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14. ABSTRACT
This study addresses questions about the causes and progression of Parkinson's disease (PD) over the life course, specifically with respect to the role of a toxic chemical exposure, chlorpyrifos (CPF), an organophosphate pesticide. To understand how early exposure to CPF affects the nervous system, genetic susceptibility to CPF, and the long-term consequences of exposure, we are studying 200 young adults in an urban community cohort, now reaching 19-20 years of age, many of whom were routinely exposed to residential pesticides, as measured by a biomarker of CPF in cord blood. We are conducting neurological assessments of stiffness and gait, cardiac measures, sleep questions, measures of tremor, olfactory status, and other neuropsychological measures. We have access to previously-collected genetic information. The assessment requires 45-50 minutes; participants are paid $100 and cost of transportation. The purpose is to identify the earliest signs of risk for later PD that may appear long before clinical and motor symptoms can be seen, and to determine who is at greatest risk. We hypothesize that the individuals who were most highly exposed to CPF during the prenatal period (based on cord blood sample) will be more likely to show pre-motor and pre-clinical symptoms on these tests, as compared to individuals with lower exposure, and that some individuals may be more susceptible to exposure based on their genetic characteristics.

15. SUBJECT TERMS
None listed.

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1. Introduction

This study addresses the role of toxic chemical exposures, organophosphate pesticides (OPs), that may contribute to our understanding of the causes and progression of Parkinson's disease over the life course. To date, there is little knowledge about how OPs inflict nerve damage potentially resulting in parkinsonian symptoms, and even less information about how early in life the non-motor and pre-clinical signs of damage can be seen. To learn more about how these chemicals attack the nervous system, genetic susceptibility to these chemicals, and the long-term consequences of exposure, we will study an urban minority birth cohort, now reaching 19-20 years of age, many of whom were routinely exposed to residential OP use, prior to the indoor residential ban in 2001. We invite 200 of these young adults to participate in an examination, including neurological measures of stiffness and gait, cardiac measures, sleep questions, measures of tremor, and other neuropsychological measures. We also have access to genetic information, previously collected on the individuals. The assessment requires 45-50 minutes, and the purpose is to identify the earliest signs of risk for later PD that may appear long before clinical and motor symptoms can be seen. We hypothesize that the individuals who were most highly exposed during the prenatal period (based on a cord blood sample) will be more likely to show pre-motor and pre-clinical symptoms, as compared to individuals with lower exposure, and that some individuals may be more susceptible to the exposure based on their genetic characteristics.

2. Keywords

Parkinson's disease
Parkinsonism
Neurodegenerative disease
Neurotoxicity
Environmental exposure
Pesticides

3. Accomplishments

3a. Major Goals

Goal 1: Identify signs of early PD risk in the form of neurological dysfunction, REM sleep behavior disorder, autonomic dysfunction, and olfactory deficits in a sample of 200 young adults selected from a prospective cohort with varying levels of prenatal CPF exposure, as previously measured

<u>Milestones associated with Goal 1</u>:

- Number of assessments to be counted as completed to achieve an average rate of 1-2 assessments/week
- Neurological examinations completed in face-to-face assessment (100% completion)
- Behavioral, olfactory and survey measures completed (100% completion)
- The Actiheart reads, meetings, processing and supervision will follow the same schedule (100% completion)
- Data entry and programming will begin in the 3rd month, after a lag time for the setting up of data entry screens, and will continue through the 40th month (100% completion)
- The review of the clinical assessments will be conducted as the examinations are completed (100% completion)

Goal 2: Measure associations between prenatal CPF concentrations (previously collected data) and signs of early PD risk (as identified in Goal 1)

Milestones associated with Goal 2 (statistical analyses are ongoing):

- Statistical analysis of associations between prenatal CPF and tremor measure (a neurological assessment) (100% completion)
- Statistical analysis of associations between prenatal CPF, neurological measures, REM sleep behavior disorder, autonomic dysfunction (Actiheart), cognition and olfactory deficits (100% completion)
- Preparation of papers and reports (50% completion)

Goal 3: Stratify the sample and measure associations between selected *PON1* gene variants and signs of early PD risk, regardless of exposure

Milestones associated with Goal 3 (statistical analyses and preparation of reports are ongoing):

- Characterization of *PON1* genotype distribution (100% completion)
- Statistical analysis of main associations between *PON1* gene variants and all indicators of early PD risk (neurological measures, REM sleep behavior disorder, autonomic dysfunction--Actiheart, cognition and olfactory deficits) (100% completion)
- Preparation of papers and reports (50% completion)

Goal 4: Test for effect modification of the primary CPF exposure-PD risk outcome by subject genotype; conduct exploratory analyses of this effect modification using various combinations of maternal and child *PON1* gene variants to potentially identify those subjects who would be expected to be most susceptible to the adverse impact of CPF exposure on PD risk symptoms

Milestones associated with Goal 4 (statistical analyses are ongoing):

- Exploratory statistical analysis of the interaction effect of CPF and genotype (*PON 108* and *PON 192*) on neurological symptoms, physiological measures, and behaviors (100% completion)
- Preparation of papers and reports (50% completion)

3b. Activities, Objectives and Results to Date

Goal 1: Identify signs of early PD risk in the form of neurological dysfunction, behavioral and cognitive anomalies, REM sleep behavior disorder, autonomic dysfunction, and olfactory deficits in a sample of 200 19-20 year old individuals selected from a prospective cohort with varying levels of prenatal CPF exposure, as previously measured

Specific Objectives:

- Conduct a 45-60 minute assessment on each recruited and consented individual
- Neurological/clinical components of the assessment to include evaluations of extrapyramidal motor dysfunction, dystonia, bradykinesia and tremor
- Behavioral and physiological components to include evaluations of non-motor symptoms, REM sleep behavior disorder, cognitive components, and autonomic dysfunction (heart rate variability), and olfactory deficits

Major Activities:

A. *Implementation of the Protocol*

The following tools/methods, comprising the neurological, behavioral and physiological protocol were completed over the duration of the study:

- UPDRS: Unified Parkinson's Disease Rating Scale
- Spiral: ten Archimedean spirals with each hand inside a 10x10 cm square on 8.5x11 inch letter-size paper, using a wireless, inked writing pen on a 9x12 inch digitizing graphics tablet (Intuos 4,Wacom technology, Vancouver, WA) connected via standard USB to a computer using proprietary software.

- UPSIT: The University of Pennsylvania Smell Identification Test
- RBDSQ: REM sleep Behavior Disorder Screening Questionnaire to facilitate the identification of subjects with REM Sleep Behavior Disorder.
- Heart Rate Variability device and software (Actiheart)

B. *Quality Control and Safety Read*

Dr. Sloan regularly reviewed all HRV data and Dr. Alcalay reviewed all neurological data. Any child scoring in the abnormal range on any measure has been contacted directly, and permission obtained to contact his/her physician for potential referral to the New York Presbyterian Hospital for clinical evaluation to confirm diagnosis of any serious disorder and to offer treatment if needed.

