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Association between depression and risk of Parkinson's disease in South Korean adults

Wonjeong Jeong [a,b], Hyunkyu Kim [b,d], Jae Hong Joo [a,b], Sung-In Jang [b,c], Eun-Cheol Park [b,c,*]

[a] Department of Public Health, Graduate School, Yonsei University, Seoul, Republic of Korea
[b] Institute of Health Services Research, Yonsei University, Seoul, Republic of Korea
[c] Department of Preventive Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea
[d] Department of Psychiatry, Yonsei University College of Medicine, Seoul, Republic of Korea

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ABSTRACT

Background: Depression is considered a predictive factor for cognitive impairments. At the same time, Parkinson's disease (PD) is a growing public health problem. The aim of this study is to examine the association between depression and PD risk among South Korean adults.

Methods: Data from 21,766 participants aged over 40, derived from the National Health Insurance Service National Sample Cohort (2002–2013), were included. Propensity score matching (1:1) was used to match participants with and without depression (case: 10,875, control: 10,875). The dependent variable was PD risk. A Cox proportional hazards regression model was built to analyze the associations between variables.

Results: People with depression had a higher risk of PD than those without depression (hazard ratio (HR) = 1.61, 95% confidence interval (CI) = 1.26–2.06). Among individuals with disabilities, those with depression had a higher risk of PD (HR = 2.31, 95% CI = 1.08–4.94). According to the Charlson Comorbidity Index (CCI) score, those with depression had a higher risk of PD than their counterparts (CCI score $\geq$ 5: HR = 1.63, 95% CI = 1.21–2.20).

Limitations: The limitations include the inability to 1) explore factors such as smoking and drinking status, which could be related to PD risk and 2) identify undiagnosed PD that already existed at the time of diagnosis of depression.

Conclusions: The results suggest that having depression places individuals at a higher risk of PD. Interventions to alleviate the risk of PD should focus on adequate depression management.

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease (Aarsland et al., 2012; Nam et al., 2018). The degeneration of dopaminergic neurons in the brain is considered to play a key role in the development of Parkinson's diseases (Mamelak, 2018). These neurons are vulnerable to degeneration because of their extensive branching and the large amounts of energy required to send nerve signals along this extensive network (Alonso et al., 2009; Mamelak, 2018). PD affects more than 1% of the global older adult population, and this rate is on the rise (Aarsland et al., 2012). Given the current trend of population aging, this disease is expected to affect over nine million people by 2030 (Nam et al., 2018). Even in South Korea, the incidence of PD has been increasing, from 41.4 per 100,000 people in 2004 to 142.5 in 2013, an average increase of 13.2% per year (Lee et al., 2017; The Korean Movement Disorder Society, 2017a). One of the reasons for this rapid increase may have been the aging society; however, PD itself is difficult to diagnose, and the advances in technology may have led to more diagnoses (The Korean Movement Disorder Society, 2017b). Considering that the per-patient medical expense of PD is twice as high as for other diseases, reducing its burden by preventing the need for treatment of modifiable risk factors has strong significance.

In the context of the global burden of disease, depression is a major contributor (World Health Organization, 2020). Specifically, in 1990, depression ranked fourth globally in disability-adjusted life years, and

* Corresponding author at: Department of Preventive Medicine & Institute of Health Services Research, Yonsei University College of Medicine, 50 Yonsei-ro, Seodaemun-gu, Seoul 03722, Republic of Korea.
E-mail address: ecpark@yuhs.ac (E.-C. Park).

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was projected to rank second after ischemic heart disease by 2020 (Chang et al., 2012). In South Korea, depression has become a major public health problem; between 2002 and 2013, there was a rise in prevalence from 2.8% to 5.3%. Considering the taboo surrounding those experiencing or seeking medical help for depression, the prevalence is likely to be underestimated (Kim et al., 2020b). Moreover, as depression is a major risk factor for suicidal mortality in the general population, treatment should be prioritized (Kim et al., 2020b).

There are reports of depression increasing the subsequent risk of many physical illnesses (Shen et al., 2013) such as cancer (Chen and Lin, 2011) and stroke (Li et al., 2012). Further, depression is highly associated with an increased risk of developing cognitive impairments like Alzheimer's disease and PD (Caraci et al., 2010). Depression has also been reported to be not only one of the most common symptoms of PD, with an average prevalence of approximately 40%, but also a factor that could worsen PD (VanderHoek et al., 2011). One study showed that taking antidepressants could place individuals at risk of developing PD (Alonso et al., 2009). However, in other studies, antidepressant use was not an independent risk factor for PD; on the contrary, depression itself increased the risk of PD because of the associated reduction in physical activity and lower level of healthcare (Bica et al., 2017; Shen et al., 2013).

