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Occurrence of Depression and Anxiety prior to Parkinson's Disease

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Abstract

OBJECTIVE—To assess the relationship between depression and anxiety and Parkinson's disease (PD).

BACKGROUND—Many people with PD suffer from depression and anxiety prior to the onset of motor symptoms. Studies suggest these psychiatric conditions may be risk factors for PD or prodromal non-motor symptoms.

METHODS—Using a population-based approach in three California counties, we recruited 371 incident PD cases, 402 population and 115 sibling controls. We recorded self-reports of lifetime depression/anxiety diagnoses and use of psychotropic medications. We adjusted for age, race, sex, pack-years of smoking, and education, and also conducted analyses after excluding (lagging) both diagnoses and medication use first occurring within 2, 5, 10, and 20 years of the index/diagnosis date.

RESULTS—Cases were more likely to have received a diagnosis of depression or anxiety at any time prior to index date (OR 1.42, 95% CI 1.01, 2.00), but were not more likely to have been both diagnosed and treated (OR 1.11, 95% CI 0.77, 1.60). Male PD patients received diagnoses combined with treatment more often than population controls within 5 years of PD diagnosis (OR 2.21, 95% CI 1.21, 4.04; *2 year lag*: OR 2.44, 95% CI 1.29, 4.61; *5 year lag*: OR 1.67, 95% CI 0.80, 3.49). We did not see any differences for females. Results for cases compared to sibling controls were similar to those for population controls.

CONCLUSION—These results suggest that depression and anxiety may be early symptoms during the prodromal phase of PD.

Keywords

Case control study; Depression; Parkinson's disease; Pre-motor phase; Risk factors in epidemiology

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Introduction

It is well-established that depression and other psychiatric disorders such as anxiety occur at higher rates in patients with Parkinson's disease (PD) than in the general population [1,2]. However, reported frequencies of depression in patients with PD vary widely with estimates from 7% to 70% [3]. A recent review of 36 studies [4] reported the mean depression prevalence to range from 17% to 35% among US and European PD patients, while a lifetime depression prevalence of 16% and a 12-month prevalence of about 7% have been documented among the general US population[5].

Depression and anxiety are significant non-motor symptoms in PD as they may be associated with a more rapid deterioration in cognitive and motor functions. [6] These psychiatric disorders are also major factors in health-related quality of life in PD [7–9]. Given the implications for clinical and quality of life outcomes, it is important to improve recognition and understanding of these disorders in PD.

Some studies have proposed that both depression and anxiety disorders precede PD development and therefore could be risk factors for PD.[10] However, it remains unclear whether depression and anxiety are independent risk factors for PD or early manifestations of the disease. Several studies have found that PD patients have more frequent histories of depression, anxiety and nervousness than controls and that these psychological symptoms were part of the prodromal phase that developed 3 to 6 years before the onset of motor dysfunction [11,12]. Therefore, if depression and anxiety are risk factors, we would expect that PD patients, referred to as cases in the following, would be more likely than controls to have both a distant (before development of PD) and recent history of depression or anxiety. If they are early manifestations, we would expect that PD cases would not be more likely to have a distant history, but would be more likely to have a recent history of depression or anxiety than controls.

Most studies concluding that depression and anxiety are risk factors for PD did not differentiate between recent and distant diagnoses [13–18]. Instead, they included all diagnoses of depression or anxiety that occurred prior to PD diagnosis. Therefore, they failed to determine whether these psychiatric symptoms might have been prodromal symptoms of PD or distant occurrences that could be considered risk factors [19]. One record-based study explored this hypothesis by examining antidepressant use separately in those who initiated treatment >2 years and ≤2 years prior to diagnosis date. However, this study was limited to a maximum of 6 years of follow-up time after initiation of anti-depressant medications and did not have the benefit of having all PD cases examined by a movement disorder specialist.[20] Another study that investigated depression/anxiety diagnoses up to 20 years before onset of PD was limited by a small sample size (196 cases total, with only 10 cases and 8 controls affected by depression up to 20 years before index date) [21]. Here we investigate the role of depression and anxiety prior to PD diagnosis by examining the distant and recent past separately.

Methods

Subjects

This is part of the UCLA Parkinson's Environment and Genes (PEG) study, a population-based case-control study that recruited incident cases and controls from Fresno, Tulare, and Kern counties in California. Cases were diagnosed within three years of enrollment and were identified through local neurologists, large medical groups (Kaiser Permanente, Kern and Visalia Medical Center, and Veteran's Administration), PD support groups, local newspapers, and local radio stations. Population control subjects were randomly selected from Medicare records or residential parcels identified from tax assessor records in the same tri-county area.

Full siblings of participating PD cases were eligible to enroll as control subjects regardless of state or county of residence. Only one sibling who never received a PD diagnosis was included for each case.

Cases were eligible if they currently lived in one of three counties (Fresno, Tulare, or Kern), had lived in California for at least five years, were not in the last stages of a terminal illness, agreed to participate, and were confirmed as having clinically probable or possible PD by a UCLA movement disorder specialist. Diagnostic criteria, explained in detail elsewhere [22], were based on those recommended previously. [23,24] A diagnosis of clinically probable or possible PD was confirmed if patients met the following criteria: 1) manifestation of at least two of the following: resting tremor, bradykinesia, or cogwheel rigidity; 2) no suggestion of a parkinsonian syndrome due to trauma, brain tumor, infection, cerebrovascular disease, other known neurologic disease, or treatment with dopamine-blocking or dopamine-depleting agents; 3) no atypical features such as prominent oculomotor palsy, cerebellar signs, vocal cord paresis, severe orthostatic hypotension, pyramidal signs, amyotrophy, or limb apraxia; 4) asymmetric onset; and 5) if treatment with levodopa had been initiated, symptomatic improvement after treatment. Probable cases met criteria one through four plus/minus criterion five. Possible cases had at least one sign from criterion one and fulfilled criteria two and three. Although sometimes included in criterion one, postural reflex impairment was excluded since it usually occurs late in PD and may typically occur early in other parkinsonian disorders, such as progressive supranuclear palsy and vascular parkinsonism.

Of the 1,167 initially invited PD cases, 604 (51.8%) were not eligible: 397 had been diagnosed with PD more than three years prior to contact, 51 denied having received a PD diagnosis, 134 lived outside the tri-county area, and 22 were too ill. Of the 563 eligible cases, 473 (84.0%) were examined by a movement disorder specialist and confirmed as having clinically “probable” or “possible” PD; the remaining 90 potential cases could not be examined. We examined but excluded another 93 patients due to other causes of parkinsonism, leaving us with 379 (67.3%) cases; of these, 371 provided all information needed for analyses.

We contacted 1,212 potential population controls by mail and/or phone for eligibility screening. Eligibility criteria were: 1) not having PD 2) being at least 35 years of age 3) currently residing primarily in one of the three counties and 4) having lived in California for at least 5 years prior to the screening. Only one person per household was allowed to enroll. 457 (37.7%) controls were ineligible: 409 were too young, 44 were terminally ill and 4 primarily resided outside of the study area. Of the 755 eligible population controls, 521 (69.0%) were enrolled and 402 (53.2%) provided all information needed for analyses.

A total of 205 potentially eligible full siblings of PD cases were contacted. Of the 157 siblings that provided all information needed for analyses, 11 were related to cases who were later re-diagnosed as not having PD, leaving 146 sibling controls. Some cases had multiple participating siblings. For these analyses, we randomly eliminated all but one sibling for each case, leaving 115 unaffected sibling controls.

All subjects provided informed consent and the study was approved by the UCLA Institutional Review Board.

Data Collection

Study participants provided self-reported medical information about previous diagnoses of depression and anxiety, including age at first diagnosis, and psychotropic medication use (medications used for depression and/or anxiety); specifically type (name), amount (pills per day/week), duration (weeks or months), and age at first and last use of each medication.

Demographic and lifestyle characteristics were collected by telephone interviewers blinded to subject's case/control status.

Participants completed the 15-item Geriatric Depression Scale (GDS) which has a score range from 0 to 15, with 1 point tallied for each 'positive' response (indicating a depressive symptom). Scores from 0 to 4 indicate no depression, 5 to 9 indicate mild to moderate depression, and 10 to 15 indicate severe depression.

Statistical analysis

Logistic regression analysis was used to calculate odds ratios (OR), which are estimates of risk, and 95% confidence intervals (CI) for depression and anxiety and PD, that is, the odds of disease (PD) developing in an individual with pre-existing depression or anxiety versus the odds of disease developing in an individual who never was diagnosed or treated for these psychiatric illnesses. Odds ratios are adjusted for sex, age at diagnosis/interview (continuous), race (Caucasian, Asian, Latino, Native American, and Black), pack-years of smoking (0, >0 to <10, ≥10 to <40, ≥40), and years of education (<12, 12, >12). We employed two models: in the first (Diagnosis Model) we defined all cases and controls who reported a history of psychiatric diagnosis (either depression, anxiety, or both) as being affected, and age at onset as the age at first diagnosis. In the second (Diagnosis + Medication Model), we defined as affected only those cases and controls who reported a history of both a psychiatric diagnosis and psychotropic medication use. Age at onset was defined as age at first use of psychotropic medication or age at first psychiatric diagnosis, whichever came first.

In all analyses we did not consider as affected cases and controls whose age at onset first occurred concurrent with or after the index date (PD diagnosis for cases, interview for controls).

In separate analyses, we limited (lagged) the diagnoses and medication use to only those that had occurred 2, 5, 10, and 20 years prior to index date. For example, in a 5-year lag, a first diagnosis or medication use was required to have occurred 5 years or more prior to the index date; in other words, depression diagnoses or medication use within zero to four years prior to the index date were excluded. We also stratified analyses by gender, education, and age at index date (≤60, >60). We also examined depression diagnoses and treatment alone i.e. after excluding anxiety diagnoses. In order to validate the self reports of previous depression and anxiety, we cross-referenced GDS scores with self-reports of current psychotropic medication use. All analyses were performed using SAS 9.1.

Results

Study participants were predominantly Caucasian, over the age of 60, and without a family history of PD (Table 1). Cases were slightly older than controls, were more often male, and had completed fewer years of education. Cases were also more likely to have never smoked or to have quit smoking. Male cases were more likely to have ever received a diagnosis of depression or anxiety than male population or sibling controls, but female population controls were more likely to have ever received a psychiatric diagnosis than female cases. Study participants who had received a psychiatric diagnosis and had been treated with psychotropic medications generally used more than one class of drug over their lifetime. Selective serotonin reuptake inhibitors (SSRIs) were most commonly reported. Less frequently reported were other anti-depressants, serotonin-norepinephrine reuptake inhibitors (SNRIs), benzodiazepines, tricyclic antidepressants, and other psychotropics.

PD cases had a slightly (40–50%) higher odds of having been diagnosed with depression and/or anxiety prior to index date than controls, but were not more likely to have reported both a psychiatric diagnosis and psychotropic medication use compared to either population or sibling

controls (Table 2). However, male cases had higher odds of having been diagnosed and treated for depression or anxiety than population or sibling controls, which was mostly due to events within a 2 to 5 year period prior to PD diagnosis. Female PD patients seemed somewhat less likely to have been diagnosed and treated than population controls, but all confidence intervals included the null value of 1. Analyses stratified by age at PD onset (<=60, >60 years) and education (<12 years, 12 years, 13–16 years, >16 years) did not reveal stratum-specific differences (results not shown). Results of depression only analyses did not differ from the results reported for depression and anxiety together (results not shown).

Finally, we calculated mean GDS scores after grouping subjects according to their reported current (at time of interview) psychotropic medication use (Table 3). We found that both cases and controls who reported current medication use scored higher on the GDS than their un-medicated counterparts (t-test p-value = 0.03 for currently medicated cases vs population controls; p-value < 0.0001 for currently un-medicated cases vs. population controls). Among currently medicated participants, more cases than population or sibling controls were moderately and severely depressed.

In order to determine whether the difference in GDS scores may be due to PD motor symptoms that overlap with depression items from the GDS, we dropped GDS questions #2 (dropping activities and interests) and #9 (preference to stay at home, rather than going out and trying new things) and re-calculated mean GDS scores, since we hypothesized that positive responses to these questions may reflect cases' motor symptom status rather than depressive symptoms. After excluding these two questions, we found that the differences in mean GDS scores between cases and controls persisted (t-test p-value = 0.04 for currently medicated cases vs population controls; t-test p-value <0.0001 for currently un-medicated cases vs population controls) suggesting that these differences reflect actual differences in depression status rather than differences due to motor symptoms.

