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RESEARCH ARTICLE

The Vulnerability Index: A weighted measure of dementia and cognitive impairment risk

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Abstract

Introduction: A brief, easily calculated and interpretable index to assess vulnerability to developing cognitive impairment is needed in clinical practice and research. To address this, we developed the Vulnerability Index (VI) with the goal of identifying individuals possessing a high risk for cognitive impairment.

Methods: Twelve easily obtained sociodemographic, medical, and functional factors were used to develop the VI, with each selectively weighted based on factor analysis and predictive modeling. This cross-sectional study examined 387 subject-partner dyads.

Results: The VI was found to accurately discriminate between cognitively normal controls and participants with cognitive impairment (area under the curve [AUC]: 0.844; 95% confidence interval [CI]: 0.776-0.913) and individuals scoring high on the VI (≥8) had worse health, functional, behavioral, cognitive, and quality of life ratings than those with lower scores.

Discussion: The VI could be used in screening asymptomatic individuals for risk of cognitive impairment and guiding the development of primary and secondary prevention plans.

KEYWORDS
Alzheimer's disease, cognitive impairment, dementia, functional assessments, health records, primary prevention, risk assessment, screening, sociodemographics

1 | INTRODUCTION

Alzheimer's disease and related dementias (ADRD) affect an estimated 6 million Americans,[1] although estimates suggest nearly two-thirds of ADRD cases remain undetected until the latter stages of impairment.[2,3] In the preclinical stages of ADRD there is an accumulation of neuropathology[4] usually without a clinically detectable effect on cognition or functioning; however, as amyloid and tau deposition increases and neuronal injury begins, cognitive decline may be first detected clinically as mild cognitive impairment (MCI), with ≈32% of patients with MCI going on to develop ADRD within 5 years.[5] As new therapies that target primary and secondary prevention become available, there will exist a need to quantify the risks for both possessing biomarkers within a population as well as progressing to the next symptomatic stage of ADRD following a positive biomarker screen.[6] To address this need, we identified 12 factors based on both modifiable and non-modifiable traits known to be associated with the development of cognitive impairment including age, biological sex, race and ethnicity, education, frailty, obesity, and comorbid medical conditions.

One of the principal risk factors of ADRD is age; above the age of 75, 13.8% of individuals are affected by ADRD, with that number increasing to 34.6% above age 85.[1] Biological sex is also strongly associated with dementia risk; women are 7.8% more likely than men to develop dementia at age 70[7] and lower levels of testosterone are associated with higher overall risk.[8] Socio-demographic factors and vascular risks prevalent in minority populations also contribute to increased risk, with African Americans and Hispanics at higher risk than Whites,[9] because fewer years are spent in formal education.[10,11] Physical functioning may be an effective metric for identifying dementia risk.[10,12,13] Comorbidities including midlife obesity,[10,12,14] midlife hypertension,[15] hypercholesterolemia,[16] heart disease,[17] and diabetes[10] often reflect lifelong compounded risks. A history of strokes is associated with an increased risk of dementia onset up to 10 years earlier.[18] Late-life depression is associated with higher dementia risk as well, due to both longitudinal neurobiological impact[19,20] and interactions with other risk factors.[21]

Combining and weighting these risk factors resulted in the creation of a single scale able to quantify the risk of developing cognitive impairment easily and independently: the Vulnerability Index (VI). The primary goal of the VI is to detect cognitively impaired individuals based on a quantified risk factor using only assessments available before any specialized assessment test is administered—much of which could be gleaned from electronic health records (EHRs)—to enable more in-depth cognitive and functional testing for diagnosis. A secondary goal is to identify cognitively normal individuals with a high risk of developing cognitive impairment in the near future to: (a) enable closer observation and referral to specialists; and (b) provide actionable data for personalized primary, secondary, and tertiary prevention plans. We compared the psychometric properties of the VI to Gold Standard assessments of cognition, function, and behavior within a cross-sectional procedure to determine its utility as a measure of vulnerability to impairment.

RESEARCH IN CONTEXT

1. **Systematic Review**: The components of the Vulnerability Index (VI; sociodemographic factors, functional assessments, health records) have each been shown to be associated with increased cognitive impairment risk, determined via a literature review conducted using traditional (e.g., PubMed) sources. Each factor's weight was determined via statistical analysis within our sample and on findings in the literature. These citations are appropriately cited in this article.
2. **Interpretation**: The aggregation into a single scale of factors known to be indicative of vulnerability to dementia may contribute to more effective screening in asymptomatic individuals and guide both primary and secondary prevention plans. Findings indicate that our weighted scale is effective at differentiating high versus low vulnerability within a research sample.
3. **Future directions**: Longitudinal examination of the VI's ability to identify future impairment is needed, as are studies that validate its performance in both clinical and research settings.

