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The Cognitive Impairment Caregiver Reported-Health Index: Development and Validation of a Caregiver-Reported Outcome Measure

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ABSTRACT

Background: There is a need for valid, disease-specific, caregiver-reported outcome measures that reliably assesses the symptomatic health of individuals across the Alzheimer's disease continuum from mild cognitive impairment to dementia.

Aims: This research describes the development and validation of the Cognitive Impairment Caregiver Reported-Health Index (CICR-HI), a disease-specific, caregiver-reported outcome measure designed according to United States Food and Drug Administration (FDA) guidance to assess the point-in-time symptomatic burden of individuals with Alzheimer's disease, mild cognitive impairment, and dementia.

Methods: Previous work identified the symptoms of greatest importance to individuals with cognitive impairment through caregiver qualitative interviews and a cross-sectional study. We selected symptomatic questions for potential inclusion in the CICR-HI based on their high importance to individuals with cognitive impairment. We conducted beta testing and test-retest reliability testing of the CICR-HI with caregivers of individuals with cognitive impairment to determine the usability and reliability of the instrument, its subscales, and its individual questions. Lastly, we determined the known groups validity and internal consistency of the final instrument.

Results: The validated CICR-HI measures eight symptomatic domains that are shown to be highly relevant to individuals with cognitive impairment. Beta testing with 12 caregivers revealed that the CICR-HI was highly relevant and easy to use. Test-retest reliability with 30 caregivers demonstrated a high intra-class correlation (0.801). Lastly, known groups analysis demonstrated that the CICR-HI is able to statistically distinguish between groups of individuals believed to have different levels of disease severity based upon demographic or clinical characteristics.

Conclusion: The CICR-HI is a regulatory-grade, disease-specific, caregiver-reported outcome measure capable of measuring disease burden across eight symptomatic domains in individuals with cognitive impairment. This instrument was developed and validated according to published FDA guidelines for use in clinical trials to serially measure how individuals with cognitive impairment feel and function. The CICR-HI adds to existing clinical trial infrastructure and provides a mechanism to quantify changes in multifaceted disease burden in cognitive impairment over time or in response to therapeutic intervention.

Keywords: Alzheimer's disease, mild cognitive impairment, dementia, outcome measure

Introduction

Alzheimer's disease is a multifactorial, neurodegenerative disorder that progresses along a clinical continuum from pre-symptomatic disease to mild cognitive impairment to dementia.[1] Alzheimer's disease has a heterogeneous symptomology demonstrated by varied cognitive presentations, functional deficits, and rates of progression.[2]

Cognitive impairment is one of the leading cause of disability and morbidity in older adults in the world.[3,4] In 2023, an estimated 416 million people worldwide were living with preclinical AD, mild cognitive impairment, or dementia.[4] A projected worldwide growth in the elderly population is anticipated to triple the number of dementia cases by 2050,[5] causing further strain on healthcare resources and caregiving social support systems.[2,4,6]

The United States Food and Drug Administration (FDA) approvals of anti-amyloid therapies for the treatment of AD were met with controversy in the global AD community, despite the growing need for therapeutic advancement.[7] The ensuing debate on the world stage challenged the use of clinicostatistical measures of cognition and function in isolation as primary outcomes and the absence of data regarding the patient's and caregiver's perspective on their symptoms, their ability to perform daily tasks, and the impact of the disease on their lives.[7,8]

Following these approvals, the FDA, the European Medicines Agency (EMA), the National Institute on Aging (NIA) and the National Institute of Neurological Disorders and Stroke (NINDS) have all acknowledged the imperative need for the use of patient-centered outcomes to determine patient-centered, clinically meaningful changes for clinical trials of AD disease-modifying treatments in Alzheimer's disease.[9–11] The utilization of patient insight to quantify cognitive, functional, and emotional health is critical for a robust assessment of the effectiveness of future AD interventions.

Individuals with more severe disease-related disruptions to memory and cognition may not be able to reliably self-report the impact of disease and treatment.[12] The intensive, proximal role of a caregiver in the life of an individual with cognitive and functional deficits renders them a valuable resource for both assessing observable symptomatic burden and quantifying changes in health over time.[10]

This study documents the development and validation of the Cognitive Impairment Caregiver Reported-Health Index (CICR-HI), a caregiver-reported outcome measure designed to quantify from the caregiver perspective how individuals with AD, dementia, or mild cognitive impairment (MCI) feel and function in response to therapeutic intervention. In prior work, we determined the extent and importance of symptoms experienced by individuals with AD, dementia, and MCI through interviews and large-scale surveys with patients and caregivers.[13] This caregiver-reported outcome measure is designed in alignment with FDA guidance to sensitively assess the multifactorial point-in-time disease burden of symptoms determined to have the greatest impact on the lives of individuals with cognitive impairment. Our work seeks to bolster existing clinical trial infrastructure by facilitating patient-meaningful therapeutic assessments in a population unable to reliably self-report.

Methods

PARTICIPANT SELECTION AND ELIGIBILITY

Study eligibility required that a participant be: (1) 18 years of age or older; (2) a caregiver for an individual diagnosed with AD, MCI, or dementia; (3) English speaking; and, (4) residing in the United States. Exclusion criteria restricted individuals from participating in this study if they did not meet all study inclusion criteria.

Study participants were recruited from the Alzheimer's Prevention Registry (Banner Health Institute), *ResearchMatch.com*, the University of Rochester (UR) AD-Care, Research, and Education (AD-CARE) program, UR Memory Care Program, and UR Clinical Translational Science Institute (CTSI) Registry. Participants provided consent by phone or online after receiving a study information letter detailing study activities and their rights as a voluntary participant. Participant information and responses were stored and protected according to United States Health Insurance Portability and Accountability Act (HIPAA) guidelines. All study activities conform to the Declaration of Helsinki and were approved by the University of Rochester's Research Subjects Review Board (RSRB).

