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Prediction of dropout from respiratory symptoms and airflow limitation in a longitudinal respiratory study

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Objectives This study investigated the possibility that employees reporting respiratory symptoms were more likely than asymptomatic workers to dropout of a respiratory study carried out in Norwegian smelters.

Methods The study included 3924 employees in 24 Norwegian smelters. They were examined annually using a respiratory questionnaire and spirometry. The employees who did not meet for the follow-up within 18 months prior to the end of the study were considered dropouts. The data were analyzed using Cox regression for time-dependent covariates.

Results The total and the median follow-up times were 16 997 and 4.9 years, respectively. The overall dropout rate was 44.5 [95% confidence interval (95% CI) 41.5–47.8 per 1000 person-years]. The hazard ratio (HR) for dropout was 1.38 (95% CI 1.15–1.66) for the workers reporting any respiratory symptom compared with the asymptomatic workers. The effect was the strongest among the employees who reported dyspnea, and it was stronger regarding symptoms at the last visit than for the baseline symptoms. Similarly, the hazard ratio for dropout for those with an airflow limitation [forced expiratory volume/forced vital capacity below the 5th percentile of the predicted value] was 1.31 (95% CI 1.01–1.69) when they were compared with employees without any airflow limitation.

Conclusions Respiratory symptoms and airflow limitation are important predictors of dropout from a longitudinal respiratory study.

Key terms occupational exposure; selection bias.

The validity of epidemiologic occupational studies depends on the health of the selected participants (1). This phenomenon may be explained by the following three mechanisms (2): (i) primary selection at the time hired (“healthy hire effect”), (ii) secondary selection during employment (“healthy worker effect”), and (iii) changes in life associated with employment (2, 3). Differences in health status related to preemployment selection can only be accounted for in the design of the study, whereby the index group and the reference group are selected using the same criteria for selection in both groups (4). Adjustment for the selective loss of employees presumes that the health status prior to the loss of follow-up is known (2). Such adjustment can be performed using

appropriate analyses of longitudinal data (5). Hence cross-sectional studies are liable to selection bias.

Selection bias represents a major concern if the health outcome studied is associated with any exposure in the occupational setting studied—“outcome dependent bias” (4). The possibility of such “outcome dependent bias” is likely to occur in studies addressing the relationship between respiratory disorders and occupational exposure to airway irritants (ie, if exposure causes respiratory symptoms and symptomatic persons are more likely to leave their jobs, a false negative association between exposure and symptoms may result). This problem has been thoroughly discussed in major textbooks in epidemiology (4, 6). However, only a few

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empirical studies have focused on this topic. In a meta-analysis of 11 longitudinal prospective studies Radon and her co-workers (2) found that dropouts had an odds ratio of 1.23 for having chronic bronchitis when compared with persons who kept working. In all of these studies respiratory symptoms were recorded at the time of inclusion into the study.

We have conducted a longitudinal respiratory study among employees in the Norwegian smelting industry. The employees were examined annually using a respiratory questionnaire and spirometry. The objective of our present report was to study the association between respiratory symptoms or airflow limitation and the risk of dropping out of the study.

Study population and methods

Altogether 24 Norwegian smelters and maintenance and otherwise related companies that were members of The Norwegian Federation for Process Industry in 1996 (today Federation of Norwegian Industries) were invited to participate in a respiratory survey carried out by the local occupational health service at each smelter. New employees were enrolled during the entire study period.

The smelters were divided into the following four groups according to the type of production: (i) ferro-silicon and silicon metal (N=11), (ii) ferromanganese, silicomanganese, and ferrochromium, (N=4) (iii) silicon carbide (N=3), and (iv) other (N=6). The productions of "other" were titanium dioxide, pig iron, calcium carbide, and ceramite (a product made from inorganic dust). An electrode-paste production plant (also calcining anthracite), a research and development facility, and a maintenance company serving the smelters were also included in the "other" productions.

