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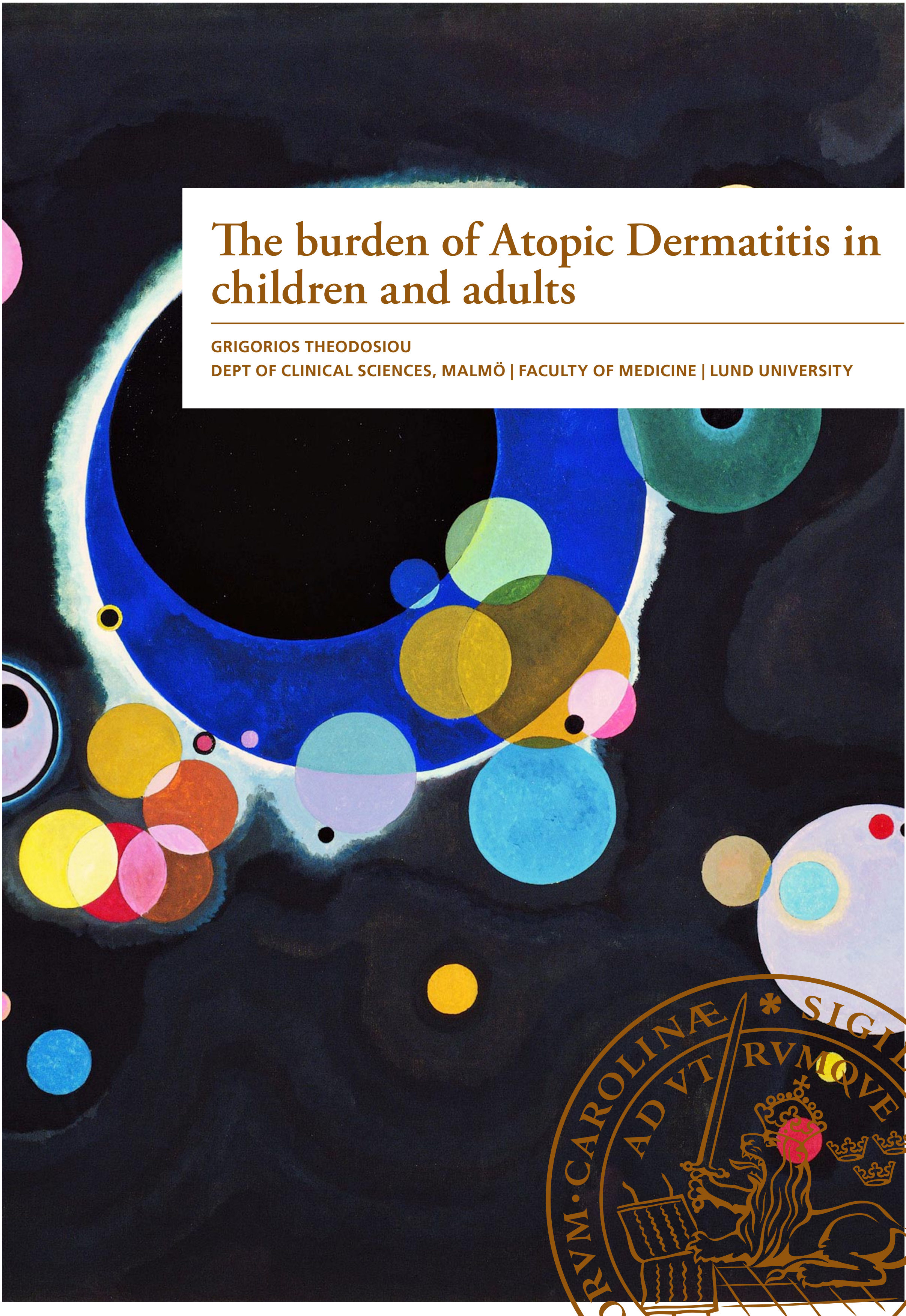

The burden of Atopic Dermatitis in children and adults

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Grigorios Theodosiou

DOCTORAL DISSERTATION
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Abstract:
Background: Atopic dermatitis (AD) is a common chronic inflammatory skin disease associated with significant itch and affecting quality of life across the lifespan.

Methods: Study I assessed prevalence and burden of AD in 34,313 Swedish adults using cross-sectional questionnaire data. Study II investigated long-term associations between adolescent AD and occupational, socioeconomic, and mental health outcomes in 205,394 Swedish men followed until ages 50–57 years. Study III developed and validated a paediatric itch questionnaire and examined itch prevalence in 443 German schoolchildren aged 6–10 years. Study IV used factor analysis to identify quality of life domains associated with AD in 9,227 Swedish schoolchildren aged 6–17 years.

Results: In Study I, adults with severe AD had markedly increased risk for severe depression (aRRR 5.62, 95% CI 4.10–7.71) and severe anxiety (aRRR 6.22, 95% CI 4.60–8.42), and the estimated burden was 526.68 DALYs (Disability-adjusted life years) per 100,000. In Study II, adolescent AD was associated with antidepressant and anxiolytic use in middle age (aHR 1.49, 95% CI 1.28–1.74) with no disadvantages in occupation, income, or marital status. In Study III, itch prevalence was 26.2% overall and 14.7% for chronic itch, with significant impairment of sleep and mood. In Study IV, the following aspects of quality of life were associated with AD: sleep disturbances were prominent in both sexes in early childhood, while adolescent girls with AD reported greater problems with body image, self-confidence, and peer relationships.

Conclusions: AD imposes a substantial multidimensional burden affecting psychological well-being, quality of life, and socioeconomic outcomes across the lifespan, with mental health associations increasing with disease severity. Age- and sex-specific patterns necessitate tailored management approaches addressing both physical symptoms and psychosocial impacts.

Key words: atopic dermatitis, atopic eczema, epidemiology, disease burden, itch, QoL

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Table of Contents

Study	Paper I	Paper II	Paper III	Paper IV
Title	Burden of Atopic Dermatitis in Swedish Adults: A Population-based Study	Associations of Atopic Dermatitis in Late Adolescence with Occupation, Mental Health, Income from Work, and Marital Status: A National Longitudinal Study	Prevalence of Itch in German Schoolchildren: A Population-based Study	Sex Differences in Assessment of Quality of Life in Children and Adolescents with Atopic Dermatitis: A School-based Study
Study Design	Cross-sectional, population-based questionnaire study	Longitudinal cohort study with registry linkage	Cross-sectional, population-based questionnaire study with pilot validation	Cross-sectional, population-based study with factor analysis
Study Population	34,313 Swedish adults ≥18 years from 5 counties (Södermanland, Uppsala, Värmland, Västmanland, Örebro)	205,394 Swedish men born 1952–1956 who underwent military conscription examination at age 17–21 years (1969–1976)	443 German schoolchildren aged 6–10 years from 9 randomly selected primary schools in Kiel, Germany	9,227 Swedish schoolchildren and adolescents aged 6–17 years from Värmland County (Student Health Database, ELSA)
AD/Itch Prevalence	AD: 14%* (95% CI 13.5–14.3%); ~10% of those with AD had severe disease	AD: 0.71%** (95% CI 0.67–0.75%); 87.6% mild AD, 12.4% severe AD	Total itch: 26.2%; Acute itch: 20.0%; Chronic itch: 14.7%*	AD: 3.63%*
Main Outcomes	Mental health (depression, anxiety, mental wellbeing), educational attainment, income, occupational status, employment, marital status, DALYs	Occupational socioeconomic group, employment status, income from work, unemployment benefits, marital status, antidepressant/anxiolytic prescriptions (2006–2009)	Prevalence and intensity of itch (VAS with smileys), itch localization, quality of life (ItchyQoL), treatment	QoL domains identified through factor analysis and used as outcomes in regression models: confidence, happiness, peer relations, physical activity, sleep, body image
Statistical Methods	Logistic and multinomial regression (OR, RRR). Adjusted for age, sex, education, childhood financial situation, asthma. DALYs calculated using WHO disability weights	Cox regression (HR), logistic regression (OR), multinomial regression (RRR). Adjusted for year of birth, cognitive function, mental illness, parental occupation, stress resilience	Descriptive statistics, Mann–Whitney U test, Wilcoxon signed-rank test, χ^2 test, Spearman correlation. Questionnaire validation: test-retest reliability, content validity	Factor analysis (eigenvalue >1.0), linear regression using factors as outcomes. Adjusted for sex, age, parental occupation, asthma, other allergies
Key Findings	Severe depression (aRRR 5.62, 95% CI 4.10–7.71) and severe anxiety (aRRR 6.22, 95% CI 4.60–8.42) increased in severe AD. Lower university degree attainment (aRRR 0.55, 95% CI 0.34–0.90) and income (≥325,000 SEK: aRRR 0.36, 95% CI 0.25–0.58) in severe AD.*** DALYs: 526.68 per 100,000.	Increased antidepressant/anxiolytic prescription in AD (HR 1.55, 95% CI 1.32–1.81; severe AD: HR 2.46, 95% CI 1.72–3.53). No association with occupational disadvantage, income, or unemployment. Mild AD: lower risk of routine jobs (aRRR 0.74, 95% CI 0.62–0.89).***	26.2% had itch (20% acute, 14.7% chronic). Mean chronic itch intensity 3.73 (VAS 0–5). Chronic itch significantly associated with impaired sleep and mood ($p<0.01$).	Children with AD: more sadness/anxiety (c 0.120, 95% CI 0.006–0.233), peer relation difficulties. Girls: physical activity problems and lower body confidence (teenage girls: c 0.187, 95% CI 0.003–0.371). Pre-school: sleep problems both sexes (c 0.274, 95% CI 0.143–0.405).***
Conclusions	AD, especially severe AD, is associated with increased mental comorbidity and adverse impact on educational and occupational outcomes. Clinicians should screen for mental health conditions.	Despite increased mental health burden, AD in adolescence is not associated with labor market disadvantage or lower income. Possible socioeconomic advantage or occupational selection may explain findings.	Itch is highly prevalent in schoolchildren and significantly impairs quality of life. Validated questionnaire suitable for epidemiological research.	AD affects multiple QoL domains with significant sex and age differences. Body image, self-confidence, and peer relations are important for teenagers, especially girls.
Journal / Status	Acta Dermato-Venereologica 2019; 99: 964–970 DOI: 10.2340/00015555-3257	Acta Dermato-Venereologica 2025; 105: adv42127 DOI: 10.2340/actadv.v105.42127	Acta Dermato-Venereologica 2022; 102: adv00718 DOI: 10.2340/actadv.v102.1063	Manuscript in preparation

Abbreviations: AD = Atopic Dermatitis; aRRR = adjusted Relative Risk Ratio; CI = Confidence Interval; DALY = Disability-Adjusted Life Years; HR = Hazard Ratio; OR = Odds Ratio; QoL = Quality of Life; SEK = Swedish Kronor; VAS = Visual Analogue Scale
**Point prevalence **Period prevalence ***Compared to individuals without AD*

Abstract

Background: Atopic dermatitis (AD) is a common, itchy, chronic inflammatory skin condition.

Aim: The overall aim of this thesis is to assess the prevalence and burden of AD in children and adults in terms of mental health comorbidity, labour market participation, and quality of life (QoL).

Methods: In Study I, a population-based, cross-sectional questionnaire study was performed among Swedish adults assessing the prevalence and severity of AD, mental health comorbidity, and educational attainment. Study II was a prospective cohort study of men in Sweden who underwent military conscription examination including physician diagnosis of AD in the late 1960s and early 1970s, with follow-up until 2009. In Study III, a questionnaire assessing the prevalence and intensity of itch was validated and distributed to schoolchildren aged 6–10 years in Germany. In Study IV, factor analysis was applied to questionnaire data from Swedish schoolchildren aged 6–17 years to examine associations between AD and pre-defined QoL domains.

Results: Study I: Adults with severe AD had substantially increased risk for severe depression (aRRR 5.62, 95% CI 4.10–7.71) and severe anxiety (aRRR 6.22, 95% CI 4.60–8.42) compared with individuals without AD. Persons with severe AD were less likely to hold a university degree (aRRR 0.55, 95% CI 0.34–0.90) compared with individuals without AD. Study II: Men with AD in adolescence more often had prescribed antidepressants and/or anxiolytics at the age of 50–57 years (aHR 1.49, 95% CI 1.28–1.74). We found no association between AD in adolescence and labour market participation, employment status, gross salary, or marital status later in adult life. Study III: The validity of the questionnaire was acceptable. Of 1,722 invited schoolchildren, 443 participated. In total, 26.2% reported itch; 20.0% acute itch and 14.7% chronic itch. Study IV: Children with AD experienced significant quality of life impairments with age- and sex-specific patterns. Sleep disturbances were prominent in both sexes in early childhood, while adolescent girls with AD reported greater problems with body image, self-confidence, and peer relationships.

Conclusions: AD is common in children and adults and is associated with increased risk for depression and anxiety, with associations strongest in those with severe disease. Itch is common in schoolchildren and is associated with decreased QoL. Although AD was related to increased mental health problems, labour market participation later in life was not altered in the military cohort compared with persons without AD in adolescence. Age- and sex-specific patterns of burden necessitate tailored management approaches addressing both physical symptoms and psychosocial impacts.

Populärvetenskaplig sammanfattning

Atopisk dermatit, på svenska oftast benämnd atopiskt eksem, är en vanlig kronisk inflammatorisk hudsjukdom som drabbar cirka 15–30 % av alla barn och 2–17 % av vuxna världen över. Sjukdomen kännetecknas av torr hud, klåda och återkommande eksemutslag, men dess konsekvenser sträcker sig långt bortom huden. Denna avhandling undersöker hur atopiskt eksem påverkar livskvalitet, psykiskt välbefinnande och sociala samt ekonomiska livsvillkor genom fyra befolkningsbaserade studier.

I den första studien analyserades enkätdata från över 34 000 vuxna i Sverige. Resultaten visade att personer med atopiskt eksem, särskilt de med svår sjukdom, hade en tydligt ökad förekomst av depression och ångest jämfört med personer utan eksem. Svårt atopiskt eksem var även kopplat till lägre utbildningsnivå och lägre inkomst.

I den andra studien användes svenska registerdata för att följa över 200 000 män från ungdomsåren till medelåldern. Män som haft atopiskt eksem i tonåren hade en ökad användning av läkemedel mot depression och ångest senare i livet. Däremot sågs inga negativa effekter på yrkesliv, inkomst eller civilstånd, vilket tyder på att långsiktiga socioekonomiska konsekvenser inte är självklara för alla med sjukdomen.

Den tredje studien fokuserade på klåda hos barn och omfattade drygt 400 tyska skolbarn i åldern 6–10 år. Klåda var vanligt förekommande och mer än var fjärde elev hade besvär. Kronisk klåda hade en tydlig negativ inverkan på sömn och humör, vilket visar hur ett ofta underskattat symtom kan påverka barns vardag och välmående.

Den fjärde studien omfattade mer än 9 000 svenska barn och ungdomar och undersökte hur atopiskt eksem påverkar livskvalitet i olika livsområden. Barn med atopiskt eksem hade sämre livskvalitet än jämnåriga utan eksem, med tydliga könsskillnader. Flickor rapporterade oftare problem med kroppsuppfattning och relationer till kamrater, medan sömnproblem var vanligt hos både flickor och pojkar, särskilt i yngre åldrar.

Sammanfattningsvis visar avhandlingen att atopiskt eksem innebär en betydande och mångdimensionell belastning genom hela livet, med effekter på psykisk hälsa, livskvalitet och i vissa fall även utbildning och ekonomi. Resultaten understryker behovet av ett helhetsperspektiv i vården, där både fysiska symtom och psykosociala konsekvenser uppmärksammas, samt vikten av individanpassade insatser som tar hänsyn till ålder och kön.

List of Papers

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

Paper I

Burden of Atopic Dermatitis in Swedish Adults: A Population-based Study. Theodosiou G, Montgomery S, Metsini A, Dalgard FJ, Svensson Å, von Kobyletzki LB. Acta Derm Venereol. 2019; 99:964–970

Paper II

Associations of Atopic Dermatitis in Late Adolescence with Occupation, Mental Health, Income from Work and Marital Status: A National Longitudinal Study.

