The Incidence of Work-related Asthma-like Symptoms and Dust Exposure in Norwegian Smelters

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***Rationale*: The prevalence of respiratory symptoms among employees in smelters is positively associated with dust exposure.**

***Objectives*: To investigate the association between the incidence of work-related asthma-like symptoms (WASTH) and dust exposure.**

***Methods*: All the employees were invited to participate in a 5-year longitudinal study. The outcome of WASTH was defined as the combination of dyspnea and wheezing improving on rest days or vacation in an individual who had no asthma previously. Information about smoking and occupational status was obtained from a questionnaire. A job exposure matrix of total dust was developed. Multivariate data analyses were performed using Cox regression.**

***Measurements and Main Results*: The total follow-up time of the employees (n = 2,476) was 8,469 years, and the median follow-up time for participants was 4.0 years. During the follow-up, 91 employees developed WASTH, and the corresponding incidence rate for WASTH per 1,000 person-years was 8.9 (7.3–10.9) (95% confidence interval in parentheses). The risk ratio of WASTH increased significantly (P = 0.0001) with dust exposure in the middle and high categories (1.0–2.9 and ≥3.0 mg/m^3). Stratified analyses showed that the effect of current dust exposure varied with both previous exposure (PE) to dust and fumes (P = 0.006) and airflow limitation (AFL) (P = 0.033). The final analyses showed that the risk ratios for WASTH per 1 mg/m^3 increase in current dust exposure were 1.1 (0.93–1.2), 1.4 (1.1–1.8), 1.6 (1.1–2.3), and 1.9 (1.2–3.0) for the categories (PE+/AFL−), (PE−/AFL−), (PE+/AFL+, and (PE−/AFL+).**

***Conclusions*: In conclusion, dust exposure was associated with an increased incidence of WASTH.**

Keywords: work-related asthma-like symptoms; incidence; dust exposure

> **AT A GLANCE COMMENTARY**
>
> **Scientific Knowledge on the Subject**
>
> A positive association between dust exposure and nonspecific respiratory symptoms has been found in employees who leave the smelter industry.
>
> **What This Study Adds to the Field**
>
> There is a positive relationship between dust exposure and the incidence of asthma-like symptoms in employees in smelters.

Increased prevalence and incidence of respiratory symptoms have been found in subjects exposed to a wide range of occupational pollutants in general populations as well as in occupational cohorts of workers exposed to nonspecific agents (1–10). In these studies, the incidence rates have varied in the range 1.5 to 7.3 cases per 1,000 person-years, with an increased rate in subjects with different occupational exposures compared with nonexposed individuals.

Norwegian smelting industry produces ferrosilicon alloys (FeSi), silicon metal (Si-metal), ferromanganese (FeMn), silicon manganese (SiMn), ferrochromium (FeCr), silicon carbide (SiC), and titanium(II) oxide (TiO_2). During production, several air pollutants are emitted to the workplace environment, foremost particulates and gases that are potentially harmful to the airways (11, 12). The effect of pollutants in smelters on the airways is most likely nonspecific because such inorganic compounds usually do not induce a specific immunologic response. In a cross-sectional study of employees in this industry, we found that the prevalence of several respiratory symptoms (dyspnea with wheeze, cough without a cold, and phlegm) was higher among subjects who worked full time in the production line (line operators) than among nonexposed workers (13). Longitudinal follow-up for 5 years of this workforce showed that line operators had more symptoms than nonexposed employees, and this effect was more pronounced among dropouts (14). We used data from this study to investigate if work-related asthma-like symptoms (WASTH) were associated with occupational dust exposure in smelter workers. Some of the results of these studies have been previously reported in the form of an abstract (15).

MATERIALS AND METHODS

Study Population

All employees aged 20 to 55 years in 18 Norwegian smelters producing FeSi/Si-metal, FeMn, SiMn, FeCr, or SiC were invited to participate in a longitudinal respiratory study. The number of employees was 3,084 (nearly 90% of the total work force), and they underwent 12,996 examinations.

The study was conducted between 1996 and 2003. The employees were followed annually with spirometry measurements and a respiratory questionnaire (16). Spirometry was performed as recommended by European Community for Coal and Steel (17); details are explained elsewhere (12, 18). On the respiratory questionnaire, participants were asked to report symptoms they experienced during the last year (16). Participants whose last examination was 18 months or more before the

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closure of the study were regarded as dropouts (19). The mean time between examinations and the number of participants at each examination are shown in Table 1.

