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# Nitrogen dioxide pollution exposure is associated with olfactory dysfunction in older US adults

**Dara R. Adams**[1], **Gaurav S. Ajmani**[1], **Vivian C. Pun**[2], **Kristen E. Wroblewski**[3], **David W. Kern**[4], **L. Philip Schumm**[3], **Martha K. McClintock**[5], **Helen H. Suh**[2], and **Jayant M. Pinto**[6]

[1]Pritzker School of Medicine, The University of Chicago, Chicago, IL, USA

[2]Department of Health Sciences, Bouve College of Health Sciences, Northeastern University, Boston, MA, USA

[3]Department of Public Health Sciences, The University of Chicago, Chicago, IL, USA

[4]Department of Psychology, Northeastern Illinois University, Chicago, IL, USA

[5]Department of Comparative Human Development and the Institute for Mind and Biology, The University of Chicago, Chicago, IL, USA

[6]Section of Otolaryngology-Head and Neck Surgery, The University of Chicago, Chicago, IL, USA

## Abstract

**Background—**Olfactory dysfunction has profound effects on quality of life, physical and social function, and mortality itself. Nitrogen dioxide ($NO_2$) is a pervasive air pollutant that is associated with respiratory diseases. Given the olfactory nerve's anatomic exposure to airborne pollutants, we investigated the relationship between $NO_2$ exposure and olfactory dysfunction.

**Methods—**The ability to identify odors was evaluated using a validated test in respondents from the National Social Life, Health, and Aging Project (NSHAP), a representative probability sample of home-dwelling, older US adults ages 57–85. Exposure to $NO_2$ pollution was assessed using measurements obtained from the US EPA AIRS ambient monitoring site closest to each respondent's home. We tested the association between $NO_2$ exposure and olfactory dysfunction using multivariate logistic regression.

**Results—**Among older adults in the US, 22.6% had impaired olfactory function, defined as ≤ 3 correct (out of 5) on the odor identification test. Median $NO_2$ exposure during the 365 days prior to the interview date was 14.7 ppb (interquartile range [IQR] 10.8–19.7 ppb). An IQR increase in $NO_2$ exposure was associated with increased odds of olfactory dysfunction (OR 1.35, 95% CI: 1.07–1.72), adjusting for age, gender, race/ethnicity, education, cognition, comorbidity, smoking, and season of the home interview (n=1,823).

Corresponding author: Jayant M. Pinto, MD, Section of Otolaryngology-Head and Neck Surgery, Department of Surgery, The University of Chicago Medicine and Biological Sciences, MC1035, 5841 South Maryland Avenue, Chicago, Illinois 60647 USA, jpinto@surgery.bsd.uchicago.edu, Telephone: 773-702-6727, Fax: 773-702-6809.

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**Conclusion—**We show for the first time that $NO_2$ exposure is associated with olfactory dysfunction in older US adults. These results suggest an important role for $NO_2$ exposure on olfactory dysfunction, and, potentially, nasal disease more broadly.

### Keywords

Aged; Air Pollutants; Air Pollution; Cross-sectional Studies; Nitrogen Dioxide; Olfaction disorders; Smell

## Background

Age-related olfactory dysfunction (presbyosmia) is a major personal and public health problem, affecting approximately 15 million older Americans and resulting in over 200,000 annual physician visits[1–8]. This sensory condition affects critical daily functions including detection of environmental hazards[9], nutrition[10–12], behavior[13], sensation of pleasure[14], sexuality[15,16], mood[17,18], and general wellbeing[19]. Further, olfactory dysfunction presages several neurodegenerative diseases, including Alzheimer's Disease and Parkinson's Disease[20–28]. We and others have shown that olfactory impairment is a major, independent risk factor for mortality[29,30]. Despite the profound impact of olfactory dysfunction on older adults, human olfaction is relatively understudied and the mechanisms that modulate age-related dysfunction are poorly understood.

The olfactory nerve is anatomically susceptible to damage by exposures to air pollutants[31]. Nitrogen dioxide ($NO_2$), a pervasive criteria airborne pollutant regulated by the US Environmental Protection Agency (EPA), is generated by fossil fuel combustion. Anthropogenic sources account for approximately 87% of US emissions and include on-road and off-road motor vehicles, as well as stationary sources such as electrical utilities and industrial processes[32–34]. Exposure to $NO_2$ has been associated with poor health outcomes, including respiratory, cardiovascular, and neurologic diseases[35–50]. Older adults may be at greater risk than younger adults for poor health outcomes associated with air pollution[45]. While the mechanisms by which $NO_2$ may cause disease are not fully understood, biochemical, cellular, and animal studies suggest a role for inflammation and oxidative stress[51–56]. Indeed, these processes have been implicated in studies of the relationship between other airborne pollutants and olfactory pathology[57].

