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Effectiveness of secondary prevention in metalworkers with work-related skin diseases and comparison with participants of a tertiary prevention program: A prospective cohort study

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Abstract

Background: In Germany, a multistep approach has been established to prevent work-related skin diseases (WRSDs).

Objectives: To evaluate the effect of a secondary individual prevention program (SIP) in metalworkers with WRSD and to compare their characteristics with those of participants of a tertiary individual prevention program (TIP).

Patients and Methods: In a prospective cohort study, metalworkers with WRSD of the hands participating either in the SIP (n = 114) or in the TIP (n = 83) were recruited. At baseline and at the respective follow-up 8–12 weeks after the SIP or at dismissal from the TIP (3–4 weeks later), questionnaires were completed and the severity of WRSD was assessed. Saliva samples were collected for assessment of filaggrin (*FLG*) mutations and an explorative genome-wide association study (GWAS).

Results: Ninety-three SIP patients (81.6%) attended the follow-up. Disease severity was significantly reduced, and knowledge and protective behavior were significantly improved compared to baseline. Significant differences between SIP and TIP patients were found regarding duration and severity of symptoms, work absenteeism, tobacco smoking, and presence of atopic dermatitis, but not regarding *FLG* mutations and by GWAS.

Conclusions: The SIP was effective in metalworkers with WRSDs. Individual factors may influence the course of the disease and the need for the TIP.

KEYWORDS

contact dermatitis, filaggrin, hand eczema, health education, metalworker, occupational, prevention, tobacco, work-related

1 | INTRODUCTION

Work-related skin diseases (WRSDs) are common and comprise mainly contact dermatitis of the hands caused by wet work and occupational exposures to irritants and/or allergens. Due to an often chronic course, they are associated with impaired health-related quality of life and a considerable socioeconomic impact, primarily owing to work absenteeism and lack of productivity.¹ In Germany, a multistep intervention approach funded by the statutory accident insurances has been established to reduce the burden of WRSDs.^{1,2} Secondary and tertiary individual prevention measures are provided depending on the severity and stage of the disease. Apart from outpatient treatment and diagnostics, patients with early or mild symptoms of WRSD are offered the opportunity to participate in a secondary individual prevention program (SIP). The set-up and content of the SIP may differ, but it usually involves an outpatient skin protection seminar with emphasis on health education. The short- and long-term effectiveness of these programs has been demonstrated before in occupations at risk.^{3–8} Patients with severe WRSD refractory to such secondary prevention measures are invited to take part in an interdisciplinary inpatient/outpatient tertiary individual prevention program (TIP).^{2,9} The TIP is based on a 3-week inpatient phase in a specialized center providing intensified diagnostics and treatment as well as health education and psychological counseling followed by a 3-week outpatient phase before returning to work. A previous multicenter study revealed that the TIP is associated with sustained improvement in terms of disease severity, ability to work, quality of life, and prognosis.^{10–12}

A high share of participants in the SIP and TIP are metalworkers (MWs),^{10,13} who frequently have contact dermatitis, with a reported life-time prevalence of 30% to 63.1%.^{14–16} The term MWs is ill-defined and summarizes a broad group of professions with varying workplace exposures. Their high risk for WRSDs is due mainly to mechanical strain, wet work, and exposure to hazardous substances, in particular metal-working fluids, with substantial irritant and allergenic potential,¹⁷ while adherence to skin protection regimens is low.¹⁴

The risk of developing WRSD and its course are modified by individual factors, including atopic skin diathesis and atopic dermatitis (AD), which may interfere with preventive efforts.¹⁸ Loss-of-function mutations in the filaggrin gene (*FLG*) cause skin barrier defects and are associated with increased prevalence and incidence of work-related hand eczema—particularly if it is combined with AD^{18–22}—a more unfavorable course of the disease, and a lower probability of remaining in the workforce.²³ Genome-wide association studies (GWAS) may help to discover other genetic variants linked to WRSDs. They have already been applied in AD and identified susceptibility loci, mostly implicated in immune dysregulation.²⁴ Furthermore, tobacco smoking may have an impact on work-related hand eczema, which is on average more severe and persistent in smokers than in nonsmokers.^{25–27}

In this prospective cohort study, we evaluated the short-term effectiveness of an SIP in MWs with WRSD. Moreover, a comparison of these patients and MWs with WRSD taking part in the TIP was conducted to reveal factors that may be associated with more severe

or persistent disease and lead to participation in tertiary preventive measures.

