

Smoking might be a risk factor for contact allergy

Allan Linneberg, MD, PhD,^{a,b} Niels Henrik Nielsen, MD, PhD,^b
Torkil Menné, MD, DMSc,^b Flemming Madsen, MD, DMSc,^c and
Torben Jørgensen, MD, DMSc^a *Copenhagen, Denmark*

Background: Contact allergy is a major public health problem in industrialized countries. Hitherto, known risk factors for contact allergy have mainly included increased exposure to allergens. There are no published data on the relation between smoking and contact allergy.

Objective: To investigate the association between smoking and contact allergy.

Methods: The study population comprised a cross-sectional, general population-based sample of 15- to 69-year-old persons living in Copenhagen, Denmark. A total of 1056 persons (73.6% of the invited) were given a patch test (TRUE test).

Contact allergy was defined as a positive patch test result to at least 1 of 23 allergens. Nickel contact allergy was defined as a positive patch test reaction to nickel. Allergic nickel contact dermatitis was defined as a history of eczema on exposure to metallic objects and a positive patch test reaction to nickel. A detailed smoking history was obtained in a questionnaire.

Results: Contact allergy (adjusted odds ratio, 1.8; 95% CI, 1.2 to 2.9), nickel contact allergy (adjusted odds ratio, 2.7; 95% CI, 1.4 to 5.2), and allergic nickel contact dermatitis (adjusted odds ratio, 3.0; 95% CI, 1.5 to 6.2) were significantly associated with a smoking history of more than 15 pack-years. Moreover, these associations showed a significant dose-response relation, and they were independent of sex, age, and exposure to nickel, as reflected by a history of ear piercing.

Conclusions: These data raise the hypothesis that smoking increases the risk of contact allergy. Further epidemiologic studies and investigations into the possible mechanisms are warranted. (*J Allergy Clin Immunol* 2003;111:980-4.)

Key words: Allergic contact dermatitis, contact allergy, delayed hypersensitivity, nickel, patch tests, smoking, tobacco

Allergic contact dermatitis is a major public health problem in industrialized countries.¹⁻⁴ Allergic contact dermatitis is the consequence of exposure to an allergen exceeding the threshold concentration in a contact-sen-

sitized individual. Contact sensitivity (contact allergy) is defined as a positive patch test, using one of the standardized technologies either the chamber test or the TRUE test.

Hitherto, known risk factors for contact allergy has mainly included increased exposure to allergens. Little is known about the role of other lifestyle factors in the development of contact allergy. To our knowledge, there is no previous study that has addressed the relation between smoking and contact allergy. A few studies have reported the association between smoking and hand dermatitis. Edman⁵ and Sprince et al⁶ found a positive association between smoking and hand dermatitis. However, Berndt et al⁷ were not able to confirm this association.

We hypothesized that smoking, which has an influence on many immunologic factors,⁸ could have an influence on the immunologic mechanisms involved in contact allergy. Thus, the aim was to investigate the relation of smoking to contact allergy in a population-based, cross-sectional study.

METHODS

Study population

The study was conducted according to a 2-stage protocol. In the first stage, a screening questionnaire on respiratory symptoms was mailed to a sample of 15- to 69-year-old subjects ($n = 8000$) living in the western part of Copenhagen, the capital of Denmark. The sample was drawn randomly from the Civil Registration System. A total of 6998 or 87.5% responded to the screening questionnaire. In the second stage, a random group and a symptom group selected among the respondents were invited to a health examination.

The symptom group comprised all respondents ($n = 788$) who had reported upper ("itchy or stuffy nose or sneezing") or lower ("shortness of breath or trouble breathing") respiratory symptoms on exposure to either pollen or furry animals in the screening questionnaire.⁹ The random group comprised 647 subjects who were randomly selected from among the remaining respondents. Subsequently, 635 (participation rate, 80.6%) and 477 (participation rate, 75.5%) subjects were examined in the symptom and random group, respectively. Thus, a total of 1112 subjects (overall participation rate, 77.5%) were examined, and of these, a total of 1056 were given the patch test. The invitational procedure and characteristics of both participants and nonparticipants have previously been described in more detail.⁹ Examinations took place between February 1990 and January 1991. The Ethics Committee of Copenhagen County approved the study. A written informed consent form was obtained from all participants before the beginning of the study.

