Association Between Cumulative Fiber Exposure and Respiratory Outcomes Among Libby Vermiculite Workers

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Objective: To examine the association between cumulative fiber exposure and health outcomes in workers ($n = 336$) with Libby amphibole exposure. **Methods:** Exposure–response relationships were explored by the use of logistic regression, with cumulative fiber exposure modeled in categories and as a continuous variable. **Results:** The use of spline functions with lifetime cumulative fiber exposure as a continuous variable showed that the odds of localized pleural thickening were significantly elevated at less than 1 f/cc-y. Odds of parenchymal abnormalities, restrictive spirometry, and chronic bronchitis were also significantly elevated at 108, 166, and 24 f/cc-y, respectively. **Conclusions:** The odds of several pulmonary health outcomes are correlated with cumulative exposure to Libby amphibole. That relatively low-lifetime cumulative exposures are associated with localized pleural thickening has implications for the non–cancer-risk assessment for Libby amphibole.

Vermiculite is a micaceous mineral that, when exposed to heat, expands in volume up to 30 times. This property has made vermiculite commercially desirable as fireproofing, as insulation, and as a soil additive. Although it was operating between the 1920s and 1990, the vermiculite mine in Libby, Montana, is believed to have produced much of the world supply of vermiculite.[1] Attic insulation made from Libby vermiculite had widespread residential use and may be present in millions of homes.[2] No adverse health effects have been associated with exposure to vermiculite itself. Nevertheless, Libby vermiculite contains amphibole fibers. These fibers have been characterized as, in decreasing order of abundance, winchite, richterite, tremolite, and actinolite.[3–5] In response to reports of pulmonary disease in Libby, the Agency for Toxic Substances and Disease Registry (ATSDR) initiated a community screening program in 2000. All participants underwent a health survey and were offered screening via spirometry and, if a participant was older than 18 years, chest radiography. By the end of the screening program in 2001, 7307 persons had been screened. Among participants, 18% had pleural abnormalities and less than 1% had parenchymal abnormalities.[6] Among former vermiculite workers, the radiographic abnormalities were more common, with 51% having pleural and 4% having parenchymal abnormalities.[6]

In this cross-sectional study, we linked data from the ATSDR screening program to estimates of cumulative fiber exposure (CFE) for former vermiculite workers. Our objective was to examine the association between CFE and radiographic abnormalities consistent with exposure to asbestos, abnormal spirometry, and respiratory symptoms and conditions.

METHODS

Subjects and Interviews

Persons who lived, worked, or played in Libby for at least 6 months before 1991 were eligible to participate in the screening program. The ATSDR actively invited participation by contacting area residents by telephone and by posting announcements in national newspapers and other media.[6] Informed consent was obtained under an institutional review board–approved protocol. We included adult participants who reported employment at the Libby vermiculite operation and could be matched to company records. All were interviewed by the use of a standardized survey in which occupational history; past exposure to Libby vermiculite and other dusts, including commercial asbestos; residential and smoking history; and reports of health outcomes were collected.

To examine the association between exposure and respiratory symptoms and conditions, we used responses to survey questions about shortness of breath (SOB—defined as being troubled by shortness of breath "when walking up a slight hill or when hurrying on level ground"); excess cough (defined as having a cough "on most days [at least 4 days of the week]"; and chronic bronchitis (defined as a worker reporting both excess cough and excess phlegm [coughing up phlegm "for at least 3 months of the year for the past 2 years"] were reported). As part of the definition of these respiratory symptoms and conditions, we excluded workers with radiographic abnormalities consistent with pneumoconiosis or restrictive spirometry.

We compared covariates of study subjects with other members of the vermiculite worker cohort ($n = 1862$), using data from ATSDR's Tremolite Asbestos Registry.

Chest Radiographs and Spirometry Measurements

Posterior–anterior chest radiographs were offered to participants aged 18 years and older who were not pregnant. The equipment and procedures used to obtain the radiographs followed guidelines developed by the Centers for Disease Control and Prevention's National Institute for Occupational Safety and Health (NIOSH).[7] All radiographs were independently read by the use of the 1980 International Labor Office Classification[8] by two primary B readers. A third B reader read each film independently for subjects for whom the first two readers disagreed about the presence of any parenchymal or pleural abnormalities. The radiographic changes examined here are parenchymal and pleural (localized [LPT] and diffuse pleural thickening [DPT]) abnormalities, all defined dichotomously (ie, present/absent). We defined parenchymal abnormalities as small opacity profusion 1/0 or more; DPT, as indicated on the International Labor Office form and accompanied by costophrenic angle obliteration[9,10] in the same hemithorax; and LPT, defined as the presence of circumscribed plaque on the chest wall (as indicated on the International Labor Office form) or diaphragm without the presence of DPT or parenchymal abnormalities (ie, for analytical purposes, subjects with concomitant LPT and DPT were categorized as DPT). As part of each one of these definitions, an abnormality must have been observed by at least two readers in the same hemithorax. Because LPT is considered a marker of asbestos exposure, although DPT can have other causes,[11] we modeled DPT and LPT separately.

