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Racial Differences in Parkinson's Disease Medication Use in the Reasons for Geographic and Racial Differences in Stroke Cohort: A Cross-Sectional Study

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Key Words
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Abstract
Background: Previous studies have suggested that African-American populations have a lower prevalence of Parkinson's disease (PD); however, because African-Americans are underrepresented in many cohorts, this relationship is poorly understood. We evaluated data from the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study to describe potential racial differences in PD prevalence. ***Methods:*** We identified subjects using PD medications from the REGARDS study, a national longitudinal cohort study of 30,000 persons over age 45 with approximately equal representation of African-Americans and Whites. ***Results:*** The prevalence of PD medication use across the cohort was 0.78% and was less among African-Americans (0.51%) than among Whites (0.97%; OR 1.90; 95% CI 1.31–2.74). There was an association of gender and PD medication use, with a prevalence of 0.61% in females and 0.97% in males (OR 1.57; 95% CI 1.13–2.18). There was no association with income, education level or geographic region of residence. ***Conclusions:*** The lower rate of PD medication use among African-Americans supports the suspected lower prevalence of PD among African-Americans suggested by other studies. While racial differences in PD diagnosis and treatment may contribute to the differences we observed, comparable disparities have not been observed in the REGARDS cohort for other diagnoses. Further studies of the REGARDS cohort may lead to important insights into potential biological differences in PD among African-Americans and Whites.

Introduction

Parkinson's disease (PD) is a debilitating neurodegenerative disorder that affects more than 4 million individuals over the age of 50 in the most populous nations, and the number of affected individuals is projected to double by the year 2030 [1]. While a small percentage of PD cases is caused by inherited genetic mutations, the overwhelming majority of PD cases are sporadic, with unknown cause [2]. Epidemiological studies have revealed that older age, male gender and environmental factors, such as rural living, are associated with an increased risk of developing PD, while caffeine consumption and smoking may protect against developing PD [3]. Studies have

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Table 1. PD medications used as surrogates for PD diagnosis

Medication	Participants
Amantadine	19
Benztropine	20
Biperiden	1
Bromocriptine	6
Carbidopa/levodopa	96
Carbidopa/levodopa/entacapone	3
Entacapone	8
Pergolide	3
Pramipexole	57
Ropinirole	30
Selegiline	4
Trihexyphenidyl	4

suggested that African and African-American populations have a lower prevalence of PD [4–14]. However, these studies have been limited by small sample size, ascertainment bias in clinic-based samples and possible racial differences in access to medical care [8].

The Reasons for Geographic and Racial Differences in Stroke (REGARDS) study is a national, population-based, longitudinal cohort study designed to follow 30,000 participants for the possible development of stroke [15]. The study was designed to enroll equal numbers of Whites and African-Americans. Because of the population-based selection process and balanced racial representation, this cohort is ideal for evaluating possible racial differences in the prevalence of PD among the general population.

The clinical diagnosis of PD requires careful evaluation of patient history and physical findings by a skilled examiner. However, direct clinical evaluation is impractical in a cohort as large as REGARDS; instead, we employed the use of PD medications as a surrogate measure. We describe differences in race, age and gender between study participants taking PD medications and those who are not.

Methods

Data from the ongoing National Institute of Neurological Disorders and Stroke-sponsored REGARDS study were used to estimate the rate of PD medication use in African-American and white populations. The REGARDS study [15] is designed to address the causes for increased stroke mortality among African-Americans and in the Southeastern US. Since January 2003, potential participants in this study were randomly selected from a commercially available national list. Data in this report are from participants enrolled and evaluated from January 2003 through May 2007, at which time approximately 27,731 persons over age 45 were available for analysis. The goals of enrollment included approximately equal representation of African-Americans and Whites and of males and females. In addition, recruitment was directed regionally in order to obtain 50% of participants from the 'Stroke Belt' (Alabama, Arkansas, Georgia, Louisiana, Mississippi, North Carolina, South Carolina and Tennessee) and the remaining 50% from the other lower 48 states. The institutional review boards of participating institutions approved the study protocol.

