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Relationships among Apathy, Health-Related Quality of Life and Function in Huntington's disease

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Dr. Fritz has no conflicts of interest to disclose.

Mr. Boileau has no conflicts of interest to disclose.

Dr. Stout has served on a Scientific Advisory Boards for Roche (2015). She has been an expert consultant to Prana Biotechnology (2011 to 2016). She is a director of Stout Neuropsych Pty Ltd, which provides clinical trial services, for Omeros (2014 to 2015), Teva (2014 to present), Vaccinex (2015 to present), and Ionis (2015 to present). She receives compensation from the Huntington's Study Group for her role as Treasurer on the Board. She serves as an expert consultant to the University of Michigan.

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Abstract

Up to 90% of individuals with Huntington's disease (HD), a progressive inherited neurodegenerative disease, experience apathy. Apathy is particularly debilitating because it is marked by a reduction in goal-directed behaviors, including self-care, social interactions, and mobility. The objective of this study was to examine relationships among apathy, functional status, physical function, cognitive function, behavioral status/emotional function, and health-related quality of life. Clinician-rated measures of physical, cognitive and behavioral function, including one clinician-rated item on apathy, and self-report measures of physical function, health-related quality of life, emotional, cognitive, and social function were collected in a single session from 193 prodromal, 186 early stage manifest and 108 late stage manifest people with the HD mutation. Multiple linear regression models were used to examine which outcomes best predicted clinician-rated apathy after controlling for disease stage. Greater apathy related to less independence, increased motor impairment, and more clinician-rated behavioral problems (i.e. anger, irritability, depression). Similarly, poorer self-reported health-related quality of life, greater chorea, greater upper and lower extremity dysfunction, greater speech and swallowing dysfunction, worse anxiety, depression and behavioral dyscontrol, worse cognitive function, and less satisfaction with social roles related to greater apathy. In summary, apathy related to physical, cognitive and behavioral dysfunction across disease stages. Future works should explore whether clinical interventions targeting different functional domains may have the potential to reduce apathy in this population.

Keywords

Huntington's Disease; Apathy; Health-Related Quality of Life

Introduction

Huntington's disease (HD) is a genetic, neurodegenerative disease characterized by motor, cognitive and behavioral changes. The behavioral changes with HD are particularly debilitating and relate to increased caregiver burden and reduced health-related quality of life (HRQOL).^{1,2} Apathy is one of the most disabling behavioral symptoms for patients and caregivers.^{3,4} Apathy affects up to 90% of individuals with HD⁴⁻⁶ and includes a marked lack of motivation, as well as reduced goal-directed behavior and action initiation, including self-care and mobility.^{7,8}

Although the diagnosis for manifest HD relies heavily on motor manifestations, apathy may either precede motor difficulties or occur early in the course of the disease,^{10,11} thereby potentially providing an informative clinical marker of disease pathophysiology. Apathy may predict disease onset,⁹ and it correlates negatively with age of disease onset,¹⁰ and positively with the number of CAG repeats among those who are at risk for HD. Apathy increased in pre-manifest individuals over a three-year period,^{9,11} suggesting that it may be

useful for marking progression over time even prior to clinical diagnosis. In manifest disease, higher levels of apathy independently predict disability¹² and correlate with longer disease duration,¹³ greater functional impairment^{14,15} and increased cognitive difficulty in attention, set-shifting, memory and sequencing.¹⁶ Apathy also relates to depression³ and irritability¹⁷ in HD, although its association to other behavioral symptoms remains to be clarified. Given the link between apathy and disability, as well as the presence of apathy across disease stages, apathy may be an important measure for tracking and monitoring disease progression in both early and late stage of HD.

While evidence suggests that higher levels of apathy relate to poorer functional, motor, cognitive and behavioral outcomes, as well as lower HRQOL in HD, a more comprehensive analysis of these associations is needed. Evidence from other neurodegenerative disease shows that apathy aligns with a greater caregiver burden, greater disability, and less rehabilitation success.¹⁸ Additionally, apathy is linked to poorer cognitive performance on executive function tasks, more severe motor impairments, and communication difficulties,¹⁹ factors that have not yet been examined in HD. A better understanding of the associations among apathy and other measures in HD may provide insights into therapeutics or rehabilitation strategies to target apathy, which is especially important given the lack of existing recommendations or treatments for apathy.²⁰ Therefore, the objective of this study was to examine associations among apathy, functional status, physical function, cognitive function, behavioral status/emotional function and HRQOL. We hypothesized that apathy would increase across disease stages, and that greater apathy would be related to worse motor, cognitive and behavioral dysfunction and poorer HRQOL in persons with HD.

