

# The Vascular Depression Subtype: Evidence of Internal Validity

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**Background:** Vascular depression has been proposed as a unique diagnostic subtype in late life, yet no study has evaluated whether the specified clinical features associated with the illness are jointly indicative of an underlying diagnostic class.

**Methods:** We applied latent class analysis to two independent clinical samples: the prospective, cohort design, Neurocognitive Outcomes of Depression in the Elderly (NCODE) study and the 8-week, multicenter, double blind, placebo-controlled Old-Old study.

**Results:** A two-class model consisting of vascular and nonvascular depressed patients provided an excellent fit to the data in both studies,  $\chi^2(6) = 2.02, p = .90$  in the NCODE study and  $\chi^2(6) = 7.024, p = .32$  in the Old-Old study. Although all of the proposed features of vascular depression were useful in identifying the illness, deep white matter lesion burden emerged with perfect sensitivity (1.00) and near-perfect specificity (.95), making it the only indicator necessary to determine class membership.

**Conclusions:** These findings, replicated across two independent clinical samples, provide the first support for the internal validity of vascular depression as a subtype of late-life depression.

**Key Words:** Cerebrovascular disease, deep white matter lesions, executive dysfunction, late-onset depression, vascular depression

Vascular depression has been proposed as a unique diagnostic subtype of late-life depression (1–4). The concept initially emerged from the finding that patients with late-onset depression (LOD) had higher rates of cerebrovascular disease as evidence by hyperintensities (HIs) on structural magnetic resonance imaging (MRI) compared to patients with early-onset depression (1,5–7). It was further observed that patients with LOD and HIs also demonstrated greater neuropsychological impairment, including, but not limited to, tests of executive dysfunction (ED) (7–10). Based on these observations, it was hypothesized that structural damage to the frontostriatal tracts resulting from ischemic cerebrovascular disease creates a vulnerability to depression in late life that is characterized by deficits in executive functioning (1).

A number of different definitions for vascular depression and other related syndromes have been proposed in the last decade using different combinations of LOD, ED, and vascular disease as core features (2,3,11–13). Despite different definitions, it has been suggested that vascular depression meets criteria for a valid diagnostic subtype based on studies of clinical profile and treatment outcome (3,11,14,15). Sneed *et al.* (16) have argued that relying on studies of clinical profile and treatment outcome (i.e., external validity) to determine diagnostic validity is problematic when each study uses different criteria to define the illness, i.e., there is no way of knowing whether the different

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definitions correspond to multiple diagnostic groups or a single, underlying diagnostic class.

Therefore, the next logical step is to evaluate the internal validity of vascular depression by determining 1) whether a subgroup can be identified among late-life depressed patients that is consistent with the vascular depression hypothesis; and 2) what combination of the core features most accurately identifies this subgroup. This study addresses this next critical step using latent class analysis (LCA) (17,18), and to evaluate the validity and generalizability of the findings, we tested the latent class models across two independent clinical studies.

## Methods and Materials

### Samples

The Neurocognitive Outcomes of Depression in the Elderly (NCODE) study (19) uses a prospective, cohort design to examine neurocognitive outcomes in depressed older adults receiving naturalistic treatment in an outpatient, academic medical setting. All depressed subjects ( $n = 367$ ) met DSM-IV criteria for single episode or recurrent major depression, were at least 60 years of age at baseline enrollment, and had baseline Mini-Mental Status Exam (MMSE) scores of greater than or equal to 25. Participants were excluded if they had another major psychiatric illness, alcohol or drug abuse or dependence, a clinical diagnosis of primary neurological illness (including dementia), or were taking medications or had a medical illness or physical disability that affected cognitive function.

