Ethnic Variation in the Manifestation of Parkinson’s Disease: A Narrative Review

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Abstract. The global prevalence of Parkinson’s disease is increasing, yet the characteristics, risk factors and genetics of PD in Black, Asian and Hispanic populations is little understood. In this paper we review the published literature on clinical variation in the symptoms and signs of Parkinson’s disease in different ethnic groups and responses to treatment. We included any study that sampled patients with Parkinson’s disease from distinct ethnic backgrounds. We conclude that whilst there is little published evidence for ethnic variation in the clinical features of Parkinson’s disease, there are substantial limitations and gaps in the current literature, which mean that the evidence does necessarily not fit with clinical observation. Possible explanations for expected differences in manifestation include genetic determinants, the co-existence of cerebrovascular disease and/or Alzheimer’s disease pathology, healthcare inequalities and socio-cultural factors.

Keywords: Parkinson’s disease, ethnic groups, epidemiology, tremor, dementia, atypical parkinsonism

INTRODUCTION

Health inequalities related to ethnicity are well recognized in clinical medicine and healthcare settings, and persist in the current era. Much of our understanding of chronic disease comes from the clinical study of White patient groups. Revolutionary advances in population-level genetics and molecular biology have not been met with similar revolution in inclusivity in research, contributing to enduring health inequalities. Ethnic inequality in inclusion in genome wide association studies is particularly stark [1]. The Parkinson’s disease (PD) research community has colluded. The global prevalence of PD doubled between 1990 and 2016 and is projected to double again over a similar interval; making PD the fastest growing neurological disorder [2, 3]. For a global phenomenon, little is understood about differing manifestations of PD in different ethnicities, including issues around diagnosis and response to treatment. Most published PD research comes from the USA and Europe, and study of mainly White subjects. Even in this group the clinical features and speed of deterioration are highly heterogenous. Attempts to disentangle heterogeneity have led to subtyping PD patients by age of onset, motor symptoms, non-motor symptoms, rate of progression, genetics and combinations of these factors [4–13].

Clinical experience and emerging evidence suggest that ethnicity is a further key determinant of heterogeneity, with differences in epidemiology, clinical manifestations and mortality observed. However, variation by ethnicity is still far from being
understood, and the studies to date report apparently contradictory findings. This review aims to summarise the evidence thus far, and outline the key directions for future research.

SEARCH STRATEGY

The Medline database (Pubmed) was searched for all articles up to April 2019. The search string included the following terms: “Parkinson’s”, “ethnicity”, “ethnic”, “race” and “racial”. We excluded any studies that identified patients based on genotype alone or the presence of a particular symptom (e.g., PD patients with REM sleep behaviour disorder). When mono-ethnic studies were reviewed the search string included the term “Parkinson’s” followed by terms related to the specific area we were searching for. For example, when searching for mono-ethnic studies that measured motor subtype in PD samples we searched for the terms; “type”, “sub-type”, “sub-type”, “sub-type”, “motor”, “postural instability”, “rigid akinesia”, “rigid-akinetic”, “rigid-akinesia”, “rigid akinesia”, “tremor-dominant” and “tremor dominant”. We also reviewed the references of these articles to identify any other relevant articles that may have been missed. Two papers were excluded that were not written in English and had no translation available, but these were mono-ethnic studies in small samples so are unlikely to substantially alter the conclusions of this article.

