Atopic dermatitis in infancy

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Table of Contents

1 Preface

Acknowledgments

The research on which this thesis is based, has been performed within the PreventADALL project and the ORAACLE Research Group at the Department of Pediatric and Adolescent Medicine at Oslo University Hospital. For three years I was a research fellow with grants from *ExtraStiftelsen Helse og Rehabiltering* (now *Stiftelsen Dam*) and later a clinical research fellow in dermatology at the Institute of Clinical Medicine, the University of Oslo and a senior consultant at the Department of Dermatology, Oslo University Hospital. I am grateful for these institutions for giving me the opportunity to explore atopic dermatitis in a scientific way.

First and foremost, I will state my deepest gratitude to all study participants in the PreventADALL project, both infants and their caregivers, for their time and effort in making the PreventADALL trial and this thesis possible.

Linn Landrø, associate professor and senior consultant in dermatology, has been my main supervisor. I am grateful to Linn, with whom I share an office at Rikshospitalet, for her dedication and hard work. As one of the key researchers in the early phase of the PreventADALL project, she could always be counted on when I needed her advice on my data and analysis. She has steadily guided me through the PhD process with no significant disagreements. I hope we can continue to share an office for many years to come!

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of clarifying things. She always turns the perspectives to the better. I highly value and respect her opinion. I am also grateful to have met and collaborated with her late husband, the always warm and welcoming *Kai-Håkon Carlsen*.

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My motivation to become a dermatologist derives from first-hand experience with atopic dermatitis within my family. This motivation became even more prominent after inspiring teaching by *Ole Fyrand* and his colleagues at Rikshospitalet during my medical studies. I did my hospital internship at Vestfold Hospital in Tønsberg. After completing two years of internal medicine there, I started as a resident at the Department of Rheumatology, Oslo University Hospital in 2011. I am very grateful that *Inge-Margrethe Gilboe* granted me this opportunity and the years I shared with great colleagues in rheumatology. In 2013, I switched to dermatology, first as part of an internal exchange program. The head of the Department Dermatology at the time, *Jan-Øivind Holm*, said during my introduction on my first day: “We shall see if the dermatitis keeps him here”. And I guess that is what happened. Some years later, Jan-Øivind sent me an email and warmly recommended joining a research team at Ullevål Hospital that aimed to prevent atopic disease. The rest is history. Thank you, Jan-Øivind!

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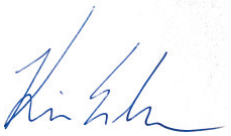
Oslo, June 2022



Kim M.A.S. Endre

Summary

Background

Atopic dermatitis (AD) is characterized by a chronic relapsing and itchy rash. The etiology is complex, and several predisposing genes and gene mutations have been identified. The observed rise in global prevalence suggests important contributions from environmental risk factors. The first symptoms often occur during infancy but may be unspecific. Data on potential sex specific variations, i.e. concerning risk factors and clinical presentation in early life, are largely lacking.

Aims

In this thesis, the aims were to identify early risk factors for AD, prevalence and persistence of AD during infancy, and the validity for established AD criteria used in infants. We also aimed to identify potential sex-specific variations on the risk, prevalence and clinical presentation of AD during infancy.

Methods

The study cohort consisted of infants in the Preventing Atopic dermatitis and Allergies (PreventADALL) study, which is a general population-based randomized controlled trial investigating whether allergic disease can be prevented by early skin care, early food introduction or a combination of the two. Pregnant women at 18 weeks of gestation (n = 2697) were recruited from three separate geographical locations, in Norway and Sweden, between December 2014 and October 2016. Their babies (n = 2397) were enrolled at birth. For aims addressing early risk factors for AD we included all infants who were not randomized to early skin care intervention, and with clinical data available from the 3- and 6-months clinical follow-ups and information on risk factors from electronic questionnaires (n=1150 in Paper I; n=1155 in Paper II). For aims addressing prevalence, clinical presentation and diagnosis of AD, we included all infants, regardless of intervention allocation, with available data from the clinical follow-ups at 3, 6 and 12 months (n = 1834). Information on risk factors, including

history of parental atopic disease, was collected in electronic questionnaires which were sent to the mothers at enrolment and at 30 weeks of pregnancy. For the studies on infants up to 6 months of age, we used outcome eczema (paper I) and *possible AD* (paper II) as proxies for AD. Eczema was defined as the presence of eczematous lesions, clinically excluding common differential diagnosis to AD. *Possible* AD was defined as eczema with the addition of parentally reported itchy rash lasting for more than 4 weeks. For the studies including all infants up to 12 months of age (Paper III and IV), we reserved the term AD for those who fulfilled the diagnostic AD criteria, i.e. the UK Working Party (UKWP) and/or the Hanifin & Rajka criteria (H&R; applied at the 12 months visit only). Skin assessments of the infants at the clinical follow-ups were performed by trained personnel.

Results

Maternal allergic disease, multiparity and birth by elective caesarean section were risk factors for AD at 3 months of age. Dry skin at 3 months of age increased the risk of AD by 6 months of age (Paper I). Parental AD increased the risk of AD by 6 months of age, particularly in offspring of matching sex of the affected parent (Paper II). A total of 628/1834 (34%) of all infants had eczema observed during infancy, of whom 212/628 (34%) fulfilled either of the two diagnostic sets of criteria for AD. Those with eczema present at 3 months as well as those with eczema on more than one follow-up visit were most likely to fulfil the criteria. About one third of infants fulfilled only one of the two diagnostic criteria sets at age 12 months. More boys than girls had eczema and AD during infancy. The clinical presentation varied between boys and girls, with more boys having eczema on the cheeks during infancy, and more girls than boys having eczema on flexor sites of the extremities at age 3 months. The trunk was a predilection site for eczema in infants, regardless of sex.

Interpretations

Atopic dermatitis in parents increased the risk of AD in offspring, mostly in infants with corresponding sex to that of the affected parent. This may be relevant for risk assessments and future genetic studies. Also, birth by elective

caesarean section increased the risk of AD, supporting the benefit of vaginal birth over caesarean section. More boys than girls had AD during infancy and the clinical distribution of eczema differed by sex, indicating possible differential disease mechanisms for AD presenting in early life.

A diagnosis of AD is challenging to confirm using present diagnostic criteria in infants. Applying both sets of criteria and at multiple timepoints may be appropriate for diagnosing AD in infants and useful in clinical research.

Sammendrag på norsk

Bakgrunn

Atopisk dermatitt (AD) kjennetegnes ved kronisk, tilbakevennende og kløende utslett. Etiologien er sammensatt og flere disponerende gener og genmutasjoner er identifisert. Den økte forekomsten i store deler av verden kan delvis forklares med ulike miljøfaktorer. Sykdommen debuterer gjerne tidlig i barndommen, men symptomene kan da være lite spesifikke. Kjønnsspesifikke variasjoner vedrørende risikofaktorer og klinisk presentasjon er i liten grad studert.

Målsetning

Vi ønsket å påvise risikofaktorer for utvikling av AD i spedbarnsalder, forekomst og persistens av eksem og AD i første leveår, samt å undersøke grunnlaget for diagnostisering av AD hos spedbarn. Vi ønsket også å identifisere potensielle kjønnsspesifikke mønstre knyttet til risiko, forekomst og klinisk presentasjon.

Metode

Studiekohorten ble hentet fra *Preventing Atopic Dermatitis and Allergies (PreventADALL)*-studien, som er en populasjonsbasert randomisert kontrollert studie med hovedmål å undersøke om allergisk sykdom kan forebygges ved tidlig hudpleie og/eller matintroduksjon. Gravide kvinner i 18. svangerskapsuke (n = 2697) ble rekruttert fra tre forskjellige geografiske steder i Norge og Sverige mellom desember 2014 og oktober 2016. Deres barn (n = 2397) ble inkludert ved fødselen. For studiene på tidlige risikofaktorer for AD (artikkel I og II) inkluderte vi alle spedbarn som ikke var randomisert til tidlig hudpleie og med kliniske data fra 3 og 6 måneders kontroll, og som hadde informasjon om mor og fars sykehistorie (n=1150 artikkel I; n=1155 artikkel II). For studiene på diagnostisering av AD og klinisk presentasjon (artikkel II og III) inkluderte vi alle spedbarn, uavhengig av intervensjonsgruppe, med tilgjengelige data fra klinisk kontroll ved 3, 6 og 12 måneders alder (n = 1834). Informasjon om risikofaktorer,

inkludert foreldrenes atopiske sykdom, ble innhentet via elektroniske spørreskjemaer sendt til mødrene ved innrullering i studien og 30. svangerskapsuke. For studiene som kun inkluderte barn opptil 6 måneders alder ble eczema, dvs. observert eksem med klinisk ekskludering av differensialdiagnoser til AD (artikkel I) og *possible* AD, definert som eczema med tillegg av kløende utslett i minst 4 uker rapportert av foreldre (artikkel II), brukt som utfallsmål og substitutter for AD. For studiene som inkluderte barn opptil 12 måneders alder, uavhengig av intervensjonsgruppe (artikkel III og IV), ble diagnosen AD forbeholdt dem som oppfylte de diagnostiske kriteriene for AD i henhold til United Kingdom Working Party (UKWP) og/eller Hanifin & Rajka kriteriene (H&R; kun brukt ved 12 måneders alder). Ved de kliniske kontrollene ble huden til barna vurdert av studiepersonell med særskilt opplæring i vurdering av spedbarnshud og de diagnostiske kriteriene for AD.

Resultater

Allergisk sykdom hos mor, flere fødsler tidligere og fødsel ved planlagt keisersnitt var risikofaktorer for AD ved 3 måneders alder (artikkel I). Tørr hud ved 3 måneders alder økte risiko for AD ved 6 måneders alder. Atopisk dermatitt hos foreldre økte risiko for AD hos barnet ved 6 måneders alder, spesielt hos avkom med samme kjønn som affisert forelder (artikkel II). Totalt 628/1834 (34%) av alle barna hadde eksem i løpet av spebarnstiden, hvorav 212/628 (34%) oppfylte minst ett av de to settene med diagnostiske kriterier for AD. Barna med eksem ved 3 måneders alder versus senere samt barna med eksem på mer enn én av kontrollene oppfylte oftere de diagnostiske kriteriene. Omtrent en tredel av barna ble diagnostisert med bruk av kun ett av de to settene når disse ble brukt samtidig ved 12 måneders alder. Flere gutter enn jenter hadde både eksem og AD i første leveår. Den kliniske presentasjonen varierte mellom gutter og jenter. Flere gutter enn jenter hadde eksem på kinn første leveår, og flere jenter enn gutter hadde eksem på bøyesider av armer og bein ved 3 måneders alder. Trunkus var et predileksjonssted for AD hos begge kjønn.

Fortolkning

Atopisk dermatitt hos mor eller far øker risiko for AD hovedsakelig hos barn med samme kjønn som affisert forelder. Dette kan danne grunnlag for risikovurderinger basert på kjønn og videre genetiske studier. Økt risiko for AD ved planlagt keisersnitt understreker fordelen ved vaginal fødsel versus keisersnitt. Flere gutter enn jenter hadde AD i løpet av spedbarnsperioden, og utbredelse av eksem på kroppen varierte mellom gutter og jenter. Dette kan tyde på ulike sykdomsmekanismer for AD hos gutter og jenter tidlig i livet.
Det kan være vanskelig å diagnostisere AD i spedbarnsalder. Anvendelse av begge kriteriesettene på flere tidspunkter gjennom første leveår kan være en nyttig fremgangsmåte i forskningssammenheng.

Abbreviations

AD	Atopic dermatitis
pAD	Possible atopic dermatitis
DLQI	Dermatological Life Quality Index
DASI	Dry skin/Ichthyosis and Severity Index
EASI	Eczema Severity and Area Index
UKWP	United Kingdom Working Party criteria for atopic dermatitis
H&R	Hanifin & Rajka's criteria for atopic dermatitis
HOME	Harmonizing Outcome Measures for Eczema
NMF	Natural moisturizing factor
OR	Odds Ratio
POEM	Patient Oriented Eczema Measure
RCT	Randomized controlled trial
SCORAD	Scoring Atopic Dermatitis Index
TEWL	Transepidermal Water Loss

List of papers

Paper I

Rehbinder EM, Endre KMA, Lødrup Carlsen KC, Asarnoj A, Stensby Bains KE, Berents TL, Carlsen KH, Gudmundsdóttir HK, Haugen G, Hedlin G, Kreyberg I, Nordhagen LS, Nordlund B, Saunders CM, Sandvik L, Skjerven HO, Söderhäll C, Staff AC, Vettukattil R, Værnesbranden MR, Landrø L.

Predicting Skin Barrier Dysfunction and Atopic Dermatitis in Early Infancy.

J Allergy Clin Immunol Pract. 2020 Feb;8(2):664-673.e5. doi: 10.1016/j.jaip.2019.09.014.

Paper II

Endre KMA, Rehbinder EM, Carlsen KL, Carlsen KH, Gjersvik P, Hedlin G, Jonassen CM, LeBlanc M, Nordlund B, Skjerven HO, Staff AC, Söderhäll C, Vettukattil R, Landrø L.

Maternal and paternal atopic dermatitis and risk of atopic dermatitis during early infancy in girls and boys.

J Allergy Clin Immunol Pract. 2020 Jan;8(1):416-418.e2. doi: 10.1016/j.jaip.2019.06.039.

Paper III

Endre KMA, *Landrø L, *LeBlanc M, Gjersvik P, Lødrup Carlsen K, Haugen G, Hedlin G, Jonassen CM, Nordlund, Rudi K, Skjerven HO, Staff AC, Söderhäll C, Vettukattil R, Rehbinder EM.

Diagnosing atopic dermatitis in infancy using established diagnostic criteria: a cohort study.

Br J Dermatol. 2021 Jan 28. doi: 10.1111/bjd.19831. Online ahead of print.

PMID: 33511639.

*Contributed equally.

Paper IV

Endre KMA, *Landrø L, *LeBlanc M, Gjersvik P, Lødrup Carlsen K, Haugen G, Hedlin G, Jonassen CM, Nordlund B, Rudi K, Skjerven HO, Staff AC, Söderhäll C, Vettukattil R, Rehbinder EM.

Clinical distribution of eczema in girls and boys during infancy: A cohort study on atopic dermatitis.

J Allergy Clin Immunol Pract. 2021 May 5:S2213-2198(21)00515-8. doi: 10.1016/j.jaip.2021.04.053. Epub ahead of print. PMID: 33964509.

*Contributed equally.

2 Atopic dermatitis: An introduction

Atopic dermatitis (AD) is the most common inflammatory skin disease worldwide, affecting around one in five.[1,2] Characteristic features include a chronic relapsing and itchy rash and a dry sensitive skin type prone to skin infections.[1,2] The symptoms usually present for the first time in early childhood[1-3] and, combined with time-consuming treatment, often results in reduced quality of life for the patents and their caretakers.[1,2,4,5] In addition, AD has a profound negative impact on national health-care resources and general economy due to frequent medical visits, costly prescriptions, loss of working days and various social benefits.[6,7]

The global disease burden of AD ranks highest of all skin diseases,[8] pointing to the importance of identifying risk factors, prevention strategies as well as tools for early and accurate diagnosis in addition to appropriate medication. The etiology of AD involves a complex interaction between genetic, immunological and environmental factors,[9] with environmental influences probably particularly important when explaining the increase in prevalence seen in many countries over the past decades.[10,11]

Terminology and diagnosis

The oldest known description of an itchy skin condition compatible with AD dates back to Egypt around 1500 B.C.[12,13] Matching descriptions under many different names have since been documented from several regions of the world.[14,15] The present nomenclature derives from early 19th century, starting with Willan & Bateman introducing the term *eczema*, derived from Greek *ekzeein*: “to boil out”.[14] Soon after, Coca & Cooke introduced the term *atopy*, from Greek *atopia*: “out of place”, to describe a tendency towards allergic reactions which had been recorded in many patients.[14] A decade later, the term

atopic dermatitis was introduced by Wise & Sulzberger in 1933.[14] Although widely accepted and adopted for clinical use, other names, most common being atopic eczema (AE) or just plain eczema, are still in use. Other synonyms for atopic dermatitis are presented in Table 1.

The lack of nomenclature consensus has resulted in an ongoing debate in dermatological and pediatric circuits. In 2004, the World Allergy Organization (WAO) proposed the use of *eczema* for cases with unknown IgE-sensitization status, and *atopic eczema/dermatitis* for cases with confirmed sensitization.[16] This definition is in line with a susceptibility for IgE-sensitization being a denominator for all atopic diseases: AD, asthma, food allergy and allergic rhinitis. However, this nomenclature has not been widely accepted and is criticized for being overly complicated and confusing for both patients and physicians.

A 2016 review of more than 33.000 publications from the period 1945 – 2016 found the term *atopic dermatitis* to be more frequently used than *atopic eczema* or just *eczema*.[17] In a survey among 77 prominent AD researchers, atopic dermatitis (AD) was preferred over atopic eczema.[18] As a result, atopic dermatitis is generally considered the recommended term when conducting research, although atopic eczema or just eczema, might be easier to understand and more useful when communicating with patients and their caretakers.[19] In the *Preventing Atopic Dermatitis and Allergies (PreventADALL)* study,[20] and the present dissertation, AD and eczema are used with different meaning; AD is reserved for those fulfilling the diagnostic AD criteria and eczema as having an eczematous rash compatible with AD.

Table 1:
Synonyms for atopic dermatitis commonly used in Northern Europe until 1980[21]

⇒ Eczema
⇒ Atopic eczema
⇒ Infantile eczema
⇒ Eczéma constitutionnel
⇒ Flexural eczema
⇒ Prurigo Besnier
⇒ Allergic eczema
⇒ Childhood eczema
⇒ Lichen Vidal
⇒ Endogenous eczema
⇒ Spätexudatives Ekzematoid
⇒ Neurodermatitis (constitutionalis)

Table 2:
Different diagnostic criteria for atopic dermatitis used in randomized controlled trials[22]

⇒ Hanifin and Rajka
⇒ UK Working Party
⇒ Japanese Dermatological Association
⇒ American Academy of Dermatology
⇒ Diepgen et al.
⇒ Zhao et al., cited in Bai et al.
⇒ Zhuan et al., cited in Wu et al.
⇒ Korean Atopic Dermatitis Association
⇒ Millennium
⇒ Seymour et al.

Diagnostic criteria for atopic dermatitis

Several diagnostic criteria have been developed in order to classify, diagnose, and differentiate AD from mimicking conditions (Table 2). In 1980, Jon Hanifin and Georg Rajka published their diagnostic criteria, later referred to as the Hanifin & Rajka´s (H&R) criteria.[23] These criteria consists of four major and 23 minor criteria, and a diagnosis of AD requires a minimum of three positive major criteria in addition to at least three positive minor criteria (Table 3). In 1994, United Kingdom Working Party (UKWP) criteria, which were derived and simplified from the H&R criteria, were published.[24] A diagnosis of AD by these criteria requires fulfilling the single major criterion of an itchy skin condition plus three out of four minor criteria (Table 4).

Later, several other AD-criteria have been developed. A 2018 meta-analysis identified 10 different diagnostic criteria for AD used in 212 randomized controlled trials (Table 2).[22] The H&R criteria was most frequently used (41%), with the UKWP criteria (9%) in second place.[22] The authors emphasized a need for harmonizing the diagnostic AD criteria in clinical studies.[22] The H&R and the UKWP criteria both have their strengths and weaknesses. Sensitivity and specificity vary between different validation studies, but are mostly high for both criteria when applied to children after the infancy period and adults.[25]

Few studies have validated the different diagnostic criteria for use in infancy.[24,26,27] Diagnosing AD in infancy, at the time when the disease manifests for the first time in most cases, may be particularly challenging as symptoms may be vague or transient and the cardinal symptom of itch may be lacking or difficult to evaluate.[28] Although eczematous rash is commonly seen in infants, it does not always represent AD. Other common conditions of infancy, such as seborrheic and contact dermatitis and dermatitis associated with immune or nutritional deficiencies , could imitate AD and thus be hard to separate using the existing diagnostic criteria.[29]

Table 3:
The Hanifin and Rajka´s diagnostic criteria for atopic dermatitis.

Hanifin and Rajka's criteria[23,30]
H = History
E = Examination
Atopic dermatitis = 3 major + 3 minor
Major criteria: 1-4
Minor criteria: 5-24

1. Pruritus (H/E)
2. Dermatitis affecting flexural surfaces in children and/or the face and extensors in infants (E)
3. Chronic or relapsing dermatitis (H)
4. Family history of atopic dermatitis, asthma or allergic rhinitis (H)
5. Dry skin (minimum 20% of skin surface) (E)
6. Ichthyosis, palmar hyper linearity or keratosis pilaris (E)
7. Hand and/or foot eczema (E)
8. Cheilitis (E)
9. Nipple eczema (E)
10. Tendency toward cutaneous infections (min. 2 episodes with e.g. S. aureus, HSV, viral warts, molluscum contagiosum, fungal infections in the last year) (H)
11. Facial pallor or facial erythema (E)
12. Perifollicular accentuation (E)
13. Pityriasis alba (E)
14. Early age of onset (before 5 years of age) (H)
15. Recurrent conjunctivitis (more than 2 episodes in the last year) (H)
16. Orbital darkening (E)
17. Dennie-Morgan lines (E)
18. Anterior neck folds (E)
19. Eczema deteriorates/exacerbates by emotional and environmental factors (H)
20. Eczema deteriorates/exacerbates by food (intolerance/allergy to food) (H)
21. Eczema/pruritus deteriorates/exacerbates by sweating (H)
22. Eczema deteriorates/exacerbates by wool (intolerance to wool) (H)
23. White dermographism (E)
24. Positive skin prick test now or before (more than 3mm) (H)

Table 4:
*The UK **Working Party criteria from 1994, modified for use in infancy.***

UK Working Party criteria, modified for use in infancy[24]

A positive diagnosis of atopic dermatitis is made if Pt1 + at least 3 out of Pt2-5.

1. Itchy skin condition, minimum 4 weeks (relapsing or chronic)
2. Previous history of rash in skin creases (elbows, knees, ankles, neck) or on extensor surfaces of arms/legs
3. Allergic rhinitis and/or asthma in patient and/or atopic disease in first degree relative
4. Dry skin since birth
5. Visible flexural dermatitis and/or visible dermatitis on cheeks, arms/legs

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Epidemiology

The reported prevalence of AD vary greatly around the globe. In 2009, the International Study of Asthma and Allergy in Childhood (ISAAC) study reported a survey-based prevalence of AD in children aged 6-7 years in 60 different countries and in children aged 13-14 years in 96 different countries.[31] The prevalence varied from 0.9% in India to 22.5% in Ecuador for children 6-7 years and 0.2% in China to 24.6% in Columbia for children 13-14 years.[31]

During the last three decades, the AD incidence has been rising in most high-income countries, but now seems to have plateaued around 15-20%, including in the Nordic countries.[32-34] At the same time, countries where prevalence used to be low, i.e. low-income countries, experience the greatest increase in prevalence.[31] Prevalence also vary within countries, depending on demographic variables and ethnicity composition; thus comparing epidemiological studies is challenging. Also, study design and outcome definitions differ, e.g. survey versus clinical data and diagnosis of AD from questionnaires, clinical judgment or diagnostic criteria. A considerable variation in diagnostic criteria leads to further challenges in description of AD epidemiology.[25]

Prevalence also vary with age and sex.[35] In most cases, AD debuts during infancy.[36] Boys are more frequently affected than girls early in life, but with a reversal of this difference around puberty.[31,35] Many will experience remission during childhood, although the prevalence in the adult population is also high, affecting up to one in ten in the USA.[2,32,37]

Regardless of epidemiological uncertainties listed above, it is safe to conclude that AD is highly prevalent worldwide, affecting both male and females, children and adults in low- and high-income countries.

Etiology and pathogenesis

Atopic dermatitis derives from a complex interplay between genetic, environmental and immunological factors.[1] Genetic factors are strongly in play, and a history of parental atopy, AD in particular, is the strongest known risk factor for developing the disease.[38] If one parent has AD, the risk increases up to 3-fold for AD in offspring, and further up to 5-fold if both parents are affected.[39] The concordance in twin studies is approximately 75%.[40] Also, presence of filaggrin null mutation increases the risk around 3-5 fold.[1,41,42] Evidence also suggest that ethnicity may influence the risk of AD.[43-45]

The marked increase in prevalence over the last 30 years or so points to the importance of environmental factors for the etiology of AD.[46] Numerous environmental factors have been connected to the development of AD, although the results from epidemiological studies are often conflicting. Some of the most consistent risk factors includes urban living,[47] high socioeconomic status and small family size,[48,49] in addition to climate conditions, such as low UV-index, humidity and temperature.[50]

The hygiene hypothesis is often discussed as a possible contributor to the rise in the prevalence of AD. This hypothesis was first introduced by Strachan in 1989 after observation of reduced prevalence of allergic rhinitis in children born into families with increasing number of older siblings.[51] The hypothesis implies that a lack of exposure to certain microorganisms leads to defects in immune tolerance, possibly increasing risk of allergic and some other diseases. The hypothesis is supported by the inverse socioeconomic gradient[52] and decreased prevalence in farming households and larger families,[48] although scientific controversy exists.[53]

The pathogenesis of AD is intricate. Central aspects are skin barrier dysfunction, type 2 immune activity and microbial dysbiosis. The epidermis, the outer layer of the skin, acts as a physical barrier from harmful environmental factors. In

patients with AD, epidermal barrier dysfunction is seen in both affected and unaffected skin.[1] The transepidermal water loss (TEWL) and pH is increased, as is the overall permeability.[54,55] Furthermore, the water retention is reduced[56] and the lipid composition altered.[55]

The cause of this barrier disruption is multifactorial. The filaggrin protein is important for both development and maintenance of an optimal skin barrier function, i.e. by the formation of the corneocytes, that is the flattened, dead cells that forms the outer layer of the epidermis.[57] Also, a natural degradation of the filaggrin protein in the epidermis essentially forms amino acids with water binding, pH-regulating and antimicrobial functions, acting as a natural moisturizing factor (NMF).[58,59] Both filaggrin mutations and environmental factors may contribute to defects in the filaggrin protein and subsequently a disrupted skin barrier,[60] however >50% of those with filaggrin mutations will not develop AD or other atopic disease.[61]

The skin barrier may also be damaged from intensive scratching as well as dysbiosis from the colonization of i.e. *Staphylococcus aureus* and *Malassezia* yeast.[1] Furthermore, immune activity may cause downregulation of genes and lipids, further worsening the underlying barrier defect.[1]

The immunological aspects and cutaneous inflammation are complex and not fully understood. The activation of T lymphocytes is central. A subset of T cells, the helper T cells (Th) are crucial for most adaptive immune responses in humans (Figure 1). Various subsets of helper T cells produce specific signal molecules, i.e. cytokines and interleukins, which contributes to the inflammatory process seen in AD. In an early phase of AD, the inflammatory skin infiltrate is dominated by Th2 cells, whereas chronic lesions may show a mixture between Th1, Th2 and other subtypes.[62] Cytokines and interleukins from Th2 cells in particular contributes to skin barrier dysfunction, i.e. by downregulating filaggrin.[62] Observed changes in unaffected skin of AD patients may show similar immunological patterns with infiltration of T cells, but less profoundly.[1] These

changes may point to underlying immunological changes rather than inflammatory, or presence of subclinical inflammation in seemingly unaffected skin. Other cells associated with inflammation in AD patients are the dendritic cells, innate lymphoid cells and Langerhans cells.[1]

The inflammation process in AD, and specifically the key driver of this process, is not clear. There is an ongoing debate on what comes first: inflammation or the skin barrier impairment. The outside-in hypothesis states than an impaired skin barrier is necessary for the inflammation to occur, and therefor precedes AD.[63] However, the inside-out hypothesis suggests that the inflammation comes first and subsequently leads to or worsen a disrupted skin barrier.[63]

Clinical characteristics

The cardinal features of AD include a chronic, relapsing and pruritic rash, a dry, sensitive skin type and a tendency towards skin infections and allergies.[2] However, as illustrated by the H&R criteria, there are several additional features associated with AD, each being more or less specific or prominent in different AD phenotypes.[30] Associated co-morbidities includes other atopic diseases, such as asthma and allergic rhinitis.[2] However, some studies also suggests an increased risk of cardiovascular diseases, some infectious diseases, certain malignancies, autoimmune diseases, ocular, and neuropsychiatric disease. [64-68]

Age

In the majority of cases, AD debuts in infancy.[3,36,69] In infants, the eczematous lesions are most frequently found in cheeks and extensor surfaces, while older children and adults are more commonly affected on the flexor sites of extremities[2] (Figure 2). The head and neck area and the hands are also commonly affected, particularly in adults.[2] These variations provides a rationale for at least 4 age-related stratifications of phenotypes, presented in 2017 by Bieber et al:[70]

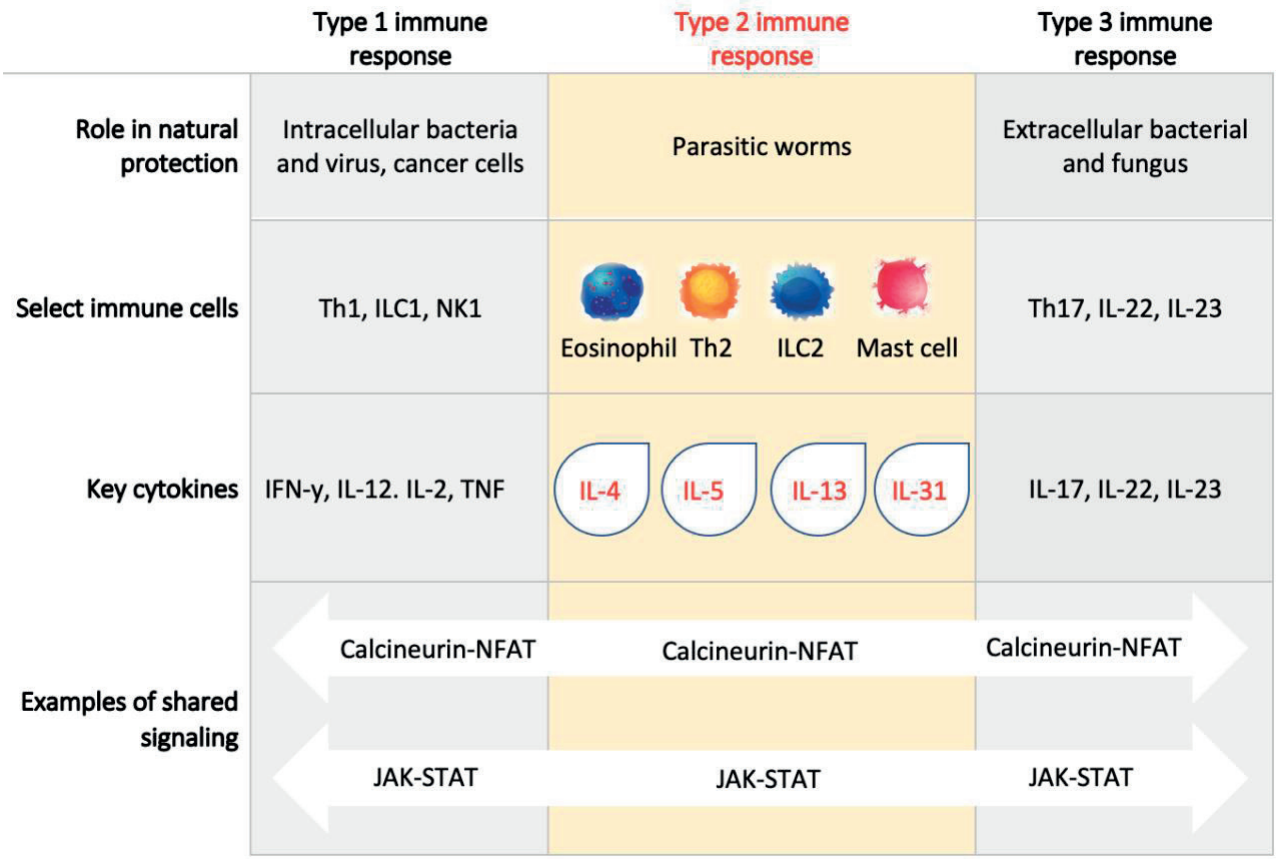

Figure 1:
Showing the three major types of immune response pathways.[71] While Type 1 and 3 immune dysregulated immune response may contribute to diseases such as psoriasis,[71] Type 2 dysregulated immune response may contribute to atopic dermatitis.[2] Figure is based on an illustration by Sanofi Genzyme.[72]

