Joint Association of Long-term Exposure to Both O-3 and NO2 with Children's Respiratory Health
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adjustment for age and smoking, urinary cadmium was higher in women of higher parity (nulliparous: 0.227 μg/g-cr; ≥3 children: 0.261 μg/g-cr), and in postmenopausal (0.254 μg/g-cr) compared with premenopausal (0.233 μg/g-cr) women.

In contrast to a previous report, no association was observed between urinary cadmium tertile and BI-RADS category, comparing BI-RADS 3 or 4 to 1 or 2 (Table). Results were similar when analysis was restricted to never-smokers (P interaction: 0.75) or postmenopausal women (P interaction: 0.34); when repeated with women with >1 μg/g-creatinine as the highest exposure group; and when BI-RADS 3 and 4 were analyzed separately.

The women in this study were recruited through the “Army of Women,” a nationwide pool of breast cancer study volunteers. Therefore, participating women may not be representative of US women, and our study sample differs from the earlier study. The range of urinary cadmium we observed was comparable with representative samples of US women, while the prevalence of high mammographic density was higher than reported for similarly aged US women. Overall, our study included an adequate range of both urinary cadmium and mammographic density to have detected an etiologic relationship, if present.

We used BI-RADS ratings recorded in routine mammography reports from participants’ community mammogram providers, a feasible approach for epidemiologic studies compared with obtaining mammogram images and measuring percent mammographic density. Moreover, good correlations between BI-RADS and percent mammographic density, and in BI-RADS assignment between readers, have been demonstrated. Thus, we expect that misclassification of BI-RADS may have modestly biased our results toward a null finding.

In summary, although cadmium is a putative “metallohormone,” we did not find evidence that cadmium exposure as measured in urine was associated with breast density. If cadmium is a risk factor for breast cancer, our findings might imply that this relationship is independent of breast density.

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Joint Association of Long-term Exposure to Both O₃ and NO₂ with Children’s Respiratory Health

To the Editor:
Recent studies have suggested associations between long-term exposure to ozone and respiratory health. These studies have generally characterized...
exposure at relatively large spatial scales (i.e., several km). Epidemiologic studies of nitrogen oxides and particulate matter have increasingly focused on intraurban variability in concentrations. These studies generally did not include O₃. In the Netherlands, we observed high negative correlations between long-term average O₃ and NO₂, suggesting that effect estimates for both NO₂ and O₃ may be biased to the null in single-pollutant analyses.³

We reported associations between NO₂ and children's respiratory health from the Dutch prospective PIAMA (Prevention and Incidence of Asthma and Mite Allergy) birth cohort study, but this study did not include O₃.⁴ In this letter, we report the joint association of long-term exposure to both O₃ and NO₂ with children’s respiratory health in the PIAMA study, taking into account the intraurban variability in both pollutants. The institutional review boards of the participating institutes approved the study protocol, and written informed consent was obtained from the parents or legal guardians of all participants.

Information on children's respiratory health was collected by questionnaire annually until age 8 years, and at ages 11 and 14 years, for 3,702 children. A medical examination, including spirometry, was performed at age 12 for 1249 children. We estimated summer average O₃ and annual average NO₂ concentrations at the participants' home addresses at birth and follow-up contacts with land-use regression models.³⁵ Summer average concentrations were used for O₃ because of its strong seasonal variation.³ We selected the same health endpoints, statistical models, and confounders as before.⁴ We report associations with exposure at the birth address for symptoms and at the current address for lung function, as before¹ (Table). Long-term average exposure to NO₂ and O₃ were highly negatively correlated (R = −0.8). In single pollutant models, O₃ tended to be negatively associated with respiratory symptoms and positively associated with lung function. In contrast, NO₂ was positively associated with respiratory symptoms and negatively associated with lung function. In two-pollutant models, effect estimates for NO₂ increased moderately and effect estimates for ozone became positive for symptoms and negative for lung function. Ozone effect estimates were moderately smaller (per interquartile range [IQRw]) than NO₂ estimates, but less precise. For example, for asthma incidence the odds ratio (95% confidence interval) per IQRw was 1.21 (1.01, 1.44) for NO₂ and 1.13 (0.88, 1.46) for O₃.

Variance inflation factors (VIFs) ranged from 2.9 to 3.5 (Table). A common guideline is that VIFs >10 indicate harmful multicollinearity, although lower, more conservative, values have also been proposed.⁶ The VIFs and consistent pattern of changes in effect estimates in two-pollutant models compared with single-pollutant models across the different endpoints suggests that the two-pollutant model effect estimates were not heavily affected by collinearity between pollutants. The change in direction of the effect estimates for O₃ probably indicates confounding by NO₂.