Therefore, it is necessary to investigate the association between depression and the risk of PD to demonstrate the importance of managing the latter to prevent premature mortality. We hypothesized that people with depression are at a higher risk of PD than those who do not have depression. Consequently, the current study examined the association between depression and the risk of PD among South Korean adults.

2. Methods

2.1. Data and sample

The data for this study were obtained from the 2002–2013 National Health Insurance Service National Sample Cohort (NHIS-NSC). The NHIS-NSC data include all medical claims from 1,025,340 individuals, which accounts for 2% of the South Korean population, by random sampling. Individuals over the age of 40 years were included in the study. The year 2002 was designated as the washout period to prevent effects of other existing diseases, which might influence the results associated with the hypothesized relationship (Kang et al., 2018). To select those who were newly diagnosed with PD, we removed those who suffered from PD in 2003 and 2004. We selected individuals who had depression without PD in 2003 and 2004 as a case group. We also excluded those who were found to have PD within one year after depression, to avoid reverse causality. We then performed 1:1 propensity score matching (matching variables: age, sex, social security, and income) to include those without depression as a control group. Consequently, a total of 21,750 individuals were included in the final study (case: 10,875, control: 10,875). All data are available in the database of the Korean National Health Insurance Sharing Service (https://nhiss.nhis.or.kr) and can be accessed upon reasonable request.

2.2. Ethical considerations

This study was based on routinely collected administrative and claims data. All individuals provided written informed consent at the time of data collection by the NHIS-NSC. This study was reviewed and approved by the International Review Board of Yonsei University's Health System (IRB number: 4-2021-0159) and adheres to the tenets of the Declaration of Helsinki. As the NHIS-NSC data do not contain any identifying information, additional approval was not required.

2.3. Variables

The risk of PD (International Classification of Diseases, 10th revision (ICD-10) code: G20) was the dependent variable. Individuals with drug-induced parkinsonism were not included. Only the data of people newly diagnosed with PD after 2006 were included in this study.

The primary independent variable was the diagnosis of depression (ICD-10: F32, F33) compared to the general population. Depression was categorized into no depression, mild depression (ICD-10: F32.0, F33.0), moderate depression (ICD-10: F32.1, F33.1), severe depression (ICD-10: F32.2, F32.3, F33.2, F33.3), and unspecified depression. Additionally, the analyses included age, social security, income, region, disability, Charlson Comorbidity Index (CCI) score, and diabetes (ICD-10: E10, E11) (Sundararajan et al., 2004).

Social security was categorized into health insurance (corporate, regional)and medical aid. The social security system in South Korea, the National Health Insurance System, covers the entire population residing within the territory of Korea except for beneficiaries of medical aid (National Health Insurance Services, 2015). The source of financing is mainly contributions from the insured and subsidies from the government. Moreover, the medical aid program is financed by both the central and local governments and is part of the Korean public assistance system (National Health Insurance Services, 2015). The government plays a direct insurance role for the poor. Therefore, the Korean government offers the medical aid program for people unable to pay for their own healthcare coverage. Disability was categorized as individuals who were registered as disabled on the NHIS information database and those who were not (National Health Insurance Service National Sample Cohort, 2017). The CCI index was calculated by attaching weights and scoring comorbid conditions using Quan's method, with additional points added to consider comorbidities that affect patients' health outcomes (Lee et al., 2020; Quan et al., 2011).

2.4. Statistical analysis

The chi-square test was used to investigate the general characteristics of the study population. A Cox proportional hazards regression model was used to calculate the association between depression and the risk of PD. Differences were considered statistically significant with a p-value < 0.05. All data analyses used SAS 9.4 software (SAS Institute Inc., Cary, NC, USA).

3. Results

Table 1 presents the general characteristics of the study population. Among the 21,750 participants, 303 (1.4%) had PD. The relationship between depression and the risk of PD was statistically significant.

Table 2 shows the association between depression and the risk of PD after controlling for all covariates. Individuals with depression had a higher risk of PD than those without depression (hazard ratio [HR] = 1.6, 95% confidence interval [CI] = 1.26–2.06). The risk of PD increased with age (61–70 years: HR = 3.92, 95% CI = 2.73–5.63, > 71 years: HR = 4.38, 95% CI = 3.07–6.25). Individuals with disabilities had a higher risk of PD compared to those without disabilities (HR = 1.37, 95% CI = 1.03–1.84). Moreover, the risk of PD increased with increasing CCI score (CCI score: 3–4: HR = 2.26, 95% CI = 1.40–3.63; CCI score ≥5: HR = 5.75, 95% CI = 3.70–8.94).

