

Original Article

# Are Inflammatory Markers an Indicator of Exposure or Effect in Firefighters Fighting a Devastating Wildfire? Follow-up of a Cohort in Alberta, Canada

Nicola Cherry<sup>1,\*</sup>, Jeremy Beach<sup>1</sup> and Jean-Michel Galarneau<sup>1</sup>

<sup>1</sup>Division of Preventive Medicine, University of Alberta Edmonton, Canada

\*Author to whom correspondence should be addressed. E-mail: [ncherry@ualberta.ca](mailto:ncherry@ualberta.ca)

Submitted 6 July 2020; revised 17 November 2020; editorial decision 18 December 2020; revised version accepted 23 December 2020.

## Abstract

**Objectives:** The Fort McMurray fire in Alberta, Canada, devastated the townsite in May 2016. First responders were heavily exposed to smoke particles. Blood samples taken from firefighters in May and August/September 2016 were used to measure concentrations of inflammatory markers in plasma and the relation of these markers to exposures and respiratory ill-health.

**Methods:** Blood samples were drawn from firefighters from two fire services, who also completed questionnaires about tasks and exposures during their deployment to the fire and about respiratory symptoms. Plasma was analysed for 42 inflammatory markers in a multiplex assay. At Service A, samples were collected twice, within 19 days of the start of the fire (early sample) and again 14–18 weeks later (late sample). At Service B, only late samples were collected, at 16–20 weeks. Principal component (PC) scores were extracted from markers in plasma from the early and late samples and, at both time periods, the first two components retained. PC scores were examined against estimated cumulative exposures to PM<sub>2.5</sub> particles, self-rated physical stressors during the fire, and time since the last deployment to an active fire. The relation of component scores and exposure estimates to respiratory health were examined, using self-ratings at the time of the blood draw, a validated respiratory screening questionnaire (the European Community Respiratory Health Survey [ECRHS]) some 30 months after the fire, and clinical assessments in 2019–2020.

**Results:** Repeat blood samples were available for 68 non-smoking first responders from Service A and late samples from 160 non-smokers from both services. In the 68 with two samples, marker concentrations decreased from early to late samples for all but 3 of the 42 markers, significantly so ( $P < 0.05$ ) for 25. The first component extracted from the early samples (C1E) was unrelated to respiratory symptoms but the second (C2E) was weakly related to increased cough ( $P = 0.079$ ) and breathlessness ( $P = 0.068$ ) and a lower forced expiratory volume in one second/forced expiratory capacity ( $FEV_1/FVC$ ) ( $\beta = -1.63$ , 95% CI  $-3.11$  to  $-0.14$ )  $P = 0.032$ . The first PC at 14–20 weeks (C1L) was unrelated

**What's important about this paper**

Firefighting results in changes in cytokines during the course of a single shift, with some changes reported to last over many weeks. Persisting elevation of key inflammatory markers was observed weeks after exposure, but was not a strong independent predictor of respiratory ill-health among firefighters. However, if confirmed in future studies, persistently elevated inflammatory markers could serve as a biomarker of exposure, valuable in assessing the risk of fire-related health outcomes.

to exposure or respiratory health but the second PC (C2L) from these late samples, drawn from both fire services, related to cumulative  $PM_{2.5}$  exposure. In a multivariate model, clustered within fire service, cumulative exposure ( $\beta = 0.19$ , 95% CI 0.09–0.30), dehydration ( $\beta = 0.65$ , 95% CI 0.04–1.27) and time since last deployed to a fire ( $\beta = -0.04$ , 95% CI  $-0.06$  to  $-0.01$ ) were all related to the C2L score. This score was also associated with respiratory symptoms of wheezing, chest tightness, and breathlessness at the time of the blood draw but not to symptoms at later follow-up. However, apart from the lower  $FEV_1/FVC$  at 15–19 days, the marker scores did not add to regression models that also included estimated cumulative  $PM_{2.5}$  exposure.

**Conclusions:** Concentrations of persisting inflammatory markers in the plasma of firefighters deployed to a devastating fire decreased with time and were related to estimates of exposure. Although not a powerful independent predictor of later respiratory ill-health, they may serve as an indicator of previous high exposure in the absence of contemporary exposure estimates.

**Keywords:** cytokines; firefighter; inflammatory markers; lung function; respiratory health

**Introduction**

The Fort McMurray fire in northern Alberta in May 2016 exposed many firefighters to high levels of heat, physical exhaustion, smoke intensity, and emotional stress, particularly in the first few days when the future of the town was in imminent danger, leading to the evacuation of some 80 000 inhabitants. In the following months, a cohort of 1234 first responders was established, comprising firefighters based throughout Alberta who had been deployed to the fire. Soon after the fire, and before the full cohort was established, blood samples for the measurement of inflammatory markers (cytokines and chemokines) were collected at two fire services. Previous work on inflammatory markers in firefighters has largely been confined to changes over a single shift (Swiston *et al.*, 2008; Greven *et al.*, 2012; Adetona *et al.*, 2017) with increases found in interleukin (IL)-8 in all three studies and IL-6 (Swiston *et al.*, 2008), with the increase in IL-8 still seen 3 months after the exposure (Greven *et al.*, 2012). Simulated exercises, without exposure to smoke particles, found cross-shift increases in IL-6 and tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ) (Walker *et al.*, 2015; Smith *et al.*, 2019), while Burgess *et al.* (2002) found a rapid decrease in IL-10, but no change in IL-8 or TNF- $\alpha$  following low-level smoke

exposure during the overhaul of structural fire incidents. Other studies have looked for inflammatory markers associated with long term exposures in firefighting. Gianniou *et al.* (2016), compared concentrations of markers including IL-8, TNF- $\alpha$ , and vascular endothelial cell growth factor (VEGF), all of which were higher in professional firefighters than trainees. Watkins *et al.* (2021) found that higher IL-6 and IL-1 $\beta$  related to the number of fire exposures in the last month among fire service instructors. Following the collapse of the World Trade Center on 11 September 2001, serum samples were collected from New York City firefighters and analysed for inflammatory markers for cases and referents drawn from a cohort of 1720 undergoing subspecialty pulmonary evaluation (SPE) (Nolan *et al.*, 2012). Cases were those with the lowest forced expiratory volume in 1 s ( $FEV_1$ ) on entry to the SPE; referents were randomly drawn from those who did not meet the criteria for airflow obstruction. Serum from the first blood sample, drawn within 6 months of 11 September, was analysed for 39 markers using a multiplex array. Cases (with low  $FEV_1$ ) had higher concentrations than referents of granulocyte-colony stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF) macrophage-derived chemokine (MDC) and

