

Review

The association of smoking with contact dermatitis and hand eczema – a review

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Abstract

Given the high prevalence of allergic contact dermatitis (ACD), irritant contact dermatitis (ICD), hand eczema (HE), and smoking, and the impact that smoking has on skin disease, the authors reviewed the existing literature to assess the association between smoking and contact dermatitis or hand eczema. Using the PubMed and SCOPUS databases, a literature search identified articles related to allergic contact dermatitis, irritant contact dermatitis, and hand eczema and a possible association with smoking. The search period included articles prior to and including April 2016. Seven of eight articles described a positive relationship between smoking and allergic or irritant contact dermatitis, while nine of nineteen articles found a positive association between smoking and hand eczema. Published studies document that smoking may be an important risk factor for both allergic and irritant contact dermatitis as well as hand eczema.

Introduction

Allergic contact dermatitis (ACD) and irritant contact dermatitis (ICD) are relatively common skin conditions, with around 19.5% of the general populace of North America and Western Europe being affected by ACD.¹ ACD is an eczematous dermatitis caused by a type four hypersensitivity reaction of the skin, while ICD is a nonspecific reaction that occurs after an irritant comes in contact with skin.^{2,3} Hand eczema (HE) is a broad term used to describe inflammation of the hands.⁴ HE is most commonly classified as ICD or ACD; it can also be atopic by nature.⁴ Other causes of HE include dyshidrotic eczema, hyperkeratotic hand eczema, and nummular hand eczema, among other diagnoses.⁴

Smoking is prevalent in the United States, with 16.8% of the population considered smokers in 2014.⁵ Smoking is associated with many disease processes in different organ systems, and the skin is no exception. According to a review by Just-Sarobé, smoking may be linked to psoriasis, pustulosis palmoplantaris, scar formation, hidradenitis suppurativa, systemic lupus erythematosus, discoid lupus erythematosus, allergic contact dermatitis, Favre-Racouchot syndrome, and lip, oral cavity, and anogenital cancers.⁶ Additionally, smoking is associated with cosmetic sequelae, including yellowing of the fingernails and

fingers, discoloration of teeth, and early wrinkle development on the face, among other problems.⁶

Given the high prevalence of allergic contact dermatitis, irritant contact dermatitis, hand eczema, and smoking, as well as the impact that smoking has on skin disease, the authors posed the question: are contact dermatitis and hand eczema associated with smoking—what is the evidence?

Materials and methods

A literature search was done primarily in April 2016 using PubMed and SCOPUS databases; the period of search included all articles prior to and including April 2016. The authors initially searched for articles relating to allergic and irritant contact dermatitis and smoking. The PubMed probe resulted in 153 articles, 11 of which were found relevant to the topic and were further reviewed. The SCOPUS search yielded approximately 146 unique articles that were distinct from the articles found through PubMed, and four additional articles were added to the review process. A subsequent inquiry was formed in both PubMed and SCOPUS using the term “hand eczema” coupled with multiple terms related to smoking, revealing 44 additional results that were reviewed. Reviewing the bibliographies of the articles revealed additional sources that

were added to the review process. Only articles published in English were included. Authors computed odds ratios for many studies based on frequency data reported in the articles.

Results

Allergic and irritant contact dermatitis and smoking

Eight articles were found relevant to the topic of ACD or ICD and smoking.

Articles showing an association between contact dermatitis and smoking

Seven articles found an association between contact dermatitis and smoking.

In a cross-sectional study by Sprince *et al.* (USA) published in 1996, the authors studied 158 individuals who worked as machine operators in auto production with exposure to metal-working fluids and 51 assemblers. Two questionnaires and one dermatologic examination were used for evaluation. The authors found an association between combined dermatitis ('definite' or 'possible' dermatitis as observed by a dermatologist) and smoking in machine operators. By logistic regression analysis, the odds ratio of being a current smoker (vs. nonsmoker) with combined dermatitis was 3.10, 95% CI: 1.34–7.18.⁷

In a cross-sectional study published in 1999 by Khalili *et al.*, authors found that smoking was associated with occupational (irritant and allergic) contact dermatitis in auto repair workers in Irbid City, Jordan. A total of 360 workers were evaluated in a cross-sectional study, which included an interview questionnaire and clinical examination. Smoking was associated with occupational contact dermatitis with 16.2% of smokers having occupational contact dermatitis ($P = 0.03$), while only 7.6% of nonsmokers had occupational contact dermatitis.⁸

In 2003, Linneberg *et al.* published a population-based, cross-sectional study that included 1056 individuals who lived in Copenhagen. The individuals were chosen from two groups: a symptom group with upper and lower respiratory symptoms, and a random group. The individuals were given a questionnaire and patch tested using the TRUE-test® (ALK-Abelló A/S, Hørsholm, Denmark). The authors found that there was an association between smoking history of greater than 15 pack-years and contact allergy, nickel contact allergy, and allergic nickel contact dermatitis (adjusted OR: 1.82, 2.7, 3.04; 95% CI: 1.15–2.89, 1.4–5.2, and 1.50–6.15, respectively). These associations were independent of sex, age, and nickel exposure. Additionally, there was a dose-response relationship between the amount smoked in pack-years and nickel contact allergy in women.⁹

Lazarov *et al.* (Israel) published a cohort study in 2005 on skin disease in hydrotherapists, who are exposed to pool water during therapy sessions. The initial cohort included 400 individuals who attended a hydrotherapy course, with 190 responding. Questions posed to hydrotherapists were about dermatologic

disease, including contact dermatitis, as well as smoking status. There was a statistically significant relationship between smoking and the incidence of contact dermatitis with $P = 0.015$. Of note, only 58.5% of 176 individuals who responded to the questionnaire were employed as a hydrotherapist when the questionnaire was given.¹⁰

In 2007, Dotterud *et al.* published a cross-sectional study showing that smoking may be a risk factor for contact sensitization in women. In the Sør-Varanger municipality of Norway, 1236 individuals were patch tested using the TRUE-test® (Pharmacia, Hillerød, Denmark). Current smoking and contact allergy (defined as one or more positive patch tests) had an OR: 0.74 (95% CI: 0.42–1.30) in men and OR: 1.42 (95% CI: 1.01–1.99) in women. However, the study found that 86.9% of women and only 5.8% of men had ear piercings, while 27.5% of women and 5.1% of men had positive patch tests to nickel.¹¹

