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Time Trends in the Incidence of Parkinson Disease

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IMPORTANCE Changes over time in the incidence of parkinsonism and Parkinson disease (PD) remain uncertain.

OBJECTIVE To investigate secular trends (period effects) and birth cohort trends in the incidence of parkinsonism and PD over 30 years in a geographically defined American population.

DESIGN, SETTING, AND PARTICIPANTS We used the medical records–linkage system of the Rochester Epidemiology Project to identify incidence cases of PD and other types of parkinsonism in Olmsted County, Minnesota, from 1976 to 2005. All cases were classified by a movement disorder specialist using defined criteria through the review of the complete medical records within the system. The analyses for this study were conducted between May 2015 and January 2016.

MAIN OUTCOMES AND MEASURES Incidence rates of parkinsonism and PD over 30 years. We tested for secular trends (period effects) using negative binomial regression models and for birth cohort effects using age–period-cohort models.

RESULTS Of 906 patients with parkinsonism, 501 were men, and the median age at onset was 74 years (interquartile range, 66-81 years). Of the 464 patients with PD, 275 were men, and the median age at onset was 73 years (interquartile range, 64-80 years). The overall incidence rates increased significantly over 30 years in men for both parkinsonism (relative risk [RR], 1.17 per decade; 95% CI, 1.03-1.33) and PD (RR, 1.24 per decade; 95% CI, 1.08-1.43). These trends were driven primarily by the older age groups. In particular, for men 70 years or older, incidence rates increased for both parkinsonism (RR, 1.24 per decade; 95% CI, 1.07-1.44) and PD (RR, 1.35 per decade; 95% CI, 1.10-1.65). The secular trends were not significant for women overall or in age strata. We observed an increased risk for both men and women born in the 1920 cohort (1915-1924). However, this birth cohort effect was significant only for PD and only in men.

CONCLUSIONS AND REVELANCE Our study suggests that the incidence of parkinsonism and PD may have increased between 1976 and 2005, particularly in men 70 years and older. These trends may be associated with the dramatic changes in smoking behavior that took place in the second half of the 20th century or with other lifestyle or environmental changes. However, the trends could be spurious and need to be confirmed in other populations.

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In 2008, Morozova et al[1] suggested that smokers have a 74% reduction in risk of Parkinson disease (PD) because some constituents of tobacco may reduce the risk of PD. Under the assumption that smoking is causally associated with PD, they postulated that the drastic decline in smoking frequency that took place in US men after the peak in the 1940s and 1950s would predict an increase in the incidence of PD several decades later.[1,2] However, to our knowledge, their predictions have not been tested empirically, and the long-term time trends for PD remain uncertain.[3-9] Therefore, we studied time trends for parkinsonism overall and for PD over 30 years in a well-defined US population.[3,10-12]

Key Points

Question Is the incidence of parkinsonism and Parkinson disease changing over time?

Findings In this study in Olmsted County, Minnesota, the incidence of both parkinsonism and Parkinson disease increased over 30 years, particularly in men 70 years old and older. In addition, an increased risk of Parkinson disease was observed in men born in the 1920 cohort (1915-1924) compared with other birth cohorts.

Meaning If these trends are confirmed in other populations, they may be associated with the dramatic changes in smoking behavior during the last 50 years or with other lifestyle or environmental changes.

Methods

Case Ascertainment

Extensive details about the case ascertainment were reported elsewhere.[3,10-12] Briefly, we ascertained cases of parkinsonism through the records-linkage system of the Rochester Epidemiology Project. This system provides the infrastructure for indexing and linking essentially all medical information of the population of Olmstead County, Minnesota.[13-16] All medical diagnoses, surgical interventions, and other procedures are abstracted and entered into computerized indexes using the *Hospital Adaptation of the International Classification of Diseases, Eighth Revision*[17] or the *International Classification of Diseases, Ninth Revision*.[18]

We ascertained potential cases of parkinsonism using a computerized screening phase and a subsequent clinical confirmation phase, as described in the original articles.[3,10-12] The complete medical records of all persons who received at least 1 of the screening diagnostic codes from 1976 through 2005 were reviewed by a movement disorders specialist using a specifically designed abstracting form (J.H.B. for 1976 to 1990 and R.S. for 1991 to 2005). In addition, we also reviewed the records for all persons who received at least 1 of the screening diagnostic codes in 2006 to 2010. This extended period of capture ensured that patients who came to clinical attention up to 5 years after the study period were appropriately counted as incident patients if the onset of symptoms had occurred during the study period (lag time between onset of symptoms and clinical diagnosis). The movement disorder specialist defined the year of onset of parkinsonism and the type of parkinsonism using specified diagnostic criteria and following a manual of instructions.[10,19-21] To be included in our study, patients were required to reside in Olmsted County at the time of onset of parkinsonian symptoms, and we excluded persons who denied authorization to use their medical records for research.[13] However, informed consent specific for this study was not required because all of the data were abstracted from medical records, and none of the patients were contacted. All study procedures and ethical aspects were approved by the institutional review boards of the Mayo Clinic and Olmsted Medical Center.

