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Childhood exposure to Libby amphibole asbestos and respiratory health in young adults

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ABSTRACT

Objectives: Vermiculite ore containing Libby amphibole asbestos (LAA) was mined in Libby, MT, from the 1920s-1990. Recreational and residential areas in Libby were contaminated with LAA. This objective of this study was to characterize childhood exposure to LAA and investigate its association with respiratory health during young adulthood.

Methods: Young adults who resided in Libby prior to age 18 completed a health and activity questionnaire, pulmonary function testing, chest x-ray and HRCT scan. LAA exposure was estimated based on participant report of engaging in activities with potential LAA exposure. Quantitative LAA estimates for activities were derived from sampling data and literature reports.

Results: A total of 312 participants (mean age 25.1 years) were enrolled and reported respiratory symptoms in the past 12 months including pleuritic chest pain (23%), regular cough (17%), shortness of breath (18%), and wheezing or whistling in the chest (18%). Cumulative LAA exposure was significantly associated with shortness of breath (aOR = 1.12, 95% CI 1.01–1.25 per doubling of exposure). Engaging in recreational activities near Rainy Creek Road (near the former mine site) and the number of instances heating vermiculite ore to make it expand or pop were also significantly associated with respiratory symptoms. LAA exposure was not associated with pulmonary function or pleural or interstitial changes on either chest x-ray or HRCT.

Conclusions: Pleural or interstitial changes on x-ray or HRCT were not observed among this cohort of young adults. However, childhood exposure to LAA was significantly associated with respiratory symptoms during young adulthood. Pleuritic chest pain, in particular, has been identified as an early symptom associated with LAA exposure and therefore warrants continued follow-up given findings of progressive disease in other LAA exposed populations.

1. Introduction

Ore mined and processed near Libby, MT provided up to 80% of the world's vermiculite from the early 1920s through 1990 in goods used in commercial and residential settings including fertilizers, gardening soils, insulation, and construction products (Kuntz et al., 2009). The open-pit mine at Zonolite Mountain was located approximately 7 miles northeast of Libby. Additional processing of vermiculite ore, including milling, screening, expansion (exfoliation) and shipping, was conducted near the mine, in Libby, and in more than 200 facilities throughout the U.S. (Horton et al., 2006; Schneider and McCumber, 2016).

Vermiculite ore mined in Libby contained naturally-occurring amphibole asbestiform minerals including winchite, richterite, and tremolite (Meeker et al., 2003). Collectively, the mixture of amphibole fibers found in vermiculite from the Libby site is referred to as Libby amphibole asbestos (LAA). Occupational exposure to LAA was first linked to chest radiographic pleural changes, pleuritic chest pain, and shortness of breath among workers at a manufacturing facility that expanded and utilized vermiculite as a lawn care products carrier in Marysville, OH (Lockey et al., 1984). A 30-year follow-up of this cohort reported pleural and parenchymal changes at low levels of cumulative fiber exposure, i.e. three to ten times less than the 45-year working lifetime U.S. OSHA asbestos standard of 4.5 fiber-year/cc (Lockey et al., 2015). Occupational exposure to LAA in Libby, where exposures were

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higher, has also been linked to increased morbidity and mortality from respiratory disease (Amandus et al., 1987; Amandus and Wheeler, 1987; McDonald et al., 2004; Sullivan, 2007).

Pulmonary disease, including pleural and interstitial abnormalities, malignant mesothelioma, and autoimmune disorders have also been reported among residents of Libby without occupational LAA exposure history (Noonan et al., 2006; Peipins et al., 2003; Vinikoor et al., 2010; Whitehouse et al., 2008). Non-occupational exposure to LAA in Libby may occur via multiple pathways including household contact with a mine worker, heating raw vermiculite in the home, the use of vermiculite insulation in the attics and walls of homes, engaging in recreational activities at or near the mining or processing facilities, and playing in vermiculite piles (Peipins et al., 2003; Noonan, 2006; Ryan et al., 2015).

Expansion of raw vermiculite ore ceased in Libby prior to 1981, and in 1990 mining operations ended. In 1999, the U.S. Environmental Protection Agency (EPA) Region 8 Emergency Response Branch began investigating the extent of LAA contamination in the Libby area and initiated cleanup activities. Subsequently, health investigations have been conducted with former mine workers and Libby residents including a community-based medical screening study by the Agency for Toxic Substances and Disease Registry (ATSDR) that reported pleural abnormalities on chest radiograph among 17.8% of the participants over age 18 (Peipins et al., 2003). Additional analyses of this population also found increased respiratory symptoms among participants ages 10–29 that was significantly associated with participating in activities with potential LAA exposure (Vinikoor et al., 2010).

Despite remediation activities, there remains ongoing concern that low-level, chronic environmental exposure to children who resided in Libby prior to clean-up may be associated with adverse health outcomes. In response, the Childhood Health Investigation and Exposure Follow-Up Study (CHIEFS) was initiated to determine if childhood exposure to LAA is associated with pulmonary disease in young adulthood. We previously developed an exposure methodology based on the EPA remediation data collected in Libby to quantitatively estimate LAA exposure during residential outdoor activities (Ryan et al., 2015). The objectives of this report are to 1) extend our previous quantitative exposure assessment to include additional childhood activities with potential LAA exposure and 2) to test the hypothesis that childhood exposure to LAA is associated with adverse pulmonary health outcomes in young adulthood, including pleural and interstitial abnormalities, decreased lung function, and increased respiratory symptoms.

2. Methods

2.1. Study participants

Eligibility for enrollment in the CHIEFS study included children who had previously enrolled in the 2000–2001 ATSDR screening and who were between the ages of 10–17 at the time of their participation and individuals who met the ATSDR medical screening eligibility criteria but did not participate in that study. Recruitment efforts included contact with the parents of the previous ATSDR participants, posts to social media, public outreach events including health fairs, and advertisements in local and regional newspapers. All participants provided written informed consent approved by the University of Cincinnati Institutional Review Board prior to participation.

2.2. Clinical evaluations and health outcomes

CHIEFS participants completed a clinical evaluation at the Center for Asbestos Related Diseases (CARD) in Libby including extensive questionnaire adapted from the ATSDR medical screening survey to obtain demographic characteristics, residential and occupational history, and respiratory health history. Participants were queried regarding the frequency and duration of engaging in activities in Libby during childhood that may have resulted in LAA exposure. The presence of respiratory symptoms in the previous 12 months was assessed by participant report of shortness of breath, wheezing/whistling in the chest, regular cough (≥ 4 / day, $\geq$ 4 days / week, $\geq$ 4 consecutive weeks), and pleuritic chest pain defined as sharp or piercing pain or cramping in the chest or upper back for 4 or more episodes/year or 1 or more episode lasting longer than 1 day.