Attwa *et al.* published a cross-sectional study in 2009 on contact dermatitis in auto repair workers in Zagazig City, Egypt. The study included 87 car repair workers who were examined over 2 weeks for signs of contact dermatitis; 10 of 16 individuals with contact dermatitis by examination were patch tested with the TRUE-test® (Mekos Laboratories A/S, Hillerød, Denmark). Statistical analysis of the eleven smokers with contact dermatitis compared to 27 smokers without contact dermatitis showed an OR: 3.59, $P < 0.05$, and 95% CI: 1.0–13.5. Thus, an association was found between the prevalence of contact dermatitis and smoking.¹²

In a cross-sectional study by Thyssen *et al.* published in 2010, the authors found an association between nickel sensitization and smoking. In Copenhagen, 3471 adults were examined and 3460 were patch tested using the TRUE-test® (Mekos Laboratories, Hillerød, Denmark) and given a questionnaire, which included questions on smoking status. A statistically significant trend, using an adjusted model, was found between smoking status and nickel sensitization, with $P < 0.05$. The authors also performed an analysis between smoking and "contact sensitization to at least one allergen," and smoking and "contact sensitization to at least one allergen but not nickel," but no strong associations were found in these two variables. However, there was a low prevalence of individuals with positive patch tests to allergens other than nickel. Of note, occasional smokers (defined as less than one cigarette, one cheroot, or one tobacco pipe daily) were excluded from the analyses.¹³

Article showing no association between contact dermatitis and smoking

One article did not find an association between contact dermatitis and smoking.

Meijer *et al.*, in a cross-sectional study published in 1995, studied nickel and cobalt sensitization in Swedish servicemen. A total of 520 individuals with a median age of 19 years were given a questionnaire and patch tested with nickel and cobalt (nickel 5.0% and cobalt chloride 1.0% in petrolatum,

Chemotechnique Diagnostics AB, Malmö, Sweden). The authors found no significant difference between smokers versus nonsmokers in nickel and cobalt sensitization frequency.¹⁴

See Table 1 for a summary of these eight studies.

Hand eczema and smoking

Nineteen original articles were found on the relationship between hand eczema and smoking.

Articles showing a positive association between hand eczema and smoking

Nine articles showed an association between hand eczema and smoking.

In a cross-sectional study published in 1988, performed in Malmö, Sweden, Edman showed that smoking was associated with vesicular palmar eczema. Overall, 425 patients were patch tested and asked about smoking habits, and instances of vesicular palmar eczema were recorded. Vesicular palmar eczema was specifically defined by the authors as “eczematous vesicles symmetrically on the volar aspects of hands and/or fingers, sometimes on the sides of fingers as well;” additionally, other areas of eczema were permitted. Vesicular palmar eczema was found in 153 individuals. A relationship was found between vesicular palmar eczema and smoking, mainly in males; 21/45 male smokers had VPE, 17/63 nonsmokers had VPE, OR: 2.4, $P = 0.029$.¹⁵

Uter *et al.* published a cohort study on 859 hairdressing apprentices in northern Germany in 1995. The hairdressers were examined and given a questionnaire. Smoking more than five cigarettes per day was significantly associated with both skin changes (OR: 1.36, 95% CI: 1.01–1.83) and HE (OR: 1.92, 95% CI: 1.27–2.91) ($P < 0.05$).¹⁶

A cross-sectional questionnaire study by Montnémy *et al.* in Sweden was published in 2005, with 9316 of 11,798 individuals responding. Questions about 1-year and lifetime prevalence of HE, as well as smoking status (defined as more than five cigarettes daily), were included. The study found that in women, the 1-year and the lifetime prevalence of HE in smokers compared to nonsmokers was statistically significant (1-year: 10.3% vs. 7.2%, $P < 0.001$; lifetime: 16.4% vs. 12.9%, $P < 0.01$). Furthermore, after a multiple logistic regression analysis was done, smoking was found to be an independent risk factor for the 1-year prevalence of HE (OR: 1.35, 95% CI: 1.04–1.75, $P = 0.022$).¹⁷

Thyssen *et al.* published a cross-sectional study of the general population in Copenhagen, Denmark, in 2010. A total of 3471 individuals were interviewed, and 3460 were patch tested. The questionnaire distinguished between current, previous, and never smokers, as well as dividing current smokers into light and heavy smokers (the study excluded occasional smokers). A statistically significant trend was found between amount smoked and HE when using a fully adjusted statistical model ($P = 0.005$).¹⁸

Meding *et al.* published a cross-sectional study of 25,428 individuals in Sweden in 2010. Questions were asked about the 1-year prevalence of HE in participants and their smoking status (daily smokers, nonsmokers, ex-smokers, occasional smokers). Confounders were identified and evaluated. Upon multivariate analysis, only ex-smokers and smokers who smoked more than 15 cigarettes daily were found to have statistically significant association with the prevalence of HE (prevalence proportion ratio 1.14 and 1.40, respectively, $P < 0.01$). Additionally, the prevalence proportion ratio of smoking (as a continuous variable) and 1-year HE prevalence was 1.05 ($P < 0.001$), with a dose-response relationship found between the two variables, indicating that with more tobacco smoking, HE prevalence increases.¹⁹

Anveden Berglind *et al.* published in 2011 a cross-sectional survey study in 27,793 individuals about the 1-year prevalence of HE and smoking in Sweden. Questions were asked about daily smoking and 1-year prevalence of HE. After multivariate analysis, the prevalence proportion ratio was 1.025 (95% CI: 1.006–1.044) for smoking status and 1-year prevalence of HE.²⁰

