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Caregiving concerns and clinical characteristics across neurodegenerative and cerebrovascular disorders in the Ontario neurodegenerative disease research initiative

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See the Supplemental Material for CRediT Contributor Roles.

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Abstract

Objectives: Caregiving burdens are a substantial concern in the clinical care of persons with neurodegenerative disorders. In the Ontario Neurodegenerative Disease Research Initiative, we used the Zarit's Burden Interview (ZBI) to examine: (1) the types of burdens captured by the ZBI in a cross-disorder sample of neurodegenerative conditions (2) whether there are categorical or disorder-specific effects on caregiving burdens, and and (3) which demographic, clinical, and cognitive measures are related to burden(s) in neurodegenerative disorders?

Methods/Design: $N = 504$ participants and their study partners (e.g., family, friends) across: Alzheimer's disease/mild cognitive impairment (AD/MCI; $n = 120$), Parkinson's disease (PD; $n = 136$), amyotrophic lateral sclerosis (ALS; $n = 38$), frontotemporal dementia (FTD; $n = 53$), and cerebrovascular disease (CVD; $n = 157$). Study partners provided information about themselves, and information about the clinical participants (e.g., activities of daily living). We used Correspondence Analysis to identify types of caregiving concerns in the ZBI. We then identified relationships between those concerns and demographic and clinical measures, and a cognitive battery.

Results: We found three components in the ZBI. The first was "overall burden" and was (1) strongly related to increased neuropsychiatric symptoms (NPI severity $r = 0.586$, NPI distress $r = 0.587$) and decreased independence in activities of daily living (instrumental ADLs $r = -0.566$, basic ADLs $r = -0.43$), (2) moderately related to cognition (MoCA $r = -0.268$), and (3) showed little-to-no differences between disorders. The second and third components together showed four types of caregiving concerns: current care of the person with the neurodegenerative

disease, future care of the person with the neurodegenerative disease, personal concerns of study partners, and social concerns of study partners.

Conclusions: Our results suggest that the experience of caregiving in neurodegenerative and cerebrovascular diseases is individualized and is not defined by diagnostic categories. Our findings highlight the importance of targeting activities of daily living and neuropsychiatric symptoms with caregiver-personalized solutions.

Keywords: Zarit's burden interview, Correspondence analysis, Neurodegenerative disorders, activities of daily living, neuropsychiatric symptoms

Key points:

- We identified multiple types of caregiving burden from the Zarit's Burden Interview across five neurodegenerative and cerebrovascular disorders.
- Overall burden showed strong relationships with neuropsychiatric symptoms (measured via Neuropsychiatric Inventory - Questionnaire) and functional dependence (measured via instrumental and basic activities of daily living).
- We found little to no differences between disorders
- Through our analyses we identified two questions that stood out with very high responses, and these two questions briefly capture the four types of burdens we identified: "Are you afraid of what the future holds for your relative?" and "Do you feel your relative is dependent on you?"

Caregiving concerns and clinical characteristics across disorders in the ONDRI study

Introduction

Informal caregivers are a critical and overlooked resource in the care of individuals with neurodegenerative disorders [1]. The personal strains of informal caregivers include physical, financial, emotional, and social stressors [2,3]. Caregivers can experience decreased health-related quality of life [4,5], elevated rates of depression and anxiety [6,7], and impaired levels of cognition compared to their age-matched peers [8]. Informal caregivers of those with dementia provide billions of dollars in uncompensated care annually [9]. As more individuals are diagnosed with neurodegenerative diseases and dementia, these costs will rise in coming years [10]. Given these personal and societal impacts, caregivers' concerns and wellbeing are a critical public health interest [11].

The last decade has seen increased interest in caregiving concerns in neurodegenerative disorders [12]. Some cross-sectional studies showed that caregivers of individuals with ALS [13,14] and with frontotemporal dementia (FTD) report higher overall concerns and [15] especially when compared with other neurodegenerative disorders, such as Alzheimer's disease (AD) [16]. Recent cross-disorder work in (AD) and Parkinson's disease (PD) showed that various types of caregiving concerns exist across—not limited to specific—diagnoses [17]. Possible contributors to caregiving concerns include participant or care partner characteristics (e.g., age, sex) and relationship role (e.g., spousal) [18], severity of communication impairment or needs driven behaviors [19], increases of and difficulty with management of neuropsychiatric symptoms [20], and decreased independence with basic and instrumental activities of daily living [21,22].

The Zarit burden interview (ZBI) [23,24] is frequently used to assess caregiving burdens in dementia and neurodegenerative disorders. Most work with the ZBI has focused on whether the ZBI captures an overall burden (unidimensional), or if it captures multiple types of burdens (multidimensional). An early study of ZBI dimensionality in the Canadian Study of Health and Aging [25] showed two burden factors: "personal" and "role strains". More recently, Oh and Kim [26] identified "social restrictions", "self-criticism", and "anger and frustration" in a Korean sample of family caregivers for individuals with ALS. Smith et al., [27] identified "impact of caregiving", "frustration/embarrassment", and "uncertainty over the future" in a UK (Scotland) sample of spousal or adult children caregivers across various diagnoses. While these showcase the variety of burdens, sometimes, the same *named* type of burdens exist across the literature. For example, Ankri et al., [28] and Springate & Tremont [29] each found three factors where one of those factors was "guilt". But these "guilt" types do not overlap.

The extant literature suggests that burdens are disorder specific. The literature also suggests a wide variety of ZBI dimensionality and burden types. But given that the majority of studies are not in representative and cross-disorder samples—and do not include comprehensive and harmonized measures and approaches—what we see may only reflect particular aspects of those studies. Therefore, it is unclear whether burdens are disorder specific, what types of burdens exist, and importantly what characteristics are related to burden(s) (e.g., relationship role, participant/partner characteristics, participant's cognition). To help resolve some of the conflicting results in the literature, we need a large and diverse sample of disorders, comprehensive and harmonized measures, and suitable analyses to uncover dimensionality of the ZBI.

The Ontario Neurodegenerative Disease Research Initiative (ONDRI) [30,31] is a multisite, prospective, observational, and longitudinal study neurodegenerative and cerebrovascular disease cohorts: Alzheimer's disease/mild cognitive impairment (AD/MCI), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), and cerebrovascular disease (CVD). A central goal of ONDRI is to collect cohort-harmonized data across clinical, neuropsychology, neuroimaging, genetics, gait and balance, oculomotor, and retinal imaging platforms to better understand the comprehensive phenotypes of each disorder, the disease impacts, and the contributions of cerebrovascular disease to dementia onset and progression. Participants were recruited from fourteen academic health sciences centers across Ontario, Canada (largely centered around six cities) and lived in a variety of communities including urban, suburban, and rural settings. Given the longitudinal study design, and the extensive data collection protocol, clinical participants were generally in early disease stages at baseline. All assessments were completed at baseline and annually thereafter for the duration of the study. In this study, we examined the following questions with the ONDRI data.

1. How many and what types of burdens are captured by the ZBI? This helps tell us what the ZBI captures and how it can be used (in research and practice).
2. Do we see categorical or spectrum-like effects for burden(s)? This helps tell us if there are effects specific to groups (e.g., FTD, spousal partners) or if there are common effects *across* groups.
3. With ONDRI's comprehensive and harmonized set of measures, which if any demographic, clinical, and cognitive measures are related to burden(s)? This helps tell us,

for examples, how memory, attention, symptoms, and disability of clinical participants are related to study partners' perceptions of burden(s).

Method

Diagnoses were based on the most recent criteria available at the time of recruitment, and participants were recruited by experienced neurologists. For complete details and references on diagnostic criteria see previous publications for recruitment targets[31] and for characteristics of the baseline sample[30] (used here). Also see *Supplemental Material*. AD/MCI participants met the NIA-AA criteria for probable AD, or single or multi-domain MCI [32,33]. PD participants were diagnosed via the UK Parkinson's Disease Society Brain Bank criteria[34]. ALS participants met the El Escorial criteria[35]. CVD participants are those that presented with ischemic stroke documented by MRI or CT more than 3 months before recruitment[36]. FTD criteria were based on various subtypes[37–40].

