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ORIGINAL RESEARCH

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Cognitive impairment, perceived medication adherence, and high-risk medication use in patients with reduced kidney function: A cross-sectional analysis

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Abstract

Background and Aims: Reduced estimated glomerular filtration rate (eGFR < 60 ml/min/1.73 m^2) is a risk factor for cognitive impairment (CI) and medication nonadherence. However, the association between CI and medication adherence in adults with reduced eGFR has not been adequately examined. Our pragmatic objectives were to assess the cross-sectional relationship between CI and self-reported medication adherence, medication number, and use of potentially high-risk medications among adults with reduced eGFR.

Methods: An observational cohort study of the epidemiology of CI in community-dwelling adults aged 45 years or older with reduced eGFR.

Results: Our analytic cohort consisted of 420 participants (202 with CI; mean age: 69.7 years) with reduced eGFR, at least one prescription medication, and nonmissing medication adherence data. Participants with CI had four times greater unadjusted odds of reporting good medication adherence than participants without CI (self-report of missing medications <4 days/month; odds ratio [OR]: 4.04, 95% confidence interval [CI]: 1.62–10.10). This difference persisted following adjustment for demographic factors and comorbidities (OR: 5.50, 95% CI: 1.86–16.28). Participants with CI were no more likely than participants without CI to report forgetfulness as a reason for missing medication doses. Participants with CI were, on average, taking more total (mean: 13.3 vs. 11.5, median: 12 vs. 11) and more high-risk (mean: 5.0 vs. 4.2, median: 5 vs. 4) medications than those without CI; these differences were attenuated and no longer significant following adjustment for demographics and comorbidities.

Conclusion: Given the well-documented association between CI and medication nonadherence, better self-reported medication adherence among those with CI may represent perceptions of adherence rather than actual adherence. Participants with CI were, on average, taking more total and more high-risk medications than those without CI, suggesting a possible increased risk for adverse drug events. Our results

highlight the potential risks of relying on self-reported medication adherence in reduced eGFR patients with CI.

KEYWORDS

cognitive impairment, chronic kidney disease, medication adherence, potentially inappropriate medications

1 | INTRODUCTION

Chronic kidney disease (CKD), reduced estimated glomerular filtration rate (eGFR < 60 ml/min/1.73 m^2), and aging are all recognized risk factors for cognitive impairment (CI).[1–8] In the Reasons for Geographic and Racial Differences in Stroke Study (REGARDS), participants with eGFR < 60 ml/min/1.73 m^2 were more likely to have CI than participants with eGFR ≥ 60 ml/min/1.73 m^2, with an adjusted odds ratio (aOR) of 1.23.[2] The BRain IN Kidney (BRINK) disease cohort also showed high rates of CI in participants with reduced eGFR, with a prevalence of 48% in those with eGFR < 60 ml/min/1.73 m^2 and 57% in those with eGFR < 30 ml/min/1.73 m^2 [5].

CI is a recognized risk factor for medication nonadherence and medication errors.[9–19] Despite this, patients with reduced eGFR are often on a large number of medications. The Atherosclerosis Risk in Communities (ARIC) observational cohort study found that participants with eGFR < 30 ml/min/1.73 m^2 took an average of 8.9 medications, compared with an average of 6.1 medications for participants without CKD.[20] These medications may include medications that are potentially inappropriate for older adults; a study in France found that 57.6% of adults aged ≥75 years with very low eGFR were on at least one potentially inappropriate medication (PIM).[21]

While reduced eGFR is associated with CI, and CI is associated with reduced medication adherence, we identified only one prior study of medication adherence in CKD that considered CI. Analysis of data from the longitudinal REGARDS study found no association between CI and self-reported medication adherence among adults with and without CKD.[22] However, rates of identified CI measured among adults with CKD in the study were low (<12%), with mean eGFR > 60 ml/min/1.73 m^2. Using baseline data from the BRINK observational cohort, we sought to re-evaluate the association of CI with self-reported medication adherence in a cohort of adults aged 45 years or older with reduced eGFR (eGFR < 60 ml/min/1.73 m^2) and a greater prevalence of CI. We hypothesized that participants with CI would self-report lower medication adherence, and more commonly report forgetfulness as a reason for missing medication doses, than participants without CI. We conducted this analysis using self-reported medication adherence among reduced eGFR participants as a pragmatic first step to understanding medication adherence in this cohort, acknowledging that gold standards for accurate recording of medication adherence require time-intensive supervision that is often lacking in usual CKD clinical management, even among patients with CI and anosognosia, the inability to recognize they are cognitively impaired.

The risks associated with poor medication adherence and medication mismanagement vary greatly by type of medication. As such, our secondary aims were to examine the total number of medications and the number and class of potentially high-risk medications; we hypothesized that participants with CI would be on more total and high-risk medications than participants without CI.

2 | MATERIALS AND METHODS

2.1 | Study design and population

The BRINK study is an observational cohort study of the epidemiology of CI in adults with and without reduced eGFR. The full methods have been previously reported.[1] In brief, community-dwelling adults aged 45 years and older were recruited from four health care institutions in Minneapolis, Minnesota. Exclusion criteria included inability to complete the Modified Mini-Mental Status Examination (3MS)[23] secondary to severe cognitive or sensory impairment, dialysis dependence or kidney transplant, chemical dependency, and long-term high-dose narcotic use. The institutional review boards of collaborating institutions approved the study (Hennepin County Medical Center, 11-3393; University of Minnesota, 1203M11122; Veterans Affairs Medical Center, 4364-B; HealthPartners, A12-282).

Participants completed a baseline in-person assessment that included cognitive testing, a medical history questionnaire, review of an active medication list from their primary care provider (PCP), self-reported medication adherence, and measurement of serum creatinine, glucose, hemoglobin A1c, weight, height, and blood pressure. Data presented in this analysis are from the baseline BRINK visit. Our analytic cohort consisted of participants with reduced eGFR, at least one prescription medication, and nonmissing medication adherence data (Figure A1).

