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PRINCIPAL INVESTIGATOR: Dr. Honglei Chen, Professor

CONTRACTING ORGANIZATION: Michigan State University
East Lansing, MI 48824

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Dr. Honglei Chen
E-Mail: hchen@epi.msu.edu

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426 Auditorium Road, RM 2
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14. ABSTRACT: In this multidisciplinary project, we proposed to examine the central hypothesis that ambient air pollutants contribute to Parkinson's disease (PD) development by initiating or exacerbating a-synuclein pathology at olfactory structures via inflammation. In the epidemiologic arm, we plan to investigate 1) the effect of long-term exposure to air pollutants on olfactory impairment (OI); 2) whether early PD pathogenesis is exacerbated by ambient air pollutants; and 3) whether lifetime use of ibuprofen modifies potential adverse effects of air pollutants on OI. The project will leverage 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. Importantly, we will objectively evaluate sense of smell of approximately 3,400 Sister Study participants, using the brief smell identification test (BSIT), efficiently administered by mail. In the first year, we have enrolled 3,018 Sister Study participants. Interim data analysis shows BSIT score distribution that is consistent with the literature, and the score clearly decreases with age. We just started DNA extraction in order to assess participants' genetic susceptibility to PD. In the second year of this project, we plan to complete DNA extraction, start genotyping, and analyze data for specific aim 1.

15. SUBJECT TERMS
Parkinson's Disease, Olfaction, Sense of Smell, Air Pollutants, Prodromal, Inflammation, Risk Factor

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1. INTRODUCTION

Olfactory impairment (OI) is an under-appreciated and under-studied health problem among older adults. More importantly, OI is an early warning for several major neurodegenerative diseases such as Parkinson's (PD) and Alzheimer's (AD) diseases. However, the causes of age-related OI and how it may contribute to neurodegenerative diseases are largely unknown. We therefore proposed a case-control study to investigate risk factors for age-related OI in order to better understand PD prodromal development. The goal of this specific project is to define the role of ambient air pollutants in OI and to explore its relevance to PD development. Specifically, we aim to 1) assess the effect of long-term exposure to air pollutants on OI; 2) investigate whether early PD pathogenesis is exacerbated by ambient air pollutants; and 3) examine whether lifetime use of non-steroidal anti-inflammatory drugs (NSAIDs), ibuprofen in particular, modifies potential adverse effects of air pollutants on OI. The project will leverage 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). Importantly, we will objectively evaluate sense of smell of approximately 3,400 selected participants from the Sister Study. We will ask these participants to take a self-administered brief smell identification test (BSIT) and to complete a survey on medical history relevant to their senses of smell and taste. In addition, we will perform genotyping to quantify their genetic risk for PD. With additional support from the NIEHS and Parkinson's Foundation, we will also identify and confirm PD diagnosis in the Sister Study. We will analyze these data together with the tremendous exposure data that the Sister Study has already collected. We expect this project will significantly improve our understanding about risk factors for OI and provide novel insights into prodromal development of PD and related neurodegenerative diseases.

2. KEY WORDS: Parkinson's Disease, Olfaction, Sense of Smell, Air Pollutants, Prodromal, Inflammation, Risk Factors

3. **ACCOMPLISHMENTS**

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

In this project, we initially proposed to assess sense of smell of 2,713 Sister Study participants using the brief smell identification test (BSIT), limited to participants ages 50-79, nonsmokers and non-movers, and without neurodegenerative diseases. By further leveraging ten years of extensive exposure data collection in the Sister Study, we aim to examine the role of ambient air pollutants in olfactory impairment (OI) and to explore its relevance to Parkinson's disease (PD). Specifically, we aim to 1) assess the effect of long-term exposure to air pollutants on OI; 2) investigate whether early PD pathogenesis is exacerbated by ambient air pollutants; and 3) examine whether lifetime use of NSAIDs, ibuprofen in particular, modifies potential adverse effects of air pollutants on OI. With additional funding from the Parkinson's Foundation, we are expanding data collection to all age-eligible Sister participants who reported a poor sense of smell, regardless of smoking, moving, or disease status. Accordingly, we expect to increase the total recruitment target to 3,417. This will allow us to more comprehensively evaluate the proposed aims with enhanced statistical power and sensitivity analyses.