2 | METHODS

2.1 | Interventions

The provision of SIP and TIP is embedded in a standard multistep procedure for patients with WRSDs applied by the German Statutory Accident Insurance (DGUV). According to this procedure, an SIP should be offered to patients with suspected WRSD shortly after notification of the statutory accident insurance body. The detailed set-up of the outpatient 2-day SIP at the study center in Osnabrück has been described before.⁵ Briefly, on one of both days, patients from various occupational fields take part in a skin protection seminar that consists of a structured group training by an experienced health educator on pathogenesis, risk factors, and prevention of WRSDs for about 5 hours (8–13 patients per group). The seminar aims at empowering the patients and improving their self-management skills, disease-specific knowledge, and motivation to perform appropriate skin protection and skin care behavior. On the other day, a dermatologist specializing in WRSDs examines the skin and provides recommendations for diagnostics and treatment. In addition, patients are counseled by a health educator on the correct use of personal protective equipment. There is a special focus on protective gloves, which are individually selected and later provided by the statutory accident insurance. SIP patients are offered an outpatient follow-up visit 8–12 weeks later to refresh their knowledge and, if necessary, to adjust the personal protective equipment. The patients are again examined by the dermatologist who adapts the previous recommendations if necessary.

The TIP is offered to patients with severe skin symptoms that are refractory to outpatient secondary prevention measures and has been described in detail elsewhere.^{9,10} Briefly, the TIP consists of a 3-week inpatient intervention phase in a specialized center including diagnostics, treatment, patient education, and individual selection of adequate personal protective equipment, which is followed by a 3-week outpatient phase of absence from work under the guidance of a local dermatologist in the patient's hometown. After the TIP, the patients ideally return to their workplaces with improved skin condition and optimized skin protection measures under continuous outpatient dermatological supervision. The statutory accident insurance organization ensures that patient receive the selected personal protective equipment and, if necessary, initiates work place visits, for example, to implement technical preventive measures or eliminate relevant allergens based on the information collected during the TIP.

2.2 | Study population and design

In an uncontrolled prospective cohort study, MWs with WRSD taking part in either the SIP or the TIP at the Institute for Interdisciplinary

Dermatologic Prevention and Rehabilitation (iDerm) at the University of Osnabrück, Germany, between June 2013 and October 2016 were recruited consecutively on a voluntary basis after informed written consent was obtained. TIP patients who had been already enrolled during an SIP were excluded from recruitment during the TIP. Controls were not recruited for ethical and legal reasons.⁴ The study protocol was approved by the ethics committee at the University of Osnabrück.

Assessments by dermatologists using standardized questionnaires were carried out in SIP patients at initial consultation (T1) and at follow-up 8–12 weeks later (T2), whereas in TIP patients only at admission to the inpatient program (T1). Basic sociodemographic data and self-reported information on work absenteeism, past treatment, occupational strain (eg, wet work, exposure to skin hazards) and individual skin protection behavior (eg, use of gloves, barrier creams, emollients) were collected.

At T1, body areas other than hands were examined for signs of AD, psoriasis, and foot eczema. An Erlangen atopy score ≥ 10 at baseline was defined as atopic skin diathesis.²⁸ At T1 and T2, the dermatologist examined the hands and used the validated Osnabrueck Hand Eczema Severity Index (OHSEI)^{29,30} to assess the severity of the disease. In TIP patients, the second examination of the hands (T2) was performed shortly before discharge, that is, 3–4 weeks after baseline. The etiology of hand eczema was based on the final diagnoses made by the dermatologists at T2. A combination of different etiological hand eczema components was possible. An atopic hand eczema component was diagnosed in patients with the presence or history of AD and/or an atopic skin diathesis in combination with evidence for an at least partially seasonal or undulating temporal course of the eczematous lesions without clear association with exposure to relevant irritants or allergens according to the patient's history (SIP and TIP patients) or the course documented during the TIP. Based on a significant exposure to known irritants and a related temporal course of the disease, irritant hand eczema component was diagnosed. Allergic contact dermatitis of the hands was diagnosed in patients with a positive patch test result to at least one allergen, with ascertained exposure that was considered relevant for the current hand eczema. The information on contact allergies was based on the patients' files in SIP patients and patch testing performed during the inpatient stay in TIP patients.

The validated, self-administered "Occupational Skin Diseases Knowledge Questionnaire (OSD-KQ)"¹³ comprising 65 items was used in SIP patients before the baseline seminar (T1) and at follow-up (T2) to determine knowledge on WRSDs and their prevention.

2.3 | Genotyping

For genetic analyses, 2 mL of saliva per individual was collected with the OG-500 Oragene DNA Self-Collection Kit (DNA Genotek, Ottawa, Canada) following the manufacturer's instructions for sampling and storage. Automated purification of genomic DNA was

performed on Autopure LS following the manufacturer's protocol (Qiagen, Hilden, Germany). The four most common *FLG* variants—R501X, 2282del4, R2447X, and S3247X—were analyzed with the TaqMan allelic discrimination method (Applied Biosystems, Carlsbad, California) as described earlier.²²

For GWAS, all subjects were genotyped on the Infinium Global Screening Array v1.0 BeadChip (Illumina, San Diego, California). Genotype calling was carried out using the Illumina GenomeStudio 2.0.4 Data-Analysis software. Sample and marker quality control (QC) was performed with PLINK (v1.9, <https://www.cog-genomics.org/plink/1.9>)³¹ as described before.²² After QC, 478839 variants and 177 individuals were eligible for analysis.