Spirometry was performed by experienced respiratory therapists using a Medgraphics Platinum Elite Series Plethysmograph in accordance with American Thoracic Society guidelines (Miller et al., 2005). Prior to study initiation, spirometry testing quality control procedures were evaluated during two on-site visits by expert members of the study team (RM, JL). Additional follow-up training was conducted and quality assurance reviews were performed throughout data collection to maintain set standards. Age-, height-, gender-, and race-adjusted spirometric reference values generated from NHANES III (Hankinson et al., 1999) were used to derive percent predicted FEV1, FVC, FEV1/FVC, and lower limits of normal (LLN). Spirometric results were also categorized as normal (FEV1/FVC $\geq$ LLN and FVC $\geq$ LLN), restrictive, (FEV1/FVC $\geq$ LLN and FVC < LLN), obstructive (FEV1/FVC < LLN and FVC $\geq$ LLN and FEV1 < LLN), or mixed (FEV1/FVC < LLN and FVC < LLN).

Participants also completed posterior-anterior chest radiographs and high resolution computed tomography (HRCT) scans at a single facility in Libby. To minimize radiation exposure, HRCTs were administered in the prone position only, with 1 mm slices taken every 15 mm moving from the costophrenic angle toward the apices, not to exceed 15 slices. Female participants were screened for pregnancy before completing imaging tests. All chest radiographic and HRCT images were read locally and digital films, masked of identifiers, were interpreted independently by three chest radiologists qualified as National Institute for Occupational Safety and Health (NIOSH) certified B-readers. The same B-readers interpreted all films as part of their standard radiologic practice.

2.3. Exposure assessment

Qualitative, semi-quantitative and quantitative approaches to LAA exposure assessment were developed for exposures occurring from birth through age 18. These relied upon participant report of engaging in activities with potential LAA exposure during childhood. Participants reported their age when first engaging in each activity, the number of years they engaged in each activity, and the average number of days per year in which they engaged in each activity. Questionnaire responses were used to qualitatively categorize participants as having 'ever' or 'never' engaged in each activity. For those reporting 'ever' participating, the frequency of engaging in each activity was calculated by multiplying the number of years participants reported engaging in the activity by the number of times per year reported. This frequency measure was the basis of our semi-quantitative exposure metric that defined individuals as 'frequently' exposed (frequency $\geq$ 75th percentile), 'sometimes' exposed (frequency < 75th percentile), or never exposed (frequency equal to zero).

Our quantitative approach combined the semi-quantitative frequency and duration exposure metrics with a quantitative estimate for 12 activities with potential LAA exposure as described in Table 1. Quantitative estimates of LAA exposure and the rationale for each were based on literature values, available activity-based sampling results, and the US EPA Contaminant Screening Survey results (Table 1). Analyses reporting phase contrast microscopy (PCM) and phase contrast microscopy equivalent (PCME) results were included in our approach due to the uncertainty in comparing results obtained from electron microscopy to phase contrast microscopy (PCM). Cumulative exposure to LAA for the 12 activities was calculated as:

Table 1
Summary of activities with potential LAA exposure.

Activity With Potential LAA Exposure ('Abbreviation)	Estimated LAA exposure (f/cc) per occurrence	Rationale for Activity and Quantitative LAA Estimate	Citation	Min Age	Max Annual Frequency	Age and Frequency Adjustment Rationale
Spending time in attic with visible vermiculite ('Attic')	0.719 f/cc	Time spent it the attic likely consisted of activities where vermiculite insulation was disturbed and times of inactivity when vermiculite was not disturbed. Thus, personal sampling for active disturbance and area samples during inactivity were included to derive the exposure estimate. The final estimate was calculated as the mean of the activity sampling and the mean of area samples prior to performing activities.	Ewing et al. 2010; Versar 2003	5	365	Min age based on 5th %-tile of participants reporting outdoor recreation activities in EPA CHAD.
Playing in games at the downtown ballfields ('Ball')	Prior to 1997: 0.06 f/cc	Downtown ballfields were located near expansion plan with large vermiculite piles and the field was surfaced with vermiculite ore. Estimate based on EPA Final Remediation Investigation Report Operable Unit 1 (OU1) - Former Export Plant Site (2009) for wetted soil disturbance / bush hogging in OU1. The Libby baseball field was centrally located in OU1, and youth baseball games occurred regularly from 1977 to 1997.	EPA 2009	5	100	Min age based on 5th %-tile of participants reporting outdoor recreation activities in EPA CHAD. Frequency dependent on climate, likely not to exceed 100 days.
Playing / digging in the yard ('Dig')	Homes with visible vermiculite: 0.45 f/cc Homes without visible vermiculite: 0.03 f/cc	Available vermiculite was added to many local yards. Estimated based on residential history combined, U.S. EPA Contaminant Screening Survey (CSS), and activity-based sampling (ABS) as described by Ryan et al. (2013)	Ryan et al. 2013	2	100	Min age based on 5th %-tile of participants reporting outdoor recreation activities in EPA CHAD. Maximum frequency limited to 100 days per year based on Libby climate data.
Fishing on the Kootenai River near the mouth of Rainy Creek ('Fish')	< 1994: 0.2 f/cc 1994 − 2005: 0.06 f/cc > 2005: 0.02 f/cc	The area surrounding Rainy Creek Road was contaminated due to its proximity to the mine and its use to haul uncovered ore from the mine to the screening plant where high occupational exposures were recorded. A conveyer belt was used to transport ore over the Kootenai River near the mouth of Rainy Creek to uncovered railroad cars on the other side of the river. Amandus et al. (1987) summarize airborne dust samples collected at the mine and mill sites, including the river office located near the mouth of Rainy Creek (0.2 f/cc). Demolition activities at the mine and mill continued through 1993 (Quivik, 2002). For years 1994 − 2005, exposures are assigned based on air sampling during soil disturbance in OU1 (0.06 f/cc). Removal of visible vermiculite was conducted in late 2004 along the frontages of Rainy Creek Road (EPA, 2008). Post 2005, exposures observed during sampling on Rainy Creek Road are assigned (0.02 f/cc).	Amandus et al. 1987; EPA 2008; Quivik 2002	5	100	Min age based on 5th %-tile of participants reporting outdoor recreation activities in EPA CHAD. Maximum frequency limited to 100 days per year based on Libby climate data.
Gardening ('Gardening')	Homes with visible vermiculite: 0.45 f/cc Homes without Visible vermiculite: 0.03 f/cc	Potential exposure to LAA due to disturbance of soil contaminated with vermiculite ore. Reported residential histories were matched with home information contained in the Libby 2 database. Presence of visible vermiculite at each home was ascertained from the CSS, or from particpant report if information was not present in the CSS. Mean LA was calculated for homes with visible vermiculite and homes without visible vermiculite for outdoor residential activities	Ryan et al., 2013	7	100	Min age based on 5th %-tile of participants reporting plant care activities in EPA CHAD. Maximum frequency limited to 100 days per year based on Libby climate data.