EPIDEMIOLOGY OF PD

The prevalence of PD appears to vary geographically [14]. The main risk factor for PD is increasing age meaning that geographical regions with older populations and higher life expectancy tend to have a higher prevalence of PD [14, 15]. However, geographic differences persist even when controlling for these factors, which suggests that ascertainment, genetic factors and competing morbidity may be important determinants [16–18]. Most studies report the highest prevalence of PD in White populations (for example 1,671.63/100,000, compared with 1,036.41/100,000 in Blacks, and 1,138.56/100,000 in Asians) [19, 20]. Geographical location is a stronger determinant of PD risk than ethnicity. The prevalence of PD in Black-Africans residing in sub-Saharan Africa (40/100,000) is much lower than the prevalence of PD amongst people of African origin living in the USA [18]. It is interesting to note that in the only published neuropathological study comparing neurologically normal White British and Black Nigerian brains a similar prevalence of incidental Lewy body disease at autopsy was found. Although these participants were not age-matched the mean age of Nigerian brains in the study was 68.8 years and the prevalence of Lewy bodies was 5.3%. The prevalence of Lewy bodies in 70–79 year olds in Europe and North America was found to be 4.7%. [21, 22]. Extrapolating from this it implies that at least some of the observed differences in the prevalence of PD might be related to case ascertainment.

MORTALITY

Several studies have reported ethnicity to be a predictor of mortality in PD. Black patients tend to have a slightly higher risk of death than White patients and this finding has been replicated across several studies [23–26]. When comparing mortality occurring after hip and pelvic fractures in PD patients Black patients also have a higher adjusted hazard ratio of mortality (HR 1.12; 95% CI 1.09–1.16), whereas rates may be lower in Hispanic patients (HR 0.87; 95% CI 0.81–0.95) [27]. In general, compared to White patients, Hispanic patients have a lower risk of death (HR 0.72; 95% CI 0.65–0.80) and the same may be true of Asian patients (HR 0.86; 95% CI 0.82–0.91) [23]. However, other studies have found contrasting results [28, 29]. This is in contrast to Alzheimer’s disease (AD) where White patients have a shorter length of survival from diagnosis (median 3.1 years) compared to Black and Hispanic patients with AD (3.7 and 4.1 years respectively) [30].

ETHNIC VARIATION IN THE MOTOR SYMPTOMS OF PD

The first reports of an atypical Parkinsonian phenotype in Black populations were from the French Antilles. It was noted that most patients had a bradykinesia-dominant disease with reduced response to levodopa and earlier dementia [31–33]. Although there is some evidence to suggest Guadeloupean-Parkinsonism may be a distinct clinico-pathological entity, Chaudhuri et al. reported an increase in atypical features (levodopa hypo-responsiveness and bradykinesia-dominant) of
Table 1 shows the proportions of each motor subtype where the motor subtype was determined in de novo PD cases [11, 28, 37–68]. It is clear that the prevalence of each motor subtype varies between studies, but it is difficult to determine patterns or correlations from these data. This is in part due to a lack of a standardised methodology for determining motor subtype and differing inclusion/exclusion criteria which confound attempts to interpret the data in a meaningful way.

There may be ethnic variation in the motor complications of PD treatment. Dyskinesia and ‘wearing off’ have been extensively studied in PD patients from North America and Europe, but research on this topic is patchy in other regions of the world, especially in multi-ethnic cohorts. Asian patients appear most likely to experience dyskinesia and as
a consequence lower doses of dopaminergic drugs are often recommended [35, 69]. In an international survey Japanese physicians reported the lowest prevalence of dyskinesia in their patients. However, they were also the least likely to use levodopa monotherapy, preferring a combination of dopamine agonists and levodopa, which could be a contributing factor [70].

ETHNIC VARIATION IN NON-MOTOR SYMPTOMS OF PD

In the past two decades, there has been significant progress in the understanding of the non-motor manifestations of PD [71]. However, there remains relatively few studies that compare non-motor symptom prevalence in ethnically diverse samples. The Non-Motor Symptom Questionnaire was designed and validated in 2006 and has been used in different populations to enable comparison (see Table 2) [72–84]. All patients, regardless of ethnicity, appear to suffer from a high burden of non-motor symptoms. It is notable in Table 2 that the prevalence of gastrointestinal non-motor symptoms appear to be highest in the East Asian studies [73, 81]. The prevalence of depression was above 60% in the Chinese, Korean, Mexican and Peruvian studies [73, 77, 80, 81], but in the studies from the UK and the USA the rate was less than 40% [82, 84]. A study comparing mood and anxiety symptoms in a multi-ethnic sample found no clear differences [85].