Diagnostic Criteria

Our diagnostic criteria included 2 steps: the definition of parkinsonism as a syndrome and the definition of the different types of parkinsonism within the syndrome. Parkinsonism was defined as the presence of at least 2 of 4 cardinal signs: rest tremor, bradykinesia, rigidity, and impaired postural reflexes. Parkinson disease was defined as parkinsonism with all 3 of the following features: no other cause (eg, repeated stroke with stepwise progression, repeated head injury, history of encephalitis, neuroleptic treatment ≤6 months before onset, hydrocephalus, or brain tumor); no documentation of unresponsiveness to levodopa at doses of at least 1 g/day in combination with carbidopa (applicable only to patients who were treated); and no prominent or early (<1 year from onset) signs of more extensive nervous system involvement (eg, dysautonomia) not explained otherwise.[10] The other types of parkinsonism were classified as reported elsewhere.[11]

Reliability and Validity of Diagnoses

The case-finding procedures were valid and reliable as described more extensively elsewhere.[10,11] In brief, an independent records review by the 2 movement disorders specialists who applied the same diagnostic criteria (J.H.B. and R.S.) showed 90% agreement on the presence of parkinsonism and 70% agreement on the exclusion of parkinsonism (sample classified by R.S. as 30 patients with parkinsonism and 10 persons free of parkinsonism from the 1991-2005 incidence study).[11] In general, the agreement on the year of onset of parkinsonism was also high (intraclass correlation coefficient, 0.85; 95% CI, 0.77-0.92).[11] Finally, a comparison of clinical diagnoses of specific proteinopathies (synucleinopathies and tauopathies) with autopsy findings in 65 patients who had died showed 81.5% agreement.[11]

Data Analysis

All individuals who met criteria for parkinsonism and were residents of Olmsted County at the time of symptom onset between January 1, 1976, and December 31, 2005, were included as incident patients. We calculated incidence rates using incident patients as the numerator and population counts from the Rochester Epidemiology Project Census as the denominator.[13] Consistent with the methods used in the initial incidence study[10] and used again in the more recent incidence study,[11] the denominator person-years were corrected by removing prevalent patients with parkinsonism.[22]

Table 1. Person-year Denominators Used to Calculate Incidence Rates

Age and Sex Groups	Person-year Denominators, No.					
	0-39 y	40-59 y	60-69 y	70-79 y	80-99 y	All Ages
Men						
1976-1985	314 404	79 569	24 498	13 910	6114	438 495
1986-1995	357 438	106 293	29 930	18 200	8170	520 031
1996-2005	383 706	156 767	39 586	24 809	11 734	616 602
All years	1 055 548	342 629	94 014	56 919	26 018	1 575 128
Women						
1976-1985	348 937	85 196	29 562	23 245	15 827	502 767
1986-1995	375 551	115 608	34 210	26 992	21 290	573 651
1996-2005	394 553	171 371	43 528	32 080	25 741	667 273
All years	1 119 041	372 175	107 300	82 317	62 858	1 743 691
Both sexes						
1976-1985	663 341	164 765	54 060	37 155	21 941	941 262
1986-1995	732 989	221 901	64 140	45 192	29 460	1 093 682
1996-2005	778 259	328 138	83 114	56 889	37 475	1 283 875
All years	2 174 589	714 804	201 314	139 236	88 876	3 318 819

We computed age-, sex-, and decade-specific incidence rates for parkinsonism (of all types) and for PD. In addition, we investigated changes in incidence rates separately for men and women in 2 broad age classes: younger than 70 years and 70 years and older. Incidence rates were directly standardized by age to the total US population from the 1990 decennial census (midpoint of the 30-year period) when overall rates were compared.[23]

We performed statistical testing of the time trends (period effects) using negative binomial regression models.[24] Negative binomial regression was used instead of Poisson regression because we had a number of zero counts and larger variance in some models.[24] The unit of observation was the incidence rate in a single calendar year (directly standardized by age to the total 1990 US population).[23] We calculated a relative risk (RR) and the corresponding 95% CI to measure the average increase in the incidence rate over 10 calendar years.

