# Cardiovascular physiology in pre-motor Parkinson disease: A Neuroepidemiologic study

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## Abstract

**Background—**Changes in cardiovascular physiology in PD are common and may occur prior to diagnostic Parkinsonian motor signs. We investigated associations of electrocardiographic (ECG) abnormalities, orthostasis, heart rate variability or carotid stenosis with the risk of Parkinson disease (PD) diagnosis in the Cardiovascular Health Study, a community-based cohort of older adults.

**Methods—**ECG abnormality, orthostasis (symptomatic or asymptomatic), heart rate variability (24-hour Holter monitoring) or any carotid stenosis ( 1%) by ultrasound were modeled as primary predictors for incident PD diagnosis using multivariable logistic regression. Incident PD cases were identified by at least one of the following: self-report, anti-Parkinsonian medication use, or ICD9. If unadjusted models were significant, they were adjusted or stratified for age, sex and smoking status and those in which predictors were still significant (p  0.05) were additionally adjusted for race, diabetes, total cholesterol, low density lipoprotein, blood pressure, body mass index, physical activity, education level, stroke and C-reactive protein.

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**Results—**Of 5,888 participants, 154 incident PD cases were identified over 14 years of follow-up. After adjusting models with all covariates, those with any ECG abnormality (Odds Ratio: 1.45, 95% CI: 1.02-2.07,p=0.04) or any carotid stenosis (OR: 2.40, 95% CI (1.40-4.09,p=0.001) at baseline had a higher risk of incident PD diagnosis. Orthostasis and heart rate variability were not significant predictors.

**Conclusions—**This exploratory study suggests that carotid stenosis and ECG abnormalities occur prior to motor signs in PD, thus serving as potential pre-motor features or risk factors for PD diagnosis. Replication is needed in a population with more thorough ascertainment of PD onset.

## Introduction

Non-motor features occur in 90% of individuals with Parkinson disease (PD).[1] Common among them is cardiovascular dysfunction, which may occur prior to mobility problems and PD diagnosis.[2] Orthostasis – a drop of blood pressure upon standing - manifests as dizziness in a majority of people with PD.[3] Also, the electrocardiogram (ECG) is now being explored as a potential tool to screen for those at risk for PD, specifically as it measures heart rate variability which is diminished in PD.[4] Carotid artery wall thickness has also been found to be low in PD compared to controls, perhaps due to hemodynamic changes in the context of hypotension.[5] Based on the hypothesis that changes in the cardiovascular system occur prior to motor dysfunction, in this longitudinal cohort we hypothesized that orthostasis, ECG abnormalities, lower heart rate variability and the absence of carotid stenosis would be associated with an elevated risk of PD diagnosis.

## Methods

### Study Population

The Cardiovascular Health Study (CHS) is a community-based cohort study of cardiovascular disease among 5888 adults aged 65 years and older who were followed longitudinally for 14 years from 1989-2003. Details of the study were previously published.[6, 7] Briefly, in 1989-90 (baseline at study year 2) 5,201 participants were recruited from a random sample of Medicare eligible persons in 4 US communities: Forsyth County, NC; Sacramento County, CA; Washington County, MD; and Pittsburgh, PA. An additional cohort of 687 African-American men and women was recruited in 1992-93, baseline at study year 5. Participants were excluded if they were institutionalized, had cancer or other life threatening diseases, were planning to move out of the area within 3 years, or required a proxy to give consent. Participants were examined yearly, alternating with telephone interviews every 6 months from 1989 through 1999 for new diagnoses, hospitalizations, and medical procedures. After 1999, study visits ceased and data collection from telephone interviews and hospitalizations continued. Health Care Finance Administration records were used to enhance surveillance of cardiovascular events and deaths. The institutional review board at each site approved the study methods, and all participants gave written informed consent.

