Modeling depression in Parkinson disease

Disease-specific and nonspecific risk factors

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ABSTRACT

Objective: To construct a model for depression in Parkinson disease (PD) and to study the relative contribution of PD-specific and nonspecific risk factors to this model.

Methods: Structural equation modeling of direct and indirect associations of risk factors with the latent depression outcome using a cross-sectional dataset of 342 patients with PD.

Results: A model with acceptable fit was generated that explained 41% of the variance in depression. In the final model, 3 PD-specific variables (increased disease duration, more severe motor symptoms, the use of levodopa) and 6 nonspecific variables (female sex, history of anxiety and/or depression, family history of depression, worse functioning on activities of daily living, and worse cognitive status) were maintained and significantly associated with depression. Nonspecific risk factors had a 3-times-higher influence in the model than PD-specific risk factors.

Conclusion: In this cross-sectional study, we showed that nonspecific factors may be more prominent markers of depression than PD-specific factors. Accordingly, research on depression in PD should focus not only on factors associated with or specific for PD, but should also examine a wider scope of factors including general risk factors for depression, not specific for PD.
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GLOSSARY

ADL = activities of daily living; **CFI** = Comparative Fit Index; **CI** = confidence interval; ***DSM-IV*** = *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition; **HAMD** = Hamilton Depression Rating Scale; **IADL** = Instrumental Activities of Daily Living; **MDS** = Movement Disorders Society; **MI** = modification index; **MMSE** = Mini-Mental State Examination; **PD** = Parkinson disease; **RMSEA** = root mean square error of approximation; **UPDRS** = Unified Parkinson's Disease Rating Scale.

Clinically relevant depressive symptoms are present in 35% of patients with Parkinson disease (PD), and depression has been identified as the most important determinant of quality of life in these patients.[1–3] Depressive disorders, in the general population as well as in patients with PD, develop in the context of multiple interacting risk and protective factors. These factors may or may not be related to PD. In the general population, longitudinal studies have shown that risk factors for depression include female sex, older age, being single, a low level of education, physical disease, a personal or family history of depression, cognitive impairment, smoking, and alcohol. Moreover, personal circumstances, such as early childhood adversity, personality traits and coping, and recent positive and negative life events, also have a role.[4–7] In cross-sectional studies, several PD-specific risk factors for depression have been identified, including more severe motor symptoms, longer disease duration, more advanced disease stage, greater limitations in disease-related activities of daily living (ADL), higher daily levodopa equivalent dose, and the presence of nonmotor symptoms such as hallucinations, sleep disturbances, and dysautonomia.[8–11] Few studies have examined the role of general risk factors for depression in PD.

Supplemental data at www.neurology.org

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The objective of this study was to construct a model for depression in PD, and to compare the relative contribution of PD-specific and nonspecific markers to this model.

METHODS

The present study was performed from the database of a cross-sectional multicenter study on anxiety disorders in PD that was conducted in 2008 and 2009, the results of which have been described in 2 reports published earlier.[12,13]

Population. The database includes 342 patients with PD, diagnosed according to the Queen Square Brain Bank clinical criteria.[14] Subjects, recruited from the movement disorders clinics and the neurology and psychiatry clinics of 6 centers in the United States, Europe, and Australia, underwent a comprehensive neurologic and neuropsychiatric assessment. Patients with neurodegenerative disorders other than PD were excluded. Patients with clinically relevant cognitive symptoms were also excluded. This was operationalized as a Mini-Mental State Examination (MMSE) score <26, following the recommendation of a Movement Disorders Society (MDS) Task Force.[15,16] All types of neurologic and psychopharmacologic medication were allowed. Patients undergoing deep brain stimulation were excluded.

Standard protocol approvals, registrations, and patient consents. The study was approved by the local Medical Ethics Committees of all participating institutions. Patients gave written informed consent before inclusion in the study.

