Parkinson's disease in the Western Pacific Region

Shen-Yang Lim, Ai Huey Tan, Azlina Ahmad-Annuar, Christine Klein*, Louis C S Tan, Raymond L Rosales, Roongroj Bhidayasiri, Yih-Ru Wu, Hui-Fang Shang, Andrew H Evans, Pramod K Pal, Nobutaka Hattori, Chong Tin Tan, Beomseok Jeon*, Eng-King Tan*, Anthony E Lang**

1·8 billion people of diverse ethnicities and cultures live in the Western Pacific Region. The increasing longevity of populations in this region is a major contributor to the exponential increase in Parkinson's disease prevalence worldwide. Differences exist between Parkinson's disease in the Western Pacific Region and in Europe and North America that might provide important insights into our understanding of the disease and approaches to management. For example, some genetic factors (such as *LRRK2* mutations or variants) differ, environmental exposures might play differential roles in modulating the risk of Parkinson's disease, and fewer dyskinesias are reported, with some differences in the profile of non-motor symptoms and comorbidities. Gaps in awareness of the disease and inequitable access to treatments pose challenges. Further improvements in infrastructure, clinical governance, and services, and concerted collaborative efforts in training and research, including greater representation of the Western Pacific Region in clinical trials, will improve care of patients with Parkinson's disease in this region and beyond.

Introduction

The prevalence of Parkinson's disease was the fastest growing of all the neurological disorders included in the Global Burden of Disease, Injuries, and Risk Factors Study (GBD; 61% increase in crude prevalence from 1990–2017), with population ageing contributing to much of that growth.[1,2] Asia will have more than 60% of the world's population aged at least 65 years by the 2030s and China alone is projected to have around 5 million patients with Parkinson's disease by 2030, accounting for 60% of patients with Parkinson's disease.[2]

The Western Pacific Region (panel 1) is therefore poised to account for the majority of patients with Parkinson's disease worldwide.[2] Furthermore, the past decade has seen a rapid increase in research output, with China, Japan, and South Korea now ranking second, seventh, and tenth globally in the number of Parkinson's disease-related scientific publications.[5] A picture is emerging of important differences in Parkinson's disease in the Western Pacific Region versus Europe and North America, such as genetic and environmental causative factors, and clinical presentation and management. An understanding of these issues gives novel insights into the aetiology, pathogenesis, natural history, and optimal treatment of the disease in general, and guides effective planning of medical resources. In this Review, we present a state-of-the-art synthesis of the differences between the Western Pacific Region and Europe and North America.

Epidemiology

Data for the incidence of Parkinson's disease in the Western Pacific Region are patchy, with a scarcity of door-to-door surveys (needed to detect undiagnosed cases); a few records-based studies after 2000 reported WHO age-standardised incidences ranging from 6·7–26·9 per 100 000 person-years.[6,7] Figure 1 shows prevalence data from studies done in high-income Western Pacific countries or territories,[6–10] and statistical estimations from GBD 2017,[1] standardised to the WHO World Standard Population 2000 to adjust for differences in the age structures of the different populations.

Despite having among the highest life expectancies and largest proportions of aged individuals in the world,[11] Japan and Singapore (a multiethnic country consisting primarily of Chinese, Malays, and Indians) had lower prevalences of Parkinson's disease compared with high-income Oceanian countries (Australia and New Zealand) and North America,[1,6,9,12] consistent with the findings of a meta-analysis of 47 studies[13] reporting lower Parkinson's disease prevalence among 70–79-year-olds in Asia compared with Europe and North America. By contrast with the well known male predominance in Parkinson's disease (global age-standardised prevalence 1·4 times higher in males),[2] female predominance was reported in Japan and Korea; possible reasons include the larger disparities between sexes in life expectancy and smoking rates in these countries.[6,7]

Few studies have examined temporal trends in the frequency of Parkinson's disease.[2,6] Studies in Japan,

Panel 1: The Western Pacific Region

The Western Pacific Region, one of six WHO-designated regions, covers 37 member-states in Asia and Oceania, stretching over a vast area, from China and Mongolia in the northwest to New Zealand in the south, and several Pacific Islands in the east. Asian countries or territories in the Western Pacific Region include (in alphabetical order): Brunei, Cambodia, China, Hong Kong, Japan, Laos, Macao, Malaysia, Mongolia, Philippines, Singapore, South Korea, and Vietnam. Oceanian countries or territories include American Samoa, Australia, Cook Islands, the Federated States of Micronesia, Fiji, French Polynesia, Guam, Kiribati, Marshall Islands, Nauru, New Caledonia, New Zealand, Niue, Northern Mariana Islands, Palau, Papua New Guinea, Pitcairn Islands, Samoa, Solomon Islands, Tokelau, Tonga, Tuvalu, Vanuatu, and Wallis and Futuna. Some of these countries are highly developed—such as Japan, South Korea, Hong Kong, Singapore, and Australia—but many are severely resource-constrained, with a large treatment gap (ie, many people not receiving appropriate treatment for their medical conditions).[3,4]

Lancet Neurol 2019; 18: 865–79

Published Online
June 4, 2019
http://dx.doi.org/10.1016/S1474-4422(19)30195-4

*Senior author

Division of Neurology, Department of Medicine, and the Mah Pooi Soo and Tan Chin Nam Centre for Parkinson's and Related Disorders, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia (Prof S-Y Lim MD, A H Tan MD, Prof C T Tan MD); **Department of Biomedical Science, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia** (A Ahmad-Annuar PhD); **Institute of Neurogenetics, University of Luebeck, Luebeck, Germany** (Prof C Klein MD); **Department of Neurology, National Neuroscience Institute, Singapore** (L C S Tan FRCP, Prof E-K Tan FRCP); **Department of Neurology and Psychiatry, University of Santo Tomas Hospital, Manila, Philippines** (Prof R L Rosales PhD); **Chulalongkorn Center of Excellence for Parkinson's Disease and Related Disorders, Department of Medicine, Faculty of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital, Thai Red Cross Society, Bangkok, Thailand** (Prof R Bhidayasiri MD); **Department of Neurology, Linkou Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Taoyuan, Taiwan** (Prof Y-R Wu MD); **Department of Neurology, West China Hospital, Sichuan University, Chengdu, China** (Prof H-F Shang MD); **Department of Neurology, Royal Melbourne Hospital, Parkville, VIC, Australia** (A H Evans MD); **Department of Neurology, National Institute of Mental Health and Neurosciences, Bangalore, India** (Prof P K Pal MD); **Department of Neurology, Juntendo University School of Medicine, Tokyo, Japan** (Prof N Hattori MD);

Department of Neurology, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, South Korea (Prof B Jeon MD); **and the Edmond J Safra Program in Parkinson's Disease and the Morton and Gloria Shulman Movement Disorders Clinic, Toronto Western Hospital, Toronto, ON, Canada** (Prof A E Lang MD)

Correspondence to: Prof Shen-Yang Lim, Neurology Laboratory, Faculty of Medicine, University of Malaya Medical Centre, 50603 Kuala Lumpur, Malaysia
sylim@ummc.edu.my

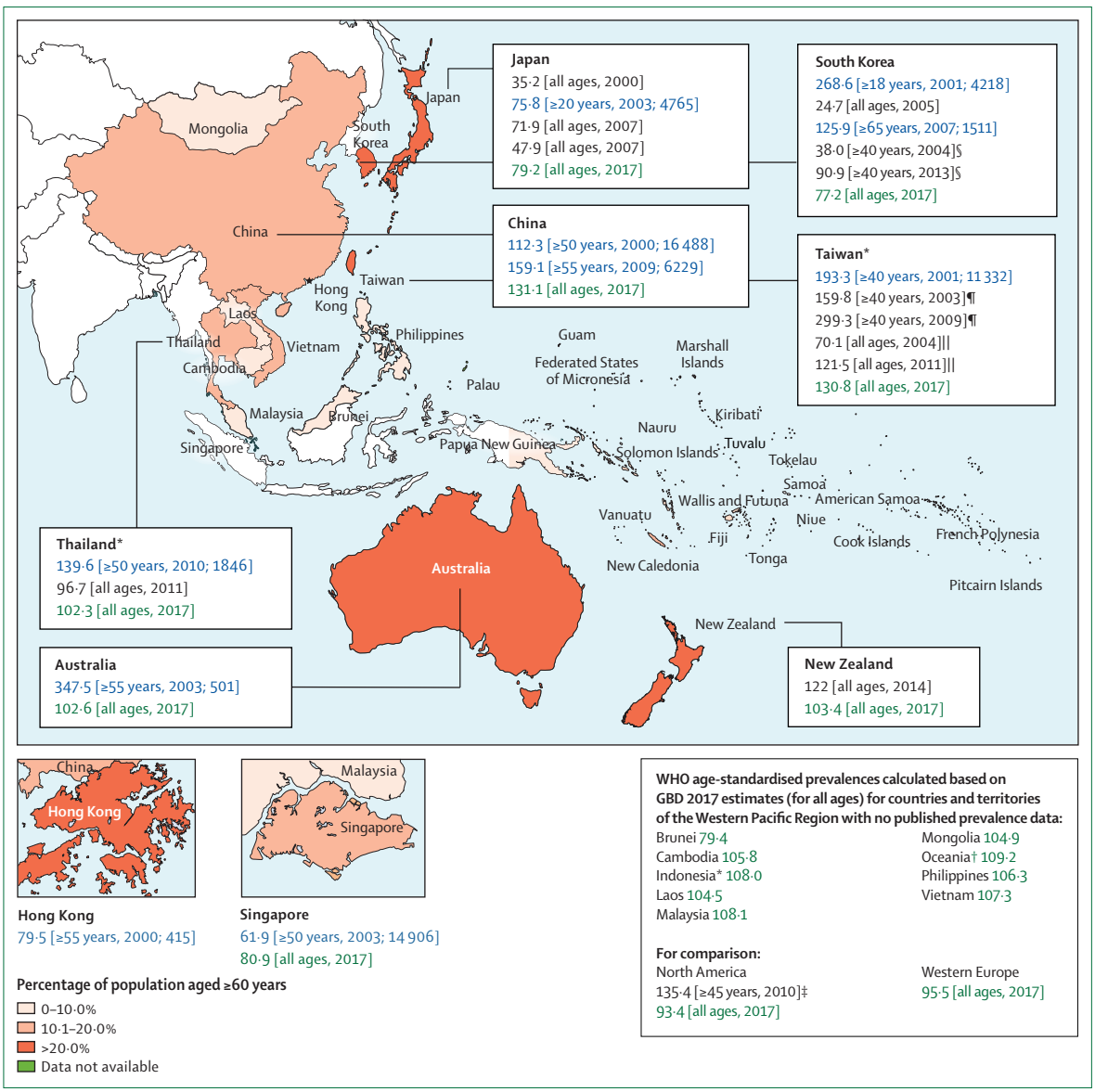

Figure 1: **Prevalence of Parkinson's disease in the Western Pacific Region**
All prevalence rates are per 100 000 population, standardised to the WHO World Standard Population 2000 (based on age-specific prevalences provided by each study, with an assumption of no prevalent cases for unreported age strata). Parentheses indicate the age strata sampled by the study, year of survey completion, and the number of individuals screened (in door-to-door surveys). Only studies with the year of survey completion from 2000 onwards[6–10] are shown (see appendix for further details). Values shown in black are from records-based surveys. Values shown in blue are from door-to-door surveys or community screening. Values shown in green are based on age-specific estimates provided by the Global Burden of Diseases, Injuries, and Risk Factors Study 2017.[1] Figures for the population aged ≥60 years were obtained from UN World Population Ageing 2017 data.[11] *Although not listed in the Western Pacific Region, Indonesia, Taiwan, and Thailand are included because of their geographical and ethnocultural interconnectedness with other member states in this region. †Oceanian countries or territories consist of American Samoa, the Federated States of Micronesia, Fiji, Guam, Kiribati, Marshall Islands, Northern Mariana Islands, Papua New Guinea, Samoa, Solomon Islands, Tonga, and Vanuatu. ‡The studies contributing to the North American meta-analysis used different case ascertainment strategies in diverse geographical regions.[12] §, ¶, and || indicate serial data extracted from three different time-trend studies.[6,7]

