ORIGINAL RESEARCH

Work-related adverse respiratory health outcomes at a machine manufacturing facility with a cluster of bronchiolitis, alveolar ductitis and emphysema (BADE)

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ABSTRACT

Objectives Four machine manufacturing facility workers had a novel occupational lung disease of uncertain aetiology characterised by lymphocytic bronchiolitis, alveolar ductitis and emphysema (BADE). We aimed to evaluate current workers' respiratory health in relation to job category and relative exposure to endotoxin, which is aerosolised from in-use metalworking fluid.

Methods We offered a questionnaire and spirometry at baseline and 3.5 year follow-up. Endotoxin exposures were quantified for 16 production and non-production job groups. Forced expiratory volume in one second (FEV_1) decline ≥10% was considered excessive. We examined SMRs compared with US adults, adjusted prevalence ratios (aPRs) for health outcomes by endotoxin exposure tertiles and predictors of excessive FEV_1 decline.

Results Among 388 (89%) baseline participants, SMRs were elevated for wheeze (2.5 (95% CI 2.1 to 3.0)), but not obstruction (0.5 (95% CI 0.3 to 1.1)). Mean endotoxin exposures (range: 0.09–28.4 EU/m^3) were highest for machine shop jobs. Higher exposure was associated with exertional dyspnea (aPR=2.8 (95% CI 1.4 to 5.7)), but not lung function. Of 250 (64%) follow-up participants, 11 (4%) had excessive FEV_1 decline (range: 403–2074 mL); 10 worked in production. Wheeze (aPR=3.6 (95% CI 1.1 to 12.1)) and medium (1.3–7.5 EU/m^3) endotoxin exposure (aPR=10.5 (95% CI 1.3 to 83.1)) at baseline were associated with excessive decline. One production worker with excessive decline had BADE on subsequent lung biopsy.

Conclusions Lung function loss and BADE were associated with production work. Relationships with relative endotoxin exposure indicate work-related adverse respiratory health outcomes beyond the sentinel disease cluster, including an incident BADE case. Until causative factors and effective preventive strategies for BADE are determined, exposure minimisation and medical surveillance of affected workforces are recommended.

Key messages

What is already known about this subject?

- A cluster of lymphocytic bronchiolitis, alveolar ductitis and emphysema (BADE) at a machine manufacturing facility indicated a previously unrecognised occupational lung disease.

What are the new findings?

- Among current workers, exposure-related respiratory symptoms, lung function loss and incident BADE highlight an ongoing risk of this novel lung disease and a burden of work-related respiratory illness beyond the sentinel cluster.

How might this impact on policy or clinical practice in the foreseeable future?

- Additional cases of BADE at this or similar manufacturing facilities merit investigation, including spirometric surveillance of co-workers, to better understand aetiology and prevent disease.

INTRODUCTION

In 2012, a National Institute for Occupational Safety and Health (NIOSH) health hazard evaluation at a manufacturing facility identified a cluster of relatively young never-smokers with lung disease. From 1995 to 2007, four workers noted insidious onset of cough, wheeze and exertional dyspnea. Each reported symptom exacerbation related to work. Lung function testing revealed obstruction and decreased diffusing capacity. Chest CT showed centrilobular emphysema.[1] Examination of lung tissue specimens revealed a distinctive histopathologic pattern characterised as B-cell lymphocytic bronchiolitis, alveolar ductitis and emphysema (BADE). The evaluation concluded the cases represented a previously unrecognised occupational lung disease.[2]

The cause of the lung disease was unclear. The facility produced large industrial machines. All four cases occurred in the facility's production areas, which comprised a machine shop, welding rooms, paint booths and an assembly area where components were pieced together. In the machine shop, steel (85%–90% of production volume), aluminium (10%–15%), cast iron (<1%) and plastics (<1%) were cut using saws, pressurised water and plasma technology. Cut materials were machined by grinders, mills and lathes that used one of two water-based metalworking fluids for cooling and

lubrication. Since the early 1990s, most machines used a non-preserved (without antibacterial biocides) mineral oil-based fluid reportedly designed, through its constituents, to promote the growth of *Pseudomonas pseudoalcaligenes*.[3] Less commonly, a preserved (with antibacterial biocides) synthetic fluid was used. Mist collectors were introduced in the late 1990s and installed on many but not all machines. Filtered air from the mist collectors was returned into the machine shop space. An administrative area was separate from production areas. At time of symptom onset, the workers with lung disease worked primarily in the machine shop or assembly area.[2] Airflow during tracer gas testing indicated the machine shop as an exposure source for the assembly area.[2]

