Patterns of Symptom Tracking by Caregivers and Patients with Dementia and Mild Cognitive Impairment: Cross-Sectional Study

Taylor Dunn, Kenneth Rockwood, Susan E Howlett, Sanja Stanojevic, Aaqib Shehzad, Justin Stanley

Submitted to: Journal of Medical Internet Research
on: April 08, 2021

Table of Contents

Patterns of Symptom Tracking by Caregivers and Patients with Dementia and Mild Cognitive Impairment: Cross-Sectional Study

Taylor Dunn[1] MSc; Kenneth Rockwood[1, 2, 3] MD; Susan E Howlett[1, 2, 4] PhD; Sanja Stanojevic[1, 5] PhD; Aaqib Shehzad[1] BDS, MHI; Justin Stanley[1] BEng

[1]Ardea Outcomes Halifax CA
[2]Division of Geriatric Medicine Dalhousie University Halifax CA
[3]Geriatric Medicine Research Unit Nova Scotia Health Authority Halifax CA
[4]Department of Pharmacology Dalhousie University Halifax CA
[5]Department of Community Health and Epidemiology Dalhousie University Halifax CA

Corresponding Author:
Kenneth Rockwood MD
Geriatric Medicine Research Unit
Nova Scotia Health Authority
1421-5955 Veterans Memorial Lane
Halifax
CA

Abstract

Background: Individuals who live with dementia or mild cognitive impairment (MCI) experience a variety of symptoms and challenges that trouble them and/or their carers. The usual remedy for this heterogeneity is to employ several standardized tests to cover the variety of problems in cognition, behaviour and function. These tests are used for diagnosis, prognosis, and to track effects of treatment. A complementary approach is to employ individualized measures. MyGoalNav™ Dementia is one such: an online tool that allows impaired individuals and their caregivers to identify and track outcomes of greatest importance to them. Such individualized outcome measurement can be a less arbitrary and more sensitive way of capturing meaningful change.

Objective: To explore the most frequent and important symptoms and challenges reported by caregivers and people with dementia and MCI, and how this varied by disease severity.

Methods: This cross-sectional observational study involved 3909 online myGoalNav™ users (mostly caregivers of people with dementia or MCI), who completed symptom profiles between 2007-2019. Users chose from a library of common dementia-related symptoms and challenges their most personally important or troublesome to track over time. Users were also asked to rank their chosen symptoms from least to most important, which we called the symptom potency. As the stage of disease for these online users is unknown, we applied a supervised staging algorithm, previously trained on clinician-derived data, to classify each profile as MCI, into these four stages: MCI, Mild, Moderate and Severe dementia. Across these stages, we compared symptom tracking frequency, symptom potency, and the relationship between frequency and potency.

Results: The staging algorithm classified 917 MCI, 1596 Mild, 514 Moderate, and 882 Severe dementia profiles. The most frequent symptoms in MCI and Mild profiles were similar and consisted of early hallmarks of dementia (e.g. recent memory, language difficulty). As the dementia stage increased to Moderate and Severe, the most frequent symptoms were characteristic of loss of independent function (e.g. incontinence) and behavioural problems (e.g. aggression). The most potent symptoms were similar between stages, and generally reflected disruptions in everyday life (e.g. problems with hobbies/games, travel, looking after grandchildren). Symptom frequency was negatively correlated with potency at all stages, and the strength of this relationship increased with increasing disease severity.

Conclusions: Our results underscore the feasibility and interpretability of patient-centricity in MCI and dementia studies. They illustrate the valuable real-world evidence that can be collected with digital tools. Here, the most frequent symptoms across the stages reflected our understanding of the typical disease progression. The symptoms ranked as most personally important by users, however, were generally among the least frequently selected. Through individualization, patient-centered instruments like myGoalNav™ can complement standardized measures by capturing these infrequent but potent outcomes.

(JMIR Preprints 08/04/2021:29219)

DOI: https://doi.org/10.2196/preprints.29219

Preprint Settings

1) Would you like to publish your submitted manuscript as preprint?

✓ **Please make my preprint PDF available to anyone at any time (recommended).**
Please make my preprint PDF available only to logged-in users; I understand that my title and abstract will remain visible to all users.
Only make the preprint title and abstract visible.
No, I do not wish to publish my submitted manuscript as a preprint.

2) If accepted for publication in a JMIR journal, would you like the PDF to be visible to the public?

✓ **Yes, please make my accepted manuscript PDF available to anyone at any time (Recommended).**
Yes, but please make my accepted manuscript PDF available only to logged-in users; I understand that the title and abstract will remain v
Yes, but only make the title and abstract visible (see Important note, above). I understand that if I later pay to participate in <a href="http

Original Manuscript

Patterns of Symptom Tracking by Caregivers and Patients with Dementia and Mild Cognitive Impairment: Cross-Sectional Study

Abstract

Background: Individuals who live with dementia or mild cognitive impairment (MCI) experience a variety of symptoms and challenges that trouble them and/or their carers. The usual remedy for this heterogeneity is to employ several standardized tests to cover the variety of problems in cognition, behaviour and function. These tests are used for diagnosis, prognosis, and to track effects of treatment. A complementary approach is to employ individualized measures. MyGoalNav™ Dementia is one such: an online tool that allows impaired individuals and their caregivers to identify and track outcomes of greatest importance to them. Such individualized outcome measurement can be a less arbitrary and more sensitive way of capturing meaningful change.

Objective: To explore the most frequent and important symptoms and challenges reported by caregivers and people with dementia and MCI, and how this varied by disease severity.

Methods: This cross-sectional observational study involved 3909 online myGoalNav™ users (mostly caregivers of people with dementia or MCI), who completed symptom profiles between 2007-2019. Users chose from a library of common dementia-related symptoms and challenges their most personally important or troublesome to track over time. Users were also asked to rank their chosen symptoms from least to most important, which we called the symptom potency. As the stage of disease for these online users is unknown, we applied a supervised staging algorithm, previously trained on clinician-derived data, to classify each profile as MCI, into these four stages: MCI, Mild, Moderate and Severe dementia. Across these stages, we compared symptom tracking frequency, symptom potency, and the relationship between frequency and potency.

Results: The staging algorithm classified 917 MCI, 1596 Mild, 514 Moderate, and 882 Severe dementia profiles. The most frequent symptoms in MCI and Mild profiles were similar and consisted of early hallmarks of dementia (e.g. recent memory, language difficulty). As the dementia stage increased to Moderate and Severe, the most frequent symptoms were characteristic of loss of independent function (e.g. incontinence) and behavioural problems (e.g. aggression). The most potent symptoms were similar between stages, and generally reflected disruptions in everyday life (e.g. problems with hobbies/games, travel, looking after grandchildren). Symptom frequency was negatively correlated with potency at all stages, and the strength of this relationship increased with increasing disease severity.

Conclusions:

Our results underscore the feasibility and interpretability of patient-centricity in MCI and dementia studies. They illustrate the valuable real-world evidence that can be collected with digital tools. Here, the most frequent symptoms across the stages reflected our understanding of the typical disease progression. The symptoms ranked as most personally important by users, however, were generally among the least frequently selected. Through individualization, patient-centered instruments like myGoalNav™ can complement standardized measures by capturing these infrequent but potent outcomes.

Keywords: dementia; mild cognitive impairment; real-world evidence; patient-centric outcomes;

machine learning; dementia stage; Alzheimer disease; symptom tracking.

Introduction

It is proving tricky to understand what constitutes successfully treated late-life dementia. This reflects in part the evolving understanding of Alzheimer disease. Contemporary thinking sees Alzheimer disease as a biological construct, defined by biomarkers that can be detected *in vivo*, or at autopsy. In this formulation, Alzheimer disease is distinguished from Alzheimer dementia, a clinical syndrome [1]. This separation is not neat, however. Over against an earlier view that a definitive diagnosis of Alzheimer disease could only be made at autopsy [2], it is now recognized that many people who meet neuropathological criteria for Alzheimer disease did not have dementia when alive [3]. Few people with late-life dementia have “pure” Alzheimer disease; in the great majority, it is present in the face of many other neuropathological features [4,5]. Even a full suite of neuropathological markers cannot distinguish between people who had dementia when alive, and those who did not; other factors such as history of delirium [6], prior hospitalization [7], and degree of frailty each are important [8]. Similarly, a range of factors, from level of education [9] to stimulating psychosocial and lifestyle experiences [10] are seen as potentially protective, even if less well-studied. A further challenge to defining successful treatment is that standard outcome measures, notably including the much-employed Alzheimer Disease Assessment Scale-Cognitive subscale (ADAS-Cog), can underestimate meaningful clinical change [11,12].

The new consensus on defining Alzheimer disease (hereafter AD) and the broader understanding of what gives rise to late-life dementia together have propelled rethinking of which outcomes to measure in dementia and pre-dementia clinical trials [13,14]. FDA guidelines in 2018 [15] have suggested that a single primary endpoint, which assesses both cognitive and functional effects (e.g. the Clinical Dementia Rating scale Sum of Boxes, CDR-SB [16,17]), may be used to evaluate treatment in early-stage patients with biomaker-defined AD. With this re-evaluation, it may be useful to consider patient-reported impacts of treatment. This could be a less arbitrary means of understanding treatment efficacy compared to changes in biomarkers that tend to correlate poorly with clinical measures [18–21].

From mild cognitive impairment (MCI), the symptomatic pre-dementia stage of AD [22], to the severe stage of dementia, patients are troubled by diverse sets of cognitive, functional, and behavioural symptoms. Even so, we lack a comprehensive inventory of symptoms across the disease spectrum and their susceptibility to treatment. Surveys of symptoms are few, in part because they are expensive. For this, the online environment can be well-suited.

Our group has shown that data on people living with MCI and dementia and their care partners can be acquired with an internet-based tool called myGoalNav™ Dementia (previously SymptomGuide® Dementia). This symptom tracking platform provides a large library from which users can identify and track dementia symptoms that are most important to them [23]. Note the distinction between a symptom being present – as in a “tick box” survey of symptom prevalence" – and one being important to individual patients and caregivers. Earlier, we had used myGoalNav™ to investigate construct validity with the Dependence Scale [24], to identify clusters of neuropsychiatric symptoms [25], to characterize the symptoms of verbal repetition [26], misplacing objects [27], and agitation [28], and to evaluate donepezil in a six-month open-label study [29]. Here, we used myGoalNav™ Dementia to better understand the patterns of dementia symptom tracking with severity of impairment, as staged by a machine learning algorithm.

Objectives

The specific aims of this cross-sectional study were three-fold: (1) to compare symptom frequency by stage, (2) to compare symptom importance by stage, and (3) to examine the relationship between frequency and importance. In doing this, our overall goal was to demonstrate the usefulness and the

types of insights gained from online symptom tracking in people with dementia and mild cognitive impairment.

Methods

Data Collection

The data come from the myGoalNav™ Dementia platform, previously called SymptomGuide™ Dementia. This was launched as a website in 2007 for people with cognitive impairment and their caregivers. Users can identify pertinent symptoms from a library and track how they change over time. In 2018, it was redesigned as an iOS and Android mobile application. Through clinician, patient, and caregiver input, the symptom library has grown to 67 symptoms, each with 2-12 (median = 9) plain-language descriptors that provide an additional level of detail into symptom manifestation.
MyGoalNav™ users first choose from the library any number of symptoms (and relevant descriptors) that are important to them and/or the person for whom they care. If they wish further personalization, users can log "Other" symptoms and descriptors which do not appear in the library. The set of initial symptoms selected by a user is called their baseline symptom profile, which they may supplement with additional demographic information such as age, gender, and living arrangements. As an optional step, users are also asked to rank their chosen symptoms from most to least important or troublesome.
MyGoalNav™ was not designed to be an inventory of every dementia-related problem an individual might experience. Rather, the library facilitates selection of those symptoms most meaningful to each participant. For this analysis, we excluded outlier profiles created by individuals who chose more than 22 symptoms (the 95th percentile).

