1 Epidemiology of Parkinson's Disease

Professor Y Ben-Shlomo

Professor of Clinical Epidemiology, Population Health Sciences, Canynge Hall, University of Bristol, 39 Whatley Road, Bristol BS8 2PS

This paper is based on and updated from an earlier published review: Ben-Shlomo Y. The epidemiology of Parkinson's disease. Baillieres Clinical Neurology. 1997; 6:55-68. For two recent reviews see publications by Asherio[1] and Bellou et al.[2]

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 or may not 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

Mortality patterns from several different countries show 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. [3-8]

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. 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 USA[3] is greater than for women (see sex differences below). This is unlikely to reflect ascertainment or treatment effects. One suggestion[9] 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 little 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.[10] Birth cohorts born between 1875-1895 do appear to have excess mortality rates.[4,6,11] It is still too soon to fully evaluate this hypothesis as cohorts born after the epidemic from the mid-30s onwards 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.[12]

Many studies have examined the relative mortality of patients with PD compared to a control population. Almost all such studies show an increased mortality for PD though in a meta-analysis of 88 studies this varied from 0.9 to 3.8 times though inception cohorts with newly diagnosed cases showed a more consistent relative mortality of 1.5 (or 50% relative increase).[13] Interestingly the best meta-analysis failed to find evidence that the relative mortality was better when comparing the post to pre-levodopa era but there were only 2 pre-levodopa studies making this estimate very imprecise.[13]

Prevalence (number of existing cases) rates in the United Kingdom have remained surprisingly consistent over time. A meta-analysis of 8 studies from 1966 to 2008 shows most rates are around 140 per 100,000 population with one notably higher rate from Aberdeen that may have been caused by the inclusion of a nursing home (with a disproportionate larger number of PD cases). [14]

Data from Rochester, Minnesota are unique in providing incidence rates from 1935 to 1979.[15-17] 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. However, like the mortality data, the rate for cases aged between 40-69 years 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.[18] 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. Similarly an analysis of incidence rates between 1999-2009 using a large UK GP database (THIN) showed a decline in annual incidence (6%). When a broader case definition was used, rates remained fairly constant over time. [19]

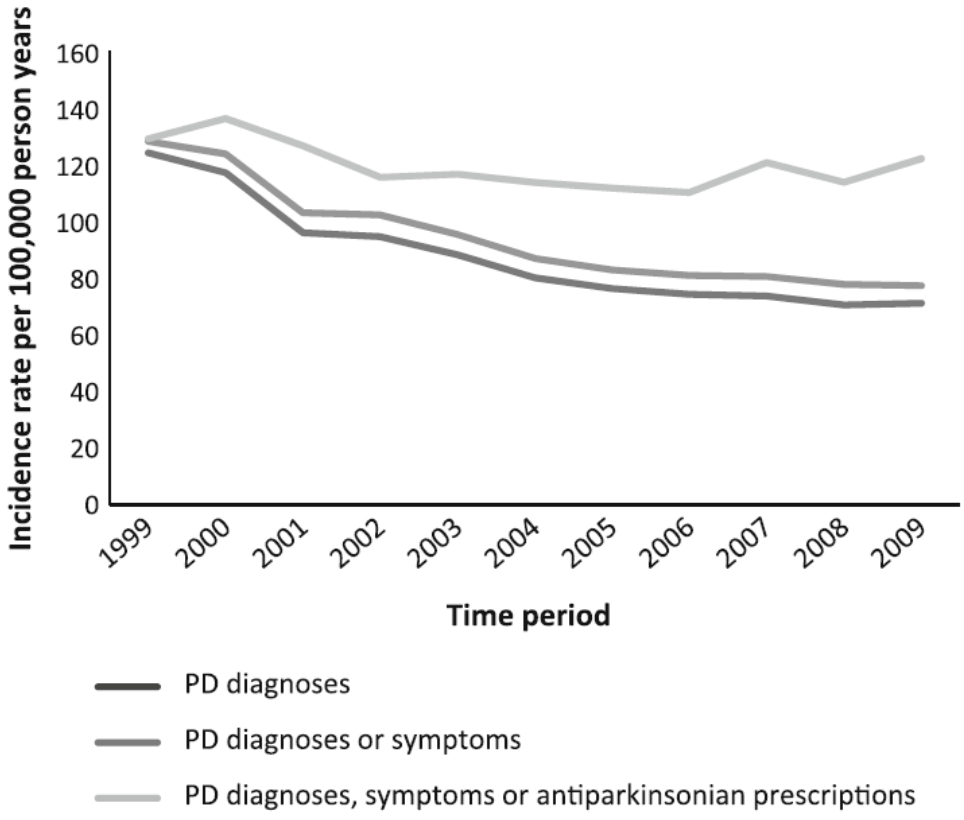

Figure 1: Temporal trends for incidence rates between 1999 to 2009 from UK primary care (Taken from ref[19])

Geographical Distribution

Early comparisons of international mortality rates showed fairly large differences (7-8 fold) between countries.[20] 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).[21] 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.[22]

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%).[23] Similar data has also been seen from a rural area of Taiwan.[24]

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.[22] However, population-based studies consistently show that prevalence rates increase continuously in an exponential fashion.[25] 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.[21] This excess is seen for both multi-source and population-based studies, but the male excess appears smaller in population-based studies.[26] 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.[27]

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.[28] Physicians were at increased risk (odds ratio 3.7, 95% CI 1.0 to 13.1) but this was based only relatively small numbers. A primary care study found slightly higher rates in patients living in more deprived areas. [19]