For willing participants, an initial telephone interview was used to obtain demographic information, medical history, cognitive function indices and measures of quality of life. After obtaining formal written consent, an in-home examination was performed to obtain blood pressure, blood and urine samples, electrocardiography, diet, residential history, and a direct inventory of current medications taken in the previous 2 weeks. These medications were coded into generic names by a team of pharmacists. From these inventories, we identified medications used primarily for PD (table 1). Those study participants that were on at least 1 of these defined medications were identified as subjects taking PD medications in order to calculate the prevalence of PD medication use. Since the REGARDS study collects only the names of medications, not dosing, use of PD medications was considered a dichotomous variable. We identified a subset of these subjects who were taking either carbidopa/levodopa and/or entacapone to confirm our initial findings with a list of PD medications less likely to be used for other medical indications.

In addition to race (African-American or white), other potential risk factors in the analysis included geographic region (classified by US Census coding into northeast, south, midwest and west), urban/rural status of the participant's residence [classified by US Census track as urban (>75% urban), rural (<25% urban) or mixed (25–75% urban)], smoking (current, past or never), sex (male or female), education (less than high school graduation, high school graduate, some college or technical school, or college graduate) and income (USD <20,000, 20,000–35,000, 35,000–75,000 or >75,000).

The prevalence of PD medication use was computed with exact 95% confidence limits. The association of risk factors and PD medication use was assessed both univariately and multivariably using logistic regression. The multivariable analysis included a saturated model (all predictor variables), and the most parsimonious model was selected using backward stepwise analysis.

In order to provide evidence that the PD medication use is a reasonable surrogate for prevalent Parkinson's disease, we examined the association between PD medication use and self-reported falls. Falls were defined as a positive response to the question: 'During the last year, have you had a fall? Do not include falls during skiing, skating, or other activities that may affect balance.'

Results

As of June 2007, there were 24,424 REGARDS participants with medication history forms available for the analysis, with baseline characteristics described in table 2; 41.7% were African-Americans and 54.1% were fe-

Table 2. Characteristics of participant population and association of risk factors with prevalence of PD medication use

		Population		Univariate analysis						Full multivariable model				Reduced multivariable model			
		n	%	patients on treatment	prevalence	OR	lower 95%	upper 95%	p value	OR	lower 95%	upper 95%	p value	OR	lower 95%	upper 95%	p value
Race	black	10,123	41.7	52	0.51	1.00	(ref)	(ref)	<0.0001	1.00	(ref)	(ref)	0.0007	1.00	(ref)	(ref)	0.0013
	white	14,242	58.3	138	0.97	1.91	1.38	2.62		1.90	1.31	2.74		1.70	1.23	2.34	
Sex	female	13,224	54.1	81	0.61	1.00	(ref)	(ref)	0.0014	1.00	(ref)	(ref)	0.0066	1.00	(ref)	(ref)	0.014
	male	11,196	45.9	109	0.97	1.60	1.20	2.13		1.57	1.13	2.18		1.44	1.08	1.93	
Age	45–54 years	2,447	10.0	11	0.45	1.00	(ref)	(ref)	0.0006	1.00	(ref)	(ref)	0.12	1.00	(ref)	(ref)	<0.018
	55–64 years	9,499	38.9	54	0.57	1.27	0.66	2.43		1.28	0.63	2.62		1.14	0.59	2.19	
	65–74 years	8,140	33.3	74	0.91	2.03	1.08	3.84		1.71	0.84	3.50		1.65	0.87	3.12	
	75–84 years	3,842	15.7	45	1.17	2.63	1.36	5.08		2.18	1.02	4.64		2.08	1.07	4.04	
	≥85 years	484	2.0	6	1.24	2.78	1.02	7.55		1.76	0.53	5.88		2.23	0.82	6.06	
Region	northeast	1,940	7.9	16	0.82	1.00	(ref)	(ref)	0.98	1.00	(ref)	(ref)	0.74				
	south	16,250	66.5	128	0.79	0.96	0.57	1.61		0.84	0.49	1.42					
	midwest	4,323	17.7	32	0.74	0.90	0.49	1.64		0.70	0.37	1.32					
	west	1,911	7.8	14	0.73	0.89	0.43	1.82		0.83	0.40	1.75					
Urban/ rural	rural	4,508	18.5	41	0.91	1.00	(ref)	(ref)	0.52	1.00	(ref)	(ref)	0.65				
	mixed	2,282	9.3	16	0.70	0.77	0.43	1.37		0.75	0.40	1.39					
	urban	17,634	72.2	133	0.75	0.83	0.58	1.18		0.94	0.64	1.38					
Smoking	never	10,746	44.2	78	0.73	1.00	(ref)	(ref)	0.73	1.00	(ref)	(ref)	0.59				
	past	10,037	41.3	80	0.80	1.10	0.80	1.50		1.02	0.72	1.43					
	current	3,548	14.6	30	0.85	1.17	0.76	1.78		1.26	0.79	2.02					
Education	LT HS	3,212	13.2	25	0.78	1.00	(ref)	(ref)	0.98	1.00	(ref)	(ref)	0.98				
	HS graduate	6,394	26.2	51	0.80	1.03	0.63	1.66		1.06	0.62	1.80					
	some college	6,517	26.7	48	0.74	0.95	0.58	1.54		1.01	0.58	1.74					
	college graduate	8,279	33.9	65	0.79	1.01	0.64	1.60		0.96	0.54	1.69					
Income USD	<20,000	4,625	21.5	35	0.76	1.00	(ref)	(ref)	0.41	1.00	(ref)	(ref)	0.39				
	20,000–35,000	6,075	28.3	57	0.94	1.24	0.81	1.90		1.02	0.66	1.58					
	35,000–75,000	7,179	33.4	55	0.77	1.01	0.66	1.55		0.79	0.48	1.27					
	≥75,000	3,601	16.8	23	0.64	0.84	0.50	1.43		0.67	0.36	1.25					
Health insurance	no	1,512	6.2	1	0.07	1.00	(ref)	(ref)	0.0011	1.00	(ref)	(ref)	0.031	1.00	(ref)	(ref)	0.032
	yes	22,891	93.8	189	0.83	12.58	1.76	89.94		8.79	1.21	63.70		8.67	1.21	62.35	

