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Immunologic effects of forest fire exposure show increases in IL-1 β and CRP

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To the Editor:

With increasing heat and droughts world-wide, wildfires are becoming a more serious global threat to the world's population. Wildfire smoke is composed of approximately 80% to 90% of fine (<2.5 μ m) and ultrafine (<1 μ m) particulate matter (PM) which are also common to ambient pollution¹; these can penetrate the bloodstream through respiration. Population health studies indicate that wildfire smoke is a serious risk to human health and increases the healthcare burden of smoke-exposed areas. Wildfires increase asthma attacks², especially asthma hospitalization in children aged 0-5 years³, and increase inflammation and cardiovascular events⁴. Both respiratory and cardiovascular events are associated with inflammation. In a recent study, we found immunological

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changes in the blood of children aged 7 to 8 years after a prescribed burn versus a wildfire⁵. Wildfire-exposed children had lower levels of type-1 T-helper cells and increased methylation of the Foxp3 gene, both of which modulate immune responses. However, plasma-derived inflammatory markers had not been tested. Therefore, in this study, our goal was to determine whether plasma markers of inflammation known to be altered by chronic air pollution were increased significantly in individuals exposed after a short period of a large 2014 wildfire in California.

We studied 67 participants (median=16 yrs, 12-25 yrs) divided into smoke-exposed vs. non smoke-exposed control groups. Smoke-exposed participants (n=25) lived in Fresno, California, 62 miles from the El Portal wildfire that burned 4689 acres for 7 days from July 26, 2014 through August 1, 2014. Hourly concentrations from four air quality monitoring stations located within the Fresno city limits and combined with other spatial temporal data were used to quantitate levels of PM_{2.5}. Prior to the El Portal fire, mean PM_{2.5} levels in Fresno were $8.73 \pm 2.98 \mu\text{g}/\text{m}^3$ (median $8.63 \mu\text{g}/\text{m}^3$). During and after the El Portal fire, mean PM_{2.5} levels in Fresno were $11.82 \pm 2.77 \mu\text{g}/\text{m}^3$ (median $11.3 \mu\text{g}/\text{m}^3$), a 1.3-fold increase in PM_{2.5} levels during the El Portal fire. The non-wildfire exposed control group (n=42) consisted of age-matched participants (median=16 yrs, 12-25 yrs) who had no obvious exposure to wildfires or prescribed fire from Fresno or the San Francisco Bay Area (160 miles away from the El Portal Fire). During the study period, mean PM_{2.5} levels in the San Francisco Bay Area were $5.1 \mu\text{g}/\text{m}^3$, approximately half of the Fresno PM_{2.5} levels during the wildfire. All smoke-exposed participants had their blood drawn either during the fire or immediately after until September 10, 2014. All participants were consented with an IRB-approved protocol. During the field office visit, each participant was given a detailed health and demographics questionnaire; vital signs and non-fasting blood samples were collected using validated techniques. Peripheral blood mononuclear cells (PBMCs) and plasma were purified from blood samples. Immune markers c-reactive protein (CRP), myeloperoxidase (MPO), interleukins IL-1 β and IL-13, and D-Dimer were assayed by the Stanford Human Immune Monitoring Center using Luminex technology. Vials from different time points and groups were mixed and run together to assure there were no batch effects. The Kruskal-Wallis test was used to compare markers between two groups.

Participant's baseline characteristics are summarized in the **Table**. There were no significant differences in baseline characteristics between groups. At the time of blood draw, asthma (defined per NHLBI guidelines) was reported in 16 (53.3%) of the 25 wildfire-exposed participants and in 10 of the 42 (40%) controls. Shown in the **Figure**, compared with control participants, the wildfire-exposed participants had significantly higher levels of CRP (median 189.5 vs 68; $p=0.017$) and IL-1 β (median 109 vs 85.12; $p=0.015$). Levels of D-Dimer, IL-18, or MPO were not significantly different between control vs. fire-exposed participants.

Our key findings that wildfire-exposed participants had significant increases in IL- β and c-reactive protein (CRP) levels compared with controls suggests a pro-inflammatory state exists after acute exposure in wildfires. These increases could lead to cardiopulmonary events associated with wildfire exposure. IL-1 β is a pro-inflammatory cytokine that plays a central role in the inflammatory processes in blood, lung, cardiac, and vascular tissues via the inflammasome, a sensor of cell injury. Increased CRP is associated with airflow obstruction and airway inflammation, and may serve as a surrogate marker of airway inflammation in asthma. In a study of 6183 adults living in a city of moderate pollution in Switzerland, exposure to PM₁₀ was shown to be associated with significantly higher levels of IL-1 β but not CRP.⁶ However, the large Framingham Heart study found short-term exposure to air pollutants, particularly PM_{2.5}, was associated with significantly higher levels of CRP in adults living in Boston, a city with moderate pollution levels⁷. Even slight increases in the distribution of inflammatory cytokines may represent a substantial health burden, particularly by increasing cardiovascular morbidity and mortality, and the significant increases in two key inflammatory markers we observed in the participants exposed to wildfire pollutants is a concern that should be further validated in a larger population. We explored changes in vital signs during the El Portal wildfire in these same participants and noted increased asthma medication use in the exposed group; no other trends for physiological parameters (Forced Expiratory Volume (FEV1), systolic blood pressure (BP) or diastolic BP, heart rate) were detected.

