Published in final edited form as:

J Parkinsons Dis. 2018 ; 8(1): 153–160. doi:10.3233/JPD-171271.

Cardiovascular Risk Factor Burden in Veterans and Non-Veterans with Parkinson Disease

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Abstract

Background—Medical comorbidities, including cardiovascular risk factors such as hypertension and diabetes, influence disease progression in Parkinson disease (PD) and may be variably present in different clinical populations.

Objective/Methods—We conducted a retrospective nested case-control study of 29 Veterans with PD and 29 non-Veteran PD controls. The groups were matched for age, gender, and disease duration. Both groups underwent clinical and imaging testing as part of their participation in a larger cross-sectional PD observational study at our research center. Veterans were recruited primarily from movement disorders neurology clinics at the Ann Arbor Veterans Affairs (VA) Health System. Non-Veterans were recruited primarily from analogous clinics at the University of Michigan Health System. We explored differences in cardiovascular risks factor burden between the groups.

Results—Veterans with PD showed higher scores on the simplified Framingham 10-year general cardiovascular disease risk calculator (FR score; 27.3% (11.5) vs. 20.7% (6.8); $t = -2.66$, $p = 0.011$) and fewer years of self-reported education (14.5 (2.5) vs. 16.7 (2.6); $t = 3.33$, $p = 0.002$). After adjusting for age, disease duration, education, and the use of antihypertensive medications,

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CONFLICTS OF INTEREST

V.K. none.

R.L.A. none.

M.L.M. none.

N.I.B. none.

FINANCIAL DISCLOSURES

Dr. Kotagal receives funding from the NIH (P30 AG024824 KL2), VA Health Systems (IK2CX0011 86 and AAVA GRECC), and the Blue Cross & Blue Shield of Michigan Foundation.

Dr. Albin serves on the editorial boards of *Annals of Neurology*, *Neurology*, *Experimental Neurology*, and *Neurobiology of Disease*. He receives grant support from the NIH and MJFF. Dr. Albin serves on the data safety and monitoring boards of the LEGATO-HD and IONISHTTRX trials.

Dr. Müller has research support from the NIH, the Michael J. Fox Foundation (MJFF), Axovant Sciences, Ltd, and the Department of Veteran Affairs.

Dr. Bohnen has research support from the NIH, the Michael J. Fox Foundation (MJFF) and the Department of Veteran Affairs.

Veterans showed higher FR scores ($t = 2.95$, $p = 0.005$) and a higher intra-subject ratio of FR score to age-and-gender normalized FR score ($t = 2.49$, $p = 0.016$), representing an elevated component of modifiable cardiovascular risk factor burden.

Conclusion—Cardiovascular comorbidities are common in Veterans with PD and may be more severe than in non-Veteran PD populations. These findings merit replication in other representative cohorts. Veterans may be a preferred population for clinical trials evaluating cardiovascular risk factor management on PD progression.

Keywords

Accidental falls; hypertension; Parkinson disease; veterans; white matter

INTRODUCTION

Medical comorbidity burden influences disease heterogeneity and progression in Parkinson disease (PD) [1]. In many cases, these comorbidities are modifiable using existing medical therapies. Identifying PD subgroups at greater risk for comorbidity-influenced clinical decline has implications on our understanding of the natural history of PD and is an important step in the design and deployment of effective future therapeutic interventions for high-risk populations in PD.

Cardiovascular risk factors are common comorbidities in PD [2] and are a leading source of chronic disability worldwide. We previously reported that diabetes in PD associates with postural instability and gait difficulty as well as cognitive impairment [3, 4]. We have also reported an association between hypertension-influenced white matter hyperintensity (WMH) burden with the severity of gait difficulties in PD [5, 6].