2.4 | Data analysis

Statistical analyses were conducted with SPSS Version 25.0 (IBM, Armonk, New York). Differences for categorical variables were assessed using the Pearson chi-square (χ^2) test. Fisher exact test was applied if at least one expected value under independence was lower than 5. To analyze differences for continuous variables, uni-factorial analysis of variance (ANOVA) was used, whereas the Mann-Whitney *U* test was applied for the OHSEI. Pearson correlation coefficients were calculated to investigate correlations between continuous variables. To further explore potential confounding effects of selected variables when comparing SIP and TIP patients, binary logistic regression analysis was performed. Differences between baseline and follow-up were calculated with paired *t* test for dependent samples for continuous variables, with Wilcoxon signed-rank test for selected variables (OHSEI, OSD-KQ), and with McNemar test for dichotomous variables. Differences were considered significant if the *P*-value was $< .05$.

For GWAS, allele frequencies were compared between the SIP and TIP patients using logistic regression models with adjustment for sex and population stratification. All analyses were conducted with PLINK (v1.9, <https://www.cog-genomics.org/plink/1.9>)³¹ and R version 3.6.1 (<https://www.r-project.org/>).

3 | RESULTS

3.1 | Basic demographic data

A total of 197 MWs were enrolled in this study. Of these, 114 took part in the SIP and 83 in the TIP. The sociodemographic characteristics of the two groups of MW at baseline are presented in Table 1. Most (>94%) participants in both groups were male. The TIP patients were significantly older than the SIP patients ($P < .001$). No significant differences were found regarding atopic skin diathesis. TIP patients reported tobacco smoking significantly more often ($P < .05$) and had a significantly higher daily cigarette consumption ($P < .05$). About half of all TIP patients (49.4%) reported to have attended a SIP in the past.

TABLE 1 Sociodemographic data and data on work-related and other skin diseases of metalworkers taking part in the secondary individual prevention program (SIP) or in the tertiary individual prevention program (TIP) at baseline (T1)

	SIP $n_{\text{total}} = 114$	TIP $n_{\text{total}} = 83$
Mean age $\pm$ SD (years)	41.07 $\pm$ 12.04***	47.46 $\pm$ 10.75
Females, n (%)	6 (5.3)	2 (2.4)
Atopic skin diathesis, ^a n (%)	40 (35.1)	26 (31.3)
FLG mutation carriers, n/ n_{total} (%)	15/106 (14.2)	9/76 (11.8)
Tobacco smokers, n (%)	39 (34.2)*	41 (49.4)
Mean daily cigarette consumption in smokers $\pm$ SD	12.98 $\pm$ 8.59*	17.22 $\pm$ 6.59
OHSI score (mean $\pm$ SD)	3.20 $\pm$ 2.70***	5.99 $\pm$ 3.26
Mean duration of WRSD $\pm$ SD (years)	4.41 $\pm$ 5.16***	8.14 $\pm$ 8.87
Days of absence from work in past 12 months due to WRSDs (mean $\pm$ SD)	7.20 $\pm$ 13.68**	17.46 $\pm$ 29.15
Diagnosis hands, n (%)		
Hand eczema ^b	109 (95.6)	76 (91.6)
Irritant contact dermatitis	102 (89.5)*	65 (78.3)
Allergic contact dermatitis	20 (17.5)	23 (27.7)
Atopic hand eczema	48 (42.1)*	49 (59.0)
Hyperkeratotic hand eczema	16 (14.1)	14 (16.9)
Palmar psoriasis	6 (5.3)	5 (6.0)
Vesicular hand eczema ^c	27 (23.7)	30 (36.1)
Diagnosis other body areas, n (%)		
Foot eczema	20 (17.5)	24 (28.9)
Psoriasis	5 (4.4)	4 (4.8)
Atopic dermatitis	17 (14.9)***	29 (34.9)
Topical treatment of hands in past 12 months, n (%)		
Corticosteroids	89 (78.1)	73 (88.0)
Calcineurin inhibitors	36 (31.6)	30 (36.1)
PUVA treatment hands in past 12 months, n (%)	23 (10.2)***	36 (43.4)
Systemic treatment of WRSDs in past 12 months, n (%)		
Corticosteroids	5 (4.4)***	16 (19.3)
Alitretinoin	5 (4.4)***	15 (18.1)
Acitretin	1 (0.9)	3 (3.6)
Cyclosporin A	0 (0)	1 (1.2)

Abbreviations: SD: standard deviation; OHSI: Osnabrueck Hand Eczema Severity Index; WRSD: work-related skin diseases; PUVA: psoralene plus ultraviolet A irradiation.

* $P < .05$.

** $P < .01$.

*** $P < .001$.

^aErlangen atopy score ≥ 10 .

^bMore than one hand eczema subtype possible.

^cAccording to OHSI.

