The burden of Parkinson’s disease (PD) is likely to increase in the years to come as many countries, particularly those in Asia, face an ageing population. As such, it has been estimated that the number of individuals suffering PD in the world will double by the year 2030. There have been many descriptive epidemiological studies conducted to understand the prevalence and incidence of PD. In this article, the prevalence and incidence of PD in Asians will be reviewed. Analytical epidemiological studies have broadly focussed on demographic and environmental factors associated with PD. Amongst the environmental factors that will be reviewed are: occupational, lifestyle, dietary, and pharmacological factors. This article will also attempt to grade the strength of the association of these epidemiological factors with PD by weighing the evidence for each of these factors. Such an approach will provide a better understanding of the association of epidemiological factors with PD so as to further the understanding of the pathogenesis of PD and to develop better therapeutic interventions.

INTRODUCTION

Parkinson’s disease (PD) is a debilitating neurodegenerative disease for which there is no cure. In recent years, several causative monogenic mutations have been found. However, these mutations likely account for only a small proportion of all PD cases. The large majority of cases are sporadic in nature. Insights into non-genetic causes are therefore needed to advance the understanding of the pathogenesis of the disease and to develop effective therapeutic interventions.

In this article, we will review both the descriptive and analytical epidemiology of PD. Descriptive epidemiologic studies enable us to understand the frequency and the geographical or temporal distribution of PD. These studies help us estimate the burden of the disease and provide etiologic clues. Analytic epidemiologic studies seek to identify specific factors that increase or decrease the risk of PD and to quantify the associated risk. Two main study types are used in analytical studies: case-control or cohort studies. Most of the epidemiological factors associated with PD have been obtained from case-control studies. However, in recent years, more prospective cohort studies have identified sufficient incident cases of PD to enable the study of risk or protective factors in PD.
from 101.9 to 439.4 per 100,000 for door-to-door surveys and 61.4 to 141.1 per 100,000 in record based studies. In the review of incidence studies, 1 door-to-door study and 2 record based studies were reviewed. The door-to-door incidence study performed in Taiwan reported at age standardized rate of 8.7 per 100,000 compared to rates of 15.4 to 27.6 in non-Asian studies. The record based studies in Asia reported rates ranged from 6.7 to 8.3 per 100,000 compared to rates of 6.1 to 17.4 (most were higher than 9.4) per 100,000 in non-Asian studies.\(^2\)\(^3\) The findings that prevalence and incidence rates in Asia are slightly less than non-Asian countries could be real or could be related to differences in study methodology.

To overcome the problems of differences in study methodology, it will be ideal to study the occurrence of PD amongst different ethnic populations using the same study method. A study in Northern California compared the incidence rate of PD amongst the different ethnic groups in a large health maintenance organization.\(^1\) Five hundred and eighty-eight incident cases of PD were identified between 1994 and 1995. The age and gender-adjusted rate per 100,000 was found to be highest among Hispanics (16.6, 95% CI: 12.0-21.3), followed by non-Hispanic Whites (13.6, 95% CI: 11.5-15.7), Asians (11.3, 95% CI: 7.2-15.3), and Blacks (10.2, 95% CI: 6.4-14.0). The study suggested that the incidence of PD varies by race/ethnicity. The results of the study are consistent with the findings of the systematic review discussed above that the occurrence of PD amongst Asians appears to be slightly less than amongst Western Caucasian populations.

To address the question whether there is a difference in the occurrence of PD amongst different ethnic groups in Asia, a study in the multi-racial country of Singapore was conducted.\(^5\) A three-phase community-based survey among a disproportionate random sample of 15,000 individuals (9,000 Chinese, 3,000 Malays, 3,000 Indians) aged 50 years and above who live in central Singapore was conducted. In phase one, trained interviewers conducted a door-to-door survey using a validated ten-question questionnaire. In phase two, medical specialists examined participants who screened positive to any of the questions. Participants suspected to have PD had their diagnosis confirmed in phase three by a movement disorders specialist. The age-adjusted prevalence rates among Chinese (0.33%, 95% CI: 0.22-0.48), Malays (0.29%, 95% CI: 0.13-0.67) and Indians (0.28%, 95% CI: 0.12-0.67) were found to be the same (p=1.0). To our best knowledge no other studies have been performed to compare the prevalence rates of PD amongst different ethnic groups in Asia. There is therefore no evidence of a significant difference in the occurrence of PD between Asians from different ethnic groups.