QUESTION SELECTION & CONTENT VALIDITY

In prior work, we utilized qualitative interviews and a large cross-sectional study of patients and caregivers to identify the symptoms with the greatest impact on individuals with cognitive impairment.[13] Semi-structured qualitative interviews were conducted with 15 caregivers (**Appendix 1**), who provided 1,097 quotes regarding the symptomatic burden experienced by individuals with cognitive impairment for whom they care.[13] Data obtained from these interviews were used to design a cross-sectional survey asking about 99 potential symptoms of importance.[13] This online survey was accessed on Research Electronic Data Capture (REDCap), a secure, HIPAA-compliant, web-based platform. This survey was completed by 329 eligible caregivers to determine the most prevalent and impactful symptoms among individuals with cognitive impairment.[13]

Data from the cross-sectional survey was used to calculate each symptom's population impact scores (PIP), which describes the relationship between a symptom and its impact on the individual's life. The PIP is a metric represented on a scale from 0 – 4, calculated as the product of the symptom's prevalence in individuals with cognitive impairment and its average impact. Symptom questions with a PIP less than 1.0 were excluded from the first version of the CICR-HI, as this indicated less relevance to individuals with cognitive impairment. Questions were also removed if they were: (1) redundant; (2) potentially offensive to future participants; (3) unlikely to be affected by a therapeutic intervention; (4) inapplicable to a broad population of individuals with cognitive impairment; (5) above an eighth grade reading level; or, (6) not directly observable by a caregiver. This methodology has been previously documented and used by our laboratory to generate instruments for over 30

different diseases.[14–25] Symptom questions that met all selection criteria were grouped into subscales, or symptomatic themes, based on the domain of patient health that they represented.

BETA INTERVIEWS – INSTRUMENT RELEVANCE & USABILITY

The first version of the CICR-HI was evaluated by caregiver participants through beta interviews. Following the online completion of the CICR-HI, caregivers participated in semi-structured interviews, providing feedback on the content, relevance, and usability of the instrument. Participants addressed if they believed that the instrument was capable of measuring how a patient feels and functions and if they were able to complete the instrument without experiencing user burden. Interview questions also inquired about the comprehension, usability, response processes, recall strategies (or timeframe of responses), and relevance of the first version of the CICR-HI. Caregivers provided feedback on any symptom questions that should be reworded for clarity, or additional symptoms they felt were missing from the first version of the CICR-HI. Participant interviews were conducted from January 2022 to September 2022. The interviews were audio-recorded, transcribed, and analyzed. Using the feedback from these interviews, modifications were made to create the second version of the CICR-HI.

TEST-RETEST RELIABILITY

Caregiver participants longitudinally completed the CICR-HI at baseline and 14 days later. A 14-day interval between baseline and retest minimizes the likelihood of symptom progression while reducing baseline recall. The instrument was administered to caregivers electronically using REDCap. Survey administration was conducted in December 2022. Test-retest reliability was quantified using a weighted kappa (WK) value for each symptom question. Less reliable questions with a WK value less than 0.40 were considered for removal from the survey.

INSTRUMENT FORMAT, SCORING, AND INTERNAL CONSISTENCY

The CICR-HI consists of symptomatic subscales representing unique domains of health for individuals with cognitive impairment as reported by their caregivers. For each symptom question, the caregiver is asked "*How much does the following impact his/her life?*" Reponses are rated on a 6-point Likert Scale. We generated a short form of the CICR-HI that included one representative question from each subscale in the CICR-HI to be used as a potential surrogate to the full form. The total score, short form, and each subscale are scored between 0 and 100, where 0 indicates no disease burden and 100 indicates maximum disease burden. Questions within subscales are weighted based on their relative importance to patients (as determined by the cross-sectional study),[13] in order to generate a total score. We determined the internal consistency of the CICR-HI and each of its subscales using Cronbach's alpha values.

KNOWN GROUPS ANALYSIS

We conducted known groups analysis for predefined patient subgroups thought to have higher or lower disease burden including: patient age (above versus equal to and below mean 80.1 years); patient sex (male versus female); patient education (grade school, high school, or technical degree versus college, masters, or doctorate degree); patient employment status (employed full-time, part-time, retired, stay-at-home parent, or other versus on disability or not working and not on disability); patient change in employment status due to disease (yes versus no); patient marital status (married or registered partner versus single, widowed, divorced, separated, or other); patient diagnosis (AD versus MCI, AD versus non-AD dementias, and non-AD dementias versus MCI); patient living situation (resides in community versus resides in assisted, independent, or skilled-nursing living facility, or other); patient fit of ability (no symptoms or significant disability, slight disability, or moderate disability versus moderately-severe or severe disability); years since onset of thinking problems (above versus equal to or below mean 7.5 years); patient receiving genetic testing (yes versus no); APOE_4 copies (one copy versus 2 copies); and, seizures (experiences versus does not experience seizures).

We also conducted known groups analysis for predefined subgroups based on caregiver characteristics including: caregiver age (above versus equal to or below mean 65.2 years); caregiver sex (male versus female); caregiver relationship to patient (son or daughter versus spouse or partner); and, the use of a home health aide (yes versus no).