Discussion

Depression and anxiety seem to be pre-clinical symptoms prior to the onset of PD motor symptoms rather than etiologic risk factors in our study. We observed a positive association between depression and anxiety diagnoses and PD among males but not females. When we restricted the definition of affected participants to only those with a psychiatric diagnosis and a history of psychotropic medication use, results were again driven by males and we did not observe any differences between PD cases and controls more than 5 years prior to index date. The results observed in males suggest that PD cases are more likely than controls to have been diagnosed with depression or anxiety up to 20 years prior to PD onset. However, the more stringent Diagnosis + Medication Model confirmed differences between male cases and controls only for the period 5 years but not 10 or 20 years prior to diagnosis. These latter results are consistent with two previous studies which also examined the timing of psychiatric disorders prior to PD.[20,21] The differences observed in our two models might be due to recall bias (male cases more frequently recalling early-life depression or anxiety diagnoses for which they did not seek treatment), or a reluctance of male PD cases to seek medical treatment for psychiatric disorders earlier in life while seeking medical care more often for non-motor symptoms and having more opportunities to be diagnosed and treated for depression in the years before PD diagnosis, or chance.

Several previous studies have reported that depression and anxiety are associated with an increased risk for PD [13–17,21], but most of these studies did not account for the prodromal phase of PD. [13] Thus the observed associations could be a result of depression occurring within 2 to 5 years before PD diagnosis, as observed in our study. The two studies most comparable in their approach to ours, in that they accounted for the timing of psychiatric events

prior to PD, support our findings that the association between PD and prior psychiatric events is mostly due to events within 2 to 5 years prior to PD diagnosis. [20,21]

Our current study is based on the largest population-based sample of incident PD cases evaluated by a movement disorder specialist in a standard protocol to explore this hypothesis. Misclassification of PD diagnosis is expected to be minimal due to our study's stringent diagnostic criteria and clinical examination (repeated if necessary) of every PD case by a movement disorder specialist. Although we recruited from a well-defined source population, there is a possibility of selection bias if history of depression is linked to participation in the study. We would expect that depression at the time of recruitment would influence participation due to apathy or other psychiatric symptoms in both cases and controls, and depressed controls may be even more reluctant than cases to enroll in a medical study. However, this pattern was not observed for females. Also, since we investigated lifetime depression, we do not expect that a history of past depression would influence study participation. We might have over-matched on genetic factors when comparing cases to sibling controls, which would be expected to result in greater similarity with regard to depression and therefore a weakening of the associations. Yet, the effect estimates from our case/sibling based analyses were similar to or stronger than the case/population control estimates, suggesting that prodromal PD rather than genetic predisposition is at play. Finally, because we assessed depression retrospectively and via self-report, misclassification of lifetime depression and anxiety diagnoses and psychotropic medication use is possible. Studies have demonstrated that self-reported age at onset of major psychiatric diagnoses is fairly reliable [25,26]. Importantly, one might speculate that exposure recall of diagnoses and medication use decades prior to the interview is unreliable and may result in misclassification that is differential, since recently diagnosed PD cases may be more inclined to recall and report depression and anxiety, but this pattern was not observed in females. We investigated whether these differences are due to differences in education but did not find evidence supporting this hypothesis. Based on a national survey conducted from 2001 to 2003, the lifetime prevalence of depression in participants above age 65 was 5.6% in males and 13.3% in females, while that of anxiety was 9.6% in males and 16.6% in females.[27] Thus, while the rates in our male controls are similar to those of the national survey, the rates in our female controls are considerably higher. These high rates of psychiatric diagnoses in female controls could be due to over-reporting, truly increased rates, selection bias, or chance.

There are several early symptoms of PD, such as fatigue, that may be mistaken for depression. We account for this in part by lagging, i.e. removing from consideration depression diagnoses in the years immediately prior to PD diagnosis when fatigue may be present and mistaken for depression. We also believe that our more stringent diagnosis plus medication requirement lessens the possibility of misclassifying depression due to fatigue, assuming that symptoms of fatigue alone would not result in both a depression diagnosis and anti-depressant treatment.

History of psychotropic medication use was employed both to confirm psychiatric diagnoses and as a marker of severity of psychiatric illness. Medication use may indicate that depression is more severe and, according to our GDS scores, there may even be some under-treated cases in our population. This is consistent with other studies that suggest depression in PD is under-diagnosed and under-treated [28,29]. Although males who developed PD had slightly higher odds of receiving psychiatric diagnoses up to 20 years or more before PD diagnosis, we did not observe differences in psychotropic medication use until 5 years before index date.