Table 3 shows the results of subgroup analysis between depression and the risk of PD, focusing on sex, social security, disability, and CCI score. Male participants with depression had a higher risk of PD than those without depression (HR = 2.50, 95% CI = 1.57–4.00). Among individuals who received medical aid or were regional subscribers, those with depression had a higher risk of PD than those without (HR = 1.80, 95% CI = 1.35–2.42). Individuals with disabilities who had depression were at a higher risk of PD than those without depression (HR = 2.31, 95% CI = 1.08–4.94). According to the CCI score, those who had depression were at a higher risk of PD (CCI score ≥ 5: HR = 1.63, 95% CI = 1.21–2.20).

Table 4 shows the results of the association between the detailed

Table 1.
General characteristics of the study population according to the risk of Parkinson's disease.[a]

Variables	Total		Risk of Parkinson's Disease				*P*-value
			Yes		No		
Total	21,750	(100.0)	303	(1.4)	21,447	(98.6)	
Depression							< 0.0001
Yes	10,875	(50.0)	204	(1.9)	10,671	(98.1)	
No	10,875	(50.0)	99	(0.9)	10,776	(99.1)	
Sex							0.7762
Male	6,942	(31.9)	99	(1.4)	6,843	(98.6)	
Female	14,808	(68.1)	204	(1.4)	14,604	(98.6)	
Age							< 0.0001
41–60	11,552	(53.1)	44	(0.4)	11,508	(99.6)	
61–70	4,694	(21.6)	105	(2.2)	4,589	(97.8)	
≥ 71	5,504	(25.3)	154	(2.8)	5,350	(97.2)	
Social Security							< 0.0001
Insurance (Corporate)	8,772	(40.3)	79	(0.9)	8,693	(99.1)	
Insurance (Regional) & Medical Aid	12,978	(59.7)	224	(1.7)	12,754	(98.3)	
Income							0.1137
Low	3,912	(18.0)	53	(1.4)	3,859	(98.6)	
Middle	7,784	(35.8)	93	(1.2)	7,691	(98.8)	
High	10,054	(46.2)	157	(1.6)	9,897	(98.4)	
Region							0.4931
Metropolitan	8,789	(40.4)	124	(1.4)	8,665	(98.6)	
City	5,264	(24.2)	65	(1.2)	5,199	(98.8)	
Rural	7,697	(35.4)	114	(1.5)	7,583	(98.5)	
Disability							< 0.0001
Yes	2,111	(9.7)	60	(2.8)	2,051	(97.2)	
No	19,639	(90.3)	243	(1.2)	19,396	(98.8)	
Charlson Comorbidity Index							< 0.0001
0–2	7,364	(33.9)	23	(0.3)	7,341	(99.7)	
3–4	7,763	(35.7)	68	(0.9)	7,695	(99.1)	
≥ 5	6,623	(30.5)	212	(3.2)	6,411	(96.8)	
Diabetes							< 0.0001
Yes	144	(0.7)	9	(6.3)	135	(93.8)	
No	21,606	(99.3)	294	(1.4)	21,312	(98.6)	

[a] The matching variables were sex, age, social security, and income.

Table 2.
Results of the association between depression and the risk of Parkinson's disease.

Variables	Risk of Parkinson's Disease			
	HR	95% CI		
Depression				
Yes	1.61	(1.26	-	2.06)
No	1.00			
Sex				
Male	1.05	(0.82	-	1.35)
Female	1.00			
Age				
41–60	1.00			
61–70	3.92	(2.73	-	5.63)
≥ 71	4.38	(3.07	-	6.25)
Social Security				
Insurance (Corporate)	1.00			
Insurance (Regional) & Medical Aid	1.22	(0.91	-	1.64)
Income				
Low	1.00			
Middle	0.83	(0.59	-	1.18)
High	0.91	(0.65	-	1.27)
Region				
Metropolitan	1.00			
City	0.92	(0.68	-	1.24)
Rural	0.89	(0.69	-	1.16)
Disability				
Yes	1.37	(1.03	-	1.84)
No	1.00			
Charlson Comorbidity Index				
0–2	1.00			
3–4	2.26	(1.40	-	3.63)
≥ 5	5.75	(3.70	-	8.94)
Diabetes				
Yes	2.13	(1.09	-	4.15)
No	1.00			

Table 3.
Subgroup analysis of the association between risk of Parkinson's disease and covariates according to depression.

