

1 **Risk factors associated with Parkinson's disease: An 11-year population-based South**
2 **Korean study**

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34

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37

38 **ABSTRACT**

39 **Objective:** To validate various known risk factors of Parkinsonism and to establish basic
40 information to formulate public health policy by using a 10-year follow-up cohort model.

41 **Methods:** This population based nation-wide study was performed using the National Health
42 Insurance Database of reimbursement claims of the Health Insurance Review and Assessment
43 Service of South Korea data on regular health check-ups in 2003 and 2004, with 10 years'
44 follow-up.

45 **Results:** We identified 7,746 patients with Parkinsonism. Old age, hypertension, diabetes,
46 depression, anxiety, taking statin medication, high body mass index, non-smoking, non-
47 alcohol drinking, and low socioeconomic status were each associated with an increase in the
48 risk of Parkinsonism (fully adjusted Cox proportional hazards model: hazard ratio (HR) 1.259,
49 95% confidence interval (CI) 1.194–1.328 for hypertension, HR 1.255, 95% CI 1.186–1.329
50 for diabetes, HR 1.554, 95% CI 1.664–1.965 for depression, HR 1.808, 95% CI 1.462–1.652
51 for anxiety, and HR 1.157, 95% CI 1.072–1.250 for taking statin medication).

52 **Conclusions:** In our study, old age, depression, anxiety, and a non-smoker status were found
53 to be risk factors of Parkinsonism, in agreement with previous studies. However, sex,
54 hypertension, diabetes, taking statin medication, non-drinking of Alcohol, and lower
55 socioeconomic status have not been described as risk factors in previous studies and need
56 further verification in future studies.

57

58 **Key words:** National Health Programs, Parkinsonism, Risk factor, Socioeconomic Status

59

60 Parkinsonism is one of the most common neurodegenerative diseases, affecting > 1% of the
61 elderly population.¹ With the marked increase in the mean age of the global population, the
62 prevalence and incidence of Parkinsonism have also increased.² The impact of Parkinsonism
63 on society is a major concern worldwide, including in South Korea. Many genetic risk factors
64 have been discovered in recent years,³ but these account for only a minor portion of
65 Parkinsonism, as the disease etiology involves an interplay of both genetic and environmental
66 factors. Most of these factors remain unknown; thus, investigating the distribution and
67 characteristics of the condition is important for identifying further etiologic factors and
68 planning public health policies.⁴

69 In South Korean, medical care is delivered via the National Health Insurance Service (NHIS)
70 in which most people are obligated to enroll. All medical health insurance-related data are
71 collected into a central database. Additionally, South Koreans receive regular health check-
72 ups with the support of the National Health Insurance Corporation (NHIC) after the age of 40
73 years. Many studies have investigated the relationship between Parkinsonism and some
74 probable risk factors.⁵⁻⁸ These include increasing age,⁵ alcohol-use disorder,⁶ urbanization
75 and exposure to pesticides,⁹ cardiovascular changes,⁷ depression¹⁰, and anxiety,¹¹ while
76 smoking has been proven to a preventative factor against development of Parkinsonism.^{12,13}
77 However, the relationship between socioeconomic status and the onset of Parkinsonism is
78 unknown.

79 We hypothesized that the relationship of known risk factors and socioeconomic status with
80 the onset of Parkinsonism could be determined using data from both the regular health check-
81 up and health insurance databases of South Korea. We therefore sought to validate the role of
82 various known risk factors for Parkinsonism and to establish a basis for formulating a public
83 health policy, using an over 10-year follow-up cohort model.

84

85 **METHODS**

86 **Statement of Ethics.** This research project was approved by the NHIS of South Korea
87 (NHIS-2017-2-542). This study was approved by the Institutional Review Board of our
88 hospital and adhered to the tenets of the Declaration of Helsinki. The need for obtaining
89 informed consent was waived. All authors contributed to the study design, results
90 interpretation, and the decision to submit the manuscript for publication. No commercial
91 support was obtained for this study.

