Effect of prednisone on woodsmoke-induced sputum inflammation in healthy volunteers: A randomized, placebo-controlled pilot study

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Background: Inhalation of biomass smoke is associated with adverse respiratory effects in those with chronic pulmonary conditions. There are few published data regarding the effects of anti-inflammatory interventions on these outcomes.
Objective: Our aim was to assess the effects of postexposure prednisone on woodsmoke (WS)-induced sputum neutrophilia.
Methods: We carried out a randomized, placebo-controlled, crossover pilot study assessing the effect of a postexposure dose of 60 mg prednisone on induced sputum inflammation after controlled exposure to WS (500 μg/m^3 for 2 hours) in healthy adults who had been identified in a separate screening protocol as being "PMN responsive" to WS. Secondary end points were sputum cytokine level and mucociliary clearance as measured by γ-scintigraphy.
Results: A total of 11 subjects yielded complete data for the primary analysis. At 24 hours after WS exposure, there was a significant increase in sputum percentage of PMNs (%PMN) versus at baseline after placebo (median = 42% [IQR = 31%-53%]) (P = .02) but not after prednisone (median = 32% [IQR = 18%-40%]) (P = .09). Prednisone reduced Δ%PMN at 24 hours, but this difference did not reach statistical significance. However, for the 8 of 11 subjects who were PMN responsive after placebo, prednisone reduced Δ%PMN significantly (P = .05). Prednisone had no significant effects on sputum levels of IL-1β, IL-6, IL-8, or TNF-α. WS exposure tended to reduce mucociliary clearance in the placebo arm but not in the prednisone arm.
Conclusions: Prednisone taken immediately after exposure to WS mitigated short-term increase in sputum %PMN among healthy volunteers selected for their underlying inflammatory responsiveness to WS. Our data support future studies assessing anti-inflammatory interventions and the role of mucus clearance in WS-induced respiratory health effects. (J Allergy Clin Immunol Global 2025;4:100347.)

Key words: *Woodsmoke, sputum, neutrophils, inflammation, prednisone, mucociliary clearance*

Inhalational exposure to smoke from burning biomass is associated with adverse respiratory health effects in healthy individuals and in those with chronic pulmonary conditions.[1] There is strong epidemiologic evidence that exposure to wildfire smoke is associated with increased exacerbations of asthma and chronic obstructive pulmonary disease; experimental models suggest that woodsmoke (WS) inhalation can trigger lung inflammation and physiologic effects, but the outcomes appear to be variable and model specific.[2] We recently reported that 68% of healthy young adult nonsmokers were "PMN responsive" to a 2-hour controlled WS exposure (ie, they had a ≥10% absolute increase in sputum percentage of PMNs [%PMN] within 24 hours).[3] However, there are few published data on the effect of anti-inflammatory interventions on these outcomes.

We carried out a pilot study with the objective of assessing the effect of a single postexposure dose of the corticosteroid prednisone on WS-induced sputum inflammation, in a setting of exposure in a controlled chamber. As an exploratory objective, we also assessed the effect of WS (and prednisone) on mucociliary clearance (MCC).

METHODS

We carried out a placebo-controlled, randomized, crossover trial to assess the effect of a single immediate postexposure dose of prednisone (60 mg by mouth) on induced sputum inflammation 6 hours and 24 hours after the start of a controlled 2-hour exposure to WS (500 μg/m^3 with intermittent exercise every 15 minutes) (Fig 1). WS was generated from smoldering red oak in a controlled exposure chamber, as previously described.[4] Subjects were healthy volunteers aged 18 to 45 years who had been identified in a separate screening protocol as being PMN responsive to WS[3]; responsiveness was defined as at least a 10% absolute increase in sputum %PMN after controlled WS exposure. Participants were randomized with an allocation of 1:1 to 1 of 2 sequences: prednisone followed by placebo or placebo followed by prednisone. Sputum was induced by inhalation of hypertonic saline, as we have previously described.[3] The primary study end point was change in sputum %PMN (Δ%PMN = postexposure %PMN – preexposure %PMN), at the 6-hour and 24-hour time points after exposure. Additional exploratory end points included levels of sputum cytokines measured by ELISA