HIGHLIGHTS

- The Vulnerability Index (VI) is a weighted scale for quantifying dementia risk
- Functional assessments, health records, and sociodemographic factors are used
- The VI is easily computed using minimal observation and commonly collected patient data
- High scores may be used to prompt more extensive evaluation of cognitive impairment
- The VI is easily integrated in computer decision support and electronic health record systems

2 | METHODS

2.1 | Study participants

We evaluated 387 participant-study partner dyads attending our center for clinical care or participating in cognitive aging research. During the visit, the participant and study partner underwent a comprehensive evaluation including the Clinical Dementia Rating (CDR) and its sum of boxes (CDR-SB),[22] physical and neurological examination, assessment of mood and physical performance, neuropsychological testing, and caregiver ratings of participant cognitive abilities, behavior, and function. All components are part of standard of care at our center.[23] A waiver of consent was obtained for retrospective review of individuals attending the clinic, and prospective research participants provided written informed consent. This study was approved by the University of Miami Institutional Review Board.

2.2 | Clinical assessment

Clinical assessments were modeled after the Uniform Dataset v3.0 from the National Institute on Aging-funded Alzheimer's Disease Research Centers[24,25] with the addition of the Hopkins Verbal Learning Test[26] for episodic memory and the Number Symbol Coding Task[27] for executive functioning. A composite z-score was computed as a summary of global cognitive performance across the nine neuropsychological tests administered. The CDR[22] was used to determine the presence or absence of dementia and to stage its severity. In most cases, a global CDR 0 indicates no dementia; CDR 0.5 represents

MCI or very mild dementia; CDR 1, 2, or 3 corresponds to mild, moderate, or severe dementia, respectively. The CDR-SB was calculated by calculating the sum of the individual CDR categories giving a score from 0-18, with higher scores supporting more severe stages. Extrapyramidal features were assessed with the Movement Disorders Society-Unified Parkinson's Disease Rating Scale, motor subscale part III (UPDRS).[28] The Charlson Comorbidity Index[29] and Functional Comorbidity Index (FCI)[30] were used to measure overall health and medical comorbidities. Global physical performance was captured with the mini-Physical Performance Test (mPPT)[31] and frailty was assessed with the Fried Frailty Scale.[32] Vascular contributions to dementia were assessed with the modified Hachinski scale[33 and a] modified form of the Cardiovascular Risk Factors, Aging, and Incidence of Dementia scale (mCAIDE).[34]

2.3 | Determination of Vulnerability Index

The Vulnerability Index (or VI) is calculated as the weighted sum of a number of factors known to be associated with an increased risk of developing cognitive impairment. Higher scores indicate a higher risk. These factors are the following.

2.3.1 | Age

Higher ages contribute significantly toward risk of dementia. Subjects older than age 75 are assigned a value of **three**, whereas subjects below 60 are assigned a value of **zero**. Between the ages of 60 and 75, a value of **one** is assigned.

2.3.2 | Biological sex

Women are more at risk of developing dementias such as AD, so they are assigned a value of **two,** whereas men are given a value of **one**.

2.3.3 | Race and ethnicity

Black and/or Hispanic subjects have been found to be more at risk compared to non-Hispanic White subjects. A value of **two** is assigned to the former, with a **one** given to the latter.

2.3.4 | Years of education

More years attending education has a protective effect, with those who attend the equivalent of high school (12 years) or less at the greatest risk of developing dementia. Subjects with 12 or fewer years of education are assigned a value of **two**, between 12 and 16 a value of **one**, and greater than 16 years assigned a value of **zero**.

2.3.5 | Obesity

Some studies suggest that obesity contributes to a greater risk of developing dementia. Subjects with a BMI score greater than 30 are assigned a value of **one**, while subjects 30 or below are assigned a value of **zero**.

2.3.6 | Frailty

Frailty has been found to be significantly correlated with cognitive impairment. The Fried Frailty Index was collected for all participants, and those with an index of two and above are assigned a value of **two**, whereas subjects below two are assigned a value of **zero**.

2.3.7 | Depression

The Hospital Anxiety and Depression Scale was administered to all subjects, although only the depression-aligned questions were used. Those with a score of 7 or below were assigned a value of **zero**, whereas those with a score of 8 or above were assigned a value of **one**.

2.3.8 | Other comorbidities

Comorbidities associated with an increased risk of dementia that are included in the VI include diabetes, stroke, heart disease, hypercholesterolemia, and hypertension. For each, a value of **one** is assigned if the subject is comorbid, or **zero** if they are not. If the patient is comorbid with either diabetes or stroke, an extra point is added due to the increased risk associated with these diseases; a value of **two** is assigned if the subject is comorbid, or **zero** if they are not.