ref = Reference; LT HS = less than high school.

males. The average (±SD) age of the cohort was 65.8 ± 9.2 years. Nearly 94% of the participants reported having some form of health insurance.

Of these participants, 190 (0.78%; 95% CI 0.67–0.90) were identified as taking at least 1 PD medication identified in table 1. PD medication use was more frequent in Whites (0.97%) compared with African-Americans (0.51%; $p < 0.0001$) and in men (0.97%) compared with women (0.61%; $p = 0.0014$; table 2). PD medication use also increased with age, from a prevalence of 0.45% for those participants aged 45–54 to 1.24% for those aged ≥85 years ($p = 0.0006$). The small group without health insurance (6.2% of the cohort) was less likely to be taking PD medications (0.07%) compared with those with some form of insurance (0.83%; $p = 0.0011$). There appeared to be no differences in PD medication use by regional distribution, urban/rural status, smoking, education or income ($p > 0.05$; table 2).

Race, sex and insurance status remained significant in a full multivariable model. There was little change in the magnitude of their association with PD medication use in the reduced model, in which variables present were race, gender, age and insurance status (table 2). The odds of PD medication use was 1.90 (95% CI 1.31–2.74) times greater for Whites than for African-Americans and 1.57 (95% CI 1.13–2.18) times greater for men than for women. Age remained significant in the reduced model, with a monotonically increasing odds of PD medication use as age increased relative to ages 45–54 (OR 2.23 for age ≥85 years; 95% CI 0.82–6.06). Factors with little evidence of an association with PD medication use in univariate analysis were not associated in multivariable analysis either.

There was an association between PD medication use and the likelihood of a fall, with 32.1% of those on PD medications reporting a fall, as compared with only 15.5% of those not on PD medications ($p < 0.0001$). This difference remained significant in logistic regression analysis adjusting for age, race and sex (OR 2.61; 95% CI 1.92–3.56; $p < 0.0001$). Poisson regression analysis estimated a 29% (95% CI 17–41) increase in the number of falls for those participants on PD medications, a difference that was somewhat mediated to a 20% increase (95% CI 8–33) by adjusting for age, race and sex.

Interaction terms were employed to assess the potential that race could be acting as an effect modifier. There was little evidence of a differential association of race by sex ($p = 0.99$), age ($p = 0.62$), smoking ($p = 0.22$), urban/rural status ($p = 0.59$), geographic region ($p = 0.92$), income ($p = 0.28$), education ($p = 0.64$) or insurance status ($p = 0.98$).

Because some of the PD medications listed in table 1 can be used less frequently for other medical indications, we limited our initial list of PD medications to those more specific for PD – carbidopa, levodopa and entacapone – and repeated our analysis. This reanalysis confirmed our initial results, showing that race, sex and age were still associated with the use of this medication subset (data not shown).