The employees were examined annually from 1997 to 2003. Their age range was 20–55 years at inclusion in the study. At each examination, the employees completed a validated respiratory questionnaire (7) and performed spirometry using a spirometer that fulfilled the specifications of the American Thoracic Society (ATS) and the European Community for Coal and Steel (ECCS) (8, 9). Spirometry was performed in a sitting position with the participants wearing a noseclip. The maximum acceptable variation between the best and the second best measurement of the forced vital capacity (FVC) was 5% or 100 ml, whichever was the highest. Details of the spirometry measurements can be found elsewhere (10). Airflow limitation was expressed as a FEV₁/FVC ratio that was less than the lower limit of normal (ie, below the 5th percentile of the predicted value as the lower limit) (10). The questionnaire also

included questions about smoking habits, previous exposure to dust and gases, and a description of job tasks during the last 12 months. The participants were regarded as current smokers if they had ever smoked during the last year. If they had quit smoking during the last year or earlier, they were regarded as former smokers. The remaining participants were regarded as never smokers. Previous exposure was defined as occupational exposure to dust, fumes, or gases before the current job. The employees working full-time on the production lines were defined as line operators, whereas those who had never worked on the production line were defined as unexposed. The remaining participants were classified as nonline operators. Two experienced industrial hygienists classified the jobs blindly without knowledge with respect to covariates such as smoking habits or health status. Three smelters were closed down during the study period.

Each employee was expected to attend an examination 12 months after his or her last examination. If an employee had his or her last examination more than 18 months prior to the termination of the study, he or she was regarded as a dropout. The total number of dropouts during the study was 759 (19.3%) [111 (24.6%) and 648 (18.7%) women and men, respectively]. The cumulative number of dropouts and the dropout rate in different covariates are shown in table 1. The study was approved by the Regional Ethics Committee.

Statistical analyses

First, we compared the crude dropout rate between employees reporting respiratory symptoms and symptom-free participants. Stratified analyses using the Mantel-Haenszel test for count-time data were also used. We chose to stratify by job classification, as we believed that it would be of considerable interest to investigate whether the association between symptoms and the dropout rate depended on job status. Multivariate analyses were performed using a Cox regression with time-dependent covariates. First, the analyses of the association between dropout and each symptom or airflow limitation at inclusion and last visit were carried out with adjustment for potential confounders. A product-term between the symptoms or airflow limitation and job classification was also included. Second, all of the symptoms and airflow limitation were included in one model that was adjusted for potential confounders. The participants were followed until the date of dropout or until the end of the follow-up. The time after inclusion in the study was used as the underlying time variable. The proportional hazard assumption was investigated using a test based on Schoenfeld's residuals (11). The data were analyzed using Stata SE 8 (12).

Results

The total follow-up time was 16 997 person-years, and the median follow-up time was 4.9 years. The number of dropouts and the dropout rates according to the different covariates at baseline and at the end of the follow-up are shown in table 1. The number of dropouts was 759, and the dropout rate was 44.5 per 1000 person-years. The participants reporting respiratory symptoms had a higher dropout rate than did the asymptomatic participants. Generally, the dropout rate was higher for the participants reporting symptoms at the last follow-up than for those reporting symptoms at baseline, except for the participants reporting "cough lasting >3 months" (table 1).

The stratified analyses indicated that there was no effect modification of the dropout rate according to job group (table 2). The multivariate Cox regression was performed in two steps. First, the dropout rate between

each symptom at baseline and at the end of the follow-up was compared using asymptomatic participants as references, with age, gender, smoking habits, job classification, and lung function as covariates (table 3). Second, all of the symptoms and the lung function were included in one model using the same covariates as already mentioned (table 4).

The hazard ratio for dropout was higher for the participants with a reduced lung function (ie, lower limit of normal) than for those with a normal lung function (table 2). The latter effect was also the most pronounced in the last follow-up. Except for phlegm, all of the respiratory symptoms were significant determinants of dropout when each symptom group was compared with the asymptomatic group in separate models (table 3).