Spirometry was offered to all participants. Spirometry testing followed American Thoracic Society guidelines[12] and was performed by a qualified technician using a Jaeger MasterScope spirometer (CareFusion, San Diego, CA). Test result quality was evaluated by the use of American Thoracic Society guidelines[10]; seven workers had results rated as "questionable" or "uninterpretable" and were excluded from the analysis of spirometry data. The following

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variables were recorded: forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), and FEV_1/FVC ratio. Predicted values based on the lower limit of normal (LLN) were calculated by the use of published reference equations.[13] We classified each subject into mutually exclusive and exhaustive categories of pulmonary function as follows: normal, $FEV_1/FVC \geq LLN$ and $FVC \geq LLN$; obstructive, $FEV_1/FVC < LLN$ and $FVC \geq LLN$; restrictive, $FEV_1/FVC > LLN$ and $FVC < LLN$; and mixed, $FEV_1/FVC < LLN$ and $FVC < LLN$.[14]

Exposure Estimates

NIOSH previously estimated CFE for Libby vermiculite workers.[15] Historical area and personal air sampling data were used to estimate the 8-hour time-weighted average (TWA)–fiber (for all fiber types) exposure for all areas of the vermiculite operation throughout the company's history on the basis of phase contrast microscopy. The proportion of each day spent at each location was calculated for each job title, and an 8-hour TWA exposure was estimated for each job at a given time. Cumulative fiber exposure for each job that a worker held was estimated by weighting the 8-hour TWA exposure for a given job held by the worker by length of time (in years) spent at that job. Finally, the total CFE for each worker was estimated by summing the CFE for each job that the worker held. Cumulative fiber exposure has the unit fibers/cubic centimeter-year (f/cc-y) and is analogous to cigarette pack years. A thorough description of how NIOSH estimated CFE for the Libby cohort is available elsewhere.[15,16] Using company records to determine workers' job titles for the period 1981 to 1993, the approximately 1981 NIOSH job-exposure matrix, and the method mentioned earlier, ATSDR supplemented the cumulative exposure estimates from the early 1980s onward with estimates of exposures that occurred between the NIOSH evaluation in the early 1980s and the closure of the Libby operation in the early 1990s.

Statistical Analysis

SAS Version 9 (SAS Institute Inc; Cary, NC) was used for all analyses. We used PROC LOGISTIC for binary logistic regression. To fit logistic models, we used backward elimination for model selection. Independent variables (ie, risk factors other than the exposure of interest) were evaluated for potential confounding of the exposure–response association through the use of a 10% or more change in the odds ratio (OR) as the threshold for their inclusion. Interaction between the exposure of interest (ie, CFE) and other independent variables was also assessed. Goodness-of-fit model was evaluated by use of the Hosmer-Lemeshow test[17]; only models with adequate fit were accepted. Because of the skewed distribution of CFE, instead of a continuous variable we categorized it as quartiles for these models. Smoking (never smoked vs current/ex-smoker) was retained in all models except LPT and DPT, because these outcomes are not generally associated with smoking. Other categorical predictor variables considered for all models were as follows:

1. Era of hire: <1974 versus ≥1974. In 1974, the vermiculite operation's dry mill and original wet mill, where some of the dustiest jobs were located, were closed.[15]
2. Body mass index (BMI) category: <25, 25 to <30, ≥30
3. Age at screening: <47, 47 to 55, 56 to 66, ≥67 (quartiles of age)
4. Sex

Potential disadvantages of converting a continuous exposure variable to categorical in this approach include falsely assuming homogeneous risk within an exposure category (ie, the category cut points may arbitrarily misclassify subjects), obscuring of the exposure–response relationship due to not using all the available exposure data, and allowing large changes in risk between categories.[18,19] In an attempt to overcome these disadvantages and allow closer examination of the low end of the exposure–response curve, we used restricted cubic spline (RCS) functions[20] of logistic regression models, with CFE as a continuous variable. Restricted cubic spline functions are piecewise polynomials with the pieces joined by knots, with the pieces before the first knot and after the last restricted to be linear.[20] Restricted cubic spline functions allow the creation of smoothed exposure–response curves, with exposure as a continuous variable.

Here we used the SAS macro %RCS_reg[20] to fit and display RCS functions of the smoothed association between health outcomes and CFE as a continuous variable, with adjustment for other covariates. For each outcome, we fit three RCS functions with three to five knots symmetrically placed at percentiles of CFE, as proposed by Durrleman and Simon,[21] at the 5th, 50th, and 95th percentiles for three knots; the 5th, 25th, 75th, and 95th percentiles for four knots; and the 5th, 25th, 50th, 75th, and 95th for five knots. We evaluated model fit by comparing Akaike information criterion values to report the best-fitting RCS function for each outcome. In these plots of RCS functions, we used the mean CFE of the lowest quartile (0.1 f/cc-y) as the reference value for calculating ORs. To make the low end of the exposure–response curve easier to visualize, we excluded workers with CFE more than 500 f/cc-y ($n = 6$) from the spline plots; such an exclusion does not affect the shape of the curve at the retained data points.

