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Australian Parkinson's Genetics Study (APGS): pilot (n=1532)

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ABSTRACT

Purpose Parkinson's disease (PD) is a neurodegenerative disorder associated with progressive disability. While the precise aetiology is unknown, there is evidence of significant genetic and environmental influences on individual risk. The Australian Parkinson's Genetics Study seeks to study genetic and patient-reported data from a large cohort of individuals with PD in Australia to understand the sociodemographic, genetic and environmental basis of PD susceptibility, symptoms and progression.

Participants In the pilot phase reported here, 1819 participants were recruited through assisted mailouts facilitated by Services Australia based on having three or more prescriptions for anti-PD medications in their Pharmaceutical Benefits Scheme records. The average age at the time of the questionnaire was 64±6 years. We collected patient-reported information and sociodemographic variables via an online (93% of the cohort) or paper-based (7%) questionnaire. One thousand five hundred and thirty-two participants (84.2%) met all inclusion criteria, and 1499 provided a DNA sample via traditional post.

Findings to date 65% of participants were men, and 92% identified as being of European descent. A previous traumatic brain injury was reported by 16% of participants and was correlated with a younger age of symptom onset. At the time of the questionnaire, constipation (36% of participants), depression (34%), anxiety (17%), melanoma (16%) and diabetes (10%) were the most reported comorbid conditions.

Future plans We plan to recruit sex-matched and age-matched unaffected controls, genotype all participants and collect non-motor symptoms and cognitive function data. Future work will explore the role of genetic and environmental factors in the aetiology of PD susceptibility, onset, symptoms, and progression, including as part of international PD research consortia.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ We used a time-effective and cost-effective recruitment method that enabled us to reach out to a random sample of individuals who have been prescribed medications for Parkinson's disease across all over Australia to invite them to participate in this study.
⇒ The identities of letter recipients remained private and confidential and were not shared with the researchers. However, those recipients who were interested and willing to participate were directed to a website where they could sign up and provide informed consent.
⇒ The source database only captures individuals who have been prescribed medications to treat Parkinson's disease in Australia and who are eligible for Medicare. Those without an official diagnosis, not receiving treatment or not eligible for government subsidies are not included.
⇒ We collected a wide range of patient-reported variables relevant to disease onset, diagnosis, symptoms, medical comorbidities, lifestyle and family history in a large cohort of participants. However, some variables might not be as accurate as when measured by a specialist clinician.
⇒ Given the 9% response rate to our single-letter invitation, there is a substantial risk of self-selection bias. Thus, patient characteristics for this cohort might differ from those of the typical population of individuals with Parkinson's disease in Australia.

INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disorder that affects 2%–3% of the global population over 65 years.[1 2] At present, over 100 000 Australians have PD, and approximately 32 new cases are diagnosed every day.[3] The economic cost of PD in Australia was estimated at almost $10 billion per year in 2015, but the prevalence and total financial cost associated with the disease have increased dramatically since then.[4] The number of newly diagnosed PD cases is expected to double over the coming decades due to population ageing, posing substantial challenges to the healthcare system, the economy and society.[5]

The pathological hallmarks of PD include nigrostriatal degeneration and widespread

intracellular accumulation of Lewy bodies in multiple brain regions. The aetiological pathways of PD are mostly unknown. Many risk factors have been explored, including certain drugs, head trauma, lifestyle factors, comorbid diseases and exposure to toxic environmental agents.[6–8] In particular, age, mood disorders, consumption of well water,[9] head injury[10] and exposure to environmental toxins[11 12] have been consistently associated with an increased PD risk. On the contrary, smoking and caffeine consumption have been inversely related to PD risk and positively correlated with a later age of onset,[13 14] suggesting a putative protective effect that needs further exploration. Associations with alcohol drinking remain controversial.[15]

The clinical manifestations of PD are highly heterogeneous. Diagnosis is based on the presence of cardinal motor symptoms, including bradykinesia, resting tremor, muscle rigidity, gait difficulty and postural instability.[1] Non-motor symptoms are also common, particularly in late-stage PD, and involve cognitive impairment (eg, executive dysfunction and attentional deficits), psychotic symptoms (eg, visual hallucinations), autonomic dysfunction (eg, orthostatic hypotension, urogenital incontinence and constipation), disorders of sleep and mood, hyposmia, fatigue and chronic pain.[16] Notably, some comorbid medical conditions such as constipation, hyposmia, Rapid Eye Movement sleep behaviour disorder, diabetes and mood disorders may precede the onset of motor disability by years or even decades and serve as prediagnostic PD symptoms.[17] Thus, it is worth noting that PD onset, clinical presentation and progression differ substantially among patients.[18]

PD has a complex genetic architecture, with both monogenic and sporadic forms. A twin study in the Swedish Twin Registry estimated heritability at 34%, with concordance rates for PD of 11% for monozygotic twins and 4% for same-sexed dizygotic twin pairs.[19] Rare coding variants detected in the *LRRK2*, *VPS12C*, *GBA* and *SNCA* genes are associated with monogenic (familial) PD forms,[20] whereas common variants around the same *GBA*, *SNCA* and *LRRK2* genes have also been associated with sporadic (non-familial) PD.[21] A recent genome-wide association study (GWAS) meta-analysis of 17 cohorts identified 90 independent single-nucleotide polymorphisms (SNPs) across 78 genomic regions associated with sporadic Parkinson's risk.[22] Despite this remarkable progress, common genetic variants only explain around 22% (95% CI 18% to 26%) of PD risk on the liability scale, implying that there are still many more unidentified genetic variants contributing to PD susceptibility. It has been pointed out that the inclusion of diverse populations in genetic studies improves the utility of genetic discovery.[23] However, genetic PD studies have focused mainly on European ancestry individuals, limiting their capacity to extrapolate results to other ethnicities. Australia is ethnically diverse, but the disease epidemiology among various ethnic groups has not been investigated.[24 25]

Treatment response in PD is complex and poorly understood.[26] Although there is currently no cure for PD, a combination of pharmacological (eg, levodopa, dopamine receptor agonists, anticholinergics) and non-pharmacological (eg, physiotherapy, deep brain stimulation) therapies are the only available treatment options. However, such interventions only ameliorate the symptoms of the illness, and their long-term use is associated with adverse side effects in some patients,[27 28] which in turn result in suboptimal medication compliance and low quality of life. Research seeking to identify the disease's genetic components that contribute to drug response variability could lead to the discovery of personalised disease-modifying therapies with great potential to improve well-being and quality of life for patients with PD.

Few studies have assessed the prevalence, risk factors, sociodemographic and genetic factors of PD in Australia. Similarly, details about disease onset, symptoms and progression and other medical comorbidities have not been collected and studied at a large scale in a nationwide sample. Long-running studies, such as the Griffith University Queensland Parkinson's Project, have made significant contributions over the past 20 years in describing risk factors and mechanisms underlying PD's pathological development and its disease progression.[29–31] However, despite continued global scientific efforts, many questions remain around early and accurate diagnosis, differentiation, prognostication, better traditional management methods and new treatment efforts such as neuroprotection and disease modification. With an ageing population, the number of individuals with PD in Australia is set to increase dramatically. Thus, it is crucial to generate reliable evidence about the epidemiology and genetic aetiology of PD to inform policy and clinical practice. Ultimately, a more extensive representation of diverse Australian participants in worldwide PD studies may also lead to discovering novel therapeutic targets and developing new therapies and interventions to prevent, stop or modify PD's clinical course in Australia and the rest of the world.

Hypothesis

We hypothesise that individual differences in PD susceptibility, symptomatology, progression and treatment response result, in part, from underlying individual genetic variability. Thus, large longitudinal cohorts of individuals with PD will be required to unravel the complex aetiology of PD heterogeneity.

Aim of the study

The Australian Parkinson's Genetics Study (APGS) aims to recruit and follow-up a large cohort of Australians with PD and unaffected controls and characterise their phenotypic, genetic and environmental diversity. Here, we describe the results of a pilot study comprising the first ~1500 participants.

Objectives

1. To recruit and follow-up a nationwide cohort of 10 000 participants with PD and 10 000 unaffected controls and characterise their genetic information.
2. To collect patient-reported data on disease onset, symptoms, comorbidities and progression; treatment

response; environmental, lifestyle and sociodemographic factors; family and medical history; and cognitive function.
3. To discover and validate genetic and environmental markers of PD susceptibility and heterogeneity and contribute to identifying and validating therapeutic molecular targets.
4. To contribute to ongoing international collaborative PD research efforts.

METHODOLOGY

The present study used a cross-sectional study design. Here, we describe the design of the Australian Parkinson's Genetics pilot study and baseline characteristics of participants, including data collection methods, sociodemographic variables, environmental and lifestyle exposures and self-reported history of medical conditions. Participants in the present study were Australian residents diagnosed with PD. The pilot project was initially conceived by researchers at the QIMR Berghofer Medical Research Institute (QIMRB).

Recruitment method

Participants were invited to participate in the study via assisted mailouts through *Services Australia* (formerly known as the Australian Government Department of Human Services) based on their pharmaceutical prescription history. *Services Australia* is an official government agency responsible for delivering a range of welfare, health, child support payments and other services to eligible Australian citizens and permanent residents, including managing the Pharmaceutical Benefits Scheme (PBS). The PBS is a programme of the Australian Government that subsidises prescription medications. Under the PBS, all Australian residents holding a current Medicare card are eligible for prescription drug subsidies to make commonly used medicines more accessible and affordable (for detailed information about the PBS and a list of all medicines on the PBS, refer to the following website https://www.pbs.gov.au/pbs/home). *Services Australia* retains records for the most recent 5 years' PBS-subsidised medicines and considers requests for assisted mailouts from external organisations for health-related research projects. External organisations must have approval from a Human Research Ethics Committee, per the National Health and Medical Research Council's guidelines. *Services Australia* then sends the approach letters to individuals meeting specific selection criteria on behalf of the research organisation. Personal data of letter recipients are not shared with the researchers requesting the mailout and thus always remains secure and confidential.

In this pilot phase, 20 000 invitation letters were sent in June 2020 to individuals who: (1) were Australian residents (Australian citizens or permanent residents), aged 40–75 years; (2) had at least three PBS claims in the last 2 years for medications commonly used in the management of symptoms of PD (see online supplemental table 1 for a list of medications and their corresponding PBS codes) according to their records in the PBS database. The invitation letters directed potential participants to a secure study website (https://www.qimrberghofer.edu.au/parkinsonsgenetics) with more detailed information about the study. Individuals who did not have PD were kindly asked to ignore the invitation letter. Those interested to participate were given the option to complete an online or a paper-based questionnaire. Participants indicated having a current clinical diagnosis for PD and the type of clinician who initially diagnosed them (eg, neurologist, geriatrician, general practitioner). Prospective participants were also asked to indicate their consent to donate a saliva sample for DNA extraction and genotyping.

Those willing to provide a saliva sample were sent a saliva DNA collection kit via mail. A small percentage of prospective participants (~10%) requested to be mailed a paper-based version of the questionnaire and consent form instead of responding the online version. Of the 1819 individuals who filled out the registration form and provided informed consent to participate (9.1% response rate for the mailouts), 1532 (84%) confirmed having a current PD diagnosis by a licensed clinician and were willing to provide a DNA sample.

Of those who consented to donate their saliva for genetic analysis, 1499 (97.8%) have returned saliva kits by mail as of August 2021. Since information about the letter recipients remained confidential, we could not follow-up with the non-respondents, some of whom may have died or moved to a new address. Refer to online supplemental table 2 for the percentage of APGS invitations sent and participant registration per Australian state or territory.

We are aware of a few cases where a letter recipient shared the invitation with other relatives or acquaintances with PD who did not initially receive an approach letter. This became evident after a few participants aged over 75 (the upper limit of our target sample for the mailout) registered in the study. Unfortunately, we cannot reliably quantify the number of participants who signed up but did not receive an invitation letter from *Services Australia*. None of the participants was excluded based on age if they met the other inclusion criteria of the study.

Patient and public involvement

During the project, we reached out to patient support groups and advocacy organisations. Notably, the Shake It Up Australia Foundation for Parkinson's Research (www.shakeitup.org.au) has become an ally of the project. When the full-fledged study is rolled out, a patient advisory group will be formed to provide input and feedback about the research agenda. Similarly, the research team will share research updates at least once a year with the participants via an electronic or physical newsletter.

Genotyping plans

Genotyping will be conducted using the Illumina Global Screening Array. Genotypes will be processed and

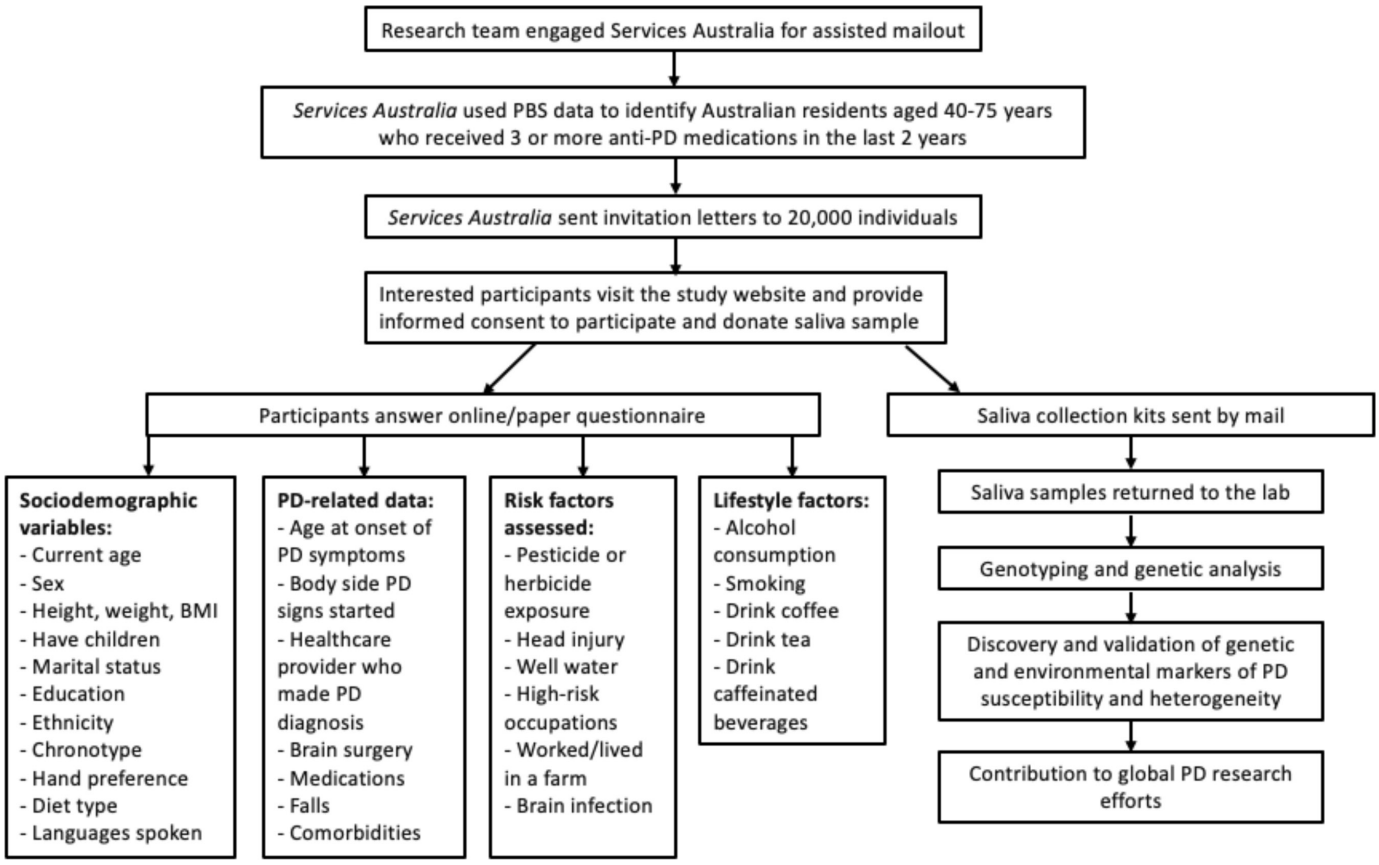

Figure 1 Overview of the recruitment strategy and questionnaire contents for the APGS pilot. APGS, Australian Parkinson's Disease Study; BMI, body mass index; PBS, Pharmaceutical Benefits Scheme medication prescription database; PD, Parkinson's disease.

subjected to quality control, and genotype imputation will be conducted using state of the art protocols. We will use available genetic controls from screened population-based studies at QIMR to perform several analyses, including estimating SNP-based heritability with the GCTA (Genome-wide Complex Trait Analysis) software package, a GWAS meta-analysis to combine our results with the summary results from previous GWASs of PD, or estimating polygenic risk scores for relevant comorbid conditions. We plan to recruit demographically matched controls in subsequent waves of the study.

Data collection

The online instruments consisted of several sections, covering sociodemographic, clinical, occupational, lifestyle and environmental factors, with a schematic of the APGS and questionnaire content shown in figure 1. As part of the informed consent process, all participants agreed to be recontacted for future related studies, understanding that their participation in future studies is voluntary. The second wave of data collection is planned for the first half of 2022. It will include questions assessing heterogeneity in PD onset and motor and non-motor disability, including the following instruments: items from the Movement Disorder Society United Parkinson's Disease Rating Scale[32]; a short scale for the assessment of motor impairments and disability in PD (the Short Parkinson's Evaluation Scale (SPES)/Scales for Outcomes in Parkinson's Disease (SCOPA) - Motor Function); the Apathy Screening Tool; Geriatric Anxiety Inventory[32 33]; Geriatric Depression Scale short-form[34]; Assessment of Psychiatric Complications in Parkinson's disease (The SCOPA-PC)[35]; and the SCOPA-sleep and Parkinson's Disease Sleep Scale scales[36] to identify sleep disorders in PD.