Assessment. Demographic and disease-related variables were assessed during an unstructured clinical interview. Motor function, disease-related decline in ADL, and complications of therapy were assessed with the Unified Parkinson's Disease Rating Scale (UPDRS).[17] Disease stage was assessed with the Hoehn & Yahr staging system.[18] Cognitive functions and instrumental ADL were assessed with the MMSE and Lawton Instrumental ADL (IADL) Scale.[15,19] Depressive symptom severity was quantified with the 17-item Hamilton Depression Rating Scale (HAMD)[20]; anxiety was assessed with the clinician-rated Hamilton Anxiety Rating Scale.[21] Patients with "on/off" fluctuations were assessed only during "on" states, as advised by an MDS Task Force.[22] Also in accordance with MDS Task Force recommendations, we followed an "inclusive" approach to rating symptoms, meaning that symptoms were scored as observed or reported, irrespective of their assumed etiology.[22] The presence of *DSM-IV*–defined depressive and anxiety disorders was determined using the Mini International Neuropsychiatric Inventory (a structured interview for *DSM-IV* disorders) sections for depression (A, B) and anxiety (D, E, F, H).[23]

Statistical analysis. Structural equation modeling was performed in M*plus* 7 (Muthén & Muthén, Los Angeles, CA) with the aim of identifying the most parsimonious model (for model fit and number of included parameters) that still accounted for a substantial part of the variance in the depression outcome.

Independent variables were chosen on the basis of their known contribution to depression in the general population and in PD from the available literature. An exploratory correlation analysis was conducted between all potential parameters to discover collinearity. If the Pearson correlation coefficient "*r*" between 2 potential parameters was both significant ($p < 0.005$ after correction for multiple testing) and >0.40, a decision was made to include only one of these parameters in the model, where general markers would have preference over PD-specific markers. An initial theoretical Multiple Indicators Multiple Causes model was constructed with the remaining parameters. Because the Multiple Indicators Multiple Causes model included continuous, binary, and ordered categorical variables, a mean- and variance-corrected weighted least-squares estimator was used.

For the sake of the analysis, on the measurement side of the model, a latent variable of "depression" was constructed by regressing the 17 items of the HAMD on a single continuous latent variable. A "latent" variable in structural equation modeling is a hypothetical construct that is not measured directly, but estimated in the model from several measured variables, in this case from the individual HAMD items. Compared with using observed HAMD total scores, this approach has the advantage that only shared variances among the items contribute to the depression factor, whereas nonshared (unique) variance is regarded as measurement error, resulting in a purer operationalization of the latent ("true") depression construct.

For the structural part of the model, direct and indirect paths of the variables theorized to influence the depression outcome were specified in an initial model (model 1). Model fit was primarily assessed by inspecting the root mean square error of approximation (RMSEA) and the Comparative Fit Index (CFI). For the RMSEA, scores ≤0.05 indicate good fit, and scores ≤0.08 indicate acceptable fit. The CFI ranges from 0 to 1 with scores ≥0.95 indicating good fit, and scores ≥0.90 indicating acceptable fit.[24] Because the χ^2 test is known to become positively biased with increasing sample size, this measure was not used to assess model fit.[24]

Based on model fit, the model was respecified via a number of consecutive steps. First, paths that did not contribute substantially ($p > 0.10$) to the model were removed in a backward 1-to-1 fashion, starting with the model with the path with the highest p value, resulting in a second model (model 2). Next, modification indices (MIs) were inspected to explore whether the model could be improved by specifying additional paths among the remaining variables. Additional paths were included based on the MIs and substantive interpretation. Finally, MIs were inspected for correlated errors (residual correlation) among variables whose specification might improve the model. This resulted in the final model.

In a last step, we examined whether PD-specific variables and PD-unrelated variables contributed equally to the depression outcome. Because a direct comparison of the joint effect of the manifest variables was not possible because of the correlated nature of individual items, 2 continuous latent variables (factors) were generated and regressed on depression. Their standardized regression coefficients were compared using a Wald test. To have both factors on the same scale, their factor variances were fixed to 1.