Excessive daytime sleepiness may be more common in PD patients from Europe and North America. Studies in Asian countries suggest a prevalence in the range of 15–32% of patients [86–89]. Whereas studies in North America and Europe suggest a prevalence of EDS between 41–57% [90–95].

Impulse control behaviours (ICB) in PD are an important complication of dopaminergic replacement therapy (particularly dopamine agonists). It is not currently clear whether certain ethnicities are more prone to ICBs, but there may be differences in the most common impulsive behaviours in different regions that could be culturally driven as demonstrated in Table 3 [96–116]. Some of the ICBs that are reported in the literature seem to be exclusive to particular cultures, for example, Otmani et al., report an “ICB mimic” that had not been reported in the literature before; excessive Qur’an reading [103].

ETHNIC VARIATION IN COGNITION IN PD

Cognitive impairment is one of the most frequent and disabling non-motor symptoms of PD [117]. The typical cognitive domains affected by PD dementia are visuospatial, executive and attention, but there can be global deficits, particularly in advanced disease. Cognitive dysfunction frequently occurs in combination with neuropsychiatric features including depression, anxiety, hallucinations and apathy, which are major determinants of morbidity [118]. The presence of cognitive impairment with a diagnosis of PD is established as a significant indicator of increased mortality [119–121].

There is evidence that Black patients with PD have higher rates of cognitive decline and progression to dementia than other ethnic groups. Chaudhuri et al. first noticed this in 2000 in London’s Black population [34] and this observation has since been substantiated by large-scale health record studies. A retrospective cohort study using the Medicare database followed up all patients with incident PD in 2002 over a six-year period (n = 138,728). 70% of the whole sample was diagnosed with dementia by the end of the study, and the proportion was highest in Black patients [23]. Black PD patients also have higher odds of being prescribed dementia medications (OR 1.33, 95% CI 1.28–1.38) compared with White PD patients which may reflect increased cognitive dysfunction [122]. Overall, unlike the inconsistencies of other non-motor and motor symptoms, current evidence supports the notion that Black patients are more at risk of dementia and cognitive impairment than White patients.

