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RESEARCH ARTICLE

Assessment of disease impact through health-related quality of life measurement in primary progressive aphasia

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Abstract

INTRODUCTION: Measurements of health-related quality of life (HRQoL) are important for capturing disease impact beyond physical health and relative to other diseases but have rarely been assessed in primary progressive aphasia (PPA).

METHODS: HRQoL was characterized overall, by sex and subtype in PPA (n = 118) using the Health Utilities Index-2/3 (HUI2/3). Multiple linear regression assessed associations between HRQoL and language severity.

RESULTS: Multi-attribute HUI2/3 summary scores indicated moderate to severe impairment. Scores did not differ by sex and were more severe for semantic than non-semantic PPA. Language severity scores showed significant associations with HUI multi-attribute scores and select single-attribute measures (hearing, sensation, cognition, and speech) with less language impairment associated with better functional capacity related to HRQoL.

DISCUSSION: This study identified poor HRQoL in a relatively large PPA cohort. HRQoL measures aid in determining patient perspective, policy decision making, and resource allocation. Results may be used to advocate for PPA support.

KEYWORDS
Alzheimer's disease, frontotemporal dementia, frontotemporal lobar degeneration, Health Utilities Index, neuropsychology, language impairment, primary progressive aphasia, quality of life, Western Aphasia Battery

Highlights

- Primary progressive aphasia (PPA) negatively impacts health-related quality of life.
- Health utilities index scores are associated with Western Aphasia Battery performance in PPA.
- Severity of language impairment in PPA is associated with poorer quality of life.

1 | INTRODUCTION

Primary progressive aphasia (PPA) is a relatively rare neurodegenerative dementia syndrome characterized by progressive and gradual impairment primarily in language.[1] PPA negatively impacts communication, activities of daily living, and quality of life (QoL).[2] However, research has typically focused on characterizing the neuropsychological impairments and neuroimaging findings associated with PPA, with less focus on quantifying the associated impact on QoL. Assessment of QoL is essential for understanding the holistic impact of PPA, beyond what might be captured in typical clinical assessments. Such information can be used to guide person-centered interventions and supportive services tailored to the needs and preferences of the family.

QoL can be measured from different perspectives; the current study examines health-related quality of life (HRQoL), which focuses on how one's perceived health, across multiple domains (e.g., physical functioning), influences overall QoL.[3] HRQoL can be assessed using generic or disease-specific measures.[4] Disease-specific measures are developed for specific health states or diseases, while comprehensive, generic measures of HRQoL are better suited for cross-disease comparisons, use in cost-effectiveness research, health policy decision making, and as outcomes for clinical trials.[5,6]

The Health Utilities Index (HUI) multi-attribute HRQoL classification tool comprises two main instruments, the HUI mark 2 (HUI2) and HUI mark 3 (HUI3).[6] These instruments are used together to provide complementary information about the ability or disability of an individual. These measures have been widely used in the HRQoL literature with reliability and validity across health conditions, including Alzheimer's disease (AD) dementia.[7–10] However, there are limited data available about HRQoL in individuals with PPA.[11–13]

The primary goal of this study was to characterize HRQoL using a generic measure, the 15-item HUI, in a relatively large cohort of individuals living with mild to moderate PPA. A secondary goal of the current study was to understand the relationship between HRQoL and language impairment severity in PPA to contextualize the impact of language loss on QoL. A previous internet survey study from a community sample with self-reported frontotemporal dementia (FTD) spectrum diagnoses (including individuals with PPA), showed the socioeconomic burden is greater for FTD than AD dementia.[12] The outcomes from this analysis will aid in characterizing HRQoL in a relatively large and well-phenotyped PPA cohort, which may inform and provide tools for advancing health care and policy decision making in PPA. Such data are particularly important as non-pharmacologic interventions are emerging and effective interventions will need to quantify the socioeconomic impact to advocate for adoption by key stakeholders including patients, clinicians, and health-care systems.[14,15]

RESEARCH IN CONTEXT

1. **Systematic Review**: The authors reviewed the literature using traditional sources (e.g., PubMed). The literature related to health-related quality of life in primary progressive aphasia (PPA) is relatively sparse, and none has assessed associations between health-related quality of life (HRQoL) and language severity.
2. **Interpretation**: Results suggest moderate to severe HRQoL for individuals living with PPA. Measurement of HRQoL was associated with language severity scores.
3. **Future directions**: Future application may include direct assessment of HRQoL from individuals with a diagnosis of PPA rather than proxy measurements from care partners as well as the comparison of the Health Utilities Index mark 2 and mark 3 to other HRQoL measures.