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Abbreviations used
BMI: Body mass index
Δ%PMN: Change in percentage of PMNs
FVC: Forced vital capacity
IQR: Interquartile range
MCC: Mucociliary clearance
%PMN: Percentage of PMNs
WBC: White blood cell
WS: Woodsmoke

(Mesoscale Discovery) and MCC measured by γ-scintigraphy before exposure and 2 hours after exposure, as previously described.[5]

The study sample size estimate (N = 12) was based on a power analysis at a significance level of .05 and target power of 80% with use of data from the WS screening study[3] and a prior study of ozone-induced sputum PMN response showing a 50% inhibition of WS-induced sputum PMN by prednisone.[6] The randomization schedule was generated by a colleague of the study statistician (H.Z.) using permuted block randomization with a block size of 4 (2 prednisone, 2 placebo) for the first treatment period of the protocol. The participants, coordinators, and investigators were blinded as to use of prednisone or placebo by maintenance of randomization codes in the investigational drug pharmacy alone. For the primary end point, data were analyzed by analysis of covariance with Δ%PMN as the dependent variable and adjustment for the difference in baseline %PMN as a covariate.[7] For other end points, WS and prednisone effects were analyzed by using descriptive statistics and the Wilcoxon matched pairs signed rank test to assess the change from the baseline.

WS exposures and all study visits were carried out at the University of North Carolina Center for Environmental Medicine, Asthma, and Lung Biology, and the US Environmental Protection Agency Human Studies Facility in Chapel Hill, North Carolina, from March 2019 to May 2023; there was an 18-month period during the coronavirus disease 2019 (COVID-19) pandemic during which recruitment was paused. The study was approved by the University of North Carolina Institutional Review Board (protocol 18-2196; initial application September 20, 2018) and listed at ClinicalTrials.gov (under the study identifier NCT03861390). We used the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines[8] (see Table E1 in the Online Repository at www.jaci-global.org).

RESULTS

Participant demographics

A total of 13 subjects enrolled; 12 of them completed the protocol (Fig 2). Of these 12, 7 (58%) self-identified as female. In terms of race and ethnicity, 1 (9%) self-identified as Asian, 2 (17%) as Black/African American, 9 (75%) as White, and 1 (9%) as Hispanic/Latino. The mean age at enrollment was 31.7 years (range 21.0-41.5 years), and the mean body mass index (BMI) was 27.5 m^2/kg (range 19.0-40.8 m^2/kg).

Technical and safety end points

The exposure chamber data for WS $PM_{2.5}$ and other monitored factors are shown in Table E2 (in the Online Repository at www.jaci-global.org). There were no serious adverse events related to the exposures. Spirometric lung function was tested before and after exposure in both study arms. Although the overall medians did not change, in the paired analysis there was a slight but statistically significant decrease in forced vital capacity (FVC) percent predicted at the time point 6 hours after exposure versus at baseline (before exposure) in both the placebo and prednisone arms. At 24 hours, FVC value did not differ from baseline in either arm (see Table E3 in the Online Repository at www.jaci-global.org). Baseline (before WS exposure) peripheral blood white blood cell count (WBC) did not differ between the arms. There was a statistically significant increase in WBC count 6 hours after WS exposure in both arms, but the difference was still within normal limits (see Table E4 in the Online Repository at www.jaci-global.org). WBC count returned to baseline by 24 hours after exposure in the placebo arm but not in the prednisone arm.

Sputum neutrophils

Samples from 11 participants yielded complete sputum cell differential data sets for the analysis. Raw data for %PMN in the sputum are shown in Fig 3. The pre-WS baseline sputum %PMNs did not differ between the placebo arm (median = 17% [interquartile range (IQR) = 6%-31%]) and the prednisone arm (median = 22% [IQR = 10%-29%]). At 24 hours after exposure, there was a significant increase in %PMN versus at baseline in the placebo arm (median = 42% [IQR = 31%-53%]) (P =.02) but not in the prednisone arm (median = 32% [IQR = 18%-40%]) (P = .09). A similar pattern was observed for number of PMNs per mg of sputum (Table I), although the increase in number of PMNs per mg of sputum did not reach statistical significance in either arm.