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Table 1 *(continued)*

Activity With Potential LAA Exposure ('Abbreviation)	Estimated LAA exposure (f/cc) per occurrence	Rationale for Activity and Quantitative LAA Estimate	Citation	Min Age	Max Annual Frequency	Age and Frequency Adjustment Rationale
Helping parents install insulation ('Insulation')	0.164 f /cc	Libby residents would frequently self-install vermiculite insulation in attics and walls. Quantitative LAA estimate based on Versar (2003) activity-based sampling scenarios for installing vermiculite insulation.	Versar 2003	7	30	Min age based on the 5th %-tile of participants reporting outdoor chores in EPA CHAD. Max frequency based on 95th %-tile of CHIEFS reported frequency.
Mowing lawn ('Mow')	Homes with Visible Vermiculite: 0.059 f/cc Homes without Visible Vermiculite: 0.014 f/cc	See rationale for 'Gardening'	Ryan et al., 2013	7	100	The minimum age was increased to 7 years. This cutpoint is based on the ages of individuals reporting outdoor chores who fall in the 5th percentile of the EPA CHAD. Maximum frequency limited to 100 days per year based on Libby climate data.
Playing in or around vermiculite piles ('Piles')	1.66 f/cc	The Cascadia Times (2001) reported it was commonplace for children to swing on ropes and drop into vermiculite piles near the WR Grace expander plant in Libby. Estimate previously used by Kelly et al. (2006). Includes maximum values recorded during removal activities at the screening and export plant in Libby (Weis, 2001). Maximum values were used to represent exposures that may have been experienced by children due to a breathing zone closer to the source. Removal activities at these sites included shoveling and pushing around vermiculite.	Fritz 2001; Kelly et al. 2006; Kelly, James, personal communication 2013; Weis 2001	5	100	Minimum age increased to 5 years. This cutpoint is based on the ages of individuals reporting outdoor recreation in EPA CHAD who fall in the 5th percentile. Maximum frequency limited to 100 days per year based on Libby climate data.
Playing along the railroad ('Rail')	< 1994: 0.2 f/cc 1994 – 2005: 06 f/cc > 2005: 0.02 f/cc	Uncovered rail cars were loaded with vermiculite ore	Amandus et al. 1987; EPA 2008; Quivik 2002	5	100	Minimum age increased to 5 years. This cutpoint is based on the ages of individuals reporting outdoor recreation in EPA CHAD who fall in the 5th percentile. Maximum frequency limited to 100 days per year based on Libby climate data.
Raking leaves ('Rake')	Homes with Visible Vermiculite: 0.014 Homes without Visible Vermiculite: 0.004	See rationale for 'Gardening'	Ryan et al., 2013	7	90	The minimum age was increased to 7 years. This cutpoint is based on the ages of individuals reporting outdoor chores in EPA CHAD who fall in the 5th percentile. Frequency dependent on climate, but does not exceed 100 days.
Recreational activities (hunting, hiking, etc) along Rainy Creek Road ('Recreation')	< 1994: 0.2 f/cc 1994 – 2005: 0.06 f/cc > 2005: 0.02 f/cc	See rationale for 'Fish'	Amandus et al. 1987; EPA 2008; Quivik 2002	5	100	Minimum age increased to 5 years. This cutpoint is based on the ages of individuals reporting outdoor recreation in EPA CHAD who fall in the 5th percentile. Maximum frequency limited to 100 days per year based on Libby climate data.
Cutting or collecting firewood near Rainy Creek Road ('Wood')	0.043 f/cc	Leading to the mine site, Rainy Creek Road was surfaced with gravel and contaminated with mine tailings. Firewood was frequently collected from this area due to its proximity to town and accessibility. Quantitative LAA estimate based on activity-based sampling reported by Hart et al. (2009) during trail maintenance performed by forestry workers. The estimate includes samples during walking and brush clearing activities.	Hart et al. 2009	7	60	Frequency not depending on climate or other factors. Minimum age increased to 7 years. This cutpoint is based on the ages of individuals reporting outdoor chores in EPA CHAD who fall in the 5th percentile.
Heating vermiculite ore to make it expand or pop ('Popping')	Count*	Expansion of raw ore was done as part of school classes and in the homes. Frequency and duration ascertained by CHIEFS questionnaire.	–	6	200	Frequency not dependent on climate or other factors. Minimum age increased to 6 years. This cutpoint is based on the ages of individuals reporting activities involving wood buring/building a fire in EPA CHAD who fall in the 5th percentile.
Share a household with a W.R.	Ever / Never	Status and duration ascertained by CHIEFS	–			

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Table 1 (*continued*)

Activity With Potential LAA Exposure ('Abbreviation)	Estimated LAA exposure (f/cc) per occurrence	Rationale for Activity and Quantitative LAA Estimate	Citation	Min Age	Max Annual Frequency	Age and Frequency Adjustment Rationale
Grace worker or contractor		questionnaire.				
Live in a home with indoor visible vermiculite ('Visible')	Years reported (0 – 18)	Residing in a home with visible vermiculite was ascertained by matching reported addresses with CSS data. If CSS data was unavailable, participant report was utilized.	–			

$$C_i = \sum_{j=1}^{12} Fij \times E_j$$

where for each individual, F_{ij} is the days individual *i* reported engaging in activity *j* through age 18 years and E_j is the estimated LAA exposure (f/cc) associated with activity *j*. A conversion to f/cc - months was applied by dividing the cumulative exposure in days by 30.44 days / month.

