

1 Epidemiology of Parkinson's Disease

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Epidemiology has essentially four roles: (i) measuring the health status of a population and identifying groups at high risk or clusters of disease, (ii) determining aetiological risk factors that may be amenable to intervention and hence preventing disease, (iii) describing the natural history of disease and measuring the impact of interventions, (iv) planning and evaluating the provision of health services. Past epidemiological effort has centred mainly on describing the frequency of Parkinson's disease (PD) with respect to time, place and person and identifying potential risk factors with relatively less concern on the natural history and planning services for PD patients.

Temporal Patterns

Temporal data are difficult to interpret, especially mortality rates, as variations may reflect chance, increased diagnostic awareness, improved survival due to treatment or secular changes in life expectancy as well as true differences in incidence of disease. Death certification data provides us with information over the longest time span, although they have additional problems with accuracy and completeness. Mortality patterns from several different countries show fairly consistent results; mortality rates amongst older populations (>75 years) show a steady increase, whilst the rates for younger populations (< 65 years) have been declining. This pattern has been seen in several different countries.^{1 2 3 4 5 6}

Almost certainly diagnostic awareness increased after the introduction of levodopa therapy in the 1970s. However, the increase in mortality appears to predate this period. It also cannot explain why the proportional increase in male mortality for England and Wales and the USA¹ is greater than for women (see sex differences below). This is unlikely to reflect ascertainment or treatment effects. One suggestion⁷ to explain this observation is that the declining mortality from other diseases, such as cardiovascular disease, has increased the pool of susceptible individuals that could develop PD. This may be true if PD and cardiovascular disease shared a common aetiology, but there is no evidence to support this idea.

The divergence of age-specific mortality rates may reflect a 'cohort' effect, whereby some cohorts of individuals born and growing up in a certain time period are uniquely at greater risk of disease than other birth cohorts due to a self-limiting exposure, such as the encephalitis lethargica epidemic.⁸ Birth cohorts born between 1875-1895 do appear to have excess mortality rates.^{2 4 9} It is still too soon to fully evaluate this hypothesis as cohorts born after the epidemic from the mid 30s are still relatively young (< 65 years) and have not reached the age when mortality rates have been shown to be increasing. The cohort hypothesis is also unlikely to explain the differential mortality increase seen for men (see above) as there was little difference in encephalitis lethargica mortality rates for men and women.¹⁰

Data from Rochester, Minnesota are unique in providing incidence rates from 1935 to 1979.^{11 12 13} The annual incidence rate has increased from 11.4 per 100,000 in 1935-1944 to 18.2 per 100,000 between 1967-1979, but the age-adjusted rates have remained fairly constant over the last 30 years.¹⁴ However, like the mortality data, the rate for cases aged between 40-69 does appear to have declined whilst that for the over 70 years has shown an increase. A re-analysis of incidence data from Rochester data between 1976 to 1990 has provided further data to help us interpret the temporal trends.¹⁵ Overall rates have remained relatively stable but the age-specific patterns are consistent with a divergence by age group (see figure 1) so that rates have been increasing for older subjects and decreasing for younger subjects.

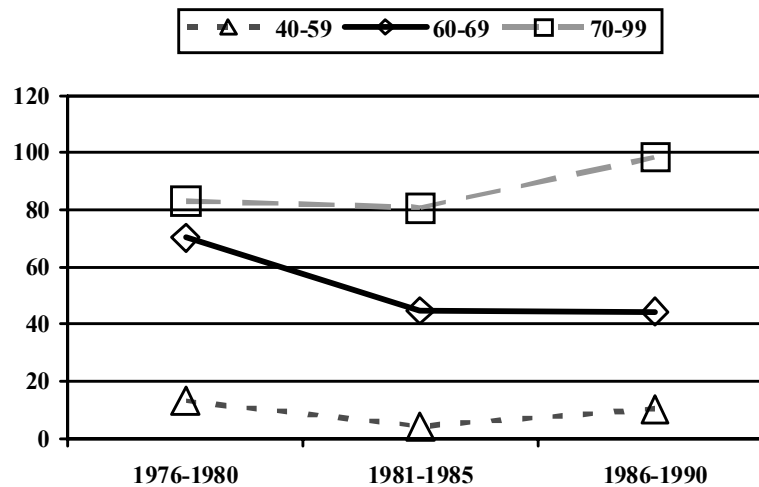


Figure 1: Temporal trends for age specific incidence rates between 1976 to 1990 from Rochester, Minnesota

Geographical Distribution

Early comparisons of international mortality rates showed fairly large differences (7-8 fold) between countries.¹⁶ However, more careful comparisons of prevalence surveys demonstrates that differences are not so marked. Age-adjusted prevalence rates suggest that a threefold difference may exist between Libya (57 per 100,000) to Iceland (182 per 100,000).¹⁴ If comparison is restricted to the 50-69 year age-range, differences between various European countries is reduced to less than two-fold (80%), excluding Iceland.¹⁷

Community door-to-door studies suggest that prevalence rates are fairly similar between both developed and some developing countries. A large cross-sectional study of both rural and urban areas in Beijing, Xian and Shanghai found the age-standardised prevalence rate for subjects 65 years or older to be 2.1% for both sexes similar to that found in Rotterdam (2.1%) and Europe (1.7%).¹⁸ Similar data has also been seen from a rural area of Taiwan.¹⁹

Sociodemographic Factors

There is little controversy as to the **increasing risk of developing PD with age**. Earlier hospital-based or multi-source prevalence studies tended to demonstrate that incidence/prevalence rates increase with age but finally fall for the oldest age-groups.¹⁷ However, population-based studies consistently show that prevalence rates increase continuously in an exponential fashion.²⁰ This supports the notion that earlier studies failed to fully ascertain older PD cases.

