

MISS KRISTIANE AASEN ENGBRETSSEN (Orcid ID : 0000-0003-0419-2698)

DR JONATHAN I SILVERBERG (Orcid ID : 0000-0003-3686-7805)

DR ALEXANDER EGEBERG (Orcid ID : 0000-0001-8257-1816)

Article type : Systematic Review

The association between atopic dermatitis and hand eczema: a systematic review and meta-analysis

S.M.D. Ruff¹, K.A. Engebretsen^{1,2}, C. Zachariae¹, J.D. Johansen², J.I. Silverberg³, A. Egeberg¹, J.P. Thyssen^{1,2}

¹Department of Dermatology and Allergy, Herlev and Gentofte Hospital, University of Copenhagen, Hellerup, Denmark

²National Allergy Research Centre, Department of Dermatology and Allergy, Herlev and Gentofte Hospital, University of Copenhagen, Hellerup, Denmark

³Feinberg School of Medicine at Northwestern University, Departments of Dermatology, Preventive Medicine, and Medical Social Sciences, Chicago, Illinois, USA

Total word count: 3,116

Number of figures/tables: 4 figures

Number of supplementary figures/tables: 14 figures/4 tables

Number of references: 72

Running head: Association between atopic dermatitis and hand eczema

Key words: atopic dermatitis, hand eczema, meta-analysis, occupational, risk

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/bjd.16147

This article is protected by copyright. All rights reserved.

Acknowledgement: Samine M. D. Ruff, Kristiane A. Engebretsen and Jacob P. Thyssen were financially supported by an unrestricted research grant from the Lundbeck Foundation. The funding source played no role in the aim, design, analysis or writing of the manuscript.

Conflicts of interest: The authors have no conflict of interest to declare

Prior presentation: The content has not been published previously and is not otherwise submitted for publication

Correspondence:

Jacob P. Thyssen, MD, PhD, DMSc

Department of Dermatology and Allergy,

Herlev and Gentofte Hospital,

Kildegaardsvej 28, DK-2900 Hellerup, Denmark

Phone: +45 38673150

E-mail: jacob.p.thyssen@regionh.dk

What is already known about this topic?

- Atopic dermatitis (AD) and hand eczema (HE) are common chronic and relapsing inflammatory pruritic skin conditions.
- While AD and HE often co-occur, the exact association estimate is unknown.

What does this study add?

- AD patients have a 3-4 fold increased prevalence of HE when compared to controls.
- Clinicians should continue to guide patients with AD away from occupations with high risk of HE.

Abstract

Atopic dermatitis (AD) and hand eczema (HE) are common chronic and relapsing inflammatory skin conditions that often co-occur. While several studies have addressed their relationship, the exact association estimate is unknown. We systematically reviewed published literature on the association between AD and HE in PubMed, Embase, and Web of Science using the following search terms; (atopic dermatitis OR atopic eczema) AND (hand dermatitis OR hand eczema). Meta-analyses were then performed to examine the association between AD and the point-, one-year- and lifetime prevalence of HE, respectively. We identified 35 relevant studies, of which 26 were included in the meta-analyses. AD was associated with an increased prevalence of HE with regards to point- (odds ratio (OR) 2.35; 95% CI: 1.47-3.76), one-year- (OR 4.29; 95% CI: 3.13-5.88), and lifetime prevalence (OR 4.06; 95% CI: 2.72-6.06). Furthermore, positive associations between AD and occupational HE were identified when assessing the one-year- 4.31 (95% CI: 2.08-8.91) and lifetime prevalence (OR 2.81; 95% CI: 2.08-3.79). Similar positive associations were found in the general population studies, i.e. OR 4.19 (95% CI: 3.46-5.08) and OR 5.69 (95% CI: 4.41-7.36). Important study limitations include the wide use of questionnaire studies, and lack of prospective studies as well as poor clinical phenotype descriptions. In conclusion, our systematic review and meta-analysis showed that patients with AD had a strongly increased prevalence of HE. Clinicians should continue to guide patients with AD away from occupations with high risk of HE.

Introduction

Atopic dermatitis (AD) is a common chronic and relapsing inflammatory pruritic skin condition that affects typical anatomical sites.¹ While most children and adults experience flexural involvement, some adult patients display particular involvement of the face, hands and feet.² The etiopathogenesis of AD is complex, but key elements include primary or secondary skin barrier impairment and a T helper (Th) cell 2 deviated immune response, caused by a cocktail of genetic risk factors, environmental exposures and skin stressors.¹

Hand eczema (HE) occurs over a lifetime in up to 20% of adults from Northern Europe, and 10% report symptoms within the past 12 months.³ HE classification systems have been proposed comprising both morphological and etiological factors.⁴ Similar to AD, the etiopathogenesis of HE is complex, and while both genetic and environmental factors play a role, pivotal risk factors include female gender, a history of AD, contact allergy, as well as domestic and occupational irritant exposures.^{3,5-8}

While several studies have shown that AD increases the risk of HE, the exact risk estimate is unknown.⁹⁻¹⁴ However, it is important to establish the magnitude of this relationship since HE is associated with disability pension and impaired quality of life.¹⁵ In this systematic review and meta-analysis, we reviewed published articles on the relationship between AD and HE to identify the strength of an association.

Materials and methods

We decided before study start to analyse AD as exposure and HE as outcome. We planned to perform stratified analysis based on gender, age, occupational relevance, study design/quality, and definition ('point', '1-year' and 'ever'). The study protocol was not registered online prior to the study.

Literature search

A systematic literature search was performed in PubMed, Embase and Web of Science in February 2016 where the following search terms were used; (atopic dermatitis OR atopic eczema) AND (hand dermatitis OR hand eczema). This provided a manageable amount of articles, but the search was limited to articles published after 1960 and only included articles written in English. Furthermore, articles were manually identified by searching the reference lists in selected publications. Post hoc, we contacted corresponding authors from studies where crude data were not available in their published articles to increase data inclusion.

Inclusion and exclusion criteria

We included all articles written in English and published after 1960, where at least 100 individuals were studied and data on the prevalence or numbers of HE in patients with AD and controls, respectively, were available. All types of HE irrespective of clinical subtype, aetiology or morphology were included. Cross-sectional data from prospective data were included in the data analysis, whereas follow-up data were excluded. Finally, we accepted terms such as ‘atopic eczema’, ‘childhood eczema’ and ‘flexural eczema’ as a proxy for AD, whereas studies using less specific terms such as ‘skin atopy’, or similar, were excluded.

Study selection

After the systematic search was conducted, duplicates were removed. Title and abstract review was performed independently by two authors (SR and KE). SR independently assessed the full text articles to identify the studies, which met the inclusion and exclusion criteria. Discrepancies were resolved by discussion. A third author (JT) was involved if there were problems with interpretation of the studies, or in case there were uncertainties regarding the inclusion or exclusion of studies.

Data extraction

Two authors, SR and KE, independently extracted information from each of the included studies. Due to differences in study designs, the prevalence of HE was divided into the following three categories; lifetime prevalence, 1-year prevalence, and point prevalence. We also performed separate meta-analyses for studies investigating the association between AD and occupational HE. Since the majority of the studies reporting the point prevalence of HE was performed in an occupational setting, we chose not to make a separate meta-analysis for the point prevalence of occupational HE. Furthermore, we performed meta-analyses on the association between AD and HE in the general population regarding the 1-year prevalence and lifetime prevalence.

For the meta-analyses, we only included studies that presented the total number of participants with AD (cases), AD and HE (positive cases), total number of participants without AD (controls) and HE

without AD (positive controls). Studies, that only provided an adjusted OR for the association between AD and HE, were excluded in the meta-analysis, but illustrated separately in supplementary tables. If the studies presented both the absolute number of cases and controls in addition to an adjusted OR, we used the absolute numbers. Finally, some studies had more than one assessment of HE (lifetime prevalence, 1-year prevalence or point prevalence) and accordingly occurred in several of the meta-analyses.^{16–19} For each meta-analysis, we also performed sensitivity analyses where the study with the largest sample size was excluded.

Qualitative synthesis

Qualitative synthesis for assessing the quality of non-randomized studies was performed by using the Newcastle-Ottawa scale (NOS).²⁰ The NOS consists of three categories: selection, comparability and outcome (case-control studies) or exposure (cohort studies). With regards to selection, there are four criteria and the maximum score is four stars. Comparability has only one criterion and the maximum score is two stars. For exposure/outcome there are three criteria and the maximum score is three stars. In total, the highest score possible is nine stars and the lowest score is zero stars. ‘Good quality’ was defined as seven stars or more, ‘fair quality’ four to six stars and ‘poor quality’ three stars or below. To investigate whether the quality of the studies influenced the outcome, we performed one meta-analysis where we only included the studies rated as ‘good quality’, and one where we included articles of ‘fair’ and ‘poor’ quality.

Statistical analysis

We calculated odds ratios (OR) with 95% confidence intervals (CIs) of HE in individuals with AD compared with controls subjects without AD, and the results were displayed graphically using forest plots. We assessed heterogeneity of the results by using the I^2 tests and Cochrane Q statistic p values. Due to significant between-study heterogeneity, random effects models with the DerSimonian and Laird method were used to estimate the pooled OR in all groups. We used funnel plots and standard errors to assess for possible publication bias. All statistical tests were 2-sided, with a significance

level of <0.05 , and analyses were performed using StatsDirect version 3.0.183 (StatsDirect Ltd., Cheshire, UK).

Results

A total of 2 273 articles were identified through our search strategy; 845 articles in PubMed, 483 articles in Embase and 945 articles in Web of Science (Fig. 1). Additionally, six articles were identified by searching the reference lists of selected publications. After removing duplicates, the title and abstract of 1 596 articles were screened, and 237 were considered eligible for full-text assessment. A total of 35 studies with 168 311 participants were included in the qualitative synthesis, and 26 studies with 90 336 participants in the quantitative synthesis. In our qualitative synthesis, two studies examined only children (<18 years), one from the birth cohort BAMSE²¹ and the other from the Odense Adolescence Cohort.¹² Furthermore, 28 studies investigated only adults^{6,9–11,13,14,16–19,22–39} and five studies investigated both children and adults.^{40–44} The studies were conducted between 1981 and 2014 and originated from 12 different countries. Four studies only studied female participants.^{16,30,31,37} In our quantitative analysis, we only identified two studies which diagnosed current AD by clinical examination,^{27,41} whereas 24 studies determined a diagnosis of AD at some point in life (AD ever), i.e. 21 by questionnaire, two by interview and one by screening medical records. Funnel plot analysis showed some evidence of publication bias, in particular regarding the point prevalence of HE (Fig. S5). Overall, I² values were high for analyses on HE (87–94.7) and occupational HE within past 12 months (95.9) (Table S4). Funnel plots and bias indicator statistics are available in the supplementary materials.

Hand eczema point prevalence

We identified seven studies reporting a point prevalence of HE in individuals with AD (Table S1). Of these, two studies based the HE diagnosis on questionnaire, and five on clinical examination. Furthermore, three studies diagnosed current AD by clinical examination, and four studies diagnosed AD by questionnaire 'AD ever'. Six studies presented sufficient data for inclusion in the meta-analysis and resulted in a combined OR of 2.35 (95% CI: 1.47–3.76) ($p=0.0003$) (Fig. 2). When we

did a sensitivity analysis, excluding the study with the largest sample size, a similar association was found (OR 2.79; 95% CI: 2.14-3.64) ($p<0.0001$). The study that was not included in the meta-analysis, due to lack of extractable data, showed that the OR between AD and HE was 2.47 (95% CI: 1.71-3.55) in fully adjusted analysis (Table S1).³⁴

Hand eczema 1- year prevalence

The 1-year prevalence of HE in individuals with AD was reported in 19 studies (Table S2). None of the studies reported current AD, but only a lifetime prevalence. Only 13 studies were eligible for inclusion in the meta-analysis resulting in a combined OR of 4.29 (95% CI: 3.13-5.88) ($p<0.0001$) (Fig. 3). A sensitivity analysis where the largest study was omitted gave a similar result (OR 4.39; 95% CI: 3.14-6.15) ($p<0.0001$). Six studies were not included in the meta-analysis as five of them only presented the adjusted OR,^{35,38,39,43,44} which ranged from 2.33 to 8.06, and one study only presented a prevalence ratio of 2.4 (95% CI: 2.0-2.9) (Table S2).³⁶

Hand eczema lifetime prevalence

The lifetime prevalence of HE in individuals with AD was reported in 14 studies (Table S3). Only 12 studies were eligible for inclusion in the meta-analysis, which resulted in a combined OR of 4.06 (95% CI: 2.72-6.06) ($p<0.0001$) (Fig. 4). A sensitivity analysis without the largest study showed a similar association (OR 3.89; 95% CI: 2.48-6.11) ($p<0.0001$). Two studies were excluded from the meta-analysis as they did not provide extractable data and only presented the adjusted OR, respectively, 5.61 (95% CI: 3.81-8.25),¹² and 6.81 (95% CI: 2.47-18.79) (Table S3).³⁷

Occupational hand eczema

We identified 17 studies, which presented data on the prevalence of occupational HE in individuals with and without AD (Table S1-S3). Of the 17 articles, 11 were conducted among health care workers. The 1-year prevalence of occupational HE was reported in 10 studies (Table S2). We only included six of these in the meta-analysis since no data could be extracted from 4 studies. However, these studies presented adjusted ORs which ranged from 2.33 to 8.06.^{35,36,38,39} The OR for the included 1-year prevalence studies was 4.31 (95% CI: 2.08-8.91) ($p<0.0001$) (Fig. S1). A sensitivity analysis

without the largest study showed a similar association (OR 3.30; 95% CI: 2.65-4.11) ($p<0.0001$). The lifetime prevalence of HE was reported by three studies and all were included in a meta-analysis (OR 2.81; 95% CI: 2.08-3.79) ($p<0.0001$) (Fig. S2).

