

It is well recognized that the incidence and prevalence of Parkinson's disease (PD) increase with age, but there is limited information on how these change among the oldest old. Utilizing the national pharmaceutical database of community dispensed medications from 2005 to 2014 in New Zealand, Myall and colleagues found the prevalence of PD to be 191 per 100000 population and an incidence of 29 per 100000 person-years, both rates were higher in men. However, the rates increased significantly until 75 years, reached its peak at 85 years and declined considerably thereafter. The drop off among the oldest old could reflect an actual decrease after 85 years or fewer in this age group got actively diagnosed with PD and/or physicians were less likely to initiate pharmacologic therapies due to advanced age and co-existent comorbidities. The authors concluded that there was a moderate increase in PD in New Zealand over 2006–2013 and the prevalence is likely to increase in the future, and suggested that PD is an age-dependent rather than aging-dependent disorder. Due to potential confounding factors in the oldest old, it would be interesting to further validate the latter hypothesis in other populations.

Parkinson's in the oldest old: Impact on estimates of future disease burden



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ARTICLE INFO

Article history:

Received 5 April 2017

Received in revised form

21 June 2017

Accepted 26 June 2017

Keywords:

Parkinson's disease

Epidemiology

Prevalence

Incidence

ABSTRACT

Background: Traditionally the risk of Parkinson's has been considered to increase monotonically with age, although there is evidence that prevalence and incidence may decrease in the oldest old. To examine this further we estimated the national prevalence and incidence of Parkinson's in New Zealand, using drug-tracing methods, to examine the relationship of Parkinson's with sex and age up to 100+.

Methods: Information on Parkinson's-related medications was extracted from the national pharmaceutical database of community-dispensed medications from 2005 to 2014. Diagnoses for a large subset of individuals were independently determined through national mortality and hospital admissions datasets. We used a Bayesian model, accommodating diagnostic uncertainty and bias, to estimate the number of people with Parkinson's.

Results: The 2013 prevalence of Parkinson's in New Zealand was 210 per 100 000 population (95% uncertainty interval 208–212) with age-standardized prevalence rates higher for males (ratio 1.6:1). Incidence was 31 per 100 000 person-years (95% uncertainty interval 30–32), also higher in males (ratio 1.8:1). Incidence and prevalence by age increased exponentially until 75 years, peaked at 85 years, and then dropped sharply.

Conclusions: The prevalence of Parkinson's in New Zealand is expected to double over a 25-year period but then increase at a slower rate due to the drop-off in prevalence and incidence in the oldest old. The findings suggest that Parkinson's disease is not an aging-dependent but an age-dependent disorder.

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1. Introduction

Parkinson's is a neurodegenerative disorder with increasing age as the primary risk factor [1]. Age-associated diseases can be classified into two types [2]: *aging-dependent*, which increase

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monotonically with the aging process, versus *age*-dependent, which tend to occur at prescribed ages. For example, stroke can be regarded as associated with the aging process itself, as the outcome of a series of accumulating degenerative damage. Thus the probability of disease increases monotonically as a person ages. Other disorders, such as multiple sclerosis and schizophrenia, are associated with onset in early or middle adulthood. Although these disease processes presumably require a certain period of time to manifest, the probability of onset does not then continue to increase with age, and indeed will begin to decrease once the age of greatest vulnerability has been reached.

The majority of epidemiological studies of Parkinson's have shown a continual increase of prevalence and incidence with age (for review see Ref. [3]). Hence Parkinson's has traditionally been viewed as an aging-dependent disease [2]. A limitation of many of those studies is that the oldest age group considered was 80+ or 85+, due to small numbers of people beyond those ages. This has limited the ability to differentiate Parkinson's as a late-stage age-dependent or aging-dependent disorder. In recent datasets which have allowed this degree of analysis [4–6], there is an indication of a drop-off in incidence of Parkinson's in the oldest old.