Unlike other PD-associated risk factors such as monogenetic risk alleles or remote environmental toxin exposures, the burden of cardiovascular risk factors (CVRFs) may be modifiable using existing treatment approaches. Of the approximately 1 million Americans affected by PD, 50,000 are US Veterans who receive care through the Veterans Affairs (VA) health system [7]. Using existing data from a cross-sectional observational study that recruited PD subjects from similar referral clinics at both a local VA specialty referral clinic and a University-affiliated medical center, we sought to explore differences in the burden of CVRFs between Veteran and non-Veteran PD subjects. Based on studies in previous VA and non-VA PD populations [2, 8], we hypothesized that a greater burden of cardiovascular risk factors would be present in Veteran subjects.

METHODS

Subjects

Subjects for this case-control study were drawn retrospectively from a single center clinical-imaging cross-sectional PD study at the University of Michigan (n total = 98). Inclusion criteria included age ≥ 50 and a PD diagnosis established according to the United Kingdom Brain Bank Clinical Diagnostic criteria for PD [9]. Exclusion criteria included a diagnosis of an atypical parkinsonian disorder, contraindications for undergoing magnetic resonance

imaging (MRI) such as indwelling metal hardware in the body, history of a large artery stroke, and subjects receiving antipsychotic medications, cholinesterase inhibitors, or anticholinergic medications. Recruitment for this study took place at the VA Ann Arbor Health System (VAAHS) Movement Disorders Neurology clinic, the University of Michigan (UM) Movement Disorders Neurology clinics, and through a posting on a University of Michigan Health studies recruitment website. Of the 98 subjects, 29 were United States Veterans. All of these 29 subjects were male. We matched each Veteran PD subject 1 : 1 with PD subjects in the remaining cohort who did not identify as Veterans. Subjects were first matched on gender, followed by approximate age and disease duration. All subjects signed informed consent documentation prior to participation. This study was approved by Institutional Review boards at the UM and the VAAHS.

Clinical testing

Clinical testing included a review of pertinent medical and PD history, current medications, and measurements of vital signs in the seated position. Subjects were asked “do you have balance or gait problems? If so, are you falling?”. If they responded affirmatively to both questions, their response was coded as a “yes”. A negative response to either portion of this question was coded as a “no”. Subject underwent the Movement Disorder Society-Unified Parkinson’s Disease Rating Scale (MDS-UPDRS) motor exam (part 3) in the dopaminergic “off-state” [10]. Subjects also underwent the MDS-UPDRS part 1 (non-motor aspects of experiences of daily living), the MDS-UPDRS part 2 (motor aspects of experiences of daily living), and the Montreal Cognitive Assessment (MoCA), the latter of which occurred after subjects took their regular PD medications.

We calculated the simplified version of the Framingham 10-year general cardiovascular risk score (FR score), which uses BMI instead of serum low-density lipoprotein (LDL), to estimate the 10-year risk of a cardiovascular event [11]. These scores were calculated using a maximum input age of 74 as per the Framingham score algorithm. The Framingham scoring system provides a unique score per individual and normal-risk score for individuals of a given age and gender once modifiable risk factors are reset to the normal age. We calculated the ratio of an individual’s true-risk-score-to-normal-risk score in order to quantify the burden of modifiable cardiovascular risk factors [6]. We categorized antihypertensive medications to include all classes of scheduled beta-blockers, angiotensin converting enzyme inhibitors, angiotensin II receptor blocking medications, diuretics, calcium channel blockers, and nitrates. We categorized cholesterol lowering medications to include statins, fibrates, niacin, and bile acid sequestrants,

Imaging methods

Brain MRIs were conducted on a 3T Philips Achieva system (Philips, Best, the Netherlands) utilizing an 8-channel headcoil. All subjects underwent T1-weighted and volumetric fluid-attenuated inversion recovery (FLAIR) MR sequences. Our group’s methods for calculation of the supratentorial WMH burden have been reported previously [5] and involve using the cerebellar white matter as reference region and then defining WMHs as voxels that are 1.65 standard deviations greater than the reference region. T1 images were segmented using the Freesurfer image analysis suite (<http://surfer.nmr.mg.harvard.edu/>). Total cortical gray matter

and white matter volumes obtained from the recon-all procedure [12] were normalized within subjects to the estimated intracranial volume.