Our study included $N = 504$ clinical participant-study partner dyads (those with available ZBI data at baseline) from: AD/MCI ($n = 120$), ALS ($n = 38$), FTD ($n = 53$), PD ($n = 136$), and CVD ($n = 157$). AD/MCI included MCI ($n = 81$), probable AD with amnestic presentation ($n = 34$), and probable AD with non-amnestic presentation ($n = 5$). FTD included behavioral variant ($n = 21$), progressive supranuclear palsy ($n = 15$), nonfluent variant primary progressive aphasia ($n = 8$), and $n = 9$ remaining individuals across semantic dementia, corticobasal syndrome, or mixed FTD diagnoses. Of the $N = 504$ in this study, 497 had neuroimaging data at baseline with stroke volume tracing [41]. Overt stroke volumes were present in 85 CVD individuals, and a combined 11 individuals across PD, FTD, and ALS. ONDRI participants were required to have study partners. Study partners were individuals that had frequent interactions with the clinical

participant (have contact at least once a month), had known the individual for more than 2 years, and had to know the participant well enough to answer questions about the participant's cognitive abilities, communication skills, mood, and daily functioning. Study partners provided information about the participant's symptoms (physical, psychological, functional, behavioral, and social abilities). Our sample included 334 male and 170 female clinical participants, with 129 male and 375 female study partners. The majority of clinical participants live in their own or family homes (n = 498) with a small number of individuals in retirement homes or nursing homes (combined n = 6). We grouped study partners into four relationship roles: domestic partners (e.g., spouses, ex spouses, long term relationships; n = 387), adult children (including grandchildren and in-laws; n = 66), siblings or parents (n = 18), and friends (n = 33). Of the study partners, 408 lived with the clinical participant where 3 individuals had spent less than a year living together, and 405 study partners and clinical participants lived together for a median of 37 years (minimum = 1 year, maximum = 65 years). Of the 96 individuals who did not live with the clinical participant, their estimated weekly time spent together was a median of 7.5 hours (minimum = 0.5 hours, maximum = 112 hours). See Table 1 for more details on demographics and clinical measures.

Table 1

(A) Distribution of study partner types across the cohorts.

N = 504	**DOMESTIC PARTNERS (N = 387)**	**CHILDREN (N = 66)**	**SIBLINGS OR PARENTS (N = 18)**	**FRIEND (N = 33)**
ADMCI (N = 120)	84	25	5	6
ALS (N = 38)	28	4	3	3

FTD (N = 53)	41	8	2	2
PD (N = 136)	116	11	4	5
CVD (N = 157)	118	18	4	17

(B) Demographics of participants and study partners, with MoCA scores of participants

	AGE (med, min-max)	**SEX (M/F)**	**SP AGE (med, min-max)**	**SP SEX (M/F)**	**LIVE TOGETHER (Y/N)**
Overall (N = 504)	68.78 [40.12 - 87.80]	334/170	64 [19 - 87]	129/375	408/96
ADMCI (N = 120)	70.93 [53.44 - 87.80]	66/54	67 [19 - 85]	39/81	92/28
ALS (N = 38)	63.71 [40.12 - 77.25]	22/16	60 [26 - 77]	14/24	31/7
FTD (N = 53)	69.13 [49.66 - 80.90]	34/19	62 [22 - 84]	12/41	41/12
PD (N = 136)	68.10 [55.08 - 85.93]	106/30	64 [22 - 85]	25/111	120/16
CVD (N = 157)	68.85 [54.95 - 85.43]	106/51	65 [22 - 87]	39/118	124/33

(C) Diagnostic history and severity

	Modified Rankin Scale (med, min-max)	**MoCA (med, min-max)**	**Zarit's Total Score (med, min-max)**
Overall (N = 504)	1 [0 - 4] Missing = 67	25 [13 - 30] Missing = 1	14 [0 - 77] Missing = 2
ADMCI (N = 120)	1 [0 - 3] Missing = 37	23 [15 - 30]	15.5 [0 - 55]
ALS (N = 38)	2 [0 - 4]	25 [19 - 30] Missing = 1	19 [4 - 45]
FTD (N = 53)	2 [0 - 4] Missing = 30	22 [13 - 29]	31 [4 - 77]
PD (N = 136)	2 [0 - 4]	26 [18 - 30]	11 [0 - 58] Missing = 1
CVD (N = 157)	1 [0 - 4]	26 [18 - 30]	9 [0 - 64] Missing = 1

Note. ADMCI = Alzheimer's Disease/Mild Cognitive Impairment, ALS = Amyotrophic Lateral Sclerosis, FTD = Frontotemporal Dementia, PD = Parkinson's Disease, CVD = Cerebrovascular Disease, MoCA = Montreal Cognitive Assessment, SP = Study Partner, med = median, min = minimum, max = maximum. Missingness is generally denoted per cell. (A) Shows the distribution of study partner types across cohorts. (B) Shows the ages and sexes of the participants and their study partners within cohorts, and the proportion of clinical participant-study partner dyads that live together. Ages are shown with median values and the minimum/maximum range of scores per cohort. Precisions differ for ages because participant age was collected with month, day, and year, where study partner age included only year. (C) modified Rankin scale, the MoCA scores for each cohort, and the Zarit's Burden Interview total score. Scores are shown with median values and the minimum/maximum range of scores per cohort.

Measures

Most data were collected within 8 weeks of consent, except fourteen participants/study partners exceeded 8 weeks, where three of those study partners completed the ZBI at 18, 26, and 35 weeks. Because of rare responses, a wide variety of possible response levels, and/or free text based responses, we recoded levels of clinical participants' education, study partner's education, household income, and study partner type. See the *Appendix* and *Supplemental Materials* for more details on recoding and mappings between levels. Not all participants had data for all measures. We note missingness as needed.

Study partners completed the ZBI, the Lawton scale for the participant's basic and instrumental activities of daily living (ADLs) [42], the Neuropsychiatric Inventory - Questionnaire (NPI-Q) [43], and demographics. Participants completed the MoCA [44] (version 7) and a cognitive battery [45] that had 26 measures from 14 neuropsychological tests across five domains (attention/working memory, executive function, language, memory, and visuospatial abilities). The brief visuospatial memory tests (BVMT; immediate and delayed recall and recognition discrimination) were not part of the protocol for the ALS cohort. We used standardized scores based on normative data or summary scores from the assessments. Some measures included cutoffs. For example, the normative scores for BVMT immediate recall contained values from 20 to 80, with "<20" or >80" to indicate values below or above that cutoff; these values were treated as ordinal. Missing data because of cognitive/behavioral issues were imputed to the worst performance for the normative scores.

The ZBI is a 22 question self-report instrument to assess caregiving burdens. Each question has five possible responses: "Never", "Rarely", "Sometimes", "Quite Frequently", and

"Nearly Always"; traditionally recoded as 0, 1, 2, 3, and 4, respectively. Those numbers are summed to compute a total score. However, individual question responses are not numeric and should not be analyzed as such [46,47]. ZBI responses are a mixture of categorical and ordinal: a categorical response of "no" (Never) vs. "yes" (any other response), with ordinal "yes" responses ("Rarely" < "Sometimes" < "Quite Frequently" < "Nearly Always").

Statistical analyses

Data recoding. We recoded the ZBI as a hybrid of "crisp" and "fuzzy" coding [48–50] that captures both the categorical "no" and the ordinal "yes". For analyses, each question was represented by three columns: a "no" column and two "yes" columns: a "low yes" and a "high yes". The "no" column is exclusively 0 or 1 when a response of "Never" occurred, and that pattern was {1 0 0}. The "yes" responses could take on values of {0 1 0} for the "lowest yes" and {0 0 1} for the "highest yes". These are all "crisp" coding. A response of "Sometimes" could take on values of {0 .667 .333}, which is an example of "fuzzy" coding. Some responses were rare (e.g., less than ~5%) and thus combined with other responses. See the *Appendix* and *Supplemental Materials* for more details and illustrations on this recoding.

Correspondence analysis. We used correspondence analysis (CA) [51], an approach akin to principal components analysis, but designed specifically to handle the complexities of the ZBI responses (i.e., hybrid categorical-ordinal). CA was designed for categorical and contingency data but accommodates mixtures of data types. CA produces orthogonal components that are new variables which are linear combinations of the original data. Components are ordered by explained variance. CA produces scores for both the rows (participants) and columns (responses to the ZBI).