See Online for appendix

South Korea, and Taiwan showed increasing prevalence over time, which could reflect population ageing, changing environmental factors (eg, decreasing rates of smoking), improvements in diagnosis, and improved survival of patients with Parkinson's disease.[6,7] The incidence of Parkinson's disease was unchanged over 25 years in Japan (1980–2004)[6] and increased in South Korea from 13·6 to 26·9 per 100 000 person-years (age-standardised to WHO World Standard Population 2000; 2004–2013);[7] opposing trends were observed between two Taiwanese studies (2002–2009 and 2004–2011), probably due to methodological issues.[6]

Geographical differences in the frequency of Parkinson's disease should be interpreted with caution due to

methodological differences across studies (appendix pp 1–5), such as differences in screening instruments and participation rates in door-to-door surveys; and case-ascertainment strategies, completeness of data sources, and access to specialised health care in records-based studies.[6,14] Many studies only surveyed populations above an arbitrary age cutoff, possibly underestimating the prevalence of Parkinson's disease.[6,10] Further confounding these assessments are the high rates (around 20–80%) of undiagnosed Parkinson's disease in the Western Pacific Region due to limitations in health-care access and the stigma of being diagnosed with the disease;[2,6,8] and the small sample sizes resulting in unrepresentative sampling.[2,6,8,10] However, despite these caveats, seven records-based studies[6] and one door-to-door survey[6] in Japan done between 1980 and 2007 across different metropolitan and rural areas showed consistently lower prevalences (35·2–75·8 per 100 000 individuals) compared with studies done during a similar period in European and North American countries (figure 1). Furthermore, studies in the USA[12] and New Zealand[9] have reported lower incidences and prevalences of Parkinson's disease in Asian, Pasifika, and Māori ethnic groups compared with white and Hispanic groups. However, there were no prevalence differences among Asian races (Chinese, Malay, and Indian) in a large study done in Singapore.[6] The lower frequency of Parkinson's disease in some Western Pacific populations could be due to racially determined genetic factors, or environmental exposures or cultural practices.[6,14,15]

Environmental or acquired factors

There is a scarcity of large epidemiological studies of environmental factors and Parkinson's disease in the Western Pacific Region and any associations are probably under-recognised and under-reported.[6,14,15] Pesticides, the strongest environmental risk factor linked to Parkinson's disease (particularly paraquat, organochlorines, organophosphates, and rotenone)[6,8,14,15] are widely used in this region,[6,8,16] with China being the largest pesticide producer in the world (a study estimates 1·5–4·0 times greater pesticide use than the global average).[16] Exposure to solvents and metals[2,14,15] might have also contributed to the increased incidence of Parkinson's disease in China, which has undergone rapid industrialisation over the past generation.[2]

Factors such as diet, smoking, exercise, and diseases other than Parkinson's disease have also had an epidemiological impact in the Western Pacific Region.[6,9,14,15,17–24] Dietary intake of coffee, black or green tea, and dairy products vary widely between countries and ethnic groups in this region.[6,15] A dose-dependent protective effect of caffeine has been extensively reported,[6,14,15] and some Western Pacific populations have a high frequency of tea drinkers. However, there is a possible differential effect between black and green tea among Chinese individuals, with only black tea being protective; researchers have postulated that the protective effect of black tea might be mediated by upregulatory effects on oestrogen-related pathways, whereas green tea might have downregulatory effects.[6,14,15]

There is a low prevalence and incidence of Parkinson's disease in New Zealand Māoris[9] that might partly relate to their high smoking rates, as well as to the high prevalences of gout and hyperuricaemia (which are associated with potential protective effects, postulated to be due to the antioxidant properties of uric acid).[6,14,15] Smoking is also very common in China, with one study of 66 752 individuals in 2014–15 reporting a 58·2% rate of current smoking among men aged 40 years and older (although the rate in women of the same age group is low, at 4·0%).[22] By contrast, smoking has declined in many parts of Europe and North America because of population health measures, leading investigators in the USA to increase the projected 2040 figures for Parkinson's disease by at least 10%.[17]

Exercise is also associated with a reduced risk of Parkinson's disease.[15] Surveys of east Asian populations (China, Japan, Singapore, and Taiwan) report lower levels of physical activity than European and North American participants.[18] However, so far, no studies have shown an association between a lack of exercise in Asian populations and the subsequent development of Parkinson's disease.

Asian people are at higher risk of type 2 diabetes, and 60% of patients with diabetes worldwide are Asian.[19] This disease has also reached epidemic proportions in many Pacific Island populations.[19] A meta-analysis of seven population-based cohort studies involving more than 1·7 million individuals reported a 38% increased risk of Parkinson's disease in people with diabetes.[20] Additionally, more than 60% of individuals with chronic hepatitis C worldwide are Asian; this infection is also associated with a 35% increased risk of Parkinson's disease.[6] *Helicobacter pylori* infection is highly prevalent in developing countries and linked both to development and worsening of Parkinson's disease.[15,21] Colonic microbiome changes in patients with Parkinson's disease (compared with control individuals without Parkinson's disease) have been reported in Japan, China, and Malaysia (and also in white patients), with a possible but controversial role suggested in Parkinson's disease causation and phenotype.[21] This field is complex and so far studies have not assessed inter-ethnic colonic microbiome differences in patients with Parkinson's disease.

Future well designed research studies into the risk and protective factors for Parkinson's disease might help to develop preventive interventions to reduce the future burden of this disease, which might have to be tailored to specific ethnocultural groups or geographical regions. For example, concerns about health problems resulting from pesticides have led to organochlorines and paraquat being banned or phased out in China, but they continue to be permitted in several Western Pacific countries or territories citing insufficient evidence of a health hazard.[16] However, the effects of environmental factors might have

a long latency (eg, pesticide exposure taking place during intrauterine life or early childhood),[17] and many decades might be required before an environmental change will modify the risk of Parkinson's disease.[16,17] Currently, evidence is probably sufficiently strong to promote exercise and, arguably, moderate doses of caffeine, for primary prevention of Parkinson's disease.[15]

Genetics

Mutations in six genes (*PRKN*, *PINK1*, *DJ1*, *LRRK2*, *SNCA*, and *VPS35*) have been conclusively linked to monogenic Parkinson's disease.[25] *PRKN*, the gene most commonly implicated in autosomal recessive early-onset Parkinson's disease, was first discovered in Japan; the discovery has increased the understanding of mitochondrial dysfunction and protein degradation pathways in neurodegenerative disorders.[25] Mutations in *PINK1*, the second most common gene causing autosomal recessive early-onset Parkinson's disease, are also common in Japanese, Filipinos, and Taiwanese people.[26] The MDSGene database[27] collates all English-language reports of cases of monogenic Parkinson's disease. Although the MDSGene database has limitations as it captures only published cases and some data can be missing in the original descriptions, it is currently the most comprehensive resource on monogenic Parkinson's disease, with stringent inclusion criteria and full curation of clinical and genetic data by both specialists in movement disorders and genetics.[27] Of all 2064 patients carrying a possibly pathogenic mutation in one of the confirmed Parkinson's disease genes (*PRKN*, *PINK1*, *DJ1*, *LRRK2*, *SNCA*, and *VPS35*), information on ethnicity is available for 1048 (appendix pp 6,7). 250 (23·9%) of these individuals are Asian, with *PRKN* accounting for the largest fraction (n=166; 39·2% of all *PRKN* mutations reported worldwide).[27] However, the 2064 MDSGene cases account for only 1·4% of the approximate 150 000 monogenic patients with Parkinson's disease worldwide (assuming that 2–3%[25] of the estimated 6·1 million cases globally[2] are attributable to a single Mendelian genetic cause). Thus, possible phenotypic differences such as age of Parkinson's disease onset or levodopa responsiveness might be explained by the preliminary nature of the observations and the small numbers of patients included.[27]

Mutations in *LRRK2* are the most frequent genetic cause of Parkinson's disease worldwide, with the most common pathogenic mutation, Gly2019Ser, accounting for 1% of sporadic and 4% of familial cases.[25] Gly2019Ser is common in white patients, and is present in up to 20% of Ashkenazi Jewish and 40% of North African Arab patients; however, it is almost completely absent in Asians.[28,29] By contrast, Asian-specific variants are found exclusively in selected populations.[28,29] For example, the *LRRK2* Gly2385Arg and Arg1628Pro variants are the most common reported genetic risk factors in Chinese individuals (each variant detected in around 5–10% of patients, versus around 2–5% in controls without Parkinson's disease).[28,29] Gly2385Arg, but not Arg1628Pro, is also common in Japanese and Korean individuals, whereas the reverse is true for ethnic Thai people.[28,29] These variants are absent or rare in white people and in other Asian groups such as Indian people.[28,29] Besides the association with Parkinson's disease development, these mutations might also confer earlier disease onset[30] and faster motor progression compared with mutation-negative patients (whereas milder progression is seen with Gly2019Ser).[31,32]

The glucocerebrosidase gene (*GBA*) is also commonly implicated in Parkinson's disease. The *GBA* Leu444Pro mutation has been associated with a more aggressive phenotype (including greater cognitive dysfunction) than other *GBA* mutations in white individuals,[33] but needs to be investigated further in other groups, including Chinese and Japanese individuals in whom this mutation is common (accounting for 62·1% of *GBA* mutations in a meta-analysis of 6536 Chinese patients).[34,35] Conversely, the *GBA* Asn370Ser mutation is rare in Chinese and Japanese populations but common in white individuals.[33]

Mutations in *CHCHD2* were first identified in late-onset autosomal dominant Parkinson's disease in Japanese populations, and have been reported primarily in other Asian populations, including mainland and Singaporean Chinese people.[36,37] This gene encodes a mitochondrial protein and its study might provide new insights into the pathogenesis of Parkinson's disease.[38]

Because monogenic forms of Parkinson's disease are rare, a polygenic model has been proposed to explain the genetic contribution to most cases of Parkinson's disease[25] (Western Pacific Region candidate gene association studies, genome-wide association studies, and meta-analyses; appendix pp 8–12). Genome-wide association studies in sporadic Parkinson's disease showed strong associations with certain loci (*SNCA*, *LRRK2*, and *MCCC1*) in both European and Asian patients with Parkinson's disease.[39] However, allelic heterogeneity occurs at *LRRK2* in east Asian patients, and European risk variants at six other loci, including *MAPT* and *GBA-SYT11*, were non-polymorphic or very rare, suggesting differences in the genetic contribution to Parkinson's disease between European and Asian populations.[39] Other studies have highlighted that inter-ethnic differences in regional linkage disequilibrium patterns at these loci might account for variances in studies between Europe and North America and the Western Pacific Region.[40] With the advent of targeted therapies, an improved understanding of the genetic and mechanistic factors underlying Parkinson's disease is becoming increasingly important,[27,41] and genetic differences between populations of the Western Pacific Region imply that successful disease-modifying therapeutic approaches might have to differ from those in European and North American patients.