Staging Dementia

In 2013, we developed an artificial neural network model to stage dementia, which was trained on data from 320 memory clinic patients [29]. That model was updated in 2020, using a support-vector machine supervised learning algorithm trained on 717 patients [30]. Patient age and symptoms served inputs to the model. Output was degree of impairment in one of four stages: MCI, or Mild, Moderate or Severe dementia. To cover the spectrum of age-related cognitive impairment, the algorithm was trained using data from a memory clinic, a long-term care study [31], and a dementia clinical trial [29]. Each employed either myGoalNav™ Dementia or goal attainment scaling (GAS), an individualized outcome measure by which patients and their families/caregivers set goals for treatment [32].

Statistical Analysis

User characteristics and demographics were summarized and differences between stages were tested. Categorical variables were summarized as percentages of users and tested with Pearson's χ^2 test. Continuous variables were summarized as means ± standard deviations or medians (lower and upper quartiles), and tested with the Kruskal-Wallis H test.
To evaluate objective 1 (comparing symptom frequency by disease stage), we first fit a logistic regression model with the number of profiles selecting each symptom in each stage as the dependent variable. Symptom name, stage, and the interaction between the two were included as independent variables. The estimates from this model were transformed to stage-specific symptom frequencies with 95% confidence intervals (CIs).
We investigated frequency differences between stages in two ways. First, we computed Pearson's correlation coefficient r on frequencies between each pair of stages, where a higher r coefficient indicates greater similarity in symptom selection. Second, we quantified the degree to which a symptom is associated with increasing or decreasing disease severity. This was accomplished by modifying our logistic regression model so that stage is treated as a monotonic predictor variable

[33], rather than a categorical variable without ordering. The estimates from this model can be interpreted as the average difference in frequency (on the log-odds scale) between adjacent stages (see the Supplementary Methods in the Multimedia Appendix for more details).

For objective 2 (comparing symptom importance by stage), we began by defining *relative* symptom importance within a symptom profile as the weighted rank, or *potency* $w_{ij}=r_{ij}/n_j$, where n_j is the number of symptoms in profile j, and r_{ij} is the rank (out of n_j) given to symptom i. Higher potency w_{ij} corresponds to higher relative importance of symptom i to the user of profile j.

Next, to model this proportion while accounting for the wide range in number of tracked symptoms among myGoalNav™ users, we used logistic regression with w_{ij} as the dependent variable, n_j as case weights, and categorical independent variables of symptom name, stage and their interaction. As with the frequency analysis, we estimated pairwise similarity in stages by computing Pearson's correlation coefficients between potency estimates.

To investigate the relationship between symptom frequency and potency (objective 3), we visualized the relationship by plotting frequency against potency estimates. We quantified the strength of these relationships using Pearson's correlation.

No missing data were imputed for this study. All analyses were performed in R version 4.0.2 [34] using tidyverse packages [35].

Ethics

Clinic data were collected after having obtained written, informed consent. Participants completed a form that allowed their anonymized data to be analyzed for research purposes. Data collection was approved by the Research Ethics Committee at Nova Scotia Health Authority. MyGoalNav™ users consented to terms of use, which included allowing their data to be aggregated and used for research purposes. Users were assured that research findings would be presented in a manner that would not disclose personally identifying information.

Results

The Sample

To date, a total of 12347 users have signed up for myGoalNav™. 34% (4213/12347) of these users created a symptom profile. After removing the profiles tracking more than 22 symptoms (the 95th percentile), our final sample size was 3909 profiles, with creation dates between 2007 and 2019.

The great majority, 96% (3753/3909), of these symptom profiles were made on the web platform, with 4% (156/3909), from the later mobile application. Most profiles were completed by caregivers, 97% (3792/ 3909), and the remaining by participants (people with cognitive impairment) on their own behalf, 3% (117/ 3909). The staging algorithm gave the following distribution of severity across the 3909 profiles: 917 (23%) MCI, 1596 (41%) Mild, 514 (13%) Moderate, and 882 (23%) Severe dementia.

Participant characteristics and demographics are summarized by stage in Table 1. With increasing severity from MCI to Moderate dementia, participants tended to be older, less well-educated, more likely to identify as women, and less likely to live on their own. A minority of caregivers (1361 of 3792 users) also provided information about themselves. Most caregivers were women (64% of 802 caregivers), between 46-55 years old (32% of 583), and spouses/partners of the participant (30% of 524).

Table 1: Baseline characteristics of the myGoalNav™ participants, stratified by stage.

Characteristic[a]	Total N=3909	MCI N=917	Mild N=1596	Moderate N=514	Severe N=882	Test statistic[b]
Age (years), mean ± SD (N=2473)						H(3)=192.8 *P*<.001
	75.4 ± 12.4	70.5 ± 13.2	74.5 ± 12.1	80.9 ± 8.7	78.2 ± 11.9	

Characteristic[a]		Total N=3909	MCI N=917	Mild N=1596	Moderate N=514	Severe N=882	Test statistic[b]
Gender, n (%) (N=2587)							$\chi^2(3)=8.00$ $P=.046$
	Man	976 (37.7)	228 (40.9)	431 (39.0)	127 (33.7)	190 (34.7)	
	Woman	1611 (62.3)	329 (59.1)	674 (61.0)	250 (66.3)	358 (65.3)	
Number of symptoms, median (quartiles) (N=3909)							H(3)=669.7 $P<.001$
		4 (2-7)	2 (1-4)	5 (3-8)	7 (4-11)	4 (2-7)	
Education, n (%) (N=1337)							$\chi^2(9)=12.7$ $P=.175$
	Secondary School or Less	625 (46.7)	117 (40.8)	283 (45.7)	99 (52.1)	126 (52.3)	
	Trade School	71 (5.3)	14 (4.9)	32 (5.2)	9 (4.7)	16 (6.6)	
	Undergraduate	439 (32.8)	108 (37.6)	211 (34.1)	53 (27.9)	67 (27.8)	
	Graduate	202 (15.1)	48 (16.7)	93 (15.0)	29 (15.3)	32 (13.3)	
Living arrangement, n (%) (N=2013)							$\chi^2(12)=126.5$ $P<.001$
	Alone	290 (14.4)	67 (14.9)	143 (15.8)	35 (12.2)	45 (12.1)	
	Assisted Living	315 (15.6)	39 (8.7)	102 (11.3)	71 (24.8)	103 (27.8)	
	With Caregiver	335 (16.6)	59 (13.1)	153 (16.9)	54 (18.9)	69 (18.6)	
	With Family/Friend	1038 (51.6)	283 (62.9)	494 (54.5)	120 (42.0)	141 (38.0)	
	With Paid Companion	35 (1.7)	2 (0.4)	14 (1.5)	6 (2.1)	13 (3.5)	

[a]N is the number of users with non-missing values.
[b]Comparisons between stages: Pearson's χ^2 test and Kruskal Wallis H test. Numbers in parentheses are degrees of freedom (df).

Symptom Frequency

Figure 1 depicts the 10 most frequent symptoms in each stage. In MCI, Mild, and Moderate profiles, the most common symptom was Memory of Recent Events: 33.4%, 36.7%, and 37.0% of profiles respectively. This early hallmark of dementia was tracked much less often at the Severe stage, where 9.8% of profiles showed it being tracked. Other symptoms were tracked more often with greater severity. For example, Sleep Disturbances tracking increased from 6.7% in MCI profiles, to 15.5% in Mild, to 25.5% in Moderate, and was the most frequently tracked symptom in Severe profiles (24.4%).

In addition to Memory of Recent Events, MCI profiles were best characterized by Repetitive Questions/Stories; no other symptom had a tracking frequency higher than 20%. Those with Mild and Moderate profiles showed more variety in symptom selection, with 6 and 8 symptoms above 20% frequency, while those with Severe profiles were slightly more uniform with 4 symptoms above that mark.

How frequencies varied is also illustrated by changes in the correlations between pairs of symptoms drawn from adjacent stages (Figure 2). By this metric, the most similar stages (highest correlation coefficient) were MCI and Mild. Indeed, those with MCI and Mild profiles shared 8 of their 10 most frequent symptoms. To a lesser degree, individuals with Moderate profiles had similar symptom frequencies to MCI and Mild profiles. There were 4 symptoms shared among the top 10 of these three stages: Attention/Concentration, Irritability/Frustration, Memory of Recent Events, and Repetitive Questions/Stories. By a large margin, Severe profiles had the most distinct set of frequent symptoms, although the correlation increased with increasing severity: r = 0.14, 0.25, and 0.48 in MCI, Mild, and Moderate profiles, respectively. The most frequent symptoms in Severe profiles were characteristic of loss of independent function (Incontinence, Mobility, Eating, Personal Care/Hygiene), and also more extreme behavioural problems (Aggression, Low Mood, Delusions & Paranoia).

Model-estimated monotonicity of frequency with dementia severity is shown for each symptom in Figure 3. More symptoms exhibited positive monotonicity (36 symptoms with lower 95% CI above 0) than negative (7 symptoms with upper 95% CI below 0). The 6 with the highest positive and negative monotonicity are visualized on the left in Figure 3.

Overall frequency and frequency by stage for each symptom is summarized in Table S1 of the

Multimedia Appendix.

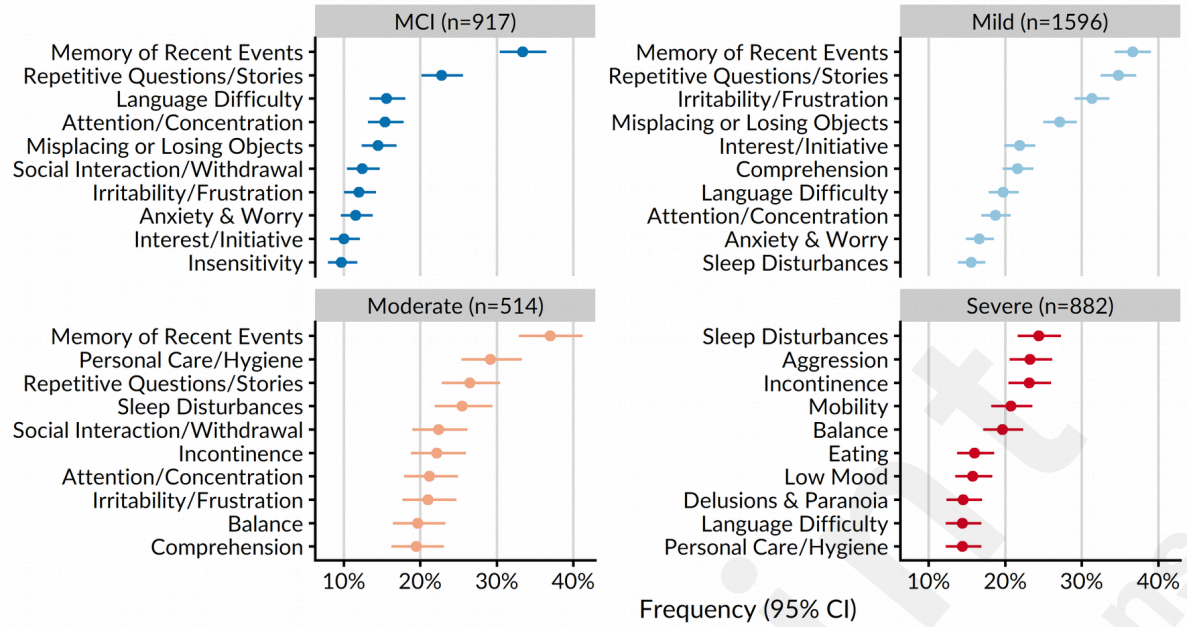


Figure 1: The 10 most frequent symptoms tracked by baseline myGoalNav™ profiles, stratified by stage. Data are presented as point estimates and 95% CIs from the logistic regression model.