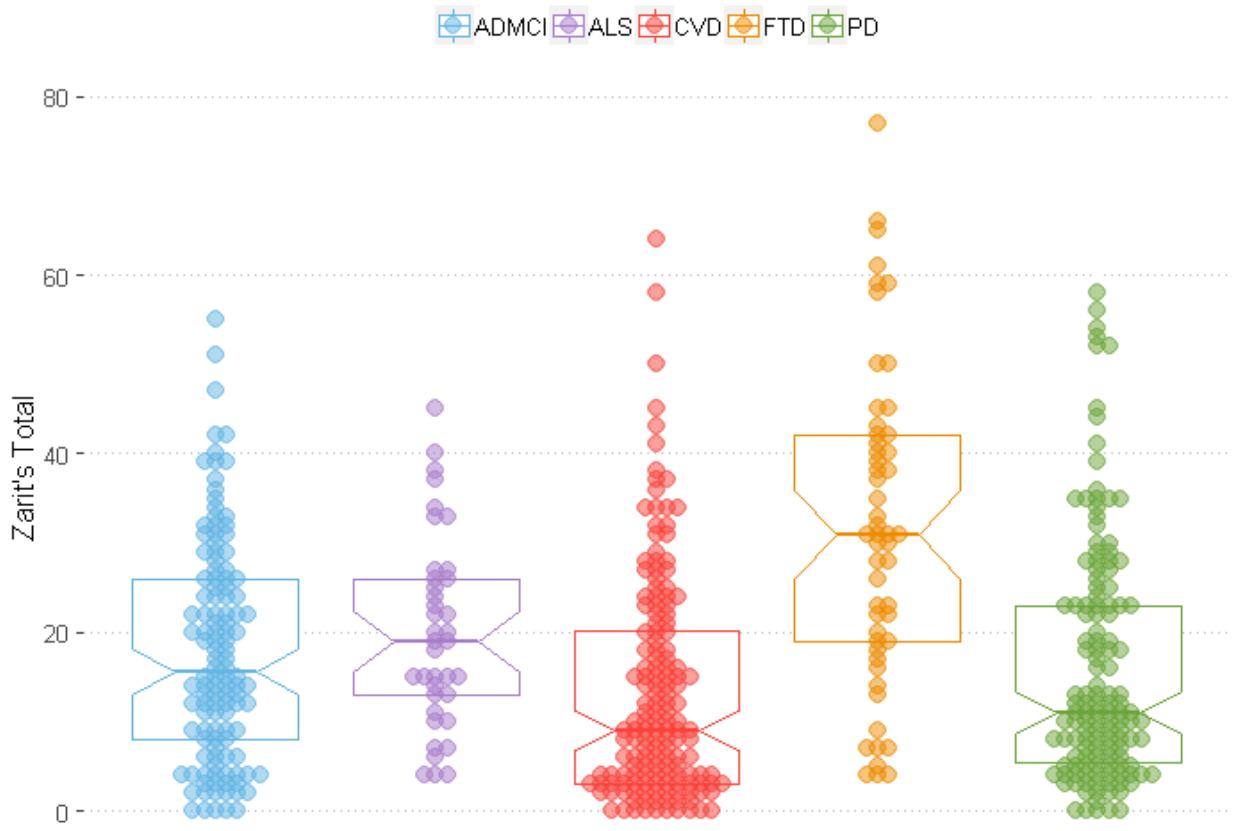
Resampling. We used split-half resampling (SHR) [52] to identify components to interpret. SHR repeatedly splits the data into two independent and equally sized sets and performs CA. Component reproducibility was estimated from the correlations between components derived from each split. We used bootstrap resampling [53] to compute bootstrap ratios [54,55] that indicate stability of responses (to each retained component). Bootstrap ratios are computed as the mean of the bootstrap distributions divided by their standard deviation (akin to a Z-score). Resampling preserved the proportions of the five cohorts. See the *Appendix* for more details on resampling.

Relationships between components and other measures. We analyzed the relationships between components and the demographic, clinical, and cognitive measures. For categorical variables (e.g., cohort, sex), we visualized distributions for levels along the component scores with beeswarm plots with the 25, 50, and 75 percentiles. For numeric data, we computed Spearman correlations between those data and the retained components. We computed permutation based *p*-values [56] and bootstrap based 95% confidence (percentile) intervals [53]. We calculated the Hellinger distance between the full (100%) permutation (null) and bootstrap (effect) distributions. Hellinger distance takes on a value of zero when the distributions are identical, and a value of one when there is no overlap.

Results

Total ZBI scores were available for $N = 502$ (two study partners each left one response blank). Table 1c and Figure 1a show the distribution of ZBI totals for each group. Our sample median ZBI was 14 (see Table 1 for each group median). For the AD/MCI and FTD subtypes, median scores were: 12 for MCI, 23 for amnestic AD, 31 for non-amnestic AD, 40 for behavioral variant FTD, 22 for progressive supranuclear palsy, 17.5 for nonfluent variant

primary progressive aphasia, and 31 for the remaining FTD subtypes. Figure 1a shows the distributions, medians, and quartiles for each cohort, and Figure 1b shows the proportion of responses. Short names for the ZBI and which questions they map to are in *Supplemental Materials*. Figure 1b helps highlight the nonlinearity in responses.



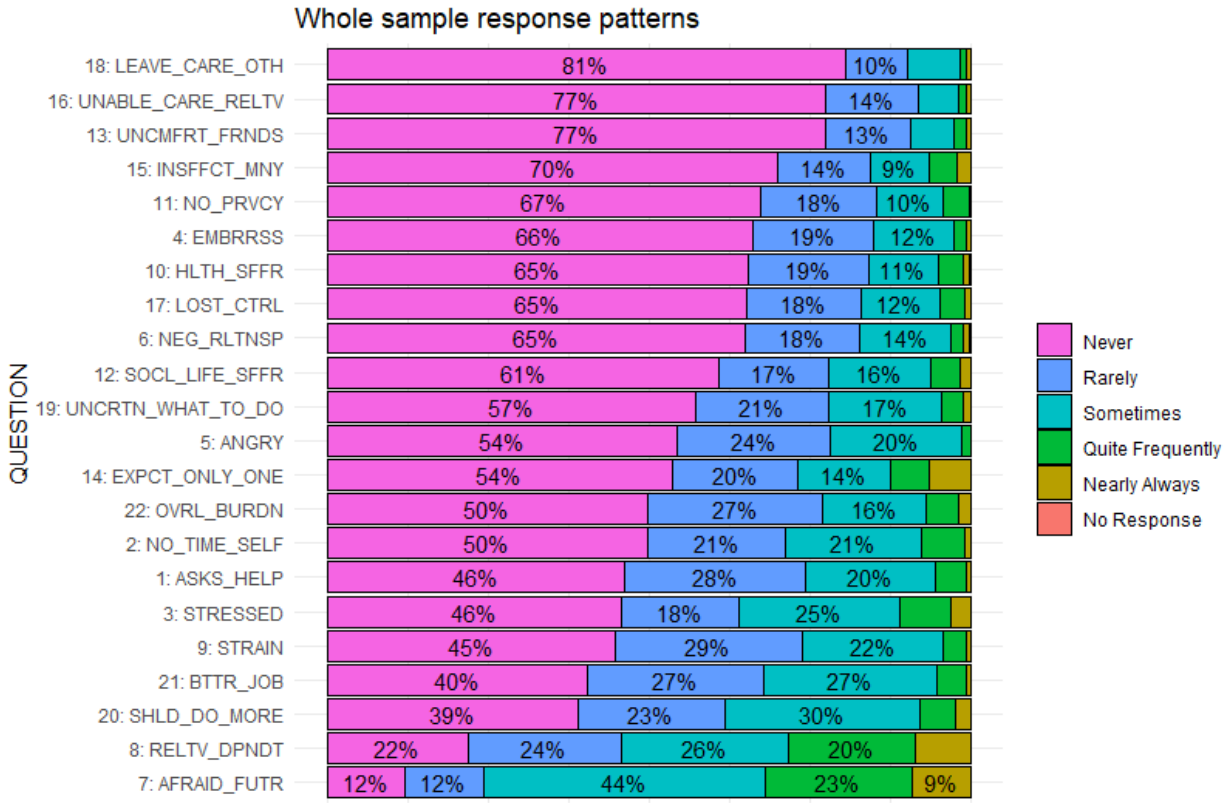


Figure 1: A (top) and B (bottom). A (top) shows the total summary scores for the N = 502 complete cases broken down by cohort, with boxplots that reflect the 25%, 50%, and 75%-iles. B (bottom) shows distributions of responses to each question for N = 504, with missing values displayed as "No Response". ADMCI = Alzheimer's Disease/Mild Cognitive Impairment, ALS = Amyotrophic Lateral Sclerosis, FTD = Frontotemporal Dementia, PD = Parkinson's Disease, CVD = Cerebrovascular Disease. In (B) we see the proportion of responses to each question (rank ordered by proportion of "Never" responses). Any unlabeled proportion is < 9%. The proportions help highlight the frequent and rare responses, and also highlight a non-linearity of responses. Each item is preceded by its question number on the Zarit's burden interview. See also Supplemental Figure 2 for recruitment cohort versions of this plot.

Missing responses for the ZBI were imputed to the mean after the hybrid crisp/fuzzy coding. Some responses were rare (e.g., less than ~5%) and combined with other responses (see *Appendix*). We flipped the signs of the components so that each component had a positive correlation with the ZBI total. Resampling was performed 1,000 times. Split-half resampling showed that the first three components had reproducibility $|r| = 0.999$, $|r| = 0.980$, and $|r| = 0.655$, with explained variance of 24.89%, 8.76%, and 4.01%, respectively (see *Appendix* for more information).

Figure 2 shows the distributions of study partner component scores colored by the participants' respective cohorts (Fig. 2a), and the responses component scores colored by the three levels used for the crisp/fuzzy coding (Fig. 2b). We used a bootstrap ratio cut-off of a magnitude of 4—approximately $p = 0.00003$ (one tailed)—for emphasis in Fig. 2b (responses with magnitudes less than 4 are denoted in grey). Component 1 shows nearly all responses are stable and that Component 1 is a gradient from "No" to "Low Yes" to "High Yes". Component 2 shows a gradient of individuals from (1) a general and low overall burdens, to (2) an absence of specific burdens, to (3) presence of specific high burdens. Component 3 shows a pattern with (1) "High Yes" responses for embarrassment and strain with "No" responses on doing a better job and should do more vs. (2) "High Yes" response to insufficient money, both "Low Yes" and "High Yes" to wanting to do a better job, and "No" responses to embarrassment and anger.


