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Depression and the Subsequent Risk of Parkinson's Disease in the NIH-AARP Diet and Health Study

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Abstract

We conducted a case-control study to examine the association between depression and Parkinson's disease (PD). Participants included 992 PD cases diagnosed after 2000 and 279,958 individuals without PD from the NIH-AARP Diet and Health Study Follow-up Survey. Physician-diagnosed depression and PD were self-reported with information on the year of diagnosis in the following categories: before 1985, 1985–1994, 1995–1999, and 2000–present. Only PD cases diagnosed after 2000 were included in the analysis. Odds ratios (ORs) and 95% confidence intervals (CIs) were derived from logistic regression models, adjusted for age, gender, educational level, marital status, smoking, and coffee drinking. Individuals with depression diagnosed after 2000 were more likely to report a concurrent diagnosis of PD than those without depression (OR=4.7, 95% CI = 3.9, 5.7). Depression diagnosed before 2000 was also associated with higher odds of PD diagnosed after 2000 (OR= 2.0, 95% CI=1.6, 2.4). This association was stronger for depression diagnosed in 1995–1999 (OR = 2.7, 95% CI = 2.0, 3.6), but was also noted for depression diagnosed in 1985–1994 (OR = 1.6, 95% CI = 1.1, 2.3) or even before 1985 (OR=1.7, 95% CI=1.3, 2.3). This association was not modified by other factors and persisted in an analysis excluding participants who reported poor health status. The results suggest that depression may either be a very early symptom of PD or share common etiological factors with PD.

Keywords

depression; Parkinson's disease; odds ratio

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INTRODUCTION

An association between depression or antidepressant use and risk of subsequent Parkinson's disease (PD) has been shown in previous epidemiological studies.^{1–12} However, the temporal relationship between depression and PD has rarely been carefully explored.^{1, 3} In addition, factors such as cigarette smoking may be associated with both depression and PD (i.e., smoking might be more prevalent among depressed patients while less prevalent among PD patients), but have seldom been taken into account in previous studies.^{3,8} In the present study, we examined depression diagnosed in various time periods in relation to PD diagnosis after 2000 in a large US population of older adults – the National Institutes of Health (NIH) – AARP (previously known as the American Association of Retired Persons) Diet and Health Study. We also examined whether other risk factors known to be associated with PD influenced this association.

METHODS

Study Population

The NIH-AARP Diet and Health Study was established in 1995–1996 by the National Cancer Institute to investigate roles of diet and lifestyle factors in cancer etiology.¹³ Participants were 566,402 AARP members aged 50 years or older from six US states (California, Florida, Pennsylvania, New Jersey, North Carolina, and Louisiana) and two metropolitan areas (Atlanta, Georgia and Detroit, Michigan) who completed a comprehensive baseline survey on diet and lifestyle.¹³ From 2004 to 2006, a follow-up survey was conducted among surviving participants of the study to update lifestyle exposures and to ascertain lifetime occurrence of major chronic diseases, including depression and PD. The year of first diagnosis for either condition was reported in the following categories: before 1985, 1985–1994, 1995–1999, and 2000–interview. A total of 187,499 men and 130,762 women participated in the follow-up survey and comprised the base population for the present study. A total of 2432 participants reported physician diagnosed PD, among whom 1338 reported a diagnosis after 2000. As we were primarily interested in examining the association between depression and subsequent PD risk as well as the temporal relationship between these two conditions, we limited our analysis to PD cases diagnosed after 2000. Of 1338 cases diagnosed after 2000, we further excluded 214 cases (16.0%) whose reports were found to be erroneous in our validation study as described below and 132 (9.9%) cases with missing information on depression. Of those who did not report a PD diagnosis (n=315,829), we excluded 35,871 participants (11.4%) with missing values on either PD status (n=7843) or depression (n=28,028). Therefore, the final analysis included 992 cases (74.1% of 1338) and 279,958 controls (88.6% of 315,829).