C. *Reimbursement for Travel and Volunteer Payment*

This was accomplished according to university policies involving a secure system to distribute and monitor cash payments at the time of the assessment.

D. *Institutional Review Board Approval*

Current

E. *Recruitment, Informed Consent, Scheduling and Testing*

Beginning with the oldest individuals in the eligible cohort, we have enrolled and tested 200 subjects. The full study team has met regularly to coordinate and monitor all start-up activities throughout the study period.

Results: In this section (Table 1) we report the distribution of scores (% deviation from normal) on the subscales of the UPDRS, showing that there is reasonable variability on this measure in a non-clinical sample (run on all subjects with neurological assessments and prenatal chlorpyrifos exposure).

Table 1.

UPDRS item	**% Deviation from Normal**
Speech	7.2
Facial Expression	11.9
Rigidity of the Neck	4.2
Rigidity of the Right Upper Extremity	20.8
Rigidity of the Left Upper Extremity	12.4
Rigidity of the Right Lower Extremity	9.9
Rigidity of the Left Lower Extremity	8.3
Finger Tapping, Right Hand	14.1
Finger Tapping, Left Hand	20.4
Finger Tapping, Dominant Hand	12.1
Finger Tapping, Nondominant Hand	22.1
Right Hand Movements	25.2
Left Hand Movements	29.3
Dominant Hand Movements	27.4
Nondominant Hand Movements	27.8
Pronation-Supination Movements of Hands, Right	4.7
Pronation-Supination Movements of Hands, Left	8.8

Goal 2: Measure associations between prenatal CPF concentrations (previously collected data) and signs of early PD risk, as identified in Goal 1

Major activities and objectives:
Statistical analyses that integrate clinical, behavioral and physiological data are ongoing.

Results:

Data analyses have been conducted using all clinical (neurological) and behavioral neurological test data as the dependent variables.

1. UPDRS Outcomes (bivariate analyses using categorical scales)

3.1 Speech
N=194: A slight deviation from 'Normal' was observed in n=14 (7.2%) of all participants, with prevalence seemingly slightly higher among females (n=8; 7.7%) than males (n=6; 6.7%) Pearson's chi-sq=.076, p=.783 (NS), and African Americans (n=7; 9.3%) vs. Dominican Americans (n=7, 5.9%) Pearson's chi-sq=.818, p=.366 (NS).
N=167: Among participants with known chlorpyrifos exposure, loss of modulation, diction or volume was observed in twice as many exposed (n=4; 11.4%) as unexposed (n=7; 5.3%) participants, yet not significantly so (Fisher's Exact test p=.176, NS).

3.2 Facial Expression
N=194: A slight deviation from 'Normal' was observed in n=23 (11.9%) of all participants with prevalence higher among males (n=13; 14.4%) than females (n=10; 9.6%), Fisher's Exact test p=.207, and among Dominican (n=16, 13.4%) versus African Americans (n=7, 9.3%) Exact test p=.266, NS.
N=167: Among participants with known chlorpyrifos exposure, minimal masked facies manifested only by decreased frequency of blinking was similarly distributed among those with higher (n=4; 11.4%) vs lower (n=17; 12.9%) exposure (Exact test p=.539). *** Slightly higher among the unexposed… but NS***

3.3 Rigidity
3.3a. Rigidity of the Neck
N=192: A slight, mild or moderate deviation from 'Normal' was observed in n=8 (4.2%) of all participants with prevalence non-significantly higher among males (n=5; 5.6%) than females (n=3; 2.9%) (Pearson's chi-squared p=.485, NS), and African Americans (n=5, 6.8%) vs. Dominican Americans (n=3, 2.5%) Fisher's Exact test p=.147.
N=165: Among participants with known chlorpyrifos exposure, rigidity of the neck was detected with activation maneuver in n=3 (9.1%) with higher exposure vs. n=4 (3.0%) with low exposure (p=.133) but the Ns were too small to reach significance (Fisher's Exact test p=.144).
Similarly, prevalence remained higher among African Americans (n=4, 6.7%) than Dominican Americans (n=3, 2.9%) but did not reach significance (Fisher's Exact test p=.218).

3.3b. Rigidity of the Right Upper Extremity
N=193: A slight or mild deviation from 'Normal' was observed in n=40 (20.7%) of all participants. Prevalence was non-significantly higher among males (n=21; 23.6%) than females (n=19; 18.3%) (Exact test p=.232, NS), and among African Americans (n=18; 24.3%) versus Dominican Americans (n=22, 18.5%) Exact test p=.214, NS).
N=165: Among participants with known chlorpyrifos exposure, rigidity of the right upper extremity was detected with activation maneuver in n=8 (23.5%) with higher exposure vs. n=19 (14.4%) with low exposure but the Ns were too small to reach significance (Pearson's chi-sq=1.657, p=.198; Fisher's Exact test p=.152).

3.3c. Rigidity of the Left Upper Extremity
N=193: A slight or mild deviation from 'Normal' was observed in n=24 (12.4%) of all participants. Prevalence was higher among males (n=13; 14.6%) than females (n=11; 10.6%), Pearson's chi-sq=.961, p=.327, NS) and among African Americans (n=10, 13.5%) than Dominican Americans (n=14, 11.8%) Pearson's chi-sq=.128, p=.720.

Note: When limited to the 166 ppts with known CPF exposure, evidence of slight or mild impairment was still higher among males (n=8; 10.1%) than females (n=6; 6.9%) but the difference was not significant (Pearson's chi-sq=.559, p=.455; Fisher's Exact test p=.319). Distribution of rigidity detected with or without action maneuver was evenly distributed between racial/ethnic groups: African Americans (n=5, 8.3%) than Dominican Americans (n=9, 8.5%) (Pearson's chi-sq=.001, p=.972 NS).

3.3d. Rigidity of the Right Lower Extremity

N=193: A Slight or Mild deviation from 'Normal' was observed in n=19 (9.9%) of all participants. Prevalence was almost (!) significantly higher among males (n=12; 13.5%) than females (n=7; 6.7%) Fisher's Exact test p=.092, NS). Distribution between racial/ethnic groups was even: African Americans n=7 (9.5%), Dominican Americans, n=12 (10.1%), Pearson chi-sq=.020, p=.887.

N=166: Among participants with known chlorpyrifos exposure, rigidity of the right lower extremity detected with activation maneuver, was slightly (non-significantly) higher among those with higher (n=3, 8.8%) vs lower (n=10, 7.6%) exposure (Exact test p=.521).