Has the occurrence of PD changed over time in Asia? To answer this question, a record based study that was first performed in Yonago City, Japan in 1980 was repeated in 1992 and 2004.\(^6\) The adjusted prevalence (standardised to 2004 Japanese population) was found to be 145.8 (95% CI, 145.2-146.5) in 1980, 147.0 (95% CI, 146.3-147.6) in 1992, and 166.8 (95% CI, 166.1-167.5) in 2004. The adjusted incidence (standardised to 1980 Yonago population) was found to be 9.8 (95% CI, 4.3-15.3) in 1992, and 10.3 (95% CI, 4.7-15.9) in 2004. This study found that while the crude prevalence rate had increased as a result of a more aged population, the age and sex-adjusted prevalence rates remained fairly stable between 1980 and 1992, but significantly increased in the 2004 study. When incidence rates were analysed, the age and sex-adjusted incidence rates were found not to have changed significantly between 1980 and 2004. As incidence rates are a more accurate determination of disease risk as they are not influenced by factors that determine disease survival, these results demonstrate that the occurrence and risk of developing PD has remained stable over the past 25 years in Yonago City in Japan.

The number of people with PD is likely to grow in Asia as a result of our rapidly ageing population and an increasing life expectancy. It has been predicted that the patient load of PD will rise more than 2 times between 2005 and 2030.\(^7\) 2030 is the year when many countries in the world, including those in Asia, will bear the brunt of its ageing population. This problem is also related to an increased life expectancy in many countries as a result of the advances in the prevention and treatment of diseases. It has been extrapolated that in many developed countries, at least 50% of the babies born today will live to 100 years of age. In Japan for example, 50% of the babies born 2007 is expected to live to the age of 107 years.\(^7\) As the incidence of PD increases with age, we can expect more patients to develop PD. Asia will experience the full impact of the rise in PD population as 60% of the world’s population (more than 4 billion people) currently resides here.
ANALYTICAL EPIDEMIOLOGY: FACTORS ASSOCIATED WITH PD

There exist a multitude of epidemiological studies that explore the association between PD and various demographic and environmental factors. Amongst the environmental factors studied are: occupational, lifestyle, dietary, and pharmacological factors. These factors have been summarized in the Table 1. One challenge in reviewing these factors is to understand the strength of their association with PD. An attempt to do this has been presented in the Table using the criteria for grading evidence adapted from the American Institute for Cancer Research. The Table presents epidemiological risk factors that are graded as convincing, probably or limited, based on the current evidence of their association with PD.

Table 1: Epidemiological factors associated with PD

<table>
<thead>
<tr>
<th>Factors / Grading of Evidence</th>
<th>Convincing</th>
<th>Probable</th>
<th>Limited</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic Factors</td>
<td>Age ↑</td>
<td></td>
<td>Male ↑</td>
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<td>Environmental Factors</td>
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<td>Occupation Factors</td>
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<td>Pesticide ↑</td>
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<td>Heavy metal exposure ↑</td>
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<td>Head injury ↑</td>
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<td>Lifestyle Factors</td>
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<tr>
<td>Smoking ↓</td>
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<td>Alcohol ↓</td>
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<td>Caffeine ↓</td>
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<td>Tea ↓</td>
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<tr>
<td>Physical activity ↓</td>
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<td></td>
<td>Obesity ↑</td>
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<tr>
<td>Dietary Factors</td>
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<tr>
<td>Diary products/milk ↑</td>
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<td>Total calories ↑</td>
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<tr>
<td>Uric acid ↓</td>
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<td></td>
<td>Carbohydrates ↑</td>
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<td>Fat ↑</td>
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<td>Unsaturated FA ↓</td>
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<td>Cholesterol ↓</td>
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<td>Iron ↑</td>
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<td>Vitamin B6 ↓</td>
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<td>Vitamin E ↓</td>
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<td>Vitamin B6 ↓</td>
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<tr>
<td>Pharmacological Factors</td>
<td>Nonaspirin NSAIDs ↓</td>
<td>Oestrogens ↓</td>
<td>Statins ↓</td>
</tr>
</tbody>
</table>

↑ - indicate increased risk for PD  
↓ - indicates reduced risk for PD

Ref: Adapted from Criteria for grading evidence, American Institute for Cancer Research; food, nutrition, physical activity, and the prevention of cancer workgroup, 2007

**Convincing**

A convincing association/relationship should be robust enough to be highly unlikely to be modified in the foreseeable future as new evidence accumulates. The following are required:
- evidence from more than 1 study type  
- evidence from at least 2 independent cohort studies  
- no substantial unexplained heterogeneity within or between study types or in different populations  
- good quality studies  
- presence of a plausible biological gradient (dose-response)  
- strong and plausible experimental evidence

**Probable**

For evidence strong enough to support a judgement of a probable association/relationship. The following are required:
- evidence from at least 2 independent cohort studies, or at least 5 case-control studies  
- no substantial unexplained heterogeneity within or between study types or in different populations  
- good quality studies  
- evidence for biological plausibility

**Limited**

Evidence that is too limited to permit a probable or convincing association, but where there is evidence suggestive of a direction of effect. The evidence may have methodical flaws, be limited in amount, or have inconsistency of direction of effect.
DEMOGRAPHIC FACTORS

Age
Increasing age has been found to be the most consistent risk factor for the development of PD. This has been found in numerous descriptive epidemiological studies and prospective cohort studies from different parts of the world. Approximately 5% of PD patients have an onset before the age of 50 years. The prevalence of PD increases with age to affect approximately 2% of those aged 65 years and above.

Male gender
A number of studies have found that males have a 1.5 to 2 fold increased risk of developing PD compared to females. Other studies have however reported no gender differences. Investigations on gender differences are limited because women have historically been under represented in study populations. A male preponderance, if confirmed in future population-based studies, could be attributed to the role of sex hormones in protecting females, increased sex-linked genetic disposition, or greater exposure to causative environmental factors.

African race
A systemic review of epidemiological studies in 13 African countries showed that PD prevalence and incidence were lower in than those reported in Western populations. A study in Northern California that compared the incidence rate of PD amongst different ethnic groups also found the incidence of PD to be lowest amongst African Americans. This difference could due to different genetic backgrounds between races or to different health seeking behaviour, and warrant further investigations.

OCCUPATION FACTORS

Pesticides
A recent meta-analysis on the relationship of pesticide use and PD evaluated 39 case-control studies, 4 cohort studies and 3 cross-sectional studies. A summary relative risk of 1.62 (95% CI: 1.4, 1.88) for pesticide exposure (ever vs never) was found. The summary estimates for subclasses of pesticides indicated a positive association with herbicides and insecticides, but not with fungicides. There was however substantial heterogeneity between studies that was attributed to differences in the method of exposure assessment.

Rotenone, an insecticide, is a plausible cause of PD because of its mechanism of action. Like 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a toxicant known to cause parkinsonism in humans, rotenone directly inhibits mitochondrial complex I. In experimental models, both MPTP and rotenone cause selective injury of dopaminergic neurons in the substantia nigra, a key pathological feature of PD. Paraquat is another common pesticide that is one of the most widely-used herbicides in the world. It is known to experimentally produce subcellular changes associated with PD, including increased production of reactive oxygen species, alpha-synuclein aggregation, and selective nigral injury.

