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Original Article

Difficulty with taking medications and the future risk of Alzheimer's disease and related dementias: Health and Retirement Study of Americans

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Abstract: Background: This study aims to determine if self-reported issues with managing medication could be an early sign of cognitive decline, possibly pointing to a future diagnosis of Alzheimer's Disease and Related Dementias (ADRD). There is currently very little information available about the link between issues with medication management and the later diagnosis of an ADRD, despite the potential clinical importance of such a link. Methods: We analyzed Health and Retirement Study participants present and interviewed at Wave 11 (2012) and followed them through Wave 16 (2020). Medication-taking difficulty (R11MEDS) was classified as no difficulty/don't do vs. difficulty/can't do. Separate cohorts excluded prevalent dementia (R11DEMENE) or AD (R11ALZHEE). Incident outcomes were first respondent-reported physician diagnoses (RwDEMENE, RwALZHEE). Kaplan-Meier curves and multivariable Cox models estimated associations. Results: Of 18,878 dementia-free and 19,348 AD-free HRS respondents at Wave 11, 3.0-3.9% reported difficulty/could not take medications. Kaplan-Meier curves diverged early between exposure groups. In fully adjusted Cox models, medication-taking difficulty predicted higher hazards of incident all-cause dementia (HR 1.59, 95% CI 1.23-2.06) and AD (HR 1.57, 95% CI 1.09-2.27), with corroborating pooled logistic estimates. Conclusion: Difficulty in Managing Medications is considered to be a robust prodromal indicator of ADRD, regardless of demographic influences. Therefore, the evaluation of an individual's ability to manage medications within routine assessment may represent a practical, costeffective means to identify cognitive decline and develop appropriate management strategies.

Keywords: Medication adherence, Alzheimer's disease and related dementias (ADRD), cognitive decline, cohort study, Health and Retirement Study (HRS)

Introduction

According to the latest reports, about one-fourth of the population of the U.S. [1] will be 65 years old or older by 2060 (approximately 100 million people) [2], and there is evidence that the elderly will continue to experience higher rates of depression as a result of the loss of family and friends, the increase in financial difficulties, and the added burden of having many different health problems that might lead to some form of mental or cognitive impairment (Dementia) [3-5]. In addition, dementia is now the seventh leading cause of death worldwide

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and is a leading factor in developing disabilities, especially among the elderly, who have to rely on others for care. Finally, Alzheimer's disease (AD) remains the most commonly diagnosed type of dementia, making up between 60% and 70% of all the current diagnoses [6].

Chronic disease states are one of the most significant barriers to adherence to treatment in patients with chronic illness and low social support, high levels of depressive symptoms, and low medication self-efficacy [7]. In the older adult population within the United States, the vast majority (95%) of older adults have at least 1 chronic condition that requires the ongoing use of medications. Furthermore, approximately 65% of older adults are taking multiple medications (i.e., polypharmacy), and approximately 40% of older adults are using five or more medications on a daily basis. Aside from the financial factors associated with adherence (such as the increased costs of medications), the difficulties associated with adherence for older adults are frequently compounded by a variety of non-financial factors. These factors may include cognitive problems (particularly in regard to executive functioning and memory), physical limitations (such as visual impairment or loss of dexterity), mental health problems (such as depression and anxiety), and social isolation [8, 9]. While cost-related non-adherence is a significant issue, functional and cognitive barriers often emerge earlier and are more directly indicative of neurodegenerative processes. Medication adherence suffers when aging affects cognition and physical function, causing timing/dosage mistakes [10, 11]. These errors interact dangerously with slower drug metabolism in older adults, creating a high-risk pathway for adverse drug events [12]. Therefore, differentiating between adherence issues driven by cost versus those driven by cognitive or functional ability is crucial for identifying early signs of dementia.

Functional disability has been linked to demographics, lifestyle risks, and chronic diseases in earlier work [13-15]. Some researchers thus categorized 13 diseases into four patterns showing disability risk, while some others grouped 14 diseases into five patterns tied to physical functional decline [16, 17]. Empirical evidence on Western disability trends shows inconsistencies. U.S. research presents diverging conclusions, declines in the 65+ cohort post-1980s versus plateaus/increases in the 53-88 group (1996-2010) [18-20]. European disability patterns vary widely [21-24]. In China, key limitations affect trend analyses: non-representative sampling, outdated (pre-2010) datasets, and exclusive focus on ADL impairment [25-28].

Functional Task Evaluations are shown through research to significantly enhance early detection of cognitive disorders within an aging population [29]. The primary purpose of this type of assessment is to evaluate functional abilities and provide information about whether individuals possess the ability to function independently or if they require assistance. This includes basic self-care, such as feeding, bathing, getting dressed etc., but it also includes more complex tasks necessary for independent living or functioning as an adult in society. Examples of these types of functional tasks are the Activities of Daily Living (ADLs), such as getting out of bed, grooming, eating, etc. and the Instrumental Activities of Daily Living (IADLs). Many IADL's require the use of higher level of cognitive processing and are used to assess the severity of decline in cognitive ability or mental status [30-32]. Examples of the types of IADLs include managing medications, household duties (e.g., shopping, cooking), using a telephone, managing personal finance and driving. All of these tasks require individuals to integrate their higher level of cognitive processing to be successful [33]. Strategic planning and task prioritizing skills directly impact an individual's ability to follow prescribed medication regimens and to successfully do grocery shopping. It is also noted that the onset of disability in IADLs often occurs earlier than in ADLs [34].