Regarding the primary study outcome, which was *change* in sputum percentage of neutrophils versus at the pre-WS baseline (Δ%PMN), prednisone was associated with a reduced median Δ%PMN at 24 hours after exposure, but this difference did not reach statistical significance (P = .29 [Fig 4, *A*]). However, for the 8 subjects who were PMN responsive according to the study's predetermined criterion, as indicated by at least a 10% increase in absolute %PMNs versus at baseline in the placebo arm, the prednisone effect on Δ%PMN was statistically significant at 24 hours (P = .05 [Fig 4, *B* and see Table E5 in the Online Repository at www.jaci-global.org]). It should be noted that the baseline, pre-placebo sputum %PMN for the 3 PMN nonresponders ranged from 24% to 83% (ie, higher values than for most of the PMN responders, whose baseline values ranged from 2% to 29%).

Other sputum inflammatory end points

At 24 hours after exposure, the percentages of macrophages in the sputum were significantly decreased versus at baseline in the placebo arm but not in the prednisone arm, as expected from the results for % PMN. Macrophage numbers per mg of sputum at 24 hours were decreased significantly versus at baseline in the prednisone arm. Most participants had few or no sputum eosinophils, and there was no significant overall effect of either WS exposure (vs baseline) or prednisone (vs placebo) on percentage of eosinophils in the sputum, but the 2 participants who appeared to have WS-induced sputum eosinophilia (<1% eosinophils at baseline and ≥5% eosinophils after WS with placebo arm) both had 0% eosinophils after prednisone. In the analysis of sputum cytokines (Table II), there was a significant increase in IL-1β level versus at baseline in prednisone arm but not in

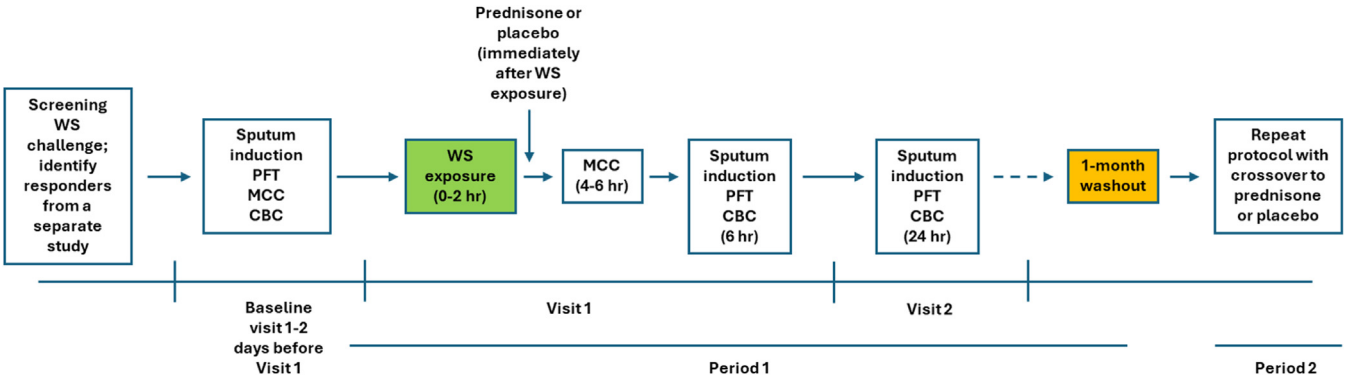

FIG 1. Study protocol diagram. *CBC*, Complete blood count; *PFT*, pulmonary function test (spirometry); *WSP*, WS particles.

