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Controlled Chamber Studies Showed Protective Effect of Nonsteroidal Antiinflammatory Drugs against Ozone Exposure: The Stage Was Set for Broader Epidemiologic Investigation

To the Editor:

I read with interest the recent article by Gao and colleagues (1) titled, "Nonsteroidal Antiinflammatory Drugs Modify the Effect of Short-Term Air Pollution on Lung Function," which examined the role of nonsteroidal antiinflammatory drugs (NSAIDs) in particulate matter (PM)-induced changes in lung function in the Normative Aging Study cohort. In the Discussion section, the authors state, "To the best of our knowledge, this is the first study on the subclinical preventive effects of NSAIDs against the adverse effects of air pollution on lung function." I respectfully submit to the authors that, with regard to examining the potential role that NSAIDs play in modifying respiratory effects of air pollution exposure, that stage had already been set, albeit not using epidemiologic studies, but rather using controlled human chamber exposure studies. For example, Alexis and colleagues (2) examined the pretreatment effect of the NSAID indomethacin in both individuals with asthma and healthy individuals exposed for 2 hours to 400-ppb ozone (not PM). That study reported that indomethacin significantly attenuated ozone-induced decreases in FVC and FEV_1 in healthy subjects but not subjects with asthma; furthermore, there was a marked attenuation of ozone-induced decrements in forced expiratory flow (FEF) at 75% of the FVC and FEF at 60% of the FVC based on partial flow volume curves in subjects with asthma but not in healthy subjects. Alexis and colleagues concluded that cyclooxygenase metabolites of the arachidonic acid pathway, such as prostaglandin $F_{2\alpha}$, contribute to restrictive changes in healthy individuals and obstructive small airway changes in individuals with asthma. Other studies by Schelegle and colleagues (3), Eschenbacher and colleagues (4), Ying and colleagues (5), and Hazucha and colleagues (6) also used indomethacin (or similar NSAIDs), not only to implicate the involvement of cyclooxygenase metabolites as a potential mechanism of response in air pollution (ozone)-induced spirometric responses but also to demonstrate NSAIDs' mitigating effect on lung function decrement after ozone exposure. In particular, Hazucha and colleagues (6) showed that the NSAID ibuprofen blunted the ozone-induced decrease in FEV_1 (7% vs. 17%) and caused a concomitant inhibition of increases in respiratory tract prostaglandin E_2 and thromboxane B2 concentrations.

The study by Gao and colleagues, together with previous controlled chamber studies with ozone, expands the potential beneficial role of NSAIDs as protectors against both gaseous and PM-induced health effects, the latter involving fine PM ($PM_{2.5}$) and black carbon, at ambient concentrations. The strengths of the study by Gao and colleagues lie in its use of a large epidemiologic data set (3,220 medical visits of 1,078 white participants between 1995 and 2012 with available data of lung function, PM exposures, and NSAID use), strong statistical modeling (time-varying linear mixed-effects regression with random participant-specific intercepts), and the inclusion of nongaseous air pollutants $PM_{2.5}$ ($\mu g/m^3$) and black carbon ($\mu g/m^3$). ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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Reply to Alexis

From the Authors:

We appreciate the valuable opinion shared by Dr. Neil E. Alexis on our article on the modifying effect by nonsteroidal antiinflammatory

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drugs (NSAIDs) on the association of short-term air pollution with lung function (1). We highly agree with him that similar modifying effects of NSAIDs had been previously described by controlled human chamber exposure studies with ozone. Chamber exposure studies have great advantages in that they allow to control both the exposure and the NSAID treatment. Yet, they are typically small in scale and may benefit from investigations that generalize their results in population studies. To the best of our knowledge, our study is the first larger-scale study on the modifying effects of NSAIDs among elderly adults (>55 yr-old).

To confirm our statement, we searched PubMed again for articles published up to February 18, 2020 that investigated the effect of NSAIDs on lung function decline in response to air pollution. We used the search terms "nonsteroidal antiinflammatory agents", "aspirin", "lung function", "air pollution", "$PM_{2.5}$", "black carbon", "ozone", "particle number", "carbon monoxide", "sulfur dioxide", and "nitrogen dioxide" in various combinations. We did not identify any population-based studies of older adults. Hence, together with the controlled human studies from Dr. Alexis' (2) and other teams, our cohort findings are important to support the hypothesis that NSAIDs treatment may protect against the adverse effects of air pollution on lung function. The evidence to date indicates the need for further validations based on well-powered randomized controlled clinical trials on NSAIDs in elderly adults.

We welcome continued dialogue and collaborations with pulmonologists, clinical research specialists, epidemiologists, and environmental health scientists to help elucidate the roles of NSAIDs in the prevention of air pollution–related pulmonary outcomes. Collaboration among all relevant parties will be instrumental in the potential implementations of NSAIDs and other antiinflammatory agents for environmental respiratory health research. ■

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