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CONTACT DERMATITIS

Metalworking exposures and persistent skin symptoms in the ECRHS II and SAPALDIA 2 cohorts

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Background: Diseases of the skin are important and often preventable conditions occurring among workers with dermal exposures to irritant and sensitizing agents.

Objective: We conducted this analysis to assess the associations between metalworking exposures and current and persistent skin symptoms among male and female participants in two population-based epidemiologic studies.

Methods: We pooled data from the European Community Respiratory Health Survey II (ECRHS II) and the Swiss Cohort Study on Air Pollution and Lung and Heart Disease in Adults 2 (SAPALDIA 2), two prospective cohort studies in Europe. Each participant completed interviewer-administered questionnaires to provide information about symptoms and exposures related to selected occupations, including metalworking, during the follow-up periods. We assessed associations between skin symptoms and the frequency of metalworking exposures among 676 ECRHS II/SAPALDIA 2 respondents.

Results: Current skin symptoms were reported by 10% of metalworkers and were associated with frequent use, defined as four or more days per week, of oil-based metalworking fluids [prevalence ratio (PR): 1.76, 95% confidence interval (CI): 1.25–2.49)] and organic solvent/degreasing agents (PR: 2.06, 95% CI: 1.21–3.50).

Conclusions: Skin symptom prevalence is associated with increasing frequency of oil-based metalworking fluid and degreasing agent use. Our findings justify assessing strategies for reducing the frequency of metal-related exposures.

Key words: contact dermatitis; epidemiology; metals; occupational diseases; occupational exposure.

Conflicts of interest: The authors have declared no conflicts.

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Irritant and allergic contact dermatitis are important and often preventable conditions occurring in workplaces with dermal exposures to irritant and sensitizing agents. Metalworking has been identified as a high-risk occupation for irritant contact dermatitis (1–5) and particularly for hand or forearm dermatitis. Industry-based epidemiological research indicates that components of metalworking fluids and solvents may be the key exposures associated with skin symptoms (6).

We conducted this analysis to assess the associations between metalworking exposures and skin symptoms among participants in the European Community Respiratory Health Survey II (ECRHS II) and Swiss Cohort Study on Air Pollution and Lung and Heart Disease in Adults 2 (SAPALDIA 2) studies. Existing evidence for an association between metalworking exposures and occupational dermatoses is strong, and thus, our analyses build on previous evidence by assessing the prevalence of skin symptoms with increasing frequency of exposure among male and female participants of two international population-based epidemiological studies.

Methods

The ECRHS is a prospective population-based cohort study of respiratory health among adults living near 28 study centres in 13 countries. The study design and methods have been described previously (7–9). Summarized briefly, the ECRHS is a longitudinal study with a fixed cohort; initial survey of the population began in 1991 (ECRHS I), and in 1998–1999, follow-up of the cohort included an occupational survey component for 22 centres located in 10 European countries (ECRHS II). Comparable baseline (SAPALDIA 1) and follow-up (SAPALDIA 2) protocols were followed in eight centres in Switzerland for the SAPALDIA study (10, 11). Data collected from participants in the two cohort studies are easily pooled for a joint analysis (12). The questionnaires completed by participants in each study contained a screening questionnaire to determine whether respondents would complete one or more of the seven occupational modules included in the follow-up surveys. The occupational modules, including one module addressing metalworking occupations, were designed to collect information about specific work-related exposures encountered in jobs held at any time during the study follow-up periods. Institutional review boards at the participating study centres approved the study protocol and instruments, and participants provided written informed consent.

In the ECRHS II and SAPALDIA 2 populations, 753 participants reported working in jobs that involved production, processing, or handling of metal or metallic objects during the follow-up period. All 753 participants completed the occupational module about metalworking tasks and exposures. We excluded 77 respondents with missing responses to questions about the metalworking exposures ($n = 61$) or the outcomes ($n = 16$) included in our analyses. These exclusions resulted in a final population of 676 metalworkers from ECRHS II ($n = 404$) and SAPALDIA 2 ($n = 272$).

