Hovedoppgave

NTNU
Norges teknisk-naturvitenskapelige universitet
Fakultet for medisin og helsevitenskap

Åshild Øksnevad Solvin

Eczema and Cardiovascular Risk Factors and Diseases: The HUNT Study, Norway

Hovedoppgave i Medisin
Veileder: Ingrid Snekvik, Marit Saunes, Mari Løset
August 2020

NTNU
Kunnskap for en bedre verden

Eczema and Cardiovascular Risk Factors and Diseases: The HUNT Study, Norway

Åshild Øksnevad Solvin[1], Ingrid Snekvik[2,3], Marit Saunes[3], Mari Løset[1,3]

[1]K.G. Jebsen Center for Genetic Epidemiology, Department of Public Health and Nursing, NTNU, Norwegian University of Science and Technology, Trondheim, Norway
[2]Department of Clinical and Molecular Medicine, NTNU, Norwegian University of Science and Technology, Trondheim, Norway
[3]Department of Dermatology, St. Olavs hospital, Trondheim University Hospital, Trondheim, Norway

Table of contents

Acknowledgements
Abbreviations
Summary in English
Sammendrag på norsk
1. Introduction 1
1.1 Eczema 1
1.1.1 Clinical course and presentation 1
1.1.2 Prevalence 1
1.1.3 Etiology and pathophysiology 2
1.1.4 Management and treatment 3
1.1.5 Comorbidities 3
1.2 Predisposition for cardiovascular risk factors and cardiovascular diseases 4
1.2.1 Eczema and cardiovascular risk factors 4
1.2.2 Eczema and cardiovascular diseases 4
2. Study aims 5
3. Study population and methods 6
3.1 The HUNT-Study 6
3.2 Classification of exposure and outcomes 6
3.2.1 Exposure: Eczema 6
3.2.2 Classification of outcomes 6
3.3 Ethics and personal protection 8
3.4 Statistical analyses 8
4. Results 10
4.1 Characteristics of study population 10
4.2 Cardiovascular risk factors according to eczema 10
4.2.1 Continuous cardiovascular risk factors 10
4.2.2 Dichotomous cardiovascular risk factors 12
4.3 Cardiovascular disease outcomes 12
5. Discussion 14
5.1 Summary and interpretation of main findings 14
5.1.1 Cardiovascular risk factors 14
5.1.2 Established cardiovascular disease 16
5.2 Methodological considerations 16
5.2.1 Precision 16
5.2.2 Validity 17

5.2.3 Causation 19
6. Conclusion and future perspectives 20
7. List of references 21

Acknowledgements

This research has been conducted using data from the HUNT Study. The HUNT Study is a collaboration between HUNT Research Centre (Faculty of Medicine and Health Sciences, NTNU, Norwegian University of Science and Technology), Nord-Trøndelag County Council, Central Norway Regional Health Authority, and the Norwegian Institute of Public Health.

Abbreviations

BMI	Body mass index
CI	Confidence interval
CRP	C-reactive protein
CVD	Cardiovascular disease
CVRF	Cardiovascular risk factor
DBP	Diastolic blood pressure
EHR	Electronic health record
FLG	Filaggrin
G-6-PDH	Glucose-6-phosphate dehydrogenase
HDL	High density lipoprotein
HUNT	The Nord-Trøndelag Health Study
IgE	Immunoglobulin E
IL-1/-4/-14	Interleukin-1/-4/-14
KIF3A	Kinesin-like protein 3 a
MI	Myocardial infarction
MR	Mendelian randomization
OR	Odds ratio
pH	Potential of hydrogen
SBP	Systolic blood pressure
TEWL	Trans-epidermal water loss
Th2	T helper cell type 2
UK	United Kingdom
USA	United States of America

Summary in English

Background: In recent years, possible associations between eczema and cardiovascular risk factors (CVRFs) and cardiovascular diseases (CVDs) have been explored. Studies have found positive associations between eczema and certain CVRFs including increased body mass index (BMI) and abdominal adiposity and CVDs including increased risk of myocardial infarction, angina pectoris and stroke. However, the results are conflicting and have not been thoroughly explored in Norwegian populations.

Objectives: To investigate the cross-sectional association of eczema with CVRFs and CVDs in a large Norwegian population.

Materials and methods: We obtained data from the third survey of the Nord-Trøndelag Health Study (HUNT3). HUNT3 is a population-based study, carried out from 2006 to 2008. All inhabitants in Nord-Trøndelag County aged 20 years or older were invited, and a total of 50 800 adults participated (54%). We classified participants as having eczema and CVDs according to self-reported information in HUNT3 and used objective measurements of CVRF from measurements collected in HUNT3. Linear and logistic regression were used to estimate adjusted associations between CVRFs and self-reported CVDs in three distinct, mutually exclusive groups; no eczema, participants with eczema on hands, and participants with eczema on hands and childhood eczema.

Results: A total of 5757 participants reported ever having had eczema on hands and among them, 4206 (73.0%) participants answered a supplementary hand eczema questionnaire. In this questionnaire, 1311 (31.2%) participants reported having had eczema in childhood. In total, our study included a total of 45018 participants with no eczema, 4446 individuals with eczema on hands and 1311 individuals with eczema on hands and childhood eczema. We found that eczema on hands was positively associated with increased waist circumference (mean 93.8, 95% CI 93.6-93.9) and increased BMI (mean 27.7, 95%CI 27.5-27.8) compared to the group with no eczema (means 93.5, 95%CI 93.4-93.5 and 27.1, 95%CI 27.1-27.1 respectively). In addition, eczema on hands was positively associated with verified hyperglycemia (OR 1.26, 95% CI 1.13-1.41), angina pectoris (OR 1.49, 95%CI 1.05-1.50), heart failure (OR 1.37, 95%CI 1.01-1.85) and other heart diseases (OR 1.49, 95% CI 1.27-1.76), compared individuals with no eczema. Participants reporting both eczema on hands and childhood eczema had marginally higher levels of micro C-reactive protein than the group with no eczema (means 3.1, 95% CI 2.8-3.4 and 2.7, 95% CI 2.7-2.8, respectively) and we observed a positive association concerning “other heart diseases” (OR 1.47, 95% CI 1.06-2.05) when comparing the group with eczema on hands and in childhood to the group with no eczema. We found no association between eczema on hands and childhood eczema for diastolic blood pressure, blood glucose, blood lipids, myocardial infarctions or stroke.

Conclusions: In this cross-sectional, population-based study, we found that eczema was positively associated with measures of adiposity, verified hyperglycemia, as well as angina pectoris, heart failure and “other heart diseases”. For the latter association, we observed a stronger association in the group that also reported childhood eczema.

Sammendrag på norsk

Bakgrunn: Mulige assosiasjoner mellom eksem og kardiovaskulære risikofaktorer (KVRF) og kardiovaskulære sykdommer (KVS) blitt undersøkt i nylige år. Studier har funnet positive assosiasjoner mellom eksem og visse KVRF-er som økt kroppsmasseindeks (KMI) og abdominal fedme, samt KVS-er, inkludert økt risiko for hjerteinfarkt, angina pectoris og slag. Ikke desto mindre er disse resultatene motstridende og har ikke blitt grundig undersøkt i norske populasjoner.

Formål: Å undersøke den tverrsnittsbaserte assosiasjonen av eksem med KVRF-er og KVS-er i en stor norsk populasjon.

Materialer og metode: Vi innhentet data fra den tredje undersøkelsen av Helseundersøkelsen i Nord-Trøndelag (HUNT3). HUNT3 er en populasjonsbasert studie gjennomført fra 2006 til 2008. Alle innbyggere i Nord-Trøndelag fylke på 20 år eller eldre ble invitert og totalt 50 800 (54%) deltok. Vi klassifiserte deltakere til å ha eksem og KVS-er etter selvrapportert informasjon i HUNT3 og brukte objektive mål på KVRF-er fra målinger samlet inn i HUNT3. Lineær og logistisk regresjon ble brukt for å estimere justerte assosiasjoner mellom KVRF-er og selvrapporterte KVS-er i tre distinkte, disjunkte grupper; ingen eksem, deltakere med eksem på hender, og deltakere med eksem på hender og barndomseksem.

Resultater: Totalt 5757 personer rapporterte å ha hatt eksem på hendene og blant dem, besvarte 4206 (73.0%) deltakere et tilleggsskjema om håndeksem. I dette spørreskjemaet rapporterte 1311 (31.2%) å ha hatt eksem i barndommen. Vår studie inkluderte totalt 45018 deltakere med ingen eksem, 4446 deltakere med eksem på hendene and 1311 deltakere med eksem på hendene og barndomseksem. Vi fant at eksem på hender var positivt assosiert med økt midjemål (gjennomsnitt 93.8, 95% CI 93.6-93.9) og økt KMI (gjennomsnitt 27.7, 95% CI 27.5-27.8) sammenliknet med gruppen med ingen eksem (gjennomsnitt henholdsvis 93.5, 95% CI 93.4-93.5 og 27.1, 95% CI 27.1-27.1). I tillegg var eksem på hender positivt assosiert med bekreftet hyperglykemi (OR 1.26, 95% CI 1.13-1.41) angina pectoris (OR 1.49, 95% CI 1.05-1.50), hjertesvikt (OR 1.37, 95% CI 1.01-1.85) og «annen hjertesykdom» (OR 1.49, 95% CI 1.27-1.76), sammenliknet med individer uten eksem. Deltakere som rapporterte både eksem på hender og barndomseksem hadde marginalt høyere nivåer av micro C-reaktivt protein enn gruppen med ingen eksem (gjennomsnitt henholdsvis 3.1, 95% CI 2.8-3.4 og 2.7, 95% CI 2.7-2.8) og vi observerte en positiv assosiasjon for «annen hjertesykdom» når man sammenliknet gruppen med eksem på hender og i barndom med gruppen uten eksem (OR 1.47, 95% CI 1.06, 2.05). Vi fant ingen assosiasjon mellom eksem på hender og barndomseksem for diastolisk blodtrykk, blodsukker, hjerteinfarkt eller slag.

