From the Department of Medicine Solna, Dermatology and Venereology Unit
Karolinska Institutet, Stockholm, Sweden

ATOPIC DERMATITIS IN ADULTS: EPIDEMIOLOGICAL STUDIES OF COMORBIDITY AND STUDIES OF PATIENTS ON SYSTEMIC TREATMENT

Lina Ivert

Stockholm 2021

Published by Karolinska Institutet.
Printed by Universitetsservice US-AB, 2021

ISBN 978-91-8016-256-2
Cover illustration: Design by Charlotta Larsdotter

Atopic dermatitis in adults: epidemiological studies of comorbidity and studies of patients on systemic treatment

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

Lina Ivert

The thesis will be defended in public in the Nanna Svartz Hall, Karolinska Universitetssjukhuset, Solna.

Wednesday, 23 June 2021 at 09h00

Principal Supervisor:
Professor Maria Bradley
Karolinska Institutet
Department of Medicine Solna,
Dermatology and Venereology Unit

Co-supervisor(s):
Senior Professor Carl-Fredrik Wahlgren
Karolinska Institutet
Department of Medicine Solna,
Dermatology and Venereology Unit

Emma Johansson, MD, PhD
Karolinska Institutet
Department of Medicine Solna,
Dermatology and Venereology Unit

Professor Bernt Lindelöf
Karolinska Institutet
Department of Medicine Solna,
Dermatology and Venereology Unit

Opponent:
Professor Emeritus Chris Anderson
Linköping University
Department of Clinical and Experimental Medicine

Examination Board:
Associate Professor Amra Osmancevic
University of Gothenburg
Department of Dermatology and Venereology

Associate Professor Oliver Seifert
Linköping University
Department of Clinical and Experimental Medicine

Professor Kilian Eyerich
Karolinska Institutet
Department of Medicine Solna,
Dermatology and Venereology Unit

ABSTRACT

Background: Atopic dermatitis (AD) is one of the most common chronic skin disorders globally. It is an itchy inflammatory skin disease that can have a detrimental impact on health-related quality of life. In recent years, AD has been associated with non-atopic conditions, though this requires further exploration. Novel understanding of AD pathogenesis has recently led to development of the first biological treatment. The overall aims of the thesis were to assess cardiovascular disease (CVD), autoimmune disease and depression among adults with AD, and to investigate the response to, and some adverse events from, systemic treatment that includes the first biological for AD.

Methods: Register-based, case-control studies were conducted to assess CVD and autoimmune comorbidity among patients with AD. The source population comprised the entire Swedish population aged ≥ 15 years. Cases, including all those with an inpatient diagnosis of AD (from 1968) and/or a specialist outpatient diagnosis of AD (from 2001) through 2016, were matched by sex and age to healthy controls (104,832 cases of AD, 1,022,435 controls). Patients were classified as having severe AD if they had received systemic pharmacotherapy for AD or had been treated in a dermatological ward with AD as the main diagnosis. Otherwise, AD was classified as non-severe. The clinical cohort studies and the case-series used data from a register containing prospectively collected data from adult patients with AD on systemic treatment at the Karolinska University Hospital from 2017. The register was launched for national use in 2019.

Result: *Studies I–II:* After multivariable adjustments for comorbidities and socioeconomic status, AD was associated with angina pectoris (adjusted odds ratio (aOR) 1.13, 95% confidence interval (CI) 1.08–1.19). Non-severe AD was associated with myocardial infarction (aOR 1.15, 95% CI 1.07–1.23) among men. Severe AD was associated with ischaemic stroke, with similar estimates in men and women (aOR 1.19, 95% CI 1.07–1.33). Diabetes mellitus, hyperlipidaemia, and hypertension were more prevalent in patients with severe AD than in controls, and hyperlipidaemia and hypertension were also more prevalent in patients with non-severe AD than in controls. Having AD was significantly associated with having one or more autoimmune diseases as compared with controls: (aOR 1.97, 95% CI 1.93–2.01), and this association was significantly stronger for having multiple autoimmune diseases than for having only one. The association was strongest for autoimmune disorders involving the skin, the gastrointestinal tract or the connective tissue. *Studies III–V*: In a case-series of 10 patients with severe, long-lasting AD and most often also previous eye disease, 9/10 developed eye complications during dupilumab treatment, most commonly conjunctivitis (7/10). In a cohort study of patients treated with dupilumab (n = 12), weight gain (mean 6.1 kg, range 0.1–18.0 kg, p = 0.002) was seen after 1 year on treatment. In spite of these adverse events, dupilumab was very effective and safe. More than half of patients with moderate-to-severe AD eligible for systemic treatment (n = 60) had depressive symptoms, 25% of whom presented with moderate-to-severe depression and 5% of whom had pronounced suicidal ideation. Systemic treatment for AD significantly reduced depressive symptoms, in addition to relieving symptoms of AD.

Conclusion: AD was associated with CVD and several autoimmune disorders. More than half of the patients with moderate-to-severe AD in routine dermatological care had depressive symptoms. Dupilumab was very effective and safe overall, but was associated with ocular adverse events and weight gain in these small studies. Systemic treatment for AD significantly reduced depressive symptoms in parallel with reducing AD symptoms.

LIST OF SCIENTIFIC PAPERS

I. **Ivert LU**, Johansson EK, Dal H, Lindelöf B, Wahlgren CF, Bradley M. Association between atopic dermatitis and cardiovascular disease: A nationwide register-based case-control study from Sweden. Acta Derm Venereol 2019;99:865-870.

II. **Ivert LU**, Wahlgren CF, Lindelöf B, Dal H, Bradley M, Johansson EK. Association between atopic dermatitis and autoimmune diseases: a population-based case-control study. Br J Dermatol 2020 Oct 22. doi: 10.1111/bjd.19624.

III. **Ivert LU**, Wahlgren CF, Ivert L, Lundqvist M, Bradley M. Eye complications during dupilumab treatment for severe atopic dermatitis. Acta Derm Venereol 2019;99(4):375-378.

IV. Johansson EK, **Ivert LU,** Bradley B, Lundqvist M, Bradley M. Weight gain in patients with severe atopic dermatitis treated with dupilumab: a cohort study. BMC Dermatology 2020;20(1):8.

V. **Ivert LU**, Svedbom A, Wahlgren CF, Bradley M, Johansson EK. The impact of systemic treatment of atopic dermatitis on depressive symptoms: a prospective clinical register study. Manuscript.

CONTENTS

LIST OF ABBREVIATIONS

AD	Atopic dermatitis
BMI	Body mass index
CAD	Coronary artery disease
CVD	Cardiovascular disease
DLQI	Dermatology Life Quality Index
DM1	Diabetes mellitus type 1
DM2	Diabetes mellitus type 2
EASI	Eczema Area and Severity Index
FLG	Filaggrin gene
HOME	Harmonising Outcome Measures for Eczema
HRQoL	Health-related quality of life
ICD	International Classification of Disease system
IgE	Immunoglobulin E
IL	Interleukin
JAK-STAT	Intracellular janus kinase and signal transducer and activator of transcription
LISA	The Longitudinal Integration Database for Health Insurance and Labour Market Studies
MADRS-S	Montgomery-Åsberg Depression Rating Scale–Self-report
MI	Myocardial infarction
MS	Multiple sclerosis
MTX	Methotrexate
NBHW	National Board of Health and Welfare
NPR	The National Patient Register
NRS-11	Peak pruritus numerical rating scale (11 scale steps 0 to 10)
POEM	Patient-Oriented Eczema Measure
RA	Rheumatoid arthritis
SCB	Statistics Sweden (Statistiska centralbyrån)
SwedAD	National Swedish quality register for Atopic Dermatitis
Th2 cells	Type 2 helper T cells

TNF	Tumour necrosis factor
VAS	Visual analogue scale
WAO	World Allergy Organization

1 INTRODUCTION

Atopic dermatitis (AD), also known as atopic eczema, is a common chronic inflammatory skin disease. Depending on its severity, AD can have a detrimental impact on health. There is increasing evidence for an association between AD and several non-atopic comorbidities, although causative mechanisms are largely unknown. Increased understanding of AD-associated comorbidities, in combination with reduction of risk factors, may aid prevention of certain comorbidities. Moreover, there has long been a lack of effective, safe and long-term treatments for moderate-to-severe AD. Novel understanding of AD pathophysiology has led to rapid development of new AD therapies, including biological therapies. The first biologics have recently been introduced and it seems that a new era with target-specific treatment has just begun. There is a need for more knowledge on the benefits and safety of new and emerging therapies.

The overall aims of the thesis were to assess cardiovascular disease (CVD), autoimmune disease and depression among adults with AD, and to investigate the response to, and some adverse events from, systemic treatment that includes the first biological for AD.

2 LITERATURE REVIEW

2.1 ATOPIC DERMATITIS

2.1.1 Nomenclature of AD

The earliest description of what may have been AD is found in the Roman historian Suetonus' description of Emperor Augustus (from 69 A.D.) (1). The emperor suffered from cardinal features of AD, such as intense pruritus and eczematous lesions. During the 20th century, many names have been proposed for AD, including eczema, atopic eczema, atopic dermatitis, childhood eczema, flexural eczema and prurigo Besnier (2). Controversy persists regarding the ideal nomenclature and definition (3).

In 2004, the World Allergy Organization (WAO) published a consensus statement where eczema was divided into atopic eczema – for cases associated with immunoglobulin E (IgE) sensitisation to one or more common environmental allergens – and non-atopic eczema – for cases without such sensitisation (4). In this classification, specific IgE has to be detected through a positive skin prick test or in serum. However, this definition has not been generally adopted among dermatologists (5). Up to two thirds of patients with typical clinical manifestations of AD have no IgE-mediated sensitisation to common allergens (6). Moreover, IgE-associated AD and non-IgE-associated AD show substantial overlap and cannot be clinically separated from each other. Sometimes non-IgE-associated AD develops into IgE-associated AD, which complicates the WAO classification (7).

Though the term eczema is the one most commonly used among patients and some doctors, it is highly unspecific (2). There are many different types of eczema and different underlying causes within the 'eczema family', e.g., seborrheic eczema, contact dermatitis (irritant or allergic) and nummular eczema (8). A recent meta-analysis showed that AD is the term most commonly used in scientific publications, and the authors suggested AD be the only term used, to achieve specificity and establish international agreement (2). In addition, AD is the Medical Subject Headings term used for indexing articles for PubMed. Hence, AD is the preferred term, regardless of IgE sensitisation. Therefore, it is used in this thesis.

2.1.2 Clinical features

Cardinal features of AD are generalised dry skin, recurrent eczematous lesions and pruritus, but clinical features have a wide spectrum (9). Symptoms can vary from minimal eczema to generalised erythroderma in severe cases. The word eczema is derived from the Greek word for 'boiling out' (1) and may reflect the oozing papulovesicles and erosions that can be seen in the acute phase of the disease. In contrast, chronic lesions usually have dry, scaly patches and plaques with lichenification and excoriations (9). Furthermore, clinical features can differ between ethnic groups. A follicular type with perifollicular accentuation and papules on the extensor surfaces of the extremities and on the trunk is more common in dark-skinned individuals (10). The patterns of AD usually have an age-related clinical

appearance that can be classified into three phases (9, 11). The ‘infantile phase’ (up to 2 years of life) generally involves the face, trunk and extensor surfaces of the limbs, whereas the napkin area is commonly spared. The ‘childhood phase’ (from age 1–2 years) typically involves the flexural folds in the elbows and knees, ankles, wrists and buttocks. The ‘adolescent/adult phase’ (from approximately 12 years) usually has a similar distribution as in childhood, but frequently affects the face, head, neck and hands. Hand eczema may be the only manifestation in adults. Recently, a new subgroup of AD in age > 60 years has been described (12). In this group, the cubital and popliteal extensor areas are commonly involved, but the flexural areas tend to be spared (13). AD in the elderly has been observed to have a strong pruritic component and extensive erythematosus lesions up to erythroderma (12). There are many differential diagnoses in each age group. For example, among patients 16 years or older, cutaneous T-cell lymphoma is one of the diagnoses that should be excluded (14). Several other skin diseases sometimes resemble AD, including psoriasis, pityriasis rosea, pityriasis rubra pilaris and scabies. The possibility of allergic contact eczema should always be kept in mind (14).

2.1.3 Diagnostic criteria

Diagnosis may be a challenge, especially since no specific laboratory tests or histological findings have been identified (9). Several diagnostic criteria have been used to define AD, but few have been validated (15). The first widely used AD criteria were Hanifin’s and Rajka’s diagnostic criteria created in 1980 (15). These emphasise itch as a basic feature, with a comprehensive list of other features; a set number of major and minor features must be present for a diagnosis. These criteria are still sometimes used, but have been criticised as unrealistic for use in routine practice (15). The U.K. Working Party’s diagnostic criteria for AD, also known as Williams’s criteria, are a simplified and refined version of Hanifin’s and Rajka’s diagnostic criteria (Table 1) (16). These are the most well-validated and commonly used in clinical practice as well as in clinical trials and epidemiological/population-based studies (17). In a systematic review, the U.K. Working Party’s criteria showed a sensitivity of 10–100% and specificity of 89–99% (17). They have been validated in several different ethnic groups. The lowest sensitivity (10%) was found in an Iranian study, while all other hospital-based studies have shown high sensitivity.

Table 1. The U.K. Working Party's diagnostic criteria for AD (1994).

Must have:

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

Plus 3 or more of the following:

- History of involvement of the skin creases such as folds of elbows, back of knees, fronts of ankles or around the neck (including cheeks in children under 10 years).
- A personal history of asthma or hay fever (or a history of atopic disease in a first-degree relative in children under 4 years).
- A history of generalized dry skin in the last year.
- Visible flexural eczema (or eczema involving the cheeks/forehead and outer limbs in children under 4 years).
- Onset under the age of 2 years (not used if the child is under 4 years).

2.1.4 Epidemiology

AD may be one of the most common chronic inflammatory diseases globally (18). Based on annual self-reported estimates, the prevalence is up to 20% among children and 10% among adults in high-income countries (14). Typically, AD has an early onset, with 60% of cases starting within the first year of life, but it can start in any age (9). Recent studies support that adult onset is more common than previously thought. A recent meta-analysis showed that 1 in 4 adults with AD reported adult onset (19). Some authors have questioned if this is 'fact or fancy' (20). One cannot exclude that participants had forgotten AD symptoms early in life and that persistence into adulthood might be a reflection of more severe cases (20). There are sparse and conflicting data regarding the long-term course of AD. Another recent meta-analysis of population-based cohorts of patients, followed longitudinally beyond childhood, suggested that outgrowing AD was less common than previously assumed (21). In a large Swedish hospital-based cohort of adult AD patients, followed up using questionnaires after 25–38 years, the majority of patients still reported the presence of AD (22). Nevertheless, in a Swedish general population-based study of children with preschool AD, half of the children were in complete remission by school age (from 4 through 16 years of age) (23).

2.1.5 Pathophysiology

The pathogenesis of AD is multifactorial and characterised by a complex interaction between epidermal barrier dysfunction and immune dysregulation (24, 25). Epidermal barrier dysfunction can be mediated through several factors, e.g., filaggrin gene (*FLG)* mutations – the most established cause of stratum corneum abnormalities – or by secondary mechanisms from itch-scratch and environmental exposures (9). The inflammatory response triggers epidermal disruption and itch, thus creating a vicious 'itch-scratch cycle' (18, 26). Much remains unknown regarding the mechanisms of chronic itch, but

psychological stress is one triggering factor among others (26). Skin barrier abnormalities have been observed in both eczematous lesions and non-lesioned skin in patients with AD, resulting in decreased skin hydration, increased skin pH, decreased sebum, and entry of allergens/irritants and infectious agents (18).

AD is associated with a disordered microbiota, with a low bacterial diversity, which contributes to barrier dysfunction (14, 27). In normal skin, the bacterial microbiota produces inhibitors of *Staphylococcus aureus,* but in AD flares the altered skin microbiota allows proliferation of single strains of *S. aureus* (28). *S. aureus* expresses numerous virulence factors that contribute to the pathogenesis of AD. This involves release of toxins acting as T cell-activating 'superantigens', and proteases contributing to epidermal barrier damage (28). The reason for adherence of *S. aureus* to AD skin is unclear, but changes to the composition of the stratum corneum are likely to contribute (28). AD is also associated with colonisation of *Malassezia* yeasts, which have been observed to trigger AD, especially in a subset of AD patients with head-and-neck type AD (29).

The effect of the inflammatory cascade is central in the pathogenesis of AD. The disrupted epidermal barrier, allergens, irritants and microbes stress keratinocytes to release proinflammatory and inflammatory cytokines. This activates dendritic epidermal cells, Langerhans cells and innate lymphoid cells (25, 30). The latter contribute to activation of Type 2 helper T (Th2) cells, which are considered to be key drivers of inflammation (25). Langerhans cells and dendritic cells pick up allergens and antigens that are presented to Th2 cells (25). The activated dendritic cells stimulate Th2 cells to secrete interleukin (IL)-4, IL-5, IL-13, IL-33 and IL-31 (30). The key inflammatory cytokines, IL-4 and IL-13, along with IL-5, activate the intracellular Janus kinase (JAK) and signal transducer and activator of transcription (STAT) pathway (31). Effects of this pathway include exaggeration of Th2 response by increasing proinflammatory cytokines and downregulating antimicrobial peptides (31). It also promotes IgE class switching in B cells and eosinophil expression (14). IL-4 and IL-13 have been observed to reduce the expression of *FLG* and other proteins involved in the barrier function (25). IL-31 has been identified as an important mediator of pruritus, along with IL-4, IL-13, histamine and neuropeptides, through activity on sensory neurons (25). This completes the 'itch-scratch cycle'. In the acute phase, the cutaneous cellular infiltrate in AD is characterised by Th2 and Th22 immune responses (25). It has been observed that Th1, Th22 and Th17 cells are activated and contribute to the pathology in chronic AD, for instance causing epidermal thickening and abnormal keratinocyte proliferation (30). Knowledge of the pathogenesis of AD is evolving rapidly. In summary: itch, barrier deficiencies, the microbiota and Th2-driven inflammation are currently considered to play important roles in AD.

2.1.6 Genetics

The strongest risk factor for AD is a family history of AD (14). This is supported by twin studies, where monozygotic twins are more often concordant for AD (72%) than dizygotic

twins (23%) (32). Several AD susceptibility genes have been identified through genetic studies. However, they explain less than 20% of the estimated heritability for AD (9).

The strongest known genetic risk factor for AD is null mutation in *FLG*, which encodes the important epidermal structural protein filaggrin. Filaggrin facilitates the terminal differentiation of the epidermis, forming the skin barrier (33). Filaggrin-deficient skin is associated with increased skin surface pH, allergen penetration, decreased hydration of the stratum corneum and increased colonisation with *Staphylococcus aureus* (33). *FLG* mutations are well-known to be the underlying genetic cause of ichthyosis vulgaris, a skin disease characterised by dry scaling skin, palmar hyper-linearity and keratosis pilaris (18). These features are also associated with AD. In European populations, approximately 10% carry a single null *FLG* mutation and have a mild ichthyosis vulgaris and a three-fold increased risk of having AD (9). Although *FLG* mutations are a strong genetic factor, especially in severe cases, more than 50% of carriers never develop AD (18). This indicates that multiple, as-yet unknown, genetic factors are involved in the pathogenesis. Genetic studies of AD patients in Ethiopia show that *FLG* mutations are very rare compared with in European and Asian AD patients, suggesting that genetic causes of AD may vary between ethnic groups (34).

2.1.7 Environmental risk factors

The increased prevalence of AD over the last 50 years, especially in high-income communities and urban settings, has generated several hypotheses regarding environmental risk factors of AD (35). These include a 'Western diet' (high intake of refined grains, red meat, saturated and unsaturated fatty acids), broad-spectrum antibiotic exposure (repeated exposure before 5 years of age), living in an urban setting, low UV exposure or dry climate and small family size (35). A systematic review found that a higher prevalence of AD was associated with both active and passive smoking (36). However, it remains unclear if the disease burden of AD in terms of sleep disturbance and stress triggers smoking, or if smoking can directly aggravate AD (37, 38).

In 1989, Strachan proposed the 'hygiene hypothesis'. It implied that living in small families with improved household and personal hygiene led to an increased prevalence of allergic (atopic) disease by reducing the exposure to infections early in life (39). The hypothesis was supported by the recognition of the Th1 cytokine release pattern, induced by bacterial and virus exposure, which suppressed the Th2 response involved in IgE-mediated allergy (39). On the other hand, more recent epidemiological studies show that childhood infections (e.g., colds, measles) do not protect against allergic (atopic) disorders and there is no solid evidence that hygiene and cleanliness are the main cause of allergies (40). Some authors suggested that the hygiene hypothesis is 'too clean to be true' (41, 42), and increasing evidence supports the biodiversity hypothesis (41, 43). This suggests that non-harmful microbes, acquired from the skin, gut and respiratory tract of other humans, and microorganisms from the natural environment may reduce the risk of immune

dysregulation. Thus, biodiversity loss related to an urbanised world may predispose to allergic and autoimmune disorders (44).

2.1.8 The Harmonising Outcome Measures for Eczema initiative

The Harmonising Outcome Measures for Eczema (HOME) initiative was established in 2010 with the main purpose to standardise outcome measures that should be included in clinical AD trials (45). Before 2010, several AD treatments suffered a lack of high-quality evidence. This was partly due to the heterogeneity of outcome measures used in AD research and difficulties in comparing results between studies. HOME has identified four core outcome domains for AD: clinical signs, symptoms, quality of life and long-term control (46). The domains include specific validated and reliable outcome measures also feasible for the monitoring of patients in clinical practice. The outcome measures are valid until new studies refine or develop new scales (45).