92

93 **Database.** The management of the NHIS is divided into two independent institutions: the
94 NHIC and Health Insurance Review and Assessment Service of Korea (HIRA). The NHIC
95 has accumulated data (National Health Insurance Database; NHID) of the insured person,
96 premium imposition, and regular health check-up, while HIRA has accumulated data on
97 health insurance claims, which are accompanied by data regarding diagnostic codes,
98 procedures, prescribed medication, personal information, information about the hospital, the
99 direct medical costs of both inpatient and outpatient care, and dental services.¹⁴ Therefore, we
100 utilized the combined data from the NHIC database of regular health check-ups in 2003 and
101 2004, and the HIRA database of reimbursement claims from 2003 to 2013.

102 Blue-collar workers can undergo annual health check-ups, while white-collar workers and
103 self-employed individuals, such as independent businessmen, farmers, fishermen, housewives,
104 and retirees, can do so every other year. The following are regular health check-up items:

- 105 1. Body index measurements: height, body weight, waist circumference, body mass index
106 (BMI).
- 107 2. History: smoking, alcohol use, and medication history. Medication history includes the
108 drugs used for hypertension, diabetes, and hyperlipidemia.

109 3. Screening test: visual, hearing, oral hygiene, and laboratory tests (total cholesterol,
110 aspartate aminotransferase, alanine aminotransferase, gamma-guanosine triphosphate,
111 fasting blood glucose, urine protein, plasma creatinine, hemoglobin), and chest X-rays
112 were performed.

113 After the first health check-up, patients suspected of hypertension or diabetes mellitus (DM)
114 undergo a second health check-up.

115

116 **Study Sample.** NHIS and HIRA use the Korean Classification of Diseases (KCD) as disease
117 classification codes; these are modified from the International Classification of Diseases. Of
118 the 5,147,950 people who underwent regular health check-ups from 2002 to 2003, 10% were
119 randomly selected (514,795 subjects) for inclusion in this study.

120 Based on HIRA data, we defined patients with Parkinsonism as those who had KCD codes
121 for Parkinsonism or Parkinson disease (not-otherwise-specified, idiopathic, primary) (G20).
122 We excluded the codes for secondary Parkinsonism (G21) and Parkinsonism in disease
123 classified elsewhere (G22).

124

125 **Definition of Risk factors.** We defined the following as risk factors: age, hypertension, DM,
126 alcohol drinking, smoking, socioeconomic status, statin medication use, depression, and
127 anxiety. Risk factors were assigned according to the presence of codes in health insurance
128 claims: hypertension (I10 to I15), DM (E10 to E14), depression (F32, F33), and anxiety (F40
129 or F41). Statin medication use was defined by drug codes for statins in the health insurance
130 claims.

131 Based on the Asian standard, BMI was classified into five grades, i.e., < 18.5 as
132 underweight, 18.5–22.9 kg/m² as normal, 22.9–24.9 kg/m² as overweight, 25–29.9 kg/m² as
133 moderately obese, and 30–35 kg/m² severely obese. Smoking history was classified into non-

134 smokers, ex-smokers, current smokers. Drinking history was divided into the following five
135 grades: no drinking, drinking 1–2 times a week, 2–3 times a week, 3–4 times a week,
136 drinking virtually daily.

137

138 **Classification of socioeconomic status by health insurance premium rate.** We assumed
139 that the health insurance premium rate reflects the socioeconomic status of subjects. The
140 health insurance premium payment was divided into three types: “self-employed insured,”
141 “employed insured,” and Medicaid. Medicaid provides medical care for old or disabled
142 individuals who have little income or property. The population on Medicaid pays a part or
143 none of their medical bills, although there are regulations and legal limits to the use of the
144 medical system.

145 The premium rate of employees is set by a standard that is based on their monthly salary,
146 but as the income of self-employed individuals could not be determined exactly, their
147 premium rate is set according to conversion points that include the insurance holder’s
148 property, such the cost of their house, whether they possess a car, economic activity by age
149 and sex, and total income.

150 The health insurance premium rate is divided into 10 quantiles for each type of premium
151 payment. We divided socioeconomic status into nine groups according to the premium
152 payment system (self-employed, employed, Medicaid) and premium rate (four grades) (Table
153 1).

