AMBIENT AIR POLLUTION AND ITS ASSOCIATION WITH OLFACTION IN U.S. WOMEN

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ABSTRACT

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Olfaction impairment (OI) is an often underreported, common sensory deficit that can lead to a host of adverse health conditions, quality of life issues, and is a predictor of 5-year mortality. Environmental exposures, including very fine particulate matter ($PM_{2.5}$), are believed to be a potential risk factor in the loss of smell but previous research into this association has been limited. We therefore collaborated with the National Institute of Environmental Health Sciences' Sister Study, which had been originally designed to examine the relationship between environmental exposures and cancer, to test a large sub-sample (n=4020) of their population in order to identify participants with olfaction impairment. Our multivariable logistic regression analysis found that those in the highest exposure group were more likely to suffer from olfaction impairment when compared to those in the lowest exposure group, with an OR = 1.55 (95% CI: 1.40, 1.72) after adjusting for all relevant confounders. Results were similar for all instances of $PM_{2.5}$ yearly average measurements. Further quantile regression analyses showed that the greatest effect of ambient air pollutants on olfaction was for those whose smell tests fell below the 42^{nd} quantile, indicating that $PM_{2.5}$ may exacerbate OI rather than instigate it. We conclude that higher levels of $PM_{2.5}$ were associated with olfaction impairment and that the effect may have been greater for those with an already declining sense of smell.

Dedicated to Heidi, Story and Collins.
For your support, love and understanding.

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INTRODUCTION

Olfaction impairment (OI) is an often unnoticed, significant public health problem, with a prevalence estimated to be between 14% and 30% in older adults in the United States, aged >60.[1,2] This sensory deficit has been linked to poor life quality, with ramifications including decreased sex drive, an inability to detect household dangers such as gas leaks or fires, and potentially depressive symptoms. Additional adverse health outcomes are associated with OI, as the loss of the sense of smell is considered an important prodromal symptom of neurodegenerative diseases such as Parkinson's (PD) and Alzheimer's (AD).[3,4] Previous research has also found that OI is an independent predictor of both short- and long-term mortality among older adults,[5,6] making it an essential sensory deficit to examine further. However, potential causes of olfaction impairment in older adults are not well understood.

Environmental exposures, especially those that can be inhaled through the nose, present a potential vehicle for the deterioration in a person's sense of smell. Fine particulate matter ($PM_{2.5}$), airborne matter with diameter ≤ 2.5 μm (approximately 3% the width of a human hair), can be inspired through the nose and bind to olfactory sensory neurons in the olfactory epithelium.[7] Sensory signals are then sent through the cribriform plate and into the olfactory bulb, where further translation down the first cranial nerve will lead to the olfactory cortex. Further connections transfer these signals to other areas of the brain, including the thalamus, hypothalamus and amygdala.[8]

Although these pollutants are present in every inhaled breath, research using computational fluid dynamics has shown that only 2%-16% of inspired air reaches the olfaction regions within the

cavity.[9] However, this amount may still be significant enough to initiate a deterioration in olfaction and potentially lead to other negative effects. For example, research performed in Mexico City has found that particulate matter accumulates in the olfactory bulb,[10] potentially leading to increased inflammation and neuropathologies of AD and/or PD.[11]

With an easily accessible point of interaction in the nasal cavity, and a direct mechanistic pathway to all parts of the olfaction system, environmental inhalants have long been suspected as a factor in declining sense of smell. Previous studies have reported that other potential inhaled odorants, such industrial chemicals[12] or pesticides and insecticides,[13,14] can adversely impact the sense of smell. However, these exposures tend to be acute, of high concentrations and only affect a small portion of a general population and don't account for long-term, ambient effects.[15]

Evidence has shown that air pollutants, specifically $PM_{2.5}$, are associated with adverse health outcomes, at levels commonly experienced during everyday activities; for example, higher exposure to ambient $PM_{2.5}$ was associated with greater risk of breast cancer,[16] asthma,[17] and chronic bronchitis,[18] cardiovascular disease and potentially with neurodegenerative diseases.[11] Despite the potential harm exhibited by persistent exposure to $PM_{2.5}$, few studies have examined the direct effect it may have on olfaction. Preliminary data has indicated a link between air pollution and OI;[19,20,21,22] however, significant weaknesses limit interpretation of these data. Many of these studies had small sample sizes (< 90 participants), based on convenience samples or samples from specific regions or cities. Additionally, pollutants were usually compared between low and high exposure groups, providing a lack of robust analysis that considers potential confounding factors or examining the roles of individual toxins. One recent, provocative study[23] analyzed data from ~2000 older US urban residents (aged 57-85). This

research found that olfaction impairments was associated with $PM_{2.5}$ (OR: 1.28, 95% CI 1.05, 1.55) and had the strongest association with those aged 57-64.