2.2 | Cognitive function

The primary exposure was cognitive function. Cognitive function was assessed using tests of three cognitive domains: memory, processing speed/executive function, and verbal fluency/language (Figure A2). Normal cognition was defined as scores within 1.0 standard deviation (SD) of the appropriate norm for all domains. CI was defined as a score >1.0 SD below the mean published norm in one or more domains; moderate-to-severe CI was defined as scores >1.5 SD

below the mean published norm in one or more domains. Further details regarding cognitive testing and classification have been previously reported.[1,5]

2.3 | Medications

Our primary outcomes were self-reported medication adherence and self-reported reasons for missing medication doses from our Medication Adherence Assessment (MAA) instrument designed for this study. The MAA was adapted from pharmacy-generated medication adherence forms used at Hennepin County Medical Center (Figure A3). The MAA included participant self-report of number of medications/day, number of missed medication doses monthly, reasons for missing doses, and a pillbox filling exercise. Self-reported reasons for missing medications were analyzed only among participants who reported missing a dose of medication at least one day per month. Participants who self-managed ≥4 medications were eligible for a pillbox filling exercise and were asked to bring their medication bottles to the study visit. Medication self-management was defined as a response of "self" to the question, "who sets up your medications?". Eligible participants who brought their medication bottles to the study visit filled one day in a pillbox with their medications and study staff checked the pillbox for accuracy.

Our secondary outcomes were the total number of medications and the number and type of potentially high-risk medications. These data were obtained from the PCP-generated medication list. As-needed (PRN) medications were included in the total medication count. Potentially high-risk medications were defined as medications potentially inappropriate in the elderly (PIMs)[24]: opioids, tramadol, benzodiazepines, nonbenzodiazepine benzodiazepine receptor agonist hypnotics ("Z-drugs"), first-generation antihistamines, and muscle relaxants or medications that may be harmful if taken in excess or if doses are missed (antihypertensives, oral diabetic agents, insulin, gabapentin, antipsychotics, anticoagulants, antiplatelets, and aspirin).[25] These medications were categorized according to pharmacologic class and Food and Drug Administration-approved indications.[26]

2.4 | Other measures

Demographic data were self-reported. The National Kidney Foundation and American Society of Nephrology CKD-EPI (CKD-Epidemiology Collaboration) equation refitted without the race variable was used to calculate eGFR using the baseline BRINK visit serum creatinine.[27] In accordance with Kidney Disease: Improving Global Outcomes guidelines,[28] we defined a reduced eGFR as eGFR <60 ml/min/1.73 m^2. Diabetes was defined as a random glucose ≥ 200, hemoglobin A1c% ≥ 6.5 or self-report of diabetes requiring medication. Hypertension was defined as systolic blood pressure (SBP) ≥ 140 mmHg, diastolic blood pressure (DBP) ≥ 90 mmHg or self-report of hypertension requiring an antihypertensive. Cardiovascular disease (CVD) was defined as a history of myocardial infarction, angina, congestive health failure, or peripheral vascular disease. A history of stroke or transient ischemic attack (TIA) was defined as at least one positive response on the Questionnaire for Verifying Stroke-Free Status.[29] Depression was defined as a Patient Health Questionnaire-9[30] score of ≥10 or self-report of depression requiring daily medication. History of traumatic brain injury, history of chemical dependency, any fall in the past year, and use of glasses and hearing aids were based on self-report.

2.5 | Statistical analysis

Descriptive statistics for demographic factors, comorbidities, PCP-generated medication list data, and MAA data are reported overall and by the CI group to demonstrate the complex associations with CI, our primary exposure variable. Unadjusted associations were evaluated using two-sample *t* tests of means for continuous variables and the χ^2 test or Fisher's exact test for categorical variables. Fisher's exact test was used for categorical variables when cell counts were too small to obtain a valid χ^2 test.

For the primary outcome of medication adherence, univariate logistic regression models were used to evaluate the associations between self-reported medication adherence and CI, demographic factors, and comorbidities. A multiple logistic regression model evaluated the association between medication adherence and CI, adjusted for the total number of medications, demographic factors, and comorbidities. Given the high prevalence of CI in Black participants compared to participants of other races in the BRINK cohort,[5] we assessed for interactions between Black race and CI and between Black race and demographic factors and comorbidities significant in the adjusted models for each outcome of interest.

Reasons for missing medication doses, limited to the subset of participants who reported missing a medication dose at least once monthly, are presented overall and by the CI group. All forgetfulness reasons were combined for a χ^2 test of association with CI; statistical tests of association were not conducted for each individual reason because participants could pick more than one reason for missing medications.

For our secondary outcomes, the total number of medications and the number and type of potentially high-risk medication are presented overall and by cognitive status. Univariate and multivariate linear regression models were used to evaluate the associations between these two secondary outcomes (total number of medications and number of high-risk medications) and CI, demographic factors, and comorbidities. Due to multiple combinations of high-risk medications and multiple comparison concerns, univariate tests of association with CI were limited to χ^2 tests of the proportion of participants taking any high-risk medications, the proportion taking any PIMs, and two-sample *t* tests of the mean for the total number of high-risk medications, PIMs, and antihypertensive medications.

Sensitivity analyses limited to the 379 participants who reported self-management of their medications were conducted. Alpha significance level for all tests was set at 0.05; all tests were two-

sided. Data analysis was completed using SAS version 9.4 (SAS Institute, 2013).

3 | RESULTS

3.1 | Baseline characteristics

Our analytic cohort consisted of 420 adults with a mean age of 69.7 years (Table 1). Almost half (202, 48%) of participants were classified with CI. More than half of participants with CI had moderate-to-severe CI (123/202 (61%), not shown in the table). Participants with CI were more likely than participants without CI to self-identify as Black race (25% vs. 8%), have diabetes (57% vs. 46%), and report a history of stroke or TIA (25% vs. 13%) and CVD (60% vs. 45%). Participants with CI had, on average, fewer years of education (13.7 vs. 14.2 years, $p = 0.048$) and lower eGFR (33.9 vs. 37.5 ml/min/1.73 m^2, $p = 0.002$) than participants without CI. Participants with and without CI otherwise had similar baseline characteristics. The comparatively high prevalence of CI in Black BRINK participants has been previously reported.[5] It may be partially attributable to higher rates of diabetes (67% vs. 49%) and TIA/stroke (29% vs. 17%), greater prevalence of a history of chemical dependency (22% vs. 2%), and fewer average years of education (12.3 vs. 14.3 years), among Black participants compared to participants of other races in this analytic cohort (Table A1).