To investigate the association between $NO_2$ exposure and olfactory dysfunction, we used data from the National Social Life, Health, and Aging Project (NSHAP), a nationally representative probability sample of home-dwelling, older US adults ages 57–85[58].

## Materials and Methods

### Study Population

We studied 1,832 NSHAP respondents who lived within 60 km of a US EPA AIRS ambient monitoring site and had complete olfactory testing. These respondents were interviewed from 2005–6 in their homes by professional interviewers (NORC at the University of Chicago) and form a representative probability sample of the US home-dwelling population ages 57–85[59]. Weighted demographic, olfactory, and health characteristics of the study

population are presented in Table 1. Further details regarding the design, data collection, and baseline characteristics of NSHAP respondents are available elsewhere[58]. The study was approved by the Institutional Review Boards of the University of Chicago and NORC; all respondents provided written, informed consent.

## Olfactory Assessment

Olfactory function was assessed with the odor identification portion of the Olfactory Function Field Exam, a validated test for field studies[1,60–62]. Respondents were asked to identify each odor presented by Sniffin' Stick odor pens by choosing from a set of four picture/word prompts in a forced choice protocol; refusals were coded as incorrect. Respondents who identified 4–5 odors correctly were classified as normosmic, whereas respondents who identified 3 or fewer odors correctly were classified as having some form of olfactory dysfunction[62]. Odor pens were purchased from Burghart Messtechnik (Wedel, Germany) and stored and utilized according to the manufacturer's instructions.

## Nitrogen Dioxide Exposure Assessment

Exposure to $NO_2$ was assessed using hourly data from monitoring sites maintained by the EPA. We linked participant data to $NO_2$ concentrations measured at the nearest stationary ambient monitoring site within 60 km of each respondent's home address. To evaluate the effect of exposure windows on the association between $NO_2$ exposure and olfactory dysfunction, we used the 365 day moving average exposure prior to the health assessment as our main exposure window of interest. In addition, we calculated $NO_2$ exposures for shorter exposure windows, including 30, 60, 90, and 180 days, to assess whether $NO_2$ exposures over shorter time frames also impacted olfaction. For each moving average, exposures were considered valid when at least 75% of the hourly measurements within the exposure window were available.

## Potential Confounding Variables

Our analyses controlled for numerous potential confounders, including age, gender, race/ethnicity, education, cognitive function, smoking status, comorbidity, and season of the home interview. Age and gender have previously observed, consistent associations with olfactory function[4,63,64]. Race (an established olfactory risk factor[3]) and Hispanic ethnicity were measured via self-report according to standard NIH questions, and respondents were classified as White, African American, or Hispanic (those who reported their race as "Black/African American" and answered "Yes" to Hispanic ethnicity were classified as African American). Those reporting their race as "American Indian or Alaskan Native," "Asian," or "Other" were combined into a single Other category. Socioeconomic status was measured by highest educational degree or certification earned. Cognitive function (specifically memory and mental arithmetic) was measured with a modified version of the Short Portable Mental Status Questionnaire (SPMSQ, scores from 0–10)[65]. Although smoking has an unclear association with olfactory dysfunction[63,66,67], current smoking (based on either self-report or salivary cotinine level ≥ 15 ng/mL) was included as a potential confounder because of its mechanistic relevance to air pollution exposure. Comorbid diseases were measured with the Charlson Index modified for NSHAP[68]. Season of the home interview (cooler months, October–March vs. warmer months, April–September) was included because of plausible

seasonal differences in olfactory function due to infections or allergies[69]. Missing covariates were minimal: race/ethnicity was missing for 9 of 1,832 respondents, and no other covariates were missing for any respondents.

### Statistical Analysis

NSHAP had a 75.5% survey response rate, excellent for a targeted probability sample, and the non-responders were similar demographically to the responders[59]. Analyses were performed using person-level weights, accounting for non-response. Design-based standard errors were calculated using the linearization method together with the strata and Primary Sampling Unit indicators provided with the dataset. All statistical analyses were conducted using Stata Version 14.0[70].

