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Variability in medication taking is associated with cognitive performance in nondemented older adults

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Abstract Interventions to slow cognitive decline typically can do little to reverse decline. Thus, early detection methods are critical. However, tools like cognitive testing are time consuming and require costly expertise. Changes in activities of daily living such as medication adherence may herald the onset of cognitive decline before clinical standards. Here, we determine the relationship between medication adherence and cognitive function in preclinical older adults. We objectively assessed medication adherence in 38 older adults (mean age 86.7 ± 6.9 years). Our results demonstrate that individuals with lower cognitive function have more spread in the timing of taking their medications ($P = .014$) and increase the spread in the timing of taking their medications over time ($P = .012$). These results demonstrate that continuous monitoring of medication adherence may provide the opportunity to identify patients experiencing slow cognitive decline in the earliest stages when pharmacologic or behavioral interventions may be most effective.

Keywords: Medication adherence; Cognitive function; Older adults; Smart home; Continuous monitoring

1. Background

Medication adherence—taking the right medication and the right dose at the right time—is a critical element of successful health care, yet poor adherence is common [1]. Patients displaying poor adherence risk reduced treatment efficacy and increased probability of morbidity, hospitalization, and death [2–4].

Older adults are specifically vulnerable to poor medication adherence as advanced age is associated with multiple factors that are negatively associated with adherence [5–9]. In addition, mild cognitive impairment (MCI) has been linked to poor adherence [10–14]. The strong association between MCI and poor adherence suggests that cognitively impaired populations need additional support adhering to medication regimens. However, identifying the earliest stages of MCI may be difficult as the cognitive screening tools used in primary care settings may not be sensitive to transitions from normal cognition to MCI [15]. An alternative approach may be daily testing of cognitively challenging tasks of everyday cognition such as medication taking.

The present study aimed to determine the relationship between features derived from objective monitoring of medication adherence and cognitive function. Our hypotheses were threefold: (1) those with lower cognitive performance will forget to take their medications more frequently, (2) those with lower cognitive performance will display more variability or spread in the time they take their medication because of difficulties remembering to take their medications, and (3) those with lower cognitive performance will demonstrate an increase in the spread of medication taking over time.

2. Methods

2.1. Participants

This study was conducted as a retrospective analysis of data collected from the Ambient Independence Measures

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for Guiding Care Transitions trial (ClinicalTrials.gov identifier NCT02566239). This study was approved by the Oregon Health & Science University Institutional Review Board (#9944), and all participants signed informed consent before participating in any study activities. Briefly, older adults (age ≥75 years) living alone were recruited from local retirement communities for a technology study.

Thirty-eight participants who agreed to use the medication monitoring system for their medications and had used the device for at least 6 months were included.

2.2. Clinical assessments

Participants receive annual in-home clinical and cognitive evaluations using a standardized battery of tests consisting of physical, cognitive, and neurologic examinations [16]. Global cognitive function was assessed using a composite score including *z*-scores tabulated from two or three representative neuropsychological tests in each of five cognitive domains. Individual participant scores were *z*-normalized, summed, and averaged to obtain the global *z*-score.

2.3. Medication monitoring system and adherence metrics

At enrollment, each participant received a MedTracker [11,17], a 7-day pillbox developed to continuously track adherence by detecting the opening and closing of each compartment door. Participants were asked to use the device for at least one prescription medication.

We computed two measures of adherence: *the spread in the timing medications was taken* and *the percent of days that medications were missed*. We calculated the spread as the interquartile range of the timing of each door event. We calculated the percent of days that medications were missed as the percent of days where either a door was not opened at all or the door opening event occurred outside the normal timing of door events. We calculated both of these metrics for each 2-month window of data.

2.4. Data analysis

We ran three linear regressions to test our three hypotheses, each with cognitive *z*-score as the outcome variable and each controlled for age, gender, and education.

The first linear regression tested the hypothesis that individuals with lower cognitive function would miss their medications more frequently. We controlled for the number of medication-taking times (e.g., morning and evening) as more medication-taking times gives increased opportunity to miss medications. The average percent of days where medications were missed was included in the model as the independent variable.

The second regression tested the hypothesis that individuals with lower cognitive function would have more spread in the timing of taking their medications. The average spread across all available 2-month windows was calculated and included in the model as the independent variable of interest.

The final regression tested the hypothesis that individuals with lower cognitive function would increase the spread in the timing of taking their medications over time. We first fit a linear regression between time and the spread in the timing of taking medications for each participant. The slope term from this model represents the change in the spread of taking medications over time and was included as an independent variable in the final model. In this final model, we also controlled for the baseline spread of the timing of taking medications. All analyses were performed in Stata (Version 13; StataCorp, TX, USA).

3. Results

3.1. Descriptive statistics

Participants were older adults (mean age 86.7 years), mostly female (79%), and highly educated (mean years of school 15.9). Participants were followed for an average of 13.3 ± 6.5 months (Table 1).

3.2. Cognitive function and medication-taking habits

In the first model, we tested whether individuals with lower cognitive performance would forget to take their medications more frequently. Contrary to our hypothesis, the percent of days where medications were missed was not significant at the 0.05 level (Table 2; $P = .063$), although the relationship between frequency of medications and cognitive function was in the hypothesized direction.