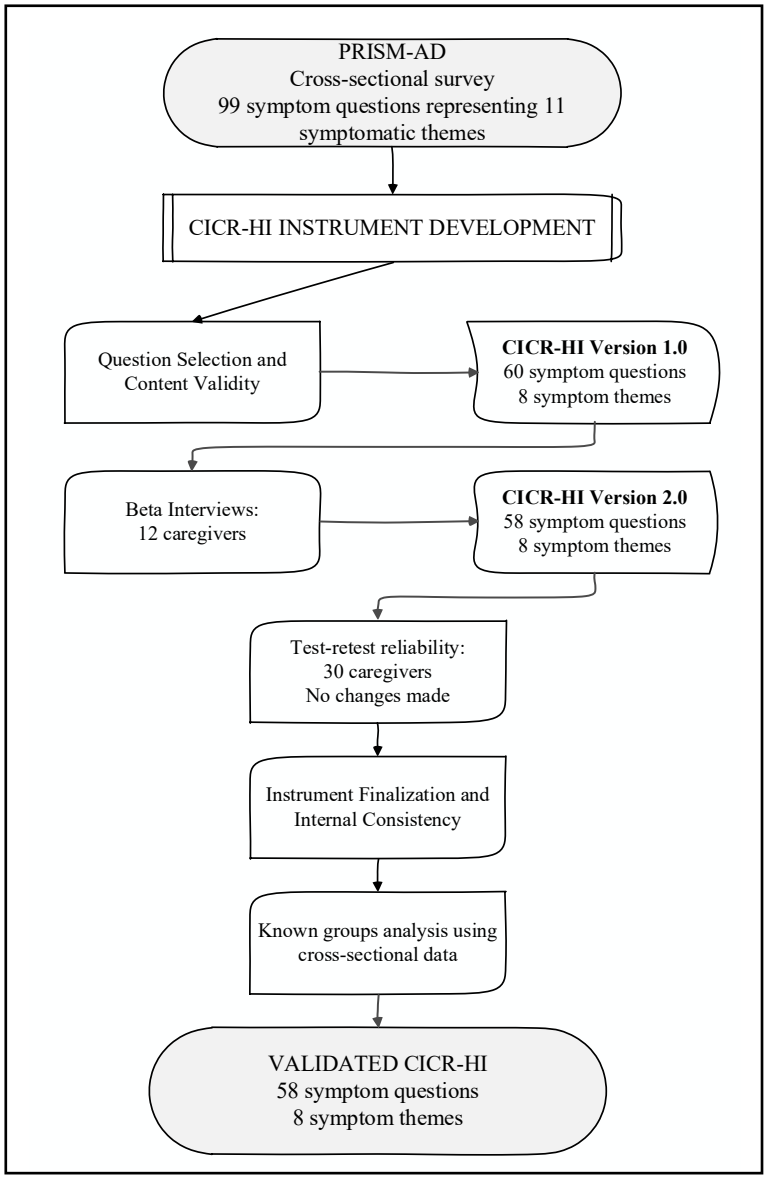
The Benjamini-Hochberg analysis was applied to the known groups analysis with a false discovery rate of 0.05 and 180 test statistics. In accordance with this statistical methodology, the p values obtained from each known groups comparison were sorted by size from smallest to largest, with the largest value of i such that $p(i) < 0.05, i/180$ was determined. The null hypothesis associated with the p values $p(1), \ldots, p(i)$ were rejected, resulting in 128 discoveries.

Results

QUESTION SELECTION AND CONTENT VALIDITY

During our initial study, we interviewed 15 caregivers and identified 173 potential symptoms of importance to individuals with cognitive impairment.[13] Our subsequent cross-sectional study evaluated the prevalence and relative importance of 99 symptomatic areas in a cohort of 329 caregiver participants.[13] Based on the cross-sectional survey responses of these initial 99 symptom questions, we eliminated 18 questions due to low population impact (PIP < 1.0), 2 questions due to redundancy, 13 questions for being non-responsive to future therapies, 2 for vague wording, and one for being deemed not observable by a caregiver. Three questions were also removed due to statistical redundancy. Following question removal, the first version of the CICR-HI consisted of 60 symptom questions representing 8 symptomatic themes. An overview of the question selection process is provided in **Figure 1**. The demographics of all study participants (caregivers) and the individuals they represented are provided in **Appendix 1**.

Figure 1: Flowchart of CICR-HI Development Methodology



BETA INTERVIEWS – INSTRUMENT RELEVANCE AND USABILITY

Twelve caregivers of individuals with cognitive impairment participated in beta interviews and provided feedback regarding the first version of the CICR-HI (**Appendix 1** provides details regarding the demographic features of these participants). Caregivers found the CICR-HI to be an appropriate way to assess disease severity and capture how the individual for whom they care feels and functions. Based on caregiver feedback, six symptom questions were reworded to enhance clarity, and two symptom questions were deleted due to redundancy. Upon completion of these revisions, the second version of the CICR-HI was developed, consisting of 58 questions representing eight symptomatic themes (8 subscales).

TEST-RETEST RELIABILITY

Thirty caregivers participated in test-retest reliability of the second version of the CICR-HI (**Appendix 1** provides details regarding the demographic features of these participants). All symptom questions demonstrated an acceptable level of reliability, with a weighted kappa greater than 0.40. Intraclass Correlation Coefficient (ICC) values for the total instrument and each of the subscales ranged from 0.633 to 0.813 (**Table 1**).

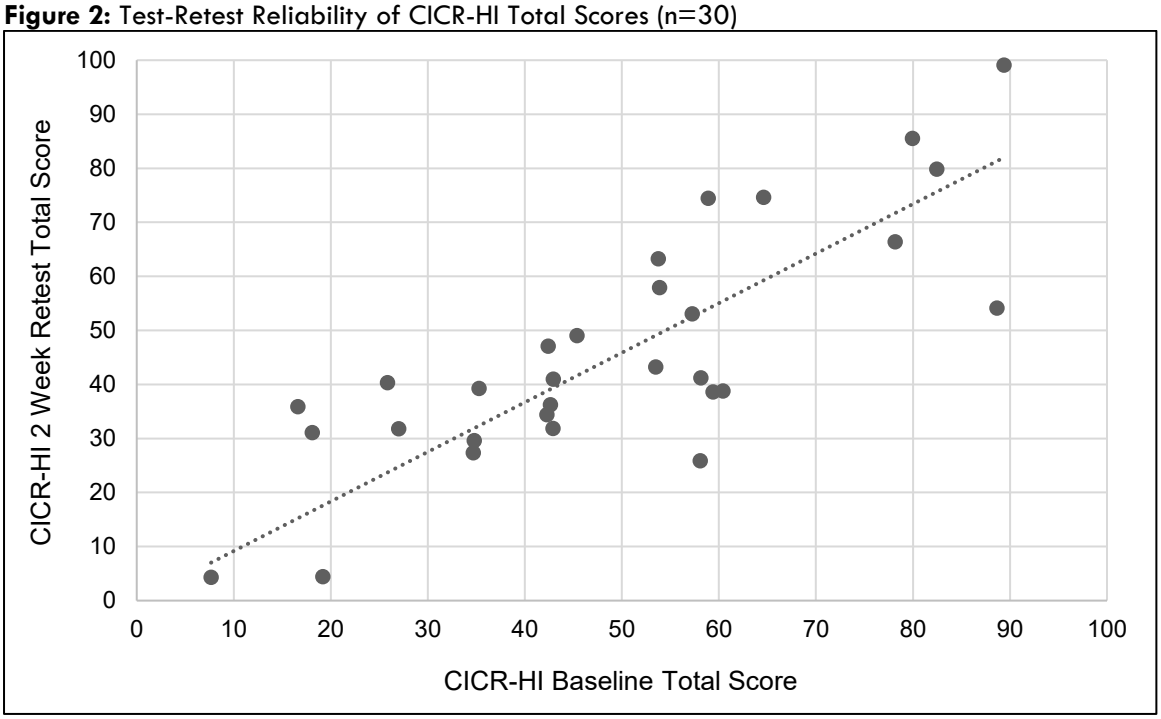
Table 1: Final Internal Consistency and Test-Retest Reliability of the CICR-HI