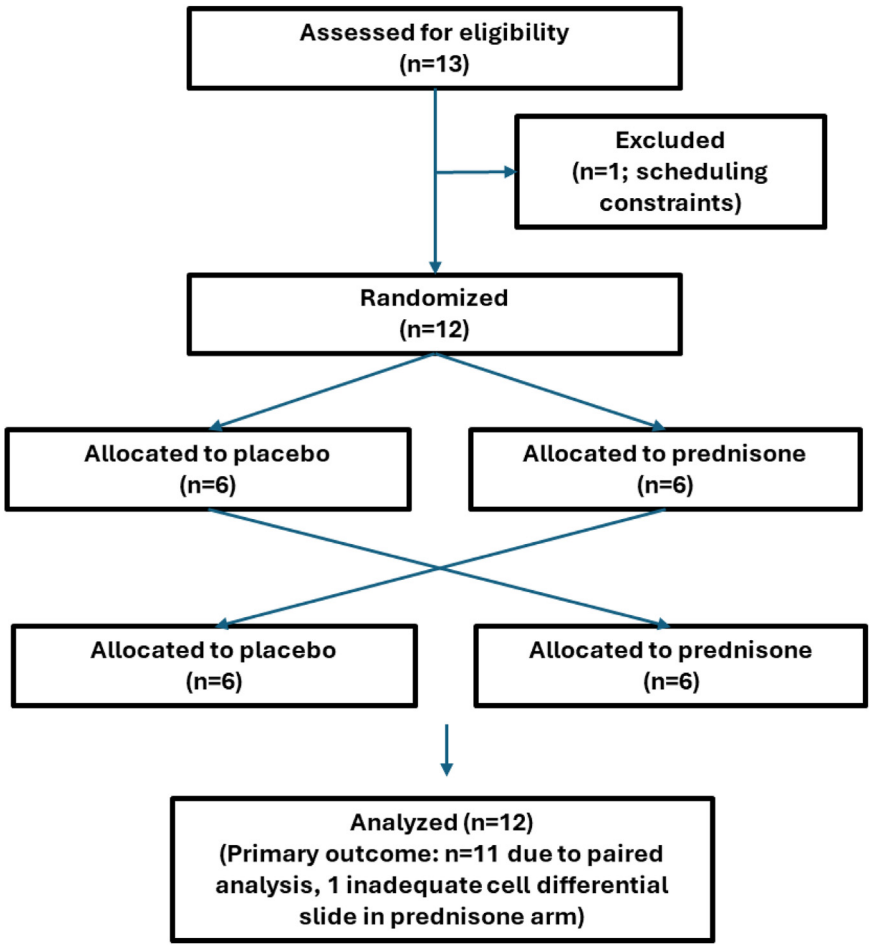

FIG 2. Study enrollment, allocation, and analysis diagram.

the placebo arm. There were no statistically significant effects of either WS or prednisone on sputum levels of IL-6, IL-8, or TNF-α.

MCC

Measurement of MCC was included in the study as an exploratory end point. In the placebo arm, MCC after WS exposure tended to be lower than before WS exposure, an effect that was statistically significant if the analysis was limited to the WS responders (Table III). In the prednisone arm, MCC was not lower after WS exposure, although the preexposure MCC appeared to be lower in that arm. Because prednisone administration after WS exposure occurred just 2 hours before the start of MCC testing, which was possibly too early to see a treatment effect, we also averaged the MCC data for each subject in the 2 arms (placebo vs prednisone). The averaged post–WS exposure MCC (median clearance value at 120 minutes = 12.7 [IQR = 10.9-16.1]) tended to be decreased versus at the preexposure

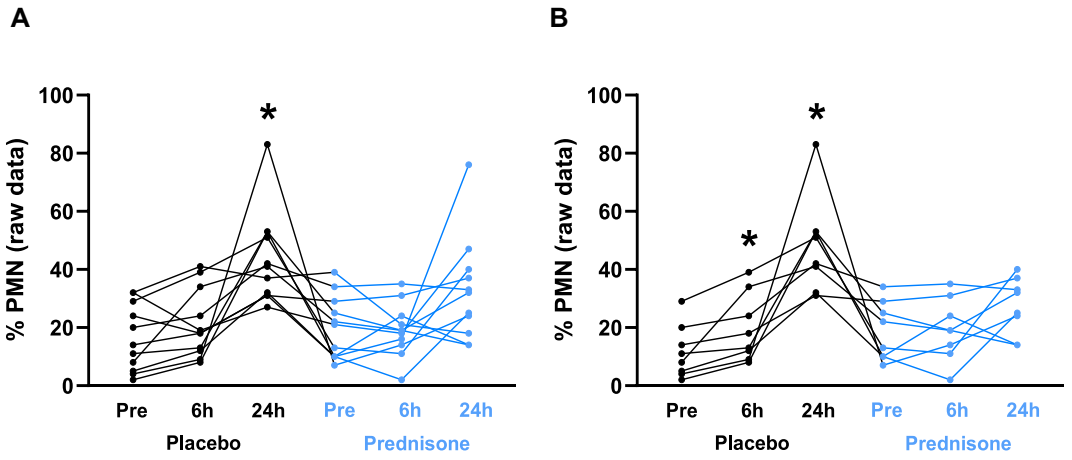

FIG 3. Raw data on sputum %PMN for all 3 time points in the placebo and prednisone arms. **A,** Data for all 11 subjects completing the protocol. **B,** Data for 8 subjects who were PMN responsive to WS (a ≥10% increase in absolute %PMN over baseline in the placebo arm). *$P < .05$ versus at the pre-WS baseline.