A verification of self-reported PD diagnosis commenced in 2007 as part of an effort to recruit cases and controls for genetic research. We requested permission from surviving self-reported cases to contact their treating neurologists and then asked the neurologists to fill out a diagnostic questionnaire and to provide a copy of the patient's medical records. The questionnaire collected information on PD cardinal signs (rest tremor, rigidity, bradykinesia, and postural instability), response to dopaminergic treatments, and clinical features that may corroborate a PD diagnosis or suggest an alternative diagnosis. The medical records were reviewed by a movement disorder specialist on the research team (XH). A case was confirmed if the diagnosis was considered clinically definite or probable by the treating neurologist, or if the medical record included a final PD diagnosis or evidence of two or more cardinal signs with one being rest tremor or bradykinesia, a progressive course, responsiveness to dopaminergic treatments, and absence of features that suggest an alternative diagnosis. In 88% of the 1069 responses we have received to date, the PD

diagnosis was confirmed. A similar protocol for verification of self-reported PD has been successfully implemented in other large cohort studies.^{14, 15}

Exposure Assessment

Information on physician-diagnosed depression was collected in the same format as PD in the follow-up survey. Although no effort was made to verify depression in the present study, self-reported physician-diagnosed depression has been deemed reliable in other validation studies using medical record review or specialist interview as a gold standard.¹⁶

Information on date of birth and sex, as well as detailed data on educational level, marital status, smoking, and coffee drinking were collected as part of the baseline survey in 1995–1996.

Statistical Analysis

Depression diagnosed before 2000 was first analyzed in its totality and later in three categories based on the year of diagnosis, i.e., before 1985, 1985–1994, and 1995–1999. The association between depression diagnosed after 2000 and PD diagnosed after 2000 was also evaluated. Odds ratios (ORs) and 95% confidence intervals (CIs) were derived from logistic regression models. We first adjusted the OR estimates for age at baseline survey (in 5-year categories) and sex, and then for educational level (less than college vs. college or higher), marital status (married/living with a partner vs. not), smoking (never, former and stopped ≥ 20 years ago, former and stopped < 20 years ago, current and 1–20 cigarettes/day, current and > 20 cigarettes/day), and coffee drinking (< 1 cup/day, 1 cup/day, 2–3 cups/day, > 3 cups/day).

To investigate whether the association between depression and PD was modified by any of the above variables, we conducted stratified analysis by median age at baseline survey (< 62 or ≥ 62 years), sex, educational level (less than college or college or higher), marital status (married/living with a partner or not), smoking (ever or never), and coffee drinking (< 1 cup/day or ≥ 1 cup/day). When applicable, finer categories of these variables were included in these subgroup analyses to mitigate potential residual confounding. We also performed tests for the significance of effect modification by adding an interaction term in corresponding models.

In the follow-up questionnaire, participants were asked to report their self-perceived health status as “excellent,” “very good,” “good,” “fair,” or “poor.” To explore whether health status might affect the validity of our analysis, we conducted an additional analysis excluding individuals who reported “poor” health in the follow-up survey. All statistical analyses were conducted using commercially available SAS software (Version 9.1, SAS Institute, Cary, North Carolina).

RESULTS

Compared to controls, PD cases were on average older and more likely to be men, married and college graduates. PD cases were less likely to smoke or drink coffee than controls, and more likely to report recently diagnosed depression (Table 1).

Depression diagnosed before 2000 was associated with 2-fold higher odds of having a PD diagnosis after 2000. The estimated ORs were similar between the age- and sex-adjusted model (OR = 1.9, 95% CI = 1.6, 2.3) and the multivariate model (OR = 2.0, 95% CI = 1.6, 2.4). Therefore, only multivariate ORs are reported. Further analysis of depression diagnosed in various calendar periods in relation to PD diagnosed after 2000 is illustrated in the Figure. The association was strongest for depression diagnosed after 2000 (OR = 4.7, 95% CI = 3.9, 5.7), attenuated for depression diagnosed in 1995–1999 (OR = 2.7, 95% CI =

2.0,3.6), and further weakened for depression diagnosed earlier. Nevertheless, even depression diagnosed before 1985, at least 15 years prior to PD diagnosis, was associated with a higher risk of PD (OR=1.7, 95% CI=1.3,2.3). Excluding participants who reported poor health status at the follow-up survey (23.1% cases and 11.1% controls) only slightly attenuated the results. The multivariate ORs were 4.2 (95% CI = 3.4,5.3) for depression after 2000, 2.4 (95% CI = 1.7,3.3) for depression in 1995–1999, 1.3 (95% CI = 0.8,2.1) for depression in 1985–1994, and 1.4 (95% CI = 1.0,2.0) for depression before 1985.