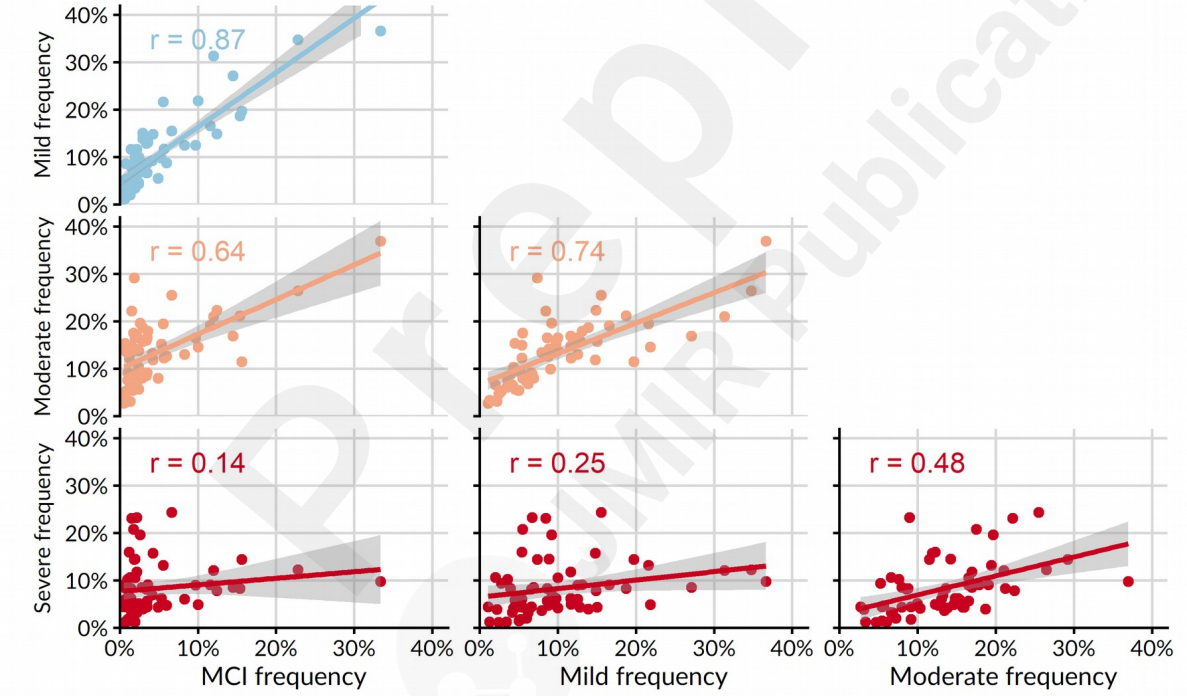


Figure 2: Pairwise relationships of symptom frequency between stages. Pearson's correlation coefficients and lines of best fit (with 95% CIs) are displayed for each pair.

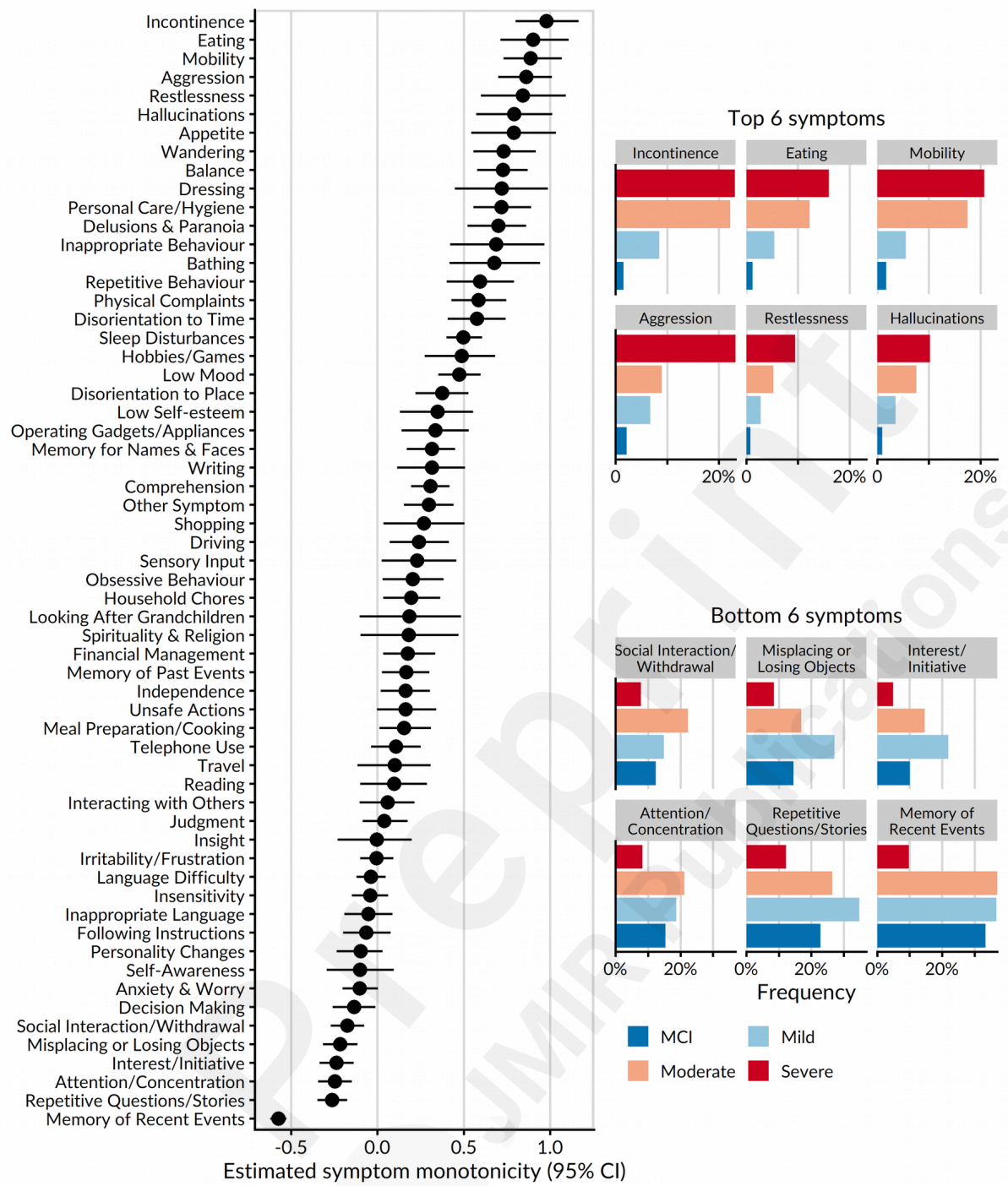


Figure 3: (Left) Estimated symptom monotonicity, where higher values indicate increasing frequency with ordered stage. Data are presented as point estimates and 95% CIs from the logistic regression model with stage as a monotonic predictor. (Right) Stage-specific frequencies for the 6 symptoms with the highest positive monotonicity, and the 6 symptoms with the highest negative monotonicity.

Symptom Potency

Since ranking of symptoms is not compulsory on myGoalNav™, the potency analysis involved 2874 symptom profiles (22% MCI, 42% Mild, 14% Moderate, and 22% Severe). The model estimates of the 10 most potent symptoms by stage are shown in Figure 4, and the rest can be found in Table S2 of the Multimedia Appendix. Two symptoms stood out as important regardless of stage: Travel and Looking After Grandchildren, which were among the top 3 most potent in each stage.

Figure 5 shows the pairwise relationship of symptom potency between stages. The most similar pairs

of stages were Moderate profiles with Mild and Severe profiles. The greatest differences in potency were MCI profiles with Moderate and with Severe profiles.

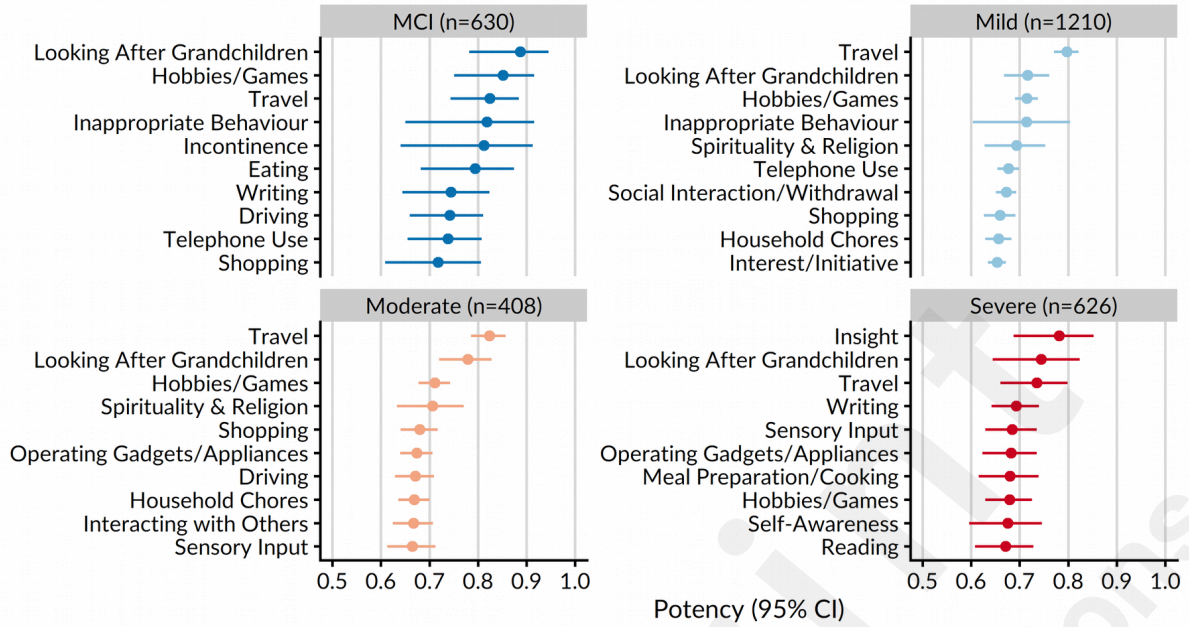


Figure 4: The 10 most potent symptoms tracked by baseline myGoalNav™ profiles, stratified by stage. Data are presented as point estimates and 95% CIs from the logistic regression model.