TABLE I. Sputum differential cell counts for PMNs, macrophages, and eosinophils

	Placebo			Prednisone		
Cell type	**Pre-WS**	**6 h after WS**	**24 h after WS**	**Before WS**	**6 h after WS**	**24 h after WS**
n	12	12	12	12	11*	11*
%PMN, median (IQR)	14 (5-29)	18 (12-34)	41* (31-53)	21 (10-29)	19 (14-24)	32 (18-40)
PMN/mg of sputum, median (IQR)	78 (27-322)	87 (50-302)	196 (50-400)	129 (47-291)	136 (115-218)	97 (36-651)
%MACs, median (IQR)	82 (68-90)	79 (64-88)	53* (45-64)	77 (69-90)	80 (75-86)	68 (55-77)
MACs/mg of sputum, median (IQR)	460 (195-1162)	554 (206-986)	220 (34-815)	530 (217-1865)	918 (481-1274)	367† (58-1146)
%EOSs, median (IQR)	0 (0-0.2)	0 (0-0)	0 (0-0.5)	0 (0-0.2)	0 (0-0.3)	0 (0-0.2)
EOSs/mg of sputum, median (IQR)	0 (0-0.5)	0 (0-0)	0 (0-0.8)	0 (0-0.7)	0 (0-0.2)	0 (0-0)

EOS, Eosinophil; *MAC*, macrophage.
*In the prednisone arm, 1 subject had inadequate sputum cells to make a differential slide at 6 hours and 24 hours.
†$P < .05$ vs preexposure baseline according to the Wilcoxon matched pairs signed rank test.

baseline (median = 16.2 [IQR = 12.6-19.8]). This change from before exposure to after exposure did not reach statistical significance ($P = .13$), but if only the PMN responder participants' data were included in the analysis, the decrease in MCC was statistically significant ($P = .04$ [Fig 5 and Table III]). The central-to-peripheral ratio for initial radioaerosol deposition associated with the MCC measurements did not vary significantly under any of the study conditions or time points. Therefore changes in central-to-peripheral ratio associated with WS exposure or prednisone versus placebo did not affect the MCC findings.[5]

DISCUSSION

The health effects of WS inhalation, especially in asthmatic individuals, are of increasing concern owing to climate change–induced increases in exposure. Experimental data in animal models suggest that inhalation of WS can induce respiratory inflammation, as evidenced by increased cytokines or inflammatory cells in lavage fluid; however, the responses in these models appear to be variable and model dependent.[9,10] In this small randomized, placebo-controlled crossover trial, we observed that healthy volunteers exposed to WS at 500 $\mu g/m^3$ for 2 hours followed by placebo had a significant increase in sputum neutrophils 24 hours later, but when WS exposure was followed by a single 60-mg dose of oral prednisone taken immediately after exposure, there was not a significant increase in sputum neutrophil levels (Fig 3). Among our volunteers who were actually PMN responsive according to the study definition in the placebo arm, the effect of prednisone was statistically significant in the primary analysis (Fig 4). Of the 3 participants with the highest BMI in the study, 2 were nonresponders. Although subgroup analyses cannot provide definitive answers in so small a study, BMI may be an important consideration in the design of future studies.

We also noted a trend toward reduction in MCC after WS exposure versus at baseline, which was not as pronounced in the prednisone arm. Although our study did not include a filtered air control arm and was not designed to provide a definitive answer for the effects of WS on MCC, our results suggest the possibility that WS exposure may inhibit mucus clearance and that WS-induced inflammation could be linked with this effect. We believe this to be the first report of a potential impact of WS exposure on MCC.