Statistical analyses

IBM SPSS Statistics (V.23) software was used for statistical analysis presented here.[37] In between-group analysis (men vs women), p values were calculated using a t-test for comparing mean values of the samples or a χ^2 test for comparing frequencies. We used a bivariate correlation test (eg, Pearson correlation coefficient) to assess a relationship between two continuous variables. We used an alpha level of 0.05 for all statistical tests.

RESULTS

We recruited 1532 participants (mean age=64±6 years; see online supplemental figures 1 and 2 for sex-stratified age distributions). Sociodemographic data were collected via web-based or paper questionnaires, with most participants (93%; n=1424) responding via the online questionnaire. Of our sample, 65% were men, and the mean body mass index of the sample was 28±5 kg/m^2.

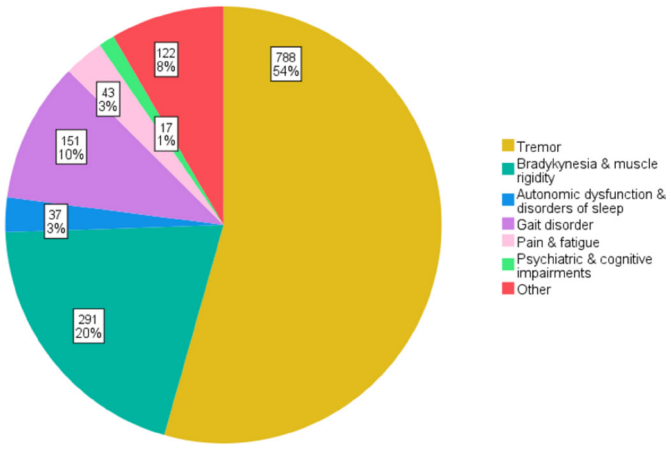

Figure 2 Frequency of patient-reported first symptom of participants in the APGS pilot cohort. 'Other' symptoms included numbness, falls, olfactory dysfunction, small handwriting, loss of taste, slurred speech. APGS, Australian Parkinson's Disease Study.

Most participants reported being diagnosed with PD by a neurologist (83%), having children (87%), being married or in a de facto relationship (81%) and being of European ancestry (92%). Nearly 60% have a post-high school qualification, and 15% speak more than one language. Tremor was the most common first symptom of PD reported in 54% of the sample, followed by bradykinesia and muscle rigidity (20%), and gait disorder (10%), with an average age at onset of the first PD symptom of 57±8 years. The frequency of the first self-reported symptom of PD in participants is presented in figure 2.

For 85% of participants, PD symptoms started on one side of the body, and more than half (44%) experienced the symptoms on the right side of the body. Most respondents (94%) were on at least one anti-PD medication at the time of the questionnaire. Patients who were not on anti-PD medication were included in the study only if they had received a deep brain stimulation surgery. Furthermore, 42% had experienced PD-related falls, and 12% reported having had brain surgery for PD. The frequencies and percentages of all self-reported sociodemographic and PD-related characteristics are outlined in tables 1 and 2, respectively.

Occupational and environmental risk factors of PD

Previously reported occupational (eg, welding, metal melting, agriculture, petrochemistry) and environmental risk factors associated with PD were examined in this cohort and included exposure to pesticides or herbicides, head injury, well water drinking, working in high-risk occupations, living on a farm for over a year and having metal poisoning or brain infection at any point across the life course. Thirty-four per cent of the sample reported being exposed to pesticides or herbicides at some point in their lives. Of those exposed to pesticides/herbicides, 390 were men, and 127 were women, with most of these cases (82%) reporting pesticide/herbicide exposure before 37 years of age.

Sixteen per cent of the sample had experienced head trauma, and the average age of head injury was 26±18 years. Of those with a previous head injury, 67% reported traumatic head injury with loss of consciousness. There was a significant positive association between the age of traumatic head injury and the age at onset of the first symptom of PD (Pearson correlation coefficient r=0.3, p<0.001) (figure 3).

Five per cent of participants reported having frequently consumed water from a well for 19±12 years on average. A third of the sample (33%) disclosed having worked in a high-risk occupation throughout their lives, including welding, metal melting, galvanisation, milling, petrochemistry, agriculture, wood processing and textile or industrial painting. Of these participants, 42% reported exposure to more than one occupational risk factor. Approximately 24% of the cohort reported having worked or lived on a farm for more than a year, 1% acquired metal poisoning and 2% encephalitis (brain infection). The occupational and environmental risk factors of PD, summarised by sex, are shown in table 3.

Lifestyle factors correlated with lower PD risk

As shown in table 4, we investigated a range of lifestyle variables that have been correlated in previous PD studies with lower PD risk. These included alcohol drinking, smoking, exposure to secondhand smoke and drinking caffeinated coffee, tea and other beverages. More than two-thirds of participants (71%) currently drink an average of 8±8 standard alcoholic drinks per week, and 20% reported consuming alcohol heavily in the past. There was a significant weak positive association between the number of alcoholic drinks consumed per week and the age at onset of the first PD symptom (Pearson correlation coefficient r=0.1, p=0.001).

Three per cent of the cohort are current cigarette, cigar or pipe smokers and smoke on average 13±8 cigarettes/cigars/pipes per day. Thirty-six per cent of the sample reported being former smokers and disclosed smoking 15±11 cigarettes/cigars/pipes a day in the past. For current smokers, there was a significant negative relationship between the number of cigarettes/cigars/pipes smoked daily and the age at onset of the first symptom of PD (Pearson correlation coefficient, r=−0.2, p=0.03).

