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Discriminant Validity and the Prevalence of Depression Among Individuals with Parkinson's Disease

By

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Degree to be awarded: Master of Public Health

Epidemiology

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Discriminant Validity and the Prevalence of Depression Among Individuals with Parkinson's Disease

By

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Bachelor of Science in Chemistry
Indiana University - Bloomington
2014

Faculty Thesis Advisor: Carolyn Drews-Botsch, PhD, MPH

An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
Master of Public Health
in Epidemiology
2018

Abstract

Discriminant Validity and the Prevalence of Depression
Among Individuals with Parkinson's Disease

By Kevin James Littrell

Background: Parkinson's Disease (PD) is currently the most prevalent movement disorder and the second-most common neurodegenerative disorder in the developed world. One area that is particularly important to achieving modern, affordable PD care is establishing the validity of psychometric tools when used among the PD population.
Methods: The observed odds ratio between PD and depression was estimated using the traditionally defined criteria for the Beck Depression Inventory - II, a score of ≥ 14 signifying depression. Then a specificity analysis and a confirmatory factor analysis, with the Apathy Scale, were conducted to investigate the influence of misclassification bias in the prevalence estimate.
Results: The observed OR for the association between PD and depression is 3.15 (0.61–16.22). While not all specificity combinations provided realistic bias-adjusted estimate, in general, as the specificity decreases, the association between depression and PD is more likely to be an overestimate. In the factors that met the inclusion criteria, the control group fit a six-factor model: general depression (factor 1), somatic depression (factor 2), cognitive depression (factor 3), dysphoria (factor 4), behavioral apathy (factor 5), cognitive apathy (factor 6). The PD case group fit a five-factor model: general depression (factor 1), frustration (factor 2), somatic changes (factor 3), dysphoria (factor 5), and self-perception (factor 6).
Conclusion: Support was found that depression is more common among individuals with PD than in other old adults. However, the study of this association is complicated by the influence of apathy and PD symptoms. In addition, when arguing that the overlapping symptoms between PD and depression causes the specificity of common depression screening tools to decrease, depression can be overestimated. However, the extent to which this is true depends on the validity of the psychometric tool used to measure depression.

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1.Background

In 1817 James Parkinson published "An Essay on the Shaking Palsy" describing an illness characterized by the progression of motor and neuropsychiatric symptoms. This illness, later defined as Parkinson's Disease (PD), is currently the most prevalent movement disorder and the second-most common neurodegenerative disorder in the developed world[1]. PD is hypothesized to be primarily caused by a loss of dopaminergic neurons in various areas of the brain, specifically the substantia nigra, and has layers of complexity[2]. Initially James Parkinson highlighted both key motor and non-motor symptoms of PD. Yet the physical symptoms (tremor, muscular rigidity, postural instability, and bradykinesia) are the most notable characteristics of PD and are usually the primary focus of research efforts[3]. Recently, the literature advocates for research initiatives that incorporate the neuropsychiatric symptoms of PD to ensure a holistic disease profile[4, 5].

The reported prevalence of PD ranges from 41 to 1,903 per 100,000 people. While these estimates do depend on setting and culture, one of the strongest factors influencing PD prevalence is age[6]. With the general United States population achieving older ages, PD poses a significant burden on society. Part of this burden comes for the neuropsychiatric aspects extending beyond the individual, and affecting their partners and families[7]. Specifically, if these neuropsychiatric complications are left untreated the cost of care has been reported to increase fourfold[8]. Common neuropsychiatric concerns include anxiety, depression, dementia, and apathy[9]. With evidence supporting a variety of treatment options, the neuropsychiatric symptoms can be addressed to ensure modern, affordable PD care[10].

One area that is particularly important to achieving a continuum of neuropsychiatric care is establishing the validity of psychometric tools when used among the PD population[11]. For example the ambiguity of certain motor symptoms, such as muscular rigidity, has been reported as a major confounder affecting the accuracy of diagnosing depression[12]. Historically, apathy has been considered a sign of depression, dementia, or another psychological condition[13]. As apathy has been more rigorously defined within the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V), the discriminant validity of common psychometric tools, especially between depression and apathy, warrants further investigation[14].