3.2 | Work-related and other skin diseases

Most patients in both groups had hand eczema (>90%) (Table 1). The most common cause was irritant contact dermatitis, which was diagnosed significantly more often in SIP patients ($P < .05$). Allergic contact dermatitis of the hands (n.s.) and atopic hand eczema ($P < .05$) were more common in TIP patients. Moreover, AD on body areas other than the hands was diagnosed more often in TIP patients than in SIP patients ($P < .001$). The duration of skin symptoms related to

WRSDs prior to recruitment had been significantly longer in TIP patients than in SIP patients ($P < .001$), and the disease severity according to OHSI was significantly higher in TIP patients than in SIP patients at baseline ($P < .001$). In the year before T1, TIP patients had a significantly higher number of days of absence from work due to WRSDs ($P < .001$) and had been treated systemically with corticosteroids significantly more often ($P < .001$) or alitretinoin ($P < .05$), or had received psoralene plus ultraviolet A irradiation (PUVA) phototherapy ($P < .001$). A logistic regression analysis adjusting for age, AD, and

tobacco smoking revealed that only age ($P < .001$) and AD ($P < .01$) were independently associated with participation in the TIP (data not shown).

3.3 | FLG mutation status

DNA was available from 182 MWs (93.0% and 91.6% of all SIP and TIP patients, respectively) and all of them were successfully genotyped for *FLG* mutations. The call rates for all four mutations were $> 99\%$ and genotype distributions were within the Hardy–Weinberg equilibrium. Fifteen SIP patients (14.2%) and nine TIP patients (11.8%) were heterozygous carriers of one of the four analyzed mutations (Table 1). Homozygous or compound heterozygous carriers were not detected. There was a higher prevalence of atopic skin diathesis (33.3% vs. 22.8%) and atopic hand eczema (62.5% vs. 48.1%) in *FLG* mutation carriers compared with noncarriers. However, these differences were not statistically significant. Similarly, no statistically significant differences were found between SIP and TIP patients regarding other genetic variants in the explorative GWAS (data not shown).

3.4 | Workplace exposures and skin protection behavior

Most of the patients worked in professions with similar occupational exposures, primarily involving in metal processing such as cutting machine operators, industrial mechanics, toolmakers, and construction mechanics/model builders (Table S1). Data on self-reported exposure to skin hazards and skin protection behavior in the SIP and TIP patients are shown in Table 2. No significant differences were found regarding prevalence of wet work or soiling > 2 hours/day. About two-thirds of MWs in both groups reported exposure to water-based metalworking fluids. In addition, other exposures and work tasks were similar in SIP and TIP patients. Only milling was reported significantly more often in SIP patients ($P < .05$). The self-reported use of protective gloves, skin barrier creams and emollients was high in both groups. However, MWs taking part in the TIP reported that they wore protective gloves for a significantly longer period each day than MWs in the SIP at baseline ($P < .05$). Notably, TIP patients who had not taken part in a SIP before, showed a significantly lower extent of glove use than the other TIP patients (data not shown). Moreover, significantly more SIP patients reported not wearing protective gloves when exposed to water-based metalworking fluids, oil-based metalworking fluids, other oils, or detergents. The frequency of handwashing was similar in both groups. The use of abrasive detergents was slightly higher in SIP patients.

3.5 | Follow-up

The disease severity was assessed again in all 83 TIP patients at discharge, revealing a significantly lower mean OHSI than at admission

(5.99 ± 3.26 vs 3.00 ± 2.22 , $P < .001$). Ninety-three SIP patients (81.6%) attended the follow-up (T2). On average, they had worked 9.71 ± 5.46 weeks between T1 and T2. No statistically significant differences in baseline characteristics between drop-outs and the remaining participants were detected, except for grinding, which was significantly less frequently reported at baseline by drop-outs ($P < .05$, data not shown). The data of the remaining 93 SIP patients at T1 and T2 is presented in Table 3. The severity of symptoms was significantly lower and the knowledge score significantly higher at T2 than at T1 (both $P < .001$). There was a significant decrease of self-reported wet work > 2 hours/day ($P < .01$) and soiling > 2 hours/day ($P < .01$), whereas self-reported use of protective gloves ($P < .05$) and amount of time wearing gloves per day ($P < .001$) significantly increased. Moreover, a significant decrease of handwashing frequency was noted. The use of abrasive detergents was significantly lower at T2 ($P < .001$).