A 2013 industrial hygiene evaluation included measurement of airborne contaminants.[2] Exposures to metals on area air sampling were low, with more than one-half of samples having concentrations below detection limits and none approaching occupational exposure limits. Similarly, concentrations of volatile organic compounds on area air sampling were orders of magnitude below existing exposure limits. Personal thoracic aerosol concentrations ranged from below detection limits in 4% of production worker samples to a maximum of 1.58 mg/m^3. Personal thoracic metalworking fluid exposures ranged from below detection limits in 43% of production worker samples to 0.32 mg/m^3, which approached but did not exceed the NIOSH recommended exposure limit of 0.4 mg/m^3. Personal airborne concentrations of endotoxin, a cell wall component of Gram-negative bacteria that can become aerosolised when colonised metalworking fluid is sprayed,[4] were detectable in 97% of production worker samples. Endotoxin concentrations exceeded the Dutch exposure limit of 90 EU/m^3 in two machine shop worker samples and were measurable in samples collected from workers in all other areas of the facility.[5]

The microbial communities of bulk metalworking fluids were assessed in 2012 and 2013 using culture and non-culture methods.[2] Culture of in-use non-preserved metalworking fluid was predominated by *P. pseudoalcaligenes*, with concentrations up to 10^9 CFU/mL. In-use preserved metalworking fluid grew Gram-negative and Gram-positive species at concentrations up to 10^6 CFU/mL. Both types of in-use metalworking fluid had lower concentrations of culturable fungi (maximum 10^3 CFU/mL) and no evidence of mycobacterial DNA by PCR testing. In addition, 16S ribosomal RNA sequencing, a technique that detects the presence of both culturable and non-culturable bacteria, revealed that both the preserved and non-preserved metalworking fluid had more complex bacterial communities than suggested by culture.

BADE is marked by proliferation of B cell lymphoid follicles in the distal airways. Bronchus-associated lymphoid tissue (BALT) is not normally present in the adult lung, but can be induced by persistent exposure to antigens.[6 7] BALT has been observed in some cases of infection, hypersensitivity pneumonitis, severe chronic obstructive pulmonary disease and autoimmune disease, and with experimental exposure to endotoxin and to cigarette smoke.[7–12] Thus, we hypothesised that exposure to bioaerosols from metalworking fluid enriched with bacteria played a pathogenic role in BADE.

Workplace lung disease clusters can serve as a sentinel for respiratory abnormalities among co-workers.[13–16] To determine whether additional cases of BADE could have occurred at the facility and if risk was ongoing, we evaluated the burden of clinical and functional abnormalities among the current workforce. To inform preventive efforts, we also assessed relationships between respiratory health and endotoxin exposure as a marker of metalworking fluid bioaerosols.

METHODS

The investigation was conducted according to NIOSH Institutional Review Board requirements for health hazard evaluations. In 2013, we offered all current workers a questionnaire and spirometry. The interviewer-administered questionnaire addressed respiratory, dermatologic, and systemic symptoms, asthma and other diagnoses, smoking history, work history and demographic information. The respiratory questions were adapted from validated survey instruments.[17–19] Work-related symptoms were defined as those that improved away from the workplace. Participants still employed at the facility 3.5 years later in 2016 were offered an additional assessment that included spirometry. Spirometry was conducted and interpreted according to published guidelines using a dry rolling-seal spirometer and national reference values.[20–22] We considered tests with ≥2 acceptable trials and forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) values within 250 mL to be interpretable. We used per cent predicted FEV_1 to classify spirometric abnormalities as mild (≥70%), moderate (60%–69%), moderately severe (50%–59%), severe (35%–49%) and very severe (<35%).[22] All participants provided written informed consent. Following the evaluation, we mailed reports to each participant at his or her home address. The reports explained individual results and provided recommendations for follow-up of abnormalities.