Component weights were determined through examining the results of factor analysis in our sample as well based on previous studies of individual or joint components.[1,7–21] Other factors considered but ultimately excluded were family history of dementia, mean arterial pressure, socioeconomic status, hearing loss, performance on the timed up-and-go task, and a history of obstructive sleep apnea, use of tobacco products, or prior head injury. Each of these was removed either due to a lack of statistical significance or because they were a covariate of another more appropriate variable.

2.4 | Statistical analyses

Analyses were conducted using statistical packages within Python, including *pingouin 0.3.9*[35] for inferential statistics; *pandas 1.2.4*[36] for descriptive statistics and data manipulation; and *scikit-learn 0.24.1*[37] for factor, cluster, and classification analysis. One-way analysis of variance (ANOVA) with either Tukey or Games-Howell post hoc tests dependent on whether the assumption of homoscedasticity was met were used on continuous data, and chi-square analyses used to

TABLE 1 Sample characteristics

	Control (N = 51)	MCI (N = 115)	Dementia (N = 221)	*P*-value
Age, y	67.25 (10.05)	73.39 (8.99)	77.07 (7.57)	<.001
Education, y	16.12 (2.22)	16.06 (2.53)	15.27 (2.90)	.035
Sex, % Female	70.59%	43.86%	39.69%	.001
ApoE, % ε4 carrier	30.95%	32.93%	40.00%	.532
QDRS – Informant	0.72 (1.06)	3.04 (3.02)	6.79 (4.00)	<.001
QDRS – Patient	0.54 (1.03)	2.62 (2.65)	5.20 (4.37)	<.001
FAQ	0.14 (0.50)	2.70 (3.86)	10.58 (7.30)	<.001
HUI-3	0.87 (0.19)	0.66 (0.24)	0.48 (0.30)	<.001
mPPT	13.02 (1.92)	11.07 (2.75)	9.48 (3.13)	<.001
MoCA	26.65 (2.55)	23.41 (3.02)	17.13 (4.35)	<.001
Composite z-score	1.17 (0.36)	0.37 (0.57)	-0.86 (0.66)	<.001
UPDRS-III	2.67 (3.57)	5.09 (7.27)	11.67 (11.23)	<.001
Charlson	1.18 (1.52)	2.37 (1.55)	2.73 (1.68)	<.001
FCI	2.43 (1.56)	4.33 (1.95)	4.06 (1.66)	<.001
Hachinski	0.51 (0.64)	0.88 (1.32)	1.15 (1.45)	.010
mCAIDE	5.06 (3.20)	7.81 (2.82)	8.45 (2.42)	<.001
CDR-SB	0.14 (0.23)	1.44 (0.88)	4.73 (1.77)	<.001

Mean (SD) or %.

Abbreviations: QDRS, Quick Dementia Rating System; FAQ, Functional Activities Questionnaire; HUI-3, Health Utilities Index-Mark3; mPPT, mini-Physical Performance Test; MoCA, Montreal Cognitive Assessment; Composite z-score , Computed summary of global cognitive performance across nine neuropsychological tests; UPDRS-III, Unified Parkinson's Disease Rating Scale-Motor Subscale; FCI, Functional Comorbidity Index; mCAIDE, Modified Cardiovascular Risk Factors, Aging, and Incidence of Dementia; CDR-SB, Clinical Dementia Rating Sum of Boxes.

examine categorical variables. The efficacy of the VI was calculated in the sample using linear and logistic regressions, and evaluated using the resulting sensitivities, specificities, positive predictive values (PPVs), negative predictive values (NPVs), positive likelihood ratios (PLRs), negative likelihood ratios (NLRs), diagnostic odds ratios (DORs), and areas under the receiver-operating characteristic (ROC) curve (AUCs). K-means cluster analysis targeting two and three clusters with 10 iterations was used to determine the risk threshold of the VI, determining that a threshold score of eight best separates high vulnerability from low vulnerability with respect to the participant's cognitive impairment status (impaired vs not-impaired and healthy controls vs mild cognitive impairment vs dementia) while maximizing classification metrics. Two other thresholds were determined to optimally identify very high risk (above a score of 10) and very low risk (score of 4 or below). Logistic regressions used L2 (ridge) regularization with class weights based on prevalence within the sample and were implemented to calculate the efficacy of the VI when thresholds were applied.