The survey module included questions about the frequency of performing specific metalworking tasks (e.g. metal smelting and metal casting), performing manual work versus operating automated machinery, working with various metals, and using selected types of products (e.g. water- and oil-based metalworking fluids and organic solvents/degreasing agent). We categorized the frequencies of exposure as <1 day/week, 1–3 day(s)/week, and 4–7 days/week. To assess the frequency of performing any metalwork, we assigned each respondent the maximum frequency category that he/she reported for any of the 18 specific work tasks.

To assess the presence of skin symptoms at follow-up, we used responses to two survey questions about skin irritation: 'have you ever had an itchy rash that was coming and going for at least six months?' and, for those with positive responses, 'have you had this itchy rash in the last 12 months?' Respondents with positive responses to both questions were identified as having skin symptoms. We identified individuals with a history of eczema and other skin allergies using one question from the baseline survey: 'have you ever had eczema or any kind of skin allergy?'

We estimated associations between metalworking exposures and skin symptoms using generalized estimating equations, specified with a binomial outcome distribution, a log link, a cluster-level variable indicating country of residence and an independent working correlation matrix structure for estimating the covariance of observations within each country. Measures of association are reported as prevalence ratios (PRs) with 95% confidence intervals (CIs), adjusted for age as a continuous variable and sex. For two of our final results, we assessed whether the PR estimates were confounded by a history of eczema, employment status, and use of respiratory protection or ventilation equipment on the job or other metalworking exposures. We categorized employment based on responses

about employment status at the time of the ECRHS II/SAPALDIA 2 surveys (employed, unemployed/not working, and other employment status). Individuals in the 'unemployed/not working' category were unemployed ($n = 13$) or not working because of illness, disability, or poor health ($n = 22$). Those in the 'other employment status' category were full-time students ($n = 3$), retired ($n = 27$), or had other employment statuses ($n = 8$). A dichotomous variable for respiratory protection or ventilation equipment was assessed as a proxy for personal protection in the workplace. All analyses were performed using SAS version 9.1 (SAS Institute Inc., Cary, NC, USA).

Results

More than 13% (90/676) of the metalworkers in our final study population reported ever having a recurrent itchy rash that lasted 6 months or more; 10% ($n = 66$) reported that the itchy rash occurred in the past 12 months and are thus identified as having persistent and current itchy skin symptoms (Table 1). Across categories of increasing frequency of performing metalworking tasks, we observed little variation in the age distribution of each population and a slightly increasing percentage of men. The percentage of respondents with a history of eczema or skin allergy was higher among individuals performing metalworking