Clinical features and comorbidities

Motor response complications

Over time, because of a combination of disease progression and treatment (particularly levodopa at higher

	Population (millions)	Number of neurologists*	Number of individuals in population per neurologist†	Number of specialist neurologists; and number of specialist neurosurgeons‡	Universal availability of oral levodopa§	Deep brain stimulation		Apomorphine infusion		Levodopa-carbidopa intestinal gel	
						Available	Widely used¶	Available	Widely used¶	Available	Widely used¶
Australia	25	500	50 000	51; 17	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Cambodia	16	11	1 455 000	0; 0	No	No	No	No	No	No	No
China	1379	20 000–100 000	14 000–69 000	500; 200	Yes	Yes	Yes	No	No	No	No
Hong Kong	7	126	56 000	14; 7	Yes	Yes	Yes	Yes	No	No	No
Indonesia‖	264	2470	107 000	1; 3	Yes	Yes	No	No	No	No	No
Japan	127	5925	21 435	930; 520	Yes	Yes	Yes	No	No	Yes	Yes
Laos	7	4	1 750 000	0; 0	No	No	No	No	No	No	No
Malaysia	32	102	314 000	14; 4	Yes	Yes	No	Yes	No	No	No
Mongolia	3	300	10 000	4; 0	Yes	No	No	No	No	No	No
New Zealand	5	46	109 000	4; 2	Yes	Yes	Yes	Yes	Yes	No	No
Philippines	103	535	193 000	10; 3	Yes	Yes	No	Yes	No	No	No
Singapore	6	103	58 000	12; 4	Yes	Yes	Yes	Yes	No	No	No
South Korea	51	2185	23 000	50; 40	Yes	Yes	Yes	No	No	No	No
Taiwan‖	24	1141	21 000	50; 22	Yes	Yes	Yes	No	No	No	No
Thailand‖	69	800	86 000	20; 10	Yes	Yes	No	Yes	No	Yes	No
Vietnam	93	300–500	186 000–310 000	5; 1	Yes	Yes	No	No	No	No	No

In most instances, official data were unavailable and information was obtained via personal enquiries of leading neurologists in the respective countries or territories. Only countries or territories with populations ≥3 million were included for pragmatic reasons; data from the Pacific Islands (many having populations <20 000) were unavailable. *There is substantial variation in the definition of neurologists from country to country and even within the same country, with some practitioners registered as such not having undergone formalised neurology training (eg, in China), or some who received training over a relatively limited duration (eg, 1 year in Vietnam). †Numbers rounded to the closest thousand. ‡For the purpose of this Review, specialists were defined as neurologists who had undergone ≥6 months of further training in movement disorders after completing general neurology training; or neurosurgeons who had undergone ≥6 months of further training in neuromodulation after completing general neurosurgical training. For Japan, the numbers were derived from membership of the Movement Disorder Society of Japan and the Japan Society for Stereotactic and Functional Neurosurgery, respectively. §Universal availability of oral levodopa was defined as wide availability of the drug in both urban and rural settings plus affordability according to the WHO definition (by which the lowest paid unskilled government worker should not have to spend more than 1 day's wages to purchase a 30-day supply of any standard treatment regimen, which could be a generic version). ¶Widely used device-aided therapies were defined as those that treating neurologists in urban centres of the country were able to provide to patients on a routine clinical basis, regardless of their socioeconomic background, because they were covered wholly or in large part by public health financing or insurance. ‖Although not listed as Western Pacific Regions, we have tabulated data for Indonesia, Taiwan, and Thailand as well, because of their geographical and ethnocultural interconnectedness with other member states in this region.

Table 1: **Management and care of patients with Parkinson's disease in Western Pacific countries or territories**

dosages),[42,43] motor fluctuations and dyskinesias develop in a majority of patients, often substantially impairing their function and health-related quality of life.[42,43] Lower rates of motor complications have been reported in Western Pacific Region populations,[42–46] probably because of the generally lower levodopa dose used compared with Europe and North America.[47–55] In two large prospective surveys of patients with Parkinson's disease recruited from tertiary centres in China (n=1558[44] and n=901[45]), only 8·5–10·3% had dyskinesias (disease duration 4·2–5·4 years). Even among patients with disease duration of at least 11 years, rates of dyskinesias and motor fluctuations were only 18·1% and 42·2%[45] (compared with around 10% of levodopa-treated patients per year who develop dyskinesias and motor fluctuations in European and North American countries).[42,43] Lower rates of dyskinesias were also reported in a retrospective study from Japan (n=1768; after 5 years, 10 years, and 15 years, dyskinesias developed in 8·4%, 35·1%, and 62·8%, and wearing-off in 21·3%, 59·4%, and 73·2%, respectively).[46]

Younger age is associated with increased risk for motor complications,[43] but this variable does not appear to be confounding, since the average age of disease onset was 60–61 years in the Chinese studies[44,45] and 57·2 years in the Japanese[46] study (ie, fairly typical of cohorts followed in specialist clinics). Some under-ascertainment is also likely, particularly in retrospective studies;[46] ideally, patients should be directly observed by movement disorder specialists during the ON-medication period using a specific dyskinesia rating scale, which was done in one of the two Chinese studies.[44]

Non-motor symptoms

In common with patients with Parkinson's disease in Europe and North America, studies in the Western Pacific Region have shown a high frequency of non-motor symptoms and a strong negative effect on health-related quality of life,[56,57] but with some possible differences in the profile of non-motor symptoms. One study showed patients of Asian ancestry to have a much higher rate of asthenia (a generalised sense of weakness) than Hispanics and Africans.[58] Constipation might also be more common in Asian patients (70% in Chinese versus 16–58% in European and North American patients, using the Non-Motor Symptoms Questionnaire), and the frequent use of anticholinergics might be a contributing factor.[56,59,60]

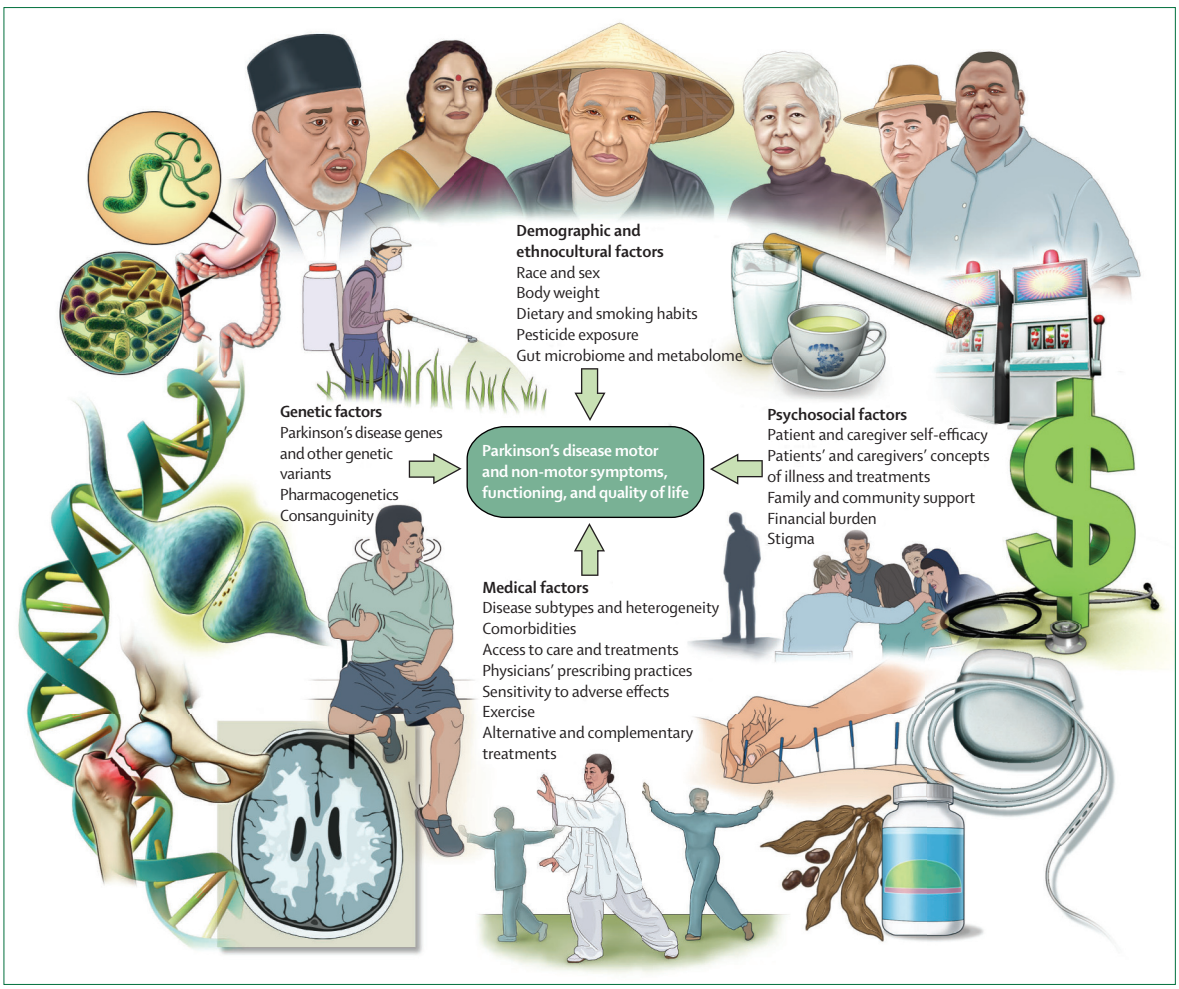

Figure 2: **Factors that might affect the development of Parkinson's disease, the expression of motor and non-motor symptoms, and quality of life**
The figure shows the genetic, demographic, ethnocultural, medical, and psychosocial factors that might have a differential effect. Selected factors or features are portrayed (clockwise from top left): colonic microbiome and *Helicobacter pylori* infection; pesticide exposure; various ethnic or cultural groups (Muslim Indonesian or Malay, Indian, Vietnamese, east Asian [Chinese, Japanese, or Korean], white Australian, and Māori); lifestyle habits (consumption of milk and green tea, and cigarette smoking); gambling slot machines; cost of medical treatment including deep brain stimulation; stigma of having Parkinson's disease; support groups; complementary and alternative medicine treatments (acupuncture, *Mucuna pruriens*, and tai chi); levodopa-induced dyskinesias; comorbidities (cerebral small vessel disease and osteoporotic hip fracture); DNA; and the nigrostriatal synapse.

Lower rates of impulsive-compulsive behaviours (such as hypersexuality and pathological gambling) than in Europe and North America have been reported in studies particularly from China and Taiwan (3·5–7·0% *vs* 13·6%), probably reflecting the lower doses of dopamine agonist used compared with Europe and North America.[60,61] Longitudinal European and North American studies indicate even higher figures of impulsive-compulsive behaviours; eg, a 46% 5-year incidence in a French multicentre study (411 patients with Parkinson's disease).[62] There is a lower rate of restless legs syndrome among Asian patients than in white patients, similar to observations in populations without Parkinson's disease.[63] The development of restless legs syndrome in white people is strongly affected by genetic factors and connected to changes in dopaminergic signalling and brain iron metabolism;[64] these factors are only beginning to be studied in Western Pacific Region populations.[65] Prodromal Parkinson's disease is an area of intense research interest, since it offers a window of opportunity to test disease-preventive treatments.[42,66] Preliminary findings suggest that the evolution of rapid-eye-movement sleep behaviour disorder into a clinical synucleinopathy might be slower in Japanese patients than in white patients.[66–68]

Management

Gaps in awareness and knowledge

Studies in the Western Pacific Region have shown major gaps in knowledge among patients, caregivers, health practitioners and the general public regarding Parkinson's disease,[69–71] with implications for health-seeking behaviours and access to appropriate treatment, adherence to

therapy, and patient and caregiver self-efficacy.[72] Examples include misconceptions that all patients with Parkinson's disease have tremor and that Parkinson's disease is usually familial.[69] Non-motor symptoms are poorly recognised among patients and caregivers, and up to a third of Asian patients and caregivers believe that Parkinson's disease is curable (compared with 15% of Australian respondents).[69] The heterogeneity and complexity of Parkinson's disease in clinical presentation and treatment response pose a barrier to patients' and caregivers' understanding of the disease.[72] Knowledge and perception of Parkinson's disease are also affected by education level, socioeconomic status, language barriers, and cultural beliefs,[69,73] which vary widely between different Western Pacific populations; thus, educational programmes need to be locally relevant, culturally sensitive, and tailored towards the different gaps in knowledge in individual countries and territories.[69]

Pharmacological treatment

Oral levodopa, the mainstay treatment for motor features of Parkinson's disease, is still not universally available in some Western Pacific countries, such as Cambodia and Laos (table 1), and several studies indicate that Parkinson's disease medications are generally used at lower doses in the Western Pacific Region than in Europe and North America.[47–55] A study of around 4000 Japanese patients with Parkinson's disease (mean disease duration 9·3 years) reported a mean levodopa dose of 382 mg/day; a follow-up study 5 years later showed that the mean dose remained relatively low at 421 mg/day.[47] Large epidemiological studies in tertiary centres in China (n=1558[44] and n=901[45])