The second model tested whether individuals with lower cognitive performance would have more spread in the timing of taking medications. Our results supported this hypothesis (Table 2): for each additional minute of spread, participants scored 0.004 points lower on their cognitive *z*-score ($P = .014$). To put this in perspective, with this beta coefficient the model would predict that a participant with the highest observed spread of 322 minutes (5.4 hours) would score 1.2 points lower on their cognitive *z*-score compared with a participant with the lowest observed spread of

Table 1
Baseline characteristics of the cohort ($n = 38$)

Characteristic	Mean (SD) or %	Range (min, max)
Age (y)	86.7 ± 6.9	(75, 99)
Gender (% female)	79%	—
Education (y)	15.9 ± 2.5	(12, 21)
Cumulative Illness Rating Scale	20.6 ± 2.5	(17, 28)
MMSE	29.1 ± 1.0	(26, 30)
Global cognitive *z*-score	0.20 ± 0.7	(−1.2, 1.9)
Follow-up period (mo)	13.3 ± 6.5	(6, 24)
Average percent of days medications were missed	31 ± 16	(7, 88)
Spread in the timing of taking medications (min)	82 ± 60	(12, 322)

Abbreviations: MMSE, Mini–Mental State Examination; SD, standard deviation.

Table 2
Results of the linear regressions comparing cognitive function as defined by a global cognitive z-score with medication-taking abilities

	Model 1: Cognitive function and missed medications		Model 2: Cognitive function and the spread in the timing of taking medications		Model 3: Cognitive function and the slope of the spread in the timing of taking medications	
	Coefficient (SD)	P value	Coefficient (SD)	P value	Coefficient (SD)	P value
Constant	−0.66 (2.07)	.75	−0.33 (2.15)	.87	0.17 (2.02)	.93
Age	−0.0066 (0.017)	.71	−0.014 (0.018)	.41	−0.019 (0.017)	.27
Sex (female)	0.44 (0.30)	.15	0.44 (0.31)	.15	0.59 (0.31)	.06
Years of education	0.088 (0.055)	.12	0.067 (0.057)	.21	0.10 (0.054)	.09
Frequency of MedTracker use per day	0.77 (0.37)	.05				
Percent of days where medications are missed	−0.015 (0.0095)	.06				
Spread in the timing of taking medications (min)			−0.0041 (0.0018)	.014		
Baseline spread in timing of taking medications (min)					−0.0032 (0.0018)	.04
Slope of spread in timing of taking medications (change over time; minutes per 2 mo)					−0.019 (0.0079)	.012

Abbreviation: SD, standard deviation.

11 minutes, holding all other variable constants. The R^2 for this model was 0.2303.

In our final model, we tested whether individuals with lower cognitive performance would increase the spread in the timing of taking their medications over time. Our results support this hypothesis: each minute increase in spread (measured over 2 months) is associated with a decrease in cognitive z-score of 0.019 points ($P = .012$). The R^2 for this model was 0.2809, 0.20 points higher than the R^2 for the basic model (0.08), which included only age, sex, and education. Accounting for both baseline spread and change in spread over time more than doubles the explained variance in z-scores compared with the basic model.

4. Discussion

In this study, medication-taking habits were monitored continuously using the MedTracker, a 7-day pillbox designed to track the timing of medication-taking events. We were able to track not only the percent of days where participants missed taking their medications, but also the spread in the timing of taking medications. We demonstrated that cognitive function is linked closely to the spread in the timing of taking medications and that individuals with poorer cognitive function exhibited a larger increase in this spread over time.

Our first hypothesis was that the percent of days where medications were missed would be linked with cognitive function. However, although better cognitive function was associated with better adherence, this relationship was not statistically significant. This may be because this cohort still maintained a relatively high level of cognitive function: only three participants had a CDR score of 0.5 suggesting MCI. Few studies have assessed the relationship between cognitive function and medication adherence in preclinical MCI older adults.

Our second and third models tested the relationship between the spread in the timing of medication adherence and cognitive function. These models demonstrated that individuals with higher cognitive function are more regular in their medication-taking routine and continue to be more regular over time. These results are consistent with previous studies on variability and cognitive function [16,18].

The participants included in this study were mostly Caucasian, well-educated older adults with few comorbidities. This may limit the generalizability of the results of the model. All participants took medications from the MedTracker at most twice per day, and 82% took medications only once per day. Follow-up studies should investigate the relationship between cognitive function and medication-taking behavior for individuals with more complicated medication schedules. Finally, because of our sample size and diverse medications taken in this cohort, we were not able to control for the type of medication taken. Future studies should investigate whether the type of medication or the patient's beliefs about medications impact the results reported here.

These results show great promise toward early detection of MCI using an everyday behavioral measure. Because this behavior can be measured daily rather than sporadically, the trajectory of decline can be captured at the earliest possible stages of change. In addition to medication-taking behavior, other in-home behaviors that relate to cognitive function include walking speed [18], computer use [16], and time out-of-home [19]. Fusing these behaviors into an objective behavioral signature of decline may enable the detection of MCI at the earliest possible stages. In this way, these techniques would not only assist patients and family members in proactively coping with cognitive decline, but also provide an ecologically valid set of metrics to speed the development of novel drug therapies.

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RESEARCH IN CONTEXT

1. Systematic review: The authors reviewed the literature using traditional (e.g., PubMed) sources. The relationship between medication adherence and cognitive function in individuals with dementia is well established, but few studies have investigated this relationship as a means of identifying cognitive changes in those at risk for dementia.
2. Interpretation: Detecting the prodromal phase of dementia is critical for the development of drugs and other therapies. Establishing a relationship between medication adherence and cognitive function provides the opportunity to detect the prodromal phase of cognitive decline from continuous medication monitoring data.
3. Future directions: This study demonstrated the relationship between cognitive function and medication adherence across a range of cognitive ability. To use medication adherence as part of an early detection system for cognitive decline, it will be necessary to develop a classifier that differentiates those who eventually convert to dementia from those who never do over several years.

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