### Identification of Incident Parkinson disease cases

Details of PD case identification with the CHS were previously published.[8] Briefly, the following data sources were used to screen for PD cases:

1. Self-report: Participants were asked if they had a physician diagnosis of PD at their baseline and in study year 11.

2. Medication inventory: At baseline and annual visits through 1999-2000, participants were asked to report on and bring all medication taken within 14 days of the visit. All medications were visually inspected, and their names, class, dose and frequency were recorded. A movement disorders specialist (S.J.) reviewed antiparkinsonian medications to screen for potential PD. These included: levodopa containing compounds (Sinemet®, Sinemet CR/ER®. Larodopa®, Dopar®. Stalevo®); pergolide (Permax®); pramipexole (Mirapex®); ropinirole (Requip®); Bromocriptine (Parlodel®); selegiline (L-deprenyl, Eldepryl®, Emsam®, Zelapar®; rasagiline (Azilect®); entacapone (Comtan®); tolcapone (Tasmar®); ethopropazine (Parsdiol®); trihexyphenidyl HCL (Artane, Tremin); procyclidine (Kemadrin®); biperiden (Akineton®); benztropine (Cogentin®); and amantadine (Symmetrel ®). Participants' response to antiparkinsonian medications is not known. This dataset precedes the time during which dopamine agonists (ropinirole and pramipexole) were widely used for restless leg syndrome (earliest FDA approval for this condition was 2005).

3. Hospitalization records: Hospitalization discharge records included information on admission date, discharge date, vital status and ICD-9 discharge codes for all hospitalizations of CHS participants. We used ICD-9 code 332.0 to identify PD patients. Through June 2006, 90% of participants in the CHS have been hospitalized.

A participant was identified as having PD if at least one of the above sources supporting PD was present and there was no evidence of parkinsonism-inducing medication use prior to or at the time of PD being identified. A date of initial diagnosis was assigned to each PD case, which was the earliest date from any of the above data sources. If this date was during the period of baseline through the first year of follow-up, the participant was defined as having prevalent PD and excluded from analyses. Those with a date of first diagnosis during subsequent follow-up were considered incident PD.

### Measurement of potential predictors and covariates

**Orthostasis—**Supine and standing blood pressures were taken after at least 20 minutes of supine rest with a mercury sphygmomanometer (Baumanometer, W.A. Baum Co., Copiague, NY) based on American Heart Association recommendations.[9] The systolic blood pressure (BP) was the first Korotkoff sound heard, and the diastolic BP was the last sound heard (Phase V). Readings were recorded to the nearest even digit. After a supine BP and heart rate were obtained, the participant was assisted to a standing position. Two minutes and twenty-five seconds after standing commenced the BP was taken. The participant was asked about any feelings of dizziness, lightheadedness or faintness during standing and if these were endorsed the procedure was aborted due to symptomatic orthostatic hypotension (OH). Asymptomatic OH was defined as a drop in systolic BP of 20 mm Hg or more from the supine to standing position at 3 minutes, a drop in diastolic BP of 10 mm Hg or more, or both. Orthostasis refers to both the asymptomatic and symptomatic categories combined.

**Electrocardiographic abnormalities—**Standard 12-lead electrocardiograms (ECG's) were recorded in all participants at study baseline following standardized protocols for ECG acquisition and quality control. Electrocardiograms were processed in a central laboratory (EPICARE Center, University of Alberta, Edmonton, Alberta, Canada, and later at Wake Forest University, Winston-Salem, North Carolina). ECG's were initially processed by the Dalhousie ECG program[10] and visually inspected for technical errors and quality. ECG wave measurements were validated on interactive graphics terminals and processing was

repeated with the 2001 version of the Marquette 12-SL program (GE Marquette, Milwaukee, WI).[11] Because PD pathology has been observed in the left ventricular myocardium, major ECG abnormalities associated with left ventricular pathology were selected. An ECG abnormality was any one or more of the following: ventricular conduction defect, major Q or QS abnormalities, minor Q or QS with ST-T-wave abnormalities, left ventricular hypertrophy, isolated major ST-T-wave changes, atrial fibrillation, and first degree atrioventricular block.

