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Saana Kauppi

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SAANA KAUPPI

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Abstract

Atopic dermatitis (AD) is the most common inflammatory skin disease worldwide, accounting for significant skin-related health burden. The clinical picture is characterized by inflamed eczematous lesions on the skin. For the patient carrying the disease, the main symptom is itch, often leading to impaired quality of life and sleep disturbance for the patients and their families. The disease course is variable.

The atopic comorbidities linked to AD are well known, but fewer studies have addressed non-atopic comorbidities. This study aimed to increase the knowledge of psychiatric and somatic diseases associated with AD.

The data sources used in this study were the Finnish Care Register for Health Care, including information from all Finnish hospitals, and the Finnish Digital Agency (previously Finnish Population Register Centre). The individuals with at least one or two recorded diagnoses of atopic dermatitis were included in the study populations, depending on the inclusion criteria of each separate article. The study periods ranged from 1987 to 2018. Different control populations were used.

This study describes the comorbidity in both children and adults with AD. AD is associated with psychiatric diseases, including eating disorders. Anxiety and depression are the most frequently diagnosed psychiatric diseases in adult AD patients, and the strongest associated eating disorder among adolescents with AD is bulimia nervosa. In addition, this study shows that pediatric AD patients have increased risk of celiac disease and dermatitis herpetiformis.

Patients with AD need to be met with a comprehensive approach, keeping in mind the possibility of associated somatic and psychiatric comorbidities. The aim of treatment should be disease control and minimizing the effect on the daily life of the patient.

Keywords: atopic dermatitis, comorbidity, epidemiology, registry study

Kauppi, Saana, Atooppisen ihottuman liitännäissairaudet
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Tiivistelmä

Atooppinen ekseema eli atooppinen ihottuma on maailmanlaajuisesti yleisin ihon tulehduksellinen sairaus, ja se aiheuttaa merkittävän osan ihosairauksiin liittyvästä kokonaistautitaakasta. Sairaus ilmenee vaihtelevan laajuisina ihottumaläiskinä. Sairauden merkittävin oire on kutina, mikä johtaa usein potilaan ja perheenjäsenten elämänlaadun heikkenemiseen ja unihäiriöihin. Atooppisen ihottuman taudinkulku on vaihteleva.

Sairauden atooppiset liitännäissairaudet tunnistetaan hyvin, mutta ei-atooppisia liitännäissairauksia on tutkittu vähemmän. Tämän tutkimuksen tavoitteena oli lisätä tietämystä atooppiseen ekseemaan liittyvistä psykiatrisista ja somaattisista sairauksista.

Tutkimuksen aineistoina käytettiin Terveyden ja hyvinvoinnin laitoksen hoitoilmoitusjärjestelmää sekä Digi- ja väestötietoviraston väestörekisteriä vuosilta 1987–2018. Sisäänottokriteerinä oli rekisteriin kirjattu atooppinen ekseema-diagnoosi, jonka tuli tutkimuksen osatyöstä riippuen esiintyä vähintään yksi tai kaksi kertaa. Tutkimuksen eri osa-alueissa käytettiin vaihtelevia verrokkiaineistoja.

Tämä tutkimus antaa lisää tietoa atooppisen ekseeman liitännäissairauksista. Atooppista ihottumaa sairastavilla on suurentunut riski psykiatrisille sairauksille, syömishäiriöt mukaan lukien. Ahdistuneisuushäiriö ja masennus ovat yleisimmin kirjatut psykiatriset liitännäissairaudet aikuisilla atoopikoilla. Nuoruusikäisillä atoopikoilla on kohonnut syömishäiriöiden riski, ja suurin riski liittyy bulimiaan. Lisäksi havaitsimme lapsilla yhteyden atooppisen ihottuman ja keliakian sekä ihokeliakian välillä.

Terveydenhuollossa atooppista ihottumaa sairastavat potilaat tulee kohdata kokonaisvaltaisesti ottaen huomioon somaattisten ja psykiatristen liitännäissairauksien mahdollisuus. Taudin hyvän hallinnan ohella hoidon tavoitteena tulisi olla mahdollisimman pieni vaikutus potilaan päivittäiseen elämään.

Asiasanat: atooppinen ekseema, epidemiologia, liitännäissairaus, rekisteritutkimus

To my son Aatu

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To my dear brothers Matti, Olli and Lauri, and my beloved mother and father, Marja and Timo († 2021). Together we have survived even the hardest of times. I know you are proud of my achievements, but especially recent years have taught us that in the end, all that matters are the people around you.

Finally, to my dearest husband Janne and my beloved son Aatu. You are my everything.

"Other things may change us, but we start and end with the family."

Anthony Brandt

Oulu, October, 2023 Saana Kauppi

Abbreviations

AD	atopic dermatitis
AN	anorexia nervosa
ANA	antinuclear antibody
BID	binge-eating disorder
BN	bulimia nervosa
BP	bullous pemphigoid
CD	celiac disease
CI	confidence interval
CRHC	The Finnish Care Register for Health Care
DH	dermatitis herpetiformis
EA	European American
EADV	European Academy of Dermatology & Venereology
EASI	Eczema Area and Severity Index
ED	eating disorder
EDNOS	eating disorder not otherwise specified
FDA	U.S. Food and Drug Administration
FLG	filaggrin
HLA	human leukocyte antigen
ICD	International Classification of Diseases
IF	immunofluorescence
IgE	immunoglobulin E
IL	interleukin
ILC2	type 2 innate lymphoid cell
ISAAC	The International Study of Asthma and Allergies in Childhood
JAK	Janus kinase
LOF	loss-of-function
MMF	mycophenolate mofetil
MTX	methotrexate
OR	odds ratio
PDE4	phosphodiesterase 4
PPV	positive predictive value
SCORAD	Scoring Atopic Dermatitis Index
TCI	topical calcineurin inhibitor
TCS	topical corticosteroid
TG	transglutaminase

Th	T helper cell
TPMT	thiopurine methyltransferase
UK	The United Kingdom
UKWP	The United Kingdom Working Party
US	The United States of America
UV	ultraviolet
UVB	ultraviolet B
WHO	World Health Organization

Original publications

This thesis is based on the following publications, which are referred to throughout the text by their Roman numerals:

I Kauppi, S., Jokelainen, J., Timonen, M., Tasanen, K., & Huilaja, L. (2019). Adult Patients with Atopic Eczema have a High Burden of Psychiatric Disease: A Finnish Nationwide Registry Study *Acta Dermato-Venereologica, 99*(7), 647–651. doi: 10.2340/00015555-3165.

II Kauppi S., Jokelainen, J., Timonen, M., Tasanen, K., & Huilaja, L. (2021). Atopic Dermatitis Is Associated with Dermatitis Herpetiformis and Celiac disease in Children. *Journal of Investigative Dermatology, 141*(1), 191–193. doi: 10.1016/j.jid.2020.05.091.

III Kauppi S., Jokelainen, J., Timonen, M., Tasanen, K., & Huilaja, L. (2021). Atopic Dermatitis and the Risk of Eating Disorders: A Population-based Cohort Study. Journal of the American Academy of Dermatology, *Journal of the American Academy of Dermatology. 87*(2),474–476. doi: 10.1016/j.jaad.2021.10.021.

Contents

1 Introduction

Atopic dermatitis (AD) is the most common inflammatory skin disease affecting 10–20% of children and 10% of adults worldwide (Silverberg & Hanifin, 2013; Williams et al., 2008). The clinical picture of AD is characterized by pruritic and inflamed eczematous lesions on the skin (Langan et al., 2020). Especially the intensive itch associated with AD causes impaired quality of life and sleep disturbance for the patients and relatives (Lee et al., 2018; Salava et al., 2021). Usually, AD has a relapsing and remitting nature, but especially continuously severe AD can be highly debilitating. Chronic skin diseases have a negative psychosocial and productivity impact comparable to other chronic diseases, such as diabetes or cardiovascular diseases (Balieva et al., 2017).

AD belongs to the category of atopic diseases, which also includes asthma and allergic rhinitis. Both genetic and environmental factors play a role in the onset of the disease (Langan et al., 2020). The key elements in the pathogenesis of AD are impaired epidermal barrier function, skin microbiome dysbiosis and immune dysregulation (Cabanillas et al., 2017; Tsakok et al., 2019). Increasing evidence shows that the inflammation in AD is not limited to the skin, since several signs of systemic inflammation are found in AD patients (Brunner et al., 2017).

During the past decades, it has become obvious that systemic inflammation plays a significant role in diseases such as rheumatoid arthritis or psoriasis and explains, at least partially, the elevated risk of comorbidities related to these diseases (Boehncke, 2018). More recently, there has been increasing interest in the dermatology community in comorbidities linked to AD – not least because of improved understanding of AD pathogenesis and vigorous ongoing search for specific systemic drugs for AD. Beyond the well-recognized atopic comorbidities, AD seems to be linked to several somatic and psychiatric diseases (Davis et al., 2022). An interesting question has been raised: are the comorbidities linked to AD caused by systemic inflammation, and could the novel drugs decrease the level of systemic inflammation in AD and thus reduce the risk of comorbidities in this patient group?

There is a limited amount of data on AD comorbidities other than atopic diseases. The aim of this study was to find out psychiatric and somatic comorbidities of AD patients in different age groups. The present study aims to increase the understanding of AD as a systemic disease. Increasing the knowledge on non-atopic comorbidities linked to AD is important for comprehensive care.

2 Review of the literature

Eczema is the Greek word for ‘to boil’, and it has been used since the 19th century to describe the acute eruption of minute vesicles arising on the eczematous skin. Historically, eczema meant pruritic and oozing skin diseases of different origin. Atopic eczema, or AD, was first reported by Ferdinand Ritter von Hebra (1816–1880), an Austrian physician and dermatologist (Kramer et al., 2017). In 1933, a more complete definition of AD was created by Fred Wise and Marion Sulzberger (Kramer et al., 2017). They defined atopic dermatitis as an eczematous skin disease with onset in infancy, localization on specific anatomic sites such as flexures, and with a genetic background for atopic diseases. Even today, the diagnosis of AD is mainly clinical, and dermatologists’ assessment is considered the gold standard (Dizon et al., 2018).

2.1 Clinical presentation

AD presents with pruritic cutaneous lesions localized on specific anatomical sites with an age-related distribution (Figure 1). The clinical presentation of AD changes with age. In infancy, eczema is usually localized on the face, especially the cheeks, but can also be widely distributed, with typical sparing of the diaper area. Flexural areas and the face are the common sites of childhood AD, and eczema is usually more localized compared to infancy. Later, adolescents and adults present with either localized or widespread eczema. Typical local cutaneous sites include face, neck, hands, flexures, and eyelids. The most severe form of AD is erythroderma, where all or most of the body surface area is affected. (Langan et al., 2020)

The skin lesions of acute AD are characterized by edema, erythema, oozing, vesicles and excoriations. In a more chronic phase, paler erythema, lichenification (thickening of the skin), scaling and xerosis (dry skin) become more prominent. Pruritus is always present. (Langan et al., 2020; Weidinger & Novak, 2016).