interferon gamma-induced protein (IP-10) but lower concentrations of IL-6 and IL-15. Further analysis suggested that elevations in GM-CSF and MDC increased the risk of continued airways obstruction. Review of these studies suggested that IL-8 and perhaps IL-6 and TNF- $\alpha$ , increased with exposures during a work shift, but that other inflammatory markers might be more relevant to long term respiratory effects of heavy exposures to fire-related particles. In the present study, blood samples were collected 15–151 days from the start of the fire and 1–146 days since last exposure to any fire. The study was designed to examine persisting inflammatory markers and their relation to exposures and respiratory health and to evaluate their potential as a biomarker of either exposure or effect

## Methods

### Participants and data collection

Firefighters from two fire services were included in the study of inflammatory markers in plasma. Firefighters from Service A, stationed close to Edmonton, the capital

city of Alberta, Canada, were deployed from day 2 of the fire. Most had only one deployment and each rotation was short (2–3 days). Those deployed included members of the Incident Management Team who were deployed early and worked many hours, but without active fire-fighting. Fire Service B was the service located in Fort McMurray, the urban centre threatened with destruction by the fire and from which all but essential workers were evacuated. These firefighters were deployed from the start of the fire and all undertook long, arduous and repeated deployments.

At both fire services, firefighters were asked to complete a questionnaire about their location, role and respiratory protection, concentrating on exposures early in the fire. Most of those from Service A completed this baseline questionnaire in the period 16–20 May 2016, while those from Service B completed it in late August or September (Table 1). Those from Service A also completed a follow-up assessment in August–September 2016: some additional firefighters from Service A completed a baseline at this time. At each contact, in addition to the task and exposure questionnaire, the firefighter

**Table 1.** Information collected from non-smoking firefighters at two fire services.

Date	Items collected	N	
		Station A	Station B
May 2016	Baseline questionnaire	68 <sup>a</sup>	–
	• Tasks, hours, location		
	• Respiratory symptoms (visual analogues)		
	• Physical stressors (visual analogues)		
	Spirometry (FEV <sub>1</sub> , FVC, FEV <sub>1</sub> /FVC)	68	–
	Blood sample for inflammatory markers	68	–
August–September 2016	Baseline questionnaire	16	76
	• Tasks, hours, location		
	• Respiratory symptoms (visual analogues)		
	• Physical stressors (visual analogues)		
	• Date attended most recent fire		
	Follow-up questionnaire	68	68
	• Respiratory symptoms (visual analogue)		
	• Date attended most recent fire		
	Spirometry (FEV <sub>1</sub> , FVC, FEV <sub>1</sub> /FVC)	84	75
	Blood sample for inflammatory markers	84	76
October 2018–January 2019	Follow-up questionnaire	72	63
	• European community health study respiratory symptom questionnaire		
July 2019–February 2020 (Stratified sample)	• Chest CT	8	14
	• Methacholine challenge	8	12
	• Pulmonary function tests	8	12

<sup>a</sup>An additional 14 did not complete the August–September follow-ups and were not included in the analysis.

reported on their respiratory and mental health and gave a urine sample (Cherry *et al.*, 2019) and a blood sample, and also gave consent to access any previous spirometry carried out through the employer. Their lung function was assessed by spirometry, following the American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines using a minimum of three and a maximum of eight manoeuvres. Questionnaires and biological samples were collected during the firefighters' normal shift rather than at a standardized collection time. Blood samples were taken by a phlebotomist using a room provided by the fire service, and immediately taken by the firefighter to a mobile clinical laboratory where the lung function assessment was carried out by a study physician. The mobile laboratory, parked immediately adjacent to the blood draw location, was equipped with a refrigerated centrifuge and  $-80^{\circ}\text{C}$  freezer. On receipt, the sample was spun down for 15 min at 200 g. Plasma was pipetted into three aliquots of 0.5 ml and stored at  $-80^{\circ}\text{C}$  immediately and then at the University of Alberta in Edmonton before being transferred on dry ice to the analytic laboratory in Calgary, Alberta.

The analysis of inflammatory markers was carried out as a multiplex array using a bead-based Luminex technology [the Luminex™ 100 system (Luminex, Austin, TX, USA)] by Eve Technologies Corp. (Calgary, Alberta, Canada). Samples were analysed in two batches. The first, in August 2016, included all but one of the paired samples from Service A that had been collected to that point. The second batch, sent for analysis in January 2017, included the balance of paired samples from Service A, Service A singleton samples, and all Service B samples.

The array estimated the concentration (pg/ml) of 42 cytokines, chemokines, and growth factors ('inflammatory markers') listed with abbreviations and full names in Appendix 1. Samples with concentrations too low to be detected were replaced, using beta substitution (Ganser and Hewett, 2010) taking the weighted values of the lowest observed values from the two batches (Appendix 2). The mean concentration of the marker in the two aliquots was used as the estimate, log-transformed to reduce skew.

### Exposure estimates

Exposure to particles ( $\text{PM}_{2.5}$ ) was estimated, as described previously (Cherry *et al.*, 2019), combining firefighter reports on dates, hours firefighting in each location with estimates of particulate matter from Alberta Environment (using results from monitoring stations and satellite imagery). For the 'key' (first) exposure, these were weighted by a factor representing smoke exposures

in the task (active firefighting being weighted higher than patrolling, for example) and a factor representing the mitigating effect of any respiratory protective equipment (RPE) used. Exposure during subsequent rotations was represented only by dates, hours and estimates of particulate exposure. The environmental exposure to  $\text{PM}_{2.5}$  on the day of highest exposure during the key rotation was also recorded. Details of these estimates are given in Appendix 3.