Changes in incidence rates of parkinsonism and PD across individuals born at different times (birth cohort effects) were investigated graphically using birth cohort curves constructed with decennium-specific incidence rates for men and women separately. Birth cohorts of 10 calendar years were considered; the central year served as the cohort label.[3] Consistent with the 10-year frame of analysis, we disaggregated the incidence rates by 10-year age classes. We also explored birth cohort effects and period effects using age-period-cohort models as described elsewhere.[25,26] For these analyses, we constructed 5-year period incidence rates and 5-year birth cohort incidence rates and used natural splines to model nonlinear effects. All statistical testing was done at the conventional α level of .05 (2-tailed). We used SAS, version 9.3 (SAS Institute Inc) and the EPI package in R (R Foundation for Statistical Computing) for analyses.[25]

Results

Secular Trends (Period Effects)

We included 906 incident cases of parkinsonism of any type with onset between January 1, 1976, and December 31, 2005.[3,10,11] **Table 1** shows the person-year denominators used to calculate the incidence rates. **Table 2** shows the age- and sex-specific incidence rates (cases per 100 000 person-years) for parkinsonism (of all types) and PD in 3 decades. **Figure 1** shows incidence rates age-standardized to the total 1990 US population estimated using single calendar year data points and negative binomial regression in men and women separately for parkinsonism and for PD. The incidence rates for parkinsonism of all types and for PD were higher in men than in women across all 3 decades (Figure 1).

Age-adjusted incidence rates of parkinsonism were stable for women over the 30-year time frame; however, they increased in men from 38.8 cases per 100 000 person-years between 1976 and 1985 to 56.0 between 1996 and 2005 (Table 2). Analyses using negative binomial regression models showed a significant increase in incidence rates for men (RR, 1.17 per decade; 95% CI, 1.03-1.33; $P = .01$, Figure 1A) but not for women. We also observed a significant sex by calendar year interaction (the slope of increase was greater in men than women). The increase in incidence rates was greater for men 70 years or older (RR, 1.24 per decade; 95% CI, 1.07-1.44; $P = .005$, Figure 1C) than in men younger than 70 years (Figure 1B). However, the age by calendar year interaction in men was not significant.

Similarly, the age-adjusted incidence rate of PD increased in men from 18.2 between 1976 and 1985 to 30.5 between 1996 and 2005 (Table 2). Analyses using negative binomial regression models showed a significant increase in incidence rates in men (RR, 1.24 per decade; 95% CI, 1.08-1.43; $P = .003$, Figure 1D) but not for women. However, the sex by calendar year interaction was not significant. The increase was greater for men 70 years or older (RR, 1.35 per decade; 95% CI, 1.10-1.65; $P = .004$, Figure 1F) than for men younger than 70 years (Figure 1E). However, the age by calendar year interaction in men was not significant. Women 70 years or older also experienced an increase in the incidence rate of PD; however, the trend was not statistically significant (RR, 1.24 per decade; 95% CI, 0.94-1.64; $P = .12$, Figure 1F).

Birth Cohort Trends

Each 10-year birth cohort contributed 3 age-specific incidence rates over 3 decades that are shown with different col-

Table 2. Age- and Sex-Specific Incidence Rates (per 100 000 Person-years) Across 3 Decades for Parkinsonism and Parkinson Disease[a]