Multivariate logistic regression was used to estimate the relationship between $NO_2$ and olfactory dysfunction, adjusting for potential confounders. Results are presented as odds ratios and 95% confidence intervals (CI). Wald tests were used to determine *p*-values. For each variable considered as an effect modifier, the corresponding model included both its main effect and interaction with $NO_2$. Statistical significance was set at $p<0.05$.

To ensure that the results were not dependent on the chosen threshold between normosmia and olfactory dysfunction, multivariate linear regression models including all covariates were fit, treating the number of odors correctly identified (0–5) as the dependent variable. To assess the sensitivity of our findings to distance from monitor, we performed additional analyses that restricted our study population to participants who lived within 40 km of an EPA monitoring site. We also conducted sensitivity analyses that included all NSHAP respondents irrespective of distance to monitor.

## Results

### $NO_2$ Exposure

Older US adults experienced a median $NO_2$ exposure level of 14.7 ppb (interquartile range [IQR] 10.8–19.7 ppb) during the 365 days prior to the interview date. Older adults' pollution exposure differed by geography: respondents in the Northeast experienced the highest median $NO_2$ exposures (19.0ppb, IQR 12.3–22.8 ppb), followed by the West (18.4 ppb, IQR 12.6–23.3 ppb) and Midwest (16.8ppb, IQR 14.7–19.8 ppb), and with the South experiencing the lowest $NO_2$ levels (11.3ppb, IQR 7.9–13.4 ppb). The highest 365 day $NO_2$ exposure for our study participants was 36.3 ppb, significantly below the 53 ppb annual mean National Ambient Air Quality Standard (NAAQS) imposed by the EPA for $NO_2$[71,72]. The World Health Organization recommends a limit of 21 ppb annual mean $NO_2$ exposure, and we found that 21.5% of older US adults faced exposure levels higher than that recommendation[33]. As expected, older adults' pollution exposure varied by season when we considered shorter exposure windows: for example, the median 30 day $NO_2$ exposure for respondents interviewed during cool months was higher than for those interviewed during warm months (16.4 vs. 12.5 ppb, $p=0.001$), consistent with known short term variability in this pollutant related to season. Median distance from an EPA monitoring site was 13.7 km. $NO_2$ exposure levels are presented in Table 2.

### Olfaction and $NO_2$

Older adults who experienced higher yearly averaged $NO_2$ exposure levels faced significantly greater odds of olfactory impairment: a 33% increase in odds of having olfactory dysfunction per 8.9 ppb (1-IQR) increase in $NO_2$ exposure (OR 1.33, 95% CI: 1.05–1.70), controlling for age, gender, race/ethnicity, and education (Table 3). This relationship was similar in adjusted models which controlled additionally for cognition, comorbidity, smoking, and season of the home interview (OR 1.35, 95% CI: 1.07–1.72; Figure 1). As has been previously reported, older adults, men, and Blacks (compared to Whites) had worse olfactory function in these models, while higher levels of education and better cognitive function were protective[2–4] (Table 3). There were no significant interactions between $NO_2$ exposure and any of our measured covariates (data not shown). Evidence of nonlinearity was assessed by use of a quadratic term, which was found to be nonsignificant.

$NO_2$ exposures averaged over 180 days was found to have a similar impact on olfaction as compared to those experienced over one year (Table 4). For example, the odds of olfactory impairment associated with an IQR increase in 180 day $NO_2$ exposures was found to be similar (OR 1.31, 95% CI: 1.02–1.67) in adjusted models controlling for all covariates. In contrast, shorter exposure windows of 30 to 90 days prior to olfactory testing showed no significant association with olfaction, although the observed associations were consistently positive.

### Sensitivity Analyses

When we restricted our study population to include only those respondents living within 40 km of an EPA monitoring site, we found the association between $NO_2$ exposure and olfactory dysfunction to be slightly stronger (OR 1.42, 95% CI: 1.11–1.80, $p$=0.006) in adjusted models controlling for all covariates.

We also re-ran the analyses to include all respondents (adding back those who lived further than 60 km from an EPA monitoring site). We found that the relationship between $NO_2$ exposure and olfactory impairment remained strong: older adults had a 21% increase in odds of impairment per 8.9 ppb (1-IQR) increase in $NO_2$ exposure (OR 1.21, 95% CI: 1.02–1.43, $p$=0.031) in adjusted models controlling for all covariates.