RESULTS

The demographic and disease characteristics of the included sample are listed in table 1. The study population comprised 207 men and 134 women with an average age of 64.8 years (SD 9.2 years). Based on the Mini International Neuropsychiatric Inventory, 48 participants (14.1%) met diagnostic criteria for a current major depressive episode, 19 (5.6%) met the diagnostic criteria for dysthymia, and 64 (18.8%) had a clinically relevant depressive symptom (defined here as a score ≥12), but did not meet the criteria for major depressive episode or dysthymia.

Results of the exploratory correlation analysis are shown in table e-1 on the *Neurology*® Web site at www.neurology.org. Based on the correlations, it was decided to exclude disease stage (Hoehn & Yahr classification) from the model because of a moderately

Table 1 Demographic and disease characteristics of the sample (n = 342)

Variable	Percentage	Mean (SD) or median (range)
Female	39	
Male	61	
Age, y		64.8 (9.2)
Duration of PD, y		8.3 (5.6)
UPDRS section 2 (ADL)		11.6 (6.8)
UPDRS section 3 (motor)		26.4 (12.4)
UPDRS section 4 (complications)		3.5 (3.5)
Hoehn & Yahr stage		2 (1–5)
On/off fluctuations	52	
Major depression	14.1	
Dysthymia	5.7	
History of depression	46.1	
History of anxiety disorder	31.9	
Family history of depression	33.4	
Family history of anxiety disorder	19.4	
Family history of PD	19.7	
HAMD score		7.7 (5.9)
HARS score		11.3 (8.5)
IADL score		7 (1.5)
MMSE score		28.5 (1.7)
Use of levodopa	85.3	
Use of dopamine agonist	61.6	
Use of antidepressant[a]	34.4	

Abbreviations: ADL = activities of daily living; HAMD = Hamilton Depression Rating Scale; HARS = Hamilton Anxiety Rating Scale; IADL = Instrumental Activities of Daily Living; MMSE = Mini-Mental State Examination; PD = Parkinson disease; UPDRS = Unified Parkinson's Disease Rating Scale.

[a] Antidepressants were used by 56% of patients who had major depressive disorder, by 42% of patients with dysthymia, and by 30% of patients without current depressive symptoms (i.e., the depressive symptoms were in remission or the antidepressant was used for other indications, such as anxiety or sleep problems).

strong correlation with UPDRS sections 2 and 3 and IADL ($r = 0.60$, $r = 0.46$, and $r = -0.51$, respectively; all $p < 0.01$). UPDRS 4 total score was excluded because of its strong correlation with off-periods ($r = 0.66$; $p < 0.01$). In addition, it was considered more informative to include separate parameters for the presence of "off-periods" and dyskinesias in the model instead of the single parameter of the UPDRS section 4. It was decided to keep both the UPDRS section 2 (ADL) and the score on the IADL Scale in the model, despite moderate correlation ($r = 0.46$; $p < 0.01$). This was done because it was thought that the UPDRS section 2 scores PD-related ADL, whereas the IADL Scale can be considered a more general measure of personal functioning. It was further decided to keep the UPDRS section 2 score in the model despite its moderate correlation with UPDRS section 3 ($r = 0.51$; $p < 0.01$).

The initial theoretical model is shown in figure 1 and specified in table 2. Nonspecific parameters included in this model were age, sex, cognitive status (MMSE total score), instrumental ADL function (IADL total score), history of depression, history of anxiety, family history of depression, and family history of anxiety. PD-specific parameters in the model were disease duration, motor symptom severity (UPDRS section 3 total score), disease-specific ADL (UPDRS section 2 total score), the presence of motor fluctuations (based on UPDRS section 4), the presence of dyskinesias (based on UPDRS section 4), the use of levodopa, and the use of a dopamine agonist. This model showed acceptable fit for RMSEA, but poor fit for CFI (RMSEA 0.069 with a 90% confidence interval [CI] = 0.064–0.074; CFI 0.644).