	Depression				
	Yes				No
	Adjusted HR	95% CI Lower		Upper	Adjusted HR
Sex					
Male	2.50	(1.57	-	4.00)	1.00
Female	1.36	(1.01	-	1.82)	1.00
Social Security					
Insurance (Corporate)	1.22	(0.77	-	1.94)	1.00
Insurance (Regional) & Medical Aid	1.80	(1.35	-	2.42)	1.00
Disability					
Yes	2.31	(1.08	-	4.94)	1.00
No	1.55	(1.19	-	2.01)	1.00
Charlson Comorbidity Index					
0–2	2.83	(1.17	-	6.86)	1.00
3–4	1.33	(0.81	-	2.18)	1.00
≥ 5	1.63	(1.21	-	2.20)	1.00

depression type and PD risk. While 569 (2.6%) participants had severe depression, 1538 (7.1%) had moderate and 4733 (21.8%) had mild depression. Individuals with mild or moderate depression were at a higher risk of PD than those without depression (mild depression: HR = 1.58, 95% CI = 1.18–2.13; moderate depression: HR = 1.76, 95% CI = 1.16–2.67). Moreover, those with unspecified depression had a higher risk of PD than those without depression (unspecified depression: HR = 1.71, 95% CI = 1.27–2.30).

Fig. 1 presents the results of the association between depression and the risk of PD according to the annual follow-up from diagnosis of

Table 4.
Results of association of detailed depression type and the risk of Parkinson's disease.

Variables	Total		Risk of Parkinson's Disease					
			Yes		No		HR	95% CI
Total	21,750	(100.0)	303	(1.4)	21,447	(98.6)		
Depression								
No	10,875	(50.0)	99	(0.9)	10,776	(99.1)	1.00	
Mild depression	4,733	(21.8)	83	(1.8)	4,650	(98.2)	1.58	(1.18-2.13)
Moderate depression	1,538	(7.1)	29	(1.9)	1,509	(98.1)	1.76	(1.16-2.67)
Severe depression	569	(2.6)	7	(1.2)	562	(98.8)	1.05	(0.49-2.27)
Unspecified depression	4,035	(18.6)	85	(2.1)	3,950	(97.9)	1.71	(1.27-2.30)