In order to minimize the potential for exposure misclassification due to recall, we winsorized the minimum age and frequency at which activities could be reported based on the EPA's Consolidated Human Activity Database (CHAD). The CHAD is a repository of person-level activity data collected from 22 studies examining daily human behaviors conducted from 1982 to 2010 (U.S. EPA, 2016). The database contains over 2 million reported activities from approximately 54,000 individuals ages 1–94 with associated demographic data including age and sex. Studies whose target population was not within the age range of CHIEFS participants were excluded. Thirteen studies in CHAD met the age criteria, representing over 1.5 million reported activities from 42,341 individuals. We identified activities in the CHAD similar to those engaged in by CHIEFS participants including outdoor leisure / play, outdoor recreation, fire building, outdoor chores and plant care activities (Table 1). We examined the distribution of ages within each of these activities and designated the 5th percentile as the minimum age to be used in the analogous CHIEFS activity (Table 1). Similarly, a maximum annual frequency was defined for each activity and CHIEFS participants who reported engaging in activities more frequently than these maximums were winsorized (Table 1).

LAA estimates associated with sharing a household with a W.R Grace worker or contractor, living in a home with visible vermiculite, or heating vermiculite ore to make it expand or pop were not available. Therefore, exposure via these pathways were defined as 1) ever or never sharing household with a W.R. Grace worker or contractor, 2) reported frequency of heating vermiculite ore to make it expand or pop, and 3) years living in a home with visible vermiculite prior to age 18.

2.4. Statistical analyses

Logistic and linear regression were used to examine the association between the three exposure metrics and the presence of respiratory symptoms and pulmonary function outcomes (%FEV1, %FVC, and %FEV1/FVC). All models were adjusted for sex and smoking status (never, former, current smoker). Due to the skewed distribution of LAA exposure estimates and the presence of zero values, the quantitative estimates for each activity and the cumulative exposure were log-transformed via a $\log_2(1+x)$ transformation in order to retain subjects with zero exposure estimates in the analysis. A log base 2 transformation was chosen for interpretation as the calculated odds ratios and 95% confidence intervals (95% CI) represent a two-fold increase in estimated LAA exposure. ANOVA was also performed as a *post hoc* analysis to compare lung function outcomes, including the %FEV1, %FVC, and %FEV1/FVC, between participants with and without respiratory symptoms.

3. Results

3.1. Study participants

A total of 312 individuals were enrolled and completed one or more portions of the study protocol. Of these, 75% (n = 234) had previously participated in the ATSDR medical screening. As shown in Table 2, the average age at enrollment was 25.1 years; 54% were female, 99% were Caucasian, and 45% were current or former smokers. The average length of residence in the Libby area through age 18 was 16.5 (SD 3.0) years. In the previous 12 months, shortness of breath, wheezing / whistling in the chest, regular cough, and pleuritic chest pain were

Table 2
Demographic and health characteristics of the CHIEFS cohort.

Demographic Characteristics	n (%)
Average Age (mean(SD))	25.1 (± 2.7)
Year of Birth	
1980–1985	157 (50%)
1986–1990	148 (48%)
1991–1992	7 (2%)
Female	167 (54%)
Race	
Caucasian	308 (99%)
Asian, Black, or Hispanic	4 (1%)
Average BMI	27.4 (± 6.2)
BMI*	
Normal	118 (39%)
Overweight	98 (32%)
Obese	88 (29%)
Smoking Status	
Never	171 (55%)
Former	51 (16%)
Current	90 (29%)
Average Pack-Years (Current and Former Smokers)	4.6 (± 3.9)
Average Length of Residence in Libby area (through age 18)	16.5 (± 3.0)
Health Outcomes	
Pleural Changes (X-ray)	0 (0%)
Pleural Changes (HRCT)	0 (0%)
Interstitial Changes (X-ray)	0 (0%)
Interstitial Changes (HRCT)	0 (0%)
Spirometry*	
Normal	284 (93.4%)
Obstructive	8 (2.6%)
Restrictive	10 (3.3%)
Mixed	2 (0.7%)
Shortness of Breath	56 (18%)
Wheezing / Whistling in Chest	57 (18%)
Regular Cough	51 (17%)
Pleuritic Chest Pain	72 (23%)

**n = 311 subjects with complete questionnaire data.
* n = 304 subjects with spirometry data, normal: FEV1/FVC > LLN and FVC > LLN, restrictive: FEV1/FVC > LLN and FVC < LLN, obstructive: FEV1/FVC < LLN and FVC > LLN and FEV1 < LLN, mixed: FEV1/FVC < LLN and FVC < LLN.

reported by 56 (18%), 57 (18%), 51 (17%) and 72 (23%) participants, respectively. There were no pleural or interstitial changes observed on either chest X-ray or HRCT scan for the 300 participants who provided these and therefore no statistical analyses were performed for these outcomes. Normal spirometry results were observed for 93% of the cohort (Table 2).

As shown in Table 3, the most frequently reported activity prior to age 18 was playing in or watching games at the downtown ball fields (64%), playing or digging in the yard (45%), playing in or around vermiculite piles (45%), and mowing lawns (44%). While 98% were born prior to the mine closing in 1990 (Table 2), only 8% (n = 24) reported ever living or sharing a household with a W.R. Grace worker or contractor (Table 3). More than one-third (35%) of participants reported indoor visible vermiculite in their home (Table 3) and nearly one-third (31%) reported heating vermiculite ore to make it expand or pop.

3.2. Quantitative estimates of LAA exposure

Assigned estimates of LAA exposure were highest for playing in or around vermiculite piles (1.66 f/cc), spending time in an attic with visible vermiculite (0.719 f/cc), and playing / digging in the yard of a home with visible vermiculite outdoors (0.45 f/cc) (Table 1). The distribution of cumulative and activity-specific estimated LAA exposure (f/cc - months) is presented in Fig. 1. The distributions were highly skewed, with estimated values > 1.5 times the interquartile range (IQR) present for most activities. The median 12-activities cumulative exposure was 4.99 f/cc - months and ranged from 0.01 to 114.3 f/cc - months. Among individual activities, median cumulative exposures were highest for playing in or around piles (6.54 f/cc - months) and spending time in an attic with visible vermiculite.