Konklusjoner: I denne populasjonsbaserte tverrsnittsstudien fant vi at eksem var positivt assosiert med mål på fedme, bekreftet hyperglykemi, i tillegg til angina pectoris, hjertesvikt og «annen hjertesykdom». For sistnevnte assosiasjon observerte vi en sterke assosiasjon i gruppen som også rapporterte barndomseksem.

1. Introduction

1.1 Eczema

1.1.1 Clinical course and presentation

Eczema is a chronic inflammatory skin disease, characterized by a relapsing-remitting disease course. Its clinical hallmarks are intense pruritus and recurrent eczematous lesions. The lesions consist of poorly defined erythema, papules, vesicles, crusting and lichenoid skin. The degree of skin changes depend on the severity of the disease and if the lesions are acute onset or chronically present (1, 2). The lesions may appear on any part of the body, but typically display an age-related distribution pattern. In infants, the lesions are most often found on the head and face, as well as on the extensor surfaces of the extremities and the diaper-area is typically spared. In toddlers and children, the lesions are typically located on the flexural surfaces of the extremities. In adults, the most common localization is on the hands, typically presented as chronic hand eczema, as well as on the neck and eyelids. In infants, toddlers and children, lesions are often acute, with intense erythema, exudations and vesicles, while in adults, the lesions are chronic in appearance, with skin thickening and visible excoriations. The clinical course may vary with season in northern countries, with many patients experience less severe symptoms in the summer months (2). Characteristic signs to the lesions include palmar hyperlinearity, Dennie-Morgan lines (lines in the skin below the eyelid) and Herthoge´s sign (a thinning of the lateral third of the eyebrow) (1). In patients with skin of color (SOC), the characteristic erythema of eczema is less noticeable and provides a diagnostic challenge. Eczema patients with SOC also tends to be more scattered, papular lesions with post inflammatory hyperpigmentation and lichenification, the latter appearing as an ashen thickening of the skin (3).

Eczema is a heterogenous disease without any specific diagnostic tests and could be divided into atopic and non-atopic subtypes. Eczema is a clinical diagnosis, and several diagnostic criteria have been proposed, where the UK working party criteria (4) or the Hanifin and Rajka criteria (5) are commonly used (1). These two sets of diagnostic criteria are developed for atopic dermatitis. However, eczema has been suggested as an umbrella term to cover both atopic and non-atopic types of dermatitis, as not all atopic dermatitis-patients show IgE mediated allergic sensitization and are therefore not strictly atopic. The terms atopic dermatitis and eczema are often used interchangeably in published literature (6).

1.1.2 Prevalence

Eczema is a common disease with an estimated prevalence 10-20% in the developed world (6) and is more prevalent in urban areas compared to rural ones (7). In Norway, the prevalence has been reported to be as high as 23% in children (8). It was previously believed to be a childhood disease with a lower prevalence in adults, however, recent studies have found the prevalence in adults to be equally high as in children (7). Furthermore, patients who may appear to have outgrown the disease, continue to have hyper-sensitive skin and may

experience recurrence of symptoms after long periods of remission (1).The lifetime prevalence for hand eczema specifically has been estimated to 15% in the general population (9).

1.1.3 Etiology and pathophysiology

Eczema is believed to arise from a complex interplay between genetic and environmental factors. I addition to genetics, skin barrier function, immunological factors and microbiota are considered to be particularly important. A family history of atopic disease is the strongest known risk factor for eczema and genome-wide association studies have linked more than 30 genetic loci to eczema across different populations (10). A systematic review which included information from 35 155 twin pairs estimated the heritability of atopic dermatitis to be approximately 75% (11), which is considered to be a high heritability for a complex trait. However, as the concordance rate in monozygotic twins is 72-86% (12), environmental influences also play a role in the development of disease.

The two main pathophysiological mechanisms associated with eczema are impaired barrier function and increased cutaneous inflammations due to an inappropriate immune response to antigens encountered (1). The clinical manifestation of eczema and efficacy of anti-inflammatory treatments such as topical corticosteroids and topical calcineurin inhibitors point to a primary dysfunction in the immune system. In addition, molecular genetics have provided evidence of mutations in the structural proteins of the stratum corneum. This causes changes in epithelial barrier function, leading to emerging inflammation as a downstream effect, rather than the primary dysfunction (13).

Filaggrin and skin barrier function

The skin is the largest organ in the human body and serves as a protective barrier against pathogens, toxins and irritants. The skin is also involved in homeostasis, regulating the loss of water and ions. The barrier function of skin is dependent on proliferation, differentiation and eventual desquamation of keratinocytes in the epidermis (14).

The most common genetic factor contributing to eczema is changes in the Filaggrin (*FLG*) gene, most commonly a loss-of-function mutation. The *FLG*-protein is vitally important in formation of the skin barrier preventing trans-epidermal water loss (TEWL) and hinders the entry of pathogens, allergens and toxins (15). Mutations in the *FLG* gene leads to barrier dysfunction through increased TEWL and changes in skin pH, leading to the clinical feature of dry skin. In turn, this leads to increased colonization of staphylococcus aureus, Th2-cell activation and pruritus (16). Mutations in *FLG* is found in up to 50% of Northern European patients with eczema (15, 17). While mutations in *FLG* are neither necessary nor sufficient for the development of eczema, carriers are more likely to have a severe clinical course and increases the probability of symptom persistence into adulthood (16). Apart from *FLG* loss-of-function mutations, other inherited factors and can impair epidermal function, such as copy number variants (1).

Immune cell dysfunction

Cutaneous inflammation and immune cell dysregulation are both central for the disease pathogenesis. The defective barrier function characteristic for eczema leads to changes in the inflammatory milieu of the skin. Firstly, an increase in pH leads to activation of Th2 cells

through an increase of IL-1 alpha and beta. Recent studies have implicated Th2 cytokines KIF3A, IL-4, and IL-13 as key molecules in the development of eczema (18). IL-4 and IL-13 are overexpressed in acute eczema lesions. In addition, these cytokines inhibit FLG production and function, and as such, skin barrier dysfunction and cutaneous inflammation act as mutually reinforcing processes. Furthermore, the Th2 cytokines help activate B-cells into IgE production, increasing the levels of IgE, which is characteristic for atopic phenotypes such as eczema (19).

Environmental factors

Certain triggers can incite flare-ups or worsening of lesions in eczema patients. These triggering factors include irritants or allergens in sensitized individuals, cold weather, humidity, or mechanical damage from repeated scratching (1, 6). Other implicated environmental exposures include rural living, air pollutants, cigarette smoking, both in utero and in adulthood, maternal stress as well as skin microbiota (20). Healthy skin acts as a barrier to pathogens and the disrupted skin barrier in atopic dermatitis leads to a dysregulated microbiome of the skin. In eczema, the microbiome is less diverse and dominated by Staphylococcus aureus and Staphylococcus epidermidis (21). The staphylococcal species produce exotoxins and superantigens which further drive cutaneous inflammation. A recent mendelian randomization study also provides evidence of a causal relationship between body mass index (BMI) and atopic dermatitis (22). The global prevalence of atopic dermatitis is increasing, underscoring the influence of environmental factors (6).

1.1.4 Management and treatment

Treatment of eczema is multifaceted, aiming at improving epidermal function and reducing inflammation to manage symptoms and obtain long-term disease control. The choice of therapy is usually based on disease severity, and includes topical-, photo-, and systemic therapies (6). A cornerstone of the treatment is topical moisturizers. Eczematous skin has a lower water and lipid content (23), leading to reduced barrier function and penetration of allergens and irritants. Other treatments to restore skin hydration and barrier function include wet wraps and oil baths (24). The two most commonly used anti-inflammatory agents in treatment of eczema are topical corticosteroids and topical calcineurin inhibitors, used in combination with a moisturizing regime. Systemic treatments include conventional immunosuppressive agents, such as oral cyclosporine and methotrexate. Recently, Dupilumab, a fully human monoclonal antibody that targets the IL4-receptor alfa, and thereby inhibits both IL-4 and IL-13 signaling has been approved for difficult-to-treat eczema in Norway (25). Dupilumab shows good efficacy and safety data in adults and adolescents (26, 27).