Determining whether Parkinson's is aging- or age-dependent has implications for understanding the disease process. It also influences the estimation of the future burden of Parkinson's disease. Under an aging-dependent assumption, as life expectancy increases the burden of Parkinson's must increase at a greater than linear rate. That is, the burden of Parkinson's is influenced not only by any change in total population size but also by the growing proportion of the population that survives into old age. On the other hand, if Parkinson's is age-dependent, then this will moderate the increase in prevalence over time as life expectancies increase. That is, as more people begin to live beyond the peak age of onset for Parkinson's, the proportion of older people with Parkinson's will be less than if the disease probability increased inexorably with age.

Use of electronic databases to estimate the rates of Parkinson's is becoming increasingly common and they have been used to provide estimates for regional populations [7–12], sub-national samples [4,13–16], and total national populations [6,17,18]. As part of New Zealand's publicly-funded healthcare system, community pharmacies are reimbursed by central government for dispensed medications. Information about each dispensing is documented within a centrally-maintained database, which can be linked to demographic information. Using this dataset, we have previously reported the prescribing patterns of anti-parkinsonian medications in New Zealand [19]. We now directly assess the prevalence and incidence of Parkinson's at the total population level and estimate future disease burden.

2. Methods

We utilised data from the New Zealand Pharmaceutical Collection database spanning a 10-year period (1 January 2005 to 31 December 2014). We extracted information for drugs that are indicated for Parkinson's and that were funded at the time by the New Zealand government. Included drugs were: 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); amantadine; and anticholinergic agents (procyclidine, orphenadrine, and bengtropine).

Within the extracted data we traced individual consumers using the patient-unique National Health Identifier (NHI) number that each resident is assigned either at birth or at first contact with the healthcare system. The NHI allows linkage to demographic

information such as date of birth, sex, ethnicity, and date of death, where applicable. We extracted data for the 10-year period beginning in 2005.

The extracted data contained over 2 million records of dispensings of anti-parkinsonian medications to over 46 000 people with each dispensing generally supplying three months of medication.

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

2.1. Parkinson's classification algorithm

After exclusions, a total of 33 917 people remained in the dataset for further classification. All data exclusions are outlined in [Supplementary Fig. 1](#). Our classification algorithm is based on specified combinations of anti-parkinsonian medications and duration of use ([Table 1](#)). The medication combinations, doses, and durations of use used in the classification groups were chosen to maximise the differentiation between Parkinson's and other medical conditions treated with these medications and are similar to those described previously [16]. Our algorithm reflects clinical knowledge (TJA) and prescribing practices in New Zealand. Each person was assigned to one of four categories to indicate the probability of a Parkinson's diagnosis (very probable, probable, possible, or unlikely). Individuals received a single classification based on their medication usage for the entire period and were included in prevalence estimates for the period they received medications.

2.2. Independent calibration of classifications

Medical diagnosis information used to calibrate our medication-based classifications was extracted from two national datasets. The Mortality Collection, a register of the underlying cause of death and the National Minimum Dataset, which contains information on each publicly-funded inpatient hospital discharge, including the primary reason for hospital stay as well as other contributing or significant medical diagnoses. Available data from the two datasets (Mortality Collection 2005 to 2013 and National Minimum Dataset 2005 to 2014) was 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 (gait). These codes were chosen to give a wide coverage of other medical conditions most likely to be treated with anti-parkinsonian drugs. Additional diagnosis information was taken from our local clinical research volunteer database, hospital neurology outpatient clinics, and a review of outpatient letters for those appearing in the database during 2011 from our local district health board region (Canterbury). Individuals were matched across data sources using NHI numbers.

2.3. Calculation of number of people with Parkinson's

To determine the probability of an individual having Parkinson's given their medication classification, sex, and 5-year age group, we formed a Bayesian hierarchical Bernoulli regression model. This model was fit using the individuals with a known Parkinson's diagnosis (ICD-10 G20 code) versus a known non-Parkinson's diagnosis (e.g., multiple sclerosis, schizophrenia, restless legs).

Table 1
Anti-parkinsonian drug combination and duration rules used to classify individuals.