The majority of studies support an **excess of male to female cases**. The average ratio of male to female standardised rates is 1.35 from prevalence studies and 1.31 from incidence studies, but the range of values is wide.¹⁴ This excess is seen for both multi-source and population-based studies, but the male excess appears smaller in population-based studies.²¹ The possibility that relative reduction of risk seen in women may be a role biological effect is supported by data from a large cohort study of women who had their ovaries removed surgically for gynaecological reasons. The risk of developing PD was more similar to that of men than control women suggesting a potential protective effect of oestrogens.²²

Socioeconomic position (or educational level in US studies) has not been examined in many studies but where it has the association has been generally found to be either inconsistent or positively associated so that higher levels of socioeconomic position or education were associated with an increased risk. A case control study from Rochester noted a doubling of risk (odds ratio 2.0, 95% CI 1.1 to 3.6) for 9 or more years of education.²³ Physicians were at increased risk (odds ratio 3.7, 95% CI 1.0 to 13.1) but this was based only relatively small numbers.

Early reports stated that PD was **less common for blacks** as compared to whites.^{24 25} Various hypotheses were put forward suggesting that the increased melanin pigmentation of blacks afforded some protection against developing PD. However, the Copiah county study demonstrated similar age-adjusted prevalence rates²⁶. Blacks were more likely to be newly diagnosed (58%) than whites (32%). A recent study from New York noted lower prevalence rates for black men and women but higher or similar incidence rates²⁷. This implies that blacks with PD have worse survival than their white counterparts. No evidence could be found that blacks presented with more severe disease or with a longer duration of symptoms. Both these studies suggest that blacks with PD have worse access to health care in the USA compared to their white counterparts.

Risk Factors

James Parkinson postulated a possible role for trauma, alcohol and long lying on the damp ground but noted that *“on the subject indeed of remote causes, no satisfactory accounts has yet been obtained from any of the sufferers.”*²⁸ A wide variety of agents have been considered, from anaesthetic exposure to years of rural residence (see Table 1).

Family History

The last decade has seen huge excitement over the discovery of new genetic forms of PD. Genome wide association studies will further elucidate common polymorphisms that are associated with disease. However from a patient’s perspective the common concern is the risk of other family members getting disease. A large and thorough Swedish twin registry found that the concordance rate amongst 132 PD cases was low with only three twin pairs (one male monozygotic and two female dizygotic) highlighting that even when one shares identical genes recurrence risk is still relatively low.²⁹ Family studies both in Iceland and Olmsted County, Minnesota suggest that siblings and offspring are at greater risk compared to the normal population (between 2 to 6 fold relative risk) but this is greater for young onset disease and in absolute term the risk of PD is still small < 5%.^{30 31}

Infections

Initial interest focussed on potential infectious agents due to the experience of post-encephalitic parkinsonism following the epidemics of Von Economo’s disease. Poskanzer and Schwab postulated a hypothesis that idiopathic PD might be related to subclinical infection.⁸ They postulated a birth cohort effect with individuals born between 1870-1900 being at greatest risk of exposure during the epidemic and hence developing PD. Whilst there has not been a major decline in PD incidence, as predicted by this hypothesis, there is some support for the possibility of a birth cohort effect (see above).

Other infectious agents have been postulated, such as intra-uterine influenza,³² measles (protective exposure)³³ and age at whooping cough infection.³⁴ Serological analysis does not however support the notion of a specific infection being any more common in cases of PD.^{35 36} Pathological examination has also failed to detect specific viral particles, inclusions or antigens in brain autopsy material.³⁷ Whilst serological data is objective, it cannot differentiate between age at infection which might be a more important predictor than infection by itself.³⁸

Neurotoxins

Enthusiasm for examining for environmental factors waned until the occurrence of MPTP-induced parkinsonism;³⁹ a “natural human experiment” of neurotoxicity. Whilst it was clear that exposure to MPTP was exceptionally rare, this provided strong impetus in searching for a more common neurotoxin. The toxic hypothesis has been given further credence by the observation that PD cases have relatively less effective detoxification systems.^{40 41} suggesting that PD may result from the combination of an inherited susceptibility and an environmental toxin.