1.1.5 Comorbidities

A growing number of epidemiological studies have established associations between eczema and multiple atopic- and non-atopic comorbidities (28, 29). Atopic comorbidities include asthma, allergic rhinitis, food allergies and eosinophilic esophagitis (30). The mechanism for the atopic comorbidities in eczema is believed to be due to the propensity for IgE production in patients, as well as transcutaneous penetration of allergens through an impaired skin barrier. In addition, increased activation of Th2 inflammatory pathways are important for the development of both eczema and asthma bronchiale (31). Large-scale genetic studies have identified shared genetic susceptibility across the atopic comorbidities, and specifically

identified common genes involved in dysregulating the expression of immune-related genes (10).

Non-atopic comorbidities that have been associated with eczema includes contact dermatitis, infections, mental illness (anxiety, depression and increased risk of suicide) (31). The increased rates of mental illnesses have been hypothesized to be due to pruritus and associated sleep disturbances, as well as social stigma and isolation (31).

1.2 Predisposition for cardiovascular risk factors and cardiovascular diseases

Cardiovascular diseases (CVDs) are the leading cause of death worldwide and most CVDs can be prevented by addressing modifiable risk factors, such as tobacco use, obesity and physical activity (32). In recent years, the possible associations between eczema and cardiovascular risk factors (CVRFs) and CVDs has gained traction. While the relationship between eczema and atopic comorbidities have been thoroughly studied and are likely causal (33), the relationship between eczema and CVRFs/CVDs is less clear, and studies have yielded conflicting results (34, 35).

1.2.1 Eczema and cardiovascular risk factors

Cardiovascular risk factors are any factors, modifiable or non-modifiable factors which increases risk for cardiovascular disease or cardiovascular death and include age, gender, family history, blood pressure, cholesterol, diabetes and smoking, to name a few (36). A positive association between increased weight and eczema has been found in North American, Asian and European populations, according to meta-analyses (22, 37). Patients with eczema in the USA have also been found to partake in behaviors known to increase cardiovascular risk, such as smoking and alcohol consumption and limited physical activity (38) and US children with eczema have been found to have higher rates of central obesity and high blood pressure (39).

1.2.2 Eczema and cardiovascular diseases

Cardiovascular diseases are diseases affecting the heart and vascular systems and include among others myocardial infarctions (MI), angina pectoris and ischemic stroke (40). While the presence of some CVRFs in eczema have been established, their clinical significance warrants further investigations. Studies from both Denmark and USA have reported associations between eczema and MI (41, 42). Another study from Taiwan found no increased risk of MI but did report a positive association between ischemic stroke and eczema (43). The discrepancies in these results may be explained by unsuitable or lack of adjusting covariates, differences in study design or due to different populations being studied (34, 38, 41, 44).

The possible links between eczema, and CVRFs and CVDs are likely complex and multifactorial. Possible explanatory mechanisms include shared genetic variants between eczema, CVRFs and CVDs, systemic low-grade inflammation, shared inflammatory pathways between eczema and atherosclerosis and a sedentary lifestyle, possibly due to asthma and skin discomfort (38).

2. Study aims

Population-based studies of the association between CVRFs and CVDs in individuals with eczema are sparse in Norwegian populations. Specifically, we are only aware of one such study, where the relationship between increased BMI and eczema was investigated (22). We therefore aimed to examine these associations in a large, population based-cohort study in Norway. CVRFs may be present without giving any symptoms and recognizing the clinical importance of these risks could introduce early initiations of preventive therapies among patients with eczema and improve individualized treatment regimens to reduce cardiovascular risk.

3. Study population and methods

3.1 The HUNT-Study

The HUNT-Study is a large, population-based cohort study performed over four periods; HUNT1 (1984-86), HUNT2 (1995-97), HUNT3 (2006-08) and HUNT4 (2017-19) (45). All inhabitants in Nord-Trøndelag county aged 20 years or older were invited to participate. The surveys included multiple questionnaires, standardized clinical examinations, urine and non-fasting venous blood samples. In the present study, we used data from HUNT3. In HUNT3, 93 860 persons were invited, and 50 800 (54%) chose to participate. In HUNT3, researchers collected baseline questionnaires with self-reported illness and certain behavioral risk factors including smoking. Anthropometric measures, vitals and venous blood samples were also collected. Participants who reported having certain diseases in the baseline questionnaire were sent additional questionnaires to more thoroughly survey a specific disease.

3.2 Classification exposure and outcomes

3.2.1 Exposure: Eczema

In the baseline assessment of HUNT3, all participants were asked to answer yes or no to the following multiple answer-question: “Do you have/have you ever had any of the following diseases? Eczema on hands”. Eczema was defined by a positive answer to this question. A total of 5757 (11.3%) participants reported to have had eczema on hands in HUNT3. We excluded 24 participants with missing information on this question. Some of the participants answering yes to this question were sent an additional, eczema specific questionnaire, provided that they were not selected for more than two other, high-priority disease-specific questionnaires, as the number of additional questionnaires was limited to three (45). A total of 5748 participants were sent this questionnaire and 4206 (73%) chose to participate. The additional, eczema-specific questionnaire asked “Did you have eczema as a child? (also called atopic dermatitis)” to which the participants could answer yes, no or don’t know. Childhood eczema was defined by having a positive answer to this question. We excluded 50 participants with missing on the eczema in childhood question. A total of 1311 (31.2%) participants asked reported having had eczema in childhood. In total, the present study included total of 45018 participants without eczema, 4446 participants with eczema on hands, and 1311 participants with eczema on hands and in childhood. As the number of study participants is high in each group, all outcome variables were assumed to be normally distributed for all groups, according to the central limit theorem.

3.2.2 Classification of outcomes

The endpoints of the present study were based on objective measures from clinical and biochemical examinations by specially trained staff in HUNT3, as well as self-reported CVRFs and CVDs

Classification of cardiovascular risk factors

Waist circumference

Waist circumference was measured after maximal expiration at the level of the umbilicus or halfway between the bottom of the ribs and the top of the hips, whichever was smaller. The participants were standing upright with arms hanging on the side. The measurements were done above light clothing and rounded to the nearest whole centimeter. We excluded 445 participants with missing information on waist circumference.

Body mass index

Height was measured without shoes and given in centimeters, with one decimal. Weight was measured with the participants wearing light clothes and without shoes. Weight was reported in kilograms with one decimal. BMI was calculated by dividing weight in kilograms by height in meters squared. We excluded 408 individuals with missing information on BMI. These participants were excluded from all analyses, as BMI was used as an adjusting covariate.

Systolic and diastolic blood pressure

Blood pressure was measured using Dinamap CARESCAPE V100 (GE Healthcare). Measurements were done with the participant in a sitting position, after being seated for two minutes with the cuff on the arm, and arm resting on a table. Cuff size was adjusted according to arm circumference. Three consecutive automatic measurements were done at one-minute intervals and rounded to the nearest 2 mmHg. The blood pressure reported in this paper is the rounded arithmetic mean of measurement two and three, if all three available. If only two measurements were available, the last measurement was used. We excluded 416 and 420 participants with missing information on systolic blood pressure (SBP) and diastolic blood pressure (DBP), respectively.

Cholesterol in serum

Serum cholesterol was measured in a non-fasted state and analyzed by cholesterol esterase methodology. Results are reported in mmol/L. We excluded 1473 participants with missing information on serum cholesterol.

High Density Lipoprotein-Cholesterol in serum

High density lipoprotein-cholesterol (HDL-cholesterol) was measured in a non-fasted state and analyzed by Accelerator selective detergent methodology. Results are reported in mmol/L. We excluded 1474 participants with missing information on serum HDL-cholesterol.

Triglycerides in serum

Serum triglycerides was measured in a non-fasted state and analyzed using Glyserol Phosphate Oxidase methodology. Results are reported in mmol/L. We excluded 762 participants with missing information on serum triglycerides.

Non-fasting glucose in serum

Serum glucose was measured in a non-fasted state and analyzed by Hexokinase/G-6-PDH methodology. Results are reported in mmol/L. We excluded 1472 participants with missing information on non-fasting glucose in serum.

micro C-reactive protein in serum

Serum micro C-reactive protein (micro CRP) was measured in a non-fasted state and analyzed by latex immunoassay methodology. Results are reported in mg/L. We excluded 763 participants with missing information on micro CRP in serum.

Self-reported cardiovascular risk factors

In the baseline questionnaire in HUNT3, all participants were asked to answer yes or no to the following questions “Has it ever been verified that you had high blood sugar (hyperglycemia)?” and “Do you take, or have you taken medication for high blood pressure?” and “Have you had, or do you have diabetes?”. Participants with positive answers were classified as having CVRFs. We excluded from the analyses participants with missing information on these questions, 35 participants for verified hyperglycemia, 29 participants for antihypertensive medication and 29 participants for diabetes.

Classification of cardiovascular diseases

Angina pectoris, myocardial infarction, heart failure, “other heart diseases” and stroke/brain hemorrhage were defined by a positive answer to the question: Do you have/have you ever had any of the following diseases? “Angina pectoris”, “Myocardial infarction”, “Heart failure”, “Other heart diseases” and Stroke/Brain hemorrhage in the baseline questionnaire in the HUNT3. We excluded participants with missing information on these questions, 28 participants for angina pectoris, 25 participants for myocardial infarction, 26 participants for heart failure, 30 participants for other heart diseases and 25 participants for stroke/brain hemorrhage.