On the first (baseline) questionnaire completed at the time of the first blood draw at each service, the firefighter was asked to indicate their worst experience during the key rotation on five physical stressors (dehydration, heat stress, noise, exhaustion, and musculoskeletal strain) recorded on a visual analogue scale, from 'no discomfort' (a score of 0) to 'worst ever experienced' (a score of 100). These scores were divided by 100 for the analysis.

The number of days/weeks from the end of the last reported deployment to the Fort McMurray fire and each blood draw was calculated, together with the number of days/weeks since exposure to any fire (including the Fort McMurray fire).

### Respiratory outcomes

Chest symptoms (cough, phlegm, undue breathlessness, wheezing or whistling, and chest tightness) were recorded at the time of each blood draw, using visual analogue scales indicating the degree to which they were bothered by the symptom on a scale from 'not at all' (a score of zero) to 'very bothered' (a score of 100).  $\text{FEV}_1$  and FVC were measured at the time of each blood draw and their ratio  $\text{FEV}_1/\text{FVC}$  used as an indicator of the degree of obstructive impairment. The most recent spirometry prior to the fire (if any were done) was obtained, with firefighter consent, from the health company carrying out periodic assessments. Once the full cohort of 1234 participants was established, including the firefighters included here, they were all followed up on two further occasions, the second being in late 2018–early 2019, 30 months or more post-fire (Table 1). On that questionnaire, the firefighters completed the screening questionnaire from the European Community Respiratory Health Study (ECRHS) (Burney *et al.*, 1994). Using the methods reported by Sunyer *et al.* (2000), a component analysis with oblique rotation was carried out with four factors extracted representing complaints of cough, phlegm, asthma, and wheeze (Appendix 4). On the questionnaire in the winter of 2018–2019 firefighters were asked also if they were still experiencing respiratory symptoms they attributed to the fire. All who reported that they were (together with a sample who were not) were invited to undergo a clinical respiratory assessment

[pulmonary function tests, methacholine challenge, high-resolution chest computed tomography (CT)]. Tobacco smokers and those who, prior to the fire, met criteria for chronic asthma or chronic obstructive pulmonary disease, were excluded from these assessments.

### Potential confounders

Information on cigarette smoking was collected and current smokers excluded from the analysis. Age and body mass index (BMI) were calculated at each contact and sex (gender), as volunteered, was recorded.

### Statistical analysis

Two groups of firefighters were used in the analyses. The first comprised non-smokers from Service A who had results from both May 2016 (early) and August/September 2016 (late) blood samples. For these, mean differences between concentrations from early and late samples were calculated for each of the 42 markers, and tested for deviations from the null, allowing for clustering within person. In order to reduce the dimensionality of the inflammatory marker arrays, a principal component analysis was used to extract uncorrelated component scores from the 42 log-transformed inflammatory markers from the May sample. The first four components were extracted and examined against exposure and respiratory outcome measures. The first two components were retained and are referred to below as component 1 early (C1E) and component 2 early (C2E). The second group was of all non-smoking firefighters from Service A and Service B who had given a blood sample in August/September. A firefighter from Service A who had given two samples contributed to both analytical groups. Differences between the two services on mean marker concentrations in the August/September

samples were computed and principal component analysis of the 42 markers was carried out, with scores on the first two components retained. These are referred to below as component 1 late (C1L) and component 2 late (C2L). The bivariate relation between the components extracted from the May and August/September samples and exposure estimates were examined by Pearson correlation. Correlations were also computed between component scores, exposure markers and markers of respiratory health. The relation of FEV<sub>1</sub>/FVC to exposure and principal component scores was examined by regression, adjusting for age, sex, FEV<sub>1</sub>/FVC before the fire (where available) and clustering within fire service. Regression analysis was also used to examine whether component scores added to estimates of PM<sub>2.5</sub> exposure in accounting for variation in symptoms. A final multivariable multilevel regression included only those exposure and respiratory outcome factors related to component scores with  $P < 0.10$  in the univariate analyses. In a supplementary analysis, multilevel generalized structural equation modelling was used in a mediation analysis of the outcomes related to exposure ([Appendix 6](#)). A  $P$  value  $\leq 0.05$  was taken as indicating statistical significance. The analysis was conducted in Stata 14.2

## Results

### Participation

Characteristics of the first responders are shown in [Table 2](#). Those from Service A were 5 years older than those from Service B, had a smaller proportion of women and fewer in a purely firefighter role. We were only able to get spirometry results before the fire for 40%. More than 80% from each service completed the screening questionnaire for pulmonary symptoms in the winter of 2018–2019. Rather more firefighters from Service

**Table 2.** Study characteristics of non-smoking first responders from these fire services.

	Service A		Service B		All	
	Mean	SD	Mean	SD	Mean	SD
Age	37.6	9.3	32.9	9.0	35.4	9.4
BMI	28.8	3.7	28.6	3.9	28.7	3.8
	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>
Male	97.6	82	86.8	66	92.5	148
Firefighter	86.9	73	97.7	72	90.6	145
Seen in both May & August/September	81.0	68	–	–	42.5	68
Results of lung function from before the fire	40.5	34	40.8	31	40.6	65
Complete ECRHS in 2018/2019	85.7	72	82.9	63	84.4	135
Included in clinical respiratory assessments	9.5	8	18.4	14	13.8	22
N	84		76		160	

B were included in the clinical assessment, reflecting a higher number reporting respiratory ill-health.

### Inflammatory markers

There were 68 non-smokers from Service A who gave blood on two occasions. The first blood samples were drawn 14–18 days (median 15.5 days) from the start of the fire and the second 106–137 days (median 107 days) from the start, with a median of 92 days between samples. At fire Service B, blood samples were collected only once, with 76 non-smoking firefighters giving samples from 121 to 151 days (median 122 days) from the start of the fire. In addition, a further 16 non-smoking firefighters from fire Service A gave blood only on the later visit, bringing the total number of late samples from fire Service A to 84.

