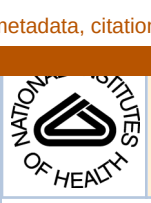

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Relations between cognitive status and medication adherence in patients treated for memory disorders

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Abstract

Medication adherence has been increasingly recognized as an important factor in elderly persons' health. Various studies have shown that medication non-adherence is associated with poor health status in this population. As part of a study of the effects of two interventions to promote medication adherence in patients treated for memory problems, information on medication adherence and cognitive status was collected at 3-month intervals. Twenty-seven participants (16 men, 11 women, age 71–92 years) were assigned to control or treatment conditions and adherence was evaluated with an electronic monitoring device. Cognitive status was evaluated at 3-month intervals beginning in April of 2003 and continuing through September of 2006. We have previously reported on the effectiveness of these interventions to promote adherence. In this paper, we examine the relations of cognitive status and adherence over time using a partial least squares path model in order to evaluate the extent to which adherence to cholinesterase medications was related to cognitive status. Adherence predicted cognitive status at later time points while cognition did not, in general, predict adherence. Results thus suggest that interventions to ensure high levels of medication adherence may be important for maintaining cognitive function in affected elderly people.

Keywords

Alzheimer; medication adherence; cognition

Introduction

Medication adherence has been increasingly recognized as an important problem in health care. While providing patients with adequate assessment and recommendations for treatment, clinicians are more and more aware that patients may not follow their recommendations.[1] Since patients with better adherence often have better health outcomes,[2–4] several authors have argued that interventions to improve medication adherence deserve serious attention.[1,5,6] The key to designing interventions to improve medication adherence is a greater understanding of the factors related to poor adherence. Previous reviews have shown that a variety of issues are related to non-adherence in the elderly, including cognitive, social and economic factors.[7,8]

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Elderly patients may thus be at especially high risk for medication non-adherence if they have memory impairments. Memory problems are often treated with cholinesterase inhibitor medications, drugs that increase levels of acetylcholine in the brain and by doing so may improve cognition and reduce the severity of its decline over time in persons with neurodegenerative disorders such as Alzheimer's disease. Adherence to a prescribed regimen of therapy may be essential to maintaining or at least reducing the rate of decline of cognitive function in affected patients. Several studies have investigated medication adherence in patients with memory impairment or Alzheimer's disease.[9–11] In spite of the importance of sustained adherence to therapy, these studies show that patients treated for Alzheimer's disease do not always take their medications regularly. Although no readily-identifiable study has investigated the effect of interventions to promote adherence in patients with Alzheimer's disease or even with memory impairments, one group has reported that providing information about medications and the importance of adherence improved medication adherence in patients with Parkinson's disease.[12] Although it is recognized that Alzheimer's and Parkinson's are pathologically and clinically distinct, patients with either disease may have significant impairments in cognition and memory. Such cognitive impairments may be serious impediments to accurate medication adherence. Although cholinesterase inhibitor medications used to treat memory problems have positive effects on cognition,[13] they have only a small effect on functional status[14,15] and have not been explicitly related to medication adherence.

In order to address this issue, the original study from which data presented here are drawn focused on the impact of two interventions on medication adherence in patients with memory problems. Participants in this study were assigned to one of three conditions: control, automated reminding, or tailored information. Participants assigned to the control condition participated in all study assessments and regular monthly visits, but did not receive any additional information about their condition, medication, or the importance of adherence. Participants in the automated reminding condition participated in regular study visits and assessments, but also received automated daily phone calls consisting of a recorded message from the investigator reminding the participant to take their medication. Participants in the tailored information condition received a 20-minute tailored information intervention at the randomization study visit that consisted of completing a questionnaire about information they wanted to receive about memory disorders and their treatment. Participants' responses to the questionnaire, their preferred language, and their level of health literacy as assessed by the Test of Functional Health Literacy in Adults[16] were read into a computer program that then created a written response that was tailored to the participant's language, level of health literacy, and requests for information. The individually-tailored information was then reviewed with the participant and given to him or her in the form of a booklet for use at home.