Definitions

Symptom and disease outcomes were based on responses to items on the survey questionnaires. The outcome of WASTH was defined as dyspnea with wheeze that improved on days off work and holidays in a participant who had not previously had asthma diagnosed by a doctor. Moreover, they should not have reported the combination of dyspnea and wheezing at the first examination of the study. Subjects were regarded as prevalent cases at each follow-up if they fulfilled the criteria for WASTH. Thereby, the total number of employees available for analyses decreased from 3,084 to 2,476. Employees reporting WASTH at inclusion to the study were classified as prevalent cases, whereas those who developed WASTH after inclusion (i.e., during the follow-up examinations) were regarded as incident cases.

Doctor-diagnosed asthma was asthma diagnosed by a physician. Allergy was considered to be present if the employee had a history of either hay fever or atopic eczema. Familial asthma was defined as current or previous asthma in parents, grandparents, sisters, or brothers.

A symptom score was constructed as the sum of positive answers (score = 1 if yes and 0 otherwise) to questions about five respiratory symptoms: dyspnea, wheezing, cough without a cold, daily cough for 3 months or longer, and phlegm. Hence, for each participant, the symptom score was an integer from 0 through 5. Participants with a score of 1 or greater were considered positive for "other respiratory symptoms."

Spirometric measurements included FEV_1 and FVC. Airflow limitation was defined as FEV_1/FVC less than the lower limit of normal (20, 21).

Exposure

Information about job category and smoking habits during the previous year was obtained from the questionnaire. Current occupational exposure was assessed using a quantitative job exposure matrix. This job exposure matrix was constructed as the geometric mean of total dust exposure in each job category in each smelter and is explained in greater detail elsewhere (11, 12). Briefly, dust from the working atmosphere was collected by personal samplers during the study period. Each employee was allocated to the geometric mean of the dust exposure for the corresponding job title of the previous year. If an employee changed job categories during the year, a time-weighted average of the relevant geometric means was used. Information on job category, and thereby qualitative as well as quantitative determination of dust exposure, was updated at each examination. The mean dust exposure (mg/m^3) by type of production is shown in Table 1.

Employees were defined as previously exposed if they answered "Yes" to the following in the baseline survey questionnaire: "Have you previously been exposed on a regular basis to fumes, dust, or irritating vapors (gases) during your work?"

The study was approved by the Regional ethics committee.

Statistical Analyses

To examine the relationship between WASTH and dust exposure, we first calculated the incidence rate (IR, per 1,000 person-years) of WASTH by different categories of several covariates (Table 2). Subjects reporting doctor-diagnosed asthma or the combination of dyspnea and wheezing at baseline were excluded from the analyses. Then, we investigated the univariate association between IR and covariates (Table 2) using the log-rank test. Second, the Mantel Haenszel test was used to investigate confounding and effect modification for the association between incident WASTH and exposure adjusted for relevant covariates that had a univariate *P* value less than 0.2 (first stage). We chose to divide dust exposure in three categories (0–0.9, 1.0–2.9, and ≥ 3.0 mg/m^3). We also investigated the effect of dividing dust exposure into tertiles (with cut points of 0.84 and 2.32 mg/m^3) and dichotomizing at 3.0 mg/m^3. The multivariate association between the incidence of WASTH and exposure was performed using Cox regression with time-dependent covariates. In these analyses we also investigated the association between the incidence of WASTH and dust exposure using dust exposure as a continuous covariate. The underlying time variable was years since inclusion in the study. In all multivariate analyses, a covariate was excluded from the model if it had a *P* value greater than 0.05 and, when deleted from the model, the coefficient for the variable of interest changed less than 20%. The proportional-hazards assumption was checked on the basis of Schoenfeld residuals (22).

Data were analyzed using the procedure stcox in Stata version 11 (StataCorp, College Station, TX).

