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Symptom Onset in the First 2 Years of Employment at a Wood Products Plant Using Diisocyanates: Some Observations Relevant to Occupational Medical Screening

Mei-Lin Wang, MD, MPH* and Edward L. Petsonk, MD

Background *Questionnaires are essential tools for medical screening, but their role in monitoring workers at increased risk of occupational asthma (OA) remains indeterminate.*
Methods *Employees who were at a newly established wood products plant without previous exposure to methylene diphenyl diisocyanate (MDI) completed an initial questionnaire and from one to four follow-up questionnaires during a 2-year period. Onset of symptoms in 132 workers was assessed by exposure groups and modeled using generalized estimating equations.*
Results *Onset of attacks of dyspnea with wheeze, attacks of dyspnea or cough at rest, and chest tightness were significantly associated with MDI exposure after controlling for age, smoking, and wood dust exposure. Onset of cough on most days was significantly related to smoking and dust. Onset of phlegm production was significantly related to both MDI and dust exposure.*
Conclusions *Onset of certain symptoms is significantly associated with MDI exposure. Early detection of MDI-associated health effects using a short screening questionnaire appears feasible.* Am. J. Ind. Med. 46:226–233, 2004. *Published 2004 Wiley-Liss, Inc.*†

KEY WORDS: occupational asthma; asthma; diisocyanate; signs and symptoms, respiratory; symptom onset; medical screening; questionnaires; occupational health services

INTRODUCTION

Occupational asthma (OA) has become the most frequently diagnosed occupational respiratory disorder in industrialized countries [Gannon and Burge, 1993; Provencher et al., 1997]. Asthma prevalence and mortality have been increasing in the United States over the past 20 years, and a significant proportion of adult asthma is related to occupational exposures [Mannino et al., 1998; Mannino, 2000]. OA frequently results in long-term health and economic consequences [Ameille et al., 1997; Gassert et al., 1998]. Diisocyanates, a group of highly reactive chemicals, are often recognized as a cause of OA. As with all occupational diseases or injuries, primary prevention is the most desirable approach and should be the highest priority. However, recent experience has indicated that even in work settings where extensive exposure controls are in place, asthma-like symptoms may develop in a considerable number of workers [Woellner et al., 1997; Petsonk et al., 2000]. Early recognition of OA and timely control of exposures has been associated with a lower risk of chronic irreversible respiratory effects, suggesting that medical screening of individuals at risk for OA, recognition of cases,

Division of Respiratory Disease Studies, National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control and Prevention, Morgantown, West Virginia
Contract grant sponsor: NIOSH.
*Correspondence to: Dr. Mei-Lin Wang, NIOSH, Mail Stop H-G900.2, 1095 Willowdale Road, Morgantown, WV 26505. E-mail: mlw4@cdc.gov

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and assessment and control of exposure for affected workers, may be an effective prevention strategy [Lemiere et al., 1996; Park and Nahm, 1997; Tarlo et al., 1997]. Standardized recommendations for medical screening are accepted occupational health practice and have been widely circulated [Wagner, 1996; International Labour Office (ILO), 1998]. Medical monitoring of workers exposed to diisocyanates has been recommended in the US and UK [National Institute for Occupational Safety and Health (NIOSH), 1996; Health and Safety Executive (UK), 2002] but no reliable biomarkers have been identified. Identification of specific early-onset symptoms and understanding their time course could facilitate the effectiveness of medical monitoring programs. In this study, we sought to identify the early onset of symptoms associated with MDI exposure, in contrast to smoking and dust exposure, and to estimate the strength and the time course of the relationship between symptom onset and exposure to MDI.

MATERIALS AND METHODS

Methods have been previously reported, and are briefly reviewed below [Petsonk et al., 2000]. The study protocol was approved by the NIOSH Institutional Review Board, and all participants gave written informed consent.