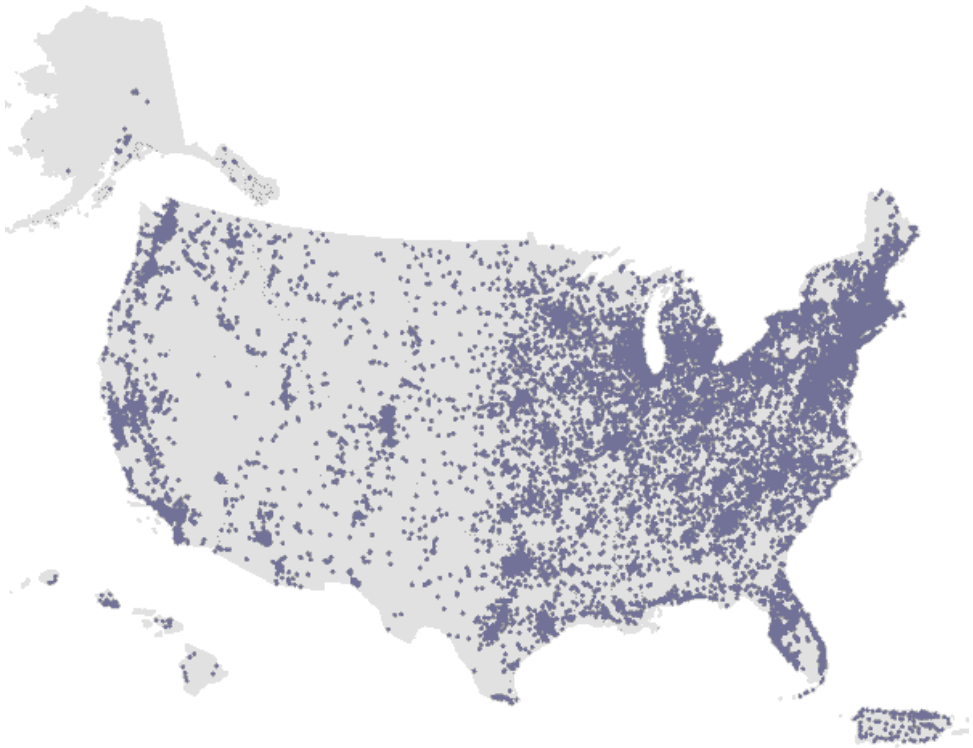
We therefore set forth to examine a large, geographically diverse population of women with residence-based measures of $PM_{2.5}$ and, through testing of their sense of smell, further delineate the role ambient air pollution plays with olfaction impairment.

METHODS AND MATERIALS

Sister Study Population

The NIEHS Sister Study is a longitudinal cohort study of U.S. women (n=50,884) from all fifty states (**Figure 1)**[24] that was originally designed to identify risk factors for breast cancer, as well as factors that influence life qualities post diagnosis.[25] Eligibility criteria were women aged 35-74, who had sisters diagnosed with breast cancer but were currently cancer free themselves. Enrollment occurred between 2003-2009 and consisted of a baseline computer-assisted telephone survey that gathered a robust set of variables regarding health diagnoses, demographic information and lifestyle information. A first follow-up was administered two years beyond baseline, with two subsequent follow-ups occurring at three-year intervals.

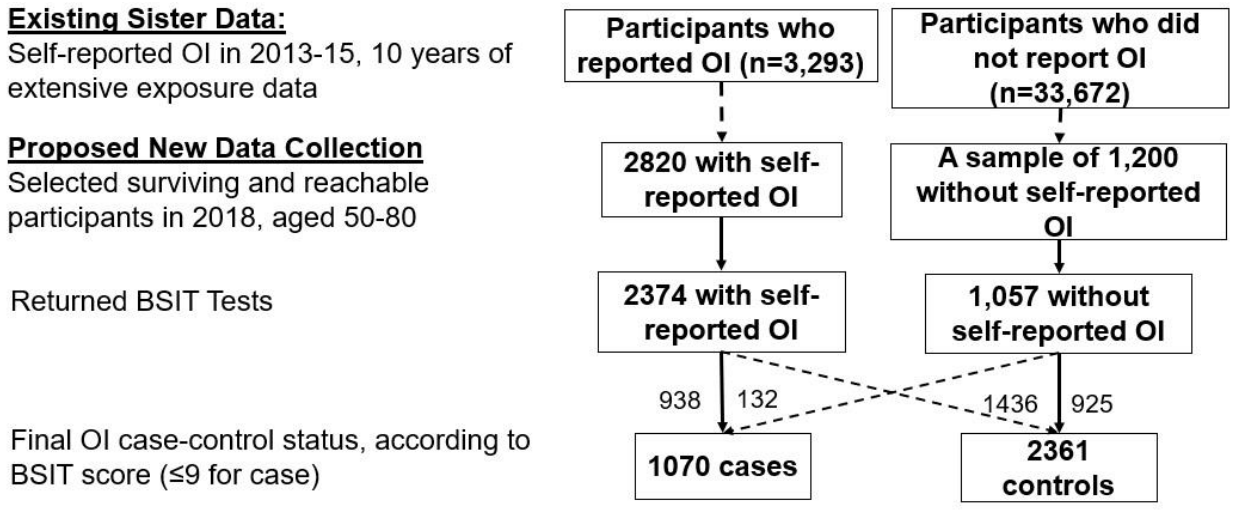
Figure 1. NIEHS Sister Study participant map