Similarity between MPTP and paraquat⁴² quickly led Canadian researchers to examine the ecological relationship between PD and the use of pesticides.⁴³ Their findings supported a toxic hypothesis as PD appeared to be more common in agricultural areas and areas of intensive market gardening, which also had the highest use of pesticides. Some case control studies have found a significant association

with pesticides^{44 45 46 47} whilst others have not.^{48 49 50 51} One important consideration is that the positive associations with pesticides reflect recall bias, cases being more likely to report exposure than controls because they believe that the exposure may have played some role in causing their disease. The dangers of this sort of bias are well illustrated from a recent German study which noted significantly raised odds ratios (1.8 and 2.3) for self-reported exposure to wood preservatives at work. However, when exposure was reclassified using a more objective “job exposure matrix” there was no difference.⁴⁷ Two papers have avoided the important concerns around recall bias. Ascherio was able to examine prospective data from a large cancer study of around 143,000 individuals who were assessed in the 1980s and followed up to 2001.⁵² From a wide list of potential toxic exposures only pesticides and herbicides had an increased risk though the relative risk was similar for exposed farmers as well as non-farmers which is slightly surprising. A case control study from California where there has been statutory notification of herbicide use mainly as crop-spraying was able to use detailed residential histories linked to archived data on dosage to create proxy exposures unrelated to specific exposure-recall.⁵³ This found a doubling of risk for those exposed to both paraquat and maneb.

The public health importance of pesticide use as a cause of PD is limited. Assuming a causal relationship, the population attributable risk, that is the percent of all PD cases that might be related to occupational pesticide use, is only around 10%, though this could vary between 2-25% (95% confidence intervals).⁴⁴ Similarly pesticides are unlikely to explain the temporal trends⁵⁴ as paraquat and other pesticides were only introduced in the last thirty years, after the increase in secular trends began. However, they might explain the relatively larger increases in mortality seen for men.

Table 1 Possible environmental risk factors for PD

Toxic exposures	Infectious exposures	Miscellaneous exposures
Pesticides/herbicides +++	Influenza +	Introvert personality ++
Solvents ++	Whooping cough +	Head trauma ++
Wood preservatives +	Shingles o	Dietary vitamin c ++
Mercury +	Chicken pox o	Dietary vitamin e +
Industrial residence +	Mumps o	Rural residence +
Lead o	Measles -	Well water +
Zinc o		Higher educational level +
Copper o		Socio-economic status o
Nickel o		Birthweight o
		Birth order o
		Prematurity o
		Alcohol -
		Coffee ---
		Smoking ----

(key: + to +++++ indicates weak to very strong evidence of an increased risk between exposure and PD, o indicates no association, - to ---- indicates weak to very strong evidence of a decreased risk between exposure and PD)

Smoking and Personality

The inverse relationship between smoking and PD has been noted since the days of the early smoking cohort studies both in the USA and UK.^{55 56} The consistency of this finding in different populations and using different methods makes it reasonable to exclude chance as an explanation for this association. This finding is also seen with early onset cases and therefore excludes the 'selective mortality' explanation⁵⁷ that smokers with a propensity to develop PD die from smoking related diseases before they develop PD.⁵⁸

There are several biologically plausible reasons why smoking may protect or retard the development of PD.^{59 60 61} However, if smoking reduced the rate of age-related nigral cell death, one would predict that smokers who developed PD would both be older in age than non-smokers and have a slower rate of disease progression. Both of these predictions are not, however, supported by empirical evidence.^{62 63 64}

If one does not believe that smoking is directly protective are there any other reasons to explain this strong association. Personality may provide the link between both an individual's smoking behaviour and Parkinson's disease. There are two possible alternatives: (a) PD may have a long preclinical latent period⁶⁵ which results in personality changes that are associated with a reduced likelihood of either taking up or continuing smoking. (b) A specific exposure or genetic susceptibility may be associated with certain personality traits. The former directly increase the risk of PD whilst indirectly influencing smoking behaviour through personality. Smokers do appear to differ in personality traits and are more likely to be extrovert or exhibit type A behaviour,⁶⁶ whilst non-smokers have higher levels of shyness and defensiveness.⁶⁷ This is consistent with the reported personality differences for PD cases, such as introversion.^{68 69} A follow-up study of a large cohort who were assessed using the MMPI has shown that anxious individuals are more likely to get PD consistent with the idea that smoking may not be causally protective (Rocca, personal communication).

Head Trauma

The idea that trauma might be causal is as old as the disease itself,²⁸ but is difficult to evaluate due to the problem of recall bias. Several studies have noted a positive association for any head injury,^{51 70} and also for severe injury resulting in loss of consciousness,⁵¹ which should be less biased as such events should be recalled equally well by both cases and controls. Only one study has examined a cohort of subjects with recorded head injuries and followed up their risk of PD. This study failed to find any increased risk but had limited statistical power.⁷¹ Recent evidence from Rochester, Minnesota using record linkage supports a potential role of head injury.⁷² They found an odds ratio of 4.3, 95% CI 1.2 to 15.2. What is important about this study is that head injury classification was not based on self-report and hence may have been biased by recall, but on linkage to medical records that had this data recorded prior to the onset of disease. A recent database linkage study from Denmark highlighted the problem of reverse causation as there was a very marked relative increase in head injury within 3 months of diagnosis.⁷³