Participants were then followed at monthly intervals for intervals of up to two years, with evaluations of cognitive function every three months. Their adherence to prescribed cholinesterase inhibitor medication (most took donepezil once a day) was evaluated using an electronic monitoring device that recorded each time their pill bottle was opened, providing an ongoing metric of medication adherence. The effectiveness of these interventions in improving medication adherence in these patients compared to controls has already been reported in our original study.[17] In this study, participants in both intervention groups showed higher levels of adherence than those in the control groups, although results did not suggest that either intervention was superior. As noted above, the effect of adherence to cholinesterase inhibitor medications on cognition has not been explicitly evaluated. The purpose of the present study was to further examine the relation between cognitive status and adherence over time, and assessing the ways that the two variables interact over time in this population.

Materials and Methods

Participants were recruited from a university-affiliated local memory disorders clinic in Miami Beach, Florida. They had previously been evaluated by a multidisciplinary team and judged to have clinically significant memory impairments. The clinic is one of several memory disorder clinics supported by the state of Florida and draws patients from all of Miami-Dade County. Approximately 50% of new patients are Spanish-speaking, and patients come from a range of socioeconomic backgrounds. Patients in this clinic are typically older than 50 years of age, and in an earlier study we showed that they have often been prescribed multiple medications for several problems, as is typical of many older people.[18]

Participants were thus included in the study if they had been clinically judged to have a memory problem and were being treated with one of the approved cholinesterase inhibitor medications (donepezil, rivastigmine, or galantamine) or memantine, and judged to be able to give informed consent for their participation as described below. Some participants were usually accompanied to the clinic by a spouse or other caregiver, such as an adult child, while others participated independently with no assistance. No participants were excluded due to an inability to provide informed consent. This study was completed under a protocol approved by the University of Miami Office of Human Subjects Protection.

Study procedure

Participants were recruited during routine clinical visits at the memory disorders clinic or from contact information available because they had participated in other research studies at the clinic. After providing written informed consent they were randomized to one of the three conditions. Participants were only included if they were judged to be able to provide informed consent based on their understanding of the nature of the study and its requirements. This was determined by the first author during the informed consent process after consideration of the participant's understanding of key elements of informed consent, such as the fact that they would participate in a research study, that their participation was voluntary, and that declining to participate would not affect their future treatment at the clinic. In cases in which participants came to study sessions with a caregiver, the caregiver was also involved in the informed consent process.

At the initial study visit, participants completed a baseline battery of evaluation criteria that included assessment of cognitive status using the Alzheimer's Disease Assessment Scale Cognitive subtest (ADAS-Cog[19]) modified to include delayed recall of a word list, and asking participants to complete a simple maze task.[20] Scores range from 0 to 70, with higher scores indicating a worse performance. At this visit they were also shown how to use the electronic device that recorded their medication adherence. Adherence to the cholinesterase inhibitor medication was assessed using a Medication Event Monitoring System (MEMS; Aaprex, Union City, CA, USA) pill bottle as the primary measure of medication adherence. The system includes a pill bottle cap that records the date and time of each opening. Each time the patient opens the pill bottle an electric switch is triggered which records the time and date. Recordings can be read into a computer and specific software is used to calculate participant adherence. The software calculates several measurements of adherence based on when medications are taken in relation to the participant's prescribed regimen. One index only evaluates the number of pills taken over the study period (*e.g.* 30 pills taken in 30 days) and another evaluates the percentage of days on which medications were taken as prescribed. Finally, the most stringent measurement evaluates the percentage of medication doses taken at appropriate dosing intervals (+/− 25% of the interval), sometimes called *timing adherence*. Each index can range from 0 to 100%.

Once assessments had been completed, participants were instructed in the use of the MEMS pill bottle, and their current anti-cholinesterase medication was transferred to it. At the second visit one month later, participant's baseline medication adherence was recorded, they were randomized to one of the three treatment conditions and followed at monthly intervals. At monthly visits, the MEMS cap was read into the computer and participants were rated on the HAM-D. At quarterly study visits (every three months), participant's cognitive status was reassessed via readministration of the ADAS-Cog with supplementary tests. Data from the baseline and quarterly follow-up cognitive status and adherence assessments were used in the analyses presented here. Although some participants did complete the full two years of the study numbers were small. Data for 19 participants were available at the 10-month follow up, allowing adherence and cognitive status from three quarterly follow-up visits to be analyzed.