154

155 **Data processing and statistical analysis.** We created a 10-year follow-up cohort model for
156 random sampling of 10% of all subjects enrolled in regular health check-ups in 2002 and
157 2003 (Figure 1). We defined Parkinsonism onset by the presence of a Parkinson’s disease
158 diagnostic code (G20) for the main or second disease in health insurance claims.

159 Descriptive statistics of the study populations are presented, and chi-square tests were
160 performed to examine the association of risk factors with Parkinsonism. Adjusted hazard
161 ratios (HRs) and 95% confidence intervals (CI) were calculated using multivariate Cox
162 proportional hazard regression. A significance level of 0.05 was selected. SAS for Windows,
163 version 9.2 (SAS Inc, Cary, NC, USA) was used to perform statistical analyses.

164

165 **RESULTS**

166 Table 2 shows the demographic data and the incidence of Parkinsonism in each group
167 among subjects who underwent regular health check-ups in 2002 and 2003. The HRs of the
168 subjects aged 50–59, 60–69, 70–79, and 80 years or older were 3.101, 8.958, 14.709, and
169 16.797, respectively, and statistically significant ($p < 0.0001$). When comparing the sexes, the
170 HR of females was 0.971, which was statistically insignificant ($p = 0.3273$) (Table 3). In
171 cases with hypertension, DM, depression, and anxiety, the HRs were 1.259, 1.255, 1.554, and
172 1.808, respectively, ($p < 0.0001$). The HR of the group taking statins was 1.157, which was
173 higher than that of the group not taking statins at the time of diagnosis.

174 The risk of Parkinsonism was higher in the highest BMI group than in the normal weight
175 group ($p < 0.0001$). The HRs of ex-smokers and current smokers were the same (0.920), but
176 was statistically significant only for current smokers. ($p < 0.0287$). The HRs of all alcohol-
177 drinking groups were < 1 and were statistically significant ($p < 0.0001$), except for the daily
178 alcohol-drinking group ($p = 0.6530$). As Medicaid was set as the standard, the HR was < 1 in
179 all groups ($p < 0.05$), indicating that socioeconomic status and Parkinsonism were closely
180 related.

181

182 **DISCUSSION**

183 The results of our study revealed that increasing age, hypertension, DM, depression, anxiety,

184 extreme overweight, statin medication use, non-smoking, non-alcohol drinking, and the
185 lowest socioeconomic class were statistically related to the onset of Parkinsonism.

186 Parkinsonism is the second most neurodegenerative disease, and its incidence has been
187 reported to increase with age in all studies.⁴ In our study, there was no difference in the
188 incidence of Parkinsonism between the sexes, but one review has reported that males have a
189 1.5- to 2-fold increased risk of developing Parkinsonism than that of females.⁴ However,
190 some large population-based cohort studies on sex and Parkinsonism have been inconsistent.
191 One study reported that men are more prone to Parkinsonism than women,⁵ and another
192 found the opposite,¹⁵ whereas other studies found no role for sex.^{5, 15, 16} Therefore, a meta-
193 analysis including large population-based cohort studies is necessary to evaluate the
194 incidence of Parkinsonism according to sex.

195 Hypertension can cause ischemic cerebrovascular lesions that involve dopaminergic or non-
196 dopaminergic subcortical structures. It also can cause hypertensive vasculopathy in basal
197 ganglia, which may injure the dopaminergic cells in the pars compacta and cause
198 Parkinsonism by breaking the neuronal connections between the substantia nigra and
199 putamen, or by decreasing expression of the β -2, α -4 subunit of the nicotinic acetylcholine
200 receptor that activates the dopaminergic pathways.¹⁷ However, most studies related to
201 hypertension and the Parkinsonism incidence yielded results contrary to our findings^{7, 13, 18, 19}
202 or showed no relationship between hypertension and Parkinsonism development.²⁰ This is
203 considered to be related to the pathophysiology and progress of Parkinsonism. Autonomic
204 nervous system dysfunction is a very common feature in Parkinsonism.¹⁹ Loss of sympathetic
205 cardiac innervation in Parkinsonism causes changes in cardiovascular physiology, which may
206 precede Parkinsonism diagnosis.^{7, 21, 22} Because the Lewy body pathology involves the dorsal
207 motor nucleus of the vagus nerve,²³ parasympathetic tone may become dysregulated, leading
208 to orthostatic hypotension and decreased heart rate variability, which are typical of autonomic