Participants and Questionnaires

A wood products plant began production in August 1995 using methylene diphenyl diisocyanate (MDI) as a binder. In April and June 1995, before initial delivery of MDI to the plant, a trained NIOSH survey team traveled to the plant and performed an initial health survey. Of all employees who had been hired at that point, about 80% (n = 214) completed the initial questionnaire (IQ). The first follow-up questionnaire (FQ) was administered in October 1995 (2 months after initial use of MDI in the plant); thereafter, the survey team administered three additional FQs (after 8, 14, and 20 months of production). The IQ and FQ respiratory health questionnaires were composed of elements from previous standard instruments, and had been pilot tested and successfully used in several field surveys prior to this study [Lebowitz and Burrows, 1976; Ferris, 1978; Burney and Chinn, 1987]. A detailed occupational history was ascertained at the first follow-up survey attended by each participant, documenting the specific job activities performed and occupational exposures to raw wood dust, diisocyanates, and composite wood product, as well as other potential hazards in the plant. The occupational history was not subsequently repeated because of the short duration of the study. Overall, occupational histories were obtained from 144 employees who had participated in the IQ and also at least one follow-up survey. Twelve workers were excluded from the analysis because their occupational histories indicated they had occupational exposure to MDI in previous jobs; the remaining 132 participants were included in this study.

Exposure Categories and Health Outcomes

Three major types of exposures were considered. Based on the occupational and smoking histories, workers who reported any contact with liquid MDI in their current job activities (either during the manufacturing process or through cleanup activities or spills—both respiratory and skin exposures were considered) were classified as MDI-exposed (n = 39). Workers from areas with potential wood dust-exposure were classified as dust-exposed (n = 74). Quantitative measurements of dust or diisocyanate exposure were not available. A smoking history was obtained at both the initial and final health surveys. Only the initial smoking status was used in the models; change in status could not be modeled because so few participants changed smoking status (five workers quit and two started smoking during follow-up). Workers who reported smoking cigarettes at the initial health survey were classified as current smokers (n = 33), while those who smoked regularly in the past but did not smoke at the time of the initial questionnaire were classified as ex-smokers (n = 18).

The study was based on symptom incidence. For each respiratory symptom, we identified the subset of workers who on the IQ denied ever experiencing the symptom. Among this subset, we recorded incidence of the symptom at each follow-up survey for which the worker had reported experiencing that symptom since the previous questionnaire. Symptom incidence was recorded at a follow-up survey regardless of whether or not the symptom had been reported on a previous or subsequent FQ. Time to occurrence was defined by the period from the initial survey to the follow-up survey at which the incident symptom was reported. Relationships with exposure categories were determined for five outcomes: attacks of dyspnea with wheeze (SOBWZ), attacks of dyspnea or cough at rest (SOBREST), chest tightness lasting more than a minute (CTIGHT), cough in the morning, during the day or at night for 4 or more days per week (COUGH), and phlegm production on most days per week (PHLEGM) (see Table I). Symptoms of rhinitis and/or conjunctivitis, including itching, burning, watery eyes, nasal congestion, and sneezing were also analyzed.

Data Analysis

All statistical analyses were accomplished with SAS software (SAS® version 8.0, 1999; SAS Institute, Inc., Cary, NC) on a personal computer. Group comparisons of symptom incidence by exposure categories (exposure to MDI, current smoking status, and wood dust exposure) were made using the χ^2 statistic, at each of the four follow-up surveys

TABLE I. Specific Respiratory Questionnaire Items Evaluated in Wood Products Workers*

Have you ever had attacks of shortness of breath with wheezing or whistling?	1: No	2: Yes
Have you had an attack of shortness of breath or coughing that came on when you were just lying in bed, or not doing any special effort?	1: No	2: Yes
Has your chest ever felt tight for longer than a minute?	1: No	2: Yes
Do you usually[a] cough on getting up, or first thing in the morning? (Exclude clearing throat or a single cough.)	1: No	2: Yes
Do you usually[a] cough during the day—or at night?	1: No	2: Yes
Do you usually[a] bring up any phlegm from your chest on getting up, or first thing in the morning? (Exclude phlegm from the nose. Count swallowed phlegm.)	1: No	2: Yes
Do you usually[a] bring up any phlegm from your chest during the day—or at night? (Accept twice or more.)	1: No	2: Yes