CICR-HI Subscale	Questions included in Final Subscale (n)	Mean Participant Scores		Internal Consistency (Cronbach's alpha)	Test-Retest Reliability (Intraclass Correlation Coefficient)
		Baseline	2 Week Retest		
Memory	11	58.2	54.2	0.96	0.813
Cognition	13	63.4	54.4	0.97	0.717
Fatigue	2	42.6	45.8	0.86	0.684
Sleep or Daytime Sleepiness	5	34.8	37.5	0.89	0.711

CICR-HI Subscale	Questions included in Final Subscale (n)	Mean Participant Scores		Internal Consistency (Cronbach's alpha)	Test-Retest Reliability (Intraclass Correlation Coefficient)
		Baseline	2 Week Retest		
Social Satisfaction	5	42.1	38.5	0.93	0.774
Communication	5	43.3	43.4	0.85	0.633
Emotional Health	7	55.3	50.3	0.93	0.746
Activity Participation	10	45.4	38.7	0.94	0.672
Total Form	50	49.1	46.0	0.98	0.801
Short Form	8	51.9	51.0	0.90	0.723

Caregivers took an average of 6.26 and 5.49 minutes to complete the baseline and 14-day time point survey, respectively. The CICR-HI total score demonstrated no floor or ceiling effects **(Figure 2)**. No modifications to the CICR-HI were required secondary to its performance during this phase of development.

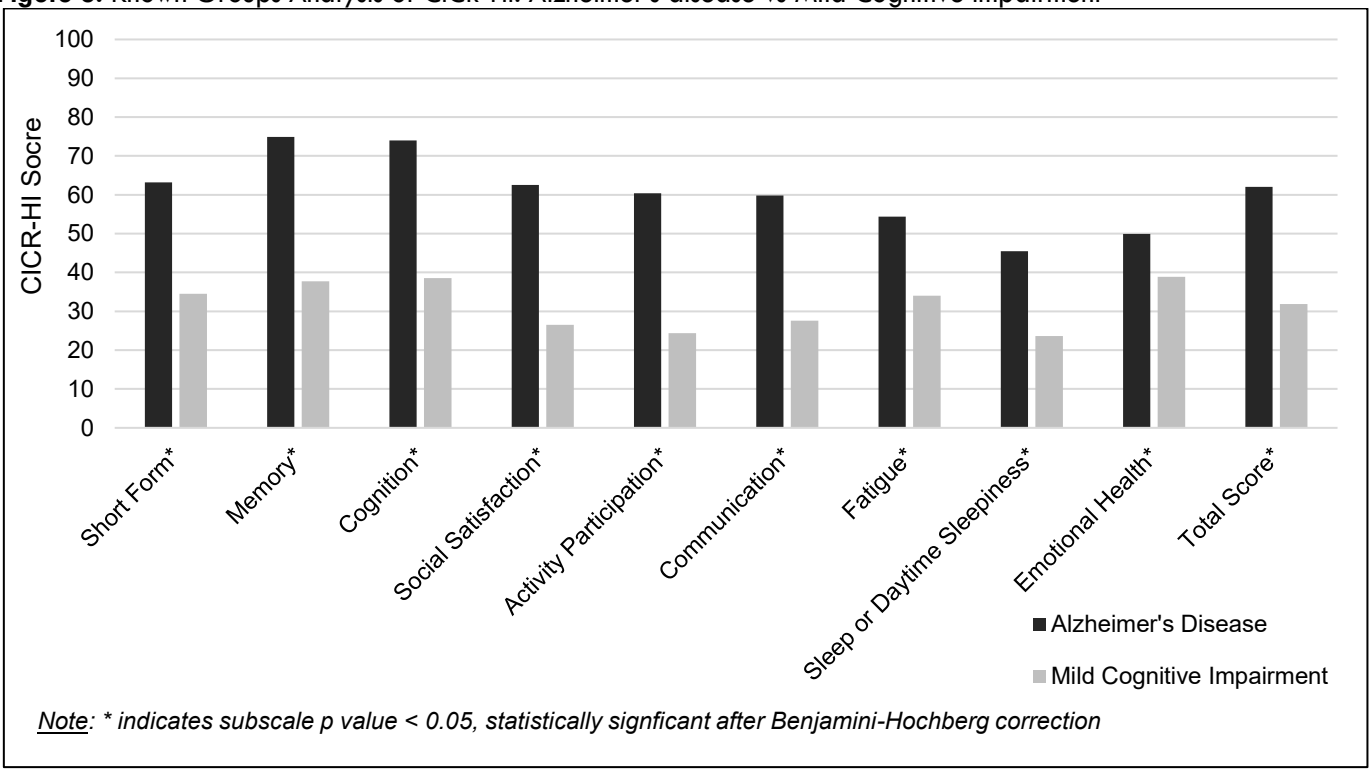
Figure 2: Test-Retest Reliability of CICR-HI Total Scores (n=30)