Very Probable	<ul style="list-style-type: none"> – Tolcapone or entacapone or apomorphine or pergolide – L-dopa and any of selegiline, amantadine, dopamine agonist, or anticholinergic – Dopamine agonist and either amantadine or anticholinergic
Probable	<ul style="list-style-type: none"> – Pramipexole only (≥ 0.75 mg/day) – L-dopa only, >180 days – L-dopa & ropinirole (>0.6 mg/day)
Possible	<ul style="list-style-type: none"> – Selegiline only – Lisuride only – L-dopa, <180 days – L-dopa & ropinirole (other dose) – Ropinirole only (>180 days)
Unlikely	<ul style="list-style-type: none"> – Pramipexole only (other dose) – Anticholinergic only – Amantadine only – Bromocriptine only – Ropinirole only (<180 days) – Bromocriptine & ropinirole

2.4. Adjustments applied to Parkinson's counts

Adjustments were then applied to account for individuals who did not appear in pharmaceutical data. One source of these cases was individuals who could not be uniquely identified in the dataset due to prescriptions that were not labelled with an NHI. Within the anti-parkinsonian medications dataset, the proportion of such cases decreased over time from 3.5% to 0.2%. If uncorrected, these cases would systematically lead to underestimation of prevalence and incidence, particularly in the earlier years of the dataset. Calibrated estimates were therefore produced by adjusting them upwards each year accordingly, under the assumption that the distribution of individuals with Parkinson's was similar between records with and without an NHI. We made a second correction to prevalence rates to account for individuals with a diagnosis of Parkinson's but who remained unmedicated. The proportion of such cases (5%, based on our clinical experience) was assumed to be constant over the years and to be evenly distributed across ages, and sex.

When calculating total new (incident) cases, we applied an additional correction for the bias due to improved identification rather than actual disease onset, which would artificially inflate new cases.

2.5. Calculation of observed prevalence and incidence rates

To arrive at population prevalence (per 100 000 people) and incidence measures (per 100 000 people per year), for the years 2006–2013, the total estimated cases and new cases by sex and by year were divided by the appropriate Statistics New Zealand estimated resident population (ERP) values at June 30 of each year.

2.6. Calculation of age-specific prevalence and incidence rates

Age-specific incidence was calculated over the period of 2006–2013 to allow for better estimation of age-specific rates in the older age groups while age-specific prevalence was averaged over the years 2006–2013.

2.7. Standardization of prevalence and incidence rates

The 2013 ERP New Zealand age and sex population structure was used as the reference population for standardisation of the overall prevalence and incidence rates for years 2006–2012. For the sex-specific rates these were standardized to the 2013 overall age population structure.

2.8. Predictions of future burden

Statistics New Zealand median, 5%, and 95% national population projections for the years 2014–2068 provided the basis for future predictions.

2.9. Software

We wrote a custom module in *Python*, run under Python 2.7, to process the raw data and classify individuals. Statistical analysis was performed in the *R* statistical environment version 3.2.1 [20]. The probabilistic language Stan [21] was used along with the *R* package *rstan* 2.14.1 to fit the Bayesian model and generate all estimates. *R* Packages *dplyr* 0.5.0 [22] and *ggplot2* [23] were additionally used to manipulate, summarise, and plot the resulting data.

2.10. Presentation of model Bayesian estimates

The means of the posterior distribution are provided, along with 95% uncertainty intervals (intervals which contain the central 95% of the posterior probability mass), indicated with square brackets after values in the text and by grey shading in figures. The number of people with Parkinson's disease was determined probabilistically, taking into account the uncertainty in diagnosis. Calculation of incidence, prevalence, and standardized rates are all direct calculations, although the uncertainty in the number of individuals with Parkinson's are propagated throughout these calculations.

3. Results

3.1. National incidence

There was a modest increase in the number of new cases of Parkinson's per year over time (Fig. 1a): 1130 [1110, 1140] per year in 2006, increasing to 1370 [1350, 1400] in 2013. This increase persisted when converted to incidence (Fig. 1c): 27 [26, 27] per 100 000 per year in 2006 increasing to 31 [30, 32] in 2013. However, the observed increase over time was largely eliminated when standardizing to the 2013 age- and sex-population structure (Fig. 1e): 30 [30, 31] per 100 000 per year in 2006 and 31 [30, 32] in 2013. That is, the apparent increase was due to a growing proportion of elderly people within the total population.