Rural Residence and Well Water

At around the same time that an excess of PD was noted in rural agricultural areas, other Canadian researchers noted an association between rural residence and well water consumption.⁷⁴ Some studies have confirmed this increased risk for rural areas^{48 49 50 75 76 77} whilst other have not.^{45 46 47 51 78 79} Demographic variables, such as rural residence are particularly sensitive to the method of recruiting controls and the possibility of selection bias. In this case it is noteworthy that the only two studies which selected proper population-based controls failed to find any association with rural residence.^{47 78} It is not surprising that studies that demonstrate a relationship between rural residence also tend to show a relationship with well water as the two exposures are closely correlated to each other.^{48 49 50} Well water could act as a carrier of a potential toxin or as a vector for an infective agent. Alternatively well water, like rural residence, may again be simply a proxy marker for another exposure which is more common in rural environments. Again any association between well water and PD could reflect selection bias, as studies with population-based controls fail to show any association.^{47 78}

Dietary Factors

There is increasing interest in the potential role of oxidative damage in the aetiology of PD⁵⁹ and hence more recent studies have examined the role of dietary anti-oxidants. Several studies have found a relationship between specific food stuffs and PD but these are rather tentative. For example, one study showed a 'protective' effect with peanut consumption only in females, and for salad with dressing only in males.⁷⁶ Nuts and seeds appeared to be harmful in yet another study.⁴⁶ An analysis of multiple food items from a food frequency questionnaire is particularly liable to significant associations by chance due to multiple significance testing (type I error). More recently results from prospective cohort studies are becoming available. These avoid the problems of both inaccuracy and recall bias. The most impressive data come from a large prospective cohort study of 41,836 women, who have been followed up for 6 years. In this study there was no association between vitamin E and PD but a significant protective effect was seen for both vitamin C and manganese consumption, whilst vitamin A was associated with an increased risk.⁸⁰ Similarly a nested case control study from the Honolulu Heart Cohort Study using previously documented data intake showed an inverse association between PD and frequency of legume intake (odds ratio 0.27).⁸¹ However, after the data was converted to a continuous measure of vitamin E intake, there was no significant protective effect. The Honolulu Heart Program follow-up has also examined coffee consumption as using a 24 hour dietary recall questionnaire. Incidence rates were calculated over a 30 year follow-up period. The adjusted relative hazard ratio for non coffee drinkers compared to those consuming ≥ 28 oz/d was 5.1 (95% CI 1.8 to 14.4), with a marked dose response effect (adjusted for age and pack-years of smoking).⁸² Recent evidence suggests that high cholesterol or treatment with simvastatin (cholesterol lowering drug) may reduce risk of PD.^{83 84} Another intriguing observation is that higher levels of serum urate (an anti-oxidant) and a clinical diagnosis of gout may be protective from PD and be associated with a better prognosis.^{85 86}

Mortality Risk

There is surprisingly little good quality data on the natural history of PD. Most work has examined mortality, either internally or by comparing rates with the general population. Levodopa treatment may have increased survival resulting in a shift of the age-specific mortality curve to the right by about 5 years.⁸⁷ Whilst it is true that PD patients have greater life expectancy today, there has been a secular increase in life-expectancy for the whole population, so that any individual would be expected to live 4-5 years longer between the 1960s and the 1980s. There is some evidence to suggest that the initial introduction of levodopa therapy may have delayed death.⁸⁸ This is supported by the observation that cohorts with relatively short follow-up are more likely to show smaller mortality differentials and these increase with further follow-up.^{89 90} More recent cohorts, where almost all patients will have been treated with levodopa still show a two-fold increased risk of death compared to the general population (Aberdeen: 2.4 95% confidence intervals 1.6-3.4)⁹¹ East Boston: 2.0 95% confidence intervals 1.6-2.6.⁹² These figures are lower but still compatible, as seen by the overlap of the confidence intervals, with the mortality seen for the pre-levodopa series of patients described by Hoehn and Yahr (Columbia: 2.9 95% confidence intervals 2.4-3.6).⁹³ Little is also known about what factors predict prognosis. Younger patients have longer survival than older patients.⁹⁴ However, given their longer life expectancy, they will lose more years of life than older patients. In fact the relatively mortality of younger patients compared to the general population is greater. Patients aged between 25-54 years were almost 4 times more likely to die whilst those between 75-84 years had twice the risk compared to a normal population control group.⁹⁵ It has also been suggested that women have worse prognosis than men.⁹⁶ However, this probably reflects selection bias in hospital-based samples.⁹⁵ Cases with tremor onset have better prognosis than those presenting with postural instability and gait disturbance.⁹⁷ This partially reflects misdiagnosis as the latter group are more likely to contain cases of multiple system atrophy or progressive supranuclear palsy,⁹⁷ and these other parkinsonian syndromes have worse mortality.⁹⁸

Summary

Epidemiological research has confirmed that Parkinson's disease is found throughout the world and increases exponentially with age. Little good quality data on the temporal incidence of Parkinson's disease is available. Differences in prevalence between identical ethnic groups in different countries supports the role of an environmental factor, as does the relatively small concordance rate from twin studies. A wide variety of aetiologic agents have been considered from infectious, toxic and other exposures. The most robust finding is that non-smokers have a greater risk of disease. Future research needs to improve on current limited methods of exposure measurement and attempt more novel designs to overcome bias. More attention should be made on examining what factors determine prognosis and using epidemiological and qualitative methods to determine needs of patients with PD.