Theodosiou G, Sterner T, Hiyoshi A, Carlberg M, Svensson Å, Montgomery S, von Kobyletzki LB. Acta Derm Venereol. 2025 Jan 14;105: adv42127

Paper III

Prevalence of Itch in German Schoolchildren: A Population-based Study. Theodosiou G, Nissen T, Weisshaar E, Plachta-Danielzik S, Augustin M, Ständer S, von Kobyletzki LB, Fölster-Holst R. Acta Derm Venereol. 2022 May 19;102: adv00718.

Paper IV

Sex differences in assessment of Quality of Life in children and adolescents with atopic dermatitis: a school-based cross-sectional study.

Theodosiou G, Svensson Å, Montgomery S, von Kobyletzki LB. In manuscript

Abbreviations

AD	Atopic Dermatitis
ADHD	Attention deficit hyperactivity disorder
ATC	Anatomical Therapeutic Chemical Codes
CDLQI	Children's Dermatology Life Quality Index
CI	Confidence Interval
CP	Chronic Pruritus
DALY	Disability-adjusted life years
EAACI	European Academy of Allergy and Clinical Immunology
FLG	Filaggrin gene
HR	Hazard Ratio
ICD-8	International Classification of Diseases version 8
IgE	Immunoglobulin E
IL	Interleukin
IQR	Interquartile range
LISA	Longitudinal Integrated Database for Health Insurance and Labour Market studies
NRS	Numerical rating scale
PDR	Prescribed Drug Registry
RRR	Relative Risk Ratio
TPR	Total Population Registry
QoL	Quality of Life
WAO	World Allergy Organization
WHO	World Health Organization

Background

Atopic Dermatitis

Background and Definitions

Atopy is a personal or familial tendency, commonly starting in childhood and adolescence to become sensitized and produce IgE antibodies after normal exposure to allergens, commonly proteins. Consequently, these persons develop typical symptoms like asthma, rhinoconjunctivitis, or eczema.[1]

Atopic dermatitis (AD) (also known as atopic eczema) is a chronic relapsing disease with multifactorial aetiology, involving immune system dysregulation and epidermal barrier dysfunction characterized by marked pruritus and recurrent cutaneous lesions. Atopic dermatitis (AD) is the most common inflammatory disease in childhood, with a prevalence of about 15-30% in children and 2-17% in adults.[2-9]

Affected individuals experience considerable distress especially from the visible skin eruptions -particularly when the face and hands are involved - and from the intense pruritus. This relentless itching causes sleep deprivation and substantial impairment in quality of life, affecting not only patients but also their families and social environment.[2-9]

Historical Perspective

The earliest documented case of what may have been atopic dermatitis likely belongs to the Roman Emperor Octavian Augustus. The historian Suetonius, writing in *Vita Caesarum*, described how the emperor experienced pruritic skin patches, chest constriction, and symptoms consistent with hay fever.[10]

The term ‘eczema’ was coined in the sixth century AD by the Greek physician Aetios from Amida who described the boiling and bubbling (εκ + ζέω= bubble up) as it can be observed in a boiling soup. Aetios from Amida himself probably did not realize how illustratively he described the modern concept of pathophysiology of spongiosis, namely the intercellular formation of edema starting in the dermis and reaching the epidermis.[11-12]

In 1923 Coca and Cooke coined the term ‘atopy’ which means "out of place" or "not in proper order". Subsequently, in 1933, Wise and Sulzberger coined the term "atopic dermatitis" to describe the chronic, relapsing skin condition characterized by intense pruritus, xerosis, and inflammatory lesions.[13,14]

Aetiology and Pathogenesis

Atopic dermatitis (AD) is a chronic inflammatory skin disease driven by the interplay between genetic susceptibility, environmental exposures, epidermal barrier dysfunction, and immune dysregulation. [2,15] Twin and family studies estimate heritability at approximately 60–70%, with substantial overlap with other atopic diseases such as asthma and allergic rhinitis.[2] A pivotal advance in understanding AD pathogenesis was the identification of loss-of-function mutations in the filaggrin (FLG) gene, a central component of the epidermal differentiation complex.[15-16] Filaggrin deficiency results in impaired stratum corneum formation, increased transepidermal water loss, altered skin surface pH, and enhanced penetration of allergens and microbes.[15-17]

Barrier disruption promotes cutaneous immune activation and a predominantly type 2 immune response, particularly in early and acute disease. Increased expression of IL-4, IL-13, and IL-5 drives IgE class switching, eosinophilia, and downregulation of epidermal barrier proteins, thereby reinforcing barrier impairment.[18] Antigen-presenting cells in AD skin, including Langerhans cells and FcεRI-expressing inflammatory dendritic epidermal cells, enhance allergen capture and T-cell activation. With disease chronicity, immune polarization broadens to include Th1, Th17, and Th22 pathways, contributing to sustained inflammation.[19-20]

Microbial dysbiosis is a critical disease-modifying factor in AD.[21] Lesional and non-lesional skin is frequently colonized by Staphylococcus aureus, whose exotoxins act as superantigens and amplify cutaneous inflammation.[22-24] Neuroimmune and vascular dysfunction further contribute to cardinal clinical features such as pruritus, erythema, and white dermatographism through altered autonomic regulation and endothelial activation.[25] Together, these mechanisms support a unified pathogenic model in which genetically determined barrier failure initiates immune activation, while immune responses, microbial factors, and neurovascular abnormalities perpetuate chronic disease.

Epidemiology

Understanding the epidemiological patterns of atopic dermatitis is fundamental to appreciating the scale of this public health challenge and informing resource allocation for prevention, treatment, and research initiatives.[2, 26]

Prevalence

Atopic dermatitis represents one of the most prevalent chronic inflammatory skin diseases worldwide, affecting individuals across all age groups and imposing substantial burden on patients, families, and healthcare systems.[26-27] AD has shown an increase in prevalence since the 1960s, though recent evidence suggests this trend may be plateauing in some developed nations.[28-29] Early studies from various countries between 1939 and 1964 reported prevalence estimates of 1.3-3.1% in different populations.[26] By the 1980s, studies documented markedly increased prevalence estimates ranging from 26% to 32%.[26]

Contemporary epidemiological data reveal substantial global variation in AD prevalence.[3,26] A systematic review by Bylund et al. demonstrated high variability in both prevalence and incidence globally, with prevalence rates reaching up to 17% in adults and 22% in children.[3] Generally, prevalence appears higher in Northern Europe and Australia compared with Asia and Eastern Europe, though notable exceptions exist.[3,4,8]

Prevalence in children

Community-based and population-based studies collectively suggest that approximately 10-30% of children in developed countries have AD, with some studies demonstrating a plateau in prevalence estimates in recent years.[3,28-32] In contrast, prevalence in developing countries has been generally lower but is increasing.[28,32]

The International Study of Asthma and Allergies in Childhood (ISAAC) has published the most comprehensive prevalence and trend data on AD to date.[29,31,33] Across three phases, ISAAC included nearly 2 million children from over 100 countries. Using the revised UK Working Party criteria via questionnaires, the ISAAC study group identified highly variable AD prevalence estimates across different countries with rates ranging from 0.9% in India to 22.5% in Ecuador among 6–7-year-old children, and from 0.2% in China to 24.6% in Colombia among adolescents aged 13-14 years. [29,31,33]

Prevalence in adults

Data on the prevalence of AD in adults are limited. The one-year prevalence in Scandinavia has been reported to be 10-14% among adults.[8,34,35] Studies from the USA, Japan, Australia, Russia, Scotland and Italy have identified prevalence rates ranging from 2-17%.[3,8,36-39] Large-scale population-based studies in the United States have documented one-year prevalence rates of 7.2-10.2%.[30,36] European studies report comparable estimates, with one-year prevalence rates of 2-10% across various adult age groups.[3,8,34,35,39]

Temporal Trends and Geographical Variations

Epidemiological evidence indicates that atopic dermatitis prevalence has increased substantially over recent decades, particularly in industrialized nations and appears to have reached a plateau.[40] Systematic reviews examining temporal trends document significant increases from the 1960s through the early 2000s, with evidence suggesting stabilization or modest decline in certain high-prevalence regions in recent years.[28,29,31,32,38,40] This temporal increase likely reflects complex interactions between genetic susceptibility and environmental factors, including changes in lifestyle, environmental exposures, dietary patterns, and hygiene practices.[38]

Geographical variations in prevalence are substantial and provide important etiological insights. The ISAAC study demonstrated that prevalence rates were generally higher in urbanized, affluent nations compared to rural areas and developing countries.[29,31,33] However, notable exceptions exist, and prevalence appears to be increasing in previously low-prevalence regions undergoing rapid economic development and urbanization.[3,6,8,27] These patterns support the hypothesis that environmental and lifestyle factors associated with modernization play important roles in disease development.

Methodological Considerations

The distinction between point prevalence, period prevalence (typically one-year), and lifetime prevalence is particularly important given the characteristically relapsing-remitting course of AD.[41] Point prevalence captures only those with active disease at a specific time and substantially underestimates disease burden. One-year prevalence provides a more comprehensive assessment by capturing individuals who experienced symptoms during a defined period, though it may miss cases in prolonged remission.[41,42] Lifetime prevalence provides the broadest measure but may be subject to recall bias, particularly when assessed through self-report in adults.[41,42]

Disease Severity

From a public health perspective, understanding the severity distribution of AD is as important as knowing overall prevalence, as severity largely determines quality of life impairment and healthcare utilization. However, research examining severity distribution within community-based populations remains limited, and published estimates vary considerably across time and setting.

Earlier population-based studies reported a predominance of mild disease.[43] More recent data, however, suggest a substantially higher proportion of moderate-to-severe presentations.[44-46] A large US survey of 10,386 children with AD reported that 67% experienced mild disease, 26% moderate symptoms, and 7% severe AD,[44] indicating a shift in the observed severity distribution compared with earlier estimates. These differences likely reflect methodological heterogeneity in severity assessment, evolving diagnostic criteria, and variation in study populations, rather than a true secular increase in disease severity.

Clinical Course and Prognosis

Atopic dermatitis typically manifests during infancy or childhood, with approximately 60-73% of paediatric cases developing before 1-2 years of age, though onset may occur at any age.[22,47] The condition follows a chronic or chronic relapsing course with considerable heterogeneity in long-term outcomes.[26,30,48]

Mortz et al., in a longitudinal cohort study reported persistent AD in adulthood in 50% of patients diagnosed in school age. [49] Kim et al., in a systematic review and meta-analysis of 45 studies encompassing over 110,000 patients with childhood-onset atopic dermatitis, demonstrated that approximately 80% achieved remission within eight years of diagnosis, with less than 5% exhibiting persistent disease at 20 years post-diagnosis.[50] These estimates reflect continuously persistent disease and exclude relapsing-remitting patterns, which may substantially affect true disease burden extending into adulthood.[51] Contemporary longitudinal studies have revealed distinct disease trajectories, with some patients experiencing persistence into adulthood, transforming what was traditionally considered a childhood condition into a potentially lifelong disorder.[52]

Multiple prognostic factors predict disease persistence. Earlier age at onset, greater baseline severity, and female sex are consistently associated with increased risk of persistent disease beyond childhood.[53-55] Patients with severe atopic dermatitis demonstrate substantially higher rates of asthma development, with approximately 70% progressing to asthma compared to 20-30% with mild disease and 8% in the general population.[56] The "atopic march" describes sequential allergic condition development, with children with AD demonstrating approximately three-fold increased odds of developing asthma and allergic rhinitis at five-year follow-up compared to children without AD.[56-57] However, recent longitudinal studies reveal that allergic disease evolution is more intricate than previously conceptualized, with only a minor fraction of children exhibiting classical atopic march trajectory profiles.[57-58] These findings underscore the clinical heterogeneity of atopic dermatitis and the importance of early identification of high-risk individuals who may benefit from intensified intervention and long-term monitoring.

Clinical Presentation and Diagnosis

Intense pruritus and cutaneous lesions are cardinal features of AD. Pruritus may fluctuate throughout the day but is typically most severe in the early evening and at night.[59] This often leads to scratching, which in turn contributes to the development of prurigo papules, lichenification, and eczematous plaques.[60] Across all stages of the disease, affected skin is usually dry and dull in appearance (xerosis).[61]

AD lesions can be classified as acute, subacute, or chronic.[62] Acute lesions are erythematous, pruritic papules and vesicles, often accompanied by excoriations and serous exudate. Subacute lesions present as erythematous, excoriated, scaling papules.[61] Chronic lesions are characterized by lichenified plaques, accentuated dermatoglyphics, and fibrotic nodules and papules resembling prurigo nodularis. In patients with chronic AD, all three lesion types can frequently coexist within the same individual.[61]

The distribution of lesions varies according to patient age. In infants, AD tends to be more acute, primarily affecting the face, scalp, and extensor surfaces of the extremities, while sparing the diaper area.[59] In older children and individuals with long-standing disease, lesions typically localize to the flexural surfaces of the extremities and present with lichenification, representing the chronic form of AD.[59-60] In adults, chronic hand eczema may constitute the predominant or sole manifestation of AD.[59]

Additional atopic stigmata—typical yet not pathognomonic signs—include hyperlinear palms and soles, infraorbital double eyelid crease (Dennie-Morgan fold), periorbital halo formation, facial pallor, and white dermographism.[61]

Figure 1: Clinical features of atopic dermatitis: erythema, oozing, oedema, scaling, crusting, excoriation, and lichenification, across multiple body sites, including the face, antecubital fossae, posterior neck, and dorsum of the foot.

Diagnostic Criteria

Atopic dermatitis is a clinical diagnosis established using validated diagnostic criteria. In 1994, a UK working group led by H. Williams developed and validated the UK Working Party's diagnostic criteria (Table 1).[63] The UK criteria have performed well in subsequent independent hospital and community validation studies, demonstrating 96% specificity and 85% sensitivity when compared with dermatologist diagnosis.[64-65] Nevertheless, the diffuse and variable morphology of lesions, absence of definitive biomarkers or laboratory diagnostic tests, and variable clinical course across the lifespan can complicate diagnosis.

Table 1: UK Working Party Diagnostic Criteria for Atopic Dermatitis

Criterion	Description
Essential criterion (must have)	An itchy skin condition (or parental report of scratching or rubbing) in the past 12 months
Plus three or more of the following:	
1.	Onset below age of 2 years*
2.	History of flexural involvement (including cheeks in children under 10 years)
3.	History of generally dry skin in the past year
4.	Personal history of other atopic disease (asthma or hay fever) **
5.	Visible flexural dermatitis as per photographic protocol (or dermatitis affecting cheeks/forehead and outer limbs in children under 4 years)

*Not used in children under 4 years
**In children under 4 years, history of atopic disease in a first-degree relative may be included

Burden of Atopic Dermatitis

Health-Related Quality of Life and Morbidity

The psychological and physical morbidity associated with chronic scratching, sleep loss and visible skin lesions substantially affects individuals with AD and their families.[66-67] In the World Health Organization's 2010 Global Burden of Disease survey, AD ranked first among common skin diseases with respect to disability-adjusted life years (DALY) and years lived with disease.[68]

The impact of AD on health-related quality of life (HRQoL) in children is comparable to that of other chronic illnesses such as asthma and diabetes.[69] Quality of life impairment correlates with disease severity.[69] A US population-based study found that 25-33% of adults with AD reported fatigue, daytime sleepiness, and/or insomnia, which were significant predictors of poorer overall health status, increased sick days, and more frequent physician visits.[70]

Children with AD experience itch or painful skin, disturbed sleep that may affect intellectual functioning, and limitations in clothing choices and participation in swimming and sports.[71] Caregivers of children with AD may also experience sleep disturbance.[71,72] The BAMSE general population cohort demonstrated that persistent AD at ages 12, 16, and 24 years was associated with worse quality of life scores on the EuroQoL visual analogue scale and limited healthcare contact.[73] Activity limitations in sports or swimming and clothing-related impairment remain significant concerns for adolescents.

