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Hand Eczema

With focus on irritant contact dermatitis and prevention

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Innehållsförteckning

Redaktörernas förord

Denna utgåva ingår i den serie av systematiska kunskapssammanställningar som ges ut av Göteborgs Universitet. Dessa kunskapssammanställningar hade ursprungligen sin bakgrund i ett behov att ange riktlinjer för hur man fastställer samband i arbetsskadeförsäkringen. Arbetet inleddes 1981 när en grupp ortopeder, yrkesmedicinare, andra arbetsmiljöforskare och läkare från LO i Läkartidningen diskuterade en modell för bedömning av vilka arbetsställningar som utgjorde skadlig inverkan för besvär i bröst och ländrygg. Gruppen pekade också på vikten av att systematiskt ställa samman kunskap inom området (Andersson 1981). Därefter publicerades flera systematiska kunskapssammanställningar med avsikt ge riktlinjer för förekomst av skadlig inverkan vid arbetsskadebedömningar (Westerholm 1995, 2002, Hansson & Westerholm 2001).

AFA Försäkring finansierar sedan 2008 ett långsiktigt projekt med avsikt att ta fram nya kunskapssammanställningar inom arbetsmiljöområdet. Arbetet samordnas av Arbets- och miljömedicin vid Sahlgrenska Akademin/Göteborgs Universitet. Dessa systematiska kunskapssammanställningar har som syfte att beskriva arbetsmiljöns betydelse för uppkomst eller försämring av sjukdom eller symptom i ett bredare perspektiv. Tillämpningen av resultaten får ske inom berörda myndigheter, arbetsplatser och försäkringsbolag.

Den nya serien av systematiska kunskapssammanställningar inleddes 2008 med en uppdaterad översikt om psykisk arbetsskada (Westerholm 2008), som sedan följdes av sammanställningar om fukt och mögel, helkroppsvibrationer och arbetets betydelse för uppkomst av depression (uppdatering), stroke, Parkinsons sjukdom, ALS, Alzheimers sjukdom, prostatacancer, reumatoid arthrit, arbete i värme, effekter av att arbeta med armarna ovan axelhöjd, riskfaktorer i arbetslivet för suicid, riskfaktorer för ”slidgigt i tommelens rodled”, arbete efter hjärtinfarkt och en analys av olika kunskapsöversikter inom arbetsmiljöområdet (Torén 2010, Burström 2012, Lundberg 2013, Jakobsson 2013, Gunnarsson 2014, 2015a, 2015b, Knutsson 2017, Kuklane 2017, Kjellström 2017, Milner 2018, Bach Lund 2018, Koch 2019, Gustavsson 2019, Järvholm 2020, Ilar 2020). Under 2016 presenterades ett uppmärksammat dokument om skador efter exponering för handöverförda vibrationer (Nilsson 2016). Under de sista åren har vi publicerat en analys om arbete efter stroke (Jood 2021), spridning av luftvägsvirus vid arbetsplatser (Löndahl 2021) samt att dokument om sambandet mellan exponering för handöverförda vibrationer och uppkomst av Dupuytrens sjukdom (Nilsson 2022). Dessutom har vi tagit fram ett mycket efterfrågat dokument om hur diabetiker klarar av olika påfrestande arbetsmiljöer (Knutsson 2013). Eftersom kunskapsläget förändras finns det ett behov av uppdateringar av gamla kunskapssammanställningar, samtidigt som det finns ett behov av kunskapssammanställningar inom nya områden.

Denna nya kunskapsöversikt syftar till att ge kunskap om hur vi bäst kan förebygga uppkomst av arbetsrelaterade handeksem Externa referenter har varit docent Jonas Brisman, Sahlgrenska universitetssjukhuset, Göteborg och docent Birgitta Meding, Karolinska institutet, Stockholm. Vi är tacksamma för författarnas gedigna arbete liksom de värdefulla och konstruktiva bidrag som referenterna har tillfört.

Umeå, Göteborg och Lund oktober 2022

Bengt Järvholm
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Sammanfattning

Handeksem (förkortat HE) är vanligt förekommande. Ca 9 procent av befolkningen har under ett år haft HE. Besvären börjar ofta tidigt i livet, cirka var tredjeperson har besvär redan före 20 års ålder och bara för cirka en tredjedel debuterar besvären efter 30 års ålder. Kvinnor har oftare HE än män. En viktig orsak är våtarbete som förekommer både i arbetet och i hemmiljö. Besvären från HE kan variera från mycket ringa besvär till svåra invalidiserande tillstånd. Personer med atopiska eksem i barndomen har betydligt högre risk för att drabbas av HE. Vid utredning av HE är det viktigt att utesluta att eksemet beror på en bakomliggande allergi. Sådan allergi identifieras med lapptest. Därför rekommenderar man att personer med svårt HE eller HE som inte läker inom tre månader utreds med lapptest.

Denna kunskapsöversikt består av två delar, den första beskriver kunskapsläget kring HE, hur de utreds, klassificeras, hur det beror på ålder, kön och vad som utlöser och försämrar/förbättrar besvären. Den andra delen består av en litteraturgenomgång av studier som utvärderat metoder för att förebygga arbetsrelaterad HE.

Kunskapsöversikten fokuserar på HE som uppkommer på grund av ämnen som skadar huden på andra sätt än genom allergi (Irritant Contact Dermatitis=ICD). Akut uppträder det oftast genom kontakt med till exempel starkt irriterande ämnen och orsaken är ofta ganska lätt att fastställa. Långvarig och upprepad kontakt med många faktorer kan leda till kroniska HE, dvs besvär som varat längre än 3 månader. Den viktigaste faktorn för arbetsrelaterad ICD är kontakt med vatten. Antingen så arbetar personen så att händerna ofta är blöta eller så kräver arbetet att man måste tvätta sig ofta. För att minska kontakten med tvål och vatten har man på senare tid börjat att använda alkoholbaserade handdesinfektionsmedel. Om detta leder till mindre risk för HE är dock oklart. Användning av handskar kan minska risken men förutsätter att de är torra på insidan och att användningstiden är begränsad. Annars kan användning av handskar bidra till HE eller att försämra HE.

Litteraturgenomgången identifierade 17 kontrollerade studier som undersökt åtgärder i arbetet för att förebygga HE. Antingen genom att minska risken för uppkomst av HE (primär prevention; 10 studier) eller genom att förebygga att personer med HE försämras i arbetet (sekundär prevention; 7 studier).

De tio primärpreventiva studierna omfattade arbetsmiljöer där det var hög risk för HE (t ex frisörer, sjuksköterskor och metallarbetare) och riktade sig mot grupper som skulle börja arbeta i sådana miljöer (lärlingar, elever vid yrkesskolor) eller personer som nyss anställts. Alla studier innehöll inslag av undervisning om hur man skulle arbeta för att minska risken. Några studier omfattade också användning av fuktgivande krämer eller så kallade barriärkrämer. Genom att studierna innehöll olika upplägg och kom till delvis lite olika resultat är det svårt att dra säkra slutsatser. Dock förefaller det som att intensiv undervisning/information skulle kunna minska risken för HE. En studie som använde IT-teknik hade sämre resultat än de studier som använde gruppundervisning direkt till personerna och trycksaker. En insats med enbart fuktkrämer var otillräcklig för att påverka förekomsten av HE. Sammantaget tyder resultaten från studier för att förebygga HE hos personer i högriskmiljöer att man kan nå viss framgång med utbildningsinsatser, men att det inte går att dra säkra slutsatser kring vilka insatser som är bäst. Eftersom HE oftast börjar tidigt i yrkeskarriären bör primärpreventiva insatser komma tidigt, dvs i samband med yrkesutbildning eller nyanställning.

Sju studier utvärderade insatser för personer med yrkesrelaterad HE. Det var personer som behandlats inom öppenvård vid sjukhus, privatmottagningar eller företagshälsovård. Åtgärderna handlade om olika utbildnings och informationsinsatser som kunde ske gruppvis eller individuellt. De kunde omfatta alltifrån ½ timmes till 2 dagars utbildning. Sammantaget visar dessa studier att man kan påverka hur kroniska och svåra besvären blir med denna typ av insatser. Bäst evidens för framgång har åtgärder som innehåller individuell rådgivning. Slutsatsen är att insatserna bör anpassas till vem som drabbas och förhållanden på arbetsplatsen. Det finns också pågående försök i Tyskland med mer omfattande insatser för personer med svår yrkesrelaterad HE. Där prövar man om 3 veckors insatser med daglig träning inom sluten vård och ytterligare 3 veckors behandling i öppen vård har effekter. Resultaten så här långt tyder på en viss framgång. Sammantaget är således evidensen starkare för att utbildningsinsatser till personer med yrkesrelaterad HE har positiva effekter än motsvarande primärpreventiva insatser. Åtgärderna behöver dock anpassas till individen och den aktuella arbetsmiljön.

Det saknas studier som utvärderar om andra typer av handrengöring än tvål och vatten kan reducera risken för HE.

Trots att det länge varit känt att våtarbete ökar risken för HE behövs betydligt mer kunskap om hur våtarbeten ska utformas eller begränsas så att risken för HE minimeras.

Abbreviations

ABHR:	Alcohol Based Hand Rubs
ACD:	Allergic Contact Dermatitis
ACHD:	Active Chlorine Hand Disinfectants
CG:	Control Group
HE:	Hand Eczema
HECOS:	Hand Eczema Care Outcome Set
HECSI:	Hand Eczema Severity Index
HR-QoL:	Health Related Quality of Life
HCW:	Health Care Workers
ICD:	Irritant Contact Dermatitis
IG:	Intervention Group
QoL:	Quality of Life
QoLHEC:	Quality of Life Hand Eczema Questionnaire

Introduction

Hand eczema is a common disease in the general population and even more common in specific occupations where hands are intensively exposed to irritants and allergens. More than 15% of the population is affected during their lifetime, females are more often affected than males, and in most cases the disease has its onset early in life. The etiology for HE is multifactorial and includes environmental exposures as well as genetic factors. For many years the focus was allergic contact dermatitis, identifying relevant allergens in the local environment of patients; however today the importance of irritant contact dermatitis, either as the primary reason or as a deteriorating factor complicating allergic, atopic or other clinical subtypes of eczema, is better understood. The prognosis for HE is discouraging, the eczema may persist for more than a decade with either chronic signs or frequent flares. Consequences of the disease are far reaching. Health-related quality of life is markedly reduced, working capacity is impaired, and for society the economic consequences are significant. However, since HE is related to exposure the preventive potential is significant. Nevertheless, despite preventive measures being attempted, the prevalence of HE in the general population seems unchanged over the last decades.

The objective of this review is to give an update on HE regarding epidemiology, classification and risk factors, to deepen the current understanding of the development of irritant contact dermatitis, and to focus on evidence-based prevention and point out possible directions for future interventions regarding the prevention of HE. The article is based on current available literature, and after each of the specific sections we have summarized, concluded and highlighted issues of special importance.

Methods

The amount of literature on hand eczema (HE) is huge, as is literature on irritant contact dermatitis (ICD) and preventive aspects. The aim of the present review is to give an updated background information on HE, comprising factors influencing prevalence and severity, irritant contact dermatitis, consequences, quality of life and prognosis. This information is given in Part one, and is based on the latest comprehensive reviews and guidelines from 2018 and 2021 (Bauer et al 2018 (Bauer et al., 2018), Jacobsen et al. 2021 (Jacobsen et al., 2021), Thyssen et al 2021 (Thyssen et al., 2021)). The article by Bauer et al. is a Cochrane systematic review. The review by Jacobsen et al. is based on an extensive review "Review of causes of irritant (toxic) contact eczema after occupational skin exposure" funded by The Danish Working Environmental Research Fund in 2017[1], and the article by Thyssen et al. is the recently updated guideline on Hand Eczema from the European Society of Contact Dermatitis (ESCD).