As expected, age-standardized incidence rates were higher for males (Fig. 2e): in 2013 males had a rate of 41 [40, 41] per 100 000

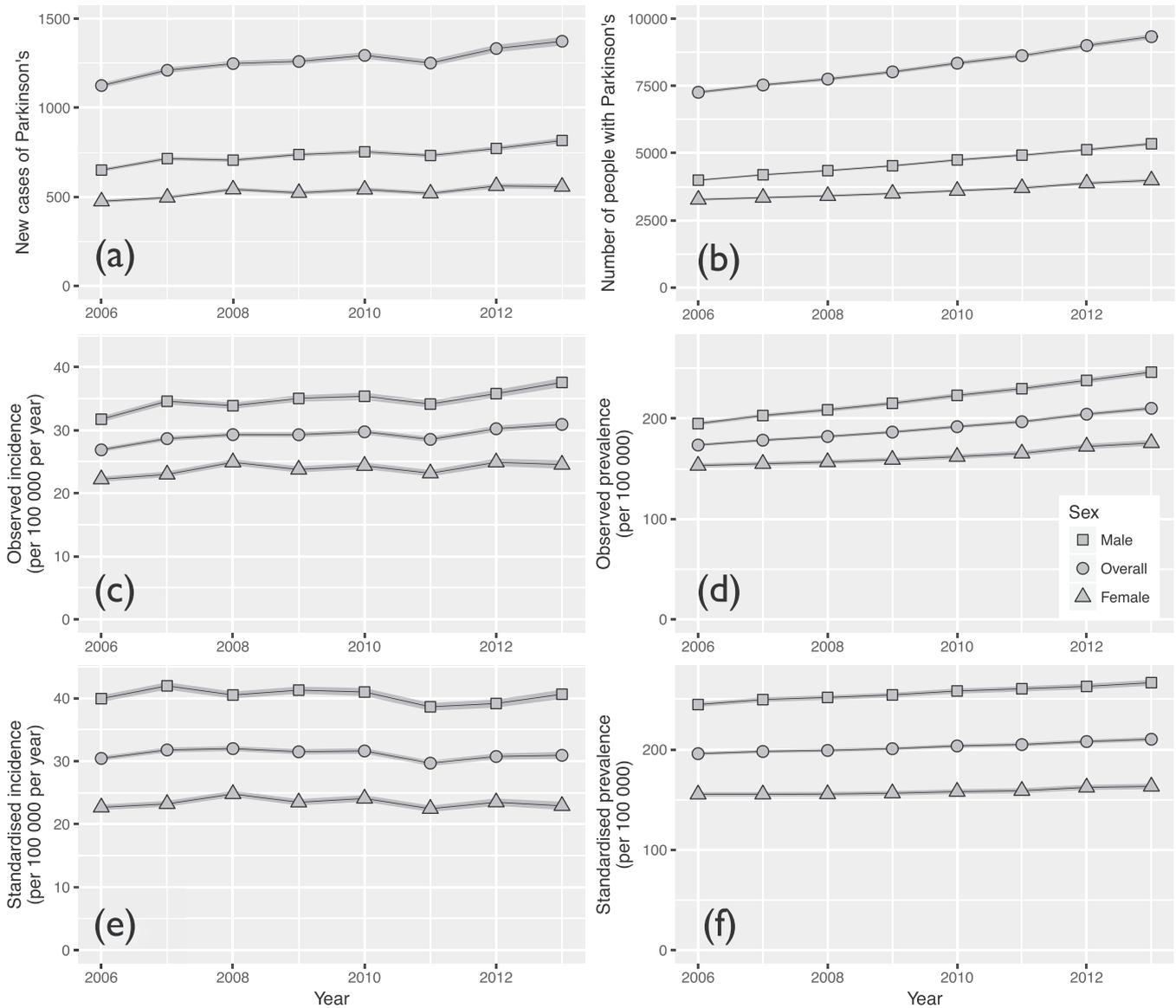


Fig. 1. Number of new individuals with Parkinson's in New Zealand (a) and total number of individuals with Parkinson's in New Zealand (b) from 2006 to 2013 by sex and overall. There has been a moderate increase in the number of new cases per year and total cases over the 8 year period. When dividing by the size of the population to get incidence (c) and prevalence (d) the relative increase over time reduces in magnitude but still persists. Following standardization to the 2013 age-sex population structure there is no evidence of an increase over time with incidence (e) but an increase over time in prevalence (f) persists. The grey bands represent the 95% uncertainty interval given the model and data.