Comorbidities

Atopic dermatitis (AD) has traditionally been recognized as the earliest manifestation of the "allergic march" (or "atopic march"), which includes the sequential development of asthma, allergic rhinitis, and food hypersensitivity.[74-77] However, contemporary research has revealed that AD is associated with a substantially broader spectrum of comorbidities beyond these classical atopic conditions. Patients with AD demonstrate increased prevalence of non-atopic disorders including chronic rhinosinusitis, nasal polyposis, urticaria, autoimmune disorders, conjunctivitis, and eosinophilic esophagitis. [78-83] Evidence from US studies indicates that comorbidity burden correlates with disease severity, with patients experiencing severe AD demonstrating higher rates of associated conditions compared to those with milder disease.[84-85]

The immunological dysregulation characteristic of AD, particularly the predominance of type 2 inflammatory pathways, appears to predispose patients to a broader range of systemic conditions. Patients with AD demonstrate increased susceptibility to infections, including bacterial (particularly *Staphylococcus aureus*), viral (eczema herpeticum), and fungal infections, due to impaired skin barrier function and altered immune responses. [86]

Beyond these associations, emerging evidence reveals significant psychiatric comorbidities, with AD patients demonstrating a higher prevalence of anxiety, depression, attention-deficit/hyperactivity disorder (ADHD), and sleep disorders.[87-90] The chronic pruritus and visible skin manifestations contribute to psychological distress, while systemic inflammation may directly affect neurological pathways.[91]

Furthermore, AD has been linked to metabolic disorders, including obesity, diabetes, dyslipidaemia as well as elevated cardiovascular risk, which may result from accumulated comorbidities and adverse lifestyle factors, or alternatively, as recent evidence suggests, from systemic inflammatory mediators related to the severity of cutaneous inflammation.[92-96] Collectively, these findings support the emerging conceptualization of AD as a systemic disease, potentially connected to its diverse comorbidities through mechanisms involving chronic inflammation or shared underlying pathophysiological risk factors.[97]

Educational Attainment and Cognitive Function

A recent cohort study of men aged 17–20 years with current or previous AD history found an association with lower stress resilience in late adolescence but no association with lower cognitive function or poorer educational attainment.[98] However, a subsequent sibling comparison study among Swedish males demonstrated that AD was associated with lower cognitive function when comparing affected and unaffected siblings, suggesting that previous null findings may have been confounded by residual confounding.[99] When severe, AD may plausibly affect educational attainment through multiple pathways including cognitive impairment, sleep disruption, and school absenteeism.

Despite these theoretical considerations, recent studies have not consistently demonstrated adverse associations with educational achievement. A systematic review by von Kobyletzki et al. highlighted the paucity of evidence on this subject; the single study meeting inclusion criteria found no association between AD and educational attainment.[100] Cultural and lifestyle factors that change over time and affect children's academic achievement may explain inter-study differences. In the study conducted by Sybilski et al., AD was more commonly observed in individuals whose mothers were more highly educated and whose families had higher incomes, factors that are generally linked to better educational opportunities for children.[101] Importantly, previous studies lacked data on patients with severe AD. It is plausible that those with mild AD do not experience adverse impacts on academic attainment, whereas individuals with severe pruritus, skin pain, extensive involvement, and substantial time requirements for skin treatment may face academic challenges.[102] Comorbid depression might further diminish educational and occupational performance.

Atopic Dermatitis, Marital Status and Sexual Health

A study by Hua T et al., which reported a 1-year prevalence of atopic dermatitis in US adults of 7.2% (95% CI 6.7-7.6%) reported significant associations between adult AD and marital status, with higher rates observed among individuals who were divorced, separated, or never married. The authors proposed that AD and its comorbidities may adversely affect social functioning and interpersonal relationships, potentially increasing the risk of marital dissolution and reducing the likelihood of marriage.[103]

A cross-sectional study conducted in Korea between 2007 and 2012 by Kim et al., including over 47,000 adults, found that Korean adults with AD were more often separated or divorced (adjusted OR: 1.3, 95% CI 1.012-1.690) and never married (adjusted OR: 1.9, 95% CI 1.513-2.482). This study found no association between AD and monthly income, education, or employment. The authors suggested that comorbid depression, anxiety, and lower self-esteem in adults with AD may be relevant factors.[104]

A multicentre cross-sectional study across 13 European countries, using item 9 of the Dermatology Life Quality Index (DLQI), identified AD as a leading cause of sexual life impairment among dermatological outpatients. Impaired sexual well-being showed a strong association with pruritus, depressive symptoms, anxiety and suicidal ideation. The cross-sectional study design precludes definitive determination of the complex interrelationships among disease onset, pruritus, anxiety and/or depression, and sexual impairment.[105]

Several studies have examined sexual health in patients with AD. Misery et al. reported that 57.5% of patients with AD experienced reduced libido, and 36.7% of their partners reported that the appearance of eczema impacted their sexual relationship.[106] Sampogna et al. found that 29% of patients with AD reported negative impacts of their skin disease on sexuality. Moreover, patients with AD tend to avoid intimacy after applying topical agents and emollients as these could be rubbed off. The presence of genital lesions in AD may also adversely affect sexual health. [105]

Several mechanisms may account for these observations. Genital involvement can directly cause pain and discomfort, while the skin's sensory and erotogenic functions mean that dermatological lesions may compromise physical intimacy. Although such concerns significantly affect patients' well-being, they are seldom addressed in routine clinical practice.[105] In the study by Niemeier et al., 96% of patients with AD indicated that their physician had never discussed this concern.[107]

Socioeconomic Burden of Atopic Dermatitis

Atopic dermatitis is associated with a substantial socioeconomic burden affecting patients, families, healthcare systems, and society at large.[108-109] At the individual level, disease burden extends beyond cutaneous symptoms and includes persistent pruritus, sleep disturbance, and functional impairment—particularly when involvement of the hands or feet interferes with manual tasks and mobility. These manifestations may contribute to impaired work performance, reduced educational participation, social stigmatization, and psychosocial distress. Sleep deprivation related to nocturnal itch further compromises cognitive functioning, productivity, and overall quality of life.[110-112]

The economic burden of AD is challenging to quantify; estimates vary considerably across countries. Beyond direct healthcare costs (primary and secondary care visits, dispensed medications) and indirect costs (parental leave to care for affected children, long-term sick leave for adults with AD), there are substantial out-of-pocket expenses borne by patients.[110-113] Across Europe, moderate-to-severe AD is estimated to generate an annual societal cost exceeding €30 billion, largely attributable to productivity losses, healthcare utilization, and patient-borne expenditures.[111-113]

Individuals with AD experience high levels of absenteeism and presenteeism, marked limitations in daily activities, and considerable out-of-pocket costs related to non-reimbursed treatments and supportive care.[113-114] In a large multi-country study, Zink et al. reported mean annual out-of-pocket expenses of €927 per patient—exceeding those observed in psoriasis or arthritis—highlighting the disproportionate financial burden borne by individuals with AD.[115]

Globally, AD accounts for the largest burden of disability among skin diseases. Knowledge regarding AD burden and at-risk populations will serve as an important policy tool for healthcare professionals and policymakers in developing AD prevention and treatment strategies. In Sweden, however, the burden of AD measured as DALY (Disability-adjusted life years) based on population-based data remains unclear.

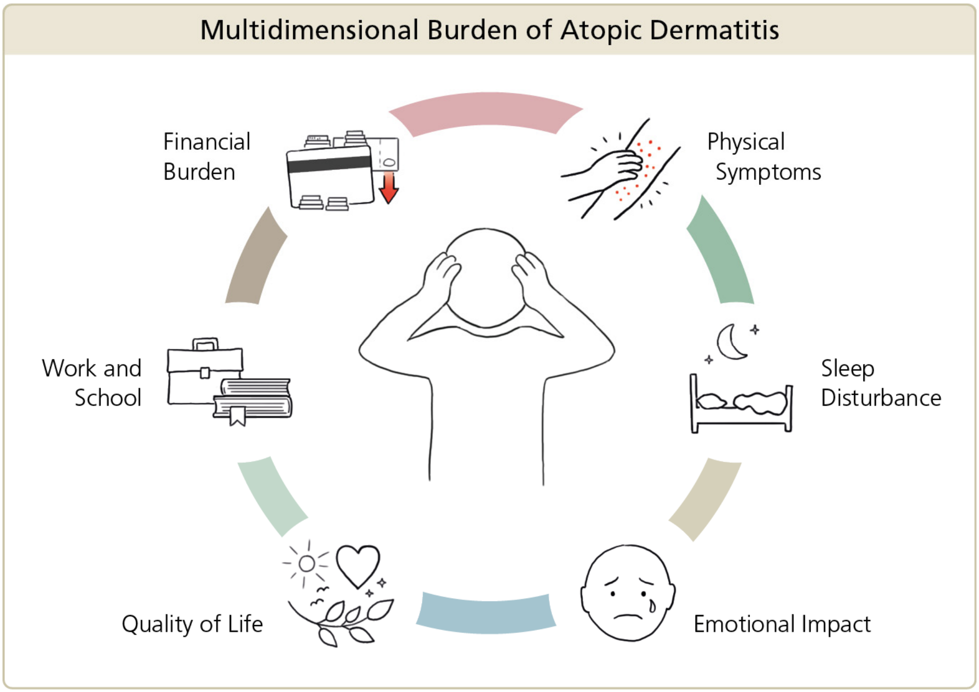

Figure 2: Multidimensional burden of AD: Infographic by Frida Nilsson © Lund University

Pruritus in Atopic Dermatitis

Historical Evolution and Contemporary Definition

The earliest formal description of itch traces back to 1660, when Samuel Hafenreffer characterized it as an unpleasant sensation that provokes the desire to scratch.[116] Pruritus is classified as either acute or chronic, with chronic pruritus (CP) defined as itch persisting for six weeks or longer, in accordance with recommendations issued by the International Forum for the Study of Itch (IFSI).[117]

Pruritus can be triggered, exacerbated, or ameliorated by diverse external and internal factors, affects both cutaneous and mucosal surfaces, and universally provokes scratching.[118] Epidemiological data on the prevalence of acute and chronic pruritus in paediatric populations remain limited. In children, the aetiology of CP is dominated by dermatological conditions, particularly AD.[119]

Global Health Impact and Clinical Significance

Pruritus represents a significant healthcare burden, contributing to an estimated 33.7 million person-years lived with disability from dermatological conditions.[7] The burden of itch extends beyond physical discomfort, causing substantial psychological and physiological stress, sleep disturbances, diminished quality of life, and considerable economic costs for affected individuals and healthcare systems.[120-124]

Pruritus is the cardinal symptom of atopic dermatitis (AD) and the principal driver of disease burden.[96,122] Patient-reported data indicate that over 90% of children and adults with AD experience itch, with daily symptoms reported by the majority of adolescents and adults, and nocturnal pruritus affecting approximately one-third of paediatric patients.[122-125] While itch predominates, overlapping sensations such as pain may coexist, complicating symptom assessment and patient-reported outcome measurement.[126]

Figure 3: Itch a cardinal feature of AD leading to excoriation and lichenification

Mechanistically, AD-associated pruritus arises from complex neuroimmune interactions. Itch is transmitted by specialized unmyelinated C-fiber sensory neurons, which interact bidirectionally with immune cells in inflamed skin.[127-128] Type 2 inflammation, driven by interleukin-4 (IL-4) and interleukin-13 (IL-13), promotes epidermal barrier dysfunction and neuronal sensitization.[128-130] Interleukin-31 (IL-31) has emerged as a key pruritogenic cytokine, directly activating sensory neurons through non-histaminergic pathways, thereby explaining the limited efficacy of antihistamines in AD.[131] Additional epithelial-derived cytokines, including interleukin-33 (IL-33) and thymic stromal lymphopoietin (TSLP), further amplify neuroimmune signalling and sustain chronic itch.[132]

Advances in understanding these pathways have transformed AD management.[132] Targeted therapies such as dupilumab, tralokinumab, and lebrikizumab which inhibit IL-4 and/or IL-13 signalling, demonstrate rapid and clinically meaningful antipruritic effects, often preceding improvement in skin lesions.[133-134] Emerging treatments targeting IL-31, TSLP, and Janus kinase (JAK) signalling further underscore the central role of pruritus as both a symptom and a therapeutic target in AD.[134]

Rationale for this thesis - Knowledge Gaps

Despite substantial research on AD epidemiology and burden, several important knowledge gaps remain:

First, although mental health comorbidity in AD is increasingly recognized, most evidence derives from cross-sectional studies, unable to establish temporal sequence. Consequently, it remains unclear whether adolescent AD predicts adverse mental health outcomes into middle age.

Second, inconsistent evidence regarding educational and occupational consequences—with studies reporting substantial disadvantage, no association, or even protective effects—demands clarification. Whether these inconsistencies reflect methodological limitations, cohort effects, or genuine heterogeneity remains uncertain.

Third, population-based data on the prevalence and burden of itch in children remain scarce, with most research conducted in healthcare-based populations. The prevalence of chronic itch in general paediatric populations and its quality-of-life associations require investigation.

Fourth, whether existing quality-of-life instruments comprehensively capture burden across developmental stages—particularly adolescence—has not been systematically examined. Identifying which domains are most affected at different ages and by sex could inform development of more appropriate assessment tools.

Fifth, national-level burden estimates using standardized metrics such as DALY (Disability-adjusted life years) are lacking for many countries, including Sweden, limiting ability to prioritize AD in healthcare policy and resource allocation decisions.

Aims

The overall aim of this thesis is to assess the prevalence and the burden of AD in schoolchildren and adults in terms of symptoms, mental health comorbidity, socioeconomic and educational aspects, as well as labour market participation, and QoL.

Specific aims

Study I-II

- To assess the prevalence and severity of AD in adults in Sweden as well as the burden of AD using the framework of DALY (Disability-adjusted life years) in a general population-based cross-sectional study.
- To assess the association of AD in adolescence with mental health later on in adult life in a longitudinal linkage study.
- To evaluate the relationship between AD in adolescence, labour market participation, and occupational characteristics, income from work, unemployment benefits, and marital status in adult life.

Study III-IV

- To develop and validate an itch questionnaire and to assess the prevalence of acute and chronic itch in a general population-based sample of schoolchildren aged 6-10 years in Kiel, Germany.
- To identify aspects of QoL which are related to AD in children 6-17 years of age, as well as to identify the strength of the relationships in a cross-sectional questionnaire study.

Materials and methods

Study Designs

This doctoral thesis comprises four studies investigating various aspects of atopic dermatitis (AD) in Swedish and German populations. The methodological approaches varied by research question: two cross-sectional population-based questionnaire studies (Papers I and IV), one prospective longitudinal registry-based cohort study (Paper II), and one combined validation and prevalence study (Paper III).

Study I

Study population

Data collection and variables

A cross-sectional, population-based study was carried out between March and June 2017. Postal questionnaires were sent to 78,004 adults aged 18 years or older in five Swedish counties (Södermanland, Uppsala, Värmland, Västmanland, and Örebro). The sample was stratified by sex, age, and municipality. A total of 34,313 individuals returned completed questionnaires, yielding a response rate of approximately 45%.[135] Attrition analyses indicated that women, older adults (>49 years), and those with higher education were more likely to respond than men, younger adults, and persons with lower education.[135]

Measures

The items in the questionnaire include measures of physical and mental health, education, employment, work environment, and social support. The question battery was derived from international questionnaires. The 5-item World Health Organization Well-Being Index (WHO5) was used to assess subjective psychological well-being.[136]

Exposure variable

AD and its severity were measured by a single self-report item asking respondents whether they had eczema: “Do you have any of the following symptoms: eczema, response categories: no; yes, mild symptoms; yes, severe symptoms."

