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Does Breathing Wood Smoke Make the Flu Worse? Sex Might Matter

We all know influenza can be bad. Aside from the fevers, cough, miserable body aches, and severe fatigue, people can actually die from it. Pregnant women, young children, and the elderly are most at risk for mortality. Recent modeling estimates (1) suggest the global mortality from seasonal influenza has been previously underestimated. From 1999 to 2015, influenza accounted for as many as 645,000 annual excess respiratory deaths, with likely many additional circulatory deaths. The highest mortality rates occurred in sub-Saharan Africa and Southeast Asia in people older than 75 years.

Air pollution can also be bad, especially in developing countries. According to the World Health Organization, ambient air pollution caused 4.2 million premature deaths in 2016, with 91% of these in low- and middle-income countries (2). This does not include the health risks for the approximately 3 billion people that cook or heat their homes with kerosene, coal, and biomass fuels, including wood.

But what if air pollution takes influenza from bad to worse? This could mean that air pollution is increasing influenza mortality, in addition to its own significant mortality. In this issue of the *Journal*, Rebuli and colleagues (pp. 996–1007), in their clinical study (3), addressed the question of whether exposure to wood smoke worsens epithelial mucosal responses to influenza virus infection. Their experimental model is nasal inoculation with the influenza virus vaccine, which is a mixture of live attenuated influenza viruses (LAIV), followed by nasal lavage. Thirty-nine healthy men and women were randomly exposed for 2 hours at rest to filtered air or wood smoke, followed by LAIV inoculation. Nasal lavage was performed before and 1 and 2 days after exposure/viral challenge, with assessment of changes in the expression of 255 genes and 30 cytokine proteins involved in inflammation. The researchers also assessed expression of viral genes as markers of infection and replication.

LAIV infection caused the expected changes in inflammatory gene expression, including the expression of viral genes, confirming infection and replication. Surprisingly, the primary analysis showed no significant wood smoke effects on any of the 255 inflammatory response genes. Only IP-10 (IFN-γ–induced protein 10 kDa) and IL-6 increased after LAIV; wood smoke partially suppressed the increase in IP-10.

However, in a planned secondary analysis, sex interacted significantly with exposure for 25 genes. Subsequent sex-specific analyses confirmed sex differences in gene expression before exposure, and in response to wood smoke. Many more genes were upregulated in men than in women before exposure. In the subjects exposed to filtered air followed by LAIV, women showed a more robust response than men. In the 8 men exposed to wood smoke compared with the 9 men exposed to filtered air, 13 genes increased expression more than twofold. In the 12 women exposed to wood smoke compared with 10 exposed to filtered air, 18 genes were differentially expressed, all downregulated, mostly less than twofold. Thus, the men had more inflammatory gene expression than women at baseline, with some genes increasing further with wood smoke and LAIV. Women had reduced gene expression at baseline, increased responses to filtered air/LAIV, and slight suppression of responses after wood smoke/LAIV. These wood smoke changes in opposite directions explain the negative outcome in the primary aggregate analysis.

Sometimes we fail to consider the possibility of sex differences in the design of clinical studies, including previous studies of wood smoke exposure (4), and Rebuli and colleagues make an important contribution in this regard. The biological differences between men and women may affect their responses to a variety of environmental insults, including air pollutants and influenza virus. Men and women differ in their ability to control a long list of viral infections, including influenza virus, and mortality from viral infections is generally greater in men

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than women (5). Humoral and cellular antiviral immune responses are stronger in women. However, this could also increase aberrant responses such as autoimmunity in women relative to men. Ghosh, and colleagues (5) have reviewed the mechanisms involved for these sex-related differences. Of course there are the hormonal influences. And it turns out that many immune response genes are encoded on the X chromosome. One of the two X chromosomes is inactivated in female cells. Thus, a loss-of-function mutation in one of these X-linked immune response genes would be expressed in one-half of the cells in women, but all the cells in men, resulting in increased X-linked immunodeficiency in men.

We know that inflammation can be both good and bad. Good is controlling infection; bad is contributing to the symptoms and tissue damage in influenza. Although men are less able than women to mount an immune defense against the influenza virus, the findings of Rebuli and colleagues suggest that men have increased expression of inflammation-related genes in the nasal mucosa relative to women at baseline, and further increase inflammatory gene responses to LAIV infection with prior exposure to wood smoke. Thus, men have more difficulty than women in fighting off influenza, and prior wood smoke exposure may enhance the inflammatory response, and hence the severity, of influenza.

There are important limitations to this study. We do not know the degree to which the sex differences in gene expression observed by Rebuli and colleagues in response to wood smoke and LAIV are the result of shifts in the type of cells recovered from the nose. We are not provided with a differential cell count for the nasal lavage, but it is likely that the observed changes in gene expression reflect in part an influx of inflammatory cells into the nose in response to these combined challenges, rather than just changes in gene expression of resident nasal epithelial cells.

Also, it needs to be kept in mind that this study was not optimally designed to examine sex differences. Such a study would ideally include equal and sufficient numbers of men and women, with restricted, balanced randomization by sex to wood smoke versus filtered air. Perhaps the biggest problem is the relatively small number of subjects in each exposure group; for example, 8 men exposed to wood smoke and 9 to filtered air. This increases the possibility of spurious results that may not hold up in a larger study. Thus, these findings should be considered hypothesis generating, and not definitive.

Despite these limitations, Rebuli and colleagues have made important contributions to our understanding of interactions among a pollutant exposure, influenza virus infection, and sex. Their data remind us that males differ from females, sometimes with opposing effects that may "cancel" each other in aggregate analyses. Sex needs to be considered in study design, especially with regard to immune and inflammatory responses. ■

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A New Tool to Capture Patients' Perceptions of the Effects of Lung Transplantation

For patients with many incurable, life-shortening lung conditions, lung transplantation offers "curative" therapy and the only therapeutic option with a reliable chance to improve their quality of life (QOL). But what is really meant by the term "QOL," and how do we measure this abstract construct?

For individuals, QOL refers to their perceptions of how well their needs and wants are met across dimensions of life that matter most to them. Thus, accurate assessments of QOL require knowledge of patients' perceptions, their needs and wants, and the dimensions of life they care about. Carefully crafted questionnaires, developed with systematically collected input from patients with the condition of interest, can capture all these things.

Until now, investigators and other stakeholders interested in examining the effect of lung transplantation on a person's QOL have had to rely on existing questionnaires (1–3). However, none of those questionnaires adequately address all of the domains that

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