per year, compared to females with a rate of 23 [22, 24] per 100 000 per year, a ratio of 1.8:1. Age-specific incidence was calculated from incident cases over 2006–2013 (Fig. 2a, details in Supplementary Table 1). Age-specific incidence increased exponentially until age 75, peaking at age 85 with a rate of 319 [313, 325] per 100 000 per year. This was followed by a sharp drop above age 85, to a rate of 115 [88, 136] per 100 000 per year for the 100+ age group.

3.2. National prevalence

There was a modest increase in the number of people with Parkinson's over time (Fig. 1b): 7270 [7200, 7330] in 2006, increasing to 9340 [9240, 9430] in 2013. This increase persisted when converted to prevalence of Parkinson's (Fig. 1d): 174 [172, 175] per 100 000 in 2006, increasing to 210 [208, 212] in 2013. In contrast to incidence, an increase in prevalence over time persisted when standardizing to the 2013 age- and sex-population structure

(Fig. 1f): 196 [194, 198] per 100 000 per year in 2006 and 210 [208, 210] in 2013.

As expected, age-standardized prevalence rates were higher for males (Fig. 1e): in 2013 males had a rate of 267 [264, 269] per 100 000, compared to females with a rate of 163 [160, 166] per 100 000, a ratio of 1.6:1. The mean 2006–2013 age-specific prevalence (Fig. 2b) increased exponentially until age 75, peaking at age 85 at a rate of 2260 [2220, 2290] per 100 000. This was followed by a sharp drop from age 90, to a rate of 760 [610, 860] per 100 000 for the 100+ age group.

3.3. Future burden and prevalence

We predicted the number of people with Parkinson's in New Zealand to increase in a linear fashion and double in the next 25 years from 9340 [9240, 9430] in 2013 to 19 700 [17 900, 21 500] in 2038. Following this, the number of people with Parkinson's is

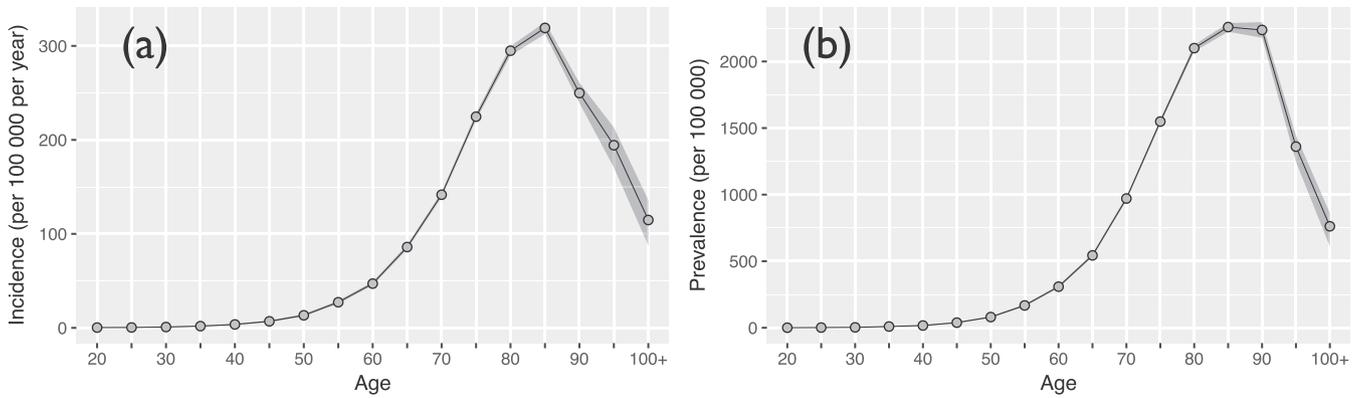


Fig. 2. 2006–2013 age-specific incidence (a) and mean 2006–2013 age-specific prevalence (b) by 5-year age groups. There is an exponential increase in incidence and prevalence from ages 20 to 75. This is followed by maximum incidence and prevalence at age 85. Rates then sharply decrease, with a greater decrease in incidence than prevalence in the oldest old. The grey bands represent the 95% uncertainty interval given the model and data.