Type of Parkinsonism	Incidence Rate (No. of Patients)						All Ages, Standardized[b]
	0-39 y	40-59 y	60-69 y	70-79 y	80-99 y	All Ages	
All types							
Men							
1976-1985	0.3 (1)	18.9 (15)	122.5 (30)	237.2 (33)	392.5 (24)	23.5 (103)	38.9
1986-1995	0.8 (3)	14.1 (15)	120.3 (36)	307.7 (56)	379.4 (31)	27.1 (141)	41.7
1996-2005	0.8 (3)	15.9 (25)	154.1 (61)	407.1 (101)	571.0 (67)	41.7 (257)	55.9
All years	0.7 (7)	16.1 (55)	135.1 (127)	333.8 (190)	468.9 (122)	31.8 (501)	47.2
Women							
1976-1985	1.4 (5)	15.3 (13)	91.3 (27)	154.9 (36)	221.1 (35)	23.1 (116)	26.8
1986-1995	0.8 (3)	7.8 (9)	46.8 (16)	166.7 (45)	169.1 (36)	19.0 (109)	20.3
1996-2005	0.0 (0)	15.2 (26)	66.6 (29)	162.1 (52)	283.6 (73)	27.0 (180)	26.0
All years	0.7 (8)	12.9 (48)	67.1 (72)	161.6 (133)	229.1 (144)	23.2 (405)	24.4
Both sexes							
1976-1985	0.9 (6)	17.0 (28)	105.4 (57)	185.7 (69)	268.9 (59)	23.3 (219)	31.1
1986-1995	0.8 (6)	10.8 (24)	81.1 (52)	223.5 (101)	227.4 (67)	22.9 (250)	28.7
1996-2005	0.4 (3)	15.5 (51)	108.3 (90)	268.9 (153)	373.6 (140)	34.0 (437)	38.4
All years	0.7 (15)	14.4 (103)	98.9 (199)	232.0 (323)	299.3 (266)	27.3 (906)	33.3
Parkinson disease							
Men							
1976-1985	0.0 (0)	11.3 (9)	73.5 (18)	129.4 (18)	81.8 (5)	11.4 (50)	18.2
1986-1995	0.3 (1)	13.2 (14)	73.5 (22)	186.8 (34)	159.1 (13)	16.2 (84)	24.2
1996-2005	0.3 (1)	10.8 (17)	90.9 (36)	201.5 (50)	315.3 (37)	22.9 (141)	30.4
All years	0.2 (2)	11.7 (40)	80.8 (76)	179.2 (102)	211.4 (55)	17.5 (275)	25.5
Women							
1976-1985	0.0 (0)	7.0 (6)	47.4 (14)	51.6 (12)	82.1 (13)	9.0 (45)	10.7
1986-1995	0.0 (0)	5.2 (6)	20.5 (7)	88.9 (24)	51.7 (11)	8.4 (48)	9.3
1996-2005	0.0 (0)	8.2 (14)	32.2 (14)	87.3 (28)	155.4 (40)	14.4 (96)	13.8
All years	0.0 (0)	7.0 (26)	32.6 (35)	77.7 (64)	101.8 (64)	10.8 (189)	11.5
Both sexes							
1976-1985	0.0 (0)	9.1 (15)	59.2 (32)	80.7 (30)	82.0 (18)	10.1 (95)	13.8
1986-1995	0.1 (1)	9.0 (20)	45.2 (29)	128.3 (58)	81.5 (24)	12.1 (132)	15.4
1996-2005	0.1 (1)	9.4 (31)	60.2 (50)	137.1 (78)	205.5 (77)	18.5 (237)	20.7
All years	0.1 (2)	9.2 (66)	55.1 (111)	119.2 (166)	133.9 (119)	14.0 (464)	17.2

[a] Incidence rates were calculated by dividing the number of observed incidence patients by the corresponding person-year denominators as reported in Table 1. We did not report confidence intervals because the study covered the target population completely (no sampling was involved).

[b] The incidence rates were directly standardized by age to the total 1990 US population. The incidence rates directly standardized by age and sex to the total 1990 US population were 31.4 for 1976-1985, 28.9 for 1986-1995, 37.9 for 1996-2005, and 33.5 for the full 30 years for parkinsonism, and they were 14.0 for 1976-1985, 15.5 for 1986-1995, 20.4 for 1996-2005, and 17.2 for the full 30 years for Parkinson disease.

