AWARD NUMBER: W81XWH-17-1-0536

TITLE: Airborne Pollutants as Triggers of Parkinson's Disease via the Olfactory System

PRINCIPAL INVESTIGATOR: Dr. Honglei Chen, Professor

CONTRACTING ORGANIZATION: Michigan State University, East Lansing, MI

REPORT DATE: December 2022

TYPE OF REPORT: Final

PREPARED FOR: U.S. Army Medical Research and Development Command
Fort Detrick, Maryland, 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
December 2022	Final	01Sep2017-31Aug2022

4. TITLE AND SUBTITLE

Airborne Pollutants as Triggers of Parkinson's Disease via the Olfactory System

5a. CONTRACT NUMBER
W81XWH-17-1-0536

5b. GRANT NUMBER
PD160021P2

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Dr. Honglei Chen

E-Mail: chenho19@msu.edu

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Michigan State University
426 Auditorium Road, RM 2
East Lansing, MI 48824-2600

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Development Command

Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT: In this project, we proposed to examine the role of air pollutants in olfactory impairment in older adults and to investigate their potential relevance to the prodromal development of Parkinson's disease (PD). Specifically, we proposed to investigate 1) the association of long-term exposures to air pollutants with olfactory impairment; 2) the association of PD polygenic risk score with olfactory impairment and potential effect modification by air pollutants; and 3) the association of lifetime uses of non-steroidal anti-inflammatory drugs with olfactory impairment and potential effect modification by air pollutants. The project leveraged ten years of extensive data collection on environmental exposures, medical history, and biospecimen from the well-established National Institute of Environmental Health Sciences' Sister Study. We selected a total of 4,020 participants from the Sister Study and enrolled 3,535 (87.9%). Of these, 3,431 (97.1%) took the Brief Smell Identification Test, and 3,358 (95.0%) have valid genomic data. Based on these data, we estimated that 13.3% of the Sister Study participants have an olfactory impairment, and the prevalence increases with age and is higher in blacks than whites. The self-awareness of this sensory deficit is low, particularly among blacks. As expected, olfactory impairment was associated with 7-8 fold higher odds of having PD. Overall, higher exposures to the air pollutants of fine particulate matters and nitrogen dioxide were not associated with olfactory impairment. However, secondary analyses suggest possible associations among younger participants and smokers. In the study of genetic data, we confirmed the strong association of PD polygenic risk score with the disease. The highest quartile of this polygenic risk score was also associated with higher odds of having an olfactory impairment. This association appears to be stronger among women with higher exposures to fine particulate matters. In our analysis of non-steroidal anti-inflammatory drugs with olfactory impairment, we found unexpected associations of regular uses of aspirin and ibuprofen with a higher risk of olfactory impairment; however, these findings were limited to never users of other types of non-steroidal anti-inflammatory drugs. In summary, this project has generated some provocative findings on a topic that has been barely investigated, which will stimulate future research. More importantly, by establishing a unique, large cohort with extensive environmental/genetic data, biospecimen, objectively assessed olfaction, and broad assessments of PD motor and nonmotor symptoms, we laid a solid foundation for future longitudinal research to investigate potential triggers and modifiers of PD prodromal development and beyond.

15. SUBJECT TERMS
Parkinson's disease, olfaction, sense of smell, air pollutants, prodromal, inflammation, non-steroidal anti-inflammatory drugs

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRDC
Unclassified	Unclassified	Unclassified	Unclassified	14	19b. TELEPHONE NUMBER *(include area code)*

TABLE OF CONTENTS

Page

1. Introduction……. 4
2. Keywords……. 4
3. Accomplishments…….. 4
4. Impact…… 8
5. Changes/Problems…… 9
6. Products……... 10
7. Participants & Other Collaborating Organizations…… 11
8. Special Reporting Requirements…… 14
9. Appendices…….. 14

1. INTRODUCTION

Olfactory impairment (OI) is an under-appreciated and under-studied health problem among older adults. Importantly, OI is an early warning for several major neurodegenerative diseases, such as Parkinson's disease (PD) and dementia. However, the causes of age-related OI and how it may contribute to neurodegenerative diseases are largely unknown. Therefore, we proposed a case-control study to investigate risk factors for age-related OI to better understand PD prodromal development. This project aims to define the role of ambient air pollutants in OI and explore its relevance to PD development. Specifically, we aim to 1) assess the effect of long-term exposure to air pollutants on OI (mPI project specific aim 5); 2) investigate whether early PD pathogenesis is exacerbated by ambient air pollutants, using PD polygenic risk score as a proxy to PD susceptibility (specific aim 6); and 3) examine whether lifetime use of non-steroidal anti-inflammatory drugs (NSAIDs) modifies potential adverse effects of air pollutants on OI (specific aim 7). The project leverages ten years of extensive data collection on environmental exposures, medical history, and biospecimen from the well-established Sister Study of the National Institute of Environmental Health Sciences (NIEHS). Specifically, we have objectively evaluated the sense of smell of 3,535 participants from the Sister Study, using a validated and self-administered brief smell identification test (B-SIT). Participants further completed a short survey on medical history relevant to their senses of smell and taste. Besides, we performed genotyping to quantify their genetic risk for PD. We have analyzed these data together with the extensive exposure data that the Sister Study has already collected to examine the proposed aims.