Study Design

We conducted a case-control study drawing upon participants from the third follow-up of Sister Study in 2013-2015. At the third follow-up, participants were asked whether they suffered from a decrease in of loss of their sense of smell, with 3,293 reporting affirmative and 33,672 reporting a normal sense of smell. Based on these samples, we sampled eligible study samples in January 2018, including all 2820 surviving Sister participants ages 50-79 who had reported olfaction impairment at the third follow-up and randomly sampled 1200 of those who had reported normal olfaction. Between March 2018 and February 2019, a total of 3431 (85.3%) study participants enrolled in the current study by taking a Brief Smell Identification Test (B-SIT) and answered a questionnaire about their sense of smell and taste, efficiently self-administered by mail. 4020 were mailed to the selected women to accurately test their sense of smell. The study protocol was approved by the Michigan State University Institutional Review Board and the NIEHS Institutional Review Board.

Figure 2. The Sister Study sense of smell design and data collection



The Sense of Smell Test

The B-SIT is an abbreviated version of the 40-item Pennsylvania Smell Identification Test, a widely-used screening test[26] for OI in epidemiological studies. In brief, participants are presented 12 common odors, delivered via individual scratch-and-sniff cards, and asked to choose from among four choices the descriptor that best matches their impression of the odor presented. Every correct answer is awarded one point, correlating to a final score ranging from 0-12, with a higher score indicating a better sense of smell.[27] As the study population are all women and are relatively young, we defined OI as a B-SIT scores ≤ 9, corresponding to about 13% in the overall Sister study population. Based on this definition, we reclassified reclassify all participants into 1070 OI cases and 2361 controls (**Figure 2**).

Exposure Measurements

Air pollutant exposures were estimated based on the primary address of study participants reported at the Sister Study enrollment in 2003-2009. Addresses were first geocoded using ArcMap version 10 (ESRI, Redlands, CA) by the University of Washington, and those locations were used for prediction of annual average ambient air pollution concentration levels. Measurements for $PM_{2.5}$ concentrations were obtained from monitors utilized by the Environmental Protection Agency (EPA) Air Quality System (AQS) database. Of 1211 $PM_{2.5}$ monitors available, 903 fit the criteria of 14 concentration measurements per quarter for the entire year. Areas with seasonal coverage or large swaths of missing data were excluded and then prediction models were fit using a universal kriging regression model.[28] Modeling was limited to the contiguous United States.

The model, in brief, considered seven geographic covariates, using buffer radii in estimation. These covariates included: 1) population, 2) pollutant emission levels for $PM_{2.5}$, 3) percentage of land use, separating between different forest types, crop and pasture, and business/residential development, 4) vegetative index, a measure of plant growth and thickness, 5) measures of impervious surfaces, 6) summation of roadway factors, such as nearness to major thoroughfares, and 7) distance to major features such as airports, railways and ports. Partial least squares estimation was used to select linear combinations and account for highly correlated covariates, and spatial smoothing was including in the final analysis. The cross-validated R^2 value for baseline $PM_{2.5}$ concentrations was 0.88.[29] This method has been widely used in the Sister Study, estimated annually from 2006-2011, as well as in other cohorts for investigations of potential adverse health effects of air pollution.

However, whenever a predicted estimate is used for exposure assessment, rather than an objective measure, it introduces the possibility of measurement error in subsequent epidemiological research.[30] To account for this possibility, the University of Washington validated their prediction model using a two-stage approach: 1) Building exposure models as described previously and 2) Utilizing the parameter bootstrap, a method to assess and correct measurement errors in predictive models.[31] They then compared their naïve model, based solely on their predictive algorithm, with models obtained after the parameter bootstrap was performed. Results showed that point estimates for both models were exactly the same up to three decimal points, indicating that any bias created by measurement error was non-significant and supported the accuracy of their predictive model.[29]

Covariate Assessment

The Sister Study comprehensively collected data on demographics, lifestyle, environmental exposures and health status at enrollment and periodically updated at the follow-up surveys. We considered the following covariates in the analysis, age (continuous), race (Non-Hispanic white, non-Hispanic black, Hispanic and other), education level (high school or less, some college or bachelor's degree, and graduate work), smoking status (never smoker, current smoker and former smoker), moving status (mover and non-mover), census region (Northeast, Midwest, South and West) and residential area type (rural, small town, suburban and urban). Age, race, education level, census region and residential area were all assessed at study enrollment. Smoking status was derived from baseline survey and updated through all subsequent follow-ups. At each of the follow-up, study participants were asked whether they had moved since the previous follow-up survey, and we defined movers as those who ever moved between Sister Study enrollment and the second follow-up, the time period that is most close to the latest $PM_{2.5}$ estimates in 2011.