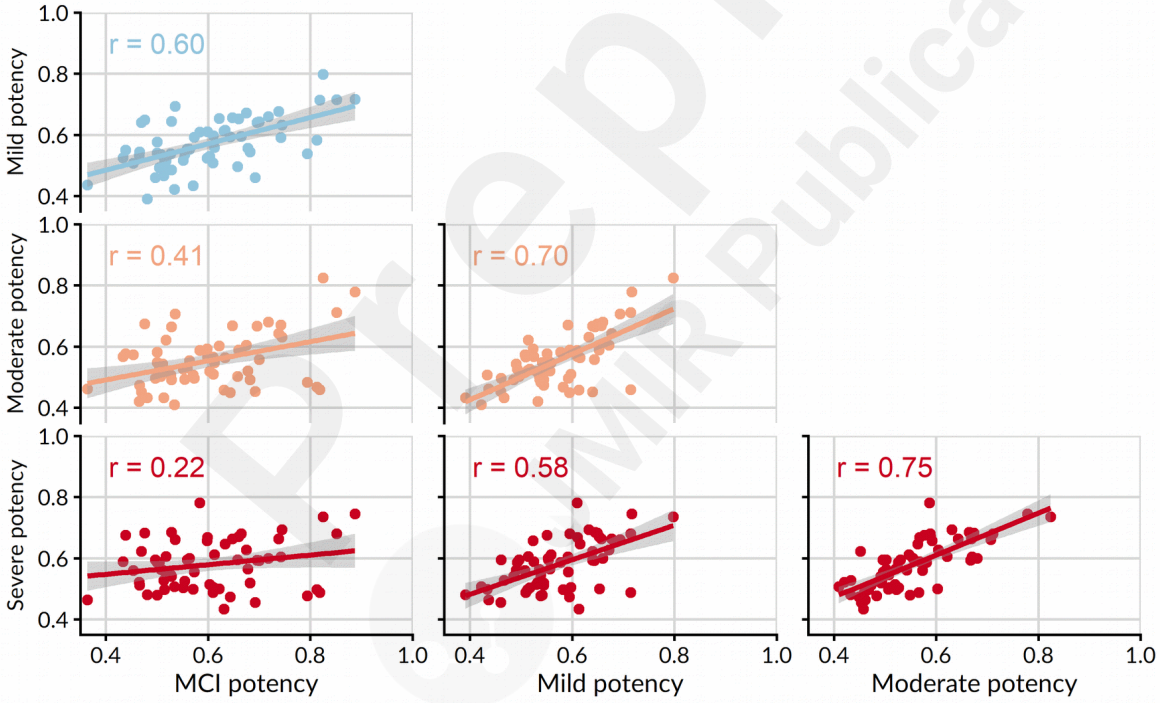


Figure 5: Pairwise relationships of symptom potency between stages. Pearson's correlation coefficients and lines of best fit (with 95% CIs) are displayed for each pair.

Frequency and Potency

We discovered a clear discrepancy between which symptoms were most frequent (Figure 1) and those which were most potent (Figure 3). Only Interest/Initiative was both highly frequent (22%) and potent (potency [95% CI] = 0.65 [0.63-0.67]) among Mild symptom profiles. Symptom frequency was negatively correlated with potency regardless of severity (Figure 6). The degree of association varied by stage from weakly correlated in MCI profiles (r = -0.18) to moderately correlated in

Severe profiles (r = -0.59). The patterns (or trajectories) of potency and frequency are visualized for a select few symptoms in Figure S1 of the Multimedia Appendix.

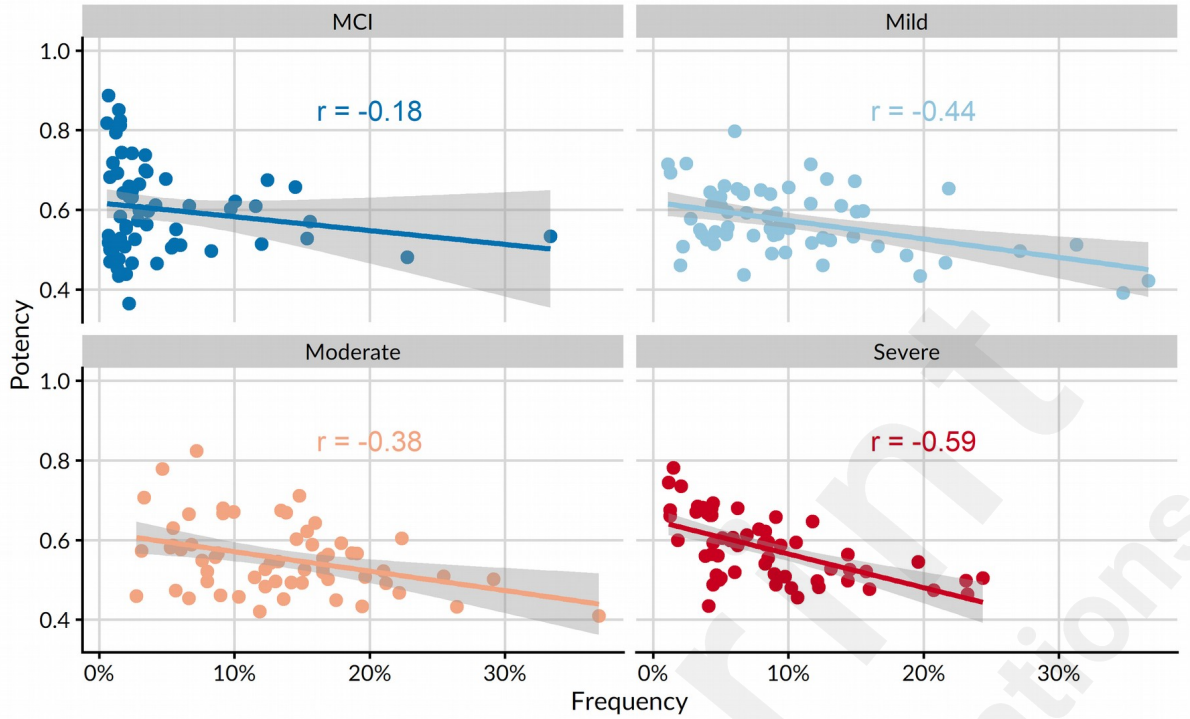


Figure 6: The relationship between symptom frequency and potency, stratified by stage. Pearson's correlation coefficients and lines of best fit (with 95% CIs) are displayed for each stage.

Discussion

This study employed a machine learning algorithm, trained with clinician-staged data, to investigate how symptom tracking in online profiles differed by severity of cognitive impairment (MCI and dementia). Our key finding was the distinction between what is common and what is most important to people with cognitive impairment and their caregivers. This reinforces the importance of capturing the patient and caregiver voice when determining clinically meaningful change in MCI and dementia trials. That we were able to discover associations that were sensible and meaningful suggests that information collected online has the potential to yield useful insights into this population. As clinical treatments that focus on single-protein abnormalities understandably exclude people who do not conform to classic profiles consistent with those abnormalities, there is a need for data on real-world experience of the larger constituency of people in whom dementia reflects a variety of disease processes.

Symptom tracking frequency was similar across MCI, Mild, and Moderate dementia profiles, with pairwise correlations between frequencies all $r>0.5$. Memory of Recent Events and Repetitive Questions/Stories were notably among the top 3 symptoms for all three stages. Neither of these symptoms, however, appeared in the 10 most frequent symptoms in Severe profiles, which differed appreciably from the other stages (all $r<0.5$). With Severe impairment, the early hallmarks of dementia (such as impaired memory) are present but become secondary to more distressing symptoms. In particular, we found that increasing disease severity was most associated with loss of independent function (Incontinence, Eating, Mobility) and behavioural problems (Aggression, Restlessness, Hallucinations).

The most potent (relatively important) symptoms were generally those related to disruptions in everyday life that, though less common, had great meaning when they occurred, e.g. problems in Looking After Grandchildren, Hobbies/Games, and Travel. Declining cognition may be a concern, but the resulting changes to routine can be especially distressing to affected people and their families. Potency was most similar between stages of similar severity. For instance, the strongest relationships are between the adjacent pairs of MCI-Mild, Mild-Moderate, and Moderate-Severe, with all $r\geq0.6$.

Across stages, symptom frequency was negatively correlated with potency, and the strength of this relationship generally increased with increasing severity. We believe this pattern reflects the nature of the disease course. Early on, and especially pre-diagnosis, gradual change in cognitive function will be both apparent and alarming to the person living with the problems and to their care partner; that likely underlies why the typical symptoms are still fairly potent. As deterioration increases, so too does the heterogeneity in their manifestation. The typical clinical presentation becomes the accepted norm (i.e. still frequent but less potent), and the impact on quality of life becomes more potent.

Although there are too many symptoms to compare all to the literature, we draw attention to a few: Repetitive Questions/Stories, Sleep Disturbance, and Interest/Initiative. The stage-specific frequencies and potencies for these symptoms are visualized in Figure S1 of the Multimedia Appendix.

We have explored the symptom of verbal repetition (here Repetitive Questions/Stories) in the ACADIE trial (open-label trial of donepezil in mild-moderate AD)[36], the VISTA trial (randomized controlled trial of galantamine in mild-moderate AD)[37], and myGoalNav™ Dementia users, staged with our earlier staging algorithm [26]. In ACADIE and VISTA, where goal attainment scaling was the primary outcome, reduction of verbal repetition was identified as a goal of treatment in 46% and 44% of patients, respectively. This symptom notably improved much more often in patients treated with galantamine than with a placebo. Our data were consistent with these secondary analyses, and with the earlier version of the staging algorithm: verbal repetition was commonly tracked (26% overall), especially in the Mild stage (35%). Hwang *et al.* also found verbal repetition to be an early sign of dementia that was troublesome to caregivers [38]. When patients are caregivers are allowed a

voice, we see that verbal repetition is important, common, and responsive, even though it typically goes unmeasured by standard tests.

We found the increasing frequency of Sleep Disturbances with severity to be compelling, especially as it was the most commonly tracked symptom in Severe profiles. Likewise, Moe *et al.* found sleep disturbances to increase with disease severity in a sample of 78 AD patients [39]. Sleep disturbances are also important at earlier stages; the prevalence in MCI patients was estimated to be 14-59% in a review of 15 studies [40]. The frequency here was 7% in myGoalNav™ MCI profiles, which is unsurprisingly lower than prevalence estimates, but still ranked as the 12th most frequent MCI symptom of 60. Growing evidence suggests that sleep disturbances are a risk factor for AD [41,42], which underlines the importance of further study at pre-dementia stages.

The symptom of Interest/Initiative describes a patient losing interest towards everyday life, and who has become disengaged from others and the world around them. It is common and distressing for caregivers [43], and a potential risk factor for progression from MCI to dementia [44]. In the VISTA trial, decreased initiation was a treatment goal for 71 of the 84 participants with mild-moderate AD (out of 130 total) who were described as having the symptom [45]. Unsurprisingly, it emerged as a noteworthy symptom in our analyses, particularly in Mild profiles where it was among both the 10 most frequent and most potent symptoms. This symptom may also be important in its sensitivity to change. In a survey of caregiver and patient judgment on changes in symptoms, apathy was the neuropsychiatric symptom that improved the most in MCI and AD patients treated with the nutritional intervention Fortasyn Connect [46].