3.2 | MAA

Associations between CI and MAA responses are reported in Table 2. Participants with CI were more likely to report good medication adherence (missing medications fewer than 4 days/month) than those without CI (97% vs. 89%, $p = 0.001$). Participants with CI were less likely to report managing their own medications (85% vs. 95%, $p < 0.001$) and knowing the purpose of all of their medications (60% vs. 76%, $p < 0.001$) than participants without CI. Two-thirds (218/333) of participants eligible for the pillbox filling exercise (self-management of ≥4 medications/day) did not complete the exercise, most commonly due to not bringing their medication bottles to the study visit ($n = 212$). Participants who completed the pillbox exercise had similar characteristics to those who did not complete the exercise (Table A2). Among the 113 participants who completed the pillbox filling exercise and had nonmissing results, the majority (98, 87%) filled the pillbox correctly

TABLE 1 Participant characteristics and associations with cognitive impairment

	Overall,[a] *N*= 420	Normal cognition, *N* = 218	Cognitive impairment,[b] *N*= 202	*p* value[c]
Age (years), mean (SD)	69.7 (9.7)	69.5 (9.2)	70.0 (10.2)	0.624
Male sex, *n* (%)	216 (51.4)	104 (47.7)	112 (55.4)	0.113
Black race,[d] *n* (%)	69 (16.4)	18 (8.3)	51 (25.2)	<0.001
Education (years), mean (SD)	14.0 (2.8)	14.2 (2.4)	13.7 (3.1)	0.048
eGFR[e] (ml/min/1.73 m^2), mean (SD)	35.8 (12.2)	37.5 (11.4)	33.9 (12.7)	0.002
Diabetes, *n* (%)	217 (51.7)	101 (46.3)	116 (57.4)	0.023
Hypertension, *n* (%)	405 (96.4)	207 (95.0)	198 (98.0)	0.091
CVD, *n* (%)	219 (52.1)	98 (45.0)	121 (59.9)	0.002
Prior stroke or TIA, *n* (%)	78 (18.6)	28 (12.8)	50 (24.8)	0.002
History of traumatic brain injury,[f] *n* (%)	13 (3.1)	8 (3.7)	5 (2.5)	0.470
Depression, *n* (%)	155 (36.9)	78 (35.8)	77 (38.1)	0.620
History of chemical dependency, *n* (%)	22 (5.2)	13 (6.0)	9 (4.5)	0.488
Any falls in past year, *n* (%)	136 (32.4)	67 (30.7)	69 (34.2)	0.454
Wears hearing aids, *n* (%)	68 (16.2)	38 (17.4)	30 (14.9)	0.473
Wears eye glasses, *n* (%)	295 (70.2)	149 (68.4)	146 (72.3)	0.379

Abbreviations: CI, cognitive impairment; CKD-EPI, Chronic Kidney Disease-Epidemiology Collaboration; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; SD, standard deviation; TIA, transient ischemic attack.

[a]Four hundred and twenty BRINK participants with reduced eGFR, ≥1 prescription medication(s), and nonmissing Medication Adherence Assessment data.

[b]Cognitive impairment (CI) is defined as a score >1 SD below the norm in one or more cognitive domains.

[c]*p* Value for two-sample *t* test of means for continuous variables and χ^2 test for categorical variables.

[d]Three hundred and thirty-two participants self-identified as White, 196 with normal cognition and 136 with CI. Nineteen participants self-identified as "other" race, 4 with normal cognition, and 15 with CI.

[e]eGFR was calculated using the American Society of Nephrology recommended creatinine-based refitted CKD-EPI equation without the race factor.

[f]Denominator is 418 participants (two participants were missing data on the history of traumatic brain injury).

TABLE 2 Medication number and MAA

	Overall,[a] N = 420	Normal cognition, N = 218	Cognitive impairment,[b] N = 202	p value[c]
PCP-generated medication list data				
Number of medications[d]				
Mean (SD)	12.3 (6.2)	11.5 (5.7)	13.3 (6.5)	0.003
Median [Q1, Q3]	11 [8, 16]	11 [7, 15]	12 [9, 18]	
4 or more medications,[d] *n* (%)	406 (96.7)	211 (96.8)	195 (96.5)	0.885
MAA (self-report)[e]				
Number of medications/day[f]				
Mean (SD)	11.2 (6.4)	10.1 (5.8)	12.4 (6.7)	<0.001
Median [Q1, Q3]	10 [6, 15]	10 [6, 14]	11 [7, 16]	
Number of times/day takes medications[g]				
Mean (SD)	2.4 (1.0)	2.3 (0.9)	2.5 (1.0)	0.027
Median [Q1, Q3]	2 [2, 3]	2 [2, 3]	2 [2, 3]	
Sets up own medications, *n* (%)	379 (90.2)	208 (95.4)	171 (84.7)	<0.001
Knows purpose of 100% of medications,[h] *n* (%)	285 (68.2)	164 (75.6)	121 (60.2)	<0.001
Spends >50/month on medications,[i] *n* (%)	171 (41.2)	93 (43.1)	78 (39.2)	0.425
Spends >100/month on medications,[i] *n* (%)	99 (23.9)	55 (25.5)	44 (22.1)	0.423
Days/month with missed medication doses, *n* (%)				0.014[o]
None	190 (45.2)	94 (43.1)	96 (47.5)	
1–3 days	200 (47.6)	100 (45.9)	100 (49.5)	
4–6 days	22 (5.2)	18 (8.3)	4 (2.0)	
7 or more days	8 (1.9)	6 (2.8)	2 (1.0)	
Missed medications <4 days/month, *n* (%)	390 (92.9)	194 (89.0)	196 (97.0)	0.001
Any forgetfulness reason for missing medications,[j] *n* (%)	181 (78.7)	99 (79.8)	82 (77.4)	0.647
Eligible for pillbox exercise,[k] *n* (%)	333 (79.7)	176 (81.1)	157 (78.1)	0.447
Pillbox completion,[l] *n* (%)				0.182
Did not complete pillbox exercise[m]	218 (65.5)	121 (68.7)	97 (61.8)	
Completed pillbox exercise	115 (34.5)	55 (31.3)	60 (38.2)	
Pillbox—100% correct,[n] *n* (%)	98 (86.7)	49 (89.1)	49 (84.5)	0.471

Abbreviations: BRINK, BRain IN Kidney; eGFR, estimated glomerular filtration rate; MAA, Medication Adherence Assessment; PCP, primary care provider; PRN, as needed; SD, standard deviation; Q1, 25th percentile; Q3, 75th percentile.

[a]Four hundred and twenty BRINK participants with reduced eGFR, ≥1 prescription medication(s), and nonmissing MAA data.

[b]Cognitive impairment is defined as a score >1 SD below the norm in one or more cognitive domains.

[c]*p* Value for two-sample *t* test of mean for continuous variables and χ^2 test for categorical variables unless otherwise indicated.

[d]Number of medications on the PCP-generated medication list, including PRN medications.

[e]See Figure A3 for all MAA questions.

[f]Self-reported number of medications from MAA: "About how many medications are you taking every day?".

[g]Self-reported medication frequency from MAA: "About how many times a day do you take medications?".

[h]Denominator is 418 participants (2 participants were missing medication purpose data).

[i]Includes $0 for those whose insurance covered all costs of prescribed meds and did not report costs for any meds. Denominator is 415 participants (5 participants were missing medication cost data).