*Respiratory health questions were modified from previous standard instruments [see Lebowitz and Burrows, 1976; Ferris, 1978; Burney and Chinn, 1987].
[a][Usually] means 4 or more days per week.

representing tenures of 2, 8, 14, and 20 months, respectively. For continuous variables, the significance of differences was evaluated by the Student's *t*-test.

Multiple logistic regression analysis for repeated measurements of symptom onset was performed using generalized estimating equations (GEE). GEE modeling was performed using the SAS procedure GENMOD including the 132 participants and up to four repeated measurements of symptom incidence. The model structure was based upon a binomial distribution, logit link function and auto-regressive (AR-1) 'working correlation'—a covariance structure with the desired property of correlations being larger for nearby times than far-apart times. The appropriateness of selection of AR-1 among other available covariance structures was confirmed by comparison of the fit criteria for the different models. For each outcome at each follow-up survey, the response was recorded as 1 if the symptom was reported at that follow-up survey but was absent at the initial survey, and 0 otherwise (those with a symptom present at the initial survey were omitted from the analysis for that particular symptom). Explanatory variables included age (years) at initial survey, liquid MDI exposure (yes/no), current smoker (yes/no), wood dust exposure (yes/no), and a time-dependent variable of duration of tenure in this plant. The model was run with independent variables for exposure groups, linear and quadratic terms for time trends, and interaction terms among the three exposures, and also between exposure and time. If a term did not enter the model ($P > 0.2$), it was removed and the model was refit using the remaining variables.

Due to the number of missing observations, it was felt necessary to assess the homogeneity of the distribution of missing values by major exposure and health categories. The GEE approach was also used to examine the potential influence of missing data on the results. An indicator variable was created, as a dependent variable for the models, indicating whether the new onset of a symptom was recorded or missing. First, the proportion of missing values among the major exposure categories was examined to determine if there was a significant difference between the exposed and non-exposed groups in the prevalence of missing values. Next, using a similar procedure, we assessed whether symptom status at a survey influenced the proportion of missing data at the subsequent survey. For example, differences in the proportion of participants missing the first follow-up survey were evaluated between participants with and without symptoms at the initial survey. Similarly, the proportion of workers who missed the second follow-up survey was compared for participants who reported the new onset of symptoms at the first follow-up survey versus those who did not report symptom onset, and so forth for each follow-up survey.

RESULTS

Table II shows overall descriptive characteristics of participating workers at the initial survey, and by MDI exposure status. The study population was relatively young and well educated. The average age was 31 years, ranging from 20 to 54, with 87% male, 99% Caucasian, 25% current smokers and 14% ex-smokers. The MDI exposed group was 3 years younger and had fewer ex-smokers than the non-exposed groups, but otherwise the groups were similar. The prevalence of the five respiratory symptoms reported at the initial survey ranged from 8 to 14%; there were no significant differences in initial symptom prevalence between the two groups of workers who subsequently were assigned to MDI exposed and non-exposed jobs.

As mentioned above, due to incomplete participation in the follow-up surveys, not all observations of incidence were available. For example, at the initial survey, 121 out of 132 workers denied the presence of wheeze. If all 121 had attended each of the four follow-up surveys, the number of observations for incidence of wheeze would be 484. However, there were only 321 observations, with 163 missing

TABLE II. Descriptive Characteristics at Initial Survey of Wood Products Workers and by MDI Exposure Status