Similar findings have been observed for Hispanic patients in some settings [23]. Hispanic patients may have a more severe form of PD dementia and/or an increased severity of behavioural and psychological symptoms in dementia [122]. The evidence regarding Asian PD patients and cognitive dysfunction is more conflicting. Willis et al. found in their 6-year retrospective cohort study that Asian patients had the lowest odds of being diagnosed with dementia during the study period (OR 0.89, 95% CI 0.79–0.99) [23]. But Asian PD patients report higher levels of subjective cognitive impairment than White patients [35]. It remains to be determined whether Asian patients suffer from different rates of cognitive dysfunction compared to other ethnicities. This is particularly true for South Asian populations that have largely been unstudied.
| Study                  | Year | Country | Total study participants | Mean years since diagnosis | Drooling (%) | Anosmia (%) | Dysphagia (%) | N&V (%) | Constipation (%) | Fecal incontinence (%) | Urinary urgency (%) | Nocturia (%) | Pain (%) | Weight change (%) | Memory problems (%) | Apathy (%) | Hallucinations (%) | Concentration problems (%) | Depression (%) | Anxiety (%) | Change in sexual interest (%) | Sexual dysfunction (%) | OH (%) | Falls (%) | EDS (%) | Insomnia (%) | Intense dreaming (%) | RBD (%) | Restless legs (%) | Leg swelling (%) | Hyperhidrosis (%) | Dyskinesia (%) | Dementia (%) |
|-----------------------|------|---------|--------------------------|----------------------------|--------------|-------------|---------------|---------|-----------------|-----------------------|---------------------|--------------|----------|-----------------|-----------------------|----------|-----------------|--------------------------|-----------------|-----------|---------------------|----------------------|------|---------|--------|------------|---------------------|--------|--------------------|----------------------|-----------------|-----------|------------|--------|------------|---------------------|--------|--------------------|----------------------|-----------------|-----------|------------|--------|------------|
| Duncan                | 2014 | UK      | 158                      | 0.5                        | 56           | 58          | 56            | 27      | 29              | 54                    | 27                  | 29           | 42       | 18              | 29                    | 27       | 29              | 42                       | 18               | 21       | 25                  | 36               | 47     | 12      | 15     | 1          |
| Romenets              | 2012 | USA     | 70                       | 3.8                        | 27           | 21          | 16            | 16      | 30              | 7                     | 41                   | 59           | 68       | 30              | 42                    | 29       | 12              | 39                       | 38               | 36       | 10                  | 41               | 34      | 38     | 47     | 12        | 19               | 15     | 1                | 1            | 1                |           | 1            | 1          |
| Hui-juan Li           | 2015 | China   | 82                       | 5.1                        | 44           | 45          | 33            | 22      | 67              | 2                    | 44                   | 55           | 87       | 48              | 29                    | 95       | 72              | 15                       | 33               | 67       | 61                  | 49               | 50      | 38     | 73     | 76        | 65               | 39     | 42                |             |                  |           |             |            |
| Cosentino             | 2013 | Peru    | 300                      | 5.8                        | 37           | 36          | 22            | 14      | 56              | 7                    | 41                   | 66           | 77       | 51              | 53                    | 61       | 44              | 20                       | 50               | 81       | 61                  | 55               | 46      | 48     | 30     | 33        | 48               | 33     | 36                |             |                  |           |             |            |
| Khedr                 | 2013 | Egypt   | 112                      | 6.2                        | 30           | 10          | 24            | 11      | 52              | 5                    | 16                   | 55           | 60       | 44              | 33                    | 30       | 38              | 13                       | 42               | 47       | 61                  | 46               | 43      | 54     | 39     | 39        | 46               | 19     | 15                |             |                  |           |             |            |
| Cheon                 | 2008 | S Korea | 74                       | 6.4                        | 32           | 28          | 31            | 23      | 66              | 5                    | 39                   | 55           | 68       | 49              | 35                    | 61       | 53              | 18                       | 51               | 65       | 48                  | 35               | 37      | 64     | 38     | 26        | 56               | 40     | 35                |             |                  |           |             |            |
| Rodriguez-Violante    | 2011 | Mexico  | 232                      | 6.6                        | 25           | 34          | 33            | 6       | 58              | 10                   | 38                   | 60           | 62       | 84              | 28                    | 47       | 34              | 19                       | 39               | 67       | 45                  | 37               | 37      | 46     | 36     | 28        | 47               | 33     | 47                |             |                  |           |             |            |
| Martinez-martin       | 2007 | International | 545                  | 7.1                        | 42           | 29          | 28            | 14      | 53              | 8                    | 30                   | 56           | 62       | 29              | 18                    | 45       | 35              | 23                       | 46               | 50       | 45                  | 34               | 32      | 28     | 28     | 31        | 46               | 34     | 36                |             |                  |           |             |            |
| Tanveer               | 2018 | Pakistan| 97                       | 7                          | 37           | 26          | 28            | 40      | 24              | 26                    | 62                   | 77           | 47          | 38       | 59           | 42                    | 30       | 35              | 52                       | 40               | -         | -                  | -               | -       | -      | -      | -          | -                 | -      | -                 |             |                  |           |             |            |
| Bostantjopoulou       | 2013 | Greece  | 166                      | 7.1                        | 19           | 26          | 14            | 11      | 46              | 1                    | 24                   | 54           | 52         | 18            | 31         | 13           | 2                    | 17               | 42       | 38                       | 37               | 33      | 28       | 8       | 9         | 26               | 33     | 27                | 29            | 18           | 21       | 11      | 2        |
| Chaudhuri             | 2010 | UK, Germany, Spain | 242                  | 8                          | 42           | 43          | 27            | 16      | 48              | 6                    | 27                   | 60           | 65       | 46              | 23                    | 51       | 34              | 17                       | 50               | 49       | 42                  | 37               | 34      | 39     | 29     | 35        | 47               | 35     | 39                |             |                  |           |             |            |
| Mukhtar               | 2018 | Pakistan| 85                       | -                          | 28           | 29          | 17            | 10      | 56              | 6                    | 11                   | 35           | 49         | 30            | 20                    | 45       | 29              | 8                       | 16               | 47       | 36                  | 30               | 30      | 40     | 19      | 13        | 29               | 22     | 11                |             |                  |           |             |            |