Methods

Data for the current analysis were collected from the baseline visit of a large cohort study that examined HRQOL in individuals with prodromal (positive gene test but no clinical diagnosis of HD), early- or late-stage HD (clinical diagnosis plus score of 7–13 for early- and 0–6 for late-HD on the TFC [described below]).²¹ Data collection occurred in conjunction with the PREDICT-HD study,²² a global cohort study with the purpose of assessing early symptoms of HD in prodromal participants.

Participant Visits

Participants were recruited through eight established HD clinics (CA, IA, IN, MD, MI, MN, MO, NJ), the National Research Roster for Huntington's Disease, online medical record data capture systems,²³ and through articles/advertisements in HD-specific newsletters and websites. Recruitment also included HD support groups and specialized nursing home units throughout the US. Participants completed an in-person assessment, and a computer-based self-report survey regarding HRQOL. Study visits lasted ~2 hours and participants were provided \$40 compensation. All data were collected in accordance with local institutional review boards and participants provided informed consent prior to their participation in study activities.

Measures

Clinician-Rated Assessments

Functional Status: Three measures from the Unified Huntington Disease Rating Scale (UHDRS) were administered to assess functional status: Total Functional Capacity (TFC),²⁵ the Functional Assessment scale (FA), and the Independence Scale. The TFC²⁵ provides a clinician-rated assessment of ability to engage in work, manage finances, complete activities of daily living (ADLs), complete chores, and live independently. Scores range from 0–13 with higher scores indicating better functioning. This measure was also used to determine HD staging (criteria highlighted above). The FA consists of 25 yes/no questions that assess the participant's ability to perform tasks such as ADLs, engage in gainful employment, manage finances, or complete chores. Total scores range from 0–25 with higher scores indicating better functioning. The Independence Scale evaluates functional independence. Scores range from 0–100 with higher scores indicating better independence. All functional status measures were based on clinical interviews with the patient and an informant (when possible).

Physical Limitations: The Total Motor Score (TMS) from the UHDRS was used to assess motor impairment across 15 different domains, including chorea, dystonia, rigidity, oculomotor function, and bradykinesia. Total scores range from 0–124 with higher scores indicating more motor impairment.

Cognition: Three measures of cognition from the UHDRS were also administered: Verbal Fluency, Symbol Digit Modalities Test (SDMT), and Stroop (Color Naming, Word Reading, and Interference). Verbal Fluency provides a measure of executive function and language and requires participants to name as many words as they can that start with a particular letter within one minute. Scores reflect the total number of named words across three different letters. The SDMT provides a measure of psychomotor processing speed, working memory, and requires participants to match symbols with numbers according to a key that is provided at the top of the page. Total scores reflect the number of correctly matched symbols provided in 90 seconds. Scores range from 0 to 120 with higher scores indicating better psychomotor processing speed. The Stroop is an executive functioning task that involves selective attention, cognitive flexibility, cognitive inhibition and information processing speed. In this three-part task, participants are required to name patches of colored ink (Color Naming), read words (i.e., either red, green or blue; Word Reading), or name the color of written words that are written in the wrong color ink (i.e., the word red written in green ink; Interference). For each Stroop task, total scores reflect the number of correct responses provided in 45 seconds; higher scores indicate better executive function.

Behavioral Status: The Problem Behaviors Assessment short form (PBAs)²⁴ was administered to evaluate eleven different behavioral problems and psychiatric symptoms (depression, suicidal ideation, anxiety, anger/aggression, irritability, apathy, obsessive compulsive behavior, perseverative thinking, delusions, hallucinations, and disoriented behavior). Severity scores for each behavior are rated from 0 (normal) to 4 (causing significant distress), while frequency scores are rated from 0 (never/almost never) to 4 (every day/at least once a day). The product of severity and frequency scores are calculated to

create a final score for each behavior which can range from 0 to 16, with higher scores indicating worse behavioral problems for each domain. Total scores reflect sum of the scores across all 11 behaviors, but given that apathy is our dependent variable of interest in the current analysis, the total PBAs scores included only the other 10 behaviors.

Self-Report Measures

Generic Measures of HRQOL

EQ-5D.²⁶ The EQ-5D is a standardized instrument that measures health status across five domains of HRQOL: mobility, pain, ability to perform regular activities, ability to care for oneself, and anxiety/depression. The EQ5D includes both an Index scores (which ranges from 0 to 25 with higher scores indicating worse health outcomes) and a Health Scale score (which ranges from 0 to 100, with lower scores indicating worse overall health).