Study partner component scores
ADMCI
ALS
CVD
FTD
PD
COMPONENT 1
COMPONENT 2
COMPONENT 3
Component Scores

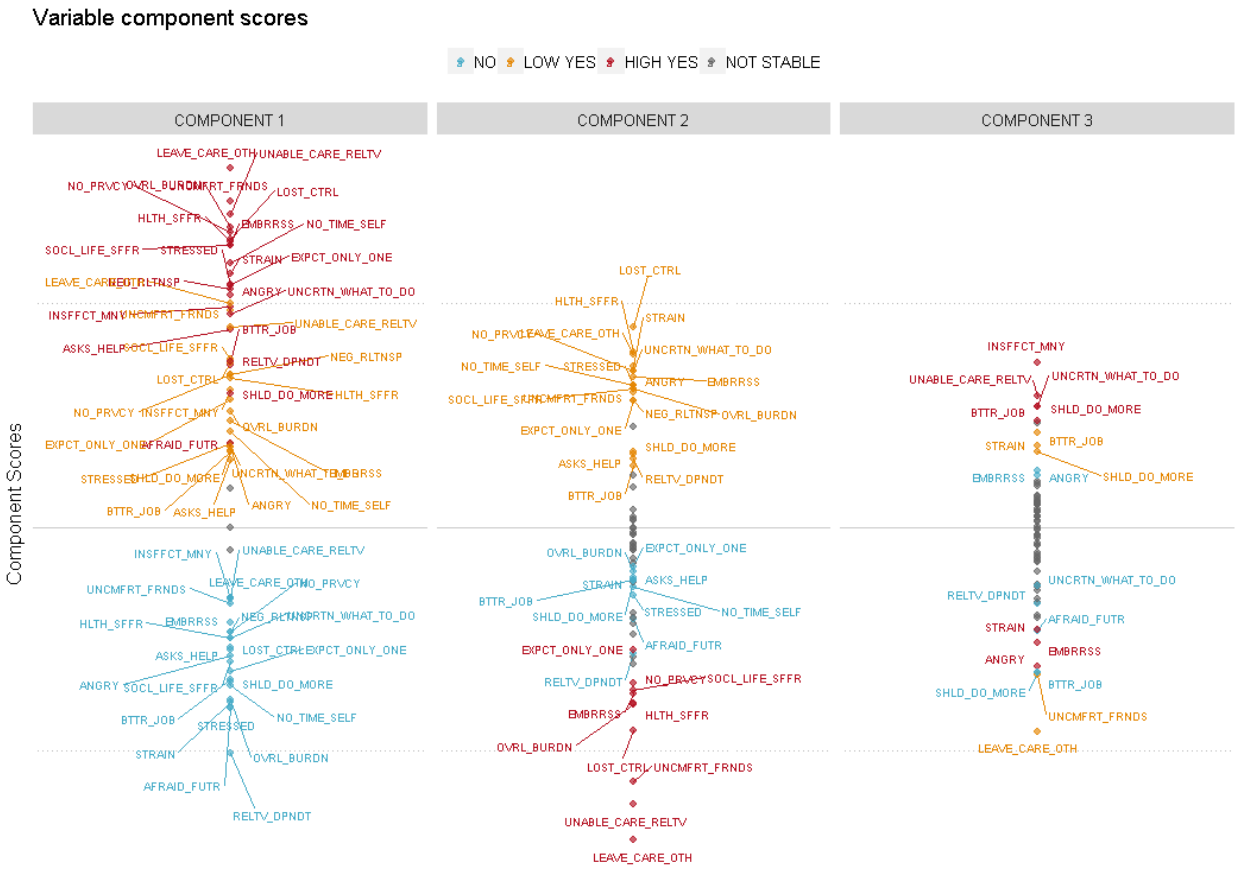
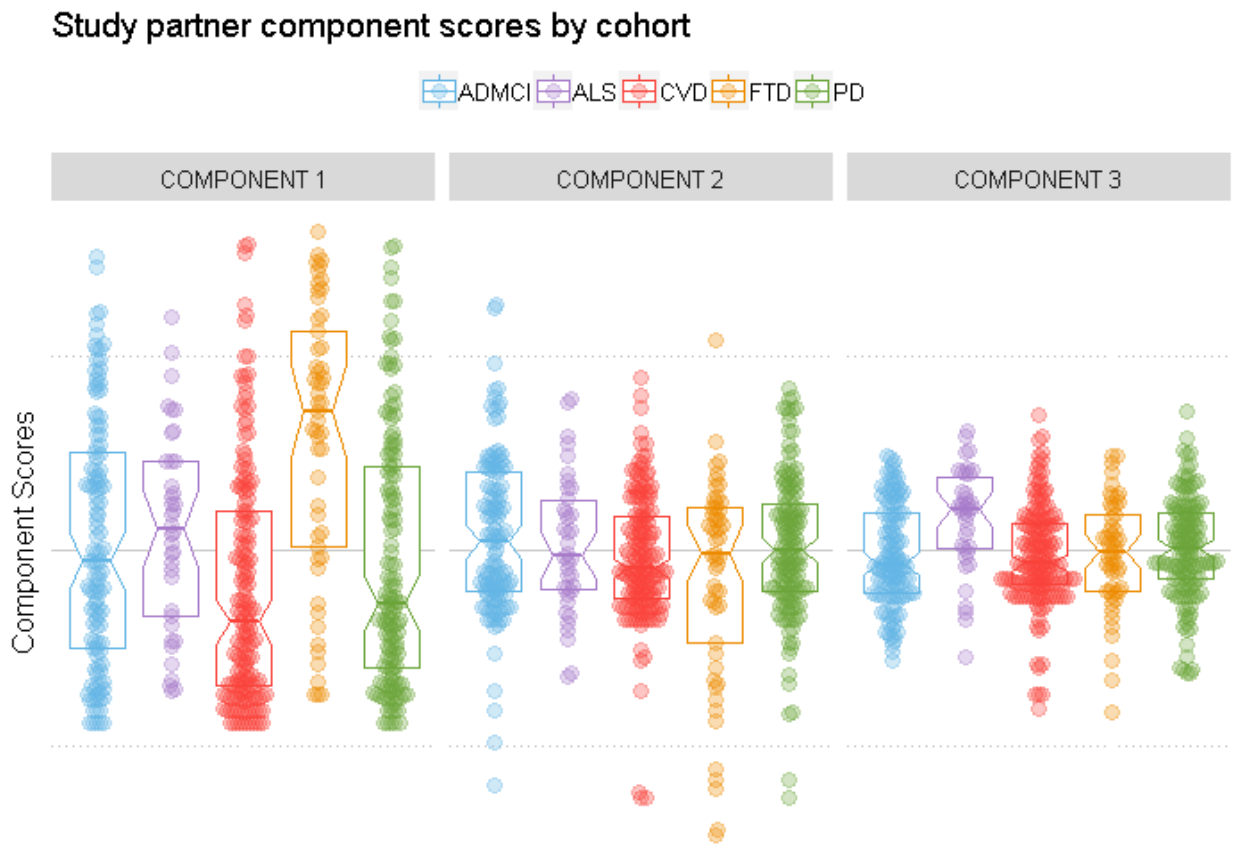


Figure 2: A (top) and B (bottom) the participant and variable component scores respectively. In both the solid horizontal line denotes zero on the Component. (A) Participant scores for the first three components, with each dot colored to represent the participant's recruitment cohort. Shown as a "beeswarm" plot, which distributes the individual dots with respect to their density (distribution). (B) Variable component scores for the first three components, with each dot colored to represent the coded response level if was stable under bootstrap resampling; else the dot is unlabeled and colored as grey. The dots are presented along a line (i.e., the component), with labels that are "repelled" from the dot to ensure readability. Each label is the short form of the question (see Supplemental Material for short codes and bootstrap ratios).

ZBI structure and demographic, clinical, and cognitive characteristics

Figure 3 shows the original component scores (see Fig. 2a), visualized separately for cohort (Fig. 3a), study partner relationship type (Fig. 3b). Notable effects include: (1) the FTD group had higher Component 1 scores (Fig. 2a), (2) the ALS group had slightly higher Component 3 scores (Fig. 2a), (3) friends and "siblings/parents" had lower Component 1 scores (Fig. 3b), and (4) "siblings/parents" had slightly higher Component 3 scores (Fig. 3b). In *Appendix*, we provide additional visualizations including participant sex, study partner sex, if they live together, participant education, study partner education, household income, and presence/absence of stroke in the participant. Generally, these show no effects.

Table 2 shows correlations between components and numeric variables. The ZBI total score was strongly correlated with the first component—$r(N = 502) = 0.987$—but weakly correlated with Components 2 and 3: $r(N = 502) = 0.207$ and $r(N = 502) = 0.156$, respectively. We emphasize interpretation of correlations where the Hellinger distances between the permutation and bootstrap distributions were at or near 1.


