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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.