2.2 COMORBIDITY OF AD

2.2.1 Atopic comorbidities

WAO has stated the following: 'Atopy is a personal and/or familial tendency, usually in childhood or adolescence, to become sensitised and produce IgE antibodies in response to ordinary exposures to allergens, usually proteins. As a consequence, these persons can develop typical symptoms of asthma, rhinoconjunctivitis, or eczema' (4). AD is associated with and may predispose to other atopic comorbidities such as food allergy, asthma, allergic rhinitis, allergic conjunctivitis and eosinophilic esophagitis (47, 48). Food allergy, asthma and allergic rhinitis are the most common comorbidities (49). In a Swedish population-based birth cohort, children with infantile AD had an increased risk of both rhinitis (OR 2.69; 95% CI, 2.22–3.26) and asthma (OR 2.22; 95% CI, 1.65–2.98) in pre-adolescence (50). Approximately one third of children with moderate-to-severe AD, and up to 10% of the adult population with AD, suffer from food allergy (18). Cow's milk, hen's egg, peanut, wheat, soy, nuts, and fish are responsible for more than 90% of food allergies in children with AD, where milk and egg allergy are the most frequent (51). Milk allergy usually resolves before the age of about three years (52). Resolution of egg allergy has been reported for more than half (68%) of 16-year-olds (52).

In general, the clinical signs of AD start before the development of food allergy, asthma and allergic rhinitis, which then follow in a progressive order (49). AD and food allergy usually dominate in early childhood, while asthma and rhinitis may persist into adulthood. This concept of an age-associated development of atopic diseases is historically referred to as the 'atopic march' and implies that AD is required for the development of IgE sensitisation, leading to other disorders (49). However, many patients develop atopic disorders without the occurrence of AD, and IgE-mediated sensitisation does not seem to be the major mechanism for driving atopic comorbidities (18). Recent studies suggest that

shared genetic loci and environmental triggers contribute to a clustering of atopic disorders, but not always in a progressive 'march' (49).

2.2.2 Non-atopic comorbidities

Associations between AD and non-atopic comorbidities, such as certain cancers, cardiovascular, autoimmune, infectious and neuropsychiatric disorders have been reported increasingly often, but the relationships of these conditions with AD are not fully understood (47, 53). Some authors conclude that the associations between AD and non-atopic comorbidities are most likely multifactorial, involving systemic low-grade inflammation, environmental exposure, genetic predispositions, medication, lifestyle and behavioural risk factors (37). Comorbidities could also be secondary to the burdensome symptoms of AD (47). Itch and pain may have a severe negative impact on health-related quality of life (HRQoL) due to disturbed sleep, as well as having a negative influence on emotions, socio-economy and daily activities (54).

2.2.3 Cardiovascular disease

In recent years, a number of epidemiological studies have explored the association between AD and CVD (53). A Danish cohort study found an association between severe AD and cardiovascular death, but the result did not remain after adjustment for socioeconomic status, smoking, comorbidities and medication use (55). The same team also conducted a systematic review and meta-analysis and did not find any association between AD and hypertension, diabetes mellitus type 2 (DM2), myocardial infarction (MI) or stroke (56). In contrast, a recent large population-based study from the United Kingdom found that severe AD had a higher risk of CVD and stroke, which remained in adjusted models for well-established cardiovascular risk factors (57). A meta-analysis, including studies up to 2017, found no overall association between AD and CVD, but did find an association between increasing AD severity and CVD. The researchers concluded that significant associations between AD and CVD were more common in cohort studies, while the effects of AD in cross-sectional studies were heterogeneous (58). In summary, epidemiological studies have shown conflicting results.

2.2.3.1 Hypotheses on a relationship between AD and cardiovascular disease

There are several hypotheses on a potential causal relationship between AD and CVD (37, 59, 60). The relationship may be influenced or explained by a number of mediators and confounders, presented in Figure 1.

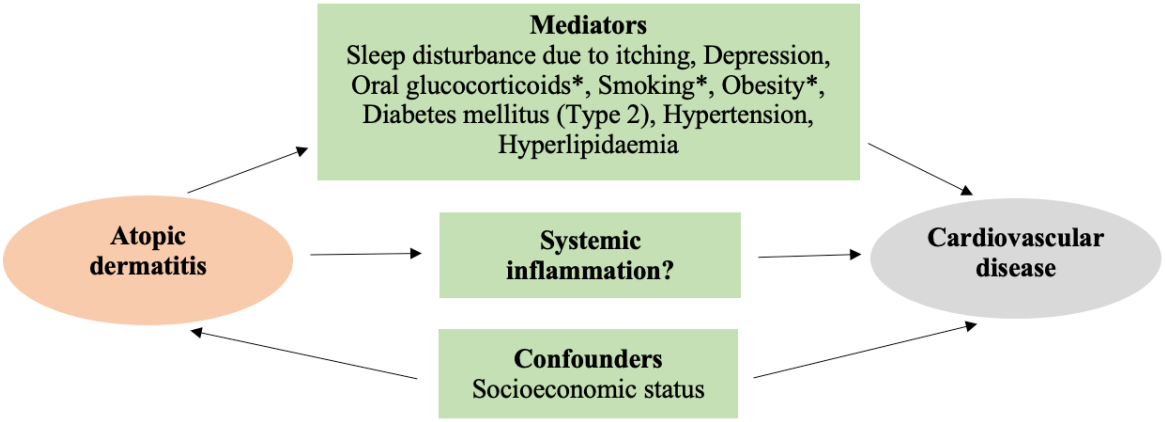

Figure 1. A model of a potential causal relationships between AD and cardiovascular disease. Potential factors considered possible as both mediators and confounders marked with *.

It has been suggested that an important mechanism for arteriosclerosis among AD patients is mediated by chronic systemic inflammation, in line with the observed risks among patients with psoriasis (61). An increase of cardiovascular risk proteins, including markers of Th1 (i.e., interferon gamma (INF-γ) and tumour necrosis factor (TNF)-β/lymphotoxin) and Th17 immune responses, has been observed in both chronic AD and psoriasis (62). However, the overall blood signatures differed in AD and psoriasis. AD has been associated with several cardiovascular risk factors such as smoking (36). Large population-based studies in the US found that AD patients had an association with sedentary lifestyle and alcohol consumption (47). A meta-analysis found an association between obesity and increased prevalence and severity of AD (63). However, in a sensitivity analysis, the association between AD and obesity was significant only in North American and Asian populations, not in European populations. Additionally, AD has been associated with multiple comorbidities (hypertension, DM2 and hyperlipidaemia) that are well-known cardiovascular risk factors (64, 65). It has been discussed if glucocorticoids may be a mediating factor between AD and CVD (59). The use of long-term systemic glucocorticoids has for various diseases been linked to adverse events including hypertension, DM2 and obesity (66). A recent systematic review found an association between use of topical glucocorticoids and development of DM2 (67). A cohort study found that exposure to > 7.5 mg of prednisolone per day for 1–5 years was associated with CVD (68). Nevertheless, long-term use of oral glucocorticoids is not among the recommendations for AD treatment in international guidelines (38).

Sleep disturbances have been associated with increased morbidity and mortality in CVD, regardless of their underlying cause (69). Several explanations have been suggested, including involvement of the autonomic nervous system, inflammation and the coagulation system. This is relevant as sleep disturbance is one of the major subjective symptoms of AD. Eczema among U.S. adults – which, however, cannot be equated with AD – has been associated with more than doubled odds of sleep disturbance, fatigue and regular daytime sleepiness compared with in healthy controls (70). The authors linked difficulties falling

asleep and premature awakening to itch. Another study, including adults with AD from several countries, found that an average of 8.4 nights had disrupted sleep during a typical AD flare (71), which could be extrapolated to at least 81 days per year and patient (70). Lastly, several studies have shown an association between depression and CVD. Depression has also been suggested as a causal risk factor for CVD (72), or as the saying goes, 'can break your heart'.

2.2.4 Autoimmune disease

Increasing evidence suggests an association between AD and several autoimmune conditions, including Crohn's disease, ulcerative colitis, coeliac disease, alopecia areata and vitiligo (64, 73). A recent systematic review found that autoimmune diseases involving skin and intestinal mucosa were more frequent in patients with AD, including systemic lupus erythematosus, while the correlations to diabetes mellitus type 1 (DM1), autoimmune thyroiditis and rheumatoid arthritis (RA) showed conflicting results and data on several major autoimmune diagnosis were limited (74). The underlying pathogenic mechanisms relating autoimmunity to AD remain unclear; some theories are presented below.

2.2.4.1 Hypotheses on a relationship between AD and autoimmune disease

Patients with moderate-to-severe AD has been observed to higher serum levels of proinflammatory markers, including IL-7, compared with controls (75). This may support AD as a systemic disorder and enhanced bioactivity in the IL-7 axis has been linked to a higher risk of DM1, RA and multiple sclerosis (MS) (75). Moreover, several studies have observed an increased risk of AD in patients with alopecia areata (76), and *FLG* mutations seem to be a strong risk factor for a severe course of alopecia areata, indicating genetic linkage (64, 77). Overlap between genetic loci in AD and other immune-mediated diseases, e.g., psoriasis and inflammatory bowel disease, has been shown, but environmental triggers are also shared, such as smoking and socioeconomic status (36, 53). Moreover, AD patients are more likely to present with multiple autoimmune comorbidities, supporting the idea of an autoimmune component of AD (78). Several studies indicate an association between AD and increased prevalence of anti-nuclear antibodies and/or IgE autoantibodies (i.e., immune response to autologous tissue, cells or proteins (78)). The latter could contribute to progression of AD and has been linked to AD disease severity.

2.2.5 Depression

The association between AD and depression and suicidal ideation is well-established (79, 80). The association has been observed to be stronger among patients with moderate-to-severe AD, although data are conflicting (79). Data on the magnitude of depression among patients with moderate-to-severe AD are scarce.

Very few studies have explored the effect of systemic AD treatment on depression symptoms. A Japanese study found that 'tight control' of AD with oral ciclosporin and topical glucocorticoids reduced depression symptoms (80). In clinical trials, dupilumab

reduced depressive symptoms (81), but whether this holds true when treatment is delivered within routine dermatological care is unknown.

2.2.5.1 Hypotheses n a relationship between AD and depression

Several symptoms of AD, such as itch and sleep disturbance, have been linked to AD severity (82). Insomnia is a well-recognised independent risk factor for development of depression, and one of the cardinal symptoms of a major depressive disorder (83). Further, the burden of disease extends beyond physical symptoms. Several factors have been assumed to cause depression among patients with AD, such as social isolation, stigmatisation due to facial eczema, restrictions in occupation and sports activities, problems in relationship and with sexuality, and financial costs (47, 84). AD patients have also been observed to have an alteration in their proinflammatory cytokine levels related to the metabolism of neurotransmitters including serotonin, norepinephrine and dopamine (85). Thus, it is possible that chronic neuroinflammation in AD may contribute to depression (86).

2.3 SYSTEMIC TREATMENT OF AD

2.3.1 Overview of AD management

At present, there is no therapeutic cure for AD. The aim of AD management is to reduce pruritus, improve HRQoL and establish long-term disease control (38). Cornerstones of basic treatment comprise avoidance of trigger factors, continuous use of emollients to restore the epidermal barrier, and topical anti-inflammatory therapy (glucocorticoids, calcineurin inhibitors) (9). Additionally, patient education of AD involving disease management and strategies to cope with the disease are important to improve HRQoL and eczema severity (87). Basic therapy is sufficient in most AD cases and is included in maintenance therapy for all AD patients. However, such interventions and phototherapy (UVB) often have limited efficacy in moderate-to-severe AD. Adults with severe AD have for many years been treated with conventional systemic drugs, such as ciclosporin, methotrexate, azathioprine and mycophenolate mofetil (14). Only ciclosporin is approved for AD; the others are used off-label (14). Long-term management with systemic glucocorticoids is not recommended due to the risk profile, and though shorter courses are common, they may cause flares (88). AD can be challenging to treat, and off-label systemic treatments may be contraindicated, ineffective or induce adverse events. Improved understanding of the immunopathogenesis of AD has led to a new era in development of systemic treatments that are more specific for certain targets, such as type 2 immunity, JAK-STAT and itch signalling pathways (18). In 2017, dupilumab, the first biologic for AD, was approved in Europe for patients with moderate-to-severe disease (31). Baricitinib, a selective inhibitor of JAK1 and JAK2, has recently been approved in Europe with the same indication (89). Several new treatments for AD may be introduced in the near future. The following section discusses the most commonly used systemic treatments, including the two recently approved drugs.

2.3.2 Conventional systemic drugs for AD

2.3.2.1 Ciclosporin

Ciclosporin, acting through inhibition of T cell proliferation, is currently the recommended first-line short-term treatment for moderate-to-severe AD in several European countries (90, 91). Multiple clinical trials have shown significant rapid effect within 2–6 weeks (often around 2 weeks), but prompt relapse of clinical and subjective symptoms of AD is common if the medication is stopped (88, 90). The most common adverse events include nephrotoxic effects and hypertension, especially with doses exceeding 5 mg/kg/day and among elderly patients. The treatment period is recommended not to exceed 2 years, although many patients have been observed to tolerate low doses for longer periods of time (92).

2.3.2.2 Methotrexate

Methotrexate (MTX), a folic acid antagonist thought to suppress several T cell activities, has been used for more than 50 years as an immunosuppressant for various dermatological diseases (93). Despite its long history in dermatology, very few published studies have explored the effects and adverse events of MTX for AD. Nevertheless, in clinical practice, it has been reported to yield a good clinical response (90). A randomised trial including 42 patients compared MTX with azathioprine (94). At week 12, both treatments were considered to achieve clinically relevant improvement and to be safe for short-term use. The average time to response has been estimated to 8–12 weeks (90). The most severe side effects reported include bone marrow suppression, hepatotoxicity and pulmonary fibrosis. Therefore, folic acid supplementation is recommended to reduce the risk of hematologic and gastrointestinal toxicity (88).

2.3.2.3 Azathioprine

Azathioprine, a purine analogue that is converted into 6-mercaptopurine (6-MP), acts by inhibiting DNA production, especially in cells with a high proliferation rate, such as B and T cells (95). Studies on efficacy and long-term safety are limited. For short-term use, it is considered to be an effective treatment – comparable with methotrexate – although one study concluded that adverse events were common (90). The most common adverse events included headache, gastrointestinal symptoms, elevated liver enzymes and bone marrow toxicity (88). During metabolism of azathioprine, thiopurine methyltransferase inactivates 6-MP. Consequently, among patients with thiopurine methyltransferase deficiency (approximately 10% of the general population), there is a risk of azathioprine toxicity even at subtherapeutic doses (95). Therefore, measurement of this enzyme is strongly recommended before initiating treatment, especially to reduce the risk of severe bone marrow suppression (95).

2.3.2.4 Mycophenolate mofetil

Mycophenolate mofetil is an immunosuppressant inhibiting B cell and T cell proliferation (88). Some case reports and clinical data indicate that mycophenolate mofetil may be

effective in AD and it is generally well-tolerated. Gastrointestinal problems are the most common side effects (90). Other observed adverse events include bone marrow suppression and infections. Data supporting the use of mycophenolate mofetil in AD are limited, and therefore it has only been recommended (off-label) if ciclosporin has failed or is not indicated (90).

2.3.3 Novel systemic drugs for AD

2.3.3.1 Dupilumab

Dupilumab is a human monoclonal antibody that inhibits IL-4 and IL-13 signalling through blockade of the shared IL-4α subunit (96). By blocking IL-4/IL-13 signalling, dupilumab effectively suppresses T helper 2-mediated inflammation and restores the skin barrier function (96). The effect is mediated through downregulation of receptor signalling downstream of the JAK-STAT pathway, which regulates many genes involved in the pathogenesis of AD (97). Dupilumab has been shown to result in significant improvement in clinical parameters and has a good safety profile. Looking at all trials published up to 2018, around 70% of the patients achieved a 75% improvement from baseline (EASI-75) during the study periods, and full clinical response was observed around week 4 (90). Approximately 15% more patients achieved EASI-75 at week 16 when dupilumab was evaluated with concomitant topical glucocorticoids (96). In 2018, a meta-analysis of adverse events in clinical trials found that dupilumab slightly increased the risk of headache and moderately increased the risk of injection site reactions compared with placebo, and conjunctivitis was observed in 8% of participants (98). In 2021, a systematic review and meta-analysis of real-world data found that dupilumab was effective and well-tolerated. The mean reduction in EASI score at week 16 was comparable with that in clinical trials. Ocular adverse events were the most common side effect and the main reason for treatment discontinuation (99).

2.3.3.2 Baricitinib

Baricitinib is an oral selective JAK1 and JAK2 inhibitor. Two independent phase III trials reported that baricitinib in monotherapy for moderate-to-severe AD improved clinical signs and symptoms, and that itch was improved within one week (100). The effect appeared to be inferior to that of dupilumab at 16 weeks' follow-up, but advantages may include rapid effect on itch, oral administration and a different profile of adverse events that may be better for some patients. Upper respiratory tract infections, creatine phosphokinase elevations and headache were the most common side effects. In pooled analyses of 8 randomised clinical trials, the most common serious adverse events were eczema herpeticum, cellulitis and pneumonia (101).

3 RESEARCH AIMS

The overall aims of the thesis were to increase knowledge on the association between AD and non-atopic comorbidities, and on the efficacy and adverse events of current and new systemic treatment for AD. The included research projects aimed more specifically to:

1. Investigate the association between AD and CVD, i.e., coronary artery diseases (CAD; angina pectoris and MI) or ischaemic stroke.
2. Investigate the association between AD and autoimmune diseases.
3. Describe ocular adverse events and weight gain from dupilumab treatment for AD in adults.
4. Describe depressive symptoms in adults with AD before and during systemic treatment.

3.1 RESEARCH FRAMEWORK

Table 2. Overview of the main research questions and related study areas.

Focus area Atopic dermatitis (AD)	Research questions	Methodological approach	Study/Outcome
Comorbidity	What is the association between AD and **coronary artery disease and/or ischaemic stroke**? Does the magnitude of such associations vary with the severity of AD?	Swedish national register data	I. Coronary artery disease and/or ischaemic stroke
	What is the association between AD and **autoimmune diseases**?		II. Autoimmune disease
	What is the prevalence of **depression** among patients with moderate-to-severe AD?	Real-life data: prospective follow-up	V. Depression
Systemic treatment	What **ocular adverse events** are associated with systemic treatment of AD?		III. Ocular adverse events
	Is dupilumab treatment of AD associated with **weight gain**?		IV. Weight gain
	How does systemic treatment of AD **impact depressive symptoms**?		V. Depressive symptoms

4 MATERIALS AND METHODS

4.1 A SUMMARY OF THE MATERIALS AND METHODS IN THE THESIS

Table 3. A summary of the studies included in the thesis.

Study	I	II	III/IV	V
Design	Case-control study	Case-control study	Case series /Cohort study	Cohort study
Study population	Swedish population age ≥ 15 years, 1968–2016	Swedish population age ≥ 15 years, 1968–2016	Patients ≥ 18 years on systemic treatment for AD at the Karolinska University Hospital 2017–2019**	Patients ≥ 18 years on systemic treatment for AD and included in SwedAD*** at the Karolinska University Hospital 2017–2020
Data source	The National Patient Register, the Medical Birth Register, the Cause of Death Register, the Swedish Prescribed Drug Register, the Total Population Register, LISA*	The National Patient Register, the Medical Birth Register, the Total Population Register, LISA* the Multi-Generation Register	Local research register with prospectively collected data	Local research register with prospectively collected data/ SwedAD***
Main factors analysed	The association between AD and coronary artery disease and/or ischaemic stroke	The association between AD and autoimmune diseases	Ocular adverse events and weight gain associated with dupilumab treatment of AD	The impact of systemic treatment of AD on depressive symptoms
Statistical analyses	Conditional logistic regression, Student's *t*-test, Pearson's χ^2 test	Conditional logistic regression, Student's *t*-test, Pearson's χ^2 test	Mann-Whitney U-test, Wilcoxon signed-rank test	Mann-Whitney U-test, Wilcoxon signed-rank test, Pearson's χ^2 test, Friedman's ANOVA[a], Spearman's rank order correlation

AD: Atopic dermatitis. *The Longitudinal Integration Database for Health Insurance and Labour Market Studies. **Study III: Treated with dupilumab ≥ 3 months, Study IV: Treated with dupilumab and/or methotrexate ≥ 6 months. ***National Swedish quality register for Atopic Dermatitis (SwedAD) [a] Friedman's repeated measurements analysis of variance (ANOVA).

4.2 DATA SOURCES

4.2.1 National registers

The history of the Swedish national population registers goes back to the 17th century. The Swedish church registers enabled the Swedish state to enrol soldiers for the army and to collect taxes (102). Today, the primary aim of the national registers, held by Statistics Sweden (SCB) and the National Board of Health and Welfare (NBHW), is to provide complete population-based data to the government and to facilitate analyses and decisions. Swedish register data have also been, and still are, an important part of Swedish medical and epidemiological research. Personal identity numbers enable linkage of data from several Swedish national and health care registers. The national registers below were used as data sources for the epidemiological studies in this thesis.

4.2.1.1 The National Patient Register

The National Patient Register (NPR) comprises data about inpatient diagnoses and hospital discharges from 1964 onward (the Swedish National Inpatient Register) and has complete national coverage since 1987. Additionally, the NPR holds the outpatient register with data from both private and public caregivers since 2001 (103). The NPR is maintained by the NBHW.

Diagnoses are coded based on the Swedish International Classification of Disease system (ICD). The coverage of inpatient diagnoses is almost 100% for all somatic (including surgery treatments) and psychiatric diagnoses. The coverage of outpatients is lower (about 80%), mainly because of missing data from private caregivers. Validation of the Swedish national inpatient register has shown a positive predictive value of about 85–95% for most diagnoses (103). The validity of the correctness of AD has, to my knowledge, not yet been investigated.

4.2.1.2 The Medical Birth Register

The Swedish Medical Birth Register, held by the NBHW, has information about all births in Sweden since 1973 (104). It contains information about pregnancy, delivery and the new-born child. Additionally, it includes detailed data of mothers registered in prenatal care, such as pre-existing diagnoses, maternal drug use, smoking habits and weight (105). Data on smoking are available from the Medical Birth Register for women registered in antenatal care after 1982.