**Heart Rate Variability**—Ambulatory ECG (Holter) monitoring was performed on a subset of 1814 volunteers at baseline for the original cohort and two years after baseline for the African American cohort. Of these, 1649 were in normal sinus rhythm and had at least 18 hours of analyzable data used in the analyses. Automatically detected beats were manually checked and corrected if needed by technicians. Edited results were reviewed (PKS) to ensure that only normal-to-normal (N-N) beats with uniformly detected onsets within each recording were included. The longest and shortest true N-N intervals were identified and intervals outside of these limits and ectopic beats were excluded. Twenty-four hour time and frequency domain heart rate variability (HRV) analysis was performed on a Sun Enterprise 450 server (Sun Microsystems, Palo Alto, CA) using validated research software. Time domain HRV measures were the percent of N-N intervals >50ms different from previous N-N intervals (pNN50), the root mean square of successive differences of N-N intervals (RMSSD) and the standard deviation of N-N intervals (SDNN). Frequency domain HRV measures were based on power spectral analysis and quantified the amount of variance in N-N intervals at different frequencies (average of five minute total power for 24 hours). Low-frequency power (LF, variations from 0.05-0.15 Hz) reflects sympathetic and parasympathetic function, while high-frequency power (HF, variations at respiratory frequencies of 0.15-0.40 Hz) primarily reflects parasympathetic function. The LF/HF ratio is thought by some investigators to reflect sympathovagal balance or sympathetic modulations.[12] HF and LF were normalized with natural logarithmic transformation.

**Carotid Ultrasound**—Trained readers insonated common and internal carotid arteries separately. Stenosis of <50% were judged visually as 1-24% or 25-49%. Stenosis of 50-74% was defined by Doppler peak flow velocity  1.5 m/s; 75-99% as flow velocity  2.5 m/s; and 100% stenosis as absent flow. In this study, carotid stenosis was quantified as either present ( 1%) or absent in the most severely affected vessel. CHS ultrasound methods and quality control results are previously published.[13]

**Covariates**—Covariate measures were obtained at baseline, including demographics (i.e., age, sex, race), smoking status, and alcohol use. Participants were current smokers if they reported smoking within the past 30 days or said they currently smoked. Former and never smokers reported no cigarette smoking in the past 30 days and were distinguished on the basis of self-reported smoking status prior to the 30 days. Baseline blood pressure was performed with participants seated, using the technique described above. Body mass index was weight (kilograms) divided by height (meters) squared. Participants were asked if a physician had ever told them that they had a stroke. Diabetes was defined as the use of insulin or oral hypoglycemic agents or a fasting glucose level of  126 mg/dL. Physical activity was assessed at baseline by use of a modified Minnesota Leisure-Time Activities questionnaire, which evaluated frequency and duration of 15 different activities during the prior 2 weeks. Education level was the highest grade or year of school completed. Coffee drinking (for the 1989-1990 cohort only) was drinking coffee at least once per week. Because survival patterns may differ among those with and without a particular cardiovascular factor and this may impact PD case ascertainment, age and comorbidity matched sensitivity analysis was planned. A modified Charlson Comorbidity Scale was used

to a quantify comorbidity at baseline. This is a scoring system for common comorbid conditions weighted by mortality risk. As in other studies of PD and risk of mortality, we used self-reported diagnoses in the disease categories of the original Charlson Index.[14, 15] The categories of cancer, HIV/AIDS and serious liver problems were omitted since participants with these conditions were excluded from the CHS cohort. Other covariates (total and low-density lipoprotein cholesterol, creatinine and C-reactive protein) were derived from baseline blood specimens sent to the Central Blood Analysis Laboratory at the University of Vermont, as detailed previously.[16]