Brans *et al.* published a prospective cohort study in Germany on patients participating in a tertiary individual prevention program in 2014. Only those with HE, 1608 participants, were studied at six time points, from admission through 3 years. At each time point, a dermatologist evaluated the patient; the Osnabrück Hand Eczema Severity Index (OHSI) was used to assess the patient's hand eczema severity. Patients were asked about smoking status and how many cigarettes they smoked daily. At admission, hand eczema was more severe in smokers than non-smokers ($P < 0.02$). Through the 6 weeks of treatment, the amount smoked daily decreased ($P < 0.01$), and though hand eczema severity decreased for both smokers and nonsmokers during the program ($P < 0.01$), HE remained more severe among smokers than nonsmokers ($P = 0.01$ at the time point of 4 weeks after returning to work). After 12 months and at 3 years, hand eczema severity remained less severe among nonsmokers than smokers (12 months: OHSI 3.1 vs. 3.7 $P < 0.01$; 3 years: OHSI 2.5 vs. 3.2 $P < 0.01$), even though hand eczema severity at 1 and 3 years showed statistically significant improvement from baseline for both smokers and non-smokers ($P < 0.01$). Smokers had more work absences because of occupational HE both in the year prior to the tertiary prevention program (37.04 vs. 25.84, $P < 0.01$) and the year after (21.89 vs. 13.94, $P = 0.02$), as well as during the subsequent 2 years (23.23 vs. 13.18, $P = 0.05$). This study did not find an association between amount smoked and occupational hand eczema severity.²¹

Molin *et al.* published a cohort study in 2015 on the relationship between chronic hand eczema and smoking on 153 patients in Munich. Patients were examined and interviewed, and asked about if they had ever smoked (‘smokers’ included past and present smokers, while ‘nonsmokers’ included never smokers). HE was characterized into categories including but

Table 1 Studies investigating the association between allergic and irritant contact dermatitis and smoking. Eight articles are included in this table; seven found a positive association between contact dermatitis and smoking

First author, year published	No. of participants	Country	Study type	Population	Determination of amount smoked	Patch-testing	Association between CD & smoking?	Details and statistics
Sprince, 1996 ⁷	158	USA	Cross-sectional	Machine operators in auto production	Not determined	Not done	Yes	CD was associated with smoking, OR 3.1, 95% CI: 1.34–7.18
Khalili, 1999 ⁸	360	Jordan	Cross-sectional	Auto repair workers	Not determined	Not done	Yes	CD was associated with smoking, $P = 0.03$
Linneberg, 2003 ⁹	1056	Denmark	Cross-sectional	General population	Never, past, light (≤ 15 g), heavy (> 15 g) smoker; pack-years also evaluated	TRUE-test®	Yes	Association found between history of > 15 pack-years smoking and contact allergy, nickel contact allergy, allergic nickel CD, adjusted OR: 1.82, 2.7, 3.04; 95% CI: 1.15–2.89, 1.4–5.2, 1.50–6.15, respectively
Lazarov, 2005 ¹⁰	190	Israel	Cohort	Attendants of a hydrotherapy course	Not determined	Not done	Yes	Relationship found between smoking and cumulative incidence of CD, $P = 0.015$
Dotterud, 2007 ¹¹	1236	Norway	Cross-sectional	General population	Not determined	TRUE-test®	Yes	Contact sensitivity was associated with smoking only in women, OR: 1.42, 95% CI: 1.01–1.99
Attwa, 2009 ¹²	87	Egypt	Cross-sectional	Auto repair workers	Not determined	TRUE-test®	Yes	Association found between the prevalence of contact dermatitis and smoking, OR: 3.59, $P < 0.05$, and 95% CI: 1.0–13.5
Thyssen, 2010 ¹³	3471	Denmark	Cross-sectional	General population	Never, past, light (≤ 15 g), heavy (> 15 g) smoker	TRUE-test®	Yes	Significant trend found between nickel sensitization and smoking, $P < 0.05$
Meijer, 1995 ¹⁴	520	Sweden	Cross-sectional	Military	Not determined	Nickel 5.0% and cobalt chloride 1.0%	No	No significant association between smoking and nickel and cobalt sensitization

CD, contact dermatitis; OR, odds ratio; CI, confidence interval.

not limited to: ACD, ICD, combined allergic and irritant contact dermatitis, and atopic dermatitis. A statistically significant association was found between the combined allergic and irritant dermatitis group and smokers versus nonsmokers (95% CI: 1.32–9.71, $P < 0.05$). No difference was found in the presence of HE when comparing past and present smokers.²²

Lai and Yew searched the 2003–2004 National Health and Nutrition Examination Survey database and evaluated data on 1301 males aged 20–59 in the United States in their cross-sectional, population-based study, and published their findings in 2016. Tobacco exposure was determined by a questionnaire; the population was stratified by amount smoked. Additionally, serum cotinine, a nicotine metabolite, was used as a biomarker for active and passive smoking (>3 ng/ml was used to classify 'smokers'). Dermatologists assessed the incidence of hand dermatitis by evaluating photographs of the participants' hands. The dermatologists found 38 cases of active hand dermatitis. Multivariate logistic regression was performed for confounding variable control. A statistically significant association was observed between current smoking status and active hand dermatitis (adjusted OR: 4.02, 95% CI: 1.13–14.24, $P = 0.031$); the odds ratio was similar for heavy smokers (adjusted OR: 4.69, 95% CI: 1.17–18.76, $P = 0.029$). Additionally, those with higher serum cotinine levels had increased risk for active hand dermatitis (OR: 2.16, 95% CI: 1.03–4.50, $P = 0.04$).²³

Articles showing no clear association between hand eczema and smoking

Three articles revealed no clear relationship between hand eczema and smoking.

In a cross-sectional study published by Meding *et al.* in 2009, the authors looked at the 1-year prevalence of HE and smoking in 13,452 Swedish bakers, dentists, and female hairdressers. The hairdressers who smoked and their controls also reported the number of cigarettes per day. When comparing hairdressers who smoke more than 10 cigarettes daily to those that smoke 0–10 daily, 22.6% (control: 14.5%) of those who smoked more than 10 cigarettes daily reported HE, while only 17.4% (control: 11.7%) of those who smoked less reported HE ($P = 0.01$, control $P = 0.06$). Also, bakers who smoked had less HE (7.7%) than those who did not smoke (12.5%, $P < 0.01$). There was no clear association between smoking and HE prevalence over 1 year; however, based on the data from the hairdresser and control group, heavier smoking may be associated with increased risk for HE.²⁴