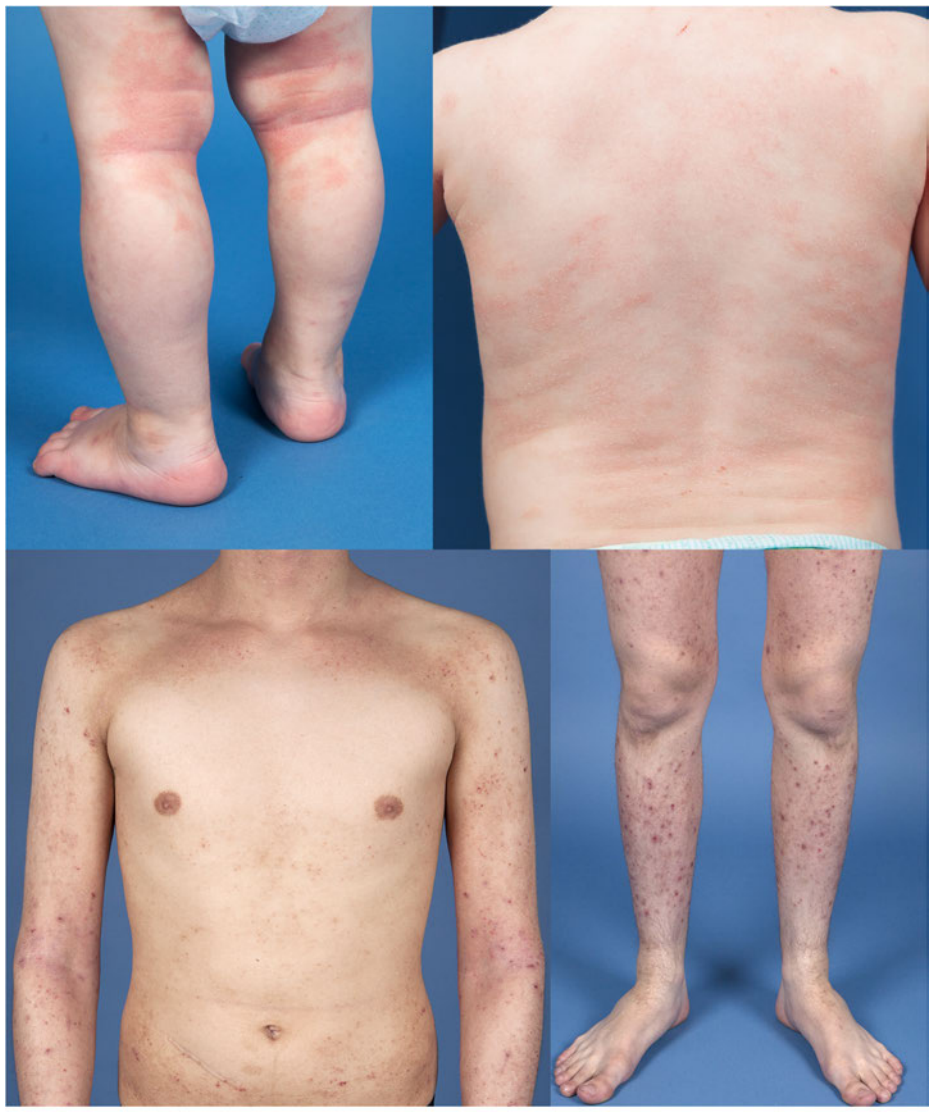

Fig 1. Clinical presentation of atopic dermatitis in a child and adult (published with consent from the Department of Dermatology, Oulu University Hospital, and from the person or the parent of the person in the photograph).

2.2 Subtypes

AD is a heterogeneous disease, and different subtypes have been classified by clinical appearance, severity of the disease, patient's age, ethnicity, filaggrin (FLG) status, immunoglobulin E (IgE) status or differences in immunologic background (Cabanillas et al., 2017; Czarnowicki et al., 2019; Girolomoni et al., 2021). Phenotype means the visible clinical features of the disease, whereas endotype is defined by the molecular mechanisms behind each phenotype (Czarnowicki et al., 2015). Studies have found specific molecular mechanisms underlying different phenotypes (Czarnowicki et al., 2015). Recognizing the molecular mechanisms behind each phenotype may help us to choose the correct therapeutic option for each AD patient in the future.

Different classifications of AD exist. The traditional classification of AD into extrinsic and intrinsic subtypes is still widely used (Czarnowicki et al., 2015). The extrinsic type, covering approximately 80% of AD patients, is characterized by elevated total and environmental serum IgE levels as well as a family history of atopic diseases (Karimkhani et al., 2015). FLG is an important epidermal structural protein in the skin. The role of FLG in AD will be discussed in detail in chapter 2.3.1. A mutation in the FLG gene is common in extrinsic AD (Karimkhani et al., 2015). Intrinsic AD (20%) is characterized by normal IgE levels, non-atopic background, female predominance, later onset, and milder disease course (Brenninkmeijer et al., 2008). The phenotype of extrinsic and intrinsic AD is similar, but the endotype of intrinsic AD shares some similarities with psoriasis compared to the extrinsic subtype (Suarez-Farinas et al., 2013). In a study of 51 patients with severe AD (extrinsic AD n = 42, intrinsic AD n = 9), the lesional skin of patients with intrinsic AD showed increased levels of T helper cell (Th)17 and Th9-type proinflammatory cytokines compared to extrinsic AD patients (Suarez-Farinas et al., 2013). Especially Th17-driven inflammation is also seen in psoriasis (Diani et al., 2016). The division of AD into extrinsic and intrinsic subtypes is, however, debatable since no consensus exists on the definition of the two entities (Roguedas-Contios & Misery, 2011). In addition, treatment of eczema seems to decrease the level of serum IgE, which makes the division to extrinsic and intrinsic AD problematic (Mandelin et al., 2010).

Definition of AD by endotype has become more relevant in terms of evolving therapeutic options and personalized medicine. There are differences in both phenotype and endotype between pediatric vs. adult, acute vs. chronic and *Staphylococcus aureus*-colonized vs. non-colonized AD (Czarnowicki et al., 2019;

Esaki et al., 2016). AD subtypes also vary between ethnicities (Czarnowicki et al., 2019). Asian AD subtype differs from European American (EA) AD by phenotype and endotype and is characterized by features of both EA AD and psoriasis. In African American AD patients, FLG mutations are infrequent (Margolis et al., 2014). The endotype is different compared to EA AD, and the phenotype is characterized by chronic and lichenified eczema (Czarnowicki et al., 2019). In a study including 193 patients with moderate-to-severe AD, 4 separate potential endotypes could be identified based on serum biomarkers, including inflammatory mediators, serum IgE and serum specific IgE antibodies against allergens (Thijs et al., 2017). Targeting the specific cytokine pathways involved in each endotype could lead to better treatment responses in the future of AD treatment.

2.3 Diagnosis

The diagnosis of AD is made clinically and based on typical signs and symptoms. AD is a heterogeneous disease lacking specific diagnostic tests, and it is difficult to define accurately. Several diagnostic criteria have been created; however, in daily practice, the diagnosis is based mainly on clinical assessment. The commonly used and most recognized diagnostic criteria for AD are the Hanifin and Rajka criteria from 1980 (Hanifin & Rajka, 1980.) The large number of different definitions for AD complicates the use of diagnostic criteria in clinical practice and for research purposes. Therefore, the United Kingdom Working Party's (UKWP) minimum list of reliable discriminators for diagnosing AD was introduced in 1994 for clinical and research purposes, and it is the most extensively validated list of criteria for AD (Brenninkmeijer et al., 2008; Williams et al., 1994, 1996). To qualify as a case, subjects are required to have:

- An itchy skin condition (or parental report of scratching or rubbing in a child)

Plus, three or more of the following:

- History of flexural involvement (including cheeks in children under 10 years)
- Onset under the age of 2 years (not used in children under 4 years)
- A personal history of asthma or hay fever (or history of asthma or hay fever in a first degree relative in children under 4 years)
- A history of generally dry skin in the last year
- Visible flexural dermatitis (or dermatitis involving the cheeks/forehead and outer limbs in children under 4 years)

Validation studies covering both hospital- and population-based settings showed sensitivity and specificity ranging from 10 to 100% and from 89 to 99% for the UKWP criteria, respectively (Brenninkmeijer et al., 2008). A Danish study tested the UKWP criteria in AD, general population, and psoriasis groups. They found a sensitivity of 71% and specificity of 96% for the UKWP criteria in general population (Thyssen et al., 2020). However, as many as 18–48% of plaque psoriasis patients met the criteria, indicating a significant problem with sensitivity (Thyssen et al., 2020). Several other criteria for AD also exist. For pediatric epidemiological research the Hanifin and Rajka criteria (Hanifin & Rajka, 1980) and the International Study of Asthma and Allergies in Childhood (ISAAC) criteria (Asher et al., 1995) for AD (Langan et al., 2020) are commonly used.

The severity of AD is mainly assessed with the Eczema Area and Severity Index (EASI) or the Scoring Atopic Dermatitis Index (SCORAD) (Chopra & Silverberg, 2018). The EASI score was first presented in 1998 (Tofte, 1998) following the development of the Psoriasis Area and Severity Index.

2.4 Natural course and prognosis

The onset of AD is usually seen during the first years of life, although onset at any age is possible (Gawkrodger et al., 1994). Several factors predict a more severe and symptomatic course of AD, including early and severe disease, high total serum IgE-level, as well as positive family history of atopic diseases (Abuabara et al., 2017; Kiiski et al., 2015). Although seen in only a part of AD patients, FLG null mutation is associated with early-onset disease and asthma (Luukkonen et al., 2017). Some AD patients are more prone to developing food allergies, allergic rhino-conjunctivitis, and asthma. The development of these atopic comorbidities in a specific sequence, typically beginning with atopic dermatitis followed by atopic rhino-conjunctivitis and asthma, is called the ‘atopic march’ (Spergel, 2010). However, in majority of patients the possible development of atopic comorbidities does not seem to follow the ’atopic march’ pattern (Haider et al., 2022). In a study of four birth cohorts, having a single atopic disease was far more common than coexistence of diseases, and most children with early-onset eczema did not develop asthma or allergic rhinitis (Haider et al., 2022). The risk of developing atopic comorbidities is inversely associated with the age of onset of atopic dermatitis (Spergel, 2010; Wan et al., 2017).

While many pediatric AD patients improve with age, recurrences are common, and some continue to have chronic persistent AD into adulthood (Abuabara et al.,

2017). In approximately 10% of adult AD patients the disease is severe (Barbarot et al., 2018). Recent studies support the fact that AD may be a chronic condition with a lifelong predisposition to clinical symptoms, since epidermal barrier dysfunction and immune dysregulation have been found even in AD patients' clinically healthy-looking skin (Abuabara et al., 2017). It may also be possible that adult-onset AD is far more common than previously thought, since studies on AD typically focus on pediatric populations (Abuabara et al., 2018). However, adult-onset AD seems to differ significantly from pediatric-onset AD by phenotype and endotype (Vakharia & Silverberg, 2019). When summarizing epidemiological studies from the US, up to one in four adult AD patients reported disease onset in adulthood (Vakharia & Silverberg, 2019). In conclusion, AD seems to be a chronic condition of any age, characterized by shifting between subclinical and clinically active disease.