3.3 Ethics and personal protection

This study was approved by the Regional Committees for Medical and Health Research Ethics in Mid-Norway (2015/586). Participation in the HUNT Study was based on a written informed consent signed before inclusion. Every participant may withdraw their consent at any time. Before data are made accessible to researchers the files are de-identified, i.e. name and identification number are converted into project numbers. We have used HUNT Cloud as our computer environment for storage of HUNT data.

3.4 Statistical analyses

To estimate the adjusted means and 95% confidence intervals (CIs) of the various CVRFs in participants with eczema and childhood eczema compared to those without eczema, univariate linear regression was used. To estimate the odds ratios (ORs) and corresponding 95% CIs for CVDs and certain CVRFs in participants with eczema and childhood eczema, compared to those without eczema, we used a binary logistic regression model. The same approaches were applied when estimating adjusted means and ORs comparing participants with childhood eczema to those with eczema in adulthood only.

We selected potential confounders based on *a priori* considerations of factors that are related to both eczema, CVRFs and CVDs. All analyses were adjusted for possible confounding by age (years), sex (women, men), smoking (never, former, occasional and current) and BMI (continuous), except BMI which was adjusted for age, sex and smoking status. We excluded participants with missing values on the confounders from the analysis (1424 participants with

missing information on smoking and 408 participants with missing information on BMI). All statistical analyses were performed using IBM SPSS statistic for Macintosh, version 25 (Chicago, IL, USA).

4. Results

4.1 Characteristics of the study population

Characteristics of the study population in given in Table 1. The self-reported prevalence of eczema on hands in HUNT3 was 11.3%, and among them 31.2% of participants asked also reported having had eczema in childhood. The present study included 45018 participants with no eczema, 4446 participants with eczema on hands and 1311 participants with eczema on hands and childhood eczema. The gender distribution was almost equal among the participants with no eczema (53.1% women), however, there were more women in both the participants with eczema on hands (65.7% women) and the participants with eczema on hands and in childhood (69.3% women). Overall in HUNT3, women were slightly overrepresented with the highest attendance in the middle-aged group.

Current smokers were more prevalent in participants with eczema on hands (21.4% current smokers) than in participants with no eczema (17.0% current smokers) and the eczema on hands and eczema in childhood group (15.9% current daily smokers). This is also reflected when comparing the proportions of participants who have never smoked. Among the participants with eczema on hands, 38.0% were never smokers, whereas an increased proportion were never-smokers in the no eczema and eczema on hands and eczema in childhood groups (43.1% and 45.6% never smokers, respectively). Proportions of former and occasional smokers are equally distributed amongst the participants with no eczema, eczema on hands and eczema on hands and in childhood groups.

Table 1. Characteristic of the study participants according to eczema-status

	HUNT3 (n = 50 800)		
	No eczema	**Eczema on hands**	**Eczema on hands and in childhood**
	(n = 45018)	**(n = 4446)**	**(n = 1311)**
Women, *n* (%)	23909 (53.1)	2922 (65.7)	908 (69.3)
Age in years, mean (SD)	53.6 (16.2)	51.3 (14.9)	45.1 (16.1)
Smoking status			
Never, *n* (%)	18832 (43.1)	1646 (38.0)	589 (45.6)
Former, *n* (%)	14262 (32.6)	1448 (33.4)	395 (30.6)
Occasional, *n* (%)	3211 (7.3)	309 (7.1)	103 (8.0)
Current, *n* (%)	7421 (17.0)	927 (21.4)	205 (15.9)

Abbreviations: HUNT3, The Nord-Trøndelag Health Study 3; SD, standard deviation

4.2 Cardiovascular risk factors according to eczema

4.2.1 Continuous cardiovascular risk factors

The adjusted mean waist circumference of the eczema on hands group was 93.8 cm (95% CI 93.6-93.9), slightly higher than the no eczema group with its adjusted mean of 93.5 cm (95% CI 93.4-93.5) (Table 2). BMI was also higher in the eczema on hands group (adjusted mean 27.7 95% CI 27.5-27.8) than in the no eczema group (adjusted mean 27.1 95% CI 27.1-27.1) and the eczema and childhood eczema group (adjusted mean 27.2 95% CI 72.0-27.5). All

three groups had a mean BMI in the overweight range (BMI ≥ 25). The SBP was lower in the group with eczema on hands and in childhood (adjusted mean 129.3, 95% CI 128.4-130.2) than in the group with no eczema (adjusted mean 130.6, 95%CI 130.5-130.7). There is a tendency towards higher levels of micro-CRP in the group with eczema and childhood eczema (adjusted mean 3.1, 95% CI 2.8-3.4) compared to the group with no eczema (adjusted mean 2.7, 95% CI 2.7-2.8) and the group with eczema on hands (adjusted mean 2.7 95% CI 2.5-2.9), despite slightly overlapping CIs. There was no difference in DBP, serum levels of cholesterol, HDL-cholesterol, triglycerides and non-fasting glucose between the three study groups.

Table 2. Means, adjusted means and 95%CIs of the continuous cardiovascular risk factors according to eczema in HUNT3.

	No eczema (n = 45018)		**Eczema on hands (n = 4446)**		**Eczema on hands and in childhood (n = 1311)**	
	Mean (SD)	*Adjusted mean (95% CI) **	*Mean (SD)*	*Adjusted mean (95% CI) **	*Mean (SD)*	*Adjusted mean (95% CI) **
Waist circumference (cm)	93.5 (12.2)	93.5 (93.4-93.5)	93.8 (12.9)	93.8 (93.6-93.9)	91.6 (12.8)	93.6 (93.3-94.0)
BMI (kg/m^2)	27.1 (4.4)	27.1 (27.1-27.1)	27.5 (4.7)	27.7 (27.5-27.8)	26.9 (4.7)	27.2 (27.0- 27.5)
SBP (mmHg)	130.8 (18.6)	130.6 (130.5-130.7)	129.1 (18.3)	130.2 (129.7-130.7)	124.9 (16.4)	129.3 (128.4-130.2)
DBP (mmHg)	73.5 (11.3)	73.4 (73.3-73.5)	72.8 (10.9)	73.5 (73.2-73.8)	71.1 (10.6)	73.0 (72.4-73.6)
Cholesterol (mmol/L)	5.5 (1.1)	5.5 (5.5-5.5)	5.5 (1.1)	5.5 (5.5-5.5)	5.4 (1.1)	5.5 (5.4-5.5)
HDL-cholesterol (mmol/L)	1.3 (0.4)	1.3 (1.3-1.4)	1.4 (0.4)	1.3 (1.3-1.4)	1.4 (0.4)	1.4 (1.3-1.4)
Triglycerides (mmol/L)	1.6 (1.0)	1.6 (1.6-1.6)	1.6 (1.0)	1.6 (1.6-1.7)	1.5 (0.9)	1.6 (1.5-1.7)
Non-fasting glucose (mmol/L)	5.6 (1.6)	5.6 (5.6-5.6)	5.5 (1.5)	5.6 (5.5-5.6)	5.3 (1.2)	5.5 (5.4-5.6)
micro CRP (mg/L)	2.7 (5.8)	2.7 (2.7-2.8)	2.8 (5.0)	2.7 (2.5-2.9)	2.9 (6.9)	3.1 (2.8-3.4)

*All variables adjusted for age, sex, smoking status and BMI, except BMI which is adjusted for age, sex and smoking status.
All values have been rounded to one decimal point

Abbreviations: SD, standard deviation; CI, confidence interval; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein; CRP, C-reactive protein

4.2.2 Dichotomous cardiovascular risk factors

Participants with eczema had an OR for an episode of verified hyperglycemia of 1.26 (95% CI 1.13-1.41) compared to non-eczema participants (Table 3). Despite the difference in verified hyperglycemia, no corresponding difference in OR was found for diabetes when comparing participants with eczema on hands to participants with no eczema. In addition, participants with eczema on hands are had no increased OR for being treated/have been treated for hypertension compared to the no eczema group (OR 1.05, 95% CI 0.96-1.15). A negative association for treatment with antihypertensive agents was found for participants with eczema on hands and in childhood compared to non-eczema participants (OR 0.79, 95% CI 0.65-0.95).

Table 3. Odds ratio (OR) of hyperglycemia, diabetes and antihypertensive treatment according to eczema in HUNT3.

	No eczema (n = 45018)	**Eczema on hands (n = 4446)**			**Eczema on hands and in childhood (n = 1311)**		
	Count	*Count*	*OR**	*95% CI*	*Count*	*OR**	*95% CI*
Verified hyperglycemia	3704	448	1.26	1.13-1.41	88	1.02	0.83-1.29
Diabetes	2047	187	1.03	0.88-1.21	28	0.77	0.52-1.12
Treatment for hypertension	10173	933	1.05	0.96-1.15	146	0.79	0.65-0.95

*Adjusted for age, sex, smoking status and BMI
All estimated values have been rounded to two decimal points
Abbreviation: OR, odds ratio; CI, confidence interval

No difference in OR for dichotomous CVRFs was found when comparing participants with eczema on hands and in childhood and those with eczema only in adulthood (Table 4).