Finally, to determine if our results were dependent on the chosen threshold between normosmia and olfactory dysfunction, we examined multivariate linear models with olfactory function scored as number of odors correctly identified. This analysis showed a similar deleterious association, with higher $NO_2$ pollution exposure associated with worse olfaction ($\beta$=−0.12 for 1-IQR increase in $NO_2$, 95% CI: −0.20 to −0.04, $p$=0.004), controlling for age, gender, race/ethnicity, education, cognition, comorbidity, smoking, and season of the home interview.

## Discussion

We show for the first time that $NO_2$ exposure is associated with olfactory dysfunction in older US adults: we found that an IQR increase in annual $NO_2$ exposure was independently associated with markedly greater odds of olfactory impairment. Importantly, this association

was found even though our study population experienced $NO_2$ exposures that were well below the EPA NAAQS of 53 ppb[71,72]. In recognition of the seriousness of the $NO_2$ threat on public health, the World Health Organization recommends a much more stringent limit of 21 ppb annual mean $NO_2$ exposure[33]. Remarkably, over one-fifth of older US adults faced exposures greater than that recommendation.

We are the first to show a relationship between olfactory dysfunction and $NO_2$ exposure; however, our results are consistent with prior studies that demonstrate an association between olfaction and air pollution. For example, residents living in severely polluted Mexico City were found to have significantly worse olfactory function than control subjects living in less polluted regions of Mexico[73,74]. Further, the Mexico City residents had ultrafine particles in their olfactory bulbs that were not found in the olfactory bulbs of control subjects[74]. Similarly, older German women living closer to a busy road, a proxy for traffic-related pollution exposure, performed worse on tests of olfactory function than women living farther from a busy road[75].

We found similar associations between $NO_2$ and olfactory dysfunction for the exposure window of 180 days, but not at shorter exposure windows. Additionally, we found no effect modification of the $NO_2$-olfaction associations by age, gender, education, and most notably by race/ethnicity. Since we found olfaction to vary significantly by race, our findings suggest that the impacts of $NO_2$ exposure on olfaction are comparable across older adults from different racial backgrounds with varying base levels of olfactory impairment.

The implications of these data are that lifetime exposure to $NO_2$ may cause olfactory decline, and by extension, have effects on the central nervous system[20–28]. The olfactory nerve is anatomically exposed to the outside environment, particularly to airborne pollutants. Odorants enter the nasal cavity through the nasal vestibule and travel superiorly to the olfactory epithelium, whose axons project through the cribriform plate to synapse in the olfactory bulb[31,76]. Along with odorants, airborne pollutants have direct access to this pathway, and damage by airborne pollutants leading to inflammation and oxidative stress may mediate olfactory dysfunction[51–56]. Further, it has been hypothesized that inhaled agents, such as pollutants or other toxins, may bypass the blood-brain barrier and access the brain via this same pathway, thereby causing or catalyzing neurodegenerative diseases (referred to as the “olfactory vector hypothesis”)[77,78]. Thus, understanding the role of airborne pollution in olfactory dysfunction may elucidate the mechanism through which olfactory dysfunction predates neurodegenerative diseases. Given the burden of neurosensory disease, understanding the mechanism of this interaction between olfactory dysfunction and $NO_2$ exposure is likely to have a major public health impact.

Residual confounding or confounding by unmeasured covariates and/or other forms of pollution (e.g., traffic, noise, or other airborne pollutants (e.g., particulate matter), etc.) is possible. Nonetheless, adjustment for several known confounding variables, including those related to socio-economic status, did not eliminate the observed associations of $NO_2$ with olfaction. We assessed $NO_2$ levels using exposures based on the nearest stationary ambient monitor within 60 km to participants’ residential addresses, with a median distance of 13.7 km. These measures do not account for spatial variability, time spent indoors, or length of

time at the current residence, and thus are imperfect proxies of personal $NO_2$ exposures and contribute to exposure misclassification. However, our sensitivity analyses suggest that exposure error in our findings may be small, as we found comparable results when restricting to a smaller buffer zone (40 km), suggesting that our findings are valid. While we do not have information on how many respondents moved within the year prior to olfactory testing, other studies have found that less than 12% of Americans move per year, and that older adults are less likely to move than younger adults[79]. Furthermore, results from several exposure studies of the elderly suggest that ambient $NO_2$ exposures are correlated with corresponding personal exposures and are thus appropriate proxies of exposures in epidemiological studies[80].