2.5 Epidemiology

2.5.1 Definition of atopic dermatitis in epidemiology

The epidemiology of AD is complicated to study since the disease presents with a broad spectrum of clinical manifestations and the definition of AD varies between studies. The most common ways to define adult AD in epidemiologic studies are the use of clinical or questionnaire-based diagnostic criteria for AD (Sacotte & Silverberg, 2018). Although epidemiological research on AD is increasing, most studies still lack validation of the diagnosis of AD (Dizon et al., 2018). In a study of validation of ICD-9 codes for AD, a recorded diagnosis of AD had excellent positive predictive value (PPV) in inpatient setting (Hsu et al., 2017). A poor PPV was found for the AD diagnosis alone in outpatient setting (Hsu et al., 2017). Incorporation of atopic comorbidity diagnoses improved the specificity of AD diagnosis (Hsu et al., 2017). Another commonly used data source in epidemiological research is medical care registers. However, these registers are not primarily designed for research purposes. A systematic review of AD disease definition in epidemiological studies revealed that the main data sources were administrative databases (insurance, birth/death, employment) and primary care databases, and that most studies used a broader definition of AD than specific diagnostic codes for AD (Dizon et al., 2018). The heterogeneity in AD definition impairs the quality of the studies and makes it more difficult to compare results.

A Finnish validation study of AD diagnostic criteria in hospital registries found that only 48.7% of patients diagnosed with AD (code L20.0 in ICD-10) fulfilled the Hanifin & Rajka criteria of AD (Kurki et al., 2023). However, a further analysis of electronic health records revealed that the PPV for a verified AD diagnosis recorded in dermatology specialty was 95.7% for 2 recorded diagnoses and 88.1% for 1 recorded diagnosis of AD, indicating that AD diagnoses recorded in dermatology specialty are reliable (Kurki et al., 2023).

2.5.2 Incidence and prevalence of atopic dermatitis

AD is most frequent in high-income countries and closely linked to urban lifestyle (Odhiambo et al., 2009). Global trends in AD were assessed in a systematic review of epidemiological studies reporting an increase in the lifetime prevalence of AD between 1990–2010 in Africa, eastern Asia, western Europe, and parts of northern Europe (Deckers et al., 2012). No clear trends could be found in other regions. Significant differences exist between self-reported and physician-diagnosed prevalence rates of AD (Pols et al., 2016). Studies on AD incidence are sparse; however, a peak in infancy can be seen (Deckers et al., 2012; Langan et al., 2020). Especially, more incidence studies on AD, especially during adulthood, are needed (Bylund et al., 2020).

The prevalence of AD is up to 20% in children and 5–10% in adults in high-income countries (Barbarot et al., 2018; Cork et al., 2020; Silverberg et al., 2021; Sinikumpu et al., 2020). Most epidemiological studies on AD focus on childhood AD, and more data on adult AD epidemiology have only recently been reported, suggesting higher prevalence rates than previously thought (Sacotte & Silverberg, 2018). According to studies from the UK, the yearly prevalence of AD is estimated to vary between 11–20% in children and 5–10% in adults (Cork et al., 2020). In a study of Finnish school children aged 13–14 years, the prevalence of AD varied from 15 to 19% (Remes et al., 1998). A recent international questionnaire study on pediatric AD found 1-year prevalence rates between 3–20% based on the ISAAC criteria for AD and self or parent report of ever being told by a physician to have AD (Silverberg et al., 2021). The overall annual pediatric AD prevalence was 8–19 % in Europe, 10–15% in North America, 3–20% in the Middle East/Eurasia, 11% in East Asia, and 10–20% in Latin America (Silverberg et al., 2021).

In a Finnish cohort study, the prevalence of AD in 46-year-old adults was 4.8%, AD being far more common than previously reported (Sinikumpu et al., 2014). The diagnosis of AD was made clinically by experienced dermatologists. No significant

prevalence difference was found between the sexes (Sinikumpu et al., 2014). Globally, the prevalence of AD is reported to be lower in males compared to females (Barbarot et al., 2018; Remes et al., 1998; Sacotte & Silverberg, 2018; Silverberg et al., 2021). A survey study in the Finnish adult population found 21.9% lifetime prevalence and 10.1% annual prevalence of AD (Kiiski et al., 2022). The highest rates, 28.5% for lifetime and 15.4% for 12-month prevalence, were found in adults between 30 and 39 years, and the prevalence rates decreased with age (Kiiski et al., 2022). In a global survey study on adult population, in which AD was defined by modified UKWP/ISAAC criteria and self-report of ever having been diagnosed with AD by a physician, point prevalence rates from 2 to 5% for AD were reported (Barbarot et al., 2018). The prevalence was 4% in the EU and Canada, 5% in the US, and 2% in Japan (Barbarot et al., 2018). Recent epidemiological studies from the US reported adult AD point prevalence of 7% (Vakharia & Silverberg, 2019). A lower annual prevalence rate of 3% was found in a study from Japan (Muto et al., 2003).

In the elderly, many age-related skin symptoms – such as skin dryness, impaired barrier function and pruritus – resemble the symptoms of AD (Williamson et al., 2020). Thus, pruritic skin conditions may be difficult to distinguish from AD. Cumulated evidence suggest a 2–3% prevalence of AD in the elderly (Williamson et al., 2020). In a cross-sectional study of Finnish elderly, the prevalence of AD was only 0.36% (Sinikumpu et al., 2020).

2.6 Pathophysiology

Both genetic susceptibility and environmental factors influence the onset and course of AD. The pathophysiology of AD is based on the three key elements of impaired epidermal barrier function, skin microbiome dysbiosis and immune dysregulation, presented in Figure 2 (Tsakok et al., 2019). These elements interact in many ways in the AD skin. Even in normal-looking skin of an AD patient, impaired epidermal barrier function and alterations in the skin microbiome, especially increased *S. aureus* colonization, compared to healthy individuals can be observed (Boguniewicz & Leung, 2011). Cutaneous *S. aureus* colonization or infection impairs epidermal barrier function and drives inflammation. In addition, the structural weakness of the epidermal barrier itself enhances inflammation and drives T-cells into the skin. The T-cell driven inflammation leads further to disturbed barrier function, itching and reduced microbial diversity on the skin, thus

creating a vicious circle.(Boguniewicz & Leung, 2011; Langan et al., 2020; Tsakok et al., 2019)

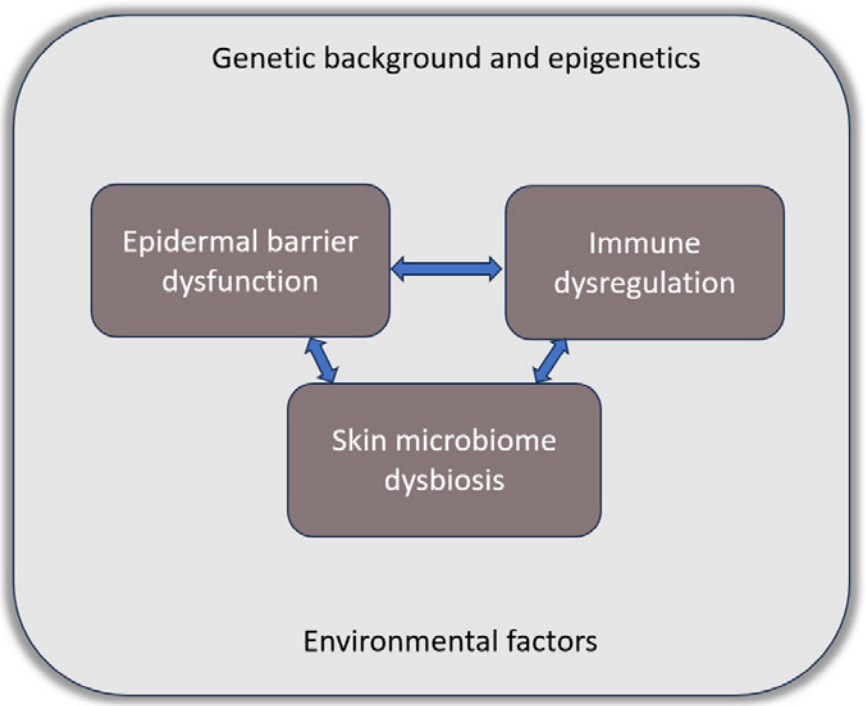

Fig 2. Pathophysiology of atopic dermatitis.

2.6.1 Genetic background and epigenetics

AD has a strong genetic background. The most important factor for the risk of developing AD is the presence of atopic disease in the family (Apfelbacher et al., 2011; Schultz Larsen, 1993). Over 60 different genes and 5 intergenic regions related to immune and barrier functions have been associated with AD (Brown, 2021; Martin et al., 2020; Paternoster et al., 2015). Recently, 5 novel AD susceptibility loci linked to immune regulation and epidermal integrity were found in a biobank study (Sliz et al., 2022). The strongest single genetic risk factor for AD is the presence of loss-of-function (LOF) mutations in the filaggrin (FLG) gene coding FLG, a key protein in epidermal structure and barrier function. Individuals with this FLG-null genotype have 3- to 5-fold risk of developing AD compared to

healthy controls (Brown & McLean, 2012). However, LOF mutations are found in only 10 to 40% of AD patients (Czarnowicki et al., 2019).

Epigenetics may partially explain the mechanisms by which environmental factors influence the development and course of AD (Martin et al., 2020). Epigenetics is the term for changes in gene expression that are not mediated by changes in DNA sequences. The epigenome seems to be dynamic and prone to alterations induced by environmental factors, such as tobacco smoke, pollutants, microbes, and diet (Liang et al., 2016).

2.6.2 Epidermal barrier dysfunction

The epidermal barrier has a vital role in preventing water loss and protecting from external mechanical, chemical and microbial stressors. The impaired epidermal barrier function in AD is characterized by increased epidermal water loss, pH and permeability, reduced water retention and altered lipid composition, and these changes can be seen in both non-lesional and lesional skin of AD patients (Langan et al., 2020). Several factors influence the epidermal function in AD. Inflammation itself, together with *S.aureus* colonization and microbial dysbiosis on AD skin, downregulate the expression of barrier genes, including the FLG gene (Beck et al., 2022; Brown & McLean, 2012; Y. Kim & Lim, 2021). Inflammation leads to pruritus and thereby, to scratching of the skin, which causes further mechanical damage to the epidermis and leads to barrier defect (Langan et al., 2020).

In AD, pruritus is mediated by nonhistaminergic pathways (Yang & Kim, 2019). The first recognized itch-mediating cytokine in AD was IL-31 produced by Th2 cells, and thereafter, epithelial-cell derived cytokines have been found to directly stimulate itch-sensory neurons (Yang & Kim, 2019). LOF mutations in the FLG gene weaken the epidermal structure and cause inflammation and T-cell infiltration into the skin; however, the mutation is found in only part of all AD patients (Brown & McLean, 2012; Luukkonen et al., 2017). Besides the FLG gene, many of the more than 60 recognized AD susceptibility genes play a role in epidermal barrier function impairing epidermal integrity (Martin et al., 2020; Paternoster et al., 2015; Sliz et al., 2022).