Table 1. Characteristics of the study population

	All	Frequency of metalworking tasks		
	Metalworkers ($n = 676$), no. (%)	<1 day/week ($n = 217$), no. (%)	1–3 day(s)/week ($n = 145$), no. (%)	4–7 days/week ($n = 314$), no. (%)
Parent study				
ECRHS II	404 (59.8)	124 (57.1)	79 (54.5)	201 (64.0)
SAPALDIA 2	272 (40.2)	93 (42.9)	66 (45.5)	113 (36.0)
Demographic characteristics				
Age at ECRHS II/SAPALDIA 2 (years)				
Mean (SD)	44.9 (9.5)	45.2 (9.3)	46.1 (9.9)	44.2 (9.5)
Median	44.2	43.9	45.0	43.7
Minimum–maximum	28.3–72.1	28.9–72.1	28.3–69.9	29.3–71.9
Country				
Belgium	25 (3.7)	2 (0.9)	2 (1.4)	21 (6.7)
Estonia	24 (3.6)	12 (5.5)	2 (1.4)	10 (3.2)
France	31 (4.6)	12 (5.5)	7 (4.8)	12 (3.8)
Germany	69 (10.2)	18 (8.3)	17 (11.7)	34 (10.8)
Italy	16 (2.4)	3 (1.4)	3 (2.1)	10 (3.2)
Norway	35 (5.2)	15 (6.9)	6 (4.1)	14 (4.5)
Spain	55 (8.1)	16 (7.4)	9 (6.2)	30 (9.6)
Sweden	105 (15.5)	23 (10.6)	26 (17.9)	56 (17.8)
Switzerland[a]	273 (40.4)	93 (42.9)	66 (45.5)	114 (36.3)
UK	43 (6.4)	23 (10.6)	7 (4.8)	13 (4.1)
Employment status				
Employed	601 (88.9)	198 (91.2)	128 (88.3)	275 (87.6)
Unemployed/not working[b]	35 (5.2)	5 (2.3)	10 (6.9)	20 (6.4)
Other employment status	40 (5.9)	14 (6.5)	7 (4.8)	19 (6.1)
Sex				
Male	618 (91.4)	190 (87.6)	130 (89.7)	298 (94.9)
Female	58 (8.6)	27 (12.4)	15 (10.3)	16 (5.1)
Health characteristics				
Atopy				
No	243 (35.9)	78 (35.9)	45 (31.0)	120 (38.2)
Yes	148 (21.9)	45 (20.7)	33 (22.8)	70 (22.3)
Unknown[c]	285 (42.2)	94 (43.3)	67 (46.2)	124 (39.5)
History of eczema or skin allergy				
No/unknown	528 (78.1)	165 (76.0)	118 (81.4)	245 (78.0)
Yes	148 (21.9)	52 (24.0)	27 (18.6)	69 (22.0)
Itchy rash skin symptoms				
No	610 (90.2)	199 (91.7)	132 (91.0)	279 (88.9)
Yes	66 (9.8)	18 (8.3)	13 (9.0)	35 (11.1)

ECRHS II, European Community Respiratory Health Survey II; SAPALDIA 2, Swiss Cohort Study on Air Pollution and Lung and Heart Disease in Adults 2.
[a]Population from Switzerland includes 1 ECRHS II participant and 272 SAPALDIA 2 participants.
[b]Not working because of illness, disability, or poor health.
[c]Atopy data are missing for 13 ECRHS II and all 272 SAPALDIA 2 respondents.

<1 day/week (24%) compared with the remaining population (21%).

Table 2 shows the associations of the frequency of metalworking tasks and use of specific metals or metalworking agents with skin symptoms. The prevalence of skin symptoms was highest among respondents who reported frequent use of hard metals (19%), oil-based metalworking fluids (18%), and/or degreasing agents (17%). Across categories of increasing frequency of oil-based metalworking fluid use, adjusted PR estimates indicate higher risks of skin symptoms in the population with the highest frequency of use (4–7 days/week: PR = 1.76, 95% CI = 1.25–2.49). This PR estimate was not notably affected by adjustment of the models for a history of eczema (PR = 1.71), manual work (PR = 1.67), or use of respiratory and/or ventilation equipment (PR = 1.76). Adjusting the model for the frequency of water-based metalworking fluid use generated a PR of 2.15 (95% CI: 1.35–3.44) and for organic solvent/degreasing agent use, a PR of 1.43 (95% CI: 1.02–2.01).

Across categories of increasing frequency of organic solvent/degreasing agent use, the prevalence of skin symptoms increased monotonically from 7% to 17% and adjusted PR estimates indicate an increase in risk across frequency categories (1–3 days/week: PR = 1.84, 95% CI = 1.14–2.97; 4–7 days/week: PR = 2.06, 95% CI = 1.21–3.50) (Table 2). The associations generated for use of organic solvent/degreasing agents were only modestly affected by adjustment for a history of eczema (1–3 days/week: PR = 1.76; 4–7 days/week:

Table 2. Associations of the frequency of tasks and use of specific metals and metalworking products with skin symptoms among European Community Respiratory Health Survey II/Swiss Cohort Study on Air Pollution and Lung and Heart Disease in Adults 2 respondents