Elderly adults can be assessed as to independent functioning through IADLs (some of which may be evaluated in everyday care) [35]. Several studies, including one conducted with a large study population, have shown that adverse (notional) outcomes related to the use of certain IADLs (telephone use, transportation, managing medications, managing money) correlate with a higher risk for developing dementia at a later date [36]. Early indicator of financial management being a negative outcome showed up as early as 10 years prior to

recognition of ADRD when an individual developed (was diagnosed with) that disorder. Including IADL indicators (such as for medications and money management) in Cognitive Screening Tools, combined with demographic and health history, is valuable for enabling the clinician to identify patients with potential need for cognitive screening [37]. While there exist tools (for example, questionnaires) for dementia detection that could stimulate further assessment of cognitive ability to perform daily activities through comprehensive health assessments, dementia assessment is not performed routinely as part of health assessments for older adults [38, 39]. As part of the older adult's health assessment, the clinician can easily evaluate a patient to assess their ability to perform IADLs and thus provide further value to their evaluation as a result of this research that found IADLs predictive of clinically relevant health outcomes [28].

The ubiquitous nature of pharmaceutical consumption, combined with the accessibility of evaluation by primary care practitioners and pharmacists during standard clinical encounters, suggests that medication management difficulties could function as an especially significant risk factor for ADRD [40]. This study centered on medication adherence difficulties as a preliminary indicator of neurocognitive deterioration, largely because of the widespread prescription medication utilization among America's elderly population and the straightforward nature of identifying such challenges [41]. Using the linked HRS and Medicare claims data, we evaluated longitudinal associations between medication management challenges and ADRD risk.

Methods

Study design and data source

In the present study, data from the Health and Retirement Study (HRS) were analyzed (2012-2020). This longitudinal cohort study has been conducted biennially by the University of Michigan since 1992, supported by the National Institute on Aging (NIA U01AG009740) and the Social Security Administration. The HRS collects detailed economic, health, and social information from a representative national sample of approximately 37,000 adults aged 50 and older in the United States. A multi-stage area probability design is employed, with oversampling of specific demographic groups (including African Americans and Hispanics) and geographical stratification. The study protocol was approved by the Institutional Review Board of the University of Rochester (# MOD00009269).

Study sample and eligibility criteria

We used the Health and Retirement Study (HRS) and defined Wave 11 (2012) as baseline, with follow-up through Wave 16. The analytic cohort was assembled in sequential steps, summarized in the CONSORT flow diagram. Participants were eligible if they were present at Wave 11 (INW11=1) and completed the Wave 11 interview (R11IWSTAT=1). We then excluded prevalent disease at baseline, creating two outcome-specific cohorts: an all-cause dementia cohort excluding respondents with R11DEMENE=1, and an Alzheimer's disease (AD) cohort excluding respondents with R11ALZHEE=1.

The exposure was baseline difficulty taking medications (R11MEDS), operationalized into two groups: No difficulty/don't do (ND) versus positive difficulty/can't do (PD); other values were treated as unclassifiable and excluded. To ensure evaluable follow-up, we required evidence of post-baseline status across Waves 12-16 (interviewed or known deceased). In the final cohorts, the all-cause dementia analysis included 18,878 participants (18,309 ND vs. 569 PD), and the AD analysis included 19,348 participants (18,590 ND vs. 758 PD).

Outcome ascertainment

Outcomes were assessed biennially at Waves 12-16 using respondent-reported physician diagnosis indicators. Incident all-cause dementia was defined as the first follow-up wave with RwDEMENE=1 among participants free of dementia at baseline. Incident AD was defined analogously using RwALZHEE=1 among those without baseline AD. Participants were followed from the Wave 11 interview until the earliest of: first outcome occurrence, death, loss to follow-up, or completion of Wave 16.

Covariates

Covariates were selected a priori from baseline (Wave 11) and coded using clinically interpre-

table groupings. Sociodemographic covariates included age, sex, race, Hispanic ethnicity, education (3 levels), marital status (3 levels), and total income category (0 income plus quartiles).

Health behaviors included smoking (never/former/current), alcohol use (0, 1-2, ≥3 drinks/day), and physical activity (vigorous, moderate, and light activity categorized by frequency).

Clinical and functional covariates included BMI, ADL limitations (0, 1-2, ≥3), depressive symptoms (CES-D high vs. low), baseline cognitive function (TICS-27), and vascular/comorbidity history (hypertension, diabetes, cancer, lung disease, heart problems, stroke).

Data analysis

We constructed two prospective cohorts from the Health and Retirement Study, anchored at Wave 11 (2012): an all-cause dementia cohort and an Alzheimer's disease (AD) cohort. Participants were required to be present and interviewed at baseline, and we excluded prevalent disease at Wave 11 using respondent-reported doctor diagnosis indicators (R11DEMENE for dementia; R11ALZHEE for AD). Medication-taking difficulty was defined at baseline from R11MEDS and collapsed into two groups: no difficulty (ND) versus positive difficulty (PD). Follow-up extended through Wave 16, with incident outcomes identified at the first wave in which a respondent reported a new doctor diagnosis while interviewed.

Baseline characteristics were summarized by exposure group using means (SD) or counts (%). Group differences were evaluated using appropriate two-sample tests (t/Wilcoxon; χ^2/Fisher), alongside standardized mean differences to describe covariate balance. Time-to-event patterns were visualized with Kaplan-Meier curves and compared using log-rank tests. Primary associations were estimated with Cox proportional hazards models, reporting hazard ratios (HR) and 95% confidence intervals. Models were sequentially adjusted: unadjusted (M0), age/sex-adjusted (M1), and fully adjusted (M2) for sociodemographic, behavioral, clinical, functional, depressive-symptom, physical-activity, and cognitive measures. As a complementary discrