

Parkinson's Disease Across Ethnicities: A Nationwide Study in New Zealand

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ABSTRACT: Background: New Zealand is an ethnically diverse country with a unified national prescribing system. This provides a good framework to use drug-tracing methodology to establish the prevalence and incidence of Parkinson's disease across different ethnic groups. The objective of this study was to determine the prevalence and incidence of Parkinson's disease in the major ethnic groups in New Zealand.

Methods: Information on Parkinson's disease-related medications was extracted from the national Pharmaceutical Collection of community-dispensed medications for the period January 1, 2005, to December 31, 2014. Diagnoses for a large subset of individuals were independently determined through national mortality and hospital admissions data sets. We used a Bayesian model, accommodating uncertainty and bias, to estimate the number of people with Parkinson's disease.

Results: We found the highest rate of Parkinson's disease in the European ethnic group and the lowest rate in the indigenous Māori. The 2006-2013 age-standardized incidence (per 100,000 population per year) was European, 33; Asian, 28; Pasifika, 27; Māori, 20. The 2013 age-standardized prevalence (per 100,000 population) was European, 223; Asian, 174; Pasifika, 160; Māori, 114.

Conclusions: There is a differential occurrence of Parkinson's disease across the major ethnic groups within the New Zealand population, with indigenous Māori showing the lowest incidence. Varying susceptibility profiles, gene-environment interactions, and inequalities in accessing health care may play a role in the variation in rates of Parkinson's disease in New Zealand. © 2018 International Parkinson and Movement Disorder Society

Key Words: Parkinson's disease; ethnic variation; prevalence; incidence; pharmacoepidemiology

Parkinson's disease is expected to affect increasing numbers of people as the proportion of individuals reaching older ages increases.^{1,2} The prevalence and incidence of Parkinson's disease has been shown to vary between ethnicities,³⁻⁵ suggesting that not all

populations will be affected to the same extent. New Zealand has an ethnically diverse population, comprising indigenous Māori and immigrants or descendants of immigrants from Europe, Asia, and neighboring South Pacific islands (Pasifika ethnic group). Thus,

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Toni L. Pitcher and Daniel J. Myall are joint first authors.

Relevant conflicts of interest/financial disclosures: Authors report no conflicts of interest. Toni L. Pitcher received funding from the Neurological Foundation of New Zealand and New Zealand Brain Research Institute. Daniel J. Myall received funding from Canterbury Medical Research Foundation, Neurological Foundation of New Zealand, and New Zealand Brain Research Institute. Michael R. MacAskill received funding from the New Zealand Brain Research Institute and Neurological Foundation of New Zealand. John F. Pearson received funding from the University of Otago. Cameron J. Lacey received funding from the University of Otago.

John C. Dalrymple-Alford received funding from the University of Canterbury. Tim J. Anderson received funding from the Canterbury District Health Board and the University of Otago.

Funding agencies: Neurological Foundation of New Zealand, New Zealand Brain Research Institute.

Contract grant sponsor: Neurological Foundation of New Zealand; **Contract grant number:** 1211 PG.

Received: 29 June 2017; **Revised:** 18 February 2018; **Accepted:** 4 March 2018

Published online 23 July 2018 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.27389

New Zealand provides a unique opportunity to study Parkinson's disease across a number of ethnic groups with the added benefit of access to health databases covering the entire national population.

Health administrative databases are increasingly being utilized for epidemiological purposes. Estimates of the prevalence and incidence of Parkinson's disease have been derived from administrative databases in the United States,^{4,5} Israel,^{6,7} Italy,⁸ Canada,⁹ Scotland,¹⁰ France,^{11,12} and Taiwan.^{13,14} New Zealand has a publicly funded health care system, providing free or subsidized health and disability services and medications to residents. Information about medications dispensed by community pharmacies is documented in a centrally maintained database, the Pharmaceutical Collection.

We have previously used the Pharmaceutical Collection to describe the prescribing patterns of antiparkinsonian medications in New Zealand¹⁵ and the national age structure of the prevalence and incidence of the disease.² Here we present an analysis of the ethnic variation in Parkinson's disease in New Zealand.