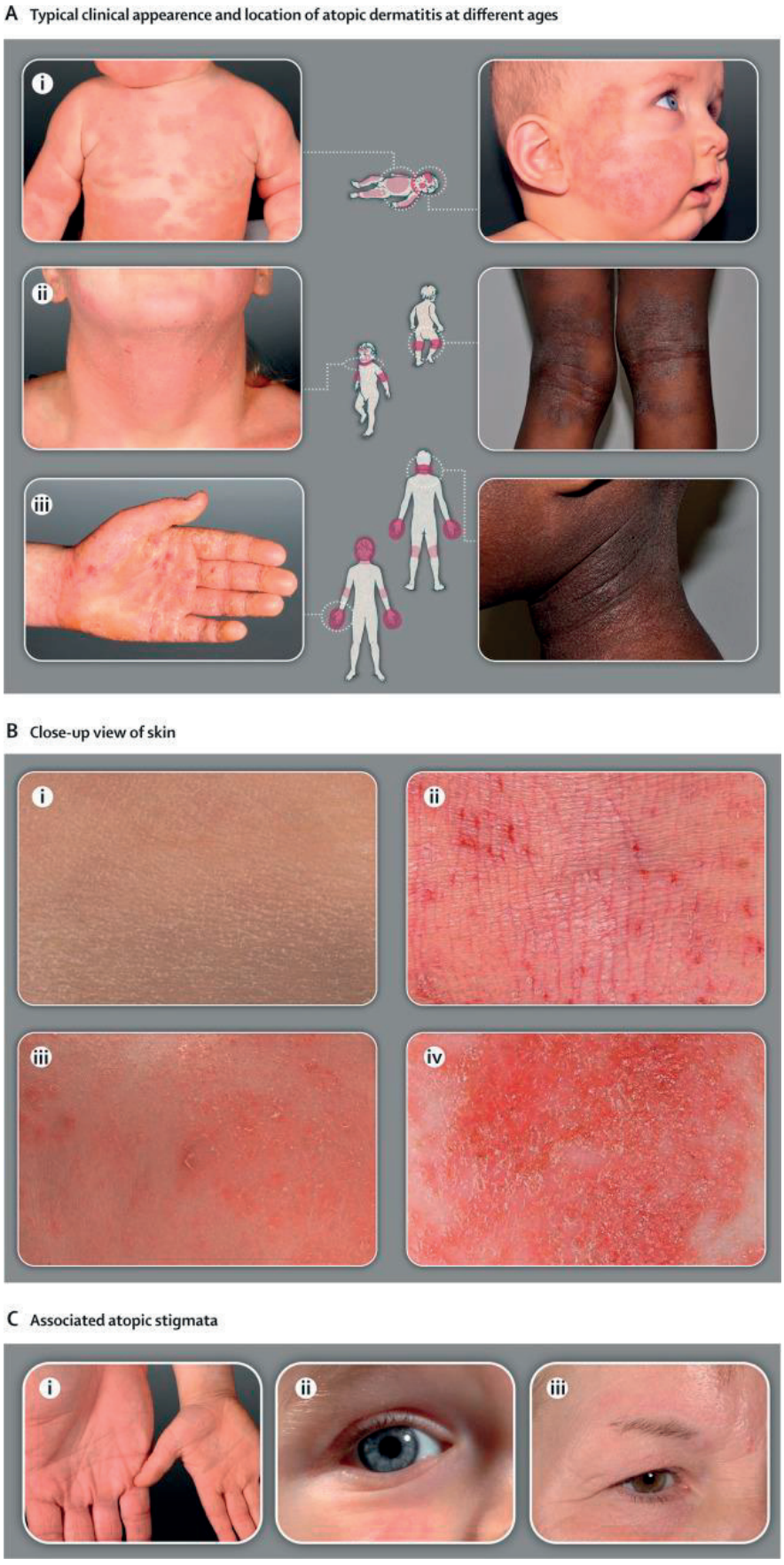

Figure 2:[1] *Typical appearance of atopic dermatitis at various ages (A), close-up views of the skin (B) showing non-lesional (Bi), acute (Bii), subacute (Biii), and chronic (Biv) atopic dermatitis. Some of the associated atopic dermatitis stigmata (C), palmar and plantar hyperlinearity (Ci), Dennie-Morgan infraorbital folds (Cii), and Hertoghe's sign (thinning of the lateral eyebrow) (Ciii) Reproduced by permission from Elsevier. License number 5287160836623*

1. Early or infantile AD (between 3 months and 2 years): Acute lesions, typically starting on the cheeks with erythema, edematous papules and vesicles, oozing and crusting, also extensor surfaces of extremities and trunk, but the diaper area spared. Co-existing cradle crap is common**.**

2. Childhood AD (age 2-12 years): Acute lesions still appearing, but chronic lesions with some lichenification is common. Popliteal and antecubital fossa (flexor sites of extremities) are predilection sites as well as face, typically the periorificial areas. Often are plaques seen, with crusting and oozing on hands and more dominant general xerosis (dry skin).

3. AD in adolescents and adults (age >12 up to 60 years): Typically, the lesions are now more fixed to head/neck, incl. periorbital area, and flexural sites of extremities. Chronic hand dermatitis is common. Some with long standing disease have more generalized erythema.

4. AD in the elderly (age>60 years): This is often a forgotten or underestimated phenotype of AD. Typically characterized by extensive eczematous lesions and/or erythroderma and/or severe pruritus. This phenotype needs further clarification and differentiation from other generalized dermatological disorders of the elderly, e.g. prurigo nodularis, asteatotic eczema and contact dermatitis.

The many features of AD, as listed in the H&R criteria, may be more or less relevant in different age groups. In a study of 221 children at 2 years of age, seeking to determine which features in the H&R criteria a 2 year old children would express, about half of the 29 investigated criteria were met in 3% or fewer of the cases.[30] This indicates that many clinical features are rare or develop over time, hence less relevant for AD occurring in children aged 2 years or under.

Severity

AD can be categorized as mild, moderate and severe based on scoring from validated tools, i.e. Eczema Severity and Area Index (EASI)[73] and the Patient Oriented Eczema Measure (POEM).[74] Both EASI and POEM are recommended as core outcome instruments by the HOME (Harmonizing Outcome Measures for Eczema) initiative,[75] with EASI grading the clinical signs and POEM the patient-reported symptoms. In addition, the Scoring Atopic Dermatitis Index, SCORAD,[76] is frequently used in both trials and clinical practice. When measuring impact on quality of life, Dermatological Life Quality Index (DLQI)[77] is often used. These tools may be useful when conducting clinical research, but also in guiding the physician to an adequate level of intervention.

Ethnicity

The cytokine profile has been shown to differ between Caucasian and Asian patients with AD.[78] Also, filaggrin mutations, a major risk factor for AD in Caucasians, were not found in South African patients with AD.[79] Immunological and genetic variations may manifest clinically in different ways. A tendency of more pronounced lichenification has been seen in AD patients from Asia.[78] Furthermore, filaggrin mutations are associated with early-onset, severe and persistent AD, higher incidence of other atopic diseases, and a predilection for eczema in exposed areas of the skin, especially the hands and cheeks.[80] Features like palmar hyperlinearity and keratosis pilaris are associated with loss of function filaggrin mutations,[81] supporting relevant clinical differences depending on ethnicity and the prevalence of such mutations.

Variations in immunological profile and the clinical characteristics may suggest that AD should not be characterized as one disease, but rather consists of many different diseases.[80] These variations also question the overall validity of the diagnostic criteria for global use.[80]

Sex

Studies exploring potential sex-related patterns of AD are limited. However, a few studies indicate relevant sex-dependent variations. Parental AD has been found to be a major risk factor AD in offspring. Arshad *et al* found evidence of an increased risk of AD in offspring of the same sex as the affected parent.[82] This observation might be explained by an epigenetic phenomenon called imprinting, favoring alleles from father to sons and mother to daughters by silencing alleles from parent of opposite sex.[82] A higher prevalence in boys than in girls has been documented in several studies, but this difference seems to be reversed around the time of puberty.[31,83] This pattern may suggests that sex hormones might play a part in the natural course of the disease.[83]

In terms of severity, a Danish study found self-reported morbidity to be highly consistent in women with AD, however not so in men.[84] Visible areas of AD appeared to affect women significantly more than men with a correlation between DLQI score and disease severity.[84]

Treatment

Although this thesis is not specifically related to therapy, this section is included to provide a complete overview of AD in children.

Treatment of AD is complex and include avoidance of trigger factors, skin barrier repair and maintenance therapy, topical anti-inflammatory treatment and phototherapy and – for severe cases – systemic agents.[1]

Several factors can increase disease activity in patients with AD. Most of these are non-allergic, such as wool and other fabrics, sweat, frequent showering or baths, detergents and alkaline soap, psychological stress and climatic factors, such as cold temperature and low humidity.[50,85-87] Although approximately one in three children with moderate to severe AD have food allergy,[88] it is rarely causative for AD, thus elimination diets are generally not recommended.[89]

Barrier repair and maintenance by frequent applications of moisturizers can improve barrier function, reduce associated xerosis, itch, flair-ups and need of anti-inflammatory medication.[90] Early life treatment with emollients has not been shown to be effective for primary prevention of AD in two large general population based randomized trials: the PreventADALL and the BEEP (Barrier Enhancement for Eczema Prevention) study.[91,92] Emollient therapy from birth did, however, reduce the risk of AD in two smaller studies on neonates at high risk of AD.[93,94]

Topical anti-inflammatory treatment is central in most cases of AD. Depending on age, localization and severity of eczema, topical steroids of appropriate strength and formulation are applied and tapered down for several weeks. Infants may be more prone to systemic uptake and are usually treated with the milder formulations.[89] Topical steroids are generally well tolerated, but fear of side effects is common and should be addressed to secure good adherence to treatment.[95]

Topical calcineurin inhibitors, without the adverse effects associated with steroids, are frequently used as a steroid-sparing agents for long term use, or in sensitive areas of the skin, in all age groups.[89] A topical phosphodiesterase 4 inhibitor has also proven safe and effective for the treatment of AD,[89] but is not marketed in the EU.

Phototherapy, i.e. narrow-band UV-B radiation, is an effective and safe treatment option for moderate to severe AD.[1,96] A treatment cycle usually consists of 2-5 treatments per week for 2-3 months.[1] Safety data for use in prepubertal children is lacking, thus phototherapy is mostly used on adults and adolescents.[89] Limitations for use are in large practical, e.g. in terms of general availability and travel time for the patients.

Systemic treatment is indicated if symptoms cannot be controlled with topical treatment and phototherapy. The choice of systemic agent depends on several

factors, such as age, disease severity, concomitant disease, cost and reimbursements, alongside patient preferences and potential side effects. Cyclosporine A, methotrexate, azathioprine and mycophenolate mofetil are all effective for treating of AD, but each with specific limitations for use.[89] Except for cyclosporine A (Figure 1) for treatment of AD in adults, treatment with these agents are off-label in Norway, i.e. not officially approved for the treatment of AD. Newer systemic treatment options include dupilumab, a human monoclonal antibody against IL-4Ra that blocks both IL-4 and IL-13 signaling, approved for children >6 years of age.[89] Also, Janus kinase (JAK) inhibitors (Figure 1) have been shown to be fast acting and effective for the treatment of AD,[89] with baracitinib and abrocitinib currently approved and available for use in Norway.

The complexity of AD requires education of both patients and healthcare professionals to increase adherence to treatments and favorable outcomes.[97] In Norway, a multidisciplinary educational program for caregivers of children with AD is offered by Oslo University Hospital, showing beneficial effects on QOL, AD severity and fear of topical steroids.[91]

3 Atopic dermatitis and the concept of disease

Philosophy, from Greek *philosophia*, meaning *love of wisdom*, is the study of general and fundamental questions.[98,99] This thesis is based on central philosophical methods, i.e. critical discussion, questioning, rational argumentation, and systematic presentation,[100] with its main focus being the disease AD. But what is disease? How does AD fit within the concept of disease?

In most cases, diseases are classified, identified and defined by etiology,[101] although a specific denominator for all diagnoses in the International Statistical Classification of Diseases and Related Health Problems (ICD-10) cannot be determined. Even so, causality is important for both our understanding and determination of a disease. When a new explanation or cause of a disease is discovered, it changes our conception of the disease and/or creates new diseases. One example is *pemphigus*, which formally referred to several diseases having blistering as a main feature.[21] With new immunological insight we now have several distinct disease entities, such as *bullous pemphigoid*, *pemphigus vulgaris* and *linear IgA dermatosis*.

Knowledge of etiology is, however, not mandatory when defining a disease. In several cases the root cause has not yet been established. The disease manifestations, rather than its etiology, will then be the defining factor.[101]

Naturalistic disease theory

A naturalistic way of understanding of the concept of disease derives from a purely descriptive definition based on biological function alone, with the term *disease* referring to a deviation from normal functioning. In 1976, Christopher Boorse, a US philosopher, gave a naturalistic definition of disease:[102]

"… a disease is a type of internal state of the organism which (i) interferes with the performance of some natural function - i.e. some species-typical contribution to survival and reproduction – characteristic of the organism's age; and (ii) is not simply in the nature of the species, i.e., is either atypical of the species or, if typical, mainly due to environmental causes."

The clinical characteristics and pathophysiology of AD fits well within a naturalistic understanding of disease, being independent of social norms and values.[101] Atopic dermatitis results in reduced skin functioning and may, in extreme cases and absence of adequate treatment, interfere with both survival (severe infections) and reproduction (isolation).

Boorse also defines disease as a statistical deviation from normal function. For AD, this fits well with *atopy*, derived from Greek *atopos*, meaning something unusual or out of place, although, in most countries, AD is relatively common, affecting around 1 in 5 children.[2] There is a widespread agreement that the increase in prevalence seen for AD and other allergic diseases over the past decades cannot be explained by genetics alone, thus AD may still fit within a naturalistic understanding of disease.

Normativist accounts of disease

Boorse´s definition of a disease is not free of limitations and controversy. What is normal function? To answer this question, a judgment needs to be made to define normality, in conflict with the naturalistic premises.[101] In contrast to the naturalistic perspective, we have the normativists who claim that disease is an inseparable value-laded concept, as highlighted by philosopher Lawrie Reznek in 1987:[103]

"The concept of disease is a normative or evaluative concept. Judging that same condition as a disease is to judge that the person with that condition is less able to lead a good or worthwhile life. And since this latter judgement is a normative

one, to judge that some condition is a disease is to make a normative judgement."

Linking disease to functional values, as some sort of dysfunction, is dependent on our concept of an ideal function, separating normal versus abnormal functioning on the basis of what is negative for an individual or a group.[101]

One can argue that *disease* is merely a word and that its concept depends on our language awareness.[101] Even the word *dis-ease*, derived from old French, has a negative value attached, meaning *a lack of ease*.[98] In contrast, *health*, from Germanic language, relates to the word *whole* and something positive.[98]

What we perceive as a disease, often connects to associations of pain and suffering.[101] As AD is classified as a disease, there is a value-laden judgement that this condition is causing discomfort for the affected. For AD patients, this discomfort can derive from itch, tendency of skin infections and time-consuming treatment, leading to reduced quality of life.[7,104]

Moral values are also connected to the concept of disease. Diseases can lead to certain limitations and become an obstacle for doing good deeds or showing good character.[101] For AD, severe itching can cause sleep disturbances, irritation and short temper. In severe cases of AD, working disability can also result in moral judgment from others. Aesthetic values may also be relevant. Disease is often perceived as something hideous, while being healthy is attractive.[101] In our time we are frequently presented with retouched images of models with flawless skin in commercials, magazines and movies. Patients affected by AD carries visible evidence of their disease which contradicts the common conception of the ideal, smooth and healthy skin.

Although most values connected to the disease concept are negative, having a disease can also be associated with something positive. AD is associated with higher socio-economic status, and patients with AD may have several social

benefits, including reimbursements for the cost of drugs and moisturizers. In Norway, some children with AD have the opportunity to participate in an organized, yearly climate therapy program in the Canary Islands. Socializing with other AD patients and receiving attention, comfort and compassion from others may also be perceived as positive aspects of having AD.

Other values connected to the concept of disease are those defined by what we can do about a disease,[101] such as performing examinations and tests to determine cause or prognosis and to figure out how to prevent or treat the disease.[101] These values may also influence our perception on what should be conceived as a disease and not. Whenever a medical diagnosis is made, it is usually based on an evaluation on several professional norms in terms of disease recognition. In most cases, a diagnosis implicate something unwanted, that the patient would be better served without the disease and that efforts should be made in terms of prevention or treatment.[101]

Although these aspects fit well for AD, paradoxically there is often a misconception between the treating physician and affected patient in terms of what is the most beneficial treatment or prevention strategy. Topical steroids are prescribed in most cases; however, compliance vary. Fear of side effects and the perception of topical steroids being more harmful than having AD, is common.[105,106] Patients and their caretakers may also misinterpret causality, e.g. blaming certain types of food for their suffering. This could result in unnecessary dietary interventions or avoidance strategies. For a growing child, this could lead to more disease, e.g. deficiency syndromes and developmental impairment.

Disease classification

Classification systems are practical to differentiate different diseases, thus making it easier to put the correct diagnosis and to provide the best treatment. Classification or diagnostic criteria are also important for clinical research.

Diseases are often organized in classification systems, and those that do not fit within these systems will not as easily be classified as a disease.

Multiple sets of criteria for the classification or diagnosis of AD have been developed.[22] Although the manifestations of AD are typical in many cases, AD can also present with non-specific symptoms, e.g. dependent on age. The diagnosis will then depend on the clinician's judgement on what is the most likely diagnosis, often by excluding mimicking conditions.

The British dermatologist Hywel Williams has introduced the term *binary thought disorder*,[21] that is a state where individuals fails to acknowledge that biological phenomena, such as a disease, do not necessarily fit neatly into all-or-nothing or either/or categories.[21,107] Similarly to other diseases, AD may be graded from barely noticeable signs and symptoms, not fulfilling any classification criteria, to very severe cases. One can therefore argue that AD should be recognized more as a continuum rather than a distinct entity or a dichotomous variable.[21] It may also be said that attaching a name to a condition may falsely give the impression of understanding the true nature of the disease.[107]

4 Aims of studies

The overall objective for this thesis was to investigate early risk factors, diagnosis and characteristics of AD during infancy, i.e. from birth up to 12 months of age.

The reporting of AD risk factors from studies are inconsistent, while large prospective observational studies, such as birth cohorts may provide further clarification. Parental atopy, and AD in particular, is a major risk factor for AD in the offspring.[39] Some studies reports a greater risk from maternal versus paternal AD,[108,109] while others have found equal effects.[110] A survey based study from 2012, including children aged 1-18 years, reported an increased risk of AD only in children of the same sex as the affected parent.[82] As a follow-up on these findings, also including clinical data, we hypothesized that a sex-dependent risk increase of AD would be present already in infancy.

Aim 1:

To identify early life risk factors for AD in infancy, and assess if the risk conferred by parental AD differ between girls and boys (Papers I, II and III)

Atopic dermatitis most often debuts during infancy, although a diagnosis of AD may be difficult to make during this period of life. Numerous criteria for diagnosing AD have been developed over the years. The H&R criteria (1980) and the UKWP criteria (1994) are most frequently used in studies.[22] Validation studies have mostly been conducted in adults and older children, thus testing the usefulness of the criteria in infancy and identifying the best diagnostic approach for AD in infants is warranted.

Aim 2:

To determine the usefulness of the diagnostic AD criteria for diagnosing AD in infancy (Papers III and IV)

Eczematous rash is common in infants, but does not necessarily represent AD. The most common differential diagnosis includes contact dermatitis and seborrheic dermatitis. A debut of AD during infancy has been associated with a risk of a more severe and persistent AD phenotype.[70,111,112] However, the risk of having AD from observations of eczema in early infancy, is unknown.

Aim 3:

To identify the risk of AD in infants with eczema at three months of age (Paper III)

The AD prevalence differs between boys and girls depending on age.[83] However, data on prevalence of AD and clinical eczema in boys and girls during infancy is lacking. Also, the clinical features of AD vary with age and ethnicity and therefore possibly also with sex.

Aim 4:

To determine if the prevalence and clinical distribution of AD differ between infant girls and boys (Paper IV)

5 Methods and subjects

Study design

The studies are based on data collected within the Preventing Atopic Dermatitis and Allergies (PreventADALL) study, which is a 2x2 factorial designed, randomized, multicenter, population-based birth cohort study in Norway and Sweden. The study's primary goal was to investigate if allergic disease can be prevented by early skin care and/or food introduction. In addition, the PreventADALL study seeks to identify factors in early life that may affect the risk of allergic and other non-communicable diseases.

The study is ongoing with a general approval by Medical Ethical committees in Norway and Sweden from 2015 until 2044; Regional Committee for Medical and Health Research Ethics in South-East Norway (2014/518) and in Sweden (2014/2242-31/4). The PreventADALL study is registered at clinicaltrials.gov (NCT02449850).

Setting and recruitment

The women were all recruited at their routine 18-week ultrasound investigation at Oslo University Hospital, Oslo, Norway; Østfold Hospital Trust, Kalnes, Norway; and Karolinska University Hospital, Stockholm, Sweden.

Study information was sent to all pregnant women with the notice of their routine ultrasound appointment. The women were then asked by the midwifes at the ultrasound appointment if they would like to participate in the study and subsequently enrolled in the study by the PreventADALL study team.

Enrollment and follow-up visits

The enrollment visits included retrieving informed, written consent, measuring general anthropometrics and blood pressure, taking blood samples and urine

samples as well as handing out equipment for home-sampling of salvia and feces. The gestational age of the infants was estimated from femur length on ultrasound. Exclusion criteria for participation were inadequate Scandinavian language skills, plans to move far away from investigation centers within their childs first year of life, three or more fetuses, and severe fetal complications/malformations.

Questionnaires during pregnancy

Electronic questionnaires were completed by the mothers at 18- and 34-weeks gestational age. Information collected included general information regarding their health status, including information on atopic disease diagnosed in the mothers and/or the fathers. Furthermore, lifestyle factors, demographics, nutrition and dietary variables were collected. Information related to the father was mainly reported in the 34-week questionnaire. All gathered information was later encrypted and securely stored.

Inclusion at birth

The newborns were enrolled by the study personnel at the maternity wards, in most cases, within two days after birth. Exclusion criteria were gestational age below 35.0 weeks, severe disease of the infant, any plans to move far away from study sites within the first year, and/or parental withdrawal. This visit also included collection of informed consent of the father/co-parent.

Anthropometric measurements and skin swabs were performed, and instructions given to parents related to which group their infants were randomized to. The randomization was determined by a system based on the date of examination and specific home district of participants. If randomized to early skin care, necessary products (bath oil and skin barrier cream) were handed to the parents at this point.

Skin assessment of the infants

All study personnel involved in clinical follow-ups were given special training in assessing infant skin by physicians with several years of experience in dermatology. Also, in order to minimize interobserver variability, annual workshops were arranged.

The skin of the infant was assessed at the clinical follow-ups at 3, 6 and 12 months of age. The investigators were masked to which intervention group the baby had been randomized to. If such information was known or accidently shared prior to the investigation, another investigator was summoned. Parents were instructed not to use any skin care products or to bathe their baby 24 hours prior to the visit.

Dry skin, defined as presence of roughness and/or scaling, were recorded for eleven predefined areas of the skin and graded as mild, moderate or severe dryness (Table 7), in accordance with the Dry skin/Ichthyosis and Severity Index (DASI).[113] Furthermore, the skin of the infant was examined for any signs of AD and/or other skin diseases, e.g. seborrheic dermatitis.

The UKWP diagnostic criteria for AD were applied in all infants with suspected AD at the 3-, 6- and 12-months visits, while the H&R diagnostic criteria were used in addition at the 12-month clinical follow up visit. Severity of AD was assessed by the Eczema Area and Severity Index (EASI) and the Patient Oriented Eczema Measure (POEM).

Skin barrier function was assessed by the transepidermal water loss (TEWL), measured at the left upper arm at the 3 months and 6 months investigations. The procedure was performed with an open chamber DermaLab USB (Cortex, Hadsund, Denmark). Prior to the measurements, the infants were undressed for 15 minutes to acclimatize. Furthermore, the procedure required a calm baby and closed room with a stable temperature close to 22ºC (between 20 and 25ºC).

Subjects

A total of 2697 women with 2701 pregnancies (4 women were included also with a second pregnancy) were recruited in Norway (n=2149) and Sweden (n=552) from December 2014 through October 2016. The mother and child cohort consisted of 2383 mothers and 2397 children (52.7% boys), including 3 children born from the same mother in two different pregnancies, and 11 children with a twin sibling. Three children were withdrawn from the study after initial inclusion, rendering 2394 mother-child pairs available for further studies.

For Paper I and II, we included all infants who were not randomized to early skin care intervention, with clinical information from the 3 and/or 6 months follow-up and information on parental atopy from e-questionnaires. The study populations were comparable, with 1150 infants included in paper I and 1155 in paper II. The baseline characteristics for paper II are presented in Table 5. Paper III and Paper IV included the 1834 infants who attended all three clinical follow-ups at 3, 6 and 12 months of age, regardless of skin intervention which did not interfere risk of AD.[91] The baseline characteristics for paper III and IV are presented in Table 6.