209 dysfunction in Parkinsonism.²⁴

210 We found DM to be a risk factor for the development of Parkinsonism. Cross-sectional
211 studies are limited in their ability to prove causality, and have not yielded concordant results.
212 In one study, patients with Parkinsonism were more likely to have DM, but another study
213 showed opposite results.^{19, 25} However, one large 18-year prospective cohort study reported
214 that type 2 DM was a risk factor for Parkinsonism development, consistent with our
215 findings.²⁶ Although the relationship between diabetes and Parkinsonism is unclear, animal
216 and in vitro studies have shown that insulin and brain dopaminergic activity are interrelated.²⁷
217 Thus, insulin dysregulation and the change in insulin action are assumed to affect the
218 pathophysiology and clinical symptoms of Parkinsonism. However, hypertension and DM
219 also increase with aging, as does Parkinsonism (excluding childhood type 1 DM and
220 secondary hypertension in the young). Therefore, we assume that hypertension and DM are
221 risk factors for development of Parkinsonism.

222 Depression and anxiety are well-known, common, non-motor symptoms of Parkinsonism.¹⁰
223 Depression is an early marker of Parkinsonism pathogenesis; significant involvement of
224 dopaminergic neurons in the substantia nigra^{10, 28} and anxiety are early symptoms of
225 Parkinsonism and are known to involve noradrenergic and serotonergic neurons in the
226 brainstem.²⁹ Previous studies have shown that depression and anxiety are significantly
227 associated with Parkinsonism.^{9, 10, 18, 20, 28} However, except for one cohort study,³⁰ these were
228 cross-sectional studies,^{9, 10, 18, 20, 28} which make it difficult to distinguish between risk factors
229 for the onset of Parkinsonism and non-motor symptoms of Parkinsonism. Nevertheless, our
230 study proved that depression and anxiety are risk factors for Parkinsonism.

231 Cholesterol is abundant in the central nervous system and plays an important protective role
232 against the early development of Parkinsonism. Higher serum cholesterol and serum
233 triglyceride levels have been reported to reduce the risk of Parkinsonism.³¹ Statin is a 3-

234 hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor of cholesterol synthesis.³² Similar
235 to our findings, a previous prospective study also demonstrated that statin use significantly
236 increased the risk of Parkinsonism. However, the findings on statin medication and
237 development of Parkinsonism have been inconsistent.^{33,34} Most of these studies were cross-
238 sectional and retrospective, making it difficult to identify causal relationships, but a recent
239 meta-analysis reported that statin medication was associated with a lower risk of developing
240 Parkinsonism.³⁵

241 Obesity is a well-known risk factor for metabolic and vascular disorders, such as type 2 DM,
242 coronary heart disease, and stroke.³⁶ Therefore, obesity is suspected as a risk factor for
243 Parkinsonism; this study showed that severe obesity elevated the risk of Parkinsonism
244 significantly. The underlying mechanism may involve reduced availability of dopamine D2
245 receptor in the striatum of obese than non-obese individuals.¹¹ However, a meta-analysis
246 reported that higher BMI did not increase Parkinsonism risk;³⁶ thus the relationship between
247 obesity and the risk of Parkinsonism remains controversial.³⁷

248 Smoking is a powerful risk factor for hypertension, atherosclerosis, and ischemic and
249 hemorrhagic stroke, but is a well-established preventative factor for Parkinsonism, as also
250 found in our study. Non-smokers more frequently developed Parkinsonism than ex-smokers
251 and current smokers.^{12, 13, 18, 22, 28, 37} Smoking increases dopamine activity by reducing MAO-
252 B activity.^{12, 28} Cytochrome P-450 family members are responsible for the metabolism and
253 detoxification of environmental toxins that cause dopaminergic neural damage. Cytochrome
254 P-450 is induced by smoking, due to the polycyclic hydrocarbons, such as benzopyrene,
255 present in cigarette smoke.^{12, 38}

256 In our study, the risk of Parkinsonism was statistically significantly reduced in all alcohol-
257 drinking groups, except for the daily alcohol-drinking group, as compared with the non-
258 alcohol drinking group.³⁹ One study reported that alcohol drinking was associated with