With no approved treatment for individuals with prodromal AD, some promise is seen in non-pharmacological interventions, especially those that combine multiple lifestyle modifications like diet and exercise [47,48]. The FINGER study showed that a multimodal intervention combining diet, exercise, cognitive training, and vascular risk monitoring might improve or maintain cognitive functioning among older individuals who are at risk of dementia [49]. Nutritional interventions are also being developed to tackle dietary deficiencies associated with AD pathology. A medical food (Fortasyn Connect) has been shown to improve memory in randomized controlled trials of mild [50,51], but not mild-to-moderate [52], AD patients over 3 and 6 months of treatment. These trials were followed by the 24-month LipiDiDiet randomized controlled trial for individuals with prodromal AD [53]. There was no significant treatment effect on the neuropsychological test battery primary endpoint, but there was evidence of cognitive and functional benefit, as assessed by the secondary CDR-SB endpoint, and this effect increased with better baseline cognition. In addition, results of the LipiDiDiet 36-month extension trial showed significant treatment effects on multiple measures of cognition, function, and disease progression [54]. Taken altogether, these studies highlight the potential for early intervention in dementia, notably with lifestyle modification, especially dietary. With this comes a need for adequately sensitive outcomes for detecting meaningful effects at early stages, for which individualized symptom tracking may be a solution [12].

Conclusions

Our results emphasize the importance of patient-centricity in evaluating interventions in MCI and dementia [55–57]. A personalized outcome of, say, a grandparent being able to travel and look after their grandchild independently, will be far more meaningful to the patient and their family compared to a 4-point change on the ADAS-Cog, which is held out as the main criterion for benefit. Asking subjects about what is most important is sensitive to change and inherently clinically meaningful [23,58,59]. This can be especially valuable in the pre-dementia stages, where standard outcomes like the ADAS-Cog and Mini-Mental State Examination lack sensitivity [60,61]. Tools like myGoalNav™ Dementia, and individualized outcome measures like goal attainment scaling [62,63], are making it more feasible to capture the patient voice in real-world and clinical trial settings.

Limitations

Our data must be interpreted with caution as it consists of observer-reported tracking data, completed mostly by caregivers of people with dementia, who were not supervised in how they described or recorded the symptoms of the people for whom they were caring. Further, as the myGoalNav™ is not a checklist of symptoms, the tracking frequencies presented here are distinct from symptom *prevalence*. There are also limitations in how the staging algorithm model was developed, such as potential bias in the training data due to clinician facilitation [30].

Acknowledgements

This study was jointly sponsored by Ardea Outcomes and Nutricia. Manuscript writing, study conceptualization, study design, data collection, data analysis and interpretation were performed by Ardea Outcomes, of which KR is co-founder and president, and TD, SH, JS, AS, and SS are employees.

Data Availability

Aggregated data are presented in Table S1 (symptom frequency) and Table S2 (symptom potency) of the Multimedia Appendix. For confidentiality reasons, user-level data cannot be made publicly available. Access to de-identified data may be provided upon reasonable request.

Conflicts of Interest

KR is President, Chief Science Officer and a shareholder of Ardea Outcomes. In the last 3 years, KR has also sat on an advisory board for Roche/Genetech and has given 2 talks sponsored by Nutricia. TD, SH, JS, AS, and SS are employees of Ardea Outcomes.

Abbreviations

- AD: Alzheimer disease
- ADAS-Cog: Alzheimer Disease Assessment Scale-Cognitive subscale
- MCI: mild cognitive impairment

References

1. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR, Kawas CH, Klunk WE, Koroshetz WJ, Manly JJ, Mayeux R, Mohs RC, Morris JC, Rossor MN, Scheltens P, Carrillo MC, Thies B, Weintraub S, Phelps CH. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's & Dementia 2011 May;7(3):263–269. PMID:21514250

2. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984 Jul;34(7):939–44. PMID:6610841

3. Jack CR, Bennett DA, Blennow K, Carrillo MC, Dunn B, Haeberlein SB, Holtzman DM, Jagust W, Jessen F, Karlawish J, Liu E, Molinuevo JL, Montine T, Phelps C, Rankin KP, Rowe CC, Scheltens P, Siemers E, Snyder HM, Sperling R, Elliott C, Masliah E, Ryan L, Silverberg N. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. Alzheimer's & Dementia 2018 Apr;14(4):535–562. PMID:29653606

4. Boyle PA, Yu L, Leurgans SE, Wilson RS, Brookmeyer R, Schneider JA, Bennett DA. Attributable risk of Alzheimer's dementia attributed to age-related neuropathologies. Annals of Neurology 2019

Jan;85(1):114–124. PMID:30421454
5. Kapasi A, DeCarli C, Schneider JA. Impact of multiple pathologies on the threshold for clinically overt dementia. Acta Neuropathologica 2017 Aug;134(2):171–186. PMID:28488154
6. Davis DHJ, Muniz Terrera G, Keage H, Rahkonen T, Oinas M, Matthews FE, Cunningham C, Polvikoski T, Sulkava R, MacLullich AMJ, Brayne C. Delirium is a strong risk factor for dementia in the oldest-old: a population-based cohort study. Brain 2012 Sep;135(9):2809–2816. PMID:22879644
7. James BD, Wilson RS, Capuano AW, Boyle PA, Shah RC, Lamar M, Ely EW, Bennett DA, Schneider JA. Hospitalization, Alzheimer's Disease and Related Neuropathologies, and Cognitive Decline. Annals of Neurology 2019 Dec;86(6):844–852. PMID:31614018
8. Wallace LMK, Theou O, Godin J, Andrew MK, Bennett DA, Rockwood K. Investigation of frailty as a moderator of the relationship between neuropathology and dementia in Alzheimer's disease: a cross-sectional analysis of data from the Rush Memory and Aging Project. The Lancet Neurology 2019 Feb;18(2):177–184. PMID:30663607
9. Wallace LMK, Theou O, Darvesh S, Bennett DA, Buchman AS, Andrew MK, Kirkland SA, Fisk JD, Rockwood K. Neuropathologic burden and the degree of frailty in relation to global cognition and dementia. Neurology 2020 Dec;95(24):e3269–e3279. PMID:32989103
10. Fratiglioni L, Marseglia A, Dekhtyar S. Ageing without dementia: can stimulating psychosocial and lifestyle experiences make a difference? The Lancet Neurology 2020 Jun;19(6):533–543. PMID:32470425
11. Rockwood K, Fay S, Gorman M. The ADAS-cog and clinically meaningful change in the VISTA clinical trial of galantamine for Alzheimer's disease. International Journal of Geriatric Psychiatry 2010;25(2):191–201. PMID:19548273
12. Rockwood K, Howlett SE, Hoffman D, Schindler R, Mitnitski A. Clinical meaningfulness of Alzheimer's Disease Assessment Scale-Cognitive subscale change in relation to goal attainment in patients on cholinesterase inhibitors. Alzheimer's & dementia : the journal of the Alzheimer's Association 2017 Oct;13(10):1098–1106. PMID:28341540
13. Sabbagh MN, Hendrix S, Harrison JE. FDA position statement "Early Alzheimer's disease: Developing drugs for treatment, Guidance for Industry". Alzheimer's & Dementia: Translational Research & Clinical Interventions 2019 Jan;5(1):13–19. PMID:31650002
14. Posner H, Curiel R, Edgar C, Hendrix S, Liu E, Loewenstein DA, Morrison G, Shinobu L, Wesnes K. Outcomes assessment in clinical trials of alzheimer's disease and its precursors: Readying for short-term and long-term clinical trial needs. Innovations in Clinical Neuroscience 2017;14(1-2):22–29. PMID:28386518
15. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). Early Alzheimer's Disease: Developing Drugs for Treatment - Draft Guidance for Industry. 2018 [cited 2020 Mar 23]. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/alzheimers-disease-developing-drugs-treatment-guidance-industy
16. Hughes CP, Berg L, Danziger W, Coben LA, Martin RL. A New Clinical Scale for the Staging of Dementia. British Journal of Psychiatry 1982 Jun;140(6):566–572. PMID:7104545
17. Morris JC. The Clinical Dementia Rating (CDR): Current version and scoring rules. Neurology 1993 Nov;43(11):2412–2412. PMID:8232972
18. Brys M, Pirraglia E, Rich K, Rolstad S, Mosconi L, Switalski R, Glodzik-Sobanska L, De Santi S, Zinkowski R, Mehta P, Pratico D, Saint Louis LA, Wallin A, Blennow K, Leon MJ de. Prediction and longitudinal study of CSF biomarkers in mild cognitive impairment. Neurobiology of Aging 2009 May;30(5):682–690. PMID:17889968
19. Fox NC, Black RS, Gilman S, Rossor MN, Griffith SG, Jenkins L, Koller M. Effects of A immunization (AN1792) on MRI measures of cerebral volume in Alzheimer disease. Neurology 2005 May;64(9):1563–1572. PMID:15883317
20. Rinne JO, Brooks DJ, Rossor MN, Fox NC, Bullock R, Klunk WE, Mathis CA, Blennow K,

Barakos J, Okello AA, LIano SRM de, Liu E, Koller M, Gregg KM, Schenk D, Black R, Grundman M. 11C-PiB PET assessment of change in fibrillar amyloid-β load in patients with Alzheimer's disease treated with bapineuzumab: a phase 2, double-blind, placebo-controlled, ascending-dose study. The Lancet Neurology 2010 Apr;9(4):363–372. PMID:20189881
21. Salloway S, Sperling R, Keren R, Porsteinsson AP, Dyck CH van, Tariot PN, Gilman S, Arnold D, Abushakra S, Hernandez C, Crans G, Liang E, Quinn G, Bairu M, Pastrak A, Cedarbaum JM. A phase 2 randomized trial of ELND005, scyllo-inositol, in mild to moderate Alzheimer disease. Neurology 2011 Sep;77(13):1253–1262. PMID:21917766
22. Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, Gamst A, Holtzman DM, Jagust WJ, Petersen RC, Snyder PJ, Carrillo MC, Thies B, Phelps CH. The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's & Dementia 2011 May;7(3):270–279. PMID:21514249
23. Rockwood K. An individualized approach to tracking and treating Alzheimers disease. Clinical Pharmacology and Therapeutics 2010;88(4):446–449. PMID:20856240
24. Rockwood K, Zeng A, Leibman C, Mucha L, Mitnitski A. Validation of an informant-reported web-based data collection to assess dementia symptoms. Journal of Medical Internet Research 2012;14(2):212–221. PMID:22411293
25. Rockwood K, Mitnitski A, Richard M, Kurth M, Kesslak P, Abushakra S. Neuropsychiatric symptom clusters targeted for treatment at earlier versus later stages of dementia. International Journal of Geriatric Psychiatry 2015;30(4):357–367. PMID:24798635
26. Reeve E, Molin P, Hui A, Rockwood K. Exploration of verbal repetition in people with dementia using an online symptom-tracking tool. International Psychogeriatrics 2017;29(6):959–966. PMID:28274302
27. McGarrigle L, Howlett SE, Wong H, Stanley J, Rockwood K. Characterizing the symptom of misplacing objects in people with dementia: findings from an online tracking tool. International Psychogeriatrics 2019 Nov;31(11):1635–1641. PMID:30698122
28. Rockwood K, Sanon Aigbogun M, Stanley J, Wong H, Dunn T, Chapman CAT, Howlett SE, Miguelez M, McGarrigle L, Baker RA. The Symptoms Targeted for Monitoring in a Web-Based Tracking Tool by Caregivers of People With Dementia and Agitation: Cross-Sectional Study. Journal of Medical Internet Research 2019 Jun;21(6):e13360. PMID:31254339
29. Rockwood K, Mitnitski A, Black SE, Richard M, Defoy I. Cognitive Change in Donepezil Treated Patients with Vascular or Mixed Dementia. Canadian Journal of Neurological Sciences / Journal Canadien des Sciences Neurologiques 2013 Jul;40(4):564–571. PMID:23786741
30. Shehzad A, Rockwood K, Stanley J, Dunn T, Howlett SE. Use of Patient-Reported Symptoms from an Online Symptom Tracking Tool for Dementia Severity Staging: Development and Validation of a Machine Learning Approach. Journal of medical Internet research 2020 Nov;22(11):e20840. PMID:33174853
31. Rockwood JK, Richard M, Garden K, Hominick K, Mitnitski A, Rockwood K. Precipitating and Predisposing Events and Symptoms For Admission to Assisted Living or Nursing Home Care. Canadian Geriatrics Journal 2014 Mar;17(1):16–21. PMID:24596590
32. Kiresuk TJ, Sherman RE. Goal attainment scaling: A general method for evaluating comprehensive community mental health programs. Community Mental Health Journal 1968;4(6):443–453. PMID:24185570
33. Bürkner P-C, Charpentier E. Modelling monotonic effects of ordinal predictors in Bayesian regression models. British Journal of Mathematical and Statistical Psychology 2020 Jan;bmsp.12195. PMID:31943157
34. R Development Core Team. R: A language and environment for statistical computing. 2010. Available from: http://www.r-project.orgISBN:3-900051-07-0
35. Wickham H, Averick M, Bryan J, Chang W, McGowan L, François R, Grolemund G, Hayes A,