4.2.1.3 The Cause of Death Register

The Swedish Cause of Death Register is one of the oldest in the world (106). The Swedish parliament introduced a nationwide reporting system for cause of death statistics in 1749. However, for more than a century, only ‘important’ causes of deaths were recorded, such as maternal death and death in an epidemic. The Cause of Death Register has full coverage since 1952, including data on cause and date of death. It also includes data on Swedish

residents who died abroad. The completeness of the register is almost 100% and 96% of individuals in the register have a specific underlying cause of death recorded. The quality of the register is closely linked to that of death certificates and therefore most reliable for those who died in hospitals. High agreement between medical records and the Cause of Death Register has been reported for several diseases, including death from cardiovascular disease (106). The Cause of Death Register is maintained by the NBHW.

4.2.1.4 The Swedish Prescribed Drug Register

The Swedish Prescribed Drug Register, held by the NBHW, contains information about all prescribed drugs dispensed at Swedish pharmacies since July 2005 (107). It includes the personal identity number of the patient, the prescriber's profession, speciality and workplace address. It has detailed information about the dispensed item (Anatomical Therapeutic Chemical [ATC] code, date of prescription, dispensing, dosage and brand name). The register does not include over-the-counter drugs and drugs used for inpatients in hospitals. It only includes some of the drugs used in outpatient care, which may be administrated in hospital day care; examples include intravenous infusions.

4.2.1.5 The Total Population Register

The Total Population Register, maintained by SCB, was established in 1968 and is since then updated with new data every year. It contains data on births, deaths, immigration/emigration, civil status and place of residence of the population alive at the end of the year (102).

4.2.1.6 The Longitudinal Integration Database for Health Insurance and Labour Market Studies

The Longitudinal Integration Database for Health Insurance and Labour Market Studies (LISA), maintained by SCB, holds information on employment, income and education for the Swedish population 16 years or older (108).

4.2.1.7 The Multi Generation Register

The Multi Generation Register, maintained by SCB, contains links to biological parents. Persons who have been registered in Sweden at any time after 1961 and who were born 1932 or later have a link to their own parents and their own biological children (109). It also holds information about adoptive parents.

4.2.2 The Swedish quality register for atopic dermatitis (SwedAD)

In 2017, the research group with which I was associated during my thesis project launched a database and quality register for patients on systemic treatment for AD (system platform DermaReg provided by Carmona, Halmstad, Sweden). The purpose was to follow up the effects and adverse events of current and new treatments for AD using established scoring systems and systematically and prospectively collected information. The establishment of

the quality register, SwedAD (Figure 2) (110), has been an important part of my thesis work and was a prerequisite for Studies III–V.

The register includes, among other things, detailed demographic data, information about working limitations due to eczema, information about atopic and non-atopic comorbidities, information about smoking and alcohol consumption, laboratory values, including *FLG* mutations and IgE sensitisation, information about contact allergies, data on duration of pharmacotherapy and adverse events from systemic treatment for AD. Patient-reported data are collected via tablets or mobile phones at each patient visit and investigator-reported data are entered through a computer. The platform has data from the Karolinska University Hospital from January 10, 2017 and was launched for national use on September 1, 2019, in dialogue with the 'Svenska Sällskapet för Dermatologi och Venereologi' and the 'Nationella programområdet (NPO) för dermatologi och venereologi'.

Figure 2. The logo of National Swedish quality register for Atopic Dermatitis (SwedAD).

4.2.2.1 Outcome measures

SwedAD includes outcome measures recommended by HOME. Additionally, SwedAD has information about depressive symptoms and other variables, as previously outlined. Outcome measures for long-term disease control are not yet included, but will be considered in the future.

The **Eczema Area and Severity Index** (EASI) is the core outcome measure of clinician-reported signs of AD at a clinical examination of the patient and measures erythema, excoriations, oedema/papulation and lichenification (46). The signs and extent of disease are weighted equally. The EASI score ranges from 0 to 72, with higher scores indicating greater severity of AD. The minimal clinically important difference for change in EASI score between two examinations has been estimated to 6.6 (111). Change in EASI scores may also be presented as improvement from baseline by 50%, 75% or 90% (46), in this thesis referred to as EASI-50, EASI-75 and EASI-90, respectively.

The **Patient-Oriented Eczema Measure** (POEM) measures patient-reported symptoms of AD in the past 7 days (112). It captures the frequency of seven symptoms, including itch, sleep disturbance, bleeding, weeping or oozing, cracking, flaking and dryness. The POEM score ranges from 0 to 28, where a higher score indicates a greater symptom burden of AD. POEM does not capture the intensity of these symptoms. An improvement by 4 points is considered to be the minimal clinically important difference for change (111).

The **Peak Pruritus Numerical Rating Scale** (NRS-11) measures the worst peak itch over the last 24 hours reported by the patient (113). The scale has 11 steps, ranging from 0 to 10, with 10 being the "worst itch imaginable". A recent validation study has suggested that a change of more than 2–4 points from baseline is clinically relevant (113). Only a few instruments are validated to estimate itch severity over the last 24 h among adults. High reliability and validity has been found between a visual analogue scale (VAS) for the last 24 h (100 mm line) and NRS-11 (114), but VAS has limited evidence for construct validity and was therefore not recommended in the HOME consensus meeting in 2019 (115). VAS for pruritus during the last 3 days was used by SwedAD until September 2019, thereafter being replaced by NRS-11, as recommended by HOME.

The **Dermatology Life Quality Index** (DLQI) is a self-report questionnaire to evaluate skin disease impact on HRQoL (116). The scale ranges from 0 to 30, with higher scores indicating greater effect on HRQoL. The questionnaire domains include symptoms and feelings, daily activities, leisure, work/school, personal relationships and treatment.

The **Montgomery Åsberg Depression Rating Scale-Self-report** (MADRS-S) is a self-rated questionnaire to evaluate depression and change of depressive symptoms (117, 118). The MADRS-S includes nine questions related to reported sadness, feelings of unease, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimism and suicidal thoughts (119). Each of these items may score between 0 and 6, and thus the sum can range between 0 and 54 points, with higher scores indicating a more severe depression. The threshold scores for different levels of depression vary between studies. The cut-off scores recommended by Svanborg and Ekselius, including the score for severe depression recommended by Snaith et al., are commonly used in Swedish studies. No depression is defined as 0–12, light depression as 13–19, moderate depression as 20–34 and severe depression as ≥ 35 points (120-122). In Study V, item 9 in MADRS-S was used to assess suicidal thoughts. For that item, 0 means 'enjoys life or takes it as it comes' and 6 means 'explicit plans for suicide when there is an opportunity'. Exhibiting marked suicidal ideation was defined as an item 9 score ≥ 4 (suicidal thoughts common/better off dead).

4.3 STUDY DESIGN AND STUDY POPULATION

4.3.1 Register-based case-control studies: Studies I–II

In Studies I–II, nationwide register-based case-control studies were conducted to investigate the association between AD and comorbidities as presented in Tables 4–6. Data were linked from several Swedish national registers. The source population comprised the entire Swedish population aged 15 years or older in the years 1968 through 2016. All patients with an inpatient diagnosis of AD (from 1968 onward) or an outpatient diagnosis of AD (from 2001 through 2016) were identified in the NPR and treated as cases. For comparison, 10 randomly selected age- and sex-matched control subjects for each case were identified from the Total Population Register. Exclusion criteria were reused personal identity numbers, incomplete records and lack of matching controls. Controls with an AD diagnosis before the age of 15 years were excluded. The final study population included 104,832 cases with AD and 1,022,435 controls. The AD diagnosis and comorbidities were identified from the NPR and from the Swedish Death Register using ICD codes (Tables 4–5).

Table 4. International Classification of Disease (ICD) codes used to identify atopic dermatitis.

	ICD-8	ICD-9	ICD-10
Atopic dermatitis	691.00	691	L20.0–L20.9

Table 5. International Classification of Disease (ICD) codes used to identify comorbidity of cardiovascular disease.

	ICD-8	ICD-9	ICD-10
Diabetes mellitus	250	250	E10, E11, E12, E13, E14
Hypertension	400, 401, 402, 403, 404	401, 402, 403, 404, 405	I10, I11, I12, I13, I15
Hyperlipidaemia	272	272	E78
Angina pectoris	413	411B, 413	I20 (I20.0, I20.1, I20.8, I20.9)
Myocardial infarction	410	410	I21, I22
Ischaemic stroke	432, 433, 434	433, 434	I63, I64

Table 6. International Classification of Disease (ICD) codes used to identify autoimmune diseases.

Group/Name*		ICD-10	ICD-9	ICD-8
Connective tissue	Bechterew's disease	M45	720A/720X 721G/721W	712.4
	Dermatomyositis	M330/M331/ M339	710D	716.0
	Polymyositis	M332	710E	716.1
	Rheumatoid arthritis	M05	714	712.0–3/712.5
	Systemic scleroderma	M34	710B	734.00
	Systemic lupus erythema-tosus	M32	710A	734.1
Dermatologic	Alopecia areata	L63	704A***	704.00
	Chronic urticaria	L508	708W	708.91
	Dermatitis herpetiformis	L130	694A	693.99
	Pemphigoid/pemphigus[a]	L12/L10	694F/694E	694
	Psoriasis	L40	696A,B	696.0–1
	Vitiligo	L80	**	709.05
Digestive	Coeliac disease	K900	579A	269.0
	Crohn's disease	K50	555	563.0
	Ulcerative colitis	K51	556	563.1
Endocrine	Addison's disease	E271	255E	255.1
	Diabetes mellitus type 1	E10	**	**
	Graves' disease	E05	242	242
	Hashimoto's disease	E063	245C	
Haematologic	Antiphospholipid syndrome	D686A		
	Autoimmune haemolytic anaemia	D591	283A	
	Pernicious anaemia	D510	281A	281.0
Hepatic	Autoimmune hepatitis	K754		
	Primary biliary cholangitis[b]	K743	571G	
Neuromuscular	Guillain-Barré syndrome	G610	357	
	Multiple sclerosis	G35	340	340
	Myasthenia gravis	G700	358	733
Vascular	Granulomatosis with polyangiitis[c]	M313	446E	446.2
	Polymyalgia rheumatica	M353	725	446.38
	Temporal arteritis	M315	446F	446.30

*Coded according to ICD-8: 1968–1986, ICD-9: 1987–1996, and ICD-10 thereafter. **Not included due to wide definition. ***Alopecia, including alopecia areata. [a] Historically, in ICD-8, the same ICD code was used for pemphigus and pemphigoid and they were therefore seen as a group in the overall analysis of disease association. When investigating the age of onset for pemphigus and pemphigoid, we analysed these diagnoses separately and restricted the analyses to ICD-9 and ICD-10 codes. [b] Previously known as primary biliary cirrhosis. [c] Previously known as Wegener's granulomatosis.

4.3.1.1 Study I

The research question addressed the association between AD and comorbidity with CVD, i.e., CAD and/or ischaemic stroke, comparing AD patients with controls and further explored if the magnitude of any such association varied with the severity of AD or with sex. Patients were classified as having severe AD if they were prescribed systemic treatment for AD (MTX, azathioprine, ciclosporin, and/or mycophenolate mofetil) or if they had been treated at a dermatological ward with AD as their main diagnosis. Otherwise, AD was classified as non-severe. Information on dispensed drugs was obtained from the Swedish Prescribed Drug Register.

Covariates: The highest attained level of education, obtained from LISA, was included as a proxy for socioeconomic status. Multivariable analyses further included cardiovascular comorbidity defined as DM1 or DM2, hyperlipidaemia and hypertension. The influence on CVD of smoking and body mass index (BMI), respectively, was examined in a subpopulation of women, using mothers registered in antenatal care between 1982 and 2016. Information about mothers was obtained from the Medical Birth Register.

4.3.1.2 Study II

This study explored the association of AD with multiple autoimmune diseases separately, but also with an organ system-based approach and with respect to sex.

Covariates: Multivariable models included education. In a sub-analysis, further adjustment was made for any parental autoimmune disease, but also for specific autoimmune diseases shared between parent and offspring. Information about heredity was obtained by linkage to the Swedish Multi-Generation Register. In sub-analyses of women, smoking was included in multivariable analyses as described in Study 1.

4.3.2 Clinical observational studies: Studies III–V

In the prospective clinical cohort studies, the overall aim was to study certain adverse events from dupilumab. An additional aim was to examine the prevalence of depression among patients with moderate-to-severe AD, and the effects of systemic treatment of AD (MTX, ciclosporin or dupilumab) on depressive symptoms. The patients started with a loading dose of 600 mg dupilumab injected subcutaneously, followed by 300 mg every other week. The dosage of other systemic drugs followed European dosing guidelines from 2018 (90). Patients who started on dupilumab had a wash-out period of at least two weeks for any previous systemic treatment. All patients in Studies III–V were on topical maintenance therapy. Outcome measures included scores on EASI, POEM, DLQI, VAS/NRS-11 and MADRS-S. These were monitored at baseline and every 3–6 months thereafter. Most of the patients were also monitored after 1 month.

The inclusion criteria were as follows: (1) age ≥ 18 years, (2) diagnosed with AD according to the U.K. Working Party's diagnostic criteria, (3) treated at the Department of Dermatology, Karolinska University Hospital, and (4) registered in the local research register/SwedAD. Additional inclusion criteria in Studies IV–V are described below.

4.3.2.1 Study III

In this case-series, ocular adverse events among AD patients treated with dupilumab (Dupixent®, Sanofi-Aventis Groupe, Paris, France) between November 2017 and June 2018 were recorded. At baseline, the patients were prescribed daily use of a Vaseline ointment (Oculentum simplex®) as a preventive measure against conjunctivitis. Assessment of ocular adverse events were diagnosed and treated by an ophthalmologist. Dupilumab had not previously been used at the department in question.

Study population: A total of 10 patients (1 woman, 9 men; age range 23–59 years) with severe AD were included. All patients had used systemic treatment for AD on and off for at least 4 years prior to initiation of dupilumab. All had a history of asthma and/or allergic rhinoconjunctivitis and three had *FLG* mutations. Half of the patients had a previous history of eye disease (conjunctivitis, blepharitis, herpes uveitis, keratoconus, bacterial keratitis and/or iridocyclitis).

4.3.2.2 Study IV

This cohort study investigated weight change during systemic treatment of AD from baseline to the 12-month follow-up. The associations between weight change and treatment response were explored, as well as reported appetite and/or disturbed sleep due to itching. The aim was to characterise these associations by comparing treatment groups (MTX vs. dupilumab). Reduced appetite was assessed with question number 4 in MADRS-S, where higher scores indicate less appetite. Disturbed night sleep due to itching was assessed with question number 2 in POEM, where higher scores indicate more severe sleep disturbance.

Additional inclusion criteria: (1) initiation of treatment with dupilumab and/or MTX between January 10, 2017 and June 30, 2019, (2) complete records on weight at the 6-month follow-up or later.

Study population: In total, 41 patients had treatment initiated within the study period, but many were excluded from the final analyses because of short follow-up periods (n = 15) and/or missing weight data (n = 8). The final cohort consisted of 12 patients with dupilumab and 8 patients with MTX treatment. Two patients had follow-up data for both MTX and dupilumab and were included in both treatment groups. The primary endpoint was weight change at the 12-month follow-up. Five patients had missing values at this timepoint and weight data from either the 6-month (n = 3) or the 9-month (n = 2) follow-up were used instead.

4.3.2.3 Study V

This cohort study comprised two parts. First, it explored the prevalence of depression and suicidal ideation among AD patients eligible for systemic treatment of AD. The primary outcome measure was MADRS-S score. Second, it evaluated the efficacy of systemic AD treatment on depressive symptoms and the correlation between MADRS-S scores and scores on EASI, POEM, DLQI, or VAS/NRS-11. Baseline data were analysed at start of the first treatment registered (within 4 weeks before start and up to 2 weeks after start). Follow-up data at 6 months (range 3–9 months) and 12 months (≥ 10 months) were also analysed.

Additional inclusion criteria: (1) complete register data for MADRS-S, EASI, POEM, DLQI and pruritus intensity at baseline, (2) initiation of systemic AD treatment from January 10, 2017 through November 10, 2020. If the patient had several treatment episodes registered, only the first was included.

Study population: In total, 60 patients were included. Patients who had changed or stopped treatment (n = 13), had too short follow-up periods (n = 8) or no follow-up data (n = 3) at the 3-month follow-up or later were excluded from all follow-up analyses. Patients who changed or stopped treatment (n = 4) or had any missing data (n = 6) at 10 months or later were excluded from analyses at 12 months. At the 6-month follow-up, a total of 36 patients were included for further analysis. In total, 26 patients had complete records at baseline, 6 months and 12 months. Information about prescriptions of antidepressants were obtained from the medical records of these patients.

4.4 STATISTICAL METHODS

All analyses were performed using SPSS, version 20 (IBM, Armonk, NY, USA). Bonferroni type adjustments were used because of multiple comparisons and the increased risk of type I errors in Study II. There were also used in a sub-analysis in Study V, as outlined below. In all other analyses, p-values < 0.05 were considered statistically significant.

4.4.1.1 Descriptive and inferential statistics (characteristics)

Baseline characteristics were expressed in proportions (%) of the total numbers of individuals observed, and continuous data as means with standard deviations (SDs) and/or medians with ranges. Independent samples were compared using Student's t-test in Studies I–II and with the Mann-Whitney U-test in Studies IV–V, respectively.

Weight change during systemic treatment were explored with non-parametric tests due to the small study population. In Study V, the primary outcome measure MADRS-S was considered to be an ordinal scale and normal distribution was not assumed for several of the other outcome measures. Therefore, non-parametric statistics were used.

4.4.1.2 χ2 tests

Categorical data and dichotomous variables were compared in terms of difference between proportions, using Pearson's χ^2 test.

4.4.1.3 Conditional logistic regression

The aim of conditional logistic regression is to describe an association between a binary outcome (e.g., disease yes/no) and possible independent variables (predictors or explanatory variables). The independent variables, often called covariates, may be continuous, dichotomous or categorical. Cases are matched with controls for at least one characteristic and the estimates are conditional on the matched set (by contrast, unconditional logistic regression is used in unmatched case-control studies). In Studies I–II, age and sex were used as matching variables. Conditional logistic regression was used to calculate odds ratios (ORs) as measures of the associations between AD and CVD and AD and autoimmune disease, respectively.

Due to the study design, AD was treated as the outcome and comorbidities as independent variables. All models used the matching variables in crude analyses. In multivariable analyses, potential confounders were included. A common cut-off for confounders is changing the OR > 10%; those were included in the adjusted odds ratio (aOR). Confounder selection was based on prior knowledge and in order to compare the study results with those of other studies within the field. This pragmatic approach to confounder selection may be used when complete knowledge on confounders is unavailable (123).

4.4.1.4 Confidence interval

A confidence interval (CI) is a range which contains the true value with a certain degree of probability. In Studies I–II, conditional logistic regression was used to calculate sex and age-adjusted crude and adjusted ORs with 95% CIs.

4.4.1.5 Wilcoxon's signed-rank test

Wilcoxon's signed-rank test was used for dependent follow-up data between start and 6 months in patients on systemic AD treatment (Studies IV–V).

4.4.1.6 Friedman's repeated measurements analysis of variance

Friedman's repeated measurements analysis of variance (ANOVA) was used to analyse long-term follow-up, and pairwise comparison with Bonferroni correction was used to compare MADRS-S score differences at start and at follow-up after 6 and 12 months (Study V).

4.4.1.7 Spearman's rank order correlation

The correlation between outcome measures (MADRS-S, EASI, POEM, DLQI and pruritus scores) was determined using Spearman's rank order correlation (Study V).

4.5 ETHICAL CONSIDERATIONS

All studies within this thesis were approved by the Swedish Ethical Review Authority (Studies I–II Dnr: 2016/2496-31, Studies III–IV Dnr: 2010/345-31/2, Study V Dnr: 2021-00394).

The four principles of medical ethics are autonomy, non-maleficence, beneficence and justice (124). This section focuses on the ethical considerations within the research project.

The respect for autonomy is linked to informed consent, where the patient makes an informed decision on whether or not to participate. Informed consent was not obtained for the case-control studies. In the Nordic countries, informed consent is rarely needed in large scale register-based research, but all research must be approved by an Ethics Committee (125). The arguments for this include that gathering informed consent would be cost-ineffective, time-consuming and often practically impossible. It may also be difficult to obtain informed consent in certain high-risk groups of the population, some individuals will

be dead at the time the study ends, etc. Studies have shown that informed consent may lead to severe selection bias in large-scale epidemiological research (126). For the clinical studies, informed consent was always obtained. The patients were verbally informed about the AD quality register, that data could be used in research and that they could withdraw from the register at any time.

The principle of non-maleficence is usually a minimal problem in large-scale epidemiological research, but all register-based studies include a risk of breaching the study person's integrity. To minimise this risk, all data were anonymised before analysis and data were stored safely in accordance with the applicable regulations. All results were presented at group level. In the case-series, there was a risk of identification of individuals. Therefore, precautions were taken not to give too detailed information in the article.

In the clinical studies, personal information was obtained through a web browser, but all communication between the web browser and the server was encrypted to protect personal data. Data in SwedAD are processed in accordance with the Swedish Personal Data Act (Personuppgiftslagen) and, as of 2018, the European Union's General Data Protection Regulation.

The clinical studies did not involve invasive procedures that could cause harm, and all tests and repeated visits were included in routine clinical care. The patients did complete several self-assessments and this may have been tiring and time-consuming, but I judge that the benefits from this standardised assessment of the AD, with the possibility for treatment modification, exceeded the 'assessment burden'.

The principle of beneficence involves a duty to benefit the patient. The clinical studies of AD patients involved a thorough check-up of the eczema, screening for adverse events and cardiovascular risk factors. If any abnormality was discovered, the patient received treatment or was referred for examinations or treatment. The study design enabled previously underreported adverse events of dupilumab to be detected and treated at an early stage.

*The principle of justic*e is often regarded as a form of fairness – in this context also distribution of risks and benefits to the participants. The case-control studies included the entire population, regardless of socioeconomic status or residence. Therefore, the results may benefit a large number of patients with AD, without causing harm to the participants.