References

1. Lilienfeld DE, Chan E, Ehland J, Godbold J, Landrigan PJ, Marsh G, et al. Two decades of increasing mortality from Parkinson's Disease among the US elderly. *Arch.Neurol.* 1990;**47**:731-734.
2. Li TM, Swash M, Alberman E. Morbidity and mortality in motor neuron disease: comparison with Multiple sclerosis and Parkinson's disease: age and sex specific rates and cohort analyses. *J.Neurol.Neurosurg.Psychiatry.* 1985;**48**:320-327.
3. Clarke CE. Mortality from Parkinson's disease in England and Wales 1921-1989. *J.Neurol.Neurosurg.Psychiatry.* 1993;**56**:690-693.
4. Ben-Shlomo Y, Finnan F, Allwright S, Davey S. The epidemiology of Parkinson's disease in Ireland: observations from routine data sources. *Irish Medical Journal* 1993;**86**:190-194.
5. Vanacore N, Bonifati V, Bellatreccia A, Edito F, Meco G. Mortality rates for Parkinson's disease and parkinsonism in Italy (1969-1987). *Neuroepidemiology.* 1992;**11**:65-73.
6. Imaizumi Y, Kaneko R. Rising mortality from Parkinson's disease in Japan, 1950-1992. *Acta.Neurol.Scand.* 1995;**91**:169-176.
7. Riggs JE, Schochet SS. Rising mortality due to Parkinson's disease and amyotrophic lateral sclerosis: a manifestation of the competitive nature of human mortality. *J.Clin.Epidemiol.* 1992;**45**:1007-1012.
8. Poskanzer DC, Schwab RS. Cohort analysis of Parkinson's syndrome. Evidence for a single etiology related to subclinical infection about 1920. *J.Chronic.Dis.* 1963;**16**:961-973.
9. Marmot MG. Parkinson's disease and encephalitis: the cohort hypothesis re-examined. In: Rose FC, ed. *Clinical Neuroepidemiology.* Kent: Pitman Medical Limited, 1980;391-401.
10. Ravenholt RT, Foege WH. 1918 Influenza, encephalitis lethargica, parkinsonism. *Lancet.* 1982;**ii**:860-864.
11. Kurland LT, Hauser WA, Okazaki H, Nobrega FT. Epidemiologic studies of Parkinsonism with special reference to the cohort hypothesis. In: Anonymous *Proceedings of the Third Symposium on Parkinsonism.* Edinburgh: E & S Livingstone, 1969;12-16.
12. Nobrega FT, Glatte E, Kurland LT, Okazaki H. Comments on the epidemiology of parkinsonism including prevalence and incidence statistics for Rochester, Minnesota, 1953-1966. In: Barbeau A, ed. *Progress in Neurogenetics.* Amsterdam: Excerpta Medica, 1969;474-485.
13. Rajput AH, Offord KP, Beard CM, Kurland LT. Epidemiology of Parkinsonism: incidence, classification and mortality. *Ann.Neurol.* 1984;**16**:278-282.
14. Zhang ZX, Roman GC. Worldwide occurrence of Parkinson's disease: an updated review. *Neuroepidemiology.* 1993;**12**:195-208.
15. Rocca WA, Bower JH, McDonnell SK, Peterson BJ, Maraganore DM. Time trends in the incidence of parkinsonism in Olmsted County, Minnesota. *Neurology* 2001;**57**:462-467.
16. Goldberg ID, Kurland LT. Mortality in 33 countries from diseases of the nervous system. *World.Neurol.* 1962;**3**:444-463.
17. Ben-Shlomo Y. How far are we in understanding the cause of Parkinson's disease? *J.Neurol.Neurosurg.Psychiat.* 1996;**61**:4-16.
18. Zhang ZX, Roman GC, Hong Z, Wu CB, Qu QM, Huang JB, et al. Parkinson's disease in China: prevalence in Beijing, Xian, and Shanghai. *Lancet* 2005;**365**:595-597.
19. Wang SJ, Fuh JL, Liu CY, Lin KP, Chang R, Yih JS, et al. Parkinson's disease in Kin-Hu, Kinmen: a community survey by neurologists. *Neuroepidemiology.* 1994;**13**:69-74.
20. Tison F, Dartigues JF, Dubes L, Zuber M, Alperovitch A, Henry P. Prevalence of Parkinson's disease in the elderly: a population study in Gironde, France. *Acta.Neurol.Scand.* 1994;**90**:111-115.
21. Morgante L, Rocca WA, Di Rosa AE, De Domenico P, Grigoletto F, Meneghini F, et al. Prevalence of Parkinson's disease and other types of Parkinsonism: a door-to-door survey in three Sicilian municipalities. *Neurology.* 1992;**42**:1901-1907.
22. Rocca WA, Bower JH, Maraganore DM, Ahlskog JE, Grossardt BR, de AM, et al. Increased risk of