2. KEY WORDS: Parkinson's disease, olfaction, sense of smell, air pollutants, prodromal, inflammation, non-steroidal anti-inflammatory drugs

3. ACCOMPLISHMENTS

3.A. What were the major goals of this project?

By objectively assessing the sense of smell of selected participants from the NIEHS Sister study and leveraging the study's extensive environmental data collection, we aim to examine the role of ambient air pollutants in OI and explore its relevance to PD, as detailed above. We initially proposed to collect data from 2,713 Sister study participants; later, with a cost-share agreement established with the Parkinson's Foundation ($151,399, details in **7.B**), we collected the sense of smell data from 3,535 participants. Importantly, beyond the specific aims, by establishing a unique, large cohort with extensive environmental/genetic data, biospecimen, objectively assessed olfaction, and broad assessments of PD motor and nonmotor symptoms, we laid a solid foundation for future longitudinal studies of the triggers and modifiers of PD prodromal development and beyond.

3.B. What was accomplished under these goals?

We started data collection (B-SIT test and questionnaire survey) in March 2018, which was completed on February 28, 2019. Of the 4,020 Sister participants we selected, 3,535 (87.9%) responded and 3,431 (85.3%) returned the B-SIT kit. The response rate was slightly higher than what we had ambitiously projected (85.0%). In May 2019, we shipped 3,696 DNA samples (including duplicates for quality control) to the National Institute on Aging (NIA) for genotyping. Genotyping was completed in 2020 at our collaborator's lab at NIA, and data were delivered in 2021. We have completed all proposed data collection and analyses. We have published two manuscript in leading specialty journals and have four more currently in review. Please refer to the *participant recruitment and data collection section* and *products section* for details.

Study participation

1. *"Obtain IRB approval or exemption from DOD and relevant study sites" by month 4.*
   Progress: We obtained standalone IRB approvals from MSU (IRB# 17-1208) on November 20, 2017, and the DoD (#A-20425) on January 10, 2018. Besides, NIEHS/SSS (Sister study contractor of NIEHS) and the University of Washington approved relevant study activities by amending their existing protocols. The Sister Study team carried out all field data collection activities. After initial approval, we made multiple minor revisions that

MSU IRB swiftly approved. All modifications did not affect the risk and benefit of study participants.

2. *"Select participants and design survey/study materials" by month 4*
   Progress: In January 2018, we selected 2,820 eligible Sister Study participants, ages 50-79 and alive, who reported a poor sense of smell at a recent survey and a random sample of 1,200 participants who did not. Study materials were ready by January 2018.

3. *"Obtain survey data from the Sister study" by month 6*
   Progress: We obtained the cohort survey data from the Sister Study first on June 1, 2018, which were updated a couple of times afterward to meet analytic needs.

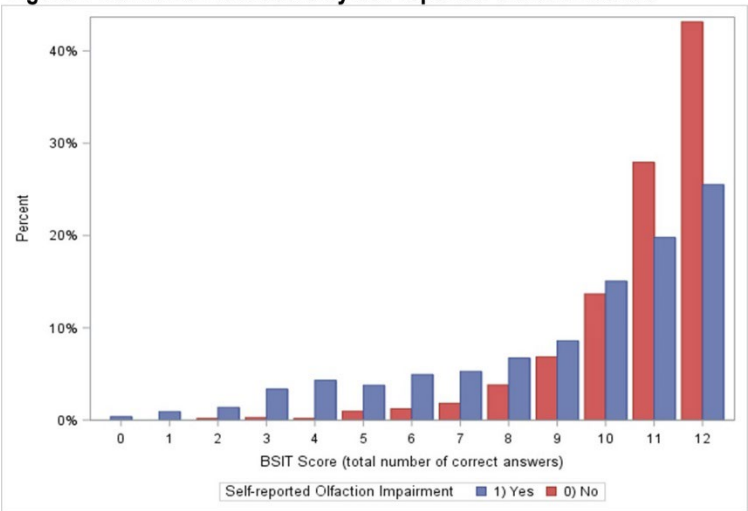
Participant recruitment and data collection

1. *"Mail/receive test kit and questionnaire" by month 18*
   Progress: We completed data collection in Feb. 2019. Of the 4,020 Sister participants selected, 3,535 (87.9%) responded, and 3,431 (85.3%) returned the sense of smell test kit. The participation rate was comparable between participants who self-reported a poor sense of smell and those who did not, and it was little affected by age or education level.