Methods

Data

Data were extracted from the national Pharmaceutical Collection for the period January 1, 2005, to December 31, 2014. We extracted information for drugs indicated for use in Parkinson's disease that were funded by the New Zealand government. They corresponded to the Anatomical and Therapeutic Chemical Classification System¹⁶ N04 anti-parkinson drug category, which includes dopaminergic agents (N04B): levodopa formulations (levodopa with benserazide, levodopa with carbidopa), dopamine agonists (apomorphine, bromocriptine, lisuride, pergolide, ropinirole, and pramipexole), catecholamine-o-methyl transferase inhibitors (tolcapone and entacapone), monoamine oxidase inhibitors (selegiline), and amantadine. Also included were anticholinergic agents from the N04A category (procyclidine, orphenadrine, and benztropine).

Within the extracted data, we traced individual consumers using the National Health Index (NHI) number. The NHI register contains demographic information such as date of birth, sex, ethnicity, and date of death, if relevant. Our extracted pharmaceutical data had a high proportion of dispensing tagged to individuals via the NHI (increasing from 92.8% in 2005 to 99.9% in 2014). The extracted pharmaceutical data contained more than 2 million records of antiparkinsonian medications dispensed to 46,605 people. Following data exclusions (as outlined in Supplementary Fig. 1), our probabilistic algorithm was applied to the remaining 33,917 people.

Medical diagnosis information potentially explaining the use of antiparkinsonian medication use was extracted from 2 national data sets as well as local sources. The national data sets were the Mortality Collection, a register of the underlying cause of death, and the National Minimum Dataset, containing information on each publicly funded inpatient hospital stay. Available data (Mortality Collection 2005-2012 and National Minimum Dataset 2005-2014) were extracted using the following International Classification of Diseases (ICD) 10-AM-III codes: G20, Parkinson's disease; G21, secondary parkinsonism; G22, parkinsonism in diseases classified elsewhere; G23.1, progressive supranuclear ophthalmoplegia; G25.8, other specified extrapyramidal and movement disorders; G31.3, Lewy body disease; G31.8, other specified degenerative diseases of nervous system; G35, multiple sclerosis; G90.3, multi-system degeneration; F20, schizophrenia; and R48.2, apraxia. These codes were chosen to give the widest coverage possible of medical conditions most likely to be treated with antiparkinsonian drugs. Locally, information from our clinical research volunteer database and hospital neurology outpatient clinics and a review of outpatient letters for those appearing in the pharmaceutical database during 2011 from our regional District Health Board (Canterbury) was also used. Individuals were matched across these data sources using NHI numbers.

Ethnicity Grouping

In New Zealand, information collected by government agencies allows for people to identify with multiple ethnicities, and hence the ethnic population numbers generated from the census are multicount numbers. That is, an individual is counted in the population of all ethnic groups with which he or she identifies. At the 2013 census, 15% of the population identified as Māori, 74% as European, 12% as Asian, 7% as Pasifika, and 1.2 % as Middle Eastern/Latin American/African (MELAA).¹⁷ The Pasifika grouping includes people originating from various islands in the South Pacific, such as Samoa, Fiji, Tonga, and Niue. The Asian grouping includes the entire Asian continent, for example, China, India, and Southeast Asian countries.

Because of the ethnic multicount system, the estimated resident population (ERP) summed over ethnicities by age group is larger than the actual total population of individuals in that age group. Selection of multiple ethnicities is largest in the younger age groups (>20% in those younger than 10 years old) and less common in the oldest age groups (<2% in those older than 70 years). The health data sources contained relatively detailed ethnicity labels (approximately 25 categories), which we mapped down to the 5 broader categories used by Statistics New Zealand for the ERP. We did not analyze the MELAA ethnic

TABLE 1. Antiparkinsonian drug combination and duration rules used to classify individuals

Very Probable

- Tolcapone or entacapone or apomorphine or pergolide
- L-Dopa and one of the following; selegiline, amantadine, dopamine agonist, anticholinergic
- Dopamine agonist and either amantadine or anticholinergic
- Pramipexole ≥ 0.75 mg/day