Table 4: Odds ratio (OR) for dichotomous cardiovascular risk factors comparing participants with eczema in childhood to those with eczema in adulthood only.

	Eczema on hands (n = 4446)	**Eczema on hands and in childhood (n = 1311)**		
	Count	*Count*	*OR**	*95% CI*
Verified hyperglycemia	448	88	0.85	0.65-1.12
Diabetes	187	28	1.03	0.65-1.63
Treatment for hypertension	933	146	1.00	0.79-1.26

*Adjusted for age, sex, smoking status and BMI.
All estimated values have been rounded to two decimal points.
Abbreviations: OR, odds ratio; CI, confidence interval.

4.3 Cardiovascular disease outcomes

Participants with eczema on hands had an OR for angina pectoris of 1.25 (95% CI 1.05-1.50), compared to those with no eczema (Table 5). Participants with eczema on hands also had higher odds of heart failure (OR 1.37, 95% CI 1.01-1.85) and “other heart diseases” (OR, 1.49,

95% CI 1.27-1.76) compared to non-eczema participants. No difference in odds of MI (OR 1.06, 95% CI 0.86-1.30) or stroke/brain hemorrhage (OR 1.14, 95% CI 0.93-1.40) was found when comparing participants with eczema on hands to non-eczema participants.
Participants with eczema on hands and childhood eczema had higher odds for "other heart diseases" (OR 1.47, 95% CI 1.06-2.05), compared to non-eczema participants, but not for angina pectoris (OR 0.83, 95% CI 0.50-1.36), MI (OR 0.69, 95% CI 0.39-1.24), heart failure (OR 0.17, 95% CI 0.02-1.22) or stroke/brain hemorrhage (OR 0.82, 95% CI 0.49-1.37).

Table 5: Odds ratio (OR) for established cardiovascular diseases in participants with eczema compared to participants with no eczema

	No eczema (n = 45018)	**Eczema on hands (n = 4446)**			**Eczema on hands and in childhood (n = 1311)**		
	Count	*Count*	*OR**	*95% CI*	*Count*	*OR**	*95% CI*
Angina pectoris	1811	166	1.25	1.05-1.50	17	0.83	0.50-1.36
Myocardial infarction	1566	121	1.06	0.86-1.30	12	0.69	0.39-1.24
Heart failure	554	56	1.37	1.01-1.85	1	0.17	0.02-1.22
Other heart diseases	1521	186	1.49	1.27-1.76	38	1.47	1.06-2.05
Stroke/Brain hemorrhage	1257	116	1.14	0.93-1.40	15	0.82	0.49-1.37

*Adjusted for age, sex, smoking status and BMI
All estimated values have been rounded to two decimal points
Abbreviations: OR, odds ratio; CI, confidence interval

No difference in OR for CVDs was found when comparing participants with eczema on hands and in childhood to those with eczema only in adulthood (Table 6).

Table 6: Odds ratio (OR) for dichotomous cardiovascular diseases comparing participants with eczema in childhood to those with eczema on hands.

	Eczema on hands (n = 4446)	**Eczema on hands and in childhood (n = 1311)**		
	Count	*Count*	*OR**	*95% CI*
Angina pectoris	166	17	0.95	0.53-1.68
Myocardial infarction	121	12	0.92	0.47-1.81
Heart failure	56	1	0.20	0.03-1.58
Other heart disease	186	38	1.29	0.85-1.96
Stroke/Brain hemorrhage	116	15	0.84	0.46-1.54

*Adjusted for age, sex, smoking status and BMI.
All estimated values have been rounded to two decimal points
Abbreviations: OR, odds ratio; CI, confidence interval.

5. Discussion

5.1 Summary and interpretation of main findings

In this population based, cross-sectional study, we found that eczema on hands was positively associated with increased waist circumference, increased BMI, verified hyperglycemia, angina pectoris, heart failure, and “other heart diseases”, compared to participants with no eczema. We found no association between eczema on hands and blood pressure, blood glucose, -lipids or -micro CRP, diabetes, MI and stroke/brain hemorrhage compared to participants with no eczema. For participants reporting both eczema on hands and childhood eczema, we found a negative association for SBP and antihypertensive treatment compared to participants with no eczema, but a positive association for micro CRP. In addition, we found a positive association for “other heart diseases” compared to participants with no eczema. There was no difference in OR for any of the dichotomous CVRFs and CVDs comparing participants with eczema on hands and in childhood to participants with eczema on hands only

5.1.1 Cardiovascular risk factors

Eczema on hands was positively associated with increased waist circumference (adjusted mean 93.8, 95% CI 93.6-93.9) compared with participants with no eczema (adjusted mean 93.5, 95% CI 93.4-93.5). The CIs of the estimated means do not overlap, however the difference between the estimates is only 0.3 cm. When analyzing large populations, CIs will be narrow and reveal subtle differences, but the clinical relevance of a 0.3 cm increase in waist circumference is questionable. Our calculations are adjusted for BMI, showing that individuals with eczema on hands have a higher propensity for gaining weight around their midsections than the group without eczema, regardless of overall weight gain. A study on an adult Korean population found increased odds of central obesity in individuals with atopic dermatitis (46) and a study on US children found increased odds for being in the upper 85th percentile for waist circumference (39). While our results somewhat support these findings, we have not investigated rates of central obesity (waist circumference >94 cm in men, >80 cm in women (47)).

Eczema on hands was also positively associated with an increased BMI (mean 27.7, 95% CI 27.5-27.8) compared to participants with no eczema (mean 27.1, 95% CI 27.1-27.1). There is no overlap of CIs and they are relatively narrow, indicating that our estimates are precise. There is also an indication that individuals with eczema on hands have higher BMIs than individuals with eczema on hands and childhood eczema (adjusted mean 27.2, 95% CI 27.0-27.5), as there is just slight overlap of the CIs. However, as for waist circumference, the difference between the adjusted means for participants with eczema on hands and no eczema is low, only 0.6 kg/m^2. This association has been reported previously, a meta-analysis found increased odds of atopic dermatitis in overweight and obese individuals in North-America and Asia, but not in Europe (37). A Mendelian randomization study including data from HUNT and UK Biobank, investigated the potential causal relationship between higher BMI and eczema. They found evidence for a small, but potential important causal effect of BMI on eczema (22).

A high SBP is an independent risk factor for CVD and a facet of cardiometabolic ill-health. Our results show no increased SBP in participants with eczema on hands compared to the no

eczema-participants, in fact, participants with eczema on hands and in childhood have a lower SBP (mean 129.3, 95% CI 128.4-130.2) than participants with no eczema (mean 130.6, 95% CI 130.5-130.7). There was no overlap of CIs, however, the absolute difference is small. SBP tends to increase with age and the group with eczema on hands and in childhood have a lower mean age than the two remaining groups. Our analyses are adjusted for age, so it is not likely that the results can be explained by increasing age alone. A possible explanation is that SBP decreases with regular physical activity (48), which may decrease with age. Also, individuals with eczema also in childhood have less likely ever been treated with antihypertensive medications compared to the control group (OR 0.79, 95% CI 0.65-0.95). Our results are in line with a study from Japan where patients with “healed” atopic dermatitis had low rates of hypertension (49). However, the results are conflicting and in contrast with three previous studies; a study of 34 525 US adults finding increased prevalence of hypertension in atopic dermatitis patients (38), a multicenter case-control study finding higher SBPs in children with atopic dermatitis (39) and a US study of insurance claims finding increased rates of essential hypertension in patients with atopic dermatitis (50). The discrepancies could be explained by different study methods, possible sample bias and demographic characteristics.

Our study did not identify any difference in measured non-fasting serum glucose between our study groups. However, individuals with eczema on hands were more likely to ever have an episode of hyperglycemia verified compared to individuals with no eczema (OR 1.26, 95% CI 1.13, 1.41). An OR of 1.26 is only suggestive and unconvincing as conclusive evidence based on a single study. Despite the increased odds for verified hyperglycemia compared to individuals with no eczema, individuals with eczema on hands did not have higher odds of diabetes (OR 1.03, 95% CI 0.96-1.15). A study of 34 535 US adults found increased prevalence in patients with atopic dermatitis of prediabetes and childhood onset diabetes, but not lifetime prevalence of diabetes unless adjusted for hay fever and asthma (38).

No differences in any blood lipids were identified between any of the groups. The CIs for all estimated means were narrow, indicating precise measurements. A study of 34 535 US adults also found an increased lifetime and 1-year prevalence of high cholesterol when adjusting for hay fever and asthma (38). In contrast, a study of three large cohorts identified no such association (34). The latter study also investigated levels of other blood lipids (HDL-cholesterol and triglycerides) and did not identify any significant association between them and eczema status (34). micro CRP is a biomarker of ongoing inflammation and high levels are associated with myocardial infarctions and death (51). In our study, we found a tendency towards increased levels of micro CRP in individuals with eczema on hands and in childhood, (adjusted mean 3.1, 95% CI 2.8-3.4) compared to participants with no eczema (mean 2.7, 95% CI 2.7-2.8), with slightly overlapping CIs. The CI of the former group is somewhat wide, indicating the need for increased sample size to increase the precision of this estimate.