SwedAD has the purpose to continually improve the treatment and follow-up of all patients with AD on systemic treatment. By enrolling in the quality register, the participants not only contributed to new knowledge but also received more optimised care.

5 RESULTS

5.1 COMORBIDITIES OF AD (I, II, V)

5.1.1 Cardiovascular disease (I)

Baseline characteristics of patients with non-severe AD and severe AD are shown in Table 7. Females were in the majority and there were more non-severe than severe AD cases. At the end of the study, participants with non-severe disease were younger than those with severe disease. The sub-analysis of women included mothers registered in antenatal care between 1982 and 2016: severe cases (n = 2,635) and non-severe cases (n = 27,985).

Table 7. Characteristics of the study population. Patients with atopic dermatitis divided into severe cases and non-severe cases.

Variable	Severe cases n = 9,558 n (%)		Controls n = 93,013 n (%)		p-value (t-test, χ^2)	Non-severe cases n = 95,274 n (%)		Controls n = 929,422 n (%)		p-value (t-test, χ^2)
Sex					0.860					0.644
Women (%)	6,149	(64.3)	59,923	(64.4)		63,101	(66.2)	616,257	(66.3)	
Age at end of study (y), mean (SD)	53.5	±15.7	53.8	±15.8	0.070	41.0	±16.7	41.3	±16.8	< 0.001
Age at end of study (y), median (range)	54.0	(15.0–80.0)	54.0	(15.0–85.0)		37.0	(15.0–86.0)	37.0	(15.0–89.0)	
Years of education					< 0.001					< 0.000
≤ 9 years (%)	1,889	(19.8)	19,442	(20.9)		13,730	(14.4)	158,116	(17.0)	
9–12 years (%)	4,634	(48.5)	41,698	(44.8)		41,484	(43.5)	414,079	(44.6)	
> 12 years (%)	3,035	(31.8)	31,873	(34.3)		40,060	(42.0)	357,227	(38.4)	
Diabetes mellitus (%)	757	(7.9)	5,844	(6.3)	< 0.001	3,222	(3.4)	32,272	(3.5)	0.146
Hyperlipidaemia (%)	571	(6.0)	4,616	(5.0)	< 0.001	2,642	(2.8)	24,128	(2.6)	0.001
Hypertension (%)	2,007	(21.0)	15,280	(16.4)	< 0.001	8,377	(8.8)	77,382	(8.3)	< 0.001

SD: standard deviation.

5.1.1.1 Overall

In the crude sex-and age-adjusted analyses, there were significant associations between AD and angina pectoris (OR 1.18, 95% CI 1.13–1.23), MI (OR 1.10, 95% CI 1.04–1.15), and ischaemic stroke (OR 1.07, 95% CI 1.02–1.13). These associations were attenuated in the adjusted model, but remained for angina pectoris and MI (Table 8). AD was not associated with death from MI or ischaemic stroke.

The adjusted estimate differed ≥ 10% when including smoking and hypertension, but not for other covariates. In line with previous studies, education, diabetes mellitus, hyperlipidaemia, and hypertension were included in the final adjustment model. Additionally, smoking and BMI were added for a subgroup of women. No effect modification between any of the included covariates was found in the overall analyses.

Table 8. Risk of coronary artery disease and stroke in patients with atopic dermatitis (AD) compared with individuals without AD.

	Cases n = 104,832 (%)	All (fully adjusted)[a] OR 95% CI		Men (fully adjusted)[a] OR 95% CI		Women (fully adjusted)[a] OR 95% CI	
Angina pectoris							
AD total	2,719 (2.59)	**1.13**	**(1.08–1.19)**	**1.10**	**(1.03–1.18)**	**1.16**	**(1.09–1.24)**
Non-severe AD	2,194 (2.09)	**1.13**	**(1.08–1.19)**	**1.12**	**(1.04–1.20)**	**1.15**	**(1.08–1.24)**
Severe AD	525 (0.50)	**1.11**	**(1.00–1.24)**	1.04	(0.89–1.21)	**1.19**	**(1.04–1.37)**
Systemic treatment[b] total	205 (0.20)	1.02	(0.87–1.21)	0.99	(0.78–1.26)	1.08	(0.85–1.35)
Myocardial infarction							
AD total	2,264 (2.16)	**1.07**	**(1.02–1.12)**	**1.12**	**(1.05–1.20)**	1.01	(0.94–1.08)
Non-severe AD	1,801 (1.72)	**1.07**	**(1.02–1.13)**	**1.15**	**(1.07–1.23)**	0.98	(0.91–1.07)
Severe AD	463 (0.44)	1.03	(0.92–1.15)	1.01	(0.87–1.18)	1.06	(0.91–1.24)
Systemic treatment[b] total	167 (0.16)	0.99	(0.82–1.18)	0.98	(0.76–1.25)	1.03	(0.79–1.34)
Stroke							
AD total	1,975 (1.88)	1.04	(0.99–1.09)	1.09	(1.01–1.17)	1.00	(0.93–1.07)
Non-severe AD	1,538 (1.47)	1.00	(0.94–1.06)	1.06	(0.98–1.16)	0.95	(0.88–1.02)
Severe AD	437 (0.42)	**1.19**	**(1.07–1.33)**	**1.20**	**(1.01–1.43)**	**1.19**	**(1.03–1.37)**
Systemic treatment[b] total	158 (0.15)	1.18	(0.98–1.41)	1.09	(0.82–1.46)	1.23	(0.98–1.56)
Death from MI/stroke							
AD total	637 (0.6)	1.01	(0.93–1.10)	1.05	(0.92–1.18)	0.98	(0.87–1.10)
Non-severe AD	463 (0.44)	0.99	(0.90–1.10)	1.04	(0.90–1.20)	0.95	(0.82–1.09)
Severe AD	174 (0.17)	1.04	(0.88–1.23)	1.05	(0.82–1.35)	1.03	(0.82–1.30)
Systemic treatment[b] total	33 (0.03)	0.84	(0.58–1.21)	0.65	(0.37–1.17)	1.02	(0.63–1.65)

a) Adjusted for cardiovascular comorbidities (diabetes mellitus, hyperlipidaemia, hypertension) and years of education. b) Subgroup of patients with severe AD receiving systemic treatment (methotrexate, azathioprine, ciclosporin or mycophenolate mofetil). Significant differences in fully adjusted models in bold. OR: odds ratio; CI: confidence interval; MI: myocardial infarction.

5.1.1.2 Non–severe atopic dermatitis

Non-severe AD was associated with a higher risk of angina pectoris (aOR 1.13, 95% CI 1.08–1.19) compared with controls and the association remained in analyses stratified by sex (Table 8). Men with non-severe AD had an association with MI (aOR 1.15, 95% Cl 1.07–1.23).

5.1.1.3 Severe atopic dermatitis

Severe AD was associated with stroke (aOR 1.19, 95% CI 1.07–1.33) in both men and women. Compared with controls, severe AD cases had a higher prevalence of diabetes mellitus, hyperlipidaemia and hypertension (Table 7). There was no association between the use of systemic treatment and CVD.

5.1.1.4 Impact of education, smoking and BMI

In the sub-analysis among mothers, severe AD cases presented with a higher prevalence of smoking (28.2% vs. 19.9%, $p < 0.001$) and obesity (12.0% vs. 9.6%, $p < 0.001$) compared with controls. In contrast, mothers with non-severe AD smoked less and were less overweight compared with controls. Among mothers with severe AD, the positive association with angina pectoris (n = 39) (OR 2.20 CI 1.50–3.24) decreased in adjusted models including smoking, BMI, education and cardiovascular comorbidities (aOR 1.51, CI 1.00–2.28); adjustment for BMI only marginally changed the estimates. Among mothers, there were no significant associations with other CAD or ischaemic stroke in adjusted models.

5.1.2 Autoimmune disease (II)

Study II was based on the same study population as Study I. Baseline characteristics revealed that patients with AD were younger than controls at first diagnosis of any autoimmune disease (42.9 vs. 45.8 years, $p < 0.001$). Overall, AD was significantly associated with having one or more autoimmune diseases. This association grew stronger among AD cases with multiple autoimmune diseases (Figure 3).

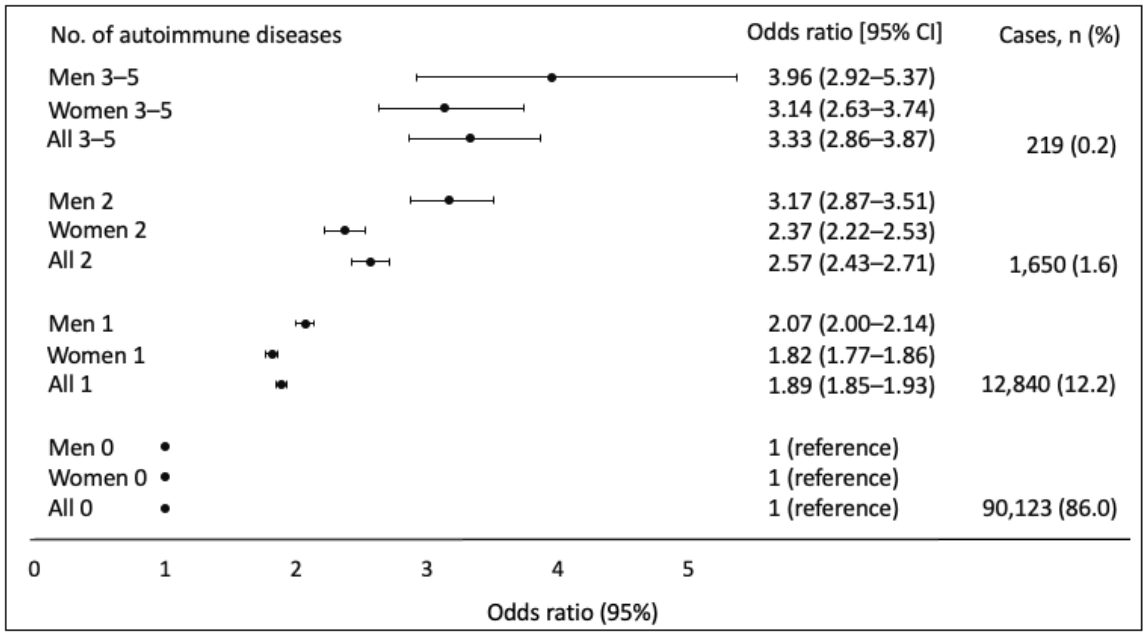

Figure 3. The number of autoimmune diseases in patients with atopic dermatitis (AD) and the overall association with AD (n = 104,832) presented with odds ratios and 95% confidence intervals (CIs).

In the adjusted analyses, including education, the odds of having any autoimmune disease were almost doubled among AD cases compared with controls (aOR 1.97, 95% CI 1.93–2.01). Associations were found between AD and diseases in several organ systems, especially for autoimmune diseases involving:

(1) the skin (aOR 3.10, 95% CI 3.02–3.18);
(2) the gastrointestinal tract (aOR 1.75, 95% CI 1.69–1.82), or
(3) the connective tissue (aOR 1.50, 95% CI 1.42–1.58).

The strongest associations between AD and autoimmune skin diseases were for dermatitis herpetiformis (aOR 9.76, 95% CI 8.10−11.8), alopecia areata (aOR 5.11, 95% CI 4.75−5.49) and chronic urticaria (aOR 4.82, 95% CI 4.48−5.19).

5.1.2.1 Gender-specific associations

Overall, men had a significantly stronger association between AD and autoimmune diseases than women ($p < 0.0013$) (Table 9). However, this sex difference was only statistically significant between AD and RA and AD and coeliac disease. Only males with AD had higher odds of DM1 (aOR 1.17 (1.08–1.27). Only females with AD had higher odds of dermatomyositis, systemic scleroderma, systemic lupus erythematosus, Hashimoto's disease, Graves' disease, MS, and polymyalgia rheumatica. Overall, no significant associations were found between AD and haematological or hepatic diseases; those results are not presented in Table 9.

Table 9. Autoimmune diseases in patients with atopic dermatitis (AD) compared with individuals without AD.

Autoimmune disease by organ/tissue type	Women (adjusted)[a] OR 95% CI	p-value	Men (adjusted)[a] OR 95% CI	p-value	Women vs. men p-value (t-test)
Any of the listed autoimmune diseases	**1.89** (1.85–1.93)	< B	**2.18** (2.10–2.25)	< B	< 0.0013
Skin	**3.01** (2.91–3.11)	< B	**3.29** (3.14–3.44)	< B	0.002
Dermatitis herpetiformis	**9.00** (7.08–11.45)	< B	**11.02** (8.20–14.82)	< B	0.299
Alopecia areata	**4.90** (4.51–5.32)	< B	**5.85** (5.04–6.78)	< B	0.040
Chronic urticaria	**4.53** (4.16–4.92)	< B	**5.98** (5.14–6.96)	< B	0.002
Pemphigoid/pemphigus	**3.22** (2.84–3.65)	< B	**3.55** (3.02–4.18)	< B	0.355
Vitiligo	**2.43** (2.15–2.75)	< B	**2.98** (2.54–3.51)	< B	0.048
Psoriasis	**2.43** (2.33–2.53)	< B	**2.71** (2.56–2.87)	< B	0.002
Gastrointestinal tract	**1.67** (1.60–1.76)	< B	**1.94** (1.81–2.08)	< B	< 0.0013
Coeliac disease	**1.80** (1.67–1.94)	< B	**2.62** (2.31–2.97)	< B	< 0.0013
Crohn's disease	**1.76** (1.62–1.92)	< B	**1.97** (1.75–2.22)	< B	0.141
Ulcerative colitis	**1.50** (1.39–1.62)	< B	**1.72** (1.56–1.90)	< B	0.033
Connective tissue	**1.46** (1.37–1.55)	< B	**1.63** (1.46–1.83)	< B	0.083
Dermatomyositis	**3.09** (2.03–4.70)	< B	1.81 (0.70–4.71)	0.223	0.314
Systemic scleroderma	**1.87** (1.40–2.49)	< B	1.86 (0.87–3.95)	0.108	0.986
SLE[b]	**1.62** (1.39–1.88)	< B	**1.97** (1.23–3.14)	0.005	0.439
Bechterew's disease	**1.51** (1.27–1.79)	< B	**1.41** (1.17–1.70)	< B	0.616
Rheumatoid arthritis	**1.35** (1.25–1.46)	< B	**1.83** (1.58–2.13)	< B	< 0.0013
Polymyositis	**1.73** (1.06–2.82)	0.028	0.44 (0.11–1.82)	0.258	0.074
Vascular	**1.32** (1.16–1.50)	< B	**1.48** (1.21–1.81)	< B	0.348
Temporal arteritis	1.42 (0.73–2.77)	0.303	**3.50** (1.26–9.77)	0.017	0.149
Granulomatosis with polyangiitis[c]	**1.52** (1.04–2.22)	0.030	**1.75** (1.04–2.93)	0.035	0.672
Polymyalgia rheumatica	**1.32** (1.15–1.51)	< B	**1.39** (1.11–1.73)	0.004	0.696
Neuromuscular	**1.26** (1.13–1.41)	< B	**1.27** (1.03–1.57)	0.027	0.952
Multiple sclerosis	**1.26** (1.12–1.42)	< B	**1.34** (1.05–1.72)	0.019	0.652
Guillain-Barré syndrome	1.41 (0.86–2.32)	0.169	1.11 (0.64–1.93)	0.705	0.526
Myasthenia gravis	1.11 (0.75–1.64)	0.598	1.04 (0.54–2.00)	0.909	0.862
Endocrine	**1.12** (1.07–1.17)	< B	**1.21** (1.12–1.30)	< B	0.088
Addison's disease	1.16 (0.78–1.71)	0.462	**2.04** (1.29–3.23)	0.002	0.066
Hashimoto's disease	**1.38** (1.22–1.55)	< B	1.16 (0.73–1.84)	0.542	0.476
Graves' disease	**1.15** (1.07–1.23)	< B	**1.39** (1.14–1.68)	0.001	0.079
Diabetes mellitus type 1	1.02 (0.95–1.10)	0.567	**1.17** (1.08–1.27)	< B	0.012

[a] Adjusted for sex, age and education. [b] Systemic lupus erythematosus. [c] Previously known as Wegener's granulomatosis. Bold indicates $P < 0.05$. B (green) indicates statistical significance ($P < 0.000427$) after Bonferroni correction. * (yellow) indicates statistical difference in odds ratios between men and women ($P < 0.00128$) after Bonferroni correction. OR: odds ratio; CI: confidence interval.

5.1.2.2 Impact of heredity and smoking

In subgroup analyses among 92,290 AD cases, after adjustment for any parental autoimmune disease, the association between AD and autoimmune disease remained stable (aOR 1.90, 95% CI 1.86–1.94 vs. OR 1.89, 95% CI 1.86–1.93). Similar results were observed in models comprising specific parent-offspring associations for 15 of the most common autoimmune diseases (data not shown). In the sub-analysis among women (n = 32,797), all associations between AD and autoimmune dermatological, gastrointestinal and rheumatological diseases and MS remained significant after adjustment for smoking (OR changed < 0.10) (data not shown).

No statistically significant interactions were found between autoimmune diseases and any of the included covariates.

5.1.3 Depression (V)

Among the 60 patients with AD eligible for analyses, females represented 38.3% (Table 10). In total, 13 (21.7%) met the criteria for moderate depression, 2 (3.3%) met the criteria for severe depression and 3 (5%) presented with marked suicidal ideation. There was no significant difference in median EASI score between the 15 (25%) patients with moderate-to-severe depression (median EASI score 19.0, range 1–46) and the 45 (75%) patients with lower MADRS-S scores (median EASI score 19.0, range 1–50).

The median EASI scores were significantly higher among males than females. More females than males had a history of hand eczema within the preceding 12 months. There were no other significant differences of baseline characteristics with respect to sex. Work limitation due to eczema was significantly associated with higher MADRS-S score ($p < 0.033$), but not hand or facial eczema.

Table 10. Baseline characteristics of patients with atopic dermatitis on systemic treatment.

Variable	All cases n = 60	Women n = 23	Men n = 37	P-value
Sex, n (%)		23 (38.3)	37 (61.7)	
Age (years), median (range)	47.5 (19–77)	48.0 (19–68)	47.0 (19–77)	0.791
MADRS-S, median (range)	13.5 (0–50)	14.0 (1–26)	13.0 (0–50)	0.426
No depression, n (%)				
MADRS-S 0–12 p	27 (45.0)	9 (39.1)	18 (48.6)	
Light depression, n (%)				
MADRS-S 13–19 p	18 (30.0)	10 (43.5)	8 (21.6)	0.251
Moderate depression, n (%)				
MADRS-S 20–34 p	13 (21.7)	4 (17.4)	9 (24.3)	
Severe depression, n (%)				
MADRS-S ≥ 35 p	2 (3.3)	0 (0)	2 (5.4)	
EASI, median (range)	19.0 (1–50)	13.0 (3–38)	22.0 (1–50)	0.047*
Education[a]				
≤ 9 years (%)	6 (10.3)	2 (9.5)	4 (10.8)	
9–12 years (%)	26 (44.8)	11 (52.4)	15 (40.5)	0.679
> 12 years (%)	26 (44.8)	8 (38.1)	18 (48.6)	
Facial eczema[b]	41 (68.3)	15 (65.2)	26 (70.3)	0.682
Hand eczema[b]	37 (61.7.)	18 (78.3)	19 (51.4)	0.037*
Work limitation due to eczema[c]	17 (37.8)	5 (27.8)	12 (44.4)	0.259
Alcohol consumption[d]				
Never	13 (22.8)	6 (30.0)	7 (18.9)	
1 time/month or less	6 (10.5)	2 (10.0)	4 (10.8)	
2–4 times/months	25 (43.9)	8 (40.0)	17 (45.9)	0.756
2–3/times/week	7 (12.3)	3 (15.0)	4 (10.8)	
4 times a week or more	6 (10.5)	1 (5.0)	5 (13.5)	
Antidepressants[e] (n)	9 (15.0)	6 (26.1)	3 (8.1)	0.058

MADRS-S: Montgomery-Åsberg Depression Rating Scale–Self-report; EASI: Eczema Area Severity Index; Independent samples were tested with the Mann-Whitney U-test. Pearsons's χ^2 test was used to compare the proportions between sexes for the following variables: education, ongoing stress, eczema location, work limitation and alcohol consumption. Significant differences marked with *.

Footnotes: [a] Missing n = 2. [b] During the preceding 12 months [c] Missing n = 15. Students, pensioners and unemployed excluded. [d] Missing n = 3. [e] Patients with antidepressants at baseline or who were prescribed antidepressants during the follow-up period.

5.2 ADVERSE EVENTS OF SYSTEMIC AD TREATMENT (III, IV)

5.2.1 Ocular adverse events (III)

In the case-series, ocular adverse events were very common: 9/10 developed eye problems (Table 11). Seven patients were diagnosed with conjunctivitis (Figure 4). Serious ocular adverse events included uveitis due to reactivation of herpes simplex virus (HSV). One patient who presented with blisters on the eyelid was 2 days later hospitalised with a diagnosis of varicella-zoster virus (VZV) meningitis. The patients with HSV and VZV

infections recovered and continued with dupilumab, but antiviral prophylaxis was added. One patient stopped dupilumab due to conjunctivitis, whereas all others improved with eye treatment (as presented in Table 11) and continued with dupilumab.

Overall, outcome measures improved during treatment. The mean EASI score at baseline was 20.7 (range 4.8–46.5). At 3 months, 2 of 10 patients showed complete clearance, 4 patients achieved EASI-90, and 2 patients achieved EASI-75. One patient who decided to stop dupilumab after 3 months due to severe conjunctivitis had almost cleared skin at that timepoint. The positive effect of dupilumab on the outcome measures overall increased and/or remained stable at follow-up after 5–7 months. However, one patient with *FLG* mutation did not achieve EASI-50.