RESULTS

Subjects

Among all screening participants, 370 reported working for the Libby vermiculite operation; of these, we were able to match 336 to company records. A comparison of these workers to the remainder of the Libby vermiculite worker cohort ($n = 1526$) is presented in Table 1. The median age of subjects at screening was 55.6 years; 93.2% were male. Compared with the rest of the worker cohort, subjects had a slightly lower-median cumulative exposure (3.6 vs 4.6 f/cc-years), a longer-median length of employment (1.5 vs 0.6 years), and a shorter-median interval between hire and December 31, 2000 (the midpoint of the screening program; 29.4 vs 48.4 years). The percentile distribution of study subjects' CFE was 0.4 for the 25th, 3.5 for the 50th, and 15.7 for the 75th.

Radiographic Pleural Abnormalities

The prevalence of pleural abnormalities consistent with pneumoconiosis was 46% ($n = 154$); 117 had LPT (35%), 18 had DPT (5%), and 74 had pleural calcification (22%). Pleural calcification was common among workers with either LPT ($n = 52$; 44%) or DPT ($n = 18$; 100%). Among the 18 workers with DPT, 7 also had LPT and 1 had parenchymal abnormalities; 4 had bilateral DPT. Compared with the CFE of the rest of the sub-cohort without pleural changes, the mean and median CFE of workers with DPT changes were greater (124.4 vs 38.5; 12.6 vs 5.6, respectively). As shown in Table 2, the prevalence of DPT increased with quartiles of age; all cases were male.

We fitted a categorical logistic regression model for DPT that retained age and era hired. Through the use of the lowest quartile as the reference, the ORs for the other quartiles ranged from 1.7 to 2.3 without monotonic trend and with 95% confidence intervals that included 1 (Table 3). The RCS function shows a monotonic increase in risk correlated to CFE, but, as with the categorical model, a 95% confidence band that includes 1 at all cumulative exposures (Fig. 1).

Excluding seven workers with coexistent DPT and/or parenchymal abnormalities, 117 workers (35%) met our definition of LPT. Compared with the rest of the sub-cohort, workers with LPT had a lower-mean CFE (32.7 vs 36.8 f/cc-year) but a greater median CFE (5.8 vs 2.1 f/cc-year). As shown in Table 2, the prevalence of LPT increased monotonically with age and BMI (Table 2). Among

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TABLE 1. Comparison of Demographics, Covariates, and Exposure Metrics Among Subjects and Other Libby Vermiculite Workers Not Included in the Study

	Subjects ($n = 336$)	Other Vermiculite Workers ($n = 1526$)
% Male (n)	93.2 (313)	97.2 (1483)
Median age at screening (25th–75th percentile)	55.6 (47.4–65.8)	. . .
% Current or ex-smoker (n)	66.7 (224)	. . .
Median BMI (25th–75th percentile)	28.6 (25.7–32.1)	. . .
Median CFE (f/cc-years; 25th–75th percentile)	3.6 (0.4–15.8)	4.6 (0.8–24.5)
Median years employed (25th–75th percentile)	1.5 (0.3–6.1)	0.6 (0.1–3.7)
Median years between hire and 12/31/2001 (25th–75th percentile)	29.4 (25.6–39.3)	48.4 (33.0–55.4)

BMI, body mass index; CFE, cumulative fiber exposure.

TABLE 2. Prevalence of Noncancer Health Outcomes Within Categories of Covariates

Outcome	Age, yr	*n* (Category %)	Body Mass Index	*n* (Category %)	Smoking	*n* (Category %)	Hire Era	*n* (Category %)	Sex	*n* (Category %)
Diffuse pleural thickening	<47	1 (1)	<25	3 (4)	Never	2 (2)	<1974	17 (8)	Male	18 (6)
	47–<56	3 (4)	25–<30	8 (6)	Ever	16 (7)	≥1974	1 (1)	Female	0 (0)
	56–<66	4 (5)	≥30	7 (5)						
	≥66	10 (12)								
Localized pleural thickening	<47	21 (25)	<25	18 (26)	Never	34 (31)	<1974	85 (42)	Male	115 (37)
	47–<56	25 (30)	25–<30	48 (35)	Ever	83 (40)	≥1974	32 (24)	Female	2 (9)
	56–<66	34 (40)	≥30	50 (38)						
	≥66	37 (44)								
Parenchymal abnormalities	<47	0 (0)	<25	3 (4)	Never	2 (2)	<1974	18 (9)	Male	17 (5)
	47–<56	0 (0)	25–<30	10 (7)	Ever	16 (7)	≥1974	0 (0)	Female	1 (4)
	56–<66	5 (6)	≥30	5 (4)						
	≥66	13 (15)								
Restrictive spirometry	<47	7 (8)	<25	4 (6)	Never	13 (12)	<1974	36 (18)	Male	44 (14)
	47–<56	7 (8)	25–<30	21 (15)	Ever	32 (14)	≥1974	9 (7)	Female	1 (4)
	56–<66	9 (11)	≥30	20 (15)						
	≥66	22 (26)								
Shortness of breath	<47	11 (19)	<25	20 (45)	Never	15 (22)	<1974	39 (46)	Male	61 (38)
	47–<56	14 (26)	25–<30	22 (32)	Ever	51 (47)	≥1974	27 (29)	Female	5 (26)
	56–<66	23 (56)	≥30	24 (37)						
	≥66	18 (69)								
Cough	<47	7 (12)	<25	11 (25)	Never	15 (22)	<1974	31 (37)	Male	43 (27)
	47–<56	12 (23)	25–<30	17 (25)	Ever	34 (31)	≥1974	18 (19)	Female	6 (32)
	56–<66	20 (49)	≥30	21 (32)						
	≥66	10 (38)								
Chronic bronchitis	<47	3 (5)	<25	7 (16)	Never	8 (12)	<1974	15 (18)	Male	24 (15)
	47–<56	9 (17)	25–<30	10 (14)	Ever	18 (17)	≥1974	11 (12)	Female	2 (11)
	56–<66	10 (24)	≥30	9 (14)						
	≥66	4 (15)								

LPT cases, 30 reported potential occupational exposure to asbestos outside of the Libby vermiculite operation.