Since depression before 1985 and in 1985–1994 had largely similar ORs as shown in the Figure, we combined these two groups in the stratified analyses to ensure sufficient statistical power. Similar results were noted across subgroups of age, sex, educational level, marital status, smoking, and coffee drinking (Table 2). None of the interaction tests was statistically significant.

DISCUSSION

In this large population of older Americans, we observed an association between depression and a higher subsequent risk of PD. The association was stronger for depression diagnosed in closer proximity to clinical PD diagnosis, but was also detected even for depression diagnosed more than 15 years prior to PD diagnosis. The depression-PD association was not explained or modified by the other PD risk factors that we took into account.

A link between depression and PD has been investigated previously, in case-control,^{1, 3, 6–9} historical cohort,^{4, 5} and prospective cohort² studies. All but one⁷ of these studies showed a positive association between depression and a higher subsequent risk of PD. Some known PD protective factors, such as smoking,¹⁷ may serve as self-medication among depressed individuals¹⁸ and therefore might alter the association of depression with PD. However, few studies have explored whether smoking or other PD risk factors might have confounded or modified the depression-PD relationship.^{3,8} Our multivariate and subgroup analyses showed that this association was neither confounded nor modified by these PD risk or protective factors.

Depression is one of the common non-motor symptoms of PD; but few data are available to describe its temporal relationship to PD, especially for depression occurring prior to PD diagnosis.^{1, 3} Shiba et al. found that depressive disorder was associated with a 1.9-fold risk of PD, but the risk elevation was limited to depressive disorder diagnosed within 5 years of PD onset.¹ Similarly, an Indian study reported a higher risk of PD among depressed patients diagnosed within 10 years prior to PD onset but not earlier (OR=1.5).³ Another two studies found a significant association between antidepressant use and the subsequent risk of PD or antiparkinson drugs use within a short time after antidepressant prescription (six months and two years respectively) but not earlier.^{11,12} Our study is larger than most of the previous studies, and we evaluated the depression-PD relationship over a longer period of time.

One explanation for these findings is that depression might be a very early marker of PD pathogenesis, before a significant involvement of dopaminergic neurons in the substantia nigra.^{19,20} It is however still under debate when PD-related pathologies begin, with most evidence pointing to a time window within 10 years of the diagnosis.^{21,22} If the 10-year time window is accurate, our finding may suggest that depression is also etiologically related to PD or, more likely, that it shares common mechanistic pathways with PD. For example, both PD and depression are characterized by impaired monoaminergic neurotransmission.²³ Another example is chronic inflammation, which may underlie both depression and PD.^{24, 25} It is possible that use of antidepressants or antipsychotics may increase the risk of PD^{11,12} which may partially account for our observation for depression.

However, it is more plausible that the findings on antidepressants were explained by the presence of depression as an early marker of PD¹². Finally, it is important to note that the depression and PD relationship is not specific. Depression belongs to a group of non-motor symptoms that many of which may predate the onset of PD.²⁶ On the other hand, depression has been related to many chronic conditions such as diabetes as a risk factor or consequence.²⁷

Major strengths of our study include the large sample size, long period of exposure assessment, and detailed information on potential confounders and effect modifiers. The analyses were however retrospective in nature. Selection bias cannot be ruled out if depressed individuals with PD were less likely to participate in the follow-up survey compared to depressed individuals without PD; if true the observed odds ratios are likely underestimated. Recall bias could also be a concern as PD patients might be more likely to recall or report depression than the PD-free participants. Although we could not directly evaluate potential impacts from this bias, our additional analysis excluding individuals with poor health status who might be more likely to over report depression, showed similar results. In such a large cohort, we had to rely on the self-report to identify depression and PD diagnoses as well as the years of first diagnoses. Misdiagnosis and under reporting are therefore unavoidable. Our ongoing verification study of PD diagnosis showed that 88% of PD cases were validated with information from their treating neurologists. Although we did not validate self-reported depression, nor did we have data on antidepressant use, in other validation studies self-reported diagnosis of depression was deemed fairly reliable compared to medical record review or specialist interview¹⁶ and self-reports have been used in other longitudinal studies²⁴.

In summary, we noted an association between depression and PD which is independent of other risk factors for PD. The significant association with depression diagnosed 15 years previously suggests that depression may be a very early symptom of PD or share common etiological factors with PD.