2 | METHODS

2.1 | Data source, design, and participant characteristics

Data were obtained from prospective PPA studies: baseline data of the Communication Bridge-2 (CB2) Clinical Trial (NCT03371706, R01AG055425), and from observational PPA research studies (R01AG056258, R01AG077444). CB2 is a prospective, stage 2, randomized controlled trial of a speech and language non-pharmacological intervention for communication difficulties in mild to moderate PPA.[15] The observational PPA studies are prospective, longitudinal multidisciplinary investigations of people with PPA.[16] Those with a diagnosis of mild-to-moderately severe PPA, based on neurologist (author A.L.) and cognitive neuroscientist and PPA expert (author E.R.) review of medical records and research assessment data (e.g., Western Aphasia Battery Aphasia Quotient [WAB-AQ], Cinical Dementia Rating [CDR] language, Boston Naming Test, and a subset of items from Peabody Picture Vocabulary Test-IV [PPVT-IV]), were included in this study. Terminal patients were not included. HUI measures were completed by co-enrolled care partners. A care partner was defined as a person who served in an informal caregiving role and assisted the participant in daily functioning. Participant data were collected from their first study visit, when the HUI and WAB assessments were both completed.[17] In instances in which participants were co-enrolled in the CB2 and PPA observational studies, assessment scores from the first chronological visit when both measures were completed were included. Participants with a diagnosis of primary progressive apraxia of speech (PPAOS) and semantic dementia were excluded because they did not meet root criteria for PPA, the focus of this study. Figure 1 details the identification and selection of 118 unique participants with consideration to the

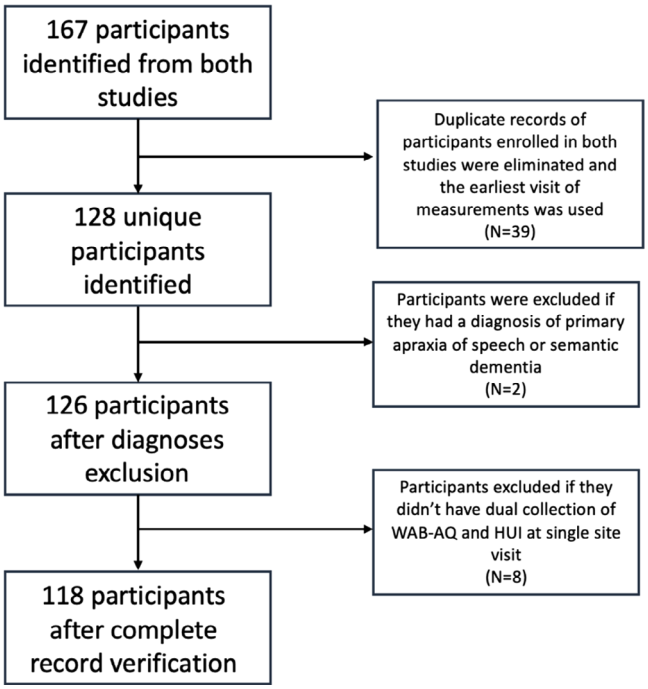

FIGURE 1 Participant inclusion flow chart. HUI2, Health Utilities Index; WAB-AQ, Western Aphasia Battery aphasia quotient.

inclusion/exclusion criteria. The research was approved by the human ethics research boards at Northwestern University and the University of Chicago.

2.2 | Measures

Variables included in the analysis were self-reported demographic and clinical history information (sex, race, age, disease duration, living situation, Charlson Comorbidity Index [CCI]), HUI2, HUI3, and the WAB-AQ scores.[17,18] The measures in this study were collected through four primary methods: video chat, phone, in person, or mailed questionnaires.

The WAB was administered in person or over video chat and was collected directly from the participant living with PPA. Previous research demonstrated the reliability of the WAB when administered via telehealth, compared to in-person administration.[19] The WAB-AQ score is a weighted average of individual WAB subtest scores relating to spoken language and auditory comprehension and was used to estimate language impairment severity in the participants with PPA.[20] While the WAB-AQ is only one measure used in the overall analysis of disease severity in PPA, previous studies have suggested scores of 80 to 85 or above in persons with PPA reflect relatively mild impairment, while scores < 60 suggest more severe impairment.[21,22]