Outcome variables

The primary outcomes included i. health variables: self-rated health status, mental health variables, healthcare utilization and prescribed medications, ii. socioeconomic factors: educational attainment and occupational status, marital status, and iii. disability-adjusted life years (DALY)

i. Health variables

Self-rated health status was derived from “How would you describe your health in general?” on a four-level scale. The *diagnosis* of depression was assessed as follows: “Do you have any of the following diagnosed illnesses: depression”. *Symptoms* anxiety, depressive mood, tiredness, sleep disturbance and stress were assessed using a three-level scale. Sick leave due to mental ill health was assessed separately for burnout, depression, stress each using: "Have you been continuously sick-listed 29 days or longer in the last 12 months?" General mental wellbeing was estimated using the measure WHO5. It was also assessed whether the individual used prescriptions of medications and how many of those.

ii. Educational attainment and occupational status

Current employment was assessed with "What is your current employment?" (employed, self-employed, on parental leave, student, unemployed, retired, on long-term sick leave). The working hours per week were also assessed. *Highest educational* attainment, occupation, country of birth, sex and age was assessed using data from Statistics Sweden which were linked to the questionnaire data. Covariates are sex, age groups, highest educational attainment, financial constraints during childhood, and country of birth (Sweden, other Nordic countries, other countries).

iii. DALY

The DALY (Disability-adjusted life years) was calculated combining estimates of the burden of symptoms of AD with the prevalence and severity of AD data of the current study. In a previous study, disability index was derived from an analysis of the comparative impact of the direct disabling consequences of AD due to mild and severe itch and disfigurement.[137] The prevalence of AD assessed in the current study in combination with the previously developed weighted average disability index was used to determine the DALY of AD in Sweden. The DALYs per 100000 in Sweden in our study was calculated as: DALYs per 100000=prevalence rate of the current study multiplied by weighted average disability weight of the WHO study. For sensitivity analysis the weighted average disability weight based on the severity distribution of our own dataset was used; combined with the prevalence of AD was assessed using data from another Swedish study.[138]

Statistical analyses

Cross-tabulation and means were used to describe the study population. Associations between AD and the outcomes were examined using logistic and multinomial regression as applicable, yielding odds ratios (OR) and relative risk ratios (RRR). In addition to the unadjusted models, the independence of AD and each outcome was assessed by adjustment for covariates based on theoretical considerations. Education, parental financial difficulties during childhood, age, sex, comorbid asthma were considered as potential confounding factors. Potential confounding factor variables were kept when confounding was evident and also based on theoretically important considerations such as education.

Analyses of depression, anxiety, mental, and socioeconomic factors were stratified by sex and a diagnosis of asthma. It was assessed if sex or asthma were an effect modifier using multiplicative and additive interaction testing if applicable for the relationship of AD and the outcomes. It was assessed whether the effect size for the AD/depression and AD/anxiety relationship increased when the individuals had asthma in addition to AD; this was assessed calculating the relative excess risk (RERI). For the continuous variable working hours, linear regression analysis was performed, and ten-year age group variables were used for adjustment in addition to education and sex.

Additional analysis was performed for the relationship of AD, highest educational outcome and occupation including individuals aged 30 years and older, adjusted for sex, age group, and parental economic situation during childhood. A p-value lower than 0.05 or 95% confidence intervals not including 1.00 was used to indicate statistical significance.

Study II

Study population

This prospective cohort study utilized Swedish population-based registry data including 205,394 men born between 1952 and 1956 who underwent military conscription examination at age 17–21 years during 1969–1976. Conscription was compulsory during this period except for individuals with severe disability or those incarcerated. Data from the conscription examinations were linked to national registers with follow-up until December 31, 2009. Men were excluded if they had missing data on key variables, were unfit for service, had emigrated or died before follow-up began, or were assessed outside the specified age window.

Data collection and setting

The conscription examination comprised a detailed medical history, physical examination, and various physical and psychological tests. The psychological examination assessed stress resilience and the ability to tolerate psychological stress in military service by a semi-structured interview creating a score from 1 to 9. Stress resilience was categorized in three groups as low (1-3), intermediate (4-6) and high (7-9). Cognitive function was assessed by a written test covering logical, spatial, verbal and technical domains, yielding a nine-level normally distributed standardized score; high values indicate better cognitive function. AD was identified using Swedish International Classification of Diseases 8th Revision (ICD-8).

Several national registries were linked to the conscription data. The Longitudinal Integrated Database for Health Insurance and Labour Market Studies (Swedish acronym, *LISA*) provided information on occupational classification, employment status, unemployment benefits, sick leave, and marital status in 2008. Data were extracted from the Prescribed Drug Registry (*PDR*), which includes data from 1 July 2005 on all pharmacy-dispensed medications, including the information of the type of medications (Anatomical Therapeutic Chemical -codes) and pharmacy dispensation dates. The Total Population Registry (*TPR*) was used to identify deaths and emigration. These databases are managed by *Statistics Sweden*-SCB and are mandatory to report to and therefore have complete population coverage. Data about head of household´s occupation was extracted from the 1960 *Population and Housing Census*. Unique personal identification numbers issued to all residents were used to link the data.

The study design and the linkage to several registers is presented in **Figure 4.**

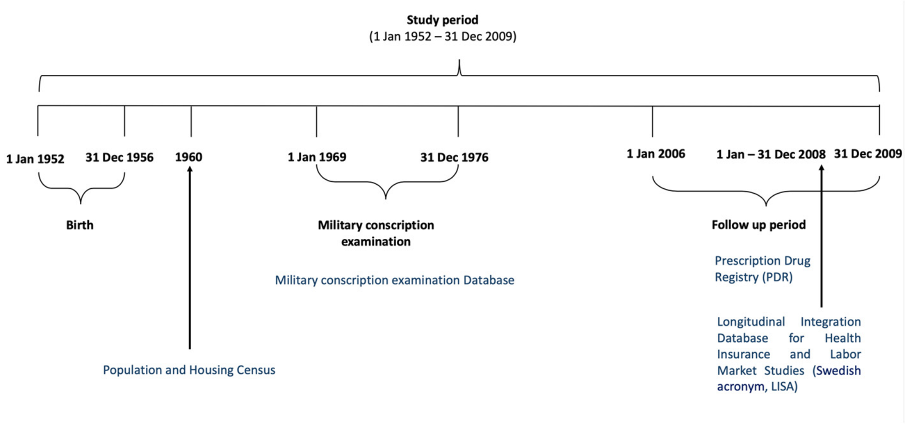

Figure 4: Schematic of the study design

Exposure variable

The exposure variable was AD and the severity of AD. Information on the exposure AD was collected by a physician from a general physical examination based on a clinical evaluation, and a medical history during the conscription assessment. The Swedish International Classification of Diseases 8th Revision (ICD-8) code 691 was used to identify AD.

Severity of atopic dermatitis was defined using the seventh digit of the AD disease code in the conscription data, indicating severity of disease (from military-medical point of view) at the conscription assessment. Codes 5-8 ("fairly significant impairment" - "no impairments, meaningless defect") were defined as "mild" and codes 0-4 ("highly significant impairment" -"considerable impairment") were defined as "severe"

Outcome variables

The information on occupation in 2008 was assessed using an occupational socioeconomic classification approximating ESeC with seven groups: i. Large employers/ higher managers/professionals; ii. lower managers/professionals, higher supervisory/technicians; iii. intermediate occupations; iv. lower supervisors and technicians; v. lower sales and service; vi. lower technical and vii. routine.

Employment status was grouped in three categories: i. Working in November 2008; ii. Not working in November 2008, and iii. Not worked during the 2008 at all. Any unemployment benefits during the whole year (yes/no) were also assessed. Income was assessed with the gross salary in 2008. Income from work was grouped in four groups: i. ≤ 244,500 SEK ii. 244,600-322,300 SEK iii. 322,400-420,000 iv. >420,000.

For marital status, data from the LISA register was used for assessment of the partnership status at the end of 2008. The data were categorized into three groups: i. Never married/registered partner; ii. Married/registered partner, widowed/partner died; and iii. Divorced.

Using the Prescribed Drug Registry (PDR), which includes data on all pharmacy-dispensed medications, and pharmacy dispensation dates, from 1 Jan 2006 until 31 Dec 2009 the first date on which the sum of dispensed anxiolytics and/or antidepressants became equivalent to the use for more than or equal to 180 days within 365 days was taken as the incidence date, indicating continuous treatment for anxiety or depression over an extended period.[139]

Covariates

Models were adjusted for year of birth, cognitive function score, stress resilience, any diagnosis of mental illness at conscription (identified by the ICD-8 codes 493, and 290 to 315), and head of household's occupation (manual workers, agricultural workers, farm owners/managers, office workers, business owners/managers, others/unknown).[140] Information on year of occupation of the head of household was obtained from the 1960 Population and Housing Census.

Statistical analyses

Descriptive analyses used cross-tabulation alongside means and median as appropriate. Logistic regression was used for the binary outcome (unemployment benefits), and multinomial regression for outcomes with more than two categories (occupational group, gross salary, marital status, employment status in November 2008). Coefficients, odds ratios (OR) and relative risk ratios (RRR) were estimated from these regression models, respectively, with 95% confidence intervals (95% CI). Cox proportional hazard regression was employed to examine the association between AD in adolescence and prescription of antidepressants and anxiolytics, yielding hazard ratios (HR). The proportional hazards assumptions were verified using Schoenfeld residuals. Analyses were additionally stratified by comorbidity status to examine whether the association may differ by having any comorbid disease. A p-value lower than 0.05 or 95% confidence intervals not including 1.00 indicated statistical significance.

Study III

This study consists of two parts: i. questionnaire construction ii. questionnaire validation and itch prevalence assessment.

i. Questionnaire construction

A novel paediatric itch questionnaire was developed through an expert consensus process after an extensive literature search.[141-147] Draft questions were adapted and simplified to be suitable and comprehensible for children and their caregivers. The questionnaire encompassed family and personal history of atopic conditions, demographic characteristics, comorbidities, itch duration, itch intensity, itch localization, disease-specific quality of life, and current treatments.

In detail, the prevalence of underlying itch-related comorbidities, such as AD, xerosis cutis, urticaria, scabies, pediculosis capitis, and other skin diseases, was assessed by the question, "were you/ was your child diagnosed by a physician with one or several of the following diseases?"

For prevalence of itch, the questions for the prevalence of acute itch were: '*Does your child experience itch? Now or within the last 24 hours? Within the last 7 days? Within the last 6 weeks*?' The questions for the prevalence of chronic itch were: '*Did your child ever experience chronic itch (≥3 days per week over a period of ≥6 weeks)? No; yes, within the last 24 hours; yes, within the last 12 months; yes, but more than 12 months ago*'.

The caregivers/children had to answer "yes" to at least one of the questions regarding the occurrence of itch for it to be classified as acute/chronic itch. The questions confirmed the presence of itch and the period in which itch developed.

Itch intensity was measured using a visual analog scale (VAS) adapted for children with five smileys-face icons grading from very happy to very sad).[148] (**Figure 5**)

5. How strong was your child's worst itch within the last 24 hours?

Please answer this question with your child and select the appropriate smiley to describe the itch intensity.

Figure 5: Question assessing the itch intensity

For the symptom-specific assessment of QoL, we used the ItchyQoL questionnaire translated in German.[149] The ItchyQoL is a validated, itch-specific assessment that measures the extent to which itch affects QoL in terms of three dimensions: symptoms, functioning, and emotions. A higher score indicates a greater adverse impact on QoL.[149]

Affected body sites were recorded using a body-silhouette line drawing, which is commonly used in dermatological assessments of skin diseases. (**Figure 6**)

6. Which parts of your child's body itched within the last 24 hours?

Please answer this question with your child and colour ALL boxes (skin areas) that itch(ed) your child.

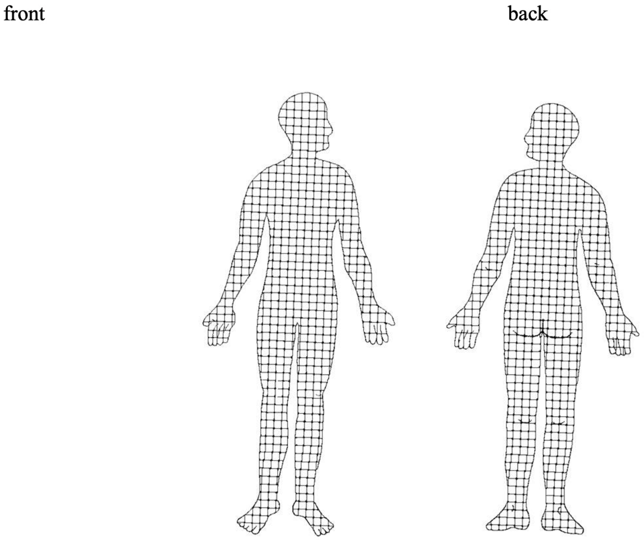

Figure 6: Assessment of the location of itch

ii. Questionnaire validation and Itch prevalence assessment

Study population

Nine of 12 randomly selected primary schools in Kiel (Schleswig-Holstein, Germany) agreed to participate. All children in grades 1-4 (age 6–10 years) were invited in September 2016 (n=1,722). Signed consent from caregivers was required before completion. The completed questionnaires from the families who gave their consent were collected.

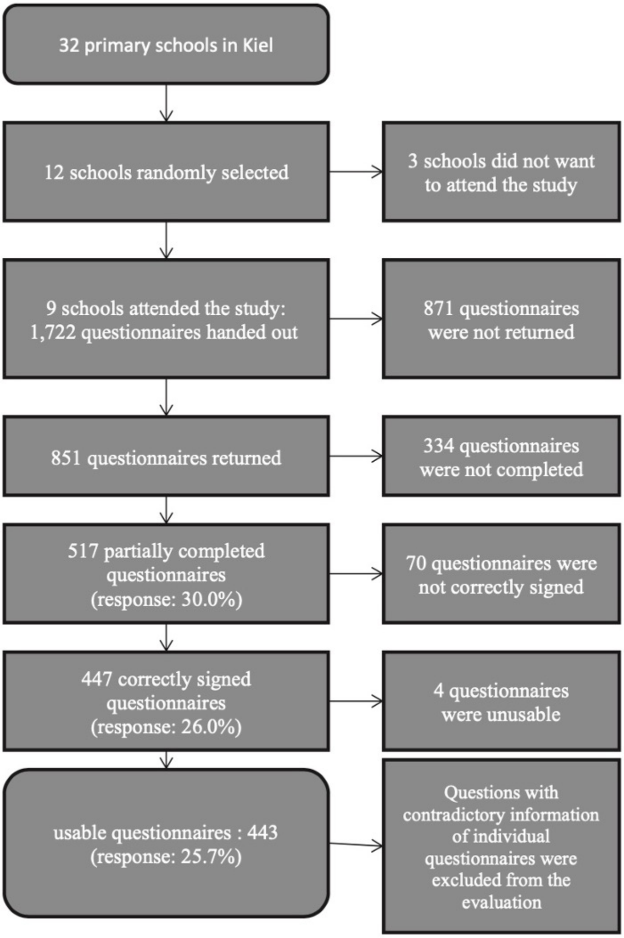

Figure 7: Flowchart of the study population

Content validation and feasibility assessment

Before deployment, the questionnaire was reviewed by clinicians, researchers with extensive itch expertise, patients, their parents, and lay individuals. All collaborators were asked for suggestions on improvements to the questionnaire. The questionnaire was adapted based on suggestions, and consensus on the final version was reached, as all collaborators either agreed or did not actively disagree. The validity of the final questionnaire was then explored.

The *content validity* of the questionnaire was assessed by conducting a semi-structured, one-to-one interview with patients and their parents at the Pediatric Consultation at the Department of Dermatology, Venereology, and Allergology of the University Hospital Kiel and non-experts. The interview started with a general discussion regarding the understanding of the itch questions and the prevalence of itch-associated conditions. The feasibility of the questionnaire was also assessed. In addition, the suitability of the content was evaluated by experts.

Test-retest reliability was evaluated by administering the questionnaire twice within a period of 3 months by 33 children, including 23 third and fourth graders from a primary school in Kiel and 10 patients from the Paediatric Clinic of the Department of Dermatology, Venereology, and Allergology of the University Hospital Kiel. The acute itch questions were not included in the second evaluation because of the time (mean 113 days) between the first and second tests.

To assess *psychometric measures,* the questionnaire was given to children visiting the Outpatient Department of Dermatology of the University Hospital of Kiel, Germany. Patients were included consecutively.