Statistical Analysis

Of the 3431 participants with B-SIT data, we excluded 74 women for missing on PM2.5 estimate and 16 missing on covariate, leaving 3341 eligible for the current analysis. In descriptive analysis, we conducted analysis of variance for the continuous variable and frequency chi-square test for categorical variables.

We defined the exposure of interest PM2.5 in three ways, using estimates from 2006, the year approximates of study enrollment, 2011 the latest available estimates, and yearly average

between 2006-2011 (**Table 1)** The exposures were further categorized into quartiles based on the exposure levels of the entire cohort.

Table 1. Quartile ranges for $PM_{2.5}$ ($\mu g/m^3$) levels for entire cohort

	2006	2011	Average Yearly 2006-2011
1st Quartile	≤8.76	≤7.70	≤8.20
2nd Quartile	8.76—10.81	7.70—9.18	8.20—9.92
3rd Quartile	10.81—12.35	9.18—10.27	9.92—11.22
4th Quartile	>12.35	>10.27	>11.22

We used multivariable logistic regression to assess the association of PM2.5 and OI, adjusting for the above defined covariates. In the analyses, we accounted for the sampling weights and participating rates to generalize the study results to the entire eligible Sister study for their follow-up participants who would be alive ages 50-79 in January 2018. Further, we used quantile regressions[32] to more comprehensively examine how $PM_{2.5}$ affected different quantiles of B-SIT scores (considered a continuous variable for the purpose of this analysis). This examination allowed us to identify whether $PM_{2.5}$ exposure universally affected all levels of olfaction or if greater affects were seen for higher or lower B-SIT scores.

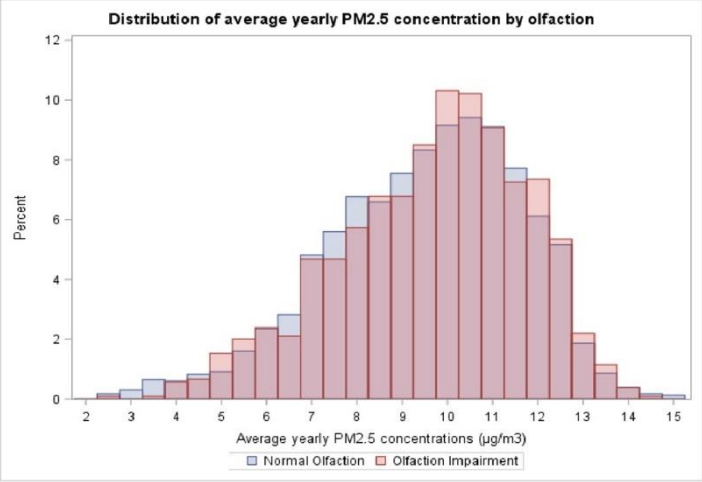
To account for stability in residence, we also conducted sensitivity analysis in two ways. First, we limited our analysis to study participants who did not move between study enrollment and the second follow-up where ambient air pollution levels and OI varied among non-movers and second, by conducting analyses based on whether participants had lived at their baseline residence for at least ten years. Further analysis was performed to identify whether unmeasured

confounding was present enough to bias the results through examination of three separate models: 1) A crude model with just the OI and $PM_{2.5}$ exposure levels, 2) The crude model with age and ethnicity included as covariates and 3) a fully-adjusted model. All analyses were performed using SAS 9.4 (SAS Institute Inc., Cary NC).

RESULTS

When comparing the distribution of average yearly $PM_{2.5}$ concentration levels by olfaction status we see that, in general, those with poor olfaction tend to have higher exposures to particulate matter while those with normal sense of smell experience lower concentrations. **(Figure 3)**

Figure 3. Distribution of average yearly $PM_{2.5}$ concentration by olfaction



Within our study sample, participants were generally more likely to have olfaction impairment if they were black, had an education level of high school or less, and were older. Conversely, whites, those with college degrees and younger participants were more likely to have normal olfaction. Region, residence type, smoking status and moving status did not appear to differ among cases and controls. (**Table 2)** Our results from the multivariable logistic regression show a significant association between higher levels of $PM_{2.5}$ exposure and likelihood of olfaction impairment, when compared to the reference group (the lowest exposure quartile). (**Table 3**) The results were consistent across all three times of exposure assessment and did not differ greatly.