3.3. Respiratory symptoms and lung function

The associations between the qualitative (ever/never) exposure metric for each activity and respiratory symptom are shown in Table 3. Participating in recreational activities along Rainy Creek Road (aOR = 1.9, 95% CI 1.1 – 3.4), cutting or collecting firewood near Rainy Creek Road (aOR = 3.1, 95% CI 1.5 – 6.4), heating vermiculite ore to make it expand or pop (aOR = 1.8, 95% CI 1.0 – 3.2), and sharing a household with a W.R. Grace worker or contractor (aOR = 3.2, 95% CI 1.3 – 7.8) were significantly associated with pleuritic chest pain. Multiple activities, including playing/digging in the yard (aOR = 1.9, 95% CI 1.0 – 3.6), fishing on the Kootenai River near the mouth of Rainy Creek (aOR = 2.7, 95% CI 1.4 = 5.2), playing in or around vermiculite piles (aOR = 2.1, 95% CI 1.1 – 3.9), playing along the railroad (aOR = 2.0, 95% CI 1.1 – 3.7), engaging in recreational activities near Rainy Creek Road (aOR = 2.8, 95% CI 1.5 – 5.2), and cutting or collecting firewood near Rainy Creek Road (aOR = 3.2, 95% CI 1.5 – 6.8), were significantly associated with shortness of breath. Increasing number of total activities reported was positively associated with each respiratory symptom but was not statistically significant (Table 3).

The association between sometimes and frequently participating in activities (for those activities for which at least 5% of the cohort reported frequently participating in) and each respiratory symptom is presented in Table 4. Frequently gardening, playing in or around vermiculite piles, and heating vermiculite were significantly associated with pleuritic chest pain (aOR = 3.0 (95% CI = 1.0 – 9.2), aOR = 2.5 (95% CI 1.1 – 5.8), and aOR = 2.7 (95% CI 1.1 – 7.0), respectively). Similar to the qualitative (ever/never) metric, sometimes and frequently fishing on the Kootenai River near the mouth of Rainy Creek and participating in recreational activities along Rainy Creek Road were significantly associated with shortness of breath (Table 4).

The adjusted odds ratios for a two-fold increase in quantitatively estimated LAA exposure and each respiratory symptom are presented in Fig. 2. Gardening (aOR = 1.2, 95% CI 1.0 – 1.3) and the frequency of heating vermiculite ore to make it expand or pop (aOR = 1.2, 95% CI 1.0 – 1.4) were significantly associated with pleuritic chest pain. Heating vermiculite ore to make it expand or pop (aOR = 1.3, 95% CI 1.1 – 1.5), playing along the railroad (aOR = 1.2, 95% CI 1.0 – 1.4), fishing on the Kootenai River near the mouth of Rainy Creek (aOR = 1.3, 95% CI 1.0 – 1.6), and cutting or collecting firewood near Rainy Creek Road (aOR = 1.9, 95% CI 1.2 – 3.4) were all significantly associated with regular cough. Similarly, multiple activities, including fishing on the Kootenai River near the mouth of Rainy Creek, gardening, playing in or around vermiculite piles, engaging in recreational activities and cutting or collecting firewood along Rainy Creek Road, and heating vermiculite ore to make it expand or pop, were significantly associated with shortness of breath (Fig. 2). Cumulative LAA exposure estimate was also significantly associated with shortness of breath (aOR = 1.1, 95% CI 1.0 – 1.3). There were no significant associations observed between any activity shown in Fig. 2 or cumulative exposure and wheezing / whistling in the chest.

Results of the linear regression models for LAA exposure and pulmonary function outcomes, including %FEV1, %FVC, and %FEV1/FVC are presented in the Supplementary Table 1 and Fig. 1. Overall, there were no significant associations observed between estimated LAA exposure, regardless of metric, and decreased lung function. The results of a post-hoc ANOVA comparing %FEV1, %FVC, and %FEV1/FVC by the presence/absence of respiratory symptoms is shown in Supplement Fig. 2. Participants reporting wheezing/whistling in the chest demonstrated significantly reduced %FEV1 compared to those who did not (99% v. 93%, $p < 0.01$). Though not statistically significant, %FEV1was also reduced among participants reporting pleuritic chest

Table 3
Association between participating (ever / never) in activities prior to age 18 with potential LAA exposure and respiratory symptoms.

Activity	n (%)	Pleuritic Chest Pain		Regular Cough		Shortness of Breath		Wheezing / Whistling in the Chest	
		aOR*	(95% CI)	aOR*	(95% CI)	aOR*	(95% CI)	aOR*	(95% CI)
Spending time in attic with visible vermiculite ('Attic')	32 (10.3%)	1.5	(0.6 – 3.5)	1.0	(0.4 – 2.7)	1.5	(0.6 – 3.7)	1.4	(0.6 – 3.6)
Playing in or watching games at the downtown ballfields ('Ball')	198 (63.5%)	0.8	(0.4 – 1.4)	**2.0**	**(1.0 – 4.2)**	1.1	(0.6 – 2.0)	1.2	(0.6 – 2.2)
Playing / digging in the yard ('Dig')	141 (45.2%)	1.4	(0.8 – 2.5)	1.2	(0.6 – 2.2)	**1.9**	**(1.0 – 3.6)**	1.4	(0.8 – 2.7)
Fishing on the Kootenai River near the mouth of Rainy Creek ('Fish')	78 (25.0%)	1.6	(0.8 – 2.9)	**2.1**	**(1.1 – 4.1)**	**2.7**	**(1.4 – 5.2)**	1.6	(0.8 – 3.1)
Gardening ('Gardening')	53 (17.0%)	1.5	(0.7 – 3.0)	0.9	(0.4 – 2.0)	1. 5	(0.7 – 3.1)	1.3	(0.6 – 2.7)
Helping parents install insulation ('Insulation')	16 (5.1%)	1.2	(0.4 – 3.6)	1.9	(0.6 – 6.2)	1.1	(0.3 – 3.7)	0.7	(0.2 – 2.6)
Mowing lawn ('Mow')	138 (44.2%)	0.7	(0.4 – 1.3)	1.8	(0.9 – 3.4)	1.2	(0.7 – 2.2)	1.7	(0.9 – 3.2)
Playing in or around vermiculite piles ('Piles')	140 (44.9%)	1.5	(0.9 – 2.7)	1.5	(0.8 – 2.8)	**2.1**	**(1.1 – 3.9)**	1.3	(0.7 – 2.5)
Playing along the railroad ('Rail')	107 (34.3%)	1.1	(0.6 – 1.9)	1.8	(0.9 – 3.5)	**2.0**	**(1.1 – 3.7)**	1.8	(0.9 – 3.4)
Raking leaves ('Rake')	115 (36.9%)	1.3	(0.7 – 2.3)	1.5	(0.8 – 2.8)	1.5	(0.8 – 2.8)	1.4	(0.8 – 2.7)
Recreational activities (hunting, hiking, etc) along Rainy Creek Road ('Recreation')	107 (34.3%)	**1.9**	**(1.1 – 3.4)**	1.1	(0.6 – 2.2)	**2.8**	**(1.5 – 5.2)**	1.0	(0.5 – 1.8)
Cutting or collecting firewood near Rainy Creek Road ('Wood')	39 (12.5%)	**3.1**	**(1.5 – 6.4)**	1.9	(0.9 – 4.4)	**3.2**	**(1.5 – 6.8)**	**2.2**	**(1.0 – 4.9)**
Heating vermiculite ore to make it expand or pop ('Popping')	98 (31.4%)	**1.8**	**(1.0 – 3.2)**	1.7	(0.9 – 3.2)	1.1	(0.6 – 2.1)	1.0	(0.5 – 1.9)
Share a household with a W.R. Grace worker or contractor	24 (7.7%)	**3.2**	**(1.3 – 7.8)**	0.6	(0.2 – 2.4)	1.5	(0.6 – 4.1)	1.9	(0.7 – 5.1)
Live in a home with indoor visible vermiculite ('Visible')	109 (34.9%)	1.0	(0.5 – 1.7)	1.5	(0.8 – 2.8)	1.0	(0.5 – 1.8)	0.8	(0.4 – 1.6)
Total Number of Activities Reported									
0	27 (8.7%)	–	–	–	–	–	–	–	–
1–3	127 (40.7%)	0.9	(0.3 – 2.6)	1.6	(0.3 – 8.0)	1.8	(0.4 – 8.6)	2.5	(0.5 – 11.9)
4–6	95 (30.5%)	0.9	(0.3 – 3.0)	2.2	(0.5 – 10.8)	2.6	(0.5 – 12.3)	2.8	(0.6 – 13.5)
7–15	63 (20.2%)	1.8	(0.6 – 5.7)	3.6	(0.7 – 17.8)	4.7	(1.0–22.7)	3.1	(0.6 – 15.5)