The questionnaire was validated by comparing itch reported via the questionnaire with the patient's medical history and examination by a physician, as described in the medical records of each patient. As no gold standard existed for assessing itch in children, the prevalence of chronic itch assessed via the questionnaire was compared with information from medical records, and the mean agreement between the measures was determined. Even comorbidities were compared with medical record data to confirm the reliability of the comorbidity questions.

Inclusion/exclusion

The inclusion criteria for the second part of the study were patients aged 6–10 years and signed informed consent. The exclusion criteria were age >10 years and <6 years at the time of the survey and absent legal guardian consent.

Statistical analyses

For the validation component, content validity, and feasibility were assessed by qualitative analysis. The reliability, item distribution characteristics, mean agreement between itch questionnaire results and medical records, and test-retest reliability were calculated. Differences between groups (children diagnosed with AD versus other conditions) were tested using the Mann–Whitney U test.

For the itch intensity, the item distribution characteristic means, standard deviation (SD), median, interquartile range (IQR), and floor and ceiling effects were assessed. Furthermore, Spearman's test was used to assess correlations of the itch prevalence and intensity with each parameter of the QoL and the strength of chronic itch in the test-retest reliability evaluation.

In the second part of the study, cross-tabulation, means, and medians were used to describe the study population. The distribution of the variables was assessed. For the daytime intensity of itch, nighttime intensity of itch, relationships, and QoL relationships, the non-parametric Wilcoxon signed-rank test (non-parametric test for paired-samples) was used. For the intensity of itch and QoL, the (non-parametric) Mann–Whitney U test was used regarding sex and underlying diseases.

For all other relationships, the chi-square test was used. For $n<5$, Fisher's exact test was used. Spearman's Rho test was used to assess correlations among QoL, chronic itch strength, and itch area and evaluate age reliability. Bonferroni's correction was used to adjust for multiple comparisons. A p-value lower than 0.05 indicated statistical significance.

Power calculation

Power was calculated assuming an itch prevalence of 15%, confidence interval of 3% and an expected response rate of 35%, which required approximately 1700 invited pupils to achieve 80% power.

Study IV

Study population

The Student Health Database (ELSA is the acronym in Swedish) was established in 2010 and collects yearly data on all children aged 6 years (pre-school class), 10 years (grade 4), 13 years (grade 7), and 16 years (first year in secondary school) in the county of Värmland, Sweden. ELSA collects data on health examinations by school nurses, and questionnaire interviews of students. For children aged 6-13 years, a parental questionnaire was also distributed. This means that data from about 9,000 - 10,000 health visits are compiled annually in ELSA. ELSA is used for mapping students' health for municipalities and county councils. The current study was based on school years 2015/16 and 9227 pupils (98%) participated. [150]

Data collection

ELSA contains validated questionnaire data on mental, physical and psychological health, social relations and family structure. The questions battery derives from the Nordic questionnaire '5-15' which examines children's mental health and other validated global assessments.[151-152] The parents' questionnaire included questions about the background of the child and family and about the health of the child. The pupil's questionnaire included questions about food and sleep habits, about physical activity and leisure, questions about school and work environment, about well-being and relationships as well as about the general health condition. For grade 7 and year 1 of upper secondary school there are also questions about tobacco/alcohol/drugs/anabolic steroids, and puberty development.

Data from questionnaires that both guardians/parents and students filled in prior to visit to the school nurse, and the school nurses' findings were registered in ELSA database. The nurse registers a diagnosis in the ELSA database only if a doctor, psychologist or speech therapist has confirmed presence of the disability or the disease. There are also questions about stress, anxiety, mental development and concentration difficulties. The school nurse enters data completely unidentified in ELSA. No identification codes are used.

Exposure variables

The exposure variable was self-reported AD, identified by the question ‘Do you have Eczema?’ (with 2 response alternatives; yes, no).

Outcome variables

The outcome variables are variables relating to state of general health and wellbeing, mental health, food habits, disturbed sleep, learning difficulties, problems with peer relationships or relationships with adults, problems with physical activities, outdoor activities and activities involving contact with water. For teenagers, outcome variables included also alcohol consumption, smoking and medications.

Covariates and background variables

Possibly important covariables were determined through a literature search assessing common associated factors for atopic dermatitis and theoretical considerations. Age, sex, comorbid asthma and comorbid allergy were considered as potential confounding factors. Paternal and maternal employment, and self-reported ADHD were considered as possible confounders or possible intermediates on the pathway.[140] Comorbid self-reported asthma and other allergic diseases such as rhinitis and conjunctivitis were considered possible effect modifiers.

The background variables included sex, parents’ occupation, the child´s birth country, number of siblings, type of family structure, and municipality. Parent´s occupation was categorized as civil servant, entrepreneur, student, worker, unemployed and other/not specified. Number of siblings was recorded as 0, 1-2, 3 or more.

Sample size

Based on previous results a sample size calculation for AD and its association with the theoretically most important dependent variable anxiety as a proxy for mental health symptoms was performed with a power of 80% and alpha error of 5%. Assuming the proportion of children with anxiety and without AD 8%, and anxiety in children with AD 13%, the maximum number needed would be 283 with AD and 5377 without AD. Thus, the sample size of the current study of more than 9000 children should be sufficient.

Statistical analyses

Summary statistics were used to describe the study population and the prevalence of all outcome- and exposure- variables for children and adolescents with AD compared with no AD. The association between AD and the outcome variables was examined using logistic and multinomial regression estimating odds ratios (OR), and relative risk ratios (RRR), respectively, as applicable. In addition to the unadjusted models, the independence of AD and each outcome was assessed by adjustment for the selected covariates based on theoretical considerations.

Factor analysis

The statistical technique of factor analysis provides a method of identifying a relatively small number of factors or factor constructs that can be used to represent the relationship between a large number of variables. These factors once identified can then be quantified with a score. The use of factors can also reduce the type I error by avoiding the use of Bonferroni correction for multiple statistical tests on related variables. In this study we applied the rotated factor analysis to a set of variables to define areas of QoL which are related to AD in children over 6 years of age, as well as, to identify the strength of the relationships. Those factors for which the variables were more correlated with each other than with variables of other factors were retained.

Each factor was interpreted according to the meaning of the variables that were loaded on it. Factors with an eigenvalue greater than 1.0 were retained. In addition, a rotated factor analysis was performed to confirm the relevance of each variable in the factors. The Kaiser-Meyer-Olkin measure of sampling adequacy for the correlation matrix was 0.9110, and the Bartlett test of sphericity was significant at a P value of .00001 or less, indicating that a factor analysis of this correlation matrix would be very appropriate. New variables, based on the factor analysis, were created and used in crude and adjusted regression analysis using the factors as the outcomes. The analyses were run both unadjusted and adjusting for parental occupation, allergy, and ADHD.

A p-value lower than 0.05 or 95% confidence intervals (95% CI) not including 1.00 was used to indicate statistical significance

All analyses were conducted using Stata MP18 statistical software (StataCorp LLC, College Station, TX, USA).

Ethical Considerations

All studies included in this thesis were conducted in accordance with the World Medical Association's Declaration of Helsinki and approved by relevant regional ethics committees in Sweden and Germany.

Study I received ethical approval from the Regional Ethics Board in Uppsala (registration number 2015/417). The study utilized anonymized questionnaire data from a large population-based survey. Participants were provided with comprehensive written information about the study aims and gave informed consent before completing the questionnaire. The questionnaire design allowed participants to decline answering any questions they found sensitive or uncomfortable.

Study II was approved by the Regional Ethics Board in Uppsala (registration numbers 2014/324 and 2019/04143). This registry-based cohort study used de-identified data from Swedish national registers linked to military conscription records. Given the register-based nature of the study and the use of historical data, individual consent was not required according to Swedish research ethics regulations. All data were handled in accordance with the Swedish Data Protection Act and the General Data Protection Regulation (GDPR).

Study III received ethical approval from the Regional Ethics Committee in Kiel, Germany (registration number A112/14). The study involved schoolchildren aged 6–10 years, and comprehensive written information was provided to both children and their parents or guardians. Participation was entirely voluntary, and participants could withdraw at any time without consequence. The questionnaires were anonymized immediately upon collection to protect participant privacy.

Study IV was approved by the Regional Ethics Board in Uppsala (registration number 2017/106). This study utilized data from the Student Health Database (ELSA), which collects routine health information from school health services. The data were completely de-identified before analysis, with no identification codes used. Parents and students provided consent for the use of anonymized health information for research purposes as part of routine school health procedures.

Across all four studies, several overarching ethical principles were maintained:

Beneficence and Non-maleficence: The research was designed to contribute knowledge about atopic dermatitis and its broader impacts on quality of life and socioeconomic outcomes, with minimal risk to participants. Survey-based and registry-based methodologies posed negligible direct risk to participants.

Confidentiality and Data Protection: Robust data-security measures were implemented throughout data collection, storage, and analysis phases. Personal identifiers were removed or encrypted, and access to data was restricted to authorized research personnel only.

Transparency and Integrity: All studies were conducted with scientific rigor and transparency. Methods, limitations, and potential conflicts of interest were clearly documented. The research adhered to good research practice guidelines and relevant regulatory frameworks.

Vulnerable Populations: Special consideration was given to the inclusion of minors in Study III, with appropriate safeguards implemented to protect their rights. In Study IV, the use of routine school health data was governed by established ethical frameworks for research with minors.

Minimization of harm: The questionnaire-based studies were designed to minimize potential psychological discomfort. Questions were formulated in clear, age-appropriate language, and participants could skip questions they did not wish to answer. For studies involving children, particular care was taken to ensure questions were understandable and non-threatening.

Results

Study I

A total of 34,313 answered the questionnaire; 54% females and 46% men. Of those, 4175 individuals had AD. The prevalence of AD was 14%, and it decreased with increasing age. Of those with AD, about 10% had severe AD. The median age was 62 years, and most individuals were born in Sweden. (**Table 2**)

Table 2: Population characteristics of adults with and without atopic dermatitis (AD) diagnosis among 34,313 randomly selected adults in central Sweden

Variables	Category	n (%)	Atopic dermatitis	
			With AD n (%)	Without AD n (%)
Age in years	18-29	5,393 (15.72)	756 (18.1)	3,991 (15.4)
	30-69	15,769 (45.96)	2,055 (49.2)	11,921 (45.9)
	70+	13,151 (38.33)	1,364 (32.7)	10,043 (38.7)
Sex	Male	15,880 (46.28)	1,811 (43.4)	12,033 (46.4)
	Female	18,433 (53.72)	2,364 (56.6)	13,922 (53.6)
Highest level of education	Compulsory schooling	8,343 (24.31)	904 (21.9)	6,090 (23.7)
	Post-compulsory school	14,688 (42.81)	1,846 (44.7)	11,076 (43.1)
	University	10,892 (31.74)	1,380 (33.4)	8,527 (33.2)
Country of birth	Sweden	30,025 (87.50)	3,701 (88.7)	22,965 (88.5)
	Other Nordic countries	1,517 (4.42)	201 (4.8)	1,108 (4.3)
	Other countries	2,771 (8.08)	273 (6.5)	1,882 (7.3)
Disposable income in thousand Swedish kronor (SEK)	146 tkr	10,976 (32.2)	1,347 (32.4)	7,988 (31.0)
	147-237 tkr	10,715 (31.4)	1,284 (30.9)	8,185 (31.7)
	238-324 tkr	6,612 (19.4)	873 (21.1)	5,044 (19.6)
	325 tkr +	5,773 (17.0)	648 (15.6)	4,578 (17.8)

DALY

The disability-adjusted life year (DALYs) per 100000 in Sweden are calculated using the prevalence, severity distribution and "disability weight". We did not wish to calculate both based on our study results as it would have implied a double impact of the current severity distribution. Therefore, we calculated the DALY taking the prevalence of the current study into account and using the standard disability weight which is used by the WHO burden of disease studies. This approach revealed a DALY of 526.68 (uncertainty interval 305-826) for individuals from Sweden. Secondly, we compared the results with an analysis using the prevalence rate of AD from the Swedish part of the population-based study by Svensson et al. and a weighted disability weight calculated based on the current data which showed a DALYs of 593.67.

Socioeconomic position and AD

Persons with severe AD had less often a university degree or higher, and had a lower income compared to persons without AD and with mild to moderate AD (table 3). For all persons with AD, crude analysis showed an increased RRR of gymnasium and university degree; potentially due to socioeconomic advantage during childhood. In adjusted analysis, the advantage was attenuated. Adults with AD were more often unemployed, and the RRR increased with AD severity. Adults with severe AD were more often on sick leave and had more often a blue-collar occupation. Adults with AD had more often on sick leave for more than 29 days, long term sick leave/on "activity stimulation" and got early pension due to disease compared to adults without AD. For all results regarding the education and occupation there was no difference for the whole group and for individuals age 30 years and older. People with AD, especially with severe AD were more often never married and they felt lonely more often than adults without AD (aRRR daily loneliness in mild AD: 2.04, 95% CI 1.52-2.74, in severe AD aRRR 4.37, 95% CI: 2.05-9.33).

Table 3: Association of atopic dermatitis (AD) and socio-economic factors, presenting as relative risk ratio (RRR) among adults in mid-Sweden in crude and adjusted analyses

Outcome variables	Category	Mild AD[#]	Severe AD[#]
		aRRR (95% CI)	aRRR (95% CI)
Income per year**(1000's SEK)	147 - 237	0.89 (0.87-1.05)	0.91 (0.75-1.21)
	238 - 324	0.94 (0.90-1.13)	0.51 (0.39-0.77)
	>325	0.76 (0.74-0.95)	0.36 (0.25-0.58)
Highest level of education***	Post-compulsory school	1.04 (0.88-1.23)	0.88 (0.56-1.40)
	University	1.05 (0.88-1.24)	0.55 (0.34-0.90)
Occupational status****	Studying or practical	0.94 (0.65-1.37)	1.54 (0.56-4.24)
	Sick leave	1.46 (1.15-1.84)	4.05 (2.46-6.68)
	Long-term sick leave	1.26 (0.85-1.88)	3.70 (1.68-8.15)
	Other	1.06 (0.75-1.50)	2.62 (1.20-5.73)
	Unemployed	1.13 (0.82-1.58)	2.52 (1.16-5.51)
Occupation*****	Managers	0.85 (0.65-1.11)	1.48 (0.53-4.10)
	Technician and associate professionals	0.98 (0.83-1.18)	1.22 (0.53-2.81)
	Small entrepreneurs	0.86 (0.67-1.10)	2.45 (1.08-5.53)
	Clerk and skilled service employees	0.99 (0.83-1.18)	1.63 (0.83-3.23)
	Skilled industrial employees	0.98 (0.79-1.22)	2.83 (1.30-6.17)
	Lower status employees	1.04 (0.83-1.32)	1.81 (0.76-4.29)
	Any employment	0.98 (0.81-1.18)	2.20 (1.10-4.40)
	Other	1.04 (0.73-1.50)	4.25 (1.71-10.57)

*Adjustments were made for sex, age group (defined as 18-29 years, 30-69 years, 70 years and older), parental economic situation during childhood. # No AD as reference. **Less than 147 thousand SEK per year as base outcome *** Compulsory schooling as base outcome ****Any employment as base outcome *****Professionals as base outcome

AD and Sleeping problems

As seen in **table** 4 the relative risk ratio of severe sleeping problems (RRR: 1.76) and severe tiredness (RRR: 2.62) were increased in adults with mild AD compared to adults without AD. Adults with severe AD had those conditions in an even higher proportion (RRR: 7.90 for severe sleeping problems and RRR: 10.18 for severe tiredness respectively). Adjustment for sex, age group, did not considerably alter the relationships.