Study partner component scores by cohort
ADMCI
ALS
CVD
FTD
PD
COMPONENT 1
COMPONENT 2
COMPONENT 3
Component Scores

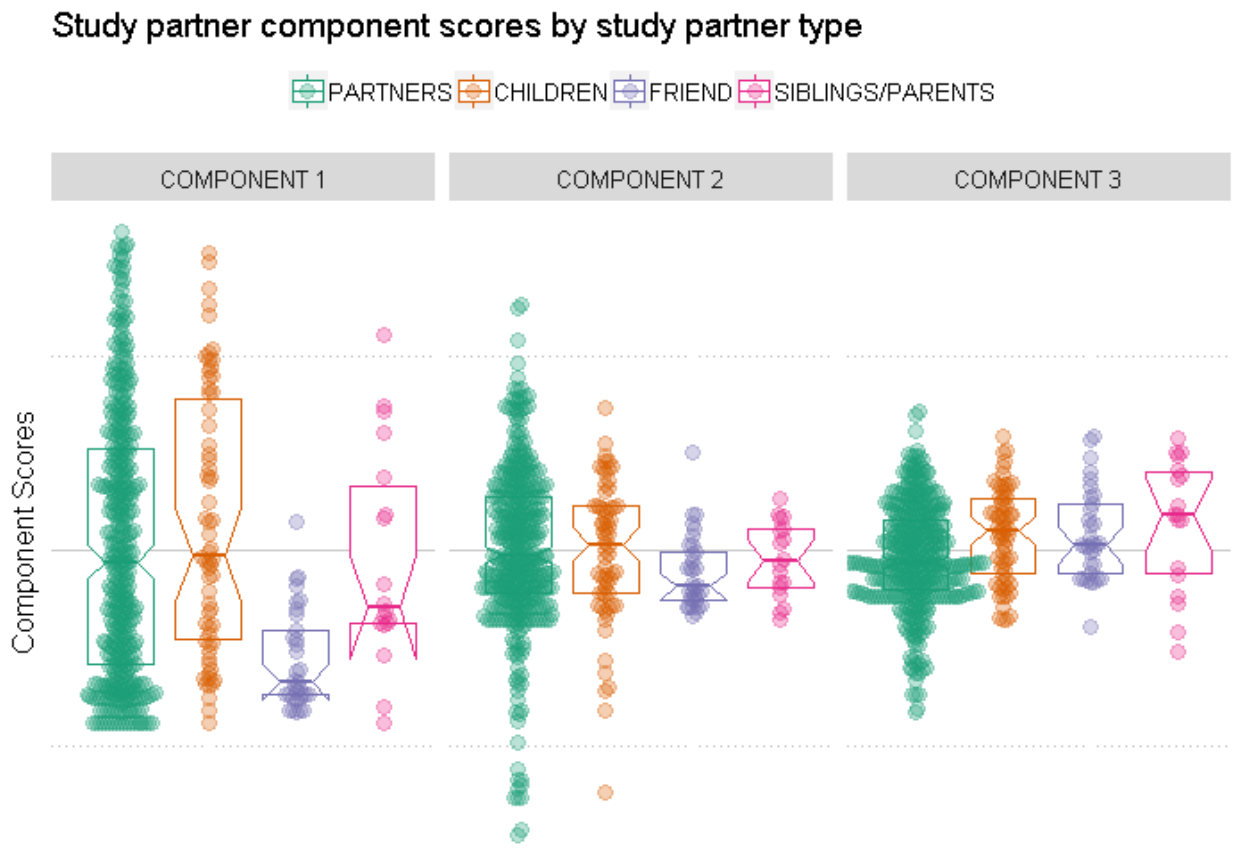


Figure 3: A (top) and B (bottom) shows the same component scores as in Figure 3a, but now broken down by cohort and study partner relationship role. The component scores across the three components shown per (A) cohort and (B) study partner relationship role. For panel (A) ADMCI = Alzheimer's Disease/Mild Cognitive Impairment, ALS = Amyotrophic Lateral Sclerosis, FTD = Frontotemporal Dementia, PD = Parkinson's Disease, CVD = Cerebrovascular Disease. All distributions are presented as "beeswarm" plots—which distribute the dots outward based on density—and notched boxplots that show the median (middle) and the 25% (bottom) and 75% (top) percentiles.

As Component 1 scores increased (1) ADL scores decreased (lower scores indicate higher levels of dependence): instrumental ADL $r(N = 475) = -.566$, $p_{perm} < 0.001$ with bootstrap CI = [-0.614, -0.511], basic ADL % $r(N = 484) = -.430$, $p_{perm} < 0.001$ with bootstrap CI = [-0.489, -0.366], and (2) NPI-Q scores increased (higher scores indicate increased severity or distress): severity $r(N = 468) = .585$, $p_{perm} < 0.001$ with bootstrap CI = [0.53, 0.633], distress $r(N = 460) = .587$, $p_{perm} < 0.001$ with bootstrap CI = [0.531, 0.636].

We saw many cognitive measures that had stable correlations with Component 1. We focus here on those with high Hellinger distances (~.95), which indicate that the permutation (null) and bootstrap (effect) distributions had little-to-no overlap. As Component 1 scores increased, MoCA scores and most of the cognitive measures decreased, including: (i) three of our seven attention & working memory measures, (ii) all six of our executive function tasks, (iii) one of our four language tasks, and (iv) five of our six memory tasks. None of our visuospatial tasks were strongly related to Component 1. See Table 2 for all of correlation values, bootstrap CIs, permutation *p*-values, and Hellinger distances between the permutation (null) and bootstrap (effect) distributions between our measures and the ZBI components. See *Appendix* for a visualization of the correlations in Table 2.

Table 2

Correlations of components with other measures.

	Component 1	Component 2	Component 3
Summary and demographics			
ZBI total (N = 502)	r = 0.987, p < 0.001 CI = [0.984, 0.989] HD = 1	r = 0.207, p < 0.001 CI = [0.118, 0.301] HD = 0.953	r = 0.156, p = 0.001 CI = [0.088, 0.227] HD = 0.907
MoCA total (N = 503)	r = -0.268, p < 0.001 CI = [-0.336, -0.201] HD = 0.995	r = -0.065, p = 0.073 CI = [-0.142, 0.008] HD = 0.484	r = 0.013, p = 0.387 CI = [-0.062, 0.093] HD = 0.152
Participant Age (N = 504)	r = -0.046, p = 0.153 CI = [-0.123, 0.029] HD = 0.373	r = 0.025, p = 0.292 CI = [-0.058, 0.1] HD = 0.209	r = -0.114, p = 0.008 CI = [-0.187, -0.045] HD = 0.767
Study Partner Age (N = 504)	r = -0.103, p = 0.016 CI = [-0.176, -0.03] HD = 0.714	r = 0.003, p = 0.479 CI = [-0.07, 0.076] HD = 0.092	r = -0.145, p = 0.001 CI = [-0.216, -0.072] HD = 0.863
Activities of daily living			
Instrumental ADLs % (N = 475)	r = -0.566, p < 0.001 CI = [-0.617, -0.515] HD = 1	r = -0.065, p = 0.078 CI = [-0.151, 0.013] HD = 0.487	r = -0.047, p = 0.144 CI = [-0.124, 0.029] HD = 0.396
Basic ADLs % (N = 484)	r = -0.43, p < 0.001 CI = [-0.493, -0.369] HD = 1	r = 0.033, p = 0.245 CI = [-0.048, 0.11] HD = 0.263	r = -0.128, p = 0.004 CI = [-0.201, -0.055] HD = 0.801
Neuropsychiatric inventory - Questionnaire			
NPI-Q Severity Total (N = 468)	r = 0.586, p < 0.001 CI = [0.534, 0.636] HD = 1	r = 0.038, p = 0.204 CI = [-0.039, 0.126] HD = 0.31	r = 0.057, p = 0.11 CI = [-0.013, 0.134] HD = 0.455
NPI-Q Distress Total (N = 460)	r = 0.587, p < 0.001 CI = [0.536, 0.638] HD = 1	r = 0.036, p = 0.222 CI = [-0.043, 0.124] HD = 0.287	r = 0.04, p = 0.208 CI = [-0.034, 0.116] HD = 0.313