* Adjusted for sex and smoking history.

pain, regular cough, and shortness of breath. %FEV1/FVC was also significantly lower among participants with regular cough and wheezing compared to participants who did not report these symptoms. No differences in %FVC were observed between participants with and without respiratory symptoms. Analyses comparing participants with pleuritic chest pain to those without any respiratory symptoms found a significantly lower %FEV1 (99% v. 96%, $p = 0.03$), and reduced, though not statistically significant, %FVC (103% v. 101%, $p = 0.20$).

4. Discussion

To our knowledge, this is the first epidemiologic study of the respiratory health of young adults with potential environmental exposure to amphibole asbestos during childhood. Importantly, there were no pleural or interstitial changes on either chest x-ray or HRCT. However, cumulative and activity-specific exposure to LAA was associated with participant-reported respiratory symptoms.

Despite being associated with only two activities, the finding that nearly one-fourth of the cohort (23%) reported pleuritic chest pain is particularly important given that this symptom has previously been identified as an early indicator associated with asbestos exposure but not previously described in an environmentally exposed cohort of young adults. Pleuritic pain, a key feature of pleurisy involving inflammation of the tissue layers lining the lungs and inner chest wall, was among the first symptoms to be reported among workers exposed to LAA in vermiculite ore at a manufacturing facility in Marysville, OH (Lockey et al., 1984). Of note, only 4.4% of the Marysville cohort had radiographic changes at the time of symptom report and initial screening (Lockey et al., 1984). However, in a 30-year follow-up of 191 workers of that cohort, 52.9% had developed pleural changes observed

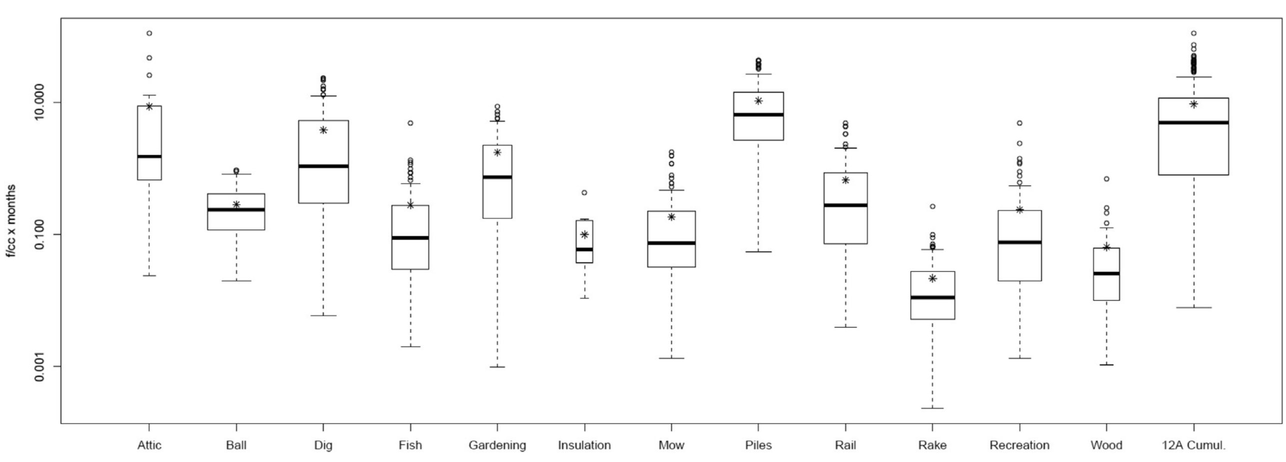

Fig. 1. Distribution of quantitative LAA exposure estimates by activity (among participants reporting ever engaging in activity)* The width of each box plot is proportional to the square root of the sample size, stars represent the mean, solid lines represent the median, boxes indicate the interquartile range (IQR), whiskers extend 1.5 times the IQR, and circles represent values that exceed the 1.5 times the IQR.

Table 4
Association between frequency of participating in activities* with potential LAA exposure and respiratory symptoms.