Of the 367 NCODE study participants, 150 provided baseline data on age at onset, a measure of ED, and HI burden. Age at onset was assessed using the Diagnostic Interview Schedule. Executive dysfunction was assessed using the Trail Making Test–Part B (Trails B) (20). The Trails B is a complex neuropsychological task involving visual scanning, psychomotor speed, and cognitive flexibility in the form of set shifting (21) and is a frequently used measure of executive functioning (22,23). T1-weighted and T2-weighted MRI scans were evaluated for the presence of HIs (i.e., deep white matter [DW] and subcortical gray matter lesions) using the Coffey modified Fazekas Rating Scale (6). Deep white matter HIs were defined as abnormalities in the frontal, parietal, temporal, or occipital lobes, and scored as 0 (absent), 1 (punctate foci), 2 (beginning confluence of foci),

and 3 (large confluent areas). Subcortical gray matter (SCG) HIs were defined as abnormalities in the caudate nucleus, putamen, globus pallidus, thalamus, and internal capsule, and were scored as 0 (absent), 1 (punctate), 2 (multipunctate), and 3 (diffuse).

The Old-Old study (24) was a large, multicenter, double-blind, randomized 8-week trial comparing citalopram with placebo in patients 75 and older ( $n = 174$ ). All depressed subjects ( $n = 174$ ) met DSM-IV criteria for single episode or recurrent major depression, were at least 75 years of age and not living in a residential setting, and had baseline 24-item Hamilton Rating Scale for Depression (HRSD) scores of at least 20. Participants were excluded if they had another major psychiatric illness, current substance abuse or dependence within the past year, current suicide intent or serious attempt within the past year, dementia, MMSE score  $\leq 18$ , or an acute, severe, or unstable medical illness.

Of the 174 Old-Old study participants, 97 provided baseline data on age at onset, a measure of ED, and HI burden. Age at onset was determined based on information obtained in the baseline Structured Clinical Interview for DSM-IV (SCID) interview, medical records, and other sources of historical information. Executive dysfunction was assessed using the Stroop Color-Word Test (25). The Stroop Color-Word Test is a complex neuropsychological task tapping attention and the ability to inhibit automatic responses (26) and is a frequently used measure of executive functioning (22,23,26). T1-weighted and T2-weighted MRI scans were evaluated for the presence of DW and SCG HIs using the Coffey modified Fazekas Rating Scale and the same definitions of severity used in the NCODE study.

### Classification

For the purposes of this study, LOD, ED, and HI burden (DW and SCG lesions) were dummy coded (1 = yes, 0 = no) in each sample to reflect the presence or absence of a feature. Participants were classified as LOD if the onset of their first episode of depression occurred after age 50 (1,3,9,27,28). Participants were classified as having deficits in ED if they scored in the highest quartile of performance within their sample (higher scores indicating greater dysfunction) (29). Participants were classified as having DW or SCG burden if they received a score of 2 or more on their severity rating scales (6). As a result, each dataset consisted of four dummy coded, manifest indicators of the vascular depression construct.

### Data Analysis

We hypothesized that there are two classes of late-life depressed patients, vascular and nonvascular, and that the diagnostic indicators of interest are imperfect measures of the class to which a patient belongs. Latent class analysis generates two types of probabilities that enable the researcher to interpret a given model. Unconditional probabilities provide information regarding the likelihood that a person is in a particular class. Unconditional probabilities are sample specific and of interest only in that they provide estimates of the base rate of the disorder in the population. Conditional probabilities represent the likelihood that an individual belonging to a class will score a certain way on a particular observed feature (30,31). Thus, conditional probabilities allow us to interpret the meaning of the classes. The conditional probabilities also enable us to estimate the sensitivity (i.e., the probability of being positive on an indicator, given you have the illness) and specificity (i.e., the probability you are negative on an indicator, given you do not have the illness) of a

**Table 1.** Descriptive Statistics for NCODE and Old-Old Study Participants with Complete and Incomplete Baseline Data on Age at Onset, Executive Dysfunction, and Hyperintensity Burden

	NCODE Study		Old-Old Study	
	Complete ( $n = 150$ )	Incomplete ( $n = 217$ )	Complete ( $n = 97$ )	Incomplete ( $n = 77$ )
Age	71	69	79	80
Sex (% women)	.67	.68	.65	.49 <sup>d</sup>
Education	13.85	12.95 <sup>a</sup>	13.70	13.86
MMSE	28.33	26.66 <sup>b</sup>	27.80	28.26
HRSD	20.34	22.40 <sup>c</sup>	24.18	24.51

HRSD, Hamilton Rating Scale for Depression; MMSE, Mini-Mental Status Exam; NCODE, Neurocognitive Outcomes of Depression in the Elderly.