The categorical model for LPT retained BMI, age, and sex. With the lowest quartile of CFE as a reference, the odds of LPT was elevated for the second and significantly elevated for the third quartile of CFE, but it was lower for the fourth quartile (Table 3). In the RCS function, the odds of LPT was statistically significant with a 95% lower confidence limit greater than 1 at lifetime CFE levels lower than 1 f/cc-y (Fig. 2). Reflecting the decrease in risk of LPT from the third to the fourth CFE quartiles in the categorical model, risk also declines above 20 f/cc-y. Because the LPT-CFE relationship may be affected or modified by latency,[10] we investigated further the impact of latency on this association. Using 28.4 years since hire (the median among all subjects) as the cut point, we stratified subjects by time since first exposure and fit spline functions. The resulting exposure–response curves (not shown) were similar in shape to the curve for all subjects but with much wider confidence bands. Finally, we excluded all workers who reported potential occupational asbestos exposure outside of the Libby vermiculite operation ($n = 62$) and fit a separate spline function. The resulting curve (not shown) was not discernibly

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TABLE 3. Risk of Pulmonary Health Outcomes From Logistic Regression Models, Controlling for Covariates and Presented by Quartiles of Cumulative Fiber Exposure (CFE) Among All Study Subjects*

Outcome	Model Covariates	CFE Quartile	*n* (CFE Category %)	OR	95% CI
DPT	CFE, age, employment before 1974	<0.4	1 (1)	1	
		0.4–3.5	4 (5)	2.3	0.2–22.6
		3.6–15.7	5 (6)	1.7	0.2–16.6
		≥15.7	8 (10)	1.9	0.2–17.6
LPT	CFE, BMI, sex, age	<0.4	17 (20)	1	
		0.4–3.5	29 (35)	1.9	0.9–3.9
		3.6–15.7	38 (45)	**2.3**	1.1–4.9
		≥15.7	33 (39)	1.8	0.8–4.0
Parenchymal	CFE, smoking, age, sex	<0.4	1 (1)	1	
		0.4–3.5	1 (1)	0.7	0.1–13.8
		3.6–15.7	2 (2)	1.3	0.1–20.9
		≥15.7	14 (17)	6.8	0.6–78.8
Restrictive spirometry	CFE, smoking, age, employment before 1974	<0.4	8 (10)	1	
		0.4–3.5	6 (7)	0.5	0.2–1.7)
		3.6–15.7	9 (11)	0.6	0.2–2.0)
		≥15.7	22 (26)	1.5	0.5–4.9)
SOB	CFE, smoking, age	<0.4	14 (23)	1	
		0.4–3.5	14 (30)	0.9	0.4–2.3)
		3.6–15.7	18 (47)	1.7	0.7–4.4)
		≥15.7	20 (32)	2.1	0.7–6.2)
Excess cough	CFE, smoking, age	<0.4	10 (16)	1	
		0.4–3.5	10 (21)	1.1	0.4–2.9
		3.6–15.7	16 (42)	2.5	0.9–6.8
		≥15.7	13 (41)	1.7	0.6–5.2
Chronic bronchitis	CFE, smoking	<0.4	5 (8)	1	
		0.4–3.5	4 (9)	1.0	0.2–4.0
		3.6–15.7	10 (26)	**3.8**	1.2–12.4
		≥15.7	7 (22)	2.9	0.8–10.4

*Significant ($P < 0.05$) adjusted associations are in bold.

BMI, body mass index; CFE, Cumulative fiber exposure; CI, confidence interval; DPT, diffuse pleural thickening; LPT, localized pleural thickening; OR, odds ratio; parenchymal, parenchymal abnormalities consistent with pneumoconiosis; SOB, shortness of breath.

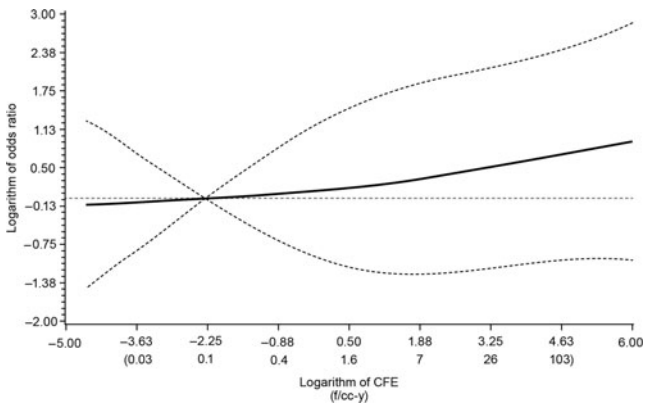

FIGURE 1. Adjusted relationship between cumulative fiber exposure (CFE; f/cc-y) and odds of radiographic diffuse pleural thickening and 95% confidence intervals (dashed lines) using a restricted cubic spline function with knots at the 5th, 50th, and 95th percentiles of CFE. All estimates are adjusted for age and employment before 1974. A CFE value of 0.1 f/cc-y was used for the calculation of all odds ratios.