	Key features of Parkinson's disease in the Western Pacific Region and differences compared with Europe and North America	Areas of uncertainty, clinical implications, and challenges and opportunities
Epidemiology	A lower prevalence of Parkinson's disease has been reported in some Western Pacific populations;[1,6–10,12,13] Japanese and Korean studies suggest a female predominance, in contrast to the higher male prevalence reported elsewhere.[2,6,7] Pesticide exposure,[6,8,14–17] reduced physical activity,[6,15,18] diabetes,[14,15,19,20] hepatitis C virus infection,[6,15] and *Helicobacter pylori* infection[15,21,53] might differentially increase risk of Parkinson's disease in this region; protective factors could include high rates of smoking (especially among men)[6,9,14,15,17,22] and tea consumption,[6,14,15] and lower consumption of dairy products.[6,14,15]	Further population-based studies are needed to accurately define the true incidence and prevalence of Parkinson's disease in the Western Pacific Region, including the less-developed countries or territories where epidemiological data are sparse or non-existent (figure 1).[1,2,6,8] To enable valid comparisons to be made, different populations should be studied using the same case-finding methods and diagnostic criteria.[14] Prospective cohort studies on risk or protective factors are needed to understand disease causation and help identify preventive interventions that might need to be tailored to specific groups.[17] Ongoing studies such as the Singapore Chinese Health Study[23] and the Shanghai Women's Health Study,[24] each involving around 60 000–70 000 individuals, are anticipated to provide greater clarity on the role of risk and protective factors for Parkinson's disease. Meanwhile, reducing pesticide exposure, increasing exercise, and moderate caffeine consumption can be advocated.[2,15]
Genetics	*PKRN*, *PINK1*, *LRRK2*, *GBA*, and *CHCHD2* mutations or variants are more common or distinctly different in this region.[25–37,39] The most obvious difference relates to *LRRK2*: Asian-specific Gly2385Arg or Arg1628Pro variants are common in Chinese, Japanese, Korean, and Thai individuals, but rare in white individuals (whereas the converse is true for the Gly2019Ser mutation).[25,28,29] According to the MDSGene[27] analysis, patients from east Asia (China, Japan, South Korea, and Taiwan) with *PRKN* mutations have a slightly earlier age at onset compared with those from France, Italy, Portugal and Spain (median 30 *vs* 32 years). All 85 east Asian patients with available data responded to levodopa while only a few European patients (three [3·8%] of 79) had no or minimal response. Fewer Asian patients or caregivers have a positive attitude towards the potential medical benefits of genetic testing (32–42%, *vs* 85–92% of Americans).[73]	Future disease-modifying therapeutic approaches might have to differ from those used in European and North American patients. For example, although LRRK2 kinase inhibitors might prove useful in patients with the Gly2019Ser mutation (in whom kinase activity is increased by around two times), it has been variously reported that the Gly2385Arg mutation is associated with reduced (by 40–50%) or increased kinase activity, and possibly acts through destabilisation of LRRK2 protein, pro-apoptotic effects, or other hitherto unknown mechanisms.[25,27,41] Possibly explained by the preliminary nature of the observations and the relatively small numbers of patients included in the database[27] to date. Further studies of genotype-phenotype correlations as well as gene-gene or gene-environment interactions are needed.[27] Attitudes are likely to change if or when genetics-based targeted treatments are proven effective.
Differential diagnosis	There are unique Asian forms of parkinsonism (eg, XDP in Filipinos); SCA2 can present with a pure Parkinson's disease phenotype in Koreans, Chinese, and Japanese[102] (appendix pp 13–15).	These conditions are important to know globally (eg, XDP might be encountered in European and North American populations[27,102] and elsewhere, since >10% of the Filipino population [>10 million people] live outside the Philippines in >100 countries).
Clinical features	Dyskinesias and motor fluctuations occur at lower rates in this region,[42–46] probably partly caused by lower levodopa dosages used,[47–55] and possibly related also to the high frequency of amantadine use.[45,52,84] Some non-motor symptoms might be more common (eg, constipation).[56,59,60] Generally lower rates of impulsive-compulsive behaviours have been reported, possibly related to lower dopamine agonist dosages used.[60–62] There is a low prevalence of restless legs syndrome in some Parkinson's disease populations in the Western Pacific Region.[63] Comorbid diabetes,[19,103] cerebral small vessel disease,[104,105] and osteoporosis[106] are highly prevalent in the Western Pacific Region.	Inter-ethnic genetic variations in metabolising enzymes, such as catechol-O-methyltransferase and monoamine oxidase B, and in dopamine turnover have been largely unexplored.[93,94,107] It has been suggested that treatment with levodopa at a dose not exceeding 400 mg/day can reduce the risk of motor complications;[43] however, using less levodopa in an attempt to avoid motor complications (and the need for expensive or often-unavailable device-aided therapies) has to be carefully balanced against under-treatment of parkinsonian features.[72,77,85] Comparative studies between different ethnocultural groups or geographical regions are scarce;[56] therefore, differences in non-motor symptoms profile are inconclusive and require further study, which should also investigate the underlying basis for such heterogeneity.[56] These comorbidities add substantially to disease burden; eg, axial motor and cognitive impairment that are difficult to mitigate.[108,109] These conditions are only beginning to be appreciated by the Parkinson's disease community and deserve particular attention both in the clinic and in research.

(Table 2 continues on next page)

	Key features of Parkinson's disease in the Western Pacific Region and differences compared with Europe and North America	Areas of uncertainty, clinical implications, and challenges and opportunities
(Continued from previous page)		
Management	Oral levodopa is not universally available (eg, in Cambodia and Laos); access to device-aided therapies is limited in many Western Pacific countries or territories (table 1).[3,4,72,77,79–82]	Where oral levodopa is not available, this needs to be urgently prioritised. The cost of device-aided therapies remains too high to be covered by government-funded health insurance in most Western Pacific countries or territories.[3,4,72,77,79] Efforts to heighten awareness of these treatment modalities among patients and physicians are also needed to improve appropriate use of these treatments.[71,98]
	Access to multidisciplinary or interdisciplinary care for Parkinson's disease[96,100,101] is limited.	There is poor awareness in many parts of the health-care community of the challenges or needs of patients with Parkinson's disease and their caregivers.[72,93,100] There is a major shortage of nurses and allied health therapists with specific expertise in Parkinson's disease in the region.[96] Health economic studies are needed in the Western Pacific Region to assess the cost-effectiveness of management by specialist professionals.[100]
	Complementary and alternative medicine treatments, including acupuncture, traditional massage, tai chi, *Mucuna pruriens* and other herbal preparations, are popular, offering a culturally relevant and holistic approach that many patients desire.[110]	High-quality studies are scarce and have produced mixed results (eg, for tai chi);[85,86,110–115] these treatments need to be tested in the same rigorous manner as for conventional therapies.[85,86] Mechanistic or molecular studies are also needed.
Psychosocial	There are major gaps in knowledge (eg, confusing Parkinson's disease with ageing, poor recognition of non-motor symptoms, and beliefs that alternative treatments can cure Parkinson's disease).[69–71]	Ongoing educational initiatives are needed, eg, free patient leaflets in multiple languages by the Movement Disorder Society;[116] numerous local guides or materials have also been published and continue to be updated.[85]
	Some Western Pacific countries or territories (eg, Cambodia and Laos) have no community support groups.	There might be opportunities for more well established support groups to assist their peers in underdeveloped areas; such efforts might be facilitated through networking or advocacy events (eg, those organised by the WPC or APPA).
	Visible movement abnormalities (eg, tremor, dyskinesias), drooling, and communication and mental difficulties contribute to stigma, a key determinant of HRQOL.[72]	Stigma related to tremor might contribute to the wide usage of anticholinergics in this region.[45,52,84] By contrast with disorders such as epilepsy, research on stigma in Parkinson's disease is scarce,[72] and there are no comparative studies between different ethnocultural groups or geographical regions.
Training and Research	There is a major shortage of clinicians with Parkinson's disease expertise, including movement disorder specialists, neurologists, and neurosurgeons in developing Western Pacific countries or territories (table 1).[3,4,72,79]	The Movement Disorder Society has an active Asian-Oceanian section that has supported around 40 teaching courses. Centre-to-centre training and visiting trainee grants for clinicians or scientists are funded with prioritisation of underserved areas. Other bodies (eg, the WFN, IAPRD, and WPC) have also contributed to education, research and advocacy. Further studies are needed to accurately project the number of Parkinson's disease clinicians required in the Western Pacific Region.
	The Western Pacific Region remains poorly represented in clinical trials[85,86] and observational cohort studies.[95]	Improvements in health-care database management (eg, electronic medical records, systematic patient data collection, and national registries) and training in good clinical practice and clinical trials methodology to ensure integrity of data are needed. There should be more validated translations of rating scales or questionnaires (eg, currently the Movement Disorder Society's Unified Parkinson's Disease Rating Scale is available in only four Asian languages, *vs* 14 from the European or Mediterranean region).[117]

XDP=X-linked dystonia-parkinsonism. SCA2=spinocerebellar ataxia type 2. WPC=World Parkinson Coalition. APPA=Asian and Pacific Parkinson Association. HRQOL=health-related quality of life. WFN=World Federation of Neurology. IAPRD=International Association of Parkinsonism and Related Disorders.

Table 2: **Summary of Parkinson's disease in the Western Pacific Region**

reported similar average levodopa doses of 375–413 mg/day (disease duration 4·2–5·4 years), as did smaller studies from Malaysia,[53] Singapore,[54] and Thailand.[55] Studies of patients from the Western Pacific Region with more advanced disease recruited for entacapone therapy to treat wearing-off symptoms and amantadine to treat dyskinesias used lower levodopa doses (440 mg/day) than those used by their European or North American counterparts (570–860 mg/day).[48–51] Additionally, Korean, Japanese, and Taiwanese patients undergoing preoperative assessment for deep brain stimulation are generally on lower medication doses than European and North American patients.[52] Studies suggest that the use of lower medication doses is partly because of intolerance to side-effects (either actual or anticipated), such as nausea, postural giddiness, dyskinesias, or hallucinations;[74,75] patients are also frequently reluctant to increase medication due to concerns regarding possible toxicity of synthetic chemicals and financial costs.[72,76] However, only a few studies have specifically explored these patient concerns, highlighting an area requiring further research efforts.[72,74–76]

Physicians are concerned about higher doses contributing to the development of disabling motor complications, and there is little access to device-aided therapies (deep brain stimulation and infusions of dopaminergic drugs) in many parts of the Western Pacific Region.[77–82] A smaller body size[43,83] and poor physician familiarity with drugs[70,71] might lead to the selection of inadequate, excessively low doses (eg, a blanket maximum of 300 mg/day of levodopa).[75] Motor symptoms should not be under-treated, particularly if these affect patients' ability to function and work.[72] Under-treatment might also partly account for differences in frequencies of non-motor symptoms such as asthenia.[58]

Western Pacific physicians also widely prescribe anticholinergics for Parkinson's disease symptoms such as tremor. 561 (38·6%) of 1453 patients in a Japanese study

received trihexyphenidyl;[84] additionally, academic hospitals in China (n=901)[45] and South Korea (n=1762)[52] reported anticholinergic use in 17·4–18·8% of patients. Amantadine, which seems to have anticholinergic properties, is also widely used (around 40% frequency in some studies),[45,52,84] even for early-stage Parkinson's disease, whereas in Europe and North America amantadine is generally reserved to treat dyskinesias.[85] This possibly contributes to the low reported incidence of dyskinesias in the Western Pacific Region.[42–46] Factors underlying the widespread use of anticholinergics include low cost, particularly in low-income and middle-income countries (although, in Japan and Korea, costs for Parkinson's disease medications are largely covered by government-funded health insurance); anticholinergics can also sometimes produce positive benefits beyond those provided by dopaminergic drugs, such as alleviating tremor or stiffness.[85] It is our general impression that patients and families in Asian societies tolerate tremor poorly, which is a highly visible and stigmatising feature of Parkinson's disease. Anticholinergic medications have been linked with cognitive decline as a short-term adverse effect, and there is also evidence suggesting a higher risk of dementia,[85,86] although it is possible that adverse effects are mitigated by the use of lower doses.[45,84] Whether Western Pacific populations have better tolerance to anticholinergic drugs than patients from Europe and North America has not been studied. Selegiline is also widely prescribed in the Western Pacific Region[84,87] and, in addition to having a mild symptomatic effect on motor features, has been suggested to slow symptom progression, with longer transition times to Hoehn and Yahr stage III.[87] Zonisamide and istradefylline are primarily used in Japan as adjunct treatments to levodopa, generally with modest efficacy;[85] these agents are rarely used for Parkinson's disease in Europe and North America.