The WS exposure protocol that we used appeared to be well tolerated, as in previous studies utilizing the same protocol. There was an increase in peripheral blood leukocyte counts after WS exposure; the increase resolved by 24 hour in the placebo arm but persisted in the prednisone arm, perhaps owing to leukocyte demargination. However, peripheral leukocyte counts remained within the normal range at all time points. Of note, our participants showed a slight and transient decrease in FVC after WS exposure in

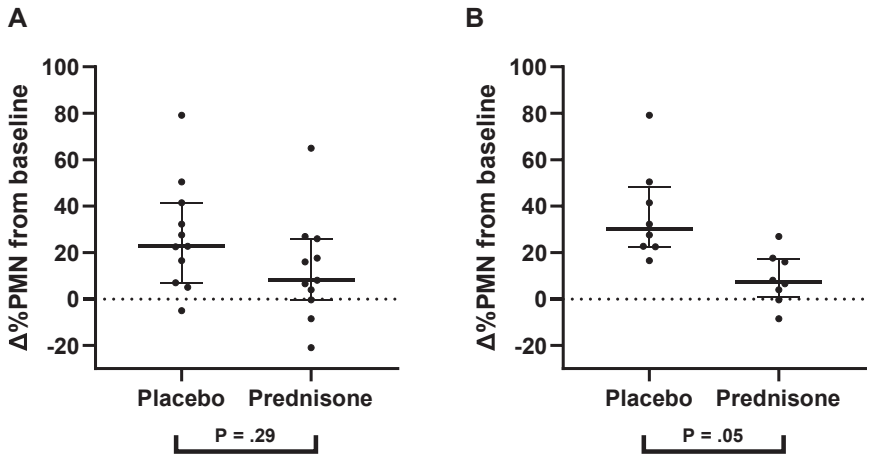

FIG 4. Effect of prednisone or placebo on WS-induced change in %PMN from baseline, at 24 hours after WS exposure. Bars indicate medians and interquartile ranges. **A**, Results for all subjects. **B**, Results for WS responders (a ≥10% increase in absolute %PMN after WS exposure + placebo).

TABLE II. Sputum cytokines

	Placebo			Prednisone		
Cytokine	**Before WS**	**6 h after WS**	**24 h after WS**	**Before WS**	**6 h after WS**	**24 h after WS**
IL-1β level (pg/mL), median (IQR)	724 (314-956)	490 (274-909)	513 (307-1058)	408 (280-636)	413 (271-643)	711* (479-1120)
IL-6 level (pg/mL), median (IQR)	295 (85-1043)	412 (118-839)	391 (106-765)	268 (117-473)	407 (170-564)	500 (226-747)
IL-8 level (pg/mL), median (IQR)	15.7 (8.8-26.1)	12.3 (9.2-24.4)	18.8 (7.6-32.0)	13.8 (3.1-22.3)	15.2 (5.3-27.2)	12.7 (6.7-41.4)
TNF-α level (pg/mL), median (IQR)	51 (3-462)	48 (1-334)	33 (1-251)	12 (1-211)	9 (1-204)	96 (19-330)

*$P < .05$ vs pre-WS baseline according to the Wilcoxon matched pairs signed rank test.

TABLE III. MCC data: Median mucociliary clearance values at 120 minutes

	Placebo			Prednisone			Avg placebo, prednisone		
Group, median (IQR)	**Before WS**	**After WS**	**Δ**	**Before WS**	**After WS**	**Δ**	**Before WS**	**After WS**	**Δ**
All participants (n = 12)	18.0 (14.5-21.3)	14.5 (12.3-17.5)	-3.0 (–5.6 to 1.0)	13.5 (10.5-21)	12.0 (7.3-17.8)	–0.2 (–4.3 to 2.7)	16.2 (12.6-19.8)	12.7 (10.9-16.1)	–1.2 (–5.6 to 0.6)
Responders only (n = 9)	19.0 (17.0-23.5)	15.0* (13.0-21.0)	-4.4 (–6.0 to 0.8)	14.0 (11.0-21.5)	11.0 (7.0-19.0)	–1.2 (–5.5 to 2.1)	16.9 (15.2-21.1)	12.7* (11.3-19.2)	–1.6 (–6.3 to –0.4)

Avg, Average.
*$P < .05$ vs Baseline (according to the Wilcoxon matched pairs signed rank test).

both treatment arms, an observation that was also made in the screening study preceding this trial.[3] Although the change observed may not be clinically important for healthy people, a similar change in FVC persisted long term in young primates exposed to wildfire smoke in a previous report.[11] Thus, it is possible that frequent or prolonged exposures to WS could induce more significant changes in lung function, which may be of concern for children or those with chronic pulmonary conditions.