The HUI2 and HUI3 measures were collected from the care partner as a proxy respondent. The HUI2 and HUI3 measures produce utility scores based on the rater's scoring of specific attributes of health. These instruments were designed to measure functional capacity and are contrasted with performance-based QoL instruments that may confound physical or cognitive capacity with personal preference, opportunities, and choices.[5] Utility scores represent the overall desirability or preference of the designated health state produced by predetermined population-based surveys.[23] The HUI2 has seven single attributes: sensation, mobility, emotion, cognition, self-care, pain, and fertility.[6] The HUI3 has eight single attributes: vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain. Each attribute score has four to six levels used to capture the range of impairment or function. The HUI2 and HUI3 are considered complementary rather than redundant measures. The HUI2 and HUI3 provide a description and enumeration of health status with: (1) aggregate multi-attribute scores comprising = all single-attribute scores and (2) individual single-attribute scores. The scoring algorithm and range of utility values for these two measures are slightly different. While scores typically range between 0.0 (dead) and 1.0 (perfect health), the measures allow for utility scores that represent "worse than death" health states with utility scores lower than 0.0 (lowest value of −0.03 for HUI2 and −0.36 for HUI3). Care partners answered the 15-item questionnaire based on the participant's function in the previous 2 weeks. For the HUI2, scores of 1.00 indicate no disability, 0.90 to 0.99 indicate mild disability, 0.80 to 0.89 indicate moderate disability, and scores < 0.80 indicate severe disability. For HUI3, scores of 1.00 indicate no disability, 0.89 to 0.99 indicate mild disability, 0.70 to 0.88 indicate moderate disability, and scores < 0.70 indicate severe disability.[24] The CCI was calculated from each PPA participant to estimate the risk of mortality due to comorbid disease states and to quantify the amount of individual comorbidity burden.[18,25]

2.3 | Statistical analyses

Demographic and clinical characteristics were summarized as frequency counts and percentages for categorical variables. Continuous variables were summarized as mean, median, standard deviation, and range values.

All analyses were performed using R statistical software (R 4.3.3, http://www.r-project.org).

Differences in HUI2 and HUI3 by self-reported sex were assessed using linear regression controlling for WAB-AQ and demographic variables as previous literature has indicated possible differences in language impairment severity and disease progression in females compared to males.[26]

PPA is commonly classified into three research subtypes based on patterns of language impairment and preservation: semantic variant (PPA-S), logopenic variant (PPA-L), and agrammatic or non-fluent variant (PPA-G).[1,27–29] These PPA subtypes were further categorized into broader PPA classes of semantic PPA and non-semantic PPA to examine differences between HUI2 and HUI3 using linear regression controlling for WAB-AQ and demographic variables. In this study, semantic variant (PPA-S) and non-semantic variant (PPA-G and PPA-L) subtypes were used because PPA-S is a clearly defined subtype with strong clinicopathological correlation whereas PPA-G and PPA-L are less distinct.[28,30,31]

The associations between multi-attribute HUI2 and HUI3 scores and WAB-AQ scores were assessed using multiple linear regression models with HUI2 and HUI3 scores as the dependent variable and WAB-AQ scores as the independent variable. These analyses adjusted for the following covariates: age, sex, disease duration, years of education, and CCI. Race and ethnicity were not included as a covariate because of the homogenous nature of the sample. A partial correlation analysis controlling for these same covariates was also performed.

The association of single attribute HUI2 and HUI3 scores and WAB-AQ scores were of interest for identifying potential salient single attributes. This additional analysis included ordinal regression to assess the association between the 14 HUI2 and HUI3 single-attribute scores (e.g., cognition, emotions, sensation, etc.) and the WAB-AQ. This analysis used the single attribute scores as ordinal dependent variables, used the WAB-AQ as the independent variable, and included the same covariates as the primary analyses. The HUI2 and HUI3 single attributes were analyzed as ordinal variables rather than continuous variables because each single-attribute has specific predetermined decrements in utility values associated with impairment.

3 | RESULTS

Baseline demographic information and clinical information are presented in Table 1 for both the person with PPA and their care partner. Overall, the sample was primarily White, highly educated, in their late sixties, and relatively balanced between men and women.

The mean multi-attribute summary scores for the HUI2 instrument and the HUI3 instrument were 0.807 and 0.667, respectively, with 0.0 indicating death and 1.0 indicating perfect health. According to the disability categorizations of the HUI instrument, the mean HUI2 multi-attribute scores indicate moderate disability and the mean HUI3 multi-attribute scores indicate severe disability.[24]

The multi-attribute summary scores for HUI2 and HUI3 were also assessed for differences by self-reported sex or by PPA semantic and non-semantic classifications. No significant difference was found between the two sexes on either HUI2 or HUI3 scores. However, there was a statistically significant difference in HUI2 and HUI3 scores between PPA subtypes, where HUI2 and HUI3 scores were higher for the non-semantic PPA subtype compared to the semantic PPA subtype ($P = 0.016$ for HUI2 and $P = 0.004$ for HUI3) indicating poorer HRQoL for those with the semantic subtype.