In 2013, we measured endotoxin levels in 101 personal air samples using the kinetic chromogenic *Limulus* amoebocyte lysate assay.[23] We developed a job group-endotoxin exposure matrix and assigned each participant an endotoxin exposure using the minimum variance unbiased estimator of the job group arithmetic mean concentration.[24] We addressed measurements below the limit of detection (n=3) with the Tobit regression method.[25] Participants were then grouped into relative low, medium and high endotoxin exposure categories using distributional tertiles.

We calculated SMRs of symptoms, diagnoses and spirometric abnormalities from comparisons with the US adult population using indirect standardisation for race/ethnicity (white, black or Mexican-American), sex, age (<40 years or ≥40 years) and cigarette smoking status (current, former or never).[19] Exposure groups were compared using χ^2 and Cochran-Armitage trend tests for binomial outcomes and the Kruskal-Wallis test and analysis of variance for continuous outcomes. Final linear models were adjusted for smoking and age (continuous). We calculated decline in FEV_1 using the longitudinal normal limit, which accounts for the expected change with ageing, and defined decline ≥10% as excessive.[26 27] We used prevalence ratio regression (PROC GENMOD in SAS with binomial distribution and log link) to examine relationships between excessive decline in FEV_1 as a dichotomous variable and participants' baseline symptoms and exposure characteristics, adjusted for smoking.

Statistical analyses were conducted using SAS software V.9.4 (SAS Institute, Inc).

RESULTS

A total of 388 (89%) current workers, including two sentinel patients with BADE, participated in the baseline health evaluation in 2013 (table 1, first column). Most participants were male (91%) and white (95%), with median age of 43 years. Median facility tenure was 14 years. About two-thirds (65%) worked in production jobs. The majority (68%) had never smoked.

Table 1 Baseline demographic, occupational, clinical and functional characteristics of participating current workers, overall and by endotoxin exposure

		Endotoxin exposure group			
		Low	Medium	High	
	Overall	<1.3 EU/m^3	1.3–7.5 EU/m^3	>7.5 EU/m^3	P value*
Questionnaire, n (%)†	388 (100)	148 (38)	115 (30)	125 (32)	
Age (years)	43 (19–65)	44 (21–64)	44 (20–65)	40 (19–64)	ns
Male	353 (91)	121 (82)	112 (97)	120 (96)	<0.0001
White race	370 (95)	146 (99)	107 (93)	117 (94)	0.04
Facility tenure (years)	14 (<1–40)	13 (<1–37)	16 (1–35)	14 (<1–40)	ns
Current production job	253 (65)	13 (9)	115 (100)	125 (100)	<0.0001
Smoking status					0.09
Current	34 (9)	6 (4)	15 (13)	13 (10)	
Former	89 (23)	36 (24)	22 (19)	31 (25)	
Never	265 (68)	106 (72)	78 (68)	81 (65)	
Dyspnea	49 (13)	10 (7)	15 (13)	24 (19)	0.002
Cough	47 (12)	10 (7)	18 (16)	19 (15)	0.03
Wheeze	129 (33)	40 (27)	44 (38)	45 (36)	0.10
Asthma symptoms	150 (39)	45 (30)	52 (45)	53 (42)	0.04
Flu-like illness	39 (10)	7 (5)	11 (10)	21 (17)	0.001
Nasal symptoms	276 (71)	103 (70)	79 (69)	94 (75)	ns
Eye symptoms	123 (32)	44 (30)	30 (26)	49 (39)	ns
Rash	47 (12)	11 (7)	15 (13)	21 (17)	0.02
WR dyspnea	17 (4)	1 (1)	6 (5)	10 (8)	0.003
WR cough	21 (5)	3 (2)	7 (6)	11 (9)	0.01
WR wheeze	33 (9)	3 (2)	13 (11)	17 (14)	0.0005
WR asthma symptoms	38 (10)	4 (3)	15 (13)	19 (15)	0.0004
WR flu-like illness	15 (4)	0	4 (4)	11 (9)	0.0002
WR nasal symptoms	54 (14)	9 (6)	14 (12)	31 (25)	<0.0001
WR eye symptoms	31 (8)	7 (5)	9 (8)	15 (12)	0.03
WR rash	9 (2)	0	0	9 (7)	0.0001
Asthma, past or current	36 (9)	15 (10)	14 (12)	7 (6)	ns
Asthma, current	23 (6)	10 (7)	9 (8)	4 (3)	ns
Hay fever	80 (21)	39 (26)	20 (17)	21 (17)	0.05
Spirometry, n (%)‡	375 (100)	142 (38)	110 (29)	123 (33)	
FEV_1, % predicted	102 (46–147)	103 (63–144)	100 (46–129)	102 (46–147)	ns
FVC, % predicted	104 (65–139)	104 (83–131)	103 (70–129)	104 (65–139)	ns
FEV_1/FVC, %	78 (41–96)	78 (48–96)	76 (41–96)	79 (53–93)	0.05
Obstruction	5 (1)	3 (2)	1 (1)	1 (1)	ns
Restrictive pattern	6 (2)	0	4 (4)	2 (2)	ns
Mixed pattern	3 (1)	0	1 (1)	2 (2)	ns
Any abnormality	14 (4)	3 (2)	6 (5)	5 (4)	ns