Kütting *et al.* published a prospective cohort study in 2011 on 1020 German metal workers. Questionnaires were sent, and the participants underwent skin examination (using the HEROS, or hand eczema score for occupational screenings, quantitative skin score). Follow-up was done at 12 months. At 1 year, dyshidrotic eczema of the hands was reported by more smokers than nonsmokers ($P = 0.027$). At the baseline exam, more smokers suffered from reported dyshidrotic vesicles when compared to

nonsmokers (25.5% vs. 19.3%, $P = 0.007$). Additionally, erythema was found in more smokers than nonsmokers ($P = 0.016$). However, there was no statistically significant difference in smoking status regarding HE (past or present) in self-reports, nor between smokers and nonsmokers in the quantitative total skin score.²⁵

Brans and John published a retrospective cohort study in Germany in 2016. A total of 723 patients with HE who took part in a tertiary prevention program (a special treatment program for individuals with suspected occupational skin disease) were studied. Dermatologists performed the history and examination, and divided HE into classes including: vesicular, hyperkeratotic, and hand eczema with erythema and desquamation. Questions were asked about smoking status; smoking more than 15 cigarettes daily was classified as heavy smoking. Vesicular hand eczema was associated with smoking, while hyperkeratotic hand eczema was inversely associated with smoking (OR: 1.94, 95% CI: 1.40–2.68, $P < 0.001$; OR: 0.38, 95% CI: 0.22–0.65, $P < 0.001$, respectively). However, there was no association between all types of hand eczema and smoking status. Given that the population studied took part in a tertiary prevention program, this study likely represents individuals with more severe hand eczema than the general population.²⁶

Articles showing no positive association between hand eczema and smoking

There are seven studies that showed no association between hand eczema and smoking.

Berndt *et al.* published a prospective cohort study in 2000 on occupational hand dermatitis in metalworker trainees in Switzerland. A total of 201 young men were studied for 2.5 years. No association was found between HE and the number of cigarettes smoked daily.²⁷

Lerbaek *et al.* published a prospective follow-up, population-based, twin cohort study in 2007. Questionnaires were given to 5610 same-gender individual twins in 1996 and again to 5048 in 2005 in Denmark. The study showed no increased risk for HE based on smoking status and did not show an association between HE and amount smoked in pack-years.²⁸

In a cross-sectional study in Oslo, Norway published in 2008, Bø *et al.* evaluated 18,747 adults using a questionnaire. The authors found no association between smoking and HE.²⁹

From a private practice setting in Denmark, Veien *et al.* published a prospective cohort study of 522 patients with HE in 2008. The authors found no relationship between smoking and HE.³⁰

Röhl and Stenberg published a cross-sectional study in 2010 that included 6095 children in upper secondary school in Sweden. The authors found that smoking was not associated with self-reported HE.³¹

Patrino *et al.* (Italy, 2014) performed a case-control, observational study of a population of 516 housewives; 214 had chronic hand eczema, and 302 were used as controls. Patrino

et al. found that smoking was not associated with the incidence of HE. However, smoking was associated with a mild form of chronic hand eczema $P < 0.05$, while a more severe type of hand eczema was associated with nonsmokers $P < 0.01$.³²

Mortz *et al.* published a prospective, population-based cohort study on hand eczema in 2014 in Denmark. Participants were followed from eighth-grade to adulthood. Smoking was not found to be associated with HE based on a 1-year logistic regression analysis on HE.³³

See Table 2 for a summary of these 19 studies.

Discussion

Smoking and contact dermatitis

Overall, seven of eight studies found positive associations between contact dermatitis^{7–12} or nickel contact dermatitis^{9,13} and smoking. The study by Meijer *et al.* (1995) was the only one to find no positive association.¹⁴ Figure 1 shows a visual representation of the data from seven of eight studies. All data in Figure 1, except for parts of data from the studies by Lazarov,¹⁰ Dotterud (males only),¹¹ and Attwa,¹² lies to the right of 1 on the graph, which is the significance point for the odds ratio. Thus, much of the study data in Figure 1 is statistically significant, including the studies by Sprince,⁷ Khalili,⁸ Linneberg,⁹ Dotterud (Females Only),¹¹ and Thyssen.¹³

Some studies do not differentiate between ICD and ACD. Khalili *et al.* studied occupational contact dermatitis, and combined allergic and irritant contact dermatitis in the data analysis.⁸ Similarly, Sprince *et al.* did not differentiate between ACD and ICD.⁷ The analysis of the study by Attwa *et al.* was done with dermatologist-diagnosed contact dermatitis, which included both ACD and ICD (most diagnoses confirmed by patch testing).¹² Lazarov *et al.* did not specifically define contact dermatitis as allergic or irritant in the study introduction or methods but does mention that the mechanism of contact dermatitis in hydrotherapists is likely irritant.¹⁰ Thus, without further analysis of the data in these studies, it is difficult to determine if there are statistically significant associations between ACD and smoking, or ICD and smoking, independently.

Five of the eight studies performed patch tests,^{9,11–14} while three did not.^{7,8,10} Most studies that performed patch testing used the TRUE-test[®],^{9,11–13} while Meijer only patch tested for nickel and cobalt.¹⁴ Additionally, the timing of patch test reading was not consistent between studies. Dotterud applied the patch tests for 2 days and read after three.¹¹ Attwa *et al.* applied patches for 2 days and read at 2 days and at 3–4 days.¹² Meijer *et al.* removed and read the patches at 2 days, with questionable reactions being reread at day three.¹⁴ Thyssen *et al.* and Linneberg *et al.* read patch tests only at day two, which may overlook some individuals with contact dermatitis, as some delayed allergic reactions may appear after 2 days.^{9,13,34} If patch tests are not read at both 2 and 4 days, there may be an

underestimation of the prevalence of ACD in the populations being studied.¹³

In determining smoking status, no studies mentioned assessing for smokeless tobacco or electronic cigarettes.^{7–14} Thus, it remains unclear if some of the 'nonsmokers' were using other types of tobacco products. Additionally, most studies did not discuss the amount smoked,^{7,8,10–12,14} and many did not discuss past use of cigarettes.^{8,10–12,14}

Controlling for all confounding variables is unattainable, but it is important to control for any possible and known confounders. Some studies did assess for multiple confounders,^{9,13} while others did not mention including the assessment of confounding in their analyses. One potentially strong confounder in these analyses is gender, given that there is a greater prevalence of contact allergy among women than men, as found in the data of some of the studies.^{9,11,13}

The populations studied in half of the articles are from Northern Europe.^{9,11,13,14} The homogeneity and background smoking rates of these study populations may make it hard to generalize findings to other populations around the world.