2. *"Data QC, entry, and delivery" by month 21*

Progress: The field team at NIEHS entered and cleaned data, which demonstrates high quality. Of those who returned the B-SIT test kit, 94.8% completed all 12 items. Only 4.1% were missing 1-2 items and 1.1% were missing three or more. The score ranges from 0 to 12 (**Figure 1**).

Figure 1 BSIT smell test score by self-reported olfaction status



Participants with self-reported OI overall scored lower than those who reported a normal sense of smell. Based on the distribution of these data in our study sample, we chose to use 9 as the cutoff for OI in the primary analysis. With this cutoff, we estimated a 13.3% (95%CI: 11.5-15.0) of the Sister Study participants, ages 50-80, have OI, and the prevalence increases with age (**Figure 2**). We also found an interesting racial disparity – blacks were twice likely to have OI than white participants, but were less likely to recognize this symptom. In both populations, the awareness of this sensory deficit and reporting accuracy was low (**Table 1**), which we found was affected by a few demographic and health factors. For example, among participants who reported OI, older age, black race, low education, underweight, fair-to-poor health, and PD were associated with higher odds of being true vs. false positives. Among those with objectively tested poor olfaction, the black race was associated with lower odds of

Figure 2. OI prevalence by age and race

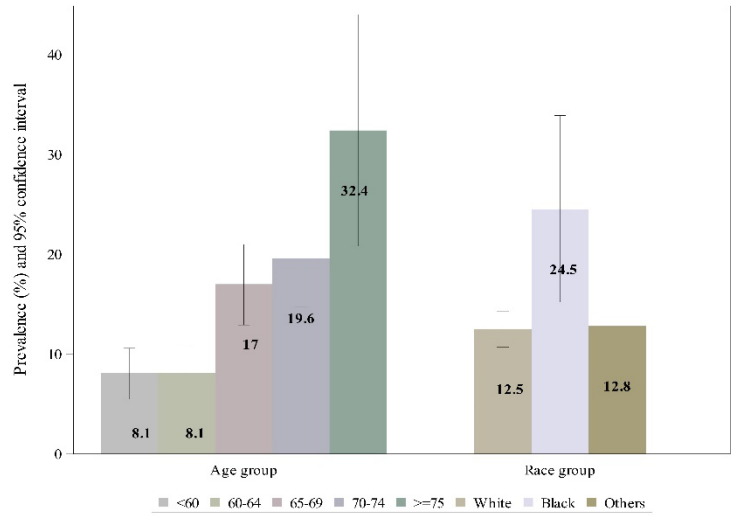


Table 1: Self-reported vs. Objectively Tested OI				
	Sensitivity	**Specificity**	**PPV**	**NPV**
Non-Hispanic Whites	24.4 (20.8,28.0)	94.5 (94.3,94.6)	38.5 (37.6,39.3)	89.8 (87.8,91.7)
Non-Hispanic Blacks	12.4 (7.0,17.8)	96.0 (94.9,97.2)	50.3 (46.5,54.0)	77.1 (67.2,87.1)
Other races	19.0 (8.3,29.7)	94.8 (93.5,96.0)	34.7 (31.1,38.3)	88.9 (81.7,96.1)
Overall	22.6 (19.6,25.6)	94.6 (94.4,94.7)	38.9 (38.0,39.7)	88.9 (87.0,90.8)
All numbers are % with 95%CI; PPV/NPV: positive/negative predictive value				

being true positives *vs.* false negatives. Given the potentially broad implications of poor olfaction on the health of older adults (including but not limited to PD and dementia), we expect our findings will generate interest in raising awareness of this common sensory deficit in older adults. The manuscript was published in 2022 in *JAMA Otolaryngology and Head and Neck Surgery*.

Specific Aim 5: To examine the association of air pollution with OI

1. "Air pollutant assessment and data delivery to MSU" by month 12

Progress: The Sister Study data delivery included air pollution estimates based on participants' baseline residential addresses as well as exposures during the Sister Study follow-ups by incorporating moving after enrollment.