**Data Analysis**—Descriptive statistics, *t*-tests and chi-square tests summarized baseline characteristics and group comparisons of incident PD cases vs. non-PD. The original cohort was combined with the minority cohort for the analyses. Logistic regression models were fit with incident PD (yes/no) as the dependent variable; and each of the following primary predictors of interest: the presence of any carotid stenosis (0 vs. 1%), any ECG abnormality (present or absent), orthostasis (present or absent), and heart rate variability measures. Interactions between the primary predictor and risk factors for PD (age, sex or smoking status) were explored. If the interaction between sex and a main predictor of interest was marginally significant (p 0.10), models were stratified by sex. If an unadjusted model demonstrated a significant primary predictor (p 0.05), then the model was fit adjusting for well-known risk factors for PD (age, sex, smoking status) (Adjusted Model 1). If Adjusted Model 1 still demonstrated a significant primary predictor (p 0.05), another model was fit with additional covariates reported to be possibly associated with both cardiovascular disease and PD (race, diabetes, total cholesterol, low density lipoprotein, systolic blood pressure, diastolic blood pressure, body mass index, physical activity, education level, stroke and C-reactive protein) (Adjusted Model 2). Coffee drinking was not included in the final models because it was not available for the African-American cohort and secondary analysis within the original 1989-1990 cohort yielded similar point estimates without changing the significance of either ECG abnormality or carotid stenosis. As a sensitivity analysis for misclassification of PD cases, analysis was repeated using only those incident PD cases identified by at least two sources. To assess impact of misclassification of incident vs. prevalent PD cases, a sensitivity analysis was also done excluding those who developed within five years of the baseline assessment instead of one. Because the survival patterns of those with ECG abnormalities or carotid stenosis may differ from those without, and this could impact incident PD case ascertainment, we fit these above models within strata matched for both age within 5 years (65-70, 71-75, 76-80, 81-85, 85-90, 90-95, >95) and comorbidity (modified Charlson score). This resulted in nine strata with sufficient numbers of participants to permit analysis. The nine strata were (Age/Charslon score): 65-70/0, 65-70/1, 65-70/2, 65-70/3, 70-75/0, 70-75/1, 75-80/1, 75-80/2, 80-85/3. Strata-specific odds ratios were combined using a random effects model[17] to obtain an overall estimate.

## Results

### Participant characteristics

PD cases (N=214) were identified over 14 years of follow-up. Sixty prevalent cases at baseline were excluded leaving 154 incident PD cases for the analyses (74 were identified by self-report, 71 by medications, 96 by ICD-9). Of these, 63 were identified by more than one data source and 24 by all three data sources). The average baseline age (SD) was 72.8 (5.6) with mean follow up of 10.4 (3.8) years (Table 1). Compared to non-PD cases, incident PD cases had higher prevalence of carotid stenosis (88.3% vs. 77.4%, p=0.001), major ECG abnormality (38.3% vs. 30.1%) and diabetes (23.3% vs. 16.1%, p=0.02) as well as higher physical activity (2109[2331] vs. 1700[2021] Kcal/day, p=0.03) at baseline. There was a

lower prevalence of women among incident PD cases (45.5% vs. 58.2%, p=0.002). All other characteristics were similar between groups (Tables 1 and 2).

### Associations between potential cardiovascular predictors and incident PD

When stratified by sex, any carotid stenosis (1-100%) was significant in men (4.05, (1.48-11.12),p=0.007) but not women (1.46,(0.81-2.64),p=0.21). This remained the case after adjusting for age and smoking (Table 3, Adjusted Model 1, stratified by sex). Sex was not a significant interaction term for any other model or with any other predictor. After additionally adjusting for race, diabetes, total cholesterol, low density lipoprotein, systolic blood pressure, diastolic blood pressure, body mass index, physical activity, education level, stroke and C-reactive protein, any carotid stenosis remained significant after combining men and women (Adjusted Model 2). The presence of ECG abnormalities was also significant in models that combined men and women (Unadjusted Model: OR 1.44(1.02-2.00),p=0.03; Adjusted Model 1: 1.41(1.00-1.99), p=0.049; Adjusted Model 2: 1.44(1.02-2.07),p=0.04)). To assess impact of misclassification of incident vs. prevalent PD cases, a sensitivity analysis was also done excluding those who developed within five years of the baseline assessment instead of one. For both carotid stenosis and ECG abnormalities, the models remained significant. Because the survival patterns of those with ECG abnormalities or carotid stenosis may differ from those without, and this could impact incident PD case ascertainment, we fit these models within strata matched for both age and comorbidity (modified Charlson score) and for both factors, a statistically significant association with risk of PD diagnosis was maintained. The significance was also maintained when adjusting for the duration of time the participant was followed in CHS (data not shown). For both carotid stenosis and ECG abnormalities, a significant association was no longer seen when restricting the classification of PD to more than one data source. Orthostasis and heart rate variability measures were not significant predictors of incident PD (Table 3). No significant interactions were found between primary predictors (ECG abnormality and carotid stenosis) and age or smoking status.