Multi-attribute summary scores for both the HUI2 and HUI3 (Figure 2) showed significant associations ($P \leq 0.001$) with the WAB-AQ scores when adjusting for the identified covariates. These results suggest less severe language impairment (i.e., higher WAB-AQ score) was associated with better functional capacity (i.e., higher HUI scores) as it relates to health-related QoL. For every 1-point increase in the WAB-AQ score, there was a 0.0029 (0.002, 0.0038) increase in the HUI2 measure ($P \leq 0.001$) and a 0.0084 (0.0066, 0.0102) increase in the HUI3 measure ($P \leq 0.001$).

The 14 single-attribute summary scores from the HUI2 and HUI3 were measured for their association with WAB-AQ scores and were

TABLE 1 Demographic and clinical characteristics of the study sample.

Variable	Number of participants (%); total $n = 118$
Self-reported sex	
Female	58 (49.2%)
Male	60 (50.8%)
Self-reported race/ethnicity	
Asian	2 (1.7%)
White, Hispanic	1 (0.8%)
White, non-Hispanic	115 (97.5%)
Age (years)	
Mean (SD)	67.5 (7.47)
Median (min, max)	68.4 (52.4, 81.9)
Education (years)	
Mean (SD)	16.5 (2.37)
Median (min, max)	16.0 (12.0, 21.0)
Living situation	
Lives alone	9 (7.6%)
With a group	4 (3.4%)
With one other person (non-spouse)	13 (11.0%)
With one other person (spouse or partner)	92 (78.0%)
Disease duration (years)	
Mean (SD)	4.11 (2.36)
Median (min, max)	3.57 (1.00, 14.5)
WAB-AQ	
Mean (SD)	80.6 (11.5)
Median (min, max)	83.2 (43.6, 97.6)
Activities of daily living questionnaire (ADLQ)	
Mean (SD)	17.2 (13.4)
Median (min, max)	13.1 (0.0, 67.9)
HUI2 score	
Mean (SD)	0.807 (0.107)
Median (min, max)	0.806 (0.360, 1.00)
HUI3 score	
Mean (SD)	0.667 (0.237)
Median (min, max)	0.699 (-0.01, 1.00)
PPA subtype	
Semantic	32 (27.1%)
Non-semantic	86 (72.8%)
CCI	
0	0 (0.0%)
1	95 (80.5%)
2	10 (8.5%)
3+	13 (11.0%)

(Continues)

TABLE 1 (Continued)

Variable	Number of participants (%); total $n = 118$
Care partner self-reported sex	
Male	46 (39.0%)
Female	72 (61.0%)
Care partner age[a]	
Mean (SD)	64.3 (10.4)
Median (min, max)	66.5 (25.8, 89.9))
Care partner relation to person with PPA	
Spouse	101 (85.6%)
Child	7 (5.9%)
Sibling	1 (0.8%)
Other relatives	3 (2.5%)
Neighbor/friend	6 (5.1%)
Care partner education (years)[b]	
Mean (SD)	16.3 (2.6)
Median (*n*, max)	16.0 (10.0, 26.0)
PROMIS depression[c]	
Mean (SD)	49.9 (2.6)
Median (min, max)	48.6 (34.2, 71.4)
PROMIS anxiety[c]	
Mean (SD)	50.6 (2.8)
Median (min, max)	51.2 (32.9, 72.8)

Abbreviations: CCI, Charlson Comorbidity Index; HUI2, Health Utilities Index mark 2; HUI3, Health Utilities Index mark 3; PPA, primary progressive aphasia; PROMIS, Patient Reported Outcomes Measurement Information System; SD, standard deviation; WAB-AQ, Western Aphasia Battery–aphasia quotient.

[a]Indicates that there is one missing age value.

[b]Indicates that there are 5 missing years of education values.

[c]Indicates *t* scores from 95 participants.

adjusted for the relevant covariates (Tables 2 and 3). The frequency of responses for each HUI2 and HUI3 single attribute and level of functional ability are shown in Figure 3(A,B), respectively. Fourteen distinct linear regression models were performed for each of the single attribute summary scores to reduce dependency. The single-attribute summary scores that showed a significant positive association with WAB-AQ scores were HUI2 sensation, HUI2 cognition, HUI3 hearing, HUI3 speech, and HUI3 cognition such that better performance on the WAB-AQ was associated with higher HRQoL in these domains. All other single-attribute summary scores were non-significant in their association with WAB-AQ scores. These findings suggest that the HUI is capturing HRQoL differences specific to the domains commonly associated with PPA compared to other domains less commonly impacted for those with PPA (i.e., self-care or pain). It should be noted that there is an overlap in the HUI2 and HUI3 cognition scores as they both are calculated from the same two questions on the HUI instrument. Similarly, the HUI2 sensation single domain score comprises the questions that relate to hearing, speech, and vision that are individually reported as three separate single domain scores for HUI3.