Activity	n (%)	Pleuritic Chest Pain		Regular Cough		Shortness of Breath		Wheezing / Whistling in the Chest	
		aOR**	(95% CI)	aOR**	(95% CI)	aOR**	(95% CI)	aOR**	(95% CI)
Playing in or watching games at the downtown ballfields ('Ball')									
Sometimes	144 (46.2%)	0.7	(0.4 – 1.3)	1.8	(0.8 – 3.8)	0.9	(0.5 – 1.8)	1.1	(0.6 – 2.2)
Frequently	54 (17.3%)	1.1	(0.5 – 2.4)	**3.0**	**(1.2 – 7.5)**	1.6	(0.7 – 3.6)	1.4	(0.6 – 3.4)
Playing / digging in the yard ('Dig')									
Sometimes	104 (33.3%)	1.6	(0.9 – 3.0)	1.0	(0.5 – 2.0)	**2.4**	**(1.3 – 4.6)**	1.5	(0.8 – 3.0)
Frequently	37 (11.9%)	0.9	(0.4 – 2.2)	1.7	(0.7 – 4.2)	0.8	(0.3 – 2.5)	1.2	(0.5 – 3.1)
Fishing on the Kootenai River near the mouth of Rainy Creek ('Fish')									
Sometimes	58 (18.6%)	1.8	(0.9 – 3.5)	1.6	(0.7 – 3.5)	**2.5**	**(1.2 – 5.1)**	1.6	(0.8 – 3.4)
Frequently	20 (6.4%)	1.0	(0.3 – 3.2)	**4.0**	**(1.4 – 11.61**	**3.3**	**(1.2 – 9.5)**	1.5	(0.5–4.7)
Gardening ('Gardening')									
Sometimes	38 (12.2%	1.0	(0.4 – 2.4)	0.9	(0.4 – 2.4)	1.1	(0.4 – 2.7)	0.9	(0.4 – 2.4)
Frequently	15 (4.8%)	**3.0**	**(1.0 – 9.2)**	0.8	(0.2 – 3.1)	2.5	(0.8 – 7.7)	2.2	(0.7 – 7.2)
Playing in or around vermiculite piles ('Piles')									
Sometimes	105 (33.7%)	1.2	(0.7 – 2.3)	1.2	(0.6 – 2.5)	1.5	(0.8 – 3.0)	1.0	(0.5 – 2.0)
Frequently	35 (11.2%)	**2.5**	**(1.1 – 5.8)**	2.3	(0.9 – 5.7)	**4.3**	**(1.8 – 10.1)**	**2.4**	**(1.0 – 5.6)**
Playing along the railroad ('Rail')									
Sometimes	78 (25.0%)	1.1	(0.6 – 2.1)	1.5	(0.7 – 3.2)	**2.3**	**(1.2 – 4.5)**	1.8	(0.9 – 3.5)
Frequently	29 (9.3%)	1.0	(0.4 – 2.6)	**2.9**	**(1.1 – 7.8)**	1.3	(0.5 – 3.6)	1.9	(0.7 – 5.1)
Raking leaves ('Rake')									
Sometimes	84 (26.9%)	1.7	(0.9 – 3.1)	1.6	(0.8 – 3.2)	1.7	(0.9 – 3.3)	**2.0**	**(1.0 – 3.9)**
Frequently	31 (9.9%)	0.6	(0.2 – 1.8)	1.2	(0.5 – 3.4)	1.0	(0.4 – 2.8)	0.5	(0.2 – 1.6)
Recreational activities (hunting, hiking, etc) along Rainy Creek Road ('Recreation')									
Sometimes	80 (25.6%)	**1.9**	**(1.0 – 3.6)**	0.9	(0.4 – 1.9)	**2.6**	**(1.3–5.0)**	0.9	(0.4 – 1.8)
Frequently	27 (8.7%)	1.9	(0.8 – 4.7)	1.9	(0.7 – 5.2)	**3.5**	**(1.4 – 8.9)**	1.2	(0.4 – 3.2)
Heating vermiculite ore to make it expand or pop ('Popping')									
Sometimes	73 (23.4%)	1.6	(0.8 – 3.0	1.0	(0.5 – 2.3)	0.82	(0.4 – 1.7)	0.8	(0.4 – 1.6)
Frequently	25 (8.0%)	**2.7**	**(1.1 – 7.095)**	**4.8**	**(1.8 – 12.8)**	2.40	(0.9–6.2)	1.8	(0.6 – 4.9)

* For those activities with > 5% of the cohort reporting frequently participating.
** Adjusted for sex and smoking history.

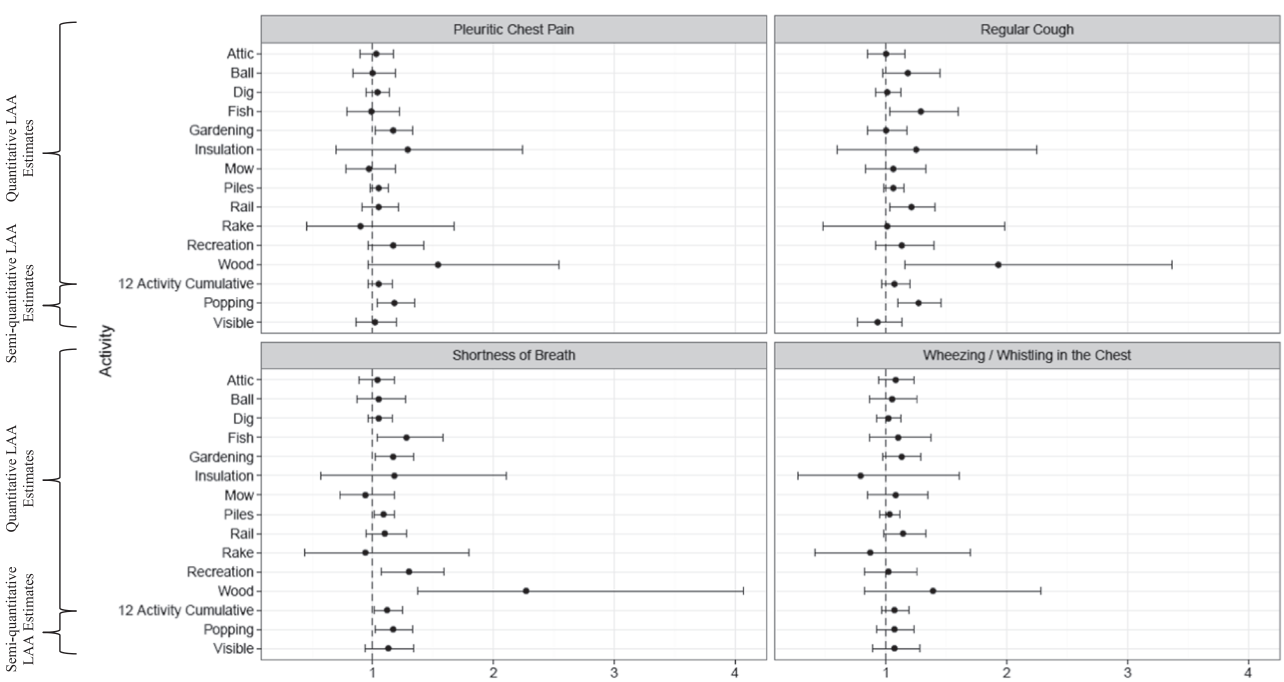

Fig. 2. Adjusted* odds ratios and 95% confidence intervals between estimates of LAA exposure due to activities with potential LAA exposure** and respiratory symptoms.

by HRCT and three had developed mesothelioma (Lockey et al., 2015; Dunning et al., 2012). While we did not observe radiographic abnormalities nor decreases in pulmonary function among CHIEFS participants, they were, on average, more than 10 years younger than the initial Marysville cohort and occupational exposures were likely more consistent than intermittent environmental exposures as described in the CHIEFS cohort. Thus, the presence of pleuritic chest pain among 23% of a young adult population may represent an early harbinger for future development of pleural disease.