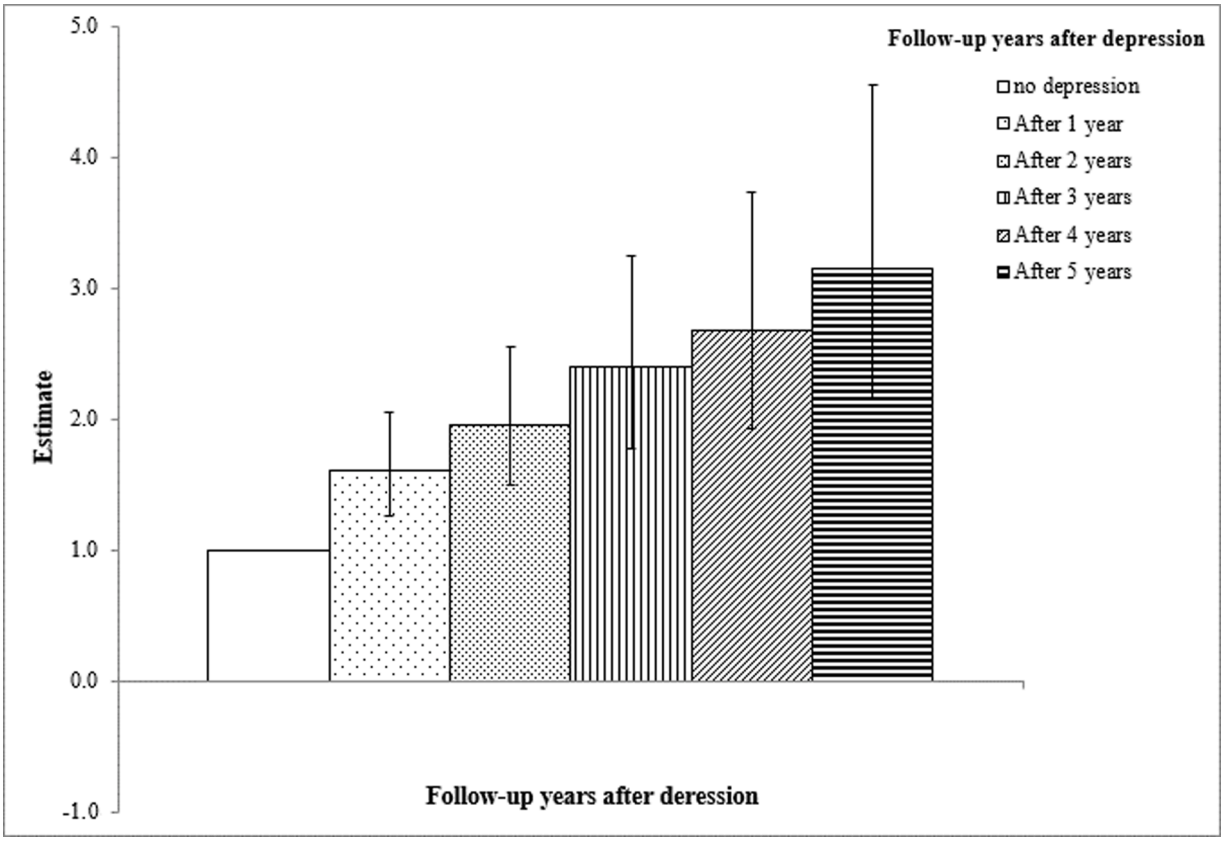

Fig. 1. Association between depression and risk of Parkinson's disease according to the years follow-up from diagnosis of depression.
Adjusted for age, sex, social security, income, region, disability, charlson comorbidity index, and diabetes. Whiskers in each bar represent error estimate of regression coefficients. Reference group is "No depression".

depression. Compared to those without depression, those who had a longer period till follow-up after the initial diagnosis of depression, had a higher risk of PD.

4. Discussion

Depression is the complex outcome of the interaction of many risk factors (Leentjens, 2015). It is the most common psychiatric disorder associated with PD (Leentjens, 2015; Schrag, 2006). Owing to the diminished quality of life of people with depression, under-diagnosed and under-treated depression lead to worsening of symptoms, which, in turn, might lead to PD (Menon et al., 2015). However, there is a paucity of studies that demonstrate PD's relationship with depression through comparisons between people with and without depression. Therefore, this study examined the association between depression and PD risk among South Korean adults.

Many people experience depression and anxiety prior to the onset of PD, which indicates that psychiatric conditions may be risk factors (Jacob et al., 2010). Depression and anxiety are significant non-motor symptoms in PD, as they may be associated with more rapid deterioration in cognitive and motor functions (Jacob et al., 2010; Uekermann et al., 2003). Since affective disorders can influence the morphological alteration of the raphe nuclei in the brainstem, depression could have a strong association with PD (Uekermann et al., 2003). In previous studies, people with depression had significantly greater cognitive decline compared to those without depression, displaying more severe impairment on tests of verbal auditory attention and fluency than the healthy controls (Kuzis et al., 1997; Uekermann et al., 2003). Nevertheless, depressive symptoms in PD often remain untreated, as an accurate assessment of depression and PD is difficult due to overlapping disease symptomatology and availability of multiple assessment tools and techniques (Early et al., 2017). Therefore, it is crucial to promptly recognize and adequately address depression to prevent the deterioration of psychological symptoms over time (VanderHoek et al., 2011).

Depression can be highly associated with PD in various dimensions. Biologically, there could be a genetic susceptibility. Other potentially

important factors include the pathophysiology of PD and medication use, and the social aspect, such as relational factors and past psychological trauma (Leentjens, 2015). The high prevalence of depression and anxiety in patients with PD before the onset of motor symptoms further supports a complex pathophysiological connection (MartínezMartín and Damián, 2010). Pathophysiological factors common to PD and other diseases occurred with a higher incidence after depression (Leentjens, 2015). Moreover, regarding social factors such as past psychological trauma, it is known that posttraumatic stress disorder (PTSD) is highly associated with neurodegenerative disorders such as Alzheimer's disease and PD (Chan et al., 2017). Exposure to extreme stress such as that in PTSD is associated with neuroanatomical change, which can induce alterations in the brain (Kibel and Drenjančević-Perić, 2008). Likewise, previous studies show that psychiatric symptoms such as psychosomatic disorders, anxiety, dysthymic disorder, and depression were highly associated with the development of PD (Bower et al., 2010; Nilsson et al., 2001; Shiba et al., 2000). Moreover, depression and anxiety are the early manifestations of PD (Cosci et al., 2015). Although there is a lack of evidence about depression directly affecting PD (Kibel and Drenjančević-Perić, 2008), it is clear that the depression and PD are strongly associated.