<sup>a</sup> $t(361) = 2.63, p = .009$ .

<sup>b</sup> $t(319.88) = -5.16, p = .001$ .

<sup>c</sup> $t(331) = -2.64, p = .009$ .

<sup>d</sup> $\chi^2(1) = 4.29, p = .038$ .

given indicator in the absence of a gold or criterion standard; that is, the conditional probabilities show what would be the sensitivity and specificity of a given indicator if a gold standard (external criterion) existed.

## Results

### Descriptive Statistics

Descriptive statistics for both the NCODE and Old-Old studies are reported in Table 1 for those who provided both complete and incomplete baseline data on age at onset, a measure of ED, and HI burden. Those with complete baseline data in the NCODE and Old-Old study were comparable in many respects. However, although formal statistical tests across samples were not performed, Old-Old study participants (with complete data) were on average older and had higher depression severity ratings than NCODE study participants with complete baseline data. Within sample, there were small differences in the NCODE study between those with and without complete baseline data on education, MMSE, and HRSD. In the Old-Old study, women were overrepresented among those with complete baseline data.

### Latent Class Analysis

The first step in LCA is to establish that there are relationships among the manifest indicators. In the absence of any relationships, there cannot be distinct latent classes. For the NCODE study data, the test of independence among the four manifest indicators was statistically significant,  $\chi^2(11) = 38.39, p = .0001$ , indicating there is covariation among the variables that is greater than chance. Next, we tested our primary hypothesis that there are two classes of late-life depressed patients. The likelihood ratio chi-square goodness-of-fit test for the two-class model was 2.02 on 6 degrees of freedom, which is nonsignificant ( $p = .90$ ). This indicates that the data are consistent with the model. We can compare the fit of these two models by taking the difference of their likelihood ratio  $\chi^2$  values where the degrees of freedom will be equal to the difference in the number of parameters between the two models. In this case, the two-class model fit significantly better than the independence model,  $\chi^2(11 - 6 = 5) = 38.39 - 2.02 = 36.37, p = .001$ . (Technical note: Although one might normally test more complex [e.g., three-class] models, the small chi-square value observed in this analysis indicates that we would not find any improvement in fit. Also, such a model would be underidentified [i.e., not all parameters would be able to be uniquely estimated]).

**Table 2.** Unconditional and Conditional Probabilities for Final Two-Class Model, NCODE Study Data

	Class 1	Class 2
Unconditional Class Probabilities	.51	.49
Conditional Probabilities of Manifest Indicators, Given Latent Class		
SCG (no)	<b>.79</b>	.35
SCG (yes)	.21	<b>.65</b>
DW (no)	<b>.88</b>	.15
DW (yes)	.12	<b>.85</b>
LOD (no)	<b>.71</b>	.44
LOD (yes)	.29	<b>.56</b>
RI (no)	<b>.91</b>	.59
RI (yes)	.09	<b>.41</b>

Note: Bold indicates sensitivity and specificity estimates of the manifest indicators.

DW, deep white matter hyperintensity burden; LOD, late-onset depression; NCODE, Neurocognitive Outcomes of Depression in the Elderly; RI, response inhibition component of executive functions; SCG, subcortical hyperintensity burden.

Table 2 reports the unconditional and conditional probabilities for the final two-class model. As can be seen from the table, there are two classes of participants in the NCODE study: those who were classified as vascular depression were high on SCG, DW, LOD, and ED (class 2) and those who were classified as nonvascular depression were low on SCG, DW, LOD, and ED (class 1). The unconditional probabilities indicate that the sample is approximately evenly split between the two classes (.51 and .49). The conditional probabilities provide estimates of the sensitivity and specificity of the manifest indicators. The highest sensitivity was for DW (.85), followed by SCG (.65), LOD (.56), and ED (.41), whereas the highest specificity was for ED (.91), followed by DW (.88), SCG (.79), and LOD (.71).