The primary purpose of this manuscript is to estimate the prevalence of depression among PD patients and evaluate the extent to which the observed association might be affected by difficulties in using common psychometric screening tools, such as the Beck Depression Inventory-II, to assess depression[15]. The overlap between PD, apathy, and depression symptoms has been reported to affect timely detection, and thus appropriate treatment, for depression [16].

2. Method

2.1 Study Population

Participants were volunteers that were recruited indiscriminant of sex or race on a rolling basis over the course of the study, largely from the metro Atlanta area, varying in age from 37 to 86, with a mean of 65. Participants with PD were recruited from existing Emory Healthcare patients who had an existing PD diagnosis. Controls were recruited from other studies conducted with Emory Healthcare or were family members of other participants. Controls are required to have no diagnosed neurological disorders or Parkinsonian symptoms. Initially, cases and controls were not aged matched, however this was added to the study protocol.

2.2 Study Design

Data were collected from a case-control cohort study that followed participants over 16-months. The study began in February 2011 and was conducted through Emory University School of Medicine and The Emory Clinic. After providing informed consent, study participants underwent a 4-hour study visit to obtain demographic information, complete a questionnaire battery, acquire vital signs, provide blood products, and undergo a research MRI sequence in a BITC scanner. Participants were excluded if they were unable to complete any aspect of the study protocol or were taking anti-psychotic medication. The Institutional Review Board of Emory University approved this study.

The questionnaire battery included the Unified Parkinson Disease Rating Scale III (UPDRS-III), Movement Disorder Society-Unified Parkinson Disease Rating Scale (MDS-UPDRS), Montreal Cognitive Assessment (MoCA), Rapid Eye Movement Behavioral Disorder – Sleep Questionnaire (RBD-SQ), Non-Motor Symptoms

Questionnaire (NMSQ), Beck Depression Inventory-II (BDI-II), Beck Anxiety Inventory (BAI), Patient Sleep Questionnaire (PSQ), Apathy Scale (AS), Fatigue Questionnaire (FQ), Freezing of Gait Questionnaire (FOG-Q), Physical Activity Scale (PAS), State-Trait Anxiety Inventory (STAI), Scales for Outcomes in Parkinson's Disease-Autonomic Questionnaire (SCOPA-AUT), Geriatric Depression Scale-15 (GDS-15).

2.3 Psychometric Tools

Depression in participants was established using the BDI-II. The BDI-II is a 21-item, 0-3 Likert scale that assesses symptoms of depression over the last 2 weeks. The BDI-II was developed for the DSM-IV criteria for major depression[17]. Reliability studies for the BDI-II in PD patients could not be located by the author. However, past literature has shown that the BDI-I has strong reliability and validity in PD patients and a Movement Disorder Society task force recommends the BDI for assessing depression in PD populations[18].

Apathy in participants was established using the AS. The AS is a 14-item, 0-3 Likert scale that assesses the symptoms of apathy. This scale is a reduced form of the original 18-item scale developed by Marin. The AS has been reported to have good psychometric properties when used in PD populations (internal consistency =.76, test-retest 1 week r=.90)[19]. A Movement Disorder Society task force classified the AS as "recommended for use" among PD populations[20].

2.4 Data Collection

Participants received most questionnaires prior to the study visit and completed them at home. Then they returned the completed questionnaires at the study visit and

were reviewed by a study coordinator to ensure completion and answer any remaining questions. The MDS-UPDRS, UPDRS-III, and the MoCA were the only questionnaires that were regularly completed at the study visit and were administer by study staff. Single data entry was completed using IBM SPSS. Data were analyzed using IBM SPSS version 24 and SAS version 9.4. Periodic auditing and range checks were done in order to assess data integrity.

2.5 Statistical Analysis

Prevalence/Specificity Analysis

The odds ratio between PD and depression was estimated in SPSS using the traditionally defined criteria for the BDI-II, a score of ≥ 14 signifying depression[21]. Due to the small sample size, no confounders were included in this analysis.