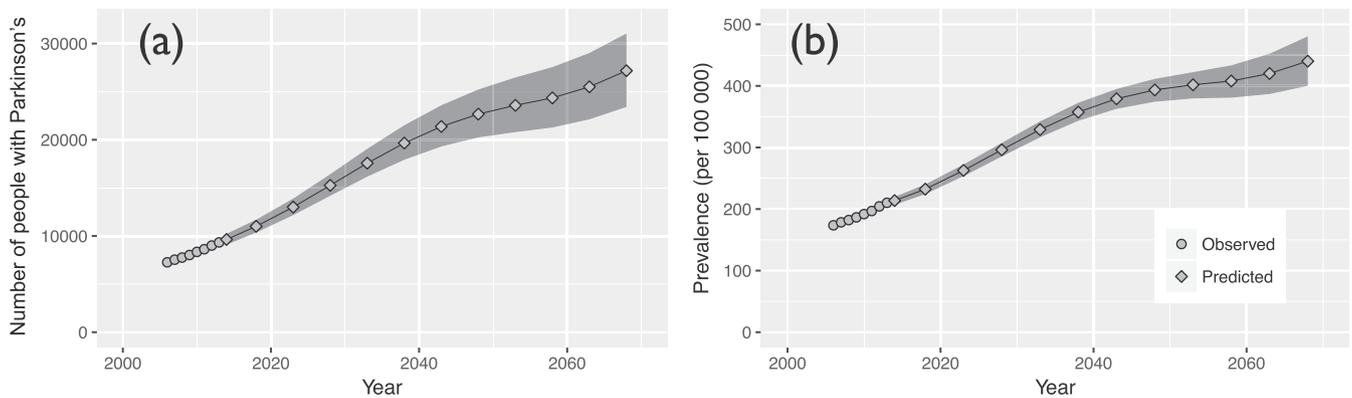


Fig. 3. Observed (years 2006–2013) and predicted (years 2014–2068) number of people with Parkinson's (a) and prevalence of Parkinson's (b) in New Zealand. The predictions are based upon Statistics New Zealand median, 5%, and 95% population projections by sex and age and the age and sex specific prevalence rates observed in 2013. There is a modest increase over the next few decades in both total number and prevalence. This is followed by a period where the rate of increase is reduced. The grey bands represent the 95% uncertainty interval given the model and data.

projected to continue to increase but at a slower rate, reaching an estimated 27 200 [23 400, 31 000] in 2068 (Fig. 3a).

The prevalence of Parkinson's in New Zealand is predicted to follow a similar trend to the number of people with Parkinson's, increasing linearly from 210 [208, 212] to 357 [343, 372] per 100 000 in 2038. Prevalence then increases at a slower rate, reaching 440 [400, 480] per 100 000 in 2068 (Fig. 3b).

4. Discussion

In this first study examining the nationwide incidence and prevalence of Parkinson's in New Zealand, we found moderately increasing incidence and prevalence rates of Parkinson's over time. We also found evidence that Parkinson's is likely a late-stage age-dependent rather than aging-dependent disease, with a sharp drop-off in incidence and prevalence after 85 years of age. Combining these findings, we predict that although there will be a linear increase in the number of people with Parkinson's and prevalence over the next 25 years, this increase will be moderated after this by the drop-off in rates in the oldest old, who will form an increasing proportion of the population. The main limitation of this study is that we indirectly inferred the probability of Parkinson's, based upon combinations of anti-parkinsonian medications and durations of their use. Those inferences were, however, calibrated using known diagnoses from a large convenience sub-sample of individuals taking those medications.

4.1. Prevalence and incidence rates in New Zealand

Our standardized incidence rates remained stable over time whereas the standardized prevalence showed an increase. This indicates that the duration of disease is increasing, which likely reflects the increasing life expectancy of the overall population (which increased by approximately 1 year over the period of this study, Statistics New Zealand Period Life Tables) as well as potentially earlier diagnosis and treatment. Stable incidence rates but increasing prevalence have also been observed in Israel [16]. Our estimate of Parkinson's prevalence is higher than previous New Zealand estimates (~110 per 100 000 [24,25]) derived from single-center ascertainment. The higher rate reported here is likely due to the aging population. No previous estimates of incidence in New Zealand exist.