259 increased risk of Parkinsonism,³⁷ while the results of other studies were similar to ours.^{13, 18}

260 One review article concluded that a weak protective association was more likely to be found
261 between alcohol drinking and Parkinsonism risk in studies at greater risk of selection and
262 recall bias. One study found that the risk of Parkinsonism was elevated in patients with
263 alcohol-abuse disorder,⁶ while our study showed that there was no lowered risk of
264 Parkinsonism in the daily alcohol-drinking group. Therefore, taken together, it is likely that
265 appropriate alcohol consumption is associated with lowered Parkinsonism risk.

266 One study reported that the incidence of Parkinsonism was not affected by socioeconomic
267 status.⁵ However, we found that the Parkinsonism risk was reduced in all health insurance
268 payment groups, as compared to the Medicaid group. This is probably because the standards
269 for determining socioeconomic status differed in the two studies, and Medicaid subscribers in
270 South Korea are mainly old individuals with no economic capacity.

271 The strengths of our study are that we used a nationwide 10-year follow-up cohort model
272 with a population > 500,000, and that the data are relatively objective and accurate, based on
273 regular health check-up data and disease diagnostic codes from HIRA. HIRA reviews claims
274 with disease codes to determine whether reimbursements are clinically valid. Thus, HIRA can
275 maintain the quality of health care and provide the standard medical service guidelines for
276 each disease. There is little chance that medical records were duplicated or omitted, because
277 all Korean residents receive a unique identification number at birth, which is used in medical
278 claims. Moreover, the relationship between the onset of Parkinsonism, various comorbidities,
279 body indexes, and various known risk factors could be verified simultaneously in the present
280 study. We also assessed socioeconomic status based on health premium payment methods. As
281 we used a retrospective cohort model, rather than a cross-sectional study, our data are useful
282 for identification of causality.

283 The study had the following limitations: subjects < 40 years old were excluded, because the

284 subjects reporting for regular health check-up are ≥ 40 years In a general multicenter
285 prospective cohort study, the same diagnostic criteria are used for data collection; however,
286 since the nationwide data cohort model uses a health insurance-related database, it is very
287 likely that the same diagnostic criteria were not applied. Smoking, BMI, and premium
288 payment type are not fixed, but may have changed during the follow-up period. If an
289 employee becomes unemployed or starts his or her business, the payment system will change
290 from Employed-insured to Self-insured, and in extreme cases, if the insurance holder has no
291 earned income or property, the premium payment form may change to Medicaid.

292

293 **Conclusion**

294 As previously reported, we found increasing age, depression, anxiety, and non-smoker status
295 to be risk factors for Parkinsonism. However, sex, hypertension, DM, statin medication use,
296 alcohol drinking, and lower socioeconomic status were also identified as risk factors, but
297 have not been reported as such in previous studies, and thus require verification in future
298 studies. Moreover, the known risk factors of Parkinsonism and socioeconomic status based
299 on the NHID has not been reported for South Korea previously. By comparing these findings
300 with the results of studies in other countries, insights into the pathophysiology and
301 epidemiology of Parkinsonism may be gained, and the results may facilitate formulation of a
302 Korean public health policy. To verify additional risk factors of Parkinsonism, it is necessary
303 to perform studies in which NHID data and genetic and environmental factors are combined.

304

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403

404

405 Table 1. Classification of socioeconomic class by health insurance premium standard (mean
406 values from 2002 to 2003)

407

Classification	Income	Employed Insured	Self-employed Insured
	Quantile	KRW (US Dollar)	KRW (US Dollar)
Group 1	10	843,945 (703.29)	982,721 (818.93)
	9	569,525 (474.60)	590,686 (492.23)
Group 2	8	384,443 (320.36)	366,403 (305.34)
	7	259,505 (216.25)	227,161 (189.30)
	6	182,225 (151.85)	140,893 (117.41)
Group 3	5	128,145 (106.79)	93,892 (78.24)
	4	83,720 (69.77)	64,603 (53.84)
Group 4	3	49,345 (41.12)	40,541 (33.78)
	2	24,625 (20.52)	29,120 (247.27)
	1	9,945 (8.29)	8,531 (7.11)