3.B. What was accomplished under these goals?

We started data collection in March 2018. Of the 4,020 Sister participants we selected, 3,018 responded and participated as of the end of August 2018. The overall participation rate was 75.1%, slightly higher than the 72.3% we projected for year-1 of this project. Please see below our proposed first-year major tasks and milestones as listed in the SOW and our detailed progress report:

a. *"Obtain IRB approval or exemption from DOD and relevant study sites" by month 4.*
   Progress: The study involves multiple sites. We obtained standalone IRB approvals from MSU (IRB# 17-1208) on Nov 20, 2017 and the DoD (#A-20425) on Jan 10th, 2018. In addition, NIEHS/SSS (Sister study contractor of NIEHS) and University of Washington approved relevant study activities by amending their existing protocols. All field data collection has been carried out by the Sister Study team at NIEHS/SSS.

   After initial approval, we made multiple minor revisions that were swiftly approved by MSU IRB. All revisions did not affect the risk and benefit of study participants, and thus are not reportable to DoD IRB.

b. *"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. All study materials were made ready by January 2018.

c. *"Obtain survey data from the Sister study" by month 6*
   Progress: We obtained relevant survey data from the Sister Study on June 1st, 2018.

d. *"Mail/receive test kit and questionnaire" by month 18*
   Progress: We started data collection in March 2018. Of the 2,820 targeted participants who reported a poor sense of smell, 2,099 participants participated. Of the 1,200 random samples who reported normal sense of smell, 919 participated. The overall response rate to date is 75.1%, higher than the projected 72.3% by the end of first year. The response rate was very comparable between participants who self-reported a poor sense of smell (74.4%) and those who did not (76.6%), and was little affected by age or

education level. To date, 88 (2.2%) participants refused participation or could not be contacted. For the rest of 914 (22.7%) non-responders, we just re-mailed the study packet, aiming to recruit another 5-10% of the study participants. We expect to finish participant contact and field data collection by the first quarter of 2019. As we have collected data from the majority of our targeted participants, we began DNA extraction in July 2018, a few months ahead of schedule.

e. "Data QC, entry, and delivery" by month 21

Interim data on sense of smell test

BSIT score	Yes (n=1837)	No (n=831)
≤6	18.84%	1.8%
≤7	24.23%	2.88%
≤8	31.09%	5.17%
≤9	39.69%	12.03%
BSIT≤9 by age		
<60 y	23.91%	7.03%
60-70 y	33.16%	8.38%
70-79 y	51.72%	19.80%

88% of received data were entered.

Progress: Data are being entered as received. To date, we have entered data from 2,668 participants or 88% of the data we had received. See **Table** for preliminary data on BSIT test results. There is no clinically validated BSIT cutoff for OI. Initially we proposed to use a cutoff of 8 or the lowest 20% among controls. Based on distribution of these preliminary data, we may choose to use 9. This is reasonable as our study population are all women and are relatively young with an average age ~67 years, and 60% of participants are younger than age 70. We will decide the final cutoff once all data are received and entered.

f. "Air pollutant assessment and data delivery to MSU"

Progress: The aforementioned Sister Study data delivery (3.B.c) included air pollution estimates based on participants' baseline residential addresses, the longest-lived addresses, and childhood addresses. Our collaborators at the University of Washington are currently updating air pollutant data by incorporating primary residential addresses after study enrollment. We expect these updated data will be delivered in the first quarter of next year.

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

Nothing to report – this project has no training component. But I did hire a graduate student to work on this project and intended to make this his thesis project.

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

Nothing to report – we are still collecting data. In the future, we will disseminate results to the scientific community and lay audience via publications and scientific meetings.

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

As described above (Accomplishments items 3.B.d-f.), we have achieved all goals proposed for year-1 other than the need to update air pollution data. We expect air pollution data update by the first quarter of next year.

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 independently predicts both short-term and long-term mortality in older adults.

Most importantly, converging evidence suggests OI is one of the earliest and most important prodromal symptoms for 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, 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) elucidate disease etiology. Current research, including ours, has focused on how OI predicts the risk of PD. We, however, also see OI research as an excellent opportunity to open the etiological "black-box" of the disease. A major challenge in such 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.