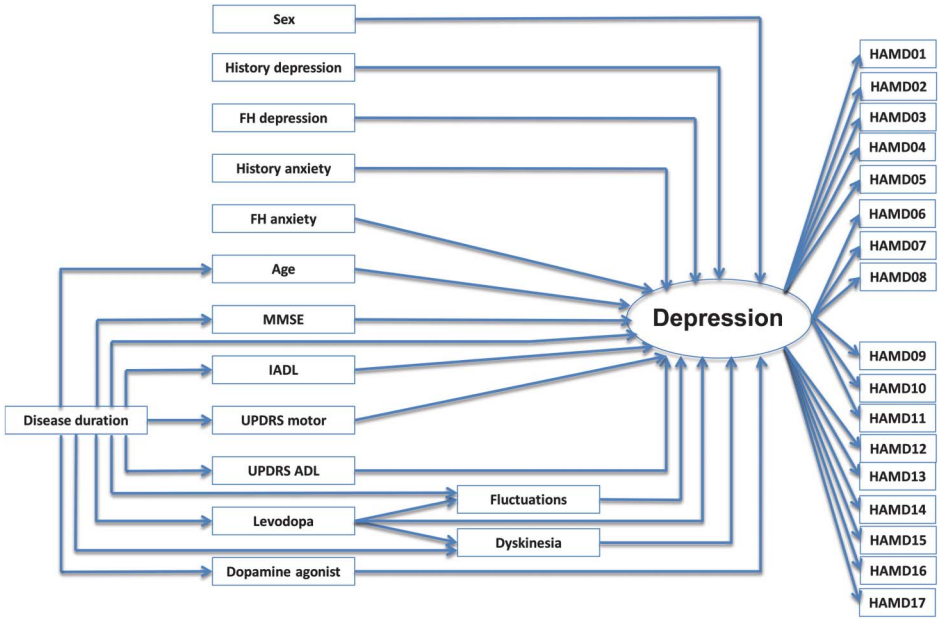
In a first revision, paths that did not contribute substantially to the model were deleted: age, family history of anxiety, the use of a dopamine agonist, the presence of dyskinesias, and the indirect effects of levodopa. This resulted in a second, simpler model showing similar fit (RMSEA 0.074 with a 90% CI = 0.069–0.080; CFI 0.675). This intermediate model is shown in figure e-1, and specified in table e-2.

A second revision, which allowed for correlated residuals among variables and extra paths, resulted in a model with better fit (RMSEA 0.051 with a 90% CI = 0.044–0.058; CFI 0.854). In this last model, the disease-specific ADL parameter was removed, and an indirect effect of the MMSE on depression through IADL function was added, as well as a correction for interaction of IADL and UPDRS section 3. This model is shown in figure 2 and specified in table 3. The model explains 41% of the observed variance in the depression outcome.

We finally compared the effects of the PD-specific and PD-unrelated variables in the model after both types of variables had been regressed on 2 latent variables. This showed that both factors were significantly associated with depression and together accounted for 69% of its variance. The PD-unrelated factor was significantly more strongly related to depression ($\beta = 0.742$, standard error = 0.078, $p < 0.001$) than the PD-specific factor ($\beta = 0.247$, standard error = 0.082, $p = 0.003$). This was confirmed in a Wald test comparing the effects of the 2 factors ($\chi^2 = 12.93$, $df = 1$, $p < 0.001$).

DISCUSSION In this study, we showed that 41% of the variance in depressive symptoms in patients with PD was explained by 9 variables: 6 variables not specific for PD, and 3 specific for PD. When both types of factors were regressed on 2 latent variables, they together explained 69% of variance. In this model, the latent variable representing the nonspecific factors had a 3-times-higher β, i.e., a 3-times-larger influence,

Figure 1 Initial model of depression in PD (model 1)



This initial model is the hypothesized model and includes all nonspecific and PD-specific variables. Model specifics and regression coefficients are given in table 2. ADL = activities of daily living; FH = family history; HAMD = Hamilton Depression Rating Scale; IADL = Instrumental Activities of Daily Living; MMSE = Mini-Mental State Examination; PD = Parkinson disease; UPDRS = Unified Parkinson's Disease Rating Scale.

than the latent variable of all PD-specific factors. However, the manifest variables most strongly associated with depression in our final model were all PD-specific markers: the UPDRS motor score, use of levodopa, and disease duration. Dopamine agonists have often been associated with mood-improving effects in patients with PD.[25] In our study, however, the use of dopamine agonists did not have a significant negative (nor positive) association with the depression outcome.