		Exposure to liquid MDI	
Characteristics	**All participants (n = 132)**	**No (n = 93)**	**Yes (n = 39)**
Mean age, year (SD)	31.1 (8.5)	32.0 (8.8)	28.8 (7.2)*
Sex, male, n (%)	115 (87.1)	78 (83.9)	37 (94.9)
Race, White, n (%)	131 (99.2)	93 (100)	38 (97.4)
Mean height, inch (SD)	69.3 (6.7)	68.9 (7.8)	70.2 (2.7)
Mean weight, lb (SD)	190.6 (37.3)	190.9 (36.1)	189.8 (40.6)
Current smokers, n (%)	33 (25)	21 (22.6)	12 (30.8)
Ex-smokers, n (%)	18 (13.6)	18 (19.4)	0 (0)**
Mean pack-years (SD)	4.2 (8.2)	4.0 (7.0)	4.7 (10.8)
Mean cigarettes/day (SD)	5.0 (11.4)	4.2 (9.1)	6.9 (15.6)
Mean education, year (SD)	13.6 (1.8)	13.4 (1.8)	14.1 (1.7)*

*$P < 0.05$.
**$P < 0.01$.

values (34%). Proportions of missing values were similar for the other symptoms: altogether, 30% of the observations for incidence were missing, and 70% were available.

Bivariate group comparisons of incidence for each of the five symptoms from each of the four follow-up surveys are shown by MDI exposure (Table IIIa) and by current cigarette smoking (Table IIIb). MDI-exposed workers had significantly higher incidence of attacks of dyspnea with wheeze (SOBWZ), chest tightness (CTIGHT), and attacks of cough or dyspnea at rest (SOBREST). The development of SOBWZ occurred as early as from 2 to 8 months of tenure, and increased over time (30 vs. 6% at 8 month tenure for MDI exposed vs. unexposed, and 39 vs. 8% at 20 month tenure). The development of CTIGHT also occurred early (30 vs. 8% at 8 month tenure), but not progressively over the 20 months of tenure observed in this study. The incidence of SOBREST progressively increased over time in the MDI-exposed group, but reached a significant level (39 vs. 8%) only at 20 months of tenure. In contrast, the onset of cough on most days (COUGH) was not consistently related to MDI exposure but increased progressively over time among current smokers. Reports of PHLEGM production on most days increased over time in both MDI exposed and current smoker groups, but did not reach a statistically significant level in the bivariate analysis. Changes in ocular or nasal symptoms did not differ significantly, comparing exposed versus non-exposed groups, at any follow-up survey. For each of the five lower respiratory symptoms, consistency of reporting within subject over time was also evaluated. Among workers who reported a new symptom at one survey and who participated in the subsequent survey, symptoms were consistently reported in 50% (range 41–58%).

TABLE IIIa. Incidence of Symptoms by Liquid MDI Exposure at Four Follow-Up Surveys Among New Employees at a Wood Products Plant (n = 132)

	Incidence (%) by liquid MDI exposure and tenure							
	2 months (n = 76)		**8 months (n = 99)**		**14 months (n = 76)**		**20 months (n = 70)**	
Symptom	**MDI+ (n = 26)**	**MDI− (n = 50)**	**MDI+ (n = 27)**	**MDI− (n = 72)**	**MDI+ (n = 20)**	**MDI− (n = 56)**	**MDI+ (n = 18)**	**MDI− (n = 52)**
SOBWZ (attacks of SOB with wheezing)	4	4	30**	6	25*	7	39**	8
SOBREST (attacks of SOB or cough at rest)	0	2	15	10	20	7	39**	8
CTIGHT (chest tightness)	4	10	30*	8	30	13	28	10
COUGH (cough most days)	0	4	22	11	15	14	17	10
Phlegm (phlegm most days)	0	2	15	8	25	14	33	13

*$P < 0.05$.
**$P < 0.01$ for MDI-exposed (MDI+) versus non-exposed (MDI−) group by χ^2 test.