[¹¹C]dihydrotetrabenazine (DTBZ) PET imaging was performed in 3D imaging mode using an ECAT Exact HR+ tomograph (Siemens Molecular Imaging, Inc., Knoxville, TN). No-carrier-added (+)-[¹¹C]DTBZ (250–1,000 Ci/mmol at the time of injection) was prepared, injected, and performed as reported previously [6]. Interactive data language image analysis software (Research Systems, Inc., Boulder, CO) was used to manually trace the striatal volume of interest (VOI) on MRI to include the caudate nucleus and putamen of each hemisphere. Total striatal distribution volume ratio (DVR) was defined as the mean of bilateral caudate and putamen regions. All image frames were spatially coregistered within participants with a rigid-body transformation. Motion-corrected PET frames were spatially coregistered to the T1-weighted MRI using standard coregistration procedures in SPM8b implemented in Matlab 2010b (The MathWorks, Natick, MA). Time activity curves for each VOI were generated from the spatially aligned PET frames. [¹¹C]-DTBZ vesicular monoamine transporter type 2 DVR was then estimated by using the Logan plot graphical analysis method as reported previously [13, 14].

Statistical analyses

Risk factors in cases and controls were summarized using descriptive statistics including means, standard deviations, and counts. Risk factor burden between Veterans and non-Veterans with PD were compared using two-sample *t*-tests and chi-square testing. In order to explore potential differences between groups independent of the effects of confounder variables, we used multivariable linear regression. In one model we used FR score as a dependent variable and in another we used the ratio of a subjects FR score to their normal-risk FR score as a way to quantify the burden of modifiable cardiovascular risk factors. Each model used subject age, gender, and years of self-reported education as covariates in order to control for the effects of these relatively immutable features on inter-group differences seen in mid-to-late life risk factors. We also controlled for the use of antihypertensive medications as a covariate in these models given that this variable influences elements of FR scoring and may be deployed differently in different health settings as well.

RESULTS

A comparison of cases and controls is presented in Table 1. There were no significant differences between groups in distribution of age, motor disease duration, striatal dopaminergic denervation as measured by DTBZ DVR, or the severity of non-motor or motor impairment as measured by the MDS-UPDRS parts 1, 2, and 3 scores respectively. Veterans reported fewer years of education than non-Veterans though MoCA scores were comparable between groups. Veterans were more likely to reporting falls at the time of study enrollment.

There were non-significant trends towards associations seen between (+)-Veteran status and several markers of cardiovascular disease burden including reporting a previous history of smoking ($X^2 = 3.61$, $p = 0.057$) and a higher severity of MRI-assessed WMH burden $t = -1.97$, $p = 0.056$). This latter MRI finding—a near difference between groups in the burden

of acquired pathological white matter lesions—is made more notable by the observation that the two groups did not differ in total adjusted volumes of white matter and cortical gray matter, lowering the possibility that these differential WMH density findings might be explained by pre-morbid volumetric differences.

Veterans showed a higher FR scores compared to non-Veterans in unadjusted analyses. In a multivariable linear regression analysis (Table 2) adjusted for age, disease duration, years of education, and the use of antihypertensive medications, (+)-Veteran status associated with higher FR scores as did higher age and the use of antihypertensive medications. In a separate model with the same covariates but using the ratio of FR score to normalized FR score as a dependent variable to quantify the modifiable component of aggregate cardiovascular risk, (+)-Veteran status also showed similar associations with higher score ratio.