*P values reflect comparison of the three endotoxin exposure groups using χ^2 and Cochran-Armitage trend tests for categorical variables and the Kruskal-Wallis test and analysis of variance for continuous variables. P values ≤0.05 were considered significant; p values ≤0.10 are presented.
†Data are presented as median (range) or n (%). Symptoms were in the last 12 months, with the exception of dyspnea and cough. Asthma symptoms were defined as at least one of the following: current use of asthma medicine, wheezing or whistling in the chest in the last 12 months, awakening with a feeling of chest tightness in the last 12 months, attack of asthma in the last 12 months.[18] Participants were considered to have flu-like illness if they answered 'yes' to the following question: 'In the last 12 months, have you had a recurring flu-like illness such as fevers, chills, aches, and tiredness?'.
‡Data are presented as mean (range) or n (%). Obstruction = FEV_1 and FEV_1/FVC below their respective lower limits of normal (fifth percentiles) with a normal FVC. Restrictive pattern=normal FEV_1/FVC ratio with FVC below the lower limit of normal. Mixed pattern = FEV_1/FVC and FVC below their respective lower limits of normal.
EU, endotoxin units; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; ns, non-significant; WR, work-related.

Nasal symptoms were most commonly reported, with a prevalence of 71% (table 1, first column). Wheeze was the most common chest symptom, with a prevalence of 33%. Thirteen per cent of participants reported dyspnea when hurrying on level ground or walking up a slight hill. Recurring flu-like illness was least common, with a prevalence of 10%. A work-related pattern was described for 19%–45% of symptoms. Doctor-diagnosed asthma was reported by 9% of participants; 6% reported current asthma.

Spirometry was interpretable in 375 of 376 participants tested. FEV_1 was repeatable within 100–150 mL in 76 (20%) and within 100 mL in 297 (79%). Mean per cent predicted FEV_1 and per cent predicted FVC exceeded 100% (table 1, first column). Mean FEV_1/FVC ratio was 78%. Fourteen (4%) participants had a spirometric abnormality.