Data analyses

Relations between cognition and medication adherence over time were evaluated using a partial least squares model calculated using SmartPLS.[21] Partial least squares (PLS) is a technique in some ways analogous to structural equation modeling but which does not depend on the parametric assumptions that underlie structural equation modeling. It is, therefore, more suitable for small samples.[22] PLS allows the creation of composite variables through an iterative process in which regression weights are assigned so as to maximize the amount of variability accounted for by each composite. Relations between composite (as in path models) are then estimated in a similar iterative fashion. This technique is thus particularly well suited for analysis of data with a large number of variables but only a small number of observed entities,[23] as its sample requirements are similar to those of simple correlation analyses. In one Monte Carlo study, for example, Winn and Newsted showed that a sample size as small as 20 could provide sufficient statistical power to detect a moderate effect size.[22]

The core model used here was developed according to two composites (cognition and adherence) each measured at four time points (Figures 1 and 2). The first composite represented participant cognitive status and was made up of the ADAS-Cog total score, the Delayed Recall trial of the ADAS-Cog word list, and time to complete a maze. The second represented adherence and was made up of the three adherence indexes, percentage of all doses taken, percentage of all doses taken on the correct day, and percentage of all doses taken at the correct time, from the Medication Event Monitoring System (MEMS; Aaprex, Inc., Union City, CA, USA). In order to investigate the interaction of cognition and adherence over time, we used a cross-lagged regression model.[24] In this model, each variable predicts itself over time to capture stability; change across time is then indirectly predicted by cross-lagged coefficients. That is, the paths between each cognitive and adherence composite and between each at time plus 1 were included in the model (*i.e*. cognition at time 1 predicted cognition at time 2, then time 3, then time 4; Figure 2). The effect of cognition on adherence at each time point was also evaluated with a path (*i.e*. cognition at time 1 predicted adherence at time 1, and so on). The ability of each composite to predict the other at the next assessment was then evaluated by paths connecting each composite at the next time point (*i.e*. cognition at time 1 predicted adherence at time 2; adherence at time 1 predicted cognition at time 2) in order to evaluate whether cognition might predict adherence or whether adherence would predict cognitive status over time. Finally, direct paths were included to account for potential confounders, including the effect of age on cognition, and the effects of a caregiver and treatment group on adherence.

Given the small sample size, it was judged advisable to evaluate the model based on multiple random samples drawn from our data using bootstrapping. Bootstrapping is a

technique that estimates population parameters from small samples through a process of drawing multiple samples with replacement from a distribution.[25] In PLS path modeling, the model is then calculated for each sample, with mean values for parameters providing an estimate of population values. The statistical significance of model parameters can then be evaluated by comparing the model parameter in relation to its standard error. The resulting statistic is tested as a *t* statistic with degrees of freedom equal to the number of samples minus one;[23] the *t* statistic, in this instance, is used to evaluate the relation of the effect size implied by the model parameter in relation to its underlying distribution as indicated by its standard error. In the analyses presented here, the model was sampled and calculated 5,000 times.

Results

Descriptive data for continuous variables in the sample are presented in Table 1. Thirty participants were recruited to the study of whom 27 were randomized to one of the treatment conditions. Among participants who had given their consent, 2 withdrew their consent before randomization while one was hospitalized before randomization and was then lost to follow up. Data collection began in April of 2003 and continued through September of 2006. Of the 27 participants who were randomized, 16 were men and 11 were women. Fifteen were English and 12 were Spanish mother tongue speakers. Fifteen had a caregiver who helped them take their medication while 12 took their medications without assistance. There were 11 participants in the control, 8 in automated reminding, and 8 in the tailored information conditions. χ^2 analyses of the relations between group assignment, language, gender, and caregiver assistance were all non-significant (all P>0.20). All patients took donepezil (Aricept; Pfizer) at either 5 or 10 mg once a day for treatment of their memory impairment. Twenty-nine participants contributed data at the first evaluation, 24 at the second, 22 at the third, and 19 at the fourth. Reasons for withdrawal from the study included withdrawal of consent after consideration of the time needed to take part and one patient who was lost to follow up after being hospitalized for a condition not related to cognition or to treatment with a cholinesterase inhibitor.