Probable

- L-Dopa only > 180 days
- L-Dopa and ropinirole > 0.6 mg/day
- Selegiline only

Possible

- Lisuride only
- L-Dopa < 180 days
- L-Dopa and ropinirole, < 0.6 mg/day
- Ropinirole only, > 180 days
- Pramipexole only, < 0.75 mg/day

Unlikely

- Anticholinergic only
- Amantadine only
- Bromocriptine only
- Ropinirole only, < 180 days
- Bromocriptine and ropinirole

L-Dopa, levodopa.

grouping because of the very small number within the New Zealand population.

The ERP data were corrected for the multicount ethnic data by assuming that multiple ethnic group selection was equally distributed between ethnicities within each age group, and hence the population by age group for each ethnicity was scaled down so the sum over ethnicities equaled the total population for that age group. Parkinson's disease counts for people with an "unknown" ethnic category were proportionally distributed across the 4 major ethnic groups, with none assigned to the small MELAA group.

Ethical approval was granted by the New Zealand Multi-Region Ethics Committee, approval number MEC/11/EXP/047.

Medication-Based Classification System

Each person was assigned to 1 of 4 categories indicating their qualitative probability of having Parkinson's disease (very probable, probable, possible, or unlikely), given their pattern of using the target medications. Our classification system is based on specified combinations of antiparkinsonian medications, the doses taken, and their duration of use (Table 1). These classifications were derived to provide the greatest separation of idiopathic Parkinson's disease from other medical conditions treated with the medications, are based on clinical knowledge of medication use, and are similar to those published elsewhere.⁶ Individuals received a single classification based on their

medication use over the entire period they appeared in the data set. The epidemiological model was applied to the 33,917 people identified as medication users.

Model for Calculating Probability of Parkinson's Disease

We formed a Bayesian Bernoulli multilevel regression model to determine the probability of each of the 33,917 individuals having Parkinson's disease, given their medication classification, ethnicity, sex, and 5-year age band. Figure 1 gives a pictorial representation of the data used in the model and the pipeline completed to arrive at the prevalence and incidence estimates. The Bayesian model was trained using the individuals with a known Parkinson's disease diagnosis (from the nonmedication data sources, such as those with an ICD-10 G20 hospital discharge code) versus those with a known non-Parkinson's disease diagnosis (such as multiple sclerosis, schizophrenia, or restless legs syndrome). The proportions of those with a confirmed Parkinson's disease diagnosis versus a confirmed non-Parkinson's disease diagnosis varied substantially across the medication categories (eg, 59% Parkinson's disease versus 5% non-Parkinson's disease in the "very probable" category, compared with 1% Parkinson's disease versus 37% non-Parkinson's disease in the "unlikely" category). This allowed the model to estimate the probability of Parkinson's disease for those without independent diagnostic information while also accounting for the markedly different distributions of age, sex, and ethnicity across the medication categories (Fig. 1). It should be noted that the model did not classify cases dichotomously, as either having or not having Parkinson's, as it is impossible to be completely confident that an individual has Parkinson's disease based on medication use alone. Rather, each individual was assigned a continuous probability of having the disease, given their medication and demographic information. Hence, our estimated total number of cases within each ethnicity was not a count of an identified subset of individuals. Instead, it was formed by summing the probabilities attached to all individuals.

Calculation of Number of People With Parkinson's Disease

Prior to calculating the standardized prevalence and incidence, we first estimated the raw total of existing and new cases in each year. To estimate the number of people with Parkinson's disease each year, we summed the probabilities of having Parkinson's disease for all individuals within each combination of factors (ethnicity, sex, and age group). To estimate the number of new cases of Parkinson's disease in each year, this procedure was repeated but limited to