Hand eczema in the general population

We identified 14 studies that reported the prevalence of HE in individuals with and without AD in the general population (Table S1-S3). Of these, nine studies presented data on the 1-year prevalence of HE and seven were included in the meta-analysis (OR 4.19; 95% CI: 3.46-5.08) ($p<0.0001$) (Fig. S3). A sensitivity analysis excluding the study with the largest study population showed similar results (OR 4.57; 95% CI: 3.96-5.26) ($p<0.0001$). Two studies with no extractable data showed adjusted ORs of, respectively, 4.5 (95% CI: 3.3-6.1),⁴³ and 3.85 (95% CI: 3.63-4.09).⁴⁴ The lifetime prevalence of HE was reported by eight studies, and seven were eligible for inclusion in the meta-analysis resulting in a combined OR of 5.69 (95% CI: 4.41-7.36) ($p<0.0001$) (Fig. S4). A sensitivity analysis showed similar results (OR 5.54; 95% CI: 3.88-7.90). One study only presented an adjusted OR of 5.61 (95% CI: 3.81-8.25).¹²

Sensitivity analysis based on study quality

By using the Newcastle-Ottawa scale, one study was given eight stars and nine studies were given seven stars, thus 10 articles were considered to be of 'good quality'. A total of 15 studies were given four to six stars and rated as being of 'fair quality'. Finally, one study was only given 3 stars and hence rated as being of 'poor quality' (Tables S1-3). We did two separate meta-analyses on the articles reporting lifetime-prevalence of HE. In the first meta-analysis, we included seven articles with ≥ 7 stars which resulted in an OR on 4.33 (95% CI: 2.99-6.27) ($p<0.0001$) (Fig. S5).^{10,13,16,24,25,33,42} In the other meta-analysis we included five articles with ≤ 6 stars which resulted in an OR of 3.68 (95% CI: 1.69-8.03) ($p=0.0011$) (Fig. S6).^{17-19,29,40} We performed sensitivity analyses omitting the largest study and found similar associations, i.e. OR 4.34 (95% CI: 2.64-7.14) ($p<0.0001$) and OR 3.20 (95% CI: 1.15-8.86) ($p=0.0253$).

Discussion

Main findings

This systematic review and meta-analysis showed that individuals with present or past AD had a strongly increased risk of having experienced HE. The association with AD was slightly weaker for point prevalence of HE compared to 1-year and lifetime prevalence of HE.

Interpretation

The observed strongly positive association between AD and HE reinforces the longstanding and well-established impression that patients with (a history of) AD have increased risk of developing HE.^{6,29}

In terms of hand eczema aetiology, three major common subtypes need to be considered, i.e. atopic, irritant and allergic, hence compromising the primary basis for the observed association in this meta-analysis.

Dermatitis on the hands can be a manifestation of AD, and it is therefore inherently problematic to associate the two disorders since they are part of the same syndrome. HE in AD patients is typically seen on the wrists and dorsal aspects.⁴⁵ Unfortunately, no studies provided any phenotype description, and it was therefore impossible to exclude HE as a part of AD in the analysis. Notably, both irritant and allergic contact dermatitis may also be present on the dorsal aspects of the hands, e.g. due to glove exposure, and result in chronic disease.

Experimental studies have convincingly shown that AD skin shows increased transepidermal water loss and has a higher penetration and absorption of irritants and allergens compared to healthy skin.^{46,47} Notably, the threshold level to the skin irritant sodium lauryl sulfate (SLS) is lower in patients with AD compared to healthy controls.⁴⁸ A recent study showed a more severe irritant-induced barrier impairment in AD patients when compared with healthy controls following exposure to SLS and sodium hydroxide (NaOH).⁴⁹ Along this line, increased susceptibility to skin irritants is observed not only in patients with a history of AD, but also in subjects with dry skin.⁵⁰ These

Accepted Article

observations are in line with epidemiological studies showing how individuals with AD, who work in occupations with a pronounced exposure to skin irritants, have an increased risk of HE.^{22,25,27}

The dysfunctional epidermal barrier in AD patients facilitates penetration of allergens through the skin, however, the exact relationship between allergic contact dermatitis and AD is controversial.^{51,52}

Hence, some, but not all, epidemiological and clinical studies have shown an increased prevalence and risk of contact allergy in individuals with AD,^{53–55} in particular to certain metals^{56–58} and ingredients found in topical products.^{59–63} While this increase could be explained by elevated exposure and concomitant enhanced penetration of allergens, experimental studies have instead shown that patients with AD in a dose-dependent manner have an increased threshold level regarding the ability to develop contact allergy.^{64,65} Based on these observations, it is difficult to estimate whether the burden of allergic contact dermatitis on the hands is differential in patients with and without AD, and hence how this could affect the observed association between AD and HE found in this study. However, interestingly in two of four studies that showed no association between AD and HE, the study design was based on patch test populations, potentially indicating that AD may be a weaker determinant for HE in case of contact allergy.^{26,28,40,42}

Due to the impaired skin barrier function, reduced inflammatory threshold, and hence increased risk of developing HE, physicians have advocated that individuals with AD should steer away from professions that include wet work and prolonged exposure to irritants and allergens. Recent studies suggest that this type of career guidance indeed have had a behavioural effect. In a recent Danish prospective cohort study, a significantly lower prevalence of AD was observed in a group of hairdressing apprentices (21.4%) compared with controls (29.8%) ($p=0.001$).⁶⁶ The same pattern was found in a Danish retrospective clinical study including 1,471 blue collar workers and 1,471 matches controls.⁶⁷ Interestingly, a Danish cross-sectional study showed that adults with filaggrin gene mutations and HE onset before 15 years of age significantly avoided occupations with irritant exposure in adulthood.⁶⁸

Limitations

A high number of studies from a wide range of countries were included, although only few non-European studies, and none from South America, Australia and Africa were available, hence making our results less generalizable. Moreover, the results may have been biased by a shortage of literature in other languages than English. Another study limitation include the different methods to diagnose both AD and HE (questionnaire vs. clinical observation), which potentially may have resulted in misclassification.

The lifetime and 12-month prevalence of HE was only assessed through questionnaires since no prospective clinical studies have been conducted with close follow-up. Interestingly, some Swedish studies have shown that the self-reported 12-month prevalence of HE tend to underestimate the true prevalence of HE,^{69,70} whereas another Swedish study examining 105 patients with self-reported HE showed that 19% in fact did not have HE.²⁸ Importantly, questions in questionnaires can be misleading and result in misclassification. For example, one study in our meta-analysis used the question “have you or have you had exanthema on hands and/or forearms?”, where exanthema represents a wide range of rashes and not just hand eczema.²⁴ Similar for AD, most studies based the diagnosis on questionnaire information, hence providing information about the lifetime prevalence of AD (AD ever) and not current AD. Importantly, five of 26 studies used the validated UK criteria to diagnose AD; criteria that holds both high sensitivity and specificity.⁷¹ Despite variations in study quality, the quality assessment by applying the Newcastle-Ottawa scale showed that studies overall had high quality, and no difference in effect estimate was found in sub analysis. Another important limitation was that most of the studies included in this systematic review, did not describe the morphological patterns of HE or etiological subtype. HE is indeed a very broad and general term and should be subtyped in clinical practice and for research purposes. However, previous studies found that morphological subtypes cannot distinguish between different aetiologies of HE.⁷² The study design did not allow us to establish cause and effect, but normally AD precedes HE, and therefore the association between HE and AD is suspected to indicate the risk of HE in patients with AD.

Conclusion

In conclusion, AD was significantly associated with an increased prevalence of HE when measuring point-, one-year- and lifetime prevalence. This also applied when making sub-analysis on occupational HE. Future studies should determine the association between AD and different types of HE.

References

- 1 Weidinger S, Novak N. Atopic dermatitis. *Lancet* 2016; **387**:1109–22.
- 2 Heede NG, Thyssen JP, Thuesen BH, *et al.* Anatomical patterns of dermatitis in adult filaggrin mutation carriers. *J Am Acad Dermatol* 2015; **72**:440–8.
- 3 Thyssen JP, Johansen JD, Linneberg A, Menné T. The epidemiology of hand eczema in the general population - prevalence and main findings. *Contact Dermatitis* 2010; **62**:75–87.
- 4 Diepgen TL, Andersen KE, Brandao FM, *et al.* Hand eczema classification: a cross-sectional, multicentre study of the aetiology and morphology of hand eczema. *Br J Dermatol* 2009; **160**:353–8.
- 5 Mahler V. Hand dermatitis - differential diagnoses, diagnostics, and treatment options. *JDDG J der Dtsch Dermatologischen Gesellschaft* 2016; **14**:7–22.
- 6 Meding B, Swanbeck G. Predictive factors for hand eczema. *Contact Dermatitis* 1990; **23**:154–61.
- 7 Nicholson PJ, Llewellyn D, English JS. Evidence-based guidelines for the prevention, identification and management of occupational contact dermatitis and urticaria. *Contact Dermatitis* 2010; **63**:177–86.
- 8 Rystedt I. Factors influencing the occurrence of hand eczema in adults with a history of atopic dermatitis in childhood. *Contact Dermatitis* 1985; **12**:185–91.
- 9 Ibler KS, Jemec GBE, Flyvholm M-A, *et al.* Hand eczema: prevalence and risk factors of hand eczema in a population of 2274 healthcare workers. *Contact Dermatitis* 2012; **67**:200–7.
- 10 Bryld LE, Hindsberger C, Kyvik KO, *et al.* Risk factors influencing the development of hand

- Accepted Article
- eczema in a population-based twin sample. *Br J Dermatol* 2003; **149**:1214–20.
- 11 Meding B, Järholm B. Hand Eczema in Swedish Adults – Changes in Prevalence between 1983 and 1996. *J Invest Dermatol* 2002; **118**:719–23.
- 12 Mortz CG, Lauritsen JM, Bindslev-Jensen C, Andersen KE. Prevalence of atopic dermatitis, asthma, allergic rhinitis, and hand and contact dermatitis in adolescents. The Odense Adolescence Cohort Study on Atopic Diseases and Dermatitis. *Br J Dermatol* 2001; **144**:523–32.
- 13 Thyssen JP, Johansen J, Zachariae C, *et al.* Xerosis is Associated with Atopic Dermatitis, Hand Eczema and Contact Sensitization Independent of Filaggrin Gene Mutations. *Acta Derm Venereol* 2013; **93**:406–10.
- 14 Bingefors K, Svensson Å, Isacson D, Lindberg M. Self-reported Lifetime Prevalence of Atopic Dermatitis and Co-morbidity with Asthma and Eczema in Adulthood: A Population-based Cross-sectional Survey. *Acta Derm Venereol* 2013; **93**:438–41.
- 15 Heede NG, Thuesen BH, Thyssen JP, *et al.* Hand eczema, atopic dermatitis and filaggrin mutations in adult Danes: a registry-based study assessing risk of disability pension. *Contact Dermatitis* 2017; **77**:95–105.
- 16 Josefson A, Färm G, Magnuson A, Meding B. Nickel allergy as risk factor for hand eczema: a population-based study. *Br J Dermatol* 2009; **160**:828–34.
- 17 Visser MJ, Verberk MM, Campbell LE, *et al.* Filaggrin loss-of-function mutations and atopic dermatitis as risk factors for hand eczema in apprentice nurses: part II of a prospective cohort study. *Contact Dermatitis* 2014; **70**:139–50.
- 18 Meding B, Liden C, Berglind N. Self-diagnosed dermatitis in adults . Results from a population survey in Stockholm. *Contact Dermatitis* 2001; **45**:341–5.
- 19 Nyrén M, Lindberg M, Stenberg B, *et al.* Influence of childhood atopic dermatitis on future worklife. *Scand J Work Env Heal* 2005; **31**:474–8.
- 20 Ottawa Hospital Research Institute [WWW Document]. URL http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp [accessed on 15 August 2017].
- 21 Grönhagen C, Lidén C, Wahlgren C-F, *et al.* Hand eczema and atopic dermatitis in

- adolescents: a prospective cohort study from the BAMSE project. *Br J Dermatol* 2015; **173**:1175–82.
- 22 Dulon M, Kromark K, Skudlik C, Nienhaus A. Prevalence of skin and back diseases in geriatric care nurses. *Int Arch Occup Env Heal* 2008; **81**:983–92.
- 23 Flyvholm M-A, Bach B, Rose M, Jepsen KF. Self-reported hand eczema in a hospital population. *Contact Dermatitis* 2007; **57**:110–5.
- 24 Holm JO, Veierød MB. An epidemiological study of hand eczema. III. Characterization of hairdressers with and without hand eczema, regarding demographic factors and medical histories. *Acta Derm Venereol Suppl (Stockh)* 1994; **187**:15–7.
- 25 Lammintausta K, Kalimo K. Atopy and hand dermatitis in hospital wet work. *Contact Dermatitis* 1981; **7**:301–8.
- 26 Lampel HP, Patel N, Boyse K, *et al.* Prevalence of Hand Dermatitis in Inpatient Nurses at a United States Hospital. *Dermatitis* 2007; **18**:140–2.
- 27 Lan C-CE, Tu H-P, Lee C-H, *et al.* Hand dermatitis among university hospital nursing staff with or without atopic eczema: assessment of risk factors. *Contact Dermatitis* 2011; **64**:73–9.
- 28 Meding B, Barregård L, Marcus K. Hand eczema in car mechanics. *Contact Dermatitis* 1994; **30**:129–34.
- 29 Rystedt I, Rystedt I. Work-related hand eczema in atopics. *Contact Dermatitis* 1985; **12**:164–71.
- 30 Smith DR, Leggat PA. Hand dermatitis among female nursing students in tropical Australia. *Nurs Heal Sci* 2004; **6**:109–13.
- 31 Smith DR, Wei N, Zhao L, Wang R-S. Hand dermatitis among nurses in a newly developing region of Mainland China. *Int J Nurs Stud* 2005; **42**:13–9.
- 32 Susitaival P, Husmant L, Horsmanheimo M, *et al.* Prevalence of hand dermatoses among Finnish farmers. *Scand J Work Env Heal* 1994; **20**:206–12.
- 33 Visser MJ, Landeck L, Campbell LE, *et al.* Impact of atopic dermatitis and loss-of-function mutations in the filaggrin gene on the development of occupational irritant contact dermatitis. *Br J Dermatol* 2013; **168**:326–32.