- parkinsonism in women who underwent oophorectomy before menopause. *Neurology* 2008;**70**:200-209.
23. Frigerio R, Elbaz A, Sanft KR, Peterson BJ, Bower JH, Ahlskog JE, et al. Education and occupations preceding Parkinson's disease: A population-based case-control study. *Neurology* 2006;**65**:1575-1583.
 24. Kessler II. Epidemiologic studies of Parkinson's disease. III. A community based survey. *Am.J.Epidemiol.* 1972;**96**:242-254.
 25. Paddison RM, Griffith RP. Occurrence of Parkinson's disease in black patients at Charity Hospital in New Orleans. *Neurology.* 1974;**24**:688-690.
 26. Schoenberg BS, Anderson DW, Haerer AF. Prevalence of Parkinson's disease in the biracial population of Copiah County, Mississippi. *Neurology.* 1985;**35**:841-845.
 27. Mayeux R, Marder K, Cote LJ, Hemenegildo N, Mejia H, Tang MX, et al. The frequency of idiopathic Parkinson's disease by age, ethnic group, and sex in Northern Manhattan, 1988-1993. *American.Journal.of.Epidemiology.* 1995;**142**:820-827.
 28. Parkinson J. An essay on the shaking palsy. *Sherwood, Neely, and Jones, London.* 1817;1-66.
 29. Wirdefeldt K, Gatz M, Bakaysa SL, Fiske A, Flensburg M, Petzinger GM, et al. Complete ascertainment of Parkinson disease in the Swedish Twin Registry. *Neurobiol.Aging* 2008;**29**:1765-1773.
 30. Sveinbjornsdottir S, Hicks AA, Jonsson T, Petursson H, Gudmundsson G, Frigge ML, et al. Familial aggregation of Parkinson's disease in Iceland. *N Engl J Med* 2000;**343**:1765-1770.
 31. Rocca WA, McDonnell SK, Strain KJ, Bower JH, Ahlskog JE, Elbaz A, et al. Familial aggregation of Parkinson's disease: The Mayo Clinic family study. *Ann Neurol.* 2004;**56**:495-502.
 32. Mattock C, Marmot M, Stern G. Could Parkinson's disease follow intra-uterine influenza?: a speculative hypothesis. *J.Neurol.Neurosurg.Psychiat.* 1988;**51**:753-756.
 33. Sasco AJ, Paffenbarger RS. Measles infection and Parkinson's disease. *American.Journal.of.Epidemiology.* 1985;**122**:1017-1031.
 34. de Pedro-Cuesta J, Gudmundsson G, Abaira V, Löve A, Tulinius H, Veiga J, et al. Whooping Cough and Parkinson's Disease. *Int.J.Epidemiol.* 1996;**25**, No.6:1301-1311.
 35. Elizan TS, Madden DL, Noble GR, Herrmann KL, Gardner J, Schwartz J, et al. Viral antibodies in serum and CSF of Parkinsonian patients and controls. *Arch.Neurol.* 1979;**36**:529-534.
 36. Martilla RJ, Arstila P, Nikostelainen J, Halonen PE, Rinne UK. Viral antibodies in the sera from patients with Parkinson's disease. *European Neurology* 1977;**15**:25-33.
 37. Schwartz J, Elizan TS. Search for viral particles and virus-specific products in idiopathic Parkinson disease brain material. *Ann.Neurol.* 1979;**6**:261-263.
 38. de Pedro-Cuesta J, Petersen IJ, Stawiarz L, Gudmundsson G, Almazan J, Tulinius H, et al. High levodopa use in periodically time-clustered, Icelandic birth cohorts. A vestige of parkinsonism etiology? *Acta.Neurol.Scand.* 1995;**91**:79-88.
 39. Langston JW, Ballard P, Tetrud JW, Irwin I. Chronic parkinsonism in humans due to a product of meperidine-analog synthesis. *Science.* 1983;**219**:970-980.
 40. Waring RH, Sturman SG, Smith MCG, Steventon GB, Heafield MTE, Williams AC. S-Methylation in motorneuron disease and Parkinson's disease. *Lancet.* 1989;**1**:356-357.
 41. Smith CAD, Gough AC, Leigh PN, Summers BA, Harding AE, Maranganore DM, et al. Debrisoquine hydroxylase gene polymorphism and susceptibility to Parkinson's disease. *Lancet.* 1992;**339**:1375-1377.
 42. Sanchez-Ramos JR, Hefti F, Weiner WJ. Paraquat and Parkinson's disease. *Neurology.* 1987;**37**:728.
 43. Barbeau A, Roy M, Bernier G, Campanella G, Paris S. Ecogenetics of Parkinson's disease: prevalence and environmental aspects in rural areas. *Can.J.Neurol.Sci.* 1987;**14**:36-41.
 44. Semchuck KM, Love EJ, Lee RG. Parkinson's disease and exposure to agricultural work and pesticide chemicals. *Neurology.* 1992;**42**:1328-1335.
 45. Hubble JP, Cao T, Hassanein RE, Neuberger JS, Koller WC. Risk factors for Parkinson's disease [see comments]. *Neurology.* 1993;**43**:1693-1697.
 46. Butterfield PG, Valanis BG, Spencer PS, Lindeman CA, Nutt JG. Environmental antecedents of young-onset Parkinson's disease. *Neurology.* 1993;**43**:1150-1158.
 47. Seidler A, Hellenbrand W, Robra BP, Vieregge P, Nischan P, Joerg J, et al. Possible environmental, occupational, and other etiologic factors for Parkinson's disease: a case-control study in Germany. *Neurology.* 1996;**1996**:1275-1284.
 48. Wong GF, Gray CS, Hassanein RS, Koller WC. Environmental risk factors in siblings with Parkinson's Disease. *Arch.Neurol.* 1991;**48**:287-289.
 49. Koller W, Vetere-Overfield B, Gray C, Alexander C, Chin T, Dolezal J, et al. Environmental risk factors in Parkinson's disease. *Neurology.* 1990;**40**:1218-1221.
 50. Jimenez-Jimenez FJ, Mateo D, Gimenez-Roldan S. Exposure to well water and pesticides in Parkinson's disease: a case-control study in the Madrid area. *Movement Disorders* 1992;**7**:149-152.
 51. Stern M, Dulaney E, Gruber SB, Golbe L, Bergen M, Hurtig H, et al. The epidemiology of Parkinson's disease: a case-control study of young-onset and old-onset patients. *Arch.Neurol.* 1991;**48**:903-907.