TABLE IIIb. Incidence of Symptoms by Current Smoking Status at Four Follow-Up Surveys Among New Employees at a Wood Products Plant (n = 132)

	Incidence (%) by current smoking status and tenure							
	2 months (n = 76)		8 months (n = 99)		14 months (n = 76)		20 months (n = 70)	
Symptom	Smk+ (n = 13)	Smk− (n = 63)	Smk+ (n = 26)	Smk− (n = 73)	Smk+ (n = 20)	Smk− (n = 56)	Smk+ (n = 16)	Smk− (n = 54)
SOBWZ (attacks of SOB with wheezing)	0	5	15	11	10	13	13	17
SOBREST (attacks of SOB or cough at rest)	0	2	12	11	5	13	19	15
CTIGHT (chest tightness)	8	8	15	14	15	18	13	15
COUGH (cough most days)	8	2	27**	10	25	11	38***	4
PHLEGM (phlegm most days)	0	2	15	8	20	16	25	17

**$P < 0.01$.
***$P < 0.001$ for current smoker (Smk+) versus non-current smoker (Smk−) group by χ^2-test.

Table IV shows the results from the GEE model. Workers exposed to liquid MDI had about two to four times greater odds of developing these specific symptoms, after controlling for age, smoking, and wood dust exposure; the association was statistically significant for all outcomes except COUGH. COUGH was the only symptom for which new onset was significantly associated with smoking in the models. The pattern of adverse effects of wood dust exposure on the new onset of symptoms appeared to more closely parallel that of current cigarette smoking, although wood dust exposure was also significantly related to PHLEGM incidence. The linear time trend effects from the models indicated that the incidence of SOBWZ, SOBREST, and PHLEGM increased significantly during the 20 months of tenure. Incidence of COUGH and CTIGHT generally increased with time as well, but this was not statistically significant. The quadratic term for time trend, interaction terms among smoking, MDI, and wood dust exposures, and the interaction terms between exposure and time trend were not significant; therefore, none of these terms was included in the final model.

Logistic modeling for missing values was performed as described above. No significant differences or trends were seen in the proportion of missing data among the major exposure categories. Similarly with regard to symptoms, the proportion of missing observations at the subsequent survey was similar between workers with and without each of the symptoms. The proportion of missing values did increase significantly with time (data not shown).

TABLE IV. The Association Between New-Onset Symptoms Reported in Four Follow-Up Surveys and Exposures to Smoking, Liquid MDI, and Wood Dust Among New Employees at a Wood Products Plant, Using Generalized Estimating Equations Approach (GEE models) (n = 132)

	GEE parameter estimates for effect of exposure status and linear time trend[a]			
Symptom	Liquid MDI (yes vs. no)	Current smoker (yes vs. no)	Wood dust (yes vs. no)	Tenure (6-month increase)
SOBWZ (attacks of SOB with wheezing)	4.2 (1.4–12.1) 0.0088	0.8 (0.3–2.5) 0.7108	0.7 (0.3–1.9) 0.4809	1.6 (1.2–2.1) 0.0023
SOBREST (attacks of SOB or cough at rest)	3.7 (1.2–11.2) 0.0232	0.9 (0.3–2.6) 0.8496	1.6 (0.6–4.7) 0.3696	1.6 (1.1–2.3) 0.0071
CTIGHT (chest tightness)	3.2 (1.2–8.7) 0.0200	0.9 (0.4–2.2) 0.8826	1.7 (0.7–4.4) 0.2537	1.2 (0.9–1.6) 0.2056
COUGH (cough most days)	2.5 (0.9–7.3) 0.0859	5.1 (1.8–14.3) 0.0018	5.0 (1.5–16.9) 0.0094	1.3 (1.0–1.7) 0.0601
PHLEGM (phlegm most days)	3.8 (1.3–11.2) 0.0146	1.6 (0.7–3.7) 0.2875	4.0 (1.4–11.5) 0.0096	1.9 (1.3–2.7) 0.0008