Taken together, both nonspecific and PD-specific variables appear to contribute to depression in PD, with PD-specific factors showing strong individual associations, while nonspecific factors seem to have a larger net effect on the depression outcome.

Published research on the relative contribution of PD-specific and nonspecific factors to the risk of depression in PD is scant. In one cross-sectional study involving 161 patients with PD, a logistic regression model consisting of 5 general, PD-nonspecific risk factors for depression (age, sex, history of depression, family history of depression, and somatic comorbidity) correctly predicted whether a patient was depressed or not in 75% of cases. Adding PD-specific risk factors into the logistic model did not increase the discriminative performance.[26] Although other studies have included some general risk factors for depression, the influence of these factors has not been directly compared with that of PD-specific factors. In line with our findings, Riedel et al.[11] and Becker et al.[9] report female sex to be associated with depression. Older age, cognitive decline, the use of nonsteroidal anti-inflammatory drugs, and physical comorbidity other than PD are also related to depression in PD.[8,11] Research seems to have moved away from the study of personality characteristics and coping in the etiology of depression in PD. Older studies report a premorbid personality in PD, characterized by inflexibility and obsessiveness, which may predispose for depression.[27] Maladaptive cognitive coping is also associated with increased feelings of depression and anxiety.[28,29] Finally, life events have been shown to have an important role in the development of major depression in PD, although its effect seems to be modified by social support and coping mechanisms.[30] These factors should receive more consideration in future studies.

Our findings have important conceptual implications for our understanding of depression in PD. They show that several PD-specific factors are indeed important markers for depression, but that their true relevance is only understood by adopting a broad multifactorial approach to depression that also includes nonspecific markers: PD-specific factors are associated with depression, but their net effect is smaller than that of a number of general risk factors for depression, not specific for PD. Based on these findings, one could hypothesize that those patients with PD who develop depression are likely to have a preexisting vulnerability because of their exposure to common risk factors for depression that are unrelated to PD. Our findings also imply that a broader

Table 2 Standardized regression coefficients of the initial (theoretical) model including 15 variables (model 1)