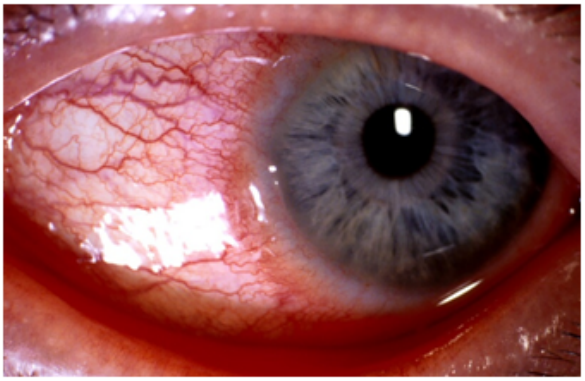

Figure 4. Severe conjunctival reaction with redness, dilated conjunctival vessels and limbal oedema with hyperaemia. Photographer: Lena Ivert.

Table 11. Characteristics of 10 patients with severe atopic dermatitis treated with dupilumab.

No.	Asthma	Allergic rhino-conjunc–tivitis	*FLG* mutation	Previous history of eye disease[a]	Adverse events	Ophthalmological treatment
1	Yes	Yes	WT	No	Conjunctivitis, photophobia, dry eyes	Vaseline eye ointment, artificial tears
2	No	Yes	WT	Atopic conjunctivitis	Worsening of conjunctivitis, dry eyes	Tacrolimus eye ointment 0.1%
3	Yes	Yes	HeZ	No	Kerato-conjunctivitis	Tacrolimus eye ointment 0.1%, artificial tears
4	Yes	Yes	HoZ	Herpes simplex virus uveitis with secondary glaucoma 2 yrs earlier	Herpes simplex virus uveitis with secondary glaucoma	Oral valaciclovir and continuing antiviral prophylaxis dexamethasone eye drops 1 mg/ml, glaucoma treatment
5	Yes	Yes	WT	Keratoconus, corneal transplant	Conjunctivitis, photophobia	Prednisolone pivalate 5 mg/g 1x1 eye ointment, artificial tears
6	Yes	Yes	WT	Atopic blepharo-conjunctivitis, marginal keratitis, bacterial keratitis	Unchanged blepharo-conjunctivitis.	Tacrolimus eye ointment 0.1%, Vaseline eye ointment
7	No	Yes	WT	Atopic blepharo-conjunctivitis, bacterial keratitis, iridocyclitis	Conjunctivitis, eyelid blisters, varicella-zoster meningitis	IV acyclovir with continuing antiviral prophylaxis
8	Yes	Yes	WT	No	Conjunctivitis	Vaseline eye ointment, artificial tears
9	Yes	Yes	HeZ	No	Keratitis, blepharitis	Dexamethasone with tobramycin 3 mg/ml/1 mg/ml eye drops, artificial tears, paraffin Vaseline ointment
10	No	Yes	WT	No	Conjunctivitis, blepharitis (The patient stopped treatment after 3 months due to conjunctivitis.)	Tacrolimus eye ointment 0.1% dexamethasone with tobramycin 3 mg/ml/1 mg/ml eye drops, artificial tears

[a]Requiring ophthalmologic examination. WT: wild-type; HeZ: heterozygous; HoZ: homozygous.

5.2.2 Weight gain (IV)

Baseline BMI was comparable between the treatment groups of dupilumab (n = 12) and MTX (n = 8). Dupilumab-treated patients presented with BMI 27.3 (95% CI 24.0–28.4), and MTX-treated patients with BMI 24.7 (95% CI 19.9–36.1). There were no significant differences in age, sex, POEM scores, pruritus scores or MADRS-S scores between the two

treatment groups at baseline, but the patients treated with dupilumab had a significantly higher EASI scores (p = 0.045) and the patients treated with methotrexate had significantly higher DLQI scores (p = 0.025).

- After one year, body weight increased by a mean of 6.1 kg, range 0.1–18.0 (p = 0.002) in AD patients treated with dupilumab, while those treated with MTX did not show any significant weight change.

5.2.2.1 Weight change in relation to treatment response

A subgroup analysis was performed among patients successfully treated with dupilumab (n = 11) or methotrexate (n = 6), in order to explore if the results remained or if they could be explained by good treatment response. Successful treatment response was defined as achievement of EASI-75 or improvement in EASI score ≥ 6.6 at the 6-month follow-up.

(1) The mean weight change among successfully treated patients with dupilumab was comparable with that of all patients treated with dupilumab. Among patients successfully treated with MTX, weight was reduced (-4.3 kg, range -17 to 2.0), but this change was not significant.
(2) Among successfully treated patients, there was no correlation between weight gain and appetite scores (all treatments).
(3) Among AD patients successfully treated with dupilumab, 5 had improved sleep at follow-up, and 5 had unchanged sleep (missing data for one person). All gained weight significantly, regardless of sleep improvement.
(4) Among patients successfully treated with MTX, all had improved night sleep during treatment and they did not gain weight (mean weight change -4.3 kg). The absolute number of nights with improved sleep tended to be lower among patients treated with MTX than among patients treated with dupilumab.

5.3 EFFECTS OF SYSTEMIC AD TREATMENT ON DEPRESSIVE SYMPTOMS AND OTHER OUTCOMES (V)

5.3.1 Outcome measures at 6 months

Among 36 patients with AD, treated with ciclosporin (n = 1), MTX (n = 8) or dupilumab (n = 27), who completed follow-up at 6 months, all outcome measures significantly improved (p < 0.001). The results remained stable both when the treatments were analysed separately and when analysed as a group, but MADRS-S scores were significantly lower in the dupilumab group at 6-month follow-up. Altogether, the median MADRS-S score change was -5.0 (range -36 to +5, $p < 0.001$). In a sensitivity analysis, the significant MADRS-S score reduction between start and 6 months remained when all patients who were on antidepressants (n = 8) during the study period were excluded (data not shown). Four patients who had used antidepressants for at least 3 months before the start of the study period and throughout follow-up tended to improve their MADRS-S score, from median 17 (range 8–25) to median 11 (range 4–14), p = 0.066.

At the 6-month follow-up, patients who achieved EASI-90 did not have a significantly different median MADRS-S score (median MADRS-S score 4.5, range 0–14) compared with patients who did not achieve EASI-90 (median MADRS-S score 7.0, range 0–22). A similar finding also applied to responders and non-responders for EASI-75 and EASI-50, respectively. Spearman's correlation coefficients for all registered MADRS-S scores (at start and 6 months) revealed a significant correlation with EASI score ($r = 0.386$, $p = 0.001$), POEM score ($r = 0.557$, $p < 0.001$), DLQI score ($r = 0.623$, $p < 0.001$) and pruritus score ($r = 0.436$, $p < 0.001$).

Of three patients with marked suicidal ideation, two were included at the 6-month follow-up. Both had improved their item 9 scores in MADRS-S to ≤ 2 ('enjoys life or takes it as it comes'/'only fleeting suicidal thoughts'). One patient changed systemic treatment to dupilumab at 3 months of the study and was therefore excluded from the follow-up analysis. The item 9 score of this subject improved to 0 at 6 months. None of the three patients with marked suicidal ideation received antidepressants during the study period.

5.3.2 MADRS-S items (0–6 months)

Sleep impairment was highest at start, with a median score of 3.0 (range 0–6). All different aspects (items) of MADRS-S were significantly improved during the follow-up period, including suicidal ideation (Figure 5). Furthermore, there was a significant correlation between sleep disturbance outcomes in POEM and in MADRS-S ($r = 0.608$, $p < 0.001$).

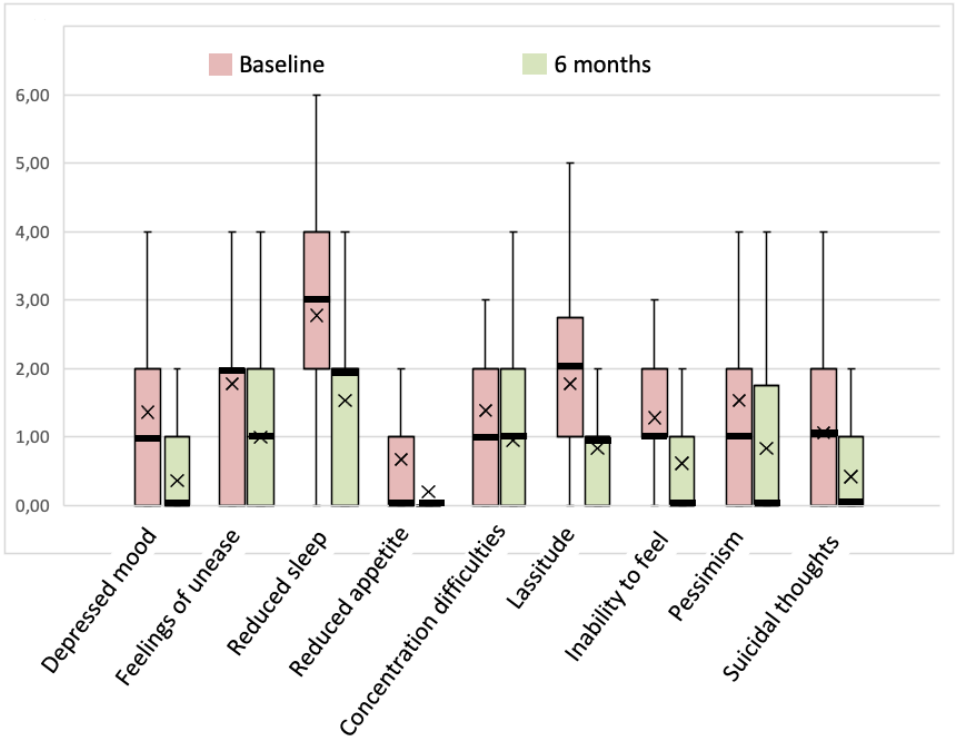

Figure 5. Boxplot showing medians, interquartile ranges and ranges of items in Montgomery-Åsberg Depression Rating Scale-Self-report (MADRS-S) at baseline and follow-up at 6 months among 36 adults with atopic dermatitis on systemic treatment. Means marked with x.

5.3.3 Outcome measures at 12 months

Among the 26 patients who completed the 12-month follow-up (Figure 6), the significant improvement of MADRS-S score and other outcome measures remained.

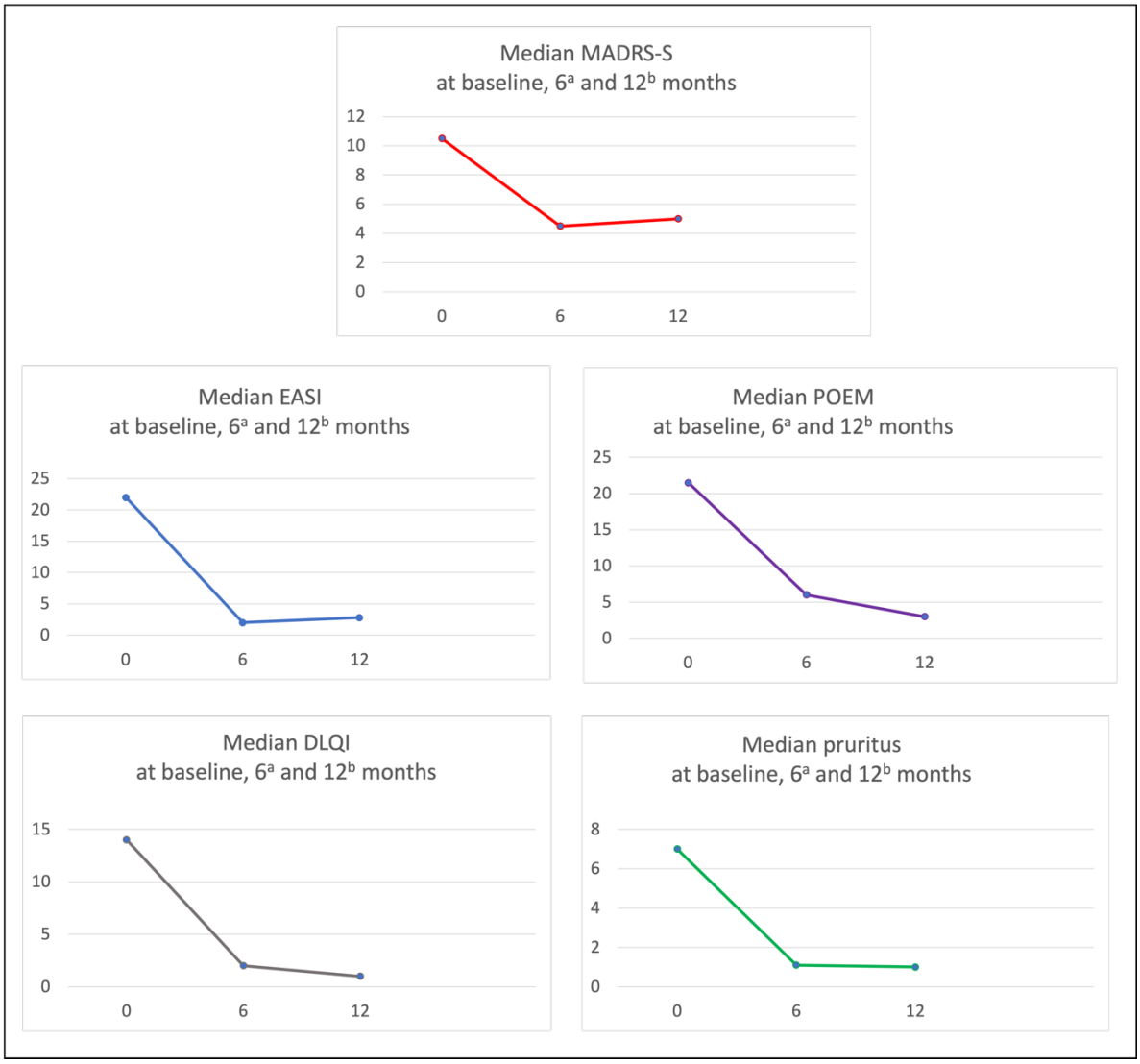

Figure 6. The effect of systemic AD treatment (dupilumab n = 23, MTX n = 3) on outcome measures in 26 patients who completed follow-up at 6 and 12 months. MADRS-S: Montgomery-Åsberg Depression Rating Scale–Self-report; EASI: Eczema Area Severity Index; POEM: Patient-Oriented Eczema Measure; DLQI: Dermatology Life Quality Index; Pruritus: 0–10 cm visual analogue scale (VAS)/0–10 numeric rating scale (NRS-11). P-values calculated with Friedman's repeated measurements analysis of variance. Footnotes: [a] Values collected at 6 ± 3 months. [b] The 12-month follow-up range for EASI was 10.0–23.0 months, and that for the other outcomes was 10–18 months. One patient had missing data for EASI at 12 months.

6 DISCUSSION

6.1 MAIN FINDINGS AND IMPLICATIONS

6.1.1 Associations between AD and CVD (I)

In Study I, an association was seen between AD and angina pectoris, MI and ischaemic stroke compared with the general population. The association between AD and ischaemic stroke was significant only among cases with severe AD. The results remained in multivariable adjustments for education and cardiovascular comorbidity. These findings are supported by previous studies (57, 58, 127), but no association between AD and cardiovascular death was found.

Subgroups were identified in which the associations varied and possible explanations were found for some, but not all, subgroup patterns. Overall, there was an association between AD and angina pectoris, but this was not found among men with severe AD. Men with non-severe AD had an association with MI, but this was not found in the severe groups or among women. Severe AD had an association with stroke among both men and women. Results stratified by sex have rarely been reported in previous studies of AD. On the other hand, the risk of MI is approximately 3 times higher among men than women in the general population. The incidence becomes more similar with increasing age, especially among women with risk factors for CVD (128). This may explain why an association between AD and MI was found among men, but not among women.

As previously discussed, several studies have explored the relation between AD and CVD, but with conflicting results (55-57, 129). Mixed findings may be due to several factors, such as differences in study design, definitions and diagnosis of AD (e.g., questionnaire-based diagnosis, diagnosis by a general practitioner or by a dermatologist). Only a few studies have adjusted for important risk factors for CVD, such as smoking. Unfortunately, adjustment for smoking was not possible among all subjects in Study I. However, in a subgroup of women, adjustments for smoking could be made and changed the estimates between severe AD and angina pectoris, but it did not change the overall estimates in the non-severe group. In study 1, our interpretation was that smoking may be an important confounder in severe cases. Nevertheless, one must be careful of generalising this result, as the subpopulation of women registered in antenatal care was younger than the main study population.

The findings are consistent with previous studies indicating that severe AD is associated with several risk factors for CVD, although data are limited (60). Among severe AD cases, there was significantly higher prevalence of cardiovascular comorbidities, including diabetes mellitus, hyperlipidaemia and hypertension, compared with controls. Subgroup analyses among women indicated that severe AD cases had significantly lower education levels, and higher prevalence rates of smoking and obesity compared with controls. Notably, mothers with non-severe AD smoked less and had less overweight than control

subjects. Additionally, in Study V, it was found that 25% of AD patients with moderate-to-severe AD presented with a moderate-to-severe depression – another possible risk factor for CVD.

Thus far, most associations between AD and CVD have been described as epidemiological. Whether or not there is a causal relationship remains unknown. Due to the design of Study I, it was not possible to explore if adults with AD were at greater risk for cardiovascular events. Nevertheless, the small effect size and lack of biological gradient did not support a causal relationship. Overall, no consistent gradient based on disease severity was seen. According to the Bradford Hill criteria, a greater exposure should generally lead to a greater incidence of the effect, and such a finding would support that the association is based on a causal relationship (130). The relative risk for CVD has been reported to be high in some high-quality studies (57), but the absolute risk may be considered low (131). Data from the large cohort study by Silverwood et al. showed that AD patients had 12 more heart attacks and 25 more strokes per 100,000 person-years compared with healthy controls (57).

In my experience, it would seem that most epidemiological studies in this field publish low odds ratios. Maybe any potential great discovery would already have been revealed by smaller studies in a clinical setting long ago, without advanced computer programs. This would be analogous to gold prospecting, where a simple gold pan was enough for gold detection in the past. Today, we need highly sensitive technological methods to find any gold at all. However, ORs in the lower range can also be important. Especially if more advanced interaction models enable the identification of subsets of patients at very high risk of CVD among millions of subjects with AD, but the average AD patient would present with an OR of about 1.0.

In summary, the findings in Study I support an association between AD and CVD, although the magnitude of this association might be considered low. Regardless of any definite causal relationship between AD and CVD, increased awareness and screening of cardiovascular risk factors may be recommended, especially among severe AD cases.

6.1.2 Associations between AD and autoimmune disease (II)

In Study II, an association was found between AD and several autoimmune diseases, especially those involving the skin, the gastrointestinal tract or the connective tissue. Overall, these findings are in line with previous studies (73, 74, 132-135). Furthermore, a dose-response relationship was observed between the number of autoimmune diseases and the association with AD. The strongest associations between AD and specific skin diseases were found for dermatitis herpetiformis, alopecia areata and chronic urticaria.

A weak association between AD and DM1 was observed among men, but not women. Previous studies have conflicting results on the association between AD and DM1 (74), supporting the view that this finding should be interpreted with caution. Furthermore, an association with MS was found – where previous data have also been conflicting, although

based on few studies – as were associations with Graves' and Hashimoto diseases, which were not found in a previous study (73). In addition to the previously discussed reasons for between-study variations, statistical cut-off points vary widely between different studies.

For most autoimmune diseases, there is a clear sex difference in prevalence: 80% of individuals with autoimmune diseases are women (136). In order to show this important aspect of comorbidity, men and women have been presented separately. Several differences between males and females were found, e.g., men with AD had a stronger association between RA and coeliac disease than women. AD was associated with several rheumatologic and endocrine diseases, and MS, in women only. Various mechanisms for sex differences in autoimmune diseases have been put forward, such as genetic predisposition and heightened immune reactivation in women (137). Speculatively, a heightened immune reactivity may also explain why females with AD have been observed to have more persistent AD than males (138).

A broad definition of autoimmune disease was used in order to replicate and compare the results with those of earlier studies that used a similar definition. The primary focus of Study II was to explore any associations between AD and autoimmune disease, not to study the mechanisms, genetics, or temporal relationship behind these associations. Nevertheless, some findings might give deeper insight into the relationship between AD and autoimmune diseases. Smoking, education and hereditary status may influence the association with several diseases, but including these variables in multivariable analyses did not change the results. Interestingly, it could be noted that patients with AD were generally diagnosed with autoimmune disease earlier in life than controls. This, and the observed dose-response relationship between AD and autoimmune diseases, may support the idea of an autoimmune component of AD and/or shared immune pathways and environmental factors yet to be discovered.

Greater awareness and screening of comorbidities among adult AD patients might relieve the disease burden of AD. Further, increased knowledge of comorbidities could enable physicians to provide more personalised treatment. Some new and emerging JAK inhibitors for AD might be used to treat both AD and autoimmune diseases. The JAK-STAT pathway is involved in the pathogenesis of multiple diseases, including RA, psoriatic arthritis, inflammatory bowel disease, and AD (139).

6.1.3 Association between AD and depression (V)

In Study V, more than half of the patients with moderate-to-severe AD eligible for systemic treatment of AD had depressive symptoms, 25% of whom presented with a moderate-to-severe depression and 5% of whom had pronounced suicidal ideation.

The high prevalence of depression was consistent with previous data (79). However, the overall prevalence of depressive symptoms was higher than in a recent meta-analysis in all ages (55% vs. 22%) (80). The explanation may be that the patients in Study V had a more

severe AD than in several other studies. Depression has been observed to be driven by AD severity (140, 141). Moreover, Study V included only adults. The prevalence of suicidal ideation was lower than in a recent meta-analysis (5% vs. 12.2%) (80). Differences may be due to diversity in study design, outcome measures and definitions of suicidal ideation. The findings of Study V were in line with a German cross-sectional study where 7 of 181 (3.9%) exhibited symptoms indicating a suicidal crisis (142).

The results supported the hypothesis that disturbed sleep due to itching is associated with depressive symptoms among AD patients. Further, an association was found with work limitation and depressive symptoms, which could have a negative impact on HRQoL and financial burden. The findings did not support that facial eczema, possibly leading to psychosocial stigmatisation, was associated with depression.