2.6.3 Role of microbiome

The microbiome is defined as a community of micro-organisms (such as bacteria, viruses, and fungi), their genomes and interactions in a particular location of the

body. The microbiome has been referred to as the 'second genome' since its functions and interactions have a remarkable impact on our personal health. AD patients' lesional and non-lesional skin present with microbial dysbiosis, including increased amounts of *S. aureus* and *Malassezia* fungi (Pothmann et al., 2019). A greater rate of *S.aureus* colonization is seen on lesional versus non-lesional skin (Pothmann et al., 2019). Impaired epidermal barrier function influences the composition of cutaneous microbiota and promotes colonization or infection with *S.aureus* (Kim & Kim, 2019). Reduced microbial diversity is found not only on the skin, but also in the gut, and the microbiota of the gut and skin also seem to interact with each other (Kim & Kim, 2019; Kong et al., 2012). Children and adults with AD have significant differences in cutaneous microbiome (Kim & Kim, 2019). Preceding and during a flare, reduced microbial diversity is seen on the skin of both children and adults (Kim & Kim, 2019).

Alterations in the microbiome influence the maturation of innate and adaptive immunity in a child (Kim & Kim, 2019). Although some evidence supports the colonization of the skin with *S. aureus* before the onset of AD, suggesting causality, more prospective longitudinal studies monitoring alterations in the cutaneous microbiome and the possible relationship with the development of AD are needed (Williams & Gallo, 2017). Similarly, the composition of gut flora in childhood may have an impact on AD pathogenesis (Pothmann et al., 2019). Previous studies on AD patients' microbiome focused primarily on the role of *S.aureus;* what remained unknown is the relationship between AD and other bacteria, fungi and viruses of the cutaneous microbiome (Kim & Kim, 2019). Normal vaginal delivery, breastfeeding and avoidance of unnecessary antibiotic treatments in early life are linked to a beneficial microbiome, and it may protect the individual from many diseases, including AD (Kim & Kim, 2019).

Interestingly, and perhaps assumably, studies demonstrate that treatment of AD with topical and systemic modalities is linked to increased microbial diversity and decreased levels of *S. aureus* on the skin (Kim & Kim, 2019; Pothmann et al., 2019; Seite et al., 2014). In addition, commensal skin bacteria have natural antimicrobial properties and can fight against pathogens, including *S.aureus* (Paller et al., 2019). Topical application of commensal skin bacteria in therapy of AD has shown promising preliminary results, but more studies are needed to find out the safety and efficacy of this biotherapy in AD (Paller et al., 2019).

2.6.4 Immunology

The human immune system is complex and consists of innate and adaptive immunity. To put it briefly, AD is driven by type 2 inflammation, and both innate and acquired immune responses are involved in the pathogenesis (Honda & Kabashima, 2020). Inappropriate activation of type 2 helper Th2 cells and type 2 innate lymphoid cells (ILC2s) lead to increased levels of mainly IL-13, IL-4 and IL-31, type 2 cytokines, on lesional AD skin (Czarnowicki et al., 2019; Moyle et al., 2019; Roediger et al., 2013; Ständer, 2021). Epidermal barrier disruption is thought to be the trigger of the inflammation in AD, leading to the release of epidermal inflammatory mediators, alarmins (Moyle et al., 2019). These danger signals activate inflammatory epidermal cells, including Th2 cells, cutaneous ILC2s, mast cells, basophils and eosinophils (Honda & Kabashima, 2020). Skin barrier disruption allows entry of various antigens into the skin, further activating antigen-specific effector Th2 cells (Honda & Kabashima, 2020). As inflammation continues, more and more effector Th2 cells accumulate into the skin. Both antigens and alarmins can activate these effector Th2 cells, highlighting the involvement of both innate and adaptive immunity in AD pathogenesis (Honda & Kabashima, 2020). As a sign of systemic inflammation, T-cell activation, inflammatory biomarkers, unique B-cell profile and elevated levels of IgE can be seen in peripheric blood of many patients with moderate to severe AD (Brunner et al., 2017; Thijs et al., 2018).

2.7 Treatment

Several guidelines for the treatment of AD exist, such as the European Academy of Dermatology & Venereology (EADV) 2018 guideline, the American Academy of Dermatology 2014 Guideline and the Finnish Current Care Guideline 2023 for treatment of AD (Atopic Dermatitis: Current Care Guidelines, 2023, Eichenfield, et al., 2014a, 2014b, Sidbury et al., 2014; Wollenberg et al., 2018a, 2018b). The following therapies are based on these guidelines and recent publications on the subject.

2.7.1 General measures

Avoidance of factors triggering and exacerbating eczema is recommended in AD. These factors may be physical, chemical or biological, such as rough textiles, wet

work or allergens. Especially in very young children with moderate to severe atopic dermatitis, food allergies may exacerbate AD (Bergmann et al., 2013). Psychological factors and mental stress influence AD severity; however, the specific mechanism behind the association is unknown (Wollenberg et al., 2018a).

2.7.2 Topical treatment

The basic principle of topical treatment in AD is regular application of emollients 1–2 times a day and courses of topical corticosteroids (TCS) for eczema flares. Regular application of emollients improves the epidermal barrier function. Between the flares, twice weekly application of TCS is recommended to reduce the risk of relapse and for better disease control. The potency of TCS and duration of the treatment are chosen based on patient's age and the area treated (Wollenberg et al., 2018a).

Topical calcineurin inhibitors (TCI), tacrolimus and pimecrolimus, are preferred when AD is not managed with TCS or when treating specific areas such as eyelids, flexures or anogenital skin (Wollenberg et al., 2018a). The efficacy of tacrolimus is comparable to middle potency corticosteroids with minor side effects, and no increased risk for infections or cancer (Ashcroft et al., 2005; Remitz & Reitamo, 2009). TCIs have also been found to be safe and effective treatment of AD in small children (Perälä et al., 2020).

Other topical treatments are crisaborole and topical Janus kinase (JAK) inhibitors. Crisaborole, a topical phosphodiesterase 4 (PDE4) inhibitor, is indicated for the treatment of mild to moderate AD; however, the efficacy seems quite limited (Paller et al., 2016). More promising results have been reported on treating AD with topical JAK inhibitors. Topical ruxolitinib was approved by the US Food and Drug Administration (FDA) for the treatment of mild to moderate AD in immunocompetent patients older than 12 years who had failed conventional topical treatments (Papp et al., 2021). The most common side effects were application site burning or pruritus, upper respiratory infection, and headache (Papp et al., 2021). Delgocitinib ointment, another topical JAK inhibitor, has been approved in Japan for the treatment of AD, and it seems effective and well tolerated in children and adults with AD (Nakagawa et al., 2021). To date, there is no long-term safety data on topical JAKs.

The main problem with topical therapy is poor adherence (Choi et al., 2020; Li et al., 2017). A study from Scotland reported fourfold lower use of emollients

compared to recommendations, and a significant underuse of TCS in AD patients (Choi et al., 2020).

2.7.3 Phototherapy

Ultraviolet (UV) radiation on the skin has antimicrobial, anti-inflammatory, immunosuppressive and immunomodulatory effects. In Europe, the mainly used UV wavelength is narrowband UVB of 311–313 nm. Phototherapy is usually given 2–3 times per week for 6–12 weeks at a medical unit with phototherapy equipment (Wollenberg et al., 2018a). The fact that the patient must repeatedly travel to the unit that offers phototherapy limits the use of this treatment modality. In addition, phototherapy is not suited for the treatment of small children or acute phase eczema. UVB phototherapy does not seem to increase the risk of skin cancers and remains a safe treatment alternative when suitable for use (E. Lee et al., 2005).

2.7.4 Conventional systemic therapy

Systemic therapy is an option for patients with moderate to severe AD unresponsive to topical treatments, and/or when phototherapy is contraindicated or inappropriate.

Oral glucocorticosteroids

Oral glucocorticosteroids have previously been prescribed for adult AD patients with severe acute eczema flare, showing moderate efficacy. However, rebound after withdrawal is typical and systemic steroids have a very unfavorable risk/benefit ratio (Wollenberg et al 2018). Systemic corticosteroids are not recommended for routine use in AD (Schmitt et al., 2010).

Immunosuppressive drugs

Cyclosporine is licensed for the treatment of AD in most European countries. It inhibits the production of ILs essential for the regulation of T-cell activation (Russell et al., 1992). It can be used either at intervals of 3 to 6 months or continuously. However, due to renal toxicity, treatment should not exceed 2 years. In a trial comparing oral cyclosporine and prednisolone for severe adult eczema, cyclosporine showed higher efficacy (Schmitt et al., 2010). Cyclosporine has also

shown lower risk for severe bacterial and opportunistic infections compared to oral prednisone in patients with severe AD (Schneeweiss et al., 2021).

Azathioprine, mycophenolate mofetil (MMF) and methotrexate (MTX) are other conventional treatment options, however novel systemic AD therapies are replacing these treatments. Some studies have addressed the role of these medicines in AD. Azathioprine seems effective in severe AD, but may cause gastrointestinal symptoms, leukopenia and liver damage, and is potentially myelotoxic, especially in patients with suppressed or lacking thiopurine methyltransferase (TPMT) activity (Berth-Jones et al., 2002). Azathioprine and methotrexate seem to be equally effective and safe in the treatment of moderate to severe AD for up to 5 years (Gerbens et al., 2018). A controlled trial comparing MMF with cyclosporine in long-term treatment of severe AD in adult patients showed equal efficacy in maintenance therapy, and longer clinical remission after discontinuation of the treatment, although cyclosporine showed faster response (Haeck et al., 2011).

2.7.5 Biologics and oral Janus kinase (JAK) inhibitors

Biologics and oral JAK inhibitors are novel expensive drugs for AD, and the possibility to use these new therapies depends on the reimbursement system of each country. In Finland, Kela, the Finnish social security institution, defines the criteria for reimbursement of systemic therapies for AD and thus guides doctors when choosing therapy for moderate to severe AD patients. Below is a list of the therapies that are currently available for treatment of AD, but new drugs are continuously in development.

Dupilumab

Dupilumab is a human monoclonal antibody against IL-4 receptor alpha, to inhibit the action of IL-4 and IL-13, which are important mediators in AD pathogenesis (Simpson et al., 2016). Dupilumab has shown long-term safety and efficacy in moderate to severe AD patients (Blauvelt et al., 2017; Deleuran et al., 2020). Injection site reactions and conjunctivitis are the most common side-effects of dupilumab (Simpson et al., 2016). Dupilumab is now also approved by the European Commission for children older than 6 months with AD.