3.3e. Rigidity of the Left Lower Extremity

N=192: A slight, mild or moderate deviation from 'Normal' was observed in n=16 (8.3%) of all participants with prevalence significantly higher among males (n=12; 13.5%) than females (n=4; 3.8%) (Pearson's chi-squared=5.858 p=.016). Racial/Ethnic differences were not significant (African American, n=10 (13.5%); Dominican n=14 (11.8%) Exact test p=.44).

N=166: Among participants with known chlorpyrifos exposure, rigidity of the left lower extremity detected with or without activation maneuver, was higher among those with higher (n=4, 11.8%) vs lower (n=8, 6.1%) exposure but not significantly so (Exact test p=.212).

<u>3.4 Finger Tapping</u>

3.4a Finger Tapping, Right Hand

N=191: Slight or mild impairment in right hand finger tapping was observed in n=27 (14.1%) of participants – fairly similarly by sex: males, n=13 (14.9%); females, n=14 (13.5%) Pearson chi-sq = .086, p=.770), but differently by race/ethnicity: African American n=18 (24.0%), Dominican American, n=9 (7.8%), Pearson chi-sq=9.899, p=.002.

N=164: Among participants with known chlorpyrifos exposure, irregular rhythm, interruptions or hesitation, slowing or amplitude decrements appeared more commonly among those with higher (n=7, 21.2%) than lower (n=14, 10.7%) CPF exposure, Exact test p=.096 (NS). No differences were observed by sex (male n=10, 13.0%; female, n=11, 12.6%), but a significant difference in distribution by racial/ethnic group was found: African American, n=12, 19.7%; Dominican, n=9, 8.7%; Pearson's chi-sq=4.102, p=.043; Exact test p=.039.

3.4b. Finger Tapping, Left Hand

N=191: Slight or mild impairment of left-hand finger tapping was observed among n=39 (20.4%) of participants. Distribution was similar by sex (males, n=17, 19.5%; females, n=22, 21.2%; Pearson's chi-sq=.076; p=.783) and race/ethnicity (African Americans, n=16, 21.3%; Dominicans, n=23, 19.9%; Pearson's chi-sq=.064; p=.801).

N=164: Among participants with known chlorpyrifos exposure, slight or mild deviations from normal appeared to be slightly more prevalent among those with lower exposure (n=27, 20.6%) vs. those with greater exposure (n=6, 18.2%) but the difference was not significant (Fisher's Exact test p=.485 NS).

There were no differences by sex (males: n=15, 19.5%; females: n=18, 20.7%; Pearson's chi-sq=.037, p=.847), or race/ethnicity (African Americans: n=12, 19.7%; Dominican Americans: n=21, 20.4%; Pearson's chi-sq=.012; p=.912) in this subset.

3.4c. Finger Tapping, Dominant Hand

N=190: (Dominance unknown for 1 participant) Slight or mild impairment in dominant hand finger tapping was observed in n=23 (12.1%) of participants, more commonly among females (n=14, 13.5%) vs. males (n=9, 10.5%) but not significantly so. Irregular rhythms, interruptions, hesitations, slowing or amplitude decrements were significantly more prevalent among African Americans (n=15, 20.0%) than Dominican Americans (n=8, 7%; Pearson's chi-sq=7.259, p=.007).

N=163: Among participants with known CPF exposure, deviations from 'normal' dominant finger tapping appeared greater among those with higher (n=5, 15.2%) vs lower (n=12, 9.2%) CPF exposure (Exact test p=.241) but not significantly so. Distribution by sex also appeared uneven but did not reach significance (males, n=6, 7.9%; females, n=11, 12.6%; Exact p=.233, NS). The significant racial/ethnic difference observed for the full sample was not maintained in the CPF subsample (African Americans, n=9, 14.8%; Dominican Americans, n=8, 7.8%; Exact test p=.129, NS).

3.4d. Finger Tapping, Nondominant Hand
N=190: Some 20.6% (n=40) of participants displayed 'slight' and 1.5% (n=3) 'mild' impairment in finger tapping with the non-dominant hand. Sex differences were minimal (males: n=21, 24.4%; females: n=22, 21.2%; Pearson's chi-sq=.287, p=.592) and racial/ethnic differences moderate (African Americans: n=19, 25.3%; Dominicans: n=24, 20.9% Pearson's chi-sq=.517, p=.472; Exact p=.293) but not significant.
N=163: No differences were observed between those with higher (n=8, 24.2%) versus lower (n=29, 22.3%) CPF exposure (Exact test p=.488). Differences by sex (males, n=19, 25.0%; females, n=18, 20.7%; Exact test p=.319) and race/ethnicity (African Americans, n=15, 24.6%; Dominican, n=22, 21.6%; Exact p=.397) did not reach significance.

3.5 Hand Movements
3.5a Right Hand Movements
N=194: Some 20.6% (n=40) of participants displayed 'slight' and 4.6% (n=9) 'mild' impairment in right hand movements. Deviations were similar among males (Slight, n=19, 21.8%; Mild, n=5, 5.7%) than females (Slight, n=21, 20.2%; Mild, n=4, 3.8%) Pearson's chi-sq=.313, p=.576, but notably more prevalent among African Americans (Slight or Mild n=27, 36.0%) than Dominican Americans (Slight or Mild, n=22, 19.0%) Pearson's chi-sq = 6.930, p=.008.

N=164: Slightly or mildly impaired right-hand movements were observed a little more frequently among those with higher (n=8, 24.2%) versus lower (n=30, 22.9%) documented exposure to CPF Exact test p=.517, NS). No significant difference in distribution by sex (males n=19. 24.7%; females, n=19, 21.8%; Exact test p=.403) was recorded. Racial/Ethnic difference persisted in the smaller sample, with slight or mild impairment recorded as follows: African Americans, n=20, 32.8%; Dominican Americans, n=18, 17.5%; Pearson's Chi-sq= 5.045, p=.025.

3.5b. Left Hand Movements
N=191: Slight (n=47, 24.6%) and Mild (n=9, 4.7%) impairment was observed among 29.3% of participants overall. At 30.8% (n=32) females demonstrated apparently greater impairment than males (27.6%, n=24), but the difference was not significant (Pearson' chi-sq= .232, p=.630). Similarly, prevalence did not differ by race/ethnicity: Africa Americans 30.7% (n=23); Dominican Americans, 28.4% (n=33) Pearson's chi-sq=.108, p=0742.
N=164: The seemingly *larger proportion of participants with lower CPF* exposure who displayed slight or mild impairment in left hand movement did not reach significance. (High exposure, n=7, 21.2%; low exposure, n=41, 31.3%; chi-sq=1.295, p=.255). Participants displaying irregular left-hand movements were equivalently distributed across sex (females= 29.9%; males = 28.6%). Apparent racial/ethnic differences in non-normal left-hand movements (African Americans 32.8%; Dominicans 27.2%) did not reach significance (Pearson's chi-sq=.581, p=.446).