Table 4: Atopic dermatitis (AD) sleeping problems and tiredness

Outcome variable	**Category**	**Mild AD**	**Severe AD**	**Mild AD**	**Severe AD**
		RRR (95% CI)	RRR (95% CI)	aRRR* (95% CI)	aRRR* (95% CI)
Sleeping problems	mild	1.24 (1.15-1.34)	1.71 (1.49-1.94)	1.27 (1.17-1.36)	1.72 (1.50-1.96)
	severe	1.76 (1.39-2.22)	7.90 (6.17-10.11)	1.82 (1.44-2.30)	7.44 (5.76- 9.59)
Tiredness	mild	1.44 (1.33 -1.56)	1.93 (1.68 -2.21)	1.47 (1.35 - 1.59)	1.97 (1.71 -2.60)
	severe	2.62 (1.93-3.53)	10.18 (7.30-14.20)	2.61 (1.93-3.52)	9.80 (6.99-13.73)

No AD as reference. * Adjustments were made for sex, age group (defined as 18–29, 30–69, 70 years and older), highest achieved education, aRRR: adjusted relative risk ratio.

AD and Mental health comorbidity

In crude analyses, adults with mild AD had elevated risk of anxiety (RRR 1.49, 95% CI 1.38–1.61 for mild anxiety; RRR 2.75, 95% CI 2.21–3.42 for severe anxiety) and depressive symptoms (RRR 1.46, 95% CI 1.35–1.58 for mild; RRR 2.64, 95% CI 2.13–3.28 for severe) compared with individuals without AD. Adults with severe AD showed substantially higher crude risks for both anxiety (RRR 2.02, 95% CI 1.24–2.35 for mild anxiety; RRR 8.79, 95% CI 6.65–11.62 for severe anxiety) and depressive symptoms (RRR 1.85, 95% CI 1.56–2.18 for mild; RRR 8.03, 95% CI 5.95–10.81 for severe), indicating a clear dose-response pattern by disease severity.

After adjustment for age, sex, and highest achieved education, the associations remained. Adults with mild AD had an elevated risk of anxiety (aRRR 1.46, 95% CI 1.35–1.58 for mild anxiety; aRRR 1.97, 95% CI 1.69–2.30 for severe anxiety) and depressive symptoms (aRRR 1.44, 95% CI 1.33–1.55 for mild; aRRR 1.78, 95% CI

1.50–2.12 for severe) compared with individuals without AD. Adults with severe AD had substantially higher adjusted risks for both anxiety (aRRR 2.48, 95% CI 1.99–3.11 for mild anxiety; aRRR 6.22, 95% CI 4.60–8.42 for severe anxiety) and depressive symptoms (aRRR 2.39, 95% CI 1.92–2.98 for mild; aRRR 5.62, 95% CI 4.10–7.71 for severe), confirming a clear dose-response relationship between AD severity and mental health burden.

Table 5: Risk of anxiety and depression among adults with AD, presented as relative risk ratios in a population from mid-Sweden in crude and adjusted analyses

Outcome variable	**Category**	**Mild AD**	**Severe AD**	**Mild AD**	**Severe AD**
		RRR (95% CI)	RRR (95% CI)	aRRR* (95% CI)	aRRR* (95% CI)
Anxiety	mild	1.49 (1.38-1.61)	2.02 (1.24-2.35)	1.46 (1.35-1.58)	2.48 (1.99-3.11)
	severe	2.75 (2.21-3.42)	8.79 (6.65–11.62)	1.97 (1.69-2.30)	6.22 (4.60-8.42)
Depressive symptoms	mild	1.46 (1.35-1.58)	1.85 (1.56-2.18)	1.44 (1.33-1.55)	2.39 (1.92-2.98)
	severe	2.64 (2.13-3.28)	8.03 (5.95–10.81)	1.78 (1.50-2.12)	5.62 (4.10-7.71)

No AD as reference. * Adjustments were made for sex, age group (defined as 18–29, 30–69, 70 years and older), highest achieved education, aRRR: adjusted relative risk ratio.

Interestingly, the odds of mental symptoms and conditions did not vary across age groups. People with AD were more likely to be on sick leave due to mental health conditions. (OR 1.30 95% CI 1.01-1.67 for mild AD and OR 2.30 95%CI 1.18-4.45 for severe AD) compared with individuals without AD.

For individuals with both AD and asthma, the relationship with both diagnosed depression (OR: 1.94, 95% CI: 1.25-3.00) and anxiety (OR: 2.24, 95% CI: 1.93-2.59 for mild anxiety, OR: 6.2, 95% CI: 5.05-7.61 for severe anxiety) was stronger compared to those with AD only. Adjustments for educational status and age group attenuated the relationships between AD and asthma and depression (aOR: 1.52, 95% CI 1.35-1.72 for mild depression; aOR: 3.51, 95% CI: 2.87-4.30 for severe depression) and anxiety (aOR for mild disease 1.60, 95% CI 1.48-1.73; and aOR 2.31, 95% CI: 1.96-2.72 for severe disease) but the relationships remained statistically significant. There was no multiplicative effect modification but a statistically significant increased excess risk for those having asthma and AD on anxiety (RERI: 0.26, p<0.001) and depression (RERI: 1.07, p<0.001). RERI > 0 indicates positive additive interaction beyond the individual effects of AD and asthma.

Study II

Description of the study population

The study population consisted of 205 394 men who underwent conscription assessment and of whom 1458 (0.71%; 95% CI 0.67-0.75%) had a diagnosis of AD at conscription assessment. Of the men diagnosed with AD at the conscription assessment, most had mild AD (n=1277, 87.6%; 95% CI 85.8-89.2%), and most had one or more comorbid conditions (n=1043, 71%; 95% CI 69.1-73.8%).

Men with AD had a much higher prevalence of asthma (n=245, 16.8%; 95% CI 14.9-18.8), tended to have lower stress resilience (n=352, 24.1%; 95% CI 22.0-26.4%) and a similar prevalence of mental illness (n=173, 11.9%; 95% CI 10.2-13.6) compared to those without AD. Further, men with AD were more often from families where the head of the household held a position with office work, compared with men without AD (35%, 95% CI 32.6-37.6%, n=511 vs. 28,1%; 27.9-28.2%, n=52 210; respectively).

Atopic Dermatitis and mental conditions

In total, 14,868 had an outcome event (antidepressant/anxiolytic medication); the median follow-up was 162 days (IQR 48-653 days). The results from unadjusted Cox regression showed that men with AD had more often prescribed antidepressant/anxiolytic medication at the age of 50-57 years (HR 1.55 95% CI 1.32-1.81) compared with men without AD (**Table 6**). HR was 1.42 for men with mild AD (95% CI 1.20-1.69) and 2.46 (95% CI 1.72-3.53) for men with severe AD.

Table 6: Association between AD and prescription of antidepressants/anxiolytics between years 2006-2009.

	Medication/total no	Unadjusted HR (95 % CI)	Adjusted HR (95 % CI) *
No AD	14,709/203,936	Reference	Reference
AD	159/1,458	1.55 (1.32 – 1.81)	1.49 (1.28 – 1.74)
-Mild AD	129/1,277	1.42 (1.20 – 1.69)	1.37 (1.16 – 1.63)
-Severe AD	30/181	2.46 (1.72 – 3.53)	2.36 (1.65 – 3.38)
AD without comorbidity			
No AD	14,709/203,936	Reference	Reference
AD	39/415	1.32 (0.96 – 1.81)	1.42 (1.03 – 1.94)
-Mild AD	33/365	1.26 (0.90 – 1.78)	1.35 (0.96 – 1.91)
-Severe AD	6/50	1.74 (0.78 – 3.88)	1.88 (0.85 – 4.19)
AD with comorbidity			
No AD	14,709/203,936	Reference	Reference
AD	120/1,043	1.64 (1.37 – 1.96)	1.52 (1.27 – 1.82)
-Mild AD	96/912	1.49 (1.22 – 1.82)	1.38 (1.13 – 1.69)
-Severe AD	24/131	2.75 (1.84 – 4.10)	2.52 (1.69 – 3.76)

* Adjusted for year of birth, cognitive function, any diagnosis of mental illness and head of household's occupation and for stress resilience.

Atopic Dermatitis and occupational socioeconomic classification

The results for the association between AD and occupational socioeconomic classification using multinomial logistic regression showed that, in 2008, men with AD had a lower risk of holding lower technical (unadjusted RRR 0.68 95% CI 0.58-0.81) and routine occupations (unadjusted RRR 0.73 95% CI 0.62-0.86) compared with men without AD in adolescence (**Table** 7). After adjusting for year of birth, cognitive function, any diagnosis of mental illness and head of household´s occupation as well as stress resilience, the association remained similar.

Table 7: Association between any atopic dermatitis at conscription examination and occupation

Outcome variables	Category	RRR (95% CI)	aRRR (95% CI)
Occupational socioeconomic classification	Large employers, higher managers/professionals	Reference	Reference
	Lower managers/professionals, higher supervisory/technicians	0.86 (0.74 – 1.01)	0.88 (0.75 – 1.04)
	Intermediate occupations	0.80 (0.66 – 0.99)	0.82 (0.67 – 1.01)
	Lower supervisors and technicians	0.81 (0.48 – 1.37)	0.81 (0.48 – 1.36)
	Lower sales and service	0.87 (0.70 – 1.07)	0.87 (0.70 – 1.08)
	Lower technical	0.68 (0.58 – 0.81)	0.73 (0.60 – 0.87)
	Routine	0.73 (0.62 – 0.86)	0.74 (0.62 – 0.89)

* Adjusted for stress resilience, year of birth, cognitive function, any diagnosis of mental illness and head of household's occupation.

AD, labour market participation and unemployment benefits

No association between AD and labour market participation in November 2008 was found in unadjusted (RRR 0.88 95% CI 0.67-1.15) or adjusted analyses (aRRR 0.90 95% CI 0.68-1.17). Analysis by AD severity showed an unadjusted RRR for not worked during the year 0.79 for men with mild AD (95% CI 0.58-1.07) and 1.55 for individuals with severe disease (95% CI 0.86-2.78). Adjusted analyses for year of birth, cognitive function, any diagnosis of mental illness and head of household´s occupation as well as further adjustment including stress resilience did not alter these estimates notably which remained not statistically significant.

AD and unemployment benefits

AD was not statistically significantly associated with higher risk of receiving unemployment benefits in crude analysis, (OR 0.93 95% CI 0.71-1.21). Adjustment for year of birth, cognitive function, any diagnosis of mental illness and SEI of the head of household as well as additional adjustment including stress resilience did not alter the estimate notably (RRR 0.95 95% CI 0.73-1.24 and RRR 0.93 95% CI 0.71-1.21, respectively).

Atopic Dermatitis and gross salary

Compared with a lower income, the unadjusted multinomial regression model showed no statistically significant increased relative risk of an income of 420 000 SEK or higher for persons with AD in adolescence (RRR 1.13, 95% CI 0.98-1.30) compared with individuals without AD (**Table 8**). Adjustment for year of birth, cognitive function, any diagnosis of mental illness and SEI of the head of household as well as additional adjustment including stress resilience did not make noticeable changes in the estimates.

Table 8: Associations between AD, gross salary in SEK and marital status

Outcome variables	Category	RRR (95% CI)	aRRR (95% CI)
Gross salary	≤ 244,500	Reference	Reference
	244,600–322,300	0.96 (0.82 – 1.11)	0.97 (0.83 – 1.12)
	322,400–420,000	1.00 (0.87 – 1.16)	1.03 (0.89 – 1.19)
	> 420,000	1.13 (0.98 – 1.30)	1.15 (0.99 – 1.34)
Marital status	Married	Reference	Reference
	Never married	1.07 (0.95 – 1.20)	1.02 (0.90 – 1.16)
	Divorced	0.94 (0.81 – 1.09)	0.93 (0.80 – 1.08)

* Adjusted for stress resilience, year of birth, cognitive function, any diagnosis of mental illness and head of household's occupation.

AD and marital status

The unadjusted analysis found that AD was not statistically significantly associated with marital status as shown in **Table 8**. The unadjusted multinomial logistic regression produced a relative risk ratio of 1.07 (95% CI 0.95-1.20) for never been married and 0.94 (95% CI 0.81-1.09) for been divorced respectively for men with AD -with married as reference category- compared with those without AD. After adjustment for year of birth, cognitive function, any diagnosis of mental illness and head of household´s occupation, the estimates did not alter notably and remained statistically not significant.

Study III

Content validity and feasibility

To assess content validity, 25 patients participated, along with physicians, non-experts, and parents. The test-retest was performed by 33 individuals: 23 students from one of the participating schools in Kiel and 10 patients from the department. The psychometric measures were assessed in 19 patients. The 25 patients and their parents found that the questionnaire was understandable and relevant to the prevalence and intensity of acute and chronic itch. The feasibility of the questionnaire was assessed as high. On average, it took 7.6 minutes to answer all itch-related and background questions.

Test-retest reliability

The mean agreement of the CCI was 0.85 (95% CI 0.59–1.00). For the VAS, the non-parametric Spearman correlation was high for nocturnal itch for the test-retest reliability (c=0.67).

Validity

The prevalence of chronic itch assessed by the questionnaire was well correlated with medical records in the 19 patients assessed. The itch of all participants could be confirmed by patient records (mean consistency=89.47%). The test performance was equally high across all self-reported conditions. Regarding the mean, SD, median, and IQR, the measurements of itch intensity and floor and ceiling effects were acceptable. The intensity of acute itch changed (either increased or decreased) in 64% (95% CI 35%–87%).

Prevalence of itch

To assess the prevalence of itch, 9/12 invited schools participated. Among all children invited (n=1722), 443 children answered the questionnaire, including 48.6% females (n=215) and 51.4% males (n=227). The response rate was 25.7%. The median age was 8 years. Most participants (98.9%) were born in Germany, and 21% had no siblings.

The total prevalence of itch was 26.2% (95% CI 19%–36%) (n=116). The prevalence of acute itch and chronic itch was 20.0% (95% CI 12%–29%) (n=87) and 14.7% (95% CI 7.0%–26%) (n=65), respectively. There were no differences in the itch prevalence by sex or age (**Table 9**). Chronic itch was reported within the previous 24 hours by 1.8% (n=8/443), within the last year by 10.0% (n=44/443), and for more than 1 year by 4.7% (n=21/443). There were no differences in age or sex.

Table 9: Prevalence of itch in German schoolchildren aged 6-10 years

		Prevalence of itch n (%)							
		Acute itch°			Chronic itch				Any* Itch
Sex	n	Within the last 24 h	Within the last 7 days	Within the last 6 weeks	Within the last 24 h	Within the last year	> 1 year	Any chronic itch	
Male	225	18 (8.1)	28 (12.4)	41 (18.2)	2 (0.9)	19 (8.4)	13 (5.7)	32 (14.1)	56 (24.7)
Female	210	22 (10.5)	32 (15.2)	46 (21.9)	6 (2.8)	25 (11.7)	8 (3.7)	33 (15.4)	60 (27.9)
Total	436	40 (9.2)	60 (13.8)	87 (20.0)	8 (1.8)	44 (10.0)	21 (4.7)	65 (14.7)	116 (26.2)

° Can overlap * Any itch=acute and/or chronic itch

Itch intensity

The intensity of acute itch assessed by VAS scores showed a mean strength of 2.61 and median of 2.5 with a lower quartile (Q1) of 2.0 and upper quartile (Q3) of 3.0. The mean intensity assessed by VAS scores (mVAS) was 2.65 in boys (n=17) and 2.57 in girls. Regarding chronic itch (n=65), the mean intensity was 3.73 with a median of 4.0, Q1 of 3.0, and Q3 of 4.0.

Itch and QoL

Itch was related to a decreased QoL; sleep and mood were disturbed in individuals with chronic itch compared with individuals without chronic itch. All dimensions of the QoL measure (sleep, concentration, leisure, mood) were significantly correlated with the itch intensity. Sleep and mood were decreased in individuals with chronic itch related to AD compared with those with chronic itch not related to AD (Mann–Whitney U test, p<0.05). Chronic itch in genital regions (p<0.001) was more closely related to mood disturbances than itch at other regions (i.e., not sensitive sites). Facial itch tended to be related to decreased concentration (p=0.015).

Concentration was better in individuals who reported chronic itch with AD and/or xerosis cutis compared with individuals with chronic itch but without either AD or xerosis (p<0.05). The presence of a comorbid condition in addition to AD did not worsen the QoL or intensity of chronic itch (Mann–Whitney U test, p<0.05, data not shown).