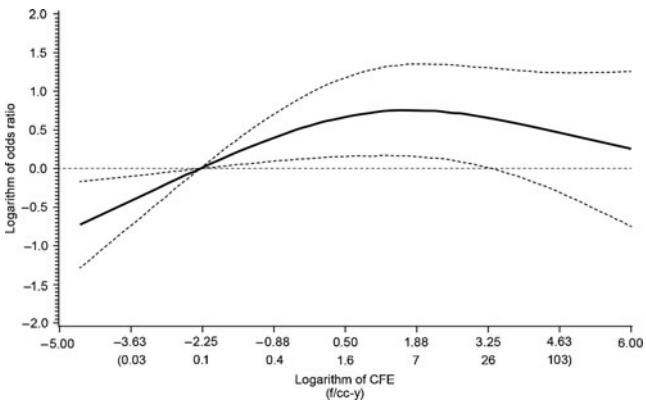

FIGURE 2. Adjusted relationship between cumulative fiber exposure (CFE; f/cc-y) and odds of radiographic localized pleural thickening and 95% confidence intervals (dashed lines), using a restricted cubic spline function with knots at the 5th, 50th, and 95th percentiles of CFE. All estimates are adjusted for body mass index, age, and sex. A CFE value of 0.1 f/cc-y was used for the calculation of all odds ratios.

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different from the curve for all subjects, but it had a much wider confidence band.

Radiographic Parenchymal Abnormalities

Eighteen workers (5%) had parenchymal changes consistent with asbestos exposure with small opacity profusion of 1/0 or more. Compared with the rest of the worker sub-cohort, these workers were older (mean 71.5 vs 56.4 years), had greater mean and median CFE (130.0 vs 29.8 f/cc-y and 47.5 vs 3.1 f/cc-y, respectively), longer time since hired (mean 44.2 vs 31.5 years), longer length of employment (mean 10.9 vs 4.6 years), and were hired earlier (mean 1956 vs 1969). The distribution of small opacity profusion was 1/0 ($n = 2$), 1/1 ($n = 5$), 1/2 ($n = 4$), 2/1 ($n = 3$), 2/2 ($n = 1$), 3/2 ($n = 2$), and 3/3 ($n = 1$). In addition to work exposures in Libby, all 18 reported nonoccupational exposure to vermiculite and 1 reported potential asbestos exposure in the military. All but two were current or ex-smokers (Table 2). All but 2 had radiographic pleural abnormalities; 10 had LPT, 10 had pleural calcification, and 6 had DPT. All workers with parenchymal abnormalities were older than 55 years at screening, and all were hired before 1974 (Table 2).

The categorical model for parenchymal abnormalities retained smoking, age, and sex as covariates and showed a nonstatistically significant increase in the OR for workers with CFE 15.7 f/cc-y or more (Table 3). In the RCS function, the exposure–response curve has a relatively linear slope that departs from the null at about 1 f/cc-y and becomes significantly elevated at 108 f/cc-y (Fig. 3).

Restrictive Spirometry

Overall, 69% of the workers had normal spirometry, whereas 11% had obstructive, 16% had restrictive, and 4% had mixed defects. Nevertheless, CFE showed no unadjusted association with obstructive and mixed spirometry (results not shown), and we subsequently focused on restrictive spirometry. The prevalence of restrictive spirometry generally increased with quartiles of age and BMI, and it was greater among smokers ($n = 35$, 31%; Table 2).

The categorical model for restrictive spirometry controlled for smoking, age, and era hired. The odds of restriction was insignificantly elevated (OR 1.5; 95% confidence intervals, 0.5 to 4.9) for CFE 15.7 f/cc-y or more (Table 3). In the spline RCS function, the risk of restriction departs from the null at about 26 f/cc-y and becomes statistically significant at 166 f/cc-y (Fig. 4).

Respiratory Symptoms and Conditions

Eighty-one workers reported any of the three symptoms/conditions examined here; 66 workers reported SOB (20%), 49 reported excess cough (15%), and 26 reported both excess cough and phlegm (ie, chronic bronchitis) (8%). Among workers reporting one or more of these outcomes, 58 were current or ex-smokers (72%) and 47 were older than 56 years at screening (58%).

The prevalence of SOB increased monotonically with age quartiles (Table 2). The categorical model controlled for smoking and age. There was an increase in the odds of SOB without statistical significance for the third and fourth quartiles of CFE (Table 3). In the spline function, the slope of the exposure–risk curve was positive but without statistical significance (Fig. 5).