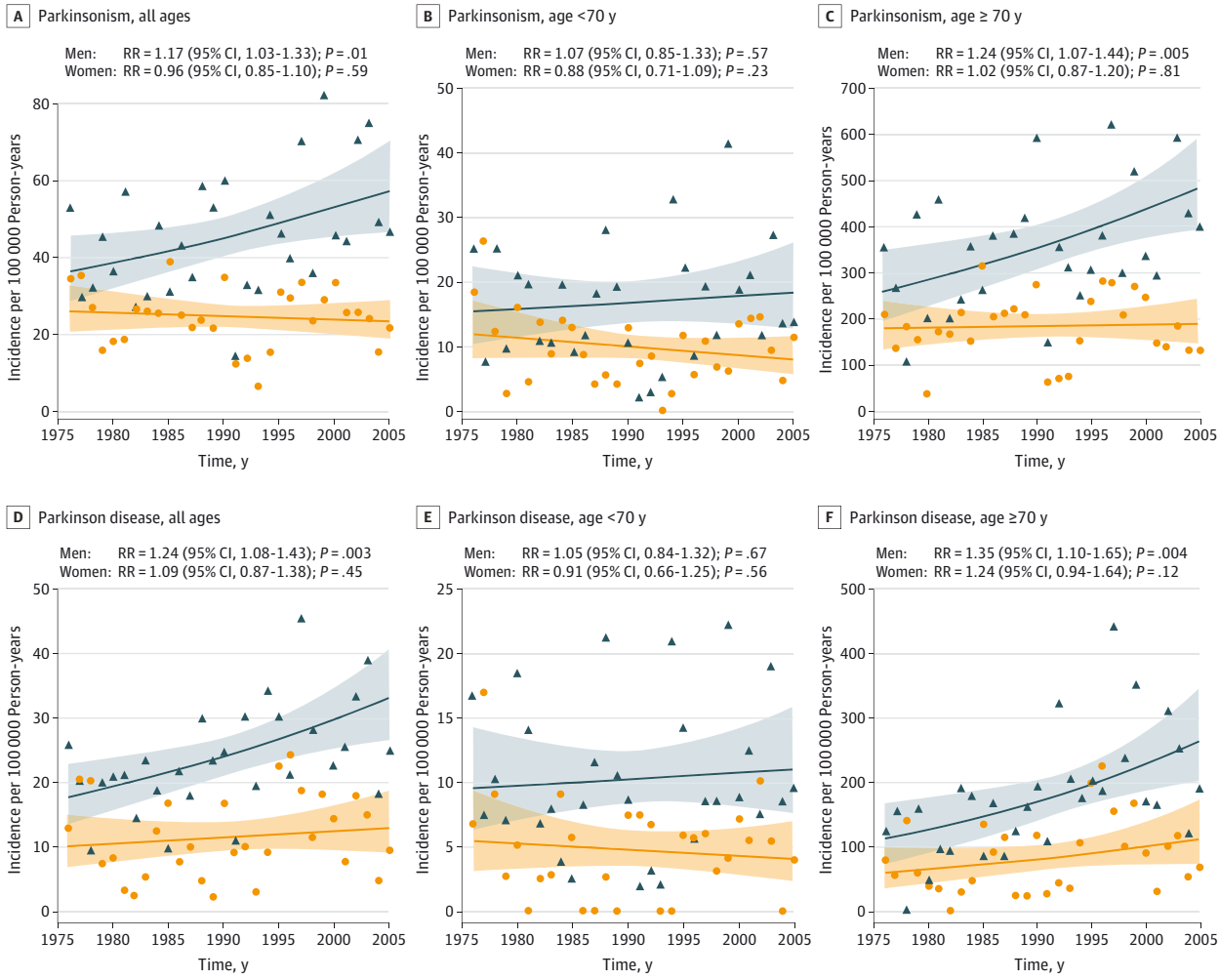
ors and symbols in **Figure 2**. Our graphical analyses of birth cohort effects revealed a possible higher incidence of both parkinsonism and PD in men and women born in the 1920 cohort. Men and women born in the 1920 cohort (1915-1924) are represented by the orange line with square symbols. However, in age-period-cohort models, the birth cohort effect was significant only for PD and only for men (**Figure 3**).

Discussion

Our study suggests an increase in the incidence of both parkinsonism of all types and of PD during the 30-year period between 1976 and 2005, particularly in men 70 years or older. Although no trend was evident overall for women, women in the age group 70 years or older experienced an increase in the incidence of PD with borderline statistical significance. We also observed higher incidence rates of PD for men born in the 1920 cohort. Our study provides evidence contrary to 2 previous US studies and 1 Canadian study that showed no trend and particularly contrary to 3 UK studies suggesting a possible decline in the occurrence of PD over time.[3-8] A study using Swiss mortality data suggested a possible birth cohort effect, with higher risk for cohorts born before the 1920s.[9]

The time trends that we observed need to be interpreted with caution. First, the trends may be an artifact caused by increased awareness of symptoms and improved access to care of patients or to increased awareness of signs and symptoms of parkinsonism by physicians. For example, the trends may be associated with a better recognition by physicians of parkinsonism and PD in the older patients in the past few decades or to a more inclusive diagnostic adjudication in the more recent segment of the study (R.S. vs J.H.B. adjudication). It is possible that in the earlier years of our study, elderly persons with cardiovascular conditions, cancer, or other diseases were not diagnosed as having parkinsonism because the symptoms of parkinsonism were not considered important in the overall clinical management and were not considered a major cause of disabil-

Figure 1. Secular Trends in Incidence Rates (Period Effects)