2. *"Data analysis and manuscript preparation/submission" by month 48*

Progress: We have analyzed the ambient concentrations of $PM_{2.5}$ and NO_2 in relation to OI. The primary analysis was based on the residence at enrollment, but we also conducted analyses using exposure levels in 2017 and average exposure between until 2017, accounting for moving after enrollment. The primary analyses were limited to 3,345 women with valid data both on the exposures and outcome of interest. Poor olfaction was defined as a B-SIT score ≤9 in the primary analysis. Overall, we found little evidence for associations of air pollutants with poor olfaction (**Table 2**). The odds ratio (OR) and 95% confidence interval (CI) of poor olfaction for each interquartile (IQR) increment of air pollutants in 2006 were 1.04 (0.91, 1.17) for $PM_{2.5}$ (per 3.3 $\mu g/m^3$) and 1.09 (0.97, 1.22) for NO_2 (per 5.7 ppb). Similar results were obtained when we analyzed the most recent (2017) or cumulative average (2006-2017) air pollutant data. When limited to participants with a stable residence pre-enrollment, we found a positive association between per IQR increase in NO_2 and poor olfaction (OR and 95% CI: 1.17 (1.00, 1.37)). Secondary analyses suggested potential effect modifications by age and smoking status. Among younger subjects (<55.2 years), the OR and 95% CI for each IQR were 1.24 (1.02, 1.51) for $PM_{2.5}$ and 1.18 (0.99, 1.41) for NO_2. The corresponding estimates among current smokers were 1.27 (0.85, 1.90) for $PM_{2.5}$ and 1.88 (1.30, 2.73) for NO_2. While, overall, this study does not find consistent evidence that air pollutants have lasting detrimental effects on the sense of smell of middle-to-old age women, we cannot exclude the possibility that $PM_{2.5}$ and NO_2 may contribute to OI among younger women and smokers. The manuscript is currently under review by *Environmental Health Perspectives*.

Table 2 Ambient air pollutants in relation to OI		
Exposure level	Multivariable OR and 95%CI	
	PM2.5 (2006)	NO2 (2006)
Quartile 1	Reference	Reference
Quartile 2	1.01 (0.79,1.29)	1.19 (0.94,1.52)
Quartile 3	1.03 (0.79,1.35)	1.04 (0.80,1.36)
Quartile 4	1.08 (0.83,1.41)	1.20 (0.90,1.60)
Per IQR	*1.04 (0.91,1.17)*	*1.09 (0.97,1.22)*
OR: odds ratio; CI: confidence interval IQR: inter-quartile range. Data weighted back to all eligible participants in the main cohort, adjusted for baseline age, race, education, BMI, health status, smoking status, census region, and residential area type		

Specific Aim 6: To examine the association of PD polygenic risk score (PRS) with OI and potential effect modification by air pollutants.

1. *"DNA extraction by Bioserve" by month 24*
   Progress: DNA extraction was completed by March 2019. In May 2019, we shipped DNA samples to NIA for genotyping.

2. *"Genotyping by NIA" by month 44*

Progress: Genotyping, quality control, and imputation were completed in 2020 by our collaborators at the NIA neurogenetic lab. The final cleaned data was delivered to MSU in 2021.

3. *"Data analysis and manuscript preparation/submission" by month 60:* This analysis included 3,358 women with both valid genetic and olfaction test data. PD PRS was calculated using 90 single nucleotide polymorphisms. OI was defined using different B-SIT cutoffs, representing the spectrum from hyposmia and anosmia. PD diagnosis was adjudicated via expert review. As expected, PD PRS was strongly associated with the odds of having PD (OR highest vs. lowest quartile = 3.79, 95%CI:1.64, 8.73). The highest PRS quartile was also modestly associated with OI, with OR ranging from 1.24 (0.98, 1.56) for the B-SIT cutoff of 9 to 1.42 (1.04, 1.92) for the cutoff of 6. For individual B-SIT items, the highest PRS quartile was generally associated with lower odds of correctly identifying the odorant, albeit only statistically significant for pineapple (0.72 (0.56, 0.94), soap (0.76 (0.58, 0.99)) and rose (0.70 (0.54, 0.92)). Overall, we found little evidence that the association of PD PRS with OI was modified by airborne environmental exposures or smoking with one possible exception. The association of PRS with OI appears to be stronger in women with higher than median exposure to $PM_{2.5}$. Taken together, these preliminary data suggest that high PD genetic susceptibility is associated with OI in middle-aged and older women. This manuscript is currently under consideration by *Movement Disorders.*

Table 3. PD poleygenic risk score and olfactory impairment

Polygenic risk score	B-SIT ≤ 9	B-SIT ≤ 8	B-SIT ≤ 7	B-SIT ≤ 6
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Quartile 1	Reference	Reference	Reference	Reference
Quartile 2	0.99 (0.78, 1.25)	1.06 (0.82, 1.38)	0.92 (0.69, 1.22)	0.97 (0.71, 1.34)
Quartile 3	1.04 (0.82, 1.32)	1.04 (0.80, 1.35)	0.82 (0.62, 1.09)	0.94 (0.69, 1.30)
Quartile 4	1.24 (0.98, 1.56)	1.34 (1.03, 1.73)	1.31 (1.00, 1.73)	1.42 (1.04, 1.92)
Per IQR	1.12 (1.00, 1.25)	1.13 (1.00, 1.28)	1.12 (0.97, 1.28)	1.18 (1.02, 1.37)
P for trend	*0.05*	*0.03*	*0.06*	*0.02*

OR: odds ratio; CI: confidence interval;
Adjusting for age, race, the first 5 principal components, self-reported sense of smell, education, smoking status, self-reported health status, PM2.5, and NO2 in 2006.