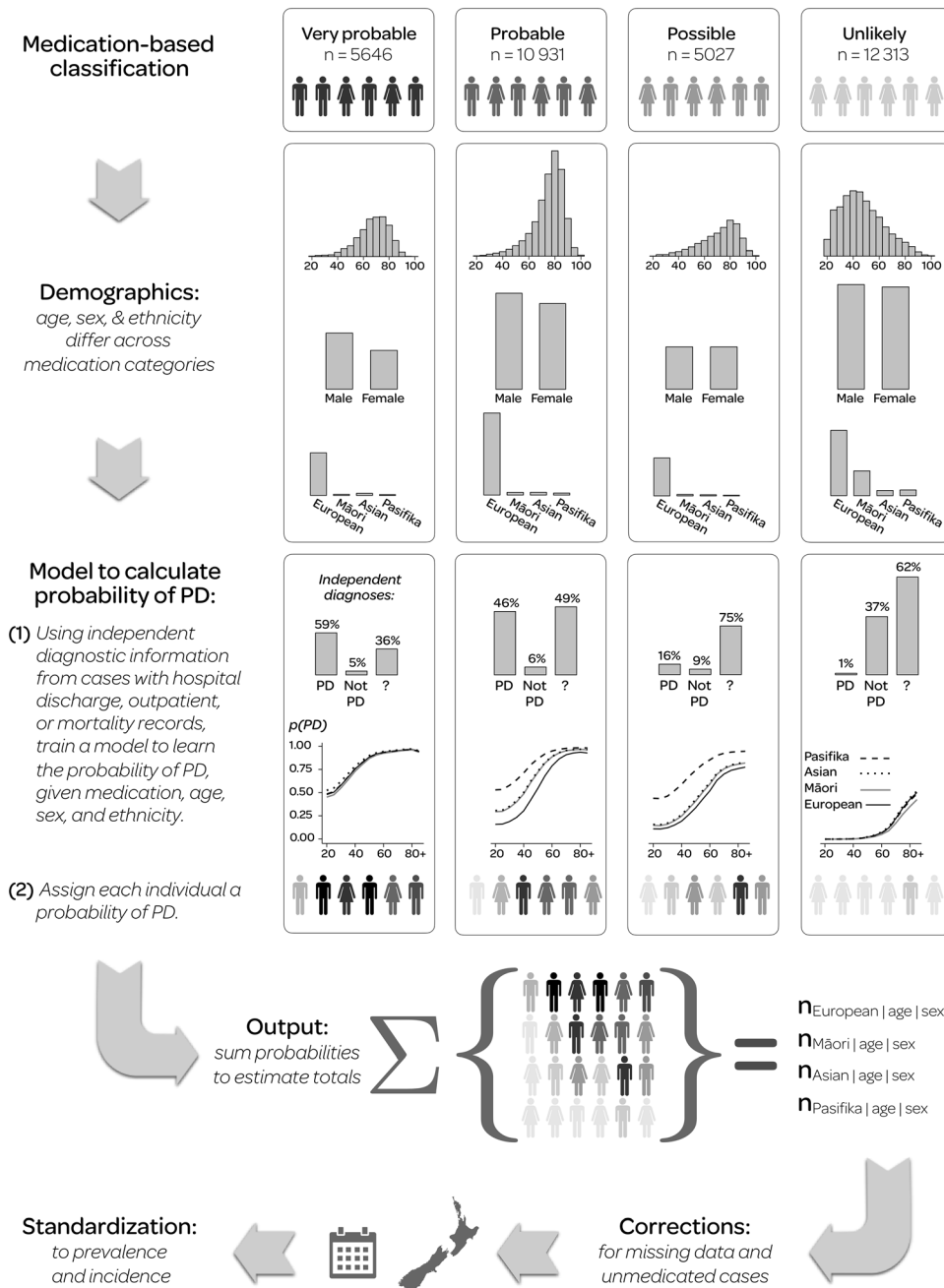


FIG. 1. A depiction of the probabilistic modeling process. Potential Parkinson's disease cases were identified by our medication-based classification (see Table 1 and Supplementary Fig. 1). Within each classification category ("very probable" through "unlikely"), individual cases started with the same (initially unquantified) probability of having Parkinson's, as indicated by the common shading of the silhouettes. The demographic characteristics were then quantified. For example, the "very probable" and "probable" categories showed age distributions and sex ratios consistent with those expected for a Parkinson's disease population. By contrast, the "unlikely" category, expected to be dominated by anticholinergic use for psychiatric purposes, was skewed toward younger cases, with a more equal male:female ratio, and overrepresentation of Māori. We then sought independent diagnostic information from other data sources, allowing us to confirm Parkinson's disease ("PD") or some other condition ("not PD") in a subset of cases. In the remaining cases, the diagnosis remained unknown ("?"). This information was used to train a model to learn the probability of a case having Parkinson's, given the patient's medication use, age, sex, and ethnicity. Each case was assigned such a probability (as indicated by the now variously shaded silhouettes). Therefore, our estimated total numbers of people with Parkinson's disease in each ethnicity are not counts of discrete, identified individuals. Rather, they are formed by summing the continuous probabilities assigned to individuals. These totals were then standardized by the census-derived national age, sex, and ethnicity distributions and each case's period of occurrence within the data set to form estimates of prevalence and incidence. Figure by MacAskill, Pitcher, and Myall (2017), distributed at DOI: 10.6084/m9.figshare.5400607 under an open CC-BY 4.0 license.

only summing the probabilities from those individuals appearing in the data set for the first time for each combination of factors (ethnicity, sex, and age group).

Adjustments Applied to Parkinson's Disease Counts

Adjustments were then applied to account for individuals who would have been missed because they did

not appear in the pharmaceutical data. One source of these cases was the individuals who could not be uniquely identified in the data set because of prescriptions that were not labeled with an NHI number. Within the antiparkinsonian medications data set, the proportion of such cases had declined to 0.2% by 2013. We made a second correction to the prevalence to account for individuals who had Parkinson's disease but who remained unmedicated. We estimated the proportion of such cases to be 5% (based on our clinical experience), which was assumed to be constant over the years and to be evenly distributed across ages and sexes.

Calculation of Prevalence and Incidence

