1.a. Full Title:
   Physical activity and incidence of Parkinson’s disease in the Atherosclerosis Risk In Communities (ARIC) study

b. Abbreviated Title (Length 26 characters):
   PD ARIC

2. Writing Group:
   Writing group members:
   Erin Suttman
   Souvik Sen, MD, MS, MPH
   Kolby Redd, PhD
   Pornpimol Anprasertporn, MD
   Xuemei Huang, MD, PhD
   Honglei Chen, MD, PhD
   Kelly Evenson PhD
   Alvaro Alonso, MD, PhD
   Wayne Rosamond, PhD, MS

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. SS [please confirm with your initials electronically or in writing]

First author: Souvik Sen
Address: 8 Medical Park, Suite 420
          Columbia, SC 29203
Phone: 803-545-6073          Fax: 803-545-6066
E-mail: souvik.sen@uscmed.sc.edu

ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

Name: Wayne Rosamond PhD, MS
Address: Phone:          Fax:
E-mail: wayne_rosamond@unc.edu

3. Timeline:
4. Rationale:

With respect to many common diseases, exercise is one of the most frequently cited methods for prevention and improving overall health – particularly cardiovascular health. [1, 2, 3] While exercise is well-known to improve quality of life for Parkinson’s disease (PD) patients after diagnosis and symptom onset, the mechanism for this treatment is not greatly understood. Current research is highly focused on exercise paradigms in PD and improved outcomes following diagnosis and symptom onset. Despite the positive therapeutic impact exercise has on outcomes for PD, research identifying the relationship between pre-onset exercise habits and the diagnosis of PD is minimal. Such analysis could provide insight to identify behavioral factors involved in the etiology of PD. Research concentrated on identifying early-stage autonomic symptoms and preventing progression prior to motor symptom onset could yield a prolific body of clinical research applied to treatment of neurodegenerative disease and improving outcomes.

Recent trials have identified various peripheral effects of the autonomic nervous system (ANS) presenting in PD patients, many of which manifest as non-motor or autonomic symptoms. 60-98% of PD patients experience sleep disturbance as a non-motor symptom, such as REM Behavior Disorder (RBD). [4] Of patients diagnosed with RBD, the 5- and 10-year risk of neurodegenerative disease is 17.7% and 40.6%, respectively, [5] and is highly concomitant with the same impaired neurological functioning observed in α-synucleinopathies. [4, 6] Study findings have associated specific pathology involving α-synuclein with the development of PD and other neurodegenerative disorders. [7, 8] Autonomic symptoms involving cardiovascular dysfunction are also associated with PD populations. Degeneration of the cardiac innervation of the autonomic nervous system within the basal ganglia has been observed prior to and in tandem with such degeneration of the motor complexes responsible for motor symptoms in PD. [9] Such findings in multidisciplinary areas of pathology support the necessity for developing of early, clinical methods for identifying non-motor symptoms characteristic of neurodegenerative diseases and early treatment paradigms to prevent further degeneration. With the existence of an exceedingly strong relationship between the cardiovascular system [3, 10] neuroprotective effects [11, 12, 13], and exercise, the proposal of exploring applications for exercise as one method of treatment for cardiovascular dysautonomia in context of PD is reasonable.

Cardiovascular dysautonomia appears as various manifestations in PD, including a low heart rate variability (HRV). In particular, reduced HRV has been observed in PD patients, including early stage patients, as an indication of ANS regulation failure. [14] Until recent analysis, it was unknown whether the reduced HRV precedes any motor or diagnostic manifestations of PD. With the use of the longitudinal data available in the ARIC database, [15] retrospectively
observed the incidence of PD in relation to low HRV at baseline, before symptom onset and diagnosis of PD, in which a positive correlation existed between low HRV at baseline and a diagnosis of PD later in life. With respect to exercise, many spectral analyses support endurance exercise producing an increase in HRV. [10] The existence of such a relationship between HRV and exercise in context of autonomic dysfunction in PD patients provides a basis for a corollary relationship between exercise and the maintaining of the autonomic functioning of the cardiovascular system, which may be further explored. While recognizing the limitations to retrospective analysis, if a relationship between high levels of physical activity and a reduced incidence of PD is observed, such indications may warrant investigation of exercise as a means for preventing the onset of motor symptoms for patients who are experiencing pre-motor, autonomic or non-motor, symptoms of PD.

Although the etiology of PD is multi-factorial (including genetic and environmental influences) and not completely understood, analysis of exercise history and its relationship to the incidence of PD may provide greater insight to lifestyle factors that either promote or prevent neurodegenerative disease. Any indications discovered supporting the use of exercise as a preventative method for patients experiencing early non-motor or autonomic symptoms could inspire the current field of research and expand knowledge of the mechanisms for the etiology and treatment of PD through exercise, in addition to other neurodegenerative disorders.

References:


5. **Main Hypothesis/Study Questions:**

   A: *Does increased physical activity prior to symptom onset have an effect on the incidence of Parkinson’s disease?*

   Subjects with a high rate of physical activity at baseline are expected to have a lower incidence of Parkinson’s disease than subjects with a lower rate of physical activity at baseline. Physical activity will be defined by the physical activity indices collected at Exam 1.