3.5c. Dominant Hand Movements
N=190: Altogether 27.4% of participants demonstrated Slight or Mild impairment in Dominant Hand movements. The distribution of non-normal movement was similarly distributed by sex (males 26.7%; females 27.9%). Hesitant, irregular, slow, or otherwise impaired dominant hand movement differed by race/ethnicity: African Americans, n=26 (34.7%); Dominican Americans, n=26 (22.6%) Exact test p= .05.

N=163: There was no difference in dominant hand movement by CPF exposure (high exposure, 24.2%; low exposure, 24.6%). Distribution of sex remained equivalent in this subset (males 23.7%; females 25.3%). Racial/ethnic differences were no longer significant: African Americans, n=19 (31.1%); Dominican Americans, n=21 (20.6%) Exact test p= .093.

3.5d. Nondominant Hand Movements
N=190: Here, 22.6% of participants showed 'Slight' and 5.2% Mild impairment in non-dominant hand movement. Neither sex differences (males 29.1%; females 26.9%) nor racial/ethnic differences (African Americans 32.0%; Dominican Americans 25.2%) in the distribution of impaired non-dominant hand movements were significant.

N=163: Impaired non-dominant hand movements were more prevalent among those with lower (n=39, 30.0%) versus higher (n=7, 21.2%) CPF exposure, but this difference was not significant (Exact test p=.219). As before, apparent differences by sex (male 30.3%; female 26.4%) and race/ethnicity (African American 34.4%; Dominican American 24.5%) were not significant.

3.6 Pronation-Supination Movements of Hands

3.6a. Pronation-Supination Movements of Hands, Right

N=191: Just 4.7% of respondents (n=9) showed a 'slight' impairment in pronation-supination movement of hands.
N=164: Eight of the nine participants with impaired performance had a known measure of CPF exposure. All of them were in the group with lower CPF exposure! No participants in the higher CPF group demonstrated anything other than 'normal' movement. There were no differences in distribution by race/ethnicity and sex.

3.6b. Pronation-Supination Movements of Hands, Left

N=191: 8.8% of participants had slight difficulty with pronation-supination of the left hand. No significant differences by sex (males: n=7, 8.0%; females: n=10, 9.6%; Pearson's chi-sq=.144, p=.704), or race/ethnicity (AA: n=8, 10.7%; DA: n=9, 7.8%; Pearson's chi-sq=.475, p=.491).
N=164: Among those with a known CPF exposure measure, slightly more were in the low exposure group (n=10, 7.6%) versus the higher exposure group (n=2, 6.1%), but the difference was not significant (Exact test p= .552). There were no significant differences by sex or race/ethnicity in the subset with known CPF exposure, although the groups with the larger percentage switched here vs the full sample.
Males: n=6 (7.8%); females: n=6 (6.9%); Pearson's chi-sq=.048, p=.826
African Americans: n=4 (6.6%); Dominican Americans: n=8 (7.8%); Fisher's Exact test p=.518

3.6c. Pronation-Supination Movements of Hands, Dominant

N=190: N=12 (6.3%) of participants demonstrated slight impairment in pronation-supination movement of the dominant hand. Prevalence was non-significantly higher among females (n=8, 7.7%) than males (n=4, 4.7%; Exact test p=.291), and among African Americans (n=7, 9.3%) than Dominican Americans (n=5, 4.3%; Exact test p=.141).
N=163: Among participants with known CPF exposure, all evidence of slight impairment presented in those with lower exposure (n=9, 6.9% vs higher exposure n=0, 0%). Despite this, the group differences were not significant (Exact test p=.123).
Prevalence remained non-significantly higher among females (n=6, 6.9%) vs. males (n=3, 3.9%; Exact test p=.319), and African Americans (n=5, 8.2%) vs Dominican Americans (n=4, 3.9%; Exact test p=.209) in the sub-sample.

3.6d. Pronation-Supination Movements of Hands, Nondominant

N=190: Slight breaks in rhythm, with one or two interruptions or hesitations, slight slowing or decrement in amplitude toward the end of the sequence of pronation-supination of the non-dominant hand were observed in n=14 (7.2%) of participants. These slight impairments were distributed evenly fairly between the sexes (male: n=6, 7.0%; female: n=8, 7.7%; Pearson's chi-sq=.035, p=.851), and racial/ethnic groups (AA: n=5, 6.7%; DA: n=9, 7.8%; Pearson's chi-sq=.089, p=.765).

N=163: Among participants with known CPF exposure, 6.7% (n=11) showed slight or mild impairment, with slightly more in the lower (n=9, 6.9%) vs higher (n=2, 6.1%) exposure group (Exact test, p=.609, NS). Prevalence was non-significantly higher among males (n=6, 7.9%) than females (n=5, 5.7%) Pearson's chi-sq=.297, p=.586, and among Dominican Americans (n=8, 7.8%) than Africa Americans (n=3, 4.9%), Exact test p=.354.

Toe Tapping

3.7a. Toe Tapping, Right Foot

N=191: Slight or Mild deviations from normal were observed in 23.0% (n=44) and 3.1% (n=6) participants respectively, representing more than a quarter of all participants (n=50, 26.2%). These were evenly distributed between males (n=23, 26.4%) and females (n=27, 26.0%), Pearson's chi-sq=.0006, p=.941). Prevalence was non-significantly higher among African Americans (n=22, 29.3%) than Dominican Americans (n=28, 24.1%), Pearson's chi-sq=.636, p=.425.

N=164: Slight or Mild impairment was equivalently distributed between participants with higher vs lower CPF exposure: higher: n=9 (27.3%); lower: n=34 (26.0%); Pearson's chi-sq=.024, p=.878. Prevalence appeared higher among males (n=22, 28.6%) than females (n=21, 24.1%) but was not significantly so (Pearson's chi-sq=.415, p=.519). In the reduced sample, prevalence remained non-significantly higher among African Americans (n=17, 27.9%) than Dominican Americans (n=26, 25.2%) Pearson's chi-sq=.137, p=.712.

3.7b. Toe Tapping, Left Foot

N=191: Impairment observed in 35.6% of participants! Slight: n=58 (30.4%); Mild: n=10 (5.2%)
Evidence of interruptions, breaks in rhythm, slight or mild slowing and/or decrements in amplitude was significantly greater among females (n=44, 42.3%) than males (n=24, 27.6%); Pearson's chi-sq=4.478, p=.034; Exact test p=.024.
Impairment was similar across racial/ethnic groups: African Americans: n=28 (37.3%); Dominican Americans: n=40 (34.5%); Pearson's chi-sq=.161, p=.688 (NS) Exact test p=.401.