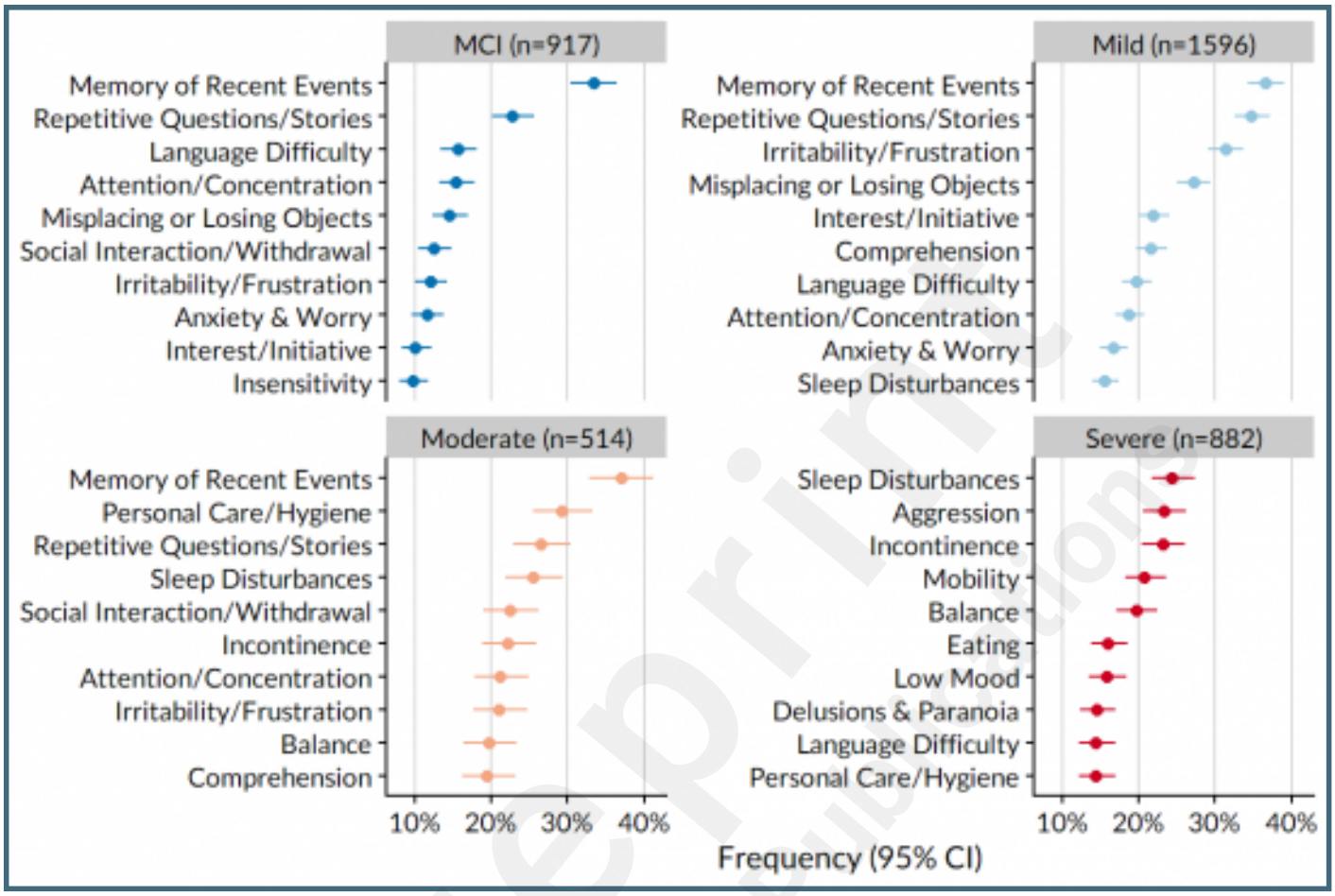
Henry L, Hester J, Kuhn M, Pedersen T, Miller E, Bache S, Müller K, Ooms J, Robinson D, Seidel D, Spinu V, Takahashi K, Vaughan D, Wilke C, Woo K, Yutani H. Welcome to the Tidyverse. Journal of Open Source Software 2019;4(43):1686. [doi: 10.21105/joss.01686]
36. Asp E, Cloutier F, Fay S, Cook C, Robertson ML, Fisk J, Dei DW, Rockwood K. Verbal repetition in patients with Alzheimer's disease who receive donepezil. International Journal of Geriatric Psychiatry 2006;21(5):426–431. PMID:16676290
37. Rockwood K, Fay S, Jarrett P, Asp E. Effect of galantamine on verbal repetition in AD: A secondary analysis of the VISTA trial. Neurology 2007;68(14):1116–1121. PMID:17404193
38. Hwang J-P, Tsai S-J, Yang C-H, Liu K-M, Lirng J-F. Repetitive Phenomena in Dementia. The International Journal of Psychiatry in Medicine 2000 Jun;30(2):165–171. PMID:11001279
39. Moe KE, Vitiello MV, Larsen LH, Prinz PN. Sleep/wake patterns in Alzheimer's disease: Relationships with cognition and function. Journal of Sleep Research 1995;4(1):15–20. PMID:10607136
40. Beaulieu-Bonneau S, Hudon C. Sleep disturbances in older adults with mild cognitive impairment. International Psychogeriatrics 2009 Aug;21(4):654–666. PMID:19426575
41. Shi L, Chen S-J, Ma M-Y, Bao Y-P, Han Y, Wang Y-M, Shi J, Vitiello MV, Lu L. Sleep disturbances increase the risk of dementia: A systematic review and meta-analysis. Sleep Medicine Reviews 2018 Aug;40:4–16. PMID:28890168
42. Minakawa E, Wada K, Nagai Y. Sleep Disturbance as a Potential Modifiable Risk Factor for Alzheimer's Disease. International Journal of Molecular Sciences 2019 Feb;20(4):803. PMID:30781802
43. Bianchetti A, Trabucchi M. Behavioural and psychological symptoms of dementia: clinical aspects. Neuroscience Research Communications 2004 Nov;35(3):173–183. [doi: 10.1002/nrc.20031]
44. Vicini Chilovi B, Conti M, Zanetti M, Mazzù I, Rozzini L, Padovani A. Differential Impact of Apathy and Depression in the Development of Dementia in Mild Cognitive Impairment Patients. Dementia and Geriatric Cognitive Disorders 2009;27(4):390–398. PMID:19339777
45. Cook C, Fay S, Rockwood K. Decreased initiation of usual activities in people with mild-to-moderate Alzheimer's disease: A descriptive analysis from the VISTA clinical trial. International Psychogeriatrics 2008;20(5):952–963. PMID:18405399
46. Bianchetti A, Perotta D, Cravello L, Ranieri P, Trabucchi M. Effectiveness of a specific nutritional supplement on cognitive, behavioral and functional symptoms in mild cognitive impairment and Alzheimer's dementia: Caregivers judgments. results of an observational survey. Journal of Gerontology and Geriatrics 2018;66(2):68–74.
47. Kivipelto M, Mangialasche F, Ngandu T. Lifestyle interventions to prevent cognitive impairment, dementia and Alzheimer disease. Nature Reviews Neurology 2018 Nov;14(11):653–666. PMID:30291317
48. Livingston G, Sommerlad A, Orgeta V, Costafreda SG, Huntley J, Ames D, Ballard C, Banerjee S, Burns A, Cohen-Mansfield J, Cooper C, Fox N, Gitlin LN, Howard R, Kales HC, Larson EB, Ritchie K, Rockwood K, Sampson EL, Samus Q, Schneider LS, Selbæk G, Teri L, Mukadam N. Dementia prevention, intervention, and care. The Lancet 2017;390. PMID:28735855
49. Ngandu T, Lehtisalo J, Solomon A, Levälahti E, Ahtiluoto S, Antikainen R, Bäckman L, Hänninen T, Jula A, Laatikainen T, Lindström J, Mangialasche F, Paajanen T, Pajala S, Peltonen M, Rauramaa R, Stigsdotter-Neely A, Strandberg T, Tuomilehto J, Soininen H, Kivipelto M. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. The Lancet 2015 Jun;385(9984):2255–2263. PMID:25771249
50. Scheltens P, Kamphuis PJGH, Verhey FRJ, Olde Rikkert MGM, Wurtman RJ, Wilkinson D, Twisk JWR, Kurz A. Efficacy of a medical food in mild Alzheimer's disease: A randomized, controlled trial. Alzheimer's and Dementia 2010;6(1). PMID:20129316