There are some differences in the treatment of non-motor symptoms in the Western Pacific Region compared with Europe and North America, although the approach is similar in general.[78] Surprisingly, olanzapine was the most commonly selected antipsychotic in surveys of physicians or neurologists from China,[71] probably due to insufficient awareness of evidence that it can aggravate parkinsonism.[86] Further studies are required to determine the prescription patterns of other typical and atypical antipsychotics in the Western Pacific Region. Another possible regional difference in treatment is that some of the newer and costlier treatments for non-motor symptoms (eg, pimavanserin for psychosis, now widely used in the USA)[86,88] are unavailable in many Western Pacific countries and territories.

Despite differences in the doses and patterns of pharmacological treatments, there are no reported differences in the rates of disease progression (eg, the time taken to reach Hoehn and Yahr stage III [ie, postural instability] in the ON-medication state)[46,89–91] and death (eg, standardised mortality ratios at 10 years)[81,89,90,92] between patients in the Western Pacific Region and those in Europe and North America. However, Western Pacific populations are poorly represented in clinical trials.[85,86] In two evidence-based reviews of studies published between 2011 and 2016, fewer than 20% of Parkinson's disease drug trials were done in this region.[85,86] This is an important issue, since there might be inter-ethnic differences in drug metabolism, therapeutic responses, and adverse effects.[93,94] A Japanese randomised controlled trial, for example, showed that entacapone used to augment levodopa effect was equally effective at half the standard dose (100 mg), with fewer adverse effects compared with the standard dose of 200 mg;[48] accordingly, this is the initial dose used in Japan and by some practitioners elsewhere in the Western Pacific Region.[78,93]

There are important caveats to consider before definitive conclusions can be drawn about pharmacological therapies for patients with Parkinson's disease in the Western Pacific Region. Geopolitical and financial constraints and local subsidies frequently decrease the availability of Parkinson's disease drugs and affect their usage patterns.[72,76] Large-scale epidemiological drug surveys are currently limited to the larger countries such as

***Panel 2:* Comorbidities**

Despite their lower body-mass index (BMI), Asian individuals have a similar or higher prevalence of diabetes than white individuals.[19] Diabetes in Parkinson's disease has been associated with worse postural instability, gait difficulty, and cognitive decline.[108] Studies assessing the effects of glycaemic control on Parkinson's disease outcomes have not yet been done; however, optimising glycaemic control to an individualised glycated haemoglobin A_{1c} (HbA_{1c}) target appears prudent. Additionally, preliminary data suggest a possible disease-modifying effect of antidiabetic drugs on Parkinson's disease, now an area of great interest for researchers.[103]

The prevalence of cerebral small vessel disease is also high in older Asians (mean age 70.1 years; up to 46·2%), and some subtypes (eg, confluent white matter hyperintensities on brain MRI) are suggested to be more prevalent in Chinese individuals than in white individuals.[104] Although studies are conflicting in terms of whether patients with Parkinson's disease have a higher risk of cerebrovascular disease than those without,[105] comorbid cerebral white matter disease might be a greater determinant of axial motor impairment (eg, balance disturbance) than nigrostriatal dopaminergic denervation in patients with Parkinson's disease, emphasising the importance of controlling cardiovascular risk factors.[104,109]

Patients with Parkinson's disease also have a higher risk of fractures, particularly hip fractures, than age-matched controls, both because of higher rates of osteoporosis (eg, due to immobility and low BMI)[83] and falls.[106] Population studies have reported higher age-standardised incidences of hip fractures (a useful surrogate for determining the global burden of osteoporosis) in certain east Asian countries and territories such as Taiwan, Singapore, and Hong Kong than in the USA and some European countries;[106] however, there are no comparative studies of Parkinson's disease populations from different geographical regions. Tools are available for screening and managing osteoporosis, including national and population-specific guidelines (eg, for east Asian populations).[106] There is evidence that patients receiving specialised Parkinson's disease care from neurologists and expert physiotherapists are less likely to sustain bone fractures, including hip fractures.[72,100]

Panel 3: Complementary and alternative medicine

Although the use of complementary and alternative medicine is widespread among patients with Parkinson's disease worldwide, its prevalence is substantially higher in Asia than in Europe and North America (61–76% *vs* 26–40%).[110] Reasons include cultural history (many traditional treatments having originated in Asia hundreds or thousands of years ago), perceived effectiveness and safety, easy access, lower cost, good therapist-patient relationship, and a desire for a more holistic approach to health care.[110]

Tai chi, a traditional mind-body exercise originating from China, is popular in the Western Pacific Region; a randomised trial with 195 patients showed an improvement in balance and reduced falls with tai chi compared with resistance training or stretching.[85] A smaller subsequent study from China of 40 individuals reported positive effects on motor function, but there was no significant improvement in balance (the primary outcome).

Acupuncture is extremely popular and has been a key component of traditional Chinese medicine for many centuries; so far, however, trials of acupuncture in patients with Parkinson's disease have not shown benefits on motor or non-motor outcomes over and above the effects of sham treatment.[85,86,110] Although acupuncture in this population is generally safe, complications such as pneumothorax and spinal cord trauma have been rarely reported.[85,110] Cupping and moxibustion (application of heated glass cups to create suction, or burning of dried mugwort herb, on particular points on the body) are thought to work along similar principles as acupuncture, but there are no high-quality studies of these techniques in patients with Parkinson's disease. A single-blinded trial of traditional massage in 60 patients reported benefits;[111] however, further evidence is still required.[110]

Mucuna pruriens, a tropical legume used in Indian ayurvedic medicine since ancient times, contains levodopa and was suggested to be effective in a double-blind crossover trial involving 18 patients with Parkinson's disease.[112] However, an analysis of commercial preparations showed that these contained widely varying concentrations of levodopa, deviating by 6–141% of individual label claims, which could potentially result in unintentional under-treatment or over-treatment of patients, or compromise the results of scientific studies on *Mucuna pruriens* products.[113]

Generally, studies of Chinese herbal medicines have been poorly undertaken, without randomised blinded assessments and standardised outcome measures.[110] In a randomised placebo-controlled trial with 111 individuals, the Chinese herbal formula Jiawei-Liujunzi Tang improved mood, cognition, and constipation; however, the primary outcome measure of Movement Disorder Society Unified Parkinson's Disease Rating Scale Part I score (ie, non-motor experiences of daily living) was not improved.[115] Yokukansan is a herbal mixture used in Japan and is reported to be well tolerated and efficacious for hallucinations, anxiety, and apathy, but studies in Parkinson's disease were open-label.[114]

Strong placebo effects are observed in Parkinson's disease and encouragingly complementary and alternative treatments have begun to be studied scientifically;[85,86,110] however, high-quality clinical trials with adequate sample sizes, and basic mechanistic and molecular studies are needed to provide an evidence-based rationale for their use.

China,[44,45] Japan,[47] and South Korea,[52] and data from smaller countries are not available for comparison, or might not be generalisable because of small sample sizes.[53–55] Between-study heterogeneity (eg, recruitment of predominantly younger patients[89] who generally show slower progression and fewer axial features, including postural instability, compared with older patients)[72] is also an important consideration when drawing conclusions from these studies. Overall, there is a need for better education and establishment of more collaborative networks, especially because global listing of cohort studies of Parkinson's disease showed that less than 10% of studies originated from the Western Pacific Region.[95]

Device-aided therapies

The financial burden of Parkinson's disease, already heavy in high-income countries,[96] is even more acute in countries where public health financing and medical insurance coverage are scarce, resulting in patients having to pay privately for treatment.[3,4,72] Thus, most patients in the Western Pacific Region have poor access to deep brain stimulation, and even poorer or no access to infusion therapies compared with patients in Europe and North America (table 1). Deep brain stimulation and infusion therapies can substantially improve motor complications and health-related quality of life at a point in the disease course when further adjustments of conventional medications yield little benefit.[97] It is estimated that more than 150 000 patients with Parkinson's disease have undergone deep brain stimulation worldwide;[97] generally, around 5–10% of patients attending movement disorder clinics in high-income countries undergo deep brain stimulation.[82] Some high-volume deep brain stimulation centres are available in China, Japan, South Korea, and Australia;[98,99] however, in the Philippines (where deep brain stimulation costs seven to 11 times the average annual family income), only 21 patients (0·04%) of an estimated 60 000 patients[1] with Parkinson's disease received deep brain stimulation between 2006 and 2016.[79] In Hong Kong, 25 (0·17%) of an estimated 15 000 patients underwent deep brain stimulation between 2009 and 2012;[80] and a Singaporean study documented use of deep brain stimulation in 1·8% of around 1800 patients.[81] The low use of deep brain stimulation might partly reflect poor physician awareness of the benefits of the procedure,[71] late referrals, and a general fear among patients of so-called Western treatments for Parkinson's disease,[98] and might affect outcomes, which typically correlate with the experience of the centre doing the procedure.[97]

Health-care resources and facilities

Patients with Parkinson's disease benefit from specialty care, which is associated with fewer admissions to hospital for Parkinson's-related complications (eg, psychosis and traumatic injury) and improved survival.[72] There is a major shortage of specialists with advanced training in Parkinson's disease in many parts of the Western Pacific Region. Of the countries and territories listed in table 1, almost half have fewer neurologists than the recommended minimum of one per 100 000 population (for comparison, the ratio in the USA is around one per 20 000).[72] The benefits of multidisciplinary or interdisciplinary management of Parkinson's disease have been increasingly recognised,[96,100,101] but descriptions of such care in the Western Pacific Region are scarce.[96] Barriers to the delivery of comprehensive care include insufficient expertise among health-care professionals

and inadequate financial support for a multidisciplinary approach.[3,4,100] Successful implementation of multidisciplinary management in the Western Pacific Region will require not only concerted collaborative efforts between neurologists and allied health-care professionals, but also improvements in the infrastructure of care.[100]

Conclusions and future directions

Differences in Parkinson's disease epidemiology, causative factors, clinical presentation, and management exist between the Western Pacific Region and Europe and North America. Figure 2 provides a visual depiction of the multitude of variables that might affect the development and clinical presentation of Parkinson's disease. Key features of Parkinson's disease in the Western Pacific Region and differences versus Europe and North America are summarised in table 2.

Further population-based studies are needed to accurately define the true incidence, prevalence, and temporal trends of Parkinson's disease in the Western Pacific Region, with harmonisation of methods between studies to facilitate comparisons between different populations.[2,14] To date, the most obvious difference in genetics relates to *LRRK2*, with ethnicity-specific mutations or variants having varying contributions to disease causation or progression[25,27–32] and pathogenesis.[25,27,41] The putative roles of diabetes,[14,15,19,20] sedentary lifestyle,[6,15,18] pesticide and chemical use,[6,8,14–17] common exposures such as tea-drinking,[6,14,15] and infections such as hepatitis C[6,15] and *H pylori*[15,21,53] require large cohort studies in the Western Pacific Region[23,24] to provide greater clarity. So far, primary preventive interventions particularly relevant in the Western Pacific Region include promotion of physical exercise,[15] prevention of diabetes,[19] and the banning or restriction of certain pesticides (such as paraquat) and adoption of proper chemical-handling practices.[6,8,14–17]

The Western Pacific Region presents many challenges to the investigation and management of Parkinson's disease, including gaps in disease awareness[69–71] and barriers to accessing specialty care and treatment.[3,4,71,72,79] Basic infrastructure and expertise for diagnostic or prognostic testing of Parkinson's disease and its mimics are still absent in many parts of the Western Pacific Region; local health-care investments and establishing collaborative networks for laboratory testing (eg, genetics)[27,39] and neuroimaging (eg, dopaminergic functional scans, such as dopamine transporter single-photon emission computed tomography or [^{18}F]dopa PET scans, which are increasingly being used to support the clinical diagnosis of Parkinson's disease)[66] will further improve the standard of care for patients with Parkinson's disease. With genetics-based targeted approaches now entering clinical trials, understanding the ethnogeographical distribution and mechanisms of action of specific genetic changes is increasingly relevant.[25,27,41] For example, *LRRK* Gly2019Ser mutations in white individuals resulting in gain-of-function effects on kinase activity could potentially be addressed using kinase inhibitors,[27] whereas the mechanisms of the common low-penetrant Asian-specific variants still need to be elucidated and might require a different approach.[25,41] Future studies of disease-modifying or prevention therapies will likely involve non-manifesting mutation carriers and patients with prodromal disease;[27,42,66,85] there are studies showing preliminary differences between non-manifesting carriers of different *LRRK2* mutations[27] that might have important implications for similar studies in the Western Pacific Region.