3 | RESULTS

3.1 | Sample characteristics

Participants had a mean age of 75.4 ± 9.3 years (range 38-98) with a mean education of 15.6 ± 2.7 years (range 6-20 y), 47.3% were female, and 36.6% were apolipoprotein E (apoE) carriers (Table 1). The sample was 93.3% non-Hispanic White, 2.3% African American, and 4.4% Hispanic. The patients had a mean montreal cognitive assessment (MoCA) score of 18.6 ± 7.1 (range 1-30) and a mean CDR-SB of 4.9 ± 4.8 (range 0-18). Participants' global ratings included 52 CDR 0, 153 with MCI or very mild dementia (CDR 0.5), 91 with mild dementia (CDR 1), 39 with moderate dementia (CDR 2), and 29 with severe dementia (CDR 3). Consensus diagnoses are 51 cognitively normal controls, 115 MCI, and 221 dementia cases, with one CDR 0 case representing a non-AD cause of MCI. The dementia cases are further classified as 78 Alzheimer's disease (or AD), 107 dementia with Lewy bodies (DLB), 21 with vascular contributions to cognitive impairment and dementia (VCID), and 15 frontotemporal degeneration (FTD) cases. The mean VI score was 9.4 ± 2.9, with a median of 9 and range of 2 (floor effect: < 0.01%) to 18 (ceiling effect: 0%), **Figure** 1A. When examining the three impairment groups, the distribution of both controls and MCI exhibited both high skewness (Controls = 0.73, standard error of skewness (SES) = 0.34; MCI = 0.78, SES = 0.23) and kurtosis (Controls = 0.98, standard error of kurtosis (SEK) = 0.66; MCI = 0.64, SEK = 0.45), whereas Dementia approached a Gaussian distribution with a skewness of 0.18 (SES = 0.16) and a kurtosis of −0.41 (SEK = 0.33), **Figure** 1B. The overall distribution also approached Gaussian, with a skewness of 0.22 (SES = 0.12) and a kurtosis of −0.25 (SEK = 0.25), **Figure** 1C.

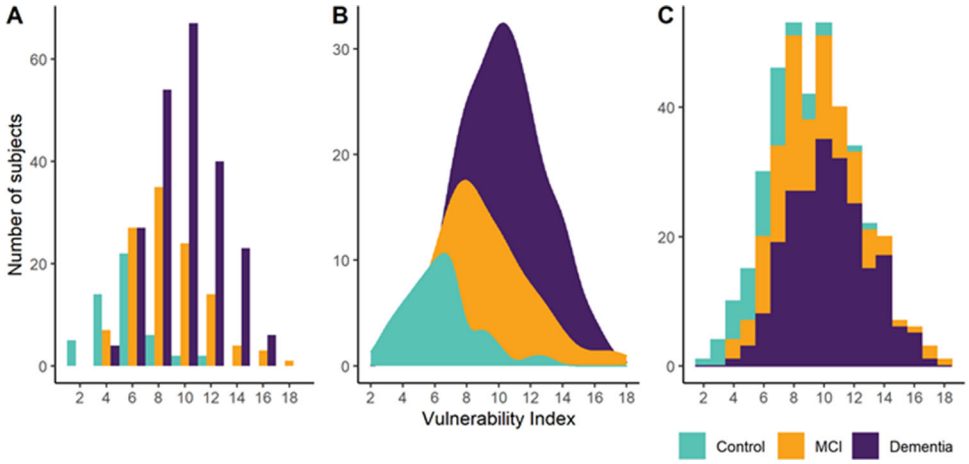

FIGURE 1 A) A split histogram depicting the number of subjects from each impairment group for each score in the Vulnerability Index (VI). (B) Curves highlighting the distribution of the VI for each impairment group. The distribution of the dementia group was not skewed, whereas the curves for both the mild cognitive impairment (MCI) and Control groups are skewed, with the majority of these subjects exhibiting lower values of the VI and tapering off toward the higher end of the scale. (C) A stacked histogram showing the overall distribution of the VI

3.2 | Vulnerability Index scores by diagnostic groups

Mean performance of the VI and its components were compared across diagnostic groups (controls, MCI, dementia) as well as between impairment status (impaired vs not impaired) in Table 2. Mean VI scores were found to differ between all three diagnostic groups, and all components other than hypertension and stroke also exhibited significant or trending differences either between all three groups or between a status of impaired (both MCI and dementia) and not impaired (controls). Examining the weighted components of the VI reveal that all components except two (hypertension and stroke) were highly associated with diagnostic groups and/or impairment status within our sample. Differences between dementia etiologies (AD, DLB, VCID, FTD) were also examined, with differences found only for sex (significantly fewer females in DLB), Fried Frailty Index (FTD with smaller scores than VCID), stroke, and the VI. Between etiologies, the VI was significantly lowest for FTD and highest for VCID. Differences between CDR stages were also examined in Table 3. Because the VI is intended to examine vulnerability to impairment, it is as expected that the VI was lowest in controls (CDR 0). Mean values of the VI do not significantly increase past CDR 1 (mild impairment), reinforcing that the VI is intended to measure vulnerability to developing impairment and not current impairment.