## Conclusion

We show for the first time that $NO_2$ exposure well below the EPA limit is associated with olfactory dysfunction in older US adults, thus adding a nasal/neurosensory phenotype to the substantial list of processes affected by airborne pollution. NSHAP is the largest, nationally representative study of olfactory function and airborne pollution to date. Our data support the recommendation that clinicians should consider screening older patients and others at risk of increased pollution exposure for olfactory loss. Given the profound biopsychosocial effects of olfactory dysfunction on quality of life, physical and social function, and mortality itself, as well as its association with neurologic outcomes, understanding the mechanism of this association is likely to have a major public health impact.

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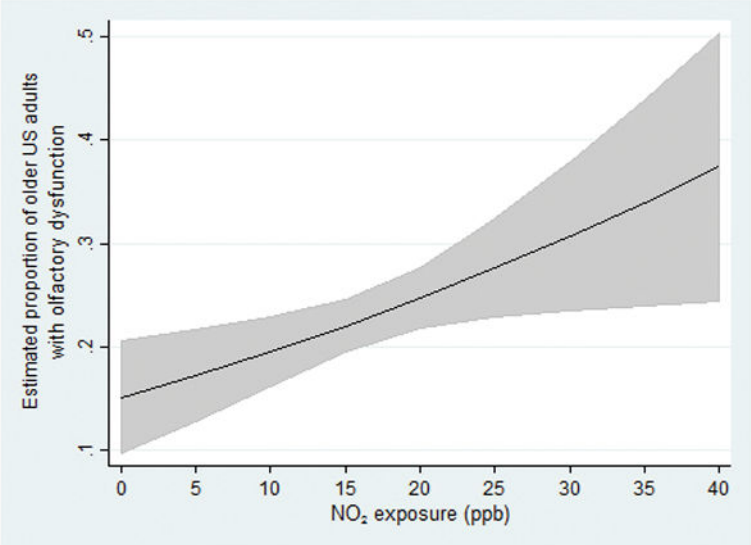


**Figure 1.**

Association among US older adults between $NO_2$ exposure (NB: 53 ppb annual mean exposure = EPA National Ambient Air Quality Standard (NAAQS)) and olfactory dysfunction (logistic regression), controlling for age, gender, race/ethnicity, education, cognition, comorbidity, smoking, and season of the home interview (n=1,823)

## Table 1

Olfactory, demographic, and health characteristics of the population (n=1,832)

| Characteristic | Weighted %* |
|---|---|
| Odors correctly identified | |
| Impaired olfaction (0–3 correct) | 22.6 |
| 0 | 1.2 |
| 1 | 2.5 |
| 2 | 5.0 |
| 3 | 13.8 |
| Normal olfaction (4–5 correct) | 77.4 |
| 4 | 28.4 |
| 5 | 49.0 |
| Age (years, weighted mean ± SD) | 67.9±7.8 |
| Gender | |
| Men | 49.3 |
| Women | 50.8 |
| Race/ethnicity (n=1,823) | |
| White | 79.4 |
| Black | 10.8 |
| Hispanic, non-Black | 7.0 |
| Other | 2.8 |
| Education | |
| <High school | 16.7 |
| High school graduate or equivalent | 24.8 |
| Some college | 30.4 |
| Bachelors or higher | 28.1 |
| Cognition (SPMSQ, weighted mean ± SD) | 9.2±1.1 |
| Modified Charlson comorbidity index (weighted mean ± SD) | 1.8±1.7 |
| Smoking | |
| Current smokers | 18.2 |
| Not current smokers | 81.8 |
| Season of the home interview | |
| Cool (October–March) | 30.8 |
| Warm (April–September) | 69.2 |
| Frequency of physical activity (n=1,829) | |
| 1+ times per week | 78.8 |
| <1 time per week | 21.2 |

| Characteristic | Weighted %* |
|---|---|
| Employment | |
| Current employed | 40.5 |
| Not current employed | 59.5 |
| Region | |
| West | 23.5 |
| Midwest | 20.2 |
| South | 33.8 |
| Northeast | 22.5 |

*Unless otherwise specified;