- 34 Apfelbacher CJ, Funke U, Radulescu M, Diepgen TL. Determinants of current hand eczema: results from case-control studies nested in the PACO follow-up study (PACO II). *Contact Dermatitis* 2010; **62**:363–70.
- 35 Lee SW, Cheong SH, Byun JY, *et al.* Occupational hand eczema among nursing staffs in Korea: Self-reported hand eczema and contact sensitization of hospital nursing staffs. *J Dermatol* 2013; **40**:182–7.
- 36 Ortengren U, Andreasson H, Karlsson S, *et al.* Prevalence of self-reported hand eczema and skin symptoms associated with dental materials among Swedish dentists. *Eur J Oral Sci* 1999; **107**:496–505.
- 37 Nilsson EJ, Knutsson A. Atopic dermatitis, nickel sensitivity and xerosis as risk factors for hand eczema in women. *Contact Dermatitis* 1995; **33**:401–6.
- 38 Smith DR, Adachi Y, Mihashi M, *et al.* Hand dermatitis risk factors among clinical nurses in Japan. *Clin Nurs Res* 2006; **15**:197–208.
- 39 Crawford GH, Katz KA, Ellis E, James WD. Use of Aromatherapy Products and Increased Risk of Hand Dermatitis in Massage Therapists. *Arch Dermatol* 2004; **140**:991–6.
- 40 Carlsen BC, Andersen KE, Menné T, Johansen JD. Sites of dermatitis in a patch test population: hand dermatitis is associated with polysensitization. *Br J Dermatol* 2009; **161**:808–13.
- 41 Heine G, Schnuch A, Uter W, Worm M. Type-IV sensitization profile of individuals with atopic eczema: results from the Information Network of Departments of Dermatology (IVDK) and the German Contact Dermatitis Research Group (DKG). *Allergy* 2006; **61**:611–6.
- 42 Nielsen NH, Linneberg A, Menne T, *et al.* The association between contact allergy and hand eczema in 2 cross-sectional surveys 8 years apart. The Copenhagen Allergy Study. *Contact Dermatitis* 2002; **47**:71–7.
- 43 Röhl K, Stenberg B. Lifestyle factors and hand eczema in a Swedish adolescent population. *Contact Dermatitis* 2010; **62**:170–6.
- 44 Stenberg B, Meding B, Svensson Å. Dermatology in public health--a model for surveillance of common skin diseases. *Scand J Public Health* 2010; **38**:368–74.

- 45 Simpson EL, Thompson MM, Hanifin JM. Prevalence and Morphology of Hand Eczema in
Patients with Atopic Dermatitis. *Dermatitis* 2006; **17**:123–7.
- 46 Cork MJ, Danby SG, Vasilopoulos Y, *et al.* Epidermal barrier dysfunction in atopic dermatitis.
J Invest Dermatol 2009; **129**:1892–908.
- 47 Coenraads P-J. Hand Eczema. *N Engl J Med* 2012; **19367**:1829–37.
- 48 Agner T. Noninvasive measuring methods for the investigation of irritant patch test reactions.
A study of patients with hand eczema, atopic dermatitis and controls. *Acta Derm Venereol
Suppl (Stockh)* 1992; **173**:1–26.
- 49 Angelova-Fischer I, Dapic I, Hoek A, *et al.* Skin Barrier Integrity and Natural Moisturising
Factor Levels After Cumulative Dermal Exposure to Alkaline Agents in Atopic Dermatitis.
Acta Derm Venereol 2014; **94**:640–4.
- 50 Tupker RA, Pinnagoda J, Coenraads PJ, Nater JP. Susceptibility to irritants: role of barrier
function, skin dryness and history of atopic dermatitis. *Br J Dermatol* 1990; **123**:199–205.
- 51 Diepgen TL, Ofenloch RF, Bruze M, *et al.* Prevalence of contact allergy in the general
population in different European regions. *Br J Dermatol* 2016; **174**:319–29.
- 52 Thyssen JP, McFadden JP, Kimber I. The multiple factors affecting the association between
atopic dermatitis and contact sensitization. *Allergy* 2014; **69**:28–36.
- 53 Cronin E, McFadden JP. Patients with atopic eczema do become sensitized to contact
allergens. *Contact Dermatitis* 1993; **28**:225–8.
- 54 Dotterud L, Smith-Sivertsen T. Allergic contact sensitization in the general adult population: a
population-based study from Northern Norway. *Contact Dermatitis* 2007; **56**:10–5.
- 55 Dotterud L, Falk E. Contact allergy in relation to hand eczema and atopic diseases in north
Norwegian schoolchildren. *Acta Paediatr* 1995; **84**:402–6.
- 56 Dotterud L, Falk E. Metal allergy in north Norwegian schoolchildren and its relationship with
ear piercing and atopy. *Contact Dermatitis* 1994; **31**:308–13.
- 57 Malajian D, Belsito D V, York N. Cutaneous delayed-type hypersensitivity in patients with
atopic dermatitis. *J Am Dermatology* 2013; **69**:232–7.
- 58 Mortz CG, Bindslev-Jensen C, Andersen KE. Nickel allergy from adolescence to adulthood in

- the TOACS cohort. *Contact Dermatitis* 2013; **68**:348–56.
- 59 Thyssen JP, Johansen JD, Linneberg A, *et al.* The association between null mutations in the filaggrin gene and contact sensitization to nickel and other chemicals in the general population. *Br J Dermatol* 2010; **162**:1278–85.
- 60 Shaughnessy CN, Malajian D, Belsito D V. Cutaneous delayed-type hypersensitivity in patients with atopic dermatitis: Reactivity to topical preservatives. *J Am Dermatology* 2014; **70**:102–7.
- 61 Vind-Kezunovic D, Johansen JD, Carlsen BC. Prevalence of and factors influencing sensitization to corticosteroids in a Danish patch test population. *Contact Dermatitis* 2011; **64**:325–9.
- 62 Rystedt I. Contact sensitivity in adults with atopic dermatitis in childhood. *Contact Dermatitis* 1985; **13**:1–8.
- 63 Herro EM, Matiz C, Sullivan K, *et al.* Frequency of contact allergens in pediatric patients with atopic dermatitis. *J Clin Aesthet Dermatol* 2011; **4**:39–41.
- 64 Jones HE, Lewis CW, McMarlin SL. Allergic contact sensitivity in atopic dermatitis. *Arch Dermatol* 1973; **107**:217–22.
- 65 Forsbeck M, Hovmark A, Skog E. Patch testing, tuberculin testing and sensitization with dinitrochlorobenzene and nitrosodimethylanilini of patients with atopic dermatitis. *Acta Derm Venereol* 1976; **56**:135–8.
- 66 Bregnhøj A, Søsted H, Menné T, Johansen JD. Healthy worker effect in hairdressing apprentices. *Contact Dermatitis* 2011; **64**:80–4.
- 67 Schwensen JF, Menné T, Veien NK, *et al.* Occupational contact dermatitis in blue-collar workers: results from a multicentre study from the Danish Contact Dermatitis Group (2003–2012). *Contact Dermatitis* 2014; **71**:348–55.
- 68 Bandier J, Ross-Hansen K, Carlsen BC, *et al.* Carriers of filaggrin gene (FLG) mutations avoid professional exposure to irritants in adulthood. *Contact Dermatitis* 2013; **69**:355–62.
- 69 Meding B, Barregård L. Validity of self-reports of hand eczema. *Contact Dermatitis* 2001; **45**:99–103.

- 70 Svensson Å, Lindberg M, Meding B, *et al.* Self-reported hand eczema: symptom-based reports do not increase the validity of diagnosis. *Br J Dermatol* 2002; **147**:281–4.
- 71 Williams HC, Jburney PG, Pembroke AC, Hay RJ. The U.K. Working Party's Diagnostic Criteria for Atopic Dermatitis. III. Independent hospital validation. *Br J Dermatol* 1994; **131**:406–16.
- 72 Agner T, Aalto-Korte K, Andersen KE, *et al.* Classification of hand eczema. doi:10.1111/jdv.13308.

Figure legends

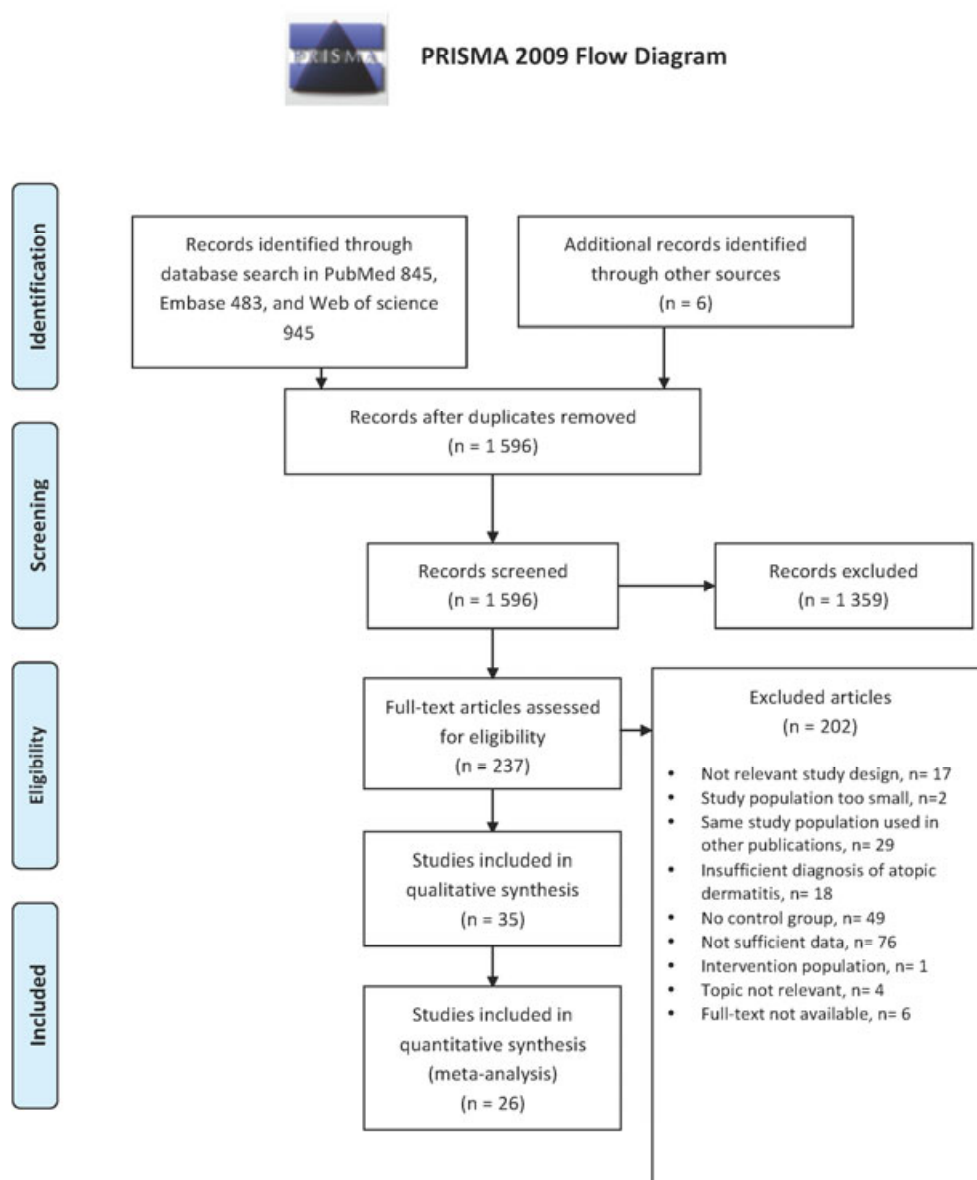
Figure 1. Flow diagram

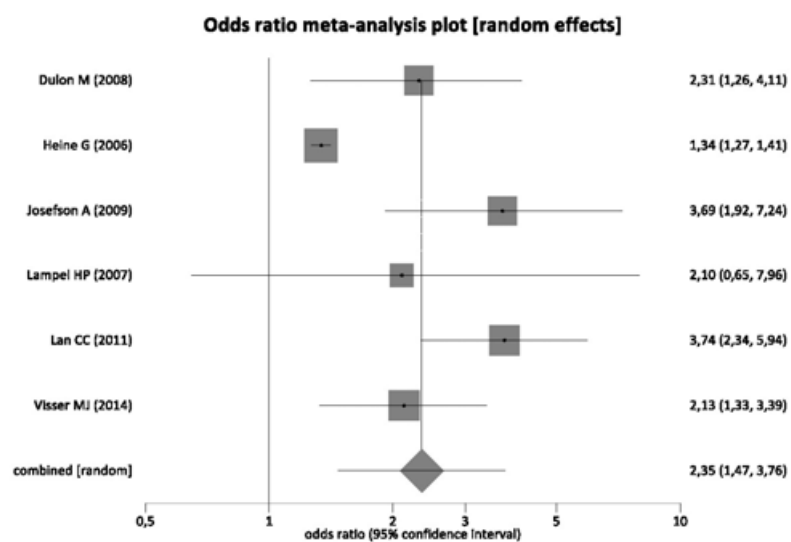
Figure 2. Forest plot of the association between current hand eczema and atopic dermatitis

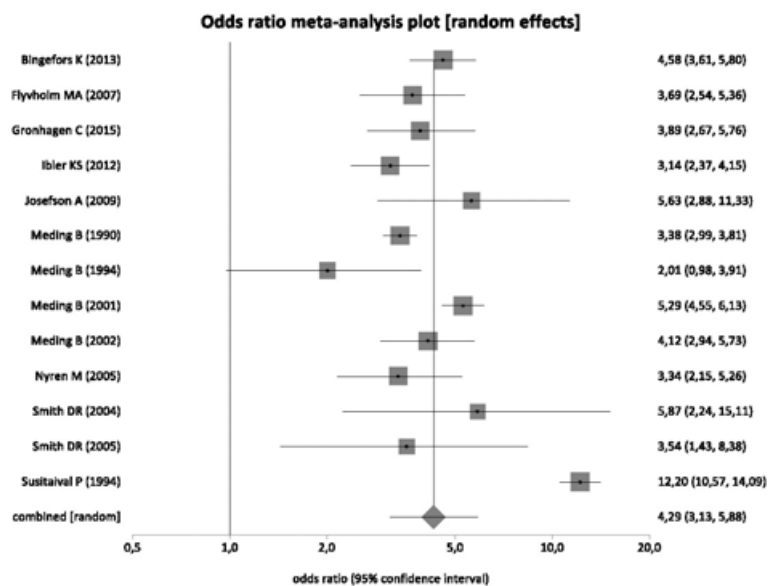
Figure 3. Forest plot of the association between hand eczema within past 1 year and atopic dermatitis