[j]Fisher's exact test.

[k]Denominator is the 230 participants who self-reported missing at least one medication dose per month. Forgetfulness reasons reported on MAA: Forgetfulness, forgetting to bring medications with when leaving the house, forgetfulness + social activity. Table 5 includes all reported reasons for missing medications.

[l]Participants with ≥4 medications who set up their own medications were eligible for the pillbox filling exercise and were asked to bring their medication bottles to the study visit. Denominator is 418 participants (2 participants were missing data on eligibility for the pillbox filling exercise).

[m]Denominator is the 333 participants who were eligible for the pillbox exercise.

[n]Reasons for not completing the pillbox exercise: Did not bring medications (*n* = 212), brought medications already set up in pillbox (*n* = 1) and unknown (*n* = 5).

[o]Denominator is the 113 participants who completed the pillbox exercise and have data for percent correct.

(correct medications and correct time(s) of day). Participants who completed the exercise were taking an average of 12.7 (SD 5.7) medications. There was no association between CI and errors on the pillbox exercise, or CI and completion of the pillbox exercise.

CI (OR: 4.04, 95% confidence interval [95% CI]: 1.62–10.10), older age (OR: 1.05 per 1 year increase in age, 95% CI: 1.01–1.09), and CVD (OR: 2.31, 95% CI: 1.05–5.06) were associated with greater self-reported medication adherence in unadjusted logistic regression models (Table 3). Depression was associated with lower self-reported adherence (OR: 0.19, 95% CI: 0.08–0.43). Following adjustment for demographic factors and comorbidities, the association between CI and medication adherence persisted (aOR: 5.50, 95% CI: 1.86–16.28). CVD was also associated with greater self-reported medication adherence in the adjusted model (aOR: 2.69, 95% CI: 1.05–6.94). History of stroke or TIA (aOR: 0.32, 95% CI: 0.11–0.94) and depression (aOR: 0.16, 95% CI: 0.06–0.42) were associated with lower self-reported medication adherence following adjustment. Interaction terms between Black race and CI and between Black race and covariates significant in the adjusted model were nonsignificant.

3.3 | Reasons for missing medications

Among the 230 participants who reported missing at least one medication dose in the past month, the most frequently reported reasons for missing medications were forgetfulness (56% overall, 53% with CI and 58% without CI) and forgetting to bring medications when leaving the house (21% overall, 22% with CI and 20% without CI; Table 4). When all reasons for missing medications due to forgetfulness were combined, participants with and without CI reported similar rates of forgetfulness (78% vs. 80%, $p = 0.647$; Table 2).

TABLE 3 Association of self-reported medication adherence[a] with cognitive impairment and other factors

	Good medication adherence[a] Univariate logistic regression models[b]		Good medication adherence[a] Multiple logistic regression model[c]	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Cognitive impairment[d] (ref = normal)	4.04 (1.62, 10.10)	0.003	5.50 (1.86, 16.28)	0.002
Covariates				
Age, 1 year increase	1.05 (1.01, 1.09)	0.018	1.01 (0.96, 1.07)	0.600
Female sex (ref = male)	0.52 (0.24, 1.13)	0.098	0.67 (0.29, 1.56)	0.351
Black race (ref = White or other race)	0.62 (0.26, 1.51)	0.293	0.55 (0.17, 1.78)	0.318
Education, each additional year	1.08 (0.95, 1.24)	0.253	1.11 (0.95, 1.31)	0.190
eGFR,[e] 1ml/min/1.73 m^2 decrease	1.00 (0.97, 1.03)	0.943	1.00 (0.97, 1.04)	0.905
Diabetes (ref = no)	0.81 (0.38, 1.70)	0.570	0.61 (0.24, 1.59)	0.311
Hypertension (ref = no)	2.07 (0.45, 9.64)	0.353	1.36 (0.23, 7.99)	0.732
CVD (ref = no)	2.31 (1.05, 5.06)	0.037	2.69 (1.05, 6.94)	0.040
Prior stroke or TIA (ref = no)	0.60 (0.26, 1.41)	0.241	0.32 (0.11, 0.94)	0.038
History of traumatic brain injury (ref = no)	0.41 (0.09, 1.93)	0.259	0.48 (0.08, 2.75)	0.412
Depression (ref = no)	0.19 (0.08, 0.43)	<0.001	0.16 (0.06, 0.42)	<0.001
Number of medications,[f] each additional	1.02 (0.96, 1.08)	0.597	1.07 (0.98, 1.16)	0.128

Abbreviations: CKD-EPI, Chronic Kidney Disease-Epidemiology Collaboration; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; PCP, Primary care provider; ref, reference; TIA, transient ischemic attack.

[a]Good medication adherence is defined as self-report of missing medications fewer than 4 days/month.

[b]Separate univariate logistic regression model results for each factor; OR (95% CI) is the estimated odds ratio (95% confidence interval) for good medication adherence for each factor.

[c]$N = 418$. Multiple logistic regression model results for each factor adjusted for other factors in the model; OR (95% CI) is the estimated adjusted odds ratio (95% CI) for good medication adherence for each factor adjusted for other factors in the model.

[d]Cognitive impairment is defined as a score > 1 SD below the norm in one or more cognitive domains.

[e]eGFR calculated using the American Society of Nephrology recommended creatinine-based refitted CKD-EPI equation without the race factor.

[f]Total number of medications from the PCP-generated medication list.

TABLE 4 Self-reported reasons for missing medications and associations with cognitive impairment

	Overall,[a] *N* = 230	Normal cognition, *N* = 124	Cognitive impairment,[b] *N* = 106
Reasons for missing medications[c]			
Forgetfulness, *n* (%)	128 (55.7)	72 (58.1)	56 (52.8)
Forgetting to bring medications with when leaving the house, *n* (%)	48 (20.9)	25 (20.2)	23 (21.7)
Forgetfulness + social activity, *n* (%)	5 (2.2)	2 (1.6)	3 (2.8)
Any forgetfulness reason[d]	181 (78.7)	99 (79.8)	82 (77.4)
Not getting prescriptions filled on time, *n* (%)	7 (3.0)	3 (2.4)	4 (3.8)
Side effects, *n* (%)	8 (3.5)	4 (3.2)	4 (3.8)
Medication not considered important, *n* (%)	1 (0.4)	0 (0.0)	1 (0.9)
No food or water to take pills, *n* (%)	1 (0.4)	1 (0.8)	0 (0.0)
High on alcohol or other drugs, *n* (%)	1 (0.4)	0 (0.0)	1 (0.9)
Other, *n* (%)	31 (13.5)	17 (13.7)	14 (13.2)

[a]Includes participants in the analytic cohort who self-reported missing at least one medication dose per month.