Tralokinumab

Tralokinumab is a human monoclonal antibody that binds to IL-13, inhibiting its binding to IL-13 receptors alpha 1 and 2 and has shown efficacy in moderate to severe AD patients (Popovic et al., 2017; Silverberg, Toth, et al., 2021; Wollenberg et al., 2021). Conjunctivitis is the most common side effect, and the drug is generally well tolerated (Wollenberg et al., 2021). Tralokinumab is not currently available in Finland.

JAK inhibitors

JAK inhibitors are orally administered anti-inflammatory drugs with a relatively short half-life. The efficacy in AD is mediated by inhibition of IL-4, IL-13, IL-31 signaling through JAK transduction pathways. (Guttman-Yassky et al., 2021) Currently, abrocitinib, baricitinib and upadacitinib are approved in Europe for treatment of moderate to severe atopic eczema (Guttman-Yassky et al., 2021; Silverberg et al., 2020; Simpson et al., 2020). Upadacitinib and abrocitinib have shown higher efficacy in moderate to severe AD compared to dupilumab (Bieber et al., 2021; Blauvelt et al., 2021). Only upadacitinib is approved for treatment of AD in over 12-year-old children. The risk-benefit profile of JAK inhibitors in AD patients seems favorable, although more data are needed about long-term safety (Blauvelt et al., 2021; Silverberg et al., 2022; Simpson et al., 2022).

2.8 Associated diseases

AD is associated with several atopic and non-atopic comorbidities (Silverberg, 2019). In recent years, the focus on AD comorbidity studies has been on non-atopic comorbidities (Brunner et al., 2017).

2.8.1 Atopic comorbidities

The well-recognized atopic comorbidities associated with AD are food allergies, asthma and allergic rhino-conjunctivitis (Andersen et al., 2017; Carlsten et al., 2013; von Kobyletzki et al., 2012). The risk for asthma is twofold and the risk for allergic rhinitis threefold compared to general population (van der Hulst et al., 2007). However, it seems that 75.4% of children with early-life AD do not develop multimorbidity of atopic comorbidities, and that no atopic disease holds priority

over any other in terms of co-occurrence, in contrast to the theory of atopic march where eczema precedes the development of asthma and allergic rhinitis (Haider et al., 2022).

2.8.2 Somatic comorbidities

Cardiovascular diseases

The studies on cardiovascular diseases and outcomes in AD patients have found conflicting results (Andersen et al., 2016; Silverberg, 2015; Silverwood et al., 2018). When summarizing the accumulated evidence, patients with severe AD seem to have elevated risk of cardiovascular comorbidities compared to general population, but the prevalence and risk is significantly lower compared to patients with severe psoriasis (Ascott et al., 2019; Egeberg et al., 2017; Roh et al., 2022). A recent systematic review and meta-analysis including fifty-one studies found higher odds of hypertension (OR 1.16, 95% CI 10.04–1.20) in AD patients compared to healthy controls (Yousaf et al., 2022). Assumably, the risk of hypertension was lower than in psoriasis patients (Yousaf et al., 2022). In addition, AD treatments, such as cyclosporine and glucocorticosteroids, may cause a confounding effect on the results by elevating blood pressure (Yousaf et al., 2022).

Autoimmune diseases

AD patients seem to have higher odds for several autoimmune diseases compared to general or control population (Davis et al., 2022; de Lusignan et al., 2022; Ivert et al., 2021; Keskitalo et al., 2023; Narla & Silverberg, 2019; Roh et al., 2022). Especially, alopecia areata and vitiligo appear to be more frequent in AD population (Ivert et al., 2021; Narla & Silverberg, 2019; Roh et al., 2022). In a large US study of hospitalized patients, the prevalence of autoimmune diseases was 7.9% (95% CI 7.3–8.5%) in adults with AD and 5.7% (CI 5.7–5.8%) in those without AD (Narla & Silverberg, 2019). AD was associated with 18 of the 32 autoimmune diagnoses studied, including diseases of the skin, endocrine, gastrointestinal, hematologic and musculoskeletal systems (Narla & Silverberg, 2019). A recent Swedish register study found association with AD and autoimmune diseases of the skin (adjusted OR 3.10, 95% CI 3.02–3.18), gastrointestinal tract (adjusted OR 1.75, 95% CI 1.69–1.82) and connective tissue (adjusted OR 1.50, 95% CI 1.42–1.58) (Ivert et

al., 2021). It is still unclear whether the associations are a consequence of long-term inflammation due to chronic AD or whether they are based on shared immunological, genetic or environmental mechanisms. Interestingly, a primary care cohort study from the UK found higher odds for pre-existing autoimmune disease in children and adults with new-onset AD, suggesting that shared genetic and/or immunologic background are potential underlying mechanisms (de Lusignan et al., 2022).

Malignancies

AD patients may have overall decreased risk of malignancies, although the risk of certain cancer types seems to be increased (Mansfield et al., 2020; Paller et al., 2018). AD patients have higher risk of lymphoma compared to controls, and the risk of lymphoma increases with severity of AD (Legendre et al., 2015; Mansfield et al., 2020). The risk of childhood acute lymphoblastic leukemia, glioma and meningioma is decreased (Linabery et al., 2010; Linos et al., 2007; H. Wang & Diepgen, 2006; M. Wang et al., 2011).

2.8.3 Psychiatric comorbidities

Depression and anxiety

AD has been associated with depression and anxiety in children and adults in several studies (Dalgard et al., 2015; Davis et al., 2022; Roh et al., 2022; Yaghmaie et al., 2013). The risk seems to increase with eczema severity (Yaghmaie et al., 2013). The odds ratios (OR) vary between 1.44–2.19 for anxiety and 1.27–2.19 for depression in different studies (Roh et al., 2022; Rønnstad et al., 2018; Yaghmaie et al., 2013). A systematic review and meta-analysis including 106 studies found higher prevalence of depression in AD patients (20.1%) versus healthy controls (14.8%) (Patel et al., 2019). In contrast, a German study did not find an association between dermatologist-diagnosed AD and anxiety or depression (Piontek et al., 2022).

Attention-deficit hyperactivity disorder and autism spectrum disorder

AD has been associated with attention-deficit hyperactivity disorder (ADHD) and autistic spectrum disorder (ASD) in children and adults in several studies (Davis et al., 2022; Lee et al., 2016; Strom et al., 2016; Yaghmaie et al., 2013). A cohort study from Taiwan followed patients diagnosed with AD by the age of 3 years and found a significantly increased risk of developing ADHD (OR 2.92, 95% CI 2.48–3.45) and ASD (OR 8.90, 95% CI 4.98–15.92) compared to patients with no AD history (Lee et al., 2016). The certainty of evidence of an association between ADHD and AD in adult studies is low (Davis et al., 2022). Survey studies carry a risk of overreporting ADHD, since public awareness on the disease has increased in recent years (Abdelnour et al., 2022). Itch and sleep disturbance caused by AD may also induce symptoms that resemble ADHD, such as difficulties with attention and hyperactive-impulsive symptoms. A German study found association between AD and ADHD, but the association was limited to AD patients with sleeping problems, indicating that disturbance of sleep may mediate the association between AD and ADHD (Romanos et al., 2010).

Other psychiatric diseases

A German regional study has examined the association between AD and other psychiatric comorbidities than depression, anxiety, ADHD or ASD. The German register-based study of adult AD patients found association between AD and affective (OR 1.83, 95% CI 1.46–2.31), stress-related and somatoform (OR 1.94, 95% CI 1.70–2.27), behavioral (1.76, 95% CI 1.22–2.55) and schizophrenic disorders (OR 2.39, 95% CI 1.35–4.40) (Schmitt et al., 2009). A recently published questionnaire-based study reported positive associations between adult AD and several psychiatric disorders, including EDs, as well as loneliness (Zhang et al., 2023).

3 Objectives

The aim of this study was to increase knowledge about non-atopic comorbidities linked to AD utilizing data from the Finnish Care Register for Health Care (CRHC). We focused on psychiatric diseases, since few previous studies addressed the risk of psychiatric comorbidities, including eating disorders (ED), in AD population. In addition, Finnish high-quality studies have found high prevalence of celiac disease (CD) and dermatitis herpetiformis (DH) in Finland (Reunala et al., 2021). It is also known that AD patients carry increased risk of autoimmune diseases (Andersen et al., 2017). Thus, we decided to investigate if AD is associated with CD and/or DH in Finnish AD population.

The specific aims of the study were:

1. to clarify possible associations between AD and psychiatric comorbidities in Finnish adult population
2. to find out the risk of CD and DH in children and adolescents with AD
3. to determine the risk of EDs in patients with AD compared to the general population.

4 Materials and methods

4.1 Databases

The CRHC is maintained by the Finnish National Institute of Health and Welfare. The CRHC includes all inpatient visits since 1987 and outpatient visits since 1998 in all Finnish hospitals, including psychiatric hospitals. Data on date of birth, sex, unique social security number, area of residence, admission and discharge days as well as primary and subsidiary medical diagnoses are recorded in the register at individual level (Sund, 2012) The CRHC does not include data recorded in primary care. The diagnosis codes are registered according to the International Classification of Diseases (ICD), and recorded by physicians. The ICD-9 version was used between 1987 and 1995, before the revised version ICD-10 which is still currently in use. The Finnish Digital Agency maintains registers that include basic information of all Finnish residents individualized by a personal identity code. In this work, the study period started on January 1st 1987 and ended on December 31st 2014 (I), 2016 (II) or 2018 (III). The ending of the study period was based on the latest data available at the time of statistical analyses.

4.2 Study population

Individuals with one (I) or at least two (II-III) diagnoses of AD (code 6918B in ICD-9, and L20.0 in ICD-10) recorded in the CRHC were included in the AD group. In the original paper I, only the AD cases aged < 25 years at the end of the study period were included, whereas in the original papers II and III, AD cases < 18 years at the time of the first AD diagnosis during the study period were included.

4.3 Control population

Different control populations were used. In the original paper I, individuals of corresponding age with at least one recorded diagnosis of melanocytic nevus registered in the CRHC (codes 2160-9A in ICD-9 and D22 in ICD-10) during the study period served as controls. Individuals with a recorded diagnosis of melanoma (code 172 in ICD-9 and C43 and D03 in ICD-10) were excluded from the control population, since melanoma may be associated with psychiatric morbidity (Beesley et al., 2015). The melanocytic nevi patients were selected as controls since we

considered their psychiatric morbidity to be comparable to that of general population. An individual with both AD and melanocytic nevus-diagnosis ended up in the AD group. For the original papers II and III, the Finnish Digital Agency permitted and delivered random samples of 250,000 individuals over 18 years of age (II) and 500,000 Finnish residents (III) to the Finnish Institute of Health and Welfare, where the control populations were searched for recorded diagnoses in the CRHC, and thereafter the data returned to our study group for analysis. The data did not include social security data and the control individuals were not identified in the study. The selection of the Finnish Digital Agency database as a source of controls was based on the intention to achieve as unselected control population as possible.