Metalworking exposures	Total	No. (%) symptomatic	Prevalence ratio (95% confidence interval)[a]	*P* value for trend
Metalworking tasks[b]				
<1 day/week	217	18 (8.3)	1.00	0.29
1–3 day(s)/week	145	13 (9.0)	1.11 (0.63–1.98)	
4–7 days/week	314	35 (11.1)	1.25 (0.80–1.96)	
Manual work				
<1 day/week	203	14 (6.9)	1.00	0.16
1–3 day(s)/week	109	10 (9.2)	1.35 (0.74–2.47)	
4–7 days/week	364	42 (11.5)	1.55 (0.85–2.83)	
Ferrous metals (iron and steel)				
<1 day/week	261	21 (8.0)	1.00	0.70
1–3 day(s)/week	118	15 (12.7)	1.55 (0.94–2.57)	
4–7 days/week	297	30 (10.1)	1.16 (0.61–2.21)	
Aluminium				
<1 day/week	463	40 (8.6)	1.00	0.20
1–3 day(s)/week	105	13 (12.4)	1.37 (0.69–2.75)	
4–7 days/week	108	13 (12.0)	1.27 (0.71–2.27)	
Other non-ferrous metals (copper)				
<1 day/week	498	45 (9.0)	1.00	0.04
1–3 day(s)/week	84	9 (10.7)	1.16 (0.78–1.71)	
4–7 days/week	94	12 (12.8)	1.42 (1.06–1.90)	
Hard metals (tungsten, cobalt, and beryllium)				
<1 day/week	602	54 (9.0)	1.00	0.04
1–3 day(s)/week	37	5 (13.5)	1.52 (1.07–2.16)	
4–7 days/week	37	7 (18.9)	1.86 (0.96–3.62)	
Water-based metalworking fluids				
<1 day/week	544	52 (9.6)	1.00	0.75
1–3 day(s)/week	58	5 (8.6)	0.93 (0.47–1.85)	
4–7 days/week	74	9 (12.2)	1.15 (0.60–2.21)	
Oil-based metalworking fluids				
<1 day/week	553	49 (8.9)	1.00	0.01
1–3 day(s)/week	49	4 (8.2)	0.89 (0.44–1.81)	
4–7 days/week	74	13 (17.6)	1.76 (1.25–2.49)	
Organic solvent/degreasing agents				
<1 day/week	495	37 (7.5)	1.00	0.003
1–3 day(s)/week	98	15 (15.3)	1.84 (1.14–2.97)	
4–7 days/week	83	14 (16.9)	2.06 (1.21–3.50)	

[a]Adjusted for age and sex.
[b]Maximum frequency of any of the following metalworking tasks: metal smelting, rolling-mill work, melting/reheating, casting, moulding/core making, annealing/tempering/hardening, drawing/extruding, plating/galvanizing, coating/spray painting, finishing/cleaning, blacksmithing/operating forging press, tool making, machine tool setting operating, metal tool operating, grinding/polishing, metal fitting/assembling, precision instrument making, motor vehicle mechanic.

PR = 2.10), manual work (1–3 days/week: PR = 1.76; 4–7 days/week: PR = 1.92), employment status (1–3 days/week: PR = 1.85; 4–7 days/-week: PR = 2.12), or use of respiratory and/or ventilation equipment (1–3 days/week: PR = 1.89; 4–7 days/week: PR = 2.09). Adjusting the model for the frequency of water-based metalworking fluids resulted in similar estimates (1–3 days/week: PR = 1.90; 4–7 days/week: PR = 2.12), as did adjusting for oil-based metalworking fluids (1–3 days/week: PR = 1.87; 4–7 days/week: PR = 1.89).