## Discussion

In this study, the presence of any carotid stenosis or major ECG abnormality was associated with significantly elevated risk of PD diagnosis. Orthostasis and heart rate variability were not significantly associated with incident PD.

Change in cardiovascular physiology is a near-universal feature in PD,[4] and may precede a diagnosis of PD. Loss of sympathetic cardiac innervation in PD has been confirmed radiographically with the most dramatic deficiencies seen in the left ventricular myocardium.[18] The neuropathological changes seen in PD (Lewy-formations) have been observed in cardiac nerves years before motor manifestations of PD[19] and in autopsy cases of incidental Lewy-body, a condition thought to be an early form of PD.[2] Lewy neuropathology has also been observed in the dorsal motor nucleus of the vagus which supplies parasympathetic tone.[20] In idiopathic rapid eye movement sleep behavior disorder, a condition in which up to 50% will go on to develop Parkinsonism, HRV is significantly lower than controls.[4] These lines of evidence have led to the conception of a pre-motor period of PD in which cardiovascular physiology is affected.

Although the prediction of ECG abnormalities associated with an elevated risk of PD was supported by the results and sensitivity analyses, it is possible this finding is spurious due to multiple statistical tests performed using multiple predictors because the 95% confidence interval for the odds ratio is only slightly above 1.0. The strength of evidence is higher for the unexpected finding of carotid stenosis being associated with an increased risk of PD diagnosis. The possible reason for these findings are that: (1) these are examples of early

non-motor features secondary to neurodegeneration during the pre-motor period of PD; (2) these are indicators of vascular disease and share common mechanisms of pathogenesis with PD; or (3) there is no association between these predictors and PD diagnosis because cases of vascular Parkinsonism were misclassified as PD. Vascular Parkinsonism is caused by cerebrovascular disease and has motor features seen in PD, and inflammation and oxidative stress are thought to contribute to both cardiovascular disease and PD.[21, 22] It is interesting that in the unadjusted sex-stratified results, the odds ratio for any Carotid Stenosis being a risk factor for the diagnosis of PD is higher in men and significant in men and not women. This may account for the significant association in models which combine men and women. However, as there are only four men with no carotid stenosis who went on to be diagnosed with PD, this number of observations is too small to warrant any definitive conclusions. Other models which combined men and women were adjusted for sex, and sex was not a significant interaction term. While the number of observations in this cohort does not allow this, it would be interesting to see how results of similar analyses may change if the cut-off for carotid stenosis is varied and sex stratified in another population.

A possible link between cardiovascular disease and PD is homocysteine, a non-protein forming amino acid involved in the recycling or elimination of the essential amino acid methionine. High concentrations of homocysteine have been associated with clinical manifestations affecting the central nervous system (e.g., cognitive decline, cerebral atrophy, epilepsy). Hyperhomocysteinemia is also a risk factor for atherosclerosis and thrombotic vascular diseases, and is independently associated with asymptomatic carotid stenosis.[23, 24] Mechanisms by which homocysteine may exert adverse effects are not completely known, but evidence suggests it is pro-oxidative contributing to endothelial damage. Elevated homocysteine has been associated with hypertrophy of the intima-media complex of the carotid artery,[25] and high concentrations of homocysteine enhances neuronal susceptibility in animal models of PD. Neuroepidemiological evidence also supports hyperhomocysteinemia as a risk factor for PD in smokers with a polymorphism known to induce high levels of homocysteine.[26] The possibility of homocysteine as risk factor spanning both cardiovascular and neurodegenerative conditions, specifically PD, is an intriguing area for future research.