N=164: Did not differ by CPF exposure (although more impairment in low exposure group!?)
Higher exposure: n=11 (33.3%); lower exposure: n=50 (38.2%) Pearson's chi-sq=.264, p=.608
Sex differences persisted: females: n=38 (43.7%) males: n=23 (29.9%); Pearson's chi-sq=3.334, p=.068; Exact test p=.048.
No difference by race/ethnicity: African Americans: n=24 (39.3%); Dominican Americans: n=37 (35.9%); Pearson's chi-sq=.192, p=.661 (Exact test p=.392.)

3.8. Leg Agility

3.8a. Leg Agility, Right Leg

N=191: Just n=10 (5.2%) of participants showed Slight impairment in right leg agility.
Breaks in rhythm via interruptions or hesitations, slight slowing, or amplitude decrements were non-significantly greater among females (n=7, 6.7%) vs males (n=3, 3.4%) Fisher's Exact test p=.248 (NS).
These impairments were significantly more likely among African Americans (n=7, 9.3%) than Dominican Americans (n=3, 2.6%) Fisher's Exact test p=.045. (Pearson's chi-sq=4.179, p=.041 but one cell has *expected* N <5 so need to report Exact test.) N=164: Slight impairment appeared more frequently among participants with higher CPF exposure (n=3, 9.1%) vs. lower exposure (n=4, 3.1%) but did not reach significance (Fisher's Exact test p=.146).
In this subset, slight impairment appeared more frequently among females (n=5, 5.7%) than males (n=2, 2.6%) but not significantly so (Fisher's Exact test p=.275). Similarly, slight impairment appeared more frequently among African Americans (n=4, 6.6%) than Dominican Americans (n=3, 2.9%) but not significantly so (Fisher's Exact test p=.233).

3.8b. Leg Agility, Left Leg

N=191: Some n=15 (7.9%) of participants showed Slight impairment in left leg agility.
Breaks in rhythm via interruptions or hesitations, slight slowing, or amplitude decrements were evenly distributed among females (n=8, 7.7%) and males (n=7, 8.0%), Pearson's chi-sq=.008, p=.928; Fisher's Exact test p=.568 (NS).
Left leg agility differed significantly between racial/ethnic groups with greater evidence of impairment among African Americans (n=11, 14.7%) than Dominican Americans (n=4, 3.4%); Pearson's chi-sq=7.922, p=.005; (Fisher's Exact test p=.006)

N=164: Slight impairment appeared more frequently among participants with higher CPF exposure (n=4, 12.1%) vs. lower exposure (n=9, 6.9%) but did not reach significance (Fisher's Exact test p=.251).
The even distribution between sexes was reproduced in the smaller sample. Females: n=7 (8.0%); Males: n=6 (7.9%); Pearson's chi-sq=.004, p=.952.
The significant difference between racial/ethnic groups persisted within the reduced sample: African Americans: n=9 (14.8%); Dominican Americans: n=4 (3.9%); Fisher's Exact test p=.016.

Inter-correlations among UPDRS scores

All variables are binary (Normal vs. Slight/Mild/Moderate)
Correlation coefficient = Spearman's Rho for non-parametric data

Correlations

			UPDRS Hand and Movements: Right, Binary (1,0)	UPDRS Hand Movements: Left, Binary (1,0)	UPDRS Hand Movements: Dominant, Binary (1,0)	UPDRS Hand Movements: Non-dominant, Binary (1,0)
Spearman's rho	UPDRS Finger Tapping: Right, Binary (1,0)	Correlation Coefficient	.347**	.069	.325**	.083
		Sig. (2-tailed)	<.001	.344	<.001	.255
		N	191	191	190	190
	UPDRS Finger Tapping: Left, Binary (1,0)	Correlation Coefficient	.208**	.216**	.214**	.207**
		Sig. (2-tailed)	.004	.003	.003	.004
		N	191	191	190	190
	UPDRS Finger Tapping: Dominant, Binary (1,0)	Correlation Coefficient	.298**	.043	.315**	.021
		Sig. (2-tailed)	<.001	.554	<.001	.773
		N	190	190	190	190
	UPDRS Finger Tapping: Non-dominant, Binary (1,0)	Correlation Coefficient	.256**	.230**	.232**	.253**
		Sig. (2-tailed)	<.001	.001	.001	<.001
		N	190	190	190	190

**. Correlation is significant at the 0.01 level (2-tailed).

Correlations

			UPDRS Pronation-Supination Movement of Hands: Right, Binary (1,0)	UPDRS Pronation-Supination Movement of Hands: Left, Binary (1,0)	UPDRS Pronation-Supination Movement of Hands: Dominant, Binary (1,0)	UPDRS Pronation-Supination Movement of Hands: Non-dominant, Binary (1,0)
Spearman's rho	UPDRS Finger Tapping: Right, Binary (1,0)	Correlation Coefficient	.123	.031	.080	.058
		Sig. (2-tailed)	.091	.665	.271	.424
		N	191	191	190	190
	UPDRS Finger Tapping: Left, Binary (1,0)	Correlation Coefficient	.010	.207**	-.025	.256**
		Sig. (2-tailed)	.891	.004	.734	<.001
		N	191	191	190	190
	UPDRS Finger Tapping: Dominant, Binary (1,0)	Correlation Coefficient	.145*	.053	.103	.081
		Sig. (2-tailed)	.046	.466	.159	.269
		N	190	190	190	190
	UPDRS Finger Tapping: Non-dominant, Binary (1,0)	Correlation Coefficient	-.002	.183*	-.037	.233**
		Sig. (2-tailed)	.976	.011	.612	.001
		N	190	190	190	190

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

Correlations

			UPDRS Toe Tapping: Right, Binary (1,0)	UPDRS Toe Tapping: Left, Binary (1,0)	UPDRS Leg Agility, Right, Binary (1,0)	UPDRS Leg Agility: Left, Binary (1,0)
Spearman's rho	UPDRS Finger Tapping: Right, Binary (1,0)	Correlation Coefficient	.305**	.075	.242**	.105
		Sig. (2-tailed)	<.001	.303	<.001	.148
		N	191	191	191	191
	UPDRS Finger Tapping: Left, Binary (1,0)	Correlation Coefficient	.201**	.274**	.114	.045
		Sig. (2-tailed)	.005	<.001	.116	.534
		N	191	191	191	191
	UPDRS Finger Tapping: Dominant, Binary (1,0)	Correlation Coefficient	.291**	.060	.274**	.131
		Sig. (2-tailed)	<.001	.415	<.001	.072
		N	190	190	190	190
	UPDRS Finger Tapping: Non-dominant, Binary (1,0)	Correlation Coefficient	.219**	.278**	.098	.028
		Sig. (2-tailed)	.002	<.001	.179	.699
		N	190	190	190	190