4 | DISCUSSION

Capturing HRQoL in individuals with PPA provides a more holistic understanding of the disease's impact.[32] This study characterized HRQoL in a relatively large sample of participants with PPA and also examined how HRQoL is associated with language impairment severity (measured by the WAB-AQ). According to the HUI disability categorizations, the multi-attribute scores indicated moderate and severe disability based on the HUI2 and HUI3 scores, respectively.[24] Further, the degree of disability on both the HUI2 and HUI3 showed significant positive relationships with the WAB-AQ scores, indicating language function is associated with HRQoL.

For every 1 unit increase in WAB-AQ scores (on a scale of 1–100), there was an associated 0.0029 increase in HUI2 and 0.0084 increase in HUI3. Previous research suggests that when assessing the minimally clinically important differences in HRQoL research and utility scoring, one can find meaningful differences in values as low as 0.01.[33] Based on this assessment, our findings suggest that the HUI3 may capture clinically meaningful differences in mild to moderate PPA; however, further research is warranted.

Key single-attribute scores, including the HUI2 and HUI3 cognition, HUI3 speech, HUI2 sensation, and HUI3 hearing were significantly associated with the WAB-AQ. Significance in the cognition, speech, and sensation attributes were expected as these attributes are related to the disease landscape of PPA. The significant association between the WAB-AQ and the single attribute HUI3 hearing score was unexpected. Further investigation is needed to better understand this association. One possibility is the care partner could be misinterpreting "hearing" for "understanding" in the two questions related to hearing, as impaired auditory comprehension can be a prominent feature of PPA.[34] The HUI questions ask about the participant's ability to hear what was said in a group conversation and about the participant's ability to hear what was said in a conversation with one other person in a quiet room. It is possible that although these items enquire about hearing capacity (as a sensory function), the language symptoms in PPA biased some care partners toward interpreting this item to indicate "communication" as a broader concept. These observations highlight the importance of expanding instrument validation efforts in rare dementias in which symptom profiles and disease impacts may affect item comprehension and response patterns.[35]

On average, HUI3 multi-attribute scores were lower than HUI2 scores in this population. Based on the proposed classifications, multi-attribute summary scores were in the moderate (HUI2) or severe (HUI3) categorization for disability.[24] However, only HUI3 disability categorizations have been externally validated in data provided from a community survey of the general Canadian population. Cautious interpretations should be made as the disability categorizations were not validated in PPA specifically.[36] Possible explanations for the differences in scores include that the HUI3 has a wider range than HUI2 in