N&V, nausea and vomiting; OH, orthostatic hypotension; EDS, excessive daytime sleepiness; RBD, REM sleep behaviour disorder. Any data that was not available is replaced with a dash.
Table 3

| Study                  | Year | Country                      | Total study participants | ICB present (%) | DA prescribed (%) | Hypersexuality (%) | Punding (%) | Hobbyism (%) | Excessive spending (%) | Gambling (%) | Excessive eating (%) | Excessive use (DDS) (%) | Excessive internet use (%) | Walkabout (%) |
|------------------------|------|------------------------------|--------------------------|----------------|------------------|-------------------|-------------|--------------|----------------------|--------------|----------------------|--------------------------|---------------------------|-----------------|
| Fan                    | 2009 | China                        | 312                      | 3.53           | 45.8             | 54.5              | –           | –            | –                    | 9.1          | 9.1                  | 18.2                     | 9.1                       | –               |
| Kenangil               | 2010 | Turkey                       | 554                      | 5.9            | –                | 42.0              | 57.0        | –            | –                    | 24.0         | 12.1                 | 27.0                     | 21.0                      | –               |
| Poletti                | 2013 | Italy                        | 805                      | 8.1            | 49.8             | 36.9              | 3.1         | –            | –                    | 12.3         | 40.0                 | 29.2                     | 3.1                       | –               |
| Weintraub              | 2010 | USA                          | 3090                     | 13.6           | 66               | 25.7              | –           | –            | –                    | 42.1         | 36.7                 | 31.4                     | –                         | –               |
| Callesen               | 2014 | Denmark                      | 490                      | 35.9           | –                | 25.0              | 30.1        | 46.5         | 19.8                 | 23.9         | 19.2                 | –                        | 14.2                      | –               |
| Valenca                | 2013 | Brazil                       | 152                      | 18.4           | 25.6             | 64.3              | –           | 57.1         | 7.1                  | 42.9         | –                    | –                        | –                         | –               |
| Corvol                 | 2018 | France                       | 426                      | 19.7           | 73.5             | 43.1              | –           | 23.3         | 19.8                 | 53.3         | –                    | –                        | –                         | –               |
| Perez-Lloret           | 2012 | France                       | 203                      | 25.0           | 79.3             | 39.8              | –           | 23.9         | 11.9                 | 55.7         | –                    | –                        | –                         | –               |
| Rodriguez-violante     | 2014 | Mexico                       | 450                      | 25.7           | 57.3             | 11.7              | *55.8       | 11.7        | 5.2                  | 33.8         | –                    | –                        | –                         | –               |
| Ramirez Gomez          | 2017 | Argentina, Colombia, Ecuador | 255                      | 27.5           | 77.2             | 35.7              | 20.0        | 1.4          | 14.3                 | 17.1         | 47.1                 | –                        | –                         | –               |
| Joutsa                 | 2012 | Finland                      | 575                      | 27.7           | 74.9             | 64.6              | 45.3        | 65.1         | 28.6                 | 25.0         | 33.3                 | –                        | –                         | –               |
| Antonini               | 2017 | Italy                        | 1095                     | 29.1           | 78                | 34.0              | 14.1        | 44.8        | 22.6                 | 18.6         | 34.6                 | 16.7                     | –                         | –               |
| Erga                   | 2017 | Norway                       | 125                      | 30.4           | 62.4             | 31.6              | 34.2        | –           | 7.9                  | –                         | –                     | –                         | –               |
| Zhang                  | 2017 | China                        | 142                      | 31.0           | 49.3             | 9.0               | 26.7        | 20.3        | 15.8                 | 22.6         | 18.1                 | 36.5                     | –                         | –               |
| Garcia-Ruiz            | 2014 | Spain                        | 233                      | 39.1           | 100               | 30.8              | 31.9        | 49.5        | 17.6                 | 9.9          | 6.6                  | 7.7                       | –                         | –               |
| Sharma                 | 2015 | India                        | 299                      | 42.8           | 81.9             | 25.8              | 29.0        | 22.0        | 19.6                 | 7.7          | 12.5                 | 18.0                     | –                         | –               |
| Kishore                | 2013 | India                        | 305                      | 31.5           | 49                | 16.0              | 50.0        | –           | 26.0                 | 14.6         | 25.0                 | 10.4                     | –                         | –               |
| Otmani H               | 2019 | Morocco                      | 125                      | 28.0           | –                | 28.6              | *40.0       | *40.0       | 34.3                 | 11.4         | 25.7                 | 0.0                       | –                         | –               |
| Giladi                 | 2007 | Israel                       | 193                      | 14.0           | 59.6             | 63.0              | –           | 22.2        | 22.2                 | 25.9         | 0.0                  | –                        | –                         | –               |
| Chiang                 | 2012 | Taiwan                       | 268                      | 5.6            | –                | 53.3              | –           | –           | 26.7                 | 6.7          | 13.3                 | –                        | –                         | –               |
| Wang                   | 2016 | China                        | 217                      | 4.2            | 46.5             | 44.4              | –           | 11.1        | 33.3                 | 11.1         | –                    | –                        | –                         | –               |
| Lee                    | 2009 | South Korea                  | 1167                     | 10.1           | 72.8             | 28.0              | 41.5        | –           | 24.6                 | 12.7         | 33.9                 | –                        | –                         | –               |

