PARKINSON'S DISEASE IN HAWAI'I:
A STUDY OF PREVALENCE AND ETHNICITY

A THESIS SUBMITTED TO THE GRADUATE DIVISION OF THE UNIVERSITY OF HAWAI'I IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF

MASTER OF SCIENCE

IN

BIOMEDICAL SCIENCES

DECEMBER 2007

By
Lois Weiss

Thesis Committee:

James Davis, Chairperson
Rosanne Harrigan
David Easa
We certify that we have read this thesis and that, in our opinion, it is satisfactory in scope and quality as a thesis for the degree of Master of Science in Biomedical Sciences.

THESIS COMMITTEE

[Signatures]
# TABLE OF CONTENTS

Acknowledgments ................................................................................................................ iii
Abstract ................................................................................................................................ iv
List of Tables .......................................................................................................................... v
List of Figures ........................................................................................................................ vi
Chapter 1: Introduction ........................................................................................................ 1
Chapter 2: Method ................................................................................................................... 3
  Study Population .................................................................................................................... 3
  Data Analysis ....................................................................................................................... 3
Chapter 3: Results ................................................................................................................... 4
  Birth Year Prevalence .......................................................................................................... 4
  Seasonal Births .................................................................................................................... 5
  Gender and Age ................................................................................................................... 6
  Ethnicity ............................................................................................................................. 7
Chapter 4: Discussion ............................................................................................................. 9
  The 1918 Influenza Pandemic ............................................................................................ 11
  Hawai’i ............................................................................................................................... 12
References ............................................................................................................................... 14
ACKNOWLEDGMENTS

This study was supported by Federal grant R25 RR019321. The author thanks James Davis, committee chairperson, and committee members Rosanne Harrigan and David Ease, for their assistance and advice.
This analysis described the population prevalence of Parkinson's disease (PD) in Hawai‘i, by birth year, season, gender, age, and ethnicity for patients 50+ years old. Inclusion criteria were a history of Parkinson's drug-treatment following the PD diagnosis, and a claims history for other secondary diagnostic or treatment codes subsequent to the 332 diagnosis. Two-thousand thirty cases met the criteria. Without age adjustments, prevalence was 145/100,000. A birth-month distribution showed a significant seasonal trend (p=.04). The male to female ratio was 1.4 to 1, modal age of death was 81 years, and mortality was 2.6 (95% CI= 2.1 to 3.2) times greater than the non-Parkinson control sample. Of the 975 who self-reported ethnicity, 58% were Japanese. Compared to Japanese men, Japanese women were 17% less likely to develop PD (p < .001). Findings suggest that multiple sources of early-exposure late-onset conditions may precipitate PD, as well as lifestyle.
LIST OF TABLES

<table>
<thead>
<tr>
<th>Table</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Unadjusted or age adjusted prevalence estimates from drug registries ......</td>
<td>4</td>
</tr>
<tr>
<td>2. Parkinson’s disease prevalence per 100,000 by gender &amp; age groups ........</td>
<td>7</td>
</tr>
</tbody>
</table>
## LIST OF FIGURES

<table>
<thead>
<tr>
<th>Figure</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Parkinson's disease prevalence by birth year</td>
<td>5</td>
</tr>
<tr>
<td>2. Seasonal birth rates for Parkinson and control groups</td>
<td>6</td>
</tr>
<tr>
<td>3. Percentage of Parkinson's disease cases by ethnicity and age group</td>
<td>8</td>
</tr>
</tbody>
</table>
CHAPTER 1

INTRODUCTION

Globally, prevalence estimates for Parkinson's disease (PD) have been acquired in a number of ways. In regions of socialized medicine, health registries and health-care agencies provided patient diagnosis and treatment histories, or in some regions, medical teams including a neurologist administered door-to-door questionnaires and neurological exams. In eleven studies, PD patients were identified from a prescription-drug data base.\(^{(1-11)}\)

A comparison of prevalence estimates between data acquired from drug registries and all other methods show variation between and within methods. For example, in Spain PD estimates are available both from drug registries and community records. Estimates per 100,000 based on drug registries in Navarra\(^{(5)}\) and Austuria,\(^{(9)}\) Spain were 162 and 199, whereas annual estimates based on community records from similar Spanish urban areas in 1999, 2002 and 2004 were 121, 901, and 122, respectively.\(^{(12-14)}\)