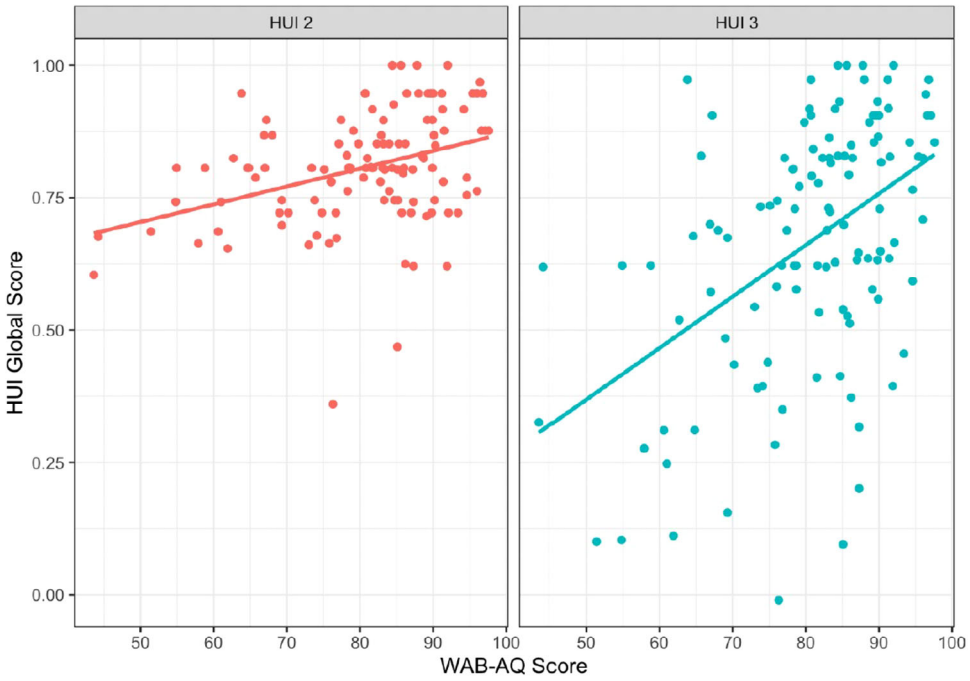

FIGURE 2 Multi-attribute HUI2 and HUI3 scores are positively associated with language severity in PPA as measured by WAB-AQ performance while accounting for demographic and clinical characteristics. The correlation between WAB-AQ scores and multi-attribute HUI2 scores was 0.398 (0.234, 0.540) and between WAB-AQ scores and multi-attribute HUI3 scores it was found to be 0.298 (0.124, 0.454). Both correlations were found to be statistically significant ($P \leq 0.001$). Negative scores are possible for multi-attribute summary scores and would indicate a state worse than death. HUI2, Health Utilities Index mark 2; HUI3, Health Utilities Index mark 3; PPA, primary progressive aphasia; WAB-AQ, Western Aphasia Battery aphasia quotient.

TABLE 2 A subset of HUI2 single attribute scores were associated with WAB-AQ scores.

HUI2 single attribute	Beta coefficient	Standard error	*P* value
Sensation	0.0808	0.0231	< 0.001*
Mobility	0.0339	0.0347	0.329
Emotion	−0.0133	0.0183	0.469
Cognition	0.0759	0.0200	< 0.001*
Self-care	−0.0011	0.0913	0.991
Pain	0.0070	0.0186	0.707

Note: Key single-domain attribute scores related to PPA were shown to have a positive association with language severity as measured by the WAB-AQ.
Abbreviations: HUI2, Health Utilities Index mark 2; WAB-AQ, Western Aphasia Battery–aphasia quotient.
*Indicates significance (*P* value ≤ 0.05).

TABLE 3 A subset of HUI3 single attribute scores were associated with WAB-AQ scores.

HUI3 single attribute	Beta coefficient	Standard error	*P* value
Vision	0.0204	0.0211	0.335
Hearing	0.0564	0.0219	0.01*
Speech	0.0817	0.0192	< 0.001*
Cognition	0.0766	0.0184	< 0.001*
Ambulation	0.0400	0.0363	0.276
Dexterity	0.0099	0.0398	0.803
Emotion	−0.0126	0.0171	0.461
Pain	−0.0084	0.0188	0.656

Note: Key single-domain attribute scores related to PPA were shown to have a positive association with language severity as measured by the WAB-AQ.
Abbreviations: HUI3, Health Utilities Index mark 3; WAB-AQ, Western Aphasia Battery–aphasia quotient.
*Indicates significance (*P* value ≤ 0.05).

multi-attribute summary scoring. While the maximum score is 1 for both the HUI2 and HUI3, the overall multi-attribute scores can be lower for HUI2 than HUI3 (−0.03, −0.36, respectively).[37] Additionally, cognition is weighed more heavily in the HUI3 versus HUI2 multi-attribute score, providing a possible factor in lower HUI3 scores.[38] Neumann et al. reported a similar difference in magnitude of HUI2 and HUI3 scores in their AD study compared to our PPA cohort.[10] The differences in HUI2 and HUI3 scores may also contribute to the varying degrees of correlation with the WAB-AQ scores (i.e., borderline moderate and moderate correlations of the HUI2 and HUI3 with the WAB-AQ, respectively, Figure 2).

There were significantly lower HUI scores in the semantic relative to the non-semantic groups, suggesting that those with semantic PPA may experience lower HRQoL. A full understanding of the underlying reasons driving this finding is unclear. One recent study found that caregivers reported a higher symptom frequency for individuals