The limitations of our study include its small sample size and a focus on short-term exposure and biologic outcomes. The clinical relevance of smoke from a single type of biomass such as that tested by us is unclear, especially when one considers the fact that many real-world exposures are from more complex fuel sources, such as burning structures at the wildland-urban interface or military burn pits.[12] In addition, sputum induction can itself introduce inflammatory artifacts with frequent serial testing,[13,14] although the low frequency and time intervals between sputum inductions in our protocol make it more likely that WS induced the inflammation observed. In addition, we previously carried out a controlled ozone exposure study that utilized the same sequence of induced sputa and included a filtered-air control, but found no increase in %PMN resulting from the inductions.[15]

Smoldering red oak has previously been shown to induce bronchoalveolar fluid neutrophilia[16] and has been analyzed chemically in a comparative study in mice; in addition, it contains polycyclic aromatic hydrocarbon and other toxins.[17] Previous human studies of controlled exposure to WS have found a variety of inflammatory and cytotoxic effects but have not consistently found evidence for short-term lower respiratory neutrophilia[18] (Table IV).[3,4,15,16,19-26] Potential sources of this variation include use of other wood species, exposure to lower concentrations of particulate matter, and differences in sampling methods for respiratory inflammation. In addition, prior studies have not selected for study participants who have previously shown PMN responsiveness to WS, as we did here. Although this preselection may limit the generalizability of our results, it may also reinforce the need to focus studies on susceptible subgroups.

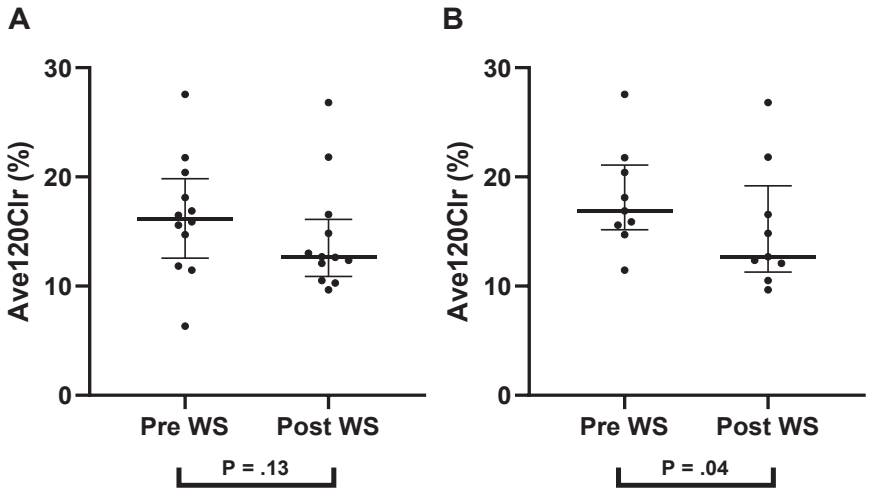

FIG 5. Averaged MCC results before versus after WS exposure for the placebo and prednisone arms. **A**, Data for all 11 subjects completing the protocol. **B**, Data for 8 subjects who were PMN responsive to WS (a ≥10% increase in absolute %PMN over baseline in the placebo arm). *$P < .05$ versus at the pre-WS baseline.

TABLE IV. Previously published studies of controlled exposure to WS in humans, with focus on respiratory inflammation results