RESULTS

The total observation time was 8,469 years, and the median observation time per participant was 4.0 years. The number of incident cases of WASTH was 91, and the overall crude IR of WASTH was 8.9×10^{-3} years. The number of subjects at baseline and the crude incidence rates of WASTH during follow-up are presented by different covariates in Table 2. The crude IR of WASTH was positively associated with smoking, airflow limitation, and dust exposure, and negatively associated with previous exposure. The Kaplan-Meier incidence plot of WASTH for the three categories of current dust exposure is shown in Figure 1. The IR varied considerably between the different production types, with higher values for FeSi-Si (15.4×10^{-3} yr) and SiMn/FeMn/FeCr (13.6×10^{-3} yr), and the lowest value for SiC (8.6×10^{-3} yr). An increased incidence of WASTH was

TABLE 1. THE NUMBER OF SMELTER EMPLOYEES AND CURRENT MEAN DUST EXPOSURE AT BASELINE AND EACH OF FIVE FOLLOW-UP SURVEYS, BY PRODUCTION TYPE

		Follow-up Surveys				
Type of Production	Baseline	1	2	3	4	5
FeSi, Si-metal						
Years after baseline	0	1.04	2.10	3.08	4.00	4.90
Number of subjects	1,687	1,514	1,281	1,138	943	538
Mean dust exposure (SD)	2.5 (2.1)	2.5 (2.1)	2.4 (2.0)	2.5 (2.1)	2.5 (2.1)	2.0 (1.8)
SiMn, FeMn, FeCr						
Years after baseline	0	1.06	2.11	3.15	4.01	4.90
Number of subjects	933	874	793	720	584	321
Mean dust exposure (SD)	1.5 (1.6)	1.5 (1.6)	1.5 (1.6)	1.5 (1.4)	1.4 (1.1)	1.3 (1.4)
SiC						
Years after baseline	0	1.12	2.16	3.34	4.06	4.90
Number of subjects	464	437	383	210	125	40
Mean dust exposure (SD)	1.9 (2.1)	1.7 (2.0)	1.6 (1.8)	1.4 (1.1)	1.3 (1.0)	1.6 (1.1)

Definition of abbreviations: FeCr = ferrochromium; FeMn = ferromanganese; FeSi = ferrosilicon; SiC = silicon carbide; Si-metal = silicon metal; SiMn = silicon manganese.

Dust exposure in mg/m^3. Individual estimates of exposure are expressed as geometric mean.

TABLE 2. NUMBER OF EMPLOYEES AT BASELINE, INCIDENCE, AND INCIDENCE RATE PER 1,000 PERSON-YEARS OF WORK-RELATED ASTHMA-LIKE SYMPTOMS BY DIFFERENT COVARIATES

	Baseline		Follow-up	
Characteristics	N	%	n	IR
Age at baseline, yr				
<35	909	36.7	20	10.1
35–44	811	32.8	27	9.7
⩾45	756	30.5	44	12.5
Sex				
Female	282	11.4	6	6.6
Male	2,194	88.6	85	11.6
Smoking habits				
Never smoked	825	33.3	16	6.2
Former smoking	509	20.6	19	9.5
Current smoking	1,067	43,1	54	15.5
Unknown	75	3.0	2	8.9
Asthma or allergy				
Familial asthma	463	18.7	21	10.4
Allergy	410	16.6	19	14.3
Airflow limitation*				
Yes	177	7.2	12	11.9
No	2,299	92.9	79	8.2
Previous exposure				
Yes	1,669	67.4	70	12.2
No	807	32.6	21	8.2
Dust exposure, mg/m^3				
<1.0	882	35.6	16	5.1
1.0–2.9	988	39.9	43	13.1
⩾3.0	606	24.5	32	16.9
Production type				
FeSi, Si-metal	1,341	54.2	56	12.5
SiMn, FeMn, FeCr	758	30.6	30	10.8
SiC	377	15.2	5	4.7
Dropout				
Yes	127	5.1	10	27.1
No	2,349	94.9	81	10.2
Respiratory symptoms				
None	1,671	67.5	30	5.4
Any	763	30.8	61	22.2
Unknown	42	1.7	0	0.0
Total	2,476	100.0	91	11.0

Definition of abbreviations: FeCr = ferrochromium; FeMn = ferromanganese; FeSi = ferrosilicon; IR = incidence rate; SiC = silicon carbide; Si-metal = silicon metal; SiMn = silicon manganese.

* Airflow limitation defined as FEV_1/FVC < lower limit of normal.

also observed in dropouts. The prevalence of WASTH during the study was, however, reasonably stable (Table 3).

The stratified analyses indicated significant effect modification of the association between the incidence of WASTH and dust exposure by previous exposure ($P = 0.006$) as well as airflow limitation ($P = 0.033$) (Table 4). Data are presented in three categories of current dust exposure: 0 to 0.9, 1.0 to 2.9, and greater than or equal to 3.0 mg/m^3. Stratified analyses regarding the remaining covariates are shown in the online supplement (*see* Table E1 in the online supplement). These analyses indicated no meaningful confounding by any of the relevant covariates. The results were broadly the same if we used alternative limits for the dust exposure, such as tertiles (data not shown). There was no evidence of interaction between smoking and dust exposure regarding the incidence of WASTH (P for effect modification, 0.87).