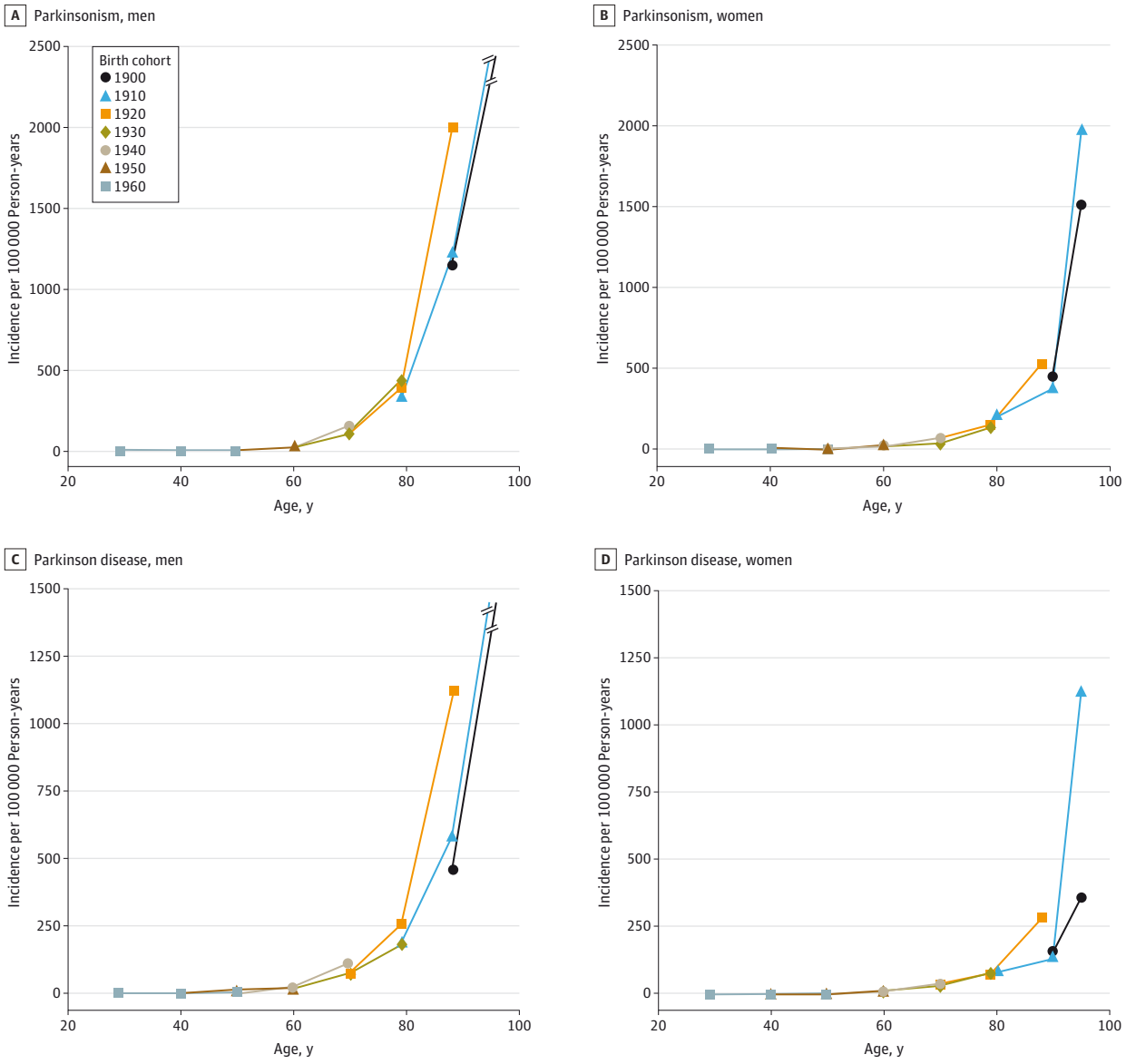


Incidence rate curves for men (blue) and women (orange) estimated using single calendar year data points (directly standardized by age to the total 1990 US population) and negative binomial regression (A-C, parkinsonism overall; D-F, Parkinson disease). The relative risk refers to the average increase in incidence rate over 10 years.

ity or of mortality. In the more recent years, physicians may have started to recognize parkinsonism even in the context of complex multimorbidity. Against a diagnostic artifact is the decline in the incidence of drug-induced parkinsonism observed in this same population during the same period (data not shown). In addition, against a diagnostic artifact is the adequate agreement between the 2 movement disorders specialists and the good validity of the clinical diagnosis compared with autopsy findings.[10,11] Finally, the observation that the time trends were more evident in men than in women may support a genuine trend in incidence because the recognition of the symptoms of parkinsonism in the context of multimorbidity should have changed similarly over time in men and women.