51. Scheltens P, Twisk JWR, Blesa R, Scarpini E, Von Arnim CAF, Bongers A, Harrison J, Swinkels SHN, Stam CJ, De Waal H, Wurtman RJ, Wieggers RL, Vellas B, Kamphuis PJGH. Efficacy of souvenaid in mild alzheimer's disease: Results from a randomized, controlled trial. Journal of Alzheimer's Disease 2012;31(1):225–236. PMID:22766770
52. Shah RC, Kamphuis PJ, Leurgans S, Swinkels SH, Sadowsky CH, Bongers A, Rappaport SA, Quinn JF, Wieggers RL, Scheltens P, Bennett DA. The S-Connect study: results from a randomized, controlled trial of Souvenaid in mild-to-moderate Alzheimer's disease. Alzheimer's Research & Therapy 2013;5(6):59. PMID:24280255
53. Soininen H, Solomon A, Visser PJ, Hendrix SB, Blennow K, Kivipelto M, Hartmann T, Hallikainen I, Hallikainen M, Helisalmi S, Lappalainen T, Liu Y, Paajanen T, Wahlund LO, Freund-Levi Y, Andreasen N, Hagman G, Lindblom S, Fassbender K, Riemenschneider M, Grimm MO, Klees-Rollmann A, Luley M, Lyros E, Schomburg R, Kennel J, Ramelli D, Frölich L, Hausner L, Laske C, Leyhe T, Mychajliw C, Koehler N, Schiekofer S, Klünemann H, Schröder J, Lütjohann D, Scheltens P, Rossum I van, Scheltens N, Bertens D, Kate M ten, Barkhof F, Henselmans JM, Roks G, Hees AM van, Ellison N. 24-month intervention with a specific multinutrient in people with prodromal Alzheimer's disease (LipiDiDiet): a randomised, double-blind, controlled trial. The Lancet Neurology 2017;16(12):965–975. PMID:29097166
54. Soininen H, Solomon A, Visser PJ, Hendrix SB, Blennow K, Kivipelto M, Hartmann T. 36-month LipiDiDiet multinutrient clinical trial in prodromal Alzheimer's disease. Alzheimer's & Dementia 2021 Jan;17(1):29–40. PMID:32920957
55. Reuben DB, Tinetti ME. Goal-Oriented Patient Care — An Alternative Health Outcomes Paradigm. New England Journal of Medicine 2012 Mar;366(9):777–779. PMID:20573919
56. Frank LB. Commentary on "Health economics and the value of therapy in Alzheimer's disease." Report from the Alzheimer's Association Research Roundtable on patient-reported outcomes and dementia research. Alzheimer's and Dementia 2007;3(3):162–165. PMID:19595932
57. Forsythe L, Heckert A, Margolis MK, Schrandt S, Frank L. Methods and impact of engagement in research, from theory to practice and back again: early findings from the Patient-Centered Outcomes Research Institute. Quality of Life Research 2018 Jan;27(1):17–31. PMID:28500572
58. Rockwood K, MacKnight C. Assessing the Clinical Importance of Statistically Significant Improvement in Anti-Dementia Drug Trials. Neuroepidemiology 2001;20(2):51–56. PMID:11359070
59. Shabbir SH, Sanders AE. Clinical Significance in Dementia Research. American Journal of Alzheimer's Disease & Other Dementiasr 2014 Sep;29(6):492–497. PMID:24526758
60. Spering CC, Hobson V, Lucas JA, Menon CV, Hall JR, O'Bryant SE. Diagnostic Accuracy of the MMSE in Detecting Probable and Possible Alzheimer's Disease in Ethnically Diverse Highly Educated Individuals: An Analysis of the NACC Database. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences 2012 Aug;67(8):890–896. PMID:22396476
61. Raghavan N, Samtani MN, Farnum M, Yang E, Novak G, Grundman M, Narayan V, DiBernardo A. The ADAS-Cog revisited: Novel composite scales based on ADAS-Cog to improve efficiency in MCI and early AD trials. Alzheimer's & Dementia 2013 Feb;9(1S):S21–S31. PMID:23127469
62. Jennings LA, Ramirez KD, Hays RD, Wenger NS, Reuben DB. Personalized Goal Attainment in Dementia Care: Measuring What Persons with Dementia and Their Caregivers Want. Journal of the American Geriatrics Society 2018 Nov;66(11):2120–2127. PMID:30298901
63. Jennings LA, Palimaru A, Corona MG, Cagigas XE, Ramirez KD, Zhao T, Hays RD, Wenger NS, Reuben DB. Patient and caregiver goals for dementia care. Quality of Life Research 2017 Mar;26(3):685–693. PMID:28000094

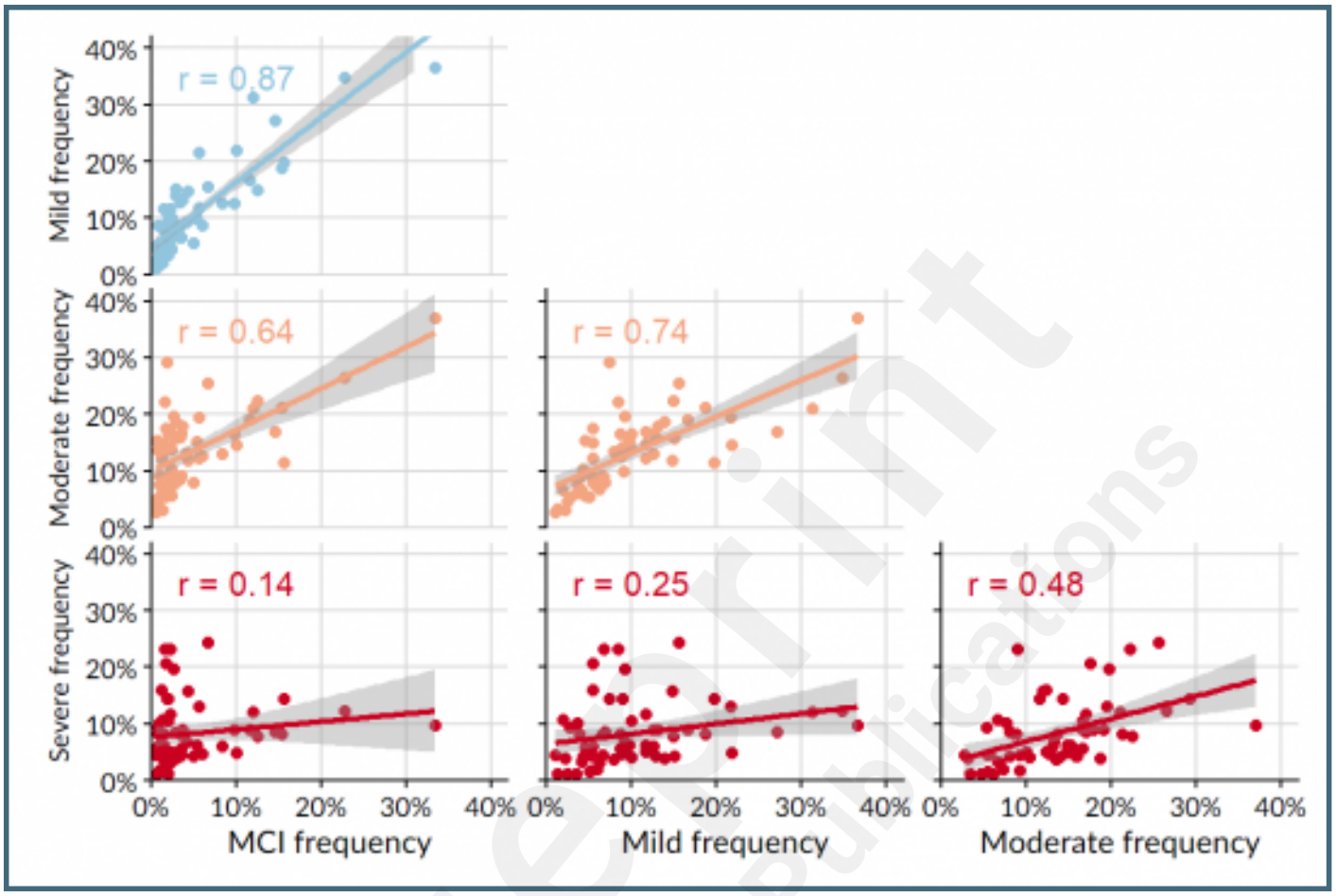
Supplementary Files

Figures

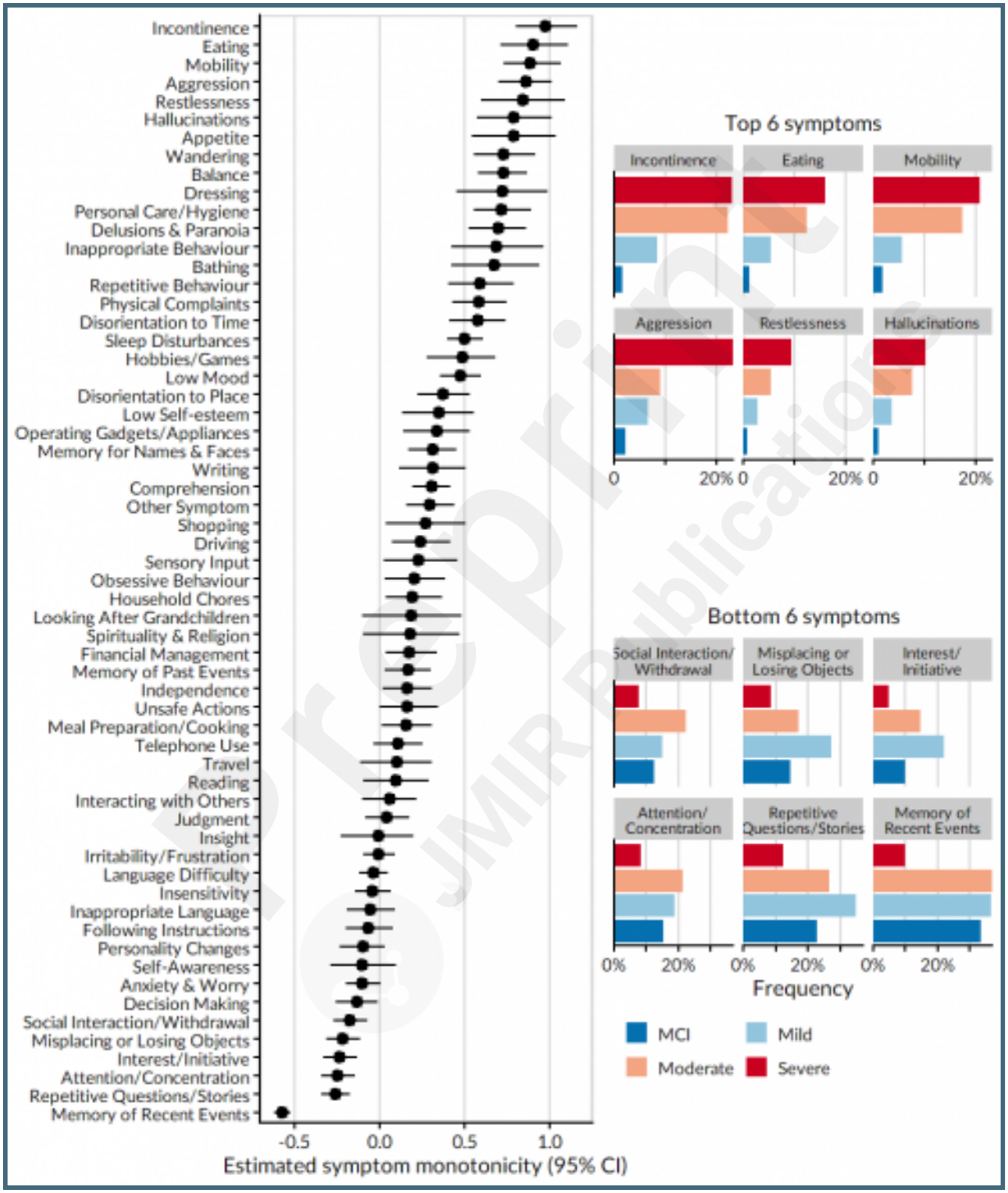
The 10 most frequent symptoms tracked by baseline myGoalNav™ profiles, stratified by stage. Data are presented as point estimates and 95% CIs from the logistic regression model.