Twenty-five of the 42 markers were significantly higher at baseline than three months after the start of the fire: none was significantly lower (Table A1, Appendix 5). The first four principal component scores were extracted from the 42 baseline marker concentrations, accounting for, respectively, 48.7, 11.6, 5.5, and 3.9% of the variance. Components 3 and 4 did not relate to particulate exposure or respiratory outcome measures and only the first component (C1E) the second (C2E) were examined further. The component weightings are shown in the first two columns of Table 3. C1E has positive and generally high weights for all markers whereas the second (C2E) weights many fewer factors (just shown with weights  $\geq 0.2$ ). High positive weights ( $>0.5$ ) were seen on C2E for seven markers (GROalpha, PDGF-AA, PDGF-BB, sCD40L IP-10, MCP-1, and IL-18).

In samples collected from the two services in August/September marker concentrations were significantly higher at Service B on 11 of the markers and lower on just 2 (Table A2, Appendix 5). Those higher at Service B included many of those highly weighted on C2E, calculated from May plasma samples. The final two columns of Table 3 show the component weightings for the first two principal components extracted from the 160 late samples, with the first component (C1L) accounting for 43.7% of the variance and the second (C2L) 11.6%. Components 3 and 4 accounted for 5.2 and 3.8% of the variance but after initial examination against exposure and respiratory outcome were not retained. Again, the weights for the first component are positive and mainly substantial. Those for the second component (C2L) are consistent with the second component (C2E) extracted from the May samples, with high positive weights ( $>0.5$ ) again seen for GROalpha, PDGF-AA, PDGF-BB, sCD40L, IP-10, MCP-1, IL-18, and here, TNF- $\alpha$ , which had a weight just  $<0.5$  in the May data. The mean of the

C1L was very similar ( $P = 0.674$ ) for Service A (mean =  $-0.03$ , SD = 1.07) and Service B (mean = 0.04, SD = 0.93) but Service B had significantly higher scores ( $P < 0.001$ ) on C2L (Service A: mean =  $-0.37$ , SD = 1.16; Service B: mean = 0.41, SD = 0.55).

### Exposures

Means of estimated exposure, highest exposure day, days since the last deployment, days since last fire and scores on the five exposure-related visual analogue scales are shown in Table 4. Exposure during the Fort McMurray fire was higher and more recent in Service B and the exposure-related experiences were all rated as worse by firefighters from Service B, with very high ratings for exhaustion. Only the time since tackling any fire (about 2 months) was similar in those from both Services.

### Respiratory outcomes

Mean symptom scores at the time of blood draw are shown in Table 5 together with mean scores on the four components extracted from the ECRHS, and FEV<sub>1</sub>/FVC from spirometry carried out by the research team. Cough, phlegm, and chest tightness improved significantly between May and August/September at Service A, but for breathlessness and wheezing the improvement was less. In the August/September results for the two services, all five symptoms were worse for those from Service B, all but cough with  $P < 0.05$ . Age, higher at Service A, was found to relate only to cough by visual analogue and weakly ( $P = 0.089$ ), to FEV<sub>1</sub>/FVC. After adjustment for age, those from Service B had significantly worse scores on cough also. Less difference was seen with factors extracted from the ECRHS  $>2$  years after the fire, but the mean wheeze score was higher ( $P = 0.055$ ) in those from Service B. FEV<sub>1</sub>/FVC did not show important differences between time points at Service A or between services in August/September: adjustment for age did not change the conclusion of no difference between the two Services. However, it appeared that, where FEV<sub>1</sub>/FVC results were available from before the fire, the ratio was lower post-fire. Twenty-two of the firefighters from these two services underwent at least one clinical respiratory assessment in the winter of 2019–2020. None of the eight from Service A were found to have asthma on the methacholine challenge or bronchial wall thickening on high-resolution chest CT. Among those tested from Service B, 6/14 were found to have asthma and 5/12 bronchial wall thickening. These differences between services were unlikely to have arisen by chance and will be reported more fully elsewhere.

**Table 3.** Weights for components 1 and 2 from principal component analysis of inflammatory markers.

	May (Service A)		August/September (both services)	
	Component 1	Component 2	Component 1	Component 2
EGF	0.687		0.621	0.301
FGF-2	0.752		0.636	0.255
Eotaxin-1	0.663	0.346	0.579	0.322
TGF- $\alpha$	0.853	-0.208	0.747	-0.245
G-CSF	0.732	0.242	0.740	
Flt-3L	0.565	0.314	0.458	
GM-CSF	0.794		0.733	
Fractalkine	0.814		0.753	
IFNa2	0.805		0.713	
IFN- $\gamma$	0.788		0.736	
GROalpha		0.703		0.737
IL-10	0.631		0.696	
MCP-3	0.792	-0.299	0.783	
IL-12P40	0.725	-0.265	0.811	
MDC	0.379		0.250	-0.208
IL-12P70	0.814		0.787	
PDGF-AA	0.212	0.882		0.882
IL-13	0.818	-0.338	0.779	-0.279
PDGF-BB	0.313	0.719		0.796
IL-15	0.848	-0.207	0.858	
sCD40L	0.475	0.539	0.262	0.782
IL-17A	0.760		0.692	
IL-1RA	0.785		0.716	-0.242
IL-1a	0.749		0.738	
IL-9	0.784		0.841	
IL-1B	0.789		0.767	
IL-2	0.810	-0.206	0.844	
IL-3	0.695	-0.268	0.778	
IL-4	0.712		0.517	0.222
IL-5	0.694	-0.401	0.741	-0.230
IL-6	0.846		0.772	
IL-7	0.831		0.724	
IL-8	0.856	0.232	0.805	
IP-10	0.213	0.572	0.270	0.512
MCP-1	0.212	0.783	0.256	0.743
MIP-1a	0.805		0.780	
MIP-1B	0.836		0.788	
RANTES	0.257	0.325		
TNF- $\alpha$	0.713	0.483	0.601	0.543
TNFB	0.803		0.756	-0.215
VEGF-A	0.845		0.773	
IL-18	0.328	0.646	0.465	0.551
N	68		160	

#### Relation of inflammatory markers to exposure and respiratory health

Table 6 shows the correlations between exposure indices and the component scores for Service A immediately

after the fire and for both services in August/September. The correlations for Service A suggest a lower C1E score with increasing exposure [found also for each of the individual markers, significantly so for 20 (Table