Many participants reported being exposed to secondhand smoke at home (56%), at work (46%) and in other areas (38%), with the mean of hours of passive smoking ranging from 2 to 5 (for details refer to table 4).

Sixty-eight per cent of participants drink tea, 73% drink coffee and 24% consume other caffeinated beverages. On average, participants drink two cups of caffeinated tea or coffee daily, ranging from half a cup to 12 cups a day. There was a significant weak positive correlation between the number of teacups consumed daily and the age at onset of PD symptoms (Pearson correlation coefficient r=0.1, p=0.001). Those who reported drinking other caffeinated beverages indicated that they consumed on average 330±335 mL of other caffeinated drinks per day.

Table 1 Sociodemographic characteristics of study participants

	Total, n (%)	Male, n (%)	Female, n (%)	P values, male vs female
Response method				0.87
Online questionnaire	1424 (92.9)	924 (92.8)	499 (93.1)	
Paper questionnaire	108 (7.1)	71 (7.2)	37 (6.9)	
Age in years				
Mean (SD)	63.9 (5.9)	64.2 (5.9)	63.5 (6.0)	0.04
Range	40–88	40–86	42–88	
Sex				
Female	536 (35.0)			–
Male	995 (64.9)			–
MTF	1 (0.06)			–
Current height in cm				
Mean (SD)	170.7 (9.9)	175.4 (7.8)	162.0 (7.2)	<0.001
Range	124–200	150–200	124–178	
Current weight in kg				
Mean (SD)	80.8 (16.9)	85.5 (15.3)	72.3 (16.5)	<0.001
Range	40–164	45–164	40–140	
Current BMI (kg/m^2)				
Mean (SD)	27.6 (5.3)	27.7 (4.8)	27.5 (6.0)	0.29
Range	16.6–55.1	17.5–50.7	16.6–55.1	
Have children	1338 (87.3)	870 (84.4)	467 (87.1)	0.86
Marital status				<0.001
Single/never married	66 (4.3)	45 (4.5)	21 (3.9)	
Married/de facto relationship	1245 (81.3)	848 (85.3)	396 (74.0)	
Separated/divorced	145 (9.5)	70 (7.0)	75 (14.0)	
Widowed	48 (3.1)	17 (1.7)	31 (5.7)	
In a relationship but not living together	26 (1.7)	13 (1.3)	13 (2.4)	
Other	2 (0.1)	2 (0.2)	0 (0.0)	
Ethnicity				0.73
European	1397 (91.6)	910 (91.5)	486 (90.7)	
East Asian	40 (2.6)	23 (2.4)	17 (3.2)	
Indigenous Australian/Torres Strait Islander	12 (0.8)	8 (0.7)	4 (0.7)	
African	2 (0.1)	2 (0.2)	0 (0.0)	
South Asian	26 (1.7)	14 (1.4)	12 (2.2)	
Pacific Islander	9 (0.6)	6 (0.6)	3 (0.6)	
Hispanics	5 (0.3)	4 (0.4)	1 (0.2)	
Mixed	21 (1.4)	16 (1.7)	5 (0.9)	
Other	13 (0.8)	8 (0.7)	5 (0.9)	
Information not provided	7 (0.4)	4 (0.4)	3 (0.6)	
Education				0.02
Junior high school or less	348 (22.7)	218 (21.9)	130 (24.3)	
Senior high school	276 (18.0)	184 (18.5)	92 (17.3)	
Certificate III/IV	196 (12.8)	124 (12.5)	72 (13.4)	
Diploma	190 (12.4)	128 (12.8)	62 (11.6)	
Bachelor's degree	235 (15.3)	163 (16.4)	71 (13.3)	

Continued

Table 1 Continued

	Total, n (%)	Male, n (%)	Female, n (%)	P values, male vs female
Graduate diploma or certificate	134 (8.7)	77 (7.7)	57 (10.6)	
Postgraduate	148 (9.7)	97 (9.7)	51 (9.5)	
Information not provided	5 (0.3)	5 (0.5)	0 (0.0)	
Hand preference				0.78
Left hand	156 (10.2)	103 (10.4)	53 (9.9)	
Right hand	1323 (86.5)	856 (86.1)	467 (87.3)	
Both hands	50 (3.3)	34 (3.4)	15 (2.8)	
Not sure	1 (0.06)	1 (0.1)	0 (0.0)	
Chronotype				<0.001
Morning-type person	800 (52.3)	518 (52.2)	282 (52.6)	
Evening-type person	376 (24.6)	212 (21.3)	163 (30.4)	
Neither	355 (23.2)	264 (26.5)	91 (17.0)	
Information not provided	1 (0.06)	1 (0.1)	0 (0.0)	
Consider themselves spiritual or religious	599 (39.1)	347 (34.9)	251 (46.8)	<0.001
Information not provided	3 (0.2)	2 (0.2)	1 (0.2)	
Diet type				0.004
Vegan	8 (0.5)	7 (0.7)	1 (0.2)	
Vegetarian	42 (2.7)	18 (1.8)	22 (4.1)	
Speak more than one language	228 (14.9)	147 (14.8)	81 (15.1)	0.88
Information not provided	1 (0.06)	1 (0.1)	0 (0.0)	

P values were calculated using a t-test for comparing mean values or a χ^2 test for comparing frequencies; sample n=1532.
BMI, body mass index; MTF, male-to-female transgender person.

Sex differences in the reported outcomes related to PD's lifestyle factors are given in table 4.

PD comorbidities

Participants reported on a range of comorbidities. PD co-occurring medical conditions included allergy, cancer, melanoma, psychological, cardiovascular, respiratory, endocrine and gastrointestinal disorders. Back problems were the most common medical condition in 47% of the respondents, and eczema was the least prevalent disorder reported by 7% of the participants (table 5).