Heavy metal exposure
Welding and exposure to heavy metals such as manganese, iron, copper, lead, amalgam, aluminium, or zinc have been hypothesised to increase the risk of PD through accumulation of metals in the substantia nigra and increased oxidative stress. Some case reports and a few case-control studies have been published. However there is only limited epidemiological evidence for an association between heavy metal exposure and risk of PD.

Head Injury
At least 10 epidemiologic studies, have reported associations of mild-to-moderate head injury with increased risk of PD but others failed to find such an association. Most of these studies were case-control studies. A recent case-control study found that overall, head injury was not associated with PD. However, in individuals carrying the long Rep1 genotype of SNCA Rep1, a gene that resides in the promoter region of alpha-synuclein, head injury was strongly associated with PD. This study postulated that head injury may initiate and/or accelerate neurodegeneration when levels of synuclein are high, as in those with Rep1 expansion.

LIFESTYLE FACTORS

Cigarette smoking
A large number of epidemiological studies have been performed on the association between smoking and PD since 1968. A meta-analyses of
44 case control and 4 cohort studies revealed that compared to never smokers, the relative risk (RR) of developing PD was 0.39 (95% CI: 0.32-0.47) in current smokers, 0.59 (95% CI: 0.54-0.63) in ever smokers, and 0.8 (95% CI: 0.69 -0.93) in past smokers.\textsuperscript{17} Below is a summary of the epidemiological findings on smoking and the development of PD:

1. There is a dose dependent relationship between no. of pack-years smoked (length of time smoked + no. of cigarettes smoked/day).
2. The decline in PD risk was diminished in former smokers.
3. A similar inverse relationship was also found with use of cigars, pipes, chewing tobacco and snuff.
4. The effect of smoking was observed in monozygotic twins discordant for PD.\textsuperscript{1}

The findings of such a strong association between smoking and PD could be due to various causes or biases such as:\textsuperscript{18}

1. Direct causal effect – as a result of a direct neuroprotective effect, protection against toxic neuronal damage, or the inhibition of free radical damage.
2. Information bias – the result of diagnostic displacement of PD by other smoking related disease. However this is unlikely in prospective cohort studies where PD cases are actively sought after.
3. Selection bias – based on the hypothesis that smokers with PD die younger than smoker without PD. However these cases are unlikely to be missed in prospective studies. An alternative hypothesis is that smokers who are genetically predisposed to develop PD die young from smoking related diseases even before their symptoms appear. Studies in monozygotic twins who have the same genes and age however revealed that smoking reduces PD risk. In addition, comparison of age-specific rates has shown that such a hypothesis is unlikely.
4. Confounding – that smoking and PD share the same genetic or environmental factor. For such a factor to exist, it has to be constant across ethnic and geographical groups, and also has to preserve the dose and time-since-quitting responses found in the association between smoking and PD. Unfortunately, no such gene or lifestyle factor correlate has been able to account for the magnitude of such an association.

5. Reverse causation – this hypothesis suggest that there is a causal effect of PD on smoking behaviour. It has been postulated that individuals predisposed to develop PD have a pre-existing personality (risk adverse, non-addictive) or underlying metabolism (genetic or early toxic insult) that makes smoking unrewarding. Such a hypothesis is difficult to disprove. However, the association between alcohol and PD is not strong and shows conflicting results.

The arguments raised above that could explain the association between smoking and PD may also be applied to the other risk factors discussed in this article.