*refers to a study which has counted hobbyism and punding as the same sub-type of ICB. Percentages represent No. of patients with that particular ICB divided by total number of patients with ICB. ICB, impulse control behaviour; DA, dopamine agonist; DDS, dopamine dysregulation syndrome. Where data was not reported/recorded in the articles they have been replaced with a dash.

CONTRIBUTORS TO ETHNIC VARIATION IN PD

Biological

Genetic factors

The commonest monogenic forms of PD are caused by mutations in genes such as LRRK2, PARK2, SNCA and DJ-1 [123]. They are associated with different phenotypes and their prevalence differs in different ethnic groups [124, 125]. For example, LRRK2 p.G2019S is the most common genetic cause of PD worldwide and accounts for 1% of sporadic PD and 4% of familial PD [126]. However the prevalence of LRRK2 p.G2019S is 30–39% in North African Berbers with PD and 26% in Ashkenazi Jewish PD cases, yet it seems to be completely absent in Nigerian PD patients [127–129].

Given their rarity, little is known about ethnic variation in the main recessive causes of PD such as parkin and DJI, but a variant of PINK1 is known to have a higher carrier frequency in Filipinos [130]. It is important to note that spinocerebellar ataxia type 3 can present in Black patients with parkinsonism and levodopa responsiveness that can be clinically identical to idiopathic PD [131].

Variation in the GBA gene is associated with an increase in the risk of PD and a reduction in the age of onset of PD in patients who carry risk variants [132, 133]. The prevalence and penetrance of GBA mutations varies by ethnicity. For example, the GBA variants 84insGG and R496H increase risk of PD exclusively in Ashkenazi Jewish populations [134].