The magnitude of depression was higher than expected, as was the number of patients with suicidal ideation. The prevalence of depression among moderate-to-severe AD patients maybe be underestimated and more attention should be paid to this. A previous case-control study found that two thirds of patients with eczema who died from suicide had visited a doctor in the month before death (143). The last visit had most often been with a family doctor, but 1 in 25 among patients with persistent eczema had visited a dermatologist at their last healthcare visit. The use of MADRS-S or other self-assessment tools can be helpful to detect depressive symptoms and suicidal ideation that are not easily captured otherwise.

6.1.4 Eye complications during dupilumab treatment (III)

In Study III, ten patients treated with dupilumab were observed and the outcome measures improved in the majority. Ocular adverse events were much higher than expected, with 90% developing eye problems (i.e., blepharitis, conjunctivitis, uveitis and keratitis). We found that 70% of the patients developed conjunctivitis, whereas clinical trials had reported a much lower incidence (8.6% to 22.1%) (144-146).

This study was among the first to report dupilumab-associated conjunctivitis as a common adverse event. The same observation has since been replicated in several real-world studies (99). In line with these observations, severe and long-lasting AD, good response to treatment and/or previous eye disease (pre-existing conjunctivitis or atopic keratoconjunctivitis) have been associated with an increased risk of conjunctivitis (147, 148). The contradictions of findings between real-world studies and clinical trials have several potential explanations. Clinical trials use strict eligibility, i.e., patients with certain comorbidities and patients with certain profiles are excluded. In most trials, AD patients were excluded if they had used systemic treatment during the run-in period (which was 4 weeks in early dupilumab trials) or topical glucocorticoids within 1 week of baseline (145). Thus, some severe AD patients may have had difficulties to qualify for or enter the trial.

The pathomechanism behind dupilumab-associated conjunctivitis is not clarified. It is also unknown why ocular adverse events are more common among patients with AD compared with patients where dupilumab is used for asthma, chronic rhinosinusitis or eosinophilic esophagitis (149). Bakker et al. performed conjunctival biopsies among 6 AD patients with dupilumab-associated conjunctivitis (150). They found a prominent inflammatory T cell infiltrate (mainly CD3+/CD4+ cells) and more eosinophils compared with in healthy controls. The most noticeable feature among AD patients was a scarcity of mucus-containing goblet cells. It has been demonstrated that IL-13 stimulates these cells to proliferation and mucus secretion, which is important for ocular surface functions (150). Therefore, effective blocking of IL-13 may cause dry eyes and conjunctival inflammation leading to keratoconjunctivitis, especially among predisposed patients (147). It has also been suggested that dupilumab increase *Demodex* numbers by compromising the Th2 signalling (151). This could cause an IL-17-mediated ocular inflammation and conjunctivitis as described in rosacea, but the role of *Demodex* in dupilumab-associated disease is debated (152). Other explanations include dupilumab-associated eosinophilia. These cells play a role in the development of allergic eye conditions (153).

Based on real-life data, where the findings of Study III contribute to the body of knowledge, conjunctivitis has been confirmed to be the most common of all dupilumab-associated adverse events (99). In light of this, new treatment algorithms have emerged (149, 154). According to these guidelines, it is appropriate to recommend preservative-free lubricating eye drops as a prophylactic treatment for patients with AD initiating dupilumab. Based on data from recent literature, most dupilumab-associated conjunctivitis resolves with conservative treatment and discontinuation of dupilumab is rarely needed (146, 149). Referral to an ophthalmologist is recommended if ocular symptoms are not relieved with conservative treatment, such as artificial tears, and/or if there are any signs of severe ocular manifestation or infection. With increased awareness of ocular adverse events, including early diagnosis and treatment, patients with AD have a higher likelihood to continue with dupilumab.

6.1.5 Weight gain during dupilumab treatment (IV)

In Study IV, we reported a significant weight gain among patients treated with dupilumab. The mean weight gain was 6.1 kg after one year of treatment. To the best of my knowledge, this is the first study reporting weight gain as a possible dupilumab-associated adverse event. We did not find any correlations between weight gain and treatment response, disturbed sleep due to itching or changed appetite. Patients with MTX treatment did not gain weight. We have not found any previous reports of weight gain through blockade of the shared IL-4α subunit, the target of dupilumab, but changes in body weight have been reported for other biologics. Patients with psoriasis have been observed to gain weight during treatment with TNF-α (155), and RA patients to gain weight during treatment with IL-6 inhibitors (156). The latter was related to significant increase in lean mass, but not fat mass.

Scratching due to itching and restlessness during disturbed night sleep may be energy-consuming. As a result of this, improved AD symptoms during treatment could hypothetically lead to increased fat mass. In Study IV, weight change was observed among patients successfully treated with dupilumab, but not among patients successfully treated with MTX. Our interpretation was that weight change might be related to the mechanisms of the treatment, without a direct link to AD treatment outcomes. We assumed that patients with MTX would have stopped treatment during the follow-up period if gastrointestinal side effects, such as nausea, were a major concern.

In conclusion, a significant weight gain among patients treated with dupilumab was observed, but possible mechanisms behind this remain unclear. Despite the limitations of a small study population, these results may serve as an indication that more attention should be paid to patients with weight gain. This may be especially important among severe AD patients with other cardiovascular risk factors. Further research and larger studies are needed to confirm and explore this novel finding.

6.1.6 The effect of systemic AD treatment on depressive symptoms (V)

In Study V, systemic treatment of AD significantly reduced all aspects of depressive symptoms, including suicidal ideation and disturbed sleep, and all other outcome measures at 6 months. This positive effect remained stable at 12 months. Studies exploring the effect of systemic treatment on depression are limited outside clinical trials, but the findings are in line with phase III trials of dupilumab where significant reduction of depressive symptoms was demonstrated. Both MTX and dupilumab improved these, but Study V suggested that dupilumab was more effective than MTX. In Study V, three patients with marked suicide symptoms radically improved their scores of suicidal ideation during systemic AD treatment without concomitant antidepressants.

There are several possible explanations why systemic treatment could reduce depressive symptoms. Itch and sleep disturbances appear to worsen with AD severity, and sleep disturbance is an independent risk factor for depression (83). Effective systemic treatment of AD, targeting both the skin inflammation, itch and sleeping disturbances, and perhaps neuroinflammatory pathways yet to be discovered, might reduce depressive symptoms. Study V supported that effective AD treatment can reduce depressive symptoms. Moreover, depressive symptoms in patients with moderate-to-severe AD might improve from systemic treatment in addition to traditional antidepressants.

6.2 METHODOLOGICAL CONSIDERATIONS

The strengths of the case-control studies (I–II) were the use of nation-wide large population-based cohorts with high-quality register data. Further, a large study population gave substantial power and enabled stratification into subgroups. The strengths of the prospective clinical cohort studies, including the case-series, were the use of validated outcome measures as defined by HOME, and AD diagnoses made by dermatologists.

Studies III–V observed outcomes for a novel treatment and contributed to new knowledge. The latter may generate hypotheses that should lead to larger studies with higher level of evidence. However, the thesis also has several limitations. The major methodological considerations are discussed below.

6.2.1 Study design

A case-control study design was used to study the association between AD and CVD or autoimmune diseases. This design has several advantages, such as being efficient in terms of money, time and effort, but it is more vulnerable to bias than comparable designs (157). By defining AD as the outcome, several exposures could be studied within the same dataset, which was very efficient. A major limitation was that it was not possible to estimate incidence rates or assess if AD was a risk factor for CVD and/or autoimmune disease. If the prevalence of an outcome is low (usually under 5%) among both those unexposed and those exposed, the odds ratio (OR) can be interpreted as an estimate of the relative risk (158). The estimated 12-month prevalence of AD (all continents included) is up to 17.1% among adults (159). Therefore, the research team considered the ORs likely to be more interesting as measures of association between AD and other diseases than as measures of how much higher the risk for AD was among people with or without CVD/autoimmune disease. If a cohort design had been used, enabling calculation of incidence rate, the study population would have been defined by their exposure status (AD vs. no AD) and followed over time to estimate the incidence of disease. The advantage would have been seen for diseases occurring later in life, such as CVD, with good coverage in the NPR and death register, and with information about date of illness onset or death. This would not apply to several of the autoimmune diseases where date of illness onset is more uncertain. Further, the date of start of symptoms with AD may be uncertain and data from primary care are not available in the NPR.

The major limitations of the clinical studies (III–V) were the small study populations, which may have led to unreliable and hard-to-replicate results, and a lack of sufficient control subjects. Unfortunately, in Study V, several of the included patients had too short follow-up periods for a longitudinal analysis. The participants with too short follow-ups were comparable with the participants included in the longitudinal analysis at baseline, and hopefully this loss-to-follow-up did not affect the findings.

6.2.2 Validity

The validity of a research project encompasses two components. External validity refers to how generalisable the results are for the population that the sample represents. Internal validity refers to if the findings within the population can be trusted and are not due to methodological errors. In other words, there is no external validity without internal validity (160). A study is valid if we can exclude systematic errors (also called bias) and random errors, thus leading to a correct assessment of the exposure and outcome. There are numerous types and sources of bias, several of which apply to this thesis. In observational

studies, the major threats to internal validity are selection bias, information bias and confounding (158).

6.2.2.1 Selection bias

Selection bias occurs when the association between an exposure and disease differs between participants and non-participants in a study (161). The result is a study population that is not a representative sample of the target population. Ascertainment bias (also known as detection bias) occurs when certain participants are more likely to be included. In the case-control studies (I–II), ascertainment bias cannot be excluded if AD patients who had seen a doctor or been hospitalised for other problems (CVD or autoimmune disease) were more likely to be diagnosed with AD. Moreover, some clinics have reimbursement systems based on diagnosis-related groups, which may have led to listing of multiple diagnoses at a visit. Bias caused by diagnosis-related groups should be minor in this study, because the majority of the autoimmune diagnoses and cardiovascular diseases have strict definitions and were made by specialists within their respective medical disciplines. In Study IV, selection bias cannot be excluded if patients gaining weight were more likely to measure their weight, and missing weight data led to an exclusion of cases without this side effect. Nevertheless, I believe this scenario was uncommon, as weight is a routine outcome measure.

6.2.2.2 Information bias

Information bias results from an incorrect measurement of exposure and/or outcome (158). It is also known as observation, classification or measurement bias. The effect of information bias will depend on the type of misclassification: non-differential or differential (160). Non-differential misclassification occurs when the bias or measurement error occurs with equal likelihood among cases and controls. In Study I, we cannot exclude non-differential measurement errors of weight and smoking reported among mothers registered at antenatal care. Such erroneous data would dilute the effect of these variables toward the null, since measurement errors most likely occurred among all mothers, regardless of a diagnosis of AD or not. Differential misclassification refers to differences in misclassification between cases and controls and will result in an estimate shifted either upward or downward from null, depending on who is misclassified. The main differential misclassification bias probably occurred in the case-control studies with misclassification of the diagnosis of AD, severity of AD and/or comorbidities. Reporting bias cannot be excluded in the clinical studies (III–IV).

Misclassification of AD may have occurred as the research team had no data from primary care and might therefore have missed some cases who had never received an AD diagnosis. However, since the AD diagnosis can be a challenge and misdiagnosis may occur, a major strength was that 80% of the AD patients had received their diagnosis in a dermatology department, thus reducing the overall risk of misclassification. It should also be recognised that some misclassification of AD can occur if a doctor is more likely to give an AD

diagnosis due to the reimbursement for this diagnosis. In some clinics, it is more favourable to make an ICD diagnosis of AD than to use the ICD code for unspecific dermatitis.

Misclassification of disease severity is linked to the study definition of severe AD vs. non-severe AD. In Study 2, we chose this definition of non-severe AD and severe AD to make that study comparable to other studies with similar definitions of disease severity. Severe AD included patients prescribed conventional systemic treatment for AD or who had been treated in a dermatological ward with AD as their main diagnosis. Patients without systemic AD treatment, even if they had been treated by a specialist, were defined as non-severe cases. Some severe AD patients probably underwent topical treatment and phototherapy because of insufficient effect of conventional systemic treatment or side effects. Unfortunately, they can have been misclassified as non-severe AD when using the study definition. Moreover, misclassification of disease severity cannot be excluded if comorbidities were an indication for treatment in dermatological wards, for example, if the patients had a mild-to-moderate AD with a flare that could not be managed at home. Speculatively, the latter would apply more to the older patients in the study. Historically, more patients were treated at dermatological wards, because there were more hospital beds and a lower threshold for admission. In 1970, Sweden had the highest number of hospital beds in Europe (all specialities included); forty years later, we had the lowest number in Europe (162). In addition, there is another explanation for the higher age among severe cases compared with non-severe cases (mean age 53.5 years vs. 41.0 years) at the end of the Study I. Before 2001, patients with a diagnosis of AD could only be identified in the inpatient register. This is a problem, since all non-severe AD cases were misclassified as controls before 2001. In summary, aside for the problem of misclassification of AD severity, some of the differences in cardiovascular comorbidities between severe and non-severe AD cases are due to age differences between these two groups. Therefore, comparisons in comorbidity can only be made between cases and age-matched controls and not between severe AD and non-severe AD.

In Study V, misclassification of depression cannot be excluded. The patients completed assessments with MADRS-S, but unfortunately, we did not have a complementary measure of depressive symptoms assessing the DSM-IV criteria of depression. On the other hand, a Swedish study has compared MADRS-S with Beck Depression Inventory II, one of the most commonly used instruments for screening and diagnosis of depression. It found good comparability and reliability across severity of depression and suggested that MADRS-S could be used for both diagnostic assessment and follow-up (163).

Misclassification of comorbidities could have occurred if AD patients were more frequently seen in the healthcare system and, therefore, were more often diagnosed with comorbidities, while non-AD patients were less frequently seen and hence underdiagnosed. The strength is the high validity of diagnoses in NPR (96). The long follow-up time enables both cases and controls to receive a diagnosis regardless of one visit due to another diagnosis, although some degree of misclassification can never be excluded in register data. I also recognise

that NPR may have a low coverage for several diagnoses managed in primary care, such as Hashimoto's disease and chronic urticaria.

In the clinical studies, *reporting bias* may have occurred during several stages of the data collection. Maybe the study subjects gave an answer they thought was of interest, or underreported undesirable behaviours, such as high alcohol consumption. I consider this a minor bias, as data were collected prospectively before the research questions were defined.

6.2.2.3 Confounding

A confounding factor is associated with both the exposure and the outcome, but is not a link in the causal pathway. It is a third factor, causing a confusion of effects (161). There are several methods to prevent confounding, including restriction, matching, stratification and multivariate techniques (158). In Studies I–II, matching by age and sex was used, and several other possible confounders were included in the multivariable models. However, one of the major limitations of Studies I–II was missing data on smoking. Smoking could have influenced several of the associations, mainly between AD and CVD, but also between AD and autoimmune diseases. In Study V, it cannot be excluded that regular follow-ups and supporting staff motivated the patients to use more moisturisers and to avoid eczema triggers. This could have improved both AD and mental health. I hope this was a minor bias, as the observers and participants could be considered blinded to the hypothesis and related research questions, which were determined several months after data collection.

6.2.2.4 Effect modification

Effect modification occurs when the effect of an exposure on the outcome differs depending on the level or value of a third variable (164). In Studies I and II, no effect modification was found for the included covariates. As previously mentioned, the research team did not have information about smoking or obesity for the entire population. Therefore, it cannot be excluded that some of the associations were different between subgroups of AD patients, such as obese vs. non-obese or smokers vs. non-smokers.

6.2.2.5 External validity

The strength of the case-control studies was the population-based design with inclusion of the entire population. Therefore, the results can be generalised to other populations with similar environmental and genetic backgrounds. In the prospective clinical studies, data were collected in a routine dermatological setting, meaning that the results are representative for how systemic AD treatment affects clinical outcomes in daily clinical practice. This is important, as existing knowledge on effects and adverse events from dupilumab is mainly based on data from clinical trials.

6.2.3 Precision

Random error is variability of data that cannot be explained or may be due to chance (164). The confidence interval provides an estimate of the variability. In Studies I–II, the large sample sizes reduced the effect of random errors and enabled precise estimates with narrow confidence intervals in general. By contrast, some precision was lost in the clinical studies due to small study populations, especially in the subgroup analyses (Studies IV–V). In Study II, the Bonferroni correction might have led to a type II error when studying the association between AD and multiple autoimmune diseases. Therefore, p-values below the common critical p-value of 5% were presented in bold, to make the data more accessible for interpretation. By way of example, an association between AD and DM1 ($p = 0.003$) was found in the overall analysis using the common critical p-value (< 0.05), but not after Bonferroni correction. However, the OR was low and probably without clinical implications for daily clinical practice (aOR 1.08, 95% CI 1.03–1.14).

7 CONCLUSIONS

I. Adult patients with AD had a positive association with angina pectoris, MI, and ischaemic stroke compared with the general population. The association was attenuated after adjustment for cardiovascular comorbidities and socioeconomic status.

II. Diabetes mellitus, hyperlipidaemia, and hypertension were more prevalent in patients with severe AD than in controls, and hyperlipidaemia and hypertension were also more prevalent in patients with non-severe AD than in controls. Subgroup analyses indicated that smoking was an important risk factor for CVD among severe AD cases.

III. Adult patients with AD had a positive association with autoimmune diseases, especially disorders involving the skin, the gastrointestinal tract and/or the connective tissue. Having multiple autoimmune diseases resulted in a stronger association with AD than having only one autoimmune disease. Men with AD had a stronger association with RA and coeliac disease than women with AD.

IV. Dupilumab was a very effective and safe treatment overall. Although the case-series was small, it was concluded that the risk of adverse events from the eyes and recurrence of herpes virus infections should be kept in mind, especially for patients with severe, long-lasting AD and previous eye disease. Dupilumab-associated conjunctivitis was the most common adverse event.

V. Weight gain was an unexpected and unexplained side effect during dupilumab treatment of AD.

VI. In routine dermatological care, more than half of the patients had depressive symptoms at the start of systemic treatment for moderate-to-severe AD, with 25% of them presenting with a moderate-to-severe depression and 5% with pronounced suicidal ideation.

VII. Systemic treatment significantly reduced depressive symptoms, in addition to relieving symptoms and signs of AD.

8 POINTS OF PERSPECTIVE

In 2016, when we started to prepare for the clinical database (to be SwedAD), no biologics with indication for AD were available on the Swedish market. The research projects have followed the journey of a new treatment and on the way, we have revised the research questions. Several new questions have arisen, where the answers could potentially relieve the disease burden in subjects with AD and give deeper insight into the pathogenesis of this disease.

I. *Can optimal treatment of AD, including topical treatment and/or systemic treatment, have an impact on the association between AD and CVD, autoimmune disease or depression? And the ultimate question, is there a causal link between AD and these comorbidities?*

II. *Do patients with multiple autoimmune diseases respond differently to systemic treatment; is there an autoimmune component making these patients more treatment-resistant? Are there subgroups of AD patients with higher risk of CVD and/or autoimmune disease?*
Real-world prospective register studies might shed some light on these questions (I+II). It is important to establish a correct diagnosis of AD, including a severity grading, and to obtain detailed information on confounding factors that have been largely unavailable in previous register studies.

III. *Why did the patients with dupilumab gain weight?*
The research group will continue to prospectively follow up this novel observation. Did the patients represent a phenotype within the AD spectrum, possibly linked to disease severity, more vulnerable to this side effect? Did they have other risk factors, e.g., for the metabolic syndrome?

IV. *How can dupilumab-associated conjunctivitis be prevented?*
Anecdotal reports found artificial tears to be effective. If a cheap and benign recommendation, such as artificial tears, can prevent patients from adverse events and treatment discontinuation, this recommendation should be added to guidelines. However, to my knowledge, this have not been studied in larger trials. This could be studied in a RCT with patients randomised to prophylactic treatment. The first step might be to further characterise patients at risk through collaboration with an opthamologists. When new research data on the pathophysiology are available, there might be other ways to prevent this side effect.

V. *What is the safest treatment option for severe AD in the current COVID-19 pandemic: conventional systemic treatment or dupilumab?*
It would be interesting to perform a cohort study using Swedish national registries to

ascertain incidence of COVID-19 in those receiving particular treatments. The findings could be important for future treatment guidelines.

VI. What is the best treatment for AD?

Treatment decision until now have often been based on disease severity and treatment options have been unspecific and limited. With emerging new therapies, this could also be based on biological pathways (endotypes) and phenotypes. We have just entered an era of personalised medicine, with increasing knowledge on AD biomarkers that can guide us to optimal treatment decisions. Another compelling research area is the exposome involved in AD pathogenesis (41), defined as the sum of external factors that an individual is exposed to during their lifetime. This includes numerous factors such as antenatal exposures, early life exposures, diet, allergens, the microbiome, urbanisation, climate, etc. Deeper understanding within this field might also change future treatment guidelines and preventive healthcare. It would be very interesting to be a small part of the ongoing research within these fields.

9 POPULÄRVETENSKAPLIG SAMMANFATTNING

Atopisk dermatit (AD), även kallat atopiskt eksem eller böjveckseksem, är en av världens vanligaste kroniska inflammatoriska hudsjukdomar och drabbar upp till 20 % av alla barn och 10 % av vuxna. Symtomen karakteriseras av torr hud och återkommande kliande utslag. De allra flesta har ett milt eksem, men beroende på svårighetsgrad kan AD påverka flera aspekter av hälsorelaterad livskvalitet. AD kan leda till sömnstörningar orsakade av klåda och rivning, liksom begränsningar av arbetsliv och sociala relationer. Depression och självmordstankar är vanligare hos dem med AD än hos normalbefolkningen. Studier under de senaste åren har visat motstridiga resultat kring huruvida det även finns ett samband mellan AD och hjärt- och kärlsjukdomar respektive autoimmuna sjukdomar.

Mild AD kan behandlas utvärtes. Svårare AD kan kräva ljusbehandling eller systemisk, invärtes behandling med t.ex. metotrexat eller cyklosporin. Systemisk behandling kan dock vara otillräcklig eller ge biverkningar. Nya revolutionerande kunskaper om AD har bidragit till utveckling av nya läkemedel under de senaste åren. Det första biologiska läkemedlet som godkändes i Europa 2017 har visat sig vara mycket effektivt och är ett genombrott för patienter med svår AD.