DISCUSSION

We report a greater degree of cardiovascular risk factor (CVRF) burden in Veterans with PD compared to non-Veterans with PD. These disparities are not fully explained by differences between groups in relevant confounders including educational attainment. We also report a higher prevalence of self-reported falls and a borderline non-significant trend towards a higher burden of WMHs in Veterans compared to non-Veterans with PD. These inter-group differences may reflect a true disparity in clinically-relevant comorbidity burden between Veterans and non-Veterans. Our regression analyses also point to the possibility that some of this aggregate cardiovascular burden may also be clinically modifiable.

Although no previous PD studies have directly explored differences between Veterans and non-Veterans in comorbidities, there are some data to support the idea that Veterans with PD may have a higher burden of CVRFs. The US Centers for Disease Control and prevention (CDC) estimate a national prevalence of diabetes of 9.4% [15]. A cross-sectional study of PD patients ($n = 1948$) receiving care at non-VA National Parkinson Foundation Clinical Centers of Excellence is in line with this estimate showed a 9% prevalence of Diabetes and an overall 36.3% prevalence of “heart/circulation” comorbidities [2]. A similar survey conducted in large national VA PD sample ($n = 14,530$) showed a self-reported prevalence of Diabetes to be much higher (22.3%). Other cardiovascular comorbidities including hypertension (52.96%), Congestive Heart Failure (20.49%), and Angina (25.05%) were common as well [8].

Differences in CVRF burden seen between Veterans and non-Veterans in our study may relate to inter-group differences in innate biological susceptibility (i.e. genetics), patient or provider health behaviors, health-system related factors, or other social determinant of health. Our study did not evaluate genotype differences between groups. Although it is possible that Veterans and non-Veterans with PD have differences in the prevalence of relevant genetic risk alleles (e.g. APO E genotype), there is no existing literature to support this idea. Veterans and non-Veterans in our cohort showed near identical findings in terms of total cortical gray and supratentorial white matter volumes, suggesting that the two study arms do not manifest the typical brain volumetric patterns that would be associated with genetic differences in APOE genotype status [16].

Our cohort did not show any inter-group differences in the use of antihypertensive or cholesterol-lowering medications. There was a non-significant trend towards an increased prevalence of a remote smoking history in Veterans with PD compared to non-Veterans. Veterans also reported a lower level of educational attainment. These factors suggest that differential cardiovascular risks between the groups may be conferred by risk factors that predate the onset of PD symptoms. On the other hand, non-significant elevations in systolic blood pressure and WMHs were both noted in the Veterans patients in our cohort. These factors are causally-linked and are known to associate with poor neurologic outcomes including balance difficulties in older individuals at risk for neurodegeneration [17, 18]. Clinical trial evidence also suggests both may be modifiable using targeted approaches with antihypertensive medications [19, 20].

Veterans manifest cardiovascular disease and the presence of certain CVRFs at higher rates than civilian populations [21–24]. Our study is not able to address the clinical impact of differences in cardiovascular risk factor burden on clinical disease burden in PD. It is certainly possible that differences between Veterans and non-Veterans with PD seen in our study are driven by long-standing common, unalterable differences in genetic or perinatal risk factors for later-in-life atherosclerosis [25–27]. An alternative possibility, however, is that modifiable patient- and provider-related health behaviors may be contributing to differences in CVRF burden. Recent studies in the United Kingdom report that, compared to guideline recommendations, PD patients are under-prescribed statin medications for CVRF modification [28, 29]. Although there are many studies that describe pathological associations between CVRFs and PD disease features [4, 30, 31], there is no direct proof in the form of a clinical trial that CVRF modification will alter disease progression in PD. There is, however, substantial evidence that appropriate CVRF modification alters one's risk for cerebrovascular disease and death [32, 33]. Large scale observational and interventional studies exploring factors associated with CVRF primary prevention heterogeneity in PD may have the potential to reveal modifiable treatment gaps in PD clinical care.