Due to the probability of misclassification bias being high, a multidimensional bias model will be used to investigate the influence of bias when screening is conducted with the Beck Depression Inventory - II. The specific bias parameters of interested are the sensitivity and specificity of the BDI-II in PD and control populations[11]. Bias analysis was conducted in Excel 14.6.7[22].

$$Bias\ adjusted\ Cases = \frac{[a - E^{+}(1 - SP_{E+})]}{[SE_{E+} - (1 - SP_{E+})]}$$

$$Bias\ adjusted\ Controls = \frac{[c - E^{-}(1 - SP_{E-})]}{[SE_{E-} - (1 - SP_{E-})]}$$

$$Bias\ adjusted\ Noncases = Total\ participants - Bias\ adjusted\ Cases$$

Factor Analysis

Based on prior literature, one reason that misclassification may occur is because the observed latent factor structure of the BDI-II and AS will not mirror the traditional latent factor structures when used among individuals with PD. A traditional three-factor model is supported for the latent factors for the BDI-II: a general depression factor, a somatic factor, and a cognitive factor[23]. A traditional three-factor model is supported for the latent factors for the AS: a cognitive factor, a behavioral factor, and an affective factor[24].

It is hypothesized that the misclassification bias is due to symptom overlap from PD and apathy with depression. A confirmatory factor analysis was used to provide evidence for the separation of depression and apathy in Parkinson's Diseases, using the hypothesis that the items from the BDI-II and AS would fall into the traditionally reported factor structure and would not cross load. The confirmatory factor analysis was conducted with statistical software IBM SPSS version 24, using a maximum likelihood approach and a Varimax rotation. Eigenvalues of 1 or greater were used for factor inclusion, with scree plots for reference to confirm the number of factors under investigation, and needed to have three or more individual components loaded appropriately. Any individual component that loaded below 0.4 and/or displayed cross loading was eliminated. The confirmatory factor analysis was conducted separately for cases and controls.

3. Results

3.1 Descriptive Characteristics

PD and control baseline visits were used for analysis, a final total of 66 PD participants and 65 control participants.

Table 1. Demographic Characteristics of Study Population

	Cases (n=66)	Controls (n=65)	Statistical Significance Value (p-value)
Age, years[a]			
n	66	65	
mean	63.18	67.05	T-test: 2.55 (.012)
s.d.	9.09	8.21	
Gender			
n	32	41	X^2: 2.83 (.093)
female	48.48%	63.08%	
Years of Education[a]			
n	64	63	
Mean	16.00	17.22	T-test: 2.86 (.005)
S.D.	2.59	2.38	
MoCA Score			
n	65	65	
Mean	26.78	27.52	T-test: 1.64 (.104)
S.D.	2.99	2.06	
Hoehn-Yahr Stage			
n	33		
Mean	2.00		
S.D.	0.00		
Disease Duration, Years			
n	44		
Mean	4.37		
S.D.	3.88		

[a]Statistically Significant Difference between Cases and Controls

Table 1 highlights general demographic information, cognitive ability, and the severity of PD among the study sample. The cases and controls had statistically significant differences in age and years of education, using an alpha value of 0.05. Regardless of statistical significance, these averages indicate that study sample is older and has a higher socio-economic status than the general population. Furthermore the Hoehn-Yahr Stage Score, which rates the clinical severity of PD; the average disease duration; and the MoCA average score suggests that the cases have low PD severity.

Table 2. Summary Statistics for Beck Depression Score for All Eligible Participants Stratified on Disease Status.

	Beck Depression Inventory Score Outcome[a]		Apathy Scale Score Outcome	
	Case	**Control**	**Case**	**Control**
n	66	65	66	65
mean	7.20	4.29	22.32	22.02
s.d.	5.85	4.39	3.49	2.88
minium	0	0	14	14
maximum	25	16	31	30
# missing	0	0	0	0
skewness	1.37	1.11	0.03	-0.004
kurtosis	1.70	0.38	-0.22	0.72

There was a statistically significant difference between the overall BDI-II scores between cases and controls (T-test value: 3.21, p-value: .002). Individuals with PD had higher scores on the BDI-II than controls. 6 cases and 2 controls were screened as having clinically significant depression. The observed OR for the association between PD and depression is 3.15 (0.61–16.22).

However, there was not a statistically significant difference between the average AS scores among cases and controls (T-test value: .541, p-value: .589).