Table 2. Population characteristics over olfaction status		
	Olfaction Impaired BSIT Score 0-9 n=1045	Olfaction Normal BSIT Score 10-12 n=2296
Covariates		
Age in years, (SD)	69.6(6.55)	65.9(7.03)
Race, (%)		
Non-Hispanic White	929(88.9)	2070(90.1)
Non-Hispanic Black	77(7.4)	105(4.6)
Hispanic	14(1.3)	64(2.8)
Other	25(2.4)	57(2.5)
Education, (%)		
High School	170(16.3)	273(11.9)
College	574(54.9)	1422(61.9)
Graduate Degree	301(28.8)	601(26.2)
Smoking Status, (%)		
Never	555(53.1)	1296(56.4)
Former	448(42.9)	913(39.8)
Current	42(4.0)	87(3.8)
Census Region, (%)		
Northeast	174(16.7)	395(17.2)
Midwest	286(27.4)	659(28.7)
South	344(32.9)	728(31.7)
West	241(23.0)	514(22.4)
Residential Area Type, (%)		
Rural	188(18.0)	404(17.6)
Small Town	402(38.5)	884(38.5)
Suburban	221(21.2)	494(21.5)
Urban	234(22.3)	514(22.4)
Moving Status, (%)		
Non-mover	821(78.6)	1815(79.1)
Mover	224(21.4)	481(20.9)

While all elevated exposure quartiles showed a significant odds ratios (OR) when compared to the lowest quartile, the largest OR occurred when comparing the highest exposure group to the lowest; OR = 1.49 (95% CI: 1.34, 1.65) for estimates from 2006, OR = 1.50 (95% CI: 1.35, 1.66) for estimates from 2011 and OR = 1.55 (95% CI: 1.40, 1.72) for the yearly averages between

2006-2011.

Table 3. Multivariable logistic regression for $PM_{2.5}$ concentration ($\mu g/m^3$) and olfaction status, Cases: n=1070 and Controls: n=2361		
	$PM_{2.5}$ Estimates	
	OR	95% CI
2006 $PM_{2.5}$ Exposure Quartiles		
1st Quartile, ≤8.76	Ref	
2nd Quartile, 8.76—10.81	1.32*	(1.20, 1.46)
3rd Quartile, 10.81—12.35	1.15*	(1.04, 1.28)
4th Quartile, >12.35	1.49*	(1.34, 1.65)
2011 $PM_{2.5}$ Exposure Quartiles		
1st Quartile, ≤7.70	Ref	
2nd Quartile, 7.70—9.18	1.27*	(1.15, 1.40)
3rd Quartile, 9.18—10.27	1.20*	(1.08, 1.33)
4th Quartile, >10.27	1.50*	(1.35, 1.66)
2006-2011 Average Yearly $PM_{2.5}$ Exposure Quartiles		
1st Quartile, ≤8.20	Ref	
2nd Quartile, 8.20—9.92	1.17*	(1.06, 1.29)
3rd Quartile, 9.92—11.22	1.19*	(1.07, 1.33)
4th Quartile, >11.22	1.55*	(1.40, 1.72)
Models all adjusted for age, race, education, smoking status, census region, residential area type and moving status. *Denotes *p*-value <0.05		

The effects were diminished when examining participants who had not moved during the first two follow-ups. (**Table 4**) Significance was lost for almost all comparisons between exposure quartiles as the confidence intervals widened with reduced sample sizes, although patterns still indicate that there may be an increased risk of OI for those exposed to higher concentrations of $PM_{2.5}$. The only remaining significance for non-movers was found within the 2011 estimates when comparing the 2nd Quartile (7.70—9.18 $\mu g/m^3$) and the 1st Quartile (≤7.70 $\mu g/m^3$), with

Table 4. Multivariable logistic regression for $PM_{2.5}$ concentration ($\mu g/m^3$) and olfaction status for non-movers only, Cases: n=821 and Controls: n=1815

	$PM_{2.5}$ Estimates	
	OR	95% CI
2006 $PM_{2.5}$ Exposure Quartiles		
1st Quartile, ≤8.76	Ref	
2nd Quartile, 8.76—10.81	1.23	(0.96, 1.58)
3rd Quartile, 10.81—12.35	1.23	(0.95, 1.60)
4th Quartile, >12.35	1.15	(0.86, 1.52)
2011 $PM_{2.5}$ Exposure Quartiles		
1st Quartile, ≤7.70	Ref	
2nd Quartile, 7.70—9.18	1.33*	(1.03, 1.71)
3rd Quartile, 9.18—10.27	1.16	(0.89, 1.51)
4th Quartile, >10.27	1.29	(0.98, 1.70)
2006-2011 Average Yearly $PM_{2.5}$ Exposure Quartiles		
1st Quartile, ≤8.20	Ref	
2nd Quartile, 8.20—9.92	1.24	(0.96, 1.59)
3rd Quartile, 9.92—11.22	1.24	(0.95, 1.62)
4th Quartile, >11.22	1.23	(0.93, 1.64)

Models all adjusted for age, race, education, smoking status, census region, and residential area type.
*Denotes *p*-value <0.05

OR=1.33 (95% CI: 1.03, 1.71). In our second analysis regarding stability of residence, we found that those who had lived in their current residence for more than ten years had greater odds of olfaction impairment, OR=1.74 (95% CI: 1.50, 2.01), than those would been residents for less than ten years, OR=1.64 (95% CI: 1.40, 1.93), when comparing the highest exposure group to the reference group. (**Table 5**) All comparisons between the lowest $PM_{2.5}$ quartile level and all higher $PM_{2.5}$ quartile levels for the stable residents were found to be significant, while

comparisons for the participants who had lived at their current residences for less than ten years at baseline were only significant for the 1st quartile, and the 2nd and 4th quartiles.