Patch tests

The patch tests used were the ready-to-apply TRUE test (ALK-Abelló A/S, Hørsholm, Denmark).¹⁰⁻¹² The haptens and mixtures of

From the ^aCentre for Preventive Medicine, Glostrup University Hospital, Copenhagen, Denmark; the ^bDepartment of Dermatology, Gentofte University Hospital, Copenhagen, Denmark; and the ^cDepartment of Internal Medicine B, Frederiksberg University Hospital, Copenhagen, Denmark.

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Reprint requests: Allan Linneberg, MD, PhD, Centre for Preventive Medicine, Glostrup University Hospital, 57 Ndr. Ringvej, Entrance 8, 7th Floor, DK-2600 Glostrup, Denmark.

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TABLE I. Prevalence of contact allergy (to at least one of 23 allergens), nickel contact allergy, allergic nickel contact dermatitis, history of ear piercing, skin prick test reactivity, and smoking among women and men

	Women % (n/total)	Men % (n/total)	P value†
Contact allergy	23.2 (133/574)	10.4 (50/482)	<.001
Nickel contact allergy	15.2 (87/574)	1.5 (7/482)	<.001
Allergic nickel contact dermatitis*	13.8 (79/573)	0.8 (4/482)	<.001
Ear piercing	70.4 (419/595)	14.1 (73/517)	<.001
Skin prick test reactivity	38.1 (226/593)	48.0 (248/517)	<.001
Smoking status			
Never	35.3 (210/595)	30.6 (158/517)	<.001 (3 df)
Previously	16.6 (99/595)	23.6 (122/517)	
≤15 g/d	33.4 (199/595)	20.5 (106/517)	
>15 g/d	14.6 (87/595)	25.3 (131/517)	
Lifetime smoking			
0 pack-years	38.5 (227/589)	33.6 (171/515)	<.001 (2 df)
≤15 pack-years	40.4 (238/589)	30.7 (158/515)	
>15 pack-years	21.1 (124/589)	35.7 (184/515)	

*Persons with history of eczema from wearing earpins or earrings, under the tightener of one's watch strap, or under the button of one's jeans and a positive patch test reaction to nickel were defined as cases of allergic nickel contact dermatitis.

†P value of χ^2 test for the comparison of women and men.

haptens in this test series comprise widely used environmental chemicals such as metals including nickel, preservatives, substances in cosmetics, glues, rubber, and medicaments. The haptens differed from the European Standard Series (Hermal-Chemi, Germany) by including thiomersal and excluding primine and formaldehyde. Directions to apply the patch tests to the upper back 2 days before the examination were mailed with the patch test. The patch tests were read one half to 1½ hours after removal. Reactions were classified according to the International Contact Dermatitis Research Group.¹³ A positive reaction (+) was defined as at least homogenous redness and palpable infiltration in the test area. Reactions not fulfilling these criteria, whether these were follicular reactions, faint erythema, or typical irritant reactions, were classified as nonallergic reactions. Contact allergy was defined as a positive patch test reaction to at least 1 of 23 allergens. Nickel contact allergy was defined as a positive patch test reaction to nickel. Nielsen read all reactions. Menné reviewed photos of the test sites, and in the case of disagreement, consensus was reached by discussion. If the tests were not applied 2 days before attending, or if the contact with the skin was poor, a new appointment was made when possible.

Skin prick test

Skin prick test reactivity against a panel of 10 common inhalant allergens was performed with the Phazet system (Pharmacia & Upjohn Diagnostics AB, Uppsala, Sweden), as previously described.⁹ Skin prick test reactivity was defined as a positive (mean wheal diameter of 3 mm or more) skin prick test to at least 1 of 10 allergens.

Questionnaire

A questionnaire about health, lifestyle, and socioeconomic factors was sent with a standard invitation letter to the participants. Information about tobacco exposure was obtained in the questionnaire in as much detail as possible. Current and previous smokers were asked about type of tobacco, daily tobacco consumption (calculated for cheroot and cigar smokers by equating 1 cheroot to 3 g tobacco and 1 cigar to 5 g tobacco), and how long a time they had smoked. Pack-years were calculated in smokers and ex-smokers as years of smoking × daily consumption in grams/20. A total of 30 previous or current smokers who stated that they had been smoking

0 years or consumed 0 grams per day were categorized as smoking 0 pack-years. These subjects did not differ from never-smokers in the prevalence of contact allergy or nickel contact allergy.