3.2 Factor Analysis

Table 3. Factor Analysis for Beck Depression Inventory-II and Apathy Scale for Controls

Individual Component	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5	Factor 6	Factor 7[a]	Factor 8[a]	Factor 9[a]	Factor 10[a]
Suicidal Thoughts (BDI-II Q9)	0.922									
Punishment Feelings (BDI-II Q6)	0.892									
Pessimism (BDI-II Q2)	0.76									
Irritability (BDI-II Q17)	*0.697*			*0.707*						
Guilty Feelings (BDI-II Q5)	0.589									
Sadness (BDI-II Q1)	0.588									
Changes in Sleeping (BDI-II Q16)	0.572									
Tiredness and Fatigue (BDI-II Q20)		0.81								
Concentration Difficulty (BDI-II Q19)		0.768								
Loss of Energy (BDI-II Q15)		0.697								
Does anything interest you? (AS Q2)[b]		-0.575								
Loss of Interest (BDI-II Q12)			0.738							
Self-Dislike (BDI-II Q7)			0.715							
Loss of Interest in Sex (BDI-II Q21)			0.663							
Past Failure (BDI-II Q3)			0.621							
Indecisiveness (BDI-II Q13)				0.768						

Self-Criticalness (BDI-II Q8)	0.714		
Agitation (BDI-II Q11)	0.558		
Are you neither happy nor sad, just in between? (AS Q13)		0.797	
Do you need a push to get started on things? (AS Q12)		0.658	
Would you consider yourself apathetic? (AS Q14)		0.605	
Are you always looking for something to do? (AS Q5)		0.458	
Do you have motivation? (AS Q7)			0.814
Are you indifferent to things? (AS Q10)			0.557
Are you interest in learning new things? (AS Q1)			0.509
Does someone have to tell you what to do each day? (AS Q9)			0.474
Do you have the energy for daily activities?			0.436

(AS Q8) Do you have plans and goals for the future? (AS Q6)	0.43				
Worthlessness (BDI-II Q14)		0.711			
Changes in Appetite (BDI-II Q18)		0.671			
Are you concerned about your condition? (AS Q3)			0.749		
Do you put much effort into things? (AS Q4)			0.646		
Are you unconcerned with many things? (AS Q11)				0.774	
Loss of Pleasure (BDI-II Q4)[b]				0.391	
Crying (BDI-II Q10)					0.835

[a] *Factor is not signficant*
[b] *Component did not load appropriately*

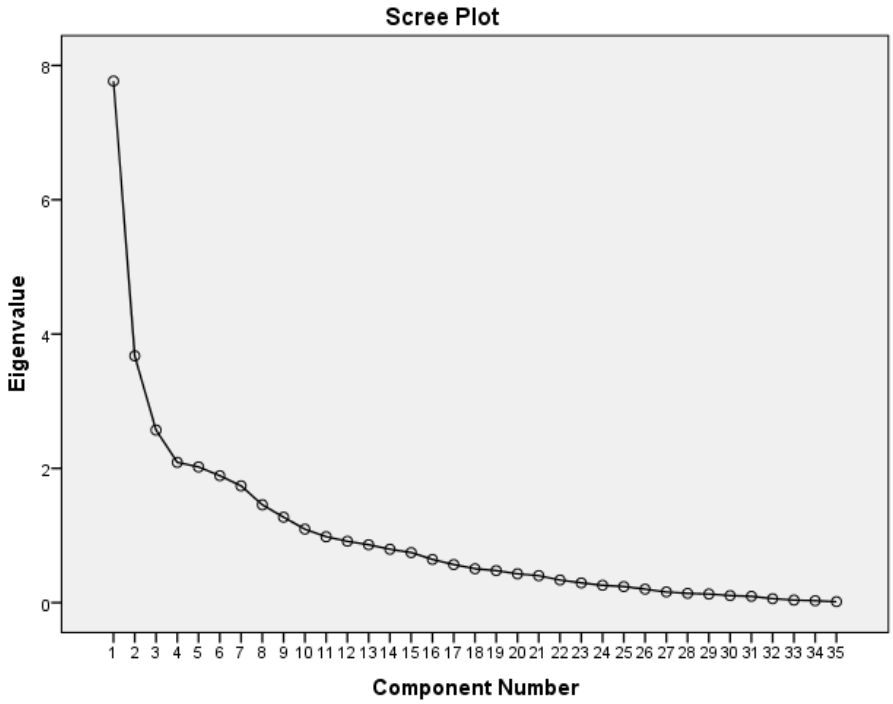

Figure 1: Scree plot for control factor analysis.