Table 5. Multivariable logistic regression sensitivity analysis for $PM_{2.5}$ concentration ($\mu g/m^3$) and olfaction status on stable residence at baseline

	$PM_{2.5}$ Estimates Current Residence ≥10 yrs Cases=591, Controls=1273		$PM_{2.5}$ Estimates Current Residence <10 yrs Cases=454, Controls=1023	
	OR	95% CI	OR	95% CI
2006 $PM_{2.5}$ Exposure Quartiles				
1st Quartile, ≤8.76	Ref		Ref	
2nd Quartile, 8.76—10.81	1.53*	(1.34, 1.75)	1.19*	(1.03, 1.39)
3rd Quartile, 10.81—12.35	1.34*	(1.16, 1.55)	1.03	(0.88, 1.23)
4th Quartile, >12.35	1.74*	(1.50, 2.01)	1.64*	(1.40, 1.93)

Models all adjusted for age, race, education, smoking status, census region, and residential area type.
*Denotes *p*-value <0.05

In our sensitivity analysis (**Table 6**) to examine whether our primary analysis suffered from unmeasured confounding, we found that the results remained significant in all three models—Model 1 OR = 1.33 (95% CI: 1.22, 1.45), Model 2 OR = 1.30 (95% CI: 1.18, 1.42) and Model 3 OR = 1.55 (95% CI: 1.40, 1.72)—when comparing the highest average yearly $PM_{2.5}$ exposure quartile with the lowest exposure quartile. The full results did not significantly differ for the 2006 $PM_{2.5}$ exposure quartiles or the 2011 $PM_{2.5}$ exposure quartiles. Additionally, the estimates move further from the null with the fully adjusted model. As we chose covariates after examining previous literature for relevant, potential confounding factors, we believe it unlikely that other unknown, unmeasured variables could be adjusted for in our analysis, that have a strong enough association with the outcome variable and exhibit a large enough difference in prevalence between exposure groups, to alter our findings to become non-significant.

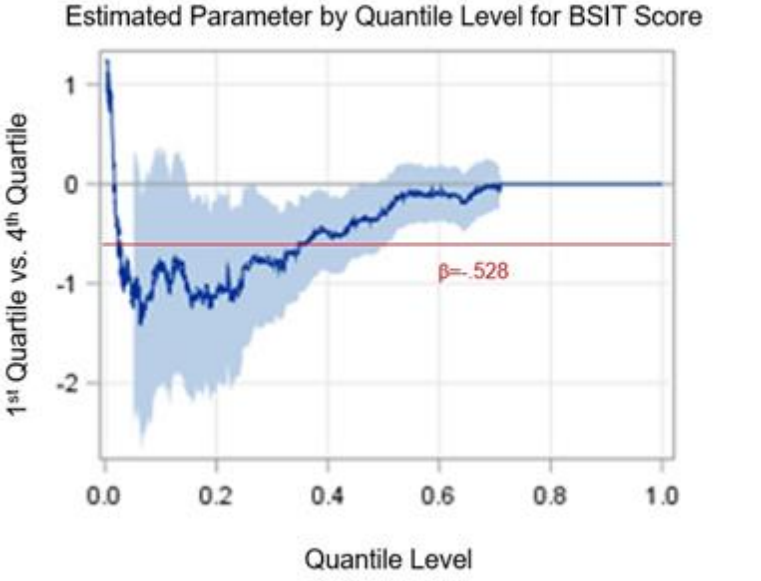
Table 6. Multivariable logistic regression sensitivity analysis for potential unmeasured confounding, Cases: n=1070 and Controls: n=2361

	Model 1		Model 2		Model 3	
	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
2006-2011 Average $PM_{2.5}$ Exposure Quartiles						
1st Quartile, ≤8.20	Ref		Ref		Ref	
2nd Quartile, 8.20—9.92	1.07	(0.97, 1.17)	1.11*	(1.01, 1.21)	1.17*	(1.06, 1.29)
3rd Quartile, 9.92— 11.22	0.99	(0.90, 1.08)	1.06	(0.96, 1.16)	1.19*	(1.07, 1.33)
4th Quartile, >11.22	1.33*	(1.22, 1.45)	1.30*	(1.18, 1.42)	1.55*	(1.40, 1.72)

Independent variables for Model 1: $PM_{2.5}$ exposure
Independent variables for Model 2: $PM_{2.5}$ exposure, age, race
Independent variables for Model 3: $PM_{2.5}$ exposure, age, race, education, smoking status, census region, and residential area type.
*Denotes *p*-value <0.05

The quantile regression showed that, when comparing the highest concentration quartile with the lowest concentration quartile, the greatest effect was shown among those with lower B-SIT scores. (**Figure 4**) Results are only shown for the average yearly $PM_{2.5}$ exposure levels, although results were similar for 2006 and 2011 estimates. Specifically, the participants whose B-SIT scores fell below the 42nd quantile were more affected by their higher exposure to $PM_{2.5}$ versus those with lower exposure levels.