Part two is a systematic review on prevention of irritant HE. A systematic literature search was conducted in PUBMED, EMBASE, and Web of Science. The search was based on MESH terms (PubMed only) "prevention of hand eczema"," prevention of hand dermatitis", "prevention of occupational hand eczema", "prevention of irritant contact dermatitis". The search string for PUBMED search was: ((((program* OR education* OR procedure*)) AND (prevent* OR treat*)) AND ("hand eczema" OR "hand dermatitis")). We updated our searches of the databases to November 2021. We also checked the bibliographies of included studies by hands for further references to relevant literature. Studies without negative patch tests were also included in the definition of irritant HE)

Flowchart of the literature search is shown in **figure 1**.

Inclusion criteria

- Articles were included complying with the following criteria:
- Original peer-reviewed studies on primary and secondary prevention of HE
- Studies with defined preventive measures for irritant HE (
- Prospective studies
- Studies with control group or cohort studies
- Studies with at least 30 participants in the intervention program
- Studies with a quantitative measure of HE as outcome (HE incidence, HE prevalence, and HE severity/ signs)
- Studies reported in English, Swedish, Danish or Norwegian languages up to November 2021 were included.

Studies on emollients were included when used as part of preventive programmes. Excluded were studies on treatment and studies without follow-up.

Quality assessment of studies

Quality assessment of the included studies was carried out by means of the Newcastle-Ottawa quality assessment form for non-randomized studies, based on selection, comparability and outcome[2], with the modification that the item comparability was changed to randomization when appropriate. This gave a 0-9 points scale, with 0-4 points being low quality, 5-7 being medium quality, and 8-9 points being high quality of the included studies. A total of 9 studies were rated high quality, 5 studies were rated medium quality, and 2 studies were of low quality. For further details see table 5 and 6.

[1] https://www.aes.dk/dokument/udredning-af-aarsager-til-irritativt-toksisk-kontakteksem - checked 2022-09-18
[2] http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp - checked 2022-09-18

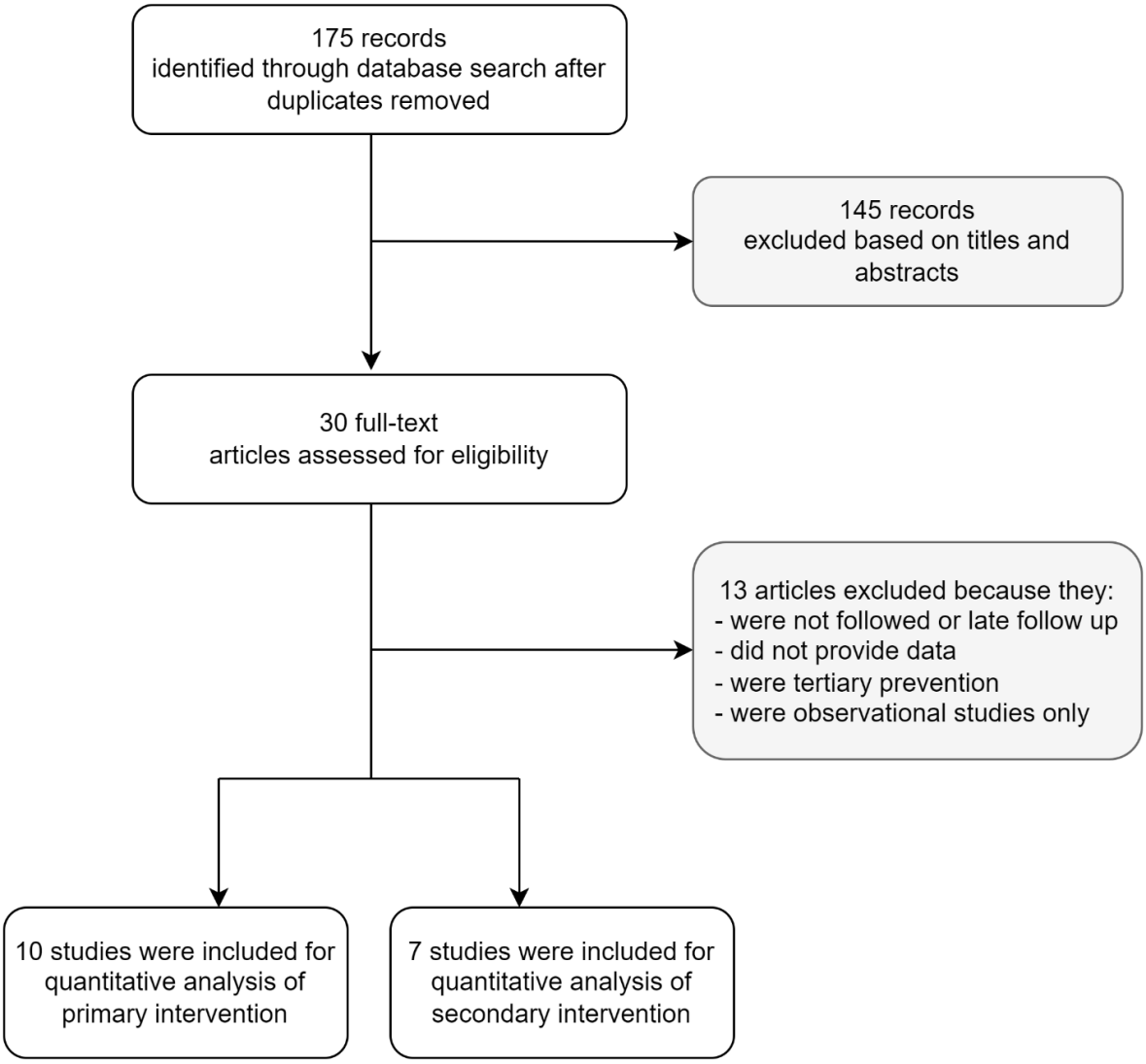

Figure 1. Flowchart for PUBMED, Embase and Web of Science search for review on occupational irritant contact dermatitis/HE.

Part one

Background and definitions

Definitions

Hand eczema (HE), also called hand dermatitis, is a common eczematous disease located on the hands or wrists. It may present as an *acute HE*, lasting for less than three months and not occurring more than once per year, or a *chronic HE*, lasting for more than three months or relapsing twice or more per year (Thyssen et al., 2021). In the acute stage during flares the dominating signs are erythema, papules, oedema and vesicles, which may later cause oozing, and in the chronic stage scaling, hyperkeratosis, lichenification and fissures are the most prominent signs (**figure 2**). Symptoms comprise itching, pain, stinging and burning. Common histological findings are spongiosis and intercellular oedema in the acute stage, whereas achantosis and hyperkeratosis may be present in the chronic stage.

Figure 2. Examples of hand eczema with fissures, scaling, erythema and vesicles

Prevalence and incidence rates

In the general population in European countries the 1-year prevalence of HE is 9.1%, while the point prevalence and life-time prevalence are 4.0% and 14.5%, respectively (Thyssen et al., 2021). HE often has an onset early in life. A Norwegian population-based study reported onset at age ≤10 years in more than 20% of HE patients (Vindenes et al., 2017), a Swedish study reported onset in 35% of women and 27% of men before age 20 (Meding and Jarvholm, 2004), and a Danish study found that the median age at first occurrence of HE was 26 years among women and 28 years among men (Hald et al., 2008). Similarly, only around 1/3 of those reporting HE presented with onset at age ≥30 years (Vindenes et al., 2017). Thus, prevalence of HE changes over a lifetime, and in a population study comprising individuals aged 70 and above, only 2.8% of the participants reported ever to have had physician-diagnosed HE (Drewitz et al., 2021), although this result may be influenced by recall bias. While the prevalence of HE decreases in the older age groups, HE tends to be more severe among the elderly (Agner et al., 2008). Ideally, questions used for assessment of prevalence should be validated, since the wording of the questions may influence the response. However, it is not clearly described in all articles whether this was the case, and this may induce a risk for bias. The fact that HE affects young individuals during a period of their life focused on education, professional career and a family life, often comprising small children, is notable when considering the impact on health-related quality of life (HR-QoL), as well as the cost to society.

The pooled incidence rate of HE was reported to be 7.3 cases/1000 person-years in a recent meta-analysis (Quaade et al., 2021), with incidence rates as well as prevalence generally reported to be 1.5-2 times higher in females than males, and most cohorts of HE-patients comprise 2/3 female and 1/3 male patients (Thyssen et al., 2010, Quaade et al., 2021). It is interesting that while prevalence of HE is higher in females than in males in the younger age groups, the female preponderance seems to decrease with age (Diepgen et al., 2009). Previous studies examining risk factors in relation to development of HE indicate that the high frequency of HE in women compared to men is caused by differences in exposures and not by genetic factors (Bryld et al., 2003). Females are generally more exposed to water than males, female-dominated occupations, such as working as hair dresser, nurse, in cleaning or kitchen work, more often comprise exposure to water/wet work, and even within the same job females seems to be more exposed than males (Anveden Berglind et al., 2009, Lund et al., 2020). The fact that the female dominance is highest during the period of their life likely to comprise young children and declines with age, could possibly be interpreted - assuming that the traditional gender roles still exist – that it is the double burden of occupational as well as domestic wet-work exposures that elicits the eczema.

Occupational HE

Occupational HE or work-related HE is eczema on the hands which is either caused or aggravated by exposure(s) at work. While the word "occupational" should be used in relation to legislation, and regarding notified or recognised cases, the word "work-related" is used in a broader and less precise context. Prevalence of work-related HE varies between countries, depending on tradition, level of industrialisation, and also on the national legislation and possibility of reimbursement. In Denmark contact dermatitis is the most frequently recognised occupational disease, and almost all cases are localised on the hands. In a Norwegian study comprising more than 50.000 individuals from the general population, 4.8% reported to have or have had HE which was relating to exposures in the workplace (Vindenes et al., 2017). In a Danish follow-up study of a population-based twin cohort notification of HE to the authorities as work related was reported by 10.1% (Lerbaek et al., 2008). Naturally, some occupations are more affected than others, depending on exposure to either irritants or to sensitizing chemicals. Examples of high-risk occupations are health care workers (HCW), with a 1-year prevalence of HE reported to be as high as 21% (Hamnerius et al., 2018), kitchen workers, workers in the cleaning sector, craftsmen and hairdressers, which are all among the top 5 jobs in terms of number of cases of recognised occupational HE in Denmark (Carøe et al., 2014). In a Danish register-based study including 1504 patients with recognised occupational contact dermatitis, ICD accounted for 70% of all cases and 68% of these were caused by wet work (Carøe et al., 2014), with wet work being recognised as the single most significant risk for the development of HE. In a recent Danish study comprising patients with recognised occupational HE high incidence rates were reported in hairdressers/beauticians, bakers, dentists and dental assistants, as well as manufacturers of windmills, with an increasing incidence rate in nursery care workers (Dietz et al., 2021b), all - except for the manufacturers of wind mills - wet work jobs. Regarding allergic contact dermatitis (ACD), the two most common culprits were rubber additives and biocides (formaldehyde and isothiazolinones as the most frequent ones), however many more industrial exposures, including epoxy, metals and hairdressing chemicals are frequent examples, and may cause occupational ACD (Carøe et al., 2014). Identification of relevant culprit allergens by patch testing is crucial to improve chances of resolution (Thyssen et al., 2021). The ratio between allergic and irritant HE is highly variable between occupations due to differences in exposures in different jobs.

Occupational HE is expensive for the society and has a negative impact on employment. A recent Danish study comprising patients with recognised occupational contact dermatitis compared the degree of employment during the 2 years prior to notification to the 2 years following notification. The study found that the degree of employment after notification was decreased on average 8.9 working hours/month, and the average number of weeks that workers were receiving unemployment benefits rose by a factor 2.5 (Dietz et al., 2021a).