Although specific diagnoses of mild cognitive impairment or Alzheimer's disease were not obtained as part of the study data collection, participants' scores on the ADAS-Cog allow characterization of cognitive status. The average total ADAS-Cog score of the sample was 22.7 (SD=11.4; range 5–59; higher scores indicate poorer performance), and the average score on the supplemental Delayed Recall subtest was 7.9 (SD=2.4; range 1–10). These scores are at levels near or even poorer than those of people diagnosed with either mild cognitive impairment or mild Alzheimer's disease in normative data published by Pyo *et al*.[26] who report that patients with a clinical diagnosis of Alzheimer's disease and clear functional impairment, as evidenced by a score of 1 on the Clinical Dementia Rating Scale, had an average ADAS-Cog score of 15.72 (SD=6.34). Current participants' scores are also consistent with a much poorer performance than normal elderly controls (mean age 72.1) whose average score was 4.98 (SD=2.25).[27]

Results of the PLS model are presented graphically in Figure 2 with path coefficients and standard errors for all paths presented in Table 2. Over time, adherence was consistently a significant predictor of cognition at the next evaluation (significant paths are indicated by bold arrows in Figure 2 and bold values in Table 2) while cognition did not predict future adherence (non-significant paths are indicated by dashed arrows in Figure 2 and presented in italics and underlined in Table 2). It should be noted that while higher levels of adherence were related to better cognitive function at the first three evaluations, higher levels of adherence were actually inversely related to cognitive status between the third and fourth evaluations. As found in earlier analyses, both of the interventions, as well as the presence

of a caregiver, resulted in improved adherence at early time points. However, this model suggests that the effects of the interventions may not have persisted over time.

Discussion

The purpose of this study was to evaluate the potentially reciprocal relations of cognition and medication adherence over time and especially to evaluate whether higher levels of adherence to cholinesterase medications were related to better cognitive status. After taking into account the presence of a caregiver and experimental interventions, adherence to anti-cholinesterase inhibitor medication predicted cognitive status three months later for the first three follow-up assessments, while cognitive status did not predict level of adherence. This finding provides evidence for the importance of medication adherence, perhaps especially to cholinesterase inhibitors, for sustained cognitive function over time in elderly subjects treated for memory problems. While these medications are known to improve cognitive function in affected individuals, the medications' effects on real-world behaviors has not been extensively demonstrated. The practical significance of this for clinicians working with patients treated for memory problems is substantial and indicates that implementing interventions to maintain high levels of adherence may be critical for these patients.

Cognition is often associated with adherence because better memory and executive function is likely to result in being better able to remember to take medications.[7,8,28,29] However, this study also suggests that adherence itself may be a factor in preserved cognitive function, at least over the short term and in subjects with memory impairment. This finding is consistent with a study by Gard[30] who argued that adherence to antihypertensive medication might itself be a factor in preserved cognitive function. In the current study, the impact of adherence on cognition might be even greater given the direct effect of cholinesterase inhibitors on cognition. The association of medication adherence with better health status and even mortality has been demonstrated in a number of studies[3,31–34] suggesting that it may be more than the result of improved treatment with specific medications.

This *healthy adherer* effect has been noted in a number of other studies that have shown that people with higher levels of medication adherence, even to placebo, may enjoy better health than those who intermittently take presumably effective treatments.[33] This effect was noted in early clinical trials of medications in their effects on risk of cardiac-related mortality[35] and has been shown to persist even after taking into account such factors as race, marital status, education, smoking, stress, and social isolation.[3,36] The presence of this effect has been noted in a number of studies in which high levels of adherence appears in itself to be an important factor in health outcomes and have been confirmed in a meta-analysis.[32] Reasons for the existence of this effect have not, therefore, been completely explained and deserve further study.[33,34]

Limitations of this study include the small sample size with potentially limited generaliz-ability and the short study period. However, although the sample size employed was small, it may be noted that few studies have been made of medication adherence over time in people treated with cholinesterase inhibitors and that even our limited data may be helpful in understanding how adherence and cognition interact over time in these patients. The time over which these patients' adherence and cognitive status was observed was a total of ten months. This is only a small portion of the time that many patients can be expected to remain on cholinesterase inhibitors as use of such medications may extend over many years. Our finding of an inverse relation between adherence and cognition at the last time point suggests that some of the relations observed may have been due to chance or to the instability of estimates, even with 5000 replications. These data, however, provide a limited window on adherence in this population and thus may also be helpful to other researchers.

Future studies should, therefore, explore the interaction of medication adherence with health outcomes including cognitive status. Whether the positive relation of adherence to cognitive status is caused by the pharmacological effects of the cholinesterase inhibitor medication or whether it is the result of some other factor that underlies the *healthy adherer* effect merits exploration. Since the *healthy adherer* effect has been observed in studies of medications that do not have direct cognitive effects, it is possible that another factor may be related to the outcomes we observed. This factor may be related to other health-related behavior not assessed in our or others' studies, or some other hitherto unexplored variable. Given the potency of the *health adherer* effect, further exploration is important.