While individuals with eczema on hands and eczema on hands and childhood eczema appear to have some increased CVRFs (increased waist circumference, BMI, verified hyperglycemia and increased micro CRP), these are only risk factors for CVDs. To establish the clinical significance of these findings, we investigated if these groups have higher OR of established CVD.

5.1.2 Established cardiovascular disease

We found that participants with eczema on hands have higher OR for angina pectoris compared to the control group (OR 1.25 95% CI 1.05-1.50). Our results are in line with two other studies (34, 42). Interestingly, one of these studies also reported a stronger association with increasing severity of atopic dermatitis(34). However, we did not investigate severity of disease. There was no increased OR for participants with eczema on hands compared to no eczema for myocardial infarction (OR 1.06 95%CI 0.86-1.30) or stroke/brain hemorrhage (OR 1.14, 95% CI 0.93-1.40), despite previously reported positive associations between both myocardial infarction (42) and stroke (43). We found increased OR for heart failure (OR 1.37 95% CI 1.02-1.85) and "other heart diseases" (OR 1.49, 95% CI 1.27-1.76) for participants with eczema on hands compared to the no eczema group. The latter association was also found when comparing the group with eczema on hands and childhood eczema to the no eczema group. The association between eczema and other heart diseases has been studied previously, with positive associations being found (42). This study investigated a total of three datasets, of which two contained "other heart diseases" as an outcome variable. In both datasets, there was an increased OR for "other heart diseases" in participants with eczema compared to no eczema. Our results show weaker associations (smaller OR), but more precise estimates, as our CIs are narrower. Eczema on hands was positively associated with heart failure compared to the no eczema participants (OR 1.37 95% CI 1.02-1.85), but not compared to the group with eczema on hands and in childhood (OR 0.20, 95% CI 0.03-1.58). Nor did the group with eczema on hands and in childhood have higher odds of heart failure than the no eczema group (OR 0.17, 95% CI 0.02, 1.22). The study of three datasets (42) identified increased odds of congestive heart failure (analogous to heart failure in our study) in patients with eczema and again, the magnitude of the association identified is larger than in our study, but less precise. Both groups with eczema on hands and eczema on hands and in childhood had higher odds of having other heart diseases than the no eczema group (OR 1.49, 95% CI 1.27-1.76 and OR 1.47, 95% CI 1.06-2.05, respectively). No difference in odds for having a stroke/brain hemorrhage was found comparing any of the three groups. This is in contrast with a population-based study of matched pairs in Taiwan, identifying increased risk of ischemic strokes in participants with atopic dermatitis.

5.2 Methodological considerations

The main aim of an epidemiological study is to present estimates of the effect of an exposure on the rate of disease in a population which is both precise and valid. There are two types of error, random and systematic error, which may in turn threaten the precision and validity of the estimates.

5.2.1 Precision

Precision refers to the degree of variation in a measurement. Random error in an experiment can arise from the "the natural, periodic fluctuation or variation in the accuracy or precision of (…) any data sampling technique or health measurement tool or scale" (52). If there is little random error, the estimate is described as precise. Random error is variation which occurs randomly and therefore equally likely to skew results in either direction (52). In our study, we used CIs as a measure of precision, with narrow CIs indicating precise estimates. Further, CIs provide information about the strength of association. In HUNT3, the clinical and lab

measurements are collected by the same group of specially trained staff for all participants, measured objectively and analyzed using the same methodology (when applicable). This reduces the risk of random errors in our study. Another way to reduce the risk of random error in a study is to increase sample size (53). In our study, there was a relatively high number of participants. This reduces the random error and increases precision. This is indicated by the relatively narrow CIs, especially for the no eczema group. However, by dividing the individuals with eczema into two subgroups, the number of participants decreases and so does precision, apparent by the wider CIs, particularly for the group with childhood eczema. The estimates for this group are more imprecise than the estimates for the no eczema-group.

5.2.2 Validity

The overall validity of a study is made up of internal and external validity. Validity is threatened by systematic error which "arises from an innate flaw in data sampling technique or measurement instrument" (52). In contrast to random error, systematic error is non-random in nature, distorting findings in one direction and is independent of sample size (52). Main types of systematic error include selection bias, information bias and confounding (53).

Selection bias

Selection bias occurs from any error in selecting individuals to participate in the study or from factors affecting participation (53). Overall, the participation rate in HUNT3 was 54% and the study was population based, which carries less risk of selection bias paralleled to hospital-based studies. Women were more likely to participate in the study than men. Women also have higher rates of eczema on their hands (54). This may cause the prevalence of eczema on hands to be falsely high. However, it seems unlikely that eczema alone played a major role in the decision to participate or not. People with no diseases may be generally less concerned with their health and less likely to participate in a medical study of this nature. This may cause the prevalence of all diseases to be falsely increased. However, a study of the non-participants in HUNT3 found that non-participants have higher prevalences of several chronic diseases, including CVDs and diabetes (55). This may be because people with severe chronic illnesses have more difficulties participating in a study which requires you to fill out a thorough questionnaire and attend a testing facility for data collection. In addition, certain individuals reporting eczema on hands were not sent the eczema-specific questionnaire if they qualified for more than two high-priority additional questionnaires. These high-priority questionnaires included diabetes and CVDs. Some of the participants classified as only "eczema on hands" may actually belong in the eczema on hands and childhood group, and their positive answers to diabetes or CVDs attributed to this group, causing the prevalence of these diseases in the childhood eczema group to be falsely low, and correspondingly, falsely high in the eczema on hands group. In addition, individuals with negative answers to the hand eczema question were not sent this questionnaire and therefore not able to indicate if they had childhood eczema at all. As some individuals have atopic dermatitis in childhood and later outgrow the disease, it is likely that individuals in our no eczema-group in fact had eczema as children. The number of patients who outgrow symptoms is estimated to be ~20% (56, 57) and we can therefore assume that a similar percentage of individuals in our no eczema group did have eczema at some point in their life. While technically selection bias, as it is an error in the selection of individuals in the childhood eczema group, the error leads to misclassification of certain individuals, a phenomenon most associated with information bias.

Information bias

Information bias occurs from errors in data collection of exposure or outcomes (53). Our study is based on self-reported eczema on hands, an instrument of HUNT3 which has not been validated. Hand eczema is one of the most common presentations of atopic dermatitis in adulthood and patients with eczema have a higher propensity for epidermal dysfunction and therefore dry and cracked skin. However, our case group likely contains individuals with irritative contact dermatitis, suggested in part by the increased proportion of women in our case groups. Additionally, “eczema on hands” is a somewhat unspecific term; some may interpret it as “dry hands” and answer affirmatively based on that. In future studies, using electronic health records (EHRs) will be useful, as diagnoses in EHRs are doctor-confirmed. The additional questionnaire asking participants with hand eczema to indicate if they had eczema in childhood lends way to recall bias. Some of the individuals may not remember if they had eczema as a child and be misclassified in the eczema on hands-group. This form of bias is further fortified by the fact that our constructed variable equaled a “no” answer with a “don’t know” answer and they were both classified ad hand eczema-only. While this made our childhood eczema group the “sincerest” atopic dermatitis group according to the U.K Working Party Diagnostic Critera, individuals in both the no eczema and eczema on hands group may belong in this group as well. As some of the outcomes (diagnosis of CVDs and certain CVRFs) are self-reported, these may be influenced by information bias, as people with one disease are more likely to be aware of any other diseases they may have, and more likely to answer yes to those questions. This way, the rate of CVDs and CVRFs may be falsely thigh in the eczema-groups or conversely, the rate of eczema may be falsely increased in people with CVDs. Additionally, individuals with any disease (e.g. eczema) are more likely to ever have been in contact with health services and are therefore more likely to have had a blood test verifying hyperglycemia. They may also be screened more frequently for other conditions, such as heart diseases and angina pectoris. It is less likely that individuals with these conditions are screened for eczema, unless presenting with a dermatological complaint.

Confounding

A confounding variable is any variable correlating positively or negatively with both the exposure and the outcome (52), but not an transitional step in the causal pathway between exposure and outcome (58). To attenuate the effect of confounders on the final result, they can be adjusted for in the analysis. In our study, we chose confounders based on *a priori* subject-matter knowledge. We chose age, sex, BMI and smoking status as confounders, adjusting for them in our analyses. We cannot, however, rule out other confounding variables effect on our results. For example, we have not adjusted for socioeconomic information. While smoking status can be viewed as a surrogate, further adjustments, for example of education levels would have been favorable, as we know that socioeconomic factors could be a risk factor for both hand eczema, CVRFs and CVDs. Further, some patients are treated with corticosteroids, which can have cardiovascular and metabolic side effects. Also, a well-known comorbidity of eczema, asthma bronchiale, may impair one's ability to exercise and therefore lead to increased blood pressure, body weight and in turn, poor cardiovascular outcomes.