The questionnaire described eczema as follows: "Eczema is an itching skin disease showing redness, dryness, and eventually vesicles and suppuration. Eczema is present in the same skin area for some time." Allergic nickel contact dermatitis was defined as an affirmative answer to the question "Have you ever had eczema from wearing earpins or earrings, under the tightener of your watch strap, or under the button of your jeans?" and a positive patch test reaction to nickel. Ear piercing was defined as an affirmative answer to the question "Have you ever had your ears pierced?"

The following socioeconomic variables were defined: vocational training (yes, no), educational level (≤9, 10 to 11, 12 to 13, ≥14 years), type of residence (house, apartment, other), ownership of residence (yes, no), and social group (self-employed, white-collar workers, skilled blue-collar workers, unskilled blue-collar workers, others).

Analysis

The association between smoking and contact allergy was expressed as odds ratios with 95% confidence intervals. Odds ratios were adjusted for sex, age (15 to 34, 35 to 49, 50 to 69 years), and ear piercing (yes, no) in a logistic regression model. First-order interactions between smoking and these variables were investigated. In further analyses, confounding by socioeconomic variables and skin prick test reactivity was investigated. All data were analyzed with SPSS for Windows (Release 10.0).

RESULTS

The prevalence of contact allergy and nickel contact allergy was substantially higher among women than among men (Table I). The prevalence of current smoking was similar among men and women, but heavy smoking (>15 g/d) was more prevalent among men. When adjusting for sex, age, and ear piercing, contact allergy was significantly associated with current smoking (>15 g/d) and previous smoking (Table II). The association was more clear and with a significant dose-response relation when

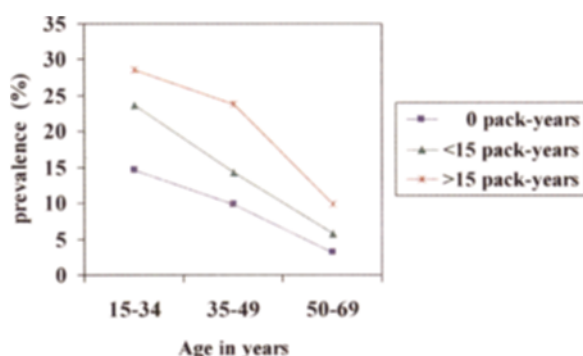


FIG 1. Prevalence of nickel contact allergy by age and smoking among women (n = 569).

TABLE II. Effect of smoking on prevalence of contact allergy (positive patch test reaction to at least 1 of 23 allergens)

	Contact allergy % (n/total)	Odds ratio* (95% CI)
Smoking status		
Never	13.6 (47/346)	1 P = .083†
Previously	19.7 (41/208)	1.88 (1.17-3.03)
≤15 g/d	19.7 (58/295)	1.37 (0.89-2.11)
>15 g/d	17.9 (37/207)	1.65 (1.01-2.69)
Lifetime smoking		
0 pack-years	13.0 (49/376)	1 P = .006†
≤15 pack-years	21.8 (82/377)	1.66 (1.11-2.47)
>15 pack-years	17.2 (51/296)	1.82 (1.15-2.89)

*Adjusted for age, sex, and ear piercing.

†P value for test for trend.

smoking was defined as pack-years. There was no statistically significant interaction between smoking and sex. Thus, the effect of smoking on the prevalence of contact allergy was similar among women and men; nor was there any statistically significant interaction between smoking and age or between smoking and ear piercing.

Among women, the prevalence of nickel contact allergy was significantly associated with current smoking, with a clear dose-response relation (Table III). Again, there was no statistically significant interaction between smoking and age or between smoking and ear piercing. Only 7 men had positive patch test reactions to nickel. None of these were never-smokers (Table III). Fig 1 shows the prevalence of nickel contact allergy by age and by smoking among women. It shows that the dose-response relation between smoking and the prevalence of nickel contact allergy was independent of age group. The test for interaction between smoking and ear piercing was not statistically significant. Thus, the association between nickel contact allergy appeared to be present both among persons with and without a history of ear piercing (Table IV).

The association between smoking and allergic nickel contact dermatitis was quite similar to, although slightly

stronger than, the association between smoking and nickel contact allergy (Table V).

The estimates for the effect of smoking on the prevalence of contact allergy, nickel contact allergy, and allergic nickel contact dermatitis were essentially similar when they were further adjusted for socioeconomic variables and skin prick test reactivity (data not shown).