Cognitive battery

Attention & Working Memory

Symbol Digit Modality Test (N = 504)	r = -0.294, p < 0.001 CI = [-0.365, -0.228] HD = 0.999	r = -0.064, p = 0.076 CI = [-0.135, 0.012] HD = 0.476	r = -0.003, p = 0.474 CI = [-0.074, 0.075] HD = 0.086
Trail Making Test – Part A (N = 499)	r = -0.199, p < 0.001 CI = [-0.271, -0.133] HD = 0.982	r = -0.036, p = 0.21 CI = [-0.109, 0.037] HD = 0.311	r = 0.002, p = 0.482 CI = [-0.079, 0.081] HD = 0.104
WAIS-III: Digit Span Forward (N = 503)	r = -0.119, p = 0.002 CI = [-0.192, -0.046] HD = 0.773	r = -0.091, p = 0.015 CI = [-0.163, -0.016] HD = 0.648	r = -0.034, p = 0.23 CI = [-0.107, 0.034] HD = 0.309
WAIS-III: Digit Span Backward (N = 502)	r = -0.115, p = 0.005 CI = [-0.196, -0.039] HD = 0.748	r = -0.028, p = 0.271 CI = [-0.105, 0.044] HD = 0.245	r = -0.075, p = 0.051 CI = [-0.145, -0.006] HD = 0.578
WAIS-III: Digit Span Total (N = 500)	r = -0.13, p = 0.001 CI = [-0.205, -0.057] HD = 0.818	r = -0.06, p = 0.079 CI = [-0.132, 0.012] HD = 0.466	r = -0.049, p = 0.123 CI = [-0.119, 0.018] HD = 0.419
DKEFS: Color naming (N = 499)	r = -0.244, p < 0.001 CI = [-0.316, -0.178] HD = 0.989	r = -0.03, p = 0.279 CI = [-0.1, 0.043] HD = 0.253	r = -0.007, p = 0.44 CI = [-0.084, 0.069] HD = 0.119
DKEFS: Word reading (N = 501)	r = -0.166, p < 0.001 CI = [-0.24, -0.097] HD = 0.915	r = -0.041, p = 0.194 CI = [-0.112, 0.028] HD = 0.316	r = -0.004, p = 0.453 CI = [-0.079, 0.072] HD = 0.081

Executive Function

Trail Making Test – Part B (N = 485)	r = -0.252, p < 0.001 CI = [-0.322, -0.183] HD = 0.994	r = -0.059, p = 0.102 CI = [-0.135, 0.017] HD = 0.446	r = -0.023, p = 0.299 CI = [-0.1, 0.058] HD = 0.217
DKEFS: Interference (N = 499)	r = -0.207, p < 0.001 CI = [-0.277, -0.138] HD = 0.977	r = -0.024, p = 0.308 CI = [-0.096, 0.048] HD = 0.215	r = -0.031, p = 0.24 CI = [-0.108, 0.042] HD = 0.258

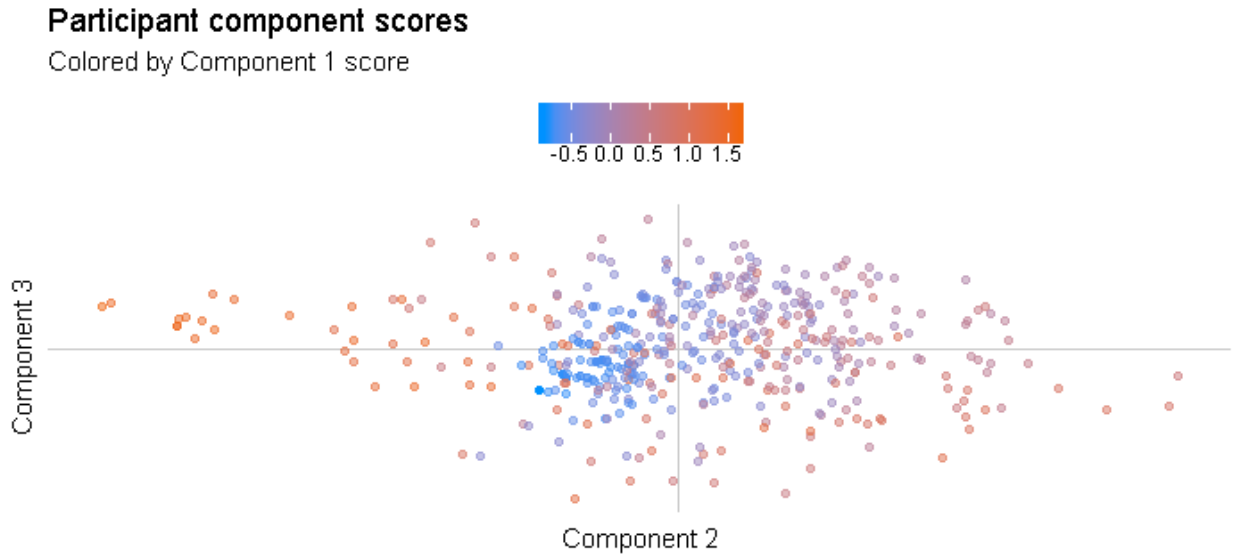
DKEFS: Switching (N = 494)	r = -0.238, p < 0.001 CI = [-0.305, -0.175] HD = 0.995	r = -0.051, p = 0.128 CI = [-0.125, 0.02] HD = 0.402	r = 0.01, p = 0.403 CI = [-0.067, 0.087] HD = 0.109
DKEFS: Letter Fluency (N = 504)	r = -0.22, p < 0.001 CI = [-0.288, -0.153] HD = 0.989	r = -0.062, p = 0.097 CI = [-0.136, 0.012] HD = 0.469	r = -0.033, p = 0.233 CI = [-0.107, 0.043] HD = 0.266
DKEFS: Category Fluency (N = 501)	r = -0.253, p < 0.001 CI = [-0.323, -0.18] HD = 0.994	r = -0.082, p = 0.032 CI = [-0.159, -0.01] HD = 0.596	r = 0.03, p = 0.256 CI = [-0.051, 0.106] HD = 0.26
WASI-II: Matrix Reasoning (N = 495)	r = -0.213, p < 0.001 CI = [-0.282, -0.145] HD = 0.983	r = -0.07, p = 0.057 CI = [-0.145, 0] HD = 0.546	r = -0.008, p = 0.43 CI = [-0.081, 0.064] HD = 0.127
Language			
Boston Naming – 15 Item (N = 429)	r = -0.145, p < 0.001 CI = [-0.22, -0.069] HD = 0.853	r = -0.075, p = 0.065 CI = [-0.158, 0.006] HD = 0.525	r = -0.077, p = 0.041 CI = [-0.151, 0.006] HD = 0.558
TAWF: Verb Naming (N = 504)	r = -0.205, p < 0.001 CI = [-0.277, -0.131] HD = 0.965	r = -0.069, p = 0.057 CI = [-0.147, 0.008] HD = 0.524	r = -0.044, p = 0.141 CI = [-0.119, 0.03] HD = 0.365
BDAE: Semantic Probe (raw) (N = 497)	r = -0.078, p = 0.032 CI = [-0.156, -0.007] HD = 0.606	r = -0.065, p = 0.074 CI = [-0.142, 0.007] HD = 0.487	r = -0.094, p = 0.02 CI = [-0.169, -0.019] HD = 0.645
WASI-II: Vocabulary (N = 489)	r = -0.153, p < 0.001 CI = [-0.233, -0.082] HD = 0.885	r = -0.054, p = 0.1 CI = [-0.131, 0.021] HD = 0.439	r = -0.011, p = 0.383 CI = [-0.089, 0.064] HD = 0.146
Memory			
RAVLT: Immediate (N = 502)	r = -0.265, p < 0.001 CI = [-0.336, -0.198] HD = 0.997	r = -0.085, p = 0.024 CI = [-0.165, -0.015] HD = 0.641	r = 0.054, p = 0.11 CI = [-0.018, 0.126] HD = 0.412
RAVLT: Long-delay (N = 501)	r = -0.18, p < 0.001 CI = [-0.254, -0.111] HD = 0.947	r = -0.06, p = 0.086 CI = [-0.141, 0.013] HD = 0.481	r = 0.08, p = 0.052 CI = [0.006, 0.154] HD = 0.573

RAVLT: Recognition Discrimination (N = 498)	r = -0.09, p = 0.019 CI = [-0.16, -0.022] HD = 0.671	r = 0.003, p = 0.475 CI = [-0.072, 0.078] HD = 0.074	r = -0.006, p = 0.429 CI = [-0.078, 0.068] HD = 0.101
BVMT-R: Immediate* (N = 466)	r = -0.258, p < 0.001 CI = [-0.328, -0.187] HD = 0.996	r = -0.102, p = 0.012 CI = [-0.177, -0.028] HD = 0.693	r = 0.004, p = 0.469 CI = [-0.08, 0.082] HD = 0.107
BVMT-R: Delayed* (N = 466)	r = -0.253, p < 0.001 CI = [-0.323, -0.18] HD = 0.988	r = -0.059, p = 0.09 CI = [-0.135, 0.02] HD = 0.446	r = -0.018, p = 0.334 CI = [-0.102, 0.062] HD = 0.19
BVMT-R: Recognition Discrimination* (N = 465)	r = -0.234, p < 0.001 CI = [-0.307, -0.159] HD = 0.994	r = -0.019, p = 0.329 CI = [-0.103, 0.056] HD = 0.207	r = 0.018, p = 0.368 CI = [-0.063, 0.095] HD = 0.151
Visuospatial			
Judgment of Line Orientation (N = 501)	r = -0.048, p = 0.137 CI = [-0.127, 0.025] HD = 0.374	r = -0.01, p = 0.419 CI = [-0.077, 0.063] HD = 0.128	r = 0.004, p = 0.461 CI = [-0.067, 0.074] HD = 0.134
VOSP: Incomplete Letters (N = 503)	r = -0.115, p = 0.003 CI = [-0.186, -0.046] HD = 0.767	r = -0.028, p = 0.264 CI = [-0.107, 0.051] HD = 0.222	r = 0.058, p = 0.092 CI = [-0.022, 0.13] HD = 0.459
BVMT-R: Copy Trial (N = 502)	r = 0.001, p = 0.486 CI = [-0.077, 0.073] HD = 0.095	r = 0.016, p = 0.367 CI = [-0.061, 0.088] HD = 0.157	r = -0.005, p = 0.425 CI = [-0.082, 0.068] HD = 0.098