Because the stratified analyses showed significant effect modification by previous exposure as well as airflow limitation on the association between current dust exposure and the incidence of WASTH, we invoked a Cox model including dichotomous covariates for airflow limitation and previous exposure, a continuous covariate for current dust exposure, and corresponding product-terms ([airflow limitation] × [dust exposure] and [previous exposure] × [dust exposure]). The P values for the product-terms were 0.014 and 0.034, respectively. We therefore decided to divide the multivariate Cox regression into five models. The results of these analyses are shown in the online supplement (Table E2). In the first model we ignored the product-terms between exposure (in mg/m^3, continuous) and previous exposure as well as airflow limitation (Table E2). As expected, the hazard ratio (HR) of WASTH and exposure differed markedly between the models, whereas HR regarding the covariates did not demonstrate noteworthy changes between the models (Table E2).

Sex and SiC did not satisfy the proportional hazard assumption and were therefore removed from the multivariate analyses. The HR (95% confidence interval [CI]) of WASTH among current smokers and former smokers was 2.0 (1.1–3.5) and 1.3 (0.68–2.7), respectively, compared with never smokers. Using the amount of tobacco consumption in three or five categories instead of three categories did not influence the association between dust exposure and the incidence of WASTH. The difference between FeSi/Si-metal smelters and FeMn/SiMn/FeCr smelters was negligible, and removal from the model did not interfere with the associations between WASTH and any of the other covariates. Type of production was therefore removed from the model. However, all the other variables as well as the global test satisfied the proportional hazard assumption. Neither airflow limitation nor previous exposure was associated with the incidence of WASTH (P values, 0.30 and 0.49, respectively). Significant associations between the incidence of WASTH and dust exposure were found in employees without previous exposures to gases or fumes ($P < 0.001$) as well as among employees with airflow limitation ($P = 0.011$) (Table E2). The association between smoking and the incidence of WASTH was less consistent than the association with dust exposure. A negative association between the incidence of WASTH and age was found in subjects with airflow limitation. See Table E2 for more details.

As we found no noteworthy confounding by the covariates on the association between the incidence of WASTH and dust exposure but strong effect modification by previous exposure as well as airflow limitation, we investigated the association between the incidence of WASTH and dust exposure stratified by the previous exposure and airflow limitation simultaneously (Figure 2). Figure 2 shows that the magnitude of the association between the incidence of WASTH and dust exposure differed significantly between the dichotomized combinations of airflow

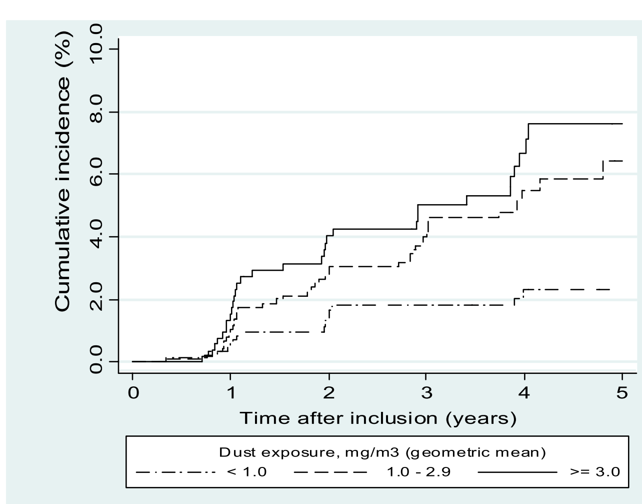

Figure 1. Kaplan-Meier incidence plot of work-related asthma-like symptoms by dust exposure (in three categories).

TABLE 3. INCIDENCE AND CUMULATIVE NUMBER OF CASES REPORTING WORK-RELATED ASTHMA-LIKE SYMPTOMS DURING THE STUDY

WASTH Subgroup	Baseline	Follow-up Surveys				
		1	2	3	4	5
Incident cases	0	41	23	11	14	2
Prevalent cases	0 (0)	41 (1.8)	32 (1.6)	18 (1.1)	21 (1.6)	7 (0.96)

Definition of abbreviations: WASTH = work-related asthma-like symptoms.
Percent of the cumulative incidence given in parentheses.

limitation (yes/no) and previous exposure to gases or dust (yes/no). The rate ratio between WASTH and dust exposure (continuous) expressed as mg/m^3 adjusted for airflow limitation and previous exposure was 1.20 (95% CI, 1.08–1.34). The *P* value for effect modification by all combinations of previous exposure and airflow limitation was 0.014.