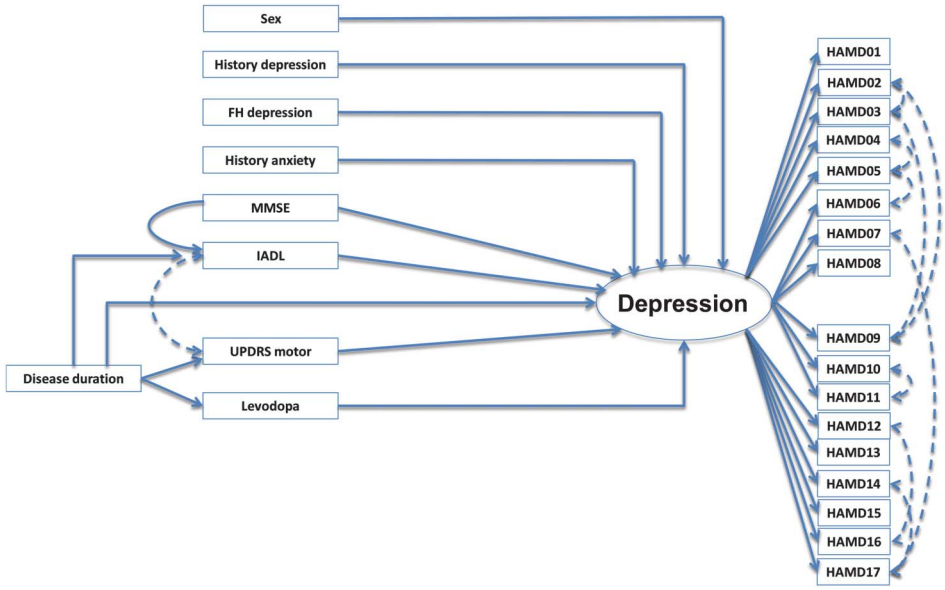
Parameter	Dependent variable	B	SE	β	*z* Statistic	*p*
Sex	Depression	−0.371	0.148	−0.151	−2.498	0.012
Age	Depression	−0.003	0.007	−0.019	−0.365	0.715
History of depression	Depression	0.544	0.165	0.226	3.297	0.001
History of anxiety	Depression	0.400	0.165	0.160	2.423	0.015
FH of depression	Depression	0.232	0.144	0.113	1.613	0.107
FH of anxiety	Depression	−0.081	0.171	−0.026	−0.471	0.638
MMSE	Depression	−0.177	0.043	−0.244	−4.162	<0.001
IADL	Depression	−0.233	0.051	−0.279	−4.583	<0.001
Disease duration	Depression	−0.096	0.026	−0.445	−3.734	<0.001
UPDRS motor (s. 3)	Depression	0.063	0.011	0.378	5.819	<0.001
UPDRS ADL (s. 2)	Depression	0.061	0.012	0.335	5.120	<0.001
Fluctuations	Depression	0.045	0.122	0.050	0.371	0.711
Dyskinesias	Depression	−0.085	0.151	−0.109	−0.563	0.573
Use of levodopa	Depression	0.328	0.275	0.349	1.194	0.232
Use of dopamine agonist	Depression	−0.084	0.083	−0.071	−1.018	0.309
Disease duration	Age	0.126	0.103	0.080	1.218	0.233
Disease duration	MMSE	−0.025	0.017	−0.086	−1.517	0.129
Disease duration	IADL	−0.068	0.014	−0.264	−4.918	<0.001
Disease duration	Levodopa	0.143	0.021	0.625	6.856	<0.001
Disease duration	Dopamine agonist	0.030	0.012	0.164	2.480	0.013
Disease duration	UPDRS s. 2	0.373	0.062	0.316	5.975	<0.001
Disease duration	UPDRS s. 3	0.274	0.072	0.214	3.808	<0.001
Disease duration	Fluctuations	0.004	0.024	0.018	0.175	0.861
Levodopa	Fluctuations	0.671	0.134	0.647	5.020	<0.001
Disease duration	Dyskinesias	−0.024	0.033	−0.087	−0.710	0.478
Levodopa	Dyskinesias	0.971	0.251	0.810	3.862	<0.001

Abbreviations: ADL = activities of daily living; FH = family history; IADL = Instrumental Activities of Daily Living; MMSE = Mini-Mental State Examination; s. = section; SE = standard error; UPDRS = Unified Parkinson's Disease Rating Scale.

approach should be followed in future studies into the etiology of depression in PD, including not only PD-specific, but also general, nonspecific risk factors.

Our study has several limitations. First, the analysis was performed on an existing database of a cross-sectional study into anxiety in patients with PD. Parameters selected to be included in the model were based on available data, which implies that other important parameters that may be considered markers of depression, such as marital status, the availability of a caregiver, personality, coping style, and past or recent life events were not included in the study. Also, protective factors, such as the use of antidepressants and recent positive life events were not included in the analysis. This may also elucidate why our final model explains 41% of the total variance in depression. Although this may seem a low percentage, it underscores that depressive syndromes are complex and etiologically multifactorial. Inclusion of more variables in the model would provide a more complete psychosomatic overview of all factors associated with depressive disturbances in PD. Notable psychological variables, such as the ones listed just above, warrant additional study given the fact that they are known risk factors for depression in the general population as well as in PD. Next, it is difficult to separate markers that are related to PD and those that are not directly related to PD. In patients with PD, cognitive decline and decline in ADL functions may be due to PD, but these are also known risk factors for depression in the general population, and hence not specific for PD. This is why the authors used the terms "PD-specific" and "nonspecific" rather than "PD-related" and "PD-unrelated" factors. Another limitation is the fact that our dataset is cross-sectional, and hence no causal interferences can be drawn. Despite these shortcomings, the database was large enough to allow structural equation modeling analysis with a