GEE model: symptom onset = age, current smoker, liquid MDI, wood dust, tenure (linear time trend effect).
The repeated binary outcome variables of new-onset symptoms were defined as symptom absent at initial questionnaire, but present at 2, 8, 14, or 20 months of tenure, respectively.
GEE model was performed based on the dataset with 132 participants, four time periods, 321 observed values (30% missing) by using the binomial distribution, logit link function and auto-regressive (AR-1) 'working correlation' structure.
Units: age at initial questionnaire (years), current smoker (yes/no), liquid MDI exposure (yes/no), wood dust exposure (yes/no), tenure in this plant (every 6-month increase).
[a] Values are adjusted odds ratio estimates, with 95% confidence interval shown in parentheses; and *P* value.

DISCUSSION

Controlling or eliminating exposure is the preferred approach to the prevention of occupational illnesses. However, in settings for which primary prevention measures have not been fully effective, such as during work with diisocyanates or other potential asthma-inducing agents, secondary prevention strategies utilizing medical monitoring are also considered desirable [Baur et al., 1998; Piirila et al., 2000]. A variety of immunologic tests, spirometry measurements, and inflammatory mediators have been evaluated for early detection of diisocyanate-induced asthma. The usefulness of bio-markers of exposure or response needs to be further validated, although the recent studies reported by Bernstein et al. [2002] suggest that diisocyanate antigen-stimulated monocyte chemoattractant protein-1 synthesis has greater test efficiency for identification of diisocyanate asthma than specific antibody tests [Bernstein and Jolly, 1999; Piirila et al., 2000; Bernstein et al., 2002]. Questionnaires on asthma symptoms are essential tools in epidemiological surveys of asthma prevalence and continue to be widely used in workplace medical monitoring programs [Venables et al., 1993; Kraw and Tarlo, 1999; Sari-Minodier et al., 1999]. They have the advantage of being inexpensive and simple to administer to large numbers of participants, and have been validated against a number of independent health measures, including spirometry and airway responsiveness testing. The sensitivity and specificity of certain questionnaire-defined symptoms have been compared to objective tests and clinical diagnosis, and have varied from study to study [Smith et al., 1989]. For example, Burney et al. conducted a validation of the International Union Against Tuberculosis and Lung Disease (IUATLD) bronchial symptoms questionnaire in four European centers [Burney et al., 1989].

In contrast to prevalent symptoms, new-onset (incident) symptoms have not been as well studied. In the workplace, employees may develop symptoms in relation to exposures to sensitizing or non-sensitizing agents, as well as to non-occupational factors, such as tobacco smoking. Thus, multiple factors may influence the specificity of responses to questionnaire items. To address these issues, we evaluated responses to a standardized respiratory questionnaire among workers in a newly established wood processing plant with potential exposures to a recognized sensitizer, MDI, as well as to wood dust. We hypothesized that the pattern of onset of respiratory tract symptoms may vary with specific exposures, and that the interpretation of medical screening questionnaires by occupational health personnel might be enlightened by improved knowledge of the association of specific questionnaire responses with type and duration of potential exposures.

The study did identify associations between the onset of specific symptoms and exposure categories defined a priori. Three questionnaire-based symptoms that have previously been associated with bronchospasm and airway hyperresponsiveness (attacks of dyspnea with wheeze, nocturnal cough or dyspnea, and chest tightness) [Mortagy et al., 1986; Enarson et al., 1987] developed in association with exposure to MDI, often within the first 8 months. In this workforce, none of these three symptoms developed in significant association with either tobacco smoking or wood dust exposure. In contrast, onset of cough occurring on most days each week was significantly associated with exposures to wood dust and also tobacco smoking, but less strongly with MDI. The proportion of workers in the study who reported phlegm production on most days increased over time, in association with exposures to MDI and to wood dust, but less strongly to tobacco smoking. It is important to note that questionnaire administration in this study was monitored by a trained NIOSH survey team. The associations, we observed between questionnaire responses and exposures are unlikely to have been greatly influenced by interviewer training, however, these questionnaire items may be less useful if administered by less experienced personnel.