**. Correlation is significant at the 0.01 level (2-tailed).

Correlations

			UPDRS Toe Tapping: Right, Binary (1,0)	UPDRS Toe Tapping: Left, Binary (1,0)	UPDRS Leg Agility, Right, Binary (1,0)	UPDRS Leg Agility: Left, Binary (1,0)
Spearman's rho	UPDRS Pronation-Supination Movement of Hands: Right, Binary (1,0)	Correlation Coefficient	.036	-.062	-.052	-.065
		Sig. (2-tailed)	.619	.393	.473	.372
		N	191	191	191	191
	UPDRS Pronation-Supination Movement of Hands: Left, Binary (1,0)	Correlation Coefficient	.148*	.075	.009	.114
		Sig. (2-tailed)	.040	.304	.901	.117
		N	191	191	191	191
	UPDRS Pronation-Supination Movement of Hands: Dominant, Binary (1,0)	Correlation Coefficient	.041	-.013	.036	.004
		Sig. (2-tailed)	.571	.855	.625	.954
		N	190	190	190	190
	UPDRS Pronation-Supination Movement of Hands: Non-dominant, Binary (1,0)	Correlation Coefficient	.152*	.042	-.066	.067
		Sig. (2-tailed)	.037	.569	.362	.359
		N	190	190	190	190

*. Correlation is significant at the 0.05 level (2-tailed).

UPDRS Factor Analysis

Factors were extracted using maximum likelihood estimation with varimax rotation to determine whether the constructs upon which the UPDRS assessment of motor signs of Parkinson's disease is based were adequately represented in our population of healthy participants in their late teens/early twenties. Items for which no variability was observed (Arising from Chair; Gait; Freezing of Gait; Postural Stability; Posture; Rest Tremor Amplitude of the right and left upper and lower extremities; Rest Tremor Amplitude of the Lip/Jaw, and Constancy of Rest Tremor) were excluded , leaving 22 itmes for the procedure.

Five factors were clearly identified using this method, despite the limitations in the data. These factors were: Tremor, Rigidity of the Extremities, Movement of the Head and Neck, Tapping/Agility of Fingers, Toes and Legs, and Hand Movement. With one exception (pronation-supination of the left hand), Right and Left side motor functions loaded together on these five factors.

Five subscales, created based on these factors, were regressed on chlorpyrifos exposure, sex of the child, racial/ethnic group and age at testing.

Rotated Factor Matrix[a]

	Factor				
	1	2	3	4	5
Speech	.061	-.033	.444	.171	.120
Facial Expression	.023	.044	.624	-.004	.081
Rigidity: Neck	-.003	-.041	.348	.078	.155
Global Spontaneity of Movement (Body Bradykinesia)	-.023	.010	.753	.150	.097
Rigidity of the Right Upper Extremity	.217	.550	.090	-.012	.126
Rigidity of the Left Upper Extremity	.298	.438	.000	-.086	-.014
Rigidity of the Right Lower Extremity	.006	.882	-.084	.018	.003
Rigidity of the Left Lower Extremity	-.020	.664	-.058	-.008	-.050
Right Finger Tapping	-.081	.009	.126	.408	.303
Left Finger Tapping	.059	-.043	.144	.390	.088
Right Hand Movement	-.136	-.011	.158	.191	.959
Left Hand Movement	.077	-.038	.176	.026	.496
Pronation-Supination Movement of Right Hand	.052	.046	.058	-.012	.295
Pronation-Supination Movement of Left Hand	.018	.024	-.016	.199	.056
Right Toe tapping	-.099	.034	.098	.673	.047
Left Toe tapping	-.021	-.130	.093	.506	-.076
Right Leg Agility	.182	.036	.002	.454	-.099
Left Leg Agility	.209	-.086	.201	.310	.001
Postural Tremor of the Right Hand	.853	-.013	-.126	.157	.026
Postural Tremor of the Left Hand	.835	.011	-.128	.114	.101
Kinetic Tremor of the Right Hand	.345	.126	.120	.005	-.008
Kinetic Tremor of the Left Hands	.464	.228	.149	-.035	.009

Extraction Method: Maximum Likelihood.

Rotation Method: Varimax with Kaiser Normalization.

a. Rotation converged in 6 iterations.

This factor loading table shows that the UPDRS is useful as a measure of slight to mild impairment, even in a non-clinical sample of young adults. Using the factors as the dependent variable for the analysis of UPDRS outcomes (using rigidity as the example), the following table shows a borderline significance for the rigidity scale.

Parameter Estimates

Parameter	B	Std. Error	95% Wald Confidence Interval		Hypothesis Test		
			Lower	Upper	Wald Chi-Square	df	Sig.
(Intercept)	2.067	1.2485	-.380	4.514	2.742	1	.098

[Chlorpyrifos Exposure >6.17pg/g=1] (Yes)	.408	.2219	-.027	.843	3.384	1	.066
[Chlorpyrifos Exposure >6.17pg/g=0]	0[a]	.	.	.	.	.	.
[Gender=2] (Male)	.348	.1572	.039	.656	4.887	1	.027
[Gender=1]	0[a]	.	.	.	.	.	.
[Ethnic background=5] (AA)	-.039	.1656	-.363	.286	.054	1	.816
[Ethnic background =3]	0[a]	.	.	.	.	.	.
UPDRS Test Age (years)	-.087	.0600	-.205	.031	2.101	1	.147
(Scale)	1[b]						

Dependent Variable: Rigidity of the Extremities

Model: (Intercept), Chlorpyrifos Exposure >6.17pg/g, Gender, Ethnic background , UPDRS Test Age (years)

a. Set to zero because this parameter is redundant.
b. Fixed at the displayed value.

Conclusion: Those with greater CPF exposure had higher Rigidity subscale scores (greater impairment) than those with less CPF exposure – almost significant (.066)

Goal 3: Stratify the sample and measure associations between selected *PON1* gene variants and signs of early PD risk, regardless of exposure; and Goal 4: Test for effect modification of the primary CPF exposure-PD risk outcome by subject genotype; conduct exploratory analyses of this effect modification using various combinations of maternal and child *PON1* gene variants to potentially identify those subjects who would be expected to be most susceptible to the adverse impact of CPF exposure on PD risk symptoms.