KNOWN GROUPS ANALYSIS

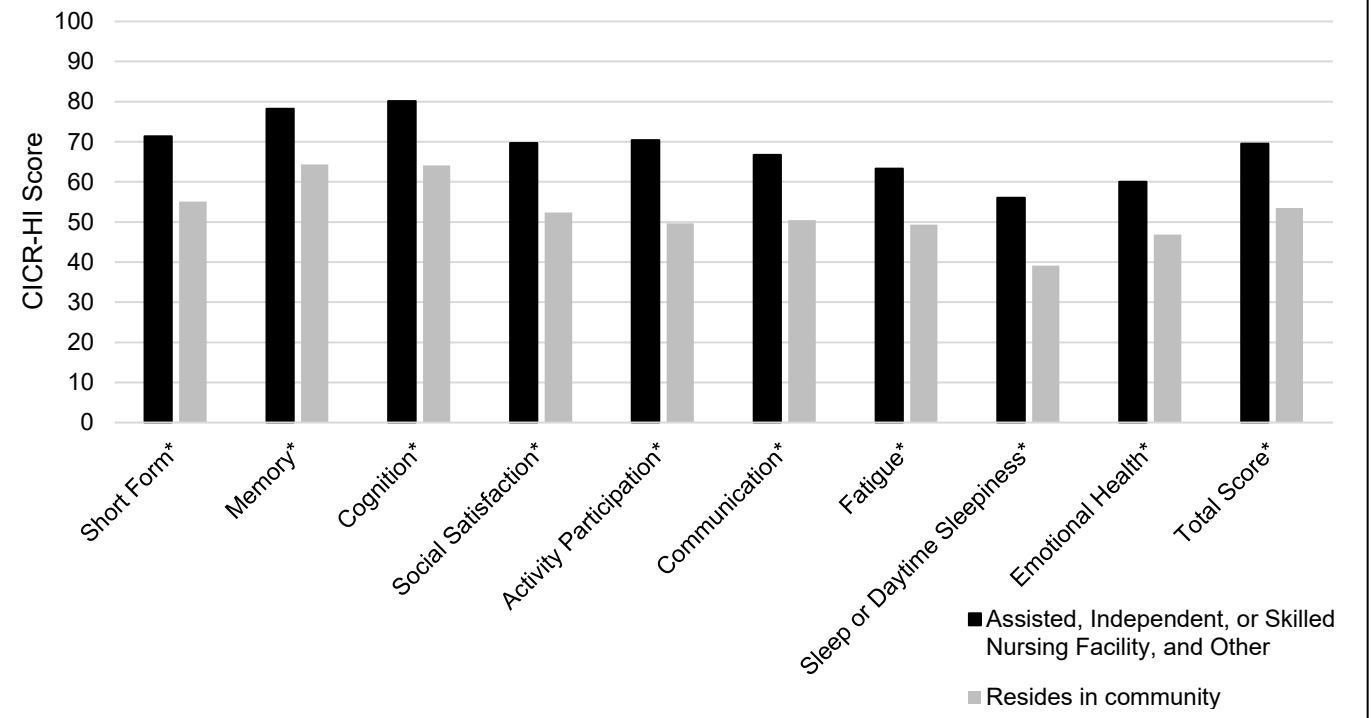
Cross-sectional data from 329 participants was used to determine the known groups validity of the CICR-HI and each of its subscales.[13] After correcting for multiple comparisons, we found significant differences among predefined subgroups (**Appendix 2**). A higher CICR-HI total score, indicating higher disease burden, was associated with: patient age (above 80.1 years); sex (female); highest education received (grade school, high school, or technical school versus college or graduate school); marital status (not married or in a registered partnership); fit of ability (moderate to severe disability versus no symptoms, slight disability, or moderate disability); living situation (resides in assisted, independent, or skilled-nursing living facility versus in the community); years since onset of thinking problems (above the 7.5 years); diagnosis (AD or non-AD dementia compared to MCI); APOE_4 copies (two copies versus one copy); and the presence of seizures **(Appendix 2)**. Additionally, a higher CICR-HI total score, indicating higher disease burden, was associated with: caregiver age (older than 65.2 years); caregiver relationship to the individual (child versus spouse); and use of a home health aide. There was no difference in CICR-HI total score based on individual with cognitive impairment's employment status, employment status change due to their disease, if the individual received genetic testing, or the caregiver's sex. Of note, higher scores were observed across CICR-HI total form, short form, and subscales based upon the individual diagnosis (AD and non-AD dementias, compared to MCI) (**Figure 3**), living situation (resides in assisted, independent, or skilled-nursing living facility versus in the community) (**Figure 4**), fit of ability (moderate-severe to severe disability versus no symptoms, slight disability, or moderate disability; and, moderate to severe disability versus no symptoms or slight disability), years since the onset of thinking problems (above mean 7.5 years), and caregiver relationship to the individual with cognitive impairment (child versus parent) (**Appendix 2**). When comparing mean score between individuals with AD versus non-AD dementias, a significant difference in scores was only observed in the Memory function subscale, with caregivers of patients with AD reporting a greater disease burden **(Appendix 2)**.

Figure 3: Known Groups Analysis of CICR-HI: Alzheimer's disease vs Mild Cognitive Impairment



*Note: * indicates subscale p value < 0.05, statistically signficant after Benjamini-Hochberg correction*

Figure 4: Known Groups Analysis of CICR-HI: Patient Living Status



*Note: * indicates subscale p value < 0.05, statistically signficant after Benjamini-Hochberg correction*

INSTRUMENT FINALIZATION AND INTERNAL CONSISTENCY

The final version of the CICR-HI consists of 58 symptomatic questions representing eight symptomatic subscales that address the following areas of disease burden: Memory function; Cognition; Fatigue; Sleep or daytime sleepiness; Social satisfaction; Communication; Emotional health; and, Activity participation **(Table 1)**. A short form of the CICR-HI consists of eight questions representative of each instrument subscale. The internal consistency of the final CICR-HI and each is its subscales is provided in **Table 1**, with the CICR-HI full form having a Cronbach's alpha score of 0.98.

Discussion

The CICR-HI is a caregiver-reported outcome measure that comprehensively measures the physical, mental, social, and disease-specific health of individuals with cognitive impairment through the caregiver perspective. This instrument, developed according to published FDA guidelines for use in clinical trials, prioritizes domains of health identified in prior research as being the most important to individuals with cognitive impairment.[13,26]

The CICR-HI was assessed by caregivers as being a comprehensive and appropriate measure of a patient's health and function while being easy to complete and

understand. On average, the CICR-HI was completed in approximately six minutes, with the short form being completed in less than one minute. Importantly, the instrument measures the symptomatic concepts that are most important to individuals with cognitive impairment, provides a reliable mechanism to quantify their multifactorial disease burden over time, and is capable of differentiating between patients with greater or lower levels of symptomatic burden.