Table 2 Standardised morbidity ratios for baseline symptoms, self-reported diagnoses and spirometric abnormalities of participating current workers

	Observed (n)	Expected* (n)	SMR† (95% CI)
Symptom or diagnosis (n=388)			
Dyspnea	49	53.7	0.9 (0.7 to 1.2)
Wheeze	**129**	**51.5**	**2.5 (2.1 to 3.0)**
Nasal symptoms	**276**	**219.2**	**1.3 (1.1 to 1.4)**
Eye symptoms	**123**	**150.4**	**0.8 (0.7 to 1.0)**
Asthma, past or current	36	28.4	1.3 (0.9 to 1.8)
Asthma, current	23	16.3	1.4 (0.9 to 2.1)
Hay fever	**80**	**54.0**	**1.5 (1.2 to 1.8)**
Spirometric abnormality (n=375)			
Obstruction (including mixed pattern)	8	14.7	0.5 (0.3 to 1.1)
Restrictive pattern	**6**	**25.1**	**0.2 (0.1 to 0.5)**

*Expected values derived from the Third National Health and Nutrition Examination Survey.[19]
†Statistically significant SMRs and 95% CIs are in bold.

SMRs are displayed in table 2. Participants had higher than expected prevalence of wheeze, nasal symptoms and hay fever compared with US adults. Spirometric abnormalities were less common than expected.

We calculated mean endotoxin exposures for 15 productions job groups and one non-production job group using 1–47 samples per job group (table 3). Production job groups fell under assembly (n=1), machine shop (n=5) and other production (n=9). Mean endotoxin exposures ranged from 0.1 EU/m^3 for welding fabrication to 28.4 EU/m^3 for new machine shop. Participants with endotoxin exposures <1.3 EU/m^3 were categorised as low exposure, those with endotoxin exposures of 1.3–7.5 EU/m^3 as medium exposure and those with endotoxin exposures >7.5 EU/m^3 as high exposure (table 1). Male sex, white race and current production job were associated with exposure (table 1).

Table 3 Job group-endotoxin exposure matrix used to assign exposures to participating current workers

		Endotoxin concentration (EU/m^3)	
Job group	**Samples (n)**	**Range**	**Mean**
Production			
Assembly	26	0.04–8.20	3.95
Machine shop			
CNC department	18	0.75–116	18.1
Machine shop general*	47	0.75–116	19.9
Machine shop help	3	1.05–15.3	6.69
New machine shop	15	1.86–94.9	28.4
Old machine shop	11	4.49–55.9	12.2
Other production			
CNC programming	2	0.75–7.61	3.24
CNC tool crib	2	13.2–13.5	13.4
Deburr/paint	1	3.39	3.39
Expediting	3	5.75–24.2	12.0
Heavy welding	3	0.43–1.09	0.85
Janitorial	2	7.93–13.9	10.7
Maintenance	3	6.75–8.91	7.51
Parts room	2	3.88–7.81	5.68
Welding fabrication	2	0.04–0.23	0.09
Non-production			
Administration	8	0.17–3.58	1.26

*This job group covered machine shop jobs not localised to one area of the machine shop. All 47 samples from the four other machine shop job groups shown were used to calculate the mean endotoxin concentration.
CNC, computer numerical control; EU, endotoxin units.

In unadjusted analyses, dyspnea, cough, asthma symptoms, flu-like illness, rash and all work-related symptoms were positively associated with endotoxin exposure (table 1). Most of these associations remained significant in adjusted analyses (figure 1). Dyspnea was nearly three-fold more common in participants exposed to high compared with low endotoxin levels (adjusted prevalence ratio=2.8; 95% CI 1.4 to 5.7). Mean FEV_1/FVC ratio was lower among participants in the medium (76%) versus low (78%) exposure category (table 1), but this difference was not statistically significant after accounting for age (p=0.09). Spirometric parameters and abnormalities were otherwise not associated with endotoxin exposure (table 1).

A total of 250 (64%) participants, including 159 production workers, had repeat spirometry in 2016. All tests were interpretable; FEV_1 was repeatable within 100–150 mL in 47 (19%) and within 100 mL in 201 (80%). Eleven (4%) had excessive decline in FEV_1, with losses of 403—2074 mL; eight were never-smokers and eight had normal baseline spirometry. At follow-up, four still had normal spirometry and four had developed new mild (n=3) or severe (n=1) abnormalities. In addition, two with abnormal baseline spirometry progressed from mild to severe and from moderately severe to severe. Among the 11 with excessive decline in FEV_1, the prevalence of chest symptoms at baseline and follow-up was: 18% and 55% for dyspnea, 18% and 36% for cough, 64% and 55% for wheeze and 64% and 64% for asthma-like symptoms.