Prevalence estimates were calculated for 2013, which maximized the amount of longitudinal data for individuals, while also having a year of postestimate prescribing to exclude new cases who might have received only 1 prescription. Incidence was calculated over the period 2006-2013 to achieve more accurate incidence estimates for ethnicities with smaller populations in the older age groups.

To calculate age-specific estimates of prevalence by ethnicity for 2013, age- and sex-specific prevalence proportions were calculated using a Bayesian multi-level normal approximation to a binomial distribution. Inputs to this model were Parkinson's disease counts and corrected ERP, both by ethnicity, sex, and age group. The sex ratio by age group in the overall New Zealand ERP was then used to generate age-specific prevalence. A similar procedure was followed to calculate age-specific incidence over the years 2006-2013.

The overall 2013 New Zealand ERP age and sex population structure was used as the reference population for age-sex standardization of the prevalence and incidence. The World Health Organization (WHO) standard population, assuming a 1:1 male:female ratio, was also used to generate internationally comparable standardized prevalence and incidence.

Software

A custom module in Python 2.7 was used to process the raw data and classify individuals. The probabilistic language Stan¹⁸ was used along with the R package rstan 2.14.1 to fit the Bayesian model and generate all estimates within the R statistical environment (version 3.2.1¹⁹). R packages dplyr²⁰ and ggplot2²¹ were used to manipulate, summarize, and plot the resulting data. The full code for this analysis is available at <https://github.com/nzbri/pdepi>.

Numbers are presented as the means of the posterior distribution, along with 95% uncertainty intervals (intervals that contain the central 95% of the posterior probability mass). These uncertainty intervals are indicated with square brackets after values in the text.

Results shown in Figure 2 show the 50% uncertainty intervals to aid group differentiation.

Results

Validation of ICD-10 Code Accuracy

Overall 42% (14,179) of the total number of people (33,917) classified by the medication algorithm had ICD-10 diagnostic codes listed in the national databases. To assess the accuracy of these codes, we compared them with the diagnostic information gathered locally from a medical record review, which included diagnoses from neurology outpatient clinics, including a movement disorders specialist. Eight hundred and seventy-six individuals had a diagnosis in both national and local data sources. Ninety-four percent of the ICD-10 diagnostic codes from the national databases were in agreement with locally derived diagnoses, with 763 people having a Parkinson's disease diagnosis from both sources (true positives) and 173 people having a non-Parkinson's disease diagnosis from both sources (true negatives). The probabilities of identifying an individual as having Parkinson's disease when they were non-Parkinson's disease, and vice versa, were similar, and hence there was no directional bias.