Specific Aim7: To examine the association of NSAID uses with OI and potential effect modification by air pollutants.

1. *Data analysis and manuscript submission by month 60*

Progress: This analysis was limited to participants with both data on NSAIDs use and olfaction. OI was defined as B-SIT score ≤9 in the primary analyses, but we also used other cutoffs of B-SIT in the analyses. Overall, NSAID uses were not associated with poor olfaction. However, we found evidence for potential multiplicative interactions. Specifically, the OR comparing regular vs. never use of aspirin was 1.8 (95%CI: 1.1, 3.2) among women who had not regularly used other NSAIDs, while the corresponding OR was 0.8 (95% CI: 0.5, 1.2) among other NSAID users (*P* for interaction =0.016). Similar observations were made in the analyses for ibuprofen. The OR comparing regular vs. never use of ibuprofen was 2.1 (95%CI: 1.1, 4) among women who never regularly used non-ibuprofen NSAIDs versus 0.8 (95% CI: 0.5, 1.2) among other NSAID users (*P* for interaction=0.010). For both aspirin and ibuprofen, longer duration, higher cumulative dosage, and continuous use pattern were associated with higher odds of having OI among women who never regularly used other types of NSAIDs. Post-hoc analyses showed that

Table 4. Regular use (vs. never) of NSAIDs through the 3rd detailed follow-up and OI

	Overall	Among never users of other NSAIDs	Among ever Users of other NSAIDs
Aspirin	1.1 (0.8,1.6)	1.8 (1.1,3.2)	0.8 (0.5,1.2)
Ibuprofen	1.0 (0.7,1.4)	2.1 (1.1, 4.0)	0.8 (0.5,1.2)
COX-2 inhibitors	1.1 (0.7,1.8)	0.5 (0.2,1.2)	1.1 (0.7,1.8)
Other NSAIDs	1.0 (0.7,1.4)	1.1 (0.4, 3.0)	1.0 (0.7,1.4)

OR and 95% CI were reported using weighted logistic models, adjusting for age, race, education, BMI, smoking, general health status, self-reported pain, and comorbidities.

the interactions could not be readily explained by unmeasured confounding, misclassification, and selection bias. COX-2 inhibitors or other NSAIDs were not related to olfaction in any analyses. To our knowledge, this is the first study to find that long-term regular use of aspirin or ibuprofen may be associated with poor olfaction among women who never regularly used other types of NSAIDs. Future studies are warranted to confirm these intriguing findings. Finally, we also examined potential interactions between NSAIDs and air pollutants on OI, and did not find meaningful patterns. This manuscript was submitted to *JAMA Otolaryngol Head Neck Surgery.*

Finally, supported by the Parkinson's Foundation, we also adjudicated PD diagnosis in the cohort. Of the 371 self-reported PD cases identified during a median of 11.6 years of follow-up, 242 PD diagnoses were adjudicated. Confirmed cases were likely to consistently report PD diagnosis, medication usage, and motor and nonmotor symptoms during follow-ups. Further, hyposmia, constipation, dream enacting behaviors, daytime saliva dribbling, and unexplained weight loss were much more commonly reported in confirmed cases. In contrast, dry mouth, dry eyes, insomnia, pain, depression, and excessive sweating were more common in unconfirmed cases. Finally, a wide range of nonmotor symptoms were associated with future PD risk, ranging from the well-studied hyposmia (OR=4.88), depression (OR=2.53), dream enacting behaviors (OR=2.20), and constipation (OR=1.86) to the less-studied unexplained weight loss (OR=4.02), dry eyes (OR=1.85), dry mouth (OR=1.91), and fatigue (OR=1.71). None but one of the negative control symptoms were associated with incident PD. Findings support the validity of PD ascertainment in this large cohort of women for environmental health research. Further, our data show that PD prodromal presentation is likely beyond its well-documented profile. This manuscript is currently under consideration by *Movement Disorders.*

3.C. What opportunities for training and professional development has the project provided?

Although this project has no training component, it supported two Ph.D. students. Mr. Zichun Cao led the analyses on the associations of air pollutants with olfaction and PD as well as PD genetics with olfaction, and Ms. Keran Wang conducted the analysis of NSAID uses and olfaction. Further, this project has generated unique statistical challenges that are often ignored in epidemiological design and analyses, for example, the analyses of secondary outcomes (i.e., B-SIT tested OI) using case-control samples selected based on a related outcome (i.e., self-reported OI), and mediation analyses with such a study design. This, in part, has led to the dissertation of Mr. Zichun Cao, a PhD candidate in Biostatistics.