External validity

External validity, or generalizability, is the degree to which any effect measured in a study reliably reveals the effect of exposure and can make inferences about populations outside the study setting (59). A prerequisite for external validity is an internally valid study. The present

study has a relatively large number of participants and the results can be assumed to apply to other Norwegian populations. Trøndelag county is considered representative for the whole country regarding sociodemographics, morbidity and mortality (60). However, we cannot establish if the results apply to other geographical areas. Additionally, as the internal validity of the present study can be called into question regarding the definition of eczema, it is likely that the associations between hand eczema and increased waist circumference, BMI and certain CVDs are generalizable, the same cannot be said for individuals with eczema used as an umbrella term.

5.2.3 Causation

Cross-sectional studies are a relatively low-cost way to investigate associations between two or more conditions in a large number of participants. However, because the associations are studied only at a set point in time, the results cannot infer causality between two conditions, just their association. Therefore, we cannot conclude that eczema on hands leads to e.g. a higher waist circumference or that eczema in childhood causes increased levels of micro CRP, just that these factors are more likely to appear together than apart. To establish causality in epidemiology, prospective or retrospective studies are needed. Observational studies are prone to bias due to confounding and reverse causation. To avoid these biases, Mendelian randomization (MR) has emerged as a powerful tool in which genetic variants are used as unbiased instrumental variables for modifiable exposures.

6. Conclusion and future perspectives

In conclusion, the present study is a population-based, cross sectional study providing evidence for the association of having eczema on hands to increasing body mass index, waist circumference, verified hyperglycemia, angina pectoris, heart failure and other heart disease. It also shows that having eczema in childhood is associated with having higher levels of micro CRP, a biomarker of inflammation and predictor of myocardial infarction. The clinical effect of this finding is unclear, as individuals with eczema in childhood only has increased odds of “other heart disease” and not the other CVD’s studied.

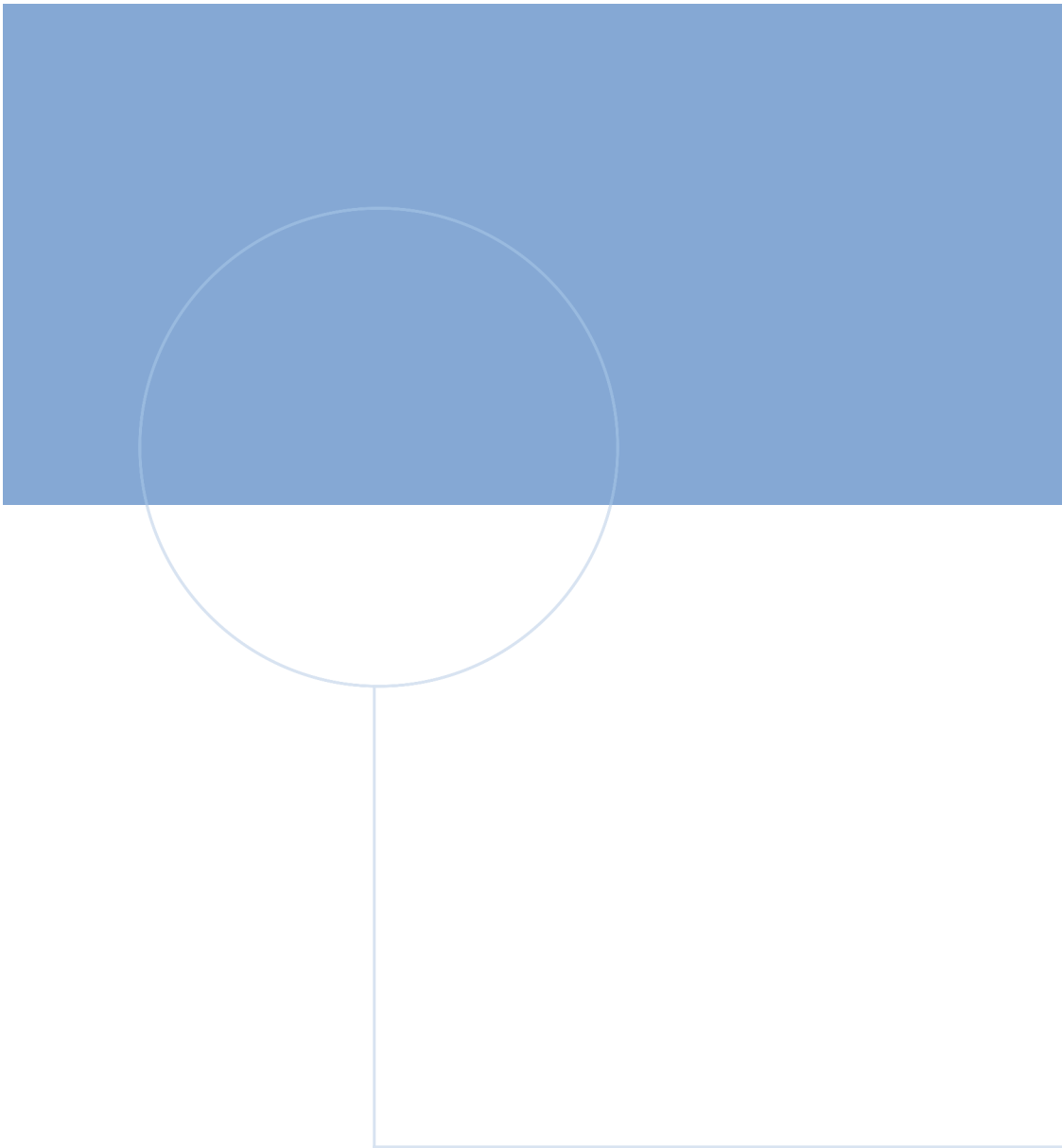
We found that participants with eczema have some increased levels of CVRFs and self-reported established CVDs. Together with previously published studies, our findings support a broad clinical approach to eczema patients. However, our study did not address causal inference and the potential underlying mechanisms of the observed associations are likely complex. Mechanistic studies are required to gain insight into these underlying relationships.

7. List of references

1. Weidinger S, Novak N. Atopic dermatitis. Lancet (London, England). 2016;387(10023):1109-22.
2. Berents TL, Saunes M, Schopf T, Vindenes HK. [Not Available]. Tidsskrift for den Norske laegeforening : tidsskrift for praktisk medicin, ny raekke. 2018;138(13).
3. Zhao CY, Hao EY, Oh DD, Daniel BS, Martin LK, Su JC, et al. A comparison study of clinician-rated atopic dermatitis outcome measures for intermediate- to dark-skinned patients. The British journal of dermatology. 2017;176(4):985-92.
4. WILLIAMS HC, JBURNEY PG, HAY RJ, ARCHER CB, SHIPLEY MJ, AHUNTER JJ, et al. The U.K. Working Party's Diagnostic Criteria for Atopic Dermatitis. British Journal of Dermatology. 1994;131(3):383-96.
5. Hanifin JM, Lobitz WC, Jr. Newer Concepts of Atopic Dermatitis. Archives of Dermatology. 1977;113(5):663-70.
6. Langan SM, Irvine AD, Weidinger S. Atopic dermatitis. Lancet (London, England). 2020;396(10247):345-60.
7. Abuabara K, Yu AM, Okhovat JP, Allen IE, Langan SM. The prevalence of atopic dermatitis beyond childhood: A systematic review and meta-analysis of longitudinal studies. Allergy. 2018;73(3):696-704.
8. Berents TL, Lødrup Carlsen KC, Mowinckel P, Sandvik L, Skjerven HO, Rolfsjord LB, et al. Vitamin D levels and atopic eczema in infancy and early childhood in Norway: a cohort study. The British journal of dermatology. 2016;175(1):95-101.
9. Thyssen JP, Johansen JD, Linneberg A, Menné T. The epidemiology of hand eczema in the general population--prevalence and main findings. Contact Dermatitis. 2010;62(2):75-87.
10. Ferreira MA, Vonk JM, Baurecht H, Marenholz I, Tian C, Hoffman JD, et al. Shared genetic origin of asthma, hay fever and eczema elucidates allergic disease biology. Nat Genet. 2017;49(12):1752-7.
11. Elmose C, Thomsen SF. Twin Studies of Atopic Dermatitis: Interpretations and Applications in the Filaggrin Era. J Allergy (Cairo). 2015;2015:902359.
12. Al-Shobaili HA, Ahmed AA, Alnomair N, Alobead ZA, Rasheed Z. Molecular Genetic of Atopic dermatitis: An Update. Int J Health Sci (Qassim). 2016;10(1):96-120.
13. O'Regan GM, Irvine AD. The role of filaggrin in the atopic diathesis. Clin Exp Allergy. 2010;40(7):965-72.
14. Eckhart L, Zeeuwen P. The skin barrier: Epidermis vs environment. Exp Dermatol. 2018;27(8):805-6.
15. Palmer CN, Irvine AD, Terron-Kwiatkowski A, Zhao Y, Liao H, Lee SP, et al. Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. Nat Genet. 2006;38(4):441-6.
16. Elias PM. Primary role of barrier dysfunction in the pathogenesis of atopic dermatitis. Experimental Dermatology. 2018;27(8):847-51.
17. Weidinger S, Illig T, Baurecht H, Irvine AD, Rodriguez E, Diaz-Lacava A, et al. Loss-of-function variations within the filaggrin gene predispose for atopic dermatitis with allergic sensitizations. The Journal of allergy and clinical immunology. 2006;118(1):214-9.
18. David Boothe W, Tarbox JA, Tarbox MB. Atopic Dermatitis: Pathophysiology. Adv Exp Med Biol. 2017;1027:21-37.
19. Poulsen LK, Hummelshoj L. Triggers of IgE class switching and allergy development. Ann Med. 2007;39(6):440-56.
20. Kantor R, Silverberg JI. Environmental risk factors and their role in the management of atopic dermatitis. Expert Rev Clin Immunol. 2017;13(1):15-26.