Unspecified depression is diagnosed when the clinician chooses not to specify the reason as the criteria are not met for a specific depressive disorder (Virginia Commission on Youth, 2017). Therefore, there is insufficient information to design more specific treatments, which could involve wrongly inferring low severity and, therefore, discourage treatment (Thomas and Seedat, 2018). The treatment using medication for anxiety or depression could be highly associated with lower development of PD (Bower et al., 2010). Moreover, among individuals with mental disorders such as depression or dementia, those who received proper care were clearly associated with low levels of PD severity (Riedel et al., 2012). Our study also found out that individuals with unspecified depression had higher risk of PD compared to those without depression. However, we found that severe depression and PD were not significantly associated, as the patients consistently receive proper medication and treatment. The current study also revealed that among individuals who received medical aid, those with depression had a higher risk of PD. Considering that patients covered by medical aid had generally more difficult economic circumstances, their use of medical services tended to be low in South Korea, which led to a lack of appropriate and timely care (Chang et al., 2011). Therefore, proper, timely care for depression is associated with low PD, given the strong association between the two diseases.

PD is diagnosed according to its motor features such as bradykinesia, tremors, rigidity, and postural instability (Pontone et al., 2016). The progression of motor symptoms parallels the worsening of daily functions, and for non-motor symptoms, depression causes additional impairments in activities of daily living (ADL) (Pontone et al., 2016; Quelhas and Costa, 2009) In the present study, individuals with disabilities who also suffered from depression were at a higher risk of PD than individuals with disabilities who did not have depression. As ADL functions in individuals with depression have been reported to decline faster than in individuals who have never experienced depression, disabilities could further increase the risk of PD (Pontone et al., 2016).

Moreover, diabetes and its complications may themselves be affected by the neurodegenerative processes leading to neuronal degeneration (Riederer et al., 2011). In a previous study, diabetes and insulin resistance were highly associated with an increased risk of PD (Driver et al., 2008). Considering that patients with diabetes have been known to have a significantly higher risk of both depression and anxiety, the presence of both depression and diabetes could accelerate the risk of PD (Clarke and Currie, 2009; Riederer et al., 2011). Moreover, PD is strongly associated with other chronic illnesses, the presence of comorbidities is an important factor of rising healthcare costs and challenges to our healthcare, which could affect overall well-being and mobility (King et al., 2014).

4.1. Limitations

First, unhealthy behaviors such as smoking and alcohol consumption, which could affect the risk of PD, were not included in this study because these were not present in the original dataset. Second, this study could not adjust the severity of PD owing to lack of data. Third, the possibility of undiagnosed PD that already existed at the time of diagnosis of depression was not considered. As our study used claims data, individuals who were not diagnosed could not be considered. Fourth, the prevalence of depression was higher in women than men in most age groups in South Korea, which might have affected the sample of our study (Kim et al., 2020a). Therefore, our study used sex as a matching variable. Finally, psychological disorders other than depression were not included. Further research with various such disorders is required.

4.2. Conclusions

Despite these limitations, this study has certain strengths. The first is the use of nationally representative data to assess the association between depression and the risk of PD, which can provide the necessary evidence to ensure that with timely care, depression does not lead to other diseases. Second, as the data spanned nearly 10 years, it is possible to make inferences about a long-term association. Third, this study included not only depression but also its severity, which could provide more accurate and detailed information. Lastly, this study emphasizes the importance of managing the risk of PD, which, despite being among the most common neurodegenerative disorders, is often ignored.

The current study identified a significant relationship between depression and the risk of PD among South Korean adults. Based on our results, individuals with mild or moderate depression were at a higher risk of PD than those without depression. Moreover, individuals with unspecified depression were at a higher risk of PD than those without depression. This highlights the importance of taking the necessary steps to ensure that those diagnosed with depression. Interventions to alleviate the risk of PD should focus on adequate depression management.

Author contributions

Wonjeong Jeong and Hyunkyu Kim conceived the study and designed the study. Wonjeong Jeong and Jae Hong Joo did the formal analysis and methodology. Wonjeong Jeong wrote the initial drafts. Sung-In Jang helped to draft the manuscript. Eun-Cheol Park is the corresponding of this work and supervised entire manuscript. All authors read and approved the final manuscript.

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Declaration of Competing Interest

The authors have no conflict of interest to declare.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2021.05.038.

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