Definitions and outcomes

Atopic dermatitis, dry skin and transepidermal water loss

The main outcome was AD. However, diagnosing AD during infancy is challenging, as symptoms may be unspecific, and the validity of the existing diagnostic criteria is uncertain during the first year of life. In the PreventADALL study, it was therefor decided to classify the AD outcome into three different levels, to be used consistently in all PreventADALL publications:[114]

> **Level 1: Atopic dermatitis (AD):** The strictest level, where the UKWP criteria and/or H&R diagnostic criteria are met (Used in Paper III and Paper IV)

Table 5: *Characteristics of the study population in paper II, similar to paper I*

Characteristics	No AD (N=833)	Possible AD (N=322)	Total (N=1155)
Age mother (years), mean, (SD, min-max)(N=1155)	32.6 (4.1, 21.0-48.0)	32.6 (4.0, 22.0-43.0)	32.6 (4.1, 21.0-48.0)
Age father (years), mean, (SD, min-max)(N=1005)	34.7 (5.5, 21.0-72.0)	35.0 (5.5, 23.0-65.0)	34.8 (5.5, 21.0-72.0)
Mother Nordic origin N (%)(N=1072)	711 (91.5)	266 (90.2)	977 (91.1)
Father Nordic origin N (%)(N=1050)	687 (90.2)	252 (87.5)	939 (89.4)
Education mother, 4 years of University or more, N (%)(N=1066)	444 (57.5)	181 (61.6)	625 (58.6)
Education co-parent, 4 years of University or more, N (%)(N=1027)	371 (49.7)	136 (48.6)	507 (49.4)
Family income N (%)(N=1056)			
Low	114 (14.9)	41 (14.0)	155 (14.7)
Middle	563 (73.7)	207 (70.9)	770 (72.9)
High	87 (11.4)	44 (15.1)	131(12.4)
BMI, mother at 18 weeks of pregnancy, mean, (SD, min-max)(N=1137)	24.8 (3.6, 18.3-39.7)	24.8 (3.6, 17.2-41.4)	24.8 (3.6, 17.2-41.4)
≥ 1 previous parity N (%)(N=1072)	317 (40.8)	126 (42.7)	443 (41.3)
Allergic disease mother, N (%) (N=1072)	488 (62.8)	204 (69.2)	692 (64.6)
Allergic disease father, N (%) (N=1072)	367 (47.4)	172 (57.7)	539 (50.3)
Atopic dermatitis mother, doctor diagnosed N (%)(N=1018)	154 (21.0)	70 (24.6)	224 (22.0)
Atopic dermatitis father, doctor diagnosed N (%)(N=995)	73 (10.1)	46 (17.0)	119 (12.0)
Asthma mother, doctor diagnosed N (%)(N=1050)	134 (17.7)	58 (19.9)	192 (18.3)
Asthma father, doctor diagnosed N (%)(N=1041)	107 (14.3)	44 (15.1)	151 (14.5)
Allergic rhinitis mother, doctor diagnosed N (%)(N=905)	167 (25.3)	62 (25.4)	229 (25.3)
Allergic rhinitis father, doctor diagnosed N (%)(N=952)	166 (23.9)	82 (32.0)	248 (26.1)
Food allergy mother, doctor diagnosed N (%)(N=947)	103 (14.7)	41 (16.6)	144 (125.2)
Food allergy father, doctor diagnosed N (%)(N=981)	67 (9.3)	31 (11.9)	98 (10.0)
Lifestyle during pregnancy			
Smoking N (%)(N=1155)	40 (4.8)	10 (3.1)	50 (4.3)
Live rural N (%)(N=1072)	71 (9.1)	21 (7.1)	92 (8.6)
Pets in general N (%)(N=1072)	195 (25.1)	60 (20.3)	255 (23.8)
Cat N (%)(N=924)	84 (12.6)	23 (8.9)	107 (11.6)
Dog N (%)(N=965)	113 (16.3)	35 (13.0)	148 (15.3)
Cat and dog N (%)(N=834)	13 (2.2)	4 (1.7)	17 (2.0)
Caesarean section, N (%)(N=1148)			
Elective N (%)(N=1035)	41 (5.5)	24 (8.4)	65 (6.3)
Acute N (%)(N=1129)	80 (10.2)	33 (11.1)	113 (10.4)
Gestational age at birth (weeks), mean (SD, min-max) (N=1138)	39.2 (1.7, 35.0-42.9)	39.4 (1.6, 35.2-45.9)	39.3 (1.7, 35.0-42.9)
Female gender N (%) (N= 1155)	405 (48.6)	133 (41.3)	538 (46.6)
Birth weight (kg), mean, (SD, min-max) (N=1132)	3.5 (0.5, 1.9-4.9)	3.6 (0.5, 2.2-5.1)	3.6 (0.5, 1.9-5.1)
Born during winter season (October – March) N (%)(N=1155)	460 (55.2)	180 (55.9)	640 (55.4)

Table 6: *Characteristics of the study population in paper III and IV*

Baseline characteristics	Included (n=1834)		Not included (n=561)		Total (n=2395)		p-value
	N	%[a]	N	%[a]	N	%[a]	
Sex							.74[b]
Male	969	52.8	292	52.0	1261	52.7	
Female	865	47.2	269	48.0	1134	47.3	
Nordic origin							
Mother	1531	90.8	432	89.3	1963	90.4	.32[b]
Father	1484	89.9	419	89.3	1903	89.8	.71[b]
Education ≥4 y University							
Mother	988	58.8	243	50.4	1231	56.9	.001[b]
Father	808	50.0	209	44.3	1017	48.7	.03[b]
Family income							.005[b]
Low	214	12.9	88	18.6	302	14.2	
Middle	1238	74.5	59.5	70.8	1572	73.7	
High	210	12.6	50	10.6	260	12.2	
≥ 1 previous parity	661	39.2	203	41.9	864	39.8	.27[b]
Atopic dermatitis	186	10.1	15	4.4	201	9.3	.001[b]
Eczema	628	34.2	57	10.2	685	36.2	.000[b]
Parental any allergic disease							
Mother	697	42.2	204	43.4	901	42.5	.65[b]
Father	607	35.8	144	31.2	751	34.8	.07[b]
Atopic dermatitis							
Mother	333	19.7	98	20.2	431	19.9	.81[b]
Father	176	10.4	44	9.5	220	10.2	.60[b]
Lifestyle during pregnancy							
Alcohol intake	110	7.4	19	4.9	129	6.9	.09[b]
Smoking	73	4.0	31	5.9	104	4.5	.07[b]
Live rural	113	6.7	45	9.3	158	7.3	.052[b]
Caesarean section							
Elective	102	6.3	39	7.9	141	6.6	.21[b]
Acute	192	11.1	60	11.6	252	11.3	.77[b]
*Born during winter season**	970	52.9	280	49.9	1250	52.2	.22[b]
	Mean	SD	Mean	SD	Mean	SD	
Gestational age at birth	39.3	1.7	39.2	1.7	39.2	1.7	.41[c]
Birth weight	3.6	.5	3.6	.5	3.6	.5	.74[c]
BMI mother	24.8	3.6	24.8	3.9	24.8	3.7	.79[c]
Age mother	32.6	4.1	31.7	4.3	32.4	4.1	.00[c]
Age father	34.9	5.3	34.1	5.9	34.7	5.5	.01[c]
3 month investigation							
Age (days)	92.9	7.9	94.4	8.9	93.1	8.1	.03[c]
Length (cm)	61.8	2.3	62.1	2.7	61.8	2.3	.09[c]
Weight (kg)	6.2	.8	6.3	.8	6.3	.8	.16[c]
6 month investigation							
Age (days)	189.7	13.3	191.6	14.8	190.0	13.5	.06[c]
Length (cm)	68.5	2.6	68.7	3.1	68.6	2.6	.39[c]
Weight (kg)	8.1	1.0	8.2	1.1	8.1	1.0	.25[c]
12 month investigation							
Age (days)	381.3	23.2	379.9	24.6	381.2	23.2	.63[c]
Length(cm)	76.5	2.9	76.3	3.2	76.5	2.9	.57[c]
Weight (kg)	10.1	1.1	10.0	1.2	10.1	1.1	.56[c]

[a] column percentages are given, [b] p-value from chi-square statistics comparing groups with complete and incomplete data, [c] p-value from 2-tailed T-test comparing groups with complete and incomplete data. Abbreviations: NA, not applicable

Level 2: Eczema: Observed eczema at the clinical investigations, also clinically excluding common differential diagnosis to AD, e.g. contact and seborrheic dermatitis (Used in Paper I, Paper III and Paper IV)

Level 3: Possible AD (pAD): All the cases where AD was either suspected at the clinical follow-ups (i.e. observed eczema) and/or from the parents reporting of an itchy rash in their child > 4 weeks (from the UKWP criteria). (Used in Paper II)

Dry skin was defined as presence of dry skin on minimum 1 out of 11 predefined areas of the skin (Table 7). Having dry skin only excluded those with coexisting eczema. (Paper I)

Unaffected skin was defined as skin without eczematous lesions or dryness. (Paper I)

Transepidermal water loss (TEWL)

In Paper I, we defined high TEWL as values above the 90th percentile, i.e. 11.3 g/m^2/h, measured in a room with stable temperature between 20 and 25ºC.

Risk factors for atopic dermatitis

Several potential predictors for AD, dry skin and high TEWL were investigated in Paper I. An overview is presented in Table 8. Although defining these variables as predictors in paper I, the specific variables related to AD also represent risk factors. The term risk factor is therefor used in the following, harmonizing terminology between the papers included in the thesis, i.e. paper I and II.

Table 7:
Table for registration of dry skin in the eleven predefined areas examined at the clinical investigations.

	Mild dryness	Moderate dryness	Severe dryness
Scalp			
Head and neck			
Cheeks			
Extensors arm and legs			
Trunk			
Flexors arms and legs			
Flexors elbows and knees			
Dorsal hands			
Palmar hands			
Feet			
Diaper area			

Table 8: *Different variables analyzed in relation to dry skin, TEWL and atopic dermatitis in paper I. Information was collected from questionnaires at 18 weeks of pregnancy (18wQ), 34 weeks of pregnancy (34wQ), the 18 weeks of pregnancy inclusion visit (18Incl.), newborn inclusion (NBIncl.) or from birth records (BR)*

Investigated variables	Variable definitions
Prenatal factors	
Age of the mother	Age of mother (18Incl.)
Age of the father	Age of the father (18wQ)
Parental Nordic origin	Nordic birth country: Norway, Sweden, Denmark, Finland, Island, (yes/no) - (18wQ)
Parental Education	>4 years of University vs. up to 4 years of University or College (18wQ)
Family income	Household income before taxes given as NOK/year. Low (<600.000), middle (600.000 - 1.400.000), high (>1.400.000) - (18wQ)
Single mother	Single (yes/no) - (18wQ)
BMI, mother	From recorded height and weight (18Incl.)
Multiparity	1 or more previous deliveries (18wQ)
Parental allergic disease (self-reported)	Atopic dermatitis, asthma, allergic rhinitis, food allergy, anaphylaxis and/or urticaria (yes/no) (18wQ mother, 34wQ father)
Parental allergic disease (diagnosed)	Doctor verified diagnosis of atopic dermatitis, asthma, food allergy, and/or allergic rhinitis, (yes/no) - (18wQ mother, 34wQ father)
Lifestyle during pregnancy	
Alcohol intake	Alcohol intake during pregnancy, (yes/no) - (18wQ and 34wQ)
Tobacco during pregnancy	Snus and/or smoking during pregnancy, (yes/no) - (18wQ and 34wQ)
Rural vs. urban living	Rural = countryside, urban = city, suburbs, town (yes/no) - (18wQ)
Exposure to humidity/mold	Exposure to humidity/mold (yes/no) - (18wQ)
Pets in general	Having pets in general (yes/no) - (18wQ)
Pets specified	No pets, cat but not dog, dog but not cat, cat and dog, only other pets, (yes/no) - (18wQ)
Perinatal factors	
Caesarian section (CS)	No CS, elective CS, acute CS (yes/no) - (BR)
Gestational age at birth (weeks)	From femur length (18Incl. and BR)
Sex of infant	(BR)
Birth weight (kg)	(BR)
Born during winter season	From October 1st to march 31st (NBIncl.)

Statistical methods

For all papers included in this thesis, the categorical variables are presented as numbers and percentages. The continuous variables are presented as means, Standard Deviation (SD) and minimum (min) – maximum (max). Means of the continuous variables were compared using two sample t-tests, while the categorical variables were compared using chi-squared tests.

In Paper I, logistic regression was used to examine potential associations between variables and outcomes. A p-value of 0.2 was set as cut-off for the primary univariate regression analysis, followed by a multivariate analysis, including all variables with <15% missing values. To investigate associations between dry skin and high TEWL in infants at 3 months of age and *eczema* in infants at 6 months, three logistic regression models were applied:

- An unadjusted model
- A model adjusted for those variables associated with dry skin, high TEWL and eczema at 3 months of age from the multivariate model
- A model also including variables associated with eczema at 6 months of age from the univariate analysis.

In Paper II, the odds ratios from the sex-stratified analysis were used to investigate potential associations between maternal and paternal AD and *possible* AD at 3 and 6 months of age. A logistic regression model was subsequently applied to test for any interactions between AD in mothers and fathers and the sex of the child. All presented results were unadjusted as the probability of confounding variables were thought to be low.

In Paper III, we first assessed potential selection bias by comparing baseline characteristics for the included study group (attended all clinical visits) to those excluded from the analysis (not attending all clinical visits). We used chi-squared tests for the categorical variables and two tailed t-tests for the continuous variables. Logistics regression models were applied to assess the potential

relationship between eczema and AD during infancy: one regression model was used to investigate the association between the number of observations of eczema during infancy and fulfilling either of the two diagnostic criteria by age 12 months. Another model was used to examine associations between having eczema first observed at 3, 6 or 12 months of age and fulfilling either of the two diagnostic criteria during infancy. Both models were also adjusted for sex of the infant and parental atopy as potential confounders.

We imputed the missing data with the best-case option, i.e. missing values were set as 0 = "no observed eczema", presuming that the caretakers would have been particularly motivated to complete the skin examination if their child had eczema. Concerning the use of topical steroids, all missing values and the "don't know" responds were set to "no use".

In Paper IV, we used chi-square statistics to compare occurrence of eczematous lesions on different locations of the skin in girls and boys. Based upon the tree most commonly affected areas with eczema, sensitivity and specificity were calculated.

Statistical level of significance was set to 5% in all publications. All statistical analyses were performed using SPSS software version 26.0, IBM, Armonk, NY, USA.

Ethical considerations

One of the primary goals of the PreventADALL is to test if atopic diseases can be prevented in a prospective, randomized interventional study with four arms:

(1) early, systematic food introduction: milk, wheat, eggs and peanut
(2) early systematic skin care: oil bath plus barrier ointment in cheeks
(3) both interventions and
(4) control group.

Pregnant women were included at 18 weeks of gestation and their infants enrolled at birth. The study is ongoing.

Sections 19 and 20 of the Declaration of Helsinki addresses research on vulnerable groups,[115] in our case represented by pregnant women and young children. Section 20 states that research on a vulnerable group can only be defended if:

- it is carried out in awareness of any special health considerations for the group,
- the research cannot be carried out on a non-vulnerable group and
- the knowledge the study generates is beneficial to the group.[115]

Although alert to these central points in the declaration of Helsinki, there is no guarantee that the knowledge generated by the study is beneficial to the study participants. The potential effects of the food intervention on the risk of disease were unknown at the time of study start. If the risk of disease were to increase with early food introduction, it can be questioned how beneficial this knowledge is to the group as guidelines recommending against such early food introduction already exists.

Informed consent by the study participant is central when conducting medical research.[115] When doing research on younger children, this is not achievable. However, section 28 of the Declaration of Helsinki allows parents to consent on behalf of their children, with a necessary requirement that all children should be exposed to an absolute minimum of risk and burden.[115] Although severe allergic reactions to e.g. peanut are quite rare, such reactions were likely to occur in our study due to the high number of children included. Different skin reactions to the skin care products, losing the grip of a slippery child after oil bath, pneumonitis from inhaling/aspirating concentrated oily bath water are other examples of potential adverse events. Although considered to be unlikely, any long-term risks

linked to the interventions cannot be completely ruled out. The overall risk of severe adverse events was, however, considered to be low.

At the clinical follow-up visits, the children underwent a clinical examination as well as a number of tests and sampling of biological material. Some children will find blood sampling painful, and parents might find the procedure unpleasant to witness. Parents may feel responsible to act as “good” study participants, pressured into allowing certain procedures to be performed. Another aspect is all the medical advice, prescriptions and referrals provided by the physicians involved in the clinical follow-ups. A doctor-patient relationship might cause further pressure on parents not to object to examinations or to withdraw their child from the study. Parents may also have different thresholds for what they are comfortable with. It may be difficult for the investigators to sense any hesitation in parents while at the same time focusing on the procedures and collecting optimal data within a limited time frame.

Various clinical findings at the follow up visits may also result in referral to other specialists. This can in turn lead to overdiagnosis, in which some children are given a diagnosis they otherwise would not have gotten, possibly without clinical relevance. Some parents might find extra clinical follow-up reassuring, but for some it may result in unnecessary concern and emotional distress.

Another ethical consideration is linked to the anonymity aspect. The identity of all study participants, including collected data, needs to be completely confidential.[115] In our study, biological material has been stored in a biobank, via KIT numbering. From this material it is possible to extract DNA, thus one can theoretically re-identify a study participant later in time.

The PreventADALL study is approved by the Regional Committee for Medical and Health Research Ethics in South-East Norway (2014/518) and in Sweden (2014/2242-31/4) and registered at clinicaltrials.gov (NCT02449850).

6 Summary of main results

Aim 1:

To identify early life risk factors for AD in infancy, also if the risk from parental AD differ between girls and boys (Paper I and Paper II)

Paper I included 1150 infants and use of outcome eczema, defined as observed eczema, clinically excluding differential diagnosis to AD.
Paper II included 1155 infants with outcome *possible* AD, defined as eczema but also including a parental reporting of itchy rash for more than 4 weeks. Listed below are our findings of pre-, peri- and postnatal risk factors for AD in early infancy:

Prenatal risk factors for AD by 3 months of age:

Multiparity, i.e. a history of one or more previous deliveries, increased risk of AD in offspring by 3 months of age, with OR being 1.63 (95% CI: 1.03-2.57).
For parental atopy, an increased risk of AD by 3 months of age was found from a history of maternal allergic disease: (OR: 1.61; 1.02-2.55) and paternal AD (OR:1.80; 1.08-3.00).

Perinatal risk factors for AD by 3 months of age:

Birth by elective caesarian section increased risk of AD by age 3 months (OR: 2.02; 1.31-3.14)

Prenatal risk factors for AD by 6 months of age:

Regardless of offspring sex, a history of paternal AD increased risk of AD by age 6 months (OR: 1.81; 1.19-2.76). Stratified by sex of the offspring, the risk increase from parental AD was statistically significant only from maternal AD and AD in daughters (OR: 1.79; 1.07-3.00) and from paternal AD and AD in sons (OR: 2.36; 1.34-4.20) (Figure 3). The sex specific risk pattern seen from parental AD was

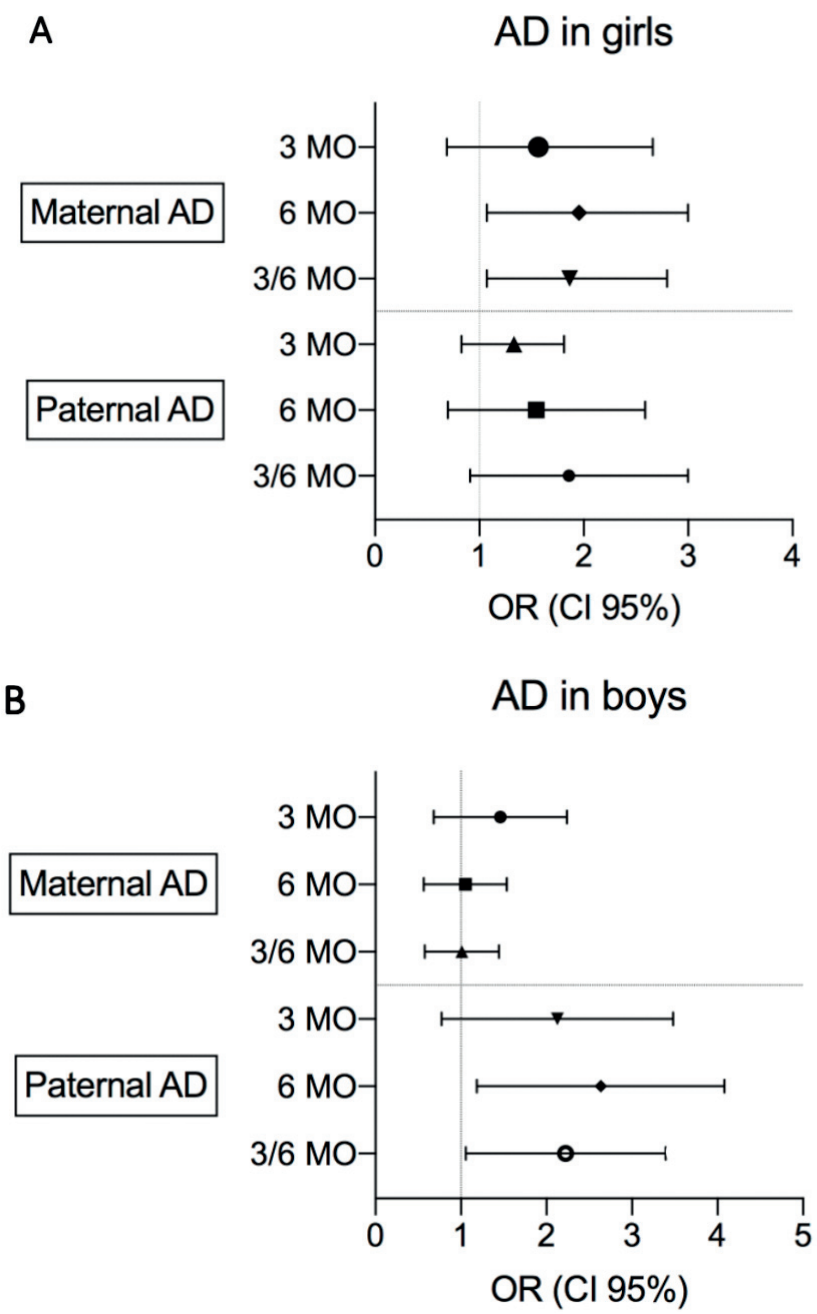

Figure 3:
Forest plots showing the risk of atopic dermatitis in girls (A) and boys (B) in early infancy from a history of maternal and paternal atopic dermatitis. The various symbols represent the Odds Ratios (ORs) while the horizontal lines represent the 95% confidence intervals (CI 95%).

Figure created using GraphPad Prism version 8.4.2 for Mac OS X, GraphPad Software, San Diego, California USA, www.graphpad.com

also present when defining the phenotype as *possible* AD at 3 and/or 6 months of age. No statistically significant findings were seen from parental AD on *possible* AD in offspring of opposite sex. A non-statistically significant interaction was seen for maternal AD and sex of the offspring by 6 months (p =0.09).

Postnatal risk factor for AD by 6 months of age:

Infants with dry skin at 3 months had double the risk of AD at the 6 months visit compared to those with unaffected skin, 21.7% versus 12.4% respectively, (OR: 1.96; (1.37-2.80). The results were similar after adjusting for covariates.

Aim 2:

To determine the usefulness of the diagnostic AD criteria, i.e. the UKWP and H&R criteria, for diagnosing AD in infancy (Papers III and IV)

In total, 628 infants (34%) had observed eczema, clinically excluding the most common differential diagnosis to AD, on at least one of three clinical visits during infancy. Among these 628 infants, 212 (34%) fulfilled the UKWP and/or the H&R diagnostic criteria for AD at least once during infancy. At 12 months of age, 156/329 (47%) fulfilled one or both sets of criteria, in which 27 (8%) fulfilled the UKWP criteria only and 65 (20%) the H&R criteria only (Figure 4). In 44/129 (34%) infants who fulfilled the H&R criteria, the itch criterion was not met. Infants with eczema observed on all three visits were most likely to fulfil the criteria (OR: 23.1; 95% CI: 12.3-43.6) compared to those with eczema on two (OR: 6.5; 95% CI: 4.3-9.9) visits or just one visit (reference).

The anatomical sites included in the UKWP and the H&R criteria were not found to correspond with the most prevalent areas of the skin to be affected with eczema during infancy (Paper IV). Truncal eczema, not included in the diagnostic criteria, was one of the three most prevalent sites of eczema throughout infancy,

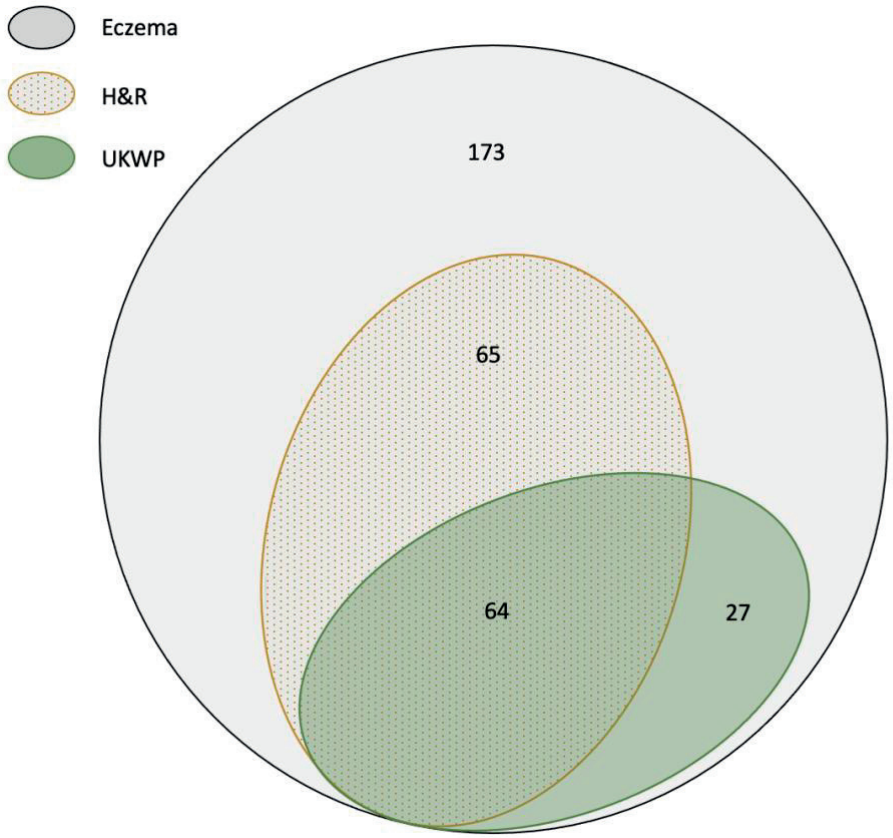

Figure 4:
An area proportional Euler diagram showing the 329 infants with observed eczema at 12 months of age and the proportions who fulfilled the H&R and/or the UKWP criteria for AD.

Figure was produced using Luana Micallef and Peter Rodgers (2014) eulerAPE: Drawing Area-proportional 3-Venn Diagrams Using Ellipses. PLoS ONE 9(7):e101717.doi:10.1371/journal.pone.0101717. http://www.eulerdiagrams.org/eulerAPE

affecting 346 (55%) of infants with eczema. Furthermore, both sensitivity and specificity for the diagnostic AD criteria were highest for eczema located on the trunk (sensitivity 51% and specificity 98%), compared to the other two most frequently affected sites: cheeks (47% and 95%) and extensors surfaces of arms and legs (43% and 97%).

Aim 3:

To identify the risk of AD in infants with eczema at three months of age (paper III)

Among the 628 infants (34%) with observed eczema on at least one clinical visit during infancy, 240 had eczema at 3 months of age, in which 87 (36%) did not have eczema on later visits and 78 (33%) had eczema on all visits (Figure 5a). Atopic dermatitis was more often diagnosed in infants with a first observation of eczema at 3 months (47%) versus first at 6 (22%) or 12 months (30%) (Figure 6).

In the regression analysis, the ORs of a criteria-based AD diagnosis during infancy were lower with eczema first observed at 6 or 12 months, (OR: 0.33; 95% CI: .22 - 0.48) and (OR: 0.49, 95% CI: 0.32 - 0.74) respectively, compared to a first observation at 3 months (reference). The results were similar after adjusting for sex of the infant and parental atopy. The risk of AD increased with eczema observed on two (OR: 6.5; 95% CI: 4.3 – 9.9) or three (OR: 23.2; 95% CI: 12.3 – 43.6) visits compared to observation at one visit only (reference).

Aim 4:

To determine if the prevalence and clinical distribution of AD differ between infant girls and boys (Paper IV)

One third of all infants (628/1834, 34%) had eczema observed at least once during infancy. At 12 months of age, 355/969 (37%) boys had eczema while eczema was observed in 273/865 (31%) girls, (p=0.02). A difference in prevalence was also seen for criteria-based AD, affecting 126 (13%) boys, compared to 86 (10%) girls, (p= 0.04).

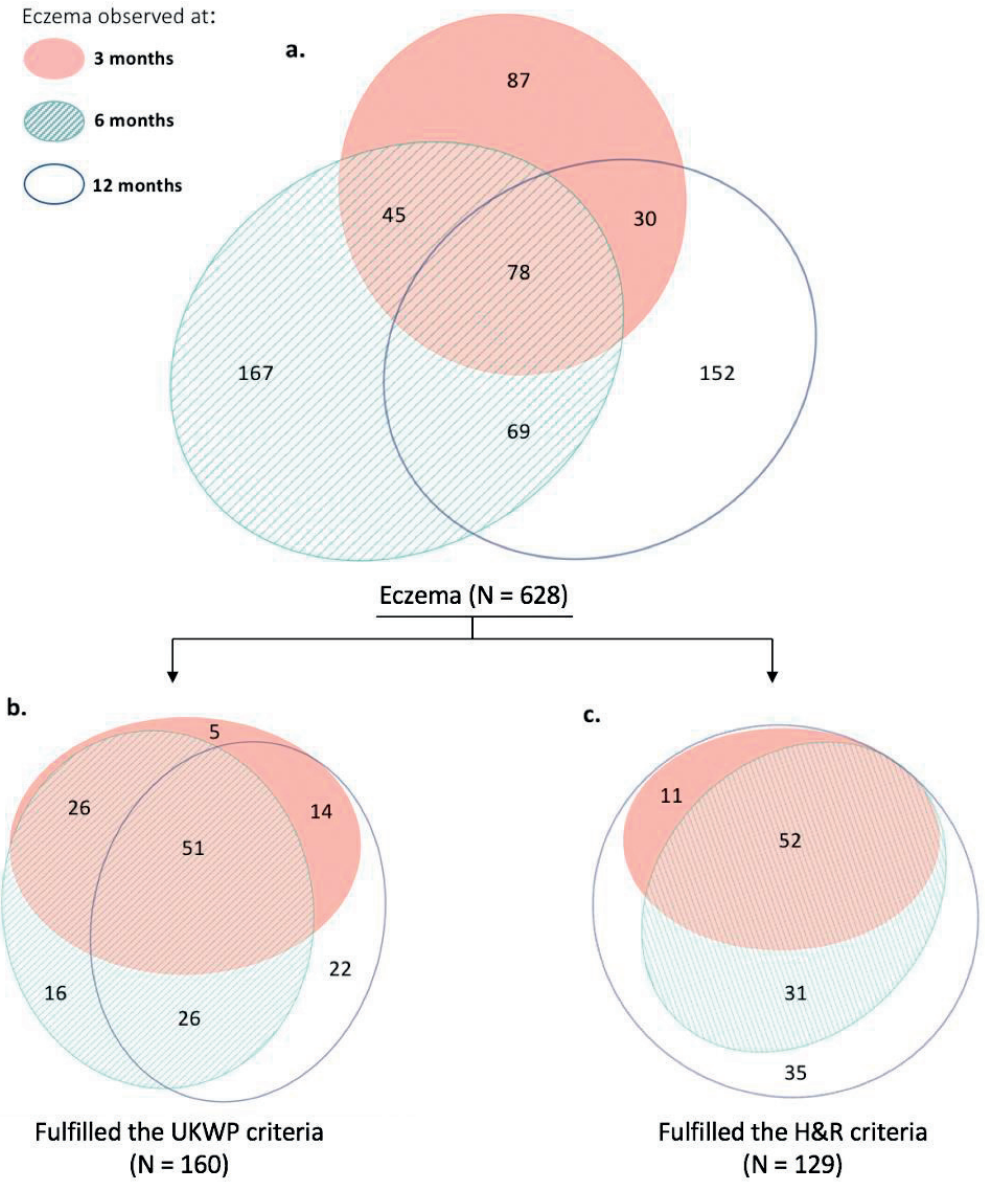

Figure 5 a-c:[116]
Area proportional Euler diagrams displaying the proportion of infants with observed eczema at the 3-, 6- and 12-months clinical follow-up:
a. The 628 infants with eczema observed during infancy
b. The 160 infants who fulfilled the UK Working Party (UKWP) criteria
c. The 129 infants who fulfilled the Hanifin & Rajka (H&R) criteria (applied at the 12 months visit only)

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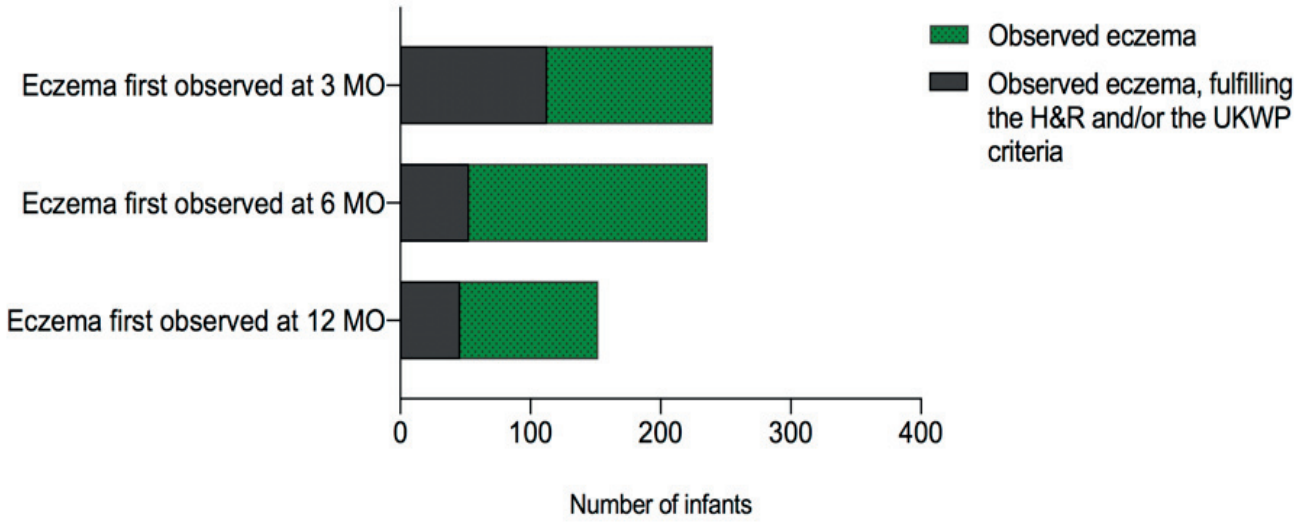

Figure 6:[116]
A stacked bar chart displaying the 628 infants who had eczema during infancy according to the timepoint of when eczema first was observed. The grey sections represent those who fulfilled the U.K. Working Party (UKWP) and/or the Hanifin and Rajka´s (H&R) criteria for atopic dermatitis by 12 months of age. The green sections represent those with eczema who did not meet any of the two criteria.