Figure 4. Forest plot of the association between a lifetime history of hand eczema and atopic dermatitis

Figure 1







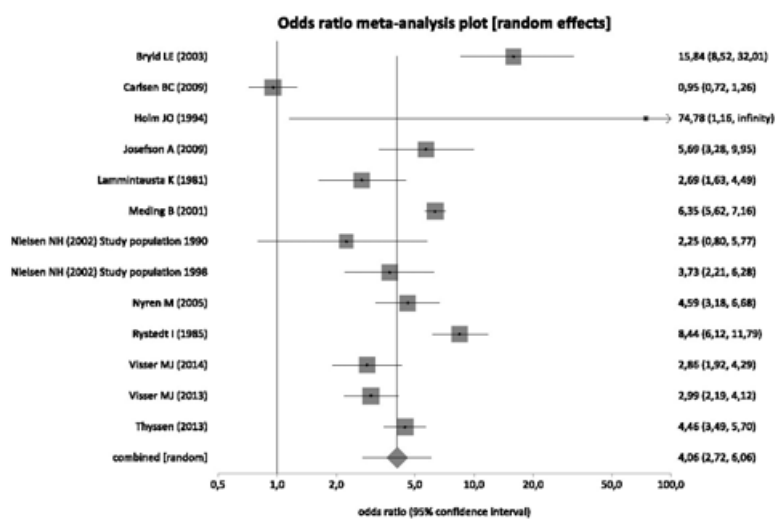


Figure S1. Forest plot of the association between 1-year prevalence of occupational hand eczema (HE) and atopic dermatitis (AD)

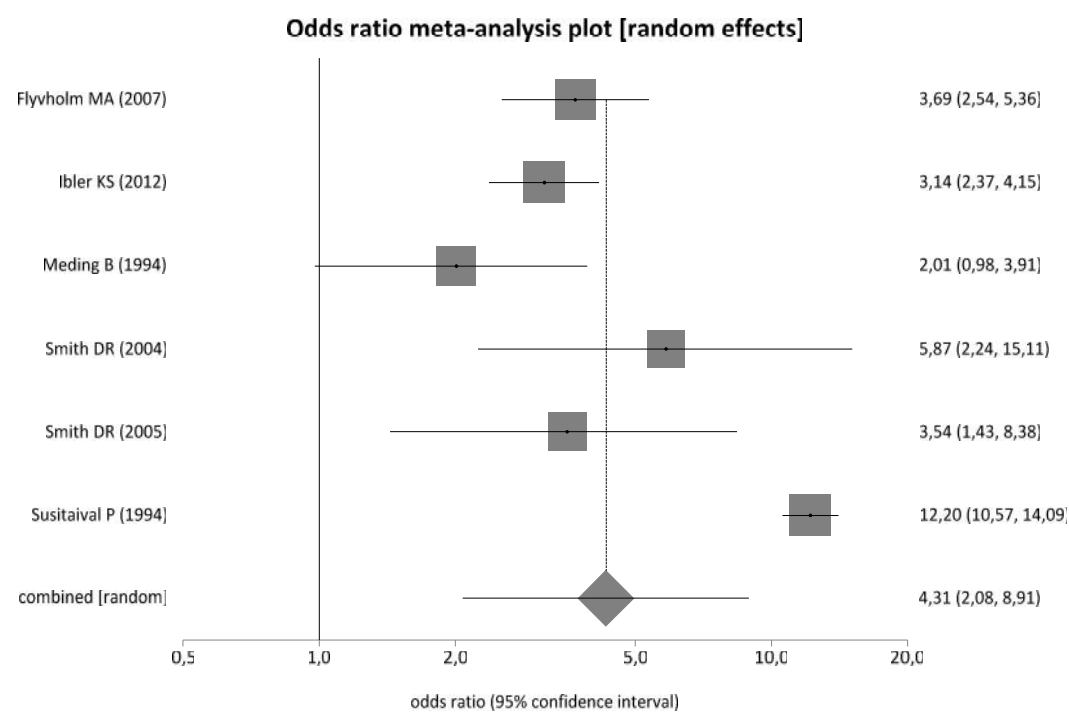


Figure S2. Forest plot of the association between lifetime prevalence of occupational HE and AD

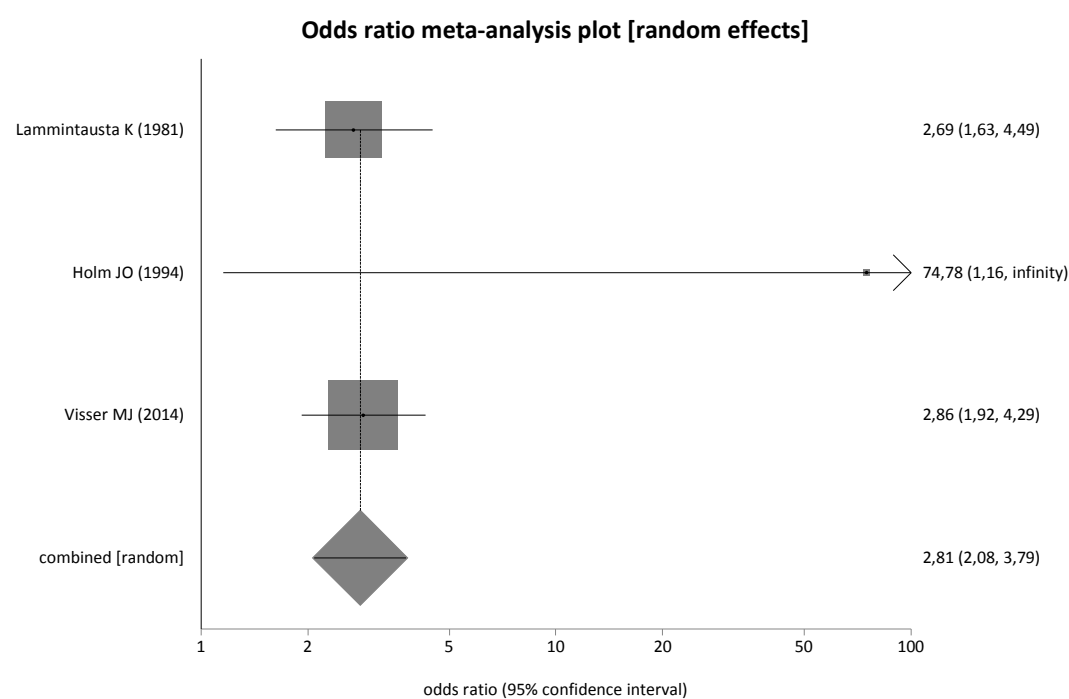


Figure S3. Forest plot of the association between 1-year prevalence of HE and AD in the general population

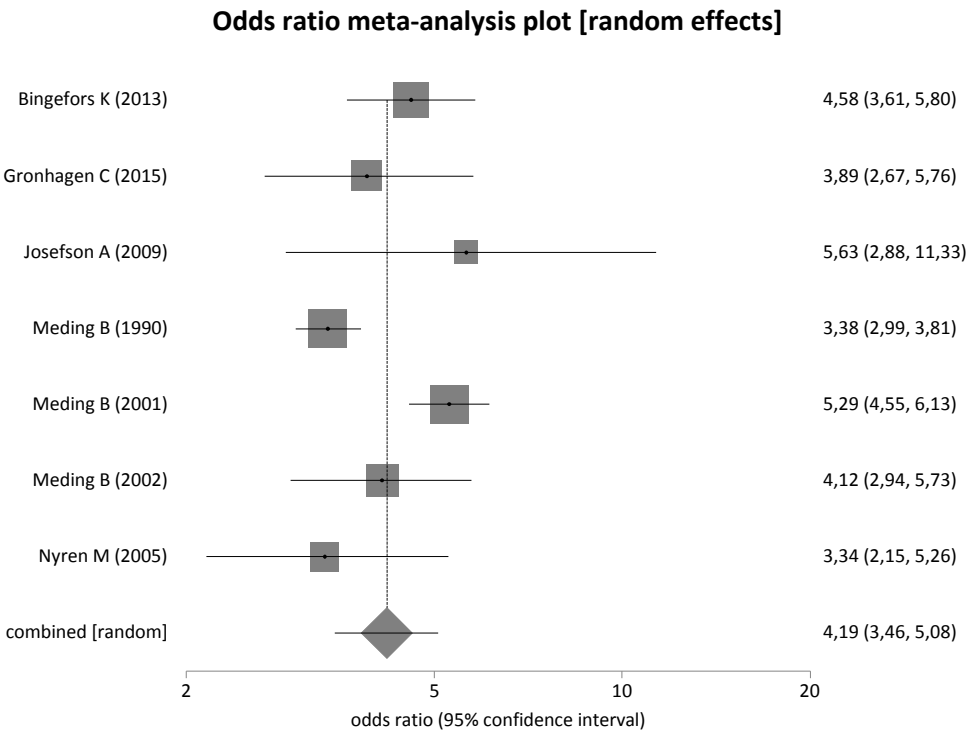


Figure S4. Forest plot of the association between lifetime prevalence of HE and AD in the general population