Both in cases of suspected exposure to risk factors for HE, and in cases of observed high prevalence of HE, inspection of and support for workplaces regarding strategies for prevention and handling of HE should be encouraged. However, data on occupational HE is based on different sources leaving considerable room for bias. Self-reported work-related HE is based on the patient´s interpretation of the interaction between eczema and exposures in the workplace. Register based studies are hampered by the fact that these are most often based on either notified or recognized cases of occupational HE. These cases are prone to a significant underreporting, and thus probably represent only the tip of the iceberg. It is also important to consider that traditions differ between occupations with respect to notification of HE as an occupational disease. Within some jobs notification of HE is not common practice, not necessarily reflecting a lack of cases, but rather due to many workers being equally affected, and the eczema being looked upon as an unavoidable part of the work. Within other jobs it may be more customary to notify HE cases as occupational, and this tradition may be self-reinforcing, so that many – including mild - cases are notified. Naturally, the attention of researchers, unions, the public and ultimately political focus will be drawn to occupations with high numbers of notified cases. However, it is important to be aware that also in occupations s with few notified cases, work-related HE may be present, and workers may be suffering from the disease in silence, out of tradition or lack of knowledge of the chance of notification and reimbursement.

HE may be complicated by the presence of bacteria. Data from a recent study comprising HE patients show that 54% were colonized with *S. aureus* on the hands compared to 2% of controls, and nasal *S. aureus* colonization was found in 72% of HE patients compared to 22% of controls (Nørreslet et al., 2020). The presence of *S. aureus* was closely associated with HE severity. Implications of colonization and risk of transmission should be considered in particular in jobs handling food and in the health care sector.

Classification

HE is a multifactorial disease with a variety of clinical presentations, and there is today no clear consensus regarding classification of HE, although it is generally agreed that a precise subclassification of cases should be attempted (Agner et al., 2015, Molin et al., 2011, Johansen et al., 2011). Development of HE depends on genetics, environmental exposures as well as some unknown trigger factors (**figure 3)**. Classification is important in the daily clinic with respect to recommendations, counselling and treatment prescribed to the patient, and also important in epidemiological studies and clinical trials, where a strict definition of included cases is required to be able to make comparisons between studies. It is generally accepted that the morphology of HE does not necessarily reflect the etiology. Classification is further complicated by the fact that often several etiological factors play important roles, and that the morphology and clinical picture may change over time.

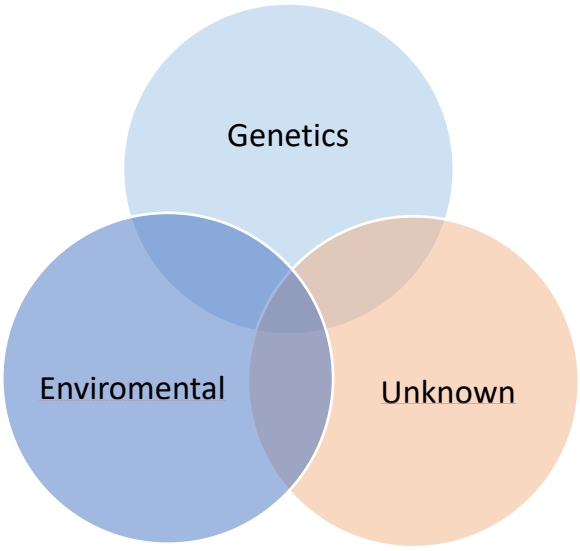

Figure 3. The etiology of hand eczema is multifactorial, including environmental and genetic factors, but much is still unknown.

The classification of acute versus chronic HE is given in **table 1** (Thyssen et al., 2021). Risk factors for chronicity has been debated, and barrier associated factors seem to be pivotal for HE to slowly develop into a chronic disease (Tauber et al., 2020a). A proposal for an etiological classification is given in **table 2**. Among the etiological subtypes ICD is the most common, however, the importance of exclusion of ACD should be emphasized, and it is recommended that all cases regardless of subtypes of HE lasting for more than three months should be patch tested (Diepgen et al., 2015, Johansen et al., 2015). Although the etiological background for HE is of less interest in the case of chronic eczema, since eliciting factors should at this time be eliminated, it is still possible that the chronicity may be due to a neglected allergen and chronic cases of HE should therefore also be patch tested. For both ICD and ACD work-related as well as domestic exposures should be considered. Protein contact dermatitis is less common, with immediate skin reactions comprising up to 5% of recognized cases of occupational HE (Carøe et al., 2014), mostly caused by exposure to food or latex proteins. Atopic HE can be diagnosed only in patients with a medical history of previous or current atopic dermatitis. Etiological subtypes are quite often combined, i.e. ICD and ACD, or ICD and atopic HE, though all combinations are possible.

Table 1. Definitions of acute and chronic hand eczema

Type	
Acute HE	Eczema, localized to the hands, lasting for less than three months and not occurring more than once per year
Chronic HE	Eczema localized to the hands, lasting for more than three months or relapsing twice or more per year

Mostly the morphology does not reflect the etiology, and since the morphology may change over time this diagnosis can be given only to reflect the current clinical picture. The clinical course, i.e. number of flares etc. should also be considered.

The diagnosis of HE is defined by location, i.e. eczema localized on the hands. The signs of eczema include vesicles, redness, oedema, scaling fissures, dryness and hyperkeratosis, and symptoms include (among others) itching and pain. Not all signs or symptoms will be present at the same time. As compared to other eczematous diseases such as atopic dermatitis there is no strict definition and no specific criteria that should be fulfilled to accept the diagnosis of HE. In epidemiological studies the question "have you ever had hand eczema?" is often used to identify patients with HE. The question has been validated and a relatively good level of agreement between self-reported HE and HE based on clinical examination has been reported (Bregnhøj et al., 2011). However, in some studies, HE as defined by self-reported signs and symptoms, give less conservative estimates of the prevalence of the disease. In a study comparing question-based and symptom-based diagnoses of HE, reports of symptoms did not contribute much to the validity of the HE diagnosis (Svensson et al., 2002). A mutual agreement on classification, as well as more specific criteria for diagnosis of HE would lead to an improved understanding of the disease and open up possibilities for specific treatment and prevention for subgroups.

Table 2. Suggestion for an etiological classification of HE, according to Guidelines from the European Society of Contact Dermatitis (Thyssen et al., 2022).

Etiological classification of HE	
Irritant HE (Irritant contact dermatitis (ICD) on the hands)	HE with a well-defined and quantified irritant exposure (e.g.: number of exposures during the workday). ACD has been excluded by patch testing.
Allergic HE (Allergic contact dermatitis (ACD) on the hands)	HE with a positive patch test (following previous sensitization) and a current exposure to the culprit allergen. A positive patch test is only relevant when a current exposure to the allergen can be confirmed.
Protein contact dermatitis /contact urticaria on the hands	HE caused by exposure to proteins, leading to immediate urticarial skin reaction which may after some time present as an eczema with scaling and infiltration. Protein contact dermatitis is often elicited by exposure to food or to latex.
Atopic HE	HE in patients with previous or current atopic dermatitis, and no documented irritant exposure or exposure to relevant contact allergens.

Instruments for severity assessment

Several instruments are available for assessment of the severity of HE. Examples are objective instruments assessing signs of eczema and the area involved to be used by dermatologists or patients (Skudlik et al., 2006, Held et al., 2005, Rönsch et al., 2019a, Carlsson et al., 2017) or for occupational screening (Weistenhöfer et al., 2011). The Hand Eczema Scoring Index (HECSI) has been validated, and is the most widely used instrument, see **table 3** (Yüksel et al., 2021a, Oosterhaven and Schuttelaar, 2020). An online version of HECSI is now available[3]. Another example is a validated photographic guide that has been much used (Coenraads et al., 2005), and in a recent systematic review an overview of outcomes that have been measured in HE trials are given (Rönsch et al., 2019a). The "HECOS" initiative (Hand Eczema Core Outcome Set) is an ongoing program with the objective to agree on a set of relevant and valid core outcome measurement instruments (Rönsch et al., 2019b). In the future new imaging techniques may take over from the clinical assessment instruments, although we are not there yet (Hald et al., 2019) .

The inclusion of patient reported outcomes has been increasingly popular in clinical studies in recent years. For HE patients focus has been on quality of life (QoL) instruments, and more recently a specific Quality of Life in Hand Eczema Questionnaire (QOLHEQ) has been developed, validated and translated into a number of languages, making the instrument available also outside Europe (Ofenloch et al., 2014).

[3] www.hecsiscore.com - checked 22022-09-18

In conclusion: Although characteristics for acute and chronic HE exists, precise criteria for the diagnosis of HE and a detailed understanding of subclasses of the disease are lacking. Data contributing to a mutual agreement on classification, as well as more specific criteria for diagnosis of HE would lead to an improved understanding of the disease and open up possibilities for specific prevention and treatment for subgroups. The fact that HE affects young individuals in particular increases the importance as well as potential for prevention of the disease, and makes HE differ from other occupational diseases in this important aspect. Occupational HE is mostly reported in wet work occupations, though not limited to these occupations, and focus on prevention of occupational HE should be broader than these occupations only.

Table 3. Hand eczema severity index (HECSI) for assessment of HE severity (Held et al., 2005). See also www.hecsiscore.com

Clinical findings* (points 0-3)	Fingertips	Fingers (not including fingertips))	Palms	Back of hands	Wrists
Erythema					
Papules/infiltration					
Vesicles					
Fissures					
Scaling					
Oedema					

*Severity of symptoms: 0= no, 1= mild, 2= moderate, 3= severe

SUM					

Extension** (points 0-4)					

** Area: 0=0%, 1= 1-25%, 2=26-50%, 3=51-75% and 4=76-100% af both hands

SUM x extension					

Total HECSI Score = ____ + ____ + _____ + ____ + ____ = (min 0; max 360)

Factors influencing prevalence and severity

Multiple risk factors have been identified regarding the development and severity of HE. The significance of environmental versus genetic risk factors was studied in a population-based twin cohort, indicating that environmental factors explain up to 59% of the etiology of HE - independent of atopic dermatitis - indicating a favorable chance of prevention (Lerbaek et al., 2007b). Environmental risk factors are discussed in the chapter on ICD below. Of all the risk factors, a history of previous HE probably weighs the heaviest.

Atopic dermatitis

Atopic dermatitis - in childhood or persistent - has for many years been considered the major risk factor for HE. Risk factors influencing the incidence of HE were evaluated in a population-based twin study, confirming atopic dermatitis as the most important factor (Bryld et al., 2003). A negative influence of atopic dermatitis on work life such as an increased risk of job changes, sick leave, and medical consultations, mainly due to HE has also been reported (Nyrén et al., 2005). Atopic dermatitis was recently reported to be associated with incident as well as persistent HE, with an OR being 3.0 and 9.0, respectively (Heede et al., 2016). Recent data shows that children suffering from atopic dermatitis had a three times increased OR of having HE at the age of 16 (Grönhagen et al., 2015). On the other hand, in a systematic review on ICD after occupational skin exposure, the presence of atopic dermatitis did not significantly influence the risk of ICD (Jacobsen et al., 2021). In a recent study examining the prognosis for occupational HE, atopic dermatitis was not

confirmed as a risk factor, while lifestyle factors were found to influence the prognosis significantly, indicating that risk factors may change over time (Olesen et al., 2019b). This trend, however, needs confirmation from more studies.