To replicate these findings, we also applied LCA to data from the Old-Old study. As expected, the complete independence model in this dataset also did not provide a good fit to the data,  $\chi^2(11) = 27.18, p = .004$ . Next, we tested the two-class model. The likelihood ratio chi-square goodness-of-fit test for the two-class model was 7.024 on 6 degrees of freedom, which is nonsignificant ( $p = .32$ ). As in the NCODE study, the two-class

**Table 3.** Unconditional and Conditional Probabilities for Final Two-Class Model, Old-Old Study Data

	Class 1	Class 2
Unconditional Class Probabilities	.52	.48
Conditional Probabilities of Manifest Indicators, Given Latent Class		
SCG (no)	<b>.87</b>	.22
SCG (yes)	.13	<b>.78</b>
DW (no)	<b>.60</b>	.00
DW (yes)	.40	<b>1.00</b>
LOD (no)	<b>.20</b>	.13
LOD (yes)	.80	<b>.87</b>
RI (no)	<b>.79</b>	.69
RI (yes)	.21	<b>.31</b>

Note: Bold indicates sensitivity and specificity estimates of the manifest indicators.

DW, deep white matter hyperintensity burden; LOD, late-onset depression; RI, response inhibition component of executive functions; SCG, subcortical hyperintensity burden.

**Table 4.** Unconditional and Conditional Probabilities for Final Two-Class Model Allowing Only LOD to Vary Across Both the NCODE and Old-Old Studies

	Class 1	Class 2
Unconditional Class Probabilities	.47	.53
Conditional Probabilities of Manifest Indicators, Given Latent Class		
SCG (no)	<b>.77</b>	.39
SCG (yes)	.23	<b>.61</b>
DW (no)	<b>.95</b>	.00
DW (yes)	.05	<b>1.00</b>
LOD (no)	<b>.54</b>	.31
LOD (yes)	.46	<b>.69</b>
RI (no)	<b>.84</b>	.66
RI (yes)	.16	<b>.33</b>

Note: Bold indicates sensitivity and specificity estimates of the manifest indicators.

DW, deep white matter hyperintensity burden; LOD, late-onset depression; NCODE, Neurocognitive Outcomes of Depression in the Elderly; RI, response inhibition component of executive functions; SCG, subcortical hyperintensity burden.

model fit significantly better than the independence model,  $\chi^2(11 - 6 = 5) = 27.18 - 7.02 = 20.16, p = .001$ .

Table 3 reports the unconditional and conditional probabilities associated with the final two-class model for the Old-Old study data. As in the NCODE study, the Old-Old study data yielded two classes of participants: vascular and nonvascular depressed. Those who were classified as having vascular depression scored high on SCG, DW, LOD, and ED, and those who were classified as not having vascular depression scored low on SCG, DW, LOD, and ED. Like the NCODE study, participants in the Old-Old study were also approximately evenly split between the two classes (52% versus 48%). Looking at the conditional probabilities in Table 3, we see a similar pattern to that observed in the NCODE study for DW (sensitivity = 1.00, specificity = .60), SCG (sensitivity = .78, specificity = .87), and ED (sensitivity = .31, specificity = .79). However, the sensitivity of LOD was much higher in the Old-Old study as compared with the NCODE study (.87 versus .56), whereas its specificity was much lower (.20 versus .71).

These findings suggest that while DW, SCG, and ED function similarly across the studies, LOD functions differently. In the NCODE study, LOD had low sensitivity and moderately high specificity, whereas in the Old-Old study, LOD had high sensitivity and low specificity. To test the hypothesis that LOD functions differently across the two studies, we estimated a complete invariance model in which we held constant the relationship between the manifest indicators and the underlying latent classes in the two samples. As expected, this model did not provide a good fit to the data,  $\chi^2(20) = 52.01, p = .0001$ , indicating that at least one of the manifest indicators functions differently across the two samples.

Next, we tested the hypothesis that it is LOD that functions differently across the samples by allowing the relationship between LOD and the latent classes to vary while holding constant the relationships for the other observed variables. This model provided a good fit to the data,  $\chi^2(18) = 15.60, p = .62$ . Table 4 reports the unconditional and conditional probabilities associated with the final, two-class model that allows LOD to vary across both the NCODE and Old-Old studies. As can be seen from this table, there are two classes of patients, one vascular (class 2) and the other nonvascular depressed (class 1). Across

the two independent clinical samples, DW has perfect sensitivity (1.00) and near perfect specificity (.95), SCG has moderate sensitivity (.61) and somewhat high specificity (.77), and finally, ED has low sensitivity (.33) but high specificity (.84). In Table 4, the average sensitivity and specificity of LOD are reported. The actual values for each sample (dataset) are at least approximately the same as in Tables 2 and 3.