Common genetic variants with small independent associations with PD are identified through genome-wide association studies (GWAS). The largest PD
GWAS (37,700 PD cases and 1.4 million controls) was recently conducted in PD patients of European ancestry [135]. Two GWASes have been conducted with Asian PD patients; the first in 2017 with 5,125 PD cases and 17,604 controls in Singapore, Hong Kong, Malaysia, Korea, mainland China and Taiwan [136]. A smaller PD GWAS was performed in Japan (2,011 PD cases and 18,381 controls) in 2009 [137]. We are not aware of any multi-ethnic GWAS and this is a priority area for further research [135]. Both the GWASes conducted in Asian patients found no association across the MAPT locus in contrast to the GWAS in a European population which found strong associations. European and Asian GWAS all found strong association signals in \textit{LRRK2}, \textit{SNCA} and \textit{MCCC1} loci [135–137].

There are many studies reporting ethnic variation in the genetics of PD [138] and it is beyond the scope of this review to fully explore ethnic variation in prevalence and penetrance in every mutation linked with parkinsonism. There have been no GWAS in African, South American, South Asian or Middle Eastern PD patients that we know of. Genetic variation almost certainly contributes substantially to the heterogeneity seen in the manifestations of PD but as with many chronic diseases, the current literature largely reflects study in populations of European ancestry [1].

\textbf{Vascular disease}

In general, African-Americans have greater cerebral vascular burden than White Americans [139, 140]. We also know that cerebral small vessel disease is associated with postural instability and gait disturbance phenotypes, freezing of gait and worse cognitive impairment [141, 142]. Separately, it has been shown that PD patients with more cardiovascular risk factors have a worse prognosis [143]. It therefore follows that ethnic variation in cerebral vascular disease is likely to be a determinant and also a confounder of PD phenotypes.

\textbf{Dementia-associated pathology}

Black and Hispanic patients with PD seem to be at higher risk of developing cognitive symptoms and frank dementia. The prevalence of Alzheimer’s disease (AD) follows a similar pattern [144, 145] which suggests the possibility that the ethnic variation observed with respect to the prevalence of cognitive symptoms in PD is driven by mixed Alzheimer’s and Lewy body pathology. African-Americans have been shown to have a higher frequency of the APOE \textit{e}4 gene [146]. Carriers of the APOE \textit{e}4 gene with PD have a faster rate of cognitive decline [147] supporting the notion of a mixed Alzheimer’s and Parkinson’s pathology driving some of the ethnic variation observed.

\textbf{Co-morbidities}

The effect of co-morbidities on risk and manifestations of PD is an important current topic in research. For example, type 2 diabetes mellitus (T2DM) has been shown to have an association with subsequent PD [148]. T2DM is very prevalent in Asia and South Asians are known to be at increased risk of T2DM which is partly determined by genetic factors in addition to diet and lifestyle [149]. The extent to which T2DM and other co-morbidities may be determining ethnic variation observed in PD is unknown at present but an important topic to further explore.

\textbf{Non-biological}

\textbf{Healthcare inequalities}

Globally there are large inequalities in the diagnosis and treatment of PD. Generally, in low-middle income countries there is less access to PD medication and neurology services. In Sub-Saharan Africa there are very few neurologists and PD medications are unreliably supplied and expensive [150, 151]. Studies comparing European PD patients to African PD patients conclude that patients in Africa have more severe disease but, despite this, are taking lower doses of levodopa. PD patients in Africa are symptomatic for longer periods before levodopa initiation and are more likely to be treated with anti-cholinergics and amantadine, compared with European patients who are more likely to be prescribed dopamine agonists, levodopa, COMT inhibitors and MAO-B inhibitors [36, 152]. Another consideration is how geopolitical circumstances affect access to medication for chronic diseases, with countries such as Cuba in Central America, and Iran in the Middle East, likely struggling to supply essential PD drugs due to political sanctions.