RAND-12.²⁷ The Rand-12 is a HRQOL measure that asks about limitations in activities in relation to physical (pain, disability) and mental (depression, apathy, anxiety) health within the past month. Separate scores are calculated for physical and mental sections of the RAND-12, where raw scores range from 0 to 100. Final scores are calculated by subtracting the participant's score from the average for their age-group, resulting in positive and negative difference scores.²⁸ Positive scores reflect above average health for an individual's age group, while negative scores reflect below average health for the participant's age group.²⁸

World Health Organization Disability Assessment Schedule 2.0 (WHODAS).²⁹ The WHODAS is a 12-item generic assessment of health and disability; it assesses mobility, cognition, self-care, participation, and activities. Total scores range from 0 to 48, with higher scores indicating more functional limitations.

Physical Ability Measures—Several physical ability measures from Quality of Life in Neurological Disorders (Neuro-QoL)³⁰ and the Huntington Disease Quality of Life (HDQLIFE) measurement system²¹ were also completed. The Neuro-QoL is designed to evaluate HRQOL in individuals with neurological conditions,³⁰ whereas HDQLIFE was developed to examine HRQOL domains specific to those living with HD. We administered Neuro-QOL Lower Extremity Functioning (mobility), Neuro-QOL Upper Extremity Functioning (ability to use hands and arms to perform tasks of ADL and fine motor movements), HDQLIFE Speech Difficulties³¹ (the ability to speak and be understood in a variety of social situations), HDQLIFE Swallowing Difficulties³¹ (the ability to swallow and fears related to choking), and HDQLIFE Chorea³² (the effects of chorea on task completion). Each item bank is scaled on a T-metric with a mean of 50 and a standard deviation of 10 (the referent group for Neuro-QOL are other individuals with neurological conditions, whereas the referent group for HDQLIFE are other individuals with HD), with higher scores on Neuro-QoL domains indicating better functioning and high scores on HDQLIFE measures indicating poorer physical functioning.

Emotional Status Measures—Study participants also completed several measures of emotional function from Neuro-QoL,³⁰ HDQLIFE,²¹ and the Patient Reported Outcomes

Measurement Information System (PROMIS).³³ Participants completed Neuro-QoL Emotional/Behavioral Dyscontrol (irritability, impatience, and impulsiveness), Neuro-QoL Positive Affect and Well-being (perceived sense of purpose and meaning), Neuro-QoL Stigma (perceived negativity of others towards the participant as a result of their symptoms), HDQLIFE Concern with Death and Dying³⁴ (end of life issues including fear of death and end of life planning), HDQLIFE Meaning and Purpose³⁴ (sense of meaning and making the most of the time they have left), PROMIS Anger, PROMIS Anxiety, and PROMIS Depression. Similar to above, each item bank is scaled on a T-metric with a mean of 50 and a standard deviation of 10 (the referent group for Neuro-QoL are other individuals with neurological conditions, whereas the referent group for HDQLIFE are other individuals with HD, and the referent group for PROMIS are individuals in the general population), with higher scores indicating worse emotional functioning (except for Neuro-QoL Positive Affect and Well-Being and HDQLIFE Meaning and Purpose, where higher scores indicate better functioning).

Cognitive Ability Measures—Two measures of cognition were administered from Neuro-QoL:³⁰ Neuro-QoL Applied Cognition-Executive Function (cognitive planning and organizing) and Neuro-QoL Applied-Cognition-General Concerns (perceived difficulty in concentration and memory). Measures are scored on a T-metric with a mean of 50 and a standard deviation of 10 (the referent group for these measures are other individuals with neurological conditions), with higher scores indicating better cognitive function.

Social Function Measures—Two measures of social function were administered from Neuro-QoL:³⁰ Satisfaction with Social Roles and Activities (SATSRA; one's contentment in obligations pertaining to family, friends, and work) and Ability to Participate in Social Roles and Activities (SRA; one's involvement in obligations pertaining to family, friends, and work). These item banks are scaled on a T-metric with a mean of 50 and a standard deviation of 10 (the referent group are other individuals with neurological conditions), with higher scores indicating better social function.

Statistical Analyses

Prior to examining the associations between clinician-rated and self-report variables and PBAs Apathy scores, we first compared the levels of PBAs Apathy across the three staging groups (prodromal, early- or late-stage HD) using one-way, two-tailed, analysis of variance. Next, we computed a series of multiple linear regressions using PBAs Apathy as the outcome and each of the clinician-rated and self-report variables as independent measures.