Discussion

The REGARDS study provides a large, well-characterized cohort in which to examine the role of demographic and environmental risk factors in developing PD. Because of nearly equal representation of African-Americans and Whites, the REGARDS study is particularly well suited to examine racial differences in disease prevalence. We found a very large difference in the rate of PD medication use in Whites as compared with African-Americans. Older age and male gender have been previously described as risk factors for PD [4, 9, 16] and were associated with increased PD medication use. There was no evidence that the effects of age, gender or health insurance status were different between African-Americans and Whites.

The first study to describe a reduced prevalence of PD in African-Americans was based on discharge diagnoses of patients from all Baltimore hospitals between 1965 and 1967 [11] and was confirmed in a follow-up study in which PD cases were tracked through community physicians [12]. Subsequent studies based on reviews of hospital or outpatient records [4, 7, 9] or on US mortality data [17] reached similar conclusions, but all of these are potentially subject to ascertainment and diagnostic bias: racial differences in access to and use of medical care are well described [18], and PD is underdiagnosed in general and, in particular, among African-Americans [5, 6].

The advantage of our study is that it is community-based and includes a geographically dispersed population with nearly 100% health insurance coverage (due to the large proportion over age 65). Study participants were selected from a commercially available national list, which is widely accepted as an excellent sampling frame [19]. The only prior study with a comparable community-based population examined the households in Copiah County, Mississippi, using questionnaires about PD symptomatology, followed by neurological examination [6]. This study did not find racial differences in the combined rates of possible and definite PD but did see higher rates of definite PD among Whites. The geographic region studied was small and may have been affected by environmental factors specific to that region. Most other studies evaluating the role of race in PD prevalence have also used patient groups limited in geographic distribution.

The main limitation of our study is our reliance on the use of PD medications as a surrogate for a clinical PD diagnosis, which itself could introduce ascertainment or diagnostic bias. Several observations suggest that this is a valid surrogate approach. Rates for PD medication use determined by pharmacy record review have been found to be comparable with rates for PD prevalence [20]. Our observation that well-established risk factors for PD, such as male gender and older age, were associated with PD medication use supports the value of this surrogate measure in the REGARDS cohort. We also noted an association between PD medication use and the likelihood of falls. Although likelihood of falls is increased in PD, we acknowledge that fall risk is not specific for the disorder. The group of PD medication users could also contain some patients who take these medications for other indications, such as tardive syndromes or restless leg syndrome. Because such alternative uses may have confounded our results, we repeated our analysis while limiting our PD medication list to carbidopa, levodopa and/or entacapone, 3 medications more specific for PD. This reanalysis confirmed our results based on the broader PD medication list.

Differences in access to medical care could result in lower recognition and treatment of PD among African-Americans, and differences among medical practitioners

could result in less frequent prescribing of medical treatment in African-Americans after they are diagnosed with PD [18]. While there may be discrepancies between African-Americans and Whites in terms of access to medical care and use of prescribed medications [18, 21], a prior study of hypertension among the REGARDS cohort showed that the African-American participants are more likely to be aware of and treated for hypertension [22]. In the present study, 91% of African-Americans had insurance, while 96% of Whites had insurance. Adjustment for socioeconomic factors, health insurance, income or educational level had little impact on the estimated racial differences in PD medication use. Thus, while we cannot entirely exclude the possibility that PD is inadequately diagnosed or treated among African-Americans, there are substantial reasons to believe that these possible confounders alone do not account for the observed strong influence of race on the prevalence of PD medication use, and our data support the view that underlying biological differences may have a central role.

Since PD is primarily a disease of the elderly, lower survival rates of African-Americans compared with Whites have also been cited as potential factors for observed racial differences in PD prevalence [8, 23]. However, we showed little evidence of a differential in the magnitude of the excess of PD medication use among white participants across the age strata.

The REGARDS cohort is uniquely suited to examine the effect of race on the occurrence and progression of PD. The REGARDS design incorporates banking of biological materials that can facilitate studies of genetic and biological risk factors. The longitudinal nature of REGARDS will also facilitate the assessment of PD incidence as well as prevalence. To pursue these goals, it will be important to identify the presence of PD in this population more directly, by employing direct assessment methods such as telephone instruments to identify Parkinsonism, more extensive review of subject medical records beyond those currently accessible in the REGARDS database, and direct physical examination of subsets of the cohort.

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