[b]Cognitive impairment is defined as a score >1 SD below the norm in one or more cognitive domains.

[c]No participants reported missing medications because their mail-order prescriptions were late, they lost the medication, they thought the medication was discontinued, they did not know the purpose of the medication, due to obligations at work or school, due to childcare or caregiving responsibilities, or secondary to cost.

[d]At least one of forgetfulness, forgetting to bring medications with when leaving the house, and forgetfulness + social activity.

3.4 | Secondary outcomes

3.4.1 | Number of medications

Participants with CI had, on average, more total medications on their PCP-generated medication list (13.3 vs. 11.5, $p = 0.003$), self-reported taking more daily medications (12.4 vs. 10.1, $p < 0.001$), and self-reported taking medications more times per day (2.5 vs. 2.3, $p = 0.027$) than those without CI (Table 2). The association between CI and medication number was attenuated and no longer significant following adjustment for demographic factors and comorbidities (Table A3; $p = 0.106$). Interaction terms between Black race and CI and between Black race and the four covariates significant in the adjusted model were nonsignificant.

3.4.2 | High-risk medications

Most participants (99% with CI, 98.6% without CI) were prescribed at least one high-risk medication (Table 5). Antihypertensives were the most common and accounted for over half of the high-risk medications. Participants with CI were, on average, prescribed more high-risk medications than those without CI (mean (SD): 5.0 (2.4) versus 4.2 (2.3), $p < 0.001$). The association between CI and the number of high-risk medications was attenuated and no longer significant following adjustment for demographic factors and comorbidities (Table A3; $p = 0.089$). Interaction terms between Black race and CI and between Black race and the four covariates significant in the adjusted model were nonsignificant. The proportion of participants taking at least one PIM was similar among participants with and without CI (33% vs. 32%, $p = 0.82$). The proportions of participants taking each class of PIMs also appeared similar (Table 5, no statistical tests completed due to multiple combinations of high-risk medications prescribed).

3.5 | Sensitivity analyses

The results did not meaningfully change in sensitivity analyses limiting the sample to participants who reported managing their own medications (379 of 420, 90%), other than loss of significance for some associations due to reduced power with the smaller sample size.

4 | DISCUSSION

In this cohort of adults with reduced eGFR, contrary to our hypothesis, participants with CI reported better medication adherence than participants without CI, an association that persisted following adjustment for demographic factors and comorbidities. Participants with CI were no more likely to report forgetfulness as a reason for missing medication doses than participants without CI. Participants with CI were, on average, taking more total medications and more high-risk medications than participants without CI; these differences were no longer significant following adjustment for demographic factors and comorbidities. Given the frequent association between CI and medication nonadherence in the literature,[9–19] our results suggest self-reported medication adherence among adults with reduced eGFR and CI may represent perceptions of adherence rather than actual adherence.

Our results add to the very limited literature on medication adherence in adults with reduced eGFR and CI. Our estimates of the prevalence of medication nonadherence in adults with reduced eGFR are similar to previous studies; a 2020 review of medication adherence in older adults with CKD found estimates of nonadherence ranging from 15% to 57%.[31] We identified one prior study of medication adherence in CKD that considered CI. A cross-sectional analysis of medication adherence in the REGARDS study found no association between CI and self-reported medication adherence among adults with and without CKD.[22] Rates of adults with CKD classified as having CI in the REGARDS analysis were low (<12%; CI was identified using only a short test of orientation and recall[32]), with relatively high average eGFR (mean eGFR > 60 ml/min/1.73 m^2; CKD was defined as eGFR < 60 ml/min/1.73 m^2 or albuminuria). The BRINK study includes a more comprehensive assessment of cognition and a focus on adults with eGFR < 60 ml/min/1.73 m^2, a strength of our analysis. Differences in the prevalence and severity of CI in the cohorts, if present, and the use of different adherence assessment tools, might partially explain the differing results.

CKD is associated with executive dysfunction,[5,6] which often includes reduced insight, and may help explain the counterintuitive positive association between CI and self-reported medication adherence. There are data to suggest self-report of medication adherence may be inaccurate in the setting of CI. A review of medication adherence in persons with CI found lower adherence in persons with CI compared to those without CI; studies not finding an association between CI and adherence generally relied on self-report.[33] A 2017 meta-analysis of medication adherence in patients with CI and a history of stroke found an association between CI and increased medication adherence when adherence was assessed using administrative databases; there was no association between dementia and adherence in studies based on self-report.[34]

The total number of medications reported by participants in BRINK was greater than what was reported by participants in the longitudinal ARIC cohort,[20] but similar to other cohorts.[35,36] Our results are consistent with previous analyses showing frequent use of PIMs and high-risk medications among adults with CKD.[20,21,35,37] Previous studies suggest that polypharmacy and PIM use are associated with adverse events in this population. The ARIC analysis of 6392 adults aged 65 years and older showed a greater number of medications, but not the use of PIMs, was associated with a greater risk of subsequent hospitalization and death.[20] A recent analysis of 3929 adults from the Chronic Renal Insufficiency Cohort found a graded association between PIM use, defined as medications to be avoided in older adults according to the 2015 American Geriatrics Society Beers criteria, and an increase