The prevalence of PD in Hawai'i is unknown. A current prevalence estimate is needed to assess healthcare costs and affect public policy on a standard-of-care for PD. The ethnic composition in the State is unique, as are local lifestyles and the physical environment. It is reasonable to anticipate that these three factors may interact and reveal a disease prevalence that substantially differs from the prevalence reported in the ethnic countries of origin. In Hawai'i, acquiring reliable data on health
issues has some unique challenges because of the inherent diversities. The intent of this current analysis was to assess the PD prevalence in Hawai‘i for individuals age 50 and older; and to describe disease prevalence by birth year, season, gender, age and ethnicity using data from a prescription drug registry.
CHAPTER 2

METHOD

Study Population

The largest insurer in Hawai‘i provided data on 4,155 members who had a diagnoses
of Parkinson’s disease or Parkinsonism (ICD-9 code 332), who were enrolled from
1999 through 2005, and were age 50 or older. From this initial group, member’s data
were entered into the study if they currently lived in Hawai‘i; had a history of
Parkinson drug- treatment following the diagnosis, and were billed for other
secondary diagnostic or treatment codes subsequent to the 332 diagnosis.

Data Analysis

The PD prevalence was derived using approximately 1.4 million enrollment years and
expressed as cases per 100,000 members. Prevalence by gender, age, and birth years
were similarly calculated using the appropriate enrollment denominators. The
statistical differences by gender, age, season, birth year, and ethnicity were calculated
using a Chi-square. Age and gender adjusted mortality ratios were estimated using
proportional hazard models. Analyses were executed in SAS 9.1 or Enterprise guide
3.0 (SAS Institute, Cary, NC).
CHAPTER 3

RESULTS

Members with PD, age 50 or older, represented 1% of the 200,499 member enrollment for 1999-2005. Two-thousand thirty members diagnosed with PD met the inclusion criteria. The PD prevalence was 145/100,000. Hawai‘i ranked fourth lowest among the prevalence estimates of the eleven drug-registry studies summarized in Table 1. The mean prevalence across studies was 185 ±57 (SD). Estimates per 100,000 from drug registries ranged from 115 to 329.(1-11)

<table>
<thead>
<tr>
<th>Country</th>
<th>Per 100,000</th>
<th>Country</th>
<th>Per 100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sweden</td>
<td>115</td>
<td>Rome, Italy</td>
<td>174</td>
</tr>
<tr>
<td>British Columbia</td>
<td>144</td>
<td>Faroe Isle, Denmark</td>
<td>183</td>
</tr>
<tr>
<td>Wales</td>
<td>144</td>
<td>NW Italy</td>
<td>196</td>
</tr>
<tr>
<td>Hawai‘i</td>
<td>145</td>
<td>Asturia, Spain</td>
<td>199</td>
</tr>
<tr>
<td>Navarra, Spain</td>
<td>162</td>
<td>L'Aquila, Italy</td>
<td>229</td>
</tr>
<tr>
<td>Denmark</td>
<td>164</td>
<td>Nebraska, US</td>
<td>329</td>
</tr>
</tbody>
</table>

Note. * Indicates unadjusted estimates
Note. Adjusted estimates were calculated using regional age distributions

Birth Year Prevalence

Figure 1 shows the prevalence of PD in Hawai‘i by birth year. The numbers inset on the figure indicate the minimum age of a member in 1999. For example, if born in 1916 a member would be 83 years-old in 1999. Prevalence was highest for members born in 1916-1918, and who were at least 81 to 83 years old in 1999.
There were 169 deaths in the study population, and the modal age of death was 81 years. Although many members with Parkinson's disease lived long lives, their mortality rate was 2.6 (95% CI = 2.1 to 3.2) times greater than the non-Parkinson control sample.

Seasonal Births

A comparison of the PD and control groups (Figure 2) for birth rates by season and unadjusted for age showed a significant ($p = .04$) seasonal trend. The control group had relatively constant percentages (8.9% - 8.0%) across the 12 calendar months.
The highest percentage of PD births occurred in March (9.5%) and April (9.8%). The lowest percentages were in September (7.5%) and October (7%). With age adjustment, the statistical significance of the seasonal difference between groups decreased slightly (p=.08).