**Caffeine**

There is convincing evidence that caffeine intake is independently associated with a lower risk of PD. Such an association has been found for both coffee and non-coffee sources of caffeine. A meta-analysis of 26 studies showed revealed a relative risk of 0.75 (95% CI: 0.68-0.82), with low to moderate heterogeneity found between studies.\textsuperscript{19} These studies revealed a liner dose response relationship between caffeine intake and PD. In females however, a U-shaped relationship was found as a result of an interaction of caffeine with postmenopausal hormone replacement therapy (HRT). Ladies with high caffeine intake and who were on HRT have an increased risk of PD.\textsuperscript{19}

Caffeine and its major metabolite, paraxantine, are adenosine A2A antagonists. These antagonists have been found to be neuroprotective and to improve motor deficits in animal models of PD.\textsuperscript{19} Clinical trials of adenosine antagonists in PD patients have revealed a reduced ‘off’ time in patients with motor fluctuations.\textsuperscript{20}

**Alcohol**

Based on the hypothesis of an addictive personality that protective for PD, a number of studies have looked at the association between alcohol intake and PD. These studies however have revealed conflicting results.\textsuperscript{15}

**Tea**

In an analyses of 11 case control and 1 cohort study on the association of tea and PD, a pooled odds ratio of 0.83 (95% CI: 0.74-0.92) was found. There was however significant heterogeneity across these studies.\textsuperscript{21} In the Singapore Chinese
Health Study, a cohort study, it was found that higher intake of black tea but not green tea was associated with a reduced risk of developing PD (HR:0.29, 95% CI: 0.13-0.65). This effect was independent of its caffeine content.  

**Physical activity**

There have been at least 3 case-control and 4 prospective cohort studies on the association between physical activity and PD. A mini meta-analysis revealed that that higher moderate to vigorous physical activities were associated with lower PD risk with an estimated odds ratio of 0.67 (95% CI 0.56–0.80) for all participants. Biologically, it is plausible for physical activity to be neuroprotective for PD by improving cerebrovascular circulation and increasing the production of neurotrophic substances.

**Obesity**

Studies have assessed the association between body mass index and other anthropometric measures with the risk of developing PD. At least 4 cohort studies have evaluated such an association. However, these studies have shown conflicting results.

**DIETARY FACTORS**

**Dairy products and milk**

There is probable evidence of an increased risk of PD amongst individuals who consume more dairy products. This was shown in a meta-analysis of 3 large cohort studies in USA with revealed a relative risk of 1.6 (95% CI: 1.3-2.0). The relationship was stronger in males than females and was not related to calcium, Vitamin D or fat in dairy products. It has been postulated that dairy products may be contaminated with toxic chemicals such as pesticides. An alternative hypothesis is that dairy products reduces uric acid levels in individuals, and this reduction in uric acid which is a natural anti-oxidant, increases the risk for PD.

**Uric Acid**

There are at least 5 cohort studies and 8 case-control studies that have assessed the association of uric acid levels, dietary uric acid or gout with PD. These studies revealed that raised uric acid levels were associated with a reduced risk of PD. This effect appears to be more apparent in males. Studies have also shown reduced uric acid levels in the CSF and substantial nigra of PD patients. Raised serum and CSF levels were also associated with better clinical outcomes in PD patients. These findings could be due to the fact that uric acid is a natural anti-oxidant, thereby preventing or reducing the neurodegenerative processes that lead to PD. Uric acid is also a scavenger of free radicals and an iron chelator. In a mouse model of PD, treatment with uric acid suppressed oxidative stress and prevented the death of dopaminergic neurons by homocysteine or iron.

**Calories and carbohydrates**

A number of case-control studies have shown an increased caloric intake amongst PD patients. Cohort studies however did not reveal such an association. Similarly, a few case-control studies and one cohort study revealed higher carbohydrate intake in PD patients. It has been suggested that these findings could be explained by the higher need for energy in PD patients.

**Fats**

Case-control studies have found that an increased total fat intake is associated with an increased risk for PD. Cohort studies however either found no such effect or an inverse effect. With regard to unsaturated fatty acids, the Rotterdam study found that an increased consumption of monounsaturated fatty acids (MUFA) and polyunsaturated FA (PUFA) were associated with a reduced risk of PD. However in the prospective health professionals follow-up study (HPFS) and nurses health study (NHS), only arachidonic acid, a polyunsaturated omega-6 fatty acid, reduced the risk of PD in women only.