<u>Major activities and objectives:</u>

Preliminary statistical analyses including 100% of data collection are reported here. (a) analyze the distribution of polymorphisms and the associations between genetic factors and chlorpyrifos blood levels in mother and infant; (b) test the main associations between CPF exposure, genotype and known level of enzyme activity; and (c) explore the interaction effect of CPF and genotype (*PON108* and *PON192*) on neurological symptoms, physiological measures, and behaviors.

Results:

We stratified our sample by the presence or absence of selected *PON1* gene variants and tested for both the main and interactive genetic effects on signs of early PD risk. First we conducted descriptive statistics to determine whether there were any race/ethnic differences in the distribution of the gene variants (Table 3). Race/ethnic differences were seen <u>only</u> for the distribution of *PON192* gene variant, suggesting that the variant was more prevalent among African American members (92.3%) as compared to Dominicans (80.5%) in our sample. However, in specific tests of interactions including exposure (CPF), the genetic variant, and race/ethnicity, there was no indication that the racial difference in the distribution of the variant explained significantly greater vulnerability to CPF in either race/ethnic group.

Table 3: Child: PON1-Q192R Pos 94775382 #rs662 * Ethnic background Crosstabulation

		Ethnic background	
		Dominican/Domin American	African American
RR or QR	Count	95	72

Child: PON1-Q192R Pos 94775382 #rs662		% within Child: PON1-Q192R Pos 94775382 #rs662	56.9%	43.1%
	QQ	Count	23	5
		% within Child: PON1-Q192R Pos 94775382 #rs662	82.1%	17.9%
Total		Count	118	77
		% within Child: PON1-Q192R Pos 94775382 #rs662	60.5%	39.5%

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	6.402[a]	1	.011	.012	.008
Continuity Correction[b]	5.388	1	.020		
Likelihood Ratio	7.032	1	.008	.012	.008
Fisher's Exact Test				.012	.008
Linear-by-Linear Association	6.369[c]	1	.012	.012	.008
N of Valid Cases	195				

In order to test whether the presence of this genetic variant was associated with increased/decreased vulnerability to the potentially adverse effects of chlorpyrifos exposure, we conducted a test of effect modification by the polymorphisms to potentially identify those subjects who would be expected to be most susceptible to the adverse impact of OP pesticide exposure on parkinsonian symptoms. First, we tested the hypothesis that subjects with variants in the serum paraoxonase 1 [which are associated with slower metabolism genotype (*PON1*$_{-108}$ and *PON1*$_{192}$)] will manifest higher levels of PD risk indicators as compared to those without the variants, regardless of environmental exposure. Second, we tested the gene X environment effect modification hypothesis such that associations between prenatal CPF blood concentrations and PD risk indicators in early adulthood will be stronger among subjects without the selected *PON1* variants as compared to those who have the variants.

<u>Final results using motor indicators as measured by speed on the Archimedes spiral drawing test</u>

1. Outcome=speed of spiral drawing test using the dominant hand

a) <u>Main effects</u>:
Linear regression of speed (dominant hand) on continuous chlorpyrifos (CPF): non-significant main effect at the 5% level (p=.756). Linear regression of speed on categorical CPF: non-significant main effect (p=.375]).

b) <u>Effect modification</u>:
Linear regression of speed with a continuous CPF x PON1108 interaction: Highly significant interaction (p = .000). For subjects with the A allele, the mean value of speed increases by .043 for each unit increase of CPF; for subjects with the G allele, the mean value of speed decreases by .289 for each unit increase of CPF; for subjects with both A and G alleles, the mean value of speed decreases by .053 for each unit increase of CPF: these 3 rates of change are significantly different from each other (p=.000).

Linear regression of speed with a categorical CPF (HICHLOP) x PON1108 interaction: Highly significant interaction (p = .000). For subjects with the A allele, the mean value of speed is 5.608 units more for subjects with high CPF than those with low CPF; for subjects with the G allele, the mean value of speed is

1.605 units less for subjects with high CPF than those with low CPF; for subjects with both A and G allele, the mean value of speed is 1.469 units less for subjects with high CPF than those with low CPF; these 3 differences are significantly different from each other (p=.000, which is the interaction p-value). Each of the above regressions was now re-run by dichotomizing PON1108 according to the presence of at least one G allele or not. A new variable PON1108_bin was given the value 1 for AG and GG and the value of 0 for AA.

Linear regression with a CPF x PON1108_bin interaction (p-value =.000). For subjects with a G allele, the mean value of speed decreases by 1.877 for each unit increase in CPF; for subjects with an A allele, the mean value of Speed increases by .043 for each unit increase in CPF: these 2 rates of change are significantly different from each other (p=.000, which is the interaction value). Linear regression with a HICHLOP x PON1108_bin interaction (p-value =.000). For subjects with the G allele, the mean value of speed is 1.762 units less for subjects with high CPF than those with low CPF; for subjects with the A allele, the mean value of speed is 5.608 units more for subjects with high CPF than those with low CPF; these 2 differences are significantly different from each other (p=.000).

2. Outcome=speed of spiral drawing test using the non-dominant hand (ND)
a) <u>Main effects</u>:
Linear regression of NDspeed on CPF: The latter was *not* a significant predictor at the 5% level (p=.209).
Linear regression of NDspeed on HICHLOP: The latter was a significant predictor (p=.025]). Subjects with high levels of CPF had a lower mean NDspeed by .501 than subjects with a lower level of CPF.
b) <u>Effect modification</u>:
Linear regression of NDspeed with a CPF x PON1108 interaction: Highly significant interaction (p = .000). For subjects with the A allele, the mean value of NDspeed increases by .041 for each unit increase of CPF; for subjects with the G allele, the mean value of NDspeed decreases by .245 for each unit increase of CPF; for subjects with both A and G alleles, the mean value of NDspeed decreases by .002 for each unit increase of CPF: these 3 rates of change are significantly different from each other (p=.000).

Linear regression of NDspeed with a HICHLOP x PON1108 interaction: Highly significant interaction (p = .000). For subjects with the A allele, the mean value of NDspeed is 3.255 units more for subjects with high CPF than those with low CPF; for subjects with the G allele, the mean value of NDspeed is .68 units less for subjects with high CPF than those with low CPF; for subjects with both A and G allele, the mean value of NDspeed is 1.301 units less for subjects with high CPF than those with low CPF; these 3 differences are significantly different from each other (p=.000, which is the interaction p-value). Each of the above regressions was rerun by dichotomizing PON1108 according to the presence of at least one G allele or not. A new variable PON1108_bin was given the value 1 for AG and GG and the value of 0 for AA.