3.3 | Strength of the association between Vulnerability Index, clinical, and cognitive measures

Construct validity was examined through bivariate correlations between the VI and clinical, functional, behavioral, informant ratings, and neuropsychological testing. The VI was moderately correlated with clinical measures but most strongly correlated with modified cardiovascular risk factors (mCAIDE) (r = .683), both Charlson and functional comorbidity indices (r = .575 and .579, respectively), and the mPPT (r = -.550). Correlations were also found with cognitive tests, with the strongest associations found between the VI and the number-symbol coding task (r = -.510), trailmaking B (r = .490), hopkins verbal learning test (HVLT) delayed recall (r = -.443), HVLT immediate recall (r = -.440), and a composite z-score of all cognitive tests (r = -.481). Moderate associations were also found with the Quick Dementia Rating System[38] patient version (r = .324) and informant version (r = .325), Functional Activities Questionnaire measuring activities of daily living[39] (r = .354), Health Utilities Index-Mark 3 measuring health-related quality of life[40] (r = -.422), and categorical verbal fluency task[25] (r = -.362).

3.4 | Discriminability of the Vulnerability Index

The predictive power of the VI and its components was examined using logistic regression analyses and areas under the ROC curve (AUCs) in Table 4. The VI produced excellent discrimination (AUC: .844; 95% CI: .776-.913) between cognitively normal controls and those with any form of cognitive impairment. The components age, sex, frailty, depression, and heart disease were found to significantly discriminate, with the Fried Frailty Index providing excellent discrimination (AUC: .818, 95% CI: .753-.884). Other components did not differ significantly between groups. Threshold determination analysis was performed, identifying a cutoff point of 8+ as the best balance between sensitivity (.807; PPV: .964) and specificity (.804: NPV: .387). The positive likelihood ratio was 4.1, whereas the negative likelihood ratio was 0.24, with a diagnostic odds ratio of 17.1. The VI correctly identified 80.7% of impaired participants with excellent accuracy (PPV: 96.4%). Further threshold analysis revealed that participants with a score of 11 and above 98.5% are likely to be impaired, with a diagnostic OR of 15.7 and a PLR of 9.94, whereas participants with a score of 4 or below are 73.3% likely to be non-impaired with a DOR of 22.8 and a NLR of 0.06.

TABLE 2 Vulnerability Index and components by diagnostic group

	Control (N = 51)	MCI (N = 115)	Dementia (N = 221)	*P*-value Two-way	*P*-value Three-way
Age, y [A]	67.25 (10.05)	73.37 (8.96)	78.27 (7.77)	**<.001**	**<.001**[a]
Weighted component	1.04 (0.89)	1.83 (1.12)	2.28 (0.98)	**<.001**	**<.001**[a]
Sex, % Female [χ]	70.59	44.35	43.44	**.001**	**.002**[b]
Weighted component	1.29 (0.46)	1.56 (0.50)	1.57 (0.50)	**<.001**	**<.001**[b]
Race, % Non-White [χ]	15.69	5.22	5.43	**.014**	.023[b]
Weighted component	1.16 (0.37)	1.05 (0.22)	1.05 (0.23)	**.010**	.020[b]
Education, y [A]	16.12 (2.22)	16.06 (2.52)	15.28 (2.81)	.154	**.014**[c]
Weighted component	0.69 (0.65)	0.75 (0.70)	1.01 (0.73)	.080	**<.001**[c]
BMI [A]	28.57 (6.35)	30.33 (11.77)	26.38 (4.60)	.475	**<.001**[c]
Weighted component	0.29 (0.46)	0.35 (0.48)	0.15 (0.36)	.320	**<.001**[c]
FFI [A]	0.94 (1.01)	1.97 (1.30)	2.88 (1.22)	**<.001**	**<.001**[a]
Weighted component	0.63 (0.94)	1.34 (0.94)	1.76 (0.66)	**<.001**	**<.001**[a]
HADS Depression [A]	4.24 (3.26)	6.25 (4.05)	6.57 (3.78)	**<.001**	**<.001**[b]
Weighted component	0.14 (0.35)	0.30 (0.46)	0.38 (0.49)	**.004**	**.004**[b]
Diabetes, % [χ]	3.92	13.91	20.36	.018	**.012**[a]
Weighted component	0.08 (0.39)	0.28 (0.70)	0.41 (0.81)	.020	**.010**[a]
Stroke, % [χ]	1.96	11.30	13.57	.042	.062[b]
Weighted component	0.04 (0.28)	0.23 (0.64)	0.27 (0.69)	.040	.060[b]
Hypertension, % [χ]	35.29	43.48	49.77	.135	.141
Weighted component	0.35 (0.48)	0.43 (0.50)	0.50 (0.50)	.140	.140
Heart disease, % [χ]	17.65	37.39	38.46	**.007**	.017
Weighted component	0.18 (0.39)	0.37 (0.49)	0.38 (0.49)	**.010**	.020[b]
Hypercholesterolemia, % [χ]	37.25	61.74	56.56	**.008**	**.012**[b]
Weighted component	0.37 (0.49)	0.62 (0.49)	0.57 (0.50)	**.010**	**.010**[b]
Vulnerability Index [A]	6.25 (2.25)	9.10 (2.83)	10.32 (2.56)	**<.001**	**<.001**[a]