For optimum symptomatic management, oral levodopa should be made widely available. Although a lower rate of motor complications, particularly dyskinesias, has been highlighted as one of the main clinical differences in the Western Pacific Region,[42–46] poor access to costly device-aided therapies for patients with disabling motor complications is currently a major unmet need[3,4,72,77,79–82] and solutions are needed to widen access to these potentially life-changing treatments.[97] Proper management of comorbid medical conditions (panel 2) and the use of complementary and alternative medicine (panel 3) are additional areas of relevance.

Academic research is vibrant in certain Western Pacific countries with highly developed economies (such as Japan and Singapore) and has provided crucial insights into areas of Parkinson's disease research, such as genetics,[25,28–30,32,33,35–40] autophagy,[118] mitochondrial dysfunction,[36,38] disease modelling,[119] and cell-based therapies;[120] however, research in most of the smaller countries and territories remains dormant with nothing or very little published, and few clinical trials are done across the region relative to the number done in Europe and North America.[85,86] Future work should consolidate areas of existing strength, and improve the quality and scope of knowledge particularly in the areas of descriptive, aetiological, and prognostic epidemiology[14] and clinical trials,[85,86] with an emphasis on well

Search strategy and selection criteria

We searched PubMed for articles published in any language from Jan 1, 2012, to April 30, 2019, using the search term "Parkinson's disease", combined with "Western Pacific Region", "Asian", "epidemiology", "incidence", "prevalence", "risk factors", "fluctuations", "dyskinesia", "non-motor", "treatment", "clinical trials", "deep brain stimulation", "apomorphine", "levodopa infusion", "support groups", "quality of life", "stigma", "awareness", "knowledge", "perception", and "employment", and all 37 countries and territories in the Western Pacific Region (we included Indonesia, Taiwan, and Thailand, because of their geographical and ethnocultural interconnectedness with other member states in this region, even though they are not listed as Western Pacific Region countries). We also used references cited in the publications retrieved. The final reference list was generated on the basis of relevance to the topics covered in this Review.

designed multinational longitudinal studies and the development of affordable, evidence-based treatments.

Contributors

S-YL initiated this Review, led the collection of the reported data, and prepared the first draft of the manuscript. AHT, AEL, E-KT, CK, and CTT further developed the concept and structure of the manuscript. AEL, E-KT, and AHT drafted parts of the manuscript. AHT led, and S-YL and LCST contributed to, the development of figure 1. S-YL, AHT, LCST, BJ, RR, RB, Y-RW, H-FS, AHE, NH, CTT, and E-KT provided data from their respective countries for table 1. S-YL and AHT led the development of figure 2. CK led the development of appendix figure 1. AHT led the development of appendix table 1. AAA led, and CK, E-KT and S-YL contributed to, the development of appendix table 2. All authors contributed to the literature search, interpretation of data, and final editing.

Declaration of interests

S-YL reports lecturing honoraria from the Asian Oceanian Association of Neurology, Chinese Neuroscience Society, Chinese University of Hong Kong, Head Foundation Singapore, International Association of Parkinsonism and Related Disorders, International Parkinson and Movement Disorder Society, Ipsen, Japan International Parkinson Disease and Movement Disorder Symposium, Korean Movement Disorders Society, Lundbeck, Medtronic, Novartis, Taiwan Movement Disorder Society, and UCB; and consultation fees from Lundbeck. AHT reports lecturing honoraria from Novartis, and grants from the University of Malaya Faculty Research Grant, University of Malaya BKP Research Grant, and Toray Science Foundation Science and Technology Grant. CK reports personal fees from Centogene and Biogen. LCST reports lecturing honoraria from the International Parkinson and Movement Disorder Society, Sichuan Medical Association, and Eisai China. RR reports lecturing honoraria from the International Parkinson and Movement Disorder Society, the International Association of Parkinsonism and Related Disorders, Asian and Oceanian Congress of Neurology; and is the overall principal investigator for the Asian Botulinum Toxin Early Post-Stroke Clinical Trials (ABCDE and ONTIME) sponsored by Ipsen. RB reports royalties from Wiley-Blackwell and Springer Publications; honoraria from Britannia, Lundbeck, Novartis, Boehringer-Ingelheim, and Abbott Pharmaceuticals; research funding from the Thailand Research Fund, Newton Fund-UK, The Neurological Society of Thailand, Chulalongkorn University Research Unit Grant, the Ratchadapiseksompoj Faculty Grant, and the Thai Red Cross Development Grant. Y-RW reports lecturing honoraria from the International Parkinson and Movement Disorder Society, the International Association of Parkinsonism and Related Disorders, the Asian Oceanian Association of Neurology, Takamatsu Symposium in Tokyo, the Korean Movement Disorder Society, the Philippine Movement Disorder Society, the Hong Kong Movement Disorder Society and UCB, Novartis, Boehringer-Ingelheim, Medtronic, Allergan, and Servier; and research funding from the Ministry of Science and Technology and Chang Gung Memorial Hospital, Linkuo. H-FS reports lecturing honoraria from the International Association of Parkinsonism and Related Disorders, International Parkinson and Movement Disorder Society, Asian and Oceanian Association of Neurology and Korean Neurological Association, Taiwan Movement Disorder Society, the Neurologist Branch of the Chinese Medical Doctor Association and Parkinson and Movement Disorders Society of China, Sichuan Medical Association, Lundbeck, Medtronic, Novartis, Boehringer-Ingelheim, Eisai China, UCB, Allergan, GlaxoSmithKline, and Sanofi China. AHE reports reimbursement of travel expenses to scientific meetings or honoraria for lecturing or consultation from UCB, Teva, Abbott, Stada, Allergan and Abbvie; and holds shares in CSL and Global Kinetics Corporation. PKP reports lecturing honoraria from the International Parkinson and Movement Disorder Society and the Asian Oceanian Association of Neurology; and grants to his institute from the Indian Council of Medical Research, Department of Science and Technology, Department of Biotechnology, and the Science and Engineering Research Board, India. NH reports grants from the Japan Agency for Medical Research and Development, the Japan Society for the Promotion of Science, the Ministry of Education, Culture, Sports, Science and Technology Japan, and the Ministry of Health, Labour and Welfare; personal fees from the International Parkinson and Movement Disorder Society, GSK KK, Acorda Therapeutics, Sanofi KK, Pfizer Japan, Alexion Pharmaceuticals, Mylan NV, MSD KK, and Lundbeck Japan; personal fees and other support from Dai-Nippon Sumitomo Pharma, Otsuka Pharmaceutical, Takeda Pharmaceutical, Kyowa Hakko-Kirin, Nippon Boehringer Ingelheim, FP Pharmaceutical Corporation, Eisai, Kissei Pharmaceutical Company, Nihon Medi-Physics, Novartis Pharma KK, Biogen Idec Japan, AbbVie, Medtronic, Astellas Pharma, and Daiichi Sankyo; non-financial support from IBM Japan; non-financial support and other support from Boston Scientific Japan; other support from Ono Pharmaceutical, Mitsubishi Tanabe Pharma, Zaiho, Hydrogen Health Medical Laboratory, ABIST, Melodian, Daiwa, Bayer Yakuhin, Nihon Pharmaceutical, Asahi Kasei Medical, MiZ, Mitsubishi Tanabe Pharma, OHARA Pharmaceutical, Meiji Seika Pharma, and Hisamitsu Pharmaceutical. BJ reports grants from Peptron, Ipsen Korea, and AbbVie Korea; lecturing honoraria from the Asian Oceanian Association of Neurology, the Chinese Neuroscience Society, the International Association of Parkinsonism and Related Disorders, the International Parkinson and Movement Disorder Society, the Japan International Parkinson Disease and Movement Disorder Symposium, the Taiwan Movement Disorder Society, the Taiwan Neurology Society, the World Federation of Neurology, the Japanese Movement Disorder Society, the Japanese Society of Neurology, and UCB; and honoraria for editorial duties for the Journal of Clinical Neuroscience. E-KT has received honoraria for editorial duties for the European Journal of Neurology and Parkinsonism and Related Disorders. AEL has served as an advisor for AbbVie, Acorda, Biogen, Bristol Myers Squibb, Janssen, Sun Pharma, Kallyope, Merck, Paladin, Theravance, and Corticobasal Degeneration Solutions; received honoraria from Sun Pharma, Medichem, Medtronic, AbbVie and Sunovion; received grants from Brain Canada, Canadian Institutes of Health Research, Corticobasal Degeneration Solutions, Edmond J Safra Philanthropic Foundation, Michael J Fox Foundation, the Ontario Brain Institute, National Parkinson Foundation, Parkinson Society Canada, and W Garfield Weston Foundation; and received publishing royalties from Elsevier, Saunders, Wiley-Blackwell, Johns Hopkins Press, and Cambridge University Press. AAA and CTT declare no competing interests.

Acknowledgments

We gratefully acknowledge the following individuals for providing data or insights from their respective countries or territories, or areas of expertise: Mandy Auyeung (Hong Kong), Samleng Chan (Cambodia), Victor SC Fung (Australia), Taku Hatano (Japan), Seong-Beom Koh (Parkinson's disease epidemiology in South Korea), Minh Le (Vietnam), Woong-Woo Lee (Parkinson's disease epidemiology in South Korea), Angus Macleod (Parkinson's disease epidemiology and mortality), Connie Marras (University of Toronto, ON, Canada) (Parkinson's disease epidemiology in North America), Victor McConvey (Australia; Allied health care), Vincent Chung Tong Mok (Hong Kong), Elena Moro (DBS), Weerasak Muangpaisan (Parkinson's disease epidemiology), Emma Nichols (Institute for Health Metrics and Evaluation; Global Burden of Disease), Yasushi Osaki (Parkinson's disease epidemiology in Japan), Eric Roberts (Public Health Institute, CA, USA, and the Parkinson's Foundation P4 group; Parkinson's disease epidemiology), Mark Simpson (New Zealand), Yu Sun (Parkinson's disease epidemiology in Taiwan), Frandy Susatia (Indonesia), Tran Ngoc Tai (Vietnam), Yeremia Tatang (Indonesia), Wesley Thevathasan (DBS in Australia), Bayasgalan Tserensodnom (Mongolia), and Somchit Vorachit (Laos). S-YL and AHT obtained funding from the University of Malaya Parkinson's Disease and Movement Disorders Research Program Fund (PV035-2017) for M G Rudakewich (Synapse Visuals, Edmonton, AB, Canada) to produce figures 1 and 2. E-KT acknowledges support from the National Medical Research Council, Singapore (STaR and Singapore Parkinson's Disease Programme Grant [SPARK 1 & 2]). Funding sources had no involvement in the writing of the manuscript or the decision to submit for publication.

References

1 GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018; **392:** 1789–858.

2 GBD 2016 Parkinson's Disease Collaborators. Global, regional, and national burden of Parkinson's disease, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol* 2018; **17:** 939–53.

3 Tan CT. Neurology in Asia. *Neurology* 2015; **84:** 623–25.

4 Jamora RDG, Miyasaki JM. Treatment gaps in Parkinson's disease care in the Philippines. *Neurodegener Dis Manag* 2017; **7:** 245–51.