Note. ZBI = Zarit's Burden Interview, MoCA = Montreal Cognitive Assessment, ADLs = activities of daily living, NPI-Q = neuropsychiatric inventory questionnaire, CI = Confidence interval, HD = Hellinger distance. Spearman correlations between additional (numeric) measures and the components. The additional measures are grouped together as (i) demographics and summary, which includes the Zarit and MoCA totals, as well as ages, (ii) percentage scores of the instrumental and basic activities of daily living (ADL), (iii) the neuropsychiatric inventory questionnaire, and (iv) individual measures from neuropsychology protocol of 14 tests, grouped by their theoretical domain; the '*' denotes the BVMT was not part of the ALS cohort's protocol. Signs of the correlations must only be interpreted with respect to the components and strictly *within* components (i.e., signs across components are arbitrary). We provide permutation-based p-values, bootstrap-based 95% confidence intervals, and the Hellinger

distance between the permutation and bootstrap distributions. See Supplemental Materials on the number of individuals imputed for each task.

Figure 4 visualizes Components 2 and 3 together, where Figure 4a shows study partner component scores and Figures 4b-c show ZBI responses. Figure 4a shows that few individuals exist strictly along Component 2 or Component 3, rather, individuals and responses exist in the quadrants. The upper right reflects “current care”, characterized by strain of caregiving, desire to do more, and should do a better job of caregiving. The upper left reflects “future care”, characterized by responses about the ability to care for much longer, insufficient money for care, and uncertainty of what to do. The lower left reflects both the *presence* of “personal” and the *absence* of “clinical participant-based” responses, with higher (“high yes”) responses to embarrassment and strain, with “never” responses to afraid of the future, the need to do more and dependence. The lower right reflects “social” responses, with generally lower (“low yes”) responses to questions on comfort around family and friends, care by others, and embarrassment.


Participant component scores
Colored by Component 1 score
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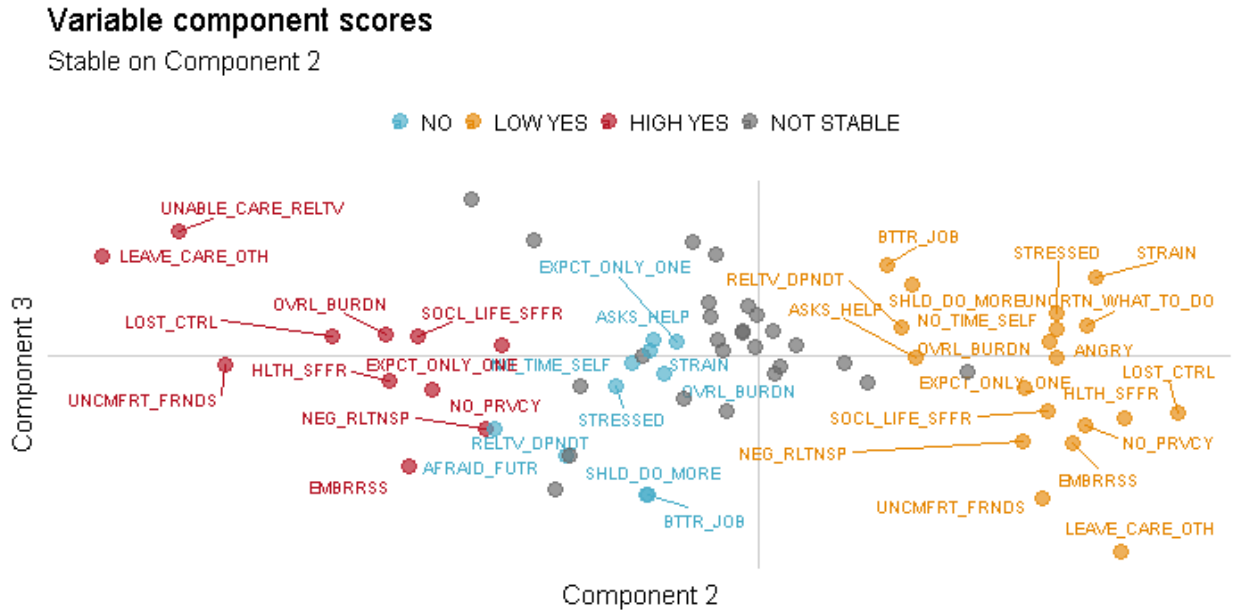
Component 3
Component 2


Variable component scores
Stable on Component 2
NO
LOW YES
HIGH YES
NOT STABLE
UNABLE_CARE_RELTV
LEAVE_CARE_OTH
LOST_CTRL
OVRL_BURDN
SOCL_LIFE_SFFR
HLTH_SFFR
UNCMFRT_FRNDS
EXPCT_ONLY_ONE
NO_TIME_SELF
NO_PRVCY
NEG_RLTNSP
RELTV_DPNDT
AFRAID_FUTR
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ANGRY
UNCMFRT_WHAT_TO_DO
Component 3
Component 2

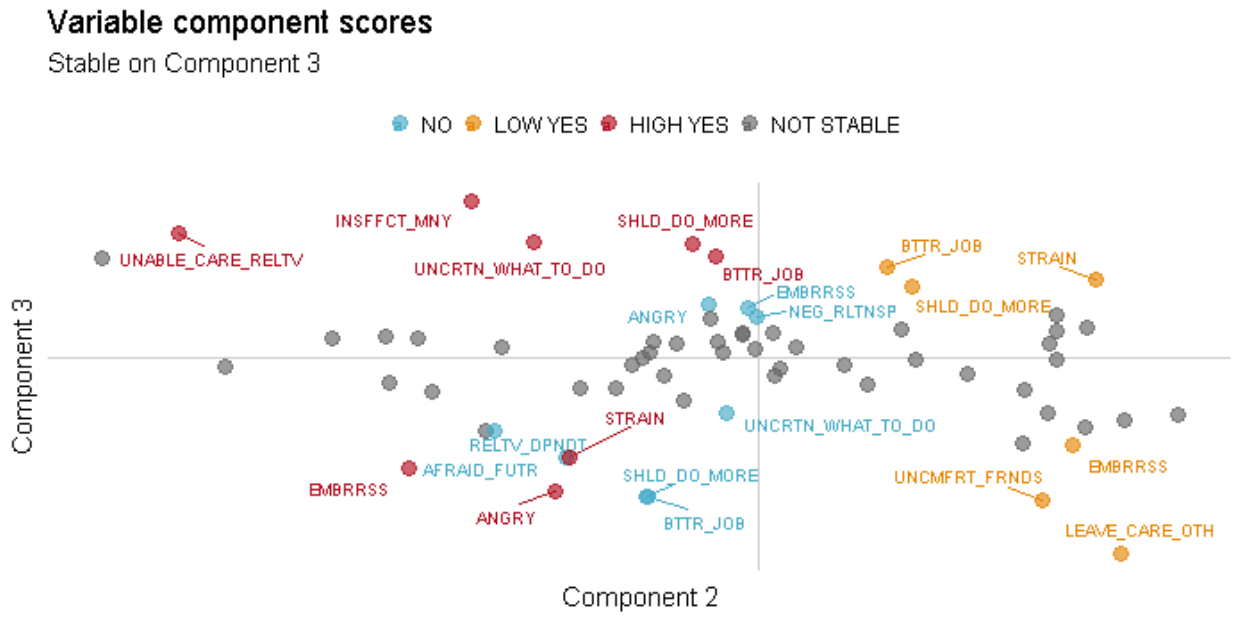

Figure 4: Visualization of Components 2 and 3 with (A) at the top and (C) at the bottom; (A) shows the participant component scores and (B-C) show the variable component scores. (A) Shows the participant component scores colored by their Component 1 score (which reflects a general overall burden from low to high). (B) Shows the variable component scores, colored by response type. Items colored only if bootstrap ratios > |4| on Component 2. (C) Shows the variable component scores, colored by response type. Items colored only if bootstrap ratios > |4| on Component 3.

Discussion

Four conclusions emerged from our study. First, we found strong relationships between Component 1 ("overall burden") and neuropsychiatric symptoms and activities of daily living. Second, study partners expressed concerns at the individual level (not necessarily diagnosis or relationship). Third, study partners expressed four types of care-related concerns (Components 2 and 3) subsequent to an overall burden (Component 1). Finally, two ZBI questions stood out that could be useful as screening questions.