A potential mechanism by which LAA exposure results in pleuritic chest pain is inflammation of the pleura surface as a direct or indirect result of chest wall or lung parenchymal deposition. LAA has also been linked to autoimmune diseases, including systemic lupus erythematosus, scleroderma, and rheumatoid arthritis among Libby residents (Noonan et al., 2006). Pleurisy and pleural effusions and thickening are common manifestations of certain autoimmune disorders, particularly rheumatoid arthritis and systemic lupus erythematosus (Olson et al., 2012). Mesothelial cell autoantibodies from Libby residents have been significantly correlated with pleural disease through increased collagen deposition, and this may result in pleural fibrosis (Serve et al., 2013). In a case series of 5 individuals who had predominately severe pleuritic chest pain and rapidly progressive pleural disease, it was postulated that an autoimmune reaction to LAA dust exposure possibly accounted for the findings (Black et al., 2014). Among another cohort of 615 silica exposed workers (mean age 67), the prevalence of chest pain among those with asbestosis, silicosis and diffuse pleural thickening was 33%, 46% and 42%, respectively, compared to 22% in an older dust exposed worker population (Park et al., 2011).

Among the strengths of our analysis is the exposure assessment methodology that expands upon prior qualitative and semi-quantitative approaches to environmental LAA exposure assessment based on participant report of the frequency of engaging in occupational and environmental exposure activities. We found that heating vermiculite, fishing on the Kootenai River, and engaging in activities along or near Rainy Creek Road were consistently associated with respiratory symptoms among CHIEFS participants. Rainy Creek Road was the primary route for transporting vermiculite ore from the mine site, and asbestos concentrations in soil up to 5% have been reported in the area prior to cleanup (Weis, 2001). An uncovered conveyor belt transporting ore over the Kootenai River to railcars was an additional source of contamination in the area. These findings are consistent with an analysis of 1003 ATSDR medical screening participants who were between 10 and 29 years of age at the time of ATSDR screening (Vinikoor et al., 2010). Similar to our results, this previous study identified frequent handling of vermiculite insulation, participation in recreational activities along Rainy Creek Road, and heating vermiculite to make it expand or pop as exposure pathways associated with respiratory symptoms including cough, shortness of breath, and bloody phlegm (Vinikoor et al., 2010).

Our study results may be applicable to other locations with potential non-occupational exposure to LAA including the vicinity of exfoliation plants (Schneider and McCumber, 2016). One such expansion facility is located in Minnesota where exposure to amphibole fibers was significantly associated with increased risk of radiographic abnormalities (Alexander et al., 2012). In this study, playing in piles and ambient air concentrations were major contributors to exposure. Playing in piles was reported by 39.0% of study participants in Minnesota compared to 45.4% of the CHIEFS population. Comparison of our exposure estimates for this activity to the Minnesota study shows the 75th percentile of cumulative exposure for CHIEFS participants was approximately 10-fold higher, 5.726 vs 0.549 f/cc – months. These higher cumulative exposure estimates may be due to the availability of numerous contaminated piles in Libby, increased frequency and duration with which the activity was reported among CHIEFS participants, differences in the exposure assessment approach, including the use of Monte Carlo simulation in the Minnesota study, or recall bias.

There are some limitations to our study that should be considered. First, the characterization of LAA exposure is based on participant report of the frequency, duration, and age of engaging in activities with potential exposure. Some error in recall is expected to be present, especially at younger ages. In an effort to minimize this recall bias we utilized the EPA's CHAD to make assumptions regarding realistic minimum ages and frequencies at which CHIEFS participants may have engaged in specific activities. Nevertheless, the potential for recall bias to result in differential exposure misclassification exists. However, the lack of any activity associated with wheezing and the consistent association between activities along Rainy Creek and respiratory symptoms provides some evidence that recall bias is not solely responsible for the study findings. It is also possible that the high prevalence of pleuritic chest pain reported by study participants is due to awareness that LAA exposure has occurred in Libby. However, given the potential importance of this symptom and previous studies suggesting that pleuritic chest pain is an early symptom of LAA exposure prior to radiographic findings we believe continued follow-up is indicated. It was not possible to conduct personal or area-based sampling to characterize exposure and therefore our exposure estimates rely upon on results from simulations of each activity. Therefore, the estimates for activities with potential LAA may over- or underestimate a participant's true exposure. However, the estimates used in this study were based on the sources cited and were made without knowledge of the participant's health status. Two potentially important activities related to exposure, heating vermiculite and living in a home with a W.R. Grace worker or contractor could not be quantitatively characterized due to lack of data. It would be useful to conduct simulation studies of popping, reported by one-third of the cohort and consistently linked to respiratory outcomes. Finally, it is possible that the odds ratios calculated using logistic regression overestimate the risk for some outcomes with higher prevalence.

Despite these limitations, the study has several strengths. We used EPA pre-remediation data to characterize exposure. When possible, data regarding the presence of visible vermiculite outside the residence of CHIEFS participants prior to remediation was also incorporated into our exposure estimates as previously described (Ryan et al., 2015). Given previous research indicating increasing health effects with additional latency in LAA exposed workers (Lockey et al., 2015), it is notable that the extensive clinical exams of residents during young adulthood provides an important baseline upon which future health outcomes can be compared.

In conclusion, our results suggest that childhood environmental exposures to LAA occurring prior to and after mining operations ceased are associated with respiratory symptoms among young adults. Of note is the high prevalence of self-reported pleuritic chest pain which was previously identified as an early symptom associated with cumulative fiber exposure in the Marysville, OH occupational cohort (Lockey et al., 1984) and warrants continued follow-up and surveillance of these young adults. The impact of this research also extends beyond Libby as raw ore was shipped to more than 200 facilities throughout the U.S. with potential occupational and environmental exposures occurring at these locations and homes throughout the U.S. containing insulation with vermiculite from the Libby, MT mine.

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Competing financial interests

The authors declare they have no competing financial interests.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.bios.2014.05.063.

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