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The clinical distribution varied with age and sex. For the 240 infants with eczema observed at age 3 months, the most prevalent sites of affection were extensors of arms and legs (65%), trunk (51%) and cheeks (40%). For the 359 infants with eczema observed at age 6 months, the most prevalent sites were trunk (50%), extensors of arms and legs (48%) and cheeks (43%). For the 329 infants with eczema at 12 months of age, the most prevalent sites were extensors of arms and legs (59%), trunk (50%) and cheeks (35%). The least frequent sites of affection during infancy were nappy area; lowest at 3 months (3%) and highest at 6 months (5%), the plantar side of hands and wrists; lowest at 6 months (2%) and highest at 12 months (6%) and the scalp; lowest at 12 months (3%) and highest at 3 months (13%).

Statistically significant differences in clinical distribution included a higher number of boys than girls having eczema on the cheeks, at 3 months: 44% vs 31% (p=0.04), 6 months: 51 % vs 33% (p=0.001) and with a trend also at 12 months: 39% vs 29% (p=0.08). Furthermore, a higher number of girls than boys had eczema on the flexor sites of arms and legs at 3 months: 45% vs. 31%, (p=0.03) (Figure 7)

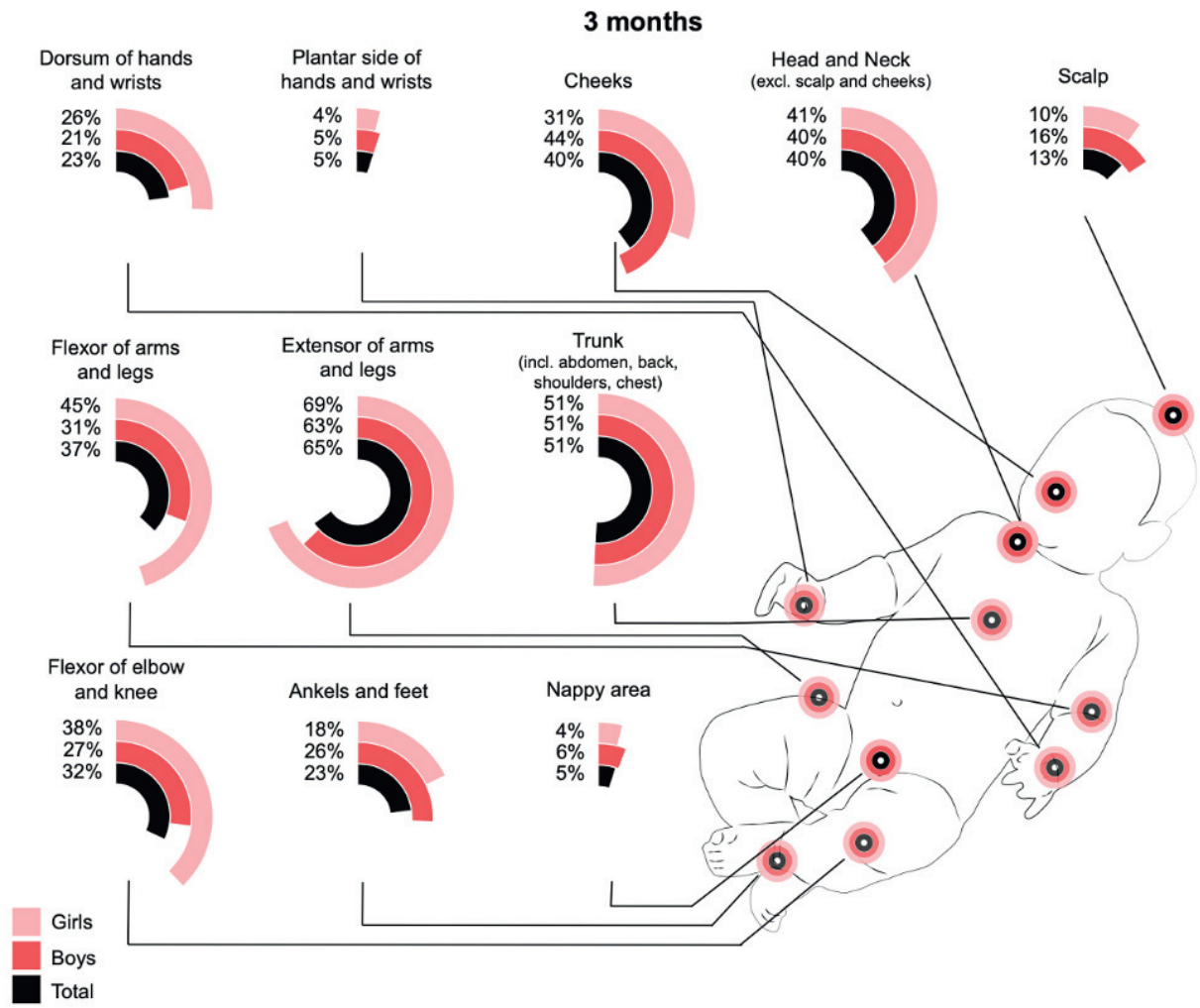


Figure 7:[117]
The clinical distribution of eczema in the 240 boys and girls with eczema at age 3 months. (Illustration by Ine Eriksen, University of Oslo)

7 Discussion

The specific aims and results of the studies in this thesis covers many aspects of AD from etiology and risk factors to prevalence, diagnosis, and clinical characteristics. The prevalence of AD in our study of infants was 12% (Paper III and IV), comparable to the results in several other epidemiological studies.[31,36]

Identifying early life risk factors for atopic dermatitis in infancy

We found parental allergic disease, multiparity and elective caesarian section to be distinct risk factors of AD by 6 months of age (Paper I). Furthermore, infants with dry skin at 3 months of age presented with AD twice as often as infants with unaffected skin (Paper I). Boys were more likely to present with AD by age 12 months compared to girls (Paper IV).

Our finding of increased risk from parental AD is in line with other studies.[2,118] Our finding of multiparity, an indicator of a larger household size, as a risk factor for AD is in contrast to the proposed hygiene hypothesis, stating that elder siblings lowers the risk of atopic disease.[49,119] However, our finding harmonize with the results from a 2010 study that did not find a risk reduction of atopic dermatitis from having elder siblings.[120] The hygiene hypothesis origins from an observation of a lower risk of allergic rhinitis in large families,[51] thus family size may have a different effect on the risk of atopic dermatitis compared to allergic rhinitis. Inconsistencies regarding the risk of AD from family size can also be partly explained by the use of different outcome definitions between studies and variations in the age of the study participants.

We have not seen other studies reporting increased risk of AD specifically from birth by elective cesarean section and not acute cesarean section. Birth by cesarean section has, however, been associated with altered immune

development, reduced microbiome diversity and an increased likelihood of allergy and asthma.[121] The majority of elective cesarean section in our study occurred prior to the rupture of amniotic membranes, thus the initial bacterial colonization of the infant skin and gut was most likely not of vaginal origin. This may have contributed to a microbiome dysbiosis which has been associated with AD development.[122]

Boys were more frequently affected with both clinical eczema and a criteria-based diagnosis of AD in our study. A higher prevalence of AD in boys than girls harmonize with the findings of others.[31,83]

Our study showed an increased risk of AD, particularly in infants of the same sex as the affected parent (Paper II), in line with the findings of Arshad *et al*,[82] but not with a cross-sectional questionnaire survey from 1992 on children aged 9-11 years.[123] However, a prospective birth cohort may be more appropriate than other study designs to answer this question, i.e. a cross-sectional study run the risk of misclassifications from the fluctuant nature of AD.[82]

Genetic risk factors may play a more crucial role for AD developing in early life.[124] Therefore, our results might have been expected to be even clearer than those of Arshad *et al* who studied older children and adolescents. In our study, the increased risk from father to sons and mothers to daughters were statistically significant by independent ORs. However, contrary to the findings of Arshad *et al*, we did not find statistically significant interactions between parental AD and sex of the offspring. This may suggest that our study was underpowered for detecting such interaction effects. We did, however, not see any statistically significant increase of risk from parental AD to offspring of opposite sex.

Several genes have been linked to the etiology of AD. A systematic literature review from 2020 reported a total of 62 genes and 5 intergenic regions associated with the development of AD.[125] How and if these genes are expressed may be influenced by environmental factors. Epigenetics, i.e. studying heritable

phenotype changes that do not include changes in the DNA-sequence,[126] addresses these aspects. An epigenetic phenomenon, i.e. genomic imprinting, may be relevant to explain the increased risk of AD in offspring of the same sex as the affected parent.[82] Genomic imprinting is defined by the silencing of a corresponding allele from DNA methylations or histone modifications, resulting in a parent-of-origin specific expression of an allele .[127,128] By these mechanisms, alleles containing AD-susceptibility genes could be expressed only in offspring matching the sex of the affected parent.

The male defining Y chromosome, passed on from fathers to sons, is also important for the regulation of immune and inflammatory responses in males[129] and may possibly play a role in the observed father to son risk increase of AD.

The usefulness of diagnostic criteria for atopic dermatitis in infancy

Around one third of all infants in the PreventADALL study presented with clinical eczema on at least one of three clinical visits, of whom one third met at least one of the two diagnostic AD criteria (Paper III). The risk of a criteria-based AD diagnosis increased with the number of observations of eczema and also if eczema was observed at 3 months compared to later in infancy (Paper III). When applying both sets of criteria at 12 months of age, almost 3 out of 5 infants with AD fulfilled only one of the two criteria (Paper III). Furthermore, we found the trunk, a site not included in the present criteria, to represent a predilection site for AD in infancy (Paper IV).

Very few studies have validated the established AD criteria for use on infants.[24,26,27] In a Turkish study, comparing the two sets on children aged 7 to 36 months, the sensitivity for the H&R criteria was 94% compared to 72% for the UKWP criteria.[26] This is in line with our finding of highest sensitivity to detect AD from the H&R criteria in comparison with the UKWP criteria. The reporting of relatively high sensitivity for both sets of criteria in certain studies including infants,[24,26] may partly be explained by the inclusion of children also older than

12 months of age. Furthermore, the recruitment of infants from a pediatric allergy or dermatology clinic, possibly with more severe AD phenotypes than in our population-based study, may also have contributed to differences in sensitivity for the diagnostic criteria.

The prevalence of AD of 12% in our study harmonize with an estimated AD prevalence of 20% and about 60% presenting their first symptoms during infancy in other studies.[31,36] Our calculation of AD prevalence is based on application of the diagnostic criteria at three consecutive timepoints during infancy. When comparing the two sets of diagnostic criteria at 12 months, the majority of infants were diagnosed by only one of the two sets, most by the H&R criteria. From other validation studies, sensitivity and specificity for the UKWP and the H&R criteria vary, but are mostly high when applied on older children and adults.[25]

Our finding of lacking overlap for diagnosing AD between the two criteria may have several explanations. Fulfilling the UKWP requires presence of itch. This is difficult to evaluate in milder cases of AD and may therefore not be recognized by the parents, who report on behalf of their child.[28] Also, the ability to demonstrate itch may not be present at 3 months of age,[130] relevant to consider when applying the criteria in early infancy. We found that one out of three infants fulfilled the H&R criteria without fulfilling the itch criterion, subsequently not fulfilling the UKWP criteria.

For the H&R criteria, a major limitation is its complexity, requiring 3 out of 4 major criteria plus 3 out of 19 minor criteria with several of the minor criteria requiring special training to investigate. Also, several of the features included in the minor criteria develop over time and therefore cannot be expected to be present already in infancy.[30] Failure to exhibit a minimum of three H&R minor criteria may result in a diagnosis of AD by the UKWP criteria only.

We found the trunk to be one of the most common sites of eczema throughout infancy. Further, truncal eczema gave the highest sensitivity and specificity of fulfilling the diagnostic criteria of the three most frequently affected sites of eczema during infancy (Paper IV). These findings point to another limitation for the two diagnostic criteria, i.e. the included anatomical sites are not well suited to represent the clinical distribution of AD during infancy. In the UKWP criteria, modified for use in infancy, the anatomical sites include arms, legs and cheeks. The H&R set includes face and extensor surfaces of arms and legs. Eczema on the trunk was not included in the UKWP criteria to avoid misclassification of seborrheic dermatitis.[24]

Some advocate that diagnostic AD criteria should be used more consistently in daily clinical practice.[131] However, our findings suggests that *both* sets of criteria should be used and on multiple occasions when diagnosing AD in infants. This approach may be useful when conducting research, but not so much in a busy clinical practice. We have demonstrated that both sets of diagnostic criteria have severe limitations for use on infants and conclude that their usefulness during infancy is limited in daily clinical practice settings.

Risk of atopic dermatitis in infants with eczema at three months of age

In our cohort, AD was significantly more often diagnosed in infants who had a first observation of eczema at 3 months of age compared to first observation at 6 or 12 months. Other studies have demonstrated that AD manifests for the first time between 3 to 6 months of age in the majority of cases.[132] Our results pinpoint this risk to be greatest around 3 months compared to 6 months of age. These findings also underline that potential future primary prevention strategies should be applied prior to 3 months of age.

About one third of infants with eczema at 3 months in our study also had eczema at the 6 and 12 months follow up, harmonizing with an early onset to be associated with a more severe and persistent AD phenotype.[70,111,112]

Prevalence and clinical distribution of eczema in girls and boys during infancy

Our finding of higher prevalence of both observed eczema and criteria-based AD in infant boys compared to girls corresponds well to studies in older children, demonstrating a higher prevalence of AD in boys than girls, but with a shift of difference around puberty.[83] This may indicate that the course of AD is influenced by modulatory effects of sex hormones on immune responses and skin barrier.[83]

Boys were more likely to have eczema on cheeks than girls during infancy, and girls were more likely to have eczema on flexor surfaces of extremities than boys at 3 months of age (Figure 8). The cheeks represent areas of the skin particularly exposed to wear and tear by local triggers.[81] It is therefore possible that sensitivity to local triggers play a more crucial role in the pathogenesis of infantile eczema in boys rather than girls, which again may contribute to the higher prevalence of AD found in boys. Our observations suggest that pathogenic factors may interact with sex in development of AD during infancy, leading to differences in both prevalence and clinical distribution between boys and girls. These findings complement the findings of sex-related patterns of AD in other studies.[82,114]

Regardless of sex, we found the trunk to be a highly prevalent site for eczema throughout infancy, also with the highest sensitivity and specificity of fulfilling the diagnostic AD criteria from the three most common sites of affection. Eczema was also commonly observed in flexural areas of arms and legs, as demonstrated in a study in 12 months old Scottish infants with flexural involvement being as common as involvement of cheeks, outer arms and legs.[27] However, this is in contrast to the assumption that typical flexural involvement develops around 2 years of age.[27,70]

Strengths and limitations

The strengths of the presented studies include their prospective design and origin from a large cohort of infants, recruited from the general population in three different geographical locations in Norway and Sweden. Clinical data was collected at three different timepoints during infancy by personnel given special training in the use of the diagnostic AD criteria. Workshops were held to minimize interobserver variability. Also, questionnaire-based data, including information on parental disease, was collected during pregnancy, thus minimizing the risk of recall bias after the potential occurrence of eczema in their child.

Limitations to consider include that the H&R criteria were used at the 12 months visit only, thus the total number with an AD diagnosis based on diagnostic criteria might have been underestimated. Treatment plans provided during the study period combined with the fluctuating nature of AD may also have led to an underestimate of eczema and AD prevalence. The majority of study participants in the PreventADALL study is of Nordic origin. Also, parents with a higher degree of education and a history of atopic disease were moderately overrepresented (Table 5 and 6). These factors may limit the generalizability of our results.

Finally, some subgroup analysis may have been statistically underpowered, i.e. when dividing into girls and boys. Also, multiple tests were performed to investigate potential differences of eczema location between girls and boys. Such factors may increase the risk of Type I and II errors.

8 Main conclusions

Based on data from a birth cohort enrolling mother-child pairs from the general population, we found that:

- Multiparity, parental atopic disease and elective caesarean section increased the risk of AD at 3 months of age.
- Infants with dry skin at 3 months had twice the risk of developing AD at 6 months of age.
- Parental AD increased the risk of AD by 6 months of age only in offspring of the same sex as the affected parent.
- One third of infants with observed eczema fulfilled the diagnostic criteria for AD.
- For infants with eczema present at 3 months, about one third did not have observation of eczema later in infancy, while one third had eczema at a second follow-up visit and one third had eczema at all three follow-up visits.
- More infants were diagnosed with AD by the H&R criteria than the UKWP criteria at 12 months of age.
- The risk of AD in infancy was highest for infants with eczema first observed at age 3 months compared to at 6 months or 12 months.
- The risk of AD increased with the number of times eczema was observed during infancy.
- Both the H&R and UKWP criteria for AD have limitations for diagnosing AD during infancy and therefore limited clinical value for use in children up to age 1 year.
- Using both sets of diagnostic criteria and at multiple timepoints might be the best approach in clinical research to increase the chance of identifying all infants with AD.
- Overall, boys were more likely to have eczema and AD during infancy than girls.

- The clinical distribution of eczema differed between girls and boys during infancy with more boys than girls having eczema on the cheeks during the whole infancy period and more girls than boys having eczema on flexor sites at 3 months.
- The flexor sites of extremities were commonly affected with eczema during the whole infancy period.
- Of the three most prevalent sites of eczema affection during infancy, cheeks, trunk and extensor surfaces of limbs, eczema on the trunk gave the highest sensitivity and specificity of fulfilling the diagnostic AD criteria.

9 Clinical implications and future perspectives

The present studies address several aspects of atopic dermatitis, from risk factors and clinical presentation to prevalence and diagnosis during the first year of life. The prospective study design, with a large cohort of infants recruited from the general population, is well suited to address these aspects.

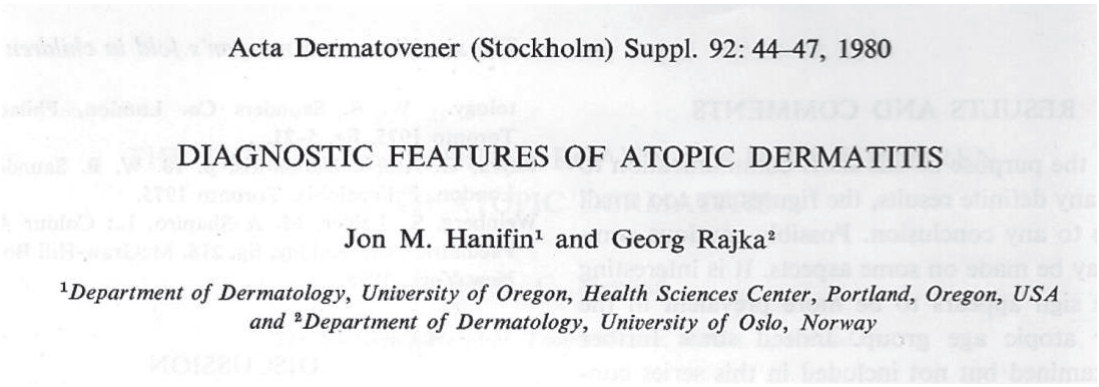
Investigating environmental risk factors seems important for increased knowledge on etiology and to pinpoint targets for future prevention strategies. Our finding of an association between birth by elective caesarean section and AD further underlines the current recommendation for choosing vaginal birth if otherwise possible. Furthermore, our finding of dry skin proceeding the occurrence of AD may support the outside-in hypothesis, with impaired skin barrier function proceeding the inflammation process. Also, although emollient treatment has not been proven effective for primary prevention of AD, infants presenting with dry skin may still benefit from frequent moisturizing treatment, possibly minimizing the severity of AD flairs.

Adding to the established risk factor for AD from parental atopy, we found parental AD to increase the risk of infant AD, particularly in offspring of the same sex as the affected parent. A clinical implication from a sex-related heredity may provide a rationale for sex-stratified risk assessments, e.g. for prevention strategies and improved diagnostic accuracy by differential weighting of hereditary criterion depending on the sex of the child and affected parent. This finding warrants additional genetic studies, i.e. translational studies, for clarification and better understanding of the genetic basis of AD.

When diagnosing AD in infants, we found the use of both the UKWP and the H&R criteria, and at multiple timepoints, may be the most appropriate approach. This may be important and feasible in clinical research studies. In most other settings,

however, the present diagnostic criteria may have limited value for diagnosing AD in infants.

Having identified the most important limitations for each set of criteria provides an opportunity to revise and improve the existing criteria or develop a whole new set of criteria for diagnosing AD in infants. A new set of criteria would need validation in a new cohort of infants, preferably selected form the general population to avoid selection bias towards the more severe phenotypes seen in a dermatological or allergy clinic. Given that Georg Rajka, with Jon Hanifin, created a set of criteria while working at Rikshospitalet in Oslo (Figure 8), it seems suitable to continue his work on diagnostic criteria at the same hospital four decades later. An accurate recognition of AD early in life is important for prognosis, follow-up, establishing rights to social benefits and reimbursements, and for harmonizing outcomes in clinical research.



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DIAGNOSTIC FEATURES OF ATOPIC DERMATITIS

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Figure 8:
A facsimile of the original publication of the Hanifin and Rajka´s criteria from 1980 with the affiliations of the two authors.

Our finding of the highest risk for AD from eczema first observed at age 3 months compared to later in infancy underlines that primary prevention interventions should begin prior to this age. Although present studies have failed to prevent

AD by regular oil bath or emollients in early life, other strategies may yet prove effective in future studies.

We found a higher risk of AD in infant boys versus girls. The finding of boys being more frequently affected with eczema in cheeks and girls more often in flexor sites of extremities give rise to a hypothesis that differential disease mechanisms may be relevant for AD presenting in early life, i.e. that boys may be more sensitive to triggering from external factors. Such effects could possibly contribute to the difference in AD prevalence between boys and girls and providers a rationale for future investigations. Also, our findings of specific sex specific variations call for studies to investigate other potential differences between AD in girls and boys, e.g. in terms of risk factors, severity and response to interventions and treatment. Our finding of the trunk being a predilection site for infant AD warrants special attention to this area when examining infant skin and underlines the need of a revised set of diagnostic criteria for use during infancy.

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Original Article

Predicting Skin Barrier Dysfunction and Atopic Dermatitis in Early Infancy

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What is already known about this topic? Skin barrier dysfunction, measured by increased transepidermal water loss (TEWL), has been found to precede atopic dermatitis (AD). Dry skin, a cardinal sign of AD, is associated with higher TEWL.

What does this article add to our knowledge? The article reveals distinctive factors predictive for dry skin, high TEWL, and AD at 3 months of age. Dry skin at 3 months was predictive for AD 3 months later.

How does this study impact current management guidelines? Recognizing predictive factors for AD early in life, including the presence of dry skin, may help targeting infants for primary prevention of AD.

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Abbreviations used
AD- Atopic dermatitis
CI- Confidence interval
FLG- *Filaggrin*
GA- Gestational age
OR- Odds ratio
PreventADALL- Preventing Atopic Dermatitis and Allergies
SD- Standard deviation
TEWL- Transepidermal water loss

BACKGROUND: Dry skin is associated with increased transepidermal water loss (TEWL), which has been found to precede atopic dermatitis (AD) in childhood.
OBJECTIVE: We aimed to identify parental, prenatal, and perinatal predictive factors of dry skin, high TEWL, and AD at 3 months of age, and to determine if dry skin or high TEWL at 3 months can predict AD at 6 months.
METHODS: From the Preventing Atopic Dermatitis and Allergies in children prospective birth cohort study, we included 1150 mother-child pairs. Dry skin, TEWL, and eczema were assessed at 3- and 6-month investigations. Eczema, used as a proxy for AD, was defined as the presence of eczematous lesions, excluding differential diagnoses to AD. High TEWL was defined as TEWL >90th percentile, equaling 11.3 g/m^2/h. Potential predictive factors were recorded from electronic questionnaires at 18- and 34-week pregnancy and obstetric charts.
RESULTS: Significant predictive factors ($P < .05$) for dry skin at 3 months were delivery >38 gestational weeks and paternal age >37 years; for high TEWL, male sex, birth during winter season, and maternal allergic disease; and for eczema, elective caesarean section, multiparity, and maternal allergic diseases. Dry skin without eczema at 3 months was predictive for eczema at 6 months (adjusted odds ratio: 1.92, 95% confidence interval: 1.21-3.05; $P = .005$), whereas high TEWL at 3 months was not.
CONCLUSION: In early infancy, distinct parental- and pregnancy-related factors were predictive for dry skin, high TEWL, and AD. Dry skin at 3 months of age was predictive for AD 3 months later.

Key words: *Dry skin; Xerosis; Skin barrier; Atopic dermatitis; Eczema; Allergic diseases; Atopy; TEWL; PreventADALL*

Atopic dermatitis (AD) is a chronic relapsing inflammatory skin disease that most often presents during early childhood.[1] The lifetime prevalence in industrialized countries is high, ranging from 15% to 20%.[2] Dry skin, erythema, and pruritus are hallmarks of the disease.[1] Diagnosis of AD is made clinically, sometimes using validated diagnostic criteria.[3,4]

The pathophysiological aspect of AD involves complex interactions between skin barrier function, immune dysregulation, and dysbiosis of the skin microbiota.[1,5] A dysfunctional skin barrier appears to be a key player in the development of the disease.[1,6] The clinical presence of dry skin, a cardinal feature of AD,[1,3,4] is indicative of an impaired skin barrier and correlates with elevated measures of transepidermal water loss (TEWL).[7,8] Recent studies suggest that increased TEWL in early infancy may precede and even predict the development of AD.[9-11] Infants with AD are at increased risk of developing food allergy, allergic rhinitis, and asthma in line with the proposed atopic march.[12,13] These findings provide a rationale for early life skin-directed treatment to enhance the barrier function and possibly prevent AD.[14-16]

The most prominent risk factors for the development of AD are parental allergic disease and the presence of mutations in the gene encoding filaggrin (*FLG*).[1,6,17] The most consistent environmental risk factors are low UV-light exposure, dry climate, urban living, small family size, high parental education level, and repeated treatment with antibiotics in early childhood.[17,18] In addition, the association between caesarean section and offspring allergic disease has been extensively investigated, however with conflicting results.[19-21] Increased knowledge of predictive factors of skin barrier dysfunction and AD in infancy is warranted to provide targeted prevention strategies. Studies aiming to identify predictors of dry skin and reduced skin barrier function measured by TEWL in early infancy have largely been lacking. We are not aware of previous studies investigating the presence and distribution of dry skin and later debut of AD in early infancy.

We recently showed in the Preventing Atopic Dermatitis and Allergies (PreventADALL) cohort that 59% of 3-month-old infants had dry skin, whereas of the 145 infants with eczema, 96% had dry skin. Dry skin without eczema on age-specific predilection sites of AD, cheeks, and extensor surfaces of extremities were significantly associated with increased TEWL.[8]

In this study, we hypothesized that dry skin or increased TEWL could predict AD in infancy. We aimed to identify factors that can predict dry skin, high TEWL, and AD at 3 months of age. Furthermore, we aimed to determine if dry skin, in general or on age-specific predilection sites of AD, or high TEWL at 3 months of age could predict AD at 6 months of age.

SUBJECTS AND METHODS

Study design

The present study included 1150 infants, attending the 3-month investigation, randomized to the 2 groups that did not receive skin care intervention from the general population-based PreventADALL study.[22] The PreventADALL multicenter, prospective, 2 × 2 factorial, interventional birth-cohort study investigates the effect of primary prevention of allergic diseases by early skin care and early complementary food introduction.

Women were recruited during the routine 18-week gestational age (GA) ultrasound examination at Oslo University Hospital, Østfold Hospital Trust (Norway) and Karolinska University Hospital (Stockholm, Sweden) between December 2014 and October 2016. Their infants, born at a GA of at least 35 weeks and without serious illnesses, were enrolled during the 1 to 2 first days of life. Infants attended follow-up visits at 3 and 6 months of age, with skin assessments performed by trained study personnel who were blinded to the randomization groups. Study information included comprehensive electronic questionnaires, weekly diaries, biological samples from mother and child, and clinical investigations. Study design, recruitment and inclusion criteria, and characteristics of the 2696 women and 2396 mother-child pairs have been described in detail in a previous paper.[22]

Informed consent forms were signed by the mother at enrollment, and by both parents (when relevant) on inclusion of the infant. The PreventADALL study was approved by the Regional Committee for

TABLE I. Baseline characteristics for pregnancy variables in 1150 infants attending the 3-month investigation, where "Unaffected skin" are infants without dry skin and eczema is defined as the presence of eczematous lesions, excluding differential diagnosis to atopic dermatitis; the table displays parental variables

Characteristics	Unaffected skin (N = 461)	Dry skin (N = 683) (139 with eczema)	Dry skin only (N = 544)	Eczema (N = 145)	Total (N = 1150)
Age mother (y), mean (SD, min-max) (N = 1150)	32.1 (4.1, 21.0-48.0)	32.9 (4.1, 21.0-47.0)	32.8 (4.1, 21.0-47.0)	33.2 (4.2, 22.0-43.0)	32.6 (4.1, 21.0-48.0)
Age father (y), mean (SD, min-max) (N = 983)	34.0 (5.0, 21.0-53.0)	35.3 (5.4, 21.0-72.0)	35.2 (5.4, 21.0-72.0)	35.3 (5.5, 23.0-55.0)	34.8 (5.3, 21.0-72.0)
Mother Nordic origin, N (%) (N = 1046)	405 (93.8)	545 (89.5)	433 (89.3)	117 (90.7)	955 (91.3)
Father Nordic origin, N (%) (N = 1026)	386 (90.8)	525 (88.1)	419 (88.6)	111 (86.7)	916 (89.3)
Education mother, >4 y of university, N (%) (N = 1040)	239 (55.5)	371 (61.4)	299 (62.2)	73 (57.0)	611 (58.8)
Education co-parent, >4 years of university, N (%) (N = 1001)	201 (48.8)	294 (50.3)	237 (51.0)	59 (47.6)	497 (49.7)
Family income, N (%) (N = 1032)					
Low	69 (16.2)	82 (13.6)	67 (14.0)	17 (13.4)	153 (14.8)
Middle	318 (74.6)	431 (71.7)	345 (72.0)	88 (69.3)	751 (72.8)
High	39 (9.2)	88 (14.6)	67 (14.0)	22 (17.3)	128 (12.4)
Single mother, N (%) (N = 1038)	6 (1.4)	11 (1.8)	8 (1.6)	3 (2.4)	17 (1.6)
BMI, mother at 18 wk of pregnancy, mean (SD, min-max) (N = 1132)	24.7 (3.7, 17.2-39.7)	24.8 (3.7, 18.4-41.4)	24.8 (3.6, 18.4-39.5)	25.2 (4.0, 19.4-41.4)	24.8 (3.7, 17.2-41.4)
≥1 previous parity, N (%) (N = 1046)	161 (37.3)	264 (43.3)	199 (41.0)	70 (54.3)	430 (41.1)
Allergic disease mother, N (%) (N = 1046)	261 (60.4)	408 (67.0)	318 (65.6)	94 (72.9)	673 (64.3)
Allergic disease father, N (%) (N = 1048)	217 (51.1)	304 (49.1)	228 (46.4)	77 (58.3)	522 (49.8)
Atopic dermatitis mother, doctor diagnosed, N (%) (N = 1046)	83 (19.2)	132 (21.7)	101 (20.8)	32 (24.8)	216 (20.7)
Atopic dermatitis father, doctor diagnosed, N (%) (N = 1048)	48 (11.3)	67 (10.8)	46 (9.4)	22 (16.7)	116 (11.1)
Asthma mother, doctor diagnosed, N (%) (N = 1046)	79 (18.3)	106 (17.4)	84 (17.3)	24 (18.6)	187 (17.9)
Asthma father, doctor diagnosed, N (%) (N = 1048)	64 (15.1)	79 (12.8)	61 (12.4)	19 (14.4)	144 (13.7)
Allergic rhinitis mother, doctor diagnosed, N (%) (N = 1046)	77 (17.8)	142 (23.3)	115 (23.7)	29 (22.5)	221 (21.1)
Allergic rhinitis father, doctor diagnosed, N (%) (N = 1048)	93 (21.9)	149 (24.1)	114 (23.2)	36 (27.3)	243 (23.2)
Food allergy mother, doctor diagnosed, N (%) (N = 1046)	56 (13.0)	81 (13.3)	67 (13.8)	14 (10.9)	137 (13.1)
Food allergy father, doctor diagnosed, N (%) (N = 1048)	34 (8.0)	59 (9.5)	48 (9.8)	12 (9.1)	94 (9.0)

BMI, Body mass index; *SD*, standard deviation.