Medication-Based Classification Numbers

A total of 33,917 individuals were classified across all years: 5646 as very probable, 10,931 as probable, 5027 as possible, and 12,313 as unlikely. The mean age of people at their first appearance in the data set was 67.5 years for the very probable group, 75.1 years for the probable group, 71.4 years for the possible group, and 47.1 years for the unlikely group. The mean follow-up period was 3.9 years (range, 1-10 years). At the end of the modeling process, it was possible to retrospectively assign a quantitative probability of having Parkinson's disease given that an individual was classified within a given category: very probable, 90% [87%, 92%]; probable, 84% [81%, 87%]; possible, 56% [48%, 62%]; unlikely, 4% [3%, 6%]. These values could be used as an approximate guide to future use of such a medication classification system in other populations.

Parkinson's Disease by Ethnicity

The age-standardized prevalence and incidence for each ethnicity is shown in Table 2, and the 5-year age group breakdown is shown in Supplementary Table 1. Māori had the lowest 2013 prevalence, followed by the Pasifika and Asian groups. Europeans had the highest prevalence. Prevalence increased with age in all ethnic groups (Fig. 2). Māori also had the lowest age-standardized incidence, calculated across years 2006-2013, with the Asian, Pasifika, and European groups having increasingly higher incidence. Incidence

TABLE 2. 2013 Prevalence and incidence of Parkinson's disease in New Zealand by ethnicity

Ethnicity	Standardized incidence ^a	Standardized Prevalence ^b	Male: female ratio of standardized incidence	WHO standardized incidence ^a	WHO standardized prevalence ^b
European	33 [32, 34]	223 [218, 228]	1.7:1 [1.6, 1.7]	20 [19, 20]	131 [128, 135]
Māori	20 [17, 22]	114 [100, 130]	1.4:1 [1.1, 1.8]	12 [10, 13]	67 [59, 76]
Pasifika	27 [23, 30]	160 [139, 183]	1.8:1 [1.3, 2.3]	16 [14, 18]	96 [84, 109]
Asian	28 [25, 31]	174 [157, 193]	1.6:1 [1.3, 2.0]	17 [15, 19]	101 [92, 112]
Total New Zealand population ^c	31 [29, 33]	210 [205, 215]	1.8:1 [1.7, 1.8]	18 [17, 19]	122 [120, 125]

Standardized prevalence values were calculated for 2013. Standardized incidence assumes that each ethnic population had the overall mean New Zealand age and sex population distribution and are calculated across the years 2006-2013.

^aIncidence is per 100,000 people per year.

^bPrevalence is per 100,000 people.

^cTotal population values are those for the total national population in 2013 (our reference year).

The World Health Organization (WHO) standardized values were calculated using the standard population values from the GPE Discussion Paper Series, No. 31, 2001 (<http://www.who.int/healthinfo/paper31.pdf>).

increased with age across all ethnicities (Fig. 2). Men outnumbered women in each of the ethnic populations (Table 2). WHO age-standardized ethnic prevalence and incidence values of Parkinson's disease in New Zealand are also listed in Table 2.

Discussion

Using drug-tracing methods encompassing an entire national population and probabilistic modeling, we estimated the prevalence and incidence of Parkinson's disease in 4 ethnic groups within New Zealand. We found that the European ethnic group had the highest prevalence and incidence of Parkinson's disease, followed by the Asian and Pasifika groups, with substantially lower prevalence and incidence in the indigenous ethnic group, Māori. Our age-specific prevalence estimates are consistent with a meta-analysis of the worldwide Parkinson's disease prevalence,³ with our 5-year age group estimates for Europeans (Supplementary Table 1) generally within the confidence intervals for the corresponding 10-year age group estimates for the European/North America/

Australia populations. Our identification of ethnic variation in Parkinson's disease also fits with results from other studies. Administrative data sources have revealed lower Parkinson's disease prevalence⁵ and incidence^{4,5} in Asians compared with whites in the United States. Lower prevalence in Asians is also supported at the meta-analysis level.³ In the United States, African Americans reportedly have a lower incidence of Parkinson's disease than white and Hispanic groups^{4,5} and lower use of Parkinson's disease medications.²² The robust finding of ethnic variation between Asians and Europeans within the same country suggests that the variation is more likely to be a result of factors other than those determined by global location.