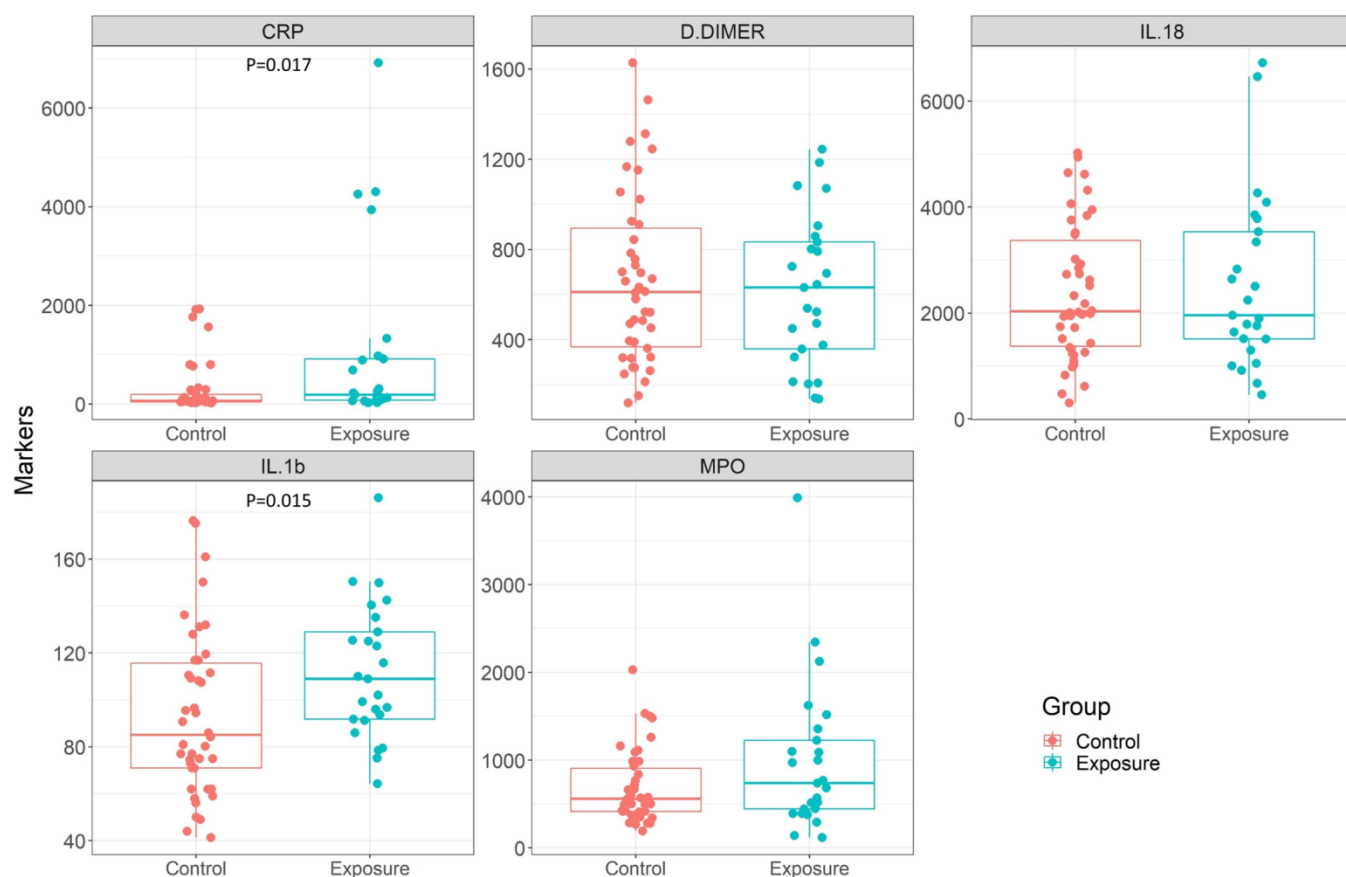
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In conclusion, this retrospective analysis in a limited number of participants showed that exposure to wildfire smoke increased two key proinflammatory markers CRP and IL-1 β . Such markers of oxidative stress and inflammasome activation have been linked to pollution exposure, particularly PM_{2.5}⁸. Respiratory and cardiovascular effects have been linked to wildfires as far as 200 to 300 miles from the fire zone⁹. Our wildfire-exposed group lived in Fresno, California, 62 miles from the El Portal fire in Yosemite Valley, whereas the control group lived in Fresno or the Bay Area during a period of time with no wildfire exposures. While this is a relatively small retrospective study and the PM levels do not distinguish from various sources including wildfires, these preliminary results suggest that future studies are needed to better understand the mechanism by which wildfire exposure can affect the immune and cardiovascular system long term.

Table. Baseline Characteristics of Control and Wildfire Exposure Participants

Demographic characteristic*	Overall	Control N=42	Exposure N=25
Age	16 [12, 25]	16 [12, 25]	17 [12, 23]
Female	32 (47.8%)	19 (45.2%)	13 (52.0%)
Ethnicity			
Hispanic	25 (48.1%)	12 (44.4%)	13 (52.0%)
African American	39 (73.6%)	18 (64.3%)	21 (84.0%)
White	27 (47.4%)	12 (37.5%)	15 (60.0%)
Chronic Asthma	26 (47.3%)	16 (53.3%)	10 (40.0%)
Cigarette smokers	13 (40.6%)	7 (41.2%)	6 (40.0%)
*Categorical and continuous variables reported as count (percent) and median (range), respectively			

Figure. Boxplots for markers for CRP, D-DIMER, IL-18, IL-1 β , and MPO for Control and wildfire-exposed (Exposure) participants.



Legend: CRP, C-reactive protein; MPO, myeloperoxidase.

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