Table 4. Factor Analysis for Beck Depression Inventory-II and Apathy Scale for Cases

Individual Component	Factor 1	Factor 2	Factor 3	Factor 4[a]	Factor 5	Factor 6	Factor 7[a]	Factor 8[a]	Factor 9[a]	Factor 10[a]
Suicidal Thoughts (BDI-II Q9)								0.854		
Punishment Feelings (BDI-II Q6)						0.827				
Pessimism (BDI-II Q2)[b]	*0.424*							*0.478*		
Irritability (BDI-II Q17)[b]					*0.493*			*0.854*		
Guilty Feelings (BDI-II Q5)[b]						*0.407*	*0.448*			
Sadness (BDI-II Q1)	0.817									
Changes in Sleeping (BDI-II Q16)			0.672							
Tiredness and Fatigue (BDI-II Q20)			0.567							
Concentration Difficulty (BDI-II Q19)							0.551			

Loss of Energy (BDI-II Q15)		0.469					
Does anything interest you? (AS Q2)[b]			-0.652				
Loss of Interest (BDI-II Q12)				0.597			
Self-Dislike (BDI-II Q7)					0.658		
Loss of Interest in Sex (BDI-II Q21)[b]			-0.462				
Past Failure (BDI-II Q3)	0.756						
Indecisiveness (BDI-II Q13)				0.651			
Self-Criticalness (BDI-II Q8)		0.757					
Agitation (BDI-II Q11)					0.792		
Are you neither happy nor sad, just in between? (AS Q13)						0.525	
Do you need a push to get started on things? (AS Q12)		0.604					
Would you consider yourself apathetic? (AS Q14)		0.483					
Are you always looking for something to do? (AS Q5)						0.659	
Do you have motivation? (AS Q7)[b]		-0.515					

Are you indifferent to things? (AS Q10)[b]	-0.535					
Are you interest in learning new things? (AS Q1)[b]		-0.654				
Does someone have to tell you what to do each day? (AS Q9)[b]		-0.54				
Do you have the energy for daily activities? (AS Q8)[b]		-0.462				
Do you have plans and goals for the future? (AS Q6)[b]	-0.49					
Worthlessness (BDI-II Q14)				0.529		
Changes in Appetite (BDI-II Q18)		0.826				
Are you concerned about your condition? (AS Q3)						0.863
Do you put much effort into things? (AS Q4)			0.738			
Are you unconcerned with many things? (AS Q11)					0.77	
Loss of Pleasure (BDI-II Q4)		0.545				
Crying (BDI-II Q10)	0.813					