Denna avhandling studerade sambandet mellan AD och hjärt- och kärlsjukdom (studie I), och mellan AD och autoimmuna sjukdomar (studie II) hos AD-patienter som var 15 år eller äldre. Detta analyserades med data från svenska nationella register. Vi jämförde 104 832 personer som hade fått diagnosen AD med 1 022 435 friska kontroller från normalbefolkningen avseende exponering för hjärt-kärlsjukdom och autoimmuna sjukdomar. De kliniska studierna (studie III–V) undersökte effekter och biverkningar av systemiska läkemedel inklusive dupilumab, det första biologiska läkemedlet. Vi studerade även förekomst och svårighetsgrad av depression hos dem med medelsvår-svår AD (studie V). De kliniska studierna baserades på data från ett kvalitets- och forskningsregister för patienter med AD vid hudkliniken vid Karolinska Universitetssjukhuset. Registret skapades 2017 som ett forskningsregister och lanserades 2019 som ett nationellt kvalitetsregister för AD (SwedAD).

Vi upptäckte ett samband mellan AD och hjärt- och kärlsjukdom och stroke, men inte mellan AD och dödsfall till följd av hjärt- och kärlsjukdom. Endast de med svårast AD hade en signifikant ökad samsjuklighet med stroke. Patienter med svår AD hade generellt sett högre förekomst av diabetes mellitus (sockersjuka), höga blodfetter och högt blodtryck jämfört med kontroller. Rökning tycktes vara en bidragande faktor till hjärt- och kärlsjukdom hos dem med svår AD, men vi hade endast underlag för att analysera detta hos en mindre grupp kvinnor. Vi påvisade även en association mellan AD och autoimmun sjukdom, som var starkare ju fler autoimmuna sjukdomar man hade. De starkaste sambanden var mellan AD och andra autoimmuna hudsjukdomar, inflammatoriska magtarmsjukdomar och reumatiska sjukdomar. De kliniska studierna visade att dupilumab är en mycket säker och effektiv behandling, men i studie III, där patienterna hade svår AD

och många hade haft ögonsjukdom tidigare, utvecklade nio av tio ögonbiverkningar, varav sju av tio fick konjunktivit (inflammation av ögats bindhinna). Nästan alla kunde fortsatta med dupilumab, men fick samtidigt behandling genom ögonläkare. Vi upptäckte även en oväntad genomsnittlig viktuppgång på 6 kg (från 0.1 till 18 kg) hos 12 patienter som stått på dupilumab i mer än ett år. Vi kunde ej förklara vad denna viktuppgång berodde på. I den sista kliniska studien (V) såg vi att mer än hälften av dem som skulle börja med systembehandling av AD var deprimerade, varav 25 % hade en medelsvår depression, och 5 % uttalade självmordstankar. Systembehandling förbättrade depressiva symptom parallellt med att förbättra AD.

Sammanfattningsvis såg vi att AD hade en samsjuklighet med flera andra sjukdomar. Genom en ökad medvetenhet om samsjuklighet vid AD, t.ex. genom screening för kardiovaskulära riskfaktorer eller autoimmuna sjukdomar, kan man kanske minska sjukdomsbördan vid AD, framför allt hos dem med svårast hudsjukdom. Dupilumab visade sig vara ett mycket effektivt och generellt säkert läkemedel för AD och minskade även depressionssymptom. En vanlig biverkan var dock konjunktivit. Nära samarbete med ögonläkare rekommenderas vid ögonsymptom, då det kan öka sannolikheten att patienten kan fortsätta behandlingen. Genom det nationella kvalitetsregistret (SwedAD) kan forskningen fortsätta att följa det långsiktiga sjukdomsförloppet av AD och effekten och biverkningarna av läkemedel. Detta kommer att bli särskilt viktigt framöver, eftersom flera nya biologiska läkemedel mot AD beräknas lanseras inom en snar framtid.

10 ACKNOWLEDGEMENTS

I am deeply grateful to all those who in various ways have helped me, supported me and contributed to this thesis.

My supervisors:

Maria Bradley, my main supervisor, I would like to express my deepest gratitude to you for taking me on as your PhD student, for teaching me about research and for your generous support. You made this journey a lot of fun and always with interesting projects! For every obstacle, you always found an even better solution and the projects grew stronger. You are a true inspiration as a much beloved and skilled doctor to your patients, an excellent researcher, and a caring mother, grandmother and dog owner. I don't know how you manage to balance all these things! I think it is your very clever positive mind and lots of coffee, and that you recognise the importance of seeing the big picture in life.

Carl-Fredrik Wahlgren, there are not enough words to describe your expertise as a clinician, researcher and teacher – I will not even try to do so. I am extremely grateful for your generous and invaluable support, your teachings, our very interesting discussions, giving me new perspectives and lots of laughs. I even learned some Russian: Pojechali! 'let's go!'

Emma Johansson, I would like to express my deepest appreciation for your invaluable hands-on advice, for your always being by my side and for sharing of your profound knowledge. Your striving for perfection and your immensely sharp mind have challenged me and helped me improve my work. But most of all, I am grateful for your true friendship.

Bernt Lindelöf, the most experienced epidemiologist. Thank you for your guidance, patience, interesting discussions, and for helping me to take my first quivering steps into the world of epidemiological research. Without you, I wouldn't even have known how to get started.

My co-authors:

Henrik Dal, statistician, thank you for your collaboration and patience. You came from a world of numbers and I from the clinic – many times, we had different ways of thinking. I have really enjoyed all our debating and conversations through millions of email. I have learned a lot and you always gave me new perspectives.

Maria Lundqvist, research nurse, thank you for helping us establish the research register and helping us, in every way imaginable, to run it in the clinic. Your positive energy, effectiveness and care for the patients have been invaluable. Thank you!

Axel Svedbom, thank you for practical support and expert guidance in how to approach clinical register data. In addition, thank you for inspiration on how to write a thesis.

Lena Ivert, researcher, skilful ophthalmologist and my aunt. Thank you for collaboration in Study III, which enabled us to give optimal care to the patients with acute ocular adverse events. I sincerely appreciate your guidance in research, and far beyond.

In addition, I would like to acknowledge the assistance of **Ylva Rodvall** for suggestions and methodological considerations in the first epidemiological study.

Thanks also to all my colleagues at the Karolinska University Hospital for creating an inspiring and fun workplace. I sincerely appreciate the open-minded atmosphere we create together. It is such a privilege to have so many close friendships at work – I think it is unique! You mean very much to me.

I would like to acknowledge the support, during the thesis work, of:

Josefin Lysell, my sharp mentor. Speaking with you always makes me happy. Our discussions regarding several of the research projects helped me more than you know. In addition, thank you for taking care of my administration for almost 6 months!

Lena Lundeberg, head of the Department of Dermatology, and **Toomas Talme**, **Maria Sund Böhme** and **Arne Wikström**, my former closest superiors, for creating a workplace where research is possible! Moreover, for all your teachings and support through the years, whatever happens in life.

Jan Lapins, one of our most reputable clinicians, I cannot thank you enough for always supporting me in my clinical work and generously sharing your immense knowledge. Thank you for our discussions regarding Study II, which helped me to find important reference articles.

To my colleagues **Maria Karlsson** and **Natalia Kuzmina**, I am extremely grateful that I have had the opportunity to learn about dermatology from the most genuine experts like you. This have been of importance when managing patients with AD of all ages. You always took the time to answer my questions, no matter the place: during lunch, in the changing room or in the elevator.

Johan Jäderstad, my great colleague and collaborative partner at the inpatient dermatology ward. Thank you for taking care of my duties and attending meetings during my absence.

Thank you **Jenny Lundgren** and **Melanie Cremer,** medical secretaries, for adapting and always finding solutions for combining research and clinical work in our schedules.

I would like also to extend my sincere thanks to the teachers and friends at the **Research school for clinicians in epidemiology, Karolinska Institutet.**

And…
Johan Heilborn, founder of Hudcentrum Hagastaden. I will always be grateful for your unwavering guidance, invaluable teachings and kindness at my first job as a specialist in dermatology – when I needed it the most.
Birgitta Kelfve, the most respected clinician, my first main supervisor in dermatology. Thank you for your support, nurturing and giving me an excellent dermatological training. Without you, none of this would have been possible.
Gina Marku, my friend, teacher and a brilliant dermatologist in Västerås. I am so grateful for our friendship. I know I can call you in the middle of the night!
Mahsa Tayefi and **Martin Gumulka**, through ups and downs, we have known each other for more than 10 years, since we started our dermatological training in Västerås. It will always be liberating to have you around – and feel like home.
Britt-Inger "Bii" Haenflein, my first dance teacher and very close friend, who taught me everything from ballet to rock 'n roll. The years spent dancing and competing with you as a teacher taught me lessons of life that have been invaluable. Your wisdom extends far beyond physical steps.

I would like to express my deepest appreciation to my family:

My father **Torbjörn Ivert** and his wife **Lisa Ivert**. My brother and sisters, **Hannes Ivert**, **Clara Ivert** and **Emelie Ivert**. Thank you for being my **beloved daughter Rebecca**'s second family and giving her experiences for life.

Thank you to my mother, **Kerstin Ivert** – despite working in Norway, you and your husband **Johnny Wahlstedt** have helped out more than seemed possible. My sister **Charlotta Larsdotter**, thank you for the cover page design! My brother, **Hampus Ivert**, I will always admire you for following your dreams and making them real.

My dear husband and closest friend, **Anders Ivert** – the completion of my dissertation would not have been possible without you.

The project would not have been possible without the support of the Swedish Asthma and Allergy Association's Research Fund, Hudfonden (The Welander-Finsen Foundation), the Stockholm County Council (ALF grants), and The Swedish Society for Dermatology and Venereology.

11 REFERENCES

1. Kramer ON, Strom MA, Ladizinski B, Lio PA. The history of atopic dermatitis. Clin Dermatol. 2017;35(4):344-8.
2. Kantor R, Thyssen JP, Paller AS, Silverberg JI. Atopic dermatitis, atopic eczema, or eczema? A systematic review, meta-analysis, and recommendation for uniform use of 'atopic dermatitis'. Allergy. 2016;71(10):1480-5.
3. Bieber T. Why we need a harmonized name for atopic dermatitis/atopic eczema/eczema! Allergy. 2016;71(10):1379-80.
4. Johansson SG, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF, et al. Revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. J Allergy Clin Immunol. 2004;113(5):832-6.
5. Hanifin JM. Atopic dermatitis nomenclature variants can impede harmonization. J Invest Dermatol. 2012;132(2):472-3; author reply 3-4.
6. Flohr C, Johansson SG, Wahlgren CF, Williams H. How atopic is atopic dermatitis? J Allergy Clin Immunol. 2004;114(1):150-8.
7. Bologna JL JJ, Schaffer JV. Dermatology 3rd ed. China: Elsevier Saunder Press. 2003.
8. Simpson EL, Hanifin JM. Atopic dermatitis. Med Clin North Am. 2006;90(1):149-67, ix.
9. Weidinger S, Novak N. Atopic dermatitis. Lancet. 2016;387(10023):1109-22.
10. Kaufman BP, Guttman-Yassky E, Alexis AF. Atopic dermatitis in diverse racial and ethnic groups -Variations in epidemiology, genetics, clinical presentation and treatment. Exp Dermatol. 2018;27(4):340-57.
11. Rajka G. Natural history and clinical manifestations of atopic dermatitis. Clin Rev Allergy. 1986;4(1):3-26.
12. Bieber T, D'Erme AM, Akdis CA, Traidl-Hoffmann C, Lauener R, Schäppi G, et al. Clinical phenotypes and endophenotypes of atopic dermatitis: Where are we, and where should we go? J Allergy Clin Immunol. 2017;139(4s):S58-64.
13. Girolomoni G, de Bruin-Weller M, Aoki V, Kabashima K, Deleuran M, Puig L, et al. Nomenclature and clinical phenotypes of atopic dermatitis. Ther Adv Chronic Dis. 2021;12:20406223211002979.
14. Langan SM, Irvine AD, Weidinger S. Atopic dermatitis. Lancet. 2020;396(10247):345-60.
15. Andersen RM, Thyssen JP, Maibach HI. Qualitative vs. quantitative atopic dermatitis criteria - in historical and present perspectives. J Eur Acad Dermatol Venereol. 2016;30(4):604-18.
16. Williams HC, Burney PG, Pembroke AC, Hay RJ. The U.K. Working Party's Diagnostic Criteria for Atopic Dermatitis. III. Independent hospital validation. Br J Dermatol. 1994;131(3):406-16.
17. Brenninkmeijer EE, Schram ME, Leeflang MM, Bos JD, Spuls PI. Diagnostic criteria for atopic dermatitis: a systematic review. Br J Dermatol. 2008;158(4):754-65.
18. Weidinger S, Beck LA, Bieber T, Kabashima K, Irvine AD. Atopic dermatitis. Nat Rev Dis Primers. 2018;4(1):1.
19. Lee HH, Patel KR, Singam V, Rastogi S, Silverberg JI. A systematic review and meta-analysis of the prevalence and phenotype of adult-onset atopic dermatitis. J Am Acad Dermatol. 2019;80(6):1526-32.e7.
20. Hanifin JM. Adult-Onset Atopic Dermatitis: Fact or Fancy? Dermatol Clin. 2017;35(3):299-302.

21. Abuabara K, Yu AM, Okhovat JP, Allen IE, Langan SM. The prevalence of atopic dermatitis beyond childhood: A systematic review and meta-analysis of longitudinal studies. Allergy. 2018;73(3):696-704.
22. Sandstrom MH, Faergemann J. Prognosis and prognostic factors in adult patients with atopic dermatitis: A long-term follow-up questionnaire study. Br J Dermatol. 2004;150(1):103-10.
23. Johansson EK, Bergstrom A, Kull I, Lind T, Soderhall C, Melen E, et al. Prognosis of Preschool Eczema and Factors of Importance for Remission. Acta Derm Venereol. 2018;98(7):630-5.
24. Bieber T. Atopic dermatitis. N Engl J Med. 2008;358(14):1483-94.
25. Guttman-Yassky E, Waldman A, Ahluwalia J, Ong PY, Eichenfield LF. Atopic dermatitis: pathogenesis. Semin Cutan Med Surg. 2017;36(3):100-3.
26. Stander S. How acute stress impacts the itch-scratch cycle in atopic dermatitis: A clinical lesson. Br J Dermatol. 2019;180(4):689-90.
27. Bjerre RD, Bandier J, Skov L, Engstrand L, Johansen JD. The role of the skin microbiome in atopic dermatitis: A systematic review. Br J Dermatol. 2017;177(5):1272-8.
28. Geoghegan JA, Irvine AD, Foster TJ. Staphylococcus aureus and Atopic Dermatitis: A Complex and Evolving Relationship. Trends Microbiol. 2018;26(6):484-97.
29. Brodská P, Panzner P, Pizinger K, Schmid-Grendelmeier P. IgE-mediated sensitization to malassezia in atopic dermatitis: More common in male patients and in head and neck type. Dermatitis. 2014;25(3):120-6.
30. Kim J, Kim BE, Leung DYM. Pathophysiology of atopic dermatitis: Clinical implications. Allergy Asthma Proc. 2019;40(2):84-92.
31. Lee DE, Clark AK, Tran KA, Shi VY. New and emerging targeted systemic therapies: A new era for atopic dermatitis. J Dermatolog Treat. 2018;29(4):364-74.
32. Schultz Larsen F. Atopic dermatitis: A genetic-epidemiologic study in a population-based twin sample. J Am Acad Dermatol. 1993;28(5 Pt 1):719-23.
33. Irvine AD, McLean WH, Leung DY. Filaggrin mutations associated with skin and allergic diseases. N Engl J Med. 2011;365(14):1315-27.
34. Winge MC, Bilcha KD, Lieden A, Shibeshi D, Sandilands A, Wahlgren CF, et al. Novel filaggrin mutation but no other loss-of-function variants found in Ethiopian patients with atopic dermatitis. Br J Dermatol. 2011;165(5):1074-80.
35. Flohr C, Mann J. New insights into the epidemiology of childhood atopic dermatitis. Allergy. 2014;69(1):3-16.
36. Kantor R, Kim A, Thyssen JP, Silverberg JI. Association of atopic dermatitis with smoking: A systematic review and meta-analysis. J Am Acad Dermatol. 2016;75(6):1119-25.e1.
37. Andersen YMF, Egeberg A, Skov L, Thyssen JP. Comorbidities of Atopic Dermatitis: Beyond Rhinitis and Asthma. Curr Dermatol Rep. 2017;6(1):35-41.
38. Wollenberg A, Barbarot S, Bieber T, Christen-Zaech S, Deleuran M, Fink-Wagner A, et al. Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: Part I. J Eur Acad Dermatol Venereol. 2018;32(5):657-82.
39. Strachan DP. Family size, infection and atopy: The first decade of the "hygiene hypothesis". Thorax. 2000;55 Suppl 1:S2-10.
40. Bloomfield SF, Rook GA, Scott EA, Shanahan F, Stanwell-Smith R, Turner P. Time to abandon the hygiene hypothesis: New perspectives on allergic disease, the human microbiome, infectious disease prevention and the role of targeted hygiene. Perspect Public Health. 2016;136(4):213-24.
41. Stefanovic N, Flohr C, Irvine AD. The exposome in atopic dermatitis. Allergy. 2020;75(1):63-74.

42. Flohr C, Pascoe D, Williams HC. Atopic dermatitis and the 'hygiene hypothesis': Too clean to be true? Br J Dermatol. 2005;152(2):202-16.
43. Haahtela T. A biodiversity hypothesis. Allergy. 2019;74(8):1445-56.
44. Rook GA, Raison CL, Lowry CA. Microbial 'old friends', immunoregulation and socioeconomic status. Clin Exp Immunol. 2014;177(1):1-12.
45. Schmitt J, Williams H. Harmonising Outcome Measures for Eczema (HOME). Report from the First International Consensus Meeting (HOME 1), 24 July 2010, Munich, Germany. Br J Dermatol. 2010;163(6):1166-8.
46. Chalmers JR, Thomas KS, Apfelbacher C, Williams HC, Prinsen CA, Spuls PI, et al. Report from the fifth international consensus meeting to harmonize core outcome measures for atopic eczema/dermatitis clinical trials (HOME initiative). Br J Dermatol. 2018;178(5):e332-41.
47. Silverberg JI. Comorbidities and the impact of atopic dermatitis. Ann Allergy Asthma Immunol. 2019;123(2):144-51.
48. Thyssen JP, Toft PB, Halling-Overgaard AS, Gislason GH, Skov L, Egeberg A. Incidence, prevalence, and risk of selected ocular disease in adults with atopic dermatitis. J Am Acad Dermatol. 2017;77(2):280-6.e1.
49. Paller AS, Spergel JM, Mina-Osorio P, Irvine AD. The atopic march and atopic multimorbidity: Many trajectories, many pathways. J Allergy Clin Immunol. 2019;143(1):46-55.
50. Ballardini N, Bergstrom A, Bohme M, van Hage M, Hallner E, Johansson E, et al. Infantile eczema: Prognosis and risk of asthma and rhinitis in preadolescence. J Allergy Clin Immunol. 2014;133(2):594-6.
51. Bergmann MM, Caubet JC, Boguniewicz M, Eigenmann PA. Evaluation of food allergy in patients with atopic dermatitis. J Allergy Clin Immunol Pract. 2013;1(1):22-8.
52. Longo G, Berti I, Burks AW, Krauss B, Barbi E. IgE-mediated food allergy in children. Lancet. 2013;382(9905):1656-64.
53. Brunner PM, Silverberg JI, Guttman-Yassky E, Paller AS, Kabashima K, Amagai M, et al. Increasing Comorbidities Suggest that Atopic Dermatitis Is a Systemic Disorder. J Invest Dermatol. 2017;137(1):18-25.
54. Drucker AM, Wang AR, Li WQ, Sevetson E, Block JK, Qureshi AA. The Burden of Atopic Dermatitis: Summary of a Report for the National Eczema Association. J Invest Dermatol. 2017;137(1):26-30.
55. Andersen YM, Egeberg A, Gislason GH, Hansen PR, Skov L, Thyssen JP. Risk of myocardial infarction, ischemic stroke, and cardiovascular death in patients with atopic dermatitis. J Allergy Clin Immunol. 2016;138(1):310-2.e3.
56. Thyssen JP, Halling-Overgaard AS, Andersen YMF, Gislason G, Skov L, Egeberg A. The association with cardiovascular disease and type 2 diabetes in adults with atopic dermatitis: A systematic review and meta-analysis. Br J Dermatol. 2018;178(6):1272-9.
57. Silverwood RJ, Forbes HJ, Abuabara K, Ascott A, Schmidt M, Schmidt SAJ, et al. Severe and predominantly active atopic eczema in adulthood and long term risk of cardiovascular disease: Population based cohort study. BMJ. 2018;361:k1786.
58. Ascott A, Mulick A, Yu AM, Prieto-Merino D, Schmidt M, Abuabara K, et al. Atopic eczema and major cardiovascular outcomes: A systematic review and meta-analysis of population-based studies. J Allergy Clin Immunol. 2018.
59. Drucker AM, Harvey PJ. Atopic dermatitis and cardiovascular disease: What are the clinical implications? J Allergy Clin Immunol. 2019;143(5):1736-8.
60. Silverberg JI, Gelfand JM, Margolis DJ, Boguniewicz M, Fonacier L, Grayson MH, et al. Association of atopic dermatitis with allergic, autoimmune, and cardiovascular comorbidities in US adults. Ann Allergy Asthma Immunol. 2018;121(5):604-12.e3.