5 Robert C, Wilson CS, Lipton RB, Arreto CD. Parkinson's disease: evolution of the scientific literature from 1983 to 2017 by countries and journals. *Parkinsonism Relat Disord* 2019; **61:** 10–18.

6 Abbas MM, Xu Z, Tan LCS. Epidemiology of Parkinson's disease: east versus west. *Mov Disord Clin Pract* 2018; **5:** 14–28.

7 Lee JE, Choi JK, Lim HS, et al. The prevalence and incidence of Parkinson's disease in South Korea: a 10-year nationwide population-based survey. *J Korean Neurol Assoc* 2017; **35:** 191–98.

8 Muangpaisan W, Siritipakorn P, Assantachai P. Development of a Thai Parkinson's disease screening tool and the prevalence of parkinsonism and Parkinson's disease, based on a community survey in Bangkok. *Neuroepidemiology* 2017; **49:** 74–81.

9 Pitcher TL, Myall DJ, Pearson JF, et al. Parkinson's disease across ethnicities: a nationwide study in New Zealand. *Mov Disord* 2018; **33:** 1440–48.

10 Zou YM, Liu J, Tian ZY, Lu D, Zhou YY. Systematic review of the prevalence and incidence of Parkinson's disease in the People's Republic of China. *Neuropsychiatr Dis Treat* 2015; **11:** 1467–72.

11 UN Department of Economic and Social Affairs. World Population Ageing 2017. New York: United Nations, 2017.

12 Marras C, Beck JC, Bower JH, et al. Prevalence of Parkinson's disease across North America. *NPJ Parkinson's Dis* 2018; **4:** 21.

13 Pringsheim T, Jette N, Frolkis A, Steeves TD. The prevalence of Parkinson's disease: a systematic review and meta-analysis. *Mov Disord* 2014; **29:** 1583–90.

14 Elbaz A, Carcaillon L, Kab S, Moisan F. Epidemiology of Parkinson's disease. *Rev Neurol* 2016; **172:** 14–26.

15 Ascherio A, Schwarzschild MA. The epidemiology of Parkinson's disease: risk factors and prevention. *Lancet Neurol* 2016; **15:** 1257–72.

16 Lai W. Pesticide use and health outcomes: evidence from agricultural pollution in China. *J Environ Economics Manage* 2017; **86**: 93–120.

17 Rocca WA. The future burden of Parkinson's disease. *Mov Disord* 2018; **33:** 8–9.

18 Yi SS, Roberts C, Lightstone AS, Shih M, Trinh-Shevrin C. Disparities in meeting physical activity guidelines for Asian-Americans in two metropolitan areas in the United States. *Ann Epidemiol* 2015; **25:** 656–60.

19 Nanditha A, Ma RC, Ramachandran A, et al. Diabetes in Asia and the Pacific: implications for the global epidemic. *Diabetes Care* 2016; **39:** 472–85.

20 Yue X, Li H, Yan H, Zhang P, Chang L, Li T. Risk of Parkinson disease in diabetes mellitus: an updated meta-analysis of population-based cohort studies. *Medicine* 2016; **95:** e3549.

21 Lubomski M, Tan AH, Lim SY, Holmes AJ, Davis RL, Sue CM. Parkinson's disease and the gastrointestinal microbiome. *J Neurol* 2019; published online Apr 30. DOI: 10.1007/s00415-019-09320-1.

22 Fang L, Gao P, Bao H, et al. Chronic obstructive pulmonary disease in China: a nationwide prevalence study. *Lancet Respir Med* 2018; **6:** 421–30.

23 Tan LC, Methawasin K, Tan EK, et al. Dietary cholesterol, fats and risk of Parkinson's disease in the Singapore Chinese Health Study. *J Neurol Neurosurg Psychiatry* 2016; **87:** 86–92.

24 Chen H, Ding D, Wang J et al. Parkinson's disease research in a prospective cohort in China. *Parkinsonism Relat Disord* 2015; **21:** 1200–04.

25 Domingo A, Klein C. Genetics of Parkinson disease. *Handb Clin Neurol* 2018; **147:** 211–27.

26 Kilarski LL, Pearson JP, Newsway V, et al. Systematic review and UK-based study of PARK2 (parkin), PINK1, PARK7 (DJ-1) and LRRK2 in early-onset Parkinson's disease. *Mov Disord* 2012; **27:** 1522–29.

27 Brüggemann N, Klein C. Will genotype drive treatment options? *Mov Disord* 2019; published online April 10. DOI:10.1002/mds.27699.

28 Xie CL, Pan JL, Wang WW, et al. The association between the LRRK2 G2385R variant and the risk of Parkinson's disease: a meta-analysis based on 23 case-control studies. *Neurol Sci* 2014; **35:** 1495–504.

29 Zhang Y, Sun Q, Yi M, et al. Genetic analysis of LRRK2 R1628P in Parkinson's disease in Asian populations. *Parkinsons Dis* 2017; **2017:** 8093124.

30 Xiao B, Deng X, Ng EY, et al. Association of *LRRK2* haplotype with age at onset in Parkinson disease. *JAMA Neurol* 2018; **75:** 127–28.

31 Saunders-Pullman R, Mirelman A, Alcalay RN, et al. Progression in the LRRK2-asssociated Parkinson disease population. *JAMA Neurol* 2018; **75:** 312–19.

32 Marras C, Alcalay RN, Caspell-Garcia C, et al. Motor and nonmotor heterogeneity of LRRK2-related and idiopathic Parkinson's disease. *Mov Disord* 2016; **31:** 1192–202.

33 Cilia R, Tunesi S, Marotta G, et al. Survival and dementia in GBA-associated Parkinson's disease: the mutation matters. *Ann Neurol* 2016; **80:** 662–73.

34 Chen J, Li W, Zhang T, Wang YJ, Jiang XJ, Xu ZQ. Glucocerebrosidase gene mutations associated with Parkinson's disease: a meta-analysis in a Chinese population. *PLoS One* 2014; **9:** e115747.

35 Li Y, Sekine T, Funayama M, et al. Clinicogenetic study of GBA mutations in patients with familial Parkinson's disease. *Neurobiol Aging* 2014; **35:** 935.

36 Funayama M, Ohe K, Amo T, et al. *CHCHD2* mutations in autosomal dominant late-onset Parkinson's disease: a genome-wide linkage and sequencing study. *Lancet Neurol* 2015; **14:** 274–82.

37 Puschmann A. New genes causing hereditary Parkinson's disease or parkinsonism. *Curr Neurol Neurosci Rep* 2017; **17:** 66.

38 Zhou W, Ma D, Sun AX, et al. PD-linked *CHCHD2* mutations impair CHCHD10 and MICOS complex leading to mitochondria dysfunction. *Hum Mol Genet* 2019; **28:** 1100–16.

39 Foo JN, Tan LC, Irwan ID, et al. Genome-wide association study of Parkinson's disease in east Asians. *Hum Mol Genet* 2017; **26:** 226–32.

40 Li H, Teo YY, Tan EK. Patterns of linkage disequilibrium at *PARK16* may explain variances in genetic association studies. *Mov Disord* 2015; **30:** 1335–42.

41 Zhang P, Fan Y, Ru H, et al. Crystal structure of the WD40 domain dimer of LRRK2. *Proc Natl Acad Sci USA* 2019; **116:** 1579–84.

42 Poewe W, Seppi K, Tanner CM, et al. Parkinson disease. *Nat Rev Dis Primers* 2017; **3:** 17013.

43 Olanow CW, Stocchi F. Levodopa: a new look at an old friend. *Mov Disord* 2018; **33:** 859–66.

44 Chen W, Xiao Q, Shao M, et al. Prevalence of wearing-off and dyskinesia among the patients with Parkinson's disease on levodopa therapy: a multi-center registry survey in mainland China. *Transl Neurodegen* 2014, **3:** 26.

45 Zhang ZX, Chen H, Chen SD, et al. Chinese culture permeation in the treatment of Parkinson disease: a cross-sectional study in four regions of China. *BMC Research Notes* 2014; **7:** 65.

46 Sato K, Hatano T, Yamashiro K, et al. Prognosis of Parkinson's disease: time to stage III, IV, V, and to motor fluctuations. *Mov Disord* 2006; **21:** 1384–95.

47 Fujimoto K, Murata M, Hattori N, Kondo T. Patients' perspective on Parkinson disease therapies: results of a large-scale survey in Japan. *Brain Nerve* 2016; **68:** 1087–98.

48 Mizuno Y, Kanazawa I, Kuno S, et al. Placebo-controlled, double-blind dose-finding study of entacapone in fluctuating parkinsonian patients. *Mov Disord* 2007; **22:** 75–80.

49 Sawada H, Oeda T, Kuno S, et al. Amantadine for dyskinesias in Parkinson's disease: a randomized controlled trial. *PLoS One* 2010; **5:** e15298.

50 Brooks DJ, Sagar H. Entacapone is beneficial in both fluctuating and non-fluctuating patients with Parkinson's disease: a randomised, placebo controlled, double blind, six month study. *J Neurol Neurosurg Psychiatry* 2003; **74:** 1071–79.

51 Oertel W, Eggert K, Pahwa P, et al. Randomized, placebo-controlled trial of ADS-5102 (amantadine) extended-release capsules for levodopa-induced dyskinesia in Parkinson's disease (EASE LID 3). *Mov Disord* 2017; **32:** 1701–09.

52 Lee JY, Kim JW, Lee WY, et al. Daily dose of dopaminergic medications in Parkinson disease: clinical correlates and a posteriori equation. *Neurol Asia* 2010; **15:** 137–43.

53 Tan AH, Mahadeva S, Marras C, et al. *Helicobacter pylori* infection is associated with worse severity of Parkinson's disease. *Parkinsonism Rel Disord* 2015; **21:** 221–25.

54 Prakash KM, Nadkarni NV, Lye WK, Yong MH, Tan EK. The impact of non-motor symptoms on the quality of life of Parkinson's disease patients: a longitudinal study. *Eur J Neurol* 2016; **23:** 854–60.

55 Kasemsap N, Onsanit S, Chiewthanakul P, et al. Efficacy and motor complications of original and generic levodopa in Parkinson's disease treatment. *Neuropsychiatr Dis Treat* 2016; **12:** 1185–89.

56 Sauerbier A, Jitkritsadakul O, Titova N, et al. Non-motor symptoms assessed by Non-Motor Symptoms Questionnaire and Non-Motor Symptoms Scale in Parkinson's disease in selected Asian populations. *Neuroepidemiology* 2017; **49:** 1–17.

57 Song W, Guo X, Chen K, et al. The impact of non-motor symptoms on the health-related quality of life of Parkinson's disease patients from Southwest China. *Parkinsonism Rel Disord* 2014; **20:** 149–52.

58 Parkinson Study Group. Pramipexole in levodopa-treated Parkinson disease patients of African, Asian, and Hispanic heritage. *Clin Neuropharmacol* 2007; **30:** 72–85.

59 Knudsen K, Krogh K, Østergaard K, Borghammer P. Constipation in Parkinson's disease: subjective symptoms, objective markers, and new perspectives. *Mov Disord* 2017; **32:** 94–105.

60 Chen W, Xu ZM, Wang G, Chen SD. Non-motor symptoms of Parkinson's disease in China: a review of the literature. *Parkinsonism Rel Disord* 2012; **18:** 446–52.

61 Chiang HL, Huang YS, Chen ST, Wu YR. Are there ethnic differences in impulsive/compulsive behaviors in Parkinson's disease? *Eur J Neurol* 2012; **19:** 494–500.

62 Corvol JC, Artaud F, Cormier-Dequaire F, et al. Longitudinal analysis of impulse control disorders in Parkinson disease. *Neurology* 2018; **91:** e189–201.

63 Yang X, Liu B, Shen H, et al. Prevalence of restless legs syndrome in Parkinson's disease: a systematic review and meta-analysis of observational studies. *Sleep Med* 2018; **43:** 40–46.

64 Schormair B, Zhao C, Bell S, et al. Identification of novel risk loci for restless legs syndrome in genome-wide association studies in individuals of European ancestry: a meta-analysis. *Lancet Neurol* 2017; **16:** 898–907.