DISCUSSION

In this study we found a significant dose–response relationship between the incidence of WASTH and dust exposure in smelters. Moreover, we found that this association was more pronounced in participants with airflow limitation or no previous exposure than among their counterparts.

This study has at least three strengths. First, the job exposure matrix was based on measurements that were obtained concurrently with the examination of employees. Second, the information from each participant was collected using a validated questionnaire that was developed in similar settings. The kappa agreement regarding dyspnea and wheezing was 0.61 and 0.57, respectively (16). Third, the application of Cox analysis in similar settings has been validated.

Nonetheless, there are some issues that have to be addressed, foremost the interpretation of the main outcome—WASTH. First, the date of onset of WASTH was not available (i.e., the incidence rate cannot be estimated with certainty). However, this problem has previously been studied by Samuelsen and Kongerud (23) in a study among potroom workers in the aluminum industry using the same questionnaire (24). Briefly, they found that the association between the incidence of WASTH and covariates was independent of the choice of time for censoring between two consecutive examinations. For several reasons, the term WASTH is not interchangeable with "work-related asthma." Studies have shown only modest association between "asthma-like symptoms" and the diagnosis of asthma in epidemiologic studies (25, 26). First, the incidence of WASTH was higher than the incidence of adult-onset asthma in the general population (27, 28), and none of the participants with doctor-diagnosed asthma fulfilled the criteria for WASTH. Hence, it is likely that the symptoms were mild. Nonetheless, airflow limitation reinforced the association between WASTH and dust exposure, indicating that WASTH may be an index of incipient work-related chronic obstructive pulmonary disease (COPD). Actually, in the aluminum industry we found a strong association between WASTH and annual decline in FEV_1 (29), although the evidence for this suggestion in the present setting is weak. Foremost, the association between the incidence of WASTH and occupational dust exposure was consistent (i.e., independent of how dust exposure was characterized in the analyses). Thus, it is reasonable to consider WASTH as an important state from the point of view of occupational health.

For occupational health care, it is desirable to identify employees having an increased risk of COPD, preferably before the disease is established (30). Guidelines for surveillance of workers with an increased risk of work-related obstructive respiratory disease are, however, lacking. The individual analyses of the measurements from repeated spirometries have several pitfalls (30, 31). Moreover, repeated spirometries in large work forces where only a minority of the employees have an elevated risk of COPD is costly. Our results indicate that it is likely that high-risk individuals can be identified using a questionnaire. Employees reporting WASTH could be selected and followed up with supplementary examinations, such as repeated spirometries. However, the sensitivity and specificity of such a strategy has to be investigated. This issue has not been investigated in the current analyses. It should be noted that a large proportion of the employees who ever reported WASTH during the study did not consistently report this combination of symptoms.

It is also worthy to note that a strong association between dust exposure and the incidence of WASTH was found, although the dust exposure level should be regarded as moderate to low (32). Thus, even employees working in an environment with low dust exposure levels should be monitored regarding their respiratory health. Because the dropout rate was significantly higher in subjects reporting WASTH compared with the remaining employees, the detection of negative health effects could be partly prevented as a result of self-selection.

The underlying pathophysiologic mechanism that corresponds to WASTH is, however, unclear. First, the combination of dyspnea and wheezing improving on rest days and holidays has

TABLE 4. NUMBER OF INCIDENT CASES, INCIDENCE RATE PER 1,000 PERSON-YEARS, CRUDE AND ADJUSTED RATE RATIOS WITH THE CORRESPONDING 95% CONFIDENCE INTERVALS FOR WORK-RELATED ASTHMA-LIKE SYMPTOMS IN THREE CATEGORIES OF CURRENT DUST EXPOSURE STRATIFIED BY RELEVANT COVARIATES USING THE MANTEL-HAENZSEL TEST

Covariate, n (IR)	Dust Exposure, mg/m^3			RR	
	0.0-0.9	1.0-2.9	⩾3.0	Crude RR (95% CI)	Adjusted RR (95% CI)
All	16 (5.1)	43 (13.1)	32 (16.9)	1.7 (1.3–2.2)	
Previous exposure*					1.7 (1.3–2.3)
Yes	12 (6.5)	38 (15.4)	20 (13.9)	1.4 (1.0–1.9)	
No	4 (3.1)	5 (6.1)	12 (26.5)	3.4 (1.9–6.0)	
Airflow limitation†					1.7 (1.3–2.3)
Yes	0 (0.0)	4 (18.0)	8 (55.5)	3.6 (1.8–7.5)	
No	16 (5.5)	39 (12.7)	24 (13.7)	1.5 (1.2–2.1)	

Definition of abbreviations: CI = confidence interval; IR = incidence rate; RR = risk ratio.