   B: *Is physical activity directly related to non-motor/autonomic symptoms?*

   Subjects with a high rate of physical activity will have reduced rates of autonomic dysfunction, measured by HRV, orthostatic hypotension, and RBD.

6. **Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodological limitations or challenges if present).**

   **Study design:**

   A cohort of subjects has been identified within the study that has been assessed and validated for a confirmed diagnosis of PD between two ancillary studies: 2009.19 Parkinson’s disease
case validation in the ARIC Study, and 2014.25 Parkinson’s disease case validation in the ARIC Study – Phase 2. Identification of a positive Parkinson’s disease diagnosis in the referenced ancillary studies will serve as the definition for Parkinson’s disease for our analysis.

**Hypothesis A:**

All participants who meet appropriate inclusion/exclusion criteria at baseline will be assessed for physical activity. Using the derived measure for (MET) to define physical activity, . Groups will be determined by categorizing physical activity levels into quartiles. Each group will be assessed for incidence of Parkinson’s disease using the Cox proportional hazards ratio analysis (CI=95%).

The Cox proportional hazards ratio will be used to identify physical activity’s effect on incidence of PD diagnosis after adjusting for significant, identifiable confounders. Several models may be run for demographic confounders (i.e. age, race, sex), as well as behavioral (i.e. smoking, alcohol consumption, etc.) confounders.

<table>
<thead>
<tr>
<th>Exposure Variable</th>
<th>Description</th>
<th>Variable Source</th>
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<td>level of physical activity at baseline (average MET-min/wk, across a year )</td>
<td>tot_metminwk_v1</td>
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| Outcome Variable | Incidence of Parkinson’s Disease | Parkinson’s disease case validation (Ancillary studies 2009.19 and 2014.25) |

<table>
<thead>
<tr>
<th>Confounding Variables</th>
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<td>Sex</td>
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<td>Smoking Status</td>
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<td>Alcohol Consumption</td>
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<td>Caffeine Consumption</td>
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<td>Socioeconomic Status</td>
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<td>Concomitant Disease</td>
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<td>Cardiovascular disease (CHD, HF)</td>
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<tr>
<th>Analysis</th>
<th>Cox proportional hazards ratio</th>
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<td></td>
<td>Spline analysis</td>
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**Hypothesis B:**

Similarly to the study design for Hypothesis A, all participants will be assessed for availability of physical activity data. Groups will be determined with similar methods to Hypothesis A according to level of physical activity as determined by the derived MET variables. An odds ratio will be measured to determine the presence of autonomic symptoms at Visit 3. Results will serve as a cross sectional analysis of correlation between physical activity and autonomic...
symptoms of PD, including: low HRV, as measured in Alonso et al. (2015) using EKG data; orthostatic hypotension, derived from the drop in systolic blood pressure by ≥20mmHg or diastolic blood pressure by ≥10mmHg between sitting and standing measurements; and diagnosis of RBD.

Limitations:

Confounding Variables: Since the etiology of PD is multi-factorial and not well-understood, the potential for confounding variables is high. Genetic, environmental, and behavioral factors are all potential confounders, and unidentified factors in the etiology of PD may exist unbeknownst to current scientific knowledge. Concomitant disease, caffeine consumption, age, race, sex, smoking status, socioeconomic status, and alcohol consumption are all examples of confounding variables that will need to be considered.

Diagnosis of PD: While diagnoses included in the analysis will have been thoroughly reviewed for accuracy, the presence of PD can only be truly confirmed in a post-mortem exam. The analysis performed is operating under the assumption that the cases diagnosed with PD are clinically assessed by the standard criteria. The possibility of misdiagnosis exists simply through the capricious nature of PD manifestation in individuals.

Inclusion

All subjects with appropriate data on physical activity at baseline will be included.

Exclusion

Subjects with missing data required for physical activity indices will be excluded. Subjects with prevalent PD at baseline will also be excluded to reduce confounding impact on analysis.

7.a. Will the data be used for non-CVD analysis in this manuscript?
____ Yes ___X__ No

b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES_OTH = “CVD Research” for non-DNA analysis, and for DNA analysis RES_DNA = “CVD Research” would be used?
____ Yes _____No
(This file ICTDER has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript?
____ Yes ___X__ No

b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value
RES_DNA = “No use/storage DNA”?
___ Yes ____ No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status. ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://www.cscc.unc.edu/ARIC/search.php
___X__ Yes _____ No

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?


11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?
___X__ Yes ____ No
11.b. If yes, is the proposal
A. primarily the result of an ancillary study (list number*2009.19, 2014.25)
B. primarily based on ARIC data with ancillary data playing a minor role (usually control
variables; list number(s)*(______________________) _________)
*ancillary studies are listed by number at http://www.cscc.unc.edu/aric/forms/

12a. Manuscript preparation is expected to be completed in one to three years. If a manuscript
is not submitted for ARIC review at the end of the 3-years from the date of the approval,
the manuscript proposal will expire.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public
has access to the published results of NIH funded research. It is your responsibility to upload
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you which journals automatically upload articles to Pubmed central.