Filaggrin is an important protein in stratum corneum, essential for the regulation of epidermal homeostasis and responsible for the skin barrier function. Individuals with mutations in the gene coding for the filaggrin are predisposed to ichthyosis vulgaris and atopic dermatitis. Filaggrin mutations can be identified in around 1/3 of patients with moderate/severe atopic dermatitis as compared to less than 10% in the background population. While filaggrin mutations in individuals without atopic dermatitis are not related to HE, several studies have confirmed an association with persistent HE in individuals with a history of atopic dermatitis, though not applying to incident HE (Heede et al., 2016, Visser et al., 2014).

Age

Age below 20 years at onset has been reported to influence the prognosis negatively (Meding et al., 2005). Since HE in patients with atopic dermatitis also has an early onset this could be a bias, however, early onset was also shown to be an independent risk factor after correction for atopic dermatitis (Meding et al., 2005). With respect to severity, moderate to severe HE was in a recent study reported to be associated with age less than 30 years or above 50 years (Cazzaniga et al., 2016).

Gender

A high incidence rate of HE has been associated with female sex, and prevalence of HE is 1.5-2 times higher among females than males in almost all studies. The general skin reactivity in tests with irritants is similar in males and females (Björnberg, 1975), and the increased prevalence in females is likely to be related to differences in exposures, since females are more often employed in wet work occupations (Anveden Berglind et al., 2009), and probably still have more wet work at home. A recent study found that independent of age and occupation, females had 78% higher odds of having wet work (Lund et al., 2019). Thus, female gender cannot be considered as a risk factor by itself, with the increased risk rather being due to increase in exposure. On the other hand, severity is often reported higher in males than females. One explanation here could be that prevalence of hyperkeratotic HE, which is often assessed as moderate or severe, is for unknown reasons higher in males (van der Heiden et al., 2018). Another explanation could be that males are less bothered by HE (Agner et al., 2008) and therefore have a more delayed contact with the health care sector and access to treatment. The impact of HE is generally more pronounced in females than in males, with increased sick leave and more impaired HR-QoL (Mollerup et al., 2014a).

Eczema localization

Data from a 15-year Swedish follow-up study of 868 individuals with HE showed that extension of HE at onset (initial examination) was associated with poor long-term prognosis of the disease (Meding et al., 2005). Thus, HE spread extensively on the hands at onset negatively influenced the prognosis, while morphology of eczema did not give the same degree of indication of prognosis (Meding et al., 2007). This study was performed before standardized instruments for estimating the severity of HE was available, and we have no indication as to whether this would have influenced the results. Widespread HE at first medical contact could also be interpreted as “patient-delay”, i.e. that the patient has waited for a long time to contact the doctor. Another study has shown that longer delay before medical attention (patient delay as well as healthcare delay) is associated with a poorer prognosis (Hald et al., 2009). Hyperkeratotic eczema occurs on palms (and soles) and is generally associated with a poorer prognosis.

Contact allergy

Having one or more contact allergies has been confirmed as a significant risk factor for the development of HE (Meding et al., 2005), and the risk has been reported to be related to strength (+ to + + +) of relevant positive patch test reactions (Bryld et al., 2003). When HE has lasted for more than three months patch testing should always be performed (Thyssen et al., 2021), and according to Danish National clinical recommendations even after 1 month´s duration of HE[4]. Patch testing should be repeated after a few years in recalcitrant cases. Strong patch test reactions are more likely to be of current clinical relevance, and relevance should in these cases be even more carefully considered.

[4] https://www.sst.dk/da/udgivelser/2016/nkr-behandling-af-haandeksem - checked 2022-09-18

Lifestyle factors

During the last decade, awareness of the influence of lifestyle factors on almost all diseases has been growing. Some lifestyle factors have been shown to be closely related to HE and to severity of the disease. Most of the data available is on tobacco smoking, which has been reported to influence the prognosis of HE negatively in numerous studies (Lukács et al., 2015). In a prospective follow-up study over 3 years of patients with occupational HE the severity of HE was at all points increased in smokers, and tobacco smoking was associated with increased sick leave from work (Brans et al., 2014). This was supported by data from a recent study reporting current tobacco smoking to be inversely associated with healing of HE (Olesen et al., 2019b). Smoking induces inflammation, delays wound healing, causes chronic damage to the microcirculation and inhibits fibroblast migration which could all be part of the explanation of the association between tobacco smoking and severity. High levels of mental stress were also identified to be negatively associated with the prognosis for occupational HE, while a high level of exercise was significantly related to healing of eczema (Olesen et al., 2019b). However, a causal relationship between lifestyle factors and HE still need to be confirmed.

In conclusion: Important factors related to the development of HE and severe disease are previous or current atopic skin disease, as well as being sensitized to contact allergens. These are factors that should be considered at an early stage in life and in relation to career choice, in particular. The high prevalence in youth is remarkable, especially for a disease with such a chronic potential, indicating that this age group should be the focus for preventive measures. Ideally, professional pre-employment counselling on skin preventive measures should be given before entering high risk jobs. The preponderance of females among HE patients is due to increased exposure and not to an increased skin susceptibility. Lifestyle factors are important, in particular regarding disease severity and should be considered in secondary prevention.

Irritant contact dermatitis (ICD)

Acute ICD is most often caused by one single powerful contact with irritants, and the cause of the irritant reaction is in most cases easily identified and understood. Further exposure can be avoided, and the healing process can be initiated. In contrast, chronic ICD is classically explained as the result of repeated exposures to irritants with a deteriorating effect on the skin barrier, each new irritation starting before recovery has been completed, and not leaving time for the healing process. This is illustrated in **figure 4**, where repetitive irritant trauma gradually leads to an impaired skin barrier function, which in the end will lead to inflammation, and the clinical disease will appear as chronic ICD (Malten, 1981). Transepidermal water loss (TEWL) is a measure for the passive diffusion of water over the stratum corneum, and the most valid and widely used method for assessment of skin barrier impairment in experimental studies (**figure 4**). Measurement of TEWL is a sensitive technique which enables detection of early changes in the skin barrier function (Tupker et al., 1989). Measurements should be performed under standardized conditions and are easily influenced by sweating and by changes in environmental temperature and humidity, which makes use of TEWL measurements difficult in fields studies or as a possible tool for surveillance of early skin damage at workplaces.

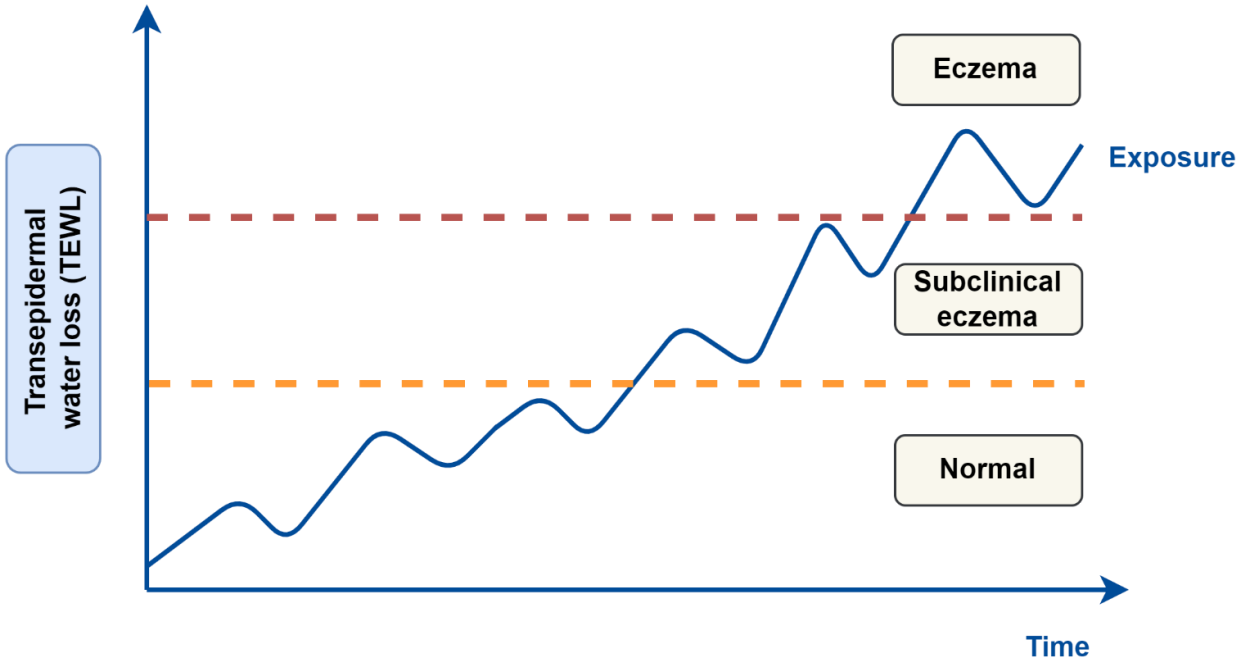

Figure 4. The development of irritant contact dermatitis is seen as a progressive deterioration of skin barrier function. The damage may be measured as an increase in transepidermal water loss (TEWL), and subsequently observed as clinically evident eczema.

Causative cumulative factors for development of ICD are many, of which exposure to wet work, cutting oils, detergents, glove occlusion, metal working fluids and mechanical trauma are just examples (Jacobsen et al., 2021). Combined effects of several irritants together may further augment the response (Schliemann et al., 2014, Pedersen et al., 2004).

Inflammatory pathways in the chronic phase of ICD are currently unknown. Neither the clinical picture nor the histological pattern allows for differentiation between ICD and ACD. Clinically, ICD is defined as dermatitis with documented irritant exposure, which is quantitatively likely to cause dermatitis, and with no relevant contact allergy (no current exposure to allergens to which the patient has reacted positively in patch tests) (Diepgen et al., 2015). Skin barrier function and development of ICD is related to individual endogenous/inherited factors, as well as to environmental exposures. When the barrier is impaired, cutaneous penetration of allergens and irritants will increase, leading to further deterioration and inflammation. Atopic dermatitis is known as a disease with an impaired skin barrier, and previous or current atopic dermatitis is a major risk factor for the development of HE (Rystedt, 1985, Ruff et al., 2018), although it seems that the significance of this risk factor may recently have changed slightly and become less important (Meding and Jarvholm, 2002, Olesen et al., 2019a, Olesen et al., 2019b). Atopic dermatitis patients with filaggrin mutations are at increased risk of development of HE (Visser et al., 2013, Heede et al., 2016), in particular of severe type (Heede et al., 2017), while filaggrin mutation without associated atopic dermatitis does not markedly increase the risk of HE (Lerbaek et al., 2007a, Visser et al., 2014). Although the focus during the last decade has been on filaggrin, other important genetic variables may also be involved. Inter-individual variation in skin susceptibility to irritants is high. The individual reactivity to irritant exposure and risk of development of ICD is further complicated by the fact that the response to one irritant does not necessarily predict the response to other irritants (Björnberg, 1974). This fact also hampers the value of attempts of using irritants for skin testing as pre-employment evaluations. Reaction to irritants is further influenced by chemical properties, and different irritants may affect the skin barrier and the skin surface in very different ways (**figure 5**). Also, concentrations and amounts applied to the skin are of importance. Chemicals, such as detergents with deteriorating influence on the skin barrier are important for the development of ICD. Chemicals with little or no negative effect on the stratum corneum may have toxic effects on deeper layers of the skin and act as important factors in the development of ICD (van der Valk et al., 1985, Agner and Serup, 1989). A combination of ICD and ACD on the hands is a common finding. The eczema may start as ICD and later when the skin barrier has deteriorated and the allergens can easily penetrate into the skin, sensitization can take place and ACD may

occur. Or alternatively, the eczema may start as ACD due to exposure to an allergen to which the person is sensitized, and when the eczema has broken the barrier ICD may further escalate the eczema. Interestingly, no significant correlation was found between sensitization to common contact allergens and susceptibility to irritants (Coenraads et al., 1975).