The control groups consisted of individuals with at least one recorded diagnosis in the CRHC. The individuals lacking any diagnosis in the CRHC were excluded, since this group of people may have undiagnosed or unrecorded diseases. Those with recorded AD diagnosis were excluded from the control groups. The AD cases and the controls were matched by age and sex (I, III). No matching was needed in the study of CD and DH since no statistical difference was found in the age or sex distribution between the AD cases and the control population (II). In the original paper III, the birth year of the control group was limited to 1979–2018, since all AD cases were born during this time period.

4.4 Evaluation of comorbidities

To investigate possible associations between AD and non-atopic comorbidities, data of preselected somatic and psychiatric diagnoses (Table 1) was gathered from the CRHC for both AD cases and controls in total and by sex. Both primary and subsidiary diagnoses were included, and the inclusion criterion was at least one recorded comorbidity diagnosis. (I-III)

Table 1. International Classification of Diseases (ICD) codes used in the study.

Disease	ICD-91	ICD-10
Major depression	2961, 2968A, 3004A	F32, F33, F34.1
Bipolar disorder and manic episodes	2962-2964, 2967A[2]	F30-F31
All psychotic disorders	295, 297, 298	F20-F29
Schizophrenia and schizotypal disorder	295	F20-F21
Anxiety, dissociative, stress-related, somatoform and other nonpsychotic mental disorders	300[3], 309[4]	F40-45, F48
Anxiety disorders	3000A-C, 3002B-D, 3002X, 3003A	F40-F42
Disorders of adult personality and behavior	301, 302[5], 3027A-H, 312	F60-69[6]
Anorexia nervosa	3071A	F50.0
Bulimia nervosa	3075B	F50.2
Binge-eating disorder[7]	NA	F50.8
Eating disorder not otherwise specified	3075A	F50.9
Dermatitis herpetiformis	6940A and 6942A	L13.0
Celiac disease	5790	K90.0

[1] The Finnish version of ICD-9 , [2] No mania diagnoses in ICD-9, [3] Excluding 3004A, [4] Excluding 3092A-B, [5] Excluding 3026A , [6] Excluding F64.2, [7] Eating disorder characterized by recurrent episodes of rapid overeating followed by feelings of quilt and depression

4.5 Statistical analyses

The statistical analyses were performed using the SAS software package (version 9.4, SAS Institute, Inc) (I-III) and the R software package (version 4.0.2) (II,III). The characteristics of the study and control populations are presented as proportions and means with standard deviations. The results are presented as ORs and 95% confidence intervals (CI). Two-sided P-values less than 0.05 were considered statistically significant (I-III). E-value was calculated to assess the possible effect of unmeasured confounders (III) (Haneuse et al., 2019). Crude and adjusted ORs were calculated between the study and control groups using logistic regression analysis (I–III). Adjusting was done for selected variables.

In the original paper I, both cases and controls were searched for psychiatric diagnoses, excluding EDs. ORs were counted comparing each AD case with controls, and adjusted ORs were calculated using age and sex as confounding variables (I). Secondly, both cases and controls were searched for the diagnoses of DH and CD recorded before the age of 18 years. Since AD patients meet dermatologists more often than controls and are thereby more likely to receive a diagnosis of CD or DH, crude and adjusted ORs were calculated using age, sex and healthcare utilization as confounding variables (II).

In the original paper III, the cumulative ED diagnoses were identified for both cases and controls, firstly, before the age of 18 years, and secondly, before the age of 30 years. ED diagnoses recorded before the age of 7 years were excluded from the study, since small children can have eating problems unrelated to EDs (III) (Manikam & Perman, 2000). We hypothesized that food allergies may bias the association between AD and EDs, since food allergies are common in AD population (Flohr et al., 2014). Similarly, depression and anxiety are common in ED patients (Lewis et al., 2021). Crude and adjusted ORs were calculated using age, sex, depression, anxiety and food allergy (defined by codes 2961, 2968A, 300-301, 3004A, 5583A and 6931A in the ICD-9, and codes F31-F33, F34.1, F40-F41, K52.2, L27.2 and T78.0 in ICD-10) as confounding variables (III).

4.6 Ethical aspects and permissions

The study and control individuals were not identified or contacted in connection with the conducted studies. Thus, a statement from the ethical committee was not required. Permission to utilize the CRHC database for study purposes was obtained from the Finnish Institute of Health and Welfare 13.4.2018. Permission to utilize the Population Information System was obtained from the Finnish Digital Agency 23.4.2018. The consent to publish clinical pictures was achieved from Oulu Department of Dermatology and by contacting the individual or the parent of the underaged individual in the picture by phone 30.8.2023 and 1.9.2023. The permissions to republish the articles were received from publishers of the original papers.

5 Results

5.1 Characteristics of study and control populations (I-III)

The CRHC database search yielded 142,745 (I), 151,822 (II) and 70,883 (III) individuals with at least one recorded diagnosis of AD during the study period (I). After the inclusion criteria described in methods, 57,690 (I), 64,975 (II) and 70,584 (III) AD cases were included in the study population. The characteristics of the study and control populations are shown in Table 2.

Table 2. Characteristics of atopic dermatitis patients and controls (modified from original papers I-III).

Group	AD	Control group
I		
N	57,690[1]	40,363
Age, years[2]	31.8 (±)16.9	45.7 (±)19.4
Female	63.2%	64.0%
Male	36.8%	36.0%
II		
N	64,975[3]	228,642
Female	47.9%	47.5%
Male	51.1%	52.5%
III		
N	70,584[4]	270,783[5]
Female	45.3%	48.3%
Male	54.7%	51.7%
Age[6] at the onset of ED	16.4 (4.19)	16.1 (3.62)

[1]In 497 cases atopic dermatitis (AD) diagnosis occurred only once

[2] Data given as mean ± standard deviation

[3] Including those AD cases with at least two recorded diagnoses of AD in the register

[4] Excluding 499 individuals from the final study population with the diagnosis AD recorded only once in the Finnish Care Register for Health Care

[5]Excluding 299,217 individuals with either no records or with a recorded diagnosis of AD in the Finnish Care Register for Health care

[6]Data given as years, mean ± standard deviation

ED = eating disorder

5.2 Association of atopic dermatitis with psychiatric disorders (I,III)

At least one mental disorder diagnosis was found in 17.2% of AD patients compared with 13.1% of melanocytic nevi controls (OR 1.25, 95% CI 1.20–1.30) (I). The most common psychiatric comorbidity diagnosis was depression, being present in 10.4% of AD patients (OR 1.33, 95% CI 1.27–1.39). As previously unreported findings, we showed that AD was associated with schizophrenia and bipolar disorders (Table 3). We also found that mental disorders were more frequent in female AD population compared to males. At least one diagnosed mental disorder was found in 18.6% of women and 14.8% of men with AD. Of all the psychiatric diagnoses, only "psychotic disorders" (present in 2.4% of women and 3.0% of men) and "schizophrenia and schizotypal disorder" (present in 1.0% of women and 1.5% of men) were more common in men. Women with AD had higher odds of having anxiety disorder (OR 1.19) compared to men with AD (OR 1.05). In contrast, men had higher odds of having psychotic disorder (OR 1.66, 95% CI 1.42 – 1.94) compared to women (OR 1.42, 95% CI 1.26 – 1.61). No other significant risk differences were found between the sexes.

Table 3. Psychiatric comorbidities in patients with atopic dermatitis (N = 57,690) and melanocytic nevi (N = 40,363) controls (modified from original paper I).

Psychiatric disorder	N (%)		OR (95% CI)	aOR (95% CI)[1]
	AD	Nevi	AD vs Nevi	AD vs Nevi
All psychiatric disorders	9,913 (17.2)	5,292 (13.1)	1.38 (1.33–1.43)	1.25 (1.20–1.30)
Major depression	6,014 (10.4)	3,257 (8.1)	1.33 (1.27–1.39)	1.23 (1.17–1.29)
Neurotic, stress-related and somatoform disorders	5,227 (9.1)	2,671 (6.6)	1.41 (1.34–1.48)	1.16 (1.10–1.22)
Anxiety disorders	2,979 (5.2)	1,453 (3.6)	1.46 (1.37–1.55)	1.14 (1.07–1.22)
All psychotic disorders	1,515 (2.6)	730 (1.8)	1.46 (1.34–1.60)	1.51 (1.37–1.66)
Disorders of adult personality and behavior	1,245 (2.2)	484 (1.2)	1.82 (1.64–2.02)	1.51 (1.35–1.68)
Bipolar disorder or manic episodes	913 (1.6)	412 (1.0)	1.56 (1.39–1.75)	1.37 (1.21–1.55)
Schizophrenia and schizotypal disorder	674 (1.2)	302 (0.8)	1.57 (1.37 – 1.80)	1.62 (1.41 – 1.88)

[1]Adjusted for age and sex

AD = atopic dermatitis, nevi = melanocytic nevi, aOR = adjusted odds ratio, OR = odds ratio, CI = confidence interval

To explore further the psychiatric burden of AD patients, we focused on EDs (III). The prevalence of ED was higher in AD patients compared to controls at the age of 18 years (0.6 vs. 0.35%) and at the age of 30 years (0.77 vs. 0.47%); however, the overall prevalence was low. The prevalence of any eating disorder was higher in female vs male AD patients being 1.10 vs. 0.18% by the age of 18 years, and 1.48 vs. 0.17% by the age of 30 years, respectively. To clarify the age of onset for EDs, the cumulative prevalence of EDs for AD cases and controls is presented in Figure 3.

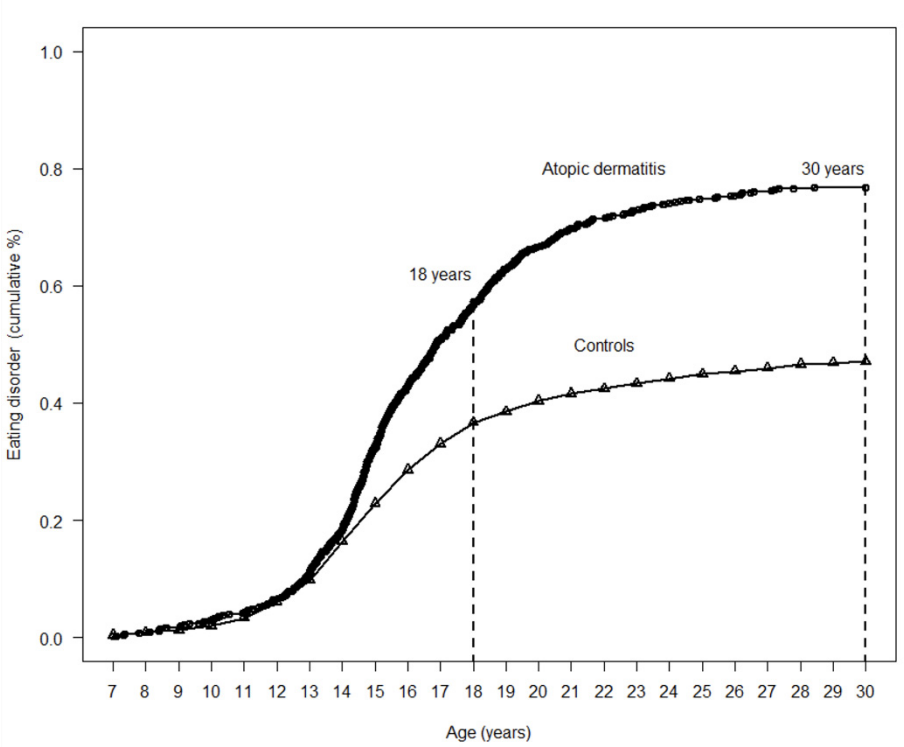

Fig 3. Cumulative prevalence of eating disorders in atopic dermatitis and control groups.