A 2014 National Institutes of Neurological Disorders and Stroke (NINDS) report [34] on PD research priorities emphasized 3 top clinical research priorities: #1) Identifying high-risk prodromal PD subgroups for enrollment in preventative proof-of-concept studies #2) Developing treatments for L-dopa-unresponsive PD features including gait and balance difficulties and #3) characterizing mechanisms that underlie disease heterogeneity in PD. To the degree that each of these goals reflect ongoing priorities among the broader PD research community, developing and trialing interventions to improve the burden of cardiovascular comorbidities among PD patients within the VA Health System may be a large scale goal worth considering. Although multidisciplinary care for PD is universally lauded [35–37], the coordination for such care for patients with chronic health conditions in the United States is generally limited [38]. The VA health system differs from this fractured model in its use of a centralized health care administration, a single electronic medical record, and strong emphasis on delivery of primary and preventative care [39]. Each of these are unique reasons that improving the burden of CVRFs among Veterans using health system-based interventions might be more feasible compared to non-VA PD populations in the US. Similar large scale interventions for treating CVRFs in high risk populations have already been

designed and conducted within the VA health system [40, 41]. Lessons learned from such CVRF-specific trials may also improve the design of future large-scale PD trials.

Our study has several limitations. We lack detailed serologic or biomarker data with which to more precisely assess CVRF burden. An age of 74 was substituted for participants older than 74 in keeping with the range of the Framingham risk score model; it is possible that such a substitution may have impacted inter-group differences even though age distribution was evenly matched between groups. This is a cross-sectional study and cannot meaningfully address questions about disparities in longitudinal disease progression. Our relatively small sample size ($n = 58$) is another limitation. These results would benefit from replication in a larger dataset. Non-Veterans in our cohort also reported a lower rate of falls compared to previous rates reported in other PD fall studies [42]. The possibility of recruitment/selection bias in Veterans and non-Veterans enrolled in this study is important to consider. For example, when we report fewer years of education in Veterans with PD, it is important to note that patients who receive care at the VA Health system, a right earned by virtue of their previous military service, may also theoretically be more likely to lack alternative sources of private insurance that might be used to obtain non-VA care. Because of this, we may be comparing Veterans with PD to a population of PD patients with access to tertiary outpatient referral care and these intergroup differences may simply reflect the influence of socioeconomic status on overall health burden. Another possibility is that Veterans may be more likely to have exposure to environmental risk factors, such as Agent Orange [43], that confer independent risks for PD and cardiovascular risk factors. These limitations linked to the possibility of selection bias are important. The reporting of falls through the use of questionnaires also raises the possibility that recall bias may impact the accuracy of our fall frequency assessment.

Nevertheless, our findings of greater CVRF burden in Veterans with PD mirror clinical impressions observations among those of us who practice clinically both the VA and in an associated University Health System. Regardless of the causal mechanism, we believe these differences between groups to be real, clinically significant, and worthy of further investigation. The long term aim of reducing health disparities in Veterans with PD has potential to improve not only their health state, but may offer meaningful lessons in the design and conduct of future PD clinical trials as well.

Acknowledgments

The authors wish to thank the study participants who contributed their time and effort toward this study.

This work was supported by the Department of Veterans Affairs (grant IK2CX001186) and the NIH (grant numbers P01 NS015655, P50 NS091856, and RO1 NS070856).

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Table 1

Comparison of Clinical and Cardiovascular risk factors between non-Veterans and Veterans with PD