In summary, this study suggests that medication adherence may be an important factor in sustained cognitive function over time in patients with memory disorders. These results confirmed the usefulness of interventions such as automated reminders or individually-tailored information in promoting medication adherence in these patients, as well as the importance of caregiver support in sustaining them. Results thus emphasize the importance of adherence to medication and the continuing importance of developing effective interventions to improve and sustain it.

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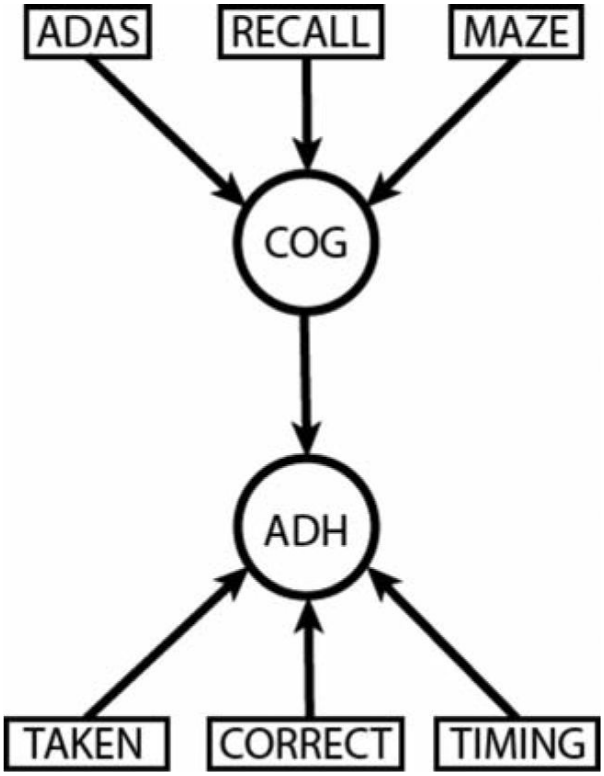

Figure 1.
Cognition and adherence composites. ADAS, Alzheimer's Disease Assessment Scale, Cognitive subtest (ADAS-Cog) total score; RECALL, Delayed Recall Trial of Word List Learning from ADAS-Cog; MAZE, time to solve maze task subtest of the ADAS-Cog; TAKEN, electronically-monitored percent of total doses taken over the interval (number of taken doses/number of days monitored times 100); CORRECT, percentage of doses taken on the correct day (number of taken doses each day/number of days monitored times 100); TIMING. Percent of total doses taken at an interval between 18 and 30 h after the previous dose (number of doses taken at the correct interval /number of intervals monitored×100).

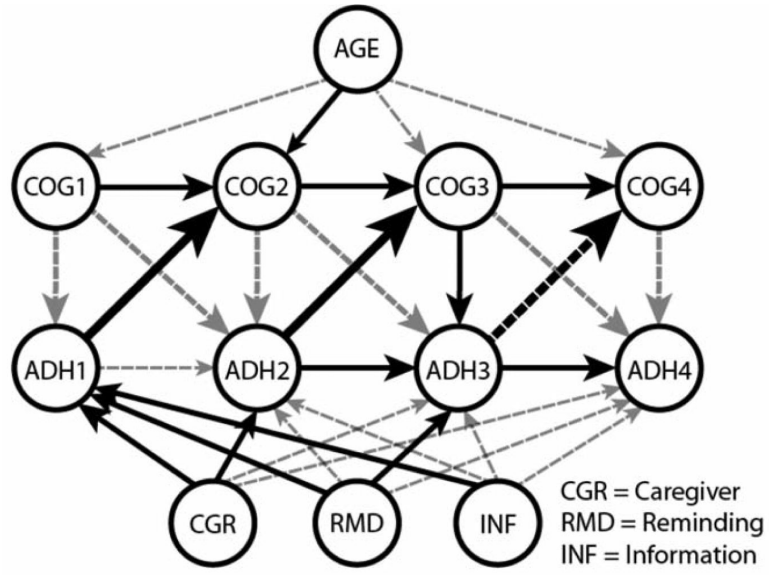

Figure 2.