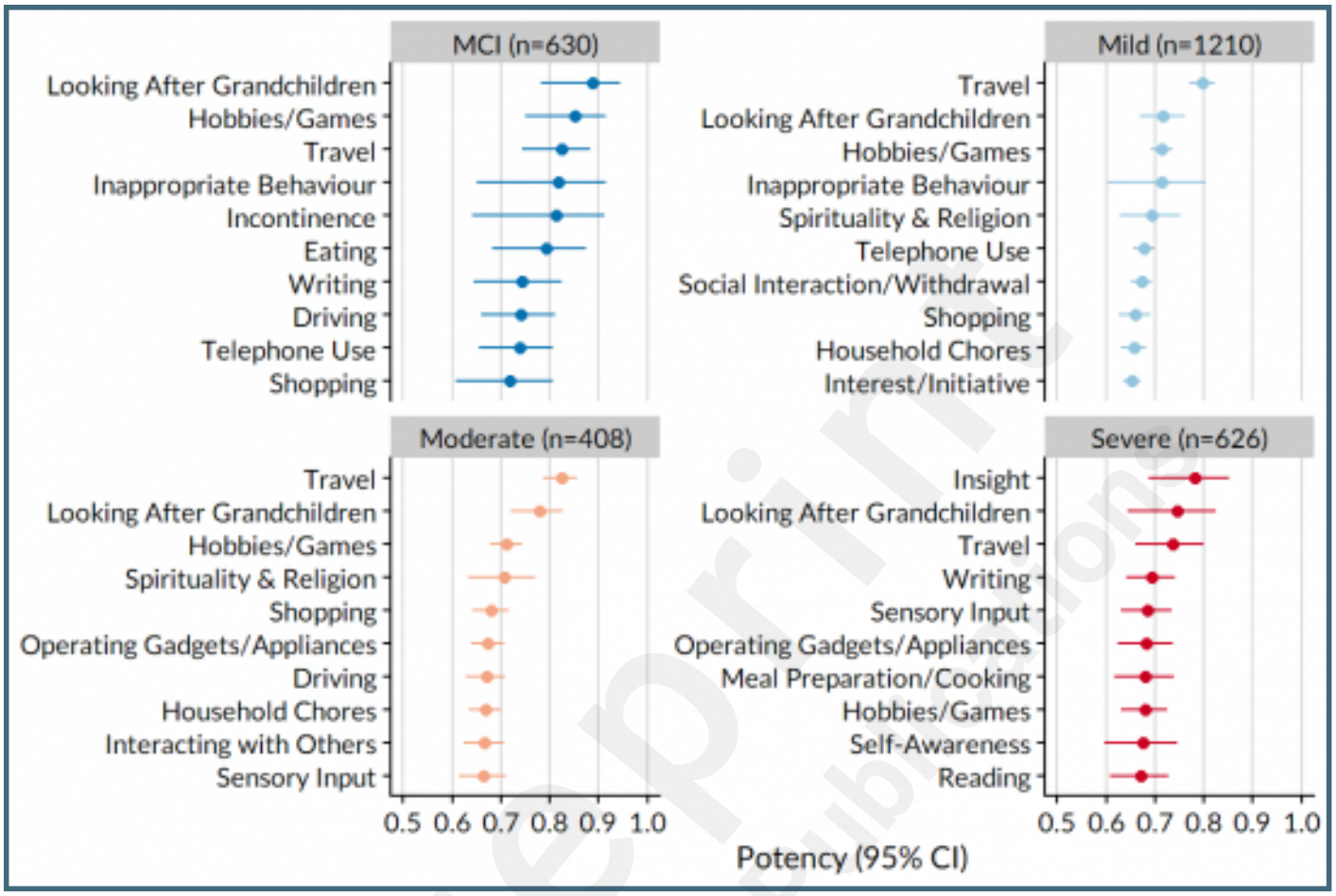
Pairwise relationships of symptom frequency between stages. Pearson's correlation coefficients and lines of best fit (with 95% CIs) are displayed for each pair.



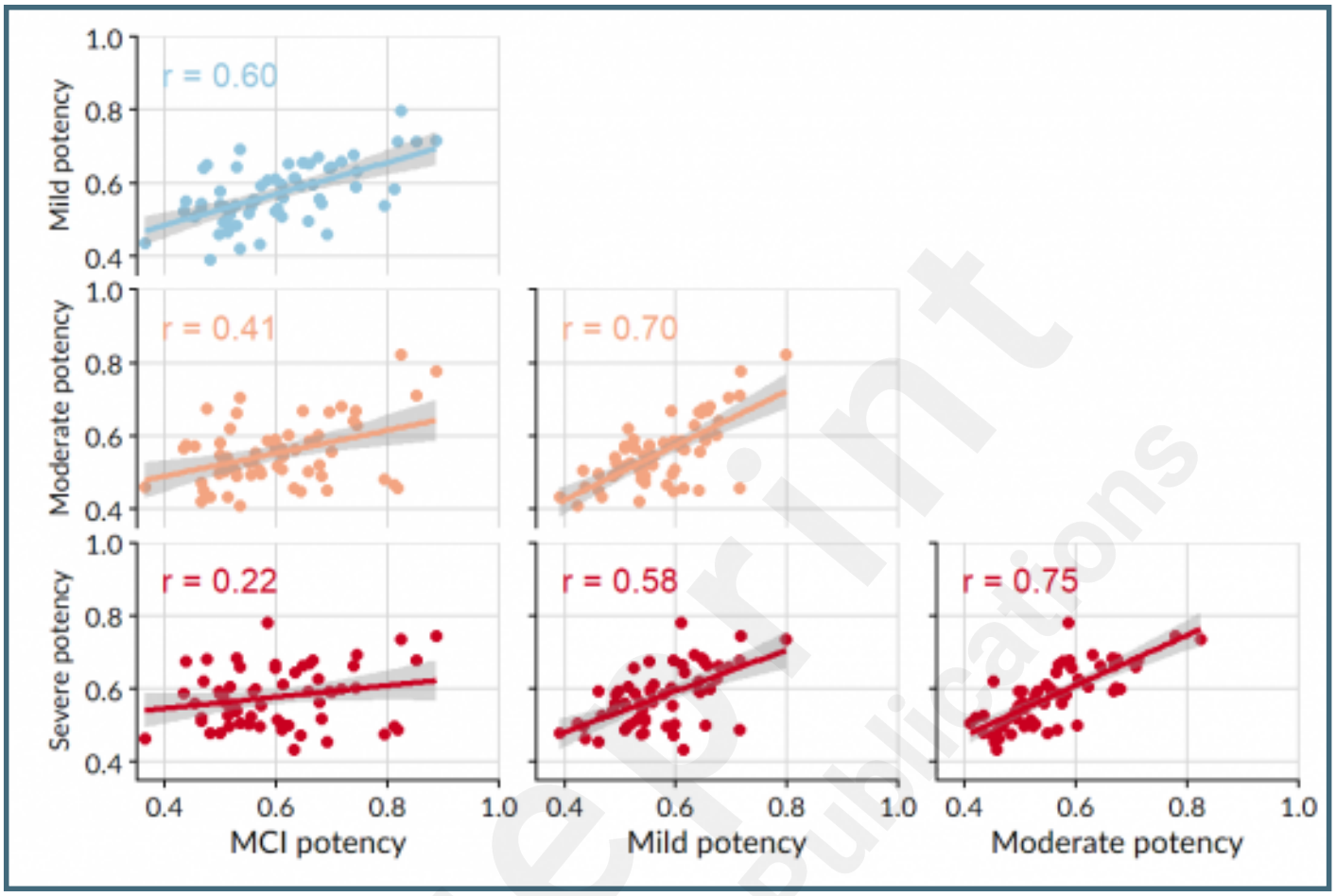
(Left) Estimated symptom monotonicity, where higher values indicate increasing frequency with ordered stage. Data are presented as point estimates and 95% CIs from the logistic regression model with stage as a monotonic predictor. (Right) Stage-specific frequencies for the 6 symptoms with the highest positive monotonicity, and the 6 symptoms with the highest negative monotonicity.



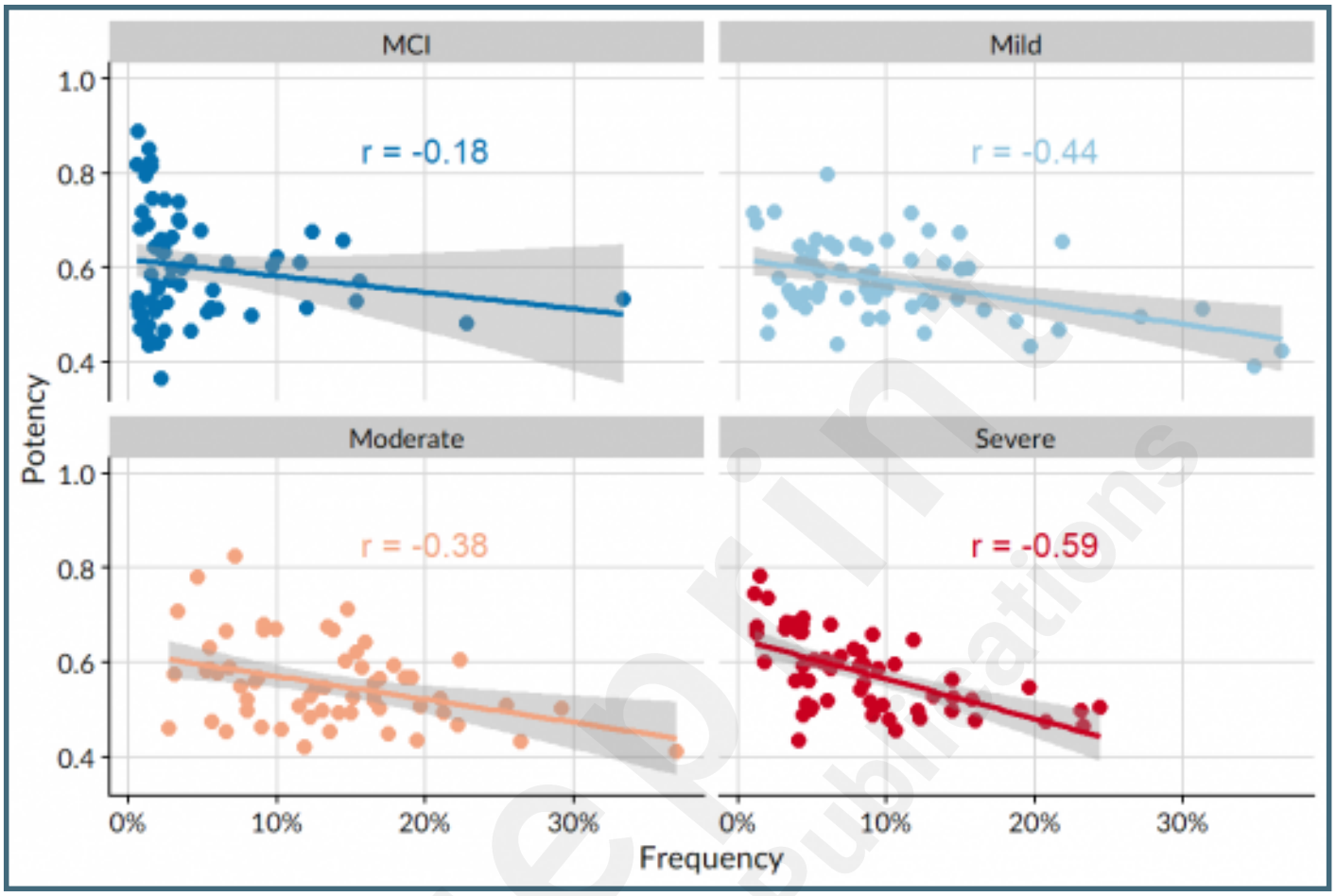
The 10 most potent symptoms tracked by baseline myGoalNav™ profiles, stratified by stage. Data are presented as point estimates and 95% CIs from the logistic regression model.



Pairwise relationships of symptom potency between stages. Pearson's correlation coefficients and lines of best fit (with 95% CIs) are displayed for each pair.



The relationship between symptom frequency and potency, stratified by stage. Pearson's correlation coefficients and lines of best fit (with 95% CIs) are displayed for each stage.



Multimedia Appendixes

Supplementary Methods, Tables and Figures.
URL: http://asset.jmir.pub/assets/25d07c41ddfbad202da21ae9fe999c78.doc