TABLE II. Baseline characteristics for pregnancy variables in 1150 infants attending the 3-month investigation, where "Unaffected skin" are infants without dry skin and eczema is defined as the presence of eczematous lesions, excluding differential diagnosis to atopic dermatitis; the table displays prenatal and perinatal variables as well as variables related to the 3-mo investigation

Characteristics	Unaffected skin (N = 461)	Dry skin (N = 683) (139 with eczema)	Dry skin only (N = 544)	Eczema (N = 145)	Total (N = 1150)
Lifestyle during pregnancy					
Alcohol intake, N (%) (N = 914)	22 (5.1)	42 (7.7)	29 (6.0)	13 (10.1)	64 (7.0)
Tobacco use in general, N (%) (N = 1128)	54 (11.8)	66 (9.9)	54 (10.2)	13 (9.2)	121 (10.7)
Smoking, N (%) (N = 1128)	24 (5.3)	26 (3.9)	19 (3.6)	8 (5.7)	51 (4.5)
Snus use, N (%) (N = 1128)	34 (7.5)	42 (6.3)	37 (7.0)	5 (3.5)	76 (6.7)
Live rural, N (%) (N = 1046)	40 (9.3)	50 (8.2)	43 (8.9)	7 (5.4)	90 (8.6)
Exposure to humidity/mold, N (%) (N = 984)	51 (12.5)	83 (14.6)	69 (15.3)	16 (13.0)	136 (13.8)
Pets in general, N (%) (N = 1046)	116 (26.9)	133 (21.8)	105 (21.6)	29 (22.5)	250 (23.9)
Cat, no dog, N (%) (N = 1046)	48 (11.1)	41 (6.7)	30 (6.2)	12 (9.3)	90 (8.6)
Dog, no cat, N (%) (N = 1046)	53 (14.0)	70 (11.5)	59 (12.2)	11 (8.5)	123 (11.8)
Cat and dog, N (%) (N = 1046)	6 (1.4)	10 (2.0)	8 (1.6)	2 (1.6)	15 (1.4)
Pets except cat and dog, N (%) (N = 1046)	9 (2.1)	12 (2.0)	8 (1.6)	4 (3.1)	22 (2.1)
Caesarean section, N (%) (N = 1137)	69 (15.2)	106 (15.6)	80 (14.8)	27 (18.8)	176 (15.5)
Elective, N (%) (N = 1137)	22 (4.9)	42 (6.2)	30 (5.6)	12 (8.3)	64 (5.6)
Acute, N (%) (N = 1137)	47 (10.4)	64 (9.4)	50 (9.3)	15 (10.4)	112 (9.9)
Gestational age at birth (wk), mean (SD, min-max) (N = 1128)	39.1 (1.8, 35.0-42.9)	39.5 (1.6, 35.1-42.9)	39.6 (1.6, 35.1-42.9)	39.5 (1.6, 35.2-42.2)	39.3 (1.7, 35.0-42.9)
Female sex, N (%) (N = 1146)	221 (48.1)	307 (45.1)	251 (46.3)	58 (40.0)	530 (46.2)
Birth weight (kg), mean (SD, min-max) (N = 1114)	3.5 (0.5, 1.9-5.1)	3.6 (0.5, 2.1-5.0)	3.6 (0.5, 2.1-4.9)	3.7 (0.5, 2.6-5.0)	3.6 (0.5, 1.9-5.1)
Born during winter season (October-March), N (%) (N = 1146)	238 (51.9)	392 (57.6)	306 (56.5)	87 (60.0)	631 (55.1)
3-month investigation					
Age (d), mean (SD, min-max) (N = 1145)	94 (9.4, 55-150)	93 (7.6, 69-134)	93 (7.9, 69-134)	94 (6.4, 83-112)	93 (8.4, 55-150)
Weight (kg), mean (SD, min-max) (N = 1118)	6.2 (0.8, 4.4-9.3)	6.3 (0.8, 4.2-8.9)	6.3 (0.8, 4.2-8.7)	6.3 (0.7, 4.4-8.9)	6.3 (0.8, 4.2-9.3)
Length (cm), mean (SD, min-max) (N = 1125)	61.7 (2.4, 54.0-70.9)	62.0 (2.3, 51.0-69.5)	62.0 (2.3, 51.0-69.5)	62.1 (2.2, 56.8-68.5)	61.9 (2.3, 51.0-70.9)
TEWL ($g/m^2/h$), mean (SD, min-max) (N = 1026)	6.7 (3.5, 1.3-32.6)	8.5 (6.3, 1.6-46.2)	7.6 (5.3, 1.6-46.2)	12.4 (8.9, 3.3-45.2)	7.8 (5.5, 1.3-46.2)

SD, Standard deviation; *TEWL*, transepidermal water loss.

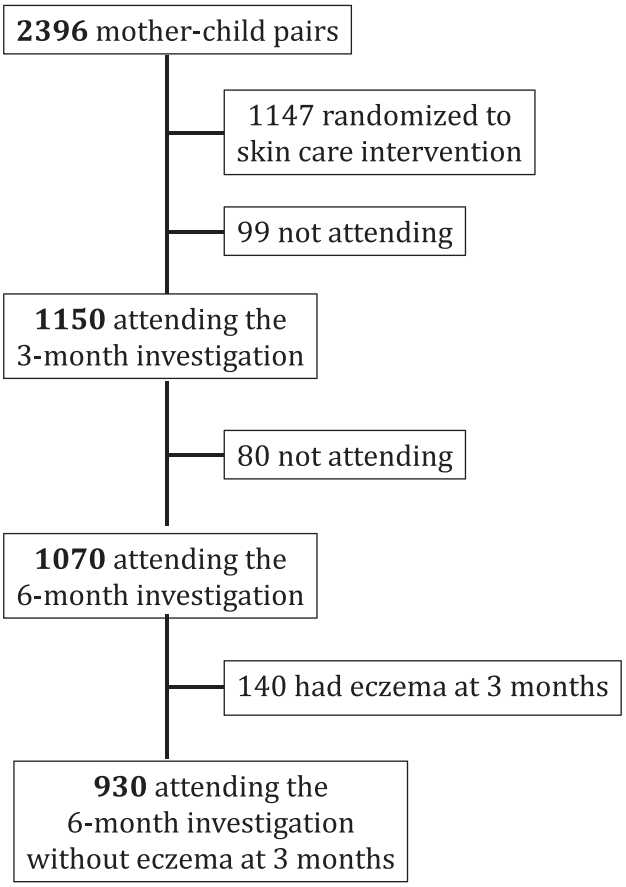

FIGURE 1. Outline of children in the present study is based on the source population of the Preventing Atopic Dermatitis and ALLergies in children (PreventADALL) with 2701 pregnancies included, resulting in a birth cohort of 2396 mother-child pairs.

Medical and Health Research Ethics in South-Eastern Norway (2014/518) and in Sweden (2014/2242-31/4), and registered at clinicaltrials.gov (NCT02449850).

Subjects

The 1150 infants had a mean GA of 39.3 weeks at birth and 46.2% were girls (Tables I and II).

For the secondary aim, we included all 930 of the 1070 infants who also attended the 6-month follow-up visit, excluding infants with eczema at the 3-month investigation, as shown in Figure 1. Detailed information on dry skin location at 3 months and eczema at 6 months was available in 913 infants.

Health personnel were trained to examine the skin by visual inspection and palpation. Observations of dry skin, presented as scaling and roughness, were recorded for 11 predefined anatomical skin areas[23] in terms of no, mild, moderate, or severe dry skin. Severity of dry skin was recorded in line with the principles of the Dry skin/Ichthyosis and Severity Index, but without their score of erythema.[24] *Mild dryness* was categorized as barely visible scaling and slight roughness when stroking the skin. *Moderate dryness* was categorized as clearly visible scaling with or without fissures, and roughness when stroking the skin. *Severe dryness* was categorized as abundant scaling and present fissures, as well as very rough skin when stroking the skin.

Eczema, used as a proxy for AD, was defined as the presence of eczematous lesions, verified by a medical doctor with the exclusion of differential diagnoses to AD.

TEWL measurements ($g/m^2/h$) were available in 1033 (89%) of the 3-month-old infants, using an open chamber DermaLab USB (Cortex, Hadsund, Denmark). We included measurements performed at room temperature between 20°C and 25°C only, in line with international recommendations,[25] while accepting humidity within the whole range 6% to 73%, mean 29%, standard deviation (SD) 12.7. Parents were instructed not to bathe the infants or use any emollients within 24 hours before the examination. Three successive measurements were performed on the left upper lateral arm after 15 minutes of acclimatization where the child was only wearing diaper, keeping the room temperature as close to 22°C as possible, noting ambient temperature and humidity. Measurements were only performed on calm children and windows and doors were kept shut.

Potential predictive factors were chosen on the basis of previously described risk factors for allergic diseases, potential relevant pregnancy-related factors, and baseline characteristics as outlined in Tables I and II.

Definitions and outcome

Unaffected skin was defined as no eczema and no dry skin. *Dry skin* included all infants with the presence of dry skin on at least 1 location, regardless of eczema. *Dry skin only* was defined as dry skin with no eczema and was further subcategorized into dry skin on cheeks, extensors, or both cheeks and extensors.

The outcomes in the present study were *Dry skin* (any location of dry skin), *Eczema*, and *High TEWL* (mean TEWL above 90th percentile) at 3 months of age and *Eczema* at 6 months of age.

Statistical analysis

Categorical variables are presented as numbers and percentages. Continuous variables are presented as means, SD, and minimum (min)-maximum (max).

Although the TEWL results did not display a perfect normal distribution, the deviation from normality was moderate, and we could therefore use parametric statistical methods for all our analyses. The independent sample *t*-test was used when comparing continuous variables, and the χ^2 test was used when comparing categorical variables.

Logistic regression analysis was used to investigate the associations between parental and pregnancy-related variables (Tables I and II) and the outcome variables *Dry skin*, *Eczema,* or *High TEWL.* We used univariate logistic regression analysis with a cutoff *P* value of .2, followed by complete-case multivariate regression analysis. The continuous variables that were found to be significant in the univariate regression analysis were analyzed as quartiles, with the lowest quartile as the reference value. If the strength of the association was higher in any quartile, we used the quartiles in the multivariate regression model. In each regression model, the assumption underlying multivariate logistic regression analysis was checked and found to be adequately met.

To investigate the impact of dry skin and high TEWL at 3 months of age on eczema at 6 months of age, the following 3 regression models were performed: Model 1: unadjusted. Model 2: the predictors from the multivariate logistic regression analyses at 3 months of age were used here. For dry skin we adjusted for the predictors found for dry skin and eczema, and for high TEWL we adjusted for the predictors found for high TEWL and eczema.

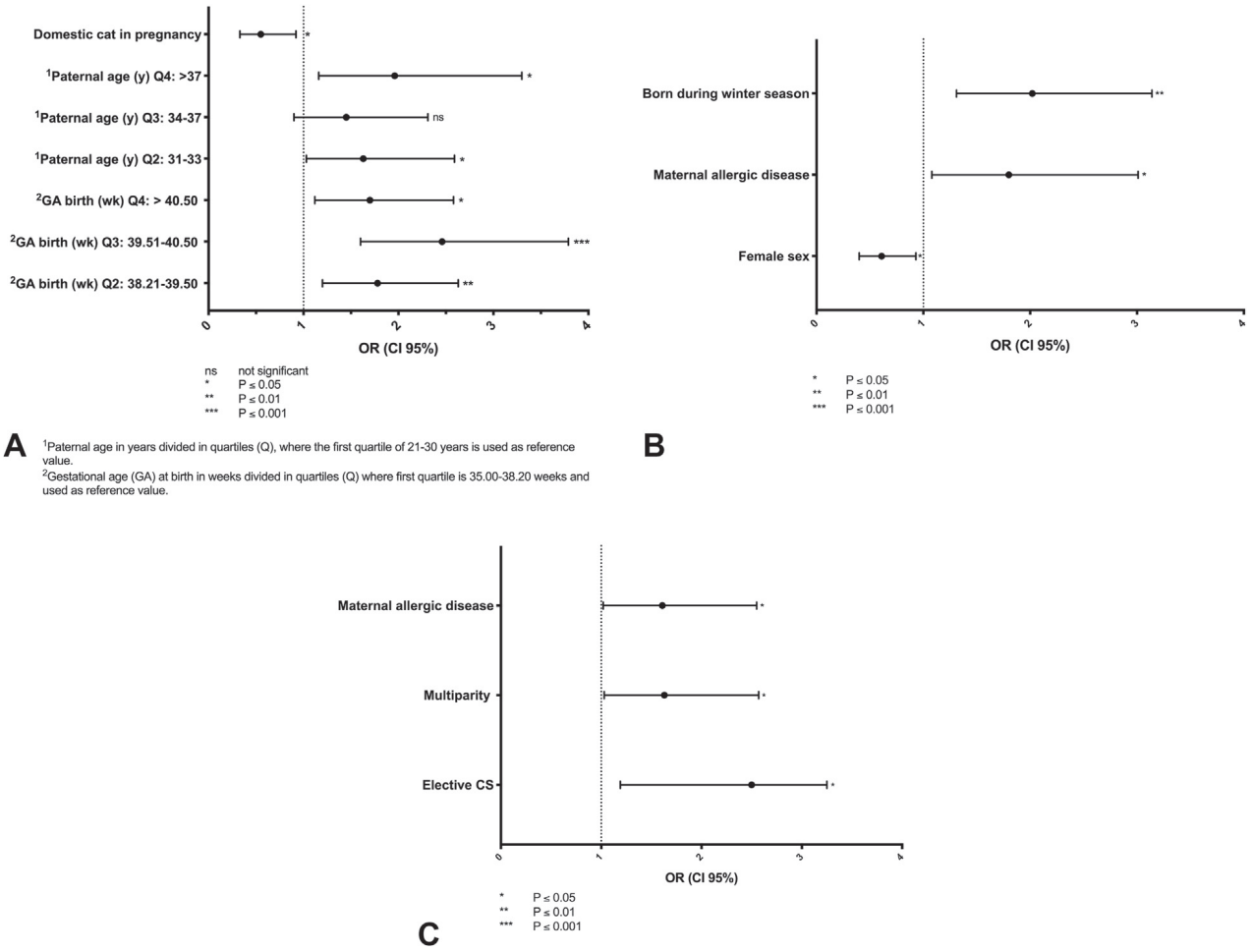

FIGURE 2. Significant predictors ($P < .05$) for dry skin (**A**), TEWL >90th percentile (11.3 g/m^2/h) (**B**), and eczema (**C**) at 3 months of age in 1150 infants, when using multivariate regression analysis shown as odds ratio and confidence intervals. **A**, Pregnancy variables with a cutoff *P* value of <.2 for predicting dry skin used in the multivariate analysis were GA at birth, birth weight, multiparity, domestic cat exposure, maternal age, paternal age, maternal allergic disease, maternal education, family income, and birth season. **B**, Pregnancy variables with a cutoff *P* value of <.2 for predicting TEWL >90th percentile (11.3 g/m^2/h) used in the multivariate analysis were female sex, birth weight, maternal allergic disease, maternal atopic dermatitis, and birth season. **C**, Pregnancy variables with a cutoff *P* value of <.2 for predicting eczema, defined as the presence of eczematous lesions, excluding differential diagnosis to atopic dermatitis, used in the multivariate analysis were female sex, birth weight, multiparity, elective caesarean section (CS), maternal age, maternal allergic disease, paternal allergic disease, snus during pregnancy, rural living, and family income. *CI*, Confidence interval; *OR*, odds ratio; *TEWL*, transepidermal water loss.

Model 3: variables from model 2 together with variables significantly associated with *Eczema* at 6 months from univariate logistic regression analysis (doctor diagnosed AD in father, alcohol consumption, and domestic cat during pregnancy). The statistical significance level was set to 5%. All analyses were performed using IBM SPSS statistics version 25 (Armonk, NY).

RESULTS

Baseline characteristics

At 3 months of age, 544 of the 1150 infants investigated had dry skin without eczema (dry skin only) and 145 had eczema. At 6 months of age, 163 of the 930 infants who attended the follow-up had eczema, excluding the infants with eczema at 3 months. Of 832 with valid TEWL measurements, 82 had high TEWL at 3 months. The clinical, socioeconomic, and demographic details of the study population are presented in Tables I and II for the infants at 3 months of age, and the details for the infants at 6 months of age are presented in Table E1 (available in this article's Online Repository at www.jaci-inpractice.org).

Predictive factors at 3 months of age

For *Dry skin*, GA and paternal age were statistical significant predictors in the multivariate analysis after including the 10 variables with a *P* value <.2 in the univariate logistic regression analysis (Figure 2, *A*, and Tables E2 and E5, available in this article's Online Repository at www.jaci-inpractice.org). When analyzed as continuous variables in univariate analyses, dry skin was significantly and positively associated with GA (odds ratio [OR]: 1.16, confidence interval [CI] 95%: 1.08-1.25; $P < .0001$) and paternal age (OR: 1.05, 95% CI: 1.02-1.07; $P = .001$). We analyzed the predictive impact by categorizing them into quartiles.

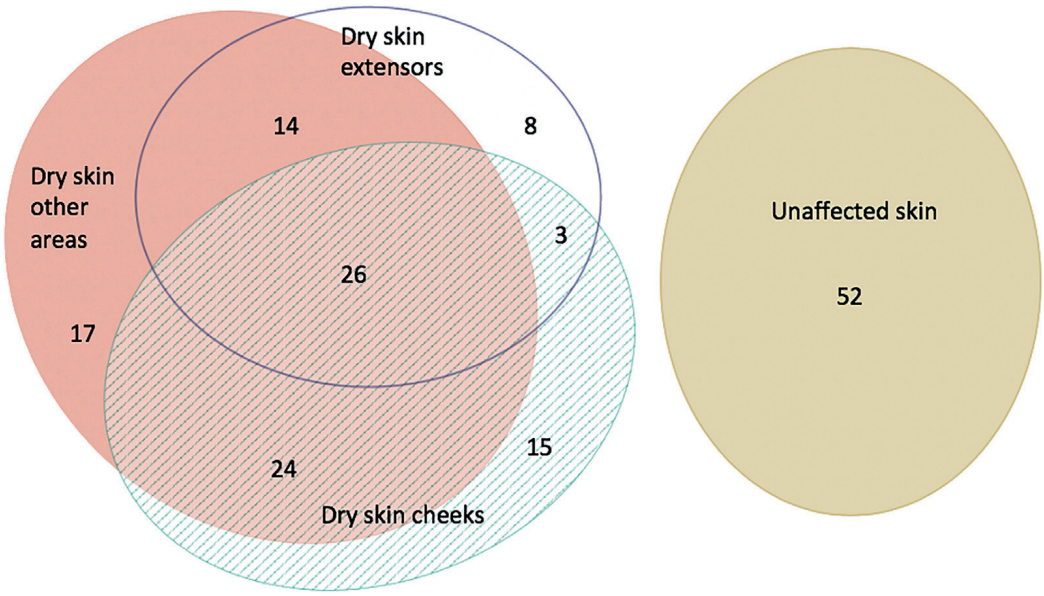

FIGURE 3. The Euler diagram depicts the distribution of dry skin at 3 months in 159 infants who at 6 months presented with eczema, used as a proxy for atopic dermatitis. Dry skin at 3 months, regardless of location, was a significant predictor for atopic dermatitis at 6 months of age with an OR (95% CI) of 1.92 (1.21-3.05) ($P = .005$), and an OR (95% CI) of 1.94 (1.20-3.15) ($P = .007$) for dry skin in the cheeks and/or the extensors specifically at 3 months. *CI*, Confidence interval; *OR*, odds ratio. Produced with courtesy of Micallef and Rodgers.[26] http://www.eulerdiagrams.org/eulerAPE.

In multivariate analyses, compared with the lower quartile of GA (35.0-38.2), the highest OR (OR: 2.46, 95% CI: 1.60-3.79; $P < .0001$) was found in the third quartile (GA 39.51-40.50), as shown in Figure 2, *A*, and Table E5 (available in this article's Online Repository at www.jaci-inpractice.org).

Similarly, for paternal age, the highest OR in multivariate analyses was found for the oldest age, with an OR: 1.96, 95% CI: 1.16 to 3.30; $P = .012$ in the fourth compared with reference (lowest) quartile. Domestic cat exposure during pregnancy was a significant protective factor for dry skin in the multivariate analysis (OR: 0.55, 95% CI: 0.33-0.92; $P = .023$).

For *High TEWL,* 3 variables were statistically significant in the multivariate analysis, namely female sex (OR: 0.61, 95% CI: 0.40-0.93; $P = .022$), maternal allergic disease (OR: 1.80, 95% CI: 1.08-3.01; $P = .025$), and birth during winter season (OR: 2.02, 95% CI: 1.31-3.14; $P = .002$) (Figure 2, *B*, and Tables E3 and E6, available in this article's Online Repository at www.jaci-inpractice.org), after including the 6 variables with a *P* value <.2 in the univariate logistic regression analysis.

For *Eczema,* 3 variables were statistically significant in the multivariate analysis, namely elective caesarean section (OR: 2.50, 95% CI: 1.19-5.25; $P = .016$), multiparity (1 or more previous deliveries) (OR: 1.63, 95% CI: 1.03-2.57; $P = .037$), and maternal allergic disease (OR: 1.61, 95% CI: 1.02-2.55; $P = .041$) (Figure 2, *C*, and Tables E4 and E7, available in this article's Online Repository at www.jaci-inpractice.org), after including 10 variables with a *P* value <.2 in the univariate logistic regression analysis. Paternal allergic disease was statistically significant in the univariate analysis (OR: 1.46, 95% CI: 1.01-2.13; $P = .046$), as well as birthweight in the fourth quartile >3.9 kg (OR: 1.89, 95% CI: 1.14-3.13; $P = .014$) compared with reference (lowest quartile).

Dry skin or *High TEWL* and *Eczema* at 6 months of age

Infants who at 3 months of age had *Dry skin only,* regardless of location, were significantly more often diagnosed with *Eczema* at 6 months of age (21.7%) compared with the infants with *Unaffected skin* (12.4%) (Figure 3), giving an unadjusted OR (95% CI) of 1.96 (1.37-2.80) ($P < .0001$). *Dry skin* at 3 months increased the risk of *Eczema* at 6 months by an OR (95% CI) of 1.92 (1.21-3.05) ($P = .005$) in the multivariate analysis adjusting for elective caesarean section, GA at birth, multiparity, paternal age, maternal allergic disease, paternal allergic disease, paternal AD, alcohol consumption during pregnancy, and domestic cat during pregnancy. Similar risk was observed using dry skin in the cheeks and/or the extensors, OR (95% CI) of 1.94 (1.20-3.15) ($P = .007$), adjusted for the same 9 variables. The prediction of *Eczema* at 6 months of age with *Dry skin* at 3 months of age had a sensitivity of 68% and a specificity of 48%.

Mean TEWL ($g/m^2/h$) in 3-month-old infants was not significantly associated with *Eczema* at 6 months as a continuous variable or by quartiles in univariate or multivariate analysis. *High TEWL* was significantly associated with *Eczema* at 6 months of age compared with mean TEWL <90th percentile (N = 750) (OR: 1.80, 95% CI: 1.07-3.04; $P = .028$) in univariate analysis, but did not remain statistically significant after adjustment for relevant factors outlined in Tables E5-E7 (available in this article's Online Repository at www.jaci-inpractice.org).

DISCUSSION

In the present population-based prospective mother-child cohort, we found increased paternal age and GA at birth to be predictive of dry skin at 3 months of age, and maternal allergic

disease, male sex, and birth season were predictive for high TEWL (>90th percentile). For eczema at 3 months the predictors were elective caesarean section, at least 1 previous delivery, and maternal allergic disease. Dry skin at 3 months of age predicted AD at 6 months of age.

Our finding of increased GA and paternal age as predictors for dry skin has, to our knowledge, not previously been assessed. As dry skin is a main feature of AD, our findings are supported by reports of increasing GA being associated with AD.[27-29] The highest risk for dry skin was found among our children with the highest GA at birth, in line with reports of inverse associations between prematurity (GA <29 weeks) and AD.[30,31] These findings may be explained by shorter exposure time to the maternal immune system and Th2 cytokines, lower levels of IgE, and a different composition of early gut and skin microbiome.[27,29,30] Post-term neonatal skin having less vernix may experience longer direct exposure to amniotic fluid, which can disrupt the stratum corneum lipid bilayer,[32,33] and promote post-term skin dryness and higher TEWL values. Pregnancy length may thus be implicated in the skin integrity.[29,30] Our finding of advanced paternal age, especially above 37 years, being a predictor for dry skin, is, to our knowledge, novel and could reflect a possible age-related increase in mutations.[34]

The protective effect of female sex on high TEWL is supported by previous findings that males have an earlier onset of AD compared with females.[29,35] Similar to our study, a recent Japanese study found significantly higher TEWL in male infants.[36] In contrast, TEWL in neonates was indistinguishable between males and females in an Indian study.[37] Our findings that infants born during fall and winter season had higher TEWL at 3 months of age than those born during spring or summer are supported by reports that birth during fall and winter has been associated with increased risk of AD.[31,38,39] These findings may be explained by cold climate and low environmental humidity that have been associated with impaired skin barrier function.[18,38,40-42] Exposure to a dry and cold winter climate may lead to depletion of filaggrin and other skin barrier proteins as well as lipids[18,43] and by lower cumulative UV irradiation before and after birth.[38]

Our finding that multiparity was a predictor of AD at 3 months is in contrast to one of the key arguments for the hygiene hypothesis where having older siblings reduces the risk of AD,[44] but more in agreement with a study showing that the risk of AD was not reduced by having older siblings.[45] In that study, a higher prevalence of eczema in children carrying *FLG* mutations was found if they had older siblings,[45] supported by larger sibships increasing the risk of severe AD.[44] Parental allergic disease, a well-known risk factor for offspring AD,[1,17] was also a predictor of AD in our population. In our cohort, elective caesarean section was predictive of eczema at 3 months, whereas acute caesarean section was not. To our knowledge, this is the first study reporting on elective caesarean section being a predictor of AD in early infancy. The vast majority of the elective caesarean sections were before rupture of amniotic membranes, and we hypothesize that a lacking exposure to the vaginal flora in elective caesarean sections (without rupture of amniotic membranes)[46] may contribute to an offspring gut and skin microbiome dysbiosis associated with AD.[5] Our results may imply that onset of AD by 3 months of age may be dominated by a genetic predisposition to allergic disease, but may be modified by mode of delivery and exposure to maternal vaginal flora.

Dry skin, but not TEWL at 3 months being a predictor of AD at 6 months, has, to our knowledge, not previously been reported. There are no direct comparable studies, nonetheless dry skin is a cardinal sign of AD,[1,8,43,47] and we[8] and others[48] have demonstrated that infants with dry skin have increased TEWL. In this study, the risk of AD at 6 months was particularly noticeable with dry skin on the cheeks and/or on the extensor surfaces of extremities at 3 months of age. Eczema of the cheeks is often the first manifestation of AD, and a recent Irish study by McAleer et al[49] demonstrated that in 188 infants the skin of the cheeks was slower to mature than the skin of the nasal tip and elbow creases, and had lower levels of natural moisturizing factor. This indicates that early-onset AD may be due to a physiological skin barrier dysfunction restricted to a specific body location, possibly enhanced by factors such as male sex, birth season, and various environmental factors.

Although high TEWL at 3 months did not predict eczema at 6 months after adjusting for potential confounders, it remains to be investigated whether TEWL can predict AD at later time points[9-11] in our cohort. The presence of clinically dry skin could precede AD without increased TEWL. Although our findings support the outside-inside hypothesis of AD,[43] dry skin at 3 months as a predictor of AD at 6 months has low sensitivity and specificity and cannot be used as a single predictive tool for such a heterogeneous disease as AD.[50,51] In line with the concept of the atopic march,[12,13] or the association between dry skin and asthma in adults,[52] early identification of dry skin may be useful as screening for targeted primary prevention provided that skin barrier enhancement is effective in reducing AD.

The strengths of our study include a large prospective cohort study from a general population, with high follow-up rate and stringent skin assessment by trained personnel as well as TEWL measurements, and parental risk factors prospectively recorded during pregnancy. The majority of the study participants originate from Nordic countries, which may to some extent limit the generalizability.[53] Our study had several limitations, including infants only born from 35 weeks of GA, genetic analysis including *FLG* mutations was not available, and we could not use the UK Working Party criteria for AD[4] at this age, mainly due to difficulties in evaluating the infant sensation of itch. The relatively high number of possible predictors for the 3-month outcomes included in the analysis together with possible bias of missing data introduces a risk of false-positive results. This must be taken into account when interpreting the results.

In conclusion, at 3 months of age, increasing paternal age and GA at birth were predictive for dry skin. Maternal allergic disease, male sex, and winter birth season were predictive for high TEWL, whereas for eczema the predictors were elective caesarean section, at least 1 previous delivery, and maternal allergic disease. Dry skin at 3 months of age, predicting AD at 6 months of age, may represent a factor in targeting infants for primary prevention of AD and possibly also food allergy and asthma.