Although the calculation of sensitivity and specificity of the manifest indicators is useful, LCA can also provide guidance regarding the classification of patients as either having or not having vascular depression. To do this, we use the unconditional and conditional probabilities in a formula related to Bayes' theorem to determine for any pattern of indicators the probability that a person with that pattern belongs to a particular class. Table 5 reports the observed and expected cell frequencies, the latent class assignment for each response pattern based on the LCA model, and the probability of correct classification.

As can be seen from Table 5, there is perfect correspondence between being classified as vascular depressed and the presence of DW lesion burden (as it should be since DW has perfect sensitivity and near perfect specificity). This indicates that DW

lesion burden is a nearly necessary and sufficient condition to be classified as vascular depressed. However, the highest rate of misclassification occurs when only DW lesion burden is present (i.e., .19 and .08 in the NCODE and Old-Old studies, respectively). Therefore, there is less certainty about diagnosis when DW is inconsistent with the other features. This suggests that while DW lesion burden is necessary to receive a diagnosis of vascular depression, our confidence in the accuracy of the classification increases with the presence of additional indicators.

**Discussion**

The results of this study provide the first support for the internal validity of vascular depression as a subtype of late-life depression. A subgroup of patients was identified by the presence of DW, SCG, ED, and LOD. Although all of the proposed core features of vascular depression were used to identify the illness, ultimately, only the presence of DW lesion burden was necessary to determine class membership. Thus, DW lesion burden emerged as the most accurate indicator of the underlying group. This is reflected by the perfect (1.00) sensitivity and near

**Table 5.** Latent Class Assignment for Each Response Pattern Based on Final, Two-Class Model Allowing LOD to Vary Across NCODE and Old-Old Studies

	Manifest Indicators				Frequencies		Latent Class	<i>p</i> (error)
	SCG	DW	LOD	RI	Observed	Expected		
NCODE	0	0	0	0	36	34.48	Non-VD	.00
	0	0	0	1	3	6.36	Non-VD	.00
	0	0	1	0	15	16.85	Non-VD	.00
	0	0	1	1	4	3.11	Non-VD	.00
	0	1	0	0	10	9.94	VD	.19
	0	1	0	1	4	4.39	VD	.08
	0	1	1	0	9	10.17	VD	.09
	0	1	1	1	5	4.81	VD	.03
	1	0	0	0	12	10.25	Non-VD	.00
	1	0	0	1	2	1.89	Non-VD	.00
	1	0	1	0	5	5.00	Non-VD	.00
	1	0	1	1	2	.92	Non-VD	.00
	1	1	0	0	13	13.23	VD	.04
	1	1	0	1	7	6.46	VD	.02
	1	1	1	0	13	14.80	VD	.02
Old-Old	0	0	0	0	3	3.92	Non-VD	.00
	0	0	0	1	1	.72	Non-VD	.00
	0	0	1	0	18	15.70	Non-VD	.00
	0	0	1	1	4	2.89	Non-VD	.00
	0	1	0	0	3	2.72	VD	.08
	0	1	0	1	2	1.29	VD	.03
	0	1	1	0	18	15.26	VD	.06
	0	1	1	1	5	7.38	VD	.02
	1	0	0	0	1	1.16	Non-VD	.00
	1	0	0	1	1	.22	Non-VD	.00
	1	0	1	0	2	4.67	Non-VD	.00
	1	0	1	1	0	.86	n/a	n/a
	1	1	0	0	2	3.99	VD	.02
	1	1	0	1	3	1.98	VD	.01
	1	1	1	0	25	22.86	VD	.01
1	1	1	1	9	11.38	VD	.00	

Note: 1 = "yes" and 0 = "no."