Known groups analysis of individuals across the Alzheimer's continuum provides insight into differences in multidimensional symptomatic burden. When comparing AD patients to patients with non-AD dementias, similar scores were observed for the CICR-HI total, short form, and subscale scores, however, AD patients reported a significantly higher symptomatic burden in the CICR-HI Memory function subscale (**Appendix 2**). This is consistent with previous findings that patients with AD experience memory deficits that are unique from those experienced by non-AD dementia patients, including severe and focused impairment related to verbal memory, recognition, and attention deficits.[27–29]

Caregivers who were children of the patient reported significantly higher CICR-HI total, short form, and subscale scores when compared to spousal caregivers (**Appendix 2**). We suspect that this difference is due to relationship-based reporting perspective and, more importantly, differences in patient age between these two groups. Specifically, child caregivers reported on behalf of older patients compared to spousal caregivers. Among primary caregivers who were the children of the patient, the average age of the patient was 85.9 years old. In contrast, for the primary caregiver who were spouses or partners to the patient with cognitive impairment, the average patient age was 74.6 years.

The CICR-HI addresses gaps in clinical trial readiness by including subscales that measure symptomatic concepts that are infrequently measured by other disease-specific instruments. The CICR-HI includes Fatigue and Sleep and daytime sleepiness subscales, domains shown to be highly relevant in Alzheimer's disease,[13,30] which are not assessed in existing instruments such as the Dementia Severity Scale and Dementia Quality of Life Instrument – Proxy Version (DEMQOL-Proxy).[31,32] Since each symptomatic domain contained in the CICR-HI is independently validated, the CICR-HI enables testing of therapeutic interventions in targeted symptomatic issues. As such, the CICR-HI is relevant for the assessment of specific symptom management therapies and multi-symptomatic disease-modifying therapies.

Individuals with cognitive impairment increasingly rely on their family and caregivers as their condition progresses.[3] Previous literature indicates that caregivers are ideally suited to observe the health of their loved one and are capable of reporting on observable symptoms such as fatigue, mobility, and activity participation,[33] all of which have been identified by individuals with cognitive impairment as being symptoms of great importance.[13] As an individual with cognitive impairment progresses, their ability to read and reliably complete a patient-reported outcome measure may decline. As such, the CICR-HI provides a much-needed option to measure small but meaningful changes in a patient's health through the direct observation of those who are engaged and optimally positioned to make this determination.

In order to advance therapeutic development for individuals with cognitive impairment, there is a need for an outcome measure capable of tracking disease burden throughout the progression of their disease. Disease progression from MCI to dementia can occur in as few as 3-5 years for 10-15% of the Alzheimer's population.[34–37] The CICR-HI will satisfy a key recommendation by the FDA with its ability to comprehensively measure disease burden early and consistently throughout disease progression.

The CICR-HI was developed by using the same methodology that has been used by our outcomes group to develop caregiver and patient-reported outcome measures for over 30 diseases.[14–21,23–25] These outcome measures have been translated and culturally validated for use in over 30 different countries, and have been used extensively in therapeutic trials worldwide.[25] Collectively, they have been found to detect meaningful changes in health during therapeutic evaluation.[22,38–42] The CICR-HI addresses a potential gap in clinical trial infrastructure for those who suffer for mild, moderate, or severe cognitive impairment. While prior studies have demonstrated the sensitivity of our instruments to detect clinical change over time,[43–45] additional studies will be needed to further evaluate the sensitivity of the CICR-HI and each its subscales in response to a specific treatment and over a longer period of time.

We acknowledge several limitations with this study. The demographic characteristics of the caregiver participants throughout this study were predominately white non-Hispanic individuals in the United States (**Appendix 1**). Requirements to participate also included an English-language proficiency. Due to this, the sampled cohort is likely not a perfect representation of all caregivers of individuals with cognitive impairment. Additionally, the nature of this study was remote, requiring internet or phone to access recruitment and study activities, likely limiting the inclusion of participants without access to these devices.

Conclusion

The CICR-HI is a comprehensive caregiver-reported outcome measure, developed and validated in accordance with FDA guidelines, and capable of measuring multifactorial levels of disease burden of individuals with cognitive impairment. Our study demonstrated reliability, relevance, consistency, and usability of the CICR-HI for measuring disease burden across the Alzheimer's continuum. The CICR-HI importantly enables individuals, who are unable to self-report due to advanced stage of disease, the opportunity to participate in clinical trials and advance therapeutic development.

Conflicts of Interest

C. Shupe has no disclosures to report.
J. Seabury has no disclosures to report.
J. Weinstein has no disclosures to report.

C. Engebrecht has no disclosures to report.
C. Irwin has no disclosures to report.
P. Kanagaiah has no disclosures to report.
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APPENDIX

Appendix 1: Participant Demographic Characteristics

	Primary Interviews[13]	Cross Sectional Study[13]	Beta Interviews	Test Retest Reliability
Total Participants	**15**	**329**	**12**	**30**
Caregiver Demographics				
Age (years)				
Mean (SD)	67.7 (11.1)	65.13 (9.28)	64.8 (16.3)	65.7 (8.9)
Range	45-85	20-86	29-89	40-79
Sex, n (%)				
Female	10 (66.7)	256 (77.31)	8 (66.7)	24 (80.0)
Male	5 (33.3)	71 (21.58)	4 (33.3)	6 (20.0)
Race, n (%)				
American Indian/ Alaska Native	-	4 (1.2)	-	-
Asian	-	3 (0.9)	1 (8.3)	-
Black	2 (13.3)	5 (1.5)	1 (8.3)	1 (3.3)
White	13 (86.7)	306 (93.0)	10 (83.3)	28 (93.3)
Hawaiian/Pacific Islander	-	-	-	1 (3.3)
Other	-	5 (1.52)	-	-
Relationship to Individual with Cognitive Impairment, n (%)				
Spouse	12 (80.0)	152 (46.2)	7 (58.3)	11 (36.7)
Son/Daughter	2 (13.3)	146 (44.4)	3 (25.0)	12 (40.0)
Home Health Aide	1 (6.7)	7 (2.1)	-	-
Other Relative	-	17 (5.2)	2 (16.7)	4 (13.3)
Other	-	6 (1.8)	-	3 (10.0)
Caregiver Ethnicity, n (%)				
Hispanic/Latino	-	12 (3.7)	0 (0.0)	3 (10.3)
States represented, n				
	5	46	3	20
Patient Demographics				
Age (years)				
Mean (SD)	73.73 (5)	80.09 (9.29)	77.17 (6.9)	79.2 (8.1)
Range	45-85	53-103	67-86	56-95
Sex, n (%)				
Female	6 (40.0)	190 (57.8)	6 (50.0)	18 (60)
Male	9 (60.0)	136 (41.3)	6 (50.0)	12 (40)
Race of Patient, n (%)				
American Indian/ Alaska Native	-	3 (0.91)	-	-
Asian	-	4 (1.22)	1 (8.3)	-
Black	1	6 (1.82)	-	-
White	15	307 (93.3)	11 (91.7)	29 (96.7)
Hawaiian/Pacific Islander	-	-	-	1 (3.3)
Other	-	3 (0.91)	-	
Patient Ethnicity, n (%)				
Hispanic/Latino	-	12 (3.7)	0 (0)	3 (10.3)