The categorical model for excess cough controlled for smoking and age; the risk of cough was elevated for the third quartile of CFE and declined for the fourth quartile (Table 3). In the spline

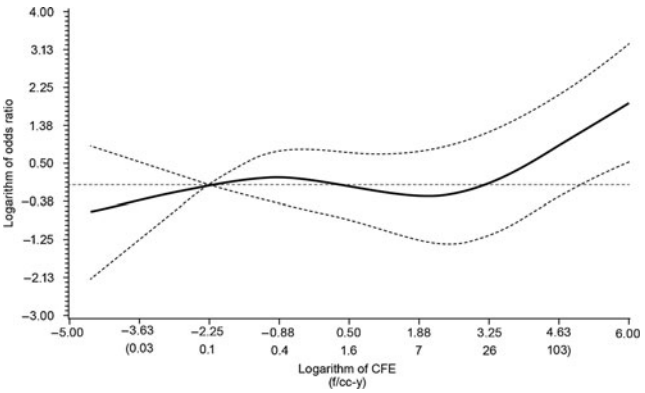

FIGURE 4. Adjusted relationship between cumulative fiber exposure (CFE; f/cc-y) and odds of radiographic restrictive spirometry and 95% confidence intervals (dashed lines) using a restricted cubic spline function with knots at the 5th, 25th, 75th, and 95th percentiles of CFE. All estimates are adjusted for smoking, age, and employment before 1974. A CFE value of 0.1 f/cc-y was used for the calculation of all odds ratios.

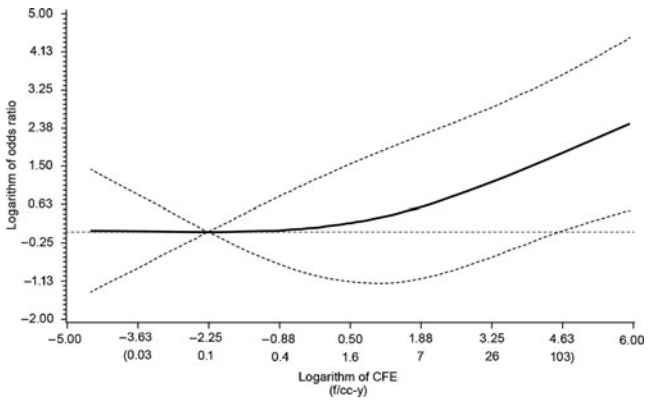

FIGURE 3. Adjusted relationship between cumulative fiber exposure (CFE; f/cc-y) and odds of radiographic parenchymal abnormalities and 95% confidence intervals (dashed lines) using a restricted cubic spline function with knots at the 5th, 50th, and 95th percentiles of CFE. All estimates are adjusted for smoking, age, and sex. A CFE value of 0.1 f/cc-y was used for the calculation of all odds ratios.

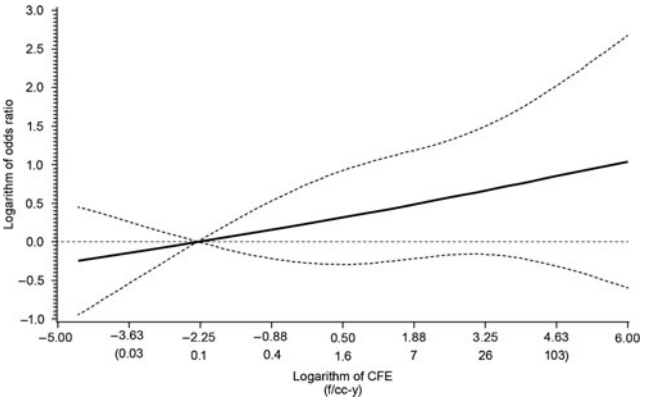

FIGURE 5. Adjusted relationship between cumulative fiber exposure (CFE; f/cc-y) and odds of radiographic shortness of breath and 95% confidence intervals (dashed lines) using a restricted cubic spline function with knots at the 5th, 50th, and 95th percentiles of CFE. All estimates are adjusted for smoking and age. A CFE value of 0.1 f/cc-y was used for the calculation of all odds ratios.

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function, the exposure–response curve had a shape similar to that of SOB and also was not statistically significant (Fig. 6).

The categorical model for chronic bronchitis controlled for smoking; the OR was significantly elevated for the third quartile of CFE (OR 3.8; 95% confidence interval, 1.2 to 12.4; Table 3). In the spline function, the exposure–response curve had a positive slope, with the OR becoming statistically significant at 24 f/cc-y (Fig. 7).

DISCUSSION

Collectively, these results provide evidence that Libby amphibole is a causative agent of pleuropulmonary morbidity. In categorical logistic models using quartiles of CFE, the exposure–response relationships are difficult to interpret, and statistical power is frequently low. Nevertheless, in RCS expansions of these logistic models for both the objective pulmonary outcomes (ie, radiographic outcomes and restrictive spirometry) and the self-reported symptoms and conditions, a positive exposure–response relationship can

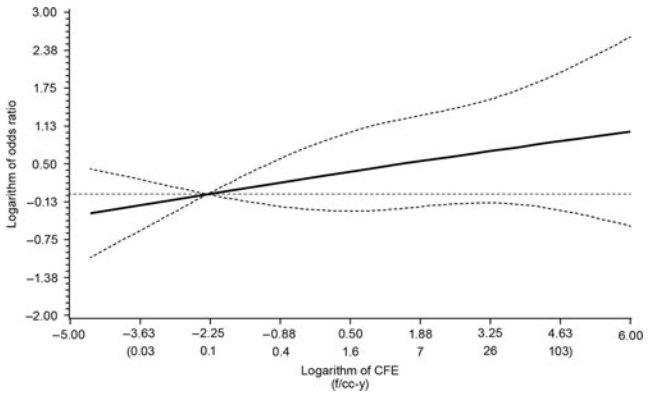

FIGURE 6. Adjusted relationship between cumulative fiber exposure (CFE; f/cc-y) and odds of excess cough and 95% confidence intervals (dashed lines) using a restricted cubic spline function with knots at the 5th, 50th, and 95th percentiles of CFE. All estimates are adjusted for smoking and age. A CFE value of 0.1 f/cc-y was used for the calculation of all odds ratios.

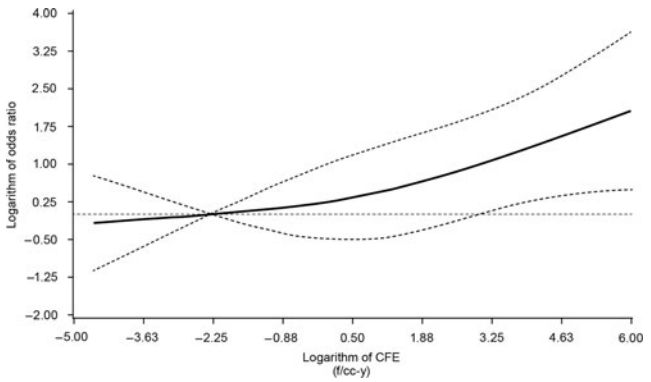

FIGURE 7. Adjusted relationship between cumulative fiber exposure (CFE; f/cc-y) and odds of chronic bronchitis and 95% confidence intervals (dashed lines) using a restricted cubic spline function with knots at the 5th, 50th, and 95th percentiles of CFE. All estimates are adjusted for smoking. A CFE value of 0.1 f/cc-y was used for the calculation of all odds ratios.

be seen at CFE levels lower than 20 f/cc-y. Although the odds for other outcomes increased monotonically with exposures above this level, the curve for LPT became attenuated and eventually declined. The exposure–response curves for LPT, parenchymal abnormalities, restrictive spirometry, and chronic bronchitis all show a region of the exposure–response curve at which risk becomes significantly elevated (ie, where the 95% lower confidence limit is > 1). The CFE level at which odds became significantly elevated ranged from a very low value of less than1 f/cc-y for LPT to 166 f/cc-y for restrictive spirometry.

In categorical models, excess risk for parenchymal abnormalities was found at 15.7 f/cc-y or more. Other investigations have found adverse effect levels for parenchymal abnormalities in the range of 15 to 53 f/cc-y for workers exposed to amosite.[22–24] Localized pleural thickening, the most common radiographic abnormality in this cohort, is associated with a wide range of asbestos-exposure levels, including exposures experienced by nonworkers, and it is frequently considered a marker of exposure, regardless of cumulative exposure.[10,25,26] This is consistent with our finding of elevated risk without a positive exposure–response relationship for pleural abnormalities at the upper three quartiles of CFE in the categorical model (OR, 1.9 to 2.3; Table 3) and in the spline function, which showed attenuation in the exposure–response curve. Attenuation of exposure–response curves has been observed in studies of other occupational cohorts and possible explanations include healthy worker survivor effect, depletion of susceptible persons, and saturation of biological pathways at high exposures.[27] The declining risk we observed for LPT may be due to a skewed distribution of exposure (only six workers had CFE > 500 f/cc-y and only one > 1000 f/cc-y) or exposure misclassification, in addition to the health worker survivor effect or self-selection bias.

Other studies of radiographic changes in Libby vermiculite workers have found elevated prevalence of parenchymal and pleural abnormalities at comparatively high-group mean or median CFE levels. Amandus et al,[28] in a study of 191 workers employed for at least 5 years during the period 1975 to 1982 with available radiographs and mean CFE of 119 f/cc-y, found that the prevalence of parenchymal and pleural abnormalities was 52.5 and 37.5, respectively. In a parallel study conducted by McDonald et al[29] of subjects who included 164 workers employed at the vermiculite operation in 1983 with a mean CFE of 40.1 f/cc-y, the prevalence of pleural and parenchymal abnormalities was 15.9 and 9.1, respectively. In another ATSDR study of 84 workers hired during 1954 to 1974 selected because of availability of their chest radiographs, the prevalence of circumscribed plaque was 98.8% at a median CFE of 44.1 f/cc-y, and parenchymal abnormalities were at 31.0% at a median CFE of 235.7 f/cc-y.[30]