DW, deep white matter hyperintensity burden; LOD, late-onset depression; n/a, indicates zero cell frequency; NCODE, Neurocognitive Outcomes of Depression in the Elderly; Non-VD, non-vascular depression; *p* (error), probability of misclassification; RI, response inhibition component of executive functions; SCG, subcortical hyperintensity burden; VD, vascular depression.

perfect (.95) specificity of DW for the illness. Importantly, the latent class model was replicated across two independent clinical samples.

Although LOD, SCG, and ED were useful in identifying the illness, they were ultimately unnecessary given the perfect sensitivity and near perfect specificity of DW lesion burden. This reality reflects the nature of the problem under investigation. As with all other psychiatric diagnoses, no gold or criterion standard exists for vascular depression; therefore, it is impossible to evaluate the sensitivity and specificity of a given indicator. Latent class analysis, however, gives us the opportunity to assess sensitivity and specificity of indicators in the absence of a gold standard. As a result, the theory underlying a given diagnostic construct must be adequately developed to identify a sufficient number of indicators. Once identified, LCA can be used to determine whether the proposed model of the illness is consistent with observed data and the sensitivity and specificity of the indicators assessed. In the present study, DW emerged with perfect sensitivity and near perfect specificity, but we would not have been able to determine this without the aid of the other indicators specified by the theory.

Executive dysfunction did not emerge as an essential feature in the classification of patients as vascular depressed. Several factors may contribute to this finding. First, the executive system encompasses a broad range of functions (e.g., planning, organizing, problem solving, and cognitive flexibility) and may be difficult to comprehensively assess (26,32–34). Although the prefrontal cortex is central to these functions (34), executive tasks activate a diffuse network of brain areas and are better described in terms of process rather than in terms of neuroanatomical location (32). Second, the NCODE and Old-Old studies used two different measures of executive functioning. The NCODE study used the Trails B, a common measure of the executive task of set shifting, whereas the Old-Old study used the Stroop Color-Word Test, a common measure of the executive task of response inhibition. Although these functions are considered to be essential to executive processes (26), including other domains of executive functioning in the LCA might change the findings observed in this report. Importantly, although the Trails B and Stroop Color-Word Test assess different cognitive processes and are largely uncorrelated (23), in the present study they functioned in similar ways with respect to sensitivity and specificity across the two independent clinical samples.

Although ED did not emerge as a defining feature of vascular depression, a recent study showed that only ED (and not LOD or hyperintensity lesion burden) predicted poor treatment response among late-life depressed patients using data from the Old-Old study (35). This raises the possibility that while the presence of DW lesion burden is both necessary and sufficient in identifying the vascular depression subtype, DW lesion burden may not adversely affect antidepressant treatment response unless it is simultaneously associated with ED.

There are a number of possibilities why LOD did not emerge as a reliable indicator of the vascular depression subtype. First, the concept of LOD incorrectly assumes that the etiology of depression in those classified as early onset is the same in early adulthood as it is in later adulthood when it is distinctly possible that the same person could experience different major depressive episodes at different points in life for very different reasons (36). Second, the classification of patients as LOD is based on patient self-report, which is problematic due to retrospective reporting bias (37). Research suggests that 20% of the critical details associated with personal events are irretrievable after 1

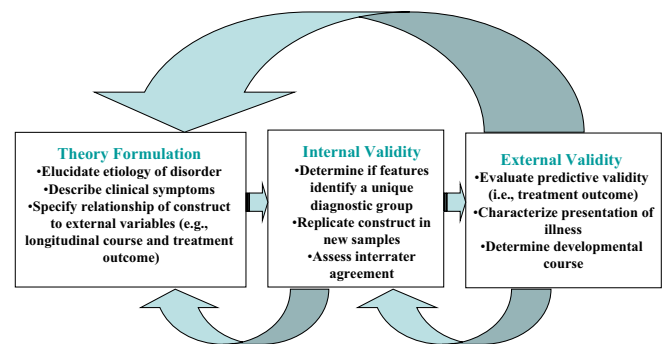
year and as much as 60% are irretrievable after 5 years (37). This is a remarkable fact when you keep in mind that we are asking older adults to recall and distinguish between syndromal and subsyndromal depression over the course of their entire lives. Given these conceptual and methodological problems, it is not surprising that LOD emerged as an unreliable indicator.