TABLE 5 High-risk medication use, overall[a] and by cognitive impairment status

High-risk medications on PCP-generated medication list	Overall,[a] *N* = 420	Normal cognition, *N* = 218	Cognitive impairment,[b] *N* = 202	*p* value[c]
High-risk medications[d]: Any, *n* (%)	415 (98.8)	215 (98.6)	200 (99.0)	1.00
PIMs[e]: Any, *n* (%)	135 (32.1)	69 (31.7)	66 (32.7)	0.823
Benzodiazepines: Any, *n* (%)	41 (9.8)	21 (9.6)	20 (9.9)	
First-generation antihistamines: Any, *n* (%)	23 (5.5)	11 (5.1)	12 (5.9)	
Muscle relaxants: Any, *n* (%)	17 (4.1)	6 (2.8)	11 (5.5)	
Opioids[f]: Any, *n* (%)	63 (15.0)	30 (13.8)	33 (16.3)	
Tramadol: Any, *n* (%)	28 (6.7)	16 (7.3)	12 (5.9)	
Z-drugs: Any, *n* (%)	19 (4.5)	9 (4.1)	10 (5.0)	
Anticoagulants: Any, *n* (%)	44 (10.5)	19 (8.7)	25 (12.4)	
Antihypertensives: Any, *n* (%)	393 (93.6)	200 (91.7)	193 (95.5)	
Antiplatelets other than aspirin: Any, *n* (%)	39 (9.3)	12 (5.5)	27 (13.4)	
Antipsychotics: Any, *n* (%)	10 (2.4)	7 (3.2)	3 (1.5)	
Aspirin: Any, *n* (%)	249 (59.3)	120 (55.1)	129 (63.9)	
Gabapentin: Any, *n* (%)	51 (12.1)	24 (11.0)	27 (13.4)	
Insulin: Any, *n* (%)	123 (29.3)	56 (25.7)	67 (33.2)	
Oral diabetic agents: Any, *n* (%)	93 (22.1)	44 (20.2)	49 (24.3)	
Number of medications				
High-risk medications[d]				
Mean (SD)	4.6 (2.4)	4.2 (2.3)	5.0 (2.4)	<0.001
Median [Q1, Q3]	4.5 [3, 6]	4 [2, 6]	5 [3, 7]	
PIMs[e]				
Mean (SD)	0.5 (0.9)	0.5 (0.8)	0.5 (0.9)	0.402
Median [Q1, Q3]	0 [0, 1]	0 [0, 1]	0 [0, 1]	
Antihypertensives				
Mean (SD)	2.4 (1.3)	2.2 (1.3)	2.6 (1.3)	0.009
Median [Q1, Q3]	2 [1, 3]	2 [1, 3]	2.5 [2, 4]	

Abbreviations: BRINK, BRain IN Kidney; eGFR, estimated glomerular filtration rate; PIM, potentially inappropriate medications; Q1, 25th percentile; Q3, 75th percentile; SD, standard deviation.

[a]Four hundred and twenty BRINK participants with reduced eGFR, ≥1 prescription medication(s), and nonmissing medication adherence assessment data.

[b]Cognitive impairment is defined as a score >1 SD below the norm in one or more cognitive domain.

[c]*p* Value for Fisher's exact test for any high-risk medications, χ^2 test for any PIMs, two-sample *t* test for mean numbers of medications; no statistical tests were run for individual medications as participants were often prescribed more than one high-risk medication or PIM.

[d]Antihypertensives, oral diabetic agents, insulin, gabapentin, antipsychotics, anticoagulants, antiplatelets, aspirin, opioids, tramadol, benzodiazepines, Z-drugs, first-generation antihistamines, muscle relaxants.

[e]PIMs: opioids, tramadol, benzodiazepines, Z-drugs, first-generation antihistamines, muscle relaxants.

[f]Excluding tramadol.

in subsequent hospitalizations and mortality.[35] Polypharmacy and use of some PIMs have also been associated with increased mortality in adults aged 65 years and older with CI.[38] To our knowledge, our analysis is the first to consider cognition in the assessment of medication burden and PIM use in adults with CKD. Future studies are needed to objectively assess medication adherence in adults with reduced eGFR, using methods such as prescription claims data and caregiver or patient surrogate report; to further explore reasons for nonadherence; to identify strategies for more accurately assessing adherence in the clinical setting; and to elucidate the likely complex relationship between cognition, reduced eGFR, and the prospective effects of polypharmacy and PIM use on outcomes such as hospitalizations and mortality.

The strengths of our study include rigorous cognitive testing and a relatively large sample size of reduced eGFR participants at high-

risk for CI. The largest limitation is that medication adherence was based on self-report, sometimes in the presence of CI. Self-report instruments are known to be subject to social desirability and recall bias,[32] biases that may be accentuated in the setting of CI. However, all of the studies identified by the 2020 review of medication adherence in CKD used self-reported medication adherence.[21] Self-reported medication adherence has been associated with adverse drug events in adults with reduced eGFR. In a cohort of 293 adults with reduced eGFR, individuals with self-reported lower medication adherence were 20% more likely than individuals with high self-reported medication adherence to have had a medication safety event, such as a fall attributed to the use of a particular medication, in the previous year.[39] Finally, self-report is commonly used to assess medication adherence in routine clinical practice, a setting in which CI is often unrecognized.[15,40] The absence of psychometric data on the MAA is also a limitation; the MAA is derived from a medication assessment tool used clinically by the pharmacy department at Hennepin Healthcare. Taken together, we believe our results reflect a "real-world" picture of medication adherence as assessed in clinical practice, and the self-perception of medication adherence among patients with reduced eGFR. Additional limitations include no assessment for underprescribing of evidence-based medications, such as statins; inability to assess adherence to specific medications (e.g., opioids, where lower adherence may be safer than greater adherence); and use of study-specific procedures with limited generalizability (e.g., the pillbox filling exercise).

We found, contrary to our hypothesis, that participants with reduced eGFR and CI reported better medication adherence than participants with reduced eGFR and normal cognition. The non-subjective finding that participants with CI were on more high-risk medications than those without CI, which increases their risk of adverse drug events, has implications for patient safety in the outpatient setting. Our results thus highlight the potential adverse outcomes when self-reported medication adherence is used clinically with no assessment of cognition. Cognitive screening in patients with eGFR < 60 ml/min/1.73 m^2 could be considered to identify patients who may benefit from medication management assistance, as CI is often undiagnosed in patients with reduced eGFR.[40] More objective measures of medication adherence are needed in future studies of medication adherence in CKD populations.

AUTHOR CONTRIBUTIONS

Kerry M. Sheets: Conceptualization; methodology; writing—original draft; writing—review and editing. **Cynthia S. Davey:** Data curation; formal analysis; software; validation; writing—review and editing. **Wendy L. St. Peter:** Writing—review and editing. **Scott A. Reule:** Writing—review and editing. **Anne M. Murray:** Conceptualization; funding acquisition; investigation; methodology; supervision; writing— review and editing. All authors have read and approved the final version of the manuscript. Kerry Sheets, Cynthia Davey, and Anne Murray had full access to all of the data in this study and take complete responsibility for the integrity of the data and the accuracy of the data analysis.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data are available on request due to privacy/ethical restrictions.

TRANSPARENCY STATEMENT

Kerry M. Sheets, the lead author, affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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APPENDIX A

See Table A1, A2, and A3 and Figure A1, A2, and A3.