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TABLE E1. Baseline characteristics in 930 infants attending 6-month investigation, grouped into No eczema and Eczema, defined as the presence of eczematous lesions, excluding differential diagnosis to AD*

Characteristics	No eczema 6 mo (N = 767)	Eczema 6 mo (N = 163)	Total (N = 930)
Age mother (y), mean (SD, min-max) (N = 927)	32.6 (4.1, 21.0-47.0)	32.3 (3.7, 25.0-42.0)	32.5 (4.1, 21.0-47.0)
Age father (y), mean (SD, min-max) (N = 804)	34.8 (5.3, 21.0-72.0)	34.7 (5.1, 25.0-51.0)	34.8 (5.3, 21.0-72.0)
Mother Nordic origin, N (%) (N = 854)	648 (91.8)	135 (91.2)	783 (91.7)
Father Nordic origin, N (%) (N = 837)	621 (89.6)	128 (88.9)	749 (89.5)
Education mother, >4 y of university, N (%) (N = 849)	409 (58.3)	97 (65,5)	506 (59.6)
Education co-parent, >4 y of university, N (%) (N = 817)	344 (50.7)	68 (49.3)	412 (50.4)
Family income, N (%) (N = 842)			
Low	105 (15.1)	18 (12.2)	123 (14.6)
Middle	510 (73.4)	110 (74.8)	620 (73.6)
High	80 (11.5)	19 (12.9)	99 (11.8)
BMI, mother at 18 wk of pregnancy, mean (SD, min-max) (N = 918)	24.8 (3.7, 18.3-39.5)	24.5 (3.2, 17.2-36.1)	24.8 (3.6, 17.2-39.5)
≥1 previous parity, N (%) (N = 854)	286 (40.5)	49 (33.1)	335 (39.2)
Allergic disease mother, N (%) (N = 854)	449 (63.6)	94 (63.5)	543 (63.6)
Allergic disease father, N (%) (N = 853)	334 (47.6)	82 (54.3)	416 (48.8)
Atopic dermatitis mother, doctor diagnosed, N (%) (N = 854)	141 (20.0)	28 (18.9)	169 (19.8)
Atopic dermatitis father, doctor diagnosed, N (%) (N = 774)	65 (10.1)	22 (16.5)	87 (11.2)
Asthma mother, doctor diagnosed, N (%) (N = 854)	123 (17.4)	28 (18.9)	151 (17.7)
Asthma father, doctor diagnosed, N (%) (N = 826)	96 (14.2)	22 (14.9)	118 (14.3)
Allergic rhinitis mother, doctor diagnosed, N (%) (N = 778)	150 (23.3)	26 (19.5)	176 (22.6)
Allergic rhinitis father, doctor diagnosed, N (%) (N = 781)	157 (24.3)	41 (30.6)	198 (25.4)
Food allergy mother, doctor diagnosed, N (%) (N = 808)	99 (14.8)	17 (12.2)	116 (14.4)
Food allergy father, doctor diagnosed, N (%) (N = 812)	60 (8.9)	15 (10.6)	75 (9.2)
Lifestyle during pregnancy			
Alcohol intake, N (%) (N = 774)	33 (5.4)	15 (11.3)	48 (6.5)
Tobacco use in general, N (%) (N = 915)	78 (10.4)	15 (9.3)	93 (10.2)
Smoking, N (%) (N = 915)	33 (4.4)	3 (1.9)	36 (3.9)
Snus use, N (%) (N = 915)	51 (6.8)	12 (7.4)	63 (6.9)
Live rural, N (%) (N = 854)	67 (9.5)	13 (8.8)	80 (9.4)
Exposure to humidity/mold, N (%) (N = 806)	87 (13.1)	27 (19.0)	114 (14.1)
Pets in general, N (%) (N = 854)	180 (25.5)	27 (18.2)	207 (24.2)
Cat, no dog, N (%) (N = 854)	69 (9.8)	5 (3.4)	74 (8.7)
Dog, no cat, N (%) (N = 854)	86 (12.2)	17 (11.5)	103 (12.1)
Cat and dog, N (%) (N = 854)	12 (1.7)	2 (1.4)	14 (1.6)
Pets except cat and dog, N (%), (N = 854)	13 (1.8)	3 (2.0)	16 (1.9)
Caesarean section, N (%) (N = 918)	104 (13.7)	27 (18.0)	133 (14.4)
Elective, N (%) (N = 918)	33 (4.4)	12 (7.5)	45 (4.9)
Acute, N (%) (N = 918)	71 (9.4)	17 (10.6)	88 (9.6)
Gestational age at birth (wk), mean (SD, min-max) (N = 913)	39.3 (1.7, 35.0-42.9)	39.4 (1.6, 35.2-42.9)	39.3 (1.7, 35.0-42.9)
Female sex, N (%) (N = 927)	370 (48.2)	70 (43.2)	440 (47.5)
Birth weight (kg), mean (SD, min-max) (N = 897)	3.6 (0.5, 1.9-4.9)	3.6 (0.5, 2.2-5.1)	3.5 (0.5, 1.9-5.1)
Born during winter season (October-March), N (%) (N = 927)	429 (56.1)	84 (51.9)	513 (55.3)
6-mo investigation			
Age (d), mean (SD, min-max) (N = 927)	190 (13.5, 146-248)	189 (11.7, 155-224)	190 (13.2, 146-248)
Weight (kg), mean (SD, min-max) (N = 907)	8.1 (1.0, 5,3-11,9)	8.1 (1.0, 5.2-12.3)	8.1 (1.0, 5.2-12.3)
Length (cm), mean (SD, min-max) (N = 913)	68.5 (2.6, 52.0-82.3)	68.6 (2.7, 62,3-77.0)	68.5 (2.7, 52.0-82.7)

AD, Atopic dermatitis; *BMI*, body mass index; *SD*, standard deviation.
*Those with eczema at the 3-month investigation have been excluded.

TABLE E2. Results of univariate analysis for dry skin as a dependent variable presented as complete case analysis showing N (%) of individuals included in the analysis with OR (95% CI) and *P* value

Pregnancy variables	N (%) of 1150 included in analysis (complete cases for dry skin as outcome)	OR (95% CI)	*P* value
Maternal age (y)			
Q1 (21-29)	1150 (100%)	Ref.	
Q2 (30-32)		1.20 (0.86-1.65)	.28
Q3 (33-35)		1.66 (1.17-2.35)	.004
Q4 (>35)		1.81 (1.27-2.56)	.001
Paternal age (y)			
Q1 (21-30)	983 (85.5%)	Ref.	
Q2 (31-33)		1.55 (1.06-2.26)	.024
Q3 (34-37)		1.53 (1.06-2.20)	.023
Q4 (>37)		2.04 (1.40-2.97)	<.0001
Education mother, >4 y of university	1040 (90.4%)	1.30 (1.01-1.67)	.039
Education co-parent, >4 y of university	1001 (87%)	1.06 (0.82-1.36)	.649
Family income			
Low	1032 (89.7%)	Ref.	
Middle		1.17 (0.82-1.65)	.388
High		1.91 (1.17-3.11)	.010
BMI, mother at 18 wk of pregnancy	1132 (98.4%)	1.01 (0.98-1.04)	.641
≥1 previous parity	1046 (91%)	1.25 (0.97-1.61)	.082
Allergic disease mother	1046 (91%)	1.32 (1.02-1.70)	.035
Allergic disease father	1023 (89%)	0.93 (0.72-1.19)	.549
Atopic dermatitis mother, doctor diagnosed	1046 (91%)	1.16 (0.86-1.58)	.334
Atopic dermatitis father, doctor diagnosed	954 (83%)	0.92 (0.62-1.37)	.695
Asthma mother, doctor diagnosed	1046 (91%)	0.93 (0.67-1.28)	.638
Asthma father, doctor diagnosed	1014 (88.2%)	0.83 (0.58-1.18)	.291
Allergic rhinitis mother, doctor diagnosed	952 (82.8%)	1.48 (1.08-2.02)	.014
Allergic rhinitis father, doctor diagnosed	957 (83.2%)	1.16 (0.86-1.56)	.342
Food allergy mother, doctor diagnosed	975 (84.8%)	1.07 (0.74-1.54)	.724
Food allergy father, doctor diagnosed	990 (86.1%)	1.20 (0.76-1.86)	.411
Alcohol intake	914 (79.5%)	1.33 (0.78-2.27)	
Smoking	1128 (98.1%)	0.71 (0.40-1.24)	.228
Snus use	1128 (98.1%)	0.84 (0.53-1.35)	.478
Rural living	1046 (91%)	0.89 (0.57-1.37)	.592
Exposure to humidity/mold	984 (85.6%)	1.16 (0.80-1.68)	.430
Pets (no pets as ref.)	1046 (91%)		
Cat, no dog		0.56 (0.36-0.87)	.01
Dog, no cat		0.89 (0.61-1.30)	.544
Cat and dog		1.12 (0.40-3.11)	.827
Pets except cat and dog		0.90 (0.37-2.15)	.807
Caesarean section (vaginal as ref.)			.344
Elective	1137 (98.9%)	1.29 (0.76-2.20)	
Acute		0.90 (0.61-1.34)	.903
Birth GA (wk)			
Q1 (35.00-38.20)	1088 (94.6%)	Ref.	
Q2 (38.21-39.50)		1.87 (1.33-2.63)	<.0001
Q3 (39.51-40.50)		2.50 (1.75-3.60)	<.0001
Q4 (>40.50)		1.84 (1.32-2.60)	<.0001
Female sex	1146 (99.7%)	0.89 (0.70-1.13)	.338
Birth weight (kg)			
Q1 (1.50-3.30)	1099 (95.6%)	Ref.	
Q2 (3.31-3.60)		1.22 (0.87-1.71)	.255
Q3 (3.61-3.90)		1.28 (0.91-1.79)	.159
Q4 (>3.90)		1.65 (1.17-2.33)	.005
Born during winter season (October-March)	1146 (99.7%)	1.28 (1.01-1.63)	.040

BMI, Body mass index; *CI*, confidence interval; *GA*, gestational age; *OR*, odds ratio; *Q*, quartile.

TABLE E3. Results of univariate analysis for high TEWL as a dependent variable presented as complete case analysis showing N (%) of individuals included in the analysis with OR (95% CI) and *P* value

Pregnancy variables	N (%) of 1033 included in analysis (complete cases for high TEWL as outcome)	OR (95% CI)	*P* value
Maternal age (y)			
Q1 (21-29)	1024 (99.1)	Ref.	
Q2 (30-32)		1.14 (0.68-1.90)	.621
Q3 (33-35)		1.09 (0.63-1.86)	.766
Q4 (>35)		1.02 (0.59-1.75)	.958
Paternal age (y)			
Q1 (21-30)	876 (84.8%)	Ref.	
Q2 (31-33)		0.78 (0.43-1.42)	.415
Q3 (34-37)		0.73 (0.41-1.30)	.290
Q4 (>37)		0.97 (0.55-1.71)	.919
Education mother, >4 y of university	925 (89.5%)	1.15 (0.77-1.71)	.508
Education co-parent, >4 y of university	892 (86.4%)	1.03 (0.69-1.52)	.900
Family income			
Low	919 (89.0%)	Ref.	
Middle		0.90 (0.51-1.57)	.701
High		1.45 (0.72-2.93)	.298
BMI, mother at 18 wk of pregnancy	1007 (97.5%)	1.02 (0.97-1.07)	.392
≥1 previous parity	931 (90.1%)	1.09 (0.73-1.61)	.683
Allergic disease mother	931 (90.1%)	1.88 (1.20-2.94)	.006
Allergic disease father	907 (87.8%)	1.25 (0.85-1.84)	.260
Atopic dermatitis mother, doctor diagnosed	931 (90.1%)	1.58 (1.01-2.47)	.046
Atopic dermatitis father, doctor diagnosed	840 (81.3%)	1.41 (0.81-2.45)	.221
Asthma mother, doctor diagnosed	931 (90.1%)	1.79 (1.14-2.82)	.012
Asthma father, doctor diagnosed	899 (87%)	0.77 (0.43-1.40)	.391
Allergic rhinitis mother, doctor diagnosed	853 (82.6%)	1.24 (0.77-1.99)	.372
Allergic rhinitis father, doctor diagnosed	849 (82.2%)	1.40 (0.91-2.15)	.131
Food allergy mother, doctor diagnosed	866 (83.8%)	1.67 (0.99-2.81)	.055
Food allergy father, doctor diagnosed	876 (84.8%)	0.78 (0.38-1.61)	.504
Alcohol intake	811 (78.5%)	1.55 (0.76-3.18)	.231
Smoking	1004 (97.2%)	1.28 (0.56-2.92)	.564
Snus use	1004 (97.2%)	1.17 (0.58-2.36)	.653
Rural living	931 (90.1%)	1.27 (0.65-2.49)	.483
Exposure to humidity/mold	874 (84.6%)	1.00 (0.56-1.78)	.986
Pets (no pets as ref.)	931 (90.1%)		
Cat, no dog		0.96 (0.46-1.99)	.911
Dog, no cat		1.40 (0.80-2.47)	.240
Cat and dog		1.05 (0.24-4.70)	.949
Pets except cat and dog		1.23 (0.35-4.25)	.749
Caesarean section (vaginal as ref.)			.768
Elective	1014 (98.2%)	1.12 (0.52-2.44)	
Acute		0.99 (0.53-1.82)	.965
Birth GA (wk)			
Q1 (35.00-38.20)	969 (93.8%)	Ref.	
Q2 (38.21-39.50)		1.05 (0.60-1.83)	.868
Q3 (39.51-40.50)		1.20 (0.69-2.09)	.524
Q4 (>40.50)		1.24 (0.72-2.11)	.438
Female sex	1020 (98.7%)	0.64 (0.44-0.94)	.021
Birth weight (kg)			
Q1 (1.50-3.30)	979 (94.8)	Ref.	
Q2 (3.31-3.60)		0.92 (0.52-1.63)	.771
Q3 (3.61-3.90)		1.35 (0.79-2.30)	.268
Q4 (>3.90)		1.54 (0.92-2.59)	.103
Born during winter season (October-March)	1020 (98.7%)	1.90 (1.27-2.82)	.002

BMI, Body mass index; *CI*, confidence interval; *GA*, gestational age; *OR*, odds ratio; *Q*, quartile; *TEWL*, transepidermal water loss.

TABLE E4. Results of univariate analysis for eczema as a dependent variable presented as complete case analysis showing N (%) of individuals included in the analysis with OR (CI 95%) and *P* value

Pregnancy variables	N (%) of 1150 included in analysis (complete cases for AD as outcome)	OR (95% CI)	*P* value
Maternal age (y)			
Q1 (21-29)	1150 (100%)	Ref.	
Q2 (30-32)		1.07 (0.63-1.85)	.796
Q3 (33-35)		1.62 (0.95-2.75)	.074
Q4 (>35)		1.80 (1.07-3.04)	.028
Paternal age (y)			
Q1 (21-30)	983 (85.5%)	Ref.	
Q2 (31-33)		0.78 (0.42-1.47)	.445
Q3 (34-37)		1.42 (0.82-2.47)	.207
Q4 (>37)		1.25 (0.71-2.20)	.448
Education mother, >4 y of university	1040 (90.4%)	0.92 (0.64-1.34)	.673
Education co-parent, >4 y of university	1001 (87.0%)	0.91 (0.62-1.32)	.622
Family income			
Low	1032 (89.7%)	Ref.	
Middle		1.06 (0.61-1.84)	.831
High		1.66 (0.84-3.28)	.145
BMI, mother at 18 wk of pregnancy (continuous)	1116 (97.0%)	1.04 (0.00-1.09)	.117
BMI, mother normal (BMI 18-24.9)		Ref.	
BMI, mother overweight (BMI 25-29.9)		1.23 (0.83-1.81)	.307
BMI, mother obese (BMI ≥30)		1.25 (0.68-2.29)	.483
≥ 1 previous parity	1046 (91%)	1.84 (1.27-2.67)	.001
Allergic disease mother	1046 (91%)	1.57 (1.04-2.36)	.032
Allergic disease father	1023 (89%)	1.46 (1.01-2.13)	.046
Atopic dermatitis mother, doctor diagnosed	1046 (91%)	1.31 (0.85-2.02)	.214
Atopic dermatitis father, doctor diagnosed	954 (83%)	1.75 (1.05-2.91)	.032
Asthma mother, doctor diagnosed	1046 (91%)	1.06 (0.66-1.70)	.818
Asthma father, doctor diagnosed	1014 (88.2%)	1.04 (0.62-1.75)	.885
Allergic rhinitis mother, doctor diagnosed	952 (82.8%)	1.15 (0.73-1.80)	.549
Allergic rhinitis father, doctor diagnosed	957 (83.2%)	1.34 (0.88-2.04)	.174
Food allergy mother, doctor diagnosed	975 (84.8%)	0.87 (0.48-1.57)	.643
Food allergy father, doctor diagnosed	990 (86.1%)	1.08 (0.57-2.04)	.815
Alcohol intake	914 (79.5%)	1.79 (0.94-3.4)	.076
Smoking	1128 (98.1%)	1.32 (0.61-2.87)	.483
Snus use	1128 (98.1%)	0.474 (0.10-1.20)	.114
Rural living	1046 (91%)	0.58 (0.26-1.28)	.174
Exposure to humidity/mold	984 (95.6%)	0.92 (0.53-1.61)	.780
Pets (no pets as ref.)	1046 (91%)		
Cat, no dog		1.07 (0.56-2.04)	.687
Dog, no cat		0.68 (0.36-1.31)	.254
Cat and dog		0.99 (0.22-4.44)	.994
Pets except cat and dog		1.64 (0.54-4.97)	.383
Caesarean section (vaginal as ref.)			.128
Elective	1137 (98.9%)	1.67 (0.86-3.21)	
Acute		1.12 (0.63-1.99)	.710
Birth GA (wk)			
Q1 (35.00-38.20)	1088 (94.6%)	Ref.	
Q2 (38.21-39.50)		1.16 (0.69-1.94)	.585
Q3 (39.51-40.50)		1.16 (0.68-1.98)	.590
Q4 (>40.50)		1.34 (0.81-2.22)	.259
Female sex	1146 (99.7%)	0.75 (0.52-1.01)	.107
Birth weight (kg)			
Q1 (1.50-3.30)	1099 (95.6%)	Ref.	
Q2 (3.31-3.60)		1.18 (0.68-2.03)	.559

(continued)

TABLE E4. *(Continued)*

Pregnancy variables	N (%) of 1150 included in analysis (complete cases for AD as outcome)	OR (95% CI)	*P* value
Q3 (3.61-3.90)		1.34 (0.78-2.27)	.280
Q4 (>3.90)		1.89 (1.14-3.13)	.014
Born during winter season (October-March)	1146 (99.7%)	1.26 (0.88-1.80)	.201

AD, Atopic dermatitis; *BMI*, body mass index; *CI*, confidence interval; *GA*, gestational age; *OR*, odds ratio; *Q*, quartile.

TABLE E5. Multivariate complete case logistic regression, where the dependent variable was *Dry skin* in 1150 three-month-old infants

Pregnancy variables	N = 879 OR (95% CI)	*P* value
Birth GA (wk)		
Q1 (35.00-38.20)		Ref.
Q2 (38.21-39.50)	1.78 (1.20-2.67)	.005
Q3 (39.51-40.50)	2.46 (1.60-3.79)	<.0001
Q4 (>40.50)	1.70 (1.12-2.58)	.013
Birth weight (kg)		
Q1 (1.50-3.30)		Ref.
Q2 (3.31-3.60)	1.03 (0.69-1.53)	.883
Q3 (3.61-3.90)	1.00 (0.66-1.52)	.987
Q4 (>3.90)	1.36 (0.89-2.08)	.163
Multipara	1.02 (0.75-1.41)	.882
Domestic cat exposure	0.554 (0.33-0.92)	.023
Maternal age (y)		
Q1 (21-29)		Ref.
Q2 (30-32)	0.84 (0.61-1.44)	.769
Q3 (33-35)	1.36 (0.83-2.22)	.747
Q4 (>35)	1.10 (0.63-1.90)	.747
Paternal age (y)		
Q1 (21-30)		Ref.
Q2 (31-33)	1.63 (1.03-2.59)	.037
Q3 (34-37)	1.45 (0.90-2.31)	.124
Q4 (>37)	1.96 (1.16-3.30)	.012
Maternal allergic disease	1.28 (0.95-1.712)	.106
Maternal education >4 y university	1.10 (0.81-1.49)	.565
Family income		
Low		Ref.
Middle	0.93 (0.61-1.44)	.754
High	1.34 (0.73-2.46)	.351
Born during winter season	1.29 (0.97-1.72)	.076

CI, Confidence interval; *GA*, gestational age; *OR*, odds ratio; *Q*, quartile.

TABLE E6. Multivariate complete case logistic regression, where the dependent variable was *High TEWL* (TEWL >90th percentile [11.3 g/m^2/h]) in 1150 three-month-old infants

Pregnancy variables	N = 888 OR (95% CI)	*P* value
Female sex	0.61 (0.40-0.93)	.022
Birth weight (kg)		
Q1 (1.50-3.30)	Ref.	
Q2 (3.31-3.60)	0.95 (0.52-1.76)	.879
Q3 (3.61-3.90)	1.26 (0.70-2.27)	.445
Q4 (>3.90)	1.33 (0.74-2.38)	.337
Maternal any allergic disease	1.80 (1.08-3.01)	.025
Maternal atopic dermatitis	1.29 (0.78-2.12)	.321
Maternal asthma	1.34 (0.18-2.23)	.256
Born during winter season	2.02 (1.31-3.14)	.002

CI, Confidence interval; *OR*, odds ratio; *Q*, quartile; *TEWL*, transepidermal water loss.

TABLE E7. Multivariate complete case logistic regression, where the dependent variable was *Eczema* in 1150 three-month-old infants

Pregnancy variables	N = 893 OR (95% CI)	*P* value
Sex (females)	0.83 (0.54-1.26)	.380
Birth weight (kg)		
Q1 (1.50-3.30)		Ref.
Q2 (3.31-3.60)	1.17 (0.62-2.22)	.632
Q3 (3.61-3.90)	1.50 (0.80-2.78)	.203
Q4 (>3.90)	1.77 (0.97-3.25)	.065
Elective caesarean section	2.50 (1.19-5.25)	.016
Multiparity	1.63 (1.03-2.57)	.037
Maternal age (y)		
Q1 (21-29)		Ref.
Q2 (30-32)	0.90 (0.47-1.74)	.757
Q3 (33-35)	1.41 (0.73-2.75)	.311
Q4 (>35)	1.65 (0.85-3.22)	.143
Maternal allergic disease	1.61 (1.02-2.55)	.041
Paternal allergic disease	1.41 (0.93-2.14)	.105
Snus during pregnancy	0.43 (0.15-1.24)	.120
Rural living	0.48 (0.20-1.15)	.101
Family income		
Low		Ref.
Middle	0.91 (0.47-1.75)	.777
High	1.14 (0.51-2.54)	.755

CI, Confidence interval; *OR*, odds ratio; *Q*, quartile.

II

Maternal and paternal atopic dermatitis and risk of atopic dermatitis during early infancy in girls and boys

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Clinical Implications

- Parental atopic dermatitis increases the risk of atopic dermatitis in infancy, particularly in offspring of the same sex as the affected parent. This may be an important factor to consider when selecting infants for primary prevention strategies.

TO THE EDITOR:

Parental allergic diseases, particularly atopic dermatitis (AD), have been established as major risk factors for AD in offspring,[1] with some studies reporting a greater risk from maternal AD than from paternal AD.[2] In the Isle of White study with a cohort of more than 1400 children aged 1 to 18 years, Arshad et al[3] found an increased risk of AD in female, but not male, offspring of mothers with AD, and in male, but not female, offspring of fathers with AD.[3]

Genetic factors may play a more important role in the pathogenesis of AD presenting early, rather than later, in life.[4] Following up on the findings of Arshad et al, we aimed to determine whether AD in fathers and mothers increases the risk of AD during early infancy in their sons and daughters. From the general population-based mother-child birth cohort in Norway and Sweden, Preventing Atopic Dermatitis and Allergies in Children (PreventADALL) study,[5] we included all 1155 infants not randomized to early skin care intervention, who had clinical assessment at age 3 and/or 6 months and available information on parental atopic disease (see Table E1 in this article's Online Repository at www.jaci-inpractice.org). Recruitment of pregnant women occurred from December 2014 through October 2016. The infants, 617 boys and 538 girls, were born at gestational week 35 or later. Information on parental doctor-diagnosed AD was collected by electronic questionnaires sent to the mother at weeks 18 and 34 of pregnancy. Skin assessment of the infants was performed by trained health care personnel, and additional skin symptoms and signs were recorded in electronic questionnaires by parents at 3 and 6 months.

The primary outcome, used as a proxy for AD, was *possible AD* (pAD), defined as observed eczema in infants by study personnel, excluding differential diagnoses to AD, and/or parent-reported intermittent or persistent itchy exanthema in their child for more than 4 weeks. Odds ratios (ORs) from sex-stratified analysis were used to assess the association of maternal and paternal AD with pAD at age 3 and 6 months. A logistic regression model was used to test for interaction between sex of the child and parental AD. Because AD is a strong risk factor for other allergic diseases, we did not adjust for parental AD comorbidities. The possibility of confounding variables was considered to be low.

At age 3 and 6 months, regardless of sex, only paternal AD significantly increased the risk of pAD in the offspring, with ORs of 1.80 and 1.81, respectively (Table I). When stratified by offspring sex, the parental effects were statistically significant at 6 months only, with an increased risk from mothers to daughters (OR, 1.79; 95% CI, 1.07-3.00) and from fathers to sons (OR, 2.36; 95% CI, 1.34-4.20) (Table II). When defining the offspring phenotype as pAD at age 3 *and/or* 6 months, the same sex-specific pattern was seen (Table II). No significant effects were found on pAD from parental AD to the group of offspring of opposite sex. When using the full regression model, a non-statistically significant interaction was found for maternal AD and offspring sex by age 6 months ($P = 0.09$) while the other interactions shown in Table E2 in this article's Online Repository at www.jaci-inpractice.org had a P value of more than .1. Significant associations with offspring sex were seen in all logistic regression models, adding further support to the theory of a sex-dependent risk increase (see Table E2).

To our knowledge, this is the first study observing a sex-specific increased risk of AD in early infancy associated with parental AD. We found an increased risk of AD in female offspring by maternal AD and in all offspring by paternal AD, with some evidence of a stronger paternal effect in boys than in girls. The maternal signal in girls and paternal signals in boys were stronger and significant at age 6 months, yet present but not significant at age 3 months. The sex-related AD risk is in line with results of Arshad et al,[3] showing a sex-dependent risk increase for AD in childhood and adolescence. The lack of statistically significant interactions between parental AD and offspring sex is partially in line with their findings, but in contrast to the significant interaction of maternal AD and AD in females from age 1 to 18 years. Our study is less powered to detect interaction effects than their study with its repeated measures in more than 1400 subjects over a 17-year time period.[3]

Possible differential effects on AD by maternal and paternal AD could be explained by genomic imprinting, that is, an epigenetic phenomenon that causes a specific parental allele to be expressed in a parent-of-origin specific manner, silencing the corresponding allele through DNA-methylation or histone modifications[6,7]; thus, the localization of a susceptibility gene for AD to an imprinted region could influence the inheritance pattern. Recent publications have also suggested that the Y chromosome influences the immune system and inflammatory responses in males.[8]

A strength of our study is the high number of infants recruited from the general population in 3 geographically different areas in Norway and Sweden and with data from both questionnaires and

TABLE I. pAD and OR for pAD in infants with or without parental AD

Age	Maternal AD pAD, % (n/N)	No maternal AD pAD, % (n/N)	OR (95% CI)	Paternal AD pAD, % (n/N)	No paternal AD pAD, % (n/N)	OR (95% CI)
3 mo	15 (33/221)	12 (92/788)	1.33 (0.87-2.04)	19 (22/118)	11 (98/869)	**1.80 (1.08-3.00)**
6 mo	27 (57/214)	22 (169/759)	1.27 (0.90-1.80)	33 (38/116)	21 (177/834)	**1.81 (1.19-2.76)**
3 and/or 6 mo	31 (70/224)	27 (214/794)	1.23 (0.89-1.70)	39 (46/119)	26 (225/876)	**1.82 (1.22-2.72)**

Statistically significant ORs are given in bold.

TABLE II. pAD and OR for pAD in (A) girls and (B) boys with or without parental AD

A. Girls

Age	Maternal AD pAD, % (n/N)	No maternal AD pAD, % (n/N)	OR (95% CI)	Paternal AD pAD, % (n/N)	No paternal AD pAD, % (n/N)	OR (95% CI)
3 mo	13 (13/103)	10 (35/362)	1.35 (0.69-2.66)	16 (9/58)	9 (37/402)	1.81 (0.83-3.98)
6 mo	28 (28/102)	17 (61/350)	**1.79 (1.07-3.00)**	24 (14/58)	19 (74/387)	1.35 (0.70-2.59)
3 and/or 6 mo	32 (34/105)	22 (79/365)	**1.73 (1.07-2.80)**	33 (19/58)	23 (92/405)	1.66 (0.91-3.00)

B. Boys

Age	Maternal AD pAD, % (n/N)	No maternal AD pAD, % (n/N)	OR (95% CI)	Paternal AD pAD, % (n/N)	No paternal AD pAD, % (n/N)	OR (95% CI)
3 mo	17 (20/118)	13 (57/426)	1.32 (0.76-2.30)	22 (13/60)	13 (61/467)	1.84 (0.94-3.60)
6 mo	26 (29/112)	27 (108/409)	0.97 (0.61-1.57)	41 (24/58)	23 (103/447)	**2.36 (1.34-4.20)**
3 and/or 6 mo	30 (36/119)	32 (135/429)	0.95 (0.61-1.47)	44 (27/61)	23 (133/471)	**2.02 (1.17-3.48)**

Statistically significant ORs are given in bold.

clinical investigations. The risk of biased reporting of parental AD after subsequent development of eczema in offspring was avoided because of the prospective study design. To limit the risk of misclassification of AD in early infancy, we used prespecified UK Working Party criteria modified for early infancy, as described in the "Outcome Definitions" section in this article's Online Repository at www.jaci-inpractice.org. Mothers completing the questionnaires may have reported AD, particularly in fathers with a persistent phenotype not limited to childhood. This, however, cannot account for the differential effects seen from maternal and paternal AD in girls and boys.

Our findings indicate a higher risk from maternal and paternal AD for AD in early infancy in offspring of the same sex as the affected parent. Although the associations were statistically significant at age 6 months only, our findings may provide a rationale for sex-specific risk stratification for primary prevention interventions.

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ONLINE REPOSITORY

OUTCOME DEFINITIONS

In the PreventADALL study, we have defined the following 3 levels of AD:

Level 1. AD: UK Working Party criteria and/or Hanifin and Rajka criteria are met.

Level 2. Eczema: Observed eczema at clinical investigations, clinically excluding common differential diagnosis to AD.