All but one with excessive decline in FEV_1 worked in production areas: six in assembly, two in the machine shop and two in other production areas. One production worker with excessive decline in FEV_1 of more than 2 L underwent a clinical evaluation including surgical lung biopsy and was found to have BADE; clinical details were previously described.[2] Baseline characteristics associated with excessive decline in FEV_1 were wheeze, work-related wheeze, work-related asthma symptoms, work-related nasal symptoms, past or current asthma diagnosis and medium endotoxin exposure (table 4).

DISCUSSION

We evaluated a manufacturing facility with four cases of BADE, a novel occupational lung disease. At baseline, current workers had an excess burden of wheeze and associations between chest symptoms and airborne endotoxin exposure. Through follow-up spirometry 3.5 years later, we found that most participants with excessive decline in FEV_1 were production workers; one of these proved to be a fifth BADE case. These findings demonstrate adverse respiratory health outcomes including BADE beyond the original sentinel cases at this facility.

The sentinel cases of BADE were notable for the severity of their clinical and functional abnormalities, with bilateral lung transplantation in one case to date.[2] In the context of a workplace cluster of severe lung disease, we aimed to determine the extent of respiratory impairment in the workforce and identify any other clinical cases of disease. On our baseline evaluation, we found that functional abnormalities were less common than expected, with just 4% of participants having a spirometric abnormality of any kind. Additional cases of unexplained severe lung disease were not apparent.

Nonetheless, our findings at baseline indicated adverse respiratory health effects beyond the sentinel cases that could represent additional cases of BADE, or a spectrum of occupational

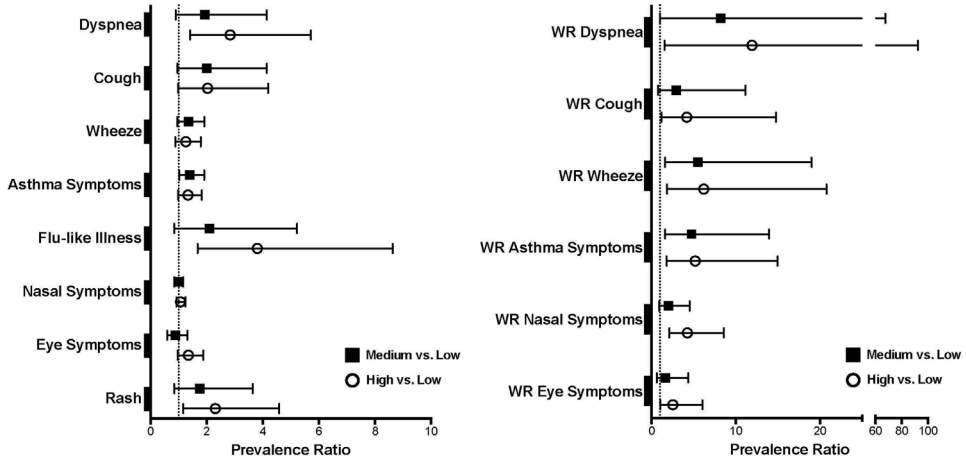

Figure 1 General symptoms (left) and work-related (WR) symptoms (right) by endotoxin exposure. Graphs show prevalence ratios (squares and circles) and 95% CIs (lines) from models using the low endotoxin exposure group as the referent, adjusted for smoking status and age. The dotted vertical lines indicate unity. Prevalence ratios for work-related flu-like illness and work-related rash could not be calculated, as these symptoms were not reported by participants in the low endotoxin exposure group.