3.D. How were the results disseminated to communities of interest?

Supported by this grant, we have published two papers, four under review, and one in preparation. Please see the publication list for details. In addition, Frank Purdy, a Master student, presented the preliminary results at the "Grand Challenges in Parkinson's Disease" meeting at the Van Andel Institute in Grand Rapids, MI, on August 21, 2019. The title of his poster is "Ambient Air Pollutants and Olfaction in A Large Cohort of Women: Preliminary Results".

3.E. What do you plan to do during the next reporting period to accomplish the goals?

N/A, as this is the final report.

4. IMPACT:

4.A. What was the impact on the development of the principal discipline(s) of the project?

The human sense of smell decreases with age, affecting 15-25% of older US adults. Although most do not even realize they have it, OI adversely affects human functioning such as detecting environmental hazards, nutrition, mood and behavior, sexuality, emotional and physical well-being, and quality of life. Further, OI is a prodromal symptom of PD and dementia and robustly predicts mortality in older adults. Preliminary findings from our group and others further show potential associations of OI with other health conditions such as pneumonia, functional decline, frailty, diabetes, and heart diseases, suggesting that OI may have broad potential implications on

the health of older adults beyond its well-known associations with mortality and neurodegeneration.

Because OI is one of the earliest and most important prodromal symptoms of PD, OI research may therefore represent an unprecedented opportunity to understand the early stages of PD development. Late-onset PD takes years, if not decades, to develop, and by the time of diagnosis, it is generally too advanced to decelerate, stop, or reverse. Research on OI may help in the war against PD in two ways: 1) characterize at-risk populations, which may eventually facilitate early diagnosis and treatment, and 2) better elucidate disease etiology. A major challenge in PD etiological research is the current lack of understanding of the decades of PD prodromal development, during which many factors may come into play to initiate pathology or modify progression. By using OI as an easily measured and noninvasive intermediate marker of PD, we expect to bring new insights into this "black-box" by identifying factors that contribute to OI and factors that modify its progression to PD, fundamentally improving understanding of the poorly understood etiology of PD. Inspired by the principles of this project, we developed another study to investigate the potential connections of pesticides, olfaction, and neurodegeneration among US farmers (R01ES029227, 2019-2024) using similar approaches. These data collection has laid a solid foundation for us to prospectively follow up these participants to advance our understanding of environmental contributions to PD during the course of its prodromal development.

4.B. What was the impact on other disciplines?

OI or hyposmia is also an early marker for several other neurodegenerative diseases such as Alzheimer's disease. Interestingly, our recent findings suggest that poor olfaction has more to tell about the health of older adults beyond its association with neurodegenerative diseases. Specifically, we recently reported that PD and dementia combined only explained ~22% of the excess mortality among older adults with poor olfaction (*Annals of Internal Medicine 2019*), and that poor olfaction was associated with a higher risk for pneumonia hospitalization (*Lancet Healthy Longevity 2021*) and a faster decline in physical functioning (*Journal Gerontology Series A: Medical Sciences, 2021*). Therefore, despite the low awareness of this common sensory deficit among the general public, OI may have profound implications for the health of older adults. Using a secondary dataset from existing cohorts of older adults (baseline mean age 75.6 yrs), we developed another project to examine potential associations of OI with a wide range of adverse health outcomes among older adults and with biological markers of age acceleration (R01AG071517, 2022-2027). With data collection supported by this project and the other R01 project among middle-aged to older adults, we are well-positioned to more rigorously examine the potential health implications of poor olfaction with repeated longitudinal assessment of olfaction and relevant health outcomes. We expect this will generate important knowledge to improve healthy aging.

4.C. What was the impact on technology transfer?

Nothing to report.

4.D. What was the impact on society beyond science and technology?

Up to a quarter of older US adults have a poor sense of smell, a sensory impairment of which most are unaware. However, poor olfaction may have broad ramifications on the health of older adults, as discussed above. In our first publication using data from this project (*JAMA Otolaryngol Head Neck Surgery, 2022),* we compared the self-reported vs. objectively tested OI and identified multiple factors that might have contributed to the low awareness. We hope our findings, together with the recent observations of olfaction loss being one of the most differentiating symptoms of COVID-19, will help to raise awareness in both the general public and medical communities of this important sensory deficit in older adults.

5. CHANGES/PROBLEMS:

5.A. Changes in approach and reasons for change

Nothing to report.

5.B. Actual or anticipated problems or delays and actions or plans to resolve them

Nothing to report.

5.C. Changes that had a significant impact on expenditures

Nothing to report.

5.D. Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Nothing to report.

6. PRODUCTS:

6.A. Publications, conference papers, and presentations *: Author(s); title; journal; volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

All manuscripts below acknowledged the support of this project.