4.2. Age-dependent disease

The drop off in the oldest old may reflect that the pool of individuals susceptible to developing Parkinson's becomes depleted, instead of Parkinson's being a disease where a progressive accumulation of cellular and organ damage over time monotonically increases the risk of developing the disease. While age-dependent diseases such as motor neuron disease have a peak incidence in middle age, it appears that for Parkinson's this peak occurs at a much older age, conflating the effects of age and aging. This may

explain why the age-related decrease remained under-recognised.

An alternative explanation for this decline could be that the oldest old aren't as actively diagnosed with Parkinson's or adequately treated. One audit of Parkinson's [26] reported that the final 2 years of life was spent in palliative care, a phase characterised in part when people with Parkinson's become unable to be administered adequate dopaminergic therapy. However, our data indicates that most people with Parkinson's in New Zealand are medicated until death (Supplementary Fig. 2).

It is also possible that it becomes more difficult, or less important, to diagnose and start treatment of Parkinson's in the oldest old, due to other comorbidities. This would cause a drop in both apparent incidence and prevalence in the oldest old. Whether such an effect could be of sufficient magnitude to explain the magnitude of the observed decline is unclear.

4.3. Future burden

Assuming no medical developments that will prevent or cure Parkinson's, the number of people with Parkinson's in New Zealand in 2038 is predicted to be double that in 2013. For Western Europe and the most populous nations the number of people with Parkinson's in 2030 has been predicted to be double that of 2005 [27]. Similarly for an analysis focusing solely on the United States, the number of people with Parkinson's in 2040 is expected to be double that of 2010 [28]. These studies all point to a relatively consistent picture of a doubling of the absolute number of people with Parkinson's in the next 25–30 years, with the longer time to doubling in the United States likely, at least in part, reflecting the lower life expectancy in the United States compared to New Zealand and Western Europe (World Bank 2104 values: New Zealand and Western Europe, 81 years; United States, 79 years).

There is inherent uncertainty in these future estimates. Although we are taking into account the uncertainty in the age-population structure, several other aspects have not been accounted for. These include the slightly increasing age-specific prevalence of Parkinson's over time due to the increase in disease duration. It is uncertain whether there will be a continual increase in disease duration due to general increases in life expectancy and/or earlier diagnosis and treatment. Furthermore, there are changes in lifestyle choices such as smoking, an activity which is correlated with lower rates of Parkinson's [29], that may influence the future incidence of Parkinson's. New Zealand has a goal of being smoke-free by 2025, a policy that will potentially increase the number of people with Parkinson's if smoking is truly protective of Parkinson's [30].

In conclusion, we have observed a moderate increase in the number of people with Parkinson's in New Zealand over the years 2006–2013, largely explained by a change in the population profile. The rate of increase in prevalence of Parkinson's disease is expected to persist in the near future, doubling from 2013 to 2038, but then increase at a slower rate after 2038. Our findings support the notion that Parkinson's disease is not an aging-dependent disorder but an age-dependent disorder.

Conflicts of interest

None.

Funding sources

This study was funded by the Neurological Foundation of New Zealand (Grant 1211 PG), and the New Zealand Brain Research Institute.

Authors' roles

1) Research project: A. Conception, B. Organization, C. Execution;

2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique;

3) Manuscript: A. Writing of the first draft, B. Review and Critique.

DJM: 1C,2A,2B,2C,3A,3B

TLP: 1A,1B,1C,2C,3A,3B

JFP: 2C,3B

JCDA: 3B

TJA: 1A, 3B.

MRM: 1A,2C,3B

Acknowledgement

We wish to thank Research Assistants, Gill Ebel and Helen Skene from the New Zealand Brain Research Institute. We are also grateful to the Ministry of Health's National Collections staff for assisting with use of data from the Pharmaceutical Collection database.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.parkreldis.2017.06.018>.

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