Figure 5. Silicone rubber replica of skin surface after exposure to different irritants (sodium lauryl sulphate, hydrochloric acid and croton oil). Examples illustrating how skin irritants affect the skin surface in different ways.

Wet work

Occupational exposure to skin irritants, in particular to wet work, is an important risk factor for HE (Anveden Berglind et al., 2009, Thyssen et al., 2010). Females are at higher risk of HE related to wet work due to more wet work exposure in females than in males (Lund et al., 2019), and more than half of all irritant HE cases are caused by wet work. Data from a Swedish population study showed that a total of 20% of the population of working age had occupational exposure to water (Anveden Berglind et al., 2009) . It is generally accepted that wet-work can be defined as activities where workers have wet hands for >2 hours per shift, or wear waterproof (occlusive) gloves for a corresponding amount of time, or wash their hands >20 times per shift/working day, **figure 6** (Behroozy and Keegel, 2014). In kitchen workers, cleaners and hairdressers 44% reported water exposure > 2 hours/day, and in HCW 22% similarly reported water exposure > 2 hours/day (Meding et al., 2016). A job-exposure matrix addressing hand exposure to wet work was recently developed, and here the highest amount of wet work was found among cleaners, butchers, fishmongers, cooks, beauticians (including hairdressers) and HCW (Lund et al., 2019). New findings show that a significantly increased risk of HE may appear at an exposure time of no more than 30 minutes of wet work per day, indicating that an up-date of the definition of wet work may be needed (Lund et al., 2020). In a recent registry-based study comprising 954 workers with occupational HE caused by wet work the effects of job change was studied, and data showed that even minor changes in exposure to wet work were associated with healing and improvement of HE (Carøe et al., 2018a). Also domestic exposure to wet work activities may be implicated in the development of HE (Meding et al., 2013). Interestingly, high degree of wet work exposure in health care workers was associated also to high exposure to wet work activities at home, indicating that frequent hand washing in this population may also be a question of behavioural habits or of socioecconomic status (Ibler et al., 2012a).

Figure 6. Wet work is today "defined" as wet hands > 2 hours/day, or glove wear > 2 hours/day, or hand washes > 20 times/day. New data indicate that a significantly increased risk of HE may appear at an exposure level of no more than 30 minutes of wet work per day (Lund et al., 2020).

Gloves

Glove use as personal protective equipment is important for protection of the skin from water, irritants and allergens, toxic chemicals and pathogenic microorganisms. However, occlusive gloves (made from latex, polyvinyl chloride and nitrile) may also play a part in the deterioration of the skin barrier, and may be a risk factor itself for the development of HE (Ramsing and Agner, 1996). Soap left on the skin before donning the glove may further reinforce the negative effect on the skin barrier (Jacobsen et al., 2021), and new findings indicate that gloves used on wet skin/hands may further intensify the negative influence on the barrier (Yüksel et al., 2021b).

Skin disinfectants

Alcohol based hand rubs (ABHR) are recommended as a substitute for hand washings in particular in the health care sector, but also more broadly during the Covid-19 pandemic. ABHR are generally considered harmless for the skin barrier (Pedersen et al., 2005), although new findings indicate that application of ABHR on hydrated/wet skin may increase susceptibility to ABHR (Plum et al., 2020), as may also the presence of atopic dermatitis (Angelova-Fischer et al., 2020). Regarding new and emerging Active Chlorine Hand Disinfectants (ACHDs), experimental results indicate that these do not affect the skin barrier function negatively (Yüksel et al., 2021c).

Moisturisers

Moisturisers are widely recommended and used during working hours or after work for the prevention of ICD, and may result in a clinically important protective effect for the primary prevention of ICD on the hands (Bauer et al., 2018). A consideration when used during working hours is that irritants and allergens may penetrate more easily through a hydrated skin (Zachariae et al., 2003, Held and Agner, 2001). Regarding "barrier creams" used before work and during working hours there are several issues that make conclusions difficult. One is that the lack of a specific definition of "barrier creams", and the decission to brand/promote the product in this way is up to the manufacturer. Another issue is, that protective creams/"barrier creams" need to be very specifically directed at specific irritants present in the work place. While "barrier creams" may in some situations be useful when directed at relevant irritants, lack of efficacy is also reported, and sometimes even aggravation of skin irritation may take place (Schliemann et al., 2013). However, so called "barrier creams" are widely used, and in spite of the complexity of the topic very little progress has been made for the last few decades to obtain a better understanding of their importance (Frosch and Kurte, 1994).

In conclusion: Understanding the concept of ICD is challenging, since it depends on numerous factors such as host suspceptibility regarding the skin barrier, the chemistry of the irritant and the exposure time and mode, the dose-response relationsship between exposure and development of ICD, and also on the preventive measures applied, of which the effect of some may be double-edged. Regarding susceptibility of the host and its interplay with the the chemistry of

the irritant, it should be emphasised that the response to one irritant does not necessarily predict the response to other irritants within the individual, and that exposure to a combination of irritants may lead to augmentation of skin response. Wet work is a significant exposure since it is common in many jobs, has a significant impact on the development of ICD on the hands, and preventive initiatives should be welcomed here. It is important to understand the dose-response relationship between exposure and disease. Simple changes such as a minor decrease in wet work or fewer working hours will have a positive influence, and legal regulations for wet work exposures could be helpful. Regarding preventive measures (gloves, substitution of hand wash with ABHR and use of moisturizers) positive effects have been documented, however sometimes the preventive measures by themselves may cause or aggravate HE. Scientific research providing data on positive and negative effects of gloves, hand disinfectants and moisturizers/barrier creams is essential for the future prevention of HE.

Consequences and HR-QoL

HR-QoL is significantly reduced in patients with HE (Diepgen et al., 2015). HE affects female patients more readily and more significantly than male patients (Agner et al., 2008, Mollerup et al., 2014a). This may be related to the tradition of females being often more involved in domestic work and that this part of their life is being affected. Interestingly, HR-QoL seems also more negatively affected in HE-patients living in metropolitan versus non-metropolitan areas (Nørreslet et al., 2018). For patients with long lasting occupational HE it was reported that job change had a positive impact on healing of the eczema, while it had a negative impact on HR-QoL, indicating that these outcomes do not always go together (Carøe et al., 2018b). A new and validated disease-specific instrument (QoLHEC) for assessment of HR-QoL in HE patients is available, and it is important to include also such patient reported outcomes for monitoring of disease activity in future intervention studies (Ofenloch et al., 2014).

Prognosis

Severity of HE varies from mild to moderate and severe cases, of which the mild cases constitute the majority. However, some patients with HE may face a chronic course, due to individual as well as environmental factors. In a fifteen years follow-up study of a population-based cohort of patients with self-reported HE, 44% reported symptoms during the previous year, and 12 % reported continuous eczema (Meding et al., 2005). In a recent study of trained hairdressers followed up after 11 years approximately one-third reported persistent and often severe HE (Havmose et al., 2021). In a study of patients with recognized occupational HE only 19.3% of patients reported complete healing at follow-up after approximately 5 years (Olesen et al., 2019b). There is a lack of understanding why the eczema takes a chronic course even when eliciting factors are eliminated. Delayed medical attention to HE, as well as long case-processing time for decision about compensation may influence prognosis in a negative direction (Dietz et al., 2021a, Hald et al., 2009). The benefits of changing job for patients with HE has been subject to discussions. A recent study compared severity of HE, as well as HR-QoL, in patients with occupational HE who after 5 years were still in the same job and those who were not, and found that more participants who changed job or left the labor market reported complete healing of HE, but that job change had a negative effect on HR-QoL (Carøe et al., 2018b). Thus, effect of job change remains controversial, and should be based on individual assessment of the specific situation.

In conclusion: While direct consequences of HE for society and up-front economic loss can be assessed, the effect of the negative impact on HR-QoL from HE experienced by the individual patient is difficult to estimate in economic terms, *although an extremely important parameter which may indirectly also influence the working ability, sickness absence and absenteeism of the patient. Involvement of patient reported outcomes in future intervention studies comprising HE patients are therefore important. Regarding the long-term prognosis of HE there is a significant knowledge gap regarding the understanding of the chronicity of the disease, and scientific studies elucidating this gap should be encouraged.*

Part two

Prevention

Acknowledging the chronic and disabling course that the HE may take, and the frequently far-reaching consequences, the importance of prevention is obvious. HE has a negative impact on HR-QoL, economics and employment, and the economic burden on society comprises medical costs, paid sick leave, unemployment costs, workers' compensation, disability and rehabilitation costs. Preventive measures should be taken, given that this could be an obvious chance to prevent such consequences. Educational programs aimed at workers in specific industries, and similar programs aimed at HE patients have been developed for primary and secondary prevention, respectively, and evaluated in follow up studies. However, preventive programs are expensive for the society, and takes a lot of effort for participants and costs for companies. Therefore, evidence should be available to ensure the positive effects of such programs. On the other hand, the effect may be difficult to assess, since many factors such as the design of the preventive effort, outcome assessments, as well as follow-up time, among others, may influence the results. In a systematic literature search articles on primary and secondary prevention of HE with either prevalence, incidence or severity as outcome have been identified, see **figure 1**. For further details on literature searches see Method section.

Intervention

Intervention is generally focused on education in safe work procedures, substitution of hazardous chemicals or procedures, and provision of personal protective measures. Preventive measures comprise protective equipment (gloves), moisturizers/barrier creams and reduced exposure time. Intervention programs applied in the primary prevention studies were directed at apprentices and workers in different high-risk jobs. Secondary prevention programs were directed at patients with occupational and non-occupational HE. With few exceptions focus was on education with respect to knowledge on skin protection and care (e.g. **table 4**). Substitution was not included in any of the studies, although the change from hand washings to ABHR as a means of hand disinfection could be seen as a matter of substitution. Preventive measures were supplies of hand creams/moisturizers/barrier creams and skin care products, and various types of protective gloves. These preventive measures were applied in several combinations although in most studies only enough for a limited period of the study period. For each study, the interventions and outcomes are briefly summarized in **tables 5 and 6.**

Table 4. Ten recommendations for use of protective equipment and skin care *(ESCD hand eczema guideline,* Thyssen et al., 2022*). Recommendations can be moderated to include more specific recommendations relevant for the job situation, e.g. for hairdressers' advice to" cut the hair before you dye" on "not to reuse disposable gloves" (Bregnhøj et al., 2012).*

Ten recommendations for use of protective equipment and skin care
• Use protective gloves for wet work and for work with hand contact with hazardous substances, both at home and at work.
• Protective gloves should be intact, clean and dry inside. Single use gloves should be worn only once.
• Protective gloves should be used when necessary but for as short a time as possible because friction, sweating and heat caused by wearing of gloves may result in irritant contact dermatitis, particularly in case of prolonged usage or skin pre-irritated e.g. by detergents.
• When protective gloves are used for more than 10 minutes, cotton gloves should be worn underneath and regularly changed to reduce occlusive effects.
• Use insulating gloves in the winter or when working in the cold.
• Hand washing is important to remove hazardous substances from the skin. However, frequent hand washing is associated with the development of HE and should be avoided.
• Wash hands in lukewarm, not hot water. Rinse and dry hands thoroughly after washing.
• Hand washing with soaps should be substituted with alcohol disinfection when hands are not visibly dirty, since alcohol is less irritating to the skin than hand washing with soap.
• Apply a fragrance-free emollient on your hands during the working day but especially after work and before bedtime. Emollients and barrier creams should be applied all over the hands, including the webs, fingertips and dorsal aspects.
• Do not wear rings or any other jewelry on the hands when performing wet work.