Mean (SD) or %.
Bold signifies significance after correction for multiple comparisons (corrected *P*-value < 0.016).
Abbreviations: BMI, body mass index; FFI, Fried Frailty Index; HADS, Hospital Anxiety and Depression Scale.
Analysis: [A] analysis of variance; [χ] chi-square.
Three-way post hoc: [a] All groups different from each other;.
[b] Control different from MCI and Dementia;.
[c] Control and MCI different from Dementia.

The VI threshold set at ≥8 also showed excellent discrimination of clinical and cognitive measures, Table 5. As individuals with high VI were older than those with low VI, we adjusted analyses controlling for age. Participants with high VI scores (≥8) were significantly different from those with low VI scores (< 7) in informant and participant-rated questionnaires, some measures of physical performance, behavior and health-related quality of life, vascular risk factors, and some cognitive domains, most notably executive function, language, and episodic memory. These age-matched results suggest that although ages did differ between groups, the VI was effective at classifying impairment status. Within diagnostic groups, the cognitive z-score in controls with high VI (0.90 ± 0.38) was significantly different than controls with low VI (1.23 ± 0.34, $P = 0.011$). This distinction was also seen in MCI individuals with high VI (0.28 ± 0.54) compared to low VI (0.58 ± 0.58, $P = 0.011$). Participants with dementia did not differ in cognitive functioning between high and low VI (-0.98 ± 0.66 vs −0.58 ± 0.90, $P = 0.044$) after correction for multiple comparisons ($\alpha = 0.016$). This suggests an ability of the VI to identify mild deficits in cognition prior to clinical detection, but an inability to stage the degree of impairment once it has progressed past a certain threshold.

4 | DISCUSSION

The VI combines easily attained modifiable and non-modifiable risk factors to generate a score of vulnerability to develop cognitive impairment. The VI is able to be generated rapidly with self-report or clinician-observed measures, with the exception of the frailty

TABLE 3 Vulnerability Index and components by CDR stages

	CDR 0 (N = 52)	CDR 0.5 (N = 153)	CDR 1 (N = 91)	CDR 2 (N = 62)	CDR 3 (N = 29)	*P*-value
Age, y [A]	67.46 (10.06)	74.42 (8.57)	76.90 (8.09)	79.97 (7.59)	79.83 (8.30)	**<.001**[a]
Sex, % Female[χ]	69.23	43.14	39.56	46.77	55.17	.010
Race, % Non-White[χ]	15.38	3.92	7.69	4.84	6.90	.070
Education, y [A]	16.19(2.27)	15.97(2.58)	15.02 (2.92)	15.61 (2.68)	14.62 (2.58)	.010
BMI [A]	28.40 (6.41)	29.35 (10.66)	26.24 (4.18)	26.45 (4.72)	26.90 (4.71)	.020
FFI [A]	0.94(1.00)	2.07(1.28)	2.68(1.23)	3.34(1.14)	3.24(0.95)	**<.001**[a]
HADS Depression [A]	4.17 (3.26)	6.03 (3.91)	7.14 (3.99)	7.35 (3.79)	4.93 (2.45)	**<.001**[b]
Diabetes, %[χ]	3.85	15.69	20.88	24.19	10.34	.030
Stroke, %[χ]	3.85	11.11	14.29	16.13	6.90	.220
Hypertension, %[χ]	34.62	46.41	52.75	46.77	41.38	.320
Heart disease, %[χ]	19.23	33.99	38.46	46.77	37.93	.040
Hypercholesterolemia, %[χ]	38.46	59.48	61.54	50.00	58.62	.050
Vulnerability Index [A]	6.33 (2.29)	9.22 (2.73)	10.38 (2.69)	10.73 (2.39)	10.24 (2.63)	**<.001**[a]

Mean (SD).
Bold signifies significance after correction for multiple comparisons (corrected *P*-value < 0.0083).
Key: .
Analysis: [A] analysis of variance; [χ] chi-square.
Post hoc: [a]CDR 0 different from CDR 0.5-3, CDR 0.5 different from CDR 1-3; CDR 1-3 not different from each other; .
[b]CDR 0 different from CDR 0.5-3, CDR 3 different from 0.5-2.