When all of the symptoms were included in one model, using reduced lung function, gender, age, smoking habits, job classification, and smelter closure as covariates, dropout was the most strongly associated with

Table 1. Number of dropouts and the dropout rates (per 1000 person-years) and their corresponding 95% confidence intervals (95% CI) according to the participants' characteristics. (FEV₁ = forced expiratory volume in 1 second, FVC = forced vital capacity, LLN = lower limit of normal)

Characteristic	Baseline				Last follow-up			
	N	%	Dropout rate	95% CI	N	%	Dropout rate	95% CI
Age at last visit								
20–34 years	345	23.2	58.4	52.6–64.9	309	29.6	65.2	58.3–72.9
35–44 years	217	16.7	36.8	32.2–42.0	220	17.4	38.1	33.4–43.4
≥45 years	197	17.3	37.5	32.6–43.2	230	14.3	35.2	30.9–40.1
Smelter closure								
No	666	19.2	42.9	39.7–46.2	. ^a	.	.	. ^a
Yes	93	20.6	61.9	50.5–75.9	. ^a	.	.	. ^a
Job classification								
Unexposed	138	25.9	62.8	53.2–74.3	148	25.3	63.7	54.2–74.9
Nonline operator	296	18.7	42.4	37.9–47.6	326	18.3	43.3	38.8–48.3
Line operator	325	17.9	41.3	37.0–46.0	285	18.3	39.7	35.3–44.6
Previous exposure								
No	243	20.9	50.5	44.5–57.3	. ^a	.	. ^a	. ^a
Yes	516	18.7	42.2	38.7–46.0	. ^a	.	. ^a	. ^a
Smoking status								
Never smoker	260	20.4	48.2	42.7–54.4	259	20.6	49.0	43.3–55.3
Former smoker	122	16.3	35.7	29.9–42.7	134	14.7	35.4	29.9–41.9
Current smoker	377	19.8	45.8	41.4–50.7	366	20.9	46.0	41.5–50.9
Symptoms								
No symptoms	374	19.3	39.8	36.0–44.1	389	15.6	37.8	34.2–41.8
Dyspnea	197	22.0	51.5	44.9–59.2	202	26.8	60.2	52.5–69.1
Wheezing	154	21.4	49.5	42.4–57.9	156	24.3	54.3	46.4–63.6
Cough	202	21.3	50.4	44.1–57.8	197	24.8	54.2	47.2–62.4
Cough >3 months	81	24.8	59.0	47.6–73.1	78	24.7	53.9	43.2–67.3
Phlegm	163	21.0	48.0	41.3–55.9	151	23.2	47.9	40.8–56.2
Any symptom	338	21.6	49.5	44.4–55.1	320	24.9	53.9	48.3–60.2
FEV ₁ /FVC ratio < LLN								
No	675	18.8	43.2	40.1–46.6	681	18.9	43.3	40.2–46.7
Yes	75	23.0	59.8	47.3–75.6	71	24.0	58.7	46.7–73.7
Total	759	19.3	44.5	41.5–47.8	. ^a	.	. ^a	. ^a

^a Identical result at baseline and at the end of the follow-up.

Table 2. Number of dropouts (N), the dropout rates (per 1000 person-years), and the dropout rate ratio for the job groups according to symptom and lung function at the end of the follow-up. (FEV1 = forced expiratory volume in 1 second, FVC = forced vital capacity, LLN = lower limit of normal)

	Line operators			Nonline operators			Nonexposed			P-value ^a
	N	Dropout rate	Dropout rate ratio	N	Dropout rate	Dropout rate ratio	N	Dropout rate	Dropout rate ratio	
Symptoms										
No symptoms	160	31.1	1	173	37.1	1	90	56.8	1	..
Dyspnea	85	52.9	1.70	87	62.6	1.69	30	83.9	1.48	0.89
Wheezing	74	53.5	1.72	62	50.8	1.37	20	73.2	1.29	0.42
Cough	102	57.0	1.83	71	47.3	1.27	24	70.2	1.24	0.13
Cough >3 months	39	56.9	1.83	31	49.9	1.35	8	60.8	1.07	0.29
Phlegm	67	42.3	1.36	62	47.3	1.27	22	84.8	1.49	0.63
FEV ₁ /FVC ratio < LLN										
No	247	40.0	1	291	42.3	1	136	62.4	1	..
Yes	35	60.5	1.18	30	53.4	1.26	9	74.3	1.12	0.60

^a P-value: test for homogeneity across the strata.