This study contributes to the growing body of literature examining the role that psychiatric disorders may play prior to PD motor symptom onset. There is evidence of a prodromal phase in PD from imaging, pathology, and clinical, epidemiological, and animal studies [11,30–32]. Estimates of duration of the prodromal period vary widely, from 3 up to 20 years, and symptoms can include olfaction deficits, dysautonomia, and sleep and psychiatric disorders[11,30,32].

While we assumed an average duration of 5 years for prodromal symptoms in this study, age and disease etiology may be important factors determining the actual length of this phase [11,30,32]. Although the pathophysiology of depression and anxiety in pre-clinical PD is not fully understood, [33] its basis may be noradrenergic, dopaminergic or serotonergic [34,35] and the neurologic structures involved may included the substantia nigra or coeruleus/subcoeruleus complex, where dysfunction occurs in Braak Stage 2, and has been estimated to begin ten years or more prior to motor symptoms.

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The additional 5 references are included at the suggestion of the reviewers.

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Table 1

Demographic characteristic and risk factor distribution of California Central valley Parkinson's study subjects

	Cases (n=371) N (%)	Controls		Cases/population controls		Cases/sibling controls	
		Population (n=402) N (%)	Sibling (n=115) N (%)	OR	95% CI	OR	95% CI
Sex							
female	163 (43.9)	202 (50.2)	68 (59.1)	ref		ref	
male	208 (56.1)	200 (49.8)	47 (40.9)	1.29	(0.97, 1.71)	1.85	(1.21, 2.82)
Mean age (in years), (SD)	68.1 (10.4)	65.9 (12.4)	65.9 (10.9)	1.02	(1.00, 1.03)	1.02	(1.00, 1.04)
1st Degree Relative with PD	56 (15.1)	38 (9.5)		1.70	(1.12, 2.24)		
Race/ethnicity							
White	299 (80.1)	315 (78.4)	96 (83.5)	ref		ref	
Black	3 (0.8)	16 (4.0)	1 (0.9)	0.20	(0.06, 0.69)	0.96	(0.10, 9.39)
Latino	49 (13.2)	42 (10.4)	7 (6.1)	1.23	(0.79, 1.91)	2.25	(0.99, 5.13)
Asian	4 (1.1)	11 (2.7)	1 (0.9)	0.94	(0.47, 1.87)	0.51	(0.23, 1.17)
Native American	16 (4.3)	18 (4.5)	10 (8.7)	0.38	(0.12, 1.22)	1.28	(0.14, 11.63)
Years of formal education							
< 12	69 (18.6)	45 (11.2)	10 (8.7)	1.18	(0.73, 1.91)	1.73	(0.78, 3.82)
12	100 (27.0)	77 (19.2)	25 (21.7)	ref		ref	
> 12	202 (54.4)	280 (69.7)	80 (69.6)	0.75	(0.63, 0.89)	0.80	(0.62, 1.03)
Cigarette (pack years)							
0	196 (52.8)	172 (42.8)	53 (46.1)	ref		ref	
0+ to 9	74 (19.9)	84 (20.9)	19 (16.5)	0.77	(0.53, 1.12)	1.05	(0.59, 1.90)
10 to 39	67 (18.1)	96 (23.9)	23 (20.0)	0.78	(0.65, 0.94)	0.89	(0.67, 1.18)
40+	34 (9.2)	45 (11.2)	17 (14.8)	0.87	(0.74, 1.03)	0.82	(0.66, 1.01)
Missing	0 (0.0)	5 (1.2)	3 (2.6)				
Depression and/or anxiety diagnosis							
Never received depression and/or anxiety diagnosis	265 (71.4)	299 (74.4)	88 (76.5)	ref		ref	
Ever received depression and/or anxiety diagnosis	106 (28.6)	103 (25.6)	27 (23.5)	1.16	(0.85, 1.60)	1.30	(0.80, 2.12)
		N (% of those diagnosed)					
Diagnosis + no psychotropic medication use	29 (27.4)	16 (15.5)	6 (22.2)	ref		ref	
Diagnosis + psychotropic medication use*	77 (72.6)	87 (84.5)	21 (77.8)	0.95	(0.67, 1.34)	1.17	(0.69, 2.00)
	N (% of those diagnosed and taking medication)						