The ONDRI ZBI score was lower than comparable studies (e.g., Hébert et al., 2000 median ZBI = 18.5; ONDRI's median ZBI = 14), and we also observed weaker relationships between clinical participants' cognition and "overall burden" than other studies [57–59]. ONDRI's ALS and FTD groups showed elevated "overall burden" compared to the other groups, where ONDRI's FTD effect was driven almost entirely by the behavioral variant subtype. The strongest relationships we saw were between "overall burden" and (higher) severity of and distress over neuropsychiatric symptoms, and (lower) activities of daily living, a finding supported by other studies [14,15,60–62]. While most studies are only within disorders [58,61,63–65], we provided a disease-agnostic approach which highlights that concerns are expressed at the individual level, not necessarily at a group level.

The literature is inconsistent regarding relationship roles. Spousal partners and adult children differ on overall burden in Alzheimer's [66] but not FTD [67]. Pinquart and Sorenson's meta-analysis [68] showed that spousal partners and adult children instead differ on types of (not overall) burdens. We showed neither: "spousal partner" and "adult children" did not differ on any

of our components. We also saw no differences for other demographic factors (e.g., education or income): a result that both agrees with [25] and contradicts [69] previous studies.

We identified four types of concerns subsequent to overall burden: current care of the person with the neurodegenerative disorder, future care of the person with the neurodegenerative disorder, personal concerns of the study partner, and social concerns of the study partner. Though we identified these four types (see Figure 4), it is worth noting that some of the individual questions may have low endorsement. For example, Figure 1 shows that a substantial majority (81%) of respondents said "Never" to "Do you wish you could leave the care of your relative to someone else?"; a question we consider a "social concern" (lower right of Figs. 4b and 4c). When our four types are considered with the overall proportions (see Figure 1), it is clear that some types have higher endorsement. In particular, we generally see that questions about current and future care have higher endorsements than other questions.

None of the concerns we identified strictly reflect objective vs. subjective concerns [20], but some reflect stress and demand [19]. Many recent efforts within [26–29] and beyond [70–72] neurodegenerative disorders also identify multiple types of concerns.

From our analyses, two questions stood out: "Are you afraid of what the future holds for your relative?" and "Do you feel your relative is dependent on you?" (see Figure 1b). A high response to the future question reflects concerns about future care, a high response to the dependence question reflects personal/dependence stressors, and a high response to both reflects high overall concern. These two questions might be useful as a screening assessment that could guide clinicians in two ways: (1) the need for additional help and resources on understanding neurodegenerative disorders, or an indicator of disease progress ("are you afraid of what the

future"), and (2) help assess the well-being of the caregiver ("is your relative dependent on you") who may require, for example, additional or external assistance with caregiving duties. However, following these two questions, clinicians should follow up with more detailed quantitative and qualitative assessments to get a more complete picture of the needs for both the individual living with a neurodegenerative disorder and the caregiver.

Limitations

Some study partners were possibly not caregivers, though the majority were spousal (N = 387/504) and/or lived with the clinical participants (N = 408/504). The number of hours spent caregiving was an overlooked measure at the time of protocol development. Our study and similar studies would benefit from clearly identifying the relationships between, and how much care a study partner provides. ONDRI did not collect valuable measures on the study partners, such as quality of life, cognitive, psychological well-being (e.g., depression, anxiety) [25], and personality measures (e.g., neuroticism, optimism, pessimism) [73]. Together, these measures and more formal measures of caregiving (e.g., specific duties, time spent, financial contributions) could help clarify the relationships between various types of burdens and well-being of the clinical participant-study partner dyads.

Our participants were recruited across numerous regions in Ontario (urban, suburban, and rural areas). Some similar effects to ours can be seen in other, more focused and smaller international studies [14,15,17,60–62]. Our sample is considerably larger than most and, importantly, includes a more diverse sample with respect to disorders. The majority of our study partners were females providing care for males, but that reflects the population of dementia caregivers [74].

For ONDRI, our participants had varying levels of impairment within and across disorders, but approximately half of each cohort (and thus whole sample) were above/below the MoCA impairment cut-off. Also, our analyses were on baseline data (i.e., recruitment into ONDRI), so many clinical participants were in early stages of disease. Because these are baseline data, severity and types of burdens could change at subsequent visits, and as disorders progress. The longitudinal component of ONDRI will be a vital resource to understand stability or change of types of caregiving burdens, especially with respect to the course(s) of disease(s).

Conclusions

We showed that caregiving concerns are multidimensional and highly individualized regardless of differing symptom profiles across neurodegenerative disorders. Our results reinforce the importance of developing caregiver support interventions and education programs that reduce the burden of completing activities of daily living and managing neuropsychiatric symptoms. Our results also highlight key caregiver concerns with planning for future care and meeting their social needs.

We can make several recommendations to address both clinical and research needs. First, research and clinical practice require better (1) general purpose and disease-specific measures of concerns and (2) definitions of concerns and burdens within, across, and beyond disorders. More accurate measurement will be critical in coming years, especially because an increasing number of individuals prefer to age at home and more likely with familial caregivers. Though it is clear that types of concerns exist across many studies—which includes our own—it is not clear what those types are or how we should define and measure them. Though we provide names for the concerns we identified in our data, others may interpret them differently.

Short assessments are beneficial to screen for and identify those in most need of support for caregiving [75]. Treatment strategies should consider both the individual living with a neurodegenerative disorder and caregivers/relatives as a unit: those with neurodegenerative disorders are assessed and treated for disorders, and caregivers/relatives are assessed on their well-being and ability to provide care. Healthcare professionals can help serve the dyadic unit by directing caregivers to more resources. One approach is to suggest resources for strategies like Goal Attainment Scaling [76], self-care [77–79], and social support [80]. Additionally, psychoeducation on disorder trajectories and characteristics, and resources on how neurodegeneration leads to physical and cognitive, as well as personality, judgement, and social functioning changes. This would be especially important—and beneficial—in low prevalence disorders.

Acknowledgments

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ONDRI data—including but not limited to the data in this article—will be accessible through the Ontario Brain Institute (https://braininstitute.ca/) to qualified researchers. Please see the Ontario Brain Institute website for information on when the data will be released and how to access the data: https://braininstitute.ca/. Code to reproduce these analyses are (currently) available upon request but will be made publicly available (see https://github.com/derekbeaton/caregiving_burdens).

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Conflicts of interest

MF is listed on a patent related to methods and kits for differential diagnosis of Alzheimer disease vs. frontotemporal dementia using blood biomarkers. CEF received grant funding from Hoffman La Roche and Vielight. DAG received honorarium for Consulting: Department of Justice Canada / Government of Canada, Sunovion; Clinical trials: CIHR, Genzyme Corporation/Sanofi Canada, Eli Lilly and Company. AEL reports consultancy support from Abbvie, Acorda, AFFiRis, Biogen, Denali, Janssen, Intracellular, Kallyope, Lundbeck, Paladin, Retrophin, Roche, Sun Pharma, Theravance, and Corticobasal Degeneration Solutions; advisory board support form Jazz Pharma, PhotoPharmics, Sunovion; other honoraria from Sun Pharma, AbbVie, Sunovion, American Academy of Neurology and the International Parkinson and Movement Disorder Society; grants from Brain Canada, Canadian Institutes of Health Research, Corticobasal Degeneration Solutions, Edmond J Safra Philanthropic Foundation, Michael J. Fox Foundation, the Ontario Brain Institute, Parkinson Foundation, Parkinson Canada, and W. Garfield Weston Foundation and royalties from Elsevier, Saunders, Wiley-Blackwell, Johns Hopkins Press, and Cambridge University Press. BL has a patent Systems, Methods, and Devices for Brain Health Assessment. U.S. Patent No. 14/928,548

pending to Baycrest and Expert consultant in legal cases concerning memory, cognition, and neurodegenerative disease. Co-developer of Goal Management Training®.

BGP receives honoraria from the American Geriatrics Society for editorial work. BGP holds United States Provisional Patent No.62/466,651 for a cell-based assay and kits for assessing serum anticholinergic activity. DS is a site investigator for a clinical trial sponsored by Hoffmann La Roche. SCS is the Chief Science Officer and a shareholder of ADMdx, Inc., Chicago, and a board member of InDoc Research, Toronto. ACR serves on the Editorial Board - Journal of Speech Language Hearing Research; Travel and Speaker Honorarium - Parkinson's Foundation; ACR holds U.S. patent Rogers, J., Xu, S., Lee, K., Ni, X., Roberts, A., Martin-Harris, B. Wireless Medical Sensors and Methods U.S. PATENT EL795244659, FEBRUARY 16, 2018. ACR has received research support - National Institute of Deafness and Communication Disorders; National Institute on Aging; Ontario Brain Institute, Parkinson's Canada; ACR is a Member Research Policy Committee Parkinson's Canada.

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