**Vitamins**

The Datatop study, a randomized, controlled clinical trial found Vit E to have no effect on the primary end point of the need to start levodopa. This study was however conducted on subjects who have already been diagnosed with PD. A meta-analyses of 1 cross sectional, 5 case control and 1 cohort study revealed a relative risk of 0.81 (95% CI: 0.67-0.98) for moderate intake of Vit E. When subjects with high intake of Vit E were analysed, the results were however not significant. Significantly elevated levels of homocysteine in the plasma of PD patients have been seen in some studies. As a deficit of Vit B causes hyperhomocystinaemia, studies were performed
to understand if any association between Vit B intake and the risk of PD existed. In the Rotterdam study, increased dietary Vit B6 intake was associated with a reduced risk for PD only in smokers. The HPFS and NHS however did not reveal any association.\(^{15,28}\)

**PHARMACOLOGICAL FACTORS**

*Nonaspirin NSAIDs*

A recent Cochrane review of 5 cohort and 9 case-control studies showed that exposure to any NSAIDs or aspirin had no effect on the risk of developing PD.\(^3^2\) Exposure to non-aspirin NSAIDs reduced the risk of developing PD by 13% (effect estimate 0.87 (95% CI 0.73 to 1.04 - random-effects model), but this did not reach statistical significance. Ibuprofen in isolation was examined in four studies and was associated with a 27% reduction in risk (effect estimate 0.73, 95% CI 0.63 to 0.85). The authors concluded that non-aspirin NSAIDs, particularly ibuprofen, may reduce the risk of developing PD.

*Oestrogens*

There is limited evidence for the association of oestrogens with PD.\(^1^5\) As discussed, the higher prevalence and incidence of PD in men in various epidemiological studies have prompted the hypothesis that female sex hormones may protect against PD. Animal models have provided evidence for a potential beneficial effect of oestrogens on PD, possible through antioxidant properties. Case-control studies on the relationship between the use of oestrogens or the length of reproductive period and PD show conflicting results.\(^1^5\) In the Nurses Health Study, a prospective cohort study, neither reproductive factors nor exogenous oestrogens were associated with the risk of PD.\(^3^3\)

*Statins*

Statins have been found to have potent anti-inflammatory and immunomodulating effects, which led to the hypothesis that statins could be neuroprotective agents. A review of epidemiological studies in 2009 however, revealed conflicting results.\(^3^4\) A large prospective study recently found that regular use of statins was associated with a modest reduction in PD risk among adults younger than 60 years of age.\(^3^5\)

**CONCLUSIONS**

In conclusion, while the occurrence of PD appears to be slightly less amongst Asians compared to the Caucasians, there does not appear to be a significant difference in rates between Chinese, Malays and Indians living in Singapore. The rates of occurrence of PD in Japan (Yonago City) also appear to be stable over the past 25 years. Nevertheless, the burden of PD in Asia will rise significantly in the years to come as a result of an increased life expectancy and an ageing population. There is therefore a need to train more doctors and health care professionals in the region to better manage and care for the increasing numbers of PD patients.

Based on the criteria adapted from the American Institute for Cancer Research, the review of the analytical epidemiology of PD revealed that there is convincing evidence that age, smoking and increased caffeine intake are associated with a reduced risk of developing PD. There is probable evidence that pesticide use and an increased intake of dairy products are associated with an increased risk for PD, while increased uric acid levels are associated with a reduced risk of PD. With regard to other demographic and environmental factors in PD, there is currently limited evidence to suggest a probable association with PD. It is important to bear in mind that the association of epidemiological factors with PD do not equate to causation or protection. These factors however provide important clues to direct further clinical and basic science studies so that the underlying pathogenic mechanisms behind PD can be unravelled. In so doing, it is hoped that novel therapeutic strategies may be developed to prevent, treat or reverse the disease process of PD.

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