Two papers published:

1) Cao Z*., Yang A.*, D'Aloisio A., Suarez, L., Deming-Halvorsend, S. Li, C., Luo, Z., Pinto, J., Werder, E., Sandler, D., Chen, H. Assessment of Self-reported Sense of Smell, Objective Testing, and Associated Factors in Middle-aged and Older Women. *JAMA Otolaryngol Head Neck Surgery.* 2022;148(5):408–417. doi:10.1001/jamaoto.2022.0069
2) Chen H, Wang K*, Scheperjans F, Killinger B. Environmental triggers of Parkinson's disease - Implications of the Braak and dual-hit hypotheses. Neurobiol Dis. 2021 Dec 23;163:105601. doi: 10.1016/j.nbd.2021.105601. Online ahead of print. PMID: 34954321

Four manuscripts supported by this grant are currently in review

1) Cao, Z.*, Yang, A.*, White, A., Purdy, F., Li, C., Luo, Z., D'Aloisio, A., Suarez, L., Deming-Halverson, S. Pinto, J., Chen, J., Werder, E., Kaufman, J., Sandler, D., Chen, H. Ambient Air Pollutants and Olfaction among Middle-to-Old Age Women. Submitted to Environmental Health Perspectives.
2) Cao, Z*., Hernandez, D., Li, C., Berhausen, J., Luo, Z., Iwaki, H., D'Aloisio, A., Huan, X., Pinto, J., Sandler, D., Singleton, A., Chen, H. Polygenic risk score of Parkinson's disease and olfaction among middle-aged to older women. Submitted to Movement Disorders.
3) Cao, Z*., Song, S*., Huang, X., Li, C., Luo, Z., D'Aloisio, A., Suarez, L., Hernandez, D., Singleton, A., Sandler, D., Chen, H. Parkinson's disease ascertainment in a nationwide cohort of women for environmental health research. Submitted to Movement Disorders.
4) Wang, K*., Li, C., Luo, Z., D'Aloisio, A., Pinto, J., Sandler, D., Chen, H. Use of nonsteroidal anto-inflammatory drugs and olfaction in middle-aged and older women. Submitted to JAMA Otolaryngol Head Neck Surgery.

* Trainees

In addition, we are preparing a manuscript that examines the association of ambient air pollutants of $PM_{2.5}$ and NO_2 with the risk of PD. Findings also suggest a potential role of NO_2 in PD development.

Books or other non-periodical, one-time publications:

Nothing to report.

Other publications, conference papers, and presentations:

Frank Purdy, a Master student, presented the preliminary results at the “Grand Challenges in Parkinson’s Disease” meeting at the Van Andel Institute in Grand Rapids, MI, on August 21, 2019. The title of his poster is “Ambient Air Pollutants and Olfaction in A Large Cohort of Women: Preliminary Results”.

6.B. Website(s) or other Internet site(s)

Nothing to report.

6.C Technologies or techniques

Nothing to report.

6.D Inventions, patent applications, and/or licenses

Nothing to report.

6.E. Other Products

Nothing to report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

7.A What individuals have worked on the project?

The followings are MSU personel’s efforts for the entire project period. Collaborators are listed separately in 7.C.

Name:	Honglei Chen
Project Role:	PI
Researcher Identifier (e.g. ORCID ID):	0000-0003-3446-7779
Nearest person month worked:	2017-2018: 3 2018-2019: 2 2019-2020: 2 2020-2021: 2 2021-2022: 2
Contribution to Project:	Oversaw all activities of the study, including study design, material development and purchase, IRB approvals, field data collection, DNA extraction, and data management and analysis.
Funding Support:	

Name:	Chenxi Li
Project Role:	Biostatistician
Researcher Identifier (e.g. ORCID ID):	0000-0003-0701-0757
Nearest person month worked:	2020-2021: 1.2
Contribution to Project:	Developed and refined analytic strategies and oversaw the statistical analysis conducted by data analysts and students
Funding Support:	
Name:	Joseph Gardiner
Project Role:	Biostatistician
Researcher Identifier (e.g. ORCID ID):	N/A

Nearest person month worked:	2017-2018: 0.6 2018-2019: 0.7 2019-2020: 0.7
Contribution to Project:	Advised the PI on statistical analyses
Funding Support:	

Name:	Aiwen Yang
Project Role:	Data analyst
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	2017-2018: 1 2018-2019: 9 2019-2020: 12 2020-2021: 8.5
Contribution to Project:	Data receiving, cleaning, management, and analyses under Dr. Chen's supervision
Funding Support:	

Name:	Zichun Cao
Project Role:	Graduate Student functions as data analyst and research assistant
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	2019-2020: 3.5 2020-2021: 6 2021-2022: 12
Contribution to Project:	Data analyses under Dr. Chen's supervision
Funding Support:	

Name:	Frank Purdy
Project Role:	Graduate Student function as a project manager
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	2017-2018: 4 2018-2019: 6 2019-2020: 2.5
Contribution to Project:	Helped Dr. Chen manage various aspects of study activities daily, conducted the preliminary data analyses
Funding Support:	

7.B. Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

The following grants were awarded during the performance period, Dr. Chen is the PI or co-PI for all these projects.