DISCUSSION

The present study describes sample characteristics of 1532 Australians with PD recruited for the APGS to unravel environmental and genetic associations with PD, along with PD heterogeneity, anti-PD medication response and adverse drug reactions.

PD incidence varies with gender, age and race or ethnicity.[38 39] We observed a higher prevalence of male participants than women (65% of men vs 35% of women), in line with most previous PD studies in various populations worldwide.[38–40] The causes of higher male-to-female ratios in PD are unknown, and it is still unclear whether male sex is an independent risk factor for PD. Although oestrogens are believed to be neuroprotective in women,[41] further research is needed to elucidate whether men could be at greater PD risk due to higher exposure to environmental or occupational risk factors.

The present study is the first to employ an assisted mailout approach to recruit PD participants from all Australian states. We found that individuals of European descent (92% of the sample group) were the most prevalent in the APGS, with a lower proportion of participants from Asian background (4%), Indigenous Australians and Torres Strait Islanders (1%), Africans (0.1%), Pacific Islanders (0.6%), Hispanics (0.3%) and in individuals of mixed ancestry (1.4%). We cannot estimate differences in PD prevalence across ethnicities, given the lack of unaffected controls. Previous Australian epidemiological studies have reported PD prevalence rates between 66 and 415 per 100 000 Australians.[42–44] Similarly, worldwide PD prevalence has been consistently reported between 60 and 335 per 100 000 individuals, with a broad spectrum of ethnic backgrounds identified. For instance, the Israel population, Native Americans and Alaska Natives have the highest prevalence (335/100 000 for Jewish Israeli and 355/100 000 for Native Americans and Alaska Natives).[45 46] At the same time, Asian and African communities report the lowest prevalence rates.[47–49] The

Table 2 Parkinson's disease specific outcomes

	Total, n (%)	Male, n (%)	Female, n (%)	P values, male vs female
Age at onset of the first PD symptom				
Mean (SD)	56.1 (8.3)	56.4 (8.2)	55.6 (8.3)	0.10
Range	27–86	30–77	27–86	
Healthcare provider who made PD diagnosis				0.001
Neurologist	1260 (82.2)	790 (79.4)	469 (87.5)	
Geriatrician	16 (1.0)	12 (1.2)	4 (0.7)	
General practitioner	237 (15.5)	178 (17.9)	59 (11.0)	
Other	15 (0.9)	12 (1.2)	3 (0.6)	
Information not provided	4 (0.3)	3 (0.3)	1 (0.2)	
Had brain surgery for PD	177 (11.5)	119 (11.9)	58 (10.8)	0.53
Take at least one medication for PD	1424 (93.9)	930 (93.5)	493 (92.0)	0.43
Experienced falls related to PD	631 (41.2)	383 (38.5)	247 (46.1)	0.004
Information not provided	13 (0.8)	8 (0.8)	5 (0.9)	
PD signs started on one side of the body	1296 (84.6)	833 (83.6)	463 (86.3)	0.12
Information not provided	9 (0.6)	6 (0.6)	3 (0.5)	
Side of the body where PD symptoms started				0.69
Left	625 (40.8)	405 (40.7)	220 (41.0)	
Right	671 (43.8)	427 (42.9)	243 (45.3)	

PD, Parkinson's disease.

significantly increased prevalence of PD among distinct ethnic groups is partly attributable to a higher occurrence of PD-linked mutations in these populations (eg, *LRRK2* G2019S and *GBA* in *Ashkenazi* Jews).[50 51] However, other factors such as variation in age groups surveyed, sampling methods and diagnostic and screening criteria cannot be ruled out.

A PD diagnosis is rare before 50, yet a significant number of patients present early-stage non-motor PD symptoms in the late 50s.[1] Therefore, ageing remains the primary risk factor for developing idiopathic PD,[52–54] with the incidence

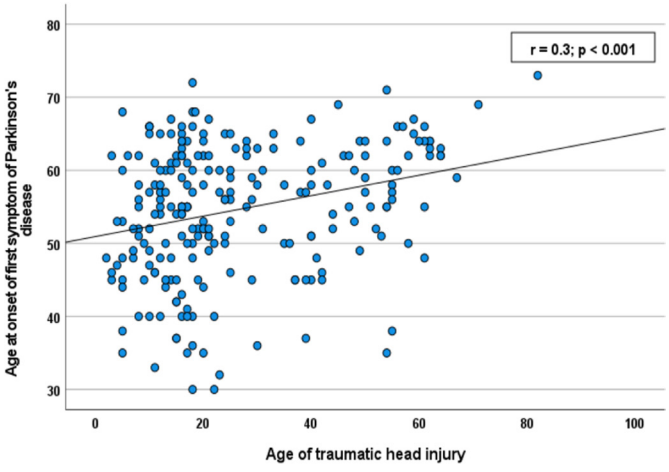

Figure 3 Traumatic brain injury is correlated with age at onset of first PD symptom. PD, Parkinson's disease.

of new cases increasing up to 10-fold between 60 and 90 years of age.[38 55 56] In our study, the mean age of onset for PD symptoms was 56 years, suggesting that self-selected PD participants may be among the younger age group, which tends to be more technology-savvy and motivated to participate in medical research. However, ageing alone is insufficient to cause PD, and a complex relationship between ageing and genetic and environmental factors prompts the disease onset.[57] Aging-associated impairments[58 59] and degeneration of dopaminergic neurons[60] may explain the steep rise in PD prevalence with age.