65 Li G, Tang H, Wang C, et al. Association of BTBD9 and MAP2K5/SKOR1 with restless legs syndrome in Chinese population. *Sleep* 2017; published online April 1; 40. DOI:10.1093/sleep/zsx028.

66 Postuma RB, Berg D. Prodromal Parkinson's disease: the decade past, the decade to come. *Mov Disord* 2019; published online March 28. DOI:10.1002/mds.27670.

67 Miyamoto T, Miyamoto M. Phenoconversion from idiopathic rapid eye movement sleep behavior disorder to Lewy body disease. *Mov Disord Clin Pract* 2018; **5:** 506–11.

68 Nihei Y, Takahashi K, Koto A, et al. REM sleep behavior disorder in Japanese patients with Parkinson's disease: a multicenter study using the REM sleep behavior disorder screening questionnaire. *J Neurol* 2012; **259:** 1606–12.

69 Tan AH, Tan CT, Marras C, et al. Knowledge of Parkinson's disease in a multiethnic urban Asian setting. *J Parkinson's Dis* 2015; **5:** 865–79

70 Bhidayasiri R, Brenden N, Viwattanakulvanid P, et al. Identifying gaps in knowledge about Parkinson disease among medical professionals in Thailand. *Neurology* 2014; **82:** 2238–40.

71 Li J, Chen D, Song W, et al. Survey on general knowledge on Parkinson's disease in patients with Parkinson's disease and current clinical practice for Parkinson's disease among general neurologists from Southwest China. *Clin Neurol Neurosurg* 2014; **118:** 16–20.

72 Lim SY, Tan AH, Fox SH, Evans AH, Low SC. Integrating patient concerns into Parkinson's disease management. *Curr Neurol Neurosci Rep* 2017; **17:** 3.

73 Scuffham TM, McInerny-Leo A, Ng SK, Mellick G. Knowledge and attitudes towards genetic testing in those affected with Parkinson's disease. *J Community Genet* 2014; **5:** 167–77.

74 Chaudhuri KR, Hu MTM, Brooks DJ. Atypical parkinsonism in Afro-Caribbean and Indian origin immigrants to the UK. *Mov Disord* 2000; **15:** 18–23.

75 Hattori N, Fujimoto K, Kondo T, Murata M, Stacy M. Patient perspectives on Parkinson's disease therapy in Japan and the United States: results of two patient surveys. *Patient Relat Outcome Meas* 2012; **3:** 31–38.

76 Deng X, Xiao B, Tan EK. Adverse effects were not the main causes for rotigotine patch withdrawal in Parkinson's disease. *J Alzheimers Dis Parkinsonism* 2015; **5:** 195.

77 Lim SY, Poewe W, Tan AH. Levodopa and Parkinson disease—myths revisited. *JAMA Neurol* 2017; **74:** 1270.

78 Chen S, Chan P, Sun S, et al. The recommendations of Chinese Parkinson's disease and movement disorder society consensus on therapeutic management of Parkinson's disease. *Transl Neurodegener* 2016; **5:** 12.

79 Diestro JDB, Vesagas TS, Teleg RA, Aguilar JA, Anlacan JP, Jamora RDG. Deep brain stimulation for Parkinson disease in the Philippines: outcomes of the Philippine Movement Disorder Surgery Center. *World Neurosurg* 2018; **115:** e650–58.

80 Chan DTM, Zhu CXL, Lau CKY, et al. Subthalamic nucleus deep brain stimulation for Parkinson disease in Hong Kong: a prospective territory-wide 2-year follow-up study. *World Neurosurg* 2016; **93:** 229–36.

81 Oosterveld LP, Allen JC Jr, Reinoso G, Seah SH, Tay KY, Au WL, Tan LC. Prognostic factors for early mortality in Parkinson's disease. *Parkinsonism Relat Disord* 2015; **21:** 226–30.

82 Fasano A, Fung VSC, Lopiano L, et al. Characterizing advanced Parkinson's disease: OBSERVE-PD observational study results of 2615 patients. *BMC Neurol* 2019; **19:** 50.

83 Tan AH, Hew YC, Lim SY, et al. Altered body composition, sarcopenia, frailty, and their clinico-biological correlates, in Parkinson's disease. *Parkinsonism Relat Disord* 2018; **56:** 58–64.

84 Yoritaka A, Shimo Y, Takanashi M, et al. Motor and non-motor symptoms of 1453 patients with Parkinson's disease: prevalence and risks. *Parkinsonism Rel Disord* 2013; **19:** 725–31.

85 Fox SH, Katzenschlager R, Lim SY, et al. International Parkinson and movement disorder society evidence-based medicine review: update on treatments for the motor symptoms of Parkinson's disease. *Mov Disord* 2018; **33:** 1248–66.

86 Seppi K, Chaudhuri KR, Coelho M, et al. Update on treatments for the non-motor symptoms of Parkinson's disease: an evidence-based medicine review. *Mov Disord* 2019; **34:** 180–98.

87 Robakis D, Fahn S. Defining the role of the monoamine oxidase-B inhibitors for Parkinson's disease. *CNS Drugs* 2015; **29:** 433–41.

88 Sellers J, Darby RR, Farooque A, Claassen DO. Pimavanserin for psychosis in Parkinson's disease-related disorders: a retrospective chart review. *Drugs Aging* 2019; published online March 29. DOI:10.1007/s40266-019-00655-y.

89 Auyeung M, Tsoi TH, Mok V, Cheung CM, et al. Ten year survival and outcomes in a prospective cohort of new onset Chinese Parkinson's disease patients. *J Neurol Neurosurg Psychiatry* 2012; **83:** 607–11.

90 Williams-Gray CH, Mason SL, Evans JR, et al. The CamPaIGN study of Parkinson's disease: 10-year outlook in an incident population-based cohort. *J Neurol Neurosurg Psychiatry* 2013; **84:** 1258–64.

91 Reinoso G, Allen JC Jr, Au WL, Seah SH, Tay KY, Tan LC. Clinical evolution of Parkinson's disease and prognostic factors affecting motor progression: 9-year follow-up study. *Eur J Neurol* 2015; **22:** 457–63.

92 Zhang Y, Wang C, Wang Y, et al. Mortality from Parkinson's disease in China: findings from a ten-year follow up study in Shanghai. *Parkinsonism Relat Disord* 2018; **55:** 75–80.

93 Bhidayasiri R, Hattori N, Jeon B, et al. Asian perspectives on the recognition and management of levodopa 'wearing-off' in Parkinson's disease. *Exp Rev Neurother* 2015; **15:** 1285–97.

94 Kim HJ, Jeon B. How close are we to individualized medicine for Parkinson's disease? *Expert Rev Neurother* 2016; **16:** 815–30.

95 Heinzel S, Lerche S, Maetzler W, Berg D. Global, yet incomplete overview of cohort studies in Parkinson's disease. *J Parkinson's Dis* 2017; **7:** 423–32.

96 Lee JM, Shine JM, Lewis SJ. What matters to people with Parkinson's disease living in Australia? *J Clin Neurosci* 2015; **22:** 338–41.

97 Antonini A, Moro E, Godeiro C, Reichmann H. Medical and surgical management of advanced Parkinson's disease. *Mov Disord* 2018; **33:** 900–08.

98 Kim MR, Yun JY, Jeon B, et al. Patients' reluctance to undergo deep brain stimulation for Parkinson's disease. *Parkinsonism Relat Disord* 2016; **23:** 91–94.

99 Poortvliet PC, Silburn PA, Coyne TJ, Chenery HJ. Deep brain stimulation for Parkinson disease in Australia: current scientific and clinical status. *Int Med J* 2015; **45:** 134–39.

100 Ypinga JHL, de Vries NM, Boonen LHHM, et al. Effectiveness and costs of specialised physiotherapy given via ParkinsonNet: a retrospective analysis of medical claims data. *Lancet Neurol* 2018; **17:** 153–61.

101 Giladi N, Manor Y, Hilel A, Gurevich T. Interdisciplinary teamwork for the treatment of people with Parkinson's disease and their families. *Curr Neurol Neurosci Rep* 2014; **14:** 493.

102 Schneider SA, Alcalay RN. Neuropathology of genetic synucleinopathies with parkinsonism: review of the literature. *Mov Disord* 2017; **32:** 1504–23.

103 De Pablo-Fernández E, Breen DP, Bouloux PM, Barker RA, Foltynie T, Warner TT. Neuroendocrine abnormalities in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 2017; **88:** 176–85.

104 Hilal S, Mok V, Youn YC, Wong A, Ikram MK, Chen CL. Prevalence, risk factors and consequences of cerebral small vessel diseases: data from three Asian countries. *J Neurol Neurosurg Psychiatry* 2017; **88:** 669–74.

105 Hong CT, Hu HH, Chan L, Bai CH. Prevalent cerebrovascular and cardiovascular disease in people with Parkinson's disease: a meta-analysis. *Clin Epidemiol* 2018; **10:** 1147–54.

106 Cheung EYN, Tan KCB, Cheung CL, Kung AWC. Osteoporosis in East Asia: current issues in assessment and management. *Osteoporosis Sarcopenia* 2016; **2:** 118–33.

107 Manson A, Stirpe P, Schrag A. Levodopa-induced-dyskinesias: clinical features, incidence, risk factors, management and impact on quality of life. *J Parkinson's Dis* 2012; **2:** 189–98.

108 Kotagal V, Albin RL, Müller ML, Koeppe RA, Frey KA, Bohnen NI. Diabetes is associated with postural instability and gait difficulty in Parkinson disease. *Parkinsonism Relat Disord* 2013; **19:** 522–26.

109 Kotagal V, Albin RL, Müller ML, Koeppe RA, Frey KA, Bohnen NI. Modifiable cardiovascular risk factors and axial motor impairments in Parkinson disease. *Neurology* 2014; **82:** 1514–20.

110 Bega D, Gonzalez-Latapi P, Zadikoff C, Simuni T. A review of the clinical evidence for complementary and alternative therapies in Parkinson's disease. *Curr Treat Options Neurol* 2014; **16:** 314.

111 Miyahara Y, Jitkritsadakul O, Sringean J, Aungkab N, Khongprasert S, Bhidayasiri R. Can therapeutic Thai massage improve upper limb muscle strength in Parkinson's disease? An objective randomized-controlled trial. *J Tradit Complement Med* 2018; **8:** 261–66.

112 Cilia R, Laguna J, Cassani E, et al. *Mucuna pruriens* in Parkinson disease: a double-blind, randomized, controlled, crossover study. *Neurology* 2017; **89:** 432–38.

113 Soumyanath A, Denne T, Hiller A, Ramachandran S, Shinto L. Analysis of levodopa content in commercial *Mucuna pruriens* products using high-performance liquid chromatography with fluorescence detection. *J Altern Complement Med* 2018; **24**: 182–86.

114 Hatano T, Hattori N, Kawanabe T, et al. An exploratory study of the efficacy and safety of yokukansan for neuropsychiatric symptoms in patients with Parkinson's disease. *J Neural Transm* 2014; **121:** 275–81.

115 Chua KK, Wong A, Chan KW, et al. A randomized controlled trial of Chinese medicine on nonmotor symptoms in Parkinson's disease. *Parkinson's Dis* 2017; **2017:** 1902708.

116 International Parkinson and Movement Disorder Society. Patient education: handouts for patient care. https://www.movementdisorders.org/MDS/Resources/Patient-Education.htm (accessed April 9, 2019).

117 International Parkinson and Movement Disorder Society. MDS rating scales. https://www.movementdisorders.org/MDS/Education/Rating-Scales.htm (accessed April 9, 2019).

118 Noorden R, Ledford H. Medicine Nobel for research on how cells 'eat themselves': Japanese biologist Yoshinori Ohsumi recognized for work on autophagy. *Nature* 2016; **538:** 18–19.

119 Sun AX, Ng HH, Tan EK. Translational potential of human brain organoids. *Ann Clin Transl Neurol* 2018; **5:** 226–35.

120 Kikuchi T, Morizane A, Doi D, et al. Human iPS cell-derived dopaminergic neurons function in a primate Parkinson's disease model. *Nature* 2017; **548:** 592–96.