	Cases (n=371) N (%)	Controls		Cases/population controls		Cases/sibling controls	
		Population (n=402) N (%)	Sibling (n=115) N (%)	OR	95% CI	OR	95% CI
selective serotonin reuptake inhibitors (SSRIs)	36 (46.8)	54 (62.1)	13 (61.9)				
other antidepressants	14 (18.2)	18 (20.7)	4 (19.0)				
serotonin norepinephrine reuptake inhibitors (SNRIs)	13 (16.9)	11 (12.6)	3 (14.3)				
benzodiazepines	14 (18.2)	9 (10.3)	3 (14.3)				
tricyclics	9 (11.7)	5 (5.7)	1 (4.8)				
other psychotropics	6 (7.8)	4 (4.6)	1 (4.8)				
missing/unspecified	30 (39.0)	31 (35.6)	10 (47.6)				

* Medication categories are not exclusive and include the following: SSRIs: citalopram, escitalopram, paroxetine, fluoxetine, fluvoxamine and sertraline; SNRIs: venlafaxine, duloxetine, and nefazadone; benzodiazepines: alprazolam, diazepam, lorazepam, chlordiazepoxide, clonazepam; tricyclics: amitriptyline, doxepin, nortriptyline, desipramine, and imipramine; other antidepressants: bupropion, mirtazapine, and trazodone; other psychotropics: buspar and miltown.

Table 2

Association between psychiatric disorders and Parkinson's disease

	Cases n (%)	Controls		Cases/population controls		Cases/sibling controls	
		Population n (%)	Sibling n (%)	OR*	95% CI	OR*	95% CI
All cases Diagnosis Model	371	402	115				
concurrent excluded	106 (28.6)	103 (25.6)	27 (23.5)	1.41	(1.01, 1.98)	1.58	(0.94, 2.65)
lag 2 years	94 (25.3)	93 (23.1)	25 (21.7)	1.37	(0.96, 1.94)	1.47	(0.86, 2.51)
lag 5 years	70 (18.9)	81 (20.1)	20 (17.4)	1.11	(0.76, 1.63)	1.41	(0.78, 2.54)
lag 10 years	54 (14.6)	63 (15.7)	12 (10.4)	1.11	(0.73, 1.68)	1.99	(0.98, 4.08)
lag 20 years	38 (10.2)	35 (8.7)	6 (5.2)	1.42	(0.85, 2.38)	2.39	(0.96, 5.99)
Diagnosis + Medication Model							
concurrent excluded	77 (20.8)	87 (21.6)	21 (18.3)	1.15	(0.80, 1.66)	1.39	(0.79, 2.44)
lag 2 years	70 (18.9)	80 (19.9)	20 (17.4)	1.12	(0.77, 1.64)	1.28	(0.72, 2.27)
lag 5 years	48 (12.9)	71 (17.7)	17 (14.8)	0.83	(0.54, 1.26)	1.03	(0.55, 1.93)
lag 10 years	35 (9.4)	58 (14.4)	11 (9.6)	0.74	(0.46, 1.17)	1.18	(0.56, 2.48)
lag 20 years	24 (6.5)	33 (8.2)	5 (4.3)	0.92	(0.52, 1.63)	1.88	(0.68, 5.23)
Males only, total Diagnosis Model	208	200	47				
concurrent excluded	54 (26.0)	26 (13.0)	8 (17.0)	2.47	(1.44, 4.22)	2.04	(0.85, 4.89)
lag 2 years	46 (22.1)	22 (11.0)	7 (14.9)	2.50	(1.41, 4.43)	1.79	(0.72, 4.44)
lag 5 years	31 (14.9)	18 (9.0)	5 (10.6)	1.99	(1.05, 3.78)	1.68	(0.59, 4.79)
lag 10 years	21 (10.1)	12 (6.0)	3 (6.4)	1.79	(0.83, 3.86)	1.57	(0.42, 5.81)
lag 20 years	14 (6.7)	5 (2.5)	2 (4.3)	2.89	(0.98, 8.52)	1.27	(0.26, 6.17)
Diagnosis + Medication Model							
concurrent excluded	40 (19.2)	20 (10.0)	7 (14.9)	2.30	(1.26, 4.21)	1.72	(0.68, 4.34)
lag 2 years	37 (17.8)	17 (8.5)	6 (12.8)	2.53	(1.34, 4.77)	1.69	(0.64, 4.46)
lag 5 years	21 (10.1)	14 (7.0)	5 (10.6)	1.68	(0.81, 3.51)	1.09	(0.37, 2.32)
lag 10 years	13 (6.3)	12 (6.0)	4 (8.5)	1.10	(0.47, 2.55)	0.70	(0.21, 2.41)
lag 20 years	8 (3.8)	6 (3.0)	2 (4.3)	1.42	(0.46, 4.36)	0.82	(0.16, 4.33)
Females only, total Diagnosis Model	163	202	68				
concurrent excluded	52 (31.9)	77 (38.1)	19 (27.9)	0.93	(0.58, 1.47)	1.35	(0.70, 2.62)
lag 2 years	48 (29.4)	71 (35.1)	18 (26.5)	0.92	(0.58, 1.48)	1.28	(0.65, 2.52)
lag 5 years	39 (23.9)	63 (31.2)	15 (22.1)	0.81	(0.50, 1.33)	1.27	(0.61, 2.63)