3.6 | Factors associated with severity of hand eczema or tobacco smoking

To assess factors associated with hand eczema severity or tobacco smoking, subgroups were analyzed, excluding patients without hand eczema and those who had stopped smoking in the past. In the remaining 89 SIP patients and 73 TIP patients, no significant associations were found between tobacco smoking and days of absence from work in the previous year or the different etiological subtypes of hand eczema (Table S2). When assessing the individual morphological variables of the OHSI separately, compared to nonsmokers, tobacco smokers among TIP patients significantly more often had values > 0 for vesicles indicating presence of vesicular hand eczema, both at T1 (48.7% vs 23.5%, $P < .05$) and T2 (51.3% vs 11.8%, $P < .001$). As presented in Table 4, the OHSI at T1 was higher in smokers than in nonsmokers both in SIP and TIP patients; however, reaching no statistical significance. No correlation was found between the number of cigarettes smoked and the OHSI (data not shown). The OHSI at T1 was significantly higher in SIP patients with an atopic skin diathesis ($P < .05$). In TIP patients, the OHSI at T1 and T2 was significantly higher in patients with an atopic skin diathesis or AD on body areas other than hands. Moreover, the duration of the disease correlated with the OHSI at T1 (Pearson 0.271, $P < .05$) and T2 (Pearson 0.286, $P < .05$) in SIP patients. In TIP patients, the OHSI at T1 correlated with days of absence from work prior to the TIP (Pearson 0.261, $P < .05$), whereas the OHSI at T2 correlated with duration of the disease (Pearson 0.271, $P < .05$). No significant associations or correlations were found between the OHSI and other variables, including age, gender, *FLG* mutation status, handwashing frequency, and protective behavior (data not shown).

4 | DISCUSSION

The SIP was effective in improving disease-specific knowledge and protective behavior in MWs with WRSDs while reducing the severity

TABLE 2 Workplace exposure and protection behavior in metalworkers taking part in the secondary individual prevention program (SIP) or in the tertiary individual prevention program (TIP) at baseline (T1)

	SIP $n_{\text{total}} = 114$	TIP $n_{\text{total}} = 83$
Wet work >2 h/day, n (%)	80 (70.2)	63 (75.9)
Soiling >2 h/day, n (%)	83 (72.8)	62 (74.7)
Work tasks, n (%)		
Lathing	49 (43.0)	32 (38.6)
Milling	55 (48.2)*	28 (33.7)
Drilling	70 (61.4)	46 (55.4)
Grinding	65 (57.0)	55 (66.3)
Workplace exposures		
Water-based metalworking fluids, n (%)	76 (66.7)	50 (60.2)
Without gloves, n/ n_{total} (%)	12/76 (15.8)*	1/50 (2.0)
Oil-based metalworking fluids, n (%)	30 (26.3)	18 (21.7)
Without gloves, n/ n_{total} (%)	10/30 (33.3)*	1/18 (5.6)
Hydraulic oils, n (%)	64 (56.1)	49 (59.0)
Without gloves n/ n_{total} (%)	6/64 (9.4)	2/49 (4.1)
Other oils/grease, n (%)	88 (77.2)	71 (85.5)
Without gloves, n/ n_{total} (%)	11/88 (12.5)*	2/71 (2.8)
Detergents, n (%)	81 (71.1)	59 (71.1)
Without gloves, n/ n_{total} (%)	10/81 (12.3)*	1/59 (1.7)
Solvents, n (%)	42 (36.8)	41 (49.4)
Without gloves, n/ n_{total} (%)	3/42 (7.1)	1/41 (2.4)
Use of skin barrier cream, n (%)	101 (88.6)	71 (85.5)
Daily application frequency (mean $\pm$ SD)	4.73 $\pm$ 3.50**	3.36 $\pm$ 2.34
Use of emollient, n (%)	106 (93.0)	77 (92.8)
Daily application frequency (mean $\pm$ SD)	3.18 $\pm$ 2.69	3.43 $\pm$ 3.02
Use of protective gloves, n (%)	103 (90.4)	80 (96.4)
Hours/day (mean $\pm$ SD)	4.33 $\pm$ 2.58*	5.13 $\pm$ 2.20
Daily handwashing frequency at work		
$\geq 5x$	48 (42.1)	27 (32.5)
$\geq 10x$, n (%)	20 (17.5)	12 (14.5)
Mean $\pm$ SD	6.14 $\pm$ 4.25	5.64 $\pm$ 3.49
Use of abrasive detergents, n (%)	56 (49.1)	30 (36.1)

Abbreviations: SD: standard deviation.

* $P < .05$.** $P < .01$.

of the disease. To the best of our knowledge, this is the first direct comparison of SIP and TIP patients from the same occupational field. The study confirms clearly that MWs with WRSDs participating in the TIP had more severe and longstanding disease than those taking part in the SIP. AD and tobacco smoking were significantly more frequent in the TIP patients.

An increase of disease-specific knowledge after participation in an SIP was already reported by Wilke et al.¹³ The mean OSD-KQ scores of their study cohort of 105 SIP patients (21.9% MWs) at baseline (38.5) and of a subcohort of 68 participants 2–3 months later (52.3) correspond well with our results. Knowledge increase does not necessarily translate into behavioral change. However, in the present

study, SIP patients reported a decrease of hazardous exposures and improvements of protective behavior at follow-up, which could be attributed to the intervention and likely led to the observed significant decrease of disease severity. Frequent handwashing and wet work, particularly when exceeding 2 hours per day, are well known risk factors for work-related hand eczema.^{32,33} At follow-up, the SIP patients reported a significant decrease of both wet work >2 hours per day and handwashing frequency. This was probably achieved by the reported significant increase in use of protective gloves in order to avoid hazardous exposures, corresponding to a significant decrease of soiling and need of abrasive detergents. In particular, the number of MWs who reported not wearing gloves when exposed to water-based