Level 3. pAD: All cases where AD has been suspected at the clinical investigations (observed eczema) and/or from parents reporting presence of an itchy rash for at least 4 weeks (from the UK Working Party criteria).

TABLE E1. Characteristics for the 1155 infants with available information on the exposure (ie, parental history of AD) and outcome (ie, pAD at 3- and/or 6-mo follow-up)

Characteristic	No AD (N = 833)	pAD (N = 322)	*P* value	Total (N = 1155)
Age mother (y), mean ± SD (min-max) (N = 1155)	32.6 ± 4.1 (21.0-48.0)	32.6 ± 4.0 (22.0-43.0)	.92	32.6 ± 4.1 (21.0-48.0)
Age father (y), mean ± SD (min-max) (N = 1005)	34.7 ± 5.5 (21.0-72.0)	35.0 ± 5.5 (23.0-65.0)	.48	34.8 ± 5.5 (21.0-72.0)
Mother Nordic origin, n (%) (N = 1072)	711 (91.5)	266 (90.2)	.49	977 (91.1)
Father Nordic origin, n (%) (N = 1050)	687 (90.2)	252 (87.5)	.21	939 (89.4)
Education mother, 4 y of university or more, n (%) (N = 1066)	444 (57.5)	181 (61.6)	.23	625 (58.6)
Education coparent, 4 y of university or more, n (%) (N = 1027)	371 (49.7)	136 (48.6)	.76	507 (49.4)
Family income, n (%) (N = 1056)*				
Low	114 (14.9)	41 (14.0)	.72	155 (14.7)
Middle	563 (73.7)	207 (70.9)	.36	770 (72.9)
High	87 (11.4)	44 (15.1)	.11	131 (12.4)
BMI, mother at 18 wk of pregnancy, mean ± SD (min-max) (N = 1137)	24.8 ± 3.6 (18.3-39.7)	24.8 ± 3.6 (17.2-41.4)	.73	24.8 ± 3.6 (17.2-41.4)
≥1 previous parity, n (%) (N = 1072)	317 (40.8)	126 (42.7)	.57	443 (41.3)
Allergic disease mother, n (%) (N = 1072)	488 (62.8)	204 (69.2)	.11	692 (64.6)
Allergic disease father, n (%) (N = 1072)	367 (47.4)	172 (57.7)	.01	539 (50.3)
AD mother, doctor diagnosed, n (%) (N = 1018)	154 (21.0)	70 (24.6)	.21	224 (22.0)
AD father, doctor diagnosed, n (%) (N = 995)	73 (10.1)	46 (17.0)	.003	119 (12.0)
Asthma mother, doctor diagnosed, n (%) (N = 1050)	134 (17.7)	58 (19.9)	.39	192 (18.3)
Asthma father, doctor diagnosed, n (%) (N = 1041)	107 (14.3)	44 (15.1)	.75	151 (14.5)
Allergic rhinitis mother, doctor diagnosed, n (%) (N = 905)	167 (25.3)	62 (25.4)	.96	229 (25.3)
Allergic rhinitis father, doctor diagnosed, n (%) (N = 952)	166 (23.9)	82 (32.0)	.01	248 (26.1)
Food allergy mother, doctor diagnosed, n (%) (N = 947)	103 (14.7)	41 (16.6)	.48	144 (125.2)
Food allergy father, doctor diagnosed, n (%) (N = 981)	67 (9.3)	31 (11.9)	.24	98 (10.0)
Lifestyle during pregnancy, n (%)				
Smoking (N = 1155)	40 (4.8)	10 (3.1)	.20	50 (4.3)
Live rural (N = 1072)	71 (9.1)	21 (7.1)	.29	92 (8.6)
Pets in general (N = 1072)	195 (25.1)	60 (20.3)	.10	255 (23.8)
Cat (N = 924)	84 (12.6)	23 (8.9)	.12	107 (11.6)
Dog (N = 965)	113 (16.3)	35 (13.0)	.20	148 (15.3)
Cat and dog (N = 834)	13 (2.2)	4 (1.7)	.64	17 (2.0)
Cesarean section, n (%) (N = 1148)				
Elective (N = 1035)	41 (5.5)	24 (8.4)	.09	65 (6.3)
Acute (N = 1129)	80 (10.2)	33 (11.1)	.64	113 (10.4)
Gestational age at birth (wk), mean ± SD (min-max) (N = 1138)	39.2 ± 1.7 (35.0-42.9)	39.4 ± 1.6 (35.2-45.9)	.08	39.3 ± 1.7 (35.0-42.9)
Sex: female, n (%) (N = 1155)	405 (48.6)	133 (41.3)	.03	538 (46.6)
Birth weight (kg), mean ± SD (minimum-maximum) (N = 1132)	3.5 ± 0.5 (1.9-4.9)	3.6 ± 0.5 (2.2-5.1)	.02	3.6 ± 0.5 (1.9-5.1)
Born during winter season (October-March), n (%) (N = 1155)	460 (55.2)	180 (55.9)	.84	640 (55.4)

BMI, Body mass index.

*Income before taxes in Norwegian kroner (NOK): Low = <600,000 NOK; Middle = 600,000-1,400,000 NOK; High = >1,400,000 NOK.

TABLE E2. Logistic regression models examining the interaction effect of parental history of AD with offspring sex at age 3, 6, and 3 and/or 6 mo by the conceptual model: pAD ~ paternal AD (yes/no) + maternal AD (yes/no) + sex (male/female) + maternal AD × sex + paternal AD × sex*

Variables in the equation	pAD at 3 mo			pAD at 6 mo			pAD at 3 and/or 6 mo		
	P value	OR	95% CI	*P* value	OR	95% CI	*P* value	OR	95% CI
Paternal AD	.14	1.72	0.83-3.53	.02	2.09	1.15-3.82	.04	1.86	1.04-3.33
Maternal AD	.99	1.00	0.53-1.88	.99	1.00	0.59-1.67	.69	0.90	0.56-1.47
Sex	.02	0.52	0.30-0.90	.03	0.64	0.42-0.96	.002	0.56	0.38-0.81
Paternal AD × sex	.70	1.24	0.41-3.78	.62	0.79	0.32-1.98	.79	1.13	0.48-2.66
Maternal AD × sex	.40	1.53	0.57-4.08	.18	1.68	0.79-3.61	.09	1.87	0.91-3.82

*Parental AD = no and sex = male were set to 0 in the indicator variables.

III

BJD
British Journal of Dermatology

Diagnosing atopic dermatitis in infancy using established diagnostic criteria: a cohort study*

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Conflicts of interest
K.M.A.E. has received honorary for presentations from AbbVie; M.L. has received honorary for presentations from MSD; and E.M.R. has received honoraria for presentations from Sanofi Genzyme, Novartis, MEDA and Omega Pharma.

L.L. and M.L. contributed equally to this study.

Summary

Background Diagnosing atopic dermatitis (AD) in infants is challenging.
Objectives To determine the incidence and persistence of eczema and AD in infants using the UK Working Party (UKWP) and Hanifin and Rajka (H&R) criteria.
Methods A cohort of 1834 infants was examined clinically at 3, 6 and 12 months of age. AD was diagnosed by UKWP (3, 6 and 12 months) and H&R (12 months) criteria. Logistic regression models were used to assess the relationship between AD and eczema.
Results Eczema was observed in 628 (34·2%) infants (n = 240, n = 359 and n = 329 at 3, 6 and 12 months, respectively), with AD diagnosed in 212 (33·7%) infants with any eczema and in 64/78 (82%) infants with eczema at all three visits. The odds of AD were lower with first presentation of eczema at 6 [odds ratio (OR) 0·33, 95% confidence interval (CI) 0·22–0·48] or 12 months (OR 0·49, 95% CI 0·32–0·74) than at 3 months, and higher in infants with eczema at three (OR 23·1, 95% CI 12·3–43·6) or two (OR 6·5, 95% CI 4·3–9·9) visits vs. one visit only. At 12 months, 156/329 (47·4%) fulfilled the UKWP and/or H&R criteria; 27 (8%) fulfilled the UKWP criteria only and 65 (20%) only the H&R criteria. Of the 129 infants who fulfilled the H&R criteria, 44 (34·1%) did not meet the itch criterion.
Conclusions Used in combination and at multiple timepoints, the UKWP and H&R criteria for AD may be useful in clinical research but may have limited value in most other clinical settings.

What is already known about this topic?

- Eczema is common in infants, while the proportion of infants with clinical eczema having atopic dermatitis (AD) is uncertain.
- Criteria-based AD in infants increases the risk of developing allergic comorbidities, and an early appearance of AD may indicate a more severe disease phenotype.
- Studies determining AD with the UK Working Party and Hanifin and Rajka criteria in the first year of life are largely lacking.

What does this study add?

- Of 34% of infants with eczema, one-third fulfilled the diagnostic criteria for AD.

*Plain language summary available online

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- Infants with eczema at 3 months vs. later in life, or with eczema at more than one visit, were most likely to fulfil the diagnostic AD criteria.
- Except for clinical research, the present diagnostic criteria for AD may have limited clinical value in infants.

Atopic dermatitis (AD) is a chronic inflammatory skin disease that affects around 20% of children in high-income countries,[1,2] and usually makes its first appearance in infancy.[3,4] The characteristics of AD, including distribution, severity, itch and persistence, vary by age group and ethnicity.[5] Although the first signs of AD often appear by 6 or 12 months of age,[6] diagnosing AD in the first year of life may be challenging, as signs of itch may be lacking and the chronicity of eczema uncertain.[7] Also, other skin conditions, for example contact dermatitis, seborrhoeic dermatitis and dermatitis associated with primary immune or nutritional deficiencies, may mimic AD.[8]

Several diagnostic criteria for AD have been developed. The Hanifin and Rajka (H&R) criteria from 1980 (revised 2003) and the H&R-derived and simplified United Kingdom Working Party (UKWP) criteria from 1994 (revised 2005) are widely used, with the UKWP criteria being most extensively validated.[9] Sensitivity and specificity vary but are generally high for both sets of criteria when applied to an adult population or children > 1 year of age.[9] However, few studies have validated the use of these diagnostic criteria in infancy.[10–12] A recent meta-analysis identified 212 randomized controlled trials, mostly including adults and older children, using 10 different diagnostic criteria for AD, with the H&R criteria the most frequently used (41%), followed by the UKWP criteria (9%).[13] The authors emphasize the need to harmonize the diagnostic criteria for AD,[13] highlighting the importance of determining the best-suited criteria for diagnosing AD in infancy.

The primary goal of this study was to determine the incidence and persistence of eczema observed at 3, 6 and 12 months of age, with a secondary goal of identifying the proportion of infants with eczema who fulfilled the UKWP and/or the H&R diagnostic criteria for AD.

Patients and methods

Design

The study was carried out within the Preventing Atopic Dermatitis and ALLergies- (PreventADALL) study, a multicentre, prospective 2 × 2 factorial interventional birth cohort study designed to investigate primary prevention strategies in AD and food allergy in infancy,[14,15] and to identify factors early in life that may be involved in the development of noncommunicable diseases.

From December 2014 to October 2016, pregnant women who consented to participate in the study at Oslo University Hospital and Østfold Hospital Trust, Norway, and at Karolinska University Hospital, Sweden, were recruited at their 18-week (between 16 and 22 + 5 weeks) routine ultrasound assessments. Exclusion criteria included inadequate skills in a Scandinavian language, plans to move away from the region shortly after birth and pregnancy with more than two fetuses. Babies of at least 35 weeks' gestational age and no severe disease were enrolled at birth. Maternal consent was obtained upon primary enrolment, with the consent of both guardians obtained shortly after birth.

Clinical follow-up visits of the infants at 3, 6 and 12 months of age included skin assessments performed by specifically trained study personnel,[15] including annual workshops, in order to minimize interobserver variability. Medical doctors with dermatological experience participated in the examinations when needed. The UKWP criteria, consisting of one major and at least three of the four minor criteria (Appendix S1; see Supporting Information) were applied at all three visits, whenever eczema was observed; the H&R criteria, requiring three of four major and three of 19 minor criteria, were additionally applied at the 12-month visit. Data on diagnosis and treatment between visits were collected by electronic questionnaires sent to infants' mothers 3, 6, 9 and 12 months after giving birth.

Baseline characteristic data were collected via electronic questionnaires at 18 and 34 weeks' gestational age. Additional information on study design, including the baseline characteristics of the 2697 mothers and 2396 babies, are reported elsewhere.[14]

The PreventADALL study is approved by the Regional Committee for Medical and Health Research Ethics in Norway (2014/518) and Sweden (2014/2242-31/4), and is registered at ClinicalTrials.gov (NCT02449850).

Patients

Of the 2396 babies enrolled in the PreventADALL study, we included 1834 infants who attended all clinical visits at 3, 6 and 12 months of age (Figure 1). One infant was withdrawn, 223 did not attend any visit and 338 attended only one or two visits. At birth, the infants (865 girls and 969 boys) had a mean gestational age of 39·3 weeks (Table 1).

Outcomes and definitions

The main outcome was observed eczema at 3, 6 and/or 12 months of age. Eczema was defined as the presence of eczematous skin lesions verified by a physician, clinically

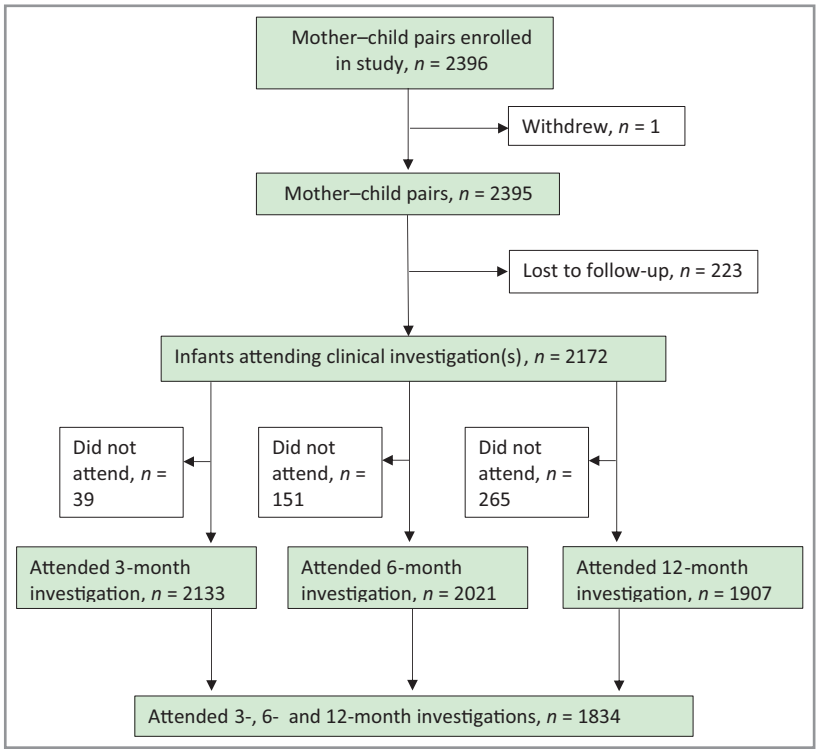

Figure 1 Enrolment of infants from the Preventing Atopic Dermatitis and ALLergies in children (PreventADALL) mother–child cohort (2701 pregnancies included).

excluding conditions with features similar to AD, for example seborrhoeic and contact dermatitis.

The secondary outcome was the proportion of children with eczema fulfilling the definition of AD by either or both the UKWP and/or the H&R diagnostic criteria at 12 months (Appendix S1). The UKWP criteria were used according to the 1994 proposed adaption of the criteria for use in infancy.[11]

Statistical analysis

Categorical variables are presented as n (%). Continuous variables are presented as mean (SD) and range. To assess selection bias, we compared the baseline characteristics for the group of PreventADALL participants included in our sample to those excluded from the present analysis, using χ^2 statistics for categorical variables and t-tests for continuous variables (Table 1). Descriptive statistics on the frequency of observed eczema in infants at the clinical visits, the use of topical steroids and a doctor's clinical diagnosis of AD between clinical visits were calculated.

Logistic regression models were used to assess the relationship between AD and eczema in infancy. As eczema is a necessary, but insufficient condition for an AD diagnosis (the probability of AD given no eczema is zero), these analyses were performed for 628 infants with eczema. A logistic regression model was used to investigate the association between one, two or three observations of eczema and the fulfilment of the diagnostic criteria by 12 months of age. A regression model was applied to examine the association between the first observation of eczema at 3, 6 or 12 months in the infants who fulfilled the diagnostic criteria. Both regression models were also adjusted for parental atopic disease and the sex of the infant.

Missing data were imputed with the best-case option, setting missing values as 0 ('no observed eczema'), assuming that parents would have been highly motivated to complete the skin examination if eczema was present. For variables concerning the use of topical steroids, missing values and 'don't know' were set to 'no use'.

All statistical analyses were performed in SPSS version 26·0 (IBM, Armonk, NY, USA). Euler diagrams were produced with eulerAPE. Bar charts were produced in GraphPad PRISM version 8·4.2 (GraphPad Software, La Jolla, CA, USA).

Results

Baseline characteristics for the included participants attending all three follow-up visits (n = 1834) were largely similar to the nonincluded group with incomplete data (n = 594), with some exceptions. Nominally statistically significant differences included a higher level of education, income, parental age and prevalence of eczema in the included participants (Table 1).

Eczema was observed in 628 infants (34·2%) on at least one of the three clinical follow-up visits (Table 2, Figure 2a). Of the 240 infants with eczema at 3 months, 87 (36·2%) did not have eczema on further follow-up visits, while 78

Table 1 Characteristics of the study population

	Included (n = 1834)	Not included (n = 561)	Total (n = 2395)	P-value
Sex				0·74[a]
Male	969 (52·8)	292 (52·0)	1261 (52·7)	
Female	865 (47·2)	269 (48·0)	1134 (47·3)	
Nordic origin				
Mother	1531 (90·8)	432 (89·3)	1963 (90·4)	0·32[a]
Father	1484 (89·9)	419 (89·3)	1903 (89·8)	0·71[a]
Education (≥ 4 years at university)				
Mother	988 (58·8)	243 (50·4)	1231 (56·9)	0·001[a]
Father	808 (50·0)	209 (44·3)	1017 (48·7)	0·03[a]
Family income				0·005[a]
Low	214 (12·9)	88 (18·6)	302 (14·2)	
Middle	1238 (74·5)	334 (70·8)	1572 (73·7)	
High	210 (12·6)	50 (10·6)	260 (12·2)	
≥ 1 previous parity	661 (39·2)	203 (41·9)	864 (39·8)	0·27[a]
AD	186 (10·1)	15 (4·4)	201 (9·3)	0·001[a]
Eczema	628 (34·2)	57 (10·2)	685 (36·2)	0·000[a]
Eczema on two visits	222 (12·1)	NA	222 (12·1)	NA
Eczema all visits	78 (4·3)	NA	78 (4·3)	NA
Eczema present at 3 months	240 (13·1)	22 (7·4)	262 (12·3)	0·005[a]
Eczema present at 6 months	359 (19·6)	31 (16·6)	390 (19·3)	0·32[a]
Eczema present at 12 months	329 (17·9)	15 (20·5)	344 (18·0)	0·57[a]
Observed possible AD later diagnosed as AD				0·012[a]
3 months	39 (2·1)	4 (1·2)	43 (2·0)	
6 months	69 (3·8)	8 (2·4)	77 (3·5)	
9 months	9 (0·5)	1 (0·3)	10 (0·5)	
12 months	69 (3·8)	2 (0·6)	71 (3·3)	
Parental allergic disease (any)				
Mother	697 (42·2)	204 (43·4)	901 (42·5)	0·65[a]
Father	607 (35·8)	144 (31·2)	751 (34·8)	0·07[a]
AD				
Mother	333 (19·7)	98 (20·2)	431 (19·9)	0·81[a]
Father	176 (10·4)	44 (9·5)	220 (10·2)	0·60[a]
Asthma				
Mother	279 (16·5)	92 (19·0)	371 (17·1)	0·20[a]
Father	213 (12·6)	66 (14·3)	279 (12·9)	0·32[a]
Allergic rhinitis				
Mother	343 (21·2)	102 (22·3)	445 (21·5)	0·63[a]
Father	412 (24·3)	98 (21·3)	510 (23·6)	0·17[a]
Food allergy				
Mother	217 (13·2)	64 (13·6)	281 (13·1)	0·83[a]
Father	152 (9·0)	45 (9·8)	197 (9·1)	0·60[a]
Lifestyle during pregnancy				
Alcohol intake	110 (7·4)	19 (4·9)	129 (6·9)	0·09[a]
Smoking	73 (4·0)	31 (5·9)	104 (4·5)	0·07[a]
Rural living	113 (6·7)	45 (9·3)	158 (7·3)	0·052[a]
Caesarean section				
Elective	102 (6·3)	39 (7·9)	141 (6·6)	0·21[a]
Acute	192 (11·1)	60 (11·6)	252 (11·3)	0·77[a]
Born in winter	970 (52·9)	280 (49·9)	1250 (52·2)	0·22[a]
Mean (SD) gestational age at birth (weeks)	39·3 (1·7)	39·2 (1·7)	39·2 (1·7)	0·41[b]
Mean (SD) birthweight (kg)	3·6 (0·5)	3·6 (0·5)	3·6 (0·5)	0·74[b]
Mean (SD) BMI of the mother (kg m^{-2})	24·8 (3·6)	24·8 (3·9)	24·8 (3·7)	0·79[b]
Mean (SD) age of the mother (years)	32·6 (4·1)	31·7 (4·3)	32·4 (4·1)	0·0[b]
Mean (SD) age of the father (years)	34·9 (5·3)	34·1 (5·9)	34·7 (5·5)	0·01[b]
3-month investigation				
Mean (SD) age (days)	92·9 (7·9)	94·4 (8·9)	93·1 (8·1)	0·03[b]
Mean (SD) length (cm)	61·8 (2·3)	62·1 (2·7)	61·8 (2·3)	0·09[b]
Mean (SD) weight (kg)	6·2 (0·8)	6·3 (0·8)	6·3 (0·8)	0·16[b]

(continued)

Table 1 (continued)

	Included (n = 1834)	Not included (n = 561)	Total (n = 2395)	P-value
6-month investigation				
Mean (SD) age (days)	189·7 (13·3)	191·6 (14·8)	190·0 (13·5)	0·06[b]
Mean (SD) length (cm)	68·5 (2·6)	68·7 (3·1)	68·6 (2·6)	0·39[b]
Mean (SD) weight (kg)	8·1 (1·0)	8·2 (1·1)	8·1 (1·0)	0·25[b]
12-month investigation				
Mean (SD) age (days)	381·3 (23·2)	379·9 (24·6)	381·2 (23·2)	0·63[b]
Mean (SD) length (cm)	76·5 (2·9)	76·3 (3·2)	76·5 (2·9)	0·57[b]
Mean (SD) weight (kg)	10·1 (1·1)	10·0 (1·2)	10·1 (1·1)	0·56[b]

Data are n (%) unless otherwise indicated. All percentages are calculated based on the total number of responses for each variable. AD, atopic dermatitis; BMI, body mass index; NA, not applicable. [a]P-value from χ^2 statistics comparing groups with complete and incomplete data; [b]P-value from two-tailed t-test comparing groups with complete and incomplete data.

(32·5%) had eczema at all three visits (Table 2, Figure 2a). Eczema was first observed at 6 months in 236 infants (12·9%) and at 12 months in 152 (8·3%) (Table 2, Figure 2a).

Diagnostic criteria for AD by 12 months of age were fulfilled for at least one of the two validated tools in 212 (33·7%) of the infants with eczema. AD was most often diagnosed in infants with eczema at 3 months of age (n = 113; 47·1%) (Table 2, Figure 3) or with eczema at all three visits (82%; Table 2). Correspondingly, any diagnostic criteria were fulfilled by only 22% and 30% of infants with eczema first observed at 6 and 12 months, respectively (Table 2, Figure 3).

The odds of criteria-based AD by 12 months of age were significantly lower with eczema first observed at 6 months [odds ratio (OR) 0·33, 95% confidence interval (CI) 0·22–0·48; $P < 0·001$] and 12 months (OR 0·49, 95% CI 0·32–0·74; $P = 0·001$) compared with 3 months (Table 3); this was still significant after adjusting for parental atopy and infant sex (Table S1; see Supporting Information). AD was more often diagnosed in infants with eczema at three (OR

Table 2 Number of infants, n (%), with eczema fulfilling the UK Working Party (UKWP) and/or Hanifin and Rajka (H&R) diagnostic criteria for atopic dermatitis at 3, 6 and/or 12 months of age

	Total (n = 1834)	UKWP 3 months	UKWP 6 months	UKWP 12 months	H&R 12 months	UKWP infancy	UKWP/ H&R infancy
Eczema at 3 months	240 (13·1)	37 (15·4)	63 (26·2)	51 (21·2)	63 (26·2)	96 (40)	113 (47)
Eczema at 3 months only	87 (4·7)	5 (5·7)	0	0	0	5 (6)	5 (6)
Eczema at 6 months	359 (19·6)	28 (7·8)	91 (25·3)	59 (16·4)	83 (23·1)	119 (33)	143 (40)
Eczema at 6 months only	167 (9·1)	0	16 (9·6)	0	0	16 (10)	16 (10)
Eczema at 12 months	329 (17·9)	22 (6·7)	54 (16·4)	91 (27·6)	129 (39·2)	113 (34)	165 (50)
Eczema at 12 months only	152 (8·3)	0	0	22 (14·5)	35 (23·0)	22 (14)	46 (30)
Eczema at 3 and 12 months	108 (5·9)	22 (20·3)	41 (38·0)	51 (47·2)	63 (58·3)	65 (60)	82 (76)
Eczema at 3 and 12 months only	30 (1·6)	4 (13·3)	0	11 (36·7)	11 (36·7)	14 (47)	18 (60)
Eczema at 3 and 6 months	123 (6·7)	28 (22·8)	63 (51·2)	40 (32·5)	52 (42·3)	77 (63)	90 (73)
Eczema at 3 and 6 months only	45 (2·4)	10 (22·2)	22 (48·9)	0	0	26 (58)	26 (58)
Eczema at 6 and 12 months	147 (8·0)	18 (12·2)	53 (36·0)	59 (40·1)	83 (56·5)	77 (52)	101 (69)
Eczema at 6 and 12 months only	69 (3·8)	0	12 (17·4)	19 (27·5)	31 (44·9)	26 (38)	37 (54)
Eczema at 3, 6 and 12 months	78 (4·2)	18 (23·1)	41 (52·6)	40 (51·3)	52 (66·7)	51 (65)	64 (82)
Eczema on at least one visit	628 (34·2)	37 (5·9)	92 (14·6)	91 (14·5)	129 (20·5)	160 (25)	212 (34)
Eczema at only one visit	406 (22·1)	5 (1·2)	16 (3.9)	22 (5.4)	35 (8·6)	43 (11)	67 (17)

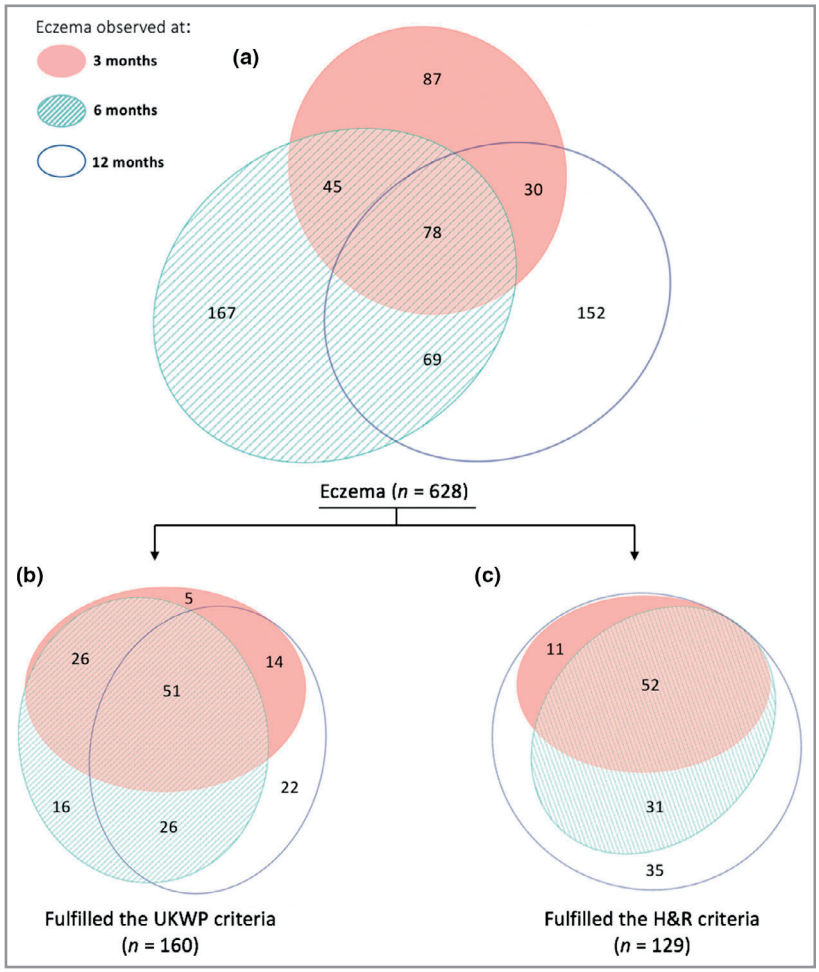

Figure 2 Area proportional Euler diagrams depicting the proportion of infants with observed eczema at the 3-, 6- and/or 12-month clinical visits in (a) the 628 infants with observed eczema in infancy; (b) the 160 infants who fulfilled the UK Working Party (UKWP) criteria; and (c) the 129 infants who fulfilled the Hanifin and Rajka (H&R) criteria (applied at 12 months only).

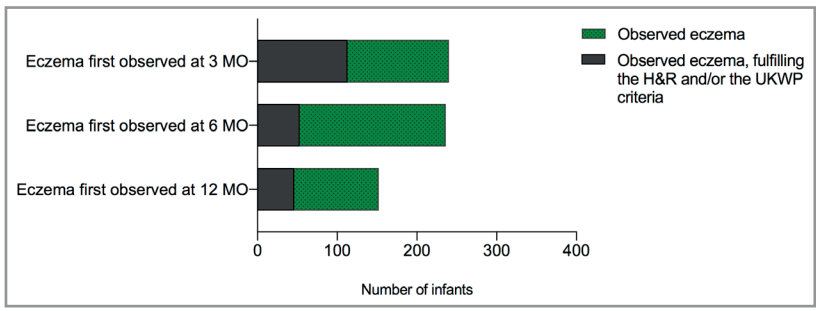

Figure 3 First observation of eczema at 3, 6 or 12 months of age in 628 infants. The grey areas illustrate those who fulfilled the UK Working Party (UKWP) and/or the Hanifin and Rajka (H&R) diagnostic criteria for atopic dermatitis by 12 months of age, while the green areas illustrate those who did not meet the criteria. The H&R criteria were applied at 12 months only.