[a] *Factor is not signficant*

[b]*Component did not load appropriately*

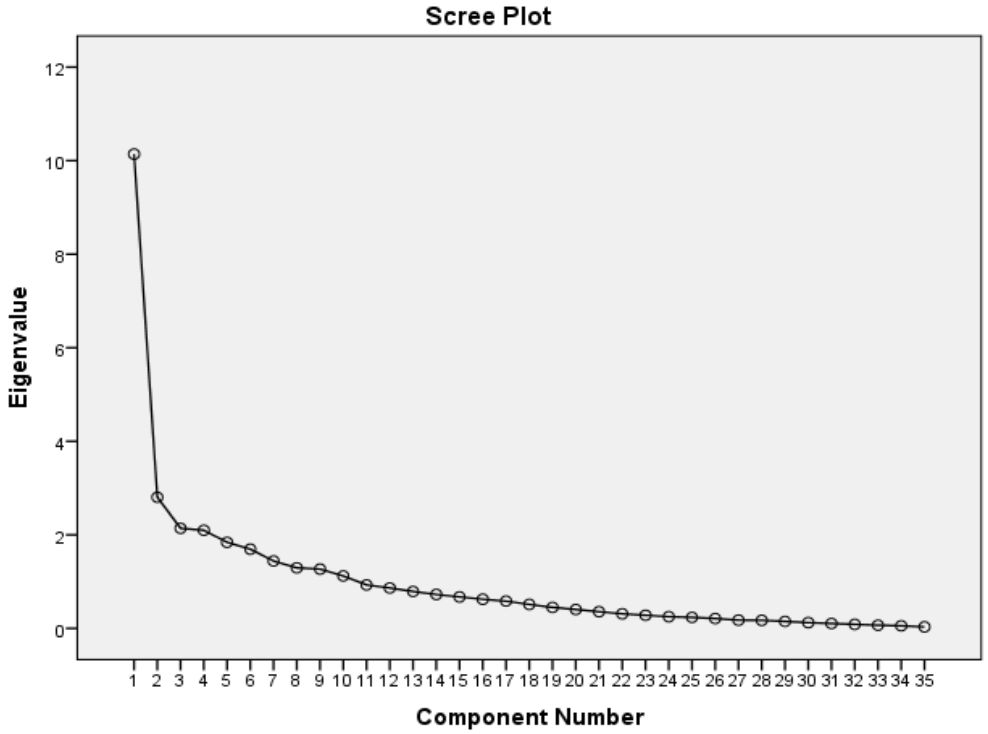

Figure 2: Scree plot for PD cases factor analysis.

Table 3 and Table 4 convey the latent factor structure of the BDI-II and AS among controls and cases, respectively. The results from both groups did not mirror the traditional factor structure, however there were commonalities between the observed factor structure in the control group and the traditional factor structure. The observed factor structure from the PD cases was not congruent with the observed factor structure from the control group or the traditional factor structure. In addition, there was a large amount of cross loading. These results suggest that the BDI-II and AS questionnaires operate differently when used among the PD population. Figure 1 and Figure 2 show the observed factor structure and the corresponding eigenvalues. A

higher eigenvalue was observed for Factor 1 among cases than controls, highlighting a larger amount of variance being accounted for by that factor.

3.3 Bias Analysis

Table 5. Bias-adjusted OR Values Using a Multidimensional Specificity Analysis for the Association Between Depression and Parkinson's Disease Using the Beck Depression Inventory-II.

		Specificity for Controls				
		0.96	*0.97*	*0.98*	*0.99*	*1*
Specificity for Cases	*0.9*	Negative	Negative	Negative	Negative	Negative
	0.91	Negative	1.22	0.09	0.05	0.03
	0.92	Negative	14.68	1.05	0.54	0.37
	0.93	Negative	28.14	2.01	1.04	0.7
	0.94	Negative	41.59	2.9	1.54	1.04
	0.95	Negative	55.05	3.8	2.04	1.38
	0.96	Negative	68.5	4.89	2.54	1.71
	0.97	Negative	81.96	5.53	3.04	2.05
	0.98	Negative	95.42	6.82	3.53	2.39
	0.99	Negative	99.59	7.78	4.03	2.72
	1	Negative	122.33	8.74	4.53	3.06

Sensitivity was kept constant throughout multidimensional bias analysis.

Table 5 displays the bias-adjusted OR values and trends from a multidimensional specificity analysis. From a priori hypotheses, the misclassification of depression among individuals with PD is due to a lack of specificity, rather than sensitivity. Thus, the sensitivity was kept constant at .92 for controls and .95 for cases. Most of the combinations of specificity did not produce realistic, non-negative, bias-adjusted estimates. However, for the combinations that did provide realistic bias-adjusted estimates, only a few suggested that depression is more common among controls than individuals with PD. Overall, Table 5 highlights how, as the specificity decreases, the association between depression and PD is more likely to be an overestimate.

4. Discussion

The prevalence of depression among individuals with PD was estimated to be 9.1% (95% CI: 2.1–16.0) in contrast to only 3.1% (95% CI: 0.0–7.3) among individuals without PD. The observed odds ratio (OR) for the association between PD and depression is 3.15 (95% CI: 0.61–16.22). While the observed OR does suggest that depression is more prevalent among individuals with PD than other older adults, there is a large amount of uncertainty because of the imprecision in the estimate.