Table 10: Relationship between chronic itch and dimensions of the self-reported quality of life

	Quality of life			
Sex	Mood	Sleep	Concentration	Leisure time
Male	n=31 Mean $2.53^{\#}$ SD 0.99 Median 3.0 IQR 2.0–3.0	n=31 Mean 2.45 SD 1.15 Median 2.0 IQR 1.0–4.0	n=25 Mean $1.92^{\#}$ SD 0.91 Median 2.0 IQR 1.0–3.0	n=30 Mean 2.23 SD 0.90 Median 2.0 IQR 2.0–3.0
Female	n=29 Mean $2.72^{\#}$ SD 0.88 Median 3.0 IQR 2.0–3.0	n=30 Mean 2.68 SD 1.28 Median 3.0 IQR 1.0–4.0	n=28 Mean $2.11^{\#}$ SD 1.10 Median 2.0 IQR 1.0–3.0	n=29 Mean 2.43 SD 0.98 Median 2.5 IQR 2.0–3.0
Total	n=60 Mean $2.63^{\#}$ SD 0.94 Median 3.0 IQR 2.0–3.0	n=61 Mean $2.57^{\#}$ SD 1.21 Median 3.0 IQR 1.0–4.0	n=53 Mean $2.02^{\#}$ SD 1.01 Median 2.0 IQR 1.0–3.0	n=59 Mean $2.33^{\#}$ SD 0.94 Median 2.0 IQR 2.0–3.0

SD: standard deviation; IQR: interquartile range. **p*<0.01 with Bonferroni’s correction (Wilcoxon signed-rank test).

Study IV

Description of the study population

The study population consisted of 9227 children and adolescents 6-17 years-old of whom 51.1% were males. Most children were born in Sweden (90.7%) although some were born in Asia (4.0%), other European countries (2.2%) or in other Nordic countries (1.4%)

Comorbidities and self-reported symptoms

AD prevalence was 3.63%. Of those reporting AD, 55.5% were girls and 70% lived with both parents. Children with AD had increased odds for comorbid asthma (OR: 3.45, 95% CI: 2.63-4.53), other allergic diseases (OR: 3.01, 95% CI: 2.38-3.81) (Table S1), disturbed sleep (OR: 2.09, 95% CI: 1.41-3.10), tiredness (OR: 1.42, 95% CI: 1.00-2.01), and anxiety (OR: 1.61, 95% CI: 1.15-2.27) compared to children without AD (Table S2). These associations strengthened after adjusting for age and sex. Children with AD did not have increased odds for ADHD (OR: 0.62, 95% CI: 0.32-1.18) or autism (OR: 0.83, 95% CI: 0.39-1.78). Pupils with AD had more frequent routine health-examinations due to illness or disability (RRR: 1.47, 95% CI: 1.13-1.92).

Analyses adjusted for sex and year of birth showed that children in grade 7 and in the first year of high school with AD were more likely to smoke cigarettes a few times per week (aRRR: 3.46, 95%CI: 1.19-10.0) compared children and adolescents without AD but no difference was shown regarding other substances; alcohol, drugs, anabolic steroids, snus in crude and adjusted models. (Data not shown).

Factor analysis – aspects of QoL related to AD

As our study sample was large, variables with eigenvalue higher than 1.0 were retained. For the whole study population aged 6 to 17 we retained the following factors: 'Do not feel good, confident, happy', 'Feel sad, anxious, angry' 'Problems with peer relations' 'Problems with physical activities which had eigenvalue over 1.0.

Children between 6 and 17 years with AD were more often sad, anxious and angry (coefficient (c):0.120 95% CI:0.006-0.233) and experienced more difficulties peer relations (c:0.120 95%CI: 0.006-0.233) compared to their peers without AD while girls with AD experienced more often problems with physical activity (c:0.161 95% CI: 0.024-0.298) compared with girls without AD (**Table 11**).

Table 11: Factor analysis on the relationship between atopic dermatitis and aspects of quality of life of children aged 6 to 17 (n=8,398)

Factors reflecting aspects of QoL	Total c (95% CI)	Girls c (95% CI)	Boys c (95% CI)
Do not feel good, confident, happy	0.073 (-0.036-0.182)	0.148 (-0.001-0.299)	-0.031 (-0.189-0.125)
Sad, anxious, angry	0.120 (0.006-0.233)	0.151 (-0.006-0.307)	0.076 (-0.089-0.241)
Problems with peer relations	0.120 (0.006-0.233)	0.151 (-0.002-0.299)	0.076 (-0.089-0.241)
Problems with physical activity	0.094 (-0.013-0.201)	0.161 (0.024-0.298)	0.009 (-0.158-0.176)
Problems with food	n.s.	n.s.	n.s.

c: coefficient, 95%CI: 95% confidence interval, *Adjusted for sex, year of birth, **Adjusted for year of birth. Similar results if additionally adjusted for parental occupation, allergy, attention-deficit disorder. n.s.: not statistically significant (p≥0.05)

Pre-school class

The factor ‘Do not feel good, confident, happy’ was positively associated with AD in girls in pre-school class (c: 0.256, 95%CI: 0.043-0.468) in crude and adjusted analyses indicating that girls with AD do not feel confident and were more often sad compared with girls without AD of the same age group. For the same age group, the factor ‘Problems with sleep’ (c:0.274 95%CI: 0.143-0.405). had a positive coefficient for both boys and girls with AD. The factors ‘Problems with peers at school’ (c:0.329 95%CI: 0.136-0.523) and ‘Problems with physical activity’ had a positive correlation with AD in children of this age-group (c: 0.244 95% CI: 0.027-0.460) (**Table 12**).

Table 12: Factor analysis on the relationship between atopic dermatitis and aspects of quality of life of children in pre-school class (n= 2,372)

Factors reflecting aspects of QoL	Total c (95% CI)	Girls c (95% CI)	Boys c (95% CI)
Do not feel good, confident, happy	0.140 (-0.015-0.295)	**0.256** **(0.043-0.468)**	0.003 (-0.222 - 0.229)
Sad, anxious, angry	n.s.	n.s.	n.s.
Problems with sleep	**0.274** **(0.143-0.405)**	**0.240** **(0.063-0.417)**	**0.313** **(0.119-0.507)**
Problems with peers at school	**0.329** **(0.136-0.523)**	**0.438** **(0.201-0.675)**	0.285 (-0.017- 0.587)
Problems with physical activity	-0.124 (-0.302 - 0.054)	**0.244** **(0.027-0.460)**	0.011 (-0.218-0.240)
Problems with walking and cycling/food	0.038 (-0.031-0.108)	-0.036 (-0.231-0.158)	0.218 (0.010-0.427)
Problems with food at school	-0.177 (-0.361-0.007)	n.s.	n.s.

c: coefficient, 95%CI: 95% confidence interval, *Adjusted for sex, year of birth, **Adjusted for year of birth. Similar results if additionally adjusted for parental occupation, allergy, attention-deficit disorder. n.s.: not statistically significant (p≥0.05)

Grade 4 class

The factor 'Do not feel good, confident, happy' had a positive coefficient in girls with AD (c 0.298 95%CI 0.059-0.537) while no statistical significance was found for boys with AD in the same age group (c: -0.272, 95%CI: -0.542-0.001). The factors 'No confident with my body/myself -Problems with peer relations' (c: 0.187, 95%CI: 0.003-0.371) 'Problems with physical activity' (c:0.329, 95%CI: 0.136-0.523) and 'Sleeping problems/anxious' (c 0.329, 95% CI: 0.140-0.508) were positively associated with AD indicating that pupils of this age group were less confident with their bodies and experienced more often problems with peer relations, physical activities and sleeping problems compared with peers without AD (**Table 13**).

Table 13: Factor analysis on the relationship between atopic dermatitis and aspects of quality of life of children in Grade 4 class (n= 2,241)

Factors reflecting aspects of QoL	Total c (95% CI)	Girls c (95% CI)	Boys c (95% CI)
Do not feel good, confident, happy	0.048 (-0.131-0.227)	**0.298 (0.059-0.537)**	-0.272 (-0.542-0.001)
Sad, anxious, angry	n.s.	n.s.	n.s.
Problems with concentration, behavior, friends	n.s.	n.s.	n.s.
Not confident with my body and myself, Problems with peer relations	**0.187 (0.003-0.371)**	**0.275 (0.012-0.538)**	0.062 (-0.195-0.318)
Problems with physical activity	**0.329 (0.136-0.523)**	**0.352 (0.104-0.600)**	0.297 (-0.009-0.603)
Sleeping problems/anxious	**0.329 (0.140-0.508)**	**0.397 (0.167-0.627)**	0.233 (-0.051-0.517)

c: coefficient, 95%CI: 95% confidence interval, *Adjusted for sex, year of birth, **Adjusted for year of birth. Similar results if additionally adjusted for parental occupation, allergy, attention-deficit disorder.
n.s.: not statistically significant (p≥0.05)

Grade 7 class

Crude and adjusted analyses for parental occupation, other allergies, and ADHD showed that the factors 'Problems with peer-relationships' (c:0.401, 95% CI: 0.134-0.667) 'Problems with swimming' (c:0.302, 95% CI: 0.034-0.570) 'Depressive mood' (c:0.361 95% CI: 0.173- 0.549) were significantly associated with self-reported AD in pupils with AD. The factor 'Do not feel good, confident and happy' was positively correlated with AD in girls in this age group (c: 0.694, 95% CI: 0.296-1.091) (**Table 14**).

Table 14: Factor analysis on the relationship between atopic dermatitis and aspects of quality of life of children in Grade 7 class (n=1851)

Factors reflecting aspects of QoL	Total c (95% CI)	Girls c (95% CI)	Boys c (95% CI)
Do not feel good, confident, happy	0.112 (-0.155-0.380)	**0.694 (0.296-1.091)**	-0.457 (-0.812 – 0.102)
Problems with peer-relationships	**0.401 (0.134-0.667)**	**0.883 (0.502-1.26)**	- 0.650 (-0.436 – 0.306)
Problems with swimming	**0.302 (0.034-0.570)**	0.308 (-0.069 -0.685)	0.223 (-0.159 – 0.605)
Sleeping problems	0.265 (-0.003-0.533)	-0.084 (-0.442-0.273)	0.389 (-0.011-0.789)
Depressive mood	**0.361 (0.173-0.549)**	**0.438 (0.201-0.675)**	0.285 (-0.018-0.587)
Difficulties with school tasks	-0.275 (-0.542 – 0.007)	-0.461 (-0.853 – 0.070)	-0.094 (-0.461 – 0.273)

c: coefficient, 95%CI: 95% confidence interval, *Adjusted for sex, year of birth, **Adjusted for year of birth. Similar results if additionally adjusted for parental occupation, allergy, attention-deficit disorder. n.s.: not statistically significant (p≥0.05)

Compulsory education class 1

The factors ‘Problems with physical activity and peer relationships’ (c: 0.231 95% CI: 0.015-0.447) ‘Not confident with my body, myself, having problems with peer relations’ (c: 0.187, 95% CI: 0.003-0.371) were statistically significant correlated with AD in pupils of this age group. Interestingly the factor ‘Do not feel good, confident, happy’ was positively associated to AD in girls of this age group (c: 0.389, 95% CI: 0.115-0.663) but negatively associated to AD in boys (c -0.404, 95% CI: -0.745 to -0.063) (**Table 15**).

Table 15: Factor analysis on the relationship between atopic dermatitis and aspects of quality of life of children in Compulsory education Grade 1 (n=1779)

Factors reflecting aspects of QoL	Total c (95% CI)	Girls c (95% CI)	Boys c (95% CI)
Do not feel good, confident, happy	0.124 (-0.091-0.340)	**0.389** **(0.115-0.663)**	**-0.404** **(-0.745 to -0.063)**
Problems with relationships with adults	n.s.	n.s.	n.s.
Problems with physical activity and peer relationships	**0.231** **(0.015-0.447)**	**0.455** **(0.179-0.730)**	-0.191 (-0.535 – 0.152)
Not confident with my body and myself, Problems with peer relations	**0.187** **(0.003-0.371)**	**0.275** **(0.012-0.538)**	0.062 (-0.195-0.318)
Feeling Anxious	n.s.	n.s.	n.s.
Feeling bad and afraid	n.s.	n.s.	n.s.

c: coefficient, 95%CI: 95% confidence interval, *Adjusted for sex, year of birth, **Adjusted for year of birth. Similar results if additionally adjusted for parental occupation, allergy, attention-deficit disorder. n.s.: not statistically significant (p≥0.05)

Discussion

This doctoral dissertation comprises four complementary population-based studies investigating various aspects of atopic dermatitis (AD) across different age groups and populations, with particular emphasis on quality of life (QoL), burden of disease, mental health comorbidity, and long-term socioeconomic outcomes. The studies collectively provide comprehensive insights into how AD affects individuals from childhood through adulthood, encompassing both immediate effects on daily functioning and long-term outcomes.

Principal Findings Across Studies

The first study demonstrated that AD affects approximately 14% of Swedish adults, with significant associations with mental health comorbidity, educational attainment, and socioeconomic position. Adults with severe AD had substantially increased risk for severe depression (adjusted relative risk ratio (aRRR) 5.62, 95% CI 4.10–7.71) and severe anxiety (aRRR 6.22, 95% CI 4.60–8.42). Importantly, persons with severe AD were less likely to have a university degree (aRRR 0.55, 95% CI 0.34–0.90) and more likely to have lower annual income compared with individuals without AD. The study calculated disability-adjusted life years (DALYs) of 526.68 per 100,000 population, comparable to the burden of diabetes in European countries.

The second study, a longitudinal investigation of 205,394 Swedish men born 1952–1956 who underwent military conscription assessment, revealed that AD in late adolescence was associated with increased risk of antidepressant and anxiolytic medication in middle age (adjusted hazard ratio [aHR] 1.49, 95% CI 1.28–1.74), with a dose-response relationship by severity. Despite this increased mental health burden, AD was not associated with disadvantage in occupational socioeconomic group, income from work, or unemployment benefits. Men with mild AD actually showed lower risk of holding routine and lower technical occupations, suggesting possible selection of occupation or residual socioeconomic confounding.

The third study validated a novel questionnaire for assessing itch prevalence and characteristics in paediatric populations and investigated the prevalence of itch in German schoolchildren aged 6-10 years, establishing that itch—the cardinal symptom of AD—is highly prevalent in the paediatric population (approximately 26% reported itch, with 20% experiencing acute itch and 15% chronic itch) and significantly affects children's daily activities, sleep (mean 2.57, SD 1.21), and mood (mean 2.63, SD 0.94). The study demonstrated that even among children without diagnosed AD, itch represents a substantial burden, highlighting the importance of symptom-based assessments alongside disease diagnoses.

The fourth study investigated quality of life across different age groups and by sex in 9,227 Swedish schoolchildren aged 6–17 years. Using factor analysis, the study identified distinct QoL domains that are particularly relevant to children with AD, including emotional wellbeing ("Do not feel good, confident, happy"), peer relationships, physical activity participation, sleep problems, and body image. Importantly, the study revealed age- and sex-specific patterns. Boys and girls in preschool class with AD had more often sleeping problems (c: 0.274 95%CI 0.143-0.405) compared to children without AD. Teenage girls with AD were less confident with their bodies (c: 0.187 95% CI 0.003-0.371) and experienced problems with physical activities and peer relationships (c: 0.231 95%CI 0.015-0.447) compared to peers without AD.

Comparison with Previous Literature

Prevalence and Epidemiology

The prevalence findings across our studies align with and extend existing epidemiological evidence. The adult AD prevalence of 14% in our first study is consistent with recent large-scale population-based studies from the United States (7.2–10.2%) and Europe (2–10%), though at the higher end of this range, which may reflect the known high prevalence in Scandinavian countries. Our finding that approximately one-quarter of adults with AD report adult-onset disease corroborates recent systematic reviews, fundamentally challenging the traditional paradigm of AD as predominantly a paediatric condition.