Table 3. Hazard ratio (HR) and its 95% confidence interval (95% CI) for dropout from the study using a Cox-regression adjusted for gender, age, smoking, job classification, and smelter closure by symptom and low lung function (lower limit of normal). Separate models for each symptom using asymptomatic persons as references. [DC = dropped due to collinearity, FEV1 = forced expiratory volume in 1 second, FVC = forced vital capacity, LLN = lower limit of normal (FEV1/FVC <5 percentile), NA = not available]

	Baseline		Last follow-up					
	HR	95% CI	Full model		Job classification excluded		Spirometry excluded	
			HR	95% CI	HR	95% CI	HR	95% CI
Symptoms versus no symptoms								
Dyspnea	0.94	0.76–1.17	1.57	1.27–1.95	1.54	1.24–1.91	1.55	1.25–1.91
Wheezing	0.99	0.78–1.25	1.35	1.06–1.72	1.33	1.05–1.68	1.36	1.07–1.72
Cough	0.99	0.80–1.23	1.39	1.12–1.74	1.36	1.09–1.70	1.37	1.10–1.70
Cough >3 months	DC	DC	1.44	1.15–1.82	1.41	1.12–1.77	1.44	1.15–1.82
Phlegm	1.10	0.89–1.38	1.12	0.89–1.41	1.10	0.88–1.37	1.12	0.89–1.40
Any symptom	1.00	0.83–1.20	1.41	1.17–1.70	1.37	1.14–1.65	1.38	1.15–1.66
FEV ₁ /FVC ratio < LLN								
Yes versus no	1.20	0.82–1.76	1.32	0.89–1.95	1.31	0.88–1.95	NA	NA

dyspnea and reduced lung function (table 4). Furthermore, a negative association between dropout and age was found, and the hazard ratio for dropout was lower for the “line operators” and “nonline operators” than for the unexposed employees. Smelter closure was also associated with an increased hazard ratio for dropout in a comparison with continued production throughout the study period. There was no association between smoking and dropout or between dropout and previous exposure to gases and dust. The product terms between symptoms or airflow limitation and job classification were all non-significant (P=0.15–0.85). Similarly, the product terms between the symptoms or airflow limitation and smelter closure were all nonsignificant (P=0.11–0.70). We also investigated 2 years as the cut-off limit for dropouts. The number of dropouts decreased to 611 employees; however, the association between dropouts and respira-

tory symptoms or decreased forced expiratory volume in 1 second (FEV₁) did not show a notable change.

There was no significant effect modification of the association between respiratory symptoms at the end of the follow-up and in the baseline examination regarding dropout. The etiologic fraction mutually adjusted for each symptom and spirometry was 30% and 24% regarding dyspnea and airflow limitation, respectively.

Discussion

In this study we found that workers reporting respiratory symptoms were more likely to drop out of our study than the asymptomatic workers were. Similarly, we also found that the employees with reduced lung

function were more likely to drop out of the study than those with a normal lung function. The association was the strongest with regard to the last follow-up and the workers reporting dyspnea.

The strength of this study is its large number of follow-ups and the long total observation time. Most of the published studies that have focused on the association between respiratory symptoms and dropout from a study, have recorded symptoms at baseline (2). We found that symptoms reported at the end of the follow-up were generally more significant than symptoms reported at baseline when it comes to dropout from a study. Likewise, reduced lung function at the end of a follow-up was an independent predictor of dropout from the study. We believe that this information is new. Fortunately, it implies that current symptoms and current FEV₁ are more important than previous symptoms and lung function with regard to selection bias in respiratory studies, the importance of the "healthy worker effect" thereby being reduced in cross-sectional studies. Nevertheless, in longitudinal respiratory studies, dropouts should be identified and taken into account when the association between symptoms, lung function, and exposure in occupational settings is analyzed because the selection effect accumulates over the study period.