A second possible cause for a spurious increase in incidence rates is a change in coding practices in the records-linkage system or the switch from *International Classification of Diseases, Eighth Revision* to *International Classification of Diseases, Ninth Revision* coding in 1994. Because our case ascertainment was a laborious process involving a sensitive screening phase (inclusion of a large set of diagnostic codes to increase sensitivity even at the expense of lower specificity) and a detailed review of the medical records of those patients who screened positive, we did not rely on electronic codes to define the disease.[10,11] Although we cannot exclude a trend in coding practices, we do not think that this was sizeable, if any. Finally, another possible cause for a spurious trend is a change over time in the percentage of people who denied authorization to use their medical records for research. However, the law requiring authorization was only introduced in 1997 (Minnesota state privacy law), and the authorization rate has always been greater than 95% since 1997.[15] In summary, during the 30 years of study, the health care practices in Olmsted County have not changed, the in and out migration has been limited, especially in the age groups at risk for parkinsonism, and the percentage of the population covered by the Rochester Epidemiology Project has remained stable.[15]

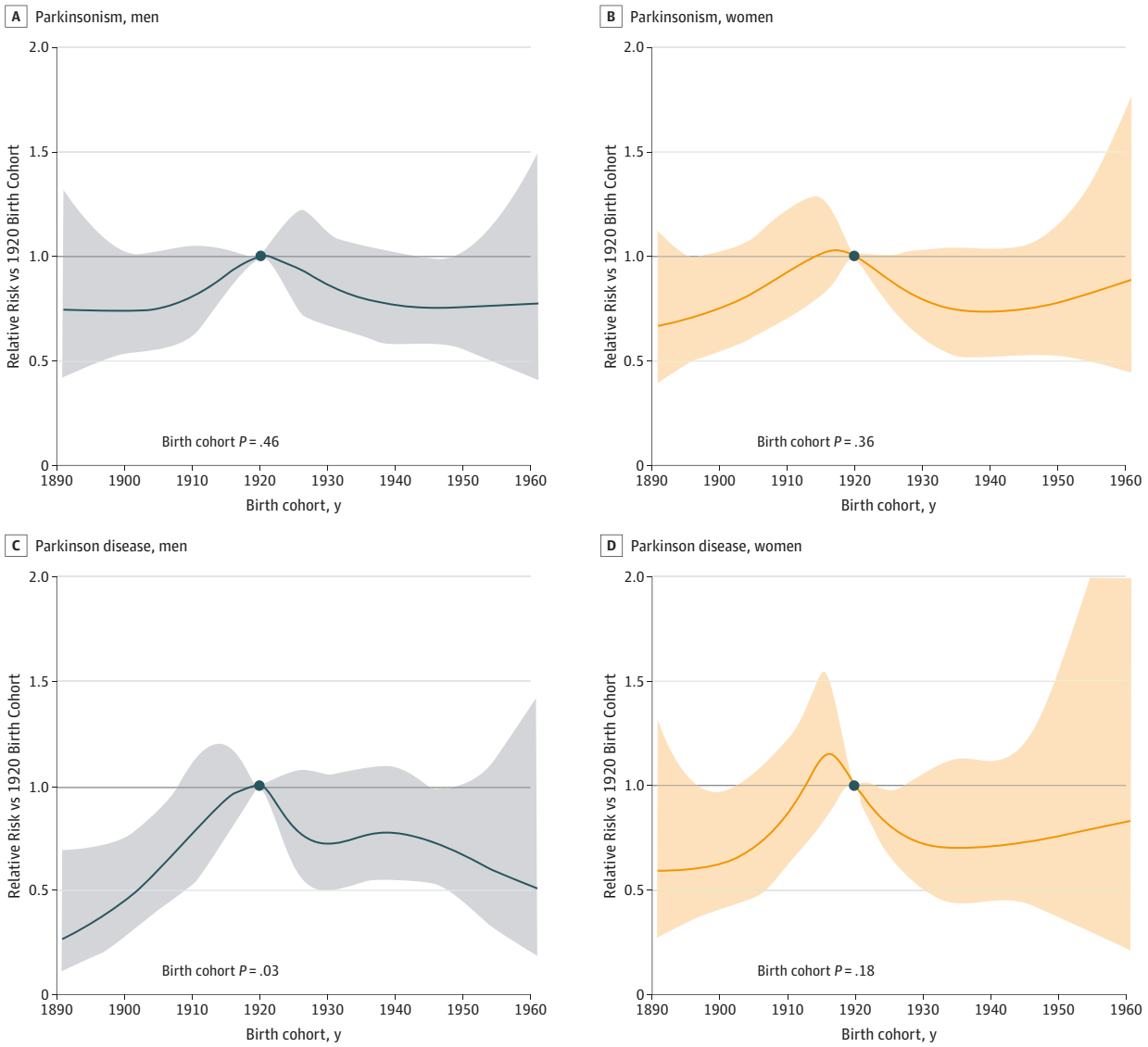
Figure 2. Birth Cohort Trends in Incidence Rates



Birth cohort curves of age- and sex-specific incidence rates for parkinsonism overall (A and B) and Parkinson disease (C and D). The central year of each 10-year birth cohort served as the cohort label. Each birth cohort contributed 3 age-specific incidence rates over 3 decades that are shown with different colors and symbols.