52. Ascherio A, Chen H, Weisskopf MG, O'Reilly E, McCullough ML, Calle EE, et al. Pesticide exposure and risk for Parkinson's disease. *Ann Neurol.* 2006;**60**:197-203.
53. Costello S, Cockburn M, Bronstein J, Zhang X, Ritz B. Parkinson's disease and residential exposure to maneb and paraquat from agricultural applications in the central valley of California. *Am.J Epidemiol.* 2009;**169**:919-926.
54. Rajput AH, Uitti RJ, Stern W, Laverty W, O'Donnell K, O'Donnell D, et al. Geography, drinking water chemistry, pesticides and herbicides and the etiology of Parkinson's disease. *Can.J.Neurol.Sci.* 1987;**14**:414-418.
55. Hammond EC. Smoking in relation to the death rates of one million men and women. *National Cancer Institute Monographs* 1966;**19**:127-204.
56. Doll R, Peto R, Wheatley K, Gray R, Sutherland I. Mortality in relation to smoking: 40 years' observations on male British doctors. *Br.Med.J.* 1994;**309**:901-911.
57. Riggs JE. Cigarette smoking and Parkinson disease: the illusion of a neuroprotective effect. *Clin.Neuropharmacol.* 1992;**15**:88-99.
58. Ben-Shlomo Y. Smoking and neurodegenerative diseases. *Lancet.* 1993;**342**:1239.
59. Jenner P. Oxidative damage in neurodegenerative disease. *Lancet.* 1994;**344**:796-798.
60. Smith PR, Cooper JM, Govan GG, Harding AE, Schapira AHV. Smoking and mitochondrial function: a model for environmental toxins. *Quarterly.Journal.of.Medicine.* 1993;**86**:657-660.
61. Gresham LS, Molgaard CA, Smith RA. Induction of cytochrome P-450 enzymes via tobacco smoke: a potential mechanism for developing resistance to environmental toxins as related to parkinsonism and other neurologic diseases. *Neuroepidemiology.* 1993;**12**:114-116.
62. Jimenez J, Mateo D, Gimenez R. Premorbid smoking, alcohol consumption, and coffee drinking habits in Parkinson's disease: a case-control study. *Movement Disorders* 1992;**7**:339-344.
63. Rajput AH, Offord KP, Beard CM, Kurland LT. A case-control study of smoking habits, dementia, and other illnesses in idiopathic Parkinson's disease. *Neurology.* 1987;**37**:226-232.
64. Haack DG, Baumann RJ, McKean HE, Jameson HD, Turbek JA. Nicotine exposure and parkinson disease. *American.Journal.of.Epidemiology.* 1981;**114**:191-199.
65. Koller WC. When does Parkinson's disease begin? *Neurology.* 1992;**42**:27-31.
66. Eysenck HJ, Tarrant M, Woolf M, England L. Smoking and personality. *Br.Med.J.* 1960;**i**:456-460.
67. Forgays DG, Bonaiuto P, Wrzesniewski K, Forgays DK. Personality and cigarette smoking in Italy, Poland and the United States. *International.Journal.of.Addiction.* 1993;**28**:399-413.
68. Eatough VM, Kempster PA, Stern GM, Lees AJ. Premorbid personality and idiopathic Parkinson's disease. *Adv.Neurol.* 1990;**53**:335-337.
69. Ward CD, Duvoisin RC, Ince SE, Nutt JD, Eldridge R, Calne DB. Parkinson's disease in 65 pairs of twins and in a set of quadruplets. *Neurology.* 1983;**33**:815-824.
70. Semchuk KM, Love EJ, Lee RG. Parkinson's disease: a test of the multifactorial etiologic hypothesis. *Neurology.* 1993;**43**:1173-1180.
71. Williams DB, Annegers JF, Kokmen E, O'Brien PC, Kurland LT. Brain injury and neurologic sequelae: a cohort study of dementia, parkinsonism, and amyotrophic lateral sclerosis. *Neurology.* 1991;**41**:1554-1557.
72. Bower JH, Maraganore DM, Peterson BJ, McDonnell SK, Ahlskog JE, Rocca WA. Head trauma preceding PD: a case-control study. *Neurology* 2003;**60**:1610-1615.
73. Rughjerg K, Ritz B, Korbo L, Martinussen N, Olsen JH. Risk of Parkinson's disease after hospital contact for head injury: population based case-control study. *BMJ* 2008;**337**:a2494.
74. Rajput AH, Utti RJ, Stern W, Laverty W. Early onset Parkinson's disease in Saskatchewan - environmental considerations for etiology. *Can.J.Neurol.Sci.* 1986;**13**:312-316.
75. Ho SC, Woo J, Lee CM. Epidemiologic study of Parkinson's disease in Hong Kong. *Neurology.* 1989;**39**:1314-1318.
76. Golbe LI, Farrell TM, Davis PH. Follow-up study of early-life protective and risk factors in Parkinson's disease. *Movement Disorders* 1990;**5**:66-70.
77. Ngim CH, Devathasan G. Epidemiologic study on the association between body burden mercury level and idiopathic Parkinson's disease. *Neuroepidemiology.* 1989;**8**:128-141.
78. Semchuck KM, Love EJ, Lee RG. Parkinson's disease and exposure to rural environmental factors: a population based case-control study. *Can.J.Neurol.Sci.* 1991;**18**:279-286.
79. Wang WZ, Fang XH, Cheng XM, Jiang DH, Lin ZJ. A case-control study on the environmental risk factors of Parkinson's disease in Tianjin, China. *Neuroepidemiology.* 1993;**12**:209-218.
80. Cerhan JR, Wallace RB, Folsom AR. Antioxidant intake and risk of Parkinson's disease (PD) in older women. *American.Journal.of.Epidemiology.* 1994;**139**:S65.
81. Morens DM, Grandinetti A, Waslien CI, Park CB, Ross GW, White LR. Case-control study of idiopathic Parkinson's disease and dietary vitamin E intake. *Neurology.* 1996;**46**:1270-1274.
82. Ross GW, Abbott RD, Petrovitch H, Morens DM, Grandinetti A, Tung KH, et al. Association of coffee and