We did not see an association between lower HRV or orthostasis and a risk of PD diagnosis, suggesting they may not predate PD diagnosis. Alternatively, the average time between measures of predictors and PD diagnosis was approximately 10 years, which may predate some cardiovascular changes in the pre-motor period. Also the number of incident PD cases may be too small to detect an association, especially in the subset of participants with HRV analyses, which included common time and frequency measures but no non-linear measures.

Our finding of diabetes being more frequent in the group that went on to develop PD is consistent with other studies suggesting diabetes as a risk factor for PD.[27-29] Our finding of baseline physical activity being higher in the Incident PD group than the non-PD group may seem unexpected as other studies have suggested either higher physical activity to lower PD risk or less physical activity is an early pre-clinical marker for PD.[29-32] However, this finding may be due to differences in study populations or methodology. The CHS cohort is older than other cohorts in which relationships between physical activity and PD have been reported. In those studies, physical activity was stratified in analyses by sex and exposure (e.g. low, medium, high), whereas our measure of activity was continuous (Kcal/day). Sex differences may also partly account for the finding, as in one study the association of higher physical activity and lower PD risk was seen in men but not women.[32]

A limitation of this study is the lack of neurological examination of all CHS participants to validate a PD diagnosis. Nor was an exact date of PD diagnosis available or duration of anti-

parkinsonian medication use. Unfortunately, most of the CHS cohort is now deceased, making clinical validation impossible. Likely, some misclassification of PD cases occurred which would have attenuated our results. We used the same types of data sources to identify PD as published in other cohorts.[33] Although vascular parkinsonism is a common comorbidity seen in 19-50% of PD patients, of particular concern is that purely vascular Parkinsonism which comprises 4-12% of all Parkinsonian cases were misclassified as PD.[34] However, the expected negative association of smoking and the risk of PD reported in CHS suggests accurate PD classification,[8] because smoking is positively associated with cerebrovascular disease. Also, the incidence rate for PD in this cohort (189 PD cases per 100 000 person years) falls well within the range of incidence rates reported for PD in this age range.[35] It is possible that significant associations were spurious due to multiple comparisons, especially in the case of ECG abnormalities where the 95% confidence interval is only slightly above 1.0. A sensitivity analysis with more restrictive criteria for PD (at least two supporting data sources) did not remain significant possibly due, in part, to the small number of remaining incident PD cases. Because of uncertainty about diagnosis dates we used logistic regression and not proportional hazards modeling and excluded all prevalent PD cases including those within the first year of follow-up. For significant predictors, sensitivity analyses with more restrictive criteria for incident PD cases (cases of PD with a date of first diagnosis >5 years after baseline) yielded results which remained significant and consistent with the primary analyses. Nonetheless, the possibility of misclassification of either PD diagnosis or time of onset cannot be excluded.

Strengths of CHS is that it is an elderly, geographically and racially diverse community-based population with over a decade of follow-up in which participants underwent extensive evaluations focused on cardiovascular disease. This exploratory study suggests another line of evidence that cardiovascular changes may occur prior to motor signs in PD. Further investigation of pre-motor features of PD is needed in more diverse, populations whose observation period began when they were younger with more thorough ascertainment and validation of PD onset.