TABLE 3 Comparison of data at baseline (T1) and at follow-up (T2) of metalworkers (n = 93) taking part in the secondary individual prevention program (SIP)

	T1	T2
OHSI (mean ± SD)	3.15 ± 2.63***	2.01 ± 2.00
OSD-KQ (mean ± SD) (n = 88)	38.50 ± 7.94***	50.74 ± 5.74
Wet work >2 h/day, n (%)	64 (68.8)**	56 (60.2)
Soiling >2 h/day, n (%)	69 (74.2)**	58 (62.4)
Workplace exposure		
Water-based metalworking fluids, n (%)	59 (63.4)	54 (58.1)
Without gloves, n/n _{total} (%)	10/59 (16.9)*	3/54 (5.6)
Oil-based metalworking fluids, n (%)	28 (30.1)	28 (30.1)
Without gloves, n/n _{total} (%)	10/28 (35.7)	8/28 (28.6)
Hydraulic oils, n (%)	53 (57.0)	53 (57.0)
Without gloves, n/n _{total} (%)	6/53 (11.3)	3/53 (5.7)
Other oils/grease, n (%)	69 (74.2)	70 (75.3)
Without gloves, n/n _{total} (%)	9/69 (13.0)	6/70 (8.6)
Detergents, n (%)	66 (71.0)	65 (69.9)
Without gloves, n/n _{total} (%)	8/66 (12.1)	4/65 (6.1)
Solvents, n (%)	38 (40.9)	37 (39.8)
Without gloves, n/n _{total} (%)	2/38 (5.3)	1/37 (2.7)
Use of skin barrier cream, n (%)	82 (88.2)	81 (87.1)
Daily application frequency (mean ± SD, n = 78)	4.90 ± 3.78	4.14 ± 2.12
Use of emollient, n (%)	86 (92.5)	88 (94.6)
Daily application frequency (mean ± SD, n = 83)	3.21 ± 2.81	3.05 ± 2.47
Use of protective gloves, n (%)	83 (89.2)*	92 (98.9)
Hours/day (mean ± SD, n = 91)	4.26 ± 2.60***	5.19 ± 2.41
Daily handwashing frequency at work		
≥ 5x, n/n _{total} (%)	43/93 (46.2)**	24/92 (26.1)
≥ 10x, n/n _{total} (%)	17/93 (18.3)*	5/92 (5.4)
Mean ± SD (n = 92)	6.30 ± 4.29**	5.01 ± 2.85
Use of abrasive detergents, n/n _{total} (%)	48/93 (51.6)***	22/91 (24.2)

Abbreviations: OHSI: Osnabrueck Hand Eczema Severity Index; OSD-KQ: Occupational skin diseases knowledge questionnaire; SD: standard deviation.

*P < .05.

**P < .01.

***P < .001.

metalworking fluids decreased. This might have been beneficial not only because of the accompanying reduction of wet work, but also because of the decrease of skin irritation caused by these usually alkaline products. Some MWs continued exposure to metalworking fluids without protective gloves. Possibly they were not allowed to wear protective gloves due to work on rotating tools and the related risk of hand injury caused by gloves trapped in the machinery. The self-reported use of skin barrier creams and emollients was already high at baseline and did not substantially increase after the SIP. Here, we assessed only short-term effects of the SIP in MWs. Previously, also long-term sustainability of the effects of the SIP or similar secondary preventions have been demonstrated in participants of various occupations.^{3-5,7} A recent study in 94 MWs with WRSD from Germany showed that 1 year after taking part in a SIP, the disease severity was

significantly lower than at baseline and 88.3% had remained in their profession.⁶

The TIP is offered to patients with severe symptoms refractory to secondary prevention measures, whereas the SIP targets patients with early and/or mild symptoms of the disease, shortly after notification of the statutory accident insurances. Accordingly, the disease severity was significantly lower and its prior duration significantly shorter in SIP patients than in TIP patients. In a previous multicenter study comprising 1788 TIP patients, the mean OHSI value at admission was 6.30,¹⁰ which was similar to the mean OHSI value of 5.99 observed among the TIP patients in our study. The higher disease severity in the TIP patients was also indicated by the more frequent systemic treatment with corticosteroids and alitretinoin as well as PUVA phototherapy in the previous year. The significantly higher number of days

TABLE 4 Severity of hand eczema at baseline (T1) and follow-up (T2) in subgroups of patients taking part in the secondary prevention program (SIP) or in the tertiary prevention program (TIP) excluding those who stopped tobacco smoking in the past