Title: Poor Sense of Smell and the Health of Older Adults
Time Commitments: Chen H, PI, 1.35 AY, 1.35 Sum month
Supporting Agency: NIH/NIA R01AG071517 (06/15/2022 – 02/28/2027)

Address: Office of Research, A209 East Fee Hall, 965 Wilson Road, East Lansing, Michigan 48824-1316
Performance Period: 06/15/2022-02/28/2027
Level of funding: total
Project Goals: We will conduct secondary analyses of data from the Health ABC and ARIC cohorts to examine poor olfaction in older adults in relation to the risk of multiple major chronic diseases above and beyond neurodegenerative diseases, declines in physical, pulmonary, and cognitive/mental functions, frailty, and epigenetic markers of age acceleration. No scientific or budgetary overlap with this project.

Title: Prodromal symptoms in the Sister Study
Time Commitments: Chen H, PI, in-kind (0% effort)
Supporting Agency: Parkinson's Foundation - PF-IMP-1825
Address: 1359 Broadway Suite 1509; New York, NY 10018
Performance Period: 06/01/2018 – 05/31/2019
Level of funding: total
Project Goals: Supplemental funding to expand data collection in the above-referenced DoD study to a larger sample which enables more comprehensive analyses of risk factors for olfactory impairment and their relevance to Parkinson's development. This was the cost-share with the current project.

Title: Determinants of depression in Parkinson's disease
Time Commitments: Chen H, co-PI, in-kind (0% effort)
Supporting Agency: Michigan State University
Address: Office of Research, A209 East Fee Hall, 965 Wilson Road, East Lansing, Michigan 48824-1316
Performance Period: 07/01/2018 – 06/30/2021
Level of funding: total
Project Goals: To evaluate the development of depressive symptoms before and after PD diagnosis. No scientific or budgetary overlap with this project.

Title: R01ES029227-01A1 Pesticides, Olfaction, and Neurodegeneration Among US Farmers
Time Commitment: Chen H, PI, 1.6 AY months & 1 Sum month
Supporting Agency: NIH/NIEHS
Address: Office of Research, A209 East Fee Hall, 965 Wilson Road, East Lansing, Michigan 48824-1316
Performance Period: 02/01/2019 – 01/31/2024
Level of funding: total
Project Goals: To investigate roles of pesticides in olfactory impairment among farmers and to examine their relevance to prodromal development of neurodegenerative diseases such as dementia and Parkinson's. No scientific or budgetary overlap with this project.

7.C. What other organizations were involved as partners?

Organization Name: The Social & Scientific Systems, Inc.
Location of Organization: Durham, North Carolina
Partner's contribution to the project: field data collection, cleaning, and delivery via purchase order contract
Lead personel: Dr. Aimee A. D'Aloisio, Ms. Lourdes Suarez, and Dr. Sandra Halverson from the Sister Study field team

Organization Name: National Institute of Environmental Health Sciences
Location of Organization: Durham, North Carolina
Partner's contribution to the project: scientific collaboration by granting data access and advising on research work, at no cost
Lead personel: Dr. Dale P. Sandler (Sister study PI)

Organization Name: ReproCell, Inc. (previously called Bioserve)
Location of Organization: Beltsville, MD
Partner's contribution to the project: DNA extraction via purchase order contract
Lead personel: Dr. Terri Lehman

Organization Name: University of Washington
Location of Organization: Seattle, WA
Partner's contribution to the project: collaboration
Partner's contribution to the project: air pollution data generation and update, via grant subcontract
Lead personel: Dr. Joel D. Kaufman

Organization Name: Chicago University
Location of Organization: Chicago, IL
Partner's contribution to the project: scientific collaborations (e.g., questionnaire design, and manuscript preparation), via grant subcontract
Lead personel: Dr. Jayant Pinto

Organization Name: National Institute on Aging
Location of Organization: Bethesda, MD
Partner's contribution to the project: scientific collaboration and genotyping, at no cost
Lead personel: Dr. Andrew B. Singleton, and Dr. Dena G. Hernandez

Organization Name: Parkinson's Foundation
Location of Organization: New York, NY
Partner's contribution to the project: Supplemental financial support as explained above

8. SPECIAL REPORTING REQUIREMENTS

8.A. COLLABORATIVE AWARDS: Other multi-PIs of this project are responsible for submitting their own reports.
8.B. QUAD CHARTS: Attached.

9. APPENDICES: Six manuscripts attached (all in pdf, two published, four in review)