**Table 4.** Exposure parameters by occasion and fire service.

	Service A				Service A		Service B		P
	May		August/September		August/September		August/September		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Log total exposure PM <sub>2.5</sub>	9.96	1.22	9.96	1.22	9.88	1.26	12.23	0.47	<0.001
Log highest day exposure	7.95	1.32	–	–	7.85	1.33	9.13	1.01	<0.001
Days since last deployment	5.53	4.25	104.13	15.57	103.25	15.35	74.74	21.37	<0.001
Days since last fire	4.22	3.6	69.66	39.54	67.64	39.21	60.14	31.23	0.186
Dehydration score	19.18	17.68	–	–	20.8	18.25	47.81	25.75	<0.001
Heat stress	14.62	13.17	–	–	17.4	15.38	50.65	25.88	<0.001
Noise	24.45	19.04	–	–	24.61	18.63	39.35	28.53	<0.001
Exhaustion	43.93	28.00	–	–	44.45	28.32	81.48	20.52	<0.001
Musculoskeletal strain	26.96	21.14	–	–	27.37	21.35	61.23	23.81	<0.001
N	68		68		84		76		

A3, Appendix 5)]. Further analysis suggested that the effect resulted in part from the inclusion of eight first responders assigned to the Incident Management Team (IMT). These had low C1E scores (firefighters: mean = 0.09, SD = 0.99; IMT: mean = -0.67, SD = 0.83;  $P = 0.043$ ) but high estimated exposure, reflecting long hours early in the fire. Increasing age was also associated ( $P = 0.084$ ) with a lower C1E score and adjustment for role and age reduced, but did not wholly eliminate, the negative relation between exposure and C1E ( $\beta = -0.19$ , 95% CI = -0.39 to 0.02,  $P = 0.071$ ). Moreover, the relation between time since leaving the fire and estimated exposure was confounded by the date of sample collection for the 68 with early samples (Fig. 1). C2E was not related to exposure.

In the August/September samples, C1L was unrelated to exposure (Table 6) but C2L scores were higher with higher exposure on all the exposure indices and lower with time since ending a deployment to the Fort McMurray or any other fire. This relation of higher marker concentration with higher exposure and lower concentrations with time since last fire is seen with several of the individual markers (GRO alpha, PDGF-AA CCD40L) contributing to C2L (Table A4, Appendix 5). In a regression analysis, allowing for clustering within service, C2L score increased with total cumulative exposure to PM<sub>2.5</sub> and with dehydration rating and decreased with time since the last fire. The fire service did not add significantly when these three exposure factors were in the equation (Table 7).

The final stage of the analysis was to examine whether exposure factors and component scores were related to poor respiratory health, and, if so, whether

the inflammatory marker scores were a better predictor of poor respiratory health than estimated exposure. In the data collected at Station A immediately post-fire, those with higher C2E scores had lower values on FEV<sub>1</sub>/FVC, having adjusted for age, sex, and particulate exposure ( $\beta = -1.63$ , -3.11 to -0.14,  $P = 0.032$ ) and there was some evidence of increased cough ( $P = 0.079$ ) and breathlessness ( $P = 0.068$ ) but, as was seen in Table 6, C2E was not related to particulate exposure or physical stressors. Neither C1E or C1L was related to either self-reports of symptoms (by visual analogue scale) at the time of the blood draw nor to the factors extracted from the ECRHS, 30 months later (data not shown). Table 8 gives the relation of these respiratory health markers and FEV<sub>1</sub>/FVC to C2L score, to cumulative exposure to PM<sub>2.5</sub>, and ratings of dehydration. C2L score correlated with visual analogue scores completed at the time of the blood draw, indicating increased breathlessness, wheezing, and chest tightness, but not to scores derived from the ECRHS completed 2 years later. Cumulative exposure to PM<sub>2.5</sub> particles was also related to breathlessness, wheeze, and tightness, and to the wheeze score and, marginally, to the asthma score derived from the ECRHS. Dehydration was related to phlegm on the visual analogue scales as well as to the three symptoms found to be related to C2L score and cumulative PM<sub>2.5</sub> exposure. It was also marginally related to wheeze score, from the ECRHS. None of these three exposure indices from August/September was significantly related to a lower FEV<sub>1</sub>/FVC in this correlation analysis.

The analysis in Table 9 tested whether C2L score had any independent effect, having allowed for statistical clustering within service and adjusted for age and



**Table 5.** Respiratory parameters by occasion and fire service.

	Service A			Service B		
	May		P	August/September		P
	Mean	SD		Mean	SD	
Visual analogue						
Cough	23.93	28.31	0.013	14.88	22.97	0.054*
Phlegm	20.79	26.96	0.020	12.68	17.84	0.008
Breathless	8.97	13.82	0.149	6.67	11.25	<0.001
Wheeze	9.01	16.85	0.129	5.83	11.09	0.005
Tightness	11.81	18.34	0.013	6.49	10.21	<0.001
N	68			83		75
ECRHS						
Cough	-0.17	0.68	-	-0.13	0.71	0.502
Phlegm	-0.07	1.57	-	-0.05	1.45	0.584
Asthma	-0.15	0.83	-	-0.16	0.83	0.157
Wheeze	-0.23	0.78	-	-0.17	0.83	0.055
N	60			72		63
Spirometry (ALL)						
FEV <sub>1</sub> /FVC	76.88	6.20	0.231	77.45	6.23	0.508**
N	68			84		75
Spirometry (with prior record)						
Prior	81.79	4.58	-	81.24	5.11	0.638
Post	77.50	6.64	0.083	78.49	5.14	0.634
P	<0.001			<0.001		
N	29			34		31