Study	Study design	WS exposure	Respiratory inflammation
Sehlstedt M et al, 2010[19]	Randomized, WS vs filtered air	Spruce and pine, 3 h, 224 μg/m^3	No impact on BALF inflammation at 24 h after WS
Stockfelt L et al, 2012[20]	Sequential exposure to air and WS at startup and burnout phase	Birch and spruce, 3 h, 146-295 μg/m^3	Increased FENO level after exposure to burnout phase
Riddervold IS et al, 2012[21]	Randomized crossover (air vs WS)	Beech, 3 h, 200-400 μg/m^3	No effect of WS on nasal inflammation
Ghio A et al, 2012[16]	Nonrandomized, crossover filtered air, then WS	Red oak, 2 h, 500 μg/m^3	Increased %PMN in BALF at 20 h after WS exposure
Muala A et al, 2015[22]	Randomized crossover (WS vs filtered air)	Birch, 3 h, 314 μg/m^3	Decreased counts of PMNs and lymphocytes in BW, BALF; increased lymphocyte and mast cell counts in endobronchial biopsy samples
Ferguson MD et al, 2016[23]	Sequential exposure to air and WS	Western larch, 1.5 h, 250 μg/m^3 and 500 μg/m^3	Increased 8-isoprostane in EBC 1 h after WS
Burbank A et al, 2019[24]	Observational before vs after WS exposure	Red oak, 2 h, 500 μg/m^3	Increased sputum %PMN at 24 h after exposure
Rebuli M et al, 2019[4]	Randomized, WS vs filtered air, followed by nasal LAIV inoculation	Red oak, 2 h, 500 μg/m^3	Sex-specific effects of WS on nasal inflammatory response to LAIV
Alexis NE et al, 2022[3]	Observational, before vs after WS exposure	Red oak, 2 h, 500 μg/m^3	50%-60% of healthy volunteers had a ≥10% increase in sputum %PMN after WS exposure
Peden DB et al, 2023[25]	Randomized crossover (γ-tocopherol vs placebo)	Red oak, 2 h, 500 μg/m^3	Reduced sputum eosinophilia with γ-tocopherol
Hansson A et al, 2023[26]	Randomized crossover (WS vs filtered air)	Birch, 2 h, 400 μg/m^3	Increased eosinophil count in BALF

Studies summarized include those reviewed by Schwartz et al (2020)[15] and additional studies found by searching PubMed for the term *controlled wood smoke exposure* from 2020 to 2024.
BALF, Bronchoalveolar lavage fluid; *BW*, bronchial washing; *EBC*, exhaled breath condensate; *FENO*, fractional exhaled nitric oxide; *LAIV*, live attenuated influenza virus.

Despite these caveats, our data suggest that an existing, widely available treatment may reduce the acute inflammatory impacts of exposure to biomass smoke. This might have clinical relevance in high-risk groups such as asthmatic individuals, in whom inflammation is a driver of disease, or in the setting of occupational or military exposures to smoke, which have been linked to reduced lung function.[27] Rosser et al[28] recently reported that exposure to particulate matter smaller than 2.5 μm in prior

year was associated with lower lung function in asthmatic children, but this was not affected by use of inhaled corticosteroids. To our knowledge, however, there are few other published data directly testing interventions for smoke exposures in humans. We speculate that "rescue" use of oral or inhaled corticosteroids targeted to the timing of exposure could be used to safely reduce acute wildfire smoke–induced airway inflammation, especially in at-risk groups. If our results are confirmed in larger studies, such interventions might be included in asthma treatment guidelines, which currently focus on avoidance of exposure on days with poor air quality. Although we did not find significant effects of WS or prednisone on a limited panel of sputum cytokines, future studies might also identify specific cytokines as therapeutic targets. In addition, our data preliminarily suggest that one mechanism underlying the clinical impacts of wildfire smoke on people with asthma and other chronic respiratory disorders could be inhibition of mucus clearance. The results of the current study will be useful in designing protocols to test such interventions more definitively. Future research should include investigations of additional topics such as specific chemical triggers of inflammation in complex smoke mixtures and specific inflammatory pathways responsible for the clinical effects of exposure in susceptible populations.

DISCLOSURE STATEMENT

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Disclosure of potential conflict of interest. The authors declare that they have no relevant conflicts of interest.

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Key messages

- **In a randomized placebo-controlled pilot study, a single dose of prednisone taken immediately after WS exposure mitigated short-term increase in sputum %PMN among healthy adult volunteers who had been selected for underlying inflammatory responsiveness to WS.**
- **WS exposure tended to reduce MCC, but the impact of prednisone on this was unclear.**
- **Our data support future studies assessing anti-inflammatory interventions and the role of mucus clearance in smoke-induced respiratory health effects, especially in at-risk groups.**

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