The low AD prevalence (0.71%) in our conscription cohort likely reflects both the historical period (late 1960s-early 1970s) when AD prevalence was genuinely lower, and potential underascertainment of mild cases during military medical examinations focused on fitness for service.[153] The prevalence of itch (26% total, 15% chronic) in German schoolchildren is novel, as no comparable population-based studies existed previously.[154-155] However, given that AD affects 15–20% of children in Northern Europe and pruritus is a cardinal feature present in over 90% of cases, our findings appear biologically plausible and likely reflect the high burden of AD and other pruritic conditions in this population.[2,3]

Mental Health Comorbidity

Our consistent findings of increased mental health burden across both cross-sectional and longitudinal studies substantially strengthen the evidence base for AD-associated psychiatric morbidity. The magnitude of association we observed between severe AD and depression/anxiety (aRRRs 5.62–6.22) in our cross-sectional study, is considerably larger than most previous reports.[156-163] Our longitudinal study demonstrating that AD in adolescence predicts antidepressant medication 3–4 decades later, with a dose-response by severity, provides stronger evidence for temporal sequence than previous cross-sectional investigations.[157,163,164]

These findings align with recent meta-analyses showing increased risk of depression (odds ratio [OR] 1.99, 95% CI 1.77–2.24) and anxiety (OR 2.19, 95% CI 1.91–2.53) in AD patients.[165-167] The finding that comorbid asthma further amplifies mental health risk (relative excess risk due to interaction [RERI] 1.07 for depression, 0.26 for anxiety) represents a novel contribution, suggesting shared immunological or inflammatory pathways may contribute to psychiatric outcomes beyond the direct burden of visible skin disease.

Socioeconomic Consequences

Our findings regarding socioeconomic outcomes present a more complex picture than suggested by previous literature. The cross-sectional study showing that severe AD is associated with lower educational attainment, income, and occupational status conflicts with our longitudinal study finding no such associations, and even protective effects of mild AD on occupational outcomes. This apparent contradiction may be explained by several factors.

First, cohort effects are substantial: men born in the 1950s experienced very different social and healthcare contexts than adults surveyed in 2017. The availability of effective AD treatments, reduced stigma, and changing occupational structures may all contribute to different life-course trajectories. Second, survival bias and healthy worker effects may operate differently in cross-sectional versus longitudinal designs. Third, our longitudinal cohort was limited to males, while sex differences in both AD and socioeconomic trajectories are well-documented.

Our cross-sectional findings align with a recent Danish cohort study showing that children with AD, particularly severe cases, had lower likelihood of completing higher education, and a systematic review identifying employment difficulties in adult AD patients.[168-169] The longitudinal study's finding that AD patients may select into less physically demanding occupations corroborates occupational dermatology literature documenting job choice influenced by skin disease.

Marital status

The association between AD and marital status has yielded contradictory findings across the two studies presented in this dissertation. In Study I, individuals with AD — particularly those with severe disease — were more often never married and reported greater loneliness compared with those without AD suggesting that the psychosocial burden of AD, including its visible manifestations and associated stigma, may adversely affect partnership formation and social connectedness. These findings were not corroborated in Study II, in which AD in late adolescence was not significantly associated with marital or registered partnership status in adulthood. This discrepancy may reflect a cohort effect: examining groups from different cohorts—defined by variations in birth period, geographic region, or distinct life experiences—may substantially influence study outcomes. In addition, period effects may play a significant role, as prior research has demonstrated that broader temporal contexts, such as historical, social, or environmental conditions, can independently affect observed results.[170-172]

Quality of Life and Functional Impairment

The consistent quality of life impairment documented across our paediatric studies extends previous work in several ways. The validation of itch-specific quality of life assessment in children addresses a recognized methodological gap, as most previous paediatric AD research relied on generic instruments or adult-derived measures. Our finding that itch affects approximately one-quarter of school-aged children, with significant impacts on sleep and mood, quantifies a burden that was previously poorly characterized in population-based samples.

The identification of age- and sex-specific domains of quality of life provides important additional insight in relation to the existing literature.[173-174] Previous studies using the Children's Dermatology Life Quality Index (CDLQI) have shown inconsistent results regarding sex differences.[175-181] Our exploratory factor analysis approach revealed that body image and self-confidence become increasingly important for adolescent girls, while physical activity limitations may be more salient for boys.

The DALY calculation of 526.68 per 100,000 provides the first Swedish national estimate and confirms findings from the Global Burden of Disease study showing AD as the leading cause of disability across skin conditions.[7] The magnitude, comparable to diabetes, supports prioritization in healthcare resource allocation.[182]

Life-course epidemiology of AD

Our studies contribute to understanding AD's natural history by documenting burden across the lifespan from childhood through late adulthood. The persistence of mental health associations into middle age in our longitudinal cohort—with effects of severe AD remaining strong despite presumably many cases achieving clinical remission—suggests that AD may have enduring neuropsychological consequences or that shared risk factors, including genetic and environmental influences, contribute to the overlap between atopic and psychiatric phenotypes.[183-185]

This interpretation aligns with emerging evidence for systemic inflammation in AD, alterations in hypothalamic-pituitary-adrenal axis function, and potential shared genetic architecture between atopic and psychiatric disorders.[23,186-189] However, our studies cannot definitively distinguish whether associations reflect causal effects of AD versus confounding by shared risk factors—a limitation common to most epidemiological investigations of comorbidity.

Methodological Considerations

Strengths

The major strength of this dissertation lies in the complementary use of multiple study designs, data sources, and analytical approaches to address similar questions across different populations and time periods. This triangulation of evidence strengthens confidence in findings that replicate across studies while also revealing important differences that reflect genuine population heterogeneity or methodological considerations.

Population-based sampling in the Swedish adult study (Study I) and German schoolchildren study (Study III) minimizes selection bias common to clinic-based studies, though modest response rates introduce potential for selective participation. The near-complete capture of Swedish males eligible for conscription (Study II) reduces selection bias for this demographic group, at the expense of female representation. The comprehensive school-based sampling in Study IV achieved 98% participation, effectively representing the general paediatric population.

The longitudinal design of Study II provides stronger evidence for temporal sequence than cross-sectional studies, with objective outcome ascertainment (prescription registry data, socioeconomic registers) eliminating recall bias and reporter effects that may inflate associations in studies relying solely on self-report. Follow-up over 30–40 years represents a relatively long-term prospective study of AD outcomes.

The validation of novel instruments for itch assessment (Study III) addresses an important methodological gap and provides tools for future epidemiological research.[190] Factor analysis in Study IV represents a more exploratory, data-driven approach to identifying relevant quality of life domains compared to imposing predetermined questionnaire structures.[191-192]

Finally, the analytical approaches employed, the comprehensive adjustment for confounders across studies, and stratified analyses by age and sex—allowed for nuanced examination of complex relationships and identification of specific vulnerable subgroups.

Limitations

Despite these strengths, several limitations warrant consideration. The cross-sectional designs of Studies I, III, and IV preclude definitive conclusions about causality.[193] Observed associations may reflect effects of AD on outcomes, effects of outcomes on AD diagnosis (reverse causation), or confounding by shared risk factors. For example, depression might increase healthcare-seeking and AD diagnosis. Bidirectional relationships may also exist.[41,42,193]

The reliance on self-reported AD diagnosis (Studies I and IV) or clinical diagnosis at a single timepoint (Studies II, III) rather than validated diagnostic criteria applied by dermatologists represents another limitation. Self-report may lead to both over-diagnosis (misidentification of other skin conditions as AD) and under-diagnosis (failure to recognize mild or past AD). This likely introduces misclassification, though validation studies suggest reasonable sensitivity and specificity for self-reported AD.

The particularly low prevalence in the conscription cohort (Study II) probably reflects both genuine historical differences and underascertainment of mild cases, limiting generalizability.[153] The low prevalence of AD in Study IV (3.63% vs. the expected 15-20%) suggests that under-diagnosis may be a significant issue, possibly because children with mild disease, those in remission, or those with late onset were missed. This under-diagnosis could bias results toward the null hypothesis, suggesting that true differences between groups may be even larger than observed.[41-42]

Response rates of approximately 25–45% in Studies I and III raise concerns about selection bias, though attrition analyses showing only modest differences between responders and non-responders by measured characteristics partially mitigate these concerns. Non-response patterns may differ by AD status and outcomes of interest, potentially biasing associations in either direction. The high response rate (98%) in Study IV effectively eliminates this concern for that investigation.

The lack of AD severity assessment in Study IV limits our ability to examine dose-response relationships or to determine whether observed associations are driven primarily by severe cases. Severity data would have enhanced understanding of which aspects of QoL are affected even by mild disease versus those primarily impacted by severe AD.

The potential for information bias exists in several forms. Social desirability bias may have affected responses to questions about mental health, relationships, and other sensitive topics across studies. However, the use of structured questionnaires and, in Study IV, the opportunity for school nurses to clarify questions likely reduced some forms of information bias.

Residual confounding remains a concern despite adjustment for measured covariates. Unmeasured factors such as detailed family history, childhood adversity, social support networks, and healthcare access may confound observed associations.

Cultural and contextual factors may also limit the generalizability of these findings. Studies I, II, and IV were conducted in Sweden, a country characterized by universal healthcare access and comprehensive social support systems, which may attenuate some of the socioeconomic consequences of AD observed in other settings. The extent to which these findings apply to populations in different healthcare and social contexts therefore remains uncertain. Although Study III, conducted in Germany, introduces some geographical diversity, all four studies were carried out in European countries, and the findings may not fully reflect the burden of AD in lower-income settings or among more ethnically and socioeconomically diverse populations.

Integration of Findings: A Life-course Perspective on AD

Taken together, these four studies provide a broad life-course perspective on AD and its multifaceted impacts. Several overarching themes emerge:

The Persistent Burden of AD Across the Lifespan

The findings challenge the traditional view of AD as a transient childhood condition. AD was associated with substantial impairment in adult quality of life (QoL) (Study I), and longitudinal analyses indicate that its effects on life trajectories may persist even when clinical symptoms attenuate (Study II). In childhood, AD affected distinct QoL domains across developmental stages (Study IV), while itch alone imposed significant functional and sleep-related burden regardless of a formal AD diagnosis (Study III). Together, these results support conceptualizing AD as a chronic, life-shaping condition rather than a time-limited disease.

Gender-Specific Patterns Across Development

Gender differences emerged consistently across studies. Adolescent girls with AD experienced greater impairments related to body image, self-confidence, and peer relationships than boys (Study IV), with parallel gender-related differences observed in adulthood (Study I). These patterns likely reflect an interaction between biological factors, including hormonal influences on immune and skin barrier function, and psychosocial mechanisms such as social norms around appearance, coping strategies, and help-seeking behaviour.[194-200] Importantly, these differences appear to emerge during adolescence and may persist into adult life.

Itch and sleep problems as key drivers of burden

Across all age groups, itch—and its impact on sleep—emerged as a central determinant of reduced QoL. Both paediatric (Studies III and IV) and adult data (Study I) identified sleep disturbance as a major contributor to functional impairment. The downstream effects of poor sleep, including cognitive difficulties, mood disturbance, and reduced daytime functioning, likely mediate many of the broader social, educational, and occupational consequences observed. These findings underscore itch control and sleep optimization as core therapeutic targets throughout the life-course.

Long-term Socioeconomic Consequences

While cross-sectional analyses indicated lower income among adults with AD (Study I), longitudinal data did not demonstrate differences in labour market participation or income from work (Study II). Nevertheless, the findings suggest that AD during adolescence may influence occupational patterns and early adulthood outcomes through indirect pathways, including educational disruption, persistent symptoms, and psychosocial effects such as reduced self-confidence. Early difficulties in peer relationships and self-esteem identified in childhood (Study IV) may represent precursors to later socioeconomic vulnerability.

Clinical and Public Health Implications

The findings of this dissertation have several important implications for clinical practice and public health policy.

In younger children, management should prioritize itch control and sleep optimization. During adolescence—particularly for girls—care should increasingly address psychosocial concerns related to body image, peer relationships, and emerging intimacy. In adulthood, comprehensive management addressing both physical symptoms and psychosocial functioning, including work-related impairment, remains essential.

Longitudinal findings demonstrate that the impact of AD extends beyond active disease periods and may influence educational, occupational, and psychosocial outcomes into middle age. These results highlight the importance of long-term follow-up, attention to educational and occupational development, and access to psychological support, particularly for individuals with severe disease or comorbid atopic conditions.

The identification of psychosocial domains inadequately captured by existing quality-of-life instruments suggests a need to expand AD-specific assessments to better reflect body image, self-esteem, and relationship concerns. Furthermore, evidence that itch-related burden extends beyond diagnosed AD supports symptom-based public health approaches aimed at early identification and management of chronic itch in paediatric populations.

Finally, the observed associations with mental health comorbidity, healthcare utilization, and functional impairment indicate that investment in effective, multidisciplinary AD care may yield substantial long-term benefits through improved quality of life, reduced healthcare costs, and enhanced educational and occupational productivity. The population-level burden—comparable to major chronic diseases such as diabetes—provides strong justification for prioritizing AD in healthcare resource allocation and policy development.

Future Research Directions

This dissertation identifies several critical priorities for future investigation. Prospective longitudinal studies with repeated assessments of AD severity, mental health, and functional outcomes across the lifespan are essential to establish causal relationships and clarify mechanisms linking AD to psychiatric comorbidity and impaired functioning. Understanding sex-specific disease trajectories warrants particular attention. Most critically, randomized controlled trials must determine whether early intensive AD treatment prevents long-term mental health and socioeconomic consequences, and whether integrated dermatological-psychological care models yield superior outcomes compared with conventional skin-directed approaches.

Methodological advances are needed to develop age-appropriate quality-of-life instruments capturing domains revealed in this research—including body image, self-confidence, and relationship functioning—that current measures inadequately address. Given the substantial population burden documented here, health economic analyses evaluating the cost-effectiveness of intensive treatment strategies would provide essential evidence for healthcare resource allocation and policy formulation

Summary of conclusions

This thesis demonstrates that atopic dermatitis represents a substantial public health burden extending far beyond skin manifestations, affecting mental health, quality of life, and potentially socioeconomic trajectories across the lifespan. The findings establish that AD affects approximately 14% of Swedish adults, challenging traditional conceptualizations of AD as predominantly a paediatric condition.

The consistent and robust associations between AD and mental health comorbidity—particularly anxiety and depression—documented across both cross-sectional and longitudinal studies establish psychiatric morbidity as a core feature requiring clinical attention. The magnitude of these associations increases with disease severity. These findings support routine mental health screening in AD patients and development of integrated care models addressing both dermatological and psychological dimensions of disease.

The impact of AD varies substantially by age, sex, and disease severity. Younger children primarily experience burden through itch-related sleep disturbance and activity limitations, while adolescents—particularly females—face additional challenges related to body image, self-confidence, and peer relationships. These developmental patterns necessitate age-appropriate and sex-specific clinical approaches, with existing quality-of-life instruments potentially inadequately capturing adolescent-specific concerns around body image and intimate relationships.

The relationship between AD and socioeconomic outcomes appears complex and context-dependent. Cross-sectional evidence demonstrates associations between severe AD and lower educational attainment, income, and occupational status in contemporary adults, while longitudinal data from an earlier birth cohort shows no such disadvantage. This discrepancy likely reflects cohort effects related to evolving treatment availability, social attitudes, and support structures, suggesting that socioeconomic consequences may be modifiable through appropriate medical and social interventions rather than representing inevitable outcomes.

The population-level burden of AD, estimated at 526.68 DALYs per 100,000—comparable to diabetes—establishes this condition as a major public health priority warranting investment in prevention research, treatment development, and healthcare system capacity. These findings challenge perceptions of AD as a minor cosmetic concern and provide empirical justification for prioritizing AD in healthcare resource allocation decisions and policy development.

Taken together, these studies advance understanding of AD's impacts across the life-course and provide evidence to support more comprehensive, personalized, and long-term approaches to AD management. The findings have implications for clinical practice, healthcare policy, and public health approaches, while also identifying important questions for future investigation. By illuminating the breadth and persistence of AD's impacts, this work contributes to a fuller understanding of the disease burden and the need for effective interventions across all life stages.

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