	Primary Interviews[13]	Cross Sectional Study[13]	Beta Interviews	Test Retest Reliability
Patient Diagnosis, n (%)				
Alzheimer's Disease	9 (60.0)	192 (59.3)	6 (50.0)	14 (46.7)
Mild Cognitive Impairment	4 (26.7)	47 (14.5)	2 (16.7)	8 (26.7)
Dementia	-	8 (2.47)	-	
Vascular Dementia	-	25 (7.72)	-	4 (13.3)
Dementia with Lewy Bodies	1 (6.7)	9 (2.78)	-	
Frontotemporal Dementia	-	9 (2.78)	-	2 (6.67)
Parkinson's Disease Dementia	1 (6.7)	-	-	1 (3.3)
I don't know	-	-	4 (33.3)	1 (3.3)
Patient Fit of Ability, n (%)				
No significant disability	3 (20.0)	18 (5.5)	-	-
Slight disability	7 (46.7)	42 (12.8)	-	-
Moderate disability	5 (33.3)	132 (40.1)	-	-
Moderately severe disability	-	104 (31.6)	-	-
Severe disability	-	32 (9.7)	-	-

Appendix 2: Known Groups Analysis of CICR-HI Scores by Subgroups (n=329)

	TOTAL SCORE	SHORT FORM	MEMORY	COGNITION	SOCIAL SATISFACTION	ACTIVITY PARTICIPATION	COMMUNICATION	FATIGUE	SLEEP OR DAYTIME SLEEPINESS	EMOTIONAL HEALTH
Patient Age										
80.1 years and younger	52.4	53.6	62.7	64.6	50.0	47.5	52.7	45.3	36.4	48.1
Older than 80.1 years	61.9	64.0	72.2	70.8	62.3	61.3	55.8	59.8	49.4	51.3
p value	**0.002***	**0.0006***	**0.005***	0.108	**0.0014***	**0.0002***	0.453	**<.0001***	**<.0001***	0.323
Patient Sex										
Male	53.9	55.7	63.1	64.8	50.6	48.3	52.8	50.5	41.3	48.8
Female	60.2	61.9	71.3	70.5	61.1	59.5	55.9	54.7	44.8	51.2
p value	**0.018***	**0.029***	**0.0046***	**0.049**	**0.004***	**0.002***	0.398	0.145	0.278	0.524
Patient Education (Highest Level Completed)										
Grade school, high school, or technical degree	61.9	62.2	72.2	72.7	62.3	59.0	56.5	55.6	48.7	56.9
College, masters, or doctorate degree	53.6	56.5	64.0	64.1	51.8	51.1	52.9	49.9	38.3	43.9
p value	**0.006***	0.107	**0.022***	**0.020***	**0.0048***	**0.035***	0.379	0.098	**0.001***	**<.0001***
Patient Employment Status										
Disabled, or not working and not on disability	60.6	63.8	65.3	69.7	64.5	56.8	57.2	54.6	51.3	57.8
Employed full-time, employed part-time, retired, stay-at-home parent, or other	57.1	58.5	68.2	67.9	55.5	54.5	54.2	52.5	42.1	49.0
p value	0.214	0.153	0.953	0.410	**0.041**	0.619	0.459	0.716	0.091	0.067
Has Patient's Employment Status Changed Due to Disease?										
Yes	62.3	63.6	71.8	72.5	63.2	58.2	60.1	56.0	49.3	56.3
No	56.5	58.2	67.1	67.3	55.5	54.0	53.8	51.6	41.8	48.7
p value	0.107	0.234	0.216	0.175	0.059	0.340	0.153	0.440	0.091	0.066

Note: p values < 0.05 are emboldened to demonstrate statistical significance

**Statistically significant p-values after Benjamini Hochberg correction*

	TOTAL SCORE	SHORT FORM	MEMORY	COGNITION	SOCIAL SATISFACTION	ACTIVITY PARTICIPATION	COMMUNICATION	FATIGUE	SLEEP OR DAYTIME SLEEPINESS	EMOTIONAL HEALTH
Patient Marital Status										
Married or registered partner	53.8	55.0	65.9	64.8	51.2	48.7	53.1	47.3	39.0	48.5
Single, widowed, divorced, separated, or other	63.0	65.4	70.8	73.0	64.8	63.8	56.9	61.0	49.9	52.4
p value	**0.003***	**0.001***	0.224	**0.029***	**0.0004***	**<.0001***	0.409	**0.0001***	**0.0008***	0.238
Patient Diagnosis										
Alzheimer's Disease	62.1	63.2	74.9	74.0	62.6	60.4	59.8	54.4	45.5	49.9
Mild Cognitive Impairment	31.8	34.5	37.8	38.6	26.5	24.4	27.6	34.0	23.6	38.9
p-value	**<.0001***	**<.0001***	**<.0001***	**<.0001***	**<.0001***	**<.0001***	**<.0001***	**<.0001***	**<.0001***	**0.014***
Alzheimer's Disease	62.1	63.2	74.9	74.0	62.6	60.4	59.8	54.4	45.5	49.9
Vascular, frontotemporal, or Parkinson's Disease dementia	62.0	64.7	66.4	72.5	59.0	63.2	59.2	62.5	47.6	55.4
p value	0.944	0.699	**0.033***	0.729	0.361	0.447	0.937	0.092	0.628	0.278
Mild Cognitive Impairment	31.8	34.5	37.8	38.6	26.5	24.4	27.6	34.0	23.6	38.9
Vascular, frontotemporal, or Parkinson's Disease dementia	62.0	64.7	66.4	72.5	59.0	63.2	59.2	62.5	47.6	55.4
p value	**<.0001***	**<.0001***	**<.0001***	**<.0001***	**<.0001***	**<.0001***	**<.0001***	**<.0001***	**<.0001***	**0.0046***
Patient Living Situation										
Resides in community	53.5	55.1	64.4	64.1	52.4	49.6	50.5	49.3	39.1	46.9
Resides in assisted, independent, or skilled-nursing living facility, or other	69.6	71.4	78.2	80.1	69.7	70.4	66.8	63.3	56.0	60.0
p value	**<.0001***	**<.0001***	**<.0001***	**<.0001***	**<.0001***	**<.0001***	**<.0001***	**0.0007***	**<.0001***	**0.0004***
Years Since Onset of Thinking Problems										
More than 7.5 years	67.2	69.9	75.7	76.9	69.0	68.0	67.4	61.5	51.5	54.3
Equal to or below 7.5 years	51.7	53.3	62.3	62.8	50.9	47.7	48.3	46.6	37.3	45.9
p value	**<.0001***	**<.0001***	**<.0001***	**<.0001***	**<.0001***	**<.0001***	**<.0001***	**0.0002***	**0.0001***	**0.015***