If the trend of increasing incidence rates is genuine and can be replicated in other populations, it has major implications for etiologic research and for public health. From a research perspective, the trend should prompt studies to identify possible environmental or lifestyle changes during the life span of the study participants.[1,27,28] If we assume that the association of smoking with reduced risk of PD has a biological basis, our findings may be explained in part by time trends in smoking.[1,2] Smoking behavior in industrialized nations, including the United States, has changed dramatically over the second half of the 20th century, with diverging patterns in men and women.[29] The prevalence of smoking in the United States peaked in the 1940s and 1950s at approximately 67% for men and in the 1960s at approximately 44% for women. However, in the past 25 years, the gap between men and women has narrowed. Between 1965 and 2009 (44 years), the frequency declined from 51.9% to 23.5% in men and from 33.9% to 17.9% in women.[30] The decline in smoking rates in men may explain in part the increasing incidence of parkinsonism and PD.[1] However, other environmental or lifestyle risk or protective factors that are related to sex may also be involved such as pesticide use, head trauma, and coffee consumption.[1,31,32] The possible higher risk of PD for men and women born in the 1920 birth cohort (1915-1924) may suggest exposures that took place during intrauterine life or in early life (eg, intrauterine infection, toxic exposure, or dietary deficiency).[33] Further studies

Figure 3. Analyses Using Age–Period-Cohort Models



Birth cohort component of the age-period-cohort models for parkinsonism overall (A and B) and Parkinson disease (C and D) in men and women separately. The birth cohort effects were displayed relative to 1920 (median year of birth for all patients with parkinsonism; circle with relative risk of 1.0) and fixing the period component to 1990 (midpoint of the study interval). For a given birth cohort year (x-axis), the figure shows the ratio of the incidence rate in that year compared with the incidence rate in the 1920 birth cohort (relative risk on the y-axis).

are needed to confirm these etiologic hypotheses. From a public health perspective, an increase in the incidence of parkinsonism and PD would modify our projections for the total number of persons with parkinsonism or PD in the coming decades.[34,35]

Our study has a number of strengths. To our knowledge, it is the first study to consider long-term secular trends in incidence (over 30 years) and to analyze the data both as secular trends (period effects) and as birth cohort trends. Our study is also unique in the extent of clinical precision. The full record of each patient was reviewed by a movement disorders specialist to confirm the diagnosis of parkinsonism and to meticulously classify different types of parkinsonism. This level of diagnostic precision is impossible when dealing with death certificate data or with administrative data (eg, billing data). Second, our study was conducted in a relatively stable population, using a population-based records-linkage system that spans across the entire life of the individuals included.[13-16] The case-finding procedures and the diagnostic criteria used in the 2 studies that were combined were similar, so the observed changes are not caused by changes in methods. In addition, all of the patients with parkinsonism were adjudicated by a movement disorders specialist at the time of medical record abstraction to reduce differences in the diagnostic criteria over time or across the different specialists. Third, all of the medical facilities in Olmsted County are included in the Rochester

Epidemiology Project,[13-16] and it is unlikely that a patient with parkinsonism would have been seen exclusively outside of the county while living in the county. To avoid the risk of underestimating incidence rates of parkinsonism in the eldest age groups, we corrected our census denominators by removing prevalent cases of parkinsonism. However, the effects of these corrections were small (data not shown).

Our study also has a number of limitations. First, our study population was somewhat small to provide stable incidence rates and to conduct more definitive age-period-cohort analyses. This limitation was insurmountable because our case finding is based on the unique records-linkage system serving Olmsted County, and a study of time trends for PD would be highly impractical in another population without the system. Second, we could not analyze the time trends in less common subtypes of parkinsonism (eg, multiple system atrophy) because of sample size limitations. Third, changes in clinical practice and the introduction of new sets of diagnostic criteria during the time frame of the 1991-2005 study could have changed the differential diagnosis by subtypes of parkinsonism, thus creating spurious trends in subtypes. As evidence against this possible bias, the overall distribution of subtypes of parkinsonism was similar in the 1976-1990 study and in the 1991-2005 study. In addition, a trend in the classification of subtypes of parkinsonism should not influence the overall trends for parkinsonism.

Conclusions

Our study suggests that the incidence of parkinsonism and PD may have increased between 1976 and 2005, particularly in men 70 years old and older. These trends may be associated with the dramatic changes in smoking behavior that took place in the second half of the 20th century or with other lifestyle or environmental changes. However, the trends could be spurious and need to be confirmed in other populations.

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Study concept and design: Rocca, Savica.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Rocca, Savica.
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Statistical analysis: Grossardt.
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