The most common ED in AD population was eating disorder not otherwise specified (EDNOS), which is recorded when the patient's disorder does not fulfill the diagnostic criteria of any specific ED diagnosis. The prevalence of EDNOS was 0.39 vs. 0.2% in the AD and control groups, respectively. At the age of 18 years the associations were found between AD and bulimia (adjusted OR 2.31, 95% CI 1.54–

3.48), followed by binge eating disorder (adjusted OR 1.86, 95% CI 1.29–2.68). The prevalence of food allergy was 31.0% in AD versus 1.43% in control population (III). The prevalence and risk of EDs in study populations before the age of 18 and 30 years are presented in the following Table 4 (III).

Table 4. Prevalence and risk of eating disorders in study populations (modified from original paper III).

Eating disorder	Group	<18 years old			<30 years old		
		N (%)	OR	aOR	N(%)	OR	aOR
All eating disorders	AD	424 (0.6)	1.74 (1.55–1.95)	1.31 (1.15-1.49)	542 (0.77)	1.64 (1.48-1.81)	1.25 (1.11-1.40
	Controls	938 (0.35)	Reference	Reference	1275 (0.47)	Reference	Reference
Anorexia nervosa	AD	214 (0.3)	1.54 (1.31–1.80)	1.15 (0.96-1.38)	266 (0.38)	1.47 (1.28–1.70)	1.09 (0.93-1.28)
	Controls	534 (0.2)	Reference	Reference	693 (0.26)	Reference	Reference
Bulimia	AD	45 (0.06)	2.79 (1.90-4.09)	2.31 (1.54-3.48)	90 (0.13)	1.75 (1.37-2.25)	1.58 (1.21-2.06)
	Controls	62 (0.02)	Reference	Reference	197 (0.07)	Reference	Reference
Binge-eating disorder	AD	57 (0.08)	2.33 (1.68–3.24)	1.86 (1.29-2.68)	82 (0.12)	2.25 (1.71-2.95)	1.68 (1.25-2.27)
	Controls	94 (0.03)	Reference	Reference	140 (0.05)	Reference	Reference
EDNOS	AD	273 (0.39)	1.91 (1.65–2.21)	1.39 (1.17-1.63)	367 (0.52)	1.84 (1.62-2.08)	1.33 (1.16-1.53)
	Controls	549 (0.2)	Reference	Reference	769 (0.28)	Reference	Reference

[1]Adjusted for age, sex, depression, anxiety, and food allergy

AD = atopic dermatitis, aOR = adjusted odds ratio, OR = odds ratio, EDNOS = eating disorder not otherwise specified

5.3 Association of atopic dermatitis with celiac disease and dermatitis herpetiformis (II)

Significant associations between DH and AD (adjusted OR 9.80, 95% CI 6.15–15.62), and between CD and AD (adjusted OR 1.92, 95% CI 1.73–2.13) were found in pediatric population. However, the overall prevalence of DH and CD was low in children with AD. Only 71 (0.1%) and 24 (0.01%) DH cases were found in AD vs. control groups, respectively. In one AD case and in 3 control cases the recorded diagnosis of DH occurred only once.

We found a similar association between AD and both DH and CD in both sexes among the pediatric AD patients. The mean age at the time of the first recorded diagnosis of AD, DH and celiac disease was 6.3, 9.6 and 8.2 years in AD population, respectively. No statistically significant difference was seen in age at onset of DH or CD between the AD and control groups.

6 Discussion

This study demonstrates that beyond the well-known atopic comorbidities, patients with AD carry a risk for non-atopic comorbidities. We found an elevated risk for psychiatric disorders, including EDs, as well as an increased risk of DH and CD in young atopics. To our knowledge, no previous studies have addressed EDs or DH in AD patients. We were also among the first to report an increased risk of schizophrenic disorders, bipolar disorder and manic episodes in adult AD patients.

6.1 Increased risk of psychiatric diseases

We found an increased risk for all psychiatric comorbidities in AD patients compared to control population (I). Overall, patients with skin diseases have more psychiatric disorders compared with the general population (Dalgard et al., 2015; Hong et al., 2008). A European questionnaire-based multicenter study investigated the burden of common skin diseases (Dalgard et al., 2015). Psoriasis, AD, hand eczema, and leg ulcers had the strongest association with depression and anxiety (Dalgard et al., 2015). In a nationwide cohort study from South Korea, AD patients (n = 25,419) were 2 times more likely to have visited a psychiatrist and 3 times more likely to have a psychiatric disorder compared to control population (Shin et al., 2016). Previously, a German study reported at least one psychiatric comorbidity diagnosis in 34% of patients with AD (Schmitt et al., 2009), compared to the 17% prevalence found in our study. The difference in prevalence may at least in part be explained by the different data sources (public hospital versus insurance-based data register) and differences in healthcare systems. We found that in AD population, mental disorders in general were more common in women compared to men, excluding psychotic disorders. This is in line with an earlier study on dermatological outpatients, where a higher prevalence of psychiatric disorders was found in females versus males (Picardi et al., 2000). In addition, schizophrenia is more common in males, and this is line with the found male predominance in psychotic disorders (McGrath et al., 2008). The risk of anxiety disorders was higher in women versus men. No risk difference between genders was found for other psychiatric diagnoses studied.

6.1.1 Depression and anxiety

The prevalence of depression was highest among psychiatric diagnoses, being

10.4 % in AD patients versus 8.1% in controls. This is in line with previous studies (Cheng et al., 2015; Shrestha et al., 2017). We found a prevalence of 5.2% for anxiety disorders compared to 3.6% in control group. Anxiety disorders were the third most common psychiatric comorbidity diagnosis group in our study of adult AD patients. Studies from the US and Korea found similar results (Shin et al., 2016; Shrestha et al., 2017). A Danish study combining questionnaire and register-based analyses found increased risk of depression, anxiety, antidepressant, or anxiolytic medication use (Thyssen et al., 2018). In the register analysis, no statistically significant risk of hospitalization or outpatient visits due to anxiety or depression was found (Thyssen et al., 2018). This result differs from other studies on this subject and may be due to use of different diagnostic criteria (UKWP) of AD. In addition, the health registry study captured only a total of 5766 patients with mild AD and 4272 patients with moderate-to-severe AD, which is markedly lower AD population compared to our study, although the population size of Finland and Denmark is similar. Differences in healthcare systems and access to specialized healthcare may have affected the results (Thyssen et al., 2018). A German study did not find association between AD and depression or suicidal ideation, however AD was associated with somatic symptoms such as back pain (Piontek et al., 2022). This result conflicts with most previously published study reports. As the authors hypothesize, somatization may be a symptom of depression(Prasad et al., 2017). In addition, a selection bias or denial of psychiatric symptoms are possible confounding variables in self-report-based studies.

6.1.2 Eating disorders

We found a previously unreported finding of an association between AD and ED. In general, the overall prevalence of EDs was relatively low in our study material, being 0.6–0.77%. Our findings are roughly in line with the results of a systematic review of 94 studies, where the point prevalence of ED was 5.7% for women and 2.2% for men (Galmiche et al., 2019). The low prevalence may also reflect resistance towards seeking medical care, which is a common phenomenon in this patient group (Smink et al., 2012). In the Finnish healthcare system, primary care physicians take care of most ED patients with mild symptoms, and only moderate to severe ED are treated in hospital setting (Eating Disorders: Current Care Guidelines, 2014). In accordance with earlier research (Treasure et al., 2020), we observed a peak onset of eating disorders in adolescence and young adulthood (Figure 3).

6.1.3 Other psychiatric diagnoses

'Neurotic, stress-related and somatoform disorders' was the second most common psychiatric diagnosis category in our study, found in 9.1% vs. 6.6% of the AD and control groups, respectively. A German study of 3,769 patients with AD reported a prevalence as high as 27.4% in this diagnosis category, and it was the most common diagnosis of AD patients in the study (Schmitt et al., 2009). The difference in prevalence may be due to differences in databases and the lack of data from psychiatric hospitals in the German study.

Although the overall prevalence of schizophrenia and schizotypal disorders was low (1.2%), we found it to be significantly associated with AD. To our knowledge, we published the first report of an association between AD and schizophrenia. In addition, we found a higher risk of bipolar disorder and manic episodes in AD patients compared to controls, with a prevalence of 1.6% vs. 1.0%, respectively. This diagnosis group was included in "affective disorders" in the German study. In line with our findings, a positive association was found between AD and affective disorders (OR 1.42, 95% CI 1.13 – 1.79) (Schmitt et al., 2009).

6.1.4 Etiology of psychiatric disease associations

Several possible etiologic factors exist that may explain the association between AD and psychiatric diseases, such as pruritus, disturbance of sleep, social stigma, emotional stress, and increased levels of inflammatory cytokines. The current understanding of the pathogenesis of psychiatric diseases includes interactions between the gut microbiome, immune system, and central nervous system (Butler et al., 2021; Wagner-Skacel et al., 2020), but the factors mediating these interactions and their possible relation to AD are widely unknown. Pro-inflammatory cytokines crossing the blood-brain barrier in prolonged eczema with constantly elevated cytokine levels have been hypothesized to function as a risk factor for autism spectrum disorders, and possibly for other psychiatric comorbidities as well (Buske-Kirschbaum et al., 2013). Another suggested mediator in the relationship between mental disorders and skin diseases is cutaneous body image (CBI), i.e., personal mental perception of the appearance of the skin, hair and nails (Gupta et al., 2004). CBI is negative in several skin diseases including AD (Hinkley et al., 2020).

Autoreactivity may play a role in the pathophysiology behind the association between AD and ED, since immune dysregulation is seen in both conditions

(Corcos et al., 2003; Narla & Silverberg, 2019). Autoreactivity means immune response against self, and it is seen in autoimmune diseases, but also in chronic inflammatory diseases that are not defined as autoimmune diseases (Santambrogio & Marrack, 2023). Female predominance is a shared feature between autoimmune diseases, major psychiatric diseases, EDs and AD (Hedman et al., 2019; Young & Pfaff, 2014). A Swedish population-based study found a bidirectional association limited to female patients between ED and several autoimmune diseases (Hedman et al., 2019). The high prevalence of food allergies in AD population does not seem to explain the co-occurrence of AD and ED. This is consistent with a prospective interview-based study of adolescents from the US, where food allergies were associated with symptoms of AN cross-sectionally, but not longitudinally. No association was found between symptoms of BN and food allergies, either (Shanahan et al., 2014). In contrast, in a Polish 5-year follow-up cohort study screening EDs with questionnaires in children with food allergies, a weak association was found between food allergies and ED (Wroblewska et al., 2018).