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	Cases n (%)	Controls		Cases/population controls		Cases/sibling controls	
		Population n (%)	Sibling n (%)	OR*	95% CI	OR*	95% CI
lag 10 years	33 (20.2)	51 (25.2)	9 (13.2)	0.89	(0.53, 1.50)	2.13	(0.89, 5.07)
lag 20 years	24 (14.7)	30 (14.9)	4 (5.9)	1.13	(0.61, 2.09)	3.04	(0.98, 9.49)
Diagnosis + Medication Model							
concurrent excluded	37 (22.7)	67 (33.2)	14 (20.6)	0.71	(0.43, 1.16)	1.23	(0.60, 2.53)
lag 2 years	33 (20.2)	63 (31.2)	14 (20.6)	0.67	(0.40, 1.11)	1.05	(0.50, 2.18)
lag 5 years	27 (16.6)	57 (28.2)	12 (17.6)	0.59	(0.34, 1.00)	0.99	(0.45, 2.17)
lag 10 years	22 (13.5)	46 (22.8)	7 (10.3)	0.62	(0.35, 1.10)	1.47	(0.57, 3.77)
lag 20 years	16 (9.8)	27 (13.4)	3 (4.4)	0.81	(0.41, 1.59)	2.87	(0.77, 10.78)

*ORs are adjusted for sex, age, race, pack-years of smoking, and education

Table 3

Distribution and mean of GDS scores stratified by current medication status.

	Cases		Population Controls		Sibling Controls	
	Males (n=57)	**Females (n=50)**	**Males (n=15)**	**Females (n=47)**	**Males (n=4)**	**Females (n=9)**
current psychotropic medication use GDS Score	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
0 to 4	27 (47.4)	28 (56.0)	13 (86.7)	34 (72.3)	2 (50.0)	7 (77.8)
5 to 9	18 (31.6)	13 (26.0)	0 (0.0)	7 (14.9)	2 (50.0)	1 (11.1)
10 +	11 (19.3)	9 (18.0)	2 (13.3)	6 (12.8)	0 (0.0)	1 (11.1)
missing	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Mean (SD)	5.16 (3.93)	5.18 (4.44)	3.41 (3.42)	3.85 (3.82)	3.51 (1.91)	3.22 (3.59)
	Males (n=151)	**Females (n=113)**	**Males (n=185)**	**Females (n=155)**	**Males (n=43)**	**Females (n=59)**
no current psychotropic medication use GDS Score	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
0 to 4	113 (74.8)	94 (83.2)	155 (83.8)	133 (85.8)	36 (83.7)	47 (79.7)
5 to 9	35 (23.2)	18 (15.9)	12 (6.5)	6 (3.9)	2 (4.7)	5 (8.5)
10 +	3 (2.0)	1 (0.9)	6 (3.2)	4 (2.6)	1 (2.3)	4 (6.8)
missing	0 (0.0)	0 (0.0)	12 (6.5)	12 (7.7)	4 (9.3)	3 (5.1)
Mean (SD)	3.01 (2.74)	2.71 (2.31)	1.69 (2.48)	1.68 (2.49)	1.30 (2.35)	1.92 (3.26)