respiratory disease including recognised health effects of metalworking fluids.[4] Current workers reported more wheeze and nasal symptoms than expected. A work-related pattern, with improvement away from the workplace, was described for many symptoms. Dyspnea and other symptoms, but not lung function, were associated with workplace endotoxin exposures. These disparate results for clinical versus functional outcomes and endotoxin are notable, and could reflect reversible irritant effects of exposure to endotoxin and associated components of metalworking fluid[28] or other unmeasured production-related respiratory irritants. In past investigations, metal workers more highly exposed to metalworking fluid have consistently reported more symptoms.[4] Another explanation for disparate results is that spirometry is insensitive for bronchiolar dysfunction, so it is possible that small airways disease (from BADE or metalworking fluid-associated asthma or hypersensitivity pneumonitis) not detected by spirometry was present in the workforce.[29–32] The facility did not have a medical surveillance programme with spirometry in place, so we were unable to determine if workers with symptoms but normal spirometry at our baseline evaluation had stable lung function or had experienced functional declines within the normal range during employment.

Table 4 Smoking-adjusted prevalence ratios of excessive decline in FEV_1 over 3.5 years of follow-up by participating current workers' baseline symptoms, self-reported diagnoses and endotoxin exposure (n=250)

Baseline characteristic	Prevalence ratio (95% CI)	P value*
Symptom		
Dyspnea	1.9 (0.4 to 8.3)	ns
Cough	2.1 (0.5 to 9.1)	ns
Wheeze	3.6 (1.1 to 12.1)	0.04
Asthma symptoms	2.8 (0.8 to 9.5)	0.09
Flu-like illness	1.9 (0.4 to 8.3)	ns
Nasal symptoms	0.5 (0.2 to 1.7)	ns
Eye symptoms	0.5 (0.1 to 2.3)	ns
Rash	2.7 (0.8 to 9.6)	ns
WR dyspnea	2.0 (0.3 to 14.1)	ns
WR cough	1.8 (0.2 to 13.0)	ns
WR wheeze	4.2 (1.2 to 14.4)	0.02
WR asthma symptoms	3.7 (1.1 to 13.0)	0.04
WR flu-like illness	–†	–†
WR nasal symptoms	4.6 (1.5 to 14.4)	0.008
WR eye symptoms	1.1 (0.2 to 8.3)	ns
WR rash	3.8 (0.5 to 26.3)	ns
Diagnosis		
Asthma, past or current	4.0 (1.1 to 14.8)	0.03
Asthma, current	1.7 (0.2 to 13.1)	ns
Hay fever	2.4 (0.7 to 8.0)	ns
Endotoxin exposure		
Medium versus low	10.5 (1.3 to 83.1)	0.03
High versus low	3.8 (0.4 to 35.8)	ns

*P values ≤0.05 were considered significant; p values ≤0.10 are presented.
†Unable to calculate due to cell with n=0.
EU, endotoxin units; ns, non-significant; WR, work-related.

Given the risk of evolving lung disease in this workforce, we conducted a follow-up evaluation 3.5 years later. We identified 11 current workers whose FEV_1 had fallen at least 10%, after accounting for ageing. Although a 15% threshold for FEV_1 decline is standard in clinical practice,[22] we chose to use a 10% threshold for epidemiologic analyses because of the high quality of our spirometry.[27] The elevated baseline prevalence of chest symptoms and the increases over time in dyspnea and cough for those meeting the 10% threshold reinforce the relevance of this approach. These analyses identified risk factors for excessive decline in FEV_1 including baseline wheeze and past or current asthma diagnosis. Decline in FEV_1 is not specific to a particular lung disease. It is possible that in at least some workers, these associations reflect progression of uncontrolled asthma or other airways disease unrelated to work, rather than development of occupational lung disease. Still, occupational contributions to the lung function losses we observed are demonstrated by the fact that all but one of the participants with excessive decline worked in production areas, and by the associations between excessive decline and several work-related chest symptoms. Furthermore, one production worker with excessive decline in FEV_1 subsequently was found to have BADE.[2] It is possible that additional cases of BADE or other occupational lung disease occurred among those with excessive decline in FEV_1, but we do not know whether others pursued clinical care or were diagnosed with lung disease after our follow-up evaluation.