408 *1\$ = 1200 Korean Won Rate

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410 Table 2. Demographic data and the incidence of Parkinsonism

Group	Subjects with Parkinsonism	Subjects without Parkinsonism	Incidence (%)
Age (years)			
40-49	648	224,862	0.13
50-59	1,478	144,470	0.29
60-69	3,447	101,583	0.67
70-79	2,088	34,265	0.41
>80	85	1,322	0.02
Total	7,746	506,502	1.51
Sex			
Men	3,574	275,276	0.69
Women	4,172	231,226	0.81
Hypertension			
Yes	3,917	132,388	0.76
No	3,829	374,114	0.74
Diabetes			
Yes	2,096	67,667	0.41
No	5,650	438,835	1.10
Depression			

Yes	1,200	24,302	0.23
No	5,258	399,874	1.24
Anxiety			
Yes	1,863	51,437	0.36
No	5,883	455,065	1.14
Statin			
Yes	938	32,537	0.18
No	6,808	473,965	1.32
BMI			
< 18.5	181	9,659	0.04
18.5–22.9	2,108	149,450	0.50
23.0-24.9	1,681	115,366	0.40
25.0-29.9	2,007	133,134	0.47
30.0-39.9	188	11,463	0.04
Smoking history (number of missing data = 21,740)			
Non-Smoker	5,691	324,584	1.16
Ex-smoker	532	43,134	0.11
Current smoker	1,217	117,350	0.25
Alcohol use history (numbers of missing data = 21,740)			

No	5,393	280,322	1.07
2-3 times/month	735	76,330	0.15
1-2 times/week	703	82,950	0.14
3-4 times/week	344	35,314	0.07
Daily	390	22,069	0.08
Socioeconomic status			
Medicaid	39	1,006	0.01
Self-employed insured grade 1	1,136	38,514	0.22
Self-employed insured grade 2	1,004	51,036	0.20
Self-employed insured grade 3	1,009	70,598	0.20
Self-employed insured grade 4	448	29,787	0.09
Employed-insured Grade 1	839	75,401	0.16
Employed-insured Grade 2	767	65,357	0.15
Employed-insured Grade 3	1,649	113,355	0.32
Employed-insured Grade 4	855	614,448	0.17

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413 Table 3. Hazard ratios of known risk factors of Parkinsonism

Variables	HR	95% Hazard Ratio Confidence Limits	P Value
Age			
40s	1		
50s	3.101	2.808-3.423	<.0001
60s	8.958	8.167-9.826	<.0001
70s	14.709	13.319-16.244	<.0001
80s	16.797	13.112-21.518	<.0001
Sex			
Male	1		
Female	0.971	0.914-1.030	0.3273
Comorbidities			
Hypertension	1.259	1.194-1.328	<.0001
DM	1.255	1.186-1.329	<.0001
Depression	1.808	1.664-1.965	<.0001
Anxiety	1.554	1.462-1.652	<.0001
Statin	1.157	1.072-1.250	0.0002
BMI			
18.5-22.9	0.933	0.808-1.078	0.3458
<18.5	1.017	0.956-1.083	0.5906

23.0-24.9	1.005	0.946-1.067	0.8739
25.0-29.9	0.932	0.806-1.078	0.3452
30.0-39.9	1.878	1.746-2.021	<.0001
Smoking History			
Non-Smoker	1		
Ex-smoker	0.920	0.831-1.018	0.1062
Current Smoker	0.920	0.854-0.991	0.0287
Alcohol Drinking History			
Non-Alcohol Drinker	1		
Drinking 2-3 times per month	0.868	0.797-0.946	0.0012
Drinking 1-2 times per week	0.810	0.740-0.887	<.0001
Drinking 3-4 times per week	0.803	0.710-0.908	0.0005
Drinking- almost everyday	0.974	0.869-1.092	0.6530
Economic status			
Medicaid	1		
Self-employed insured grade 1	0.571	0.414-0.788	0.0007
Self-employed insured grade 2	0.584	0.422-0.807	0.0011
Self-employed insured grade 3	0.544	0.393-0.751	0.0002
Self-employed insured grade 4	0.502	0.359-0.701	<.0001
Employed-insured Grade 1	0.453	0.327-0.627	<.0001