Clinician-Rated Apathy—A one-way two-tailed Analysis of Variance (ANOVA) was conducted to determine differences in PBAs Apathy scores between the three HD staging groups.

Creating Composite Scores—To minimize the number of regression models used, composite scores for each of the nine aforementioned domains (clinician-rated physical ability (TMS), clinician-rated functioning, clinician-rated cognition, clinician-rated behavioral status, generic HRQOL, self-report physical ability, self-report emotional status,

self-report cognition, and self-report social function) were created for participants with complete data. Scores on each individual measure (i.e., Verbal Fluency, Stroop, and Symbol Digits Modalities Test for clinician-rated cognition; UHDRS Independence scale, UHDRS Functional Assessment, and UHDRS Total Functional Capacity for clinician-rated functioning; the 11 behaviors on the PBAs for clinician-rated mental health; the UHDRS Total Motor Scale for clinician-rated physical ability; Neuro-QoL Emotional and Behavioral Dyscontrol, Neuro-QoL Positive Affect and Well-Being, Neuro-QoL Stigma, HDQLIFE Concern with Death and Dying, HDQLIFE Meaning and Purpose, PROMIS Depression, PROMIS Anxiety, and PROMIS Anger for self-reported emotional status; HDQLIFE Chorea, HDQLIFE Speech Difficulties, HDQLIFE Swallowing Difficulties, Neuro-QoL Lower Extremities, and Neuro-QoL Upper Extremities for self-reported physical ability; Neuro-QoL Ability to Participate in Social Roles and Activities and Neuro-QoL Satisfaction with Social Roles and Activities for social functioning; Neuro-QoL Executive Functioning and Neuro-QoL General Concerns for self-reported cognition; the WHODAS, RAND-12, and EQ-5D measures for generic HRQOL), were first recoded to ensure that higher scores indicated better outcomes. Next, these individual scores were then standardized to have a mean of 0 and standard deviation of 1. Then, these standardized scores were summed for each respective composite score (i.e., clinician-rated cognition, clinician-rated functioning, clinician-rated behavioral status, self-report emotional status, and clinician-rated physical ability, self-reported emotional status, self-report physical ability, self-report social function, self-reported cognition, generic HRQOL). The sum scores within each of the nine composite groups were then scaled with a mean of 0 and standard deviation of 1 so that each composite score was on the same scale.

Multiple Linear Regression Models

Each of the nine composite scores were entered into separate multiple linear regression models (two-tailed tests of significance at $p < .05$), where the composite measure was the predictor, staging and clinician rated depression were covariates (except when depression was included as part of the composite score [i.e., analysis examining Clinician Mental Health]), and apathy was the outcome. R^2 values were used to determine which variables accounted for the most variance in apathy scores. We considered R^2 values between .01 and .08 to be small or minimal effect sizes, values between .09 and .24 were considered moderate, and effect sizes greater than .25 to be large. These R^2 values were then compared using Fisher's R to Z transformation³⁵, which sets correlation coefficient values onto a normal distribution scale with confidence intervals that can be statistically evaluated (while similar, this is not to be confused with the Fisher's Z Distribution). Finally, the Root Mean Square Error (RMSE), which is the standard deviation of the residuals, was calculated as an additional assessment of model fit.

Results

One hundred and ninety-three (193) prodromal, 187 early-stage, and 91 late-stage manifest HD participants were assessed (Table 1). The three groups differed by age ($F[2, 468] = 43.3$; $p < .0001$), which was expected given the progressive nature of HD. The prodromal participants were approximately 8 years younger than the early stage group and 13 years

younger than the late stage group. The prodromal participants also had significantly more years of education ($F[2, 434]= 15.6; p<.0001$) than both the early and late stage groups. The groups did not significantly differ for gender ($X^2= 3.60; p=.17$). The groups did significantly differ for race (Fisher's Exact $p<.0001$); the prodromal group did not include African Americans, whereas the early and late stage groups did. The groups also differed for marital status (Fisher's Exact $p<.0001$); the prodromal group did not include any widowed individuals, and had fewer divorced/separated individuals than the other two groups.

Across the three HD groups, average PBAs apathy score was 2.5 (SD=4.0). The prodromal group had an average score of 1.4 (SD=2.9), which was significantly lower than both the early-stage (mean=3.0; SD=4.1) and late-stage (mean=3.9; SD=5.0) group ($F[2,468]=14.9; p<.0001$). Early and late-stage scores did not significantly differ. Therefore, all models were adjusted for stage of disease.