The selection of participants in a symptom and random group could potentially induce bias. However, the effect of smoking was similar in the random and symptom group. Thus, nickel contact allergy was associated with a smoking history of more than 15 pack-years both among subjects with (adjusted odds ratio, 2.9; 95% CI, 1.3 to 6.4) and without (adjusted odds ratio, 2.6; 95% CI, 0.8 to 8.9) symptoms of respiratory allergy. Similarly, the effect of smoking was similar among subjects with and without skin prick test reactivity. Furthermore, including a group variable (symptom versus random group) or skin prick test reactivity in the logistic regression models did not change the estimates substantially. In these models, neither the group variable nor skin prick test reactivity was significantly associated with outcome (contact allergy or nickel contact allergy).

DISCUSSION

We found a significant positive dose-response relation between smoking and contact allergy, nickel contact allergy, and allergic nickel contact dermatitis.

The possibility that the observed association between smoking and contact allergy is due to confounding by other factors should be considered. However, our analyses showed that the effect of smoking was independent of well-known determinants of contact allergy such as sex, age, and ear piercing. Furthermore, socioeconomic variables did not appear to explain the results. One might further speculate that smokers are more frequently exposed to, for example, nickel. In fact, a history of ear piercing was more frequent in smokers compared with never-smokers (data not shown). However, adjustment for ear piercing did not change the results substantially, and the effect of smoking was apparent both among subjects with and without a history of ear piercing (Table IV). Thus, there was no evidence to support that the observed associations were due to confounding.

The frequencies of patch test reactions were read at day 2 only. Shehade et al¹⁴ found that of 4210 allergic reactions to an extended standard series recorded at day 4 in 4271 consecutive patients, 993 (24%) were negative at day 2. Thus, the frequencies of sensitization were probably underestimated. However, we have no reason to believe that this misclassification was differential, that is, different between smokers and nonsmokers.

It should be considered whether the overrepresentation of atopic individuals in our study population could have influenced the results. However, adjusting for atopy as reflected by respiratory symptoms or skin prick test reactivity to inhalant allergens did not change the results. Furthermore, the effect of smoking on the prevalence of

TABLE III. Effect of smoking on prevalence of nickel contact allergy

	Women		Men	
	Nickel allergy % (n/total)	Odds ratio† (95% CI)	Nickel allergy % (n/total)	P value*
Smoking status				
Never	9.9 (20/202)	1 <i>P</i> = .003‡	0 (0/144)	.215 (3 <i>df</i>)
Previously	9.5 (9/95)	0.89 (0.38-2.06)	2.7 (3/113)	
≤15 g/d	19.5 (38/195)	1.80 (0.99-3.27)	2.0 (2/100)	
>15 g/d	24.4 (20/82)	2.67 (1.32-5.42)	1.6 (2/125)	
Lifetime smoking				
0 pack-years	9.6 (21/218)	1 <i>P</i> = .007‡	0 (0/158)	.112 (2 <i>df</i>)
≤15 pack-years	18.5 (43/233)	1.63 (0.91-2.92)	2.8 (4/144)	
>15 pack-years	19.5 (23/118)	2.52 (1.27-4.98)	1.7 (3/178)	

**P* value of Fisher exact test for association between smoking and prevalence of nickel allergy (odds ratios are not applicable).

†Adjusted for age and ear piercing.

‡*P* value for test for trend.

TABLE IV. Effect of smoking on prevalence of nickel contact allergy stratified by ear piercing

	Ear-pierced		Never ear-pierced	
	Nickel allergy % (n/total)	Odds ratio* (95% CI)	Nickel allergy % (n/total)	Odds ratio* (95% CI)
Smoking status				
Never	12.9 (19/147)	1 <i>P</i> = .007†	0.5 (1/199)	1 <i>P</i> = .142†
Previously	12.2 (9/74)	0.92 (0.39-2.18)	2.2 (3/134)	5.01 (0.49-51.50)
≤15 g/d	19.9 (34/171)	1.54 (0.82-2.88)	4.8 (6/124)	9.85 (1.15-84.2)
>15 g/d	26.0 (20/77)	2.67 (1.29-5.52)	1.5 (2/130)	3.81 (0.32-44.98)
Lifetime smoking				
0 pack-years	12.6 (20/159)	1 <i>P</i> = .016†	0.5 (1/217)	1 <i>P</i> = .126†
≤15 pack-years	18.6 (41/220)	1.50 (0.82-2.72)	3.8 (6/157)	9.41 (1.11-80.06)
>15 pack-years	24.1 (21/87)	2.43 (1.19-5.00)	2.4 (6/209)	6.12 (0.66-57.06)

*Adjusted for age and sex.

†*P* value for test for trend.

TABLE V. Effect of smoking on prevalence of allergic nickel contact dermatitis

	Allergic nickel contact dermatitis* % (n/total)	Odds ratio† (95% CI)
Smoking status		
Never	4.6 (16/346)	1 <i>P</i> = .001‡
Previously	5.3 (11/207)	1.45 (0.64-3.29)
≤15 g/d	12.2 (36/295)	2.23 (1.18-4.21)
>15 g/d	9.7 (20/207)	3.21 (1.55-6.65)
Lifetime smoking		
0 pack-years	4.5 (17/376)	1 <i>P</i> = .001‡
≤15 pack-years	11.4 (43/376)	2.12 (1.15-3.91)
>15 pack-years	7.8 (23/296)	3.04 (1.50-6.15)

*Persons with history of eczema from wearing earpins or earrings, under the tightener of one's watchstrap, or under the button of one's jeans and a positive patch test to nickel were defined as cases of allergic nickel contact dermatitis.

†Adjusted for age, sex, and ear piercing.

‡*P* value for test for trend.

contact allergy appeared to be present both among atopic and nonatopic subjects. Consistent with our previous report,¹⁵ there was no significant association between contact allergy and skin prick test reactivity. Thus, we did not find evidence suggesting that the overrepresentation of atopic individuals has biased the results.

To our knowledge, this is the first study to address the relation between smoking and contact allergy, and therefore further studies are warranted. However, two studies have reported a positive association between smoking and

hand dermatitis.^{5,6} A subsequent study could not confirm this association.⁷ None of these studies reported the relation between smoking and patch test reactivity to allergens. Indirect evidence was provided by a study in a population of Swedish patients with positive patch tests.¹⁶ The number of incident cancers, in particular cancer of the respiratory tract, which is related to smoking, was higher than expected, as estimated on the basis of data from The Swedish Cancer Registry.¹⁶ The authors speculated that a common failure of the immune system might predispose to both con-

tact allergy and cancer. An alternative explanation could be that smoking increases the risk of both contact allergy and cancer. Nevertheless, the authors had no data on smoking and thus were unable to test this hypothesis.

In our opinion, the results of the current study suggest that smoking is a risk factor for the development of contact allergy. The finding of a dose-response relation (in pack-years) could also indicate that smoking cessation might prevent the development of contact allergy. Nevertheless, it should be recognized that despite a high prevalence of smokers among men, the prevalence of nickel contact allergy was low. This underlines that exposure to allergens remains the most important determinant of contact allergy. The question is whether the effect of exposure to allergens is stronger in smokers than in nonsmokers. This was not indicated by our data, since there was no statistically significant interaction between smoking and ear piercing, the latter being a well-established risk factor for nickel allergy and an indirect marker of nickel exposure.¹⁷ Thus, the effect of smoking on the prevalence of nickel allergy was not greater among subjects with a history of ear piercing than among subjects without a history of ear piercing. However, more data are needed to answer this question.

The immunologic hallmark of allergic contact dermatitis is a type IV cell-mediated immune reaction, in which type 1 helper T cells and associated cytokines are predominant. It is well known that smoking has many deleterious effects on the immune system, although the exact mechanisms are not fully understood.⁸ These immunologic effects could also play a role in the regulation of type 1 helper T-cell-mediated immune reactions, thereby facilitating the development of contact allergy. Smoking might also have nonimmunologic effects, for example, by decreasing the blood flow in the skin,¹⁸ which might have an influence on patch test reactivity. In this way, it could be of interest to investigate whether smoking increases skin reactivity to irritants such as, for example, sodium lauryl sulfate.¹⁹ Thus, the possible mechanisms underlying the observed association between smoking and contact allergy remains to be elucidated.

In conclusion, we found a complex positive relation between smoking and the prevalence of contact allergy. We hypothesize that smoking might be a risk factor for contact allergy and that the prevalence of allergic contact dermatitis might be reduced by avoiding smoking or smoking cessation. Further epidemiologic studies and investigations into the possible mechanisms are warranted.

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