Previous studies have shown that a traumatic brain injury with loss of consciousness early in life is associated with late-life neurodegenerative conditions, accumulation of Lewy bodies, PD progression and increased PD risk.[61] However, the pathogenesis of brain injury and its link with neurodegenerative disorders has not been fully elucidated. We identified a significant positive association between the age of head injury and the age at onset of PD symptoms. Participants who had a head injury early in life also reported an earlier age at which the first PD symptoms were manifested. However, only a small percentage of participants reported a lifetime traumatic head injury. Thus, our results appear to support the hypothesis that traumatic brain injury may initiate or exacerbate PD. This may be due to persistent inflammation, metabolic dysfunction and abnormal protein aggregation.[62]

Lifestyle may affect PD susceptibility. For instance, alcohol,[15 63 64] tobacco[65 66] and caffeine[67 68] consumption

Table 3 Occupational and environmental risk factors

Risk factor	Total, n (%)	Male, n (%)	Female, n (%)
Exposure to pesticides or herbicides	517 (33.6)	390 (39.2)	127 (23.6)
Information not provided	25 (1.6)	16 (1.6)	9 (1.7)
Age of exposure to pesticides or herbicides			
<18 years of age	185 (12.1)	128 (12.9)	57 (10.6)
18–36	239 (15.6)	190 (19.1)	49 (9.1)
37–55	84 (5.5)	64 (6.4)	20 (3.7)
≥56	9 (0.6)	8 (0.8)	1 (0.2)
Head injury	244 (15.9)	186 (18.7)	58 (10.8)
Information not provided	21 (1.4)	12 (1.2)	9 (1.7)
Age of head injury			
Mean (SD)	26.3 (17.6)	26.2 (16.5)	26.9 (20.8)
Range	2–82	3–67	2–82
Head injury with loss of consciousness	165 (10.8)	128 (12.8)	37 (6.9)
Well water drinking	82 (5.3)	55 (5.5)	27 (5.0)
Information not provided	34 (2.2)	21 (2.1)	13 (2.4)
Number of years drinking well water			
Mean (SD)	18.7 (12.4)	18.3 (12.9)	19.4 (11.6)
Range	2–50	2–50	4–40
Worked in high-risk occupations	504 (32.9)	425 (42.7)	79 (14.7)
Number of high-risk occupations worked throughout of life			
One	293 (19.1)	226 (22.8)	67 (12.5)
Two	115 (7.5)	107 (10.7)	8 (1.5)
Three	52 (3.4)	48 (4.8)	4 (0.7)
Four	29 (1.9)	29 (2.9)	0 (0.0)
Five or more	15 (0.9)	15 (1.5)	0 (0.0)
Worked or lived on a farm for over 1 year	360 (23.5)	236 (23.7)	124 (23.1)
Information not provided	27 (1.8)	18 (1.8)	9 (1.6)
Had metal poisoning	22 (1.4)	17 (1.7)	5 (0.9)
Information not provided	34 (2.2)	21 (2.1)	13 (2.4)
Had brain infection (encephalitis)	31 (2.0)	20 (2.0)	11 (2.1)
Information not provided	21 (1.4)	12 (1.2)	1 (0.2)

High-risk occupations included welding, metal melting, galvanisation, milling, petrochemistry, agriculture, wood processing, textile or industrial painting. n=1532.

are negatively correlated with PD risk. Previous studies have found that alcohol users have a lower PD risk than non-alcohol users, and those who drink more are less susceptible to PD than those who drink less.[64] Excessive alcohol consumption has been found to reverse this protective effect, increasing PD susceptibility independent of gender.[69] We observed a positive association between alcohol use and PD age of onset in the APGS sample, whereby participants with PD who had more alcoholic drinks consumed per week reported a later age of onset of PD compared with those who consumed fewer alcoholic drinks weekly. This interim observation agrees with previous findings and may imply that alcohol has a protective effect and delays the onset of PD. However, this needs to be explored further due to the possibility of ascertainment bias (eg, alcohol consumption has negative effects on health and increases the risk of mortality).

Several longitudinal studies have reported an inverse association between smoking and PD. Compared with never smokers, a lower PD risk was observed among current and past smokers.[65 70] Notably, smoking duration and intensity have been inversely related to PD risk, with PD susceptibility decreasing up to 70% when the duration of smoking in years increased.[65] In contrast, we observed an earlier age of symptoms onset in those who smoked more cigarettes/cigars/pipes per day than those who smoked fewer. This should be interpreted with caution, given the small sample size. Also, a recent Mendelian

Table 4 Lifestyle variables

	Total, n (%)	Male, n (%)	Female, n (%)
Currently drink alcohol	1090 (71.1)	751 (75.5)	339 (63.2)
Mean number of drinks per week (SD)	7.6 (7.7)	8.3 (8.4)	5.7 (5.3)
Range	1–50	1–50	1–30
Information not provided	37 (2.4)	23 (2.3)	14 (2.6)
Consumed alcohol heavily in the past	313 (20.4)	252 (25.3)	61 (11.4)
Current cigarette/cigar/pipe smokers	50 (3.3)	28 (2.8)	22 (4.1)
Mean number of cigarettes/cigar/pipes smoked per day (SD)	13.3 (8.3)	14.3 (8.9)	12.0 (7.6)
Range	2–40	2–40	2–30
Former smokers	554 (36.2)	368 (37.0)	186 (34.7)
Mean number of cigarettes smoked per day (SD)	15.3 (11.2)	18.1 (4.6)	17.9 (3.5)
Range	1–60	10–49	10–31
Information not provided	37 (2.4)	24 (2.4)	13 (2.4)
Exposure to secondhand smoke at home	858 (56.0)	510 (51.3)	348 (64.9)
Mean number of hours per day (SD)	4.5 (3.7)	4.3 (3.6)	4.9 (3.9)
Range	0.5–20	0.5–18	0.5–20
Exposure to secondhand smoke at work	701 (45.7)	521 (52.4)	179 (33.4)
Mean number of hours per day (SD)	4.9 (3.1)	4.9 (3.2)	4.9 (2.9)
Range	0.5–12	0.5–12	0.5–12
Exposure to secondhand smoke in other areas	586 (38.2)	405 (40.7)	181 (33.8)
Mean number of hours per day (SD)	2.0 (1.7)	2.1 (1.8)	1.9 (1.6)
Range	0.5–14	0.5–14	0.5–12
Drink caffeinated tea	1043 (68.1)	668 (67.1)	375 (69.9)
Mean number of cups per day (SD)	2 (1.4)	2 (1.3)	2.3 (1.6)
Range	0.5–12	0.5–8	0.5–12
Information not provided	34 (2.2)	21 (2.1)	13 (2.4)
Drink caffeinated coffee	1120 (73.1)	761 (76.5)	359 (66.9)
Mean number of cups per day (SD)	2 (1.2)	2.1 (1.3)	1.8 (1.2)
Range	0.5–10	0.5–10	0.5–10
Information not provided	34 (2.2)	21 (2.1)	13 (2.4)
Drink other caffeinated beverages	371 (24.2)	271 (27.2)	100 (18.7)
Average volume in ml per day (SD)	330.8 (336.6)	335.8 (340.2)	317.3 (330.7)
Range	10–2000	10–2000	10–2000
Information not provided	35 (2.3)	22 (2.2)	13 (2.4)