	SIP T1 n/n _{total} (%)	SIP OHSI T1 mean ± SD	SIP T2 n/n _{total} (%)	SIP OHSI T2 mean ± SD	TIP T1/2 n/n _{total} (%)	TIP OHSI T1 mean ± SD	TIP OHSI T2 mean ± SD
Smokers	36/89 (40.4)	3.44 ± 2.97	28/72 (38.9)	1.75 ± 1.90	39/73 (53.4)	6.05 ± 3.34	3.15 ± 2.29
Nonsmokers	53/89 (59.6)	2.89 ± 2.42	44/72 (61.1)	1.80 ± 2.03	34/73 (46.6)	5.56 ± 3.31	2.68 ± 2.36
Atopic skin diathesis ^a	20/89 (22.5)	4.15 ± 3.27*	17/72 (23.6)	2.59 ± 2.48	16/73 (21.9)	7.81 ± 3.33**	4.38 ± 2.50**
No atopic skin diathesis	69/89 (77.5)	2.81 ± 2.40	55/72 (76.4)	1.53 ± 1.73	57/73 (78.1)	5.26 ± 3.11	2.53 ± 2.11
Atopic dermatitis ^b	14/89 (15.7)	4.07 ± 3.58	11/72 (15.3)	2.45 ± 1.75	28/73 (38.4)	7.32 ± 3.62**	3.68 ± 2.75*
No atopic dermatitis	75/89 (84.3)	2.93 ± 2.44	61/72 (84.7)	1.66 ± 1.99	45/73 (61.6)	4.89 ± 2.75	2.47 ± 1.89
FLG mutation	13/82 (15.9)	2.31 ± 1.80	10/69 (14.5)	1.60 ± 1.43	7/68 (10.3)	5.86 ± 2.67	2.97 ± 2.27
no FLG mutation	69/82 (84.1)	3.22 ± 2.68	59/69 (85.5)	1.85 ± 2.08	61/68 (89.7)	5.85 ± 3.39	3.86 ± 2.97

Abbreviations: OHSI: Osnabrueck Hand Eczema Severity Index; SD: standard deviation.

* $P < .05$.

** $P < .01$.

^aErlangen atopy score ≥ 10 .

^bOn body areas other than hands.

of absence from work in the previous year reported by the TIP patients is likely also related to the higher severity of the disease.

Wilke et al demonstrated that the severity of hand eczema at the time of participation in a SIP correlated with the ability to remain in the profession without the need to subsequently participate in the TIP in the following 5 years.⁵ Exogenous and endogenous factors may be involved in severity and chronicity of the disease leading to participation in tertiary preventive measures. Self-reported workplace exposures to skin hazards and work tasks were very similar in SIP and TIP patients. However, significantly more SIP patients reported occupational exposure without protective gloves to various hazardous substances, including water-based metalworking fluids, at baseline, whereas the extent of self-reported use of protective gloves was significantly higher in the TIP patients. A likely explanation for these differences is that about half of the TIP patients had previously participated in an SIP, and thus had already received guidance regarding adequate gloves and their correct use. Indeed, TIP patients who had not taken part in an SIP before showed a significantly lower extent of glove use than the other TIP patients. Overall, this points to a higher need for improvements of protective behavior in SIP than in TIP patients and to factors other than workplace exposures and inadequate skin protection behavior as reasons for the higher disease severity observed in TIP patients.

In accordance with other studies, irritant contact dermatitis was the most common diagnosis in both groups.^{6,10} Atopic skin diathesis and AD, which are associated with impaired skin barrier function, are well-recognized risk factors for developing WRSDs, particularly irritant contact dermatitis.^{18,34,35} In the present study, an atopic hand eczema component and AD observed at body areas other than the hands were significantly more common in TIP patients than in SIP patients. Notably, atopic skin diathesis and AD were associated with severity of hand eczema in TIP patients, and atopic skin diathesis also in SIP patients. AD may not only worsen the severity and course of work-related hand eczema, but may itself cause chronic and relapsing

skin symptoms. It is therefore a challenge in these patients to differentiate if symptoms leading to participation in the TIP were caused primarily by WRSD or AD. Moreover, extensive body involvement of AD may increase willingness in taking part in the TIP.

The high prevalence of FLG mutations in SIP patients (14.2%) and TIP patients (11.8%) is in accordance with other studies reporting an increased risk of developing work-related hand eczema in FLG mutation carriers,^{18,19,21} which subsequently leads to participation in the SIP and TIP. Recently, we demonstrated in 303 metal work apprentices that FLG mutations are significantly associated with incident hand eczema during apprenticeship.²² The rate of FLG mutation carriers in apprentices with incident hand eczema was 13.0% and thus corresponds well with the current results. In contrast to AD, FLG mutations were not associated with severity of hand eczema and not more common in TIP than in SIP patients in the present study. This suggests that severity of hand eczema and need for the TIP were rather linked to factors related to AD other than FLG mutations. Similarly, no significant differences between SIP and TIP patients were found by the explorative GWAS. Possible explanations were the small study size and a healthy worker effect. The duration of the disease correlated with the severity of hand eczema at baseline in SIP patients and at follow-up both in SIP and TIP patients. A longstanding disease may impair the skin regeneration capacity, thereby resulting in a more severe and persistent disease stressing the need for early interventions.