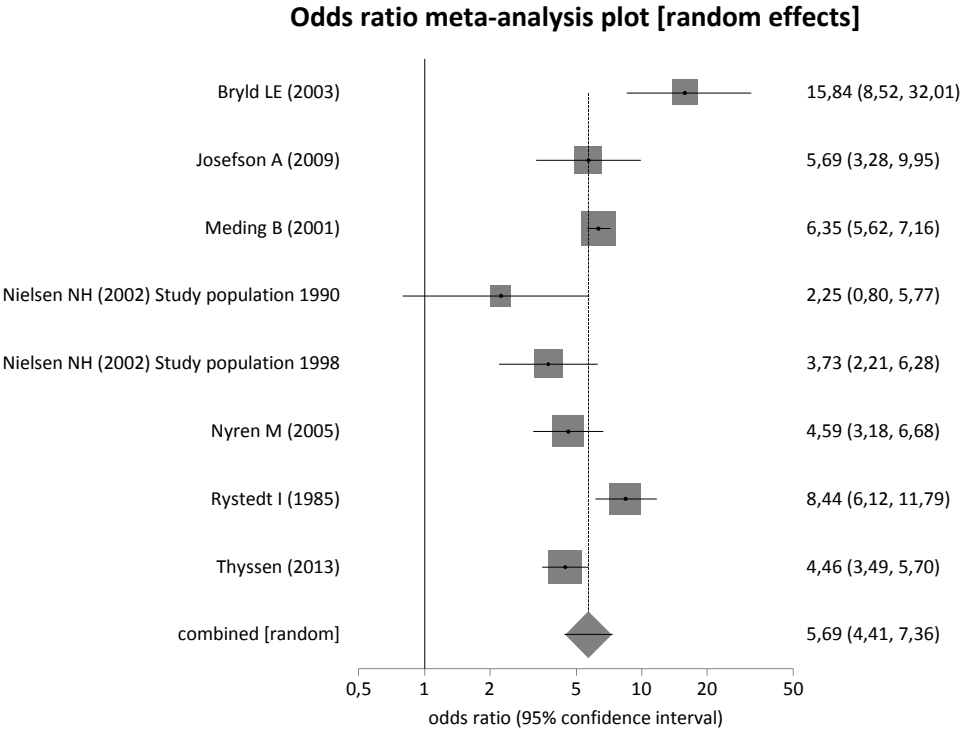


Figure S5. Forest plot of the studies rated as being of good quality

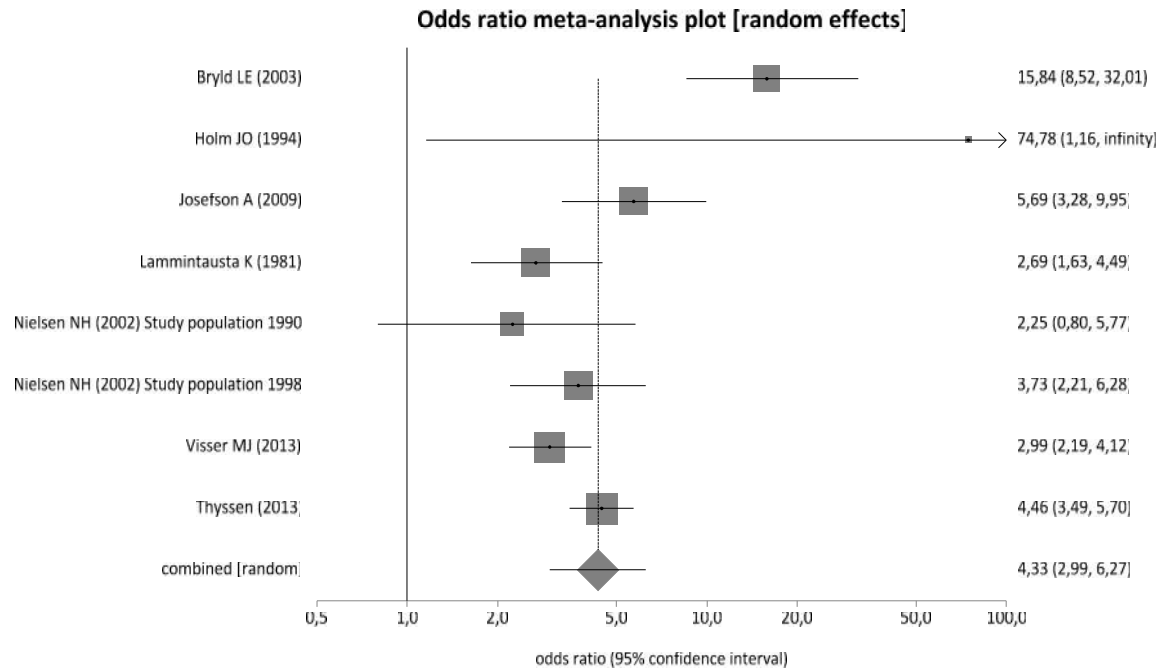


Figure S6. Forest plot of the studies rated as being of poor and fair quality

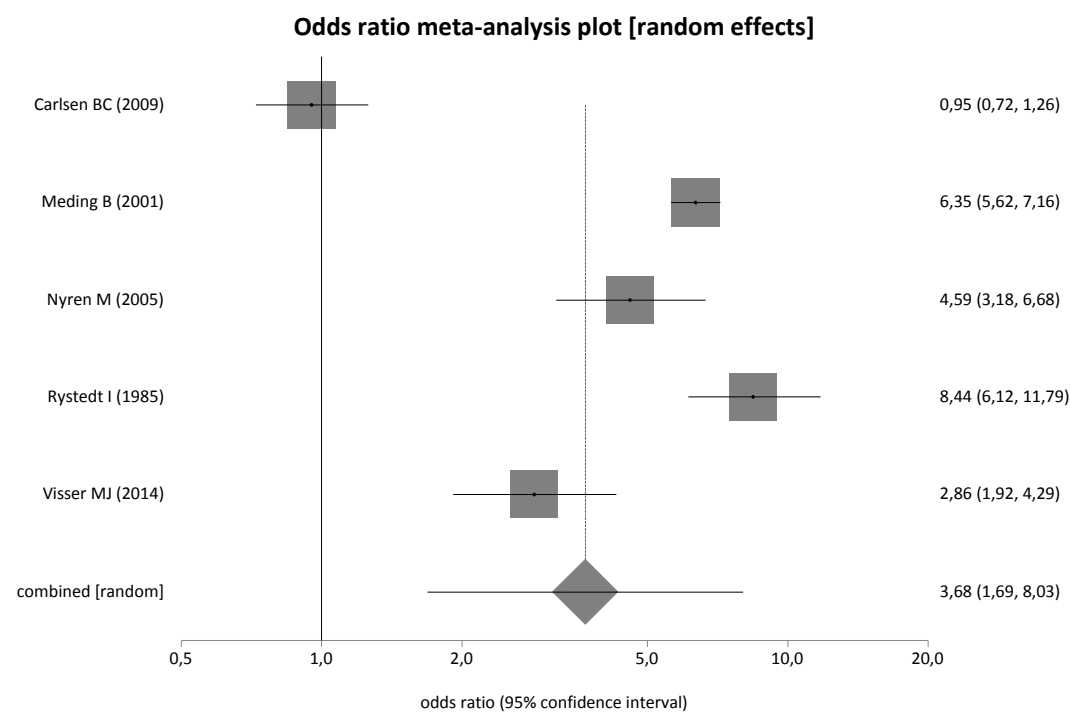


Figure S7. Funnel plot of the point prevalence of HE

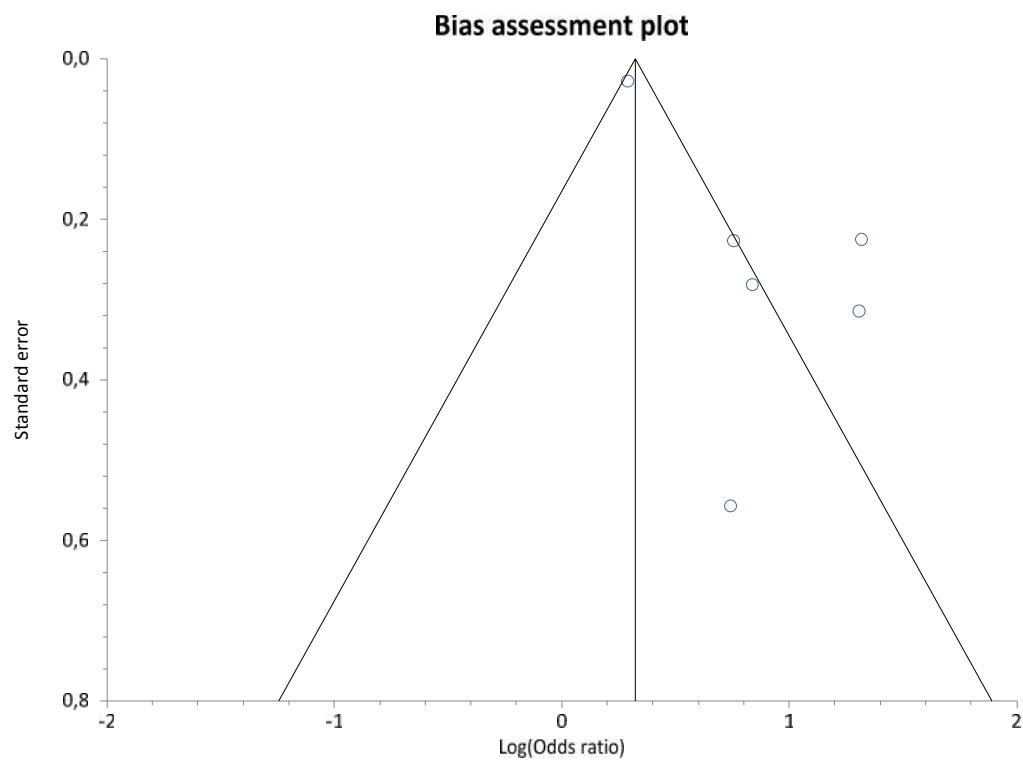


Figure S8. Funnel plot of the 1-year prevalence of HE

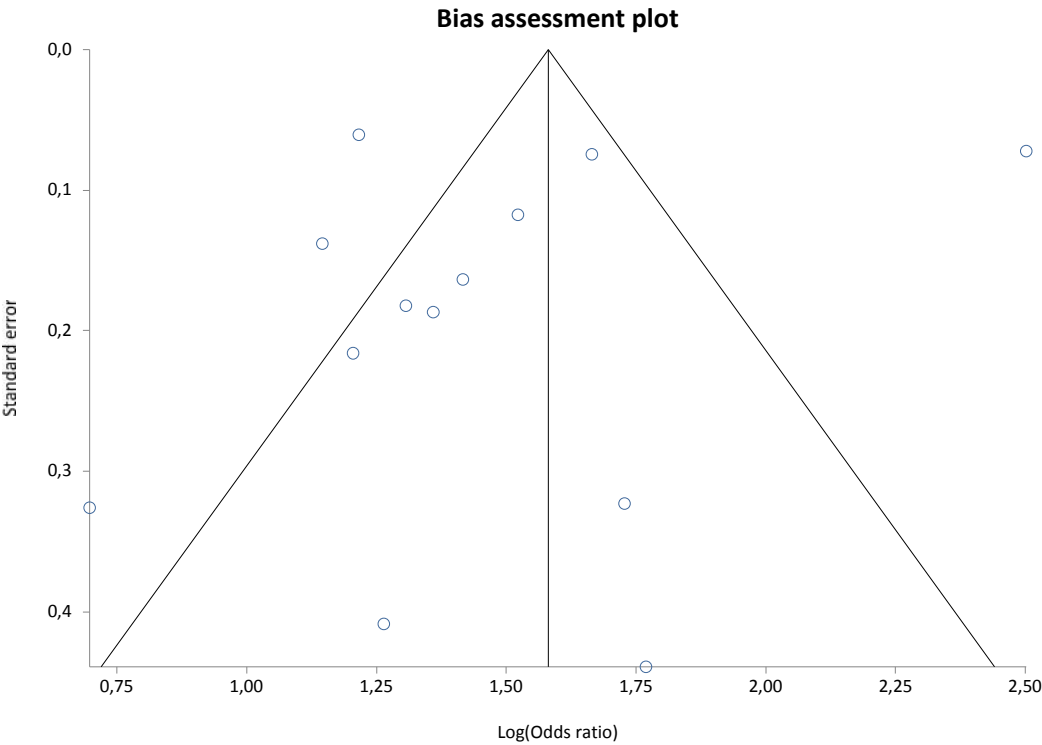


Figure S9. Funnel plot of the lifetime prevalence of HE

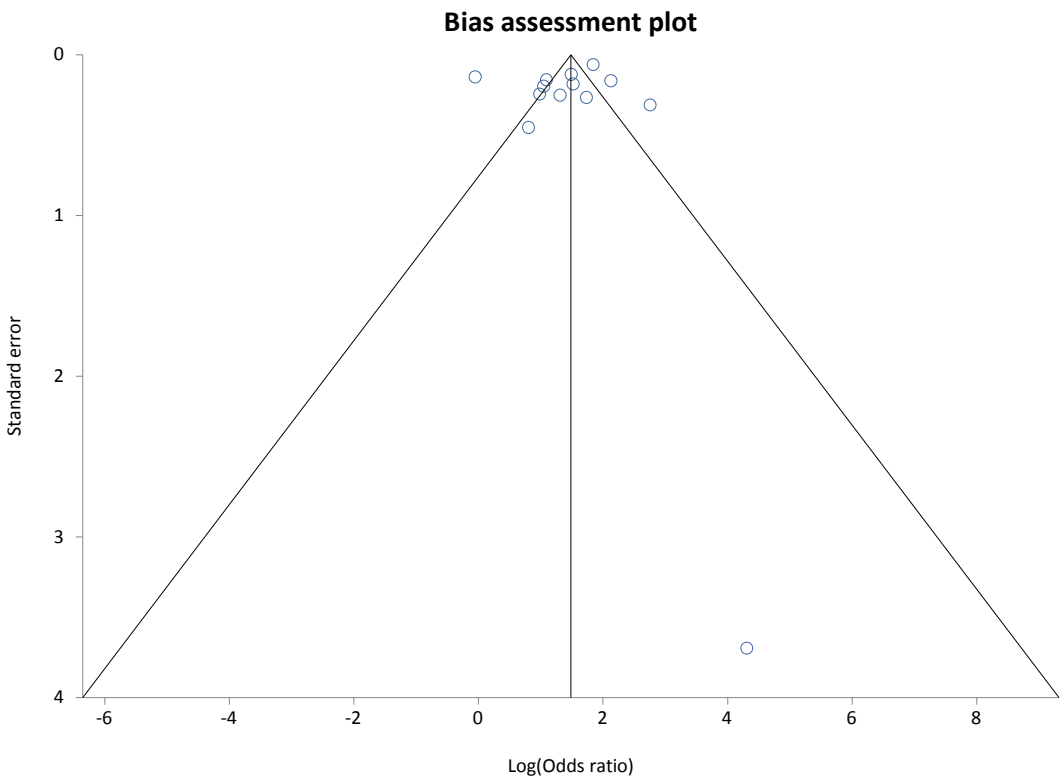


Figure S10. Funnel plot of the 1-year prevalence of occupational HE

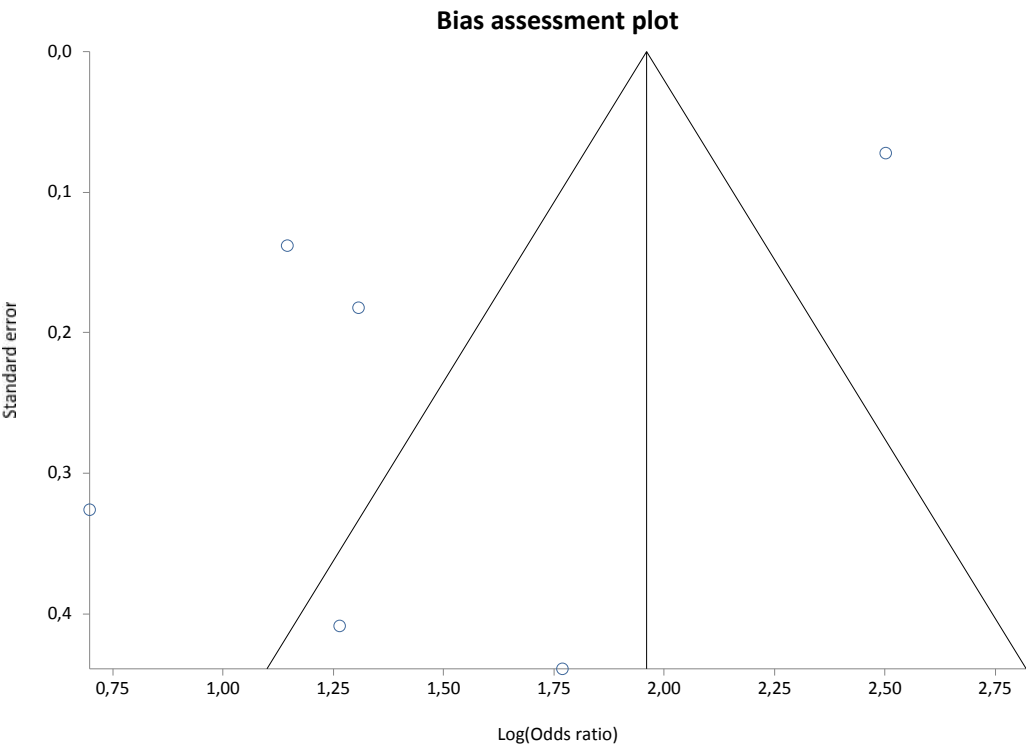


Figure S11. Funnel plot of the 1-year prevalence of HE in the general population

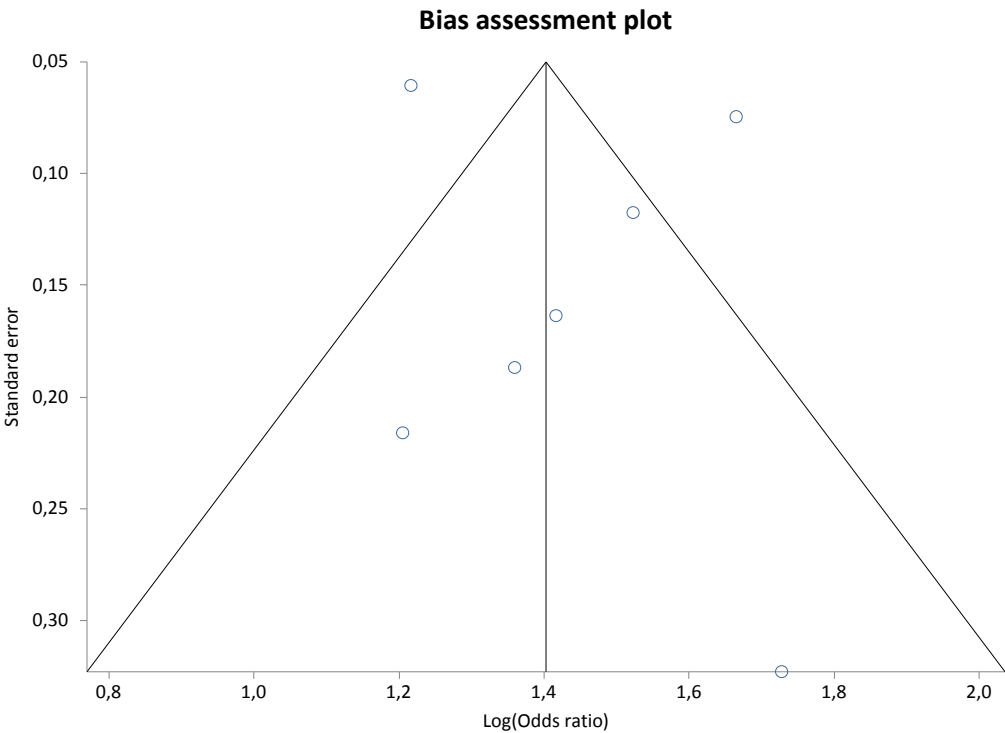


Figure S12. Funnel plot of the lifetime prevalence of HE in the general population