Determining underlying causes for the different incidence of Parkinson's disease between ethnic groups, and especially the lower incidence in Māori, could provide important information on potential risk and protective factors for Parkinson's disease. Factors that may contribute to the ethnic variation described here include data quality, inequalities in access to health care, and differing exposure to determinants of Parkinson's disease. In terms of data quality, the coverage

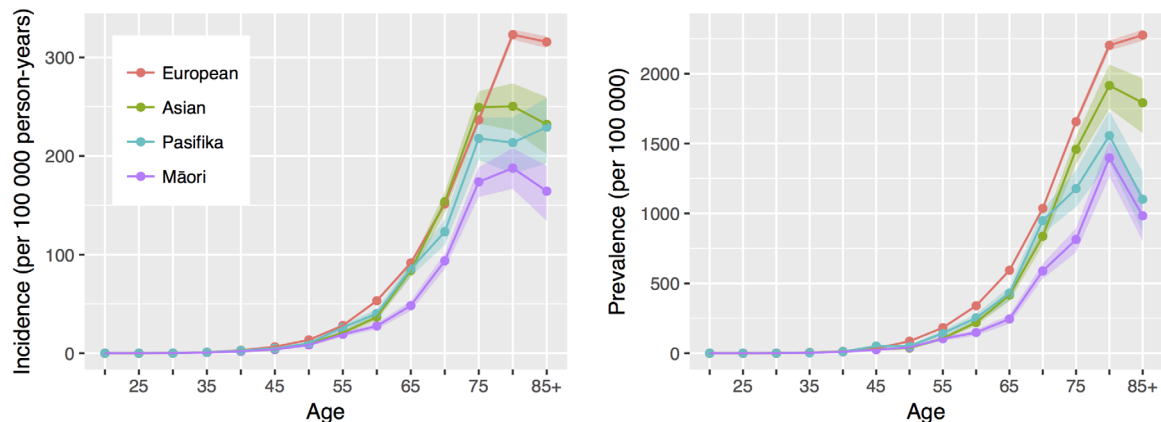


FIG. 2. Incidence and prevalence of Parkinson's disease by ethnicity and age. Age-specific incidence over the years 2006-2013 (left) and age-specific prevalence in 2013 (right). Incidence increased with age up to 75-80 years old and then plateaued. The highest incidence was observed in the European ethnic group, followed by Asian, Pasifika, and Māori ethnicities. The same ordering was observed for prevalence. Shaded areas represent 50% uncertainty intervals.

of ethnicity information within the NHI register is not complete.²³ However, fewer than 3% of people classified by our algorithm did not have an ethnic group listed. Misclassification of ethnicity is also known to occur within the health sector and differentially affects the smaller ethnic groups, such as Māori.²³ It is therefore possible that misclassification of ethnicity within the data we used (eg, someone who identifies as Māori being labeled as New Zealand European) could contribute to the ethnic variation in Parkinson's disease reported. The proportion of the difference attributable to this is unknown.

On average, Māori experience lower socioeconomic status than European and Asian New Zealanders. They are therefore more likely to be affected by known health care inequalities in New Zealand.²⁴ These inequalities include access to health care, adequate treatment once in the system, and disparities in being prescribed medications and subsequently collecting them.²⁵ All these have the potential to account for at least some of the reduced number of Māori with Parkinson's disease we observed. Reduced access to health care could result in delayed diagnosis, in delayed uptake of symptomatic treatment, or in not receiving a diagnosis at all. Once in the system, inadequate treatment could affect diagnostic accuracy, especially in ambiguous cases, or result in inappropriate or less timely medication choices being made. Further study would be required to establish if Māori are receiving adequate quality of care, including specialist referrals, in the context of Parkinson's disease. Disparity in medication collection could lead to our algorithm assigning an incorrect probability of Parkinson's disease to a person.