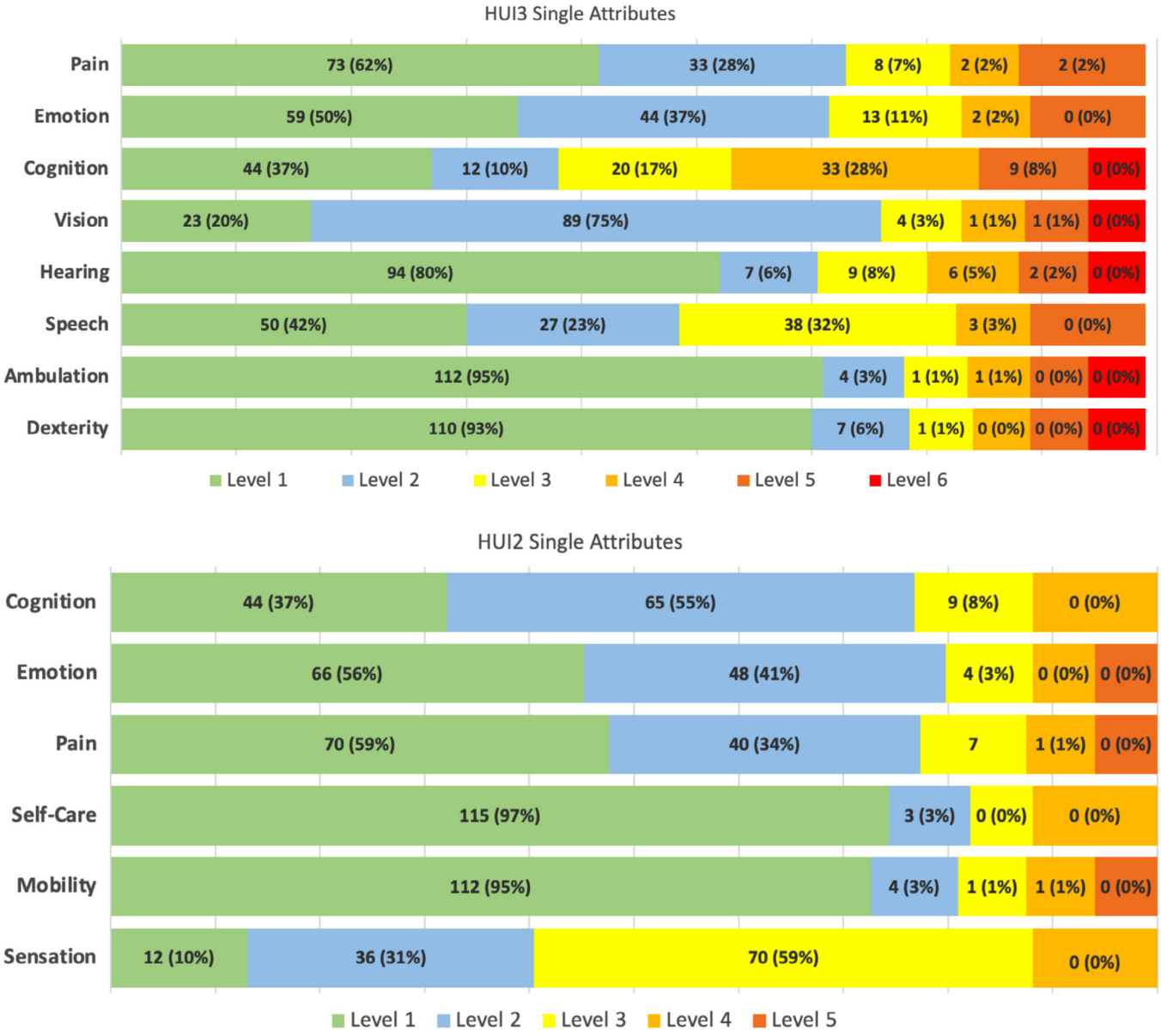

FIGURE 3 (A) Frequency of the HUI2 single attribute summary scores. (B) Frequency of the HUI3 single attribute summary scores. Numerical single summary scores for both HUI2 and HUI3 have been associated with discrete levels of HRQoL that are unique to each domain.[6] The number of discrete levels varies from four to six levels depending on the domain. Higher levels indicate a worse functional state, while a participant endorsement of level 1 indicates no problems for that domain. The number and (percent) of participants are associated with each level are provided in (A) and (B) for the HUI2 and HUI3, respectively. For the HUI2, emotion, pain, and mobility have four possible levels, while cognition, self-care, and sensation have five possible levels. For the HUI3, emotion, pain, and speech have five possible levels, while cognition, vision, hearing, ambulation, and dexterity have six possible levels. HRQoL, health-related quality of life; HUI2, Health Utilities Index mark 2; HUI3, Health Utilities Index mark 3.

with semantic (54 symptoms) compared to agrammatic PPA (44 symptoms).[39] Symptoms in both variants varied from communication issues to an inability to control movement and body functions in more severe diseases. Higher symptom frequency in the semantic relative to non-semantic PPA may contribute to the endorsement of lower HUI scores.