Both genetic and environmental factors play a role in the onset of both AD and psychiatric diseases (Culbert et al., 2015; Grotzinger et al., 2022; Silverberg, 2017). The genetic background of psychiatric diseases overlaps with major psychiatric diagnoses, and genome-wide association studies have revealed several genetic risk loci for both AD and psychiatric diseases (Cao et al., 2021; Culbert et al., 2015; Grotzinger et al., 2022; Paternoster et al., 2015; Sliz et al., 2022; Watson et al., 2019). A polygenetic analysis revealed 18 shared genetic loci between atopic diseases (asthma, hay fever and eczema) and major depression, and suggested estrogen receptor β-encoding gene ESR2 as a possible shared liability gene (Cao et al., 2021). Genetic liability to depression also seems to have a causal effect on atopic diseases, but genetic liability to atopic diseases had only a weak causal effect on depression (Cao et al., 2021). More data is needed on the possible shared genetic background of AD and other psychiatric disorders.

6.2 Increased risk of somatic diseases

In this study, we showed that AD is associated with increased risk of DH and CD compared to controls in pediatric population. We found that in pediatric AD population, the risk of CD and DH is similar between the sexes. This is in line with another somatic comorbidity study in AD patients where no significant differences were found between sexes in the risk of juvenile idiopathic arthritis (Keskitalo et al., 2023). Since DH is relatively rare, a large study population is needed to study

possible disease associations. Thus, register-based epidemiological study design is well suited for this purpose. Previous studies have found conflicting results for the risk of CD (Narla & Silverberg, 2019; Ress et al., 2014), but to our knowledge, no previous studies have addressed DH in pediatric AD population. Since DH is typically diagnosed in adulthood (Reunala et al., 2021), it is important for clinicians to be aware of possible DH in young AD patients as well. In genetically susceptible patients, gluten induces immune-mediated enteropathy – CD – and a small proportion of CD patients develop DH over time. Currently, there are no ways to predict the onset of DH in CD patients, but DH is considered a late manifestation of celiac disease (Reunala et al., 2021). We hypothesize that the skin inflammation and impaired barrier function seen in AD skin could predispose to the onset of DH. It is known that the tissue injury caused by scratching of itchy eczema lesions leads to the release of intracellular autoantigens and activates an autoimmune response against these antigens (Tang et al., 2012). This is a possible mechanism explaining the association, but there is a lack of studies on this subject.

Increasing evidence supports the fact that AD patients are at increased risk of certain somatic diseases, especially autoimmune diseases (YAndersen et al., 2017; Cipriani et al., 2017; Keskitalo et al., 2023; Narla & Silverberg, 2019). A cross-sectional US study of hospitalized AD patients found an association between AD and 18 out of 32 autoimmune disorders in adults and 13 out of 24 in children (Narla & Silverberg, 2019). Interestingly, maternal autoimmune disease increases the risk of AD in the offspring (Hamann et al., 2019).

6.2.1 Etiology of somatic disease associations

AD shares some features with autoimmune diseases, such as a relapsing-remitting course. A recent systematic review that focused on autoimmunity in AD showed that AD patients present with elevated levels of IgE class antibodies for different autoantigens of the skin and antinuclear antibodies (ANAs) compared with control subjects (Holmes et al., 2019). Both IgE and ANAs are indicators of autoimmunity. However, the mechanisms of the associations between AD and autoimmune diseases are currently largely unknown.

The genetic background of AD and autoimmune diseases has significant overlap, and most of the genetic risk loci for AD are related to immune responses (Paternoster et al., 2015; Sliz et al., 2022). A recent study by our study group showed a remarkable risk for both DH and CD in patients with bullous pemphigoid (BP) (Varpuluoma et al., 2019). It is possible that epitope spreading is one of the

mechanisms behind the association between DH/CD and BP (Ameen et al., 2000; Varpuluoma et al., 2019). Despite emerging reports of at least partially autoimmune pathomechanisms of AD (Weidinger & Novak, 2016), epitope spreading is unlikely the explanation between AD and DH/CD, since AD is not a classical autoimmune disease.

The gut microbiome is closely linked to immune system development and weight regulation, and large diversity of gut microbes is generally considered an indicator of gut health (Butler et al., 2021; Herpertz-Dahlmann et al., 2017; Kim & Kim, 2019). In contrast, reduced diversity of the gut microbiome is linked to several diseases, including autoimmune, atopic and mental diseases (Butler et al., 2021; Kim & Kim, 2019; Wagner-Skacel et al., 2020). In AD, the microbiome of both the skin and the gut is disordered and lacks diversity compared to controls, and reduction in diversity can be seen preceding eczema exacerbations (Kim & Kim, 2019; Kong et al., 2012). What remains unclear is whether alterations in gut microbiome are the outcome or the cause of diseases. It is, however, possible that gut microbiome disturbance leads to increased gut permeability predisposing self-antigens to the immune system and triggering an inadequate immune response, thus predisposing AD patients to comorbidities (Butler et al., 2021; Kim & Kim, 2019; Wagner-Skacel et al., 2020).

6.3 Strengths and limitations

The main strength of our study is the large population size. The Finnish hospital register is of high quality and completeness (Sund, 2012). It is based on exact linkage of individuals by a unique personal identification number that follows each person throughout life and is never given to another person (Thygesen & Ersboll, 2014). All the diagnoses are recorded by specialists in hospital setting, which increases the probability of correct diagnosis. In the original papers II and III, control populations were derived from random representative samples of Finnish residents. Epidemiologic study is ideal for studying rare diseases, such as DH in our study.

Our studies were limited to hospital setting since we did not have access to primary care data for this study. In Finland, mild AD cases are treated in primary care setting while moderate-to-severe AD patients are treated in hospitals. We did not assess the severity of AD in the study population, which is a limitation of our study. It is likely, that the risk of comorbidities increases together with severity of eczema (Narla & Silverberg, 2019; Patel et al., 2019; Sinikumpu et al., 2023). In

addition, we did not have access to sociodemographic and behavioral confounding factors, such as socioeconomic status, family history or smoking. In this register-based study setting we were not able to confirm the validity of the recorded diagnoses. A validation study of AD diagnosis in Finnish hospitals found that only half of the AD diagnosed individuals fulfilled the Hanifin and Rajka criteria for AD, and this is a limitation of our study in original publication I. We did however analyze where the diagnoses were recorded, and most of the AD diagnoses in the CRHC were made by dermatologists of pediatricians. To increase the validity of AD diagnosis, in the original publications II and III at least two recoded diagnoses of AD were required to be included in the study population. In the validation study, the PPV increased to 95.7% if the diagnosis was recorded at least twice in dermatology specialty (Kurki et al., 2023). The results of this study need to be interpreted with caution because in large datasets, statistical significance can be achieved with minor differences that may not be clinically relevant. Register-based studies are also prone to confounding, and we were not able to consider all possible confounding variables as we did not have access to socio-economic status, lifestyle factors or medication data. However, we evaluated the validity of our results by sensitivity analysis and found that a possible unmeasured confounder effect is unlikely to explain the results, indicating a true association (III).

Since oral glucocorticosteroids can induce psychosis, we cannot exclude that some of the recorded psychoses in AD population may be side effect of the prescribed medication. We did not include medication data in our study, and this is a limitation.

We cannot exclude misclassification of pruritic skin diseases, AD and DH, and it is possible that some of the DH diagnoses were first recorded as AD, since AD is a far more common pruritic skin disease. However, most of the DH and AD diagnoses were recorded by dermatologists, reducing the risk of misdiagnosis. Yet, young patients with AD are mainly treated by dermatologists or pediatricians, while our control subjects would primarily have visited physicians in other specialties who would be less familiar with the criteria for DH diagnosis. Therefore, DH may have been underdiagnosed in the control population. The intense pruritus in DH usually leads to a dermatology consultation; however, the median diagnostic delay varies between 8 and 12 months, and even two years or more in up to a quarter of the patients (Mansikka et al., 2018). Given the above discussed limitations in the CD and DH study, future studies are needed to assess the association between AD and CD/DH.

6.4 Clinical implications

The burden of non-atopic comorbidities in AD patients is beyond our previous understanding. This national study provides new epidemiological data about non-atopic comorbidities in AD patients. To optimize the treatment of AD, we suggest a holistic approach, keeping in mind not only atopic, but also possible psychiatric and somatic comorbidities linked to AD.

EDs threaten the normal physical and emotional development in adolescence, but early detection and treatment of ED in this vulnerable period of life can save individuals from far-reaching negative effects on overall health (Treasure et al., 2020). Dermatologists have a key role in detecting ED, since there are at least 40 cutaneous signs that can lead to the underlying diagnosis (Strumia, 2013). Individuals suffering from psychiatric diseases rarely disclose their illness. If there is any difficulty with the patients' adherence to therapy, it is wise to search for an underlying mental health problem. Similarly to psoriasis, we suggest that AD should be seen as a systemic inflammatory disease where the inflammation is not limited to the skin.

It may be possible that effective treatment of AD reduces the risk of comorbidities: more effective control of AD symptoms leads to better quality of life, improved sleep and less psychosocial distress, and may even prevent the individual from developing mental disorders. Novel therapeutics of AD seem to lead to reduction in symptoms of anxiety and depression and improvement in quality of life (Reich et al., 2023; Simpson et al., 2016). Another example of the possible prevention of comorbidities is linked to food allergies: Accumulating evidence shows that sensitization to foods happens through non-oral routes, mainly through skin. Thus, effective treatment of AD together with early oral exposure to foods with high allergy potential could possibly prevent food allergies (Barshow et al., 2021).

6.5 Future prospects

In this study, we found that AD is associated with several previously widely unknown comorbidities. It seems that comorbidities accumulate together with increasing eczema severity, but it is unclear whether patients with mild AD are spared from the disease associations found. Primary care data could give us some answers, but the data is unfortunately less reliable in terms of validity of diagnoses. Further studies are needed to clarify the underlying mechanisms and possible

endotypes behind the associations between AD and non-atopic comorbidities. Longitudinal cohort studies with standardized criteria for AD and comorbidities could give us more information about disease associations and co-occurrence or causality. New therapies make it possible to treat severe AD and some of the associated comorbidities more effectively than previously, however the pathophysiology of AD is complex and more personalized treatment is needed. A nationwide quality register for AD could aid research and help achieve real-life data on the efficacy and safety of different therapies. Future research is also needed to find out whether it is possible to prevent AD-linked comorbidities by treating AD early and effectively.

7 Conclusions

The findings of this study increase the knowledge of comorbidities associated with AD.

The following conclusions can be drawn based on studies I-III:

1. AD is associated with any psychiatric disorder in adult patients, and especially depression and anxiety are common in AD population
2. Pediatric AD patients seem to be at markedly increased risk of dermatitis herpetiformis, although the prevalence is low
3. AD is associated with eating disorders, with the strongest association seen between AD and bulimia nervosa.

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1742. Ylimartimo, Aura Tellervo (2023) Complications and outcomes of patients after emergency laparotomy

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