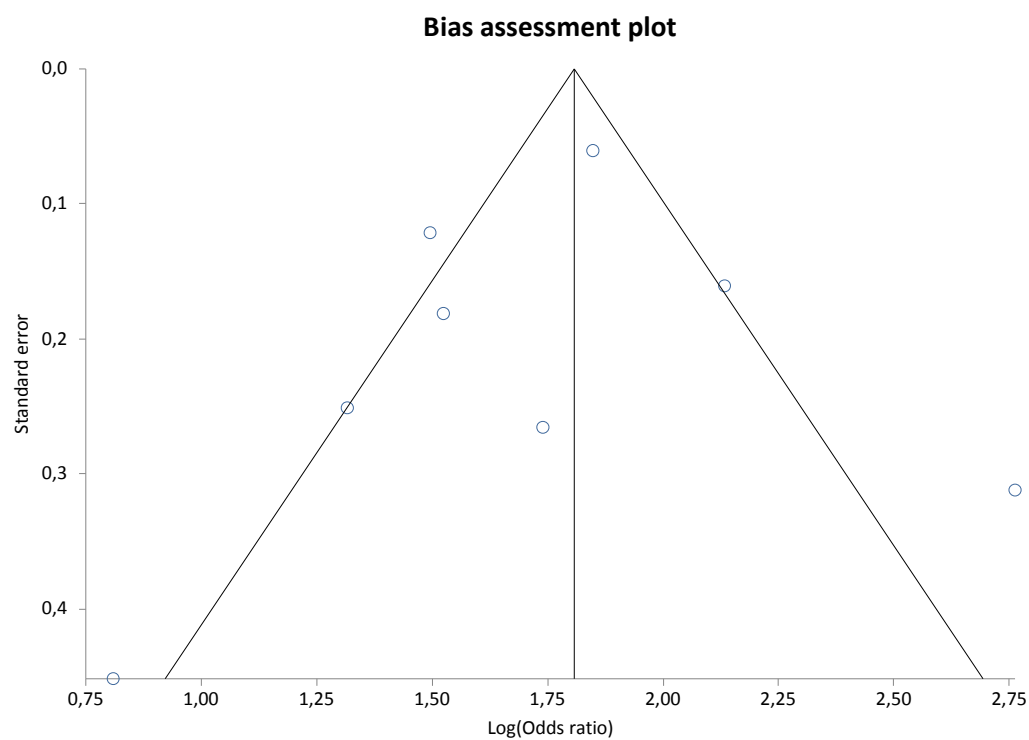


Figure S13. Funnel plot of the studies rated as being of good quality

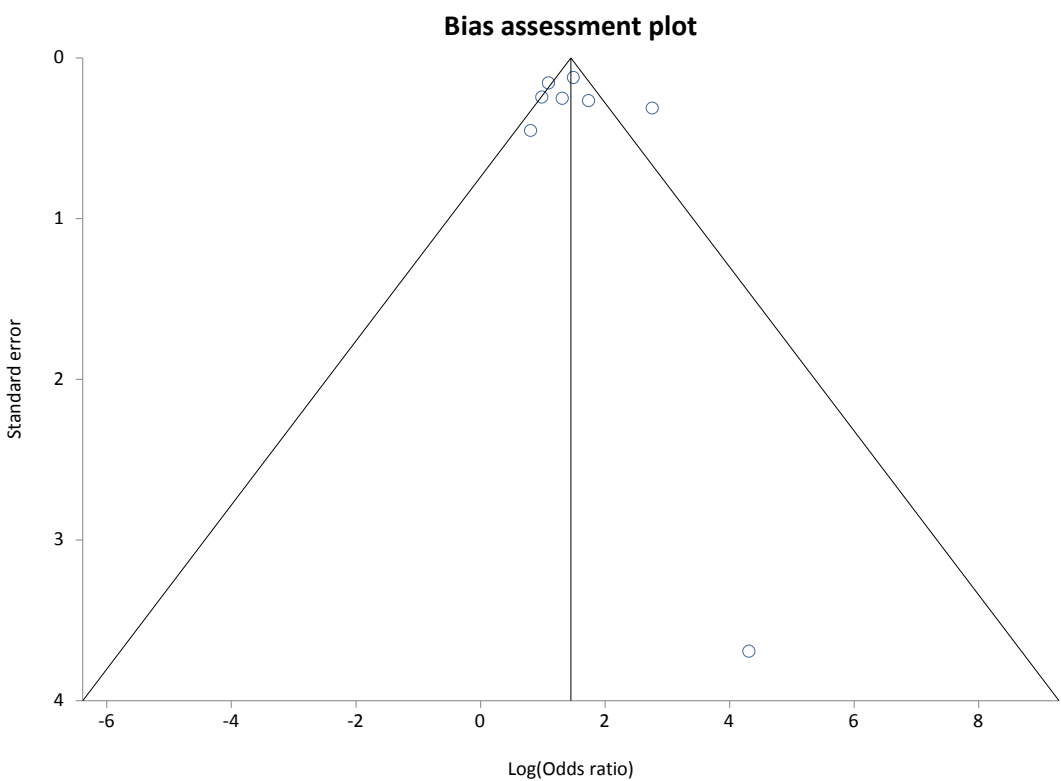


Figure S14. Funnel plot of the studies rated as being of poor and fair quality

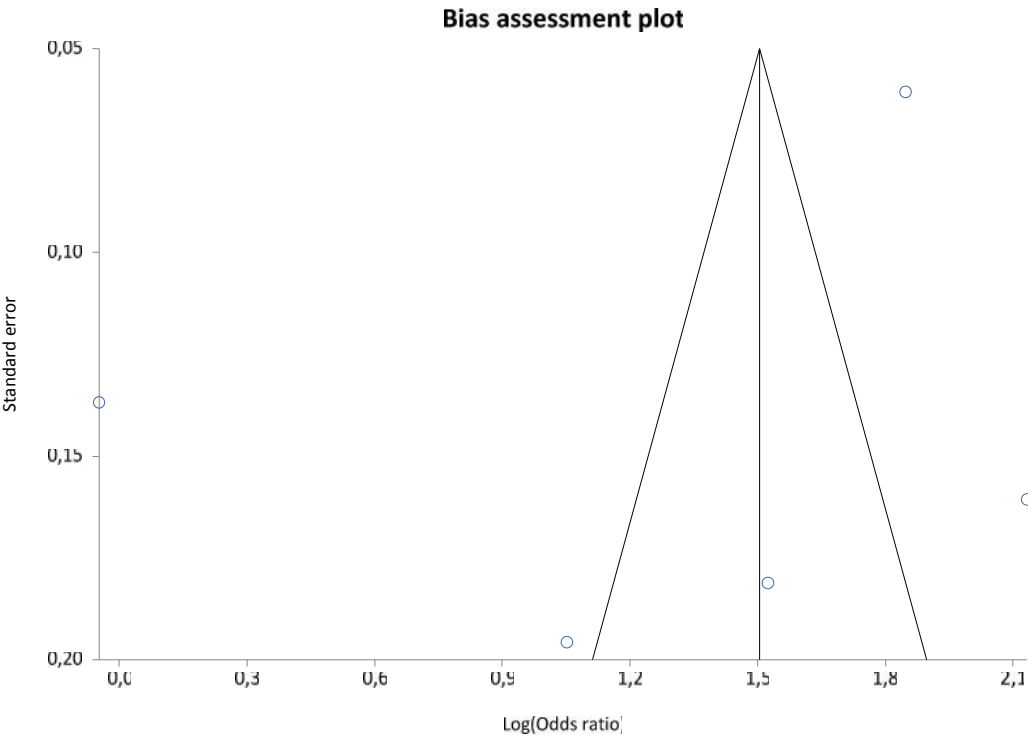


Table S1: Data from studies reporting the point prevalence of hand eczema (HE) in individuals with atopic dermatitis (AD).

First Author	Reference	Year	Country	Study design	Study population	Definition of AD	Definition of HE	NOS score	Key results relevant to meta-analysis
Lampel HP	(1)	2007	USA	Cross-sectional	Occupational Nurses (health care) n=167 Gender or age not given.	Questionnaire Self-reported history of AD, details not given.	Clinical examination	5	70.6% (12/17) of the nurses with AD had HE 53.3% (80/150) of the nurses without AD had HE
Dulon M	(2)	2008	Germany	Cross-sectional	Occupational Geriatric nurses (health care) n=1 202, F/M=1 054/148 Age not given.	Questionnaire Details not given.	Clinical examination HE assessed by the Osnabrueck Hand Eczema Severity Index (OHSI)	7	31.3% (20/64) of the nurses with AD had positive HE 16.4% (187/1 138) of the nurses without AD had positive OHSI results
Lan CC	(3)	2011	Taiwan	Cross-sectional	Occupational Nurses (health care) n=1 132, F/M=1 125/7, mean age: 31.6 years (SD $\pm$ 7.5 years)	Clinical examination Hanifin and Rajka Criteria AD was clinically diagnosed during the past year	Questionnaire 13 questions to evaluate signs and symptoms, location of affected skin areas, duration of symptoms and differential diagnoses of HE.	7	47.7% (43/90) of the nurses with AD had HE 19.7% (205/1 042) of the nurses without AD had HE
Heine G	(4)	2006	Germany, Austria and Switzerland	Cohort	Patient population Recruited from clinics in Germany, Austria and Switzerland and one control group n=24 283, F/M=15 185/9 098 Age not given.	Clinical examination Hanifin and Rajka Criteria	Clinical examination MOAHLFA-index	6	38.4% (3463/9 020) of the patients with AD had hand eczema (HE) 31.8% (4854/15 263) of the people without AD had HE
Josefson A	(5)	2009	Sweden	Cohort	General population N=364, F/M=364/0 Age not given.	Questionnaire “Have you had childhood eczema (before age 15 years?)”	Clinical examination Criteria for the diagnosis “current HE” were; 1. Erythema and papules/vesicles or	7	24.6% (32/130) of the women with AD had HE 8.1% (19/234) of the women without AD had HE

							2. Erythema, scaling and fissures and/or 3. A positive history including these signs during the previous year (at interview).		
Visser MJ	(6)	2014	Holland	Cohort	Occupational Apprentice nurses (health care) n=596 Gender or age not given.	Questionnaire U.K. Working Party's Diagnostic Criteria	Questionnaire Mild HE with presence of at least one of the following symptoms or combinations: 1. Redness and itch 2. Redness and scaling 3. Itch and scaling 4. Fissures and redness 5. Fissures and itch 6. Fissures and scaling 7. Vesicles 8. Papules all irrespective of duration or recurrence	6	26.8% (41/153) of the nurses with AD had HE 14.7% (65/443) of the nurses without AD had HE
<i>Not included in the meta-analysis, OR only</i>									
Apfelbacher CJ	(7)	2010	Germany	Case-control	Occupational Car industry Cases: n=108 mean age: 28.9 years (SD ± 1.5 years), Controls: n=119 mean age: 29.3 years (SD ± 1.7 years) Gender not given.	Clinical examination The Erlangen Atopy Score An atopic skin diathesis was assumed to be present if the summary score was above 10 points.	Clinical examination At least one of the following combinations 1. Erythema and vesicles 2. Erythema and scaling 3. Erythema and papules 4. Erythema and erosions/fissures 5. Erythema and lichenification	8	Adjusted OR for the association between HE and AD was 2.47 (95%CI: 1.71-3.55)
AD: atopic dermatitis, F/M: females/males, HE: hand eczema, n: number of participants, NOS: Newcastle-Ottawa scale, OR: odds ratio, SD: standard Deviation									

Table S2: Data from studies reporting the 1-year prevalence of hand eczema (HE) in atopic dermatitis (AD)