We found that participants in the medium endotoxin exposure group had a 10-fold higher prevalence of excessive decline in FEV_1 compared with the low exposure group. However, for the high exposure group, the prevalence ratio was lower (3.8) and the difference was not statistically significant. This pattern reflects that six of the 11 participants with excessive decline in FEV_1 were in the assembly job group, categorised as medium exposure. In contrast, the prevalence of endotoxin-associated symptoms tended to be highest in the high exposure group. It is possible that the relationships between health outcomes and endotoxin were impacted by a healthy worker survivor effect, whereby more highly exposed workers become ill and leave employment.[33] This phenomenon would tend to lower the prevalence of adverse health outcomes in the high exposure group and might disproportionately affect analyses of lung function loss, an outcome that was substantially less frequent than were most symptoms. Indeed, there is evidence of a healthy worker effect, in that two of the sentinel patients with BADE had high exposure jobs but left employment before our evaluation because of respiratory impairment.[2] Ongoing monitoring of the workforce, including those who leave employment, could help clarify the relationship of endotoxin exposure to lung function loss and BADE.

In our analyses, we considered endotoxin exposure as a marker of metalworking fluid bioaerosols more generally, which allowed us to group participants by job using an objective metric. Nonetheless, the associations between some health outcomes and endotoxin exposure among current workers could be caused by direct effects of endotoxin itself. Inhalation of high concentrations of endotoxin has been shown to cause respiratory inflammation, respiratory symptoms and FEV_1 decline, and health effects at concentrations below the Dutch exposure limit of 90 EU/m^3 also have been documented.[5 34] However, the relatively low prevalence of flu-like illness is evidence against a direct effect of endotoxin. Alternatively, measured endotoxin might have served as a surrogate for another causative exposure encountered in production areas, whether also generated from use of metalworking fluids or from another process. Metalworking fluids are complex mixtures of oil, water, chemicals, metals and microbes, and the component(s) responsible for their recognised respiratory health risks (asthma, hypersensitivity pneumonitis and humidifier fever) remain uncertain.[4 16 35] Ultimately, though our findings do not provide definitive evidence, they support the possibility of a pathogenic role of metalworking fluid-related bioaerosols in BADE and the further inquiry into the disease's aetiology, which should include examination of the dominant organism on culture of the primary metalworking fluid (*P. pseudoalcaligenes*) and other organisms identified by non-culture methods, as well as other production-related exposures.

Our study has several limitations. Although participation was high, we included only current workers. Furthermore, we assessed lung function using spirometry, which might not detect small airways disease in some cases.[29–32] Had we included former workers and more sensitive lung function tests, our estimates of disease burden might have been higher. In addition, our endotoxin exposure assessment, though extensive, occurred during 1 week in 2013. Our measurements are unlikely to be fully representative of preceding or subsequent exposures. However, our analyses depended on categorisation of endotoxin exposures into high, medium and low groups rather than exact endotoxin concentrations, and these relative groups seem less likely to change with time. Finally, the lack of follow-up clinical information on all but one of the participants with excessive decline in FEV_1 prevents us from fully describing the spectrum of lung disease in this facility and limits the conclusions that can be drawn from our analyses of health and exposure. Despite this limitation, the identification of an incident case of BADE among those with excessive decline in FEV_1 indicates an ongoing risk of this novel disease for current workers.

The recognition of an ongoing respiratory health risk in a workplace compels a response. Preventive steps can be taken even in absence of certainty about the definitive cause of disease. In addition to standard exposure reduction strategies to minimise all airborne exposures such as engineering controls, administrative policies and use of personal protective equipment, we recommended this facility establish a medical monitoring programme including respiratory symptom assessment and periodic spirometry. Our findings highlight the value of chest symptoms, particularly wheeze, and serial spirometry in early identification of workers who could be developing disease. New symptoms and new spirometric abnormalities should prompt referral to a specialist for diagnostic work-up. Furthermore, given that four participants in our study had excessive decline in FEV_1 but normal spirometry at both baseline and follow-up, attention to declines within the normal range is warranted. Finally, to better understand aetiology and prevent disease, additional cases of BADE at this or similar manufacturing facilities merit investigation.

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