Primary prevention

With respect to primary prevention a total of 10 interventional studies were identified focusing on the prevention of HE (**table 5**). Intervention took place at schools or workplaces in high risk jobs, and most studies therefore also included a minor proportion of apprentices and workers with already existing or previous HE. Participants were metal workers/apprentice metal workers, nurses/apprentice nurses/HCW, hospital cleaners and hairdresser apprentices. Numbers of participants included in each study varied between 86 and up to 1727. The design of the preventive efforts differed between studies. Few reported in detail on the content of their education programs. Education was in most studies group-based, with information provided directly, and was often combined with pamphlets or other hard cover teaching materials. Some studies used participatory working groups and education of frontline personnel/role models. In one study the intervention was an online behavioral change program. Four studies used clinical assessment of outcome, three studies used self-reported HE as outcome, two studies used a combined assessment of clinical and self-reported outcomes and one study used photographs, which were evaluated by two dermatologists. Follow-up time varied from 3 months up to 3 years.

A total of five studies reported a positive outcome of the intervention, and of these only two studies were evaluated to be of high quality (**table 5**), according to Newcastle-Ottawa quality assessment scale[5]. One was the Reich study (Reich et al., 2020) comprising metal worker apprentices, in which the intervention was group-based training including practical exercises for 90 minutes and provision of emollients and soaps. It was followed up by a leaflet after 1 and 2 years. Outcome was incident HE cases. A specific not validated definition of the HE diagnosis was used (this definition was: (a) vesicles or (b) erythema in combination with at least one of the symptoms papules, scaling, or fissures on the hands, either observed at clinical examination or self-reported). At clinical follow up after 2 and 3 years, data showed significantly reduced numbers of incident cases of HE, though, surprisingly, no difference was shown between intervention- and control group after one year, although the training was given only at the start of the study. The other high-quality study reporting a positive outcome was by Bregnhøj et al (Bregnhøj et al., 2012), comprising hairdresser apprentices, and with the intervention designed as an evidence-based training program delivered by teachers in the schools who had been specially trained in the prevention of HE. Follow-up after 18 months showed that significantly fewer in the intervention group developed self-reported HE as compared with apprentices from the control group ($p=0.04$), although more apprentices from the intervention group were working in salons than in schools, which should give a higher exposure to wet work and chemicals. Additionally, atopic dermatitis was found to have a significantly negative influence on the development of HE in the cohort irrespective of the intervention. The outcome in both studies confirmed a positive effect of intervention, however, outcome measures as well as intervention program differed markedly between the two studies (Reich et al., 2020, Bregnhøj et al., 2012). Among the studies assessed as being of lower quality Clemmensen et al (Clemmensen et al., 2015) provided a one-hour course for hospital cleaners in an uncontrolled study, and found a significant decrease in HECSI values from 2.8 to 1.8 after 3 months. The management of the cleaning department was involved in the planning of the study, which was emphasized as a positive factor. Although the results indicate a positive effect, the study was uncontrolled, and the decrease in HECSI probably below the minimal important clinical difference for this assessment tool (Yüksel et al., 2021a). Kutting et al (Kütting et al., 2010) included more than 1000 metal workers into three different intervention regimes, all focusing at preventive measures. Group 1: skin protection before work (barrier creams) + skin care after work (moisturizers), Group 2: skin protection (barrier creams) before and during work, Group 3: skin care (moisturizers) after work, and a control group (Group 4). The primary outcome was a clinical examination using a skin score assessment. Barrier creams and moisturizers were provided by the employers, and different products were used in different workplaces. At follow-up after 12 months a significant deterioration was found in the control group only. There was no difference between the intervention arms of the study, but they were all superior to the control arm. Although the findings indicate a positive effect of use of any of the interventions, the mean differences in skin score were small. In the study by Löffler et al (Löffler et al., 2006) a positive effect of an educational intervention program repeated 3 times the first year, and twice in the following years, was found at follow-up after 18 and 36 months. Outcome was a non-validated definition of HE based on clinical signs, which hampers the interpretation of results. Interestingly, the positive effect of the intervention increased rather than stagnated over time.

[5] http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp - checked 220918

Amongst the studies with insufficient evidence, Madan et al (Madan et al., 2020) used an alternative educational approach, offering an online behavioral change program as intervention, and used photos assessed by trained dermatologists for outcome assessment. This well-performed study including 1727 student nurses reported insufficient evidence to conclude whether the intervention was effective with respect to self-reported HE. The study is interesting because it was the first and only study to report results from an online intervention for HE. However, a lack of personal contact and maybe also the alternative method for outcome assessment lacking a precise definition of HE may have influenced the results of the study. In the study by Soltanipoor et al (Soltanipoor et al., 2019) HCWs were included and both the intervention group (IG) and the control group (CG) received basic education on skin care and skin protection behavior. The intervention consisted of provision of moisturizers on easily accessible areas in the workplace, and no effect on primary outcome (delta HECSI values) was reported. The results indicate that the education given to both groups was more important than accessibility to moisturizers. The Moldowan study (Moldovan et al., 2021) included apprentice nurses, the duration of education was 20 minutes applied two times in 3 months, and moisturizers and soaps were provided. The follow-up time for this study was 3 months only, and the study reported a reduction in self-reported HE, but no effect regarding HECSI values. The study by van der Meer et al (van der Meer et al., 2015) used participatory groups and role models in the intervention and outcome was self-reported HE. At follow-up after 12 months the intervention group was significantly more likely to report HE, OR 1.45 (CI 1.03-2.04). This study was the only one to report a deteriorating effect of the intervention, which could be interpreted as an effect of the increased attention to and heightened awareness of HE, following the intervention and group discussions. UVB for hardening of the skin in apprentice bakers were used in the study by Bauer et el, however a positive effect could not be confirmed (Bauer et al., 2002).

The results of the 2 high quality studies with positive outcomes, Reich et al and Bregnhøj et al (Reich et al., 2020, Bregnhøj et al., 2012), confirm the positive effects and long-term impact of intervention for participants in risk of HE. The educational part of the intervention was in both studies rather intense, although with very different approaches. Follow-up time was from 18 months to 3 years, and outcome assessed as (partly) self-reported in both studies, however none of these factors differed markedly between the studies. Among the three high quality studies with inconclusive or negative outcome, one study used online intervention and photographic assessment (Madan et al., 2020), one study had a very brief educational program, but focused on provision of hand creams (Soltanipoor et al., 2019). The study by van der Meer et al had a multifaceted strategy comprising groups discussions, which may have increased attention to HE and this way have had a negative impact and increased numbers of self-reported HE (van der Meer et al., 2015). These were all factors that may have counteracted a successful outcome.

Although no clear conclusions can be made data indicates that educational intervention has a role in prevention of HE. Group-based intervention followed by leaflets/pamphlets as reminders seems to be superior to online intervention programs, although this conclusion may be subject to change over time, as online teaching generally becomes more popular. Provision of preventive measures (moisturizers) alone does not have enough impact to influence outcome. When scrutinizing the studies, it becomes very clear that a precise and generally accepted definition of HE is lacking, resulting in a huge variation in outcomes, and that it would be of importance to reach consensus regarding this. When using clinical scores as outcomes, results should also be evaluated with respect to minimal clinical important difference.

Table 5. Intervention studies, primary prevention

Authors	Participants (number)	Participants job and eczema status	Follow-up time	Intervention	Outcome and results	Quality of the study
Bauer et al 2002 (Bauer et al., 2002)	**Total: 94** Adherence: 61 at follow-up (IG 31, CG 30)	Baker apprentices	6 months	**Education:** Both IG and CG received a training program regarding prevention of, lasting for 60 minutes. **Preventive measures:** UVB for hands (IG only)	Outcome was **clinical assessment** of incident HE cases. At T_0 no one in the IG or the CG had HE. After 6 month the point prevalence of HE was IG: 19.4% CG: 13.3% UV therapy as intervention of HE did not prove successful	Not RCT study Newcastle-Ottawa quality assessment 7 **Medium quality**
Bregnhøj A et al 2012 (Bregnhøj et al., 2012)	10 schools **Total: 502** IG: 301 CG: 201 **Adherence:** at follow-up 57%	Hairdresser apprentices	8 month and 18 months	**Education:** Intervention was based on educating teachers in the training schools. These supervisors underwent a 2-day course and were responsible for the training of the apprentices. The training program consisted of several oral presentations, a pamphlet, group work exercises, practical training and glove size measurement. **Preventive measures:** Examples of moisturizers and gloves were provided during training	Primary outcome was **self-reported** HE during study period (incidence rate): Results: At 8 months follow-up: IG: 11.0% CG: 19.2% (p=0.05) At 18 months follow-up: IG: 19.4 CG: 28.3 (p=0.04) The OR of getting hand eczema during the study period (18 months) for CG compared to IG was 1.65 (95% CI 1.02 - 2.67).	Randomization was performed on the level of included schools. Newcastle-Ottawa quality assessment: 8 **High quality**
Clemmensen K et al 2014 (Clemmensen et al., 2015)	**Total: 86** **Adherence:** at follow up: 95.3%	Hospital cleaners	3 months	**Education:** A 1 hr group course in hand protective behavior and practical exercises (hand wash, use of gloves). A hard copy card with 10 pieces of advice on prevention of HE **Preventive measures:** A bag with small free small samples of moisturizers and a certificate of participation.	Outcome: **Clinical examination.** Change in HECSI from baseline to follow-up Results: Mean HECSI decreased from 2.8 at baseline to 1.8 at follow-up (p<0.002) .	No control group Newcastle-Ottawa quality assessment: 5 **Medium quality**

Kutting et al 2009 (Kütting et al., 2010)	From 19 factories **Total: 1020** Group 1: 253 Group 2: 258 Group 3: 263 Group 4: 246 **Adherence:** At follow-up: 78.4%	Metal workers	12 months	**Education:** 0 **Preventive measures:** 4-armed study: **Provision of skin protection and care** Group 1: skin care products after work Group 2: skin protection creams before and during work Group 3: skin protection + skin care products Group 4: control (care = moisturizer) Skin protection equipment and skin care was provided by the employers and not by the study	Outcome: **Clinical examination**. The percentage change of an objective skin score from baseline to 12 months was used as primary outcome measure Results: Skin score, median values and 25/75 percentiles for baseline and follow-up, respectively: Group 1: 14 (11-19) and 15 (12-19) Group 2: 15 (12-20) and 14.5 (11-18) Group 3: 14 (11-19) and 13 (10-17) Group 4: 11 (8-15) and 13 (10-17) Significant improvement in group 1 and 2, significant deterioration in group 4 (control group). Differences between the three intervention arms were not significant, but all differences between any one intervention and control were significant ($P < 0.05$), however, total differences were small.	Randomization was performed on the level of included enterprises, assigning each of these to one of the 4 study arms Newcastle-Ottawa quality assessment: 6 **Medium quality**
Löffler H, 2006 (Löffler et al., 2006)	From 14 training schools **Total: 521** **Adherence:** At follow-up 62.3% (IG: 156 CG:169)	Nurse apprentices	3 years	**Education:** The intervention group received an educational group lecture with practical parts 3 times in the first year, and twice in the following years. **Preventive measures:** A moisturizer was provided	Outcome: HE defined by **clinical examination** as the occurrence of a morphology category (sign) of at least 'moderate' or 'severe' HE Results: HE: baseline 18 m. 3 years IG 17% 33% 16% CG 17% 48% 38% Adjusted OR for development of HE in control group was 3.3 (1.93–5.56) at 3 year follow up	Randomization was performed on the level of included training schools. Newcastle-Ottawa quality assessment: 7 **Medium quality**
Madan I et al 2020 (Madan et al., 2020)	14 intervention sites 21 control sites **Total: 1727** IG students:539 CG students:250 IG ICU:453 CG ICU:485 **Adherence:**	(i) first-year student nurses with a history of atopic conditions or (ii) intensive care unit nurses (ICU-nurses).	12-15 months	**Education:** Behavioral change program (BCP) that targeted appropriate use of gloves; washing hands, using antibacterial hand rubs and moisturizing cream. BCP was offered online or as hard copy, and the message of skin care was reinforced by the local occupational health service, control-of-infection team, and line management. CG received leaflet **Preventive measures:**	Outcome: Detectable HE by **photographic assessment.** Results: Student nurses: IG: 15.1% at baseline, 10.3% at follow up CG: 7% at baseline, 12 % at follow up ICU nurses: IG: 16.5% at baseline, 9.9% at follow-up CG: 16.5% at baseline, 13.8 at follow-up OR (95% CI) for hand dermatitis at follow-up in the intervention group relative to the controls were 0.72	Randomization was performed on the level of included sites. Newcastle-Ottawa quality assessment: 9 **High quality**