Relations of composites and covariates over four measurements. ADH1-ADH4, adherence composite at each evaluation; COG1-COG4, cognition composite at each evaluation; AGE, participant age; CGR, caregiver present; RMD, dummy variable for participants in automated reminding condition; INF, dummy variable for participants in tailored information condition. Solid arrows represent statistically significant paths. Gray dashed arrows represent paths tested but not statistically significant. Heavy dashed arrow (ADH3 to COG4) indicates a significant inverse relation.

Table 1

Descriptive statistics for continuous variables at Visit 1.

	N	Min.	Max.	Mean	SD
Age	30	71	92	79.93	5.34
ADAS COG total*	29	5.00	59.00	22.72	11.44
Delayed Word Recall°	29	1	10	7.93	2.434
Maze time (seconds)#	27	25	240	125.78	92.16
% Doses taken§	30	32	100	99.10	24.26
% Days correctly taken^	30	0	100	81.76	24.30
% Doses on schedule$	30	0	100	77.18	25.71

*Alzheimer's Disease Assessment Scale, Cognitive Subscale;

°Delayed Word Recall supplementary subtest of the ADAS-Cog;

#Maze solving supplementary subtest of the ADAS-Cog;

§Percent of total doses taken over the interval (number of taken doses/number of days monitored times 100);

^Percent of doses taken on the correct day (number of taken doses each day/number of days monitored times 100);

$Percent of total doses taken at an interval between 18 and 30 h after the previous dose (number of doses taken at the correct interval /number of intervals monitored times 100).

Table 2

Bootstrapped path coefficients and standard errors.

Path	Bootstrapped mean path coefficient	SE	*T* value	*P* value
ADHERE1 -> ADHERE2	−0.04	0.25	0.49	0.62
ADHERE1 -> COG2*	0.25	0.14	2.15	0.03
ADHERE2 -> ADHERE3	0.42	0.22	2.13	0.03
ADHERE2 -> COG3*	0.16	0.06	2.96	0.00
ADHERE3 -> ADHERE4	0.91	0.10	9.20	0.00
ADHERE3 -> COG4*	−0.14	0.08	2.02	0.04
AGE -> ADHERE1	−0.17	0.16	1.31	0.19
AGE -> COG1	0.22	0.17	1.06	0.29
AGE -> COG2	0.37	0.13	3.35	0.00
AGE -> COG3	0.21	0.11	1.23	0.22
AGE -> COG4	0.01	0.09	0.09	0.93
CG -> ADHERE1	−0.66	0.15	4.24	0.00
CG -> ADHERE2	−0.60	0.30	1.99	0.05
CG -> ADHERE3	−0.39	0.21	1.54	0.12
CG -> ADHERE4	0.00	0.17	0.15	0.88
COG1 -> ADHERE1	−0.14	0.19	0.77	0.44
COG1 -> ADHERE2°	0.62	0.37	1.18	0.24
COG1 -> COG2	0.61	0.12	4.67	0.00
COG2 -> ADHERE2	−0.62	0.43	1.09	0.28
COG2 -> ADHERE3°	0.26	0.50	1.02	0.31
COG2 -> COG3	0.68	0.12	6.15	0.00
COG3 -> ADHERE3	−0.59	0.36	2.17	0.03
COG3 -> ADHERE4°	−0.14	0.13	1.27	0.20
COG3 -> COG4	0.86	0.07	13.19	0.00
COG4 -> ADHERE4	0.15	0.21	0.71	0.48
INFO -> ADHERE1	0.92	0.19	5.02	0.00
INFO -> ADHERE2	0.48	0.36	1.37	0.17
INFO -> ADHERE3	0.34	0.23	1.35	0.18
INFO -> ADHERE4	0.06	0.24	0.42	0.68
REMIND -> ADHERE1	0.26	0.11	2.72	0.01

Path	Bootstrapped mean path coefficient	SE	*T* value	*P* value
REMIND -> ADHERE2	−0.08	0.23	0.01	0.99
REMIND -> ADHERE3	0.26	0.13	2.27	0.02
REMIND -> ADHERE4	0.02	0.15	0.26	0.80

ADHERE1–ADHERE4, adherence composite of each adherence index at each evaluation; COG1–COG4, cognition composite of total ADAS-Cog score with delayed recall and maze task performance at each evaluation; AGE, participant age; CG, caregiver present; REMIND, dummy variable for participants in automated reminding condition; INFO, dummy variable for participants in tailored information condition.

* Adherence predicting cognition at a later time;

o cognition predicting adherence at a later time.