21. Meylan P, Lang C, Mermoud S, Johannsen A, Norrenberg S, Hohl D, et al. Skin Colonization by Staphylococcus aureus Precedes the Clinical Diagnosis of Atopic Dermatitis in Infancy. The Journal of investigative dermatology. 2017;137(12):2497-504.
22. Budu-Aggrey A, Watkins SH, Brumpton B, Løset M, Tyrrell J, Modalsli EH, et al. Assessment of a causal relationship between body mass index and atopic dermatitis. The Journal of allergy and clinical immunology. 2020.
23. Imokawa G. Lipid abnormalities in atopic dermatitis. Journal of the American Academy of Dermatology. 2001;45(1, Supplement):S29-S32.
24. Chong M, Fonacier L. Treatment of Eczema: Corticosteroids and Beyond. Clin Rev Allergy Immunol. 2016;51(3):249-62.
25. Veiledende anbefalinger for bruk av biologiske legemidler ved atopisk eksem [press release]. 2019.
26. Thaçi D, Simpson EL, Beck LA, Bieber T, Blauvelt A, Papp K, et al. Efficacy and safety of dupilumab in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical treatments: a randomised, placebo-controlled, dose-ranging phase 2b trial. Lancet (London, England). 2016;387(10013):40-52.
27. Silverberg JI, Yosipovitch G, Simpson EL, Kim BS, Wu JJ, Eckert L, et al. Dupilumab treatment results in early and sustained improvements in itch in adolescents and adults with moderate to severe atopic dermatitis: Analysis of the randomized phase 3 studies SOLO 1 and SOLO 2, AD ADOL, and CHRONOS. J Am Acad Dermatol. 2020;82(6):1328-36.
28. Andersen YMF, Egeberg A, Skov L, Thyssen JP. Comorbidities of Atopic Dermatitis: Beyond Rhinitis and Asthma. Current dermatology reports. 2017;6(1):35-41.
29. Dalgard FJ, Gieler U, Tomas-Aragones L, Lien L, Poot F, Jemec GBE, et al. The psychological burden of skin diseases: a cross-sectional multicenter study among dermatological out-patients in 13 European countries. The Journal of investigative dermatology. 2015;135(4):984-91.
30. González-Cervera J, Arias Á, Redondo-González O, Cano-Mollinedo MM, Terreehorst I, Lucendo AJ. Association between atopic manifestations and eosinophilic esophagitis: A systematic review and meta-analysis. Ann Allergy Asthma Immunol. 2017;118(5):582-90.e2.
31. Silverberg JI. Comorbidities and the impact of atopic dermatitis. Ann Allergy Asthma Immunol. 2019;123(2):144-51.
32. WHO. Cardiovascular diseases: World Health Organization; 2017 [Available from: https://www.who.int/en/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds).
33. Bantz SK, Zhu Z, Zheng T. The Atopic March: Progression from Atopic Dermatitis to Allergic Rhinitis and Asthma. J Clin Cell Immunol. 2014;5(2).
34. Standl M, Tesch F, Baurecht H, Rodriguez E, Muller-Nurasyid M, Gieger C, et al. Association of Atopic Dermatitis with Cardiovascular Risk Factors and Diseases. The Journal of investigative dermatology. 2017;137(5):1074-81.
35. Ascott A, Mulick A, Yu AM, Prieto-Merino D, Schmidt M, Abuabara K, et al. Atopic eczema and major cardiovascular outcomes: A systematic review and meta-analysis of population-based studies. Journal of Allergy and Clinical Immunology. 2019;143(5):1821-9.
36. Payne RA. Cardiovascular risk. Br J Clin Pharmacol. 2012;74(3):396-410.
37. Zhang A, Silverberg JI. Association of atopic dermatitis with being overweight and obese: a systematic review and metaanalysis. J Am Acad Dermatol. 2015;72(4):606-16.e4.
38. Silverberg JI, Greenland P. Eczema and cardiovascular risk factors in 2 US adult population studies. The Journal of allergy and clinical immunology. 2015;135(3):721-8.e6.
39. Silverberg JI, Becker L, Kwasny M, Menter A, Cordoro KM, Paller AS. Central obesity and high blood pressure in pediatric patients with atopic dermatitis. JAMA Dermatol. 2015;151(2):144-52.
40. WHO. Global Atlas of cardiovascular disease, prevention and control. Geneva; 2011.
41. Andersen YM, Egeberg A, Gislason GH, Hansen PR, Skov L, Thyssen JP. Risk of myocardial infarction, ischemic stroke, and cardiovascular death in patients with atopic dermatitis. The Journal of allergy and clinical immunology. 2016;138(1):310-2.e3.

42. Silverberg JI. Association between adult atopic dermatitis, cardiovascular disease, and increased heart attacks in three population-based studies. Allergy. 2015;70(10):1300-8.
43. Su VY, Chen TJ, Yeh CM, Chou KT, Hung MH, Chu SY, et al. Atopic dermatitis and risk of ischemic stroke: a nationwide population-based study. Ann Med. 2014;46(2):84-9.
44. Paller A, Jaworski JC, Simpson EL, Boguniewicz M, Russell JJ, Block JK, et al. Major Comorbidities of Atopic Dermatitis: Beyond Allergic Disorders. Am J Clin Dermatol. 2018;19(6):821-38.
45. Krokstad S, Langhammer A, Hveem K, Holmen TL, Midthjell K, Stene TR, et al. Cohort Profile: the HUNT Study, Norway. Int J Epidemiol. 2013;42(4):968-77.
46. Lee JH, Jung HM, Han KD, Lee SH, Lee JY, Park YG, et al. Association Between Metabolic Syndrome and Atopic Dermatitis in Korean Adults. Acta Derm Venereol. 2017;97(1):77-80.
47. Owolabi EO, Ter Goon D, Adeniyi OV. Central obesity and normal-weight central obesity among adults attending healthcare facilities in Buffalo City Metropolitan Municipality, South Africa: a cross-sectional study. J Health Popul Nutr. 2017;36(1):54.
48. Cornelissen VA, Smart NA. Exercise training for blood pressure: a systematic review and meta-analysis. J Am Heart Assoc. 2013;2(1):e004473.
49. Uehara M, Sugiura H, Tanaka K. Rarity of hypertension in adult patients with atopic dermatitis. The British journal of dermatology. 2002;146(4):631-5.
50. Abramovits W, Stevenson L, Prendergast MM, Tong K. Prevalence of hypertension among patients with atopic dermatitis. The British journal of dermatology. 2003;148(2):380; author reply
51. Wang J, Tan GJ, Han LN, Bai YY, He M, Liu HB. Novel biomarkers for cardiovascular risk prediction. J Geriatr Cardiol. 2017;14(2):135-50.
52. Vetter TR, Mascha EJ. Bias, Confounding, and Interaction: Lions and Tigers, and Bears, Oh My! Anesth Analg. 2017;125(3):1042-8.
53. Tripepi G, Jager KJ, Dekker FW, Zoccali C. Selection bias and information bias in clinical research. Nephron Clin Pract. 2010;115(2):c94-9.
54. Vindenes HK, Svanes C, Lygre SHL, Hollund BE, Langhammer A, Bertelsen RJ. Prevalence of, and work-related risk factors for, hand eczema in a Norwegian general population (The HUNT Study). Contact Dermatitis. 2017;77(4):214-23.
55. Langhammer A, Krokstad S, Romundstad P, Heggland J, Holmen J. The HUNT study: participation is associated with survival and depends on socioeconomic status, diseases and symptoms. BMC Med Res Methodol. 2012;12:143.
56. Margolis JS, Abuabara K, Bilker W, Hoffstad O, Margolis DJ. Persistence of Mild to Moderate Atopic Dermatitis. JAMA Dermatology. 2014;150(6):593-600.
57. Silverberg JI. Persistence of Childhood Eczema Into Adulthood. JAMA Dermatology. 2014;150(6):591-2.
58. Hernán MA, Hernández-Díaz S, Werler MM, Mitchell AA. Causal Knowledge as a Prerequisite for Confounding Evaluation: An Application to Birth Defects Epidemiology. American Journal of Epidemiology. 2002;155(2):176-84.
59. Odibo AO, Acharya G. External validity in perinatal research. Acta Obstet Gynecol Scand. 2018;97(4):424-8.
60. Holmen J MK, Lund-Larsen PG The Nord-Trøndelag Health Study 1995-1997 (HUNT2). Norsk Epidemiologi. 2003;13(1):19-32.



NTNU

Kunnskap for en bedre verden