Figure 2 Final model of depression in PD (model 3)



This final model allows for correlated residuals (dashed lines) among variables and extra paths. Model specifics and regression coefficients are given in table 3. FH = family history; HAMD = Hamilton Depression Rating Scale; IADL = Instrumental Activities of Daily Living; MMSE = Mini-Mental State Examination; PD = Parkinson disease; UPDRS = Unified Parkinson's Disease Rating Scale.

substantial number of parameters. Finally, model fit for all models was acceptable to good for the RMSEA, although not for CFI. Hence, our reliance on the RMSEA might seem arbitrary. However, CFI tends to worsen as the number of variables increases.[31] In addition, use of the CFI (and other incremental measures of fit) has been discouraged if the baseline model has an RMSEA <0.158,[32] which is the case in our data (RMSEA of the baseline model is 0.125). Again, these analyses are exploratory and limited as outlined above. Finally, the model requires confirmation in a longitudinal design that includes more psychological and contextual variables.

In this study, we showed that individual PD-specific factors are strongly associated with depression, but that nonspecific factors, as compared with PD-specific factors, contributed to a substantially larger degree to the presence of depressive disturbances. These

Table 3 Standardized regression coefficients showing direct effects within specified paths for the final model including 8 variables (model 3)

Parameter	Dependent variable	B	SE	β	z Statistic	p
Sex	Depression	−0.442	0.163	−0.166	−2.711	0.007
History of depression	Depression	0.670	0.179	0.256	3.743	<0.001
History of anxiety	Depression	0.499	0.178	0.184	2.809	0.005
FH of depression	Depression	0.312	0.147	0.140	2.116	0.034
MMSE	Depression	−0.185	0.050	−0.242	−3.735	<0.001
IADL	Depression	−0.109	0.049	−0.120	−2.234	0.026
Disease duration	Depression	−0.067	0.023	−0.289	−2.935	0.003
UPDRS motor (s. 3)	Depression	0.056	0.012	0.302	4.722	<0.001
Use of levodopa	Depression	0.306	0.109	0.303	2.799	0.005
Disease duration	UPDRS s. 3	0.261	0.075	0.207	3.508	<0.001
Disease duration	Levodopa	0.145	0.021	0.631	6.803	<0.001
Disease duration	IADL	−0.065	0.014	−0.253	−4.753	<0.001
MMSE	IADL	0.171	0.037	0.202	4.557	<0.001

Abbreviations: FH = family history; IADL = Instrumental Activities of Daily Living; MMSE = Mini-Mental State Examination; s. = section; SE = standard error; UPDRS = Unified Parkinson's Disease Rating Scale.

data underscore the importance of understanding depression in PD within a complex multifactorial framework. Accordingly, it is critical that future studies into the etiology of depression in PD (and most likely studies addressing other psychopathologic syndromes in PD as well) have a wider scope and be designed to include general risk factors for depression that are not specific for PD, while including psychological factors and factors associated with PD. A restricted approach, limited to PD-specific factors, obscures the complex nature of psychopathologic comorbidities encountered in PD, and may subsequently lead to wrong conclusions about what might be salient targets for prevention and treatment.

AUTHOR CONTRIBUTIONS

A.F.G. Leentjens: study concept and design, acquisition of data, analysis and interpretation, writing the manuscript, study supervision. A.J.H. Moonen: acquisition of data, analysis and interpretations, critical revision of the manuscript for intellectual content. K. Dujardin, L. Marsh, P. Martinez-Martin, I.H. Richard, and S.E. Starkstein: data acquisition, interpretation of results, critical revision of the manuscript for intellectual content. S. Köhler: analysis and interpretation, critical revision of manuscript for intellectual content.

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