23·1, 95% CI 12·3–43·6) or two visits (OR 6·5; 95% CI 4·3–9·9) than at one visit only (Table 4); this was also true after adjusting for parental atopy and infant sex (Table S2; see Supporting Information).

The UKWP criteria were fulfilled in 160 of 628 infants (25·5%) with observed eczema overall, and in 15% of the 240 infants with eczema at 3 months of age (Table 2). Of the 160 infants fulfilling the UKWP criteria by 12 months of age, < 15% had eczema on one occasion only (Table 2, Figure 2b). The H&R criteria, applied exclusively at 12 months, were fulfilled in 21% of all infants with eczema and 39% of infants with eczema at 12 months (Table 2, Figure 2c).

Table 3 Logistic regression model: association between first observation of eczema and fulfilling the diagnostic criteria for atopic dermatitis (UK Working Party and/or the Hanifin and Rajka criteria) in 628 infants with at least one observation of eczema in infancy

	Eczema first observed at 3 months		Eczema first observed at 6 months		Eczema first observed at 12 months	
	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)
Fulfilling the AD criteria	–	Ref.	< 0·001	0·33 (0·22–0·48)	0·001	0·49 (0·32–0·74)

Eczema at 3 months was set as the indicator. CI, confidence interval; OR, odds ratio; Ref., reference.

Table 4 Logistic regression model: number of times eczema was seen in 628 infants with at least one observation of eczema in infancy

	Eczema observed at one of three visits		Eczema observed at two of three visits		Eczema observed at three of three visits	
	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)
Fulfilling the AD criteria	–	Ref.	< 0·001	6·5 (4·3–9·9)	< 0·001	23·1 (12·3–43·6)

Eczema observed in one of three visits was set as indicator. AD, atopic dermatitis; CI, confidence interval; OR, odds ratio; Ref., reference group.

At 12 months of age, 156 of 329 infants with eczema were diagnosed with AD, with 65 fulfilling the H&R criteria only, 27 fulfilling the UKWP criteria only and 64 fulfilling both (Table 2). Additionally, nine infants with eczema at 12 months had fulfilled the UKWP criteria prior to, but not at, 12 months. The mandatory major criteria of an itchy skin condition in the UKWP criteria was reported in 85 of 129 (65·9%) infants fulfilling the H&R criteria (Table S3; see Supporting Information).

The use of topical steroids was highest in infants with eczema at all three visits (96%) vs. one visit only (52%), and in infants with eczema who fulfilled the AD criteria (79%) vs. those who did not (48%) (Table S4 and Figure S1; see Supporting Information).

Discussion

In this large, prospective, general population-based birth cohort study, clinical eczema was observed in about one-third of 1834 infants at 3, 6 and/or 12 months of age. Of these, about one-third were diagnosed with AD based on the UKWP and/or H&R diagnostic criteria for AD. Infants with eczema at 3 months of age, as well as eczema observed on three separate visits, were more likely to meet the AD criteria by 12 months of age than infants with eczema observed first after 3 months or at fewer observations. More than two in five infants with AD at 12 months fulfilled the H&R criteria only, while fewer than one in five fulfilled the UKWP criteria only.

The incidence of approximately one in three children having clinical eczema in our study is in line with a 2013 study of nearly 5000 Australian infants, where a similar proportion developed clinical eczema by 12 months of age.[16] The 12% incidence rate of AD found in our study corresponds to an estimated prevalence of AD of 20%,[2] and to the finding that 60% of German infants presented their first AD symptoms by 12 months of age.[6] However, comparing the incidence and prevalence of eczema and AD across studies is challenging, especially in infants, as the outcome definitions vary greatly. Rather than using the term 'eczema' synonymously with AD, we defined AD as fulfilling the UKWP and/or H&R diagnostic criteria.

Our finding that approximately one-third of infants with clinical eczema were diagnosed with AD adds new information about the incidence of criteria-based AD in infancy and provides a pragmatic perspective in the debate on what should be considered as AD in the first year of life. Challenges related to early diagnosis of AD in children with eczema resembles the challenges of diagnosing asthma in infants who wheeze as a result of lower respiratory tract infections.[17,18] Diagnoses of both AD and asthma are largely based on clinical signs and symptoms that are typical, but not exclusive, for the diseases.

The likelihood of AD in our study was increased in infants with observed eczema at 3 months vs. infants with a first observation of eczema at 6 or 12 months of age. This agrees with the early onset of AD being associated with an increased risk of a more severe AD phenotype.[19–21] Early fulfilment of diagnostic AD criteria may also be important in the risk of developing allergic comorbidities. In a study of > 3000 infants in Canada, meeting the UKWP criteria for AD at 12 months of age provided the best prognostic marker of all allergic outcomes at 5 years of age vs. a clinically based or a parentally reported diagnosis of AD.[22] However, Figure 3 illustrates the low sensitivity of the UKWP and H&R criteria in infancy. Also, there may be an under-recognition of skin conditions that mimic AD, such as contact dermatitis and seborrhoeic dermatitis.

Although we found a greater risk of AD in those with eczema present at 3 months of age, no further observations of eczema in infancy were seen in approximately one-third. This may be, owing, in part, to the remitting and relapsing nature of AD, or

effective treatment. However, topical steroid treatment was reported in fewer than one of five infants with eczema exclusively at 3 months vs. more than nine of 10 infants with eczema at all three visits. This also suggests that a significant proportion of those with the earliest onset of eczema will have a mild course of disease in their first year of life.

The likelihood of being diagnosed with AD in accordance with the UKWP and/or H&R criteria increased significantly with two or three observations compared with one observation only. To the best of our knowledge, this finding has not been reported previously. More than 80% of all infants with eczema present at all three visits met at least one of the diagnostic criteria, and 96% used topical steroids. Still, several skin conditions that may mimic or coexist with AD are treated with topical steroids.

In our study, 28% of infants with observed eczema at 12 months fulfilled the UKWP criteria, while 39% met the H&R criteria for AD. The higher sensitivity for detecting AD by the H&R criteria vs. the UKWP criteria found in our study is in line with a Turkish study of 200 children aged 7–36 months, which reported sensitivities of 72% and 94% for the UKWP and H&R criteria, respectively.[10] The relatively high sensitivity for both sets of criteria in the Turkish study and others could be due, in part, to the selection of children from a paediatric allergy or dermatology clinic and/or the inclusion of older children with an established diagnosis of AD,[11,12] possibly indicating more severe AD phenotypes. Our study cohort was population based. Furthermore, the higher number of infants fulfilling the H&R criteria than the UKWP criteria may, in large part, be explained by the required major criterion of an itchy skin condition in the UKWP criteria. In our study, about one-third of infants who fulfilled the H&R criteria did so without meeting the itch criterion, thereby not fulfilling the UKWP criteria. Although itch is a hallmark of the disease, a diagnosis of AD may still be made by the H&R criteria (despite no reported or observed itch) by fulfilling the remaining three major criteria and at least three minor criteria (see Appendix S1). As the UKWP criteria correspond to four major and one minor criteria in the H&R criteria, fulfilling the major criteria but not three H&R minor criteria would result in fulfilling the UKWP criteria only. The required criterion of an itchy skin condition within the last 12 months to meet the UKWP criteria may be less prominent in infants with mild skin disease,[23,24] and under-reported by caretakers. Demonstrating itch probably requires the ability to localize targets on the skin with coordinated motor skills, which may not be developed by 3 months of age,[25] putting into question the appropriateness of the UKWP's itch criterion to diagnose AD in infants aged 3 months. Although 40% of infants with eczema at 3 months met the UKWP criteria by 12 months, only 15% did so at 3 months.

The limitations of the H&R criteria include its complexity, with several minor criteria – some of which require clinical experience or additional examinations to assess – and the combination of both present features and signs or symptoms reported on behalf of the child. Also, several of the minor criteria, for example allergy, Dennie-Morgan folds, orbital darkening and palmar hyperlinearity, may not be present at the time of AD debut in infancy.

The strengths of the present study include its prospective design and the large number of infants, enrolled from three different geographical location sites in Norway and Sweden, with clinical observations performed by trained study personnel, as well as the use of two validated diagnostic criteria for AD at three different timepoints in infancy. The investigators were masked to the randomization of the participant to the interventions.[15]

This study also has some limitations. The H&R criteria, only applied at 12 months, have consistently shown higher sensitivity than the UKWP criteria in validation studies; thus, we might have underestimated the total number of infants with criteria-based AD. The fluctuating nature of AD combined with treatment plans provided at the clinical follow-up visits may also have contributed to an underestimation of the prevalence of eczema and AD at each visit. Although we recruited from the general population, many parents had a higher education and a large proportion of them reported a history of atopic disease, perhaps motivating them to participate in the study. These aspects might influence the generalizability of our results.

In conclusion, this study documents the limitations of the UKWP and H&R criteria in diagnosing AD in the first year of life. Repeated clinical observations and applying both sets of criteria may be the most appropriate way in which to diagnose AD in infants and the most useful in clinical research. However, in most clinical situations this approach may not be feasible. This suggests that the term 'infantile eczema' may be more appropriate in some infants, postponing a diagnosis of AD until the typical characteristics have been established and the diagnostic pitfalls are fewer.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Appendix S1 Outcome definitions, UK Working Party criteria, and Hanifin and Rajka criteria.

Figure S1 Euler diagram of 1141 infants with available data from clinical visits and electronic questionnaires, illustrating proportions with observed eczema and atopic dermatitis according to the diagnostic criteria, and use of steroids in infancy.

Table S1 Adjusted logistic regression model: atopic dermatitis by UK Working Party criteria and/or Hanifin and Rajka criteria, first observation of eczema, paternal any atopy, maternal any atopy and sex of the infant.

Table S2 Adjusted logistic regression model: atopic dermatitis by UK Working Party criteria and/or the Hanifin and Rajka criteria, approximate number of times eczema observed + paternal any atopy + maternal any atopy + sex of the infant.

Table S3 The number of infants fulfilling the Hanifin and Rajka criteria, with or without fulfilling the first major criteria of pruritus/itch (reported or by visible excoriations/scratch marks at the investigation) at 12 months of age.

Table S4 Infants with eczema exclusively at various timepoints and use of topical steroids.

Powerpoint S1 Journal Club Slide Set.

Eczema distribution in girls and boys during infancy: A cohort study on atopic dermatitis

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Clinical Implications

- Different eczema distribution in girls and boys during infancy may reflect differences in sex-related factors in early atopic dermatitis. With eczema being prevalent on the trunk, we suggest adding truncal eczema to the diagnostic criteria for atopic dermatitis in infants.

Atopic dermatitis (AD) is a common chronic inflammatory skin disease characterized by eczematous skin lesions, pruritus, and dry skin.[1] The distribution of the eczema lesions in AD patients is known to vary with age and ethnicity.[2] We are not aware of data on possible differences in the clinical distribution of eczema in girls and boys during infancy. Furthermore, the clinical distribution of eczema during infancy may not be suitable for the 2 most commonly used diagnostic criteria sets for AD—the UK Working Party (UKWP) and Hanifin & Rajka (H&R) criteria.[3]

We aimed to determine prevalence and clinical distribution of eczema at 3, 6, and 12 months of age in girls and boys. Also, we aimed to determine sensitivity and specificity of fulfilling the UKWP and/or H&R criteria for AD using the areas most commonly affected by eczema.

From the PreventADALL (Preventing Atopic Dermatitis and Allergies) randomized controlled trial in a mother-child birth cohort study in Norway and Sweden,[3] we included all 1,834 infants (966 boys and 868 girls) who attended study visits at 3, 6, and 12 months of age. Skin assessment of the infants was performed by trained health care personnel. The primary outcome was eczema, defined as the presence of eczematous skin lesions, clinically excluding the differential diagnosis to AD (eg, seborrheic and contact dermatitis). Eczema on 11 specific areas of the skin[3] was registered at all 3 clinical follow-up visits. The secondary outcome, atopic dermatitis, was defined as fulfilling the UKWP and/or H&R criteria for AD. The UKWP criteria were used at all visits, whereas the H&R criteria were used at 12 months only. Comparing the occurrence of eczematous skin on different locations in girls and boys was performed using the chi-squared statistic in SPSS software version 26.0 (IBM, Armonk, NY). The sensitivity and specificity of the 2 sets of diagnostic criteria were calculated based upon the 3 areas most commonly affected with eczema.

Eczema was observed more often in boys (n = 355; 37%) than in girls (n = 273; 31%) ($P = .02$) by 12 months of age. Likewise, AD, by fulfilling 1 or both sets of diagnostic criteria at any timepoint, was diagnosed more often in boys (n = 126; 13%) than in girls (n = 86; 10%) ($P = .04$). Eczema was most often found on the cheeks, the extensor surfaces of the extremities, and the trunk (Table I, Figure 1, and Figures E1 and E2; available in this article's Online Repository at www.jaci-inpractice.org). More boys than girls had eczema on the cheeks—44% versus 31% at 3 months ($P = .04$), 51% versus 33% at 6 months ($P = .001$), 39% versus 29% at 12 months ($P = .08$), and 51% versus 37% ($P = .001$)—overall in infancy. However, more girls than boys had eczema on flexor surfaces of the extremities at 3 months (45% vs 31%; $P = .03$) (Table I, Figure 1, and Figures E1 and E2). Eczema on the trunk did not differ at any timepoint and was observed in 58% of girls and 53% of boys ($P = .29$). Sensitivity and specificity for the UKWP and/or H&R criteria using at least 1 observation of eczema at each location, independent of timepoint, were 47% and 95% for the cheeks, 43% and 97% for the extensor surfaces, and 51% and 98% for the trunk, respectively.

To the best of our knowledge, this is the first study to report the clinical distribution of eczema separately for boys and girls during infancy. Eczema on the cheeks was more common in boys at both 3 and 6 months of age, and with a trend also at 12 months of age, as was AD, whereas eczema on the flexor surfaces was more common in girls than in boys at 3 months of age. These findings are in line with studies in older children showing a slightly higher prevalence of AD in boys than in girls with a reversal after puberty.[4] Our study also adds to the recent finding of other sex-specific patterns of AD.[5] With cheeks being more exposed to wear and tear by local triggers,[6] sensitivity to such factors may play a more important role in the pathogenesis of infantile AD in boys than in girls, possibly contributing to the higher prevalence of AD observed in boys.

In all infants, regardless of sex, eczema was common in flexural areas of the extremities during infancy. This is in line with a study of AD in 12-month-old infants identifying flexural involvement to be as common as involvement of the cheeks, outer arms, and legs,[7] but, according to the authors, in contrast to others suggesting that typical flexural involvement often does not develop until about 2 years of age.[7]

In our study, the trunk was a common site for eczema during the first year of life, and had a somewhat higher sensitivity and specificity for a criteria-based diagnosis of AD than both cheeks and extensors. In the modified UKWP criteria for AD in infants, anatomical sites other than the trunk were chosen partly in order to separate infantile seborrheic dermatitis from infantile AD.[8] Although sometimes affecting the umbilical area,[9] infantile seborrheic dermatitis is not as common on the trunk as AD in infants and may also involve the sites already included in the criteria. Our findings may provide a rationale to add eczema localized on the trunk to the diagnostic criteria for AD.

The strengths of our study include the high number of infants from the general population in 3 different geographic areas in Norway and Sweden. Limitations include that the H&R criteria were used at 12 months only; we might have underestimated the total number of infants with criteria-based AD. The fluctuating

TABLE I. The clinical distribution of eczema by age and sex in the 628 infants with at least one observation of eczema in infancy

	At 3 months			At 6 months			At 12 months			During infancy		
Localization of eczema	**Girls n/N (%) (n = 105)**	**Boys n/N (%) (n = 135)**	***P****	**Girls n/N (%) (n = 162)**	**Boys n/N (%) (n = 197)**	***P****	**Girls n/N (%) (n = 140)**	**Boys n/N (%) (n = 189)**	***P****	**Girls n/N (%) (n = 273)**	**Boys n/N (%) (n = 355)**	***P****
Scalp	10 (10)	22 (16)	.13	14 (9)	15 (8)	.72	4 (3)	6 (3)	.87	23 (8)	39 (11)	.29
Cheeks	33 (31)	60 (44)	**.04**	53 (33)	100 (51)	**.001**	41 (29)	73 (39)	.08	102 (37)	180 (51)	**.001**
Head and neck (excluding scalp and cheeks)	43 (41)	54 (40)	.88	70 (43)	83 (42)	.84	37 (26)	51 (27)	.91	109 (40)	142 (40)	.99
Trunk (abdomen, back, shoulders, and chest)	54 (51)	69 (51)	.96	78 (48)	100 (51)	.62	75 (54)	88 (47)	.21	157 (58)	189 (53)	.29
Extensors of arms and legs	72 (69)	85 (63)	.37	71 (44)	100 (51)	.19	83 (59)	111 (59)	.92	166 (61)	229 (65)	.34
Flexors of arms and legs	47 (45)	42 (31)	**.03**	54 (33)	64 (33)	.87	43 (31)	68 (36)	.32	123 (45)	141 (40)	.18
Flexor of elbows and knees	40 (38)	36 (27)	.06	49 (30)	61 (31)	.88	40 (29)	43 (23)	.23	105 (38)	114 (32)	.10
Dorsum of hands and wrists	27 (26)	28 (21)	.36	26 (16)	21 (11)	.13	30 (21)	26 (14)	.07	65 (24)	64 (18)	.08
Plantar side of hands and wrists	4 (4)	7 (5)	.61	4 (3)	3 (2)	.52	9 (6)	10 (5)	.66	15 (5)	19 (5)	.94
Ankles and feet	19 (18)	35 (26)	.15	30 (19)	34 (17)	.76	27 (19)	24 (13)	.10	65 (24)	73 (21)	.33
Nappy area†	4 (4)	8 (6)	.46	5 (3)	6 (3)	.98	6 (4)	11 (6)	.53	14 (5)	24 (7)	.40

*P values $< .05$ are given in bold. A conservative level of statistical significance by Bonferroni's correction for multiple testing: $P = .05/11 \times 3 = .0015$.
†Nappy area indicates the area of the skin covered by a standard sized diaper.

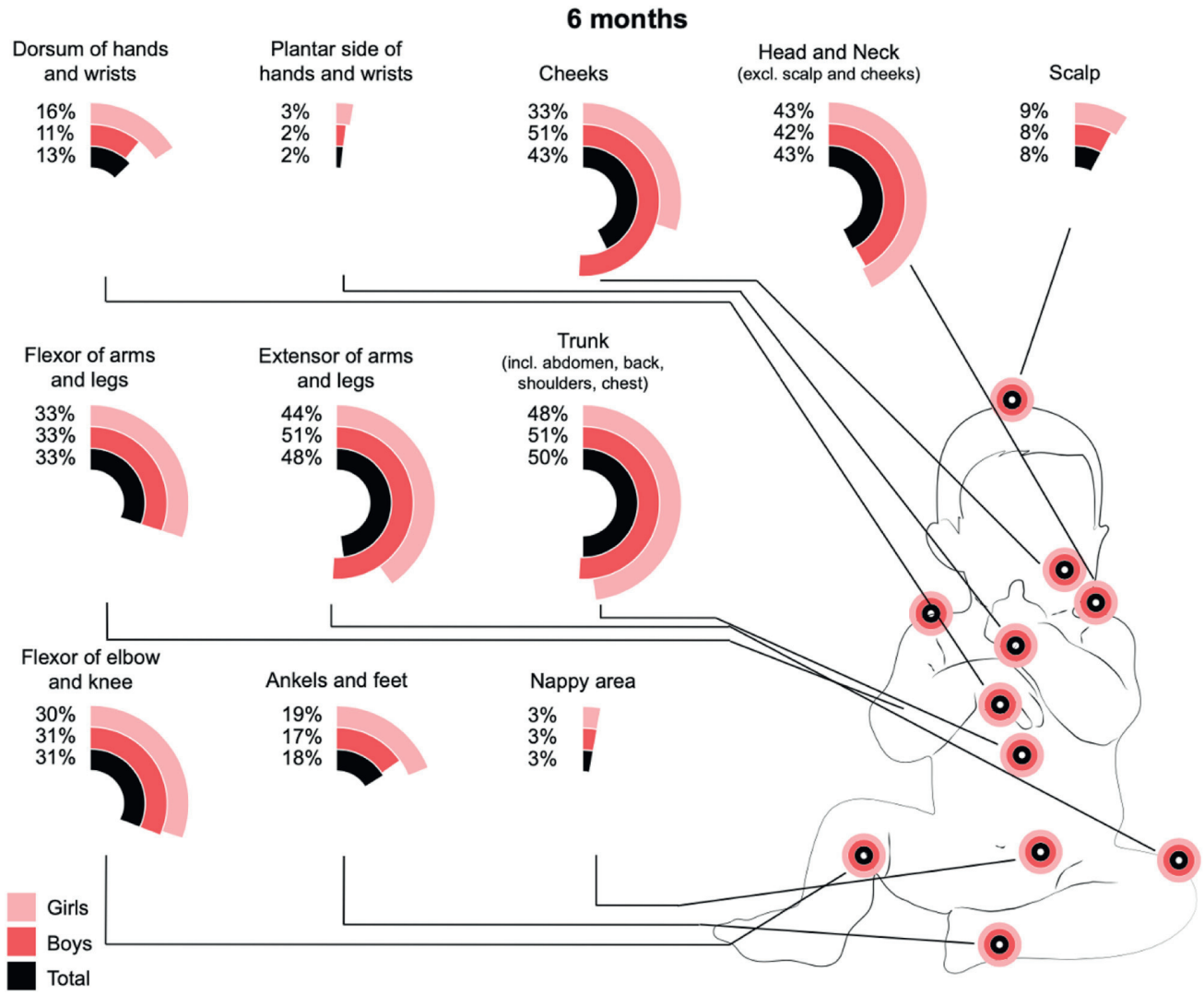

FIGURE 1. The distribution of eczema in the 359 girls and boys with observed eczema at 6 months of age. (Illustration by Ine Eriksen, University of Oslo, Oslo, Norway.) *Nappy area indicates the area of the skin covered by a standard sized diaper.

nature of AD and treatment effects during the study period may also have contributed to an underestimation of the prevalence of eczema. Although recruiting from the general population, parents with higher education and atopic disease were somewhat overrepresented,[3] which may limit the generalizability of the results.

In conclusion, the clinical distribution of eczema in infants differed between girls and boys, which may be relevant for our understanding of the pathogenesis of AD in boys and girls. With the finding of the trunk being a predilection site for infantile eczema, we suggest adding the trunk to the diagnostic criteria for AD in infants.

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The PreventADALL study is approved by the Regional Committee for Medical and Health Research Ethics in Norway (2014/518) and Sweden (2014/2242-31/4) and is registered at clinicaltrials.gov (NCT02449850).

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Conflicts of interest: K. M. A. Endre has received honorary for presentations from AbbVie. M. LeBlanc has received honorary for presentations from MSD. E. M. Rehbinder has received honoraria for presentations from Sanofi Genzyme, Novartis, MEDA and Omega Pharma. The rest of the authors declare that they have no relevant conflicts of interest.

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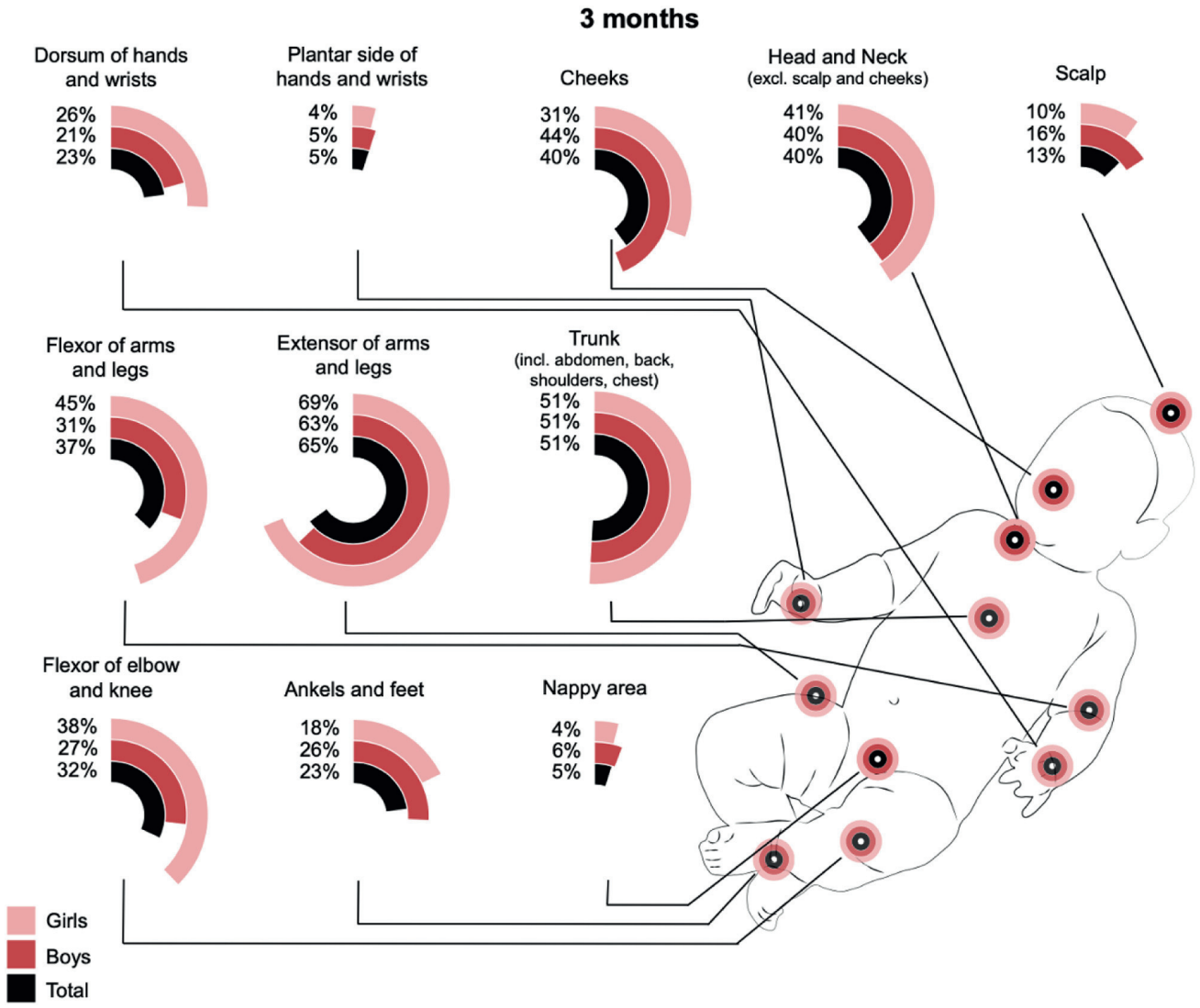

FIGURE E1. The distribution of eczema in the 240 girls and boys with observed eczema at 3 months of age. (Illustration by Ine Eriksen, University of Oslo, Oslo, Norway.) (Illustration by Ine Eriksen, University of Oslo, Oslo, Norway.) *Nappy area indicates the area of the skin covered by a standard sized diaper.

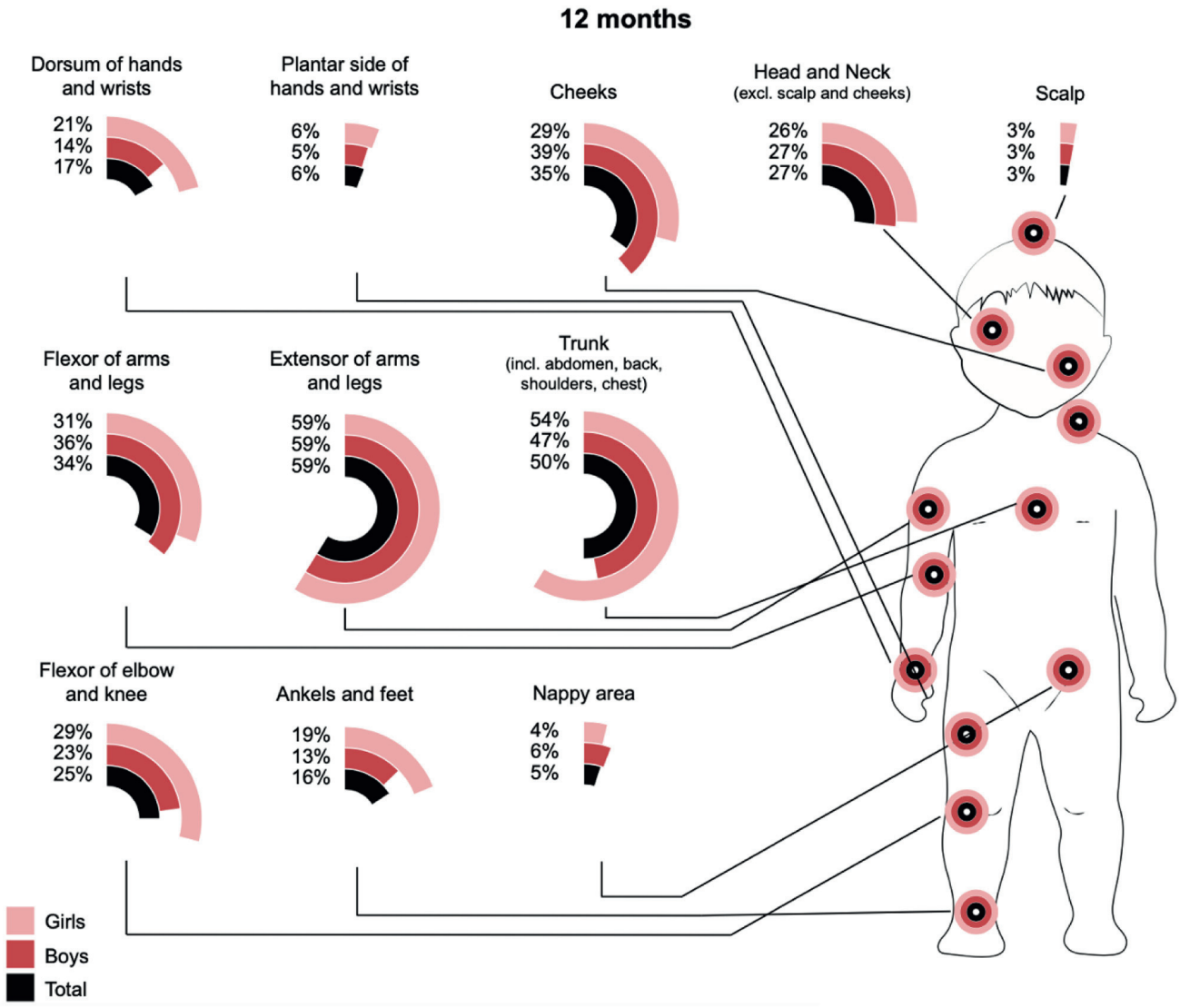

FIGURE E2. The distribution of eczema in the 329 girls and boys with observed eczema at 12 months of age. (Illustration by Ine Eriksen, University of Oslo, Oslo, Norway.) *Nappy area indicates the area of the skin covered by a standard sized diaper.