### Implications for DSM-IV

Although the current study focused on patients with major depressive disorder, it has not been established that the mood disorder associated with DW lesion burden is restricted to major depression. Patients with DW lesion burden may have clinically significant depressive symptomatology but not meet criteria for any mood disorder recognized in DSM-IV. Patients with DW lesion burden might also present with cognitive deficits, falls, gait disturbance, and urinary incontinence without depressed mood or anhedonia (14,38). Thus, vascular depression may be viewed as part of a larger category of cerebral white matter lesion syndrome in which patients may or may not present with depressive symptomatology (14,38). In attempting to establish a new diagnosis, we should not be bound by the current classification system.

The method used in this study also has important implications for the process of establishing valid diagnoses. Sneed *et al.* (16) articulated the psychometric approach to diagnostic validity (39–41), which is represented in Figure 1. According to this approach, the first step in establishing diagnostic validity is the specification of a theory. Given a specified theoretical model, the next step is to evaluate internal validity, which becomes the focus of attention “whenever no criterion or universe of content is accepted as entirely adequate to define the quality to be measured” (42, p. 282). In the absence of a gold or criterion standard, it must be shown that the proposed features of the illness identify an unobserved (inferred) construct that represents the theoretically specified diagnostic subgroup. This study represents the first evidence of this kind for vascular depression. Given sufficient evidence of internal validity, which includes replication across different samples as in this study, the next and final step in the validation process is to examine external validity, i.e., clinical presentation, treatment outcome, and developmental course (43). Thus, studies of internal validity serve as a critical starting point but cannot serve as an end point in the process of establishing diagnostic validity (36).

The statistical models that were used to evaluate the internal validity of vascular depression required certain assumptions that place limits on our ability to discern the “truth” about the construct. First, we took as given that the observed variables



**Figure 1.** A construct validation framework for psychiatric classification. (Adapted from Skinner [41].)

would be dichotomized and at what point they would be dichotomized. Each could be questioned, but we were investigating the latent structure that could be inferred if the current definitions of these variables were correct. It would be of interest to investigate the issue of whether these variables should be dichotomized and if so, at what point in future research. We also assumed that the underlying structure of vascular depression is categorical rather than continuous. This is consistent with the hypothesis that vascular depression is a subtype of late-life depression. However, it is possible that the underlying structure of vascular depression is continuous, which deserves further research and requires different statistical models such as taxometrics (44). However, the application of taxometrics to clinical studies is often precluded because of the statistical requirements of the model, such as very large sample sizes, a sufficient number of manifest indicators, and correlations among these indicators that are large enough to be able to separate the putative taxon and complement class to detect the taxonomic boundary should it exist (44).

### Limitations

First, there is no consensus regarding how LOD should be defined. While most have used an age threshold of 50 years (1,3,9,27,28), others have used an age threshold of 60 years (7,45) or even 65 years (10). In the present study, it is possible that using different cutoffs would have yielded different results. Second, small differences were observed between those with and without complete baseline data (Table 1). However, these differences only affect the unconditional probabilities of the LCA and not the conditional probabilities, which are our primary interest. The conditional probabilities tell us the probability of being positive on an indicator given latent class, and this is independent of the rate of the illness in the sample. Third, we were unable to examine the additive influence of certain clinical features that have been associated with vascular depression (e.g., psychomotor retardation, family history of mental illness), as these variables were not available across both studies. However, because different definitions of vascular depression have been used to study clinical presentation (11,13), it is unclear whether the features that have been identified are in fact part of the vascular depression syndrome (16).

### Conclusion

This study provides the first support for the internal validity of vascular depression as a subtype of late-life depression. The application of a systematic, empirically grounded, psychometric approach to diagnostic validity may substantially improve on previous efforts that relied primarily on expert consensus. In fact, vascular depression may serve as a prototype for the DSM-V in that the criteria for the diagnosis are based on both phenomenology (symptoms of major depressive disorder) and laboratory tests (e.g., DW lesion burden on MRI), and the method of establishing diagnostic validity is based on evidence of both internal and external validity.

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