	At follow-up 57.6% (IG students:185 CG students:142 IG ICU:334 CG ICU:333)			Provision of moisturising creams	(0.33–1.55) and 0.62 (0.35–1.10) for student and intensive care unit nurses, respectively. Although all the statistical analyses suggested a small benefit from the intervention, none were statistically significant.	
Moldovan HR et al 2021 (Moldovan et al., 2021)	**Total: 230** IG: 132 CG: 98 **Adherence:** 60% at follow-up	Nurse apprentices	3 months	**Education:** 20 minutes group training program, lecture about skin biology, eczema and proper use of soap, disinfectants, and emollients. **Preventive measures:** Provision of emollients and soaps to be used during the practical activities in the hospital, in sufficient quantities for 3 months	Outcome: **Self-reported** 3-month prevalence of HE by **clinical examination** (HECSI score) Results, self-reported HE: IG: Baseline: 19.6%, follow-up 9.3% CG: Baseline 19.1%, follow-up 19.1% No statistics available on these data. Results, HECSI score IG: baseline 1.02, follow-up 0.18 CG: baseline 1.00, follow-up 0.31 No significant difference in HECSI between T1 and T2	Control group recruited from different hospital Not RCT Newcastle-Ottawa quality assessment: 3 **Low quality**
Reich A et al 2020 (Reich et al., 2020)	**Total: 303** IG: 131 CG: 172 **Adherence:** 1 year: 86.5% 2 year: 80.2% 3-year: 58.8%	Metal worker apprentices (MWA)	1- 2-3 years	**Education:** 90-minute training consisting of an interactive, and dialogue-oriented presentation, combined with hands-on practical exercises, directed at MWA on correct use of protective gloves, barrier creams, and skin care products. Training was group-based with a maximum of 25 MWA in each group. A leaflet after 1 and 2 years summarizing the training program. **Preventive measures:** Free samples of emollients and barrier creams offered together with leaflets after 1 and 2 years	Outcome: Incident cases of HE were defined as signs either observed at **clinical examination** or **self-reported** occurring after T_0. The following signs were included: (a) vesicles or (b) erythema in combination with at least one of the symptoms papules, scaling, or fissures on the hands, Results: **At 1-year:** Incidence rate IG 6.9%, CG (MWA) 7.6% **At 2-years:** Incidence rate IG 9.2%, CG (MWA) 20.9% **At 3-year**s: Incidence rate IG 12.2%, CG (MWA) 32.6% No significant difference in number of incident cases between IG and CG after 1 year.	Randomization was performed on the level of included schools Not RCT Newcastle-Ottawa quality assessment: 8 **High quality**

					After 2 years and 3 years increased OR for incident HE cases in the CG compared to IG were OR 2.63 (CI 1.31 to 5.28) and OR 3.47, (CI 1.88 to 6.40), respectively.	
Soltanipoor M et al 2018 (Soltanipoo r et al., 2019)	19 wards **Total: 501** IG: 285 CG: 216 **Adherence:** 60% at follow-up	HCW	12 months	**Education:** The HCWs were instructed to use hand creams. (Both the IG and the CG received basic education on skin care and skin protection behavior every 3 months from baseline to the end of the study. This education program took the form of a short small-group lesson lasting 5 to 10 minutes). **Preventive measures:** For IG only: Provision of hand cream dispensers, at accessible locations in the wards, continuous electronic monitoring of cream use, and feedback on cream use at ward level by means of posters	Primary outcome was **clinical assessment** (change in HECSI score). Results: Reduction in HECSI score: IG: −6.2 points (95%CI: −7.7 to −4.7) CG: −4.2 points (95%CI: −6.0 to −2.4). Although there was no significant effect on the primary outcomes, the intervention showed overall positive effects on the HECSI score.	Cluster randomized, parallel-group controlled trial with blinded outcome assessments. Newcastle-Ottawa quality assessment: 9 **High quality**
van der Meer et al (van der Meer et al., 2015)	48 different departments **Total: 1649** **Adherence:** 66.4 % at follow-up (IG: 609 CG 486)	HCW	12 months	**Education:** A multifaceted implementation strategy comprising participatory working groups, role models, an educational program, including reminders, and a leaflet. All components were guided by a trained occupational nurse. The leaflet was also given to the control group. **Preventive measures:** All workers who were present at the educational session received a bag with one moisturizer, a pair of cotton under-gloves, and two disinfectants.	Outcome was **self-reported** prevalence of HE presence in the past 3 months, as measured by the Nordic Occupational Skin Questionnaire Results: Hand eczema: IG: baseline 7.3 %, follow-up 11.3% CG: baseline 10.3 %, follow-up 9.7% IG was significantly more likely to report HE, OR 1.45 (95% CI 1.03-2.04)	Randomization was performed on the level of included departments Newcastle-Ottawa quality assessment: 9 **High quality**

Quality assessment of the papers is based on the Newcastle-Ottava assessment scale.
IG = intervention group; CG = control group. HECSI: Hand eczema severity index, an objective score assessing signs and extent of HE

Secondary prevention

Our literature research identified a total of 7 studies evaluating the outcome of secondary intervention. Patients included were HE-patients from hospital outpatient clinics and from private clinics, and occupational HE-patients from workplaces. Preventive efforts varied between group education and individual education or both and the time spent on the intervention varied between 30 minutes - 1 hour, and up to 2 days (**table 6**). Five studies had clinical assessment as primary outcome, while in 2 studies the outcome was self-reported HE severity (**table 6**). Follow-up time varied between 8-12 weeks and up to 12 months. Four studies were evaluated as high quality RCT studies (**table 6**). Of these van Gils et al (van Gils et al., 2012) included HE- patients from a hospital setting with a broad range of severity, provided multidisciplinary integrated care with focus on topical treatment, use of gloves and hands washing on an individual basis, while usual care was provided to the control group. The outcome was assessed after 6 months as difference in HECSI between baseline and follow-up, which was 10.7 points. This difference in HECSI in favor of the intervention is above the minimal clinical important difference, and results from this high quality RCT study clearly confirm the positive effects of intervention. Ibler et al (Ibler et al., 2012b) included HCW with HE recruited from the workplace, provided individual training in prevention of HE (**table 4**) and counselling based on patch tests, while treatment consisted of usual care in the intervention as well as the control group. HECSI was used for outcome assessment 5 months after the intervention. Delta HECSI from baseline to follow-up after 5 months in the intervention group was 3.56 points higher than in the control group, which was a statistically significant difference, although below the cut-off for clinically important change (Yüksel et al., 2021a). Since participants were recruited from workplaces and not from a dermatology practice or hospital clinic cases were mild, which may have influenced the result. However, both studies (van Gills and Ibler) clearly confirm that education/counselling on an individual basis is superior to usual care with respect to improvement of HE severity. Two uncontrolled studies, Brans et al (Brans et al., 2020) and Tauber et al (Tauber et al., 2020b), used group-based education for metal workers with HE and for chronic HE patients, respectively. They both used clinical examination for outcome assessment, and both studies supported a significant although minor effect of the intervention. In another study assessed as being of lower quality, Schürer et al (Schürer et al., 2005) included geriatric nurses with HE in the intervention group and ordinary HE patients as controls, and provided counselling on an individual basis. Self-reported signs of HE was used as outcome, which was significantly better in the intervention than in the control group. Two high quality studies did not unanimously support a positive outcome of the intervention. One of these, Mollerup et al (Mollerup et al., 2014b) recruited two groups of HE patients, one from a hospital setting and one from a private clinic. The intervention was an individual questionnaire, as well as a website with information and the opportunity to contact the trial team. Outcome was difference in HECSI points, and while no significant difference was found between intervention and control group, a post-hoc sub-analysis including patients from the hospital setting only, showed significantly improved HECSI score in the intervention group. The explanation for this could be that quite a few patients recruited from the private clinic received regular treatment at the clinic, and therefore already had close access to therapy. The other study, Fisker et al (Fisker et al., 2018) recruited patients with notified occupational HE with different professional backgrounds, offered a 2-hour group-based education session, and had self-assessed severity after 12 months as primary outcome. Overall, a positive effect of the intervention could not be confirmed. However, in a sub-analysis excluding patients from HCW-jobs a positive but statistically insignificant effect of the intervention was found (p=0.06). In this study the relatively high number of participants with mild HE at entry may possibly have diluted the effect of the intervention, as may the time lapse between intervention and follow-up, which was longer than in any of the other studies. Results from this study also illustrate that a one-time 2-hour group-based educational intervention is not enough to have an impact on HE after 12 months.

Results from the secondary prevention studies in general support the conclusion that intervention may have a positive impact on severity of HE. The best evidence is available for the effect of individual counselling. With respect to the population to which the intervention is given, this clearly influences the outcome. Examples of this are education programs being effective for hospital patients but not for patients recruited from private clinics (Mollerup et al., 2014b), and another program being detrimental to HCW and beneficial in all other occupations (Fisker et al., 2018). The results point in the direction that “one size does not fit all” and that tailor-made models and more individualized approaches may be the way to obtain successful interventions. A few studies investigated the difference in effectiveness of programs in subgroups such as atopic patients, young patients, or differences between sexes.

None of the studies on primary or secondary intervention comprise data on substitution, although substitution of hand wash with disinfection is widely used. More data on substitution used in relation to ICD would be interesting. Further, none of the studies have focused on reduced exposure time, which due to the dose-dependent relationship between exposure and eczema, would be expected to have a positive impact.