TABLE 4 Discriminability of the Vulnerability Index and its components

				95% Confidence Interval	
Test Result Variable(s)	**AUC**	**SE**	***P*-value**	**Lower Bound**	**Upper Bound**
Age, y	.779	.038	<.001	.705	.853
Sex	.338	.046	.002	.247	.428
Race, binary	.431	.055	.187	.324	.539
Education, y	.441	.048	.259	.347	.536
Body mass index	.442	.052	.262	.340	.543
Fried Frailty Index	.818	.033	<.001	.753	.884
HADS Depression	.635	.051	.009	.536	.735
Diabetes	.559	.048	.256	.464	.654
Stroke	.556	.048	.282	.461	.650
Hypertension	.570	.051	.177	.471	.669
Heart disease	.617	.046	.025	.526	.707
Hypercholesterolemia	.569	.051	.185	.468	.670
Vulnerability Index	.844	.035	<.001	.776	.913

Abbreviation: AUC, Area under the receiver-operating characteristic (ROC) curve; HADS, Hospital Anxiety and Depression Scale; SE, Standard Error.

component; however, an assessment of frailty is generally a component of geriatric evaluations included in initial preventive physical exams and annual wellness visits covered by Medicare.[41] Overall performance was high across participant characteristics and ADRD etiologies; however, there was little ability to discriminate between impairment severities above CDR 1. This is due to the components of the VI—including Fried Frailty Index, BMI, HADS depression, and age—being known risk factors for dementia but not necessarily predictors of progression, and thus were able to discriminate in our sample between CDR 0 (no impairment) and CDR 0.5 (mild impairment) or above but not between different CDR stages past 1 (Table 3). As a result, the VI should not be used as a staging tool and is not intended as such, as once impairment is already manifest a measure of vulnerability to impairment is no longer necessary. We included a range of individuals from age 38-98 years of age that includes similar proportions of individuals with and without impairment below age 65 (16 non-impaired, 23 impaired), with the lowest aged control (age 38) matched with a similarly aged case (age 39). This suggests that the VI could be used to examine risk of ADRD in younger individuals and offer paths for early intervention. The VI showed moderate to high correlations with cognitive and clinical measures, particularly for executive function, which is one of the earliest domains to change.[27,42,43] Individuals rated high in vulnerability (≥8) displayed worse functional, behavioral, and cognitive health and had lower health-related quality of life ratings than individuals with lower scores.

Given its high accuracy metrics (sensitivity, specificity, diagnostic odds ratio) and that the VI examines only demographic, medical, and easily administered physical functioning information, much of which is easily extractable from the EHR, it would be highly useful in both clinical and research contexts to assess potential risk of cognitive impairment. Potential clinical use of the VI could be in identifying patients likely to benefit most from

TABLE 5 Comparison of clinical and cognitive measures by Vulnerability Index threshold

Variable	Low Vulnerability (N = 106)	High Vulnerability (N = 281)	Adjusted *P*-value*
Clinical Measures			
Age, y	67.41 (8.04)	78.37 (7.82)	<**.001**
Education, y	16.34 (2.40)	15.35 (2.73)	.012
QDRS – Informant	3.51 (4.94)	7.60 (6.03)	<**.001**
QDRS – Patient	2.45 (3.55)	5.49 (5.12)	<**.001**
FAQ	4.65 (8.16)	11.54 (9.84)	<**.001**
HUI-3	0.72 (0.29)	0.44 (0.32)	<**.001**
TUG	8.76 (3.37)	12.97 (6.92)	.010
mPPT	12.53 (1.90)	8.98 (3.46)	<**.001**
UPDRS-III	5.01 (7.82)	12.46 (14.92)	<**.001**
Charlson	1.38 (1.19)	2.83 (1.63)	<**.001**
FCI	2.86 (1.64)	4.34 (1.75)	<**.001**
Hachinski	0.47 (0.72)	1.15 (1.47)	.003
mCAIDE	5.20 (2.82)	8.78 (2.34)	<**.001**
Mean arterial pressure	115.64 (15.23)	121.04 (15.06)	.431
Hippocampal volume	7.10 (1.11)	5.99 (1.13)	.180
Cognitive Measures			
MoCA	22.41 (7.07)	17.12 (6.62)	.007
Numbers Forward	6.98 (1.55)	6.49 (1.46)	.101
Numbers Backward	4.90 (1.66)	4.05 (1.57)	**.002**
Trailmaking A	42.71 (33.16)	69.09 (46.15)	.014
Trailmaking B	84.68 (42.66)	132.97 (46.13)	<**.001**
HVLT – Immediate	18.81 (6.90)	12.57 (5.98)	<**.001**
HVLT – Delay	6.50 (3.79)	2.84 (3.01)	<**.001**
HVLT – Recognition	10.21 (2.59)	8.16 (3.31)	.045
Number Symbol Coding	40.25 (12.37)	25.51 (11.90)	<**.001**
Animal Naming	17.12 (6.49)	11.99 (6.03)	**.001**
Composite z-score	0.69 (0.84)	-0.33 (0.90)	<**.001**
CDR-SB	2.55 (4.15)	5.81 (4.70)	.003

Mean (SD) or %.