Notes: SD=Standard deviation

**Table 2**

365 day $NO_2$ exposure for the population (n=1,832)

| | **Measured $NO_2$ (ppb)** |
|---|---|
| Mean ± SD | 15.6±7.0 |
| Median | 14.7 |
| $25^{th}$–$75^{th}$ percentile | 10.8–19.7 |
| Interquartile range | 8.9 |
| Cool season, Mean ± SD | 17.7±8.2 |
| Warm season, Mean ± SD | 13.0±7.1 |

Notes: All values are weighted. SD=Standard deviation

## Table 3

Effects of $NO_2$ exposure on olfactory dysfunction, controlling for age, gender, race/ethnicity, and education (logistic regression, Model A), and additionally for cognition, comorbidity, smoking, and season of the home interview (Model B) (n=1,823)

| | **Odds Ratio (95% Confidence Interval)** ***p-Value*** | |
|---|---|---|
| **Covariates** | **Model A** | **Model B** |
| **$NO_2$ exposure (per 1-IQR: 8.9ppb)** | 1.33 (1.05,1.70) 0.022 | 1.35 (1.07, 1.72) 0.013 |
| **Age (decades)** | 2.11 (1.77, 2.51) <0.001 | 1.98 (1.67, 2.34) <0.001 |
| **Gender (men vs. women)** | 1.52 (1.15, 2.02) 0.004 | 1.57 (1.18, 2.09) 0.003 |
| **Race/ethnicity** | | |
| White (ref) | -- | -- |
| Black | 2.48 (1.72, 3.58) <0.001 | 2.23 (1.54, 3.23) <0.001 |
| Hispanic, non-Black | 1.00 (0.56, 1.80) 0.998 | 0.92 (0.50, 1.68) 0.770 |
| Other | 1.49 (0.72, 3.10) 0.277 | 1.35 (0.66, 2.78) 0.407 |
| **Education** | | |
| <High school (ref) | -- | -- |
| High school graduate or equivalent | 0.68 (0.49, 0.95) 0.023 | 0.76 (0.56, 1.04) 0.083 |
| Some college | 0.50 (0.34, 0.74) 0.001 | 0.58 (0.40, 0.84) 0.005 |
| Bachelors or higher | 0.46 (0.30, 0.73) 0.001 | 0.55 (0.34, 0.87) 0.013 |
| **Cognition (SPMSQ)** | -- | 0.80 (0.71, 0.90) <0.001 |
| **Comorbidity (modified Charlson index)** | -- | 1.04 (0.97, 1.11) 0.244 |
| **Current smoking** | -- | 0.94 (0.69, 1.29) 0.688 |
| **Season of the home interview (cool vs. warm)** | -- | 0.83 (0.60, 1.16) 0.278 |

Notes: IQR=Interquartile Range

**Table 4**

Effect of $NO_2$ sampling window on detecting relationship between olfactory dysfunction and $NO_2$ exposure in logistic regression Models A and B (n=1,823)

| | 30 day $NO_2$ | 60 day $NO_2$ | 90 day $NO_2$ | 180 day $NO_2$ | 365 day $NO_2$ |
|---|---|---|---|---|---|
| **$NO_2$ exposure IQR** | 10.0 | 9.5 | 9.1 | 9.2 | 8.9 |
| **Model A** | | | | | |
| **OR per 1-IQR increase in $NO_2$ exposure** | 1.17 | 1.18 | 1.21 | 1.29 | 1.33 |
| **95% CI** | (0.90,1.51) | (0.91,1.52) | (0.95,1.55) | (1.00,1.66) | (1.05,1.70) |
| ***p*-Value** | 0.237 | 0.200 | 0.122 | 0.046 | 0.022 |
| **Model B** | | | | | |
| **OR per 1-IQR increase in $NO_2$ exposure** | 1.21 | 1.23 | 1.26 | 1.31 | 1.35 |
| **95% CI** | (0.94,1.57) | (0.95,1.59) | (0.98,1.61) | (1.02,1.67) | (1.07,172) |
| ***p*-Value** | 0.141 | 0.118 | 0.066 | 0.034 | 0.013 |

Notes: IQR=Interquartile Range, OR=Odds Ratio, CI=Confidence Interval

Model A adjusted for age, gender, race/ethnicity, and education

Model B adjusted for age, gender, race/ethnicity, education, cognition, comorbidity, smoking, and season of the home interview