All studies, except for one cohort study,¹⁰ are cross-sectional studies,^{7–9,11–14} which are limited in value. Performing more prospective cohort studies on this topic would be beneficial to grow the base of evidence. Randomized control studies are not feasible to explore the dermatological impact of smoking on individuals.

Smoking and hand eczema

Overall, 9 of 19 studies found a positive association between hand eczema and smoking.^{15–23} One of these studies only looked at a subtype of HE, vesicular palmar eczema.¹⁵ Three studies are cohort studies,^{16,21,22} while the others are cross-sectional.^{15,17–20,23}

Three studies of nineteen did not show a direct relationship between HE and smoking but did report on or speculate about a possible relationship. In the cross-sectional study by Meding *et al.*, a potential dose-response relationship was found between smoking and HE in the group of hairdressers and their controls, while bakers who smoked had less HE than nonsmokers.²⁴ Kütting *et al.*, in a prospective cohort study, found that smoking status had no statistically significant association with HE, but dyshidrotic hand eczema, dyshidrotic vesicles, and erythema were associated with smoking.²⁵ A retrospective cohort study by Brans and John showed that vesicular hand eczema was associated with smoking, but hyperkeratotic hand eczema was associated with not smoking.²⁶ Overall, these three studies show an unclear relationship between smoking and HE.

Seven of nineteen studies failed to show an association between smoking and HE.^{27–33} Four of the seven studies are prospective cohort studies,^{27,28,30,33} one, a case-control study,³² and two are cross-sectional studies.^{29,31}

Figure 2 shows a visual representation of the data for some of the studies found on the association between HE and

Table 2 Studies investigating the association between hand eczema and smoking. Nineteen articles are included in this table; nine show an association between HE and smoking, three are indeterminate, and seven show no association between HE and smoking

First author, year published	No. of participants	Country	Study type	Population	Determination of amount smoked	Association between HE & smoking?	Details and statistics
Edman, 1988 ¹⁵	425	Sweden	Cross-sectional	Individuals with dermatitis suspicious for contribution from contact allergy	Not determined	Yes	Vesicular palmar eczema was associated with male smokers, OR: 2.4, $P = 0.029$
Uter, 1995 ¹⁶	859	Germany	Cohort	Hairdressing apprentices	Only measured smoking >5 cigarettes daily	Yes	Smoking >5 cigarettes daily was associated with skin changes, OR: 1.36, 95% CI: 1.01–1.83, and HE, OR: 1.92, 95% CI: 1.27–2.91; $P < 0.05$
Montrémery, 2005 ¹⁷	9316	Sweden	Cross-sectional	General population	Not determined	Yes	Smoking was associated with 1-year prevalence of HE, OR: 1.35, 95% CI 1.04–1.75, $P = 0.022$
Thyssen, 2010 ¹⁸	3471	Denmark	Cross-sectional	General population	Never, past, light (≤ 15 g), heavy (>15 g) smoker	Yes	Statistically significant trend found between amount smoked and HE, using a fully adjusted statistical model, $P = 0.005$
Meding, 2010 ¹⁹	25,428	Sweden	Cross-sectional	General population	Never, past, occasional, smoking 1–7, 8–15, >15 cigarettes daily	Yes	Dose–response relationship found between smoking status and HE, prevalence proportion ratio 1.05, $P < 0.010$
Anveden Berglind, 2011 ²⁰	27,793	Sweden	Cross-sectional	General population	Not determined	Yes	Association found between 1-year prevalence of HE and smoking status, prevalence proportion ratio 1.025, 95% CI: 1.006–1.044
Brans, 2014 ²¹	1608	Germany	Prospective cohort	Individuals with occupational HE participating in a tertiary prevention program	Number of cigarettes smoked	Yes	HE was more severe in smokers than nonsmokers initially, $P < 0.02$; irritant CD was more common in nonsmokers, 85.8%, than smokers, 78.7%, $P = 0.01$; after 1 and 3 years, HE severity was lower in nonsmokers than smokers, $P < 0.01$; smokers had more work absences because of occupational HE than nonsmokers in the year prior to the program, $P < 0.01$, the year after, $P = 0.02$, and over the subsequent 2 years, $P = 0.05$
Molin, 2015 ²²	153	Germany	Cohort	Individuals with chronic HE	Not determined	Yes	Association found between combined allergic and irritant dermatitis group and smoking, 95% CI: 1.32–9.71, $P < 0.05$
Lai, 2016 ²³	1301	USA	Cross-sectional	General population	Never, past, light (≤ 15 g), heavy (>15 g), exposure at work/home, cotinine level (>3 ng/mL = smoker, ≤ 3 ng/mL = non-smoker)	Yes	Significant associations found between active HE and current smoking, adjusted OR: 4.02, $P = 0.031$, heavy smoking, adjusted OR: 4.69, $P = 0.029$, and serum cotinine level OR: 2.16, $P = 0.04$