First Author	Reference	Year	Country	Study design	Study population	Definition of AD	Definition of HE	NOS score	Key results relevant to meta-analysis
Meding B	(8)	1990	Sweden	Cross-sectional	General population n=16 584 Gender or age not given.	Questionnaire “Did you have childhood eczema?”	Questionnaire “Have you during the past 12 months had HE on some occasion?”	7	27.2% (47/1 725) of the individuals with AD had HE 10.0% (1 488/14 859) of the individuals without AD had HE
Meding B	(9)	1994	Sweden	Cross-sectional	Occupational Car mechanics n=801, mean age: 33 years Gender not given.	Questionnaire Questions on childhood eczema, details not given.	Questionnaire Question on HE on some occasion during the last 12 months.	4	25.0% (14/56) of the mechanics with AD had HE 14.2% (106/745) of the mechanics without AD had HE
Susitaival P	(10)	1994	Finland	Cross-sectional	Occupational Farmers n=10 847, F/M=5 266/5 581 Women: mean age: 46.1 years, Men: mean age: 44.7 years	Questionnaire “Do you have or have you had infantile eczema or eczema on antecubital fossae or knee flexures?”	Questionnaire Participants were asked to mark the areas of their eczema on a picture. The hand and forearm were together in the same area.	6	49.0% (532/1 086) of the farmers with AD had HE 7.3% (712/9 761) of the farmers without AD had HE
Meding B	(11)	2001	Sweden	Cross-sectional	General population n=10 950 Gender or age not given.	Questionnaire “Have you had childhood eczema?”	Questionnaire “Have you had HE on any occasion during the past 12 months?”	5	23.0% (378/1 643) of the individuals with AD had HE 5.4% (498/9 307) of the individuals without AD had HE
Meding B	(12)	2002	Sweden	Cross-sectional	General population n=2 218, F/M=1 130/1 088, age: 20-65 years	Questionnaire “Did you have childhood eczema?”	Questionnaire “Have you during the past 12 months had HE on some occasion?”	6	25.2% (69/275) of the individuals with AD had HE 7.5% (146/1 943) of the individuals without AD had HE

Smith DR	(13)	2004	Australia	Cross-sectional	Occupational Nurses (health care) n=232, F/M=232/0, mean age: 25.6 years (SD ± 8.8 years)	Questionnaire Questions on the presence of atopy, details not given.	Questionnaire “Have you had one of the following symptoms at your hands or fingers in the past 12 months?”: 1. Red and swollen hands or fingers 2. Red hands or fingers and fissures 3. vesicles on the hands or between the fingers 4. Scaling hands or fingers with fissures 5. Itching hands or fingers with fissures A positive case was registered when two or more symptoms occurred in the past 12 months and had persisted for more than three weeks or reoccurred.	6	<u>50</u> % (13/ <u>26</u>) of the nurses with AD had HE <u>14.6</u> % (30/20 <u>6</u>) of the nurses without AD had HE
Smith DR	(14)	2005	China	Cross-sectional	Occupational Nurses (health care) n=282, F/M=282/0, mean age for the different hospital departments ranged from 32.8-37.6 years	Questionnaire Self-reported AD, details not given.	Questionnaire Same criteria as used in the study by Smith et al. (2004) (previously described in this table).	6	38.7% (12/31) of the nurses with AD had HE 15.1% (38/251) of the nurses without AD had HE
Flyvholm MA	(15)	2007	Denmark	Cross-sectional	Occupational Hospital staff (health care) n=1 076, mean age: 42.9 years Gender not given.	Questionnaire Nordic Occupational Skin Questionnaire (NOSQ-2002)	Questionnaire Nordic Occupational Skin Questionnaire (NOSQ-2002)	5	47.1% (72/153) of the individuals with AD had HE 19.4% (179 out of 923) individuals without AD had HE
Ibler KS	(16)	2012	Denmark	Cross-sectional	Occupational Physicians, nurses, nursing auxiliaries and bio technicians in 3	Questionnaire U.K. Working Party’s Diagnostic Criteria	Questionnaire Self-reported HE was defined by the question:	6	40.9% (115/281) of the individuals with AD had HE 18.1% (282/1 562) of the individuals without AD had HE

					hospitals (health care) n=1 843, F/M=1 598/242 (gender not given for 3 responders), mean age: 46.2 years (SD ± 10.3 years)		“Have you had HE within the past year?”		
Bingefors K	(17)	2013	Sweden	Cross-sectional	General population n=4 875, F/M=2 630/2 245, age: 18-84 years	Questionnaire “Have you had childhood eczema?”	Questionnaire “Have you had HE during the past 12 months?”	6	20.7% (138/666) of the individuals with AD had HE 5.4% (227/4 209) of the individuals without AD had HE
Nyren M	(18)	2005	Sweden	Cohort	General population n=783, F/M=441/342 Age not given.	Medical records indicating AD Symptoms or findings suggestive of AD were, for example, itchy eczema on the flexural area of the arms and legs.	Questionnaire “Have you had HE on any occasion during the past 12 months?”	6	24.2% (98/405) of the individuals with AD had HE 8.7% (33/378) of the individuals without AD had HE
Josefson A	(5)	2009	Sweden	Cohort	General population N=364, F/M=364/0 Age not given.	Questionnaire “Have you had childhood eczema (before age 15 years?)”	Questionnaire “Have you had HE on any occasion during the past 12 months?”	7	29.2% (38/130) of the women with AD had HE 6.8% (16/234) of the women without AD had HE
Gronhagen C	(19)	2015	Sweden	Cohort	General population (birth cohort) Children were consecutively recruited at birth and prospectively followed up to 16 years of age. n=2 927, F/M=1 494/1 433, age: 0-16 years	Questionnaire Dry skin and itchy rash with typical localization and/or doctors diagnosis of eczema.	Questionnaire “Have you had HE on any occasion during the past 12 months?”	6	8.8% (111/1 249) of the adolescents with AD had HE 2.4% (41/1 678) of the adolescents without AD had HE
<i>Not included in the meta-analysis, OR only</i>									
Ortengren U	(20)	1999	Sweden	Cross-sectional	Occupational Dentists n=3 082, F/M=1 464/1 618 Age not given.	Questionnaire “Did you experience childhood eczema?”	Questionnaire 1. “Do you often experience dry and rough skin on your hands?” 2. “Do you have or have you had HE?” If yes to question 2;	6	Adjusted prevalence ratio for the association between HE and AD was 2.4 (95%CI: 2.0-2.9)

							“What year did the HE start?” “Have you on any occasion experienced HE during the past 12 months?” “If you have experienced HE, but not during the last 12 months, when was your last experience of HE?” “Has your HE been diagnosed by a physician?” “Have you, in relation to the HE, been patch-tested at a dermatological clinic?”		
Smith DR	(21)	2006	Japan	Cross-sectional	Occupational Nurses (health care) n=860, F/M=843/17, mean age: 33 years	Questionnaire Self-reported AD, details not given.	Questionnaire Same criteria as used in the study by Smith et al. (2004) (previously described in this table)	6	Adjusted OR for the association between HE and AD was 2.7 (95%CI: 1.8-4.0)
Rohrl K	(22)	2010	Sweden	Cross-sectional	General population n=6 095, F/M=3 663/2 432, mean age: 17.4 years	Questionnaire “Have you ever had itching eczema in flexural folds on arms or legs (flexural eczema)”	Questionnaire “Have you had HE on any occasion during the past 12 months?”	6	Adjusted OR for the association between HE and AD was OR 4.5 (95%CI: 3.3-6.1)
Stenberg B	(23)	2010	Sweden	Cross-sectional	General population n=65 261 Gender or age not given.	Questionnaire “Have you had childhood eczema?”	Questionnaire “Have you had HE on any occasion during the past 12 months?”	6	Adjusted OR for the association between HE and AD was 3.85 (95%CI: 3.63-4.09)
Crawford GH	(24)	2014	USA	Cross-sectional	Occupational Massage therapist n=292, F/M=246/43 (gender not given for 3 responders), mean age: 42.9 years (SD ± 10.7 years)	Questionnaire Nordic Occupational Skin Questionnaire (NOSQ-2002)	Questionnaire Nordic Occupational Skin Questionnaire (NOSQ-2002)	6	Adjusted OR for the association between HE and AD was 8.06 (95%CI: 3.39-19.17)
Lee SW	(25)	2013	Korea	Cross-sectional	Occupational Nurses, assistant nurses and nurses ‘aides (health care)	Questionnaire History of AD, details not given.	Questionnaire The participants were questioned about their opinions on whether or not they had HE. They were	6	Adjusted OR for the association between HE and AD was 2.33 (95%CI: 1.06-5.15)

					n=525, F/M=510/15, mean age: 30.8 years (range 21-58 years)		allowed to compare and check their symptoms, if any, by proving a common list of symptoms of HE		
AD: atopic dermatitis, F/M: females/males, HE: hand eczema, n: number of participants, NOS: Newcastle-Ottawa scale, OR: odds ratio, SD: standard Deviation									

Table S3: Data from studies reporting the lifetime prevalence of hand eczema (HE) in atopic dermatitis (AD)

First Author	Reference	Year	Country	Study design	Study population	Definition of AD	Definition of HE	NOS score	Key results relevant to meta-analysis
Lammintausta K	(26)	1981	Finland	Cross-sectional	Occupational Hospital staff (health care) n=586, F/M=557/29 Age not given.	Interview AD was defined as recurrent infantile dermatitis on the face or pruritic dry dermatitis on the exposed surfaces at crawling age, with other symptoms later in childhood, or as a typical flexural eczema in childhood or adulthood..	Clinical examination Registration of the occurrence of HE once, twice or more than twice. Redness of the skin with edema, vesicles/vesicopapules and/or scaling.	7	65.1% (56/86) of the individuals with AD had HE 41 % (205/500) of the individuals without AD had HE
Holm JO	(27)	1994	Norway	Cross-sectional	Occupational Hairdressers n=203, mean age for the different groups ranged from 26-28 years Gender not given.	Questionnaire Used by the doctor during personal interview The diagnosis of previous or present AD was made by the respondent's physician, and confirmed by the interviewer	Questionnaire "Have you or have you had exanthema on hands and/or forearms?"	8	100% (15/15) of the hairdressers with AD had HE 73.4% (138/188) of the hairdressers without AD had HE
Meding B	(11)	2001	Sweden	Cross-sectional	General population n=10 950 Gender or age not given.	Questionnaire "Have you had childhood eczema?"	Questionnaire "Have you ever had hand eczema?"	5	42.0% (690/1 643) of the individuals with AD had HE 10.2 % (953/9 307) of the individuals without AD had HE

Nielsen NH	(28)	2002	Denmark	Cross-sectional Two surveys, 8 years apart.	General population 1990: n=312 1998: n=482 Age range: 15-41 years Gender not given.	Questionnaire “Have you ever had eczema in the flexures of your arms or legs?”	Questionnaire “Have you ever had HE?”	7	1990: 29.6% (8/27) of the individuals with AD had HE <u>15.8 % (45/285) of the individuals without AD had HE</u> 1998: 50.6% (42/83) of the individuals with AD had HE 21.6% (86/399) of the individuals without AD had HE
<u>Thyssen JP</u>	(35)	<u>2013</u>	<u>Denmark</u>	<u>Cross-sectional</u>	<u>General population</u> <u>n=3 335, F/M=1 844/1 491, age range: 18-69 years</u>	<u>Questionnaire</u> “ <u>Has your doctor ever told you that you suffered from AD?</u> ” “ <u>Have you ever had dry skin all over your body?</u> ”	<u>Questionnaire</u> “ <u>Have you ever had HE?</u> ”	<u>7</u>	<u>50.6% (163/322) of the individuals with AD had HE</u> <u>18.7 % (535/2863) of the individuals without AD had HE</u>
Rystedt I	(29)	1985	Sweden	Cohort	General population n=1 376, F/M=610/766 Age not given.	Questionnaire and interview Participants in group 1 had been hospitalized at the department of	Questionnaire and interview Details not given.	3	54.9% (524/955) of the individuals with AD had HE 12.6% (53/421) of the individuals without AD had HE

						dermatology, Karolinska University Hospital with the diagnosis AD. Participants in group 2 had visited the outpatient clinic because of AD, but had not been hospitalized.			
Bryld LE	(30)	2003	Denmark	Cohort	General population n=1 076, F/M=697/379, age: 20-44 years	Questionnaire U.K. Working Party's Diagnostic Criteria	Questionnaire “Have you ever had eczema on your hands?” “Do you have eczema on your hands now?” “Has a doctor ever told you that you had HE?” HE was diagnosed if positive answer to one of the three questions above.	7	89.8% (106/118) of the individuals with AD had HE 35.8% (343/958) of the individuals without AD had HE
Nyren M	(18)	2005	Sweden	Cohort	General population n=783, F/M=441/342 Age not given.	Medical records indicating AD Symptoms or findings suggestive of AD were, for example, itchy eczema in the flexural part of the arms and legs.	Questionnaire “Have you ever had HE?”	6	41.7% (169/405) of the individuals with AD had HE 13.5% (51/378) of the individuals without AD had HE
Josefson A	(5)	2009	Sweden	Cohort	General population n=364, F/M=364/0 Age not given.	Questionnaire “Have you had childhood eczema?”	Questionnaire “Have you ever had HE after age 15 years?”	7	44.6 % (58/130) of the women with AD reported HE 12.4% (29/234) of the women without AD reported HE
Visser MJ	(6)	2014	Holland	Cohort	Occupational Apprentice nurses (health care) n=596 Gender or age not given.	Questionnaire U.K. Working Party's Diagnostic Criteria	Questionnaire	6	65.4% (100/153) of the individuals with AD had HE 39.7% (176/443) of the individuals without AD had HE
Carlsen BC	(31)	2009	Denmark	Case-control	Patient population Subjects were recruited from a hospital patch test population.	Questionnaire U.K. Working Party's Diagnostic Criteria,,	Questionnaire The responders were asked where the dermatitis was located at the time of first appearance.	6	63.8% (244/385) of the individuals with AD had HE 64.5% (374/580) of the individuals without AD had HE

					n=965 Gender or age not given.				
Visser MJ	(32)	2013	Holland	Case-control	Cases: Patients with chronic contact dermatitis of the hands n=634, F/M=392/236 (no gender given from 6 patients), mean age: 43 years (range 31-51 years) Control group: Workers in high risk occupations n=393, F/M=244/149, mean age: 19 years (range 18-22 years)	Questionnaire, interview and clinical examination Cases: Interview where a full medical and dermatological history was taken, including information regarding sex, age, diagnosis, age at onset of contact dermatitis and history of flexural eczema. Control group: Questionnaire including information on skin and atopic symptoms. A subsample of the control group was clinically examined.	Clinical examination Cases: HE diagnosis was verified by clinical examination or medically verified in the past.	7	77.8% (249/320) of the individuals with AD had HE 54 % (361/669) of the individuals without AD had HE
<i>Not included in the meta-analysis, OR only</i>									
Mortz CG	(33)	2000	Denmark	Cohort	General population Adolescents n=1 438, F/M=713/725, mean age: 14.1 years (range 12-16 years)	Questionnaire and clinical examination The lifetime prevalence of AD in the study participants was diagnosed by questionnaire (maternal reporting of skin symptoms, asthma, hay fever or genetic predisposition to atopic diseases). The 1-year prevalence and point prevalence of AD was diagnosed by clinical examination using the Hanifin and Rajka Criteria.	Questionnaire Criteria for a history of HE was eczema (rash) on the fingers, finger webs, palms or back of hands, which had appeared once and continued for at least two weeks, had appeared several times or had been persistent.	6	Adjusted OR for the association between past or present HE and past or present AD was 5.61 (95%CI: 3.81-8.25)