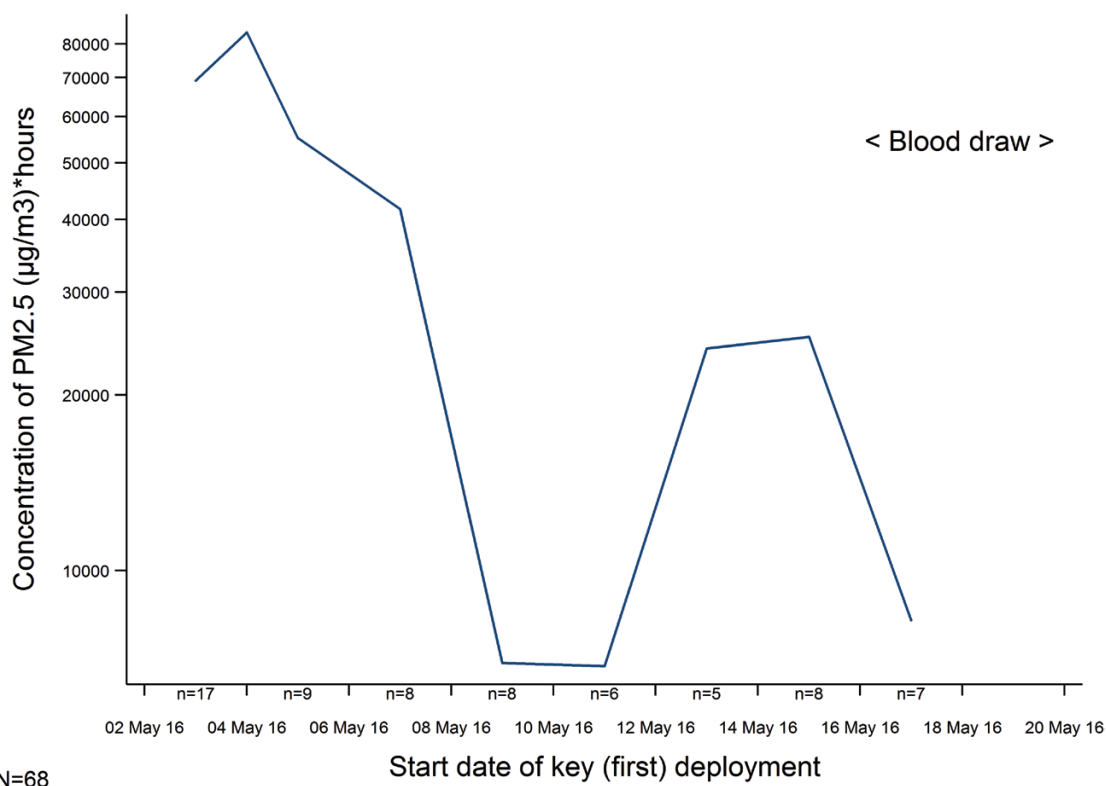
\* P = 0.009 after adjustment for age.

\*\* P = 0.237 after adjustment for age.

**Table 6.** Relation of exposure indices to component scores.

	May				August/September			
	Service A				Both services			
	Component 1		Component 2		Component 1		Component 2	
	<i>R</i> <sup>a</sup>	<i>P</i>	<i>R</i>	<i>P</i>	<i>R</i>	<i>P</i>	<i>R</i>	<i>P</i>
Log total exposure	-0.32	0.008	0.03	0.791	-0.00	0.992	0.38	<0.001
Log highest day exposure	-0.25	0.037	0.00	0.972	-0.09	0.277	0.20	0.010
Days since last deployment	-0.06	0.621	0.01	0.919	0.02	0.766	-0.24	0.003
Days since last fire	-0.13	0.311	0.17	0.166	0.02	0.760	-0.21	0.008
Dehydration	-0.15	0.223	0.12	0.268	0.01	0.935	0.32	<0.001
Heat stress	-0.03	0.784	-0.05	0.701	0.04	0.593	0.28	<0.001
Noise	-0.12	0.355	-0.16	0.209	-0.05	0.538	0.20	0.011
Exhaustion	-0.17	0.168	0.00	0.987	-0.02	0.764	0.33	<0.001
Musculo-skeletal strain	0.07	0.600	-0.17	0.890	0.069	0.390	0.28	<0.001
<i>N</i>	68				160			

<sup>a</sup>Pearson regression coefficient.

**Figure 1.** Mean exposure to PM<sub>2.5</sub> by start of key(first) deployment.

sex, in addition to the relationship to estimated cumulative PM<sub>2.5</sub> exposure. The table includes each respiratory health outcome, which was seen to relate, in [Table 8](#), to

either exposure measure. In this analysis, the inflammatory marker scale did not contribute to a multivariable model that included estimated cumulative exposure for

**Table 7.** Regression of second component score from late samples on exposure indices and fire service, allowing for clustering within service ( $N = 159$ ).

	Univariate <sup>a</sup>			Multivariate <sup>a</sup>			Final Model <sup>a</sup>		
	$\beta$	95% CI	$P$	$\beta$	95% CI	$P$	$\beta$	95% CI	$P$
Log cumulative exposure	0.25	0.15 to 0.34	<0.001	0.12	-0.03 to 0.26	0.107	0.19	0.09 to 0.30	<0.001
Weeks since last deployment	0.00	-0.05 to 0.06	0.899						
Weeks since last fire	-0.03	-0.06 to -0.01	0.019	-0.03	-0.06 to -0.01	0.015	-0.04	-0.06 to -0.01	0.010
Dehydration	0.62	-0.02 to 1.26	0.059	0.53	-0.11 to 1.16	0.102	0.65	0.04 to 1.27	0.036
Heat stress	0.22	-0.47 to 0.90	0.532						
Noise	0.37	-0.23 to 0.98	0.226						
Exhaustion	0.46	-0.11 to 1.03	0.115						
Musculoskeletal strain	0.24	-0.40 to 0.87	0.463						
Service B	0.79	0.50 to 1.07	<0.001	0.33	-0.13 to 0.79	0.161	-	-	-
Constant				-1.33	-2.77 to 0.10	0.069	-2.00	-3.10 to -0.90	<0.001

<sup>a</sup> Allowing for clustering within service.

**Table 8.** Correlation of component 2 score, cumulative exposure and dehydration with respiratory health indices (August/September, both services).