* *P* value for effect modification of the association between the incidence of WASTH and dust exposure by previous exposure = 0.006.

† *P* value for effect modification of the association between the incidence of WASTH and dust exposure by airflow limitation = 0.033.

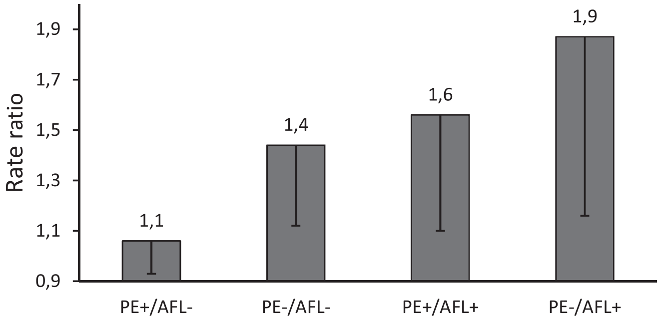

Figure 2. Stratum-specific rate ratios for the association between the incidence of work-related asthma-like symptoms and current dust exposure (continuous) per mg/m^3 by combined status of previous exposure to dust and fumes and airflow limitation, using Mantel Haenszel test. Vertical lines indicate lower 95% confidence interval bounds (*P*-trend, 0.014). AFL = airflow limitation; PE = previously exposed.

many similarities with occupational asthma. The Third Jack Pepys Workshop on Asthma in the Workplace held in Montreal, Canada in May 2007 subdivided asthma at the workplace as work-related asthma and occupational asthma (33). Work-related asthma was subclassified into "irritant asthma" and "work-aggravated asthma." This categorization has also been used by others (34). The environment in smelters does not contain substances that are likely to act as sensitizers, but rather irritants like sulfur dioxide, nitrogen oxides, and particulates. Thus, we believe that the symptoms are mediated by a nonspecific mechanism, such as an innate immune response. The exposure level of these substances should be regarded as moderate or low. Hence, it not likely that subjects reporting WASTH have "reactive airways dysfunction syndrome" (35), although short episodes of high peak exposure cannot be excluded. However, in their consensus statement, the American College of Chest Physicians suggests that repeated low-dose exposure to irritants constitutes a separate subgroup of occupational asthma (36). It is likely that WASTH fulfills this definition of occupational asthma. Moreover, subjects reporting WASTH have not had asthma diagnosed by a doctor. Thus, WASTH can hardly be classified as work-aggravated asthma. As the association between WASTH and exposure increased after exclusion of cases reporting the combination of dyspnea and wheezing, it is not likely that they had a latent asthma that has not been diagnosed by a doctor beforehand. Alternatively, it could also represent an incipient symptom of work-related COPD, as the association between the incidence of WASTH and exposure was aggravated by airflow limitation.

Because WASTH was strongly associated with occupational dust exposure, it is likely that the questionnaire is suitable for monitoring employees regarding work-related respiratory problems among employees exposed to dust. This association was quite uniform across the different types of production in these settings. Moreover, a comparable result was also found in the aluminum industry (24), where the pollutants in the workplace atmosphere are similar to the environment in the smelter industry. Accordingly, it is likely that subjects reporting WASTH may respond to nonspecific agents in the workplace air. Finally, the concept "previous exposure to fumes and gases" is problematic. Nonetheless, it has been adapted from other Norwegian studies (37, 38) since the seventies and should be considered as a surrogate index of air pollution at the workplace. Finally, we want to mention that the incidence of WASTH in the highest exposure group was the same magnitude as the incidence of WASTH among current smokers.

The main limitation is that the outcome (WASTH) lacks a diagnostic classification, which is shared by workers in several other workplaces where nonspecific airways irritants represent the main pollutants, like the work environment of welders (39).

In conclusion, the incidence of WASTH among employees in smelters is associated with dust exposure, and this association was amplified by airflow limitation. The nature and mechanism of this entity are, however, unknown.

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