61. Hjuler KF, Bottcher M, Vestergaard C, Deleuran M, Raaby L, Botker HE, et al. Increased Prevalence of Coronary Artery Disease in Severe Psoriasis and Severe Atopic Dermatitis. Am J Med. 2015;128(12):1325-34.e2.
62. Brunner PM, Suárez-Fariñas M, He H, Malik K, Wen HC, Gonzalez J, et al. The atopic dermatitis blood signature is characterized by increases in inflammatory and cardiovascular risk proteins. Sci Rep. 2017;7(1):8707.
63. Zhang A, Silverberg JI. Association of atopic dermatitis with being overweight and obese: A systematic review and metaanalysis. J Am Acad Dermatol. 2015;72(4):606-16.e4.
64. Paller A, Jaworski JC, Simpson EL, Boguniewicz M, Russell JJ, Block JK, et al. Major Comorbidities of Atopic Dermatitis: Beyond Allergic Disorders. Am J Clin Dermatol. 2018;19(6):821-38.
65. Silverberg JI, Greenland P. Eczema and cardiovascular risk factors in 2 US adult population studies. J Allergy Clin Immunol. 2015;135(3):721-8.e6.
66. Rice JB, White AG, Scarpati LM, Wan G, Nelson WW. Long-term Systemic Corticosteroid Exposure: A Systematic Literature Review. Clin Ther. 2017;39(11):2216-29.
67. Phan K, Smith SD. Topical corticosteroids and risk of diabetes mellitus: Systematic review and meta-analysis. J Dermatolog Treat. 2019:1-5.
68. Wei L, MacDonald TM, Walker BR. Taking glucocorticoids by prescription is associated with subsequent cardiovascular disease. Ann Intern Med. 2004;141(10):764-70.
69. Tobaldini E, Fiorelli EM, Solbiati M, Costantino G, Nobili L, Montano N. Short sleep duration and cardiometabolic risk: From pathophysiology to clinical evidence. Nat Rev Cardiol. 2019;16(4):213-24.
70. Silverberg JI, Garg NK, Paller AS, Fishbein AB, Zee PC. Sleep disturbances in adults with eczema are associated with impaired overall health: A US population-based study. J Invest Dermatol. 2015;135(1):56-66.
71. Zuberbier T, Orlow SJ, Paller AS, Taïeb A, Allen R, Hernanz-Hermosa JM, et al. Patient perspectives on the management of atopic dermatitis. J Allergy Clin Immunol. 2006;118(1):226-32.
72. Hare DL, Toukhsati SR, Johansson P, Jaarsma T. Depression and cardiovascular disease: A clinical review. Eur Heart J. 2014;35(21):1365-72.
73. Andersen YM, Egeberg A, Gislason GH, Skov L, Thyssen JP. Autoimmune diseases in adults with atopic dermatitis. J Am Acad Dermatol. 2017;76(2):274-80.e1.
74. Cipriani F, Marzatico A, Ricci G. Autoimmune diseases involving skin and intestinal mucosa are more frequent in adolescents and young adults suffering from atopic dermatitis. J Dermatol. 2017;44(12):1341-8.
75. Thijs JL, Strickland I, Bruijnzeel-Koomen C, Nierkens S, Giovannone B, Knol EF, et al. Serum biomarker profiles suggest that atopic dermatitis is a systemic disease. J Allergy Clin Immunol. 2018;141(4):1523-6.
76. Barahmani N, Schabath MB, Duvic M. History of atopy or autoimmunity increases risk of alopecia areata. J Am Acad Dermatol. 2009;61(4):581-91.
77. Betz RC, Pforr J, Flaquer A, Redler S, Hanneken S, Eigelshoven S, et al. Loss-of-function mutations in the filaggrin gene and alopecia areata: Strong risk factor for a severe course of disease in patients comorbid for atopic disease. J Invest Dermatol. 2007;127(11):2539-43.
78. Holmes J, Fairclough LC, Todd I. Atopic dermatitis and autoimmunity: The occurrence of autoantibodies and their association with disease severity. Arch Dermatol Res. 2019;311(3):141-62.

79. Thyssen JP, Hamann CR, Linneberg A, Dantoft TM, Skov L, Gislason GH, et al. Atopic dermatitis is associated with anxiety, depression, and suicidal ideation, but not with psychiatric hospitalization or suicide. Allergy. 2018;73(1):214-20.
80. Patel KR, Immaneni S, Singam V, Rastogi S, Silverberg JI. Association between atopic dermatitis, depression, and suicidal ideation: A systematic review and meta-analysis. J Am Acad Dermatol. 2019;80(2):402-10.
81. Simpson EL AB, Ardeleanu M. Correspondence. Two Phase 3 Trials of Dupilumab versus Placebo in Atopic Dermatitis. N Engl J Med. 2017;376(11):1090-1.
82. Bender BG, Ballard R, Canono B, Murphy JR, Leung DY. Disease severity, scratching, and sleep quality in patients with atopic dermatitis. J Am Acad Dermatol. 2008;58(3):415-20.
83. Fang H, Tu S, Sheng J, Shao A. Depression in sleep disturbance: A review on a bidirectional relationship, mechanisms and treatment. J Cell Mol Med. 2019;23(4):2324-32.
84. Ring J, Zink A, Arents BWM, Seitz IA, Mensing U, Schielein MC, et al. Atopic eczema: Burden of disease and individual suffering - results from a large EU study in adults. J Eur Acad Dermatol Venereol. 2019;33(7):1331-40.
85. Buske-Kirschbaum A, Geiben A, Hellhammer D. Psychobiological aspects of atopic dermatitis: An overview. Psychother Psychosom. 2001;70(1):6-16.
86. Nicholas MN, Drucker AM. Depression and anxiety in atopic dermatitis: Increasing recognition and opportunities to intervene. Br J Dermatol. 2019;181(3):442-3.
87. Sy W, Lamb AJ. Atopic Dermatitis Disease Education. Adv Exp Med Biol. 2017;1027:179-84.
88. Sidbury R, Davis DM, Cohen DE, Cordoro KM, Berger TG, Bergman JN, et al. Guidelines of care for the management of atopic dermatitis: section 3. Management and treatment with phototherapy and systemic agents. J Am Acad Dermatol. 2014;71(2):327-49.
89. King B, Maari C, Lain E, Silverberg JI, Issa M, Holzwarth K, et al. Extended Safety Analysis of Baricitinib 2 mg in Adult Patients with Atopic Dermatitis: An Integrated Analysis from Eight Randomized Clinical Trials. Am J Clin Dermatol. 2021.
90. Wollenberg A, Barbarot S, Bieber T, Christen-Zaech S, Deleuran M, Fink-Wagner A, et al. Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: Part II. J Eur Acad Dermatol Venereol. 2018;32(6):850-78.
91. Roekevisch E, Spuls PI, Kuester D, Limpens J, Schmitt J. Efficacy and safety of systemic treatments for moderate-to-severe atopic dermatitis: A systematic review. J Allergy Clin Immunol. 2014;133(2):429-38.
92. van der Schaft J, Politiek K, van den Reek J, Christoffers WA, Kievit W, de Jong E, et al. Drug survival for ciclosporin A in a long-term daily practice cohort of adult patients with atopic dermatitis. Br J Dermatol. 2015;172(6):1621-7.
93. Bangert CA, Costner MI. Methotrexate in dermatology. Dermatol Ther. 2007;20(4):216-28.
94. Schram ME, Roekevisch E, Leeflang MM, Bos JD, Schmitt J, Spuls PI. A randomized trial of methotrexate versus azathioprine for severe atopic eczema. J Allergy Clin Immunol. 2011;128(2):353-9.
95. Chavez-Alvarez S, Herz-Ruelas M, Villarreal-Martinez A, Ocampo-Candiani J, Garza-Garza R, Gomez-Flores M. Azathioprine: Its uses in dermatology. An Bras Dermatol. 2020;95(6):731-6.
96. Gooderham MJ, Hong HC, Eshtiaghi P, Papp KA. Dupilumab: A review of its use in the treatment of atopic dermatitis. J Am Acad Dermatol. 2018;78(3 Suppl 1):S28-s36.

97. Seegräber M, Srour J, Walter A, Knop M, Wollenberg A. Dupilumab for treatment of atopic dermatitis. Expert Rev Clin Pharmacol. 2018;11(5):467-74.
98. Ou Z, Chen C, Chen A, Yang Y, Zhou W. Adverse events of Dupilumab in adults with moderate-to-severe atopic dermatitis: A meta-analysis. Int Immunopharmacol. 2018;54:303-10.
99. Halling AS, Loft N, Silverberg JI, Guttman-Yassky E, Thyssen JP. Real-world evidence of dupilumab efficacy and risk of adverse events: A systematic review and meta-analysis. J Am Acad Dermatol. 2021;84(1):139-47.
100. Simpson EL, Lacour JP, Spelman L, Galimberti R, Eichenfield LF, Bissonnette R, et al. Baricitinib in patients with moderate-to-severe atopic dermatitis and inadequate response to topical corticosteroids: Results from two randomized monotherapy phase III trials. Br J Dermatol. 2020;183(2):242-55.
101. Bieber T, Thyssen JP, Reich K, Simpson EL, Katoh N, Torrelo A, et al. Pooled safety analysis of baricitinib in adult patients with atopic dermatitis from 8 randomized clinical trials. J Eur Acad Dermatol Venereol. 2021;35(2):476-85.
102. Ludvigsson JF, Almqvist C, Bonamy AK, Ljung R, Michaëlsson K, Neovius M, et al. Registers of the Swedish total population and their use in medical research. Eur J Epidemiol. 2016;31(2):125-36.
103. Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim JL, Reuterwall C, et al. External review and validation of the Swedish national inpatient register. BMC Public Health. 2011;11:450.
104. The National Board of Health and Welfare. The swedish medical birth register [updated 2020, December 8]. Available from: https://www.socialstyrelsen.se/en/statistics-and-data/registers/register-information/the-swedish-medical-birth-register/. Accessed 2021, March 21.
105. Axelsson O. The Swedish medical birth register. Acta Obstet Gynecol Scand. 2003;82(6):491-2.
106. Brooke HL, Talbäck M, Hörnblad J, Johansson LA, Ludvigsson JF, Druid H, et al. The Swedish cause of death register. Eur J Epidemiol. 2017;32(9):765-73.
107. Wettermark B, Hammar N, Fored CM, Leimanis A, Otterblad Olausson P, Bergman U, et al. The new Swedish Prescribed Drug Register--opportunities for pharmacoepidemiological research and experience from the first six months. Pharmacoepidemiol Drug Saf. 2007;16(7):726-35.
108. Ludvigsson JF, Svedberg P, Olén O, Bruze G, Neovius M. The longitudinal integrated database for health insurance and labour market studies (LISA) and its use in medical research. Eur J Epidemiol. 2019;34(4):423-37.
109. Statistics Sweden. Background Facts, Population and Welfare Statistics 2017:2, Multi-generation register 2016. A description of contents and quality.
110. Swedish quality register of Atopic Dermatitis (SwedAD). Svenskt kvalitetsregister för atopisk dermatit (Swedish) [updated 2021, March 15]. Available from: https://swedad.nu/vardgivare/om-swedad/. Accessed 2021, March 23.
111. Schram ME, Spuls PI, Leeflang MM, Lindeboom R, Bos JD, Schmitt J. EASI, (objective) SCORAD and POEM for atopic eczema: Responsiveness and minimal clinically important difference. Allergy. 2012;67(1):99-106.
112. Spuls PI, Gerbens LAA, Simpson E, Apfelbacher CJ, Chalmers JR, Thomas KS, et al. Patient-Oriented Eczema Measure (POEM), a core instrument to measure symptoms in clinical trials: A Harmonising Outcome Measures for Eczema (HOME) statement. Br J Dermatol. 2017;176(4):979-84.
113. Yosipovitch G, Reaney M, Mastey V, Eckert L, Abbé A, Nelson L, et al. Peak Pruritus Numerical Rating Scale: Psychometric validation and responder definition for assessing itch in moderate-to-severe atopic dermatitis. Br J Dermatol. 2019;181(4):761-9.

114. Phan NQ, Blome C, Fritz F, Gerss J, Reich A, Ebata T, et al. Assessment of pruritus intensity: Prospective study on validity and reliability of the visual analogue scale, numerical rating scale and verbal rating scale in 471 patients with chronic pruritus. Acta Derm Venereol. 2012;92(5):502-7.
115. Thomas KS, Apfelbacher CA, Chalmers JR, Simpson E, Spuls PI, Gerbens LAA, et al. Recommended core outcome instruments for health-related quality of life, long-term control and itch intensity in atopic eczema trials: Results of the HOME VII consensus meeting. Br J Dermatol. 2020.
116. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)—a simple practical measure for routine clinical use. Clin Exp Dermatol. 1994;19(3):210-6.
117. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry. 1979;134:382-9.
118. Svanborg P, Asberg M. A new self-rating scale for depression and anxiety states based on the Comprehensive Psychopathological Rating Scale. Acta Psychiatr Scand. 1994;89(1):21-8.
119. Wikberg C, Pettersson A, Westman J, Björkelund C, Petersson EL. Patients' perspectives on the use of the Montgomery-Asberg depression rating scale self-assessment version in primary care. Scand J Prim Health Care. 2016;34(4):434-42.
120. Mattsson S, Olsson EMG, Carlsson M, Johansson BBK. Identification of Anxiety and Depression Symptoms in Patients With Cancer: Comparison Between Short and Long Web-Based Questionnaires. J Med Internet Res. 2019;21(4):e11387.
121. Svanborg P, Ekselius L. Self-assessment of DSM-IV criteria for major depression in psychiatric out- and inpatients. Nord J Psychiatry. 2003;57(4):291-6.
122. Snaith RP, Harrop FM, Newby DA, Teale C. Grade scores of the Montgomery-Asberg Depression and the Clinical Anxiety Scales. Br J Psychiatry. 1986;148:599-601.
123. VanderWeele TJ. Principles of confounder selection. Eur J Epidemiol. 2019;34(3):211-9.
124. Gillon R. Medical ethics: Four principles plus attention to scope. Bmj. 1994;309(6948):184-8.
125. Ludvigsson JF, Håberg SE, Knudsen GP, Lafolie P, Zoega H, Sarkkola C, et al. Ethical aspects of registry-based research in the Nordic countries. Clin Epidemiol. 2015;7:491-508.
126. Kho ME, Duffett M, Willison DJ, Cook DJ, Brouwers MC. Written informed consent and selection bias in observational studies using medical records: systematic review. Bmj. 2009;338:b866.
127. Su VY, Chen TJ, Yeh CM, Chou KT, Hung MH, Chu SY, et al. Atopic dermatitis and risk of ischemic stroke: A nationwide population-based study. Ann Med. 2014;46(2):84-9.
128. Millett ERC, Peters SAE, Woodward M. Sex differences in risk factors for myocardial infarction: Cohort study of UK Biobank participants. Bmj. 2018;363:k4247.
129. Silverberg JI. Association between adult atopic dermatitis, cardiovascular disease, and increased heart attacks in three population-based studies. Allergy. 2015;70(10):1300-8.
130. Olsen J, Jensen UJ. Causal criteria: Time has come for a revision. Eur J Epidemiol. 2019;34(6):537-41.
131. Thyssen JP, Egeberg A. Cardiovascular disease and atopic dermatitis: Epidemiological strengths and limitations. Br J Dermatol. 2018;179(4):1014-5.
132. Narla S, Silverberg JI. Association between atopic dermatitis and autoimmune disorders in US adults and children: A cross-sectional study. J Am Acad Dermatol. 2019;80(2):382-9.

133. Schmitt J, Schwarz K, Baurecht H, Hotze M, Folster-Holst R, Rodriguez E, et al. Atopic dermatitis is associated with an increased risk for rheumatoid arthritis and inflammatory bowel disease, and a decreased risk for type 1 diabetes. J Allergy Clin Immunol. 2016;137(1):130-6.
134. Mohan GC, Silverberg JI. Association of Vitiligo and Alopecia Areata With Atopic Dermatitis: A Systematic Review and Meta-analysis. JAMA Dermatol. 2015;151(5):522-8.
135. Ghazanfar MN, Kibsgaard L, Thomsen SF, Vestergaard C. Risk of comorbidities in patients diagnosed with chronic urticaria: A nationwide registry-study. World Allergy Organ J. 2020;13(1):100097.
136. Rubtsova K, Marrack P, Rubtsov AV. Sexual dimorphism in autoimmunity. J Clin Invest. 2015;125(6):2187-93.
137. Ngo ST, Steyn FJ, McCombe PA. Gender differences in autoimmune disease. Front Neuroendocrinol. 2014;35(3):347-69.
138. Kim JP, Chao LX, Simpson EL, Silverberg JI. Persistence of atopic dermatitis (AD): A systematic review and meta-analysis. J Am Acad Dermatol. 2016;75(4):681-7.e11.
139. Nezamololama N, Fieldhouse K, Metzger K, Gooderham M. Emerging systemic JAK inhibitors in the treatment of atopic dermatitis: A review of abrocitinib, baricitinib, and upadacitinib. Drugs Context. 2020;9.
140. Silverberg JI, Gelfand JM, Margolis DJ, Boguniewicz M, Fonacier L, Grayson MH, et al. Symptoms and diagnosis of anxiety and depression in atopic dermatitis in U.S. adults. Br J Dermatol. 2019;181(3):554-65.
141. Schonmann Y, Mansfield KE, Hayes JF, Abuabara K, Roberts A, Smeeth L, et al. Atopic Eczema in Adulthood and Risk of Depression and Anxiety: A Population-Based Cohort Study. J Allergy Clin Immunol Pract. 2020;8(1):248-57.e16.
142. Dieris-Hirche J, Gieler U, Petrak F, Milch W, Te Wildt B, Dieris B, et al. Suicidal Ideation in Adult Patients with Atopic Dermatitis: A German Cross-sectional Study. Acta Derm Venereol. 2017;97(10):1189-95.
143. Drucker AM, Thiruchelvam D, Redelmeier DA. Eczema and subsequent suicide: A matched case-control study. BMJ Open. 2018;8(11):e023776.
144. Wollenberg A, Ariens L, Thurau S, van Luijk C, Seegraber M, de Bruin-Weller M. Conjunctivitis occurring in atopic dermatitis patients treated with dupilumab-clinical characteristics and treatment. J Allergy Clin Immunol Pract. 2018;6(5):1778-80.e1.
145. Simpson EL, Bieber T, Guttman-Yassky E, Beck LA, Blauvelt A, Cork MJ, et al. Two Phase 3 Trials of Dupilumab versus Placebo in Atopic Dermatitis. N Engl J Med. 2016;375(24):2335-48.
146. Akinlade B, Guttman-Yassky E, de Bruin-Weller M, Simpson EL, Blauvelt A, Cork MJ, et al. Conjunctivitis in dupilumab clinical trials. Br J Dermatol. 2019;181(3):459-73.
147. Touhouche AT, Cassagne M, Bérard E, Giordano-Labadie F, Didier A, Fournié P, et al. Incidence and risk factors for dupilumab associated ocular adverse events: A real-life prospective study. J Eur Acad Dermatol Venereol. 2021;35(1):172-9.
148. Treister AD, Kraff-Cooper C, Lio PA. Risk Factors for Dupilumab-Associated Conjunctivitis in Patients With Atopic Dermatitis. JAMA Dermatol. 2018;154(10):1208-11.
149. Agnihotri G, Shi K, Lio PA. A Clinician's Guide to the Recognition and Management of Dupilumab-Associated Conjunctivitis. Drugs R D. 2019;19(4):311-8.

150. Bakker DS, Ariens LFM, van Luijk C, van der Schaft J, Thijs JL, Schuttelaar MLA, et al. Goblet cell scarcity and conjunctival inflammation during treatment with dupilumab in patients with atopic dermatitis. Br J Dermatol. 2019;180(5):1248-9.
151. Thyssen JP. Could conjunctivitis in patients with atopic dermatitis treated with dupilumab be caused by colonization with Demodex and increased interleukin-17 levels? Br J Dermatol. 2018;178(5):1220.
152. de Bruin-Weller M, Graham NMH, Pirozzi G, Shumel B. Could conjunctivitis in patients with atopic dermatitis treated with dupilumab be caused by colonization with Demodex and increased interleukin-17 levels?: Reply from the authors. Br J Dermatol. 2018;178(5):1220-1.
153. Ferreira S, Torres T. Conjunctivitis in patients with atopic dermatitis treated with dupilumab. Drugs Context. 2020;9.
154. Thyssen JP, Heegaard S, Ivert L, Remitz A, Agner T, De Bruin-Weller M, et al. Management of Ocular Manifestations of Atopic Dermatitis: A Consensus Meeting Using a Modified Delphi Process. Acta Derm Venereol. 2020;100(16):adv00264.
155. Wu MY, Yu CL, Yang SJ, Chi CC. Change in body weight and body mass index in psoriasis patients receiving biologics: A systematic review and network meta-analysis. J Am Acad Dermatol. 2020;82(1):101-9.
156. Tournadre A, Pereira B, Dutheil F, Giraud C, Courteix D, Sapin V, et al. Changes in body composition and metabolic profile during interleukin 6 inhibition in rheumatoid arthritis. J Cachexia Sarcopenia Muscle. 2017;8(4):639-46.
157. Schulz KF, Grimes DA. Case-control studies: Research in reverse. Lancet. 2002;359(9304):431-4.
158. Grimes DA, Schulz KF. Bias and causal associations in observational research. Lancet. 2002;359(9302):248-52.
159. Bylund S, von Kobyletzki LB, Svalstedt M, Svensson Å. Prevalence and Incidence of Atopic Dermatitis: A Systematic Review. Acta Derm Venereol. 2020;100(12):adv00160.
160. Delgado-Rodríguez M, Llorca J. Bias. J Epidemiol Community Health. 2004;58(8):635-41.
161. Rothman KJ. Epidemiology : An introduction. New York: NY: Oxford Press; 2012.
162. Borquist L, Andre M. Läkartidningen. 2016;113:D43E.
163. Wikberg C, Nejati S, Larsson ME, Petersson EL, Westman J, Ariai N, et al. Comparison Between the Montgomery-Asberg Depression Rating Scale-Self and the Beck Depression Inventory II in Primary Care. Prim Care Companion CNS Disord. 2015;17(3).
164. Vetter TR, Mascha EJ. Bias, Confounding, and Interaction: Lions and Tigers, and Bears, Oh My! Anesth Analg. 2017;125(3):1042-8.