In contrast with these other radiographic surveys, Rohs et al[31] found strong associations for pleural plaque at low lifetime cumulative exposures in another occupational cohort exposed to Libby amphibole in Marysville, Ohio. Compared with the Marysville cohort, we found weaker associations despite the greater cumulative exposure experienced by Libby workers as a group. This may be due to the fact that Rohs et al did not separate risks of DPT and LPT, as we did in this study, or it may be due to exposure misclassification resulting from non–occupational-amphibole exposure. The nonoccupational exposure that occurred in Libby has been shown to cause pleural plaques in residents without occupational exposure.[6,30] This non–occupational-amphibole exposure was unlikely to have occurred among the Marysville cohort. Evidence for the potential influence of non–occupational-amphibole exposure in our study compared with that of Rohs et al can be found by a comparison of the prevalence of pleural abnormalities from the lowest quartiles of CFE: although less than 4% of Marysville workers with CFE less than 0.25 f/cc-y had pleural abnormalities, we found 25% with CFE less than 0.4 f/cc-y. That all the workers studied here reported

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multiple non–occupational-exposure pathways may have blunted ORs that otherwise would have been similar to those seen by Rohs et al. Rohs et al[31] also found parenchymal abnormalities and DPT at mean CFE levels of 11.9 and 9.0 f/cc-y, respectively.

When stratified by short/long time since first exposure, the exposure–response curves were similar in shape, indicating that time since first exposure had only minor impact on the CFE-LPT association. Studies of other cohorts have shown that LPT may be better related to latency than to cumulative exposure.[10,26] Similarly, the RCS function excluding workers who reported potential occupational exposure to asbestos outside of the Libby operation was similar in shape to that of all workers. This suggests that there was little exposure misclassification related to these other asbestos exposures. In this study, the positive association between cumulative exposures below 20 f/cc-y and LPT was unlikely to have been confounded by latency or biased by exposure misclassification related to other asbestos exposures.

Although restrictive spirometry is commonly associated with nonmalignant–asbestos-related diseases,[10] only 13% of the workers had this type of abnormality, and its risk was only slightly elevated for the highest quartile of exposure (Table 3). Nevertheless, the spline function shows a marked association with higher CFE, again illustrating the potential limitation of categorical analysis. Results from another study showed significant reductions in FEV_1 and FVC associated with cumulative exposure to crocidolite.[32]

In general, respiratory symptoms are less specific for asbestos exposure than are objective findings.[10] Here, we found increasing odds of excess cough and SOB with CFE, albeit without statistical significance. Results from another study show correlations between respiratory symptoms and frequency of handling vermiculite among participants in the ATSDR screening program aged 10 to 29 years.[33] Shortness of breath has been significantly associated with cumulative exposures of 10 f/cc-y or more to mainly chrysotile.[34] Cumulative exposure and smoking have been shown to be synergistic in increasing chronic bronchitis and SOB in asbestos-cement workers.[35]

The weaknesses of this study include potential selection bias of participating workers, exposure misclassification due to potential error in the CFE estimates, and non–occupational-amphibole exposure, and the use of self-reported data. As shown in Table 1, only 18% of the eligible population (336/1862) participated. Study subjects self-selected to participate in the screening program, and as a group, they had lower CFE and tended to work later in the vermiculite operation's history, when process controls had been implemented to reduce exposures. Thus, a variation of the healthy worker survivor effect may have resulted in workers with lower exposures remaining healthy enough to participate in the screening program. Also, workers with greater cumulative exposure may have already been diagnosed with asbestos-related health outcomes and opted not to participate. In particular, for LPT, this source of selection bias may have resulted in a lower prevalence at high-CFE levels. Because the latency of LPT is typically considered to be greater than 20 years after initial exposure,[10] the prevalence of LPT in this study may be lower than expected because participating workers had a lower median time since first exposure than the rest of the cohort. In addition, parenchymal abnormalities are typically associated with higher CFE[36,37]; thus, the prevalence among our study subjects may underrepresent that of the entire worker cohort.

Exposure misclassification may have resulted from error in the exposure estimates. When the exposure estimates were originally developed, many judgments were made to make use of the available air sampling data.[15] These data were collected over a long period by the vermiculite operation and by state and federal agencies. Relatively few samples were taken before 1969 and none before 1956. Before 1967, many samples were collected by the use of a midget impinger, whereas later samples were collected with a membrane filter. A conversion factor was used to convert the average respirable dust content of the impinger results to fiber exposure. Finally, most sampling results were from area samples from which the 8-hour TWA had to be estimated. Additional exposure misclassification may have resulted from community-amphibole exposure, although it seems likely that the impact of such misclassification would have been greatest among workers with very low-occupational exposures.

Finally, self-reports of respiratory symptoms may have been biased by a worker's belief that his or her health was affected by occupational amphibole exposure or by hypersensitivity to symptoms that otherwise would have been ignored.

CONCLUSIONS

We have analyzed the exposure–response relationship between Libby amphibole and several pulmonary health outcomes in a subset of the vermiculite worker cohort. For several outcomes, we detected an exposure level at which the odds of the outcome becomes elevated to the point of statistical significance. For LPT, this level is less than 1 f/cc-y—a level far below what would be experienced by a worker exposed at the current permissible exposure level of 0.1 f/cc-y over a working life of 45 years (ie, 4.5 f/cc-y). The shape of the exposure–response curves generally correlates with CFE less than 400 f/cc-y for the objective outcomes, providing evidence that Libby amphibole is a causative agent of adverse pulmonary outcomes. Because Libby vermiculite was so widely disseminated, these results have implications for public health policy and for the non–cancer-risk assessment for Libby amphibole.

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