Linear regression with a CPF x PON1108_bin interaction (p-value =.000). For subjects with a G allele, the mean value of NDspeed decreases by .086 for each unit increase in CPF; for subjects with an A allele, the mean value of Speed increases by .041 for each unit increase in CPF: these 2 rates of change are significantly different from each other (p=.000). Linear regression with a HICHLOP x PON1108_bin interaction (p-value =.000). For subjects with the G allele, the mean value of NDspeed is 1.271 units less for subjects with high CPF than those with low CPF; for subjects with the A allele, the mean value of NDspeed is 3.255 units more for subjects with high CPF than those with low CPF; these 2 differences are significantly different from each other (p=.000).

Summary of results: Linear regression of Dspeed with a CPF x PON1108 interaction: Highly significant interaction (p = .000). For subjects with the A allele, the mean value of Dspeed increases by .056 for each unit increase of CPF; for subjects with the G allele, the mean value of Dspeed decreases by .362 for each unit increase of CPF; for subjects with both A and G alleles, the mean value of Dspeed decreases by .015 for each unit increase of CPF: these 3 rates of change are significantly different from each other (p=.000, which is the interaction p-value) *Linear regression of Dspeed with a HICHLOP x PON1108 interaction: Highly significant interaction (p = .000). For subjects with the A allele, the mean value of Dspeed is 2.925 units more for subjects with high CPF than those with low CPF; for subjects with the G allele, the mean value of Dspeed is 2.712 units less for subjects with high CPF than those with low CPF; for subjects with both A and G allele, the mean value of Dspeed is .53 units less for subjects with high CPF than those with low CPF; these 3 differences are significantly different from each other (p=.000, which is the interaction p-value)

3c. Opportunities for training and professional development

Nothing to report

3d. Dissemination of results to communities of interest

Nothing to report

3e. Plans for the next reporting period to accomplish goals

No further reporting periods.

4. Impact

4a. Impact on the development of the principal discipline(s)

Although we are still in the initial stages of data analysis and report writing, our findings suggest small yet significant impact of prenatal CPF exposure on a range of neurological tests in early adulthood. This would be the first report of the effect of prenatal CPF exposure on neurological tests that were selected because they are sensitive to symptoms of parkinsonism. Although we do not see clinical parkinsonism in this young adult sample, and the signal is modest, nevertheless, these measureable changes using a well-validated test could predate the development of further symptoms associated with PD. Such findings potentially provide a very early window into the pathogenic process, much earlier than other studies of emerging parkinsonism. Further, if we can show that certain genetic variants may affect individual susceptibility to the toxic effects of this pesticide, this knowledge will add to our understanding of early risk and the need for further screening.

4b. Impact on other disciplines

From a public health perspective, the landscape has changed in recent years with respect to the registration of chlorpyrifos for agricultural use. Although the US Environmental Protection Agency banned chlorpyrifos in 2021, a very recent decision by the 8th District Court overturning the ban could affect the states of Minnesota, Iowa, North Dakota, South Dakota, Nebraska, Missouri and Arkansas. This means that CPF could be put back in use for agricultural purposes, exposing agricultural workers and nearby populations, including pregnant women, to additional risk. Demonstration that this exposure may be associated with early risk for parkinsonism would add to the evidence supporting a total ban.

4c. Impact on technology transfer

Nothing to report

4d. Impact on society beyond science and technology

Nothing to report

5. Changes/Problems

5a. Changes in approach and reasons for change

No changes. We have received a 12-month no-cost extension to allow time to analyze the data following the completion of data collection.

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

No problems or delays anticipated.

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

Subject compensation for travel and volunteer payments were reduced during the COVID pause (when a partial assessment was completed requiring less subject time). The cost savings has permitted us to bring those subjects into the office to complete the remainder of the testing in person (neurological exam and heart rate variability) for which they have been compensated. We were able to complete the assessments and accomplish some of the data analytic activities during the 12-month no-cost extension.

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

- Significant changes in use or care of human subjects None noted
- Significant changes in use or care of vertebrate animals NA
- Significant changes in use of biohazards and/or select agents NA

6. Products

- **Publications, conference papers, and presentations**
  In preparation
- **Website(s) or other Internet site(s)**
  Nothing to report
- **Technologies or techniques**
  Nothing to report
- **Inventions, patent applications, and/or licenses**
  Nothing to report
- **Other Products**
  Nothing to report

7. Participants & Other Collaborating Organizations

Name:	*Virginia A. Rauh, ScD*
Project Role:	*PI*
Researcher Identifier (e.g. ORCID ID):	*0000-0003-3164-9892*
Nearest person month worked:	*1.0*
Contribution to Project:	*Dr. Rauh has overseen all aspects of the project, including hiring training, protocol development, Human Subjects approvals, and met regularly with the research team.*
Funding Support:	*NA*

Name:	*Kwei, Kimberly, MD*
Project Role:	*Movement disorders neurologist (junior faculty)*
Researcher Identifier (e.g. ORCID ID):	*0000-0002-0907-2807*
Nearest person month worked:	*2.0 cal months*
Contribution to Project:	*Dr. Kwei has clinically examined study participants, including administration of the MDS-UPDRS.*
Funding Support:	*NA*

Name:	*Elinol Lopez*

Project Role:	*Research Assistant*
Researcher Identifier (e.g. ORCID ID):	*0000-0002-6744-9924*
Nearest person month worked:	*5.0 cal months*
Contribution to Project:	*Ms. Lopez has made recruitment calls, consented and administered all questionnaires and cognitive tests.*
Funding Support:	*NA*

Name:	*Wanda Garcia*
Project Role:	*Project Coordinator*
Researcher Identifier (e.g. ORCID ID):	*0000-0002-5559-2432*
Nearest person month worked:	*6.00 cal months*
Contribution to Project:	*Ms. Garcia has overseen all protocol activities, including the finalization of measures, IRB tasks, compensation of participants, scheduling, and data collection. She has organized regular staff meetings and ongoing internal reports.*
Funding Support:	*NA*

Name:	*Grace Liu*
Project Role:	*RA for Heart Rate Variability Analysis-Data Manager*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*No change*

Contribution to Project:	*Responsibilities include collection and recording of data on each physiological signal. She is responsible for file storage on a shared, secured server; visual review of each type of data; and manually correcting invalid data points and/or annotating segments of unusable data via keyboard input.*
Funding Support:	*NA*

Name:	*David Merle*
Project Role:	Database Programmer
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*No change*
Contribution to Project:	*Merle is conducting data cleaning, entry and management*
Funding Support:	*NA*

Name:	*Judith Austin, PhD*
Project Role:	*Associate Research Scientist*
Researcher Identifier (e.g. ORCID ID):	

Nearest person month worked:	*1.0*
Contribution to Project:	Judy Austin has conducted the data analyses for the neurological outcomes (UPDRS)
Funding Support:	*NA*

- **Change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period**

8. Special Reporting Requirements

- **QUAD CHARTS:**

9. Appendices