Differential exposure to factors that may mediate risk of Parkinson's disease is possible. There are lifestyle factors and medical comorbidities that potentially mediate Parkinson's disease risk and are known to occur with differing frequencies across ethnic groups in New Zealand. Smoking is known to be negatively associated with Parkinson's disease,²⁶ and a high proportion of Māori report being current or past smokers.²⁷ Low levels of uric acid are associated with Parkinson's disease,^{28,29} and Māori and Pasifika have a high prevalence of gout and hyperuricemia.³⁰ This raises the question of whether the high prevalence of these other medical conditions might in turn reduce the risk of Parkinson's disease among Māori and Pasifika. Counter to this is the lower incidence of Parkinson's disease in Māori and Pasifika despite these groups having a high prevalence of type 2 diabetes,³¹ a condition associated with an *increased* risk of Parkinson's disease.^{32,33} We are not aware of differential exposure to other known factors that may mediate the risk of Parkinson's disease. For example, New Zealand has an extensive agricultural economy, and thus

there is the potential for exposure to pesticides or consumption of well water to contribute to an individuals' risk of Parkinson's disease. However, the population is largely urbanized³⁴; hence, any such risk is unlikely to contribute substantially to the ethnic variation across the entire population. There is also the potential for differences in genetic determinants of Parkinson's disease. Specific genotypes and haplotypes for both increasing risk^{35,36} and protecting against Parkinson's disease³⁷⁻³⁹ have been identified. Māori have low frequencies of genetic mediators of multiple sclerosis risk⁴⁰ and are 3 times less likely to be diagnosed with multiple sclerosis than non-Māori,⁴¹ demonstrating that varying genetic susceptibility exists within this population.

Strengths of this study include its coverage of a total national population, with the ability to assess Parkinson's disease across ethnic groups using the same methodology within the same national environment. In addition, the relatively long period of data collection allowed us to make more informed classification decisions, such as capturing if an individual's drug use moved toward more Parkinson's disease-specific combinations over time. We also independently confirmed diagnoses for a large subset of the people taking anti-parkinsonian drugs. Limitations of this study include the potential for bias in our estimates between ethnicities because of differing access to treatment and differing proportions of missing data by ethnicity. It is also difficult to independently assess the accuracy of our model. The model assigns a continuous probability of having Parkinson's disease to each person, rather than making categorical disease/nondisease decisions. This means we cannot meaningfully calculate traditional measures of sensitivity and specificity by comparing the model judgments against a small subset of patients with a known diagnosis. An optimum alternative would be to test the predicted number of people with Parkinson's disease against the number of diagnoses in a large national-level independent data set. Several years have passed since the data cutoff for this study, and so it will be feasible in the near future to validate the model by testing its performance on the cohort of new individuals identified within the Pharmaceutical Collection.

We have provided further evidence of lower prevalence and incidence of Parkinson's disease in people of Asian versus European descent. We have also provided the first estimates of the prevalence and incidence of Parkinson's disease in Māori and Pasifika populations. Despite our grouping of South Pacific Island populations together into a single Pasifika ethnic group, prevalence and incidence estimates reported here will provide a useful comparison should any studies be conducted within individual island nations in the future. Inclusion of WHO age-standardized values will

also facilitate comparison of our results with future studies.

Our methodology will allow for monitoring of Parkinson's disease incidence and prevalence across the ethnic groups in New Zealand over time. Given that the life expectancy of Māori is increasing at rates greater than non-Māori,⁴² it might be expected that the standardized prevalence of Parkinson's disease among Māori will increase faster than the remainder of the population, potentially reducing the differences reported here. ■

Acknowledgments: Gill Ebel and Helen Skene, New Zealand Brain Research Institute, and Ministry of Health National Collections staff.

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Supporting Data

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