TABLE A1 Associations of Black race with demographic factors, comorbidities, medication number, and self-reported medication adherence

	Black race, *N* = 69	White or other race,[a] *N* = 351	*p* value[b]
Male, *n* (%)	35 (50.7)	181 (51.6)	0.898
Age (years), mean (SD)	63.4 (8.7)	71.0 (9.4)	<0.001
Education (years), mean (SD)	12.3 (3.1)	14.3 (2.6)	<0.001
eGFR[c] (ml/min/1.73 m^2), mean (SD)	30.3 (13.0)	36.9 (11.7)	<0.001
Diabetes, *n* (%)	46 (66.7)	171 (48.7)	0.006
Hypertension, *n* (%)	67 (97.1)	338 (96.3)	1.00[g]
CVD, *n* (%)	35 (50.7)	184 (52.4)	0.796
Prior stroke or TIA, *n* (%)	20 (29.0)	58 (16.5)	0.015
History of traumatic brain injury,[d] *n* (%)	2 (2.9)	11 (3.2)	1.00[g]
Depression, *n* (%)	29 (42.0)	126 (35.9)	0.335
History of chemical dependency, *n* (%)	15 (21.7)	7 (2.0)	<0.001
Any falls in the past year, *n* (%)	27 (39.1)	109 (31.1)	0.190
Wears hearing aids, *n* (%)	3 (4.4)	65 (18.5)	0.004
Wears eyeglasses, *n* (%)	42 (60.9)	253 (72.1)	0.063
Any cognitive impairment, *n* (%)	51 (73.9)	151 (43.0)	<0.001
Moderate/severe cognitive impairment, *n* (%)	37 (53.6)	86 (24.5)	<0.001
Total number of medications,[e] mean (SD)	13.0 (6.6)	12.2 (6.1)	0.329
Missed medications <4 days/month[f]	62 (89.9)	328 (93.5)	0.306[g]

Abbreviations: CKD-EPI, Chronic Kidney Disease-Epidemiology Collaboration; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; PCP, primary care provider; SD, standard deviation; TIA, transient ischemic attack.

[a]White: *n* = 332 (79.1% of analysis cohort of 420 participants); other race: *n* = 19 (4.5%).

[b]*p* Value for two-sample *t* test of mean for continuous variables and χ^2 test for categorical variables, unless otherwise indicated,

[c]eGFR calculated using the American Society of Nephrology recommended creatinine-based refitted CKD-EPI equation without the race factor.

[d]Fisher's exact test.

[e]Denominator is 418 participants with data on the history of traumatic brain injury.

[f]Total number of medications from the PCP-generated medication list.

[g]Self-reported medication adherence.

TABLE A2 Associations of pillbox completion and participant characteristics among the 333 participants eligible for the pillbox exercise[a]

	Completed pillbox exercise		
	Yes, *N* = 115	No,[b] *N* = 218	*p* value[c]
Male, *n* (%)	52 (45.2)	121 (55.5)	0.074
Age (years), mean (SD)	69.5 (9.6)	69.5 (9.3)	0.995
Education (years), mean (SD)	13.9 (2.7)	14.0 (2.6)	0.852
eGFR (ml/min/1.73 m^2), mean (SD)	34.9 (12.6)	35.5 (12.2)	0.660
Diabetes, *n* (%)	58 (50.4)	125 (57.3)	0.229
Hypertension, n (%)	112 (97.4)	216 (99.1)	0.345[g]
CVD, *n* (%)	61 (53.0)	123 (56.4)	0.556
Prior stroke or TIA, *n* (%)	18 (15.7)	43 (19.7)	0.361
History of traumatic brain injury,[d] *n* (%)	2 (1.7)	8 (3.7)	0.503[g]
Depression, *n* (%)	46 (40.0)	85 (39.0)	0.858
History of chemical dependency, *n* (%)	7 (6.1)	13 (6.0)	0.964
Any falls in the past year, *n* (%)	40 (34.8)	70 (32.1)	0.622
Wears hearing aids, *n* (%)	14 (12.2)	42 (19.3)	0.100
Wears eyeglasses, *n* (%)	87 (75.7)	151 (69.3)	0.220
Any cognitive impairment, *n* (%)	60 (52.2)	97 (44.5)	0.182
Moderate/severe cognitive impairment, *n* (%)	28 (24.4)	63 (28.9)	0.376
Total number of medications,[e] mean (SD)	12.7 (5.7)	12.9 (5.4)	0.846
Missed medications <4 days/month[f]	106 (92.2)	205 (94.0)	0.515

Abbreviations: CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; PCP, primary care provider; SD, standard deviation; TIA, transient ischemic attack.

[a]Participants with ≥4 medications who set up their own meds were eligible for the pillbox filling exercise and asked to bring their medication bottles to the study visit.

[b]Reasons for not completing the pillbox exercise: Did not bring medications (*n* = 212), brought medications already set up in pillbox (*n* = 1), and unknown (*n* = 5).

[c]*p* Value for two-sample *t* test of the mean for continuous variables and χ^2 test for categorical variables, unless otherwise indicated.

[d]Fisher's exact test.

[e]Denominator is 332 participants with data on the history of traumatic brain injury (115 who completed the pillbox exercise, 217 who did not complete the pillbox exercise).

[f]Total number of medications from the PCP-generated medication list.

[g]Self-reported medication adherence.

TABLE A3 Association of the total number of medications and number of high-risk medications with cognitive impairment and other factors

	Total number of medications[a] Univariate regression models[b]		Total number of medications[a] Multiple regression model,[c] $N = 417$		Number of high-risk medications[d] Univariate regression models[e]		Number of high-risk medications[d] Multiple regression model,[f] $N = 417$	
	β (SE)	p value	β (SE)	p value	β (SE)	p value	β (SE)	p value
Cognitive impairment[g] (ref = normal)	1.8 (0.6)	0.003	0.91 (0.56)	0.106	0.79 (0.23)	<0.001	0.34 (0.20)	0.089
Covariates								
Age, 1 year increase	−0.03 (0.03)	0.315	−0.01 (0.03)	0.855	−0.02 (0.01)	0.078	−0.011 (0.011)	0.331
Female sex (ref = male)	0.39 (0.60)	0.515	0.65 (0.55)	0.237	−0.13 (0.23)	0.577	0.006 (0.194)	0.976
Black race (ref = White or other race)	0.79 (0.81)	0.329	−0.82 (0.81)	0.307	0.75 (0.31)	0.016	0.008 (0.284)	0.978
Education, each additional year	−0.13 (0.11)	0.246	0.02 (0.10)	0.862	−0.10 (0.04)	0.013	−0.046 (0.036)	0.193
eGFR[h] (1 ml/min/1.73 m^2) decrease	0.07 (0.02)	0.003	0.04 (0.02)	0.076	0.02 (0.01)	0.009	0.004 (0.008)	0.600
Diabetes (ref = no)	4.96 (0.55)	<0.001	3.98 (0.56)	<0.001	2.55 (0.19)	<0.001	2.12 (0.20)	<0.001
Hypertension (ref = no)	5.54 (1.60)	<0.001	2.88 (1.47)	0.050	3.71 (0.60)	<0.001	2.45 (0.52)	<0.001
CVD (ref = no)	2.71 (0.59)	<0.001	1.15 (0.58)	0.046	1.09 (0.23)	<0.001	0.49 (0.20)	0.016
Prior stroke or TIA (ref = no)	2.97 (0.76)	<0.001	1.55 (0.71)	0.031	0.88 (0.29)	0.003	0.21 (0.25)	0.395
History of traumatic brain injury (ref = no)	3.12 (1.73)	0.071	2.64 (1.53)	0.085	1.38 (0.66)	0.038	1.25 (0.54)	0.021
Depression (ref = no)	2.89 (0.61)	<0.001	1.98 (0.58)	<0.001	0.67 (0.24)	0.005	0.23 (0.20)	0.260

Abbreviations: CKD-EPI, Chronic Kidney Disease-Epidemiology Collaboration; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; PCP, Primary care provider; ref, reference; TIA, transient ischemic attack.