Within a single country, there is good evidence that healthcare inequalities exist in the detection, diagnosis and treatment of PD. The only studies comparing national healthcare inequalities in PD have been conducted in the USA, a country with greater healthcare inequalities than many other countries in the world [153]. It is unknown whether the findings are applicable to other countries and it would be interesting to know whether the results reproduce in countries
Table 4
Future directions to ameliorate ethnic inequalities in PD research

- Future cross-sectional and cohort studies in ethnically diverse samples of PD cases
- A drive to ensure future GWAS studies are as representative of the global population as possible
- Sharing of raw UPDRS data to enable meta-analysis of mono-ethnic studies
- Developing a standardised method of determining the motor sub-type
- Analysis of ethnic variation in cognitive impairment and neuropsychiatric features that are major determinants of morbidity and mortality in PD
- Establish culturally fair definitions of cognitive impairment
- Investigate role of vascular risk factors in ethnic variation in PD
- Exploration of the role that ethnic and geographic variation in comorbidities have as determinants of ethnic variation in PD
- Further assessment of the contribution of co-morbid Alzheimer’s pathology in shaping ethnic variation seen in PD
- Improving awareness of ethnic healthcare inequalities in the diagnosis and treatment of PD and ameliorating them where possible
- Neuropathological studies in ethnically diverse PD cases

with universal healthcare systems. For other medical conditions, ethnic health inequalities exist even in countries such as the UK which have universal healthcare systems [154]. Black patients in the USA are less likely to be treated by a neurologist than White patients [155, 156]. This may in-part explain some of the suspected under-ascertainment of PD in patients from certain ethnic backgrounds. For PD patients, being treated by a neurologist was inversely associated with residing in a nursing home, hip fractures and likelihood of death [155, 157]. Dahodwala et al., showed that African-Americans are four times less likely than White patients to receive PD treatment (OR 0.24; 95% CI 0.09–0.64) [158]. This finding has been replicated [157, 159] and there is evidence the inequalities extend to the treatment of depression and advanced therapies in PD patients as well [160–162]. Amongst the minority ethnic patients that do receive treatment prescribing errors are more likely; Hispanic PD patients have an increased probability of being co-prescribed an anticholinesterase inhibitor and a high potency anticholinergic; a frank prescribing error [122]. To summarise, PD patients from minority ethnic backgrounds in the USA are less likely to be cared for by a neurologist, receive a diagnosis and be treated adequately for their PD.

One major limitation in the existing literature on ethnic variation of cognitive changes in PD is the definition of dementia using conventional neuropsychological instruments that are known to lack cultural fairness [163, 164]. Future studies will need to consider this source of confounding in order to establish whether there are true biological differences in the incidence of cognitive decline in PD. Data on the relative prominence of neuropsychiatric features among ethnic groups is largely lacking, and will be important to study further given their strong association with morbidity and care burden [118], as well as their potential to reflect specific underlying patterns of neuropathological change [165].

Under-reporting of symptoms
Another factor which could affect ascertainment is the fact that African-Americans and Chinese-Americans are more likely to perceive PD symptoms as a normal part of aging than White-Americans [166]. This may explain findings showing that Black patients under-report their symptoms and could account for some differences in the severity of PD seen [167]. In a multi-ethnic study of PD knowledge in Asia, significant differences in PD knowledge according to ethnicity were found; people of Chinese ethnicity were more aware of the non-motor symptoms of PD compared to Malay people (p < 0.001) and Chinese people were more likely than Indians to be aware that not all patients with PD have a tremor (p = 0.009) [168].

CONCLUSIONS
It seems probable that there are geographic and ethnic differences in the clinical manifestations, epidemiology and mortality of PD. What is unclear is the exact nature of these differences and their cause. Black and Hispanic PD patients seem to be at increased risk of cognitive impairment but whether this is due to modifiable vascular risk factors, different rates of Alzheimer’s pathology, genetic factors or healthcare inequalities is unknown. In Table 4 we have set out what we believe should be research goals in this field. Further prospective clinico-pathological studies in multi-ethnic populations and in Black and Asian populations in countries other than Europe and the USA are important research goals.
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CONFLICT OF INTEREST

The authors have no conflict of interest to report.

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