RespiratoryHealthIndicator	Component 2		Cumulative exposure		Dehydration	
	$R^a$	$P$	$R$	$P$	$R$	$P$
<b>Visual analogue (2016)</b>						
Cough	0.10	0.202	0.07	0.407	0.05	0.525
Phlegm	0.14	0.071	0.10	0.229	0.16	0.043
Breathlessness	0.18	0.027	0.30	<0.001	0.23	0.003
Wheezing	0.18	0.021	0.24	0.002	0.27	0.001
Tightness	0.20	0.010	0.28	<0.001	0.17	0.035
N	158		158		158	
<b>ECRHS (2018–2019)</b>						
Cough	0.08	0.358	0.04	0.671	0.06	0.480
Phlegm	0.02	0.822	-0.10	0.267	-0.00	0.995
Asthma	0.02	0.783	0.16	0.061	0.08	0.387
Wheeze	0.13	0.122	0.22	0.012	0.16	0.065
N	135		135		135	
FEV <sub>1</sub> /FVC	-0.12	0.122	-0.05	0.499	-0.09	0.270
	159		159		159	

<sup>a</sup> Pearson correlation coefficient.

any of the symptoms, either those recorded by visual analogue in August/September 2016 or the 2018/2019 follow-up. However higher scores on C2L did appear to be associated ( $P = 0.099$ ) with lower FEV<sub>1</sub>/FVC, having adjusted for age, sex and clustering within service, consistent with the relation of C2E to FEV<sub>1</sub>/FVC reported above.

In a mediation analysis (Appendix 6) it was found that 20.0% of the effect of exposure on wheeze from the ECRSQ was mediated through the inflammatory marker

component 2, with similar proportions (22.8%, breathless; 21.3% wheezing; 21.4%; chest tightness) of the effect mediated for the visual analogue scores

Finally, we examined the relation to the respiratory health of the two markers, GM-CSF and MDC reported as being related to declining lung function in New York City firefighters after the World Trade Centre disaster. GM-CSF was unrelated to any of the respiratory health outcomes considered in Tables 8 and 9. Among those undergoing clinical assessment, mean log GM-CSF

**Table 9.** Regression of respiratory health indices on component 2 score and cumulative PM<sub>2.5</sub> exposure, allowing for clustering within service and adjusting for age and sex.

	Univariate						Multivariate					
	Component 2			Cumulative exposure			Component 2			Cumulative exposure		
	$\beta$	95% CI	P	$\beta$	95% CI	P	$\beta$	95% CI	P	$\beta$	95% CI	P
Visual analogue												
Breathless	0.97	-2.20 to 4.14	0.548	4.15	2.19 to 6.12	<0.001	1.47	-1.70 to 4.63	0.364	3.79	1.68 to 5.90	<0.001
Wheeze	1.84	-1.12 to 4.80	0.224	3.29	1.47 to 5.11	<0.001	1.97	-0.95 to 4.89	0.187	2.80	0.84 to 4.75	0.005
Tightness	1.70	-1.84 to 5.24	0.347	0.83	-2.54 to 4.20	0.629	2.46	-1.10 to 6.01	0.176	3.61	1.23 to 5.99	0.003
N = 158												
ECRSQ												
Asthma	0.01	-0.15 to 0.17	0.903	0.08	-0.02 to 0.19	0.128	-0.04	-0.21 to 0.14	0.682	0.09	-0.02 to 0.21	0.116
Wheeze	0.12	-0.04 to 0.28	0.130	0.14	0.03 to 0.24	0.011	0.06	-0.10 to 0.23	0.466	0.12	0.01 to 0.23	0.030
N = 135												
FEV <sub>1</sub> /FVC	-0.83	-1.83 to 0.16	0.099	-0.37	-1.03 to 0.30	0.280	-0.73	-1.80 to 0.34	0.180	-0.18	-0.90 to 0.53	0.614
N = 159												

concentrations were higher (but not significantly so) in those with positive methacholine challenge tests, bronchial wall thickening detected on chest CT and in the three firefighters with FEV<sub>1</sub>/FVC <70. The only one of these differences to approach significance was with bronchial wall thickening, where mean log GM-CSF in those with thickening (N = 5) was 3.54 ng/ml and those without (N = 17) 1.50 ng/ml (P = 0.082). MDC concentrations were negatively correlated with visual analogue symptoms at the time of the blood draw (meaning those with higher concentrations were less bothered by the symptoms) and unrelated to FEV<sub>1</sub>/FVC as measured by the research team or to the results in the clinical assessment.

## Discussion

Blood samples were collected from firefighters deployed to the Fort McMurray fire to assess whether inflammatory markers were related to respiratory ill-health. The analyses reported here show that, following a fire of high intensity with extended burning and overhaul, inflammatory markers measured in plasma were higher in the period soon after early deployment than when re-measured in plasma from the same firefighters 3–4 months later. Principal components extracted from the 42 markers at the two time periods had a similar structure. The second component from late samples gave scores that were higher with greater cumulative exposure to PM<sub>2.5</sub>, with reports of more intense dehydration early in the fire and decreased with time since attending any

fire. This component related to contemporaneous ratings of wheeze, chest tightness and breathlessness and, more weakly, to changes in FEV<sub>1</sub>/FVC ratio that suggested increased airway obstruction since the fire. Estimated cumulative exposure to PM<sub>2.5</sub> was a better predictor of respiratory symptoms than the inflammatory marker component. Specific markers related to worsening obstructive lung disease in New York City firefighters following the World Trade Center disaster (Nolan *et al.*, 2012) did not show any marked relation to respiratory health in this study.