Previous literature has rarely assessed HUI scores in PPA. Participants in our study had higher (i.e., better perceived HRQoL) HUI3 measurements (0.67 vs. 0.09) than in a community sample of people with PPA reported by Galvin et al.[12] The higher HUI3 scores in our cohort could be due to the exclusion of individuals classified with terminal PPA in our study compared to the Galvin et al. study, which included terminal patients. Additionally, HUI3 scores in our study were higher than those of the behavioral variant of frontotemporal dementia (bvFTD; 0.13), FTD with motor neuron disease (0.10), and those with progressive supranuclear palsy (0.04) reported by Galvin et al.[12] However, these cohorts also included terminal patients, limiting the direct comparison to the current study. Because Galvin et al. relied

on an online community sample with self-reported diagnosis, it makes it difficult to ascertain diagnostic accuracy or comparative severity of language impairment, further limiting direct comparison across studies. Our findings are contextually similar to that of Neumann et al. in AD, showing worse HRQoL (measured by HUI) was associated with greater clinical severity (measured by WAB-AQ for PPA and CDR scale for AD).[10] Finally, the sub-analysis assessing the association between sex and HUI2 and HUI3 scores was performed because a previous study showed females had greater impairment in language and more aggressive rates of decline.[26] Although our findings for analysis based on sex were non-significant, females did have lower mean reported HUI2 and HUI3 multi-attribute scores.

Having a usable HRQoL measure to capture general health impairments in people with PPA is critical for clinical practice and decision making.[40] Cost-effectiveness research uses generic HRQoL measures and utility scores in the calculation of the benefit when assessing treatment and intervention effectiveness. HRQoL in the benefit calculation of effectiveness helps elucidate the QoL that could be extended with potential treatments. These HRQoL measures can also be used in clinical decision making to capture what the potential benefit could be from certain treatment options on an individual level, such as in a recently published paper assessing the cost effectiveness of aducanumab in AD and another summary with potential policy implications.[41,42] Finally, HRQoL measures can be used in health-care policy decision making and resource allocation.[43] Thus, a useful HRQoL measure has implications beyond the accurate capture of patient perspective.

One limitation is the HUI measurements were only collected from the care partner, not directly from the participant. Capturing the HUI2 and HUI3 from the proxy care partner was done in part to allow for consistent collection of data across the studies and to reduce the respondent burden on the participant with PPA. In doing so, the potential for proxy bias was introduced. Previous studies have documented that caregivers' psychological distress and perceived burden can be a predictor of proxy reports of psychosocial scores for the patient.[44] In our study, the Patient Reported Outcomes Measurement Information System (PROMIS) Depression and PROMIS Anxiety measures were captured for the care partners in a subset of the respondents (i.e., care partners from the CB2 trial). Mean *t* scores with standard error were 49.9 (2.6) and 50.6 (2.8), for the PROMIS Depression and Anxiety measures, respectively, suggesting anxiety and depression were not elevated for the care partners on average. Additionally, the presence and impact of proxy response and participant self-report have been unclear in PPA and related syndromes (e.g., AD) using the HUI instruments.[10,11,45] Ruggero et al. found no significant or consistent evidence of proxy bias report of QoL for PPA.[11] Other studies have stated that while the two reports cannot be used interchangeably, collection of proxy-report data when self-report data are not available (or are not feasible to collect) is preferable to imputing missing data.[46] Furthermore, it remains unclear whether the mode of administration of the HUI (i.e., in-person data collection or mail responses) had an effect on the care partner responses.[47] One direction for future research is to examine the feasibility and validity of different administration modes and of collecting proxy and self-report measurements of HRQoL in PPA.

Another limitation is the racial–ethnic homogeneity of the participant sample. The sample was primarily White, non-Hispanic, and highly educated. Additionally, the participant sample comprised primarily participants with mild-to-moderate PPA due to the CB2 study enrollment criteria. This observed homogeneity limits the generalizability of these findings beyond the study sample. Prior studies reporting the influence of race/ethnicity, education, and socioeconomic status on HRQoL underscores the importance of understanding the intersection of these factors with QoL in people living with PPA.[48–50] While aphasia was the prominent deficit for each participant, it is possible deficits in additional domains could have contributed to worse HRQoL; however, this could not be statistically assessed in the current sample.

Overall, this study shows poor HRQoL in a relatively large PPA sample. Measurement of HRQoL was associated with language impairment severity scores. Collectively, these data may be used for advocating for additional health-care and policy support for PPA as the HRQoL measurements used can be contextualized across diseases.

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CONFLICT OF INTEREST STATEMENT

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CONSENT STATEMENT

Informed consent was gathered from all human subjects prior to enrollment in their respective study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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