Gender and Age

The mean age for PD detection among men and women was 76 years. The prevalence per 100,000 in Hawai‘i by gender was 86 for men and 61 for women (a ratio of 1.4 to 1). Table 2 shows disease prevalence stratified by gender and age. There was a progressive increase in the number of cases across decades 50-80 and a markedly higher prevalence among men at each decade. Seventy-seven percent of members were 70 to 89 years old.
Table 2. Parkinson’s disease prevalence per 100,000 by gender & age groups

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age Groups</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>50-59</td>
<td>60-69</td>
</tr>
<tr>
<td>Men</td>
<td>Cases</td>
<td>66</td>
</tr>
<tr>
<td></td>
<td>Prevalence</td>
<td>24</td>
</tr>
<tr>
<td>Women</td>
<td>Cases</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td>Prevalence</td>
<td>18</td>
</tr>
<tr>
<td>Total</td>
<td>Cases</td>
<td>119</td>
</tr>
<tr>
<td></td>
<td>Prevalence</td>
<td>20</td>
</tr>
</tbody>
</table>

Ethnicity

Forty-eight percent (n=975) of the 2030 cohort reported ethnicity. Fifty-eight percent (n= 567) were Japanese, and of those 53% were men. The remaining members were 16% Caucasian, 8% Chinese, 7% Filipino, 6% Hawaiian, 1% Korean, and 4% other ethnicities. Compared to Japanese men in Hawai‘i, Japanese women were 17% less likely to develop PD (p < .001) and were 10% more likely than all other women (p < .001). A comparison of the age distribution between Japanese to all other ethnicities was statistically different (p < .001). Figure 3 shows Japanese members acquired Parkinson’s symptoms later and were more likely to live with the symptoms to an older age.
Figure 3 Percentage of Parkinson's disease cases by ethnicity and age group.
This analysis, based on historical drug registry data, revealed PD prevalence in Hawai‘i ranked fourth among twelve studies that used similar drug data bases, and suggested that prevalence was to some extent a function of ethnicity, age, and gender. Specific findings suggest an ethnic influence on PD acquisition, namely, Japanese members were older at first diagnosis and lived longer. Also, compared to women of other ethnicities, Japanese women had a substantially greater risk of developing PD. Furthermore, the environmental or lifestyle influence may be revealed by comparing gender difference between PD data from citizens in Japan\(^{(15-17)}\) and Japanese members in Hawai‘i. That is in Japan, PD predominates in women, whereas in Hawai‘i, Japanese women had significantly less risk of developing PD, than did Japanese men.

With PD, the initial disease symptoms result from a premature loss of dopamine producing neural cells in sub-cortical brain structures. The selective neural cell loss is attributed to a mitochondrial dysfunction in the central nervous system,\(^{(18,19)}\) which may result from a neuro-toxicity that ultimately blocks mitochondrial flow,\(^{(20-22)}\) or to an enzyme deficiency found in mitochondrial brain activity, as well as in other tissues of Parkinson patients.\(^{(23)}\) Selective neuro-cells loss may result from exposure to environmental neuro-toxins,\(^{(24-27)}\) or the interaction between exposure subsequent to genetic predisposition.\(^{(24)}\)
Hawai‘i has a long agricultural history using potentially neuro-toxic pesticides and heavy-metal herbicides to control invasive plant growth.\textsuperscript{[24,28]} Petrovich et. al.\textsuperscript{[29]} examined agricultural exposure among Japanese-American men from the Honolulu Heart Program who were born between 1900 and 1919. Compared to workers in other environments, the authors found a significant risk (RR=1.7-1.9) of developing PD among men who worked more than 10 years on a plantation. Given these findings, it is likely that a large number of agricultural workers are represented among the oldest members in our analysis, and they are included among those born before or during the peak birth years 1916-1918.