Figure 4. Quantile Regression Analysis for $PM_{2.5}$



DISCUSSION

Results from this nationwide study suggest a positive association between long-term exposures to $PM_{2.5}$ and the prevalence of OI among middle-to-older age women. There was a clear dose-response relationship in the overall analysis, independent of a range of potential confounders. While the association was modestly attenuated when the analyses were restricted to non-movers, we found a stronger association when the analysis focused on those who had a stable residence for ten or more years prior to baseline. This discrepancy is possibly due to misclassification error of the moving status over multiple follow-ups, leading to inaccurate exposure measures. The stability of residence analysis is less likely to suffer from the same issue and we believe it better represents the true effect of ambient air pollution on olfaction for those with consistent exposure. Further, quantile regression analysis further showed a potential stronger adverse effect of $PM_{2.5}$ on olfaction among women whose sense of smell has already been compromised, indicating that ambient PM2.5 exposure may be an exacerbating factor rather than an initiator with regards to olfaction decline.

Despite the fact that many studies have established the profound impact olfaction impairment has on the health of older adults,[33,34,35,36] it is still a relatively understudied sensory deficit with exact mechanisms and causes not fully understood. As the olfactory epithelium is directly exposed to the outside environment, the olfactory nerve is therefore uniquely susceptible to environmental influences,[7] specifically ambient air pollutants such as $PM_{2.5}$,[37] and offers a biologically plausible site of initiation for olfactory decline, as well as a mechanism for adverse health outcomes caused by $PM_{2.5}$, such as asthma, chronic bronchitis, cardiovascular disease and cognitive health.[17,18,19,38,39] Again, the specific nature what role $PM_{2.5}$ has in the etiology of these outcomes

is still unclear, although cellular and animal studies indicate that air pollutants may increase inflammation and oxidative stress.[40,41]

For example, the role olfaction impairment plays as a prodromal symptom to Parkinson's disease and Alzheimer's disease has been well established,[3,4,42,43] but these conditions, often diagnosed later in life, and their pre-clinical pathogenesis are still poorly delineated.[44] Currently, treatments exist to treat and slow the symptoms of PD and AD, but the progression of the diseases cannot be halted and will eventual lead to physical and mental deterioration.[45] It has been hypothesized that the toxicity of $PM_{2.5}$ can lead to inflammation processes and oxidative stress within the brain,[46] which then stimulates the progression of neurodegeneration within susceptible populations.[47,48] Therefore, by identifying environmental exposures that may increase the risk of developing neurodegenerative pathologies, preventative steps may be taken to delay or stop the clinical symptoms. This relationship between ambient air pollution and neurodegenerative diseases is still speculative at this time, but underscores the importance of illuminating the exact relationship between ambient air pollution and olfaction impairment.

This research helps further our understanding the effects of ambient air pollution on sense of smell and strengthens the findings of previous research. While earlier studies have identified a link between elevated levels of air pollution and poor olfaction, they have been severely limited in design and executions. Many of the first epidemiological studies were undertaken in Mexico City,[19,22,49] where air pollution levels are notably high, and surrounding areas of lesser exposure as controls. However, these studies assumed that the exposure levels of ambient air pollution were equal if the participants lived in the same location; this uniform distribution is unlikely even over short distances.[50] Additionally, sample sizes were small (the largest was n=82 and the smallest n=30) and the populations examined were not representative of the general population

(i.e., over-sampled younger populations[19] or significant gender differences between case and control groups[22]). Subsequent studies followed similar geographical models, but focused on differences in olfaction between industrialized countries like Poland and Germany (considered high exposure risks) and non-industrialized regions such as Bolivia and Cook's Islands.[20,21] Such variety in locale increases the likelihood of unknown factors or cultural confounders affecting the accuracy of any results.

Two other studies have specifically examined the effects of $PM_{2.5}$ on olfaction.[23,51] In the first, Ranft et al. found, when examining 399 German women aged 68-79, that olfactory disfunction was associated with higher exposure to $PM_{2.5}$. However, this study did not measure levels of $PM_{2.5}$, but instead used distance to the nearest roadway as a proxy exposure for $PM_{2.5}$ levels instead. In the second, Ajmani et al. used data from the National Social Life, Health and Aging Project, a cohort of nationally representative participants of older adults, aged 57-85. Although secondary analyses we performed regarding rural participants, the primary analysis for this study only focused on 2,221 non-rural residents. Their results for this group indicated that the strongest association was found for the 6-month average exposure (OR 1.28, 95% CI 1.05, 1.55), with the youngest age group, 57-64, suffering the worst effects.