Tobacco smoking is thought to induce proinflammatory mechanisms and tissue damage in the skin.³⁶ Accordingly, we recently found a significant association between tobacco smoking and incident hand eczema in metalwork apprentices.²² However, data on associations between tobacco smoking and hand eczema are contradictory.³⁷ Previously we revealed that work-related hand eczema was more severe and persistent in smokers than in nonsmokers among TIP patients and that tobacco smoking was associated with work absenteeism and leaving the workforce.²⁵ Others also showed that tobacco smoking is

associated with severity and impaired healing of work-related hand eczema.^{26,27} In the present study, self-reported tobacco smoking was significantly more common among TIP patients than SIP patients. This may indicate that tobacco smoking contributed to severity and persistence of the disease leading to the TIP. However, when adjusting for age and AD, tobacco smoking was not independently associated with the TIP. The severity of hand eczema at baseline and work absenteeism in the previous year were higher in smokers than in nonsmokers among both TIP and SIP patients. However, these differences did not reach significance, which may be related to the small study size. Of interest, tobacco smoking was significantly associated with vesicular hand eczema in TIP patients. In addition, in a previous study focusing on the different morphological subtypes of hand eczema in TIP patients, vesicular hand eczema was the only clinical subtype associated with self-reported tobacco smoking.³⁸ In line with our current findings, Kütting et al demonstrated in metalworkers with irritant hand dermatitis that smokers had significantly higher hand eczema score values than nonsmokers for both erythema and vesicles.³⁹ Thus tobacco smoking may, in particular, have an influence on the occurrence and course of vesicular hand eczema.

Regarding limitations of our study, as mentioned earlier, a controlled study design was not possible.⁴ Another limitation is that no long-term results were available, including information on how many of the SIP patients participated in the TIP afterwards. Some of the data were self-reported, which may have compromised accuracy. Furthermore, the small study size hampered the genetic analyses, particularly the GWAS. Because the study was done in MWs only, it is difficult to draw any conclusions regarding patients working in other occupations, even though it is likely that some of the results would be similar.

In conclusion, the SIP was effective in improving disease-specific knowledge and protective behavior in MWs with WRSD, while reducing the severity of the disease. Individual factors, including particularly AD, may confer a higher severity and persistence of the disease leading to participation in the TIP.

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CONFLICT OF INTEREST

There are no conflicts of interest.

AUTHOR CONTRIBUTIONS

Richard Brans: Conceptualization; data curation; formal analysis; funding acquisition; investigation; project administration; supervision; writing-original draft; writing-review and editing. **Annika Wilke:** Conceptualization; investigation; supervision; writing-review and editing. **Elke Rodriguez:** Formal analysis; investigation; writing-review and editing. **Nicole Boraczynski:** Formal analysis; investigation; writing-review and editing. **Stephan Weidinger:** Conceptualization; resources; supervision; writing-review and editing. **Anna Reich:** Conceptualization; writing-review and editing. **Johannes Geier:** Conceptualization; funding

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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Supplemental Table 1. Professions of metalworkers taking part in the secondary individual prevention program (SIP) and in the tertiary individual prevention program (TIP)

Profession n (%)	SIP n _{total} = 114	TIP n _{total} = 83
Cutting machine operator	46 (40.4) *	21 (25.3)
Industrial mechanic	31 (27.2)	26 (31.3)
Tool maker	13 (11.4)	8 (9.6)
Construction mechanic/model builder	9 (7.9)	9 (10.8)
Car mechanic	8 (7.0)	8 (9.6)
Process mechanic	5 (4.4)	6 (7.2)
Other	2 (1.8)	5 (6.0)

* $P < .05$

Supplemental Table 2. Comparison of smokers and non-smokers among patients with hand eczema taking part in the secondary prevention program (SIP) or in the tertiary individual prevention program (TIP) excluding those who stopped smoking in the past

SIP	SIP Smokers n=36	SIP Non-smokers n=53	TIP Smokers n=39	TIP Non-smokers n=34
Days of absence from work due to HE in 12 months prior to T1 (mean $\pm$ SD)	9.28 $\pm$ 15.25	5.23 $\pm$ 9.21	19.00 $\pm$ 31.78	16.26 $\pm$ 23.62
Subtypes of HE n (%)				
• ICD	34 (94.4)	50 (94.3)	35 (89.7)	27 (79.4)
• ACD	4 (11.1)	13 (24.5)	13 (33.3)	9 (26.5)
• Atopic HE	18 (50.0)	20 (37.7)	27 (69.2)	19 (55.9)
• Hyperkeratotic HE	5 (13.9)	5 (9.4)	5 (12.8)	7 (20.6)
Vesicular HE [†] T1 n (%)	9 (25.0)	11 (20.8)	19 (48.7) *	8 (23.5)
Vesicular HE [†] T2 n (%)	5 (17.9)	7 (15.9)	20 (51.3) ***	4 (11.8)

HE: hand eczema; SD: standard deviation; ICD: irritant contact dermatitis, ACD: allergic contact dermatitis

[†]according to Osnabrueck Hand Eczema Severity Index

T1: at baseline; T2: at follow-up

* $P < .05$; *** $P < .001$