The prevalence of symptoms observed in this study appears to be in the range observed among other studies in similar settings [Herbert et al., 1995]. Overall, about 13% of participants in the current study reported new asthma-like symptoms, while symptom onset exceeded 30% among certain exposed subgroups. Although inhalation challenges were not performed in the current study, previous reports have documented specific sensitization in about half of symptomatic isocyanate-exposed workers [Mapp et al., 1988]. If isocyanate sensitization occurred in a comparable proportion in the current study, the prevalence of illness would be in the range of the estimated OA prevalence (16–18%) among another group of similarly exposed workers [Woellner et al., 1997]. In contrast, incidence rates among isocyanate production workers may be much lower [Ott et al., 2000].

In this study, the incidence of ocular and nasal symptoms did not differ significantly by exposure groupings. In a previous report by Jakobsson et al. [1997], the prevalence of episodes of irritative eye symptoms and nasal congestion was much higher among pipelayers exposed to thermal degradation products from MDI-based polyurethane than among unexposed controls. Possible explanations for the different results include differences in study design and exposures.

Use of GEE methods requires an assumption that the pattern of missing data is independent of the response. Workers who develop symptoms may fail to return due to illness, although workers with symptoms may also have increased motivation to participate in health surveys. To investigate these issues, we tested for any association between the presence of asthma-like symptoms on the initial questionnaire and missing data at the first follow-up survey, and between incident asthma-like symptoms on the first,

second, or third follow-up questionnaire and missing data at the subsequent health survey. No trends or associations were noted between these symptom responses and participation at subsequent follow-up surveys, suggesting that the assumption of randomly distributed missing data appears to be valid for this population. However, only 26 out of the 132 individuals were observed at all four follow-up surveys (38 were observed at three, 35 at two, and 33 at one, follow-up surveys). To further assess the potential for missing data to influence the inferences drawn, a logistic regression analysis was performed to examine differences in the presence of missing values between the two exposure groups (MDI exposure, yes/no), including linear and quadratic terms for time trend and group–time interaction terms. This analysis did not indicate a significant difference between the exposure groups in terms of time trend and group/time interactions for prevalence of missing values, although both groups showed a significant increasing quadratic time trend of missing values. We did not find any specific reasons for drop outs in this study, and the results from these statistical approaches suggest that failure to attend a health survey was a random event. Despite this, confidence in a study's inferences decreases as the amount of missing data increases, and missing data represent a major limitation of our study.

Screening examinations in an occupational setting are offered to individuals who are deemed to be at increased risk of developing a work-related illness, such as OA. The screening procedure does not diagnose the illness, which generally requires a rigorous and systematic evaluation [Bernstein and Jolly, 1999; Friedman-Jimenez et al., 2000; Rabatin and Cowl, 2001]. Rather, screening is intended to identify workers for whom further investigation is warranted, before the individual would otherwise seek medical attention. If the screening process lacks sensitivity, many workers with disease will be missed. Conversely, if the process lacks specificity, resources will be required to evaluate a large number of workers, most of whom will not be found to have work-related illnesses. For this reason, an evidence-based understanding of the operating characteristics of the screening process can facilitate interpretation of the results, and improve effectiveness and efficiency. The findings of this study should assist health care professionals who evaluate screening questionnaires from workers at risk of OA, in identifying symptom patterns that are associated with the sensitizing exposures, and warrant further investigation. Future research is needed to address the operating characteristics of these questionnaire items with respect to subsequent development of clinically confirmed health outcomes.

We conclude that onset of certain symptoms appears to be associated with MDI exposure. Early detection of MDI-associated health effects using a short form questionnaire appears feasible for medical screening; since new onset of symptoms continued to be observed throughout the 20-month study, questionnaires should be given to new employees at intervals for at least 2 years. The onset of symptoms that have been associated with MDI exposure should trigger an evaluation of the worker and the worker's exposures.

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