Table 2 Continued

First author, year published	No. of participants	Country	Study type	Population	Determination of amount smoked	Association between HE & smoking?	Details and statistics
Meding, 2009 ²⁴	13,452	Sweden	Cross-sectional	Bakers, dentists, female hairdressers, and their controls	Only determined for hairdressers and their controls – number of cigarettes daily (divided by 0–10 and >10)	Indeterminate	Comparing hairdressers smoking >10 cigarettes daily to those smoking 0–10 daily, 22.6% (control: 14.5%) of heavier smokers reported HE, while only 17.4% (control: 11.7%) lighter smokers reported HE; $P = 0.01$ (control: $P = 0.06$); bakers who smoked had less HE, 7.7%, than nonsmokers, 12.5%, $P < 0.01$; no clear association found between smoking and HE prevalence over 1 year
Kütting, 2011 ²⁵	1020	Germany	Prospective cohort	Metal workers	Not determined	Indeterminate	More smokers reported dyshidrotic HE at 1 year than non-smokers, $P = 0.027$; more smokers reported dyshidrotic vesicles than nonsmokers; 25.5% versus 19.3%, $P = 0.007$; more smokers had erythema than nonsmokers, $P = 0.016$; however, no statistically significant difference found in self-reports of HE (past or present) nor in the quantitative total skin score
Brans, 2016 ²⁶	723	Germany	Retrospective cohort	Individuals with occupational HE participating in a tertiary prevention program	Nonsmokers, ex-smokers, current smokers, heavy smokers defined as >15 cigarettes daily	Indeterminate	Vesicular HE associated with smoking, OR: 1.94, 95% CI: 1.40–2.68, $P < 0.001$; hyperkeratotic HE inversely associated with smoking status, OR: 0.38, 95% CI: 0.22–0.65, $P < 0.001$; no association found between all types of HE and smoking status
Berndt, 2000 ²⁷	201	Switzerland	Prospective cohort	Metalworker trainees	Number of cigarettes smoked daily	No	No association found between HE and number of cigarettes smoked daily
Lerbaek, 2007 ²⁸	5610, then 5048	Denmark	Prospective twin cohort	General population, twins	Never, past, and current smokers, and evaluation of pack-years ($0 \leq 15$, and > 15)	No	No increased risk for hand eczema based on smoking status, no association found between HE and amount smoked in pack-years
Bø, 2008 ²⁹	18,747	Norway	Cross-sectional	General population	Never, past, and current smoker; past and current smoking (< 20 , ≥ 20 cigarettes daily)	No	No association found between smoking and HE
Veien, 2008 ³⁰	522	Denmark	Prospective cohort	Patients with HE	Not determined	No	No relationship found between smoking and HE
Röhl, 2010 ³¹	6095	Sweden	Cross-sectional	Upper secondary school children	Not determined	No	Smoking was not associated with self-reported HE
Patruno, 2014 ³²	516	Italy	Case-control	Housewives with chronic HE and controls	Nonsmokers, smokers; 1–10, 11–20, and 21–30 cigarettes daily	No	Smoking was not associated with incidence of HE; smoking was associated with a mild form of chronic HE, $P < 0.05$; a more severe type of HE was associated with nonsmokers, $P < 0.01$

Table 2 Continued

First author, year published	No. of participants	Country	Study type	Population	Determination of amount smoked	Association between HE & smoking?	Details and statistics
Mortz, 2014 ³³	1206	Denmark	Prospective cohort	Initial cohort of 8th grade schoolchildren who were later evaluated as young adults	Not determined	No	Smoking was not associated with HE based on a 1-year logistic regression analysis

OR, odds ratio; CI, confidence interval; HE, hand eczema; CD, contact dermatitis.

smoking. Although most of the studies include slightly dissimilar characteristics (see the large number of symbols in the figure legend representing differences, including how smoking is classified and specific classifications of hand eczema), odds ratios were either found or calculated for 12 of 19 studies. Six of the odds ratios, including data from studies by Edman,¹⁵ Uter,¹⁶ Montn  mery,¹⁷ Thyssen,¹⁸ Mending (calculation specific to never and daily smokers >15 cigarettes daily),¹⁹ and Lai²³ lie to the right of 1 and have confidence intervals that do not cross 1, which is statistically significant, showing a trend toward an association between HE and smoking. A number of studies have 95% confidence intervals that cross the significance number of 1; these include data from one Meding study (calculation specific to never and daily smokers),¹⁹ data from a different Meding study,²⁴ both values calculated from K  tting's study,²⁵ both values from B  's study,²⁹ and data from studies by R  hrl,³¹ Patruno,³² and Mortz.³³ Data from these studies indicate that there is no statistically significant association between HE and contact dermatitis. Only four studies have odds ratios less than 1; these include data from Meding's study,²⁴ both values from B  's study,²⁹ and data from studies by R  hrl³¹ and Patruno,³² however, all of their upper confidence intervals cross 1, so no statistically significant association is seen between smoking and HE in these studies.

Many of the 19 studies did not look in detail into the smoking habits of individuals; for example, smokeless tobacco products were generally not assessed.^{15–21,24,25,27–33} Eight studies did not quantify the amount smoked,^{15,17,20,22,25,30,31,33} and 12 did not study or mention studying past smokers who quit smoking.^{15–17,20,21,24,25,27,30–33} However, Lai and Yew did use a laboratory measurement, serum cotinine—a nicotine metabolite, as a surrogate marker for the amount of nicotine used by their study participants.²³

Some studies primarily used questionnaires for their analyses, without dermatologic skin examinations;^{17,19,20,24,28,29} while this may increase the number of participants available to be studied, recall bias may occur, along with a false measurement of disease prevalence.

In the studies that looked at the association between HE and smoking, all but one were done in Europe,^{15–22,24,25,27–33} and most were performed in northern Europe.^{15,17–20,24,28–31,33} The only study done outside of Europe was performed in the United States.²³ Thus, the homogeneity of the populations studied may make it difficult to extend these conclusions to other populations across the world.

Of note, the two studies by Thyssen appear to have used the same population of individuals, although one study focused on contact dermatitis,¹³ while the other studied HE.¹⁸

It is important to note that HE is a broad term that includes multiple subtypes, including ACD, ICD, atopic contact dermatitis, and combined variants. Not all articles mention the specific type of HE discussed. However, a number of articles split HE into component subtypes (such as ACD, ICD, and atopic