- caffeine intake with the risk of Parkinson disease. *JAMA* 2000;**283**:2674-2679.
83. Huang X, Abbott RD, Petrovitch H, Mailman RB, Ross GW. Low LDL cholesterol and increased risk of Parkinson's disease: prospective results from Honolulu-Asia Aging Study. *Mov Disord.* 2008;**23**:1013-1018.
 84. Wolozin B, Wang SW, Li NC, Lee A, Lee TA, Kazis LE. Simvastatin is associated with a reduced incidence of dementia and Parkinson's disease. *BMC Med* 2007;**5**:20.
 85. Alonso A, Rodriguez LA, Logroscino G, Hernan MA. Gout and risk of Parkinson disease: a prospective study. *Neurology* 2007;**69**:1696-1700.
 86. Schwarzschild MA, Schwid SR, Marek K, Watts A, Lang AE, Oakes D, et al. Serum urate as a predictor of clinical and radiographic progression in Parkinson disease. *Arch.Neurol.* 2008;**65**:716-723.
 87. Kurtzke JF, Murphy FM. The changing patterns of death rates in parkinsonism. *Neurology.* 1990;**40**:42-49.
 88. Clarke CE. Does levodopa therapy delay death in Parkinson's disease? A review of the evidence. *Movement Disorders* 1995;**10**:250-256.
 89. Cedarbaum JM, McDowell FH. Sixteen-year follow-up of 100 patients begun on Levodopa in 1968: emerging problems. In: Yahr MD, ed. *Advances in Neurology*. New York: Raven Press, 1986;469-472.
 90. Curtis L, Lees AJ, Stern G, Marmot MG. Effect of L-Dopa on course of Parkinson's disease. *Lancet.* 1984;**2**:211-212.
 91. Ebmeier KP, Calder SA, Crawford JR, Stewart L, Beeson JAO, Mutch WJ. Parkinson's disease in Aberdeen: survival after 3.5 years. *Acta.Neurol.Scand.* 1990;**81**:294-299.
 92. Bennett DA, Beckett LA, Murray AM, Shannon KM, Goetz CG, Pilgrim DM, et al. Prevalence of Parkinsonian signs and associated mortality in a community population of older people. *N.Engl.J.Med.* 1996;**334**:71-76.
 93. Hoehn MM, Yahr MD. Parkinsonism: onset, progression, and mortality. *Neurology.* 1967;**17**:427-442.
 94. Diamond SG, Markham CH, Hoehn MM, McDowell FH, Muentner MD. Effect of age at onset on progression and mortality in Parkinson's disease. *Neurology.* 1989;**39**:1187-1190.
 95. Ben-Shlomo Y, Marmot MG. Survival and cause of death in a cohort of patients with parkinsonism: possible clues to aetiology. *J.Neurol.Neurosurg.Psychiatry.* 1995;**58**:293-299.
 96. Diamond SG, Markham CH, Hoehn MM, McDowell FH, Muentner MD. An examination of male-female differences in progression and mortality of Parkinson's disease. *Neurology.* 1990;**40**:763-766.
 97. Rajput AH, Pahawa R, Pahwa P, Rajput A. Prognostic significance of the onset mode in Parkinsonism. *Neurology.* 1993;**43**:829-830.
 98. Wenning GK, Ben-Shlomo Y, Magalhes M, Daniel SE, Quinn NP. Clinical features and natural history of multiple system atrophy: an analysis of 100 cases. *Brain.* 1994;**117**:835-845.