In addition to being predisposed by a history of toxic exposure in adulthood, a permanent but select inflammatory reaction to cytotoxic agents during fetal development or early in life may result in an enzyme deficiency that reduces mitochondrial function.\textsuperscript{[30]} A maternal immune response to an intrauterine viral infection is one source for a cytotoxic agent, which may interfere with necessary cell development and result in a premature depletion of dopamine as one ages.\textsuperscript{[31]} To assess the relative risk of developing PD following intrauterine viral exposure, Mattock et al.\textsuperscript{[32]} reported birth ratios of a Parkinson cohort matched to controls, at five-year intervals, during the influenza pandemic and epidemics in London during 1890-1930. Compared to births in other years, risk (≥ 1.66) of PD increased in 1892, 1904, 1909, 1918, 1919, and 1929. Similarly, a 1976 meta-analysis of PD incidence and age-of-onset in the United States, concluded that incidence and modal age-of-
onset were essentially unchanged during the previous 100 years with the exception of a notable disease increase during the 1920-1930 viral encephalitis epidemic.\(^{(33)}\)

The 1918 Influenza Pandemic

The influenza pandemic in Europe most likely originated in France, purportedly in the summer of 1918, and spread through Europe and America by troop movements during WWI.\(^{(34)}\) However, evidence supports the possibility of an early or pre-pandemic outbreak in New York City that quickly spread down the Atlantic coastline. Olsen et al.\(^{(35)}\) analyzed monthly New York City age-specific mortality data from 1911 to 1921. They found a strong, characteristic pandemic shift in mortality occurred toward adolescents and young adults first during the winter of 1917, followed by a devastating outbreak in the fall of 1918, and fewer reported cases in 1919. For the young pregnant women who survived exposure to influenza during the pandemic, fetal health was a concern. State Health and Human Service data from the Baltimore area in Maryland showed virus strength increased in mid to late September, 1918. Subsequently, stillbirths increased 60% during October through December of that year.\(^{(36)}\)
Hawai`i

Hawai`i has a long history of immigration from Western Europe, Asia, and the Americas. The general mobility of people on the islands during the early twentieth century was similar to other countries, creating similar risks of exposure to the influenza pandemic. The Hawai`i Board-of-Health, Bureau of Vital Statistics began reporting pandemic influenza cases in 1919. Reported incidence during the period was 1,088 in 1919; 17,411 in 1920; and 1,268 in 1921, after which the number of cases substantially decreased. Similar to the reports of increased stillbirths in Maryland, Hawai`i stillbirths nearly tripled during 1919-1921 with annual reports of 312, 370, and 334. The death rate in the State due to influenza was highest (10/1000) in 1920.

The 1918 pandemic virus did not occur simultaneously in all areas of all countries, nor was its virulence geographically consistent. The peak birth years, 1916-1918, of disease prevalence in the current Hawai`i cohort represents individuals born in varied geographic locations. The seasonal preponderance of the March and April births (figure 2) are not unique, seasonal shifts are reported throughout historic literature. It is noteworthy that the first trimester of these birth months occurred during the Fall when viral exposure increased.

In conclusion, the unique ethnic composition of this cohort demonstrates the effect environment or lifestyle may have on the development of PD. The analysis of birth year prevalence suggests multiple sources of early exposure – late onset conditions
that may precipitate the development of PD. Together, birth-year prevalence, the seasonal birth effect, and the general co-occurrence of these events during the 1918 influenza pandemic make a compelling observation that warrants further study. Alternative explanations for the observed PD prevalence patterns in Hawai`i may include exposure to environmental neuro-toxins, or a convergence of increased longevity with a greater death rate in the very old.
REFERENCES

29. Helen Petrovitch MGWR, MD; Robert D. Abbott, PhD; Wayne T. Sanderson, PhD,CIH; Dan S. Sharp, MD,PhD; Caroline M. Tanner, MD,PhD; Kamal H. Masaki, MD; Patricia L. Blanchette, MD,MPH; Jordan S. Popper, MD; Daniel Foley, MS; Lenore Launer, PhD; Lon R. White, MD,MPH. Plantation Work and Risk of Parkinson Disease in a Population-Based Longitudinal Study Arch Neurol. 2002;59(11):1787-92.
34. Patterson SW. The Pathology of Influenza in France. From the Medical Journal of Australia. 1920 March 6;1(10).