Table 6.
Intervention studies, secondary prevention

Authors	Participants (number)	Participants job and eczema status	Follow-up time	Intervention	Outcome and results	Quality of the study
Brans et al 2020 (Brans et al., 2020)	**Total: 114** **Adherence:** 81.5% a at follow-up	Metal workers with occupational HE, consecutively recruited	8-12 weeks	**Education:** 2-day seminar including group education on pathogenesis, risk factors, and prevention, (8–13 patients per group), followed by individual clinical examination and recommendations for diagnostics and treatment and counselling on the correct use of personal protective equipment **Preventive measures:** Correct gloves provided later	Outcome: **Clinical examination** (change in OHSI objective score) Results: OHSI score: Baseline 3.15 +/-2.63, follow-up: 2.01+/-2.00 (p<0.001)	Prospective cohort study No control group Newcastle-Ottawa quality assessment: 7 **Medium quality**
Fisker M et al 2018 (Fisker et al., 2018)	**Total: 756** **Adherence:** 71.5% at follow-up (IG: 274 CG: 260)	Patients with notified occupational HE, consecutively recruited	12 months	**Education:** One-time, 2-hour, group-based education session on skin-protective behavior. Leaflet **Preventive measures**: 0	Outcome: **Self-reported** severity of HE assessed by a validated photographic guide (clear, mild, moderate, severe, very severe). Results: The ordinal odds of scoring worse on self-reported hand eczema severity was 15% lower in the intervention compared with the control group (p=0.34) corresponding to OR 0.85 (95% CI:0.61–1.18). No significant effect on self-reported severity.	RCT study Individually randomized Newcastle-Ottawa quality assessment 8 **High quality**
Ibler et al 2012 (Ibler et al., 2012b)	**Total:255** IG: 123 CG: 132 **Adherence:** 96.8% at follow-up	HCWs with HE	5 months	**Education:** Individual education and counselling (20-30 minutes) based on patch and prick testing and assessment of work- and domestic related exposures. Education based on a skin care program. Practical training. Leaflet **Preventive measures: 0**	Outcome: **Clinical examination** (difference in HECSI at follow-up between IG and CG) Results: Delta (IG-CG) of means for HECSI: −3.56 (95% confidence interval −4.92 to −2.14)	RCT Individual randomization Newcastle-Ottawa quality assessment 9 **High quality**

Mollerup A et al 2014 (Mollerup et al., 2014b)	**Total:306** **Adherence:** 70.5% at follow-up	HE patients referred for diagnostic work-up in hospital or private clinic	6 months	**Education:** Nurse-lead training program based on: 1) baseline questionnaire with the purpose to focus on the relevant areas for individual counselling. 2) a secure website with information, educational videos, and tools for self-monitoring. 3) Support for self-management by ad hoc communication and networking **Preventive measures:** The patients could contact either the intervention team or with other trial participants by use of the website.	Outcome: **Clinical examination.** HE-severity at follow-up, assessed as change in HECSI from baseline to follow-up Results: IG: Baseline: 42 (20-82), follow-up:24 (12-46) CG: Baseline: 44 (20-72), follow-up: 25 (10-45) (p=0.08) At post-hoc evaluation of subgroups the intervention had a positive outcome in patients from a hospital setting: IG: Baseline 42 (20-91, follow-up 25 (11-46) CG: Baseline 38 (18-64), follow-up: 23 (10-57) (p=0.01)	RCT study Individual (block) randomization Newcastle-Ottawa quality assessment 9 **High quality**
Schürer NY 2005 et al (Schürer et al., 2005)	Total: 209 IG: 102 CG: 107 Adherence: 77% at follow up (IG: 82 CG: 78)	Geriatric nurses with HE	6 months	**Education:** An exploratory interview (duration 45 min/participant), recommendation of individualized protective measures (barrier creams). Hands-on training in the correct use of protective gloves and barrier creams, and skin care, during the first appointment (duration 20 min/participant). **Preventive measures:** If required pastes with zinc and tar were prescribed. Participants were provided with cotton gloves and protective gloves	Outcome: **Self-reported** decrease in signs (erythema, xerosis and fissures significantly different from control group) Results: Participants with HE: IG baseline: 73, follow-up 42 CG baseline 70, follow-up 55 (p<0.01) Questionnaires 3 months after study completion revealed skin lesions in 53% of IG and 82% of CG (p<0.01).	Prospective controlled study. Control group consisted of ordinary HE patients Newcastle-Ottawa quality assessment 7 **Medium quality**
Tauber M et al 2019 (Tauber et al., 2020b)	**Total: 71** **Adherence:** 81.6% at follow-up	Chronic HE patients, consecutively recruited	3 months	**Education:** Group education including terms of knowledge and self-management. Definition of the disease, a review of aggravating conditions (particularly irritating and identified allergic factors), and the treatment modalities **Preventive measures: 0**	Outcome: **Clinical examination** (mTLSS is a severity score based on signs and including severity of symptoms as well). Results: mTLSS baseline 7.1 +/- 2.9, follow-up 3.9 +/- 3.0 (follow-up data interpreted from a table) mTLSS significantly improved (p<0.01),	Single-centre prospective study No control group Newcastle-Ottawa quality assessment 4 **Low quality**

van Gils et al 2012 (van Gils et al., 2012)	**Total: 196** IG: 101 CG: 95 **Adherence:** 63% at follow up	HE patients	26 weeks	**Education:** Individual integrated, multidisciplinary care, comprising evaluation by a dermatologist, and specialized nurse/physician assistance in terms of counselling on compliance with topical treatment and with regard to hand washing and gloves. Occupational physician involved if work-relation was suspected **Preventive measures:** Not described	Outcome: **Clinical examination** (difference in improvement in HECSI between groups). Results: Improvement in HECSI: IG – 22.4 points CG: - 11.7 points (CI) 0.3–21.1 Clinically significant improvement in IG as compared to CG	RCT Individual (block) randomisation Newcastle-Ottawa quality assessment 9 **High quality**

Quality assessment of the papers is based on the Newcastle-Ottava assessment scale.

IG = intervention group; CG = control group. HECSI: Hand eczema severity index, an objective score assessing signs and extent of HE. OHSI = Osnabrück Hand Eczema Severity Index, an objective score assessing signs and extent of HE. mTLSS= Modified total lesion symptom score, an evaluation of hand eczema signs and symptoms.

Other intervention studies

Although not fulfilling our criteria for inclusion of studies with HE incidence, prevalence, or severity as outcome, the following older studies may contribute with information regarding prevention.

In a study from 2002 a total of 375 wet work employees participated in an intervention study with a skin care program provided to front line personnel (10-20 acting as a participatory team). Outcome was registration of skin symptoms/problems, and not on identification of HE cases (Held et al., 2002). In two studies from 2005 Danish cheese dairy workers and gut cleaners, respectively, were offered a skin care program (Flyvholm et al., 2005, Sell et al., 2005), with outcome being self-reported eczema or skin symptoms on hands or forearms. All three studies reported reduced symptoms after intervention. They were not included due to a mix up of hands and forearms, and a lack of definitions of HE. The studies illustrate that it is hard to define the line dividing “damaged/shabby skin” from eczema.

Tertiary prevention

As well as primary and secondary intervention, tertiary prevention has also been introduced in Germany as an opportunity for patients with chronic occupational HE. Tertiary prevention is performed as a 6-week program that can be offered to patients with severe skin symptoms, not responding to secondary prevention measures. In Germany it is designed as a 3-week inpatient intervention phase in a specialized center, comprising diagnostics and treatment, patient education, training in personal protective equipment, followed by a 3-week outpatient phase of sickness-absence under the guidance of a dermatologist. The intention is that the patients ideally return to their workplaces after the end of tertiary prevention, and the studies provide some evidence for success (Brans et al., 2016, Breuer et al., 2015).

Conclusions

HE is still a major challenge within occupational health despite decades of research into its cause, and two decades of studies into prevention. Systematic search, however, revealed only 17 controlled studies in systematic preventive measures, directed at either primary or secondary prevention. Obviously, the documentation of prevention of HE is challenging due to its multifactorial origin, the need for long term follow-up, and the need for substantial retention of participants to the intervention program. The 17 studies represented a variety of settings, study groups and designs. The results showed only limited evidence for the beneficial effects of primary education programs applied in high risk trades. The teaching programs vary, and the evidence does not support any clear conclusion as to which interventions are best/most effective, though it appears that very brief programs have less effect than more intense ones. Due to the early onset of HE, it seems obvious that that the intervention should be delivered early, i.e. to apprentices. Furthermore, 3 studies found some protective effect of teaching programs given to hairdresser apprentices (Bregnhøj), nurse apprentices (Löffler) and metal worker apprentices (Reich). All 5 studies on apprentices were well conducted and of high or medium quality (Newcastle-Ottawa scale >7). In particular, the Reich study (Reich 2020) combines an initiating education program with an annual follow-up leaflet to enhance the preventive effect.

With respect to secondary prevention, there is more evidence for the positive effects of intervention, and here education programs with an individual focus seem to be most successful. There is also some evidence for the provision and use of emollients/moisturizers/barrier creams, but information on specific ingredients, amount and timing is still obscure.

We identified no studies on substitution of irritants or irritative procedures, or reduced exposure time. The substitution of hand washing with ABHR has been made subsequently during the past years and it may have prevented an increase in the prevalence of HE during the covid-19 pandemic. But this has not been scientifically evaluated in any controlled studies.

The most urgent task is the development of a safety strategy for the huge amount of wet work jobs in industry and households; how could they be turned into safe jobs avoiding an increased risk of HE? Second is the establishment of safe guidelines for the use of protective gloves without

increased risk of development of ICD on the hands. Third is the implementation of the evidence-based teaching programs in all vocational training in high-risk jobs.

Future recommendations

Since the prevalence and course of HE has been unchanged for decades, it is time to apply new perspectives to diagnostics and prevention. Based on the summary of the background for the disease, and on the systematic literature search on prevention of HE we suggest that the following issues should be the focus for future research:

Focus on children and adolescents. Focus on women

Since HE starts early in life and has the potential to turn into a chronic disease, the younger age group is
of particular concern. Having atopic dermatitis and being sensitized to an allergen should be considered
early in life. Vocational guidance prior to or at the start of a career is suggested to this vulnerable
group.
The fact that females apparently have a coping strategy different from men should be investigated further, and different approaches for prevention in females and males may be appropriate.

HE-prevention in students/ apprentices

Good results were reported from studies on groups of apprentices (e.g. nurses and metal workers). This
calls for further including HE-prevention in the educations leading to jobs with high risk of HE. Though not documented, it seems important to address HE during the vocational training into high-risk jobs. It is probably also necessary to repeat the training during the entire education.

For occupational HE the focus should be on wet work. Contact allergy should not be overlooked.

It is evident that wet work is a major culprit regarding the development and severity of HE, and should be the focus for preventive initiatives. We suggest a threshold limit value for wet work to be set lower than the 2 hours, which are currently considered safe. There is an urgent need for research in preventive strategies for people with wet work. How can wet work be

organized to minimize the impact on the skin barrier, and which protective measures are efficient? Are there other strategies than simply reducing exposure time? However, we suggest that surveys should also be carried out in occupations with fewer notified cases to avoid overlooking a silent problem in occupations with little tradition for notification of skin diseases. Prevention should further focus on occupations with current and specific problems relating to contact allergy.

Lifestyle factors are important regarding severity and prognosis for HE, and this understanding should be communicated to the patients

During the last decade it has become clear that an association between HE- severity, and probably also HE-prevalence is associated with lifestyle factors such as tobacco smoking, mental stress and lack of physical activity. The causal relationship should be clarified, and lifestyle factors should even now be included in educational programs for HE patients.

The dose-dependency of ICD should be understood and utilised in prevention.

A reduction of irritant stimuli may prevent the development of HE or lead to improvement or healing. The dose-response-relationsship, such as reducing time spent doing wet work should be considered in work-places. Legal regulation of exposure time to irritant stimuli, i.e. wet-work, may be helpful

Further research should clarify effects and side effects of preventive measures such as gloves, moisturisers and substitution of soap with disinfectants.

Preventive measures are needed and also recommended in educational programs. However, these may
be double-edged and have side effects. This should be a focus for future studies, aiming at reducing
side effects for preventive measures. Based on experimental data ABHR are believed to be less irritant than soap and water for hand desinfection. This needs to be to be confirmed in occupational real-life settings.

Improved diagnostic criteria for classification of subtypes of HE and for eczema outcome measures.

More data enlightening this area is important – not only to be able to communicate in a more precise way using a distinctive terminology, but also because by attempting to classify HE, a deeper understanding of the complexity of the diagnosis can be reached and will lead to a more differentiated view of HE. More precise diagnosis and eczema outcome

measures will help the interpretation of intervention studies and facilitate specific prevention and treatment for subgroups.

Research on chronicity

HE cases may vary from mild cases which may be easily treated and to severe chronic cases. More knowledge on risk factors for chronicity is needed to be able to direct prevention of HE to groups at risk of becoming chronic cases.

Early identification of severe cases in need of systemic therapy and early access to medical treatment

Early treatment may be an important factor for prevention of severe eczema and development of chronicity.

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