Early reports stated that PD was **less common for blacks** as compared to whites.[29,30] 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 rates[31]. 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 rates[32]. 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*."[33] A wide variety of agents have been considered, from anaesthetic exposure to years of rural residence. A recent umbrella review of meta-analyses identified 75 unique meta-analyses of which 21 had results that were significant at $p < 0.001$ (using random effect models). However most of these had strong evidence of heterogeneity and the potential for small study bias (i.e. smaller positive studies with less good methods more likely to be published hence resulting in a misleading meta-analysis). However two risk factors, constipation and physical activity showed strong class I evidence (highly suggestive) of an association and two others, smoking and anxiety and depression, showed class II (suggestive) evidence. Both constipation and anxiety and depression are now considered as non-motor phenotypes of PD and the other two behaviours may also be secondary to PD pathology hence these associations may reflect reverse causation rather than a true protective effect.[34] The following will examine some of the commonly postulated risk factors in greater detail

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.[10] 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,[35] measles (protective exposure)[36] and age at whooping cough infection.[37] Serological analysis does not however support the notion of a specific infection being any more common in cases of PD.[38,39] Pathological examination has also failed to detect specific viral particles, inclusions or antigens in brain autopsy material.[40] Whilst serological data is objective, it cannot differentiate between age at infection which might be a more important predictor than infection by itself.[41]

Neurotoxins

Enthusiasm for examining for environmental factors waned until the occurrence of MPTP-induced parkinsonism;[42] 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.[43,44] suggesting that PD may result from the combination of an inherited susceptibility and an environmental toxin.

Similarity between MPTP and paraquat[45] quickly led Canadian researchers to examine the ecological relationship between PD and the use of pesticides.[46] 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[47-50] whilst others have not.[51-54] 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.[50] 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.[55] 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.[56] This found a doubling of risk for those exposed to both paraquat and maneb. The same research group have also found that self-reported household pesticide use was more common in cases than controls (with the possibility of recall bias) but this association was much stronger in PON1 genotypes, which are involved in detoxifying chemicals. So exposure to organophosphorus pesticides was associated with an odds ratio of 1.03 with non-carriers byt 2.62 with the QQ homozygotes (p for interaction <0.05). [57]

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).[47] Similarly pesticides are unlikely to explain the temporal trends[58]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.

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.[59,60] 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' explanation[61] that smokers with a propensity to develop to develop PD die from smoking related diseases before they develop PD.[62]

There are several biologically plausible reasons why smoking may protect or retard the development of PD.[63-65] 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.[66-68]

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 period[69] 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,[70] whilst non-smokers have higher levels of shyness and

defensiveness.[71] This is consistent with the reported personality differences for PD cases, such as introvertism.[72,73] 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. [74]

Head Trauma

The idea that trauma might be causal is as old as the disease itself,[33] but is difficult to evaluate due to the problem of recall bias. Several studies have noted a positive association for any head injury,[54,75] and also for severe injury resulting in loss of consciousness,[54] 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.[76] Recent evidence from Rochester, Minnesota using record linkage supports a potential role of head injury.[77] 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 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.[78]

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.[79] Some studies have confirmed this increased risk for rural areas[51-53,80-82] whilst other have not.[48-50,54,83,84] 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.[50,83] 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.[51-53] 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.[50,83]

Life style factors

There is increasing interest in the potential role of oxidative damage in the aetiology of PD[63] 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.[81] Nuts and seeds appeared to be harmful in yet another study.[49] 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.[85] 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).[86] 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).[87] Several studies have failed to support the Another intriguing observation is that higher levels or serum urate (an anti-oxidant) and a clinical diagnosis of gout may be protective from PD and be associated with a better prognosis.[88,89] An on-going phase 3 RCT of inosine is currently underway in the USA to see if these observations are supported by a clinical RCT. Similarly, some evidence exists that anti-inflammatory drugs, specifically ibuprofen may have protective effects. [90] Some[91], but not all, studies have suggested that low cholesterol or cholesterol lowering drugs[92,93] may be associated with a reduced risk of PD. However after adjustment for cholesterol levels or a clincal diagnosis of hyperlipidaemia the "protective" effect of statins is attenuated[94]. There is also no evidence that better stain adherence is associated with a reduced risk of PD.[95] Finally genetic approaches using a technique known as Mendelian Randomization[96,97] have failed to find

supportive evidence that genetic variants associated with lower cholesterol have an increased risk of PD but the 95% confidence interval around the estimates are wide so one cannot rule out an effect.[98] The on-going double blind PD Stat RCT will report on any evidence of disease modification with statins. Other life style factors such as exercise and physical activity have also been linked with PD so that more activity appears to be beneficial. Evidence from the Health Professionals follow-up show a strong dose-response effect with increased months of strenuous activity being more protective even after adjustment for smoking status and other potential confounders. [1] Once again it is possible, like with smoking behaviour that a parkinsonian pre-morbid personality is itself the driver of physical activity levels hence we cannot be sure that any association is truly causal or reflects reverse causation.

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 and what exists fails to find a relative mortality benefit from levodopa therapy. 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.[99] A wide variety of aetiologic agents have been considered from infectious, toxic and other exposures. The most robust findings relate to constipation, less physical activity, non-smoking and anxiety and depression. Recent observational associations with statin, some anti-inflammatory agents and uric acid have generated therapeutic hypothesis that are or can be tested with RCTs. Future research needs to improve on current limited methods of exposure measurement and attempt more novel designs, such as Mendelian Randomization, to overcome confounding and 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.

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