While the observed prevalence estimate falls within the lower end of the reported range of 8-37%, there are reasons to believe that depression may not be accurately measured in the PD population[25]. To highlight the potential influence of misclassification on the observed OR, and by extension the prevalence, a multidimensional bias analysis was conducted. It is expected that the specificity of the BDI-II decreases due to overlapping symptoms of PD and depression. Conditional on the bias model being accurate, as the specificity for cases decreases, the bias-adjusted estimates for the odds ratio describing the association between PD and depression increase. This trend enforces the idea that depression is overestimated. However, the specificity ranges that were used are not congruent with the published specificity ranges of the BDI-II among either the cases or controls. The ranges used in Table 5 were the values that provided a non-negative bias-adjusted estimate.

In the factors that met the inclusion criteria, the control group fit a six-factor model: general depression (factor 1), somatic depression (factor 2), cognitive depression (factor 3), dysphoria (factor 4), behavioral apathy (factor 5), cognitive apathy (factor 6). The PD case group fit a five-factor model: general depression (factor

1), frustration (factor 2), somatic changes (factor 3), dysphoria (factor 5), and self-perception (factor 6). These results contribute to the growing body of literature suggesting an entangled relationship between two psychiatric states, depression and apathy, in PD populations. The observed latent factors from the PD group did not provide a clear separation and support the idea that apathy can influence the estimation depression.

Furthermore, an "overlapping PD and mood symptoms" factor should be included with the BDI-II and AS latent factor structure. The "overlapping symptoms" factor would account for loss of interest and pleasure, as well as other physical complaints. Our results support this additional factor, since many of the somatic components, which are common symptoms of PD, load onto a single factor. Using an overlapping symptoms factor, individual components or symptoms that lead to a false positive diagnosis of minor or major depression disorders could be identified. Hypothetically, minor depression can be easily misdiagnosed if a patient has loss of interest or loss of pleasure plus an additional symptom associated with PD.

The current study had numerous strengths. Both psychometric tools are supported by the Movement Disorder Society to assess mental health concerns among individuals with PD. In addition, this study offers a careful evaluation of how the psychometric tools work in PD patients.

The current study has several limitations. First and foremost, this study did not use psychiatric interviews and DSM-V diagnoses. This would have allowed participants to be separated by depression severity, minor or major. Another weakness is that the study sample size was relatively small, which is highlighted in the large range of

uncertainty surrounding our estimates. Finally, the generalizability of these results to the greater PD population is questionable. The sample was obtained from a quaternary healthcare system, Emory University Healthcare, and in this paper, being used for a secondary analysis. It can be argued that the participants in this study have a higher socioeconomic status than the general population, which is supported by the relatively high number of years of education completed. Participants had to have a high enough health status to complete the study protocol, which exclude any cases that had advance stages of PD. Another point of caution is that the higher prevalence of depression among individuals with PD does not guarantee a higher incidence of depression among individuals with PD. The higher prevalence of depression could be a result of individuals with PD having longer durations of depressive episodes, and thus are more easily detected by clinicians. The extent of, and how, incidence or duration influence the higher prevalence of depression is unknown and not explored in this study.

5. Conclusion and Future Directions

While the use of psychometric tools for detecting mental health disorders can assist clinicians in identifying patients at risk, it is important that the tools provides accurate and meaningful results to base further clinical decisions. Support was found that depression is more common among individuals with PD than in other old adults. However, the study of this association is complicated by the influence of apathy and PD symptoms. In addition, when arguing that the overlapping symptoms between PD and depression causes the specificity of common depression screening tools to decrease, depression can be overestimated. However, the extent to which this is true depends on the validity of the psychometric tool used to measure depression. Thus, the discriminant validity of two common mental health screening tools, BDI-II and AS, when using among the PD population requires future research.

Future studies are needed to examine depression in individuals with PD and how to measure it. Assessing the reliability of the BDI-II when used among the PD population should be an immediate goal for future research studies. Then, estimating the incidence of depression among individuals with PD could clarify the reasoning behind the reported prevalence estimates. In addition, studies investigating the relationship between depression, apathy, and cognition are warranted. Several studies have found common mental health disorders to be associated with impaired executive functioning, which is another common comorbidity of PD.

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