Multiple Linear Regression Models

Table 2 highlights findings from the multiple linear regression models, after controlling for HD disease stage. For clinician-rated assessments, better behavioral status ($t[1]= -12.77; p<.0001$) was associated with better apathy scores (Table 2). There was no association between apathy and clinician-rated cognition ($t[1]= -0.85; p=.3955$), clinician-rated functioning ($t[1]= -1.15; p=.2504$), nor clinician-rated physical ability ($t[1]=-0.86; p=.3928$). The adjusted R^2 value for behavioral status was large at 0.30, while the adjusted R^2 values for physical ability, functioning, and cognition were all moderate (0.20, 0.14 and 0.18, respectively).

For self-reported HRQOL, better scores on the generic composite measure ($t[1]= -2.33; p=.0201$), emotional status ($t[1]= -3.74; p<.0001$), cognition ($t[1]= -5.04; p<.0001$), and social functioning ($t[1]= -6.25; p<.0001$) were all significantly associated with better apathy outcomes (Table 2). Self-reported physical ability ($t[1]= -1.46; p=.1445$) was not associated with apathy. Adjusted R^2 values for generic HRQOL (.21), physical ability (0.19), emotional status (0.22), cognition (0.24) were moderate, and social function (0.26) had a large effect size.

Comparisons of R^2 Effect Sizes

The Fisher's R to Z transformations revealed significant differences between R^2 values for each of the 8 composite measures. The composite score with the highest R^2 value was clinician-rated problem behaviors ($R^2=0.30$; Table 2). The R^2 value for clinician-rated problem behaviors did not significantly differ from generic HRQOL ($R^2=0.21; z = 1.79; p=.0735$). The R^2 value for clinician-rated problem behaviors was, however, significantly higher than clinician-rated physical functioning ($R^2=0.20; z=2.03; p=.04$), clinician rated functioning ($R^2=0.14; z=2.99; p=.0028$), clinician rated cognition ($R^2=0.18; z=2.18; p=.0324$), and self-reported physical functioning ($R^2=0.19; z=2.21; p=.0271$). Additionally, self-reported social functioning ($R^2=0.26$) had a higher adjusted R^2 value than clinician rated functioning ($R^2=0.14; z=2.26; p=.0238$). Generic HRQOL, self-report emotion, and self-reported cognition had similar adjusted R^2 values with all other composite measures.

Discussion

This study examined associations among apathy and functional status, physical ability, cognition, behavioral status/emotional health and HRQOL in participants with prodromal and manifest HD. As expected, apathy levels differed by stage of disease, with individuals in the prodromal group demonstrating less apathy than participants in the early and late stage groups. These findings support other research that suggests that apathy increases with HD progression.¹⁰

In our cohort, worsened functional capacity and behavioral status were associated with higher levels of apathy. In addition, apathy related to almost all self-reported assessments of these same constructs, as well as with cognition. These findings are largely consistent with the extant literature in HD, which indicates that greater apathy relates to lower functional status and reduced independence^{14,15,36}. Our findings are somewhat discrepant from other research in HD, PD, and AD suggesting that increased apathy relates to worse objectively measured cognitive function.^{16,19} While previous research shows correlations between objective cognition and apathy, our study did not find such associations. One explanation for this is that our study measured different domains of cognitive function than previous studies. The cognitive measures used in this study (Stroop, Verbal Fluency, and SDMT) primarily measure executive functioning, processing speed, attention, and language, whereas other studies have utilized the Mini-Mental State Exam¹⁹, which measures orientation, registration, calculation, and recall or the Mattis Dementia Rating Scale¹⁶, which measures initiation, construction, conceptualization, and memory. Therefore, it is possible that different domains of objective cognition have different associations with apathy. Although apathy did not correlate with objective assessments of cognition, there was a significant association between apathy and self-reported cognitive function. One explanation for this discrepancy is that subjective measures of memory and cognition are often stronger indicators of overall emotional distress, rather than an objective evaluation of cognition.³⁸ Additionally, anosognosia, or symptom unawareness, is common in HD and therefore may play a role in this discrepancy; previous studies have shown that participants with greater cognitive deficits are more likely underreport cognitive symptoms.³⁹

Although little is known about the association between apathy and emotional and behavioral status in HD, our results are consistent with prior work showing associations among apathy, depression and irritability.^{3,17} In our cohort, clinician-rated behavioral problems, self-reported emotional problems/symptoms, and lower levels of positive affect/well-being and feelings of meaning/purpose were all associated with higher levels of apathy.

With regard to HRQOL, greater apathy related to worse overall HRQOL, and less social satisfaction and participation. Such findings support previous work in HD^{40,41} and PD.¹⁹ This study builds upon prior work by including five different measures of HRQOL in a large cohort of individuals with HD across stages of disease.

To our knowledge, no existing clinical treatments have targeted the reduction of apathy. Our results, however, identify associations of apathy, such as depression and behavioral dyscontrol that may be manageable with pharmacological and non-pharmacological

interventions. These results align with studies in PD and AD, suggesting that many associations with apathy may be common among neurodegenerative conditions. As depression and behavioral dyscontrol are quite common in HD, future work is needed to determine if interventions that target these specific domains may vicariously reduce apathy as a result.

Although this study highlights a number of important findings with regard to apathy in HD, it is also important to acknowledge several study limitations. First, findings are based on a convenience sample of individuals with HD, and thus may not represent the HD population at large. Second, although apathy is considered a multidimensional construct,^{7,8} this study utilized a single clinician-rated item of apathy and did not include a self-report measure of apathy. Future work should include a more comprehensive assessment of apathy that includes multiple aspects of motivation. In addition, participants completed the clinician-rated assessments and self-report measures within a two-week window and not necessarily within the same session, weakening analyses focused on the associations between clinician-rated apathy and self-report assessments for some participants.

Conclusions

Our data suggest that apathy relates to functional status, physical function, self-report cognitive function, behavioral status/emotional function, and HRQOL in HD. These findings are consistent with work in other neurodegenerative diseases and suggest that clinical interventions should consider targeting apathy, since it appears to be rather pervasive in terms of affecting multiple aspects of functioning and HRQOL. In addition, future work should focus on further characterizing the different aspects of apathy that have been established in other neurological diseases.

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Table 1

Demographics of the three staging groups

Variable	Prodromal (N=193)	Early (N=187)	Late (N=91)	All (N=471)
Age(Years) *				
M (SD)	43.1 (12.1)	51.5 (12.8)	56.2 (10.4)	48.9 (13.1)
Gender (%)				
Female	64.8	55.6	57.1	59.7
Male	35.2	44.4	42.9	40.3
Race (%) *				
White	98.5	95.7	94.5	96.6
African American	0.0	1.6	5.5	1.7
Other	1.0	2.7	0.0	1.5
Not Provided	0.5	0.0	0.0	0.2
Ethnicity (%)				
Not Hispanic or Latino	93.3	92.5	97.2	93.8
Hispanic or Latino	1.0	4.3	0.9	2.3
Not Provided	5.7	3.2	1.9	3.9
Education (# of years) *				
M (SD)	16.0 (2.8)	14.8 (2.8)	14.2 (2.6)	15.2 (2.9)
Marital Status (%) *				
Single, Never Married	14.4	15.7	8.2	13.8
Married	69.5	56.2	67.1	63.8
Separated/Divorced	13.9	21.4	22.4	18.4
Widowed	0.0	2.8	2.3	1.6
Living with Partner	2.2	3.9	0.0	2.4
CAG Repeats				
M (SD)	42.1 (2.5)	43.2 (3.9)	43.3 (2.8)	43.0 (3.4)

Note.

* indicates significant group differences.

Table 2

With Standardized Composite/Aggregate Scores

Variable	N	Adjusted R ²	T-value	RMSE	Significant Adjusted R ² Comparisons
A. Clinician-rated Physical Functioning	462	0.20	-0.86	3.52	A < D
B. Clinician-rated Functioning	305	0.14	-1.15	4.03	B < D, I
C. Clinician-rated Cognition	270	0.18	-0.85	3.74	C < D
D. Clinician-rated Behavioral Health	455	0.30	-12.69**	3.33	A, B, C, F < D
E. Generic HRQOL Measure	429	0.21	-2.33**	3.49	E = A-I
F. Self-Report Physical Function	438	0.19	-1.46	3.62	F < D
G. Self-Report Emotion	433	0.22	-3.74*	3.52	G = A-I
H. Self-Report Cognition	434	0.24	-5.04**	3.47	H = A-I
I. Self-Report Social Function	433	0.26	-6.25**	3.42	B < I

All predictors are standardized with a mean of 0 and SD of 1

RMSE: Root Mean Square Error (smaller is better)

* p<.05

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*** p<.0001