[a]Total number of medications from the PCP-generated medication list.

[b]Multiple linear regression model results for each factor adjusted for other factors in the model; β (SE) is the estimated mean (standard error) increase in the total number of PCP medications for each factor (relative to reference group for categorical factors or for a 1 unit increase or decrease as indicated for continuous factors) adjusted for other factors in the model.

[c]High-risk medications: Antihypertensives, oral diabetic agents, insulin, gabapentin, antipsychotics, anticoagulants, antiplatelets, aspirin, opioids, tramadol, benzodiazepines, Z-drugs, first-generation antihistamines, and muscle relaxants.

[d]Separate linear regression model results for each factor; β (SE) is the estimated mean (standard error) increase in the total number of PCP medications for each factor (relative to reference group for categorical factors or for a 1 unit increase or decrease as indicated for continuous factors).

[e]Separate linear regression model results for each factor; β (SE) is the estimated mean (standard error) increase in the number of high-risk medications for each factor (relative to reference group for categorical factors or for a 1 unit increase or decrease as indicated for continuous factors).

[f]Multiple linear regression model results for each factor adjusted for other factors in the model; β (SE) is the estimated mean (standard error) increase in the number of high-risk medications for each factor (relative to reference group for categorical factors or for a 1 unit increase or decrease as indicated for continuous factors) adjusted for other factors in the model.

[g]Cognitive impairment is defined as a score >1 SD below the norm in one or more cognitive domains.

[h]eGFR calculated using the ASN recommended creatinine-based refitted CKD-EPI equation without the race factor.

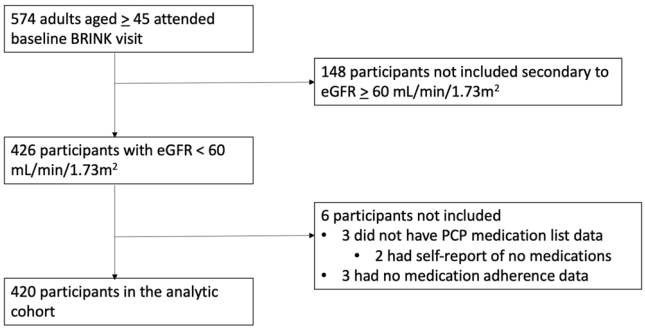

FIGURE A1 Participant flow diagram

As previously described[1,2], cognitive function was assessed at the baseline BRINK visit using the following assessments:

Tests of memory:

1. Verbal memory (Hopkins Verbal Learning Test-Revised, HVLTR[3])
2. Visual-spatial/memory (Brief Visuospatial Memory Test-Revised, BVMTR[4])

Tests of processing speed and executive function:

1. Concentration and processing speed (Symbol Digit Modalities Test, SDMT[5])
2. Processing speed and executive function (Color Trails Tests 1 and 2, CTT-1 and CTT-2[6])

Tests of verbal fluency and language:

1. Animal naming portion of 3MS (Modified Mini-Mental Status Examination, 3MS[7,8])
2. Verbal fluency/language and semantic memory (Controlled Oral Word Association Test, COWAT[9])

Scores were assessed as T-scores adjusted for age, sometimes education (SDMT, COWAT, CTT-1, and CTT-2), and sometimes race (COWAT[10]). Cognition was categorized according to the number of standard deviations (SDs) below the mean published norm. Cognitive impairment (CI) was defined as a score >1.0 SD below the mean published norm in one or more domains (memory, processing speed/executive function, and/or verbal fluency/language); moderate-to-severe CI was defined as scores ≥1.5 SD below the mean published norm in one or more domains.

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FIGURE A2 BRain IN Kidney baseline cognitive assessments

1. About how many medications are you taking every day?
2. About how many times a day do you take medications?
3. About what percentage of your mediations do you know the purpose of? (0%, 1-24%, 25-49%, 50-74%, 75-99%, 100%)
4. Who sets up your medications?
5. When did you start taking the particular combination of medications that you're taking now?
6. Many people find it difficult to follow a medication schedule exactly, especially if they have to keep doing it for a long time. About how many days in a month do you think you miss a dose of your prescription medications? (0 days, 1-3, 4-6, 7+)
7. Which medications do you most often miss taking?
8. What are the most common reasons you miss taking your medications?[1]
9. Does your insurance pay for 100% of the cost of drugs that your doctor prescribes for you?
    a. Is it that you have to pay a part of the cost (make a copayment) every time you fill a prescription, that only certain drugs are covered, that your insurance doesn't pay for drugs at all, or what?
    b. About how much money do you spend per month on all of your medications?
10. Which of the following insurance companies cover you?

Pillbox.[2] I would like you to set up one day of your medications in this pillbox as you would normally take them. Please hand me the bottle after you place the medication.

FIGURE A3 Medication adherence assessment. [1]Participants were given a list of possible reasons: (1) forgetfulness, (2) not getting a prescription filled on time, or having a problem getting a prescription filled at the pharmacy, (3) mail-order medications late, (4) lost medication, (5) not considered an important medication, (6) thought s/he was not supposed to take the medication, (7) did not know medication purpose, therefore did not take medication, (8) being high on alcohol or drugs, (9) forgetting to take your medication with you when you leave the house/are at a social activity, (10) there was no food or water available with which to take your pills, (11) work/school, (12) childcare, other caregiving responsibilities, (13) side effects, (14) could not afford, (15) other, (16) not applicable (16) forgetfulness+ not filling a prescription, (17) could not afford + other, (18) forgetfulness + social activity. [2]The pillbox portion of the MAA was completed only if participants (1) were taking four or more prescription medications, (2) were responsible for managing their own medications, and (3) brought their medication bottles to the study visit.