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FIG. 1. Depression diagnosed at various calendar periods in relation to Parkinson's disease diagnosed after 2000. Odds ratios and 95% confidence intervals were adjusted for age, gender, educational level, marital status, smoking, and coffee drinking.

TABLE 1

Characteristics of Parkinson's disease cases diagnosed after 2000 and controls

Characteristics	Cases (N=992)	Controls (N=279,958)
Age at baseline in years, mean (SD)	64.4 (4.8)	61.8 (5.3)
Gender, n (%)		
Men	744 (75.0)	164,491 (58.8)
Women	248 (25.0)	115,467 (41.2)
Educational level, n (%)		
Less than college	481 (48.5)	150,420 (53.7)
College or higher	490 (49.4)	123,303 (44.0)
Unknown	21 (2.1)	6,235 (2.3)
Marital status, n (%)		
Married/living with a partner	751 (75.7)	196,825 (70.3)
Not married	236 (23.8)	81,511 (29.1)
Unknown	5 (0.5)	1,622 (0.6)
Smoking, n (%)		
Never	414 (41.7)	106,705 (38.1)
Former	512 (51.6)	142,469 (50.9)
Current	54 (5.4)	27,386 (9.7)
Unknown	12 (1.2)	3,398 (1.2)
Coffee drinking, n (%)		
<1 cup per day	291 (29.3)	74,775 (26.7)
≥1 cup per day	695 (70.1)	204,105 (72.9)
Unknown	6 (0.6)	1,078 (0.4)
Year of first depression diagnosis, n (%)		
No depression	722 (72.8)	239,587 (85.6)
Before 1985	52 (5.2)	12,699 (4.5)
1985–1994	30 (3.0)	8,414 (3.0)
1995–1999	51 (5.1)	8,063 (2.9)
2000-interview	137 (13.8)	11,195 (4.0)

Percentages may not add up to 100% due to rounding.

TABLE 2

Preceding depression and the risk of Parkinson's disease in stratified analyses

	No depression	First diagnosis of depression		P-values for interaction
		1995–1999	Before 1995	
Age at baseline				0.94
<62 years	194/114,470	16/4,796	24/11,948	
OR (95%CI)	1	2.3 (1.4, 3.8)	1.4 (0.9, 2.1)	
≥62 years	528/125,117	35/3,267	58/9,165	
OR (95%CI)	1	3.0 (2.1, 4.2)	1.8 (1.4, 2.4)	
Gender				0.35
Men	559/146,949	38/3,711	47/8,451	
OR (95%CI)	1	3.2 (2.3, 4.4)	1.6 (1.2, 2.1)	
Women	163/92,638	13/4,352	35/12,662	
OR (95%CI)	1	2.0(1.1, 3.4)	1.7 (1.2, 2.5)	
Educational level				0.56
Less than college	333/127,539	27/4,737	43/11,240	
OR (95%CI)	1	2.8 (1.9, 4.2)	1.9 (1.4, 2.7)	
College or higher	374/106,834	22/3,115	38/9,358	
OR (95%CI)	1	2.6 (1.7, 4.0)	1.5 (1.0, 2.1)	
Marital status				0.40
Married/living with a partner	557/172,380	40/5,114	52/11,781	
OR (95%CI)	1	3.1 (2.3, 4.3)	1.7 (1.3, 2.2)	
Not married	162/65,864	11/2,887	30/9,182	
OR (95%CI)	1	1.9 (1.0, 3.5)	1.6 (1.1, 2.4)	
Smoking				0.98
Never	319/92,789	16/2,735	34/7,400	
OR (95%CI)	1	2.1 (1.3, 3.5)	1.6 (1.1, 2.3)	
Ever	397/143,928	32/5,202	47/13,448	
OR (95%CI)	1	3.0(2.1, 4.3)	1.7 (1.2, 2.3)	
Coffee drinking				0.79
>1 cup per day	511/175,780	36/5,693	58/14,513	
OR (95%CI)	1	2.9(2.0, 4.0)	1.8 (1.3, 2.3)	
≤1 cup per day	205/62,902	15/2,330	24/6,519	
OR (95%CI)	1	2.5 (1.5, 4.3)	1.5 (1.0, 2.3)	

Adjusted for age, gender, educational level, marital status, smoking, and coffee drinking; numbers are shown as cases/controls.