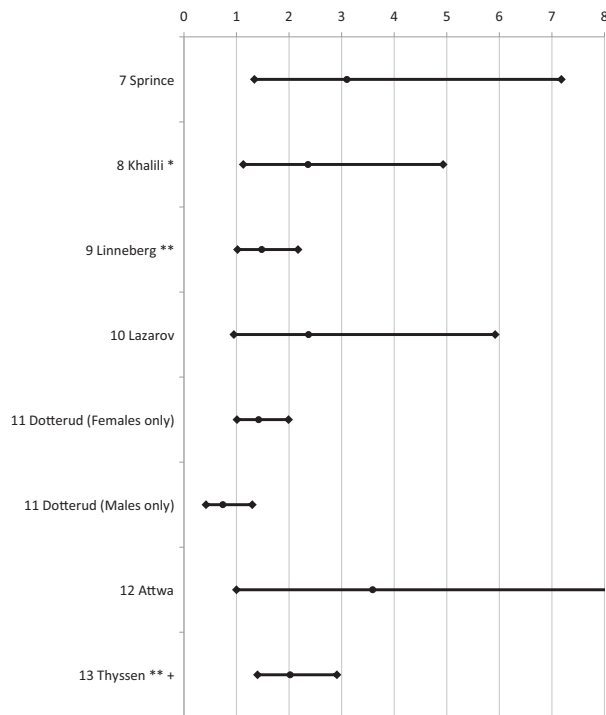


Figure 1 Studies investigating the association between contact dermatitis and smoking, odds ratio and 95% confidence intervals. Data from seven of eight of the studies were analyzed and included in this figure. The odds ratio and confidence interval relate to the association between contact dermatitis and smoking. If an odds ratio is greater than 1, and the confidence interval associated does not include 1 and is greater than 1 within the interval, then there is a statically significant association between contact dermatitis and smoking. The figure shows the 95% confidence interval as a line with diamonds at each end, with the odds ratio as the round point within the line. Significance is seen when the left diamond does not cross 1 on the graph. The odds ratios and confidence intervals of studies 7, 10, and 11 are from adjusted models, while studies 8, 9, 12, and 13 are statistics from crude analysis. The study by Meijer (14) did not include an odds ratio, confidence interval, or numbers for calculations of this association. Note: numbers correspond to the references section. *Odds ratio and 95% confidence interval were calculated from the paper's data; **Odds ratio and 95% confidence interval were calculated from the papers' data, comparing current smokers to never smokers; +Data limited to nickel sensitization and smoking

dermatitis, combined variants, or other variants) and their relation to smoking.^{18,21,22,26} Others divided HE by morphology (such as by vesicular or hyperkeratotic types, erythema, or papules, among other classifications),^{25,26} while Edman specifically studied vesicular palmar eczema in relation to smoking.¹⁵ As HE can be classified in multiple ways, it is important to distinguish the association between smoking and the specific types of HE, which many articles did not discuss. As the subtypes of HE, including ACD, ICD, and atopic dermatitis, are different disease entities with different causes and modulating factors, not

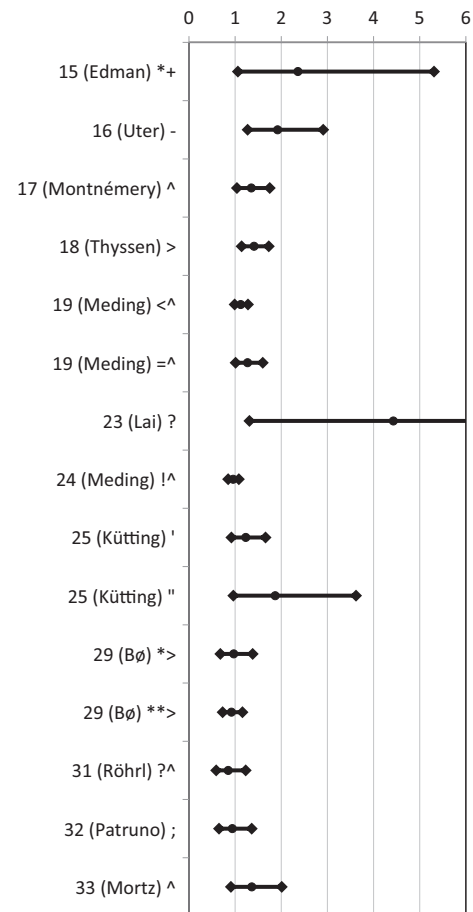


Figure 2 Studies investigating the association between hand eczema and smoking, odds ratio and 95% confidence intervals. Data are included from 12 studies. The odds ratio and confidence interval relate to the association between hand eczema and smoking. If an odds ratio is greater than 1, and the confidence interval associated does not include 1 and is greater than 1 within the interval, then there is a statically significant association between hand eczema and smoking. The figure shows the 95% confidence interval as a line with diamonds at each end, with the odds ratio as the round point within the line. Significance is seen when the left diamond does not cross 1 on the graph. The odds ratios and confidence intervals of studies 16, 17, 29, 31 are from adjusted models, while the ratios and confidence intervals of studies 15, 18, 19, 23, 24, 25, 32, and 33 are calculated from the data in the papers. Studies 20, 21, 22, 26, 27, 28, and 30 were not included as the data from these papers could not be used for odds ratio calculations comparable to the studies included in the figure. Note: numbers correspond to the references section. *Males; **Females; + calculation specific to vesicular palmar eczema; - calculation specific to smoking >5 cigarettes daily; > calculation comparing never and current smokers; < calculation comparing never and daily smokers; = calculation comparing never and daily smokers > 15 cigarettes daily; ? calculation specific to current smokers; ! calculation specific to current smokers, included are groups: Bakers, Dental Technicians, Hairdressers, and their controls; ; calculation specific to past hand eczema, baseline exam; ^ calculation specific to past hand eczema, 1 year follow-up; ' calculation specific to chronic hand eczema; " calculation for 1 year prevalence

separating the entities in the analysis between HE and smoking is a source of bias and possible confounding.

Reviews on smoking and hand eczema

In addition to the 19 original studies, two reviews were found on the relationship between hand eczema and smoking.

A systematic review of 20 articles in 2015 by Sørensen *et al.* looked at the link between tobacco smoking and hand eczema. Overall, there was inconsistency in the study results on hand eczema and smoking. About half of the articles showed a positive association between hand eczema and smoking, while about half showed no association, and one study reported that smoking was protective for hand eczema. Taken as a whole, there may be a positive association between smoking and hand eczema, especially in those with high-risk occupations. However, the authors felt that more studies were needed and found that there were few prospective studies in their search.³⁵

Lukács *et al.* published a systematic review and meta-analysis in 2015 about the possible link between smoking and hand dermatitis. There were three studies, all from Sweden, that met inclusion criteria. The meta-analysis showed no significant difference between hand dermatitis and smoking (OR: 0.99, 95% CI: 0.88–1.11). Additionally, there was a high amount of heterogeneity across the studies ($I^2 = 72\%$). These authors express a need for more studies on the topic.³⁶

Sørensen *et al.* discusses how smoking affects the skin, including increasing pro-inflammatory cytokines, such as TNF-alpha, TNF-alpha receptors, and interleukin-6, as well as delaying wound healing through smoking's effects on vasculature and blocking fibroblast migration to damaged skin.³⁵ Lukács *et al.* adds that smoking also decreases anti-inflammatory cytokines including interleukin-10, along with increasing pro-inflammatory cytokines including interleukin-1 and interleukin-8, and that smoking induces microvascular vasoconstriction in the skin.³⁶

These two systematic reviews on the possible association between hand eczema and smoking are inconclusive; more robust studies are needed on the topic. An association between smoking and hand dermatitis cannot be excluded.