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. Therefore, this project may eventually help understand a common pathway that leads to neurodegeneration.

4.C. What was the impact on technology transfer?
Nothing to report

4.D. What was the impact on society beyond science and technology?
Nothing to report during this period, but eventually data from this project will raise public awareness of the importance of sense of smell in aging, especially brain aging.

5. CHANGES/PROBLEMS:

5.A. Changes in approach and reasons for change
There was no substantial change to the project or its direction. As explained above (Accomplishments - 3.A.), with additional funding from the Parkinson's Foundation, we are able to extend data collection to all age-eligible Sister participants, regardless of their smoking, moving, or disease status. Our initial proposal to limit to nonsmokers and non-movers was mainly constrained by the budget allocation of the project ($1.5 million per study team). This addition does not affect scientific goals, study protocol, or risks and benefits of study participants, and brings substantial benefits to this project and beyond. With an expected total of 3,417 participants as compared to 2,713 initially planned, we will be able to more comprehensively examine the proposed specific aims with larger statistical power and possibilities of sensitivity analyses. Although this does not change the scope of work, we did obtain approval from Dr. Stephen Grate, DoD project office, via email on Jan 19, 2018. DoD IRB approval also covers this additional data collection.

5.B. Actual or anticipated problems or delays and actions or plans to resolve them
Nothing to report other than a slight delay in updating air pollutants data. To date, we have had a slightly higher participation rate than we had expected.

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

As of August, we spent a total of $373,552.06 which is 8.3% less than the year-1 budget. This was mainly due to a slightly delay in the start of this project. In year-2, we plan to use this saving for a third mailing, if needed, to boost the response rate to ~85%, and to support relevant data analyses.

5.D. Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents
Nothing to report. Human subject study protocol was approved as detailed in 3.B.a.

6. PRODUCTS:

6.A. Publications, conference papers, and presentations
Nothing to report.

Journal publications: Nothing to report
Books or other non-periodical, one-time publications: Nothing to report
Other publications, conference papers, and presentations: Nothing to report

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
As reported earlier in 3.B. We have collected the sense of smell data from 3,018 participants of the NIEHS Sister Study, creating one of the largest databases on the sense of smell among middle to old aged women. In addition, we just began to extract DNA samples from Sister Study participants, using blood samples the Sister Study has already collected.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

7.A What individuals have worked on the project?

Name:	Honglei Chen
Project Role:	PI
Researcher Identifier (e.g. ORCID ID):	0000-0003-3446-7779
Nearest person month worked:	3
Contribution to Project:	Oversaw all activities of the study, including study design, material development and purchase, IRB approvals, filed data collection, and coordinate DNA extractions.
Funding Support:	

Name:	Frank Purdy
Project Role:	Graduate Student function as project manager
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	4
Contribution to Project:	Helped Dr. Chen manage various aspects of study activities on a daily basis, received and managed Sister Study data, conducted preliminary data analyses.
Funding Support:	

Name:	Aiwen Yang
Project Role:	Data analyst
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	1
Contribution to Project:	Under Dr. Chen's supervision, conducted 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?

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: $151,399 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 as detailed in 3.A. & 5.A.

Title: Determinants of depression in Parkinson's disease
Time Commitments: Chen H, co-I, 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: $299,975 total
Project Goals: To determine role of appendectomy in depression among Parkinson's patients
Specific Aims: To evaluate appendectomy in relation to depression in Parkinson's disease using data from the Swedish Patient Registry. 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: collaboration

Organization Name: National Institute of Environmental Health Sciences
Location of Organization: Durham, North Carolina
Partner's contribution to the project: collaboration

Organization Name: ReproCell, Inc. (previously called Bioserve)
Location of Organization: Beltsville, MD
Partner's contribution to the project: collaboration

Organization Name: University of Washington
Location of Organization: Seattle, WA
Partner's contribution to the project: collaboration

Organization Name: Chicago University
Location of Organization: Chicago, IL
Partner's contribution to the project: collaboration

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 co-PI will submit their own reports
8.B. QUAD CHARTS: attached.

9. APPENDICES: Nothing to report