That current symptoms were generally more important predictors of dropout than previous symptoms is not a surprising finding. However, it is hard to explain why workers reporting persistent cough for 3 months or longer had a higher dropout rate at baseline than at the end of the follow-up. Probably, the workers reporting persistent cough have had their symptoms for several years, and the time to quit a job may have been more arbitrary.

When all of the symptoms were included in one model, dyspnea persisted as the only significant predictor of dropout. Dyspnea is probably more cumbersome than any of the other symptoms investigated. As the symptoms, as well as lung function, are mutually confounded, one can ask whether it is acceptable to put them in the same multivariate model. First, this choice of model selection is not in conflict with the assumption underlying the Cox regression. Second, we have selected the same variables in a cross-sectional study of the same cohort and similar variables in a study of respiratory symptoms and subsequent mortality from respiratory diseases (13, 14).

In addition to respiratory symptoms and lung function, age, job classification, and smelter closure were significant predictors for dropout from the study. The dropout rate was negatively associated with increasing age. This finding indicates that employees are less likely to quit their jobs as they get older. When the study was designed, we decided to limit age at inclusion to 20–55 years. This decision was made in order to limit

Table 4. Hazard ratios (HR) and their 95% confidence intervals (95% CI) for dropout from the study using a Cox regression (one model). All of the variables were recorded at the last visit. (FEV₁ = forced expiratory volume in 1 second, FVC = forced vital capacity, LLN = lower limit of normal)

	HR	95% CI
Female versus male	1.15	0.92–1.45
Age during follow-up		
20–34 years	1	..
35–44 years	0.52	0.36–0.75
≥45 years	0.37	0.21–0.63
Smelter closure		
No	1	..
Yes	1.24	0.98–1.58
Job classification		
Unexposed	1	..
Nonline operator	0.70	0.56–0.88
Line operator	0.60	0.47–0.75
Symptoms		
No symptoms	1	..
Dyspnea	1.42	1.13–1.78
Wheezing	1.04	0.81–1.32
Cough	1.20	0.97–1.49
Cough >3 months	1.16	0.89–1.51
Phlegm	0.90	0.72–1.12
FEV ₁ /FVC ratio < LLN		
No	1	..
Yes	1.31	1.01–1.69

the number of short-term employees, such as students working during vacation, and workers giving up their job for health reasons, most likely persons older than 55 years of age (15).

The risk of dropout was lower for the line operators and nonline operators than for the unexposed persons. This observation can probably be explained by the fact that the former group would be more interested in finding out if occupational exposure to gases and dust at work is harmful to their health. Alternatively, previous selection may have resulted in a stronger survivor effect among the "line operators" than among the unexposed employees. There was, however, no effect modification of the association between the dropout rate and respiratory symptoms.

The observation that smelter closure was associated with an increased risk of dropout, compared with smelters continuing production throughout the study period, is not surprising. People probably try to find a new job before the closure of the smelter. Thus they were lost from the study.

The major limitation of our study was apparently the definition of dropout. First, 18 months as a limit may be perceived as arbitrary. As the standard deviation of the time difference between consecutive examinations was 0.3 years, only 5% were expected to have longer inter-

vals than 18 months between follow-ups (16). Moreover, using 2 years between the last examination and the end of the study yielded almost the same hazard ratio for dropout with regard to respiratory symptoms. However, using 2 years as the dropout limit would have reduced the number of dropouts and thereby reduced the power of the study.

Finally, dropout does not imply that the person has left the industry. It only means that he or she was lost from follow-up. For the interpretation of the results, it is not crucial whether the person was lost from the study because he or she left the smelter or for another reason.

In conclusion, both the presence of respiratory symptoms and reduced lung function were associated with an increased loss of follow-up in this longitudinal study. The effect was strongest regarding the status at the last survey, and dyspnea appeared to be the most important symptom in this regard. Thus dropouts should be identified and taken into account when data are analyzed in respiratory studies.

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