Our study, with the accuracy of the addressed-based $PM_{2.5}$ exposure, large sample size, participants with primary residences in rural and urban locations in all 50 states, corrects the limitations of previous research, and confirms the relationship between higher $PM_{2.5}$ concentration levels and OI, for both the entire study population and those who had lived in their residence for more than ten years prior to baseline. In addition, our results from our quantile regression suggest that $PM_{2.5}$ has a greater effect on those whose sense of smell is already

declining, hasn't been examined before and warrants further research to identify the ramifications of this result.

Strengths

This study has several notable strengths. First, the participants in the Sister Study are a widespread, geographically diverse group. This allows us to examine ambient air pollution beyond the context of just rural versus urban, as many previous studies have done, while controlling for potential confounders and allow our results to be more generalizable to a general female population. Additionally, by utilizing location-specific exposure measurements based on the address of primary residences, we were able avoid issues of misclassification and more finely analyze how levels of $PM_{2.5}$ affect sense of smell. This model improves upon previous methods to measure pollutant exposure such as distance to nearest road proxies and regional estimates mentioned in previous research, as it incorporated land-use regression models with spatial smoothing to accurately predict exposure levels. The meticulous and dedicated nature of data collection within the Sister Study, with response rates for all three follow-ups above 91%, ensured not only the accuracy of the data, but also limited the amount of missing data. Our varied analyses allowed us the ability to examine perspectives of ambient air pollution and olfaction that previous studies had not done, including differences between moving status and residential stability, and our quantile regression suggested that the $PM_{2.5}$ exposure has a greater effect on those whose sense of smell has declines, the ramifications of which need to be investigated further in future studies.

Limitations

Our study also has several notable have limitations. First, our population is predominantly health conscious white women with relatively high education level, potentially making study findings less generalizable to the general population within the United States. As the OI are about twice as common in men and in blacks,[52] future studies should examine this potential association among men and black persons. Second, as discussed above, the sensitivity analysis using moving status has the potential for bias in the results. The additional use of a potentially more accurate measure of residential stability, length of time in residence prior to baseline, helps mitigate this limitation. Third, the time between the most recent exposure estimates for $PM_{2.5}$ and when the B-SIT was administered was approximately five years. This could lead to misclassification of the exposure quartile, but as noted previous publications, air pollutant levels are generally declining nationally[18] and historically, $PM_{2.5}$ concentrations tend to remain consistent over multiple years.[53] Our own correlation analyses for the yearly $PM_{2.5}$ levels showed very high correlation (~0.9), indicating that even with more recent exposure data, the results would be similar but it would be prudent to re-examine the results as more updated exposure data becomes available. Third, exposure data was only estimate for the primary residence of each participant at baseline; those who moved during the follow-up period were not revised and thus, the analyses that used exposure data from after they moved may be biased. The Sister Study is currently working with the University of Washington to correctly identify the exposures levels for each participant's new address and subsequent analyses should reflect that change. Lastly, the B-SIT was only given at a single time, producing a single time point in an outcome that is known to decline over time. Additional assessments of the sense of smell may further our knowledge of how ambient air pollution levels affect OI, and whether variability in $PM_{2.5}$

concentrations over time plays a role in the speed of the decline in a person's sense of smell as they age.

Future Study

Currently, the Sister Study and the University of Washington are in the process of updating their air pollution data. This involves two main revisions: 1) providing more current estimates of $PM_{2.5}$ and other pollutants and 2) providing estimates for the new addresses of those who moved during the duration of the study. These updates will eliminate or reduce the limitations mentioned above. When those data are available, a reanalysis of this study is warranted to refine the results further.

Moreover, Michigan State University is working in conjunction with Penn State University and the NIEHS Sister Study to accurately adjudicate cases of Parkinson's disease, based on self-reported information and physician-provided medical records. Once this process is complete, the natural continuation of this research, identifying the association between ambient air pollution and PD, with olfaction impairment as a potential mediator or step on the etiological pathway, can be assessed.

Finally, $PM_{2.5}$ is a heterogenous airborne mixture comprised of many different types of particles (i.e., dust, metals, wood, chemicals) that varies based on geographical sources and meteorological factors,[54] making it a fascinating substance to study with regards to adverse health outcomes. Developing studies are beginning to examine how the component clusters of $PM_{2.5}$ affects human health, with one recent manuscript from the Sister Study identifying clusters that were associated with an increased risk of invasive breast cancer.[55] Similar analysis of

clusters and olfaction impairment or neurodegenerative diseases could provide further enlightenment as to the risk factors for both health events.

Conclusion

In conclusion, we found that higher levels of $PM_{2.5}$ were associated with olfaction impairment and that the effect may have been greater for those with an already declining sense of smell.

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