Nilsson EJ	(34)	1995	Sweden	Cross-sectional	Patient population Subjects were recruited from a dental clinic due to suspicion that dental fillings caused somatic symptoms. n=195, F/M=195/0, mean age: 51.2 years	Interview by phone Itching, relapsing dermatitis starting in infancy or childhood with a typical distribution. “Have you always had unusually dry skin (xerosis)?” “Do you get itchy if you have rough material such as wool or synthetic clothing on the skin?” “Do you get itchy when sweating?”	Interview by phone 1. Dry and chapped skin with rashes and small cracks (dry erythemas) 2. Itching red macular and popular skin lesions (maculopapules) 3. Small vesicles (vesicles) 4. Ruptured vesicles or excoriated skin (erosions) 5. Rough skin with cracks and scaling (hyperkeratosis) Yes to ≥ 1 of the questions	6	Adjusted OR for the association between HE and AD was 6.81 (95%CI: 2.47-18.79)
------------	------	------	--------	-----------------	--	---	---	---	--

AD: atopic dermatitis, F/M: females/males, HE: hand eczema, n: number of participants, NOS: Newcastle-Ottawa scale, OR: odds ratio, SD: standard Deviation

References

1. Lampel HP, Patel N, Boyse K, O'Brien SH, Zirwas MJ. Prevalence of Hand Dermatitis in Inpatient Nurses at a United States Hospital. *Dermatitis* [Internet]. 2007 Sep [cited 2016 Nov 4];18(3):140–2. Available from: <http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=01206501-200709000-00004>
2. Dulon M, Kromark K, Skudlik C, Nienhaus A. Prevalence of skin and back diseases in geriatric care nurses. *Int Arch Occup Env Heal*. 2008;81:983–92.
3. Lan C-CE, Tu H-P, Lee C-H, Wu C-S, Ko Y-C, Yu H-S, et al. Hand dermatitis among university hospital nursing staff with or without atopic eczema: assessment of risk factors. 2010;
4. Heine G, Schnuch A, Uter W, Worm M. Type-IV sensitization profile of individuals with atopic eczema: results from the Information Network of Departments of Dermatology (IVDK) and the German Contact Dermatitis Research Group (DKG). *Allergy* [Internet]. 2006 May [cited 2016 Nov 4];61(5):611–6. Available from: <http://doi.wiley.com/10.1111/j.1398-9995.2006.01029.x>
5. Josefson A, Färm G, Magnuson A, Meding B. Nickel allergy as risk factor for hand eczema: a population-based study. *Br J Dermatol* [Internet]. 2009 Apr [cited 2016 Nov 4];160(4):828–34. Available from: <http://doi.wiley.com/10.1111/j.1365-2133.2008.09006.x>
6. Visser MJ, Verberk MM, Campbell LE, McLean WHI, Calkoen F, Bakker JG, et al. Filaggrin loss-of-function mutations and atopic dermatitis as risk factors for hand eczema in apprentice nurses: part II of a prospective cohort study. *Contact Dermatitis* [Internet]. 2014 Mar [cited 2016 Nov 7];70(3):139–50. Available from: <http://doi.wiley.com/10.1111/cod.12139>
7. Apfelbacher CJ, Funke U, Radulescu M, Diepgen TL. Determinants of current hand eczema: results from case-control studies nested in the PACO follow-up study (PACO II). *Contact Dermatitis* [Internet]. 2010 Jun [cited 2016 Nov 4];62(6):363–70. Available from: <http://doi.wiley.com/10.1111/j.1600-0536.2010.01729.x>
8. Meding B, Swanbeck G. Predictive factors for hand eczema. *Contact Dermatitis* [Internet]. 1990 Sep

[cited 2016 Sep 22];23(3):154–61. Available from: <http://doi.wiley.com/10.1111/j.1600-0536.1990.tb04776.x>

9. Meding B, Barregård L, Marcus K. Hand eczema in car mechanics. *Contact Dermatitis* [Internet]. 1994 Mar [cited 2016 Nov 7];30(3):129–34. Available from: <http://doi.wiley.com/10.1111/j.1600-0536.1994.tb00692.x>
10. Susitaival P, Husmant L, Horsmanheimo M, Notkola V, Husman K. Prevalence of hand dermatoses among Finnish farmers. *Scand J Work Env Heal*. 1994;2020:206–12206.
11. Meding B, Liden C, Berglind N. Self-diagnosed dermatitis in adults . Results from a population survey in Stockholm. *Contact Dermatitis* [Internet]. 2001 Dec [cited 2016 Nov 7];45(6):341–5. Available from: <http://doi.wiley.com/10.1034/j.1600-0536.2001.450604.x>
12. Meding B, Järvholm B. Hand Eczema in Swedish Adults – Changes in Prevalence between 1983 and 1996. *J Invest Dermatol*. 2002;118(4):719–23.
13. Smith DR, Leggat PA. Hand dermatitis among female nursing students in tropical Australia. *Nurs Heal Sci* [Internet]. 2004 Jun [cited 2016 Nov 7];6(2):109–13. Available from: <http://doi.wiley.com/10.1111/j.1442-2018.2004.00181.x>
14. Smith DR, Wei N, Zhao L, Wang R-S. Hand dermatitis among nurses in a newly developing region of Mainland China. *Int J Nurs Stud*. 2005;42:13–9.
15. Flyvholm M-A, Bach B, Rose M, Jepsen KF. Self-reported hand eczema in a hospital population. *Contact Dermatitis* [Internet]. 2007 Aug [cited 2016 Nov 7];57(2):110–5. Available from: <http://doi.wiley.com/10.1111/j.1600-0536.2007.01134.x>
16. Ibler KS, Jemec GBE, Flyvholm M-A, Diepgen TL, Jensen A, Agner T. Hand eczema: prevalence and risk factors of hand eczema in a population of 2274 healthcare workers. *Contact Dermatitis* [Internet]. 2012 Oct [cited 2016 Sep 22];67(4):200–7. Available from: <http://doi.wiley.com/10.1111/j.1600-0536.2012.02105.x>
17. Binge-fors K, Svensson Å, Isacson D, Lindberg M. Self-reported Lifetime Prevalence of Atopic Dermatitis and Co-morbidity with Asthma and Eczema in Adulthood: A Population-based Cross-sectional Survey. *Acta Derm Venereol* [Internet]. 2013 [cited 2016 Sep 22];93(4):438–41. Available

from: <http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1522>

18. Nyrén M, Lindberg M, Stenberg B, Svensson M, Svensson Å, Meding B. Influence of childhood atopic dermatitis on future worklife. *Scand J Work Env Heal*. 2005;3131(6):474–8.
19. Grönhagen C, Lidén C, Wahlgren C-F, Ballardini N, Bergström A, Kull I, et al. Hand eczema and atopic dermatitis in adolescents: a prospective cohort study from the BAMSE project. *Br J Dermatol* [Internet]. 2015 Nov [cited 2016 Nov 7];173(5):1175–82. Available from: <http://doi.wiley.com/10.1111/bjd.14019>
20. Ortengren U, Andreasson H, Karlsson S, Meding B, Barregard L. Prevalence of self-reported hand eczema and skin symptoms associated with dental materials among Swedish dentists. *Eur J Oral Sci* [Internet]. 1999 Dec [cited 2016 Nov 7];107(6):496–505. Available from: <http://doi.wiley.com/10.1046/j.0909-8836.1999.eos107612.x>
21. Smith DR, Adachi Y, Mihashi M, Kawano S, Ishitake T. Hand dermatitis risk factors among clinical nurses in Japan. *Clin Nurs Res* [Internet]. 2006 Aug [cited 2016 Nov 7];15(3):197–208. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16801359>
22. Röhrl K, Stenberg B. Lifestyle factors and hand eczema in a Swedish adolescent population. *Contact Dermatitis* [Internet]. 2010 Mar [cited 2016 Nov 7];62(3):170–6. Available from: <http://doi.wiley.com/10.1111/j.1600-0536.2009.01679.x>
23. Stenberg B, Meding B, Svensson A. Dermatology in public health--a model for surveillance of common skin diseases. *Scand J Public Health*. 2010;38(4):368–74.
24. Crawford GH, Katz KA, Ellis E, James WD. Use of Aromatherapy Products and Increased Risk of Hand Dermatitis in Massage Therapists. *Arch Dermatol*. 2004;140:991–6.
25. Lee SW, Cheong SH, Byun JY, Choi YW, Choi HY. Occupational hand eczema among nursing staffs in Korea: Self-reported hand eczema and contact sensitization of hospital nursing staffs. *J Dermatol* [Internet]. 2013 Mar [cited 2016 Nov 7];40(3):182–7. Available from: <http://doi.wiley.com/10.1111/1346-8138.12036>
26. Lammintausta K, Kalimo K. Atopy and hand dermatitis in hospital wet work. *Contact Dermatitis* [Internet]. 1981 Dec [cited 2016 Nov 7];7(6):301–8. Available from:

<http://doi.wiley.com/10.1111/j.1600-0536.1981.tb04085.x>

27. Holm JO, Veierød MB. An epidemiological study of hand eczema. III. Characterization of hairdressers with and without hand eczema, regarding demographic factors and medical histories. *Acta Derm Venereol Suppl* (Stockh) [Internet]. 1994 [cited 2016 Nov 7];187:15–7. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/9868491>
28. Nielsen NH, Linneberg A, Menne T, Madsen F, Frolund L, Dirksen A, et al. The association between contact allergy and hand eczema in 2 cross-sectional surveys 8 years apart. The Copenhagen Allergy Study. *Contact Dermatitis* [Internet]. 2002 Aug [cited 2016 Nov 7];47(2):71–7. Available from: <http://doi.wiley.com/10.1034/j.1600-0536.2002.470203.x>
29. Rystedt I, Rystedt I. Work-related hand eczema in atopsics. *Contact Dermatitis* [Internet]. 1985 Mar [cited 2016 Nov 1];12(3):164–71. Available from: <http://doi.wiley.com/10.1111/j.1600-0536.1985.tb01087.x>
30. Bryld LE, Hindsberger C, Kyvik KO, Agner T, Menne T. Risk factors influencing the development of hand eczema in a population-based twin sample. *Br J Dermatol* [Internet]. 2003 Dec [cited 2016 Sep 22];149(6):1214–20. Available from: <http://doi.wiley.com/10.1111/j.1365-2133.2003.05678.x>
31. Carlsen BC, Andersen KE, Menné T, Johansen JD. Sites of dermatitis in a patch test population: hand dermatitis is associated with polysensitization. *Br J Dermatol* [Internet]. 2009 Oct [cited 2016 Nov 7];161(4):808–13. Available from: <http://doi.wiley.com/10.1111/j.1365-2133.2009.09287.x>
32. Visser MJ, Landeck L, Campbell LE, McLean WHI, Weidinger S, Calkoen F, et al. Impact of atopic dermatitis and loss-of-function mutations in the filaggrin gene on the development of occupational irritant contact dermatitis. *Br J Dermatol* [Internet]. 2013 Feb [cited 2016 Nov 7];168(2):326–32. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/23039796>
33. Mortz CG, Lauritsen JM, Bindslev-Jensen C, Andersen KE. Prevalence of atopic dermatitis, asthma, allergic rhinitis, and hand and contact dermatitis in adolescents. The Odense Adolescence Cohort Study on Atopic Diseases and Dermatitis. *Br J Dermatol* [Internet]. 2001 Mar [cited 2016 Sep 22];144(3):523–32. Available from: <http://doi.wiley.com/10.1046/j.1365-2133.2001.04078.x>
34. Nilsson EJ, Knutsson A. Atopic dermatitis, nickel sensitivity and xerosis as risk factors for hand

eczema in women. *Contact Dermatitis* [Internet]. 1995 Dec [cited 2016 Nov 7];33(6):401–6.

Available from: <http://doi.wiley.com/10.1111/j.1600-0536.1995.tb02075.x>

35. Thyssen J, Johansen J, Zachariae C, Menné T, Linneberg A. Xerosis is Associated with Atopic Dermatitis, Hand Eczema and Contact Sensitization Independent of Filaggrin Gene Mutations. *Acta Derm Venereol* [Internet]. 2013 [cited 2016 Sep 22];93(4):406–10. Available from: <http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1539>

Table S4: Data on the I2 value from each meta-analysis.

Meta-analyses	I2 (%)
Point prevalence of HE	87
Sensitivity analysis on the point prevalence of HE	13.3
1-year prevalence of HE	94.7
Sensitivity analysis on the 1-year prevalence of HE	93.4
Lifetime prevalence of HE	94.4
Sensitivity analysis on the lifetime prevalence of HE	93.1
1-year prevalence of occupational HE	95.9
Sensitivity analysis on the 1-year prevalence of occupational HE	12.4
Lifetime prevalence of occupational HE	0
1-year prevalence of HE in the general population	75.8
Sensitivity analysis on the 1-year prevalence of HE in the general population	29.2
Lifetime prevalence of HE in the general population	78
Sensitivity analysis on the lifetime prevalence of HE in the general population	79.9
Good quality	77.3
Sensitivity analysis on good quality	80.2
Poor quality	97.8
Sensitivity analysis on poor quality	97.4

HE: hand eczema