Bold signifies significance after correction for multiple comparisons (corrected p-value < 0.0026).

Threshold for High Vulnerability set at ≥8.

*All values (except for age) are adjusted for age.

Abbreviations: QDRS, Quick Dementia Rating System; FAQ, Functional Activities Questionnaire; HUI-3, Health Utilities Index-Mark3; QPAR, Quick Physical Activity Rating; CLAS, Cognitive Leisure Activities Scale; AMPS, Applied Mindfulness Process Scale; TUG, Timed Up and Go; mPPT, mini-Physical Performance Test; UPDRS-III, Unified Parkinson's Disease Rating Scale-Motor Subscale; FCI, Functional Comorbidity Index; mCAIDE, Modified Cardiovascular Risk Factors, Aging, and Incidence of Dementia; MoCA, Montreal Cognitive Assessment; HVLT, Hopkins Verbal Learning Test; Composite z-score, Computed summary of global cognitive performance across nine neuropsychological tests; CDR-SB, Clinical Dementia Rating Sum of Boxes.

regular cognitive screening procedures and adhering to primary prevention strategies. The VI could be integrated into clinical decision support systems that examine the EHR and automatically flag patients, enabling seamless integration into clinical practice.[44] Identifying high vulnerability in asymptomatic individuals could improve early-stage screening for primary prevention studies, while mildly symptomatic patients could be targeted for secondary prevention.[6,45]

A cutoff score of 8 for determining high/low vulnerability was chosen for our sample due to its balanced sensitivity and specificity in addition to a high diagnostic OR, along with our aim of developing an effective screen for further cognitive testing. Within our sample, a large percentage of healthy controls were scored between 5 and 7 (mean = 6.25) while impaired subjects scored significantly higher than the cutoff (mean = 9.10 for MCI) (Table 2), meaning that a single point in the positive direction could have caused the average control to be

marked as impaired using our 8+ cutoff, whereas one point would not have altered the designation of the average impaired subject (**Figure** 1). This paired with our comparatively fewer numbers of controls led to low NPVs when selecting a threshold of 8+, with the benefit of higher PPVs. We have identified other thresholds that more favor sensitivity and NPV (11+) or specificity and PPV (5+) and reinforce the need for clinical validation to determine ideal thresholds.

Several other limitations exist in this study. The VI was developed and validated in an academic research setting where patients tended to be highly educated and predominantly White. In addition, the prevalence of MCI and dementia within our sample was high. Validation in other clinical and research settings, in individuals from more diverse racial, ethnic, and cultural backgrounds, and from other countries is needed. Our sample also consisted of a disproportionate number of male participants in the impaired category, likely skewed due to the comparatively high number of DLB subjects as a result of an interest in DLB by the senior author. Frailty and old age both greatly increase the risk of cognitive impairment, which is why the VI assigns them higher weight than other measures, but individually they cannot be used to determine if a single individual is at greater risk than another individual. Furthermore, both hypertension and stroke were found to be non-significant between impairment status in our sample, in contrast to the found association between these comorbidities and cognitive impairment in other studies.[15,18] Obesity was also more common in non-impaired than impaired subjects. Exclusion of these factors resulted in reduced predictive accuracy, likely due to trending effects; although these irregularities present within our sample may have contributed to reduced performance of the VI in this study, additional examination in other settings would be expected to result in increased overall performance. This was a cross-sectional study; thus the VI's longitudinal properties and predictive power will need to be evaluated in future studies. However, this project was critical to develop weighted scores and thresholds for establishing what is "normal" and what is "abnormal" by including both cognitively normal controls and individuals with various forms of impairment.

The strengths of the VI are derived from its ability to determine vulnerability to impairment using commonly collected health records, patient data, and easily obtained frailty measures. It is able to be calculated without regard to cognitive status or dementia etiology and may be useful for screening and risk determination of cognitive impairment or dementia, with high scores (≥8) used to trigger more extensive evaluations in patients or research participants.

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CONFLICTS OF INTEREST

James E. Galvin is the creator of the Number Symbol Coding Task and Quick Dementia Rating System scale used in this study. James E. Galvin and Michael J. Kleiman are creators of the Vulnerability Index. The other authors report no conflicts of interest.

DATA AVAILABILITY STATEMENT

A de-identified data set is available at Open Science Framework DOI 10.17605/OSF.IO/AKWV5. For questions regarding this data set, please contact Michael J. Kleiman, PhD at mjkleiman@med.miami.edu

DISCLOSURES

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MJK has nothing to disclose.

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