	Non-Veterans with PD	Veterans with PD	<i>t</i> -test/ χ^2 , <i>p</i> -value
	Mean (standard deviation) or Count		
Age	64.2 (6.3)	65.6 (7.1)	<i>t</i> = -0.77, <i>p</i> = 0.446
Motor disease duration	5.6 (3.3)	5.7 (4.2)	<i>t</i> = -0.05, <i>p</i> = 0.959
Gender	M = 29, W = 0	M = 29, W = 0	χ^2 = 0.00, <i>p</i> = 1.00
Systolic Blood Pressure (mm Hg)	120.4 (11.3)	125.8 (14.1)	<i>t</i> = -1.60, <i>p</i> = 0.115
Diabetes	No = 27, Yes = 2	No = 27, Yes = 2	χ^2 = 0.00, <i>p</i> = 1.00
History of Smoking	No = 21, Yes = 7 [<i>n</i> = 28]	No = 13, Yes = 13 [<i>n</i> = 26]	χ^2 = 3.61, <i>p</i> = 0.057
Body Mass Index	27.0 (4.2)	28.8 (4.9)	<i>t</i> = -1.54, <i>p</i> = 0.130
Years of Education	16.7 (2.6)	14.5 (2.5)	<i>t</i> = 3.33, <i>p</i> = 0.002
Montreal Cognitive Assessment	26.2 (2.3)	25.2 (2.9)	<i>t</i> = 1.45, <i>p</i> = 0.153
Use of antihypertensive medications	No = 21, Yes = 8	No = 19, Yes = 10	χ^2 = 0.32, <i>p</i> = 0.570
Use of cholesterol lowering medications	No = 14, Yes = 15	No = 16, Yes = 13	χ^2 = 0.27, <i>p</i> = 0.599
Levodopa Dose Equivalents	682.2 (615.1)	719.8 (520.7)	<i>t</i> = -0.25, <i>p</i> = 0.802
Hoehn & Yahr stage	2.33 (0.49)	2.36 (0.743)	<i>t</i> * = 0.19, <i>p</i> = 0.813
MDS-UDPRS part 1 score (non-motor aspects of daily living)	6.4 (8.0)	6.7 (5.1)	<i>t</i> * = -0.14, <i>p</i> = 0.891
MDS-UDPRS part 2 score (motor aspects of daily living)	7.6 (6.8)	8.6 (6.8)	<i>t</i> = -0.60, <i>p</i> = 0.551
MDS-UDPRS part 3 score (motor exam)	29.2 (16.0)	32.7 (15.0)	<i>t</i> = -0.86, <i>p</i> = 0.394
Self-reported falls	No = 26, Yes = 3	No = 18, Yes = 11	χ^2 = 6.03 , <i>p</i> = 0.014
Striatal DTBZ DVR	1.94 (0.27)	1.89 (0.24) [<i>n</i> = 28]	<i>t</i> = 0.67, <i>p</i> = 0.503
Cortical Gray Matter Volume ratio	0.283 (0.031)	0.283 (0.043)	<i>t</i> = 0.06, <i>p</i> = 0.953
Supratentorial White Matter Volume ratio	0.337 (0.038)	0.337 (0.046)	<i>t</i> = -0.09, <i>p</i> = 0.931
White Matter Hyperintensity burden	8.76×10^{-6} (2.1×10^{-6}) [<i>n</i> = 25]	9.9×10^{-6} (1.9×10^{-6}) [<i>n</i> = 21]	<i>t</i> = -1.97, <i>p</i> = 0.056
10 year Framingham Risk score	20.7% (6.8)	27.3% (11.5)	<i>t</i>* = -2.66, <i>p</i> = 0.011

*t** = Satterthwaite *t*-test due to unequal variances.

Table 2

Multivariable linear regression analyses

Dependent variable	Model Characteristics	(+) Veteran Status	Covariates		
			Age	Disease Duration	Education
Framingham General Cardiovascular Risk Score	F = 13.12 p < 0.0001	t = 2.95, p = 0.005	t = 4.12, p = 0.0001	t = -0.62, p = 0.537	t = 1.00, p = 0.320
Ratio of Framingham score to normalized Framingham score	F = 5.87, p = 0.0002	t = 2.49, p = 0.016	t = -2.24, p = 0.029	t = -0.47, p = 0.641	t = 0.68, p = 0.502
					t = 5.29, p < 0.0001
					t = 4.20, p = 0.0001