Previous studies have reported both positive and negative correlations between long-term average concentrations of O₃ and NO₂.² The high negative correlation between NO₂ and O₃ levels in our study can be explained by the scavenging of O₃ by primary nitrogen oxide emissions.² A French study on atopic and respiratory outcomes in schoolchildren reported a negative correlation of −0.76 between 3-year average O₃ and NO₂ measured at urban background sites.² In two-pollutant models, inverse associations with NO₂ observed in single-pollutant models disappeared, while adverse effects of O₃ remained.⁷ In a study on lung function growth conducted in the US, the correlation between community mean levels of NO₂ and daytime O₃ was −0.23. In two-pollutant models, effect

### TABLE. Summary of Single- and Two-pollutant Adjusted Associations for O₃ and NO₂

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Single-pollutant Model</th>
<th>Two-pollutant Model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NO₂</td>
<td>O₃</td>
</tr>
<tr>
<td>Asthma incidence</td>
<td>1.13 (1.02, 1.25)</td>
<td>0.91 (0.78, 1.05)</td>
</tr>
<tr>
<td>Asthma symptoms</td>
<td>1.08 (1.00, 1.17)</td>
<td>0.96 (0.86, 1.08)</td>
</tr>
<tr>
<td>Hayfever</td>
<td>1.10 (0.98, 1.24)</td>
<td>0.95 (0.79, 1.13)</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>1.12 (1.00, 1.25)</td>
<td>0.88 (0.75, 1.03)</td>
</tr>
<tr>
<td>Allergic sensitization</td>
<td>1.08 (0.99, 1.17)</td>
<td>0.91 (0.81, 1.04)</td>
</tr>
</tbody>
</table>

OR per IQRw,² change in exposure at the current address

<table>
<thead>
<tr>
<th>% change per IQRw,² change in exposure at the current address</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1</td>
</tr>
<tr>
<td>−1.5 (−2.5, −0.5)</td>
</tr>
<tr>
<td>1.0 (−0.4, 2.4)</td>
</tr>
<tr>
<td>−2.0 (−3.4, −0.5)</td>
</tr>
<tr>
<td>−0.9 (−2.8, 1.0)</td>
</tr>
<tr>
<td>3.0</td>
</tr>
<tr>
<td>3.0</td>
</tr>
<tr>
<td>FVC</td>
</tr>
<tr>
<td>−1.1 (−2.0, −0.1)</td>
</tr>
<tr>
<td>0.8 (−0.5, 2.1)</td>
</tr>
<tr>
<td>−1.3 (−2.7, 0.1)</td>
</tr>
<tr>
<td>−0.5 (−2.3, 1.4)</td>
</tr>
<tr>
<td>3.0</td>
</tr>
<tr>
<td>3.0</td>
</tr>
<tr>
<td>FEF25–75</td>
</tr>
<tr>
<td>−2.5 (−5.6, 0.7)</td>
</tr>
<tr>
<td>1.6 (−2.7, 6.1)</td>
</tr>
<tr>
<td>−3.4 (−7.6, 1.0)</td>
</tr>
<tr>
<td>−1.6 (−7.2, 4.3)</td>
</tr>
<tr>
<td>2.9</td>
</tr>
<tr>
<td>2.9</td>
</tr>
</tbody>
</table>

All associations adjusted for sex, maternal education, parental allergies, breastfeeding, maternal smoking during pregnancy, smoking in the child's home, use of gas for cooking, mold/dampness in the child's home, pets at home, daycare attendance during 1st year of life, and neighborhood percentage low-income households. Associations for lung function were additionally adjusted for ln age, ln height, ln weight, respiratory infections during the past 12 weeks and short-term exposure to NO₂.

³ All associations adjusted for sex, maternal education, parental allergies, breastfeeding, maternal smoking during pregnancy, smoking in the child’s home, pets at home, daycare attendance during 1st year of life, and neighborhood percentage low-income households. Associations for lung functions additionally adjusted for ln age, ln height, ln weight, respiratory infections during the past 12 weeks and short-term exposure to NO₂.

³⁸ 4.4 µg/m³ for NO₂ and 6.7 µg/m³ for O₃.

³⁹ FEF25–75 indicates forced expiratory flow between 25% and 75% of the vital capacity; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity.
estimates for both NO₂ and O₃ increased by about 30%.⁸

Our study adds to this limited evidence that health effects of NO₂ and O₃ are underestimated in single-pollutant analyses in settings where these pollutants are negatively correlated.

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