Sample n=1532.

randomisation study[71] suggested that continuing the smoking habit rather than smoking heaviness (ie, numbers of cigarettes smoked per day) may exert the protective effect of smoking over PD risk.

Prospective studies assessing lifetime coffee and tea consumption and PD highlight a negative correlation between the caffeine in coffee or tea and PD risk,[72] and the effect is more pronounced among men than women who regularly drink coffee or tea.[67 73 74] But there is substantial between-study heterogeneity across reported effect estimates. Our correlations between caffeinated tea consumption and age of onset of PD are similar to those previously reported by others,[75] with regular tea consumers reporting a later age of symptom onset than non-habitual tea consumers. The precise mechanisms underlying this relationship between lifestyle variables and PD susceptibility are poorly understood.

Consistent with previous findings, we observed high rates of comorbidities including constipation,[76 77] depression,[78 79] anxiety disorder,[80] melanoma[81 82] and diabetes.[83] In particular, the incidence of melanoma is known to be twofold higher in patients with PD than among the general population.[84–86] In addition, the Australian population exhibits high rates of melanoma due to predominantly fair-skin populations living under high levels of ultraviolet radiation. Further investigation is needed to unravel the underlying mechanisms linking PD with melanoma. Although the prevalence estimates of

Table 5 Self-reported history of comorbidities in the study sample

Condition/disorder	n	%
Back problems	722	47.1
Constipation	533	36.1
Depression	514	33.6
High blood pressure	506	33.0
High cholesterol	430	28.1
Frequent acid reflux	377	24.6
Cold sores	336	21.9
Migraine	264	17.2
Anxiety	262	17.1
Melanoma	243	15.9
Sleep apnoea	241	15.7
Insomnia	202	13.2
Cancer	201	13.1
Asthma/COPD	194	12.7
Pneumonia	192	12.5
REM sleep behaviour disorder	177	11.6
Diabetes	156	10.2
Osteoporosis	126	8.2
Eczema	107	7.0

Sample n=1532.
COPD, chronic obstructive pulmonary disease; REM, Rapid Eye Movement.

common comorbidities in our cohort are higher than in the general population,[87–90] our results support the body of evidence that these particular conditions are substantially more common among individuals with PD and thus may share a common aetiology.

The study design and data analysis methods limitations warrant some cautions when interpreting our interim findings. Notably, our mailout targeted participants aged 40–75 years old regardless of their disease duration since onset. We acknowledge that a large proportion of PD cases have an onset above 75,[91] and thus, our selected age range could have led to a selection bias as many individuals with PD could have been missing from the study. It would be ideal to recruit and follow-up all patients at diagnosis or at least from the early stages of the disease. In future recruitment phases, we will prioritise the recruitment of older participants and employ other recruitment methods such as movement disorder clinics, patient support groups and a public media campaign.

Furthermore, although the 9% response rate in the pilot mailout is comparatively higher than similar studies targeted at individuals with depression, bipolar disorder, alcohol dependence and Alzheimer's disease,[92] it remains low and susceptible to selection bias. In the next stage of our study, we plan to compare the background characteristics of participants recruited through different recruitment channels to identify differences in response rates and potential selection biases. This will also help us identify the most efficient mode of recruitment.

The current pilot study did not have a comparator age-matched and sex-matched control cohort. We also hope to recruit unaffected controls via referral from PD participants in the future. We will ask each participant to invite one or two friends of the same sex and within a 10-year age range from similar regional and ethnic backgrounds but without PD.

Although most participants (97%) reported being diagnosed with PD by a neurologist or general practitioner, ideally, participants included in a PD study would have their diagnosis confirmed by case note review or in-person evaluation to validate the identification of PD, but this was not feasible in our pilot phase due to limited research funds and a large number of participants.

In summary, we report the baseline characteristics of the APGS pilot cohort. The APGS aims to characterise and improve our understanding of the sociodemographic, genetic and environmental basis of PD susceptibility, symptoms and progression in Australia. We used an innovative and highly efficient recruitment approach through assisted mailouts, establishing feasibility and laying the groundwork for expanding and extending the study's scale and reach in the future. The results of this study will provide an important opportunity for generating evidence on the epidemiology and genetic aetiology of PD in the country. Ultimately, a more extensive representation of diverse Australian participants in worldwide PD studies may lead to a better understanding of the causes of PD and help in the discovery and validation of novel therapeutic targets and the development of new therapies and interventions to prevent, stop or modify the clinical course of PD in Australia and the rest of the world.

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Competing interests CRS has collaborated with Pfizer, Opko, Proteome Sciences, Genzyme; has consulted for Genzyme; has served as Advisor to the Michael J. Fox Foundation, NIH, Department of Defense; is on the Scientific Advisory Board of the American Parkinson Disease Association; has received funding from the NIH, the U.S. Department of Defense, the Harvard NeuroDiscovery Center, the Michael J. Fox Foundation and American Parkinson Disease Association.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by QIMR Berghofer Medical Research Institute's Human Research Ethics Committee (P3711). Participants gave informed consent to participate in the study before taking part.

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