The study has limitations. The negative relation between estimated PM<sub>2.5</sub> and inflammatory markers in plasma from the blood draw 15–19 days from the start of the fire was unexpected and may indicate that these early markers are reflecting, in part, other factors known to reflect cytokine concentrations such as physical exercise (Pedersen *et al.*, 2001) or heat stress (Wright-Beatty *et al.*, 2014; Watkins *et al.*, 2021) rather than simply PM<sub>2.5</sub> exposure. Interpretation was complicated by the non-linear relationship between the intensity of particulate exposure and time since last exposure, which limited also the interpretation of urinary 1-hydroxypyrene in this sample (Cherry *et al.*, 2019). Moreover, there will be an error in the estimates of exposure, not least the likely overestimation in the Incident Management Team. A further limitation is that spirometry results before the fire were available only for a subgroup of firefighters and these were carried out for routine health assessment using different equipment and operators than measures carried out by the research

team. While it is interesting that the observed mean  $FEV_1/FVC$  after the fire was lower than in the earlier spirometry reports, it would be unsafe to assert that this was due to exposures during the fire. The absence of any relationship between estimated  $PM_{2.5}$  exposure and  $FEV_1/FVC$  in firefighters from these two services should also be noted. An important weakness was the homogeneity of exposures within the fire service which resulted in an analysis which reflected largely the difference between rather than within groups, although in the final model the fire service was no longer found to be important. Finally, there may have been unmeasured events immediately prior to the fire or post fire that influenced the concentration of inflammatory markers measured. Medication taken since the fire was examined and only intermittent use of anti-inflammatories for muscle pain was noted, suggesting that this was not an important effect modifier.

Use of principal component analysis to extract a small number of factors from the 42 inflammatory markers reduced the likelihood of extraneous significance associated with making multiple comparisons. Nevertheless, it was appropriate to examine certain individual markers that had been reported previously as associated with firefighting. Despite the uncertainty over the cause of the higher inflammatory markers in May, it is of interest that those markers (IL-6, IL-8, TNF- $\alpha$ ) reported in cross shift studies to increase with acute exposure (Swiston *et al.*, 2008; Greven *et al.*, 2012; Adetona *et al.*, 2017) were lower at the second blood draw, consistent with the high levels found soon after exposure in the earlier studies, and with IL-8, reported by Swiston *et al.* (2008) to still show the elevation at 3 months, declining less than IL-6.

The main finding of interest was the extraction, at each time period, of a second principal component that was found, in the August/September samples, to relate systematically to estimated  $PM_{2.5}$  exposure, to self-reports of dehydration and to time since the last fire. Since these exposures were related to respiratory outcomes, it seemed possible that this component might be a biomarker useful in predicting effect. In the current study, where it was possible to make a quantitative estimate of exposure, the biomarker score was not uniquely useful, but such an approach might be of value where blood samples could be taken (as with the New York City firefighters) some weeks after a fire for which exposure could not easily be estimated. A high C2L score for such a firefighter might suggest exposures sufficient to affect health. The indication of lower  $FEV_1/FVC$  with higher C2E and C2L would

support such an interpretation. Accurate estimation of exposure and collection of biological samples to a pre-determined schedule may be prohibitively difficult in the early stages of a devastating fire. With such conflagrations becoming more frequent with changes in climate, the use of persistent biomarkers, as indicated here, may be helpful in attributing health effects to deployment, and potentially for assessing the effects of mitigation efforts, including RPE and rapidly rotating schedules. While it would be important to repeat the marker analysis in other cohorts, the present analysis suggests a role for this approach in the assessment of firefighters coming from fires with high and extended exposures.

## Funding

The study was funded, in part, by the OHS Futures program of Alberta Labour.

## Ethics

The protocol was approved by the Health Ethics board of the University of Alberta (Pro00065284).

## Conflicts of Interest

The authors declare no conflict of interest.

## References

- Adetona AM, Adetona O, Gogal RM Jr *et al.* (2017) Impact of work task-related acute occupational smoke exposures on select proinflammatory immune parameters in wildland firefighters. *J Occup Environ Med*; 59: 679–90.
- Burgess JL, Nanson CJ, Hysong TA *et al.* (2002) Rapid decline in sputum IL-10 concentration following occupational smoke exposure. *Inhal Toxicol*; 14: 133–40.
- Burney PG, Luczynska C, Chinn S *et al.* (1994) The European Community Respiratory Health Survey. *Eur Respir J*; 7: 954–60.
- Cherry N, Aklilu Y, Beach J *et al.* (2019) Urinary 1-hydroxypyrene and skin contamination in firefighters deployed to the Fort McMurray fire. *Ann Work Expo Health*; 63(4): 448–58.
- Ganser GH, Hewett P. (2010) An accurate substitution method for analyzing censored data. *J Occup Environ Hyg*; 7: 233–44.
- Gianniou N, Katsaounou P, Dima E *et al.* (2016) Prolonged occupational exposure leads to allergic airway sensitization and chronic airway and systemic inflammation in professional firefighters. *Respir Med*; 118: 7–14.
- Greven FE, Krop EJ, Spithoven JJ *et al.* (2012) Acute respiratory effects in firefighters. *Am J Ind Med*; 55: 54–62.

- Nolan A, Naveed B, Comfort AL *et al.* (2012) Inflammatory biomarkers predict airflow obstruction after exposure to World Trade Center dust. *Chest*; **142**: 412–8.
- Pedersen BK, Steensberg A, Fischer C *et al.* (2001) Exercise and cytokines with particular focus on muscle-derived IL-6. *Exerc Immunol Rev*; **7**: 18–31.
- Smith DL, Friedman NMG, Bloom SI *et al.* (2019) Firefighting induces acute inflammatory responses that are not relieved by aspirin in older firefighters. *J Occup Environ Med*; **61**: 617–22.
- Sunyer J, Basagaña X, Burney P *et al.* (2000) International assessment of the internal consistency of respiratory symptoms. *Am Thorac Soc J*; **162**: 930–5.
- Swiston JR, Davidson W, Attridge S *et al.* (2008) Wood smoke exposure induces a pulmonary and systemic inflammatory response in firefighters. *Eur Respir J*; **32**: 129–38.
- Walker A, Keene T, Argus C *et al.* (2015) Immune and inflammatory responses of Australian firefighters after repeated exposures to the heat. *Ergonomics*; **58**: 2032–9.
- Watkins ER, Hayes M, Watt P *et al.* (2021) Extreme occupational heat exposure is associated with elevated haematological and inflammatory markers in Fire Service Instructors. *Exp Physiol*; **106**: 233–43.
- Wright-Beatty HE, McLellan TM, Larose J *et al.* (2014) Inflammatory responses of older firefighters to intermittent exercise in the heat. *Eur J Appl Physiol*; **114**: 1163–74.