Discussion

We took advantage of data available from two large international population-based surveys to assess the prevalence of an important occupational disease in a high-risk population. If metalworking fluids are associated with skin symptoms, then frequent or unprotected use of these agents may heighten the risk among metalworkers, hobbyists, and other exposed individuals. In these analyses, we observed increasing skin symptom prevalence and adjusted PRs with increasing frequency of metalworking exposures and particularly for use of oil-based metalworking fluids or organic solvent/degreasing agents four or more days per week. The adjusted associations increase with increasing frequency of use and do not appear to be confounded by a history of eczema, the frequency of performing manual metalworking tasks, employment status, or use of protective respiratory or ventilation equipment, used here as a proxy for personal protection in the workplace.

In previous analysis of ECRHS II data, Harrop et al. reported on geographic variation in the prevalence of all eczema and specifically in atopic eczema, which was defined as the presence of eczema and specific immunoglobulin E (IgE) to any of the four allergens tested (13). Because Harrop et al. also assessed non-occupational risk factors, the definition used to identify individuals with eczema was further restricted to include only individuals with the skin symptoms in the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears, or eyes. We chose not to use this more restrictive definition because of its obvious exclusion of hand dermatitis, which would most likely be associated with irritant exposures among metalworkers. As a consequence, our results are not directly comparable to those of Harrop et al.; we are unable to identify the symptoms as atopic or non-atopic eczema and instead have opted to assess skin symptoms more broadly defined.

In our analysis, assessment of the role of atopy was limited by the small size of our metalworking population and by the number of individuals with missing information about atopic status. For example, for 13 ECRHS II respondents and for all 272 SAPALDIA 2 respondents, we did not have information to identify atopic status. Using the remaining population ($n = 391$), we were able to identify respondents as atopic based on specific serum IgE levels >0.35 kU/l to at least one of four common environmental allergens (dust mite, cat, Timothy grass, and *Cladosporium herbarum*) at the time of the baseline and follow-up surveys. Among the 148 respondents with positive tests from either survey (i.e. atopic) and among the remaining 243 respondents (i.e. non-atopic), stratifying the model in which we assessed oil-based metalworking fluid exposures resulted in distinct estimates in the highest exposure categories for the atopic (PR = 2.83) and non-atopic (PR = 0.80) strata (data not shown). These estimates were computed using only eight exposed and symptomatic individuals with atopy and four without atopy, and therefore, our data cannot be used to thoroughly investigate the role of atopy. However, because of this difference, the extent to which the metalworking and skin symptom associations may be modified by atopic status warrants further assessment. In addition, the percentage of respondents with a history of eczema or skin allergy was higher among individuals performing metalworking once per week or less. If this difference indicates an early selection effect in which individuals with skin allergies might avoid more frequent exposures, then the associations generated here may underestimate the potential burden of more frequent exposure.

The metalworking exposures considered here are correlated with one another. For example, 77% of those who reported using water-based metalworking fluids ≥1 day(s)/week also reported using oil-based metalworking fluids ≥1 day(s)/week. The 76% increase in relative risk observed with frequent use of oil-based metalworking fluids was attenuated to a 44% increase in risk when adjusted for frequency of degreasing agent use, and when adjusted for the frequency of water-based metalworking fluids, the PR was elevated farther away from unity (PR = 2.16). The 106% increase in relative risk observed with frequent use of organic solvent/degreasing agents was not notably attenuated following adjustment for water-based or oil-based metalworking fluids, suggesting that the elevations observed are not largely attributable to these other, albeit closely related, exposures. More thorough investigation of the impact of combining the metals and metalworking fluid exposures on both absolute and relative risk is limited by the small number of