Employed-insured Grade 2	0.518	0.374-0.717	<.0001
Employed-insured Grade 3	0.564	0.409-0.776	0.0004
Employed-insured Grade 4	0.553	0.400-0.766	0.0004

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415 **Figure Legend**

416 Figure 1. Flowchart of the study design

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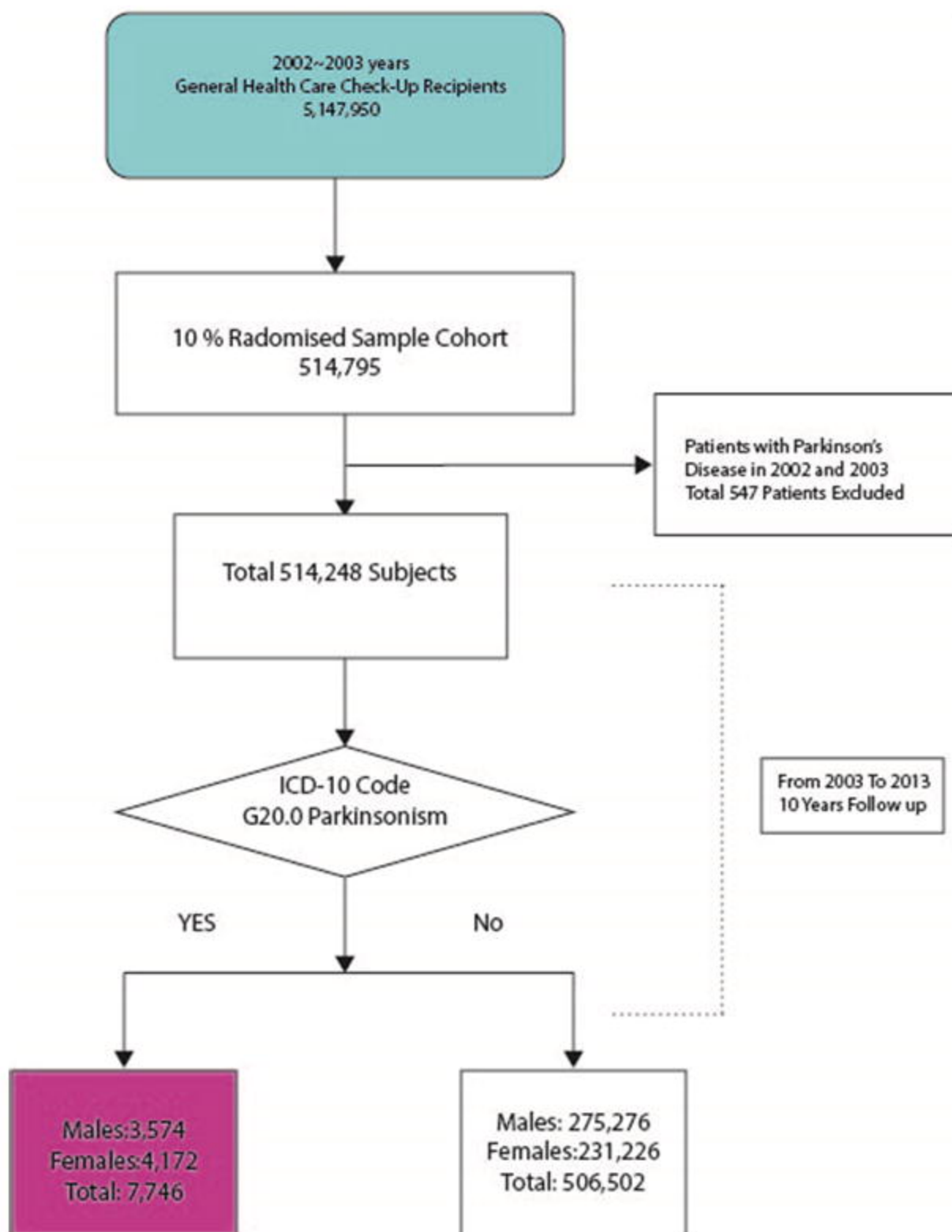


Figure 1