## Acknowledgments

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**Table 1**

Participant Demographic Characteristics

| | Incident PD group (go on to develop PD motor signs) | Non-PD group (did not develop PD motor signs) | CHS Cohort (excluding prevalent PD cases at baseline) |
|---|---|---|---|
| **Number of Participants** | 154 | 5674 | 5828 |
| **# women** | 70 (45.5%) [*] | 3300 (58.2%) | 3370 (57.8%) |
| **Mean Baseline Age in years (SD)** | 72.44 (5.0) | 72.83 (5.6) | 72.82 (5.6) |
| **Smoking** | | | |
| **Never and former** | 143 (92.9%) | 4984 (87.9%) | 5127 (88.1%) |
| **Current** | 11 (7.1%) | 684 (12.1%) | 695 (11.9%) |
| **Race** | | | |
| **Caucasian** | 129 (83.77%) | 4740 (83.5%) | 4869 (83.5%) |
| **African-American and Other** | 25 (16.2%) | 934 (16.5%) | 959 (16.5%) |

[*] $p < 0.05$ vs. non-PD group

**Table 2**

Baseline Measures of Interest in Participants

| | Incident PD group (go on to develop PD motor signs) | Non-PD group (did not develop PD motor signs) | CHS Cohort (excluding prevalent PD cases at baseline) |
|---|---|---|---|
| **Presence of** | | | |
| **Any carotid stenosis** | 136 (88.3%) [*] | 4364 (77.4%) | 4500 (77.7%) |
| **Major ECG abnormality** | 57 (38.3%) [*] | 1653 (30.1%) | 1710 (30.4%) |
| **Orthostasis** | 27 (18.0%) | 970 (17.9%) | 997 (17.9%) |
| **Heart Rate Variability Measures** | | | |
| **Number of Participants** | N=44 | N=1543 | N=1587 |
| *Time domain(SD)* | | | |
| **pNN50** | 0.83 (1.6) | 0.98 (1.5) | 1.51 (1.0) |
| **RMSSD** | 3.18 (0.5) | 3.21 (0.5) | 3.21 (0.5) |
| **SDNN** | 121.88 (32.7) | 119.27 (34.7) | 119.34 (34.6) |
| *Frequency domain(SD)* | | | |
| **LF** | 5.86 (0.8) | 5.77 (0.9) | 5.77 (0.9) |
| **HF** | 4.75 (1.0) | 4.81 (1.0) | 4.79 (1.0) |
| **LF/HF** | 1.30 (0.6) | 1.22 (0.6) | 1.25 (0.6) |
| **Diabetes** | 36 (23.4%) [*] | 905 (16.1%) | 941 (16.3%) |
| **Stroke** | 8 (5.2%) | 235 (4.1%) | 243 (4.2%) |
| **Alcohol consumption (drinks/wk)(SD)** | 2.64 (5.8) | 2.58 (10.9) | 2.58 (10.8) |
| **C-reactive protein (SD)** | 4.08 (8.8) | 4.81 (8.2) | 4.79 (8.2) |
| **Systolic blood pressure (SD)** | 135.9 (19.0) | 136.5 (21.9) | 136.53 (21.9) |
| **Diastolic blood pressure (SD)** | 70.60 (10.7) | 70.72 (11.4) | 70.71 (11.4) |
| **Body Mass Index (SD)** | 26.59 (4.1) | 26.69 (4.7) | 26.68 (4.7) |
| **Physical Activity (Kcal/day) (SD)** | 2109 (2331) [*] | 1700 (2020) | 1711.31 (2030.2) |
| **Total Cholesterol(SD)** | 206 (40.6) | 211 (39.2) | 211 (39.3) |
| **Low-density lipoprotein** | 128 (34.9) | 130 (35.7) | 129.90 (35.7) |
| **Charlson Comorbidity Scale (SD)** | 1.47(1.3) | 1.48 (1.3) | 1.48 (1.3) |