exposed individuals with the highest risk of skin symptoms and by an even smaller number ($n = 70$) who reported never performing any of the specific metalworking tasks in the questionnaire and thus could be considered completely unexposed. These unexposed individuals were plumbers and pipe fitters, shop attendants, medical assistants, machinery repair technicians, teaching professionals, safety and health inspectors, and others who may have metalworking-related exposures but who may not perform the specific tasks included in the questionnaire. The lack of a completely unexposed comparison population may be the reason that our estimates of the relative risk among exposed individuals are fairly low; if the groups with <1 day/week of each individual exposure are exposed to the other metals and/or solvents, then the PRs generated here may underestimate the actual risks. We initially intended to contrast the prevalence of skin symptoms among metalworkers to that among individuals in professional/administrative occupations, as defined in previous analyses of ECRHS data (14, 15). In this case, however, the high prevalence of skin symptoms in this non-metalworking comparison population (13%) as well as the suggestion that individuals who work in office settings may be at risk for itchy skin symptoms because of low humidity and other characteristics of the indoor workplace (16) suggest that this population may not be an appropriate comparison group to assess the risk of occupational exposures and skin symptoms.

Our analyses also have several important limitations related to the identification of individuals with skin symptoms. The primary objectives of the ECRHS and SAPALDIA studies were to assess respiratory outcomes, not dermatoses, and therefore, our use of two questionnaire items as a proxy for skin symptoms may not fully reflect the symptom prevalence in these populations. Indeed, our use of these two questionnaire items to identify individuals with skin symptoms, but without any specific reference to symptoms on the hands, was a practical approach to use survey-based information, despite this recognized gap in the survey instrument. Using these data, we are unable to estimate how many of the individuals we identified with skin symptoms may have reported skin symptoms but did not have these symptoms on their hands. However, the association between hand eczema and metalworking has been reported previously and recently (1, 2, 5); in our study, if individuals without hand symptoms have been incorrectly classified because of the low specificity of our disease definition, then our results may be biased downward and towards unity. Reducing misclassification of dermatoses in further follow-up of the ECRHS and SAPALDIA cohorts may show stronger associations with increasing frequency of metalworking tasks than those generated in our analyses.

Previous research provides evidence that identification of hand dermatitis using self-reported questionnaire data may incorrectly estimate the actual prevalence of the disease (17, 18). Here, we highlight relative risks rather than absolute risks and note that using our survey-based identification of skin symptoms, we are not able to draw conclusions about the prevalence of hand eczema or diagnosed skin conditions. And finally, we are unable to assess whether the self-reported symptoms are consistent in appearance with contact dermatitis, atopic eczema, or urticaria. In this metalworking population, we have self-reported evidence of workplace exposures to potential skin irritants. A temporal relationship is supported by the evidence of new-onset symptoms, although analysis of the incidence of symptoms is limited by the small number of metalworkers without eczema or other skin allergy symptoms at the time of ECRHS I but who reported skin symptoms in the ECRHS II survey ($n = 15$). Additional information about whether the distribution of the skin symptoms is consistent with dermal exposure that may correspond to the job tasks reported, about non-occupational exposures, and about whether the symptoms improve away from the workplace would strengthen the evidence of the reported symptoms as being occupational in nature. In addition, occupational exposure histories and information about the timing of onset of skin symptoms would improve the ability to identify the work-relatedness of the symptoms. The effects of a reduced epidermal barrier function should also be carefully investigated.

Occupational skin diseases are largely preventable conditions for which prevention is especially important because of their potentially poor prognoses – that is because of the likelihood that many individuals with occupational dermatoses will continue to have exacerbations of their symptoms, medical expenses, and absences from work. Secondary prevention measures such as workplace education and symptom treatments may enable individuals with existing symptoms to ease the severity or frequency of their symptoms. Education programmes aimed at secondary individual prevention have been assessed in several workplace environments (19, 20), and the extent to which they may be effective in addressing occupational skin diseases among metalworkers remains unknown. If such programmes prove to be effective in workplaces where metals and metalworking fluids are in use, they could be a sensible addition to other prevention and treatment programmes. Our findings

justify further exploration of primary prevention methods to reduce the frequency of exposures to specific metals and to metalworking fluids in this population. Possible interventions may include substitution of fluids or additives, reduced exposure through automation, improvements in the use of personal protective equipment, and heightened efforts to educate potentially exposed workers about the health hazards of these agents.

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