Smoking and nickel exposure

One potential confounding variable in this review is that tobacco and cigarettes can be sources for nickel exposure. Citing two articles by Sunderman *et al.* and Szadkowski *et al.*, Beckno mentions that there is an estimated amount of 1.1–3.1 µg of nickel in each cigarette.³⁷ Similarly, Mastromatteo cites a US Environmental Protection Agency source in his chapter on nickel, mentioning that there is 1–3 µg of nickel in one cigarette.³⁸ Stojanović, *et al.*, found that there is a large amount of nickel in cigarettes and tobacco (2.32–4.20 mg/kg in cigarettes, and 2.20–4.91 mg/kg in tobacco).³⁹ Also, Stojanović *et al.* tested the urine of smokers and nonsmokers and found a higher

concentration of nickel in smokers' urine (median 1.20 µg/l smokers, median 0.50 µg/l nonsmokers, $P < 0.05$).³⁹ Nickel is one of the most common sensitizers in ACD; if smoking exposure directly causes nickel sensitization, then a large amount of data could be biased in studies assessing the relationship between smoking and ACD or HE.

Cigarette components as a direct cause of allergic contact dermatitis

A review by Glick *et al.* in 2009 found that the components of cigarettes might directly cause allergic contact dermatitis.⁴⁰ The review includes discussions on various components that may cause contact dermatitis, including filters, paper, and tobacco leaves, as well as additives such as cocoa, menthol, licorice, colophony, and formaldehyde.⁴⁰ The discussion includes information on the use of patch testing for cigarette components.⁴⁰ Thus, cigarette smoking can be a direct cause of allergic contact dermatitis.

Conclusion and Recommendations

Smoking may be a risk factor for both allergic and irritant contact dermatitis, as well as hand eczema.

Given the small number of studies on the relationship between smoking and contact dermatitis, the uniformity of population studied and of study type used, and the limited control on confounding variables, a definitive statement on the possible link between smoking and contact dermatitis cannot be made. However, seven of the eight studies found statistically significant data showing a relationship between smoking and contact dermatitis.

Regarding hand eczema and smoking, nineteen original studies were found on this topic, and a larger variety of study types were used. However, the uniformity of population studied and limited confounding variable analyses make it difficult to make a definitive statement on the relationship between hand eczema and smoking. Furthermore, nine of nineteen studies found a positive relationship between smoking and hand eczema, while three were inconclusive, and seven showed no relationship. While no definitive statement on the relationship between hand eczema and smoking can be made, the scope of this review was limited to a description of published work.

More studies are needed on the topic of smoking and its relationship with contact dermatitis and hand eczema. Given the recent increase in use of electronic cigarettes, as well as the population of individuals using smokeless tobacco, including a detailed history of smoking status and the use of smokeless tobacco products, or even measuring surrogate markers for nicotine, would provide useful and potentially more accurate data for future studies on this topic.

Continuing to propose study types with a stronger level of evidence, particularly prospective cohort studies, is encouraged. Additionally, including a wider range of population types from across the world would make the data more generalizable.

Finally, in the analysis of contact dermatitis, patch testing is recommended, particularly in the study of allergic contact dermatitis.

Limitations to this study include only using articles available in English, as well as limiting the search to the PubMed and SCOPUS databases. Thus, the restricted search criteria used in this review may not find all possible articles on this topic.

As smoking might be associated with contact dermatitis and hand eczema, it is recommended to encourage all patients, particularly those with contact dermatitis and hand eczema, to refrain from using tobacco products. Ask, advise, assess, assist, arrange.⁴¹

Questions (answers provided after references)

- 1 Approximately how much of the populace of North America and Western Europe is affected by allergic contact dermatitis?
 - a. 5%
 - b. 10%
 - c. 20%
 - d. 30%
 - e. 40%
- 2 What was the prevalence of smoking in the United States in 2014?
 - a. 10.4%
 - b. 16.8%
 - c. 18.9%
 - d. 21.4%
 - e. 25.0%
- 3 Which disease may smoking be associated with?
 - a. Hidradenitis Suppurativa
 - b. Psoriasis
 - c. Pustulosis Palmoplantaris
 - d. Systemic Lupus Erythematosus
 - e. All of the above
- 4 Which type of dermatitis is a type 4 hypersensitivity reaction?
 - a. Allergic Contact Dermatitis
 - b. Atopic Dermatitis
 - c. Irritant Contact Dermatitis
 - d. Occupational Contact Dermatitis
- 5 Which type of dermatitis is related to exposure at work but is not necessarily a hypersensitivity reaction?
 - a. Allergic Contact Dermatitis
 - b. Atopic Dermatitis
 - c. Occupational Contact Dermatitis
- 6 What is a surrogate marker for tobacco exposure?
 - a. Hair norcocaine
 - b. Serum cholyglycine
 - c. Serum cotinine
 - d. Urine benzoylecgonine
 - e. Urine cannabinoids
- 7 What is the most common metal sensitizer in allergic contact dermatitis?
 - a. Chromium
 - b. Gold
 - c. Mercury
 - d. Nickel
 - e. Silver
- 8 Which components of cigarettes may directly cause allergic contact dermatitis?
 - a. Filters
 - b. Formaldehyde
 - c. Licorice
 - d. Tobacco leaves
 - e. All of the above
- 9 What test can help differentiate between allergic contact dermatitis and irritant contact dermatitis?
 - a. Patch Testing
 - b. Serum Eosinophils
 - c. Skin Examination
 - d. Skin Prick Testing
- 10 What are some of the A's that can assist the clinician in advising their patient to quit smoking?
 - a. Advise
 - b. Arrange
 - c. Ask
 - d. Assess
 - e. Assist
 - f. All of the above

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Answers to questions

1. c, 2. b, 3. e, 4. a, 5. c, 6. c, 7. d, 8. e, 9. a, 10. f