[*] p<0.05 vs. non-PD group

**Table 3**

**Associations between Cardiovascular factors and incident Parkinson disease[*]**

| Cardiovascular Predictor | Analysis[*] (Men are women are combined unless otherwise noted) | $N_{PD}$ | $N_{non-PD}$ | Odds Ratio | 95% CI |
|---|---|---|---|---|---|
| | Unadjusted Model | | | | |
| | Men | 84 | 2364 | 4.05 | 1.48-11.12 |
| | Women | 70 | 3274 | 1.46 | 0.81-2.64 |
| | Combined | 154 | 5638 | 2.21 | 1.34-3.62 |
| | Adjusted Model 1 | | | | |
| | Men | 84 | 2361 | 4.26 | 1.55-11.72 |
| | Women | 70 | 3271 | 1.60 | 0.88-2.90 |
| Any Carotid Stenosis [*] | Combined | 154 | 5632 | 2.21 | 1.34-3.65 |
| | Adjusted Model 2 | 147 | 5400 | 2.40 | 1.40-4.09 |
| | Sensitivity Analyses of Adjusted Model 2 | | | | |
| | Alternative classification of PD ( 2 data sources) | 61 | 5400 | 2.05 | 0.92-4.61 |
| | Alternative classification of incidence | 110 | 5400 | 1.96 | 1.11-3.43 |
| | Matched for age & comorbidity (Charlson Scale) | 130 | 4397 | 1.79 | 1.08-3.00 |
| | Unadjusted Model | 149 | 5484 | .44 | 1.02-2.00 |
| | Adjusted Model 1 | 149 | 5479 | 1.41 | 1.00-1.99 |
| | Adjusted Model 2 | 142 | 5249 | 1.45 | 1.02-2.07 |
| Major ECG Abnormality [*] | Sensitivity Analyses of Adjusted Model 2 | | | | |
| | Alternative Classification of PD ( 2 data sources) | 59 | 5249 | 1.27 | 0.73-2.21 |
| | Alternative classification of incidence | 106 | 5249 | 1.57 | 1.04-2.37 |
| | Matched for age & comorbidity (Charlson Scale) | 133 | 4544 | 1.51 | 1.02-2.25 |
| Orthostasis | Unadjusted Model | 115 | 5410 | 0.96 | 0.59-1.57 |

| Cardiovascular Predictor | | | Analysis[*] (Men are women are combined unless otherwise noted) | $N_{PD}$ | $N_{non-PD}$ | Odds Ratio | 95% CI |
|---|---|---|---|---|---|---|---|
| **Heart Rate Variability Measures** | Time domain | pNN50 | Unadjusted Model | 44 | 1543 | 0.92 | 0.67-1.26 |
| | | RMSSD | Unadjusted Model | 44 | 1543 | 0.89 | 0.48-1.66 |
| | | SDNN | Unadjusted Model | 44 | 1543 | 1.00 | 0.99-1.01 |
| | Frequency domain | LF | Unadjusted Model | 36 | 1440 | 1.13 | 0.76-1.67 |
| | | HF | Unadjusted Model | 36 | 1440 | 0.95 | 0.68-1.32 |
| | | LF/HF | Unadjusted Model | 36 | 1440 | 1.13 | 0.62-2.04 |

$N_{PD}$ = number of incident PD cases; $N_{non-PD}$ = total number of participants without PD

Adjusted Model 1: If stratified by sex, adjusted for age and smoking (if not stratified, adjusted for sex as well).

Adjusted Model 2: Additionally adjusted for race, diabetes, total cholesterol, low density lipoprotein, systolic blood pressure, diastolic blood pressure, body mass index, physical activity, education level, stroke and c-reactive protein

Alternative classification of PD: PD cases identified with two or more data sources, adjusted as in Model 2

Alternative classification of incidence: excluding PD cases within the first 5 years of follow up, adjusted as in Model 2

Matched for age and comorbidity: Participants were matched by categories of age in years (65-70, 71-75, 76-80, 81-85, 85-90, 90-95, >95) and a modified Charlson morbidity index score

[*]
Analyses were stratified by sex only if it was a marginally significant interaction term (p 0.10). Adjusted Model 1 was only applied if the unadjusted model was significant (p 0.05). Adjusted Model 2 and Sensitivity analyses were only performed if Adjusted Model 1 was significant (p 0.05)