Note: p values < 0.05 are emboldened to demonstrate statistical significance
**Statistically significant p-values after Benjamini Hochberg correction*

	TOTAL SCORE	SHORT FORM	MEMORY	COGNITION	SOCIAL SATISFACTION	ACTIVITY PARTICIPATION	COMMUNICATION	FATIGUE	SLEEP OR DAYTIME SLEEPINESS	EMOTIONAL HEALTH
Patient Fit of Ability										
Moderately-severe, or severe disability	75.2	77.6	84.1	85.7	76.7	81.7	72.2	71.5	58.4	55.1
No symptoms or significant disability, slight, and moderate disability	44.6	45.7	56.1	55.0	41.8	35.2	41.6	39.7	31.9	46.1
p value	**<.0001***	**<.0001***	**<.0001***	**<.0001***	**<.0001***	**<.0001***	**<.0001***	**<.0001***	**<.0001***	**0.005***
Moderate, moderately-severe, or severe disability	63.8	65.9	74.1	75.1	64.1	62.9	60.9	58.9	48.3	52.8
No symptoms and no significant disability, or slight disability	27.6	28.0	38.8	34.7	21.2	16.7	24.2	25.6	18.3	36.4
p value	**<.0001***	**<.0001***	**<.0001***	**<.0001***	**<.0001***	**<.0001***	**<.0001***	**<.0001***	**<.0001***	**<.0001***
Has Patient Received Genetic Testing?										
Yes	56.8	58.9	67.0	67.3	56.9	53.6	54.2	51.7	42.3	48.7
No	51.2	52.0	62.2	60.5	47.1	50.5	46.7	47.5	35.2	50.3
p value	0.267	0.175	0.613	0.392	0.169	0.747	0.200	0.452	0.185	0.807
If Received Genetic Testing, Which Risk Factor?										
APOE_4 (One copy)	34.0	36.1	42.8	42.9	25.2	24.4	24.7	38.8	27.3	42.3
APOE_4 (Two copies)	57.5	57.8	81.0	63.1	51.7	66.0	47.7	46.8	31.9	57.9
p value	**0.031***	**0.021***	**0.014***	0.090	0.121	**0.006***	**0.014***	0.583	1	0.440
Patient Experiencing Seizures										
Yes	69.9	75.7	77.1	78.9	67.8	71.8	72.1	66.3	58.3	54.3
No	56.7	58.4	67.3	67.2	55.9	53.6	53.6	52.1	42.4	49.9
p value	**0.029***	**0.011***	0.113	**0.024***	0.111	**0.022***	**0.020***	0.119	0.064	0.600

Note: p values < 0.05 are emboldened to demonstrate statistical significance
**Statistically significant p-values after Benjamini Hochberg correction*

	TOTAL SCORE	SHORT FORM	MEMORY	COGNITION	SOCIAL SATISFACTION	ACTIVITY PARTICIPATION	COMMUNICATION	FATIGUE	SLEEP OR DAYTIME SLEEPINESS	EMOTIONAL HEALTH
Caregiver Age										
65.2 years or younger	51.7	53.0	63.7	63.0	48.5	48.6	48.8	48.0	36.1	43.9
Older than 65.2 years	63.4	65.3	72.3	73.4	64.7	61.2	60.3	57.8	50.4	56.0
p value	**<.0001***	**<.0001***	**0.006***	**0.001***	**<.0001***	**0.0003***	**0.0006***	**0.008***	**<.0001***	**0.0001***
Caregiver Sex										
Male	52.9	53.6	65.8	63.6	53.8	51.2	50.8	45.5	34.6	43.7
Female	58.5	60.5	68.2	69.1	57.2	55.5	55.3	54.6	45.3	51.6
p value	0.184	0.082	0.869	0.422	0.476	0.328	0.325	**0.045**	**0.009***	**0.033***
Caregiver Relationship to Patient										
Son or daughter	66.5	68.2	76.6	76.7	68.0	67.2	61.0	62.5	52.3	55.2
Spouse or partner	47.3	48.9	58.9	58.4	43.4	41.4	46.8	42.4	32.7	42.7
p value	**<.0001***	**<.0001***	**<.0001***	**<.0001***	**<.0001***	**<.0001***	**0.0001***	**<.0001***	**<.0001***	**0.0002***
Use of Home Health Aide?										
Yes	69.4	72.5	75.7	79.7	72.4	75.6	66.0	66.4	52.9	52.2
No	53.4	54.7	65.1	63.9	51.2	47.9	50.5	48.8	40.0	49.0
p value	**<.0001***	**<.0001***	**0.004***	**<.0001***	**<.0001***	**<.0001***	**<.0001***	**<.0001***	**0.001***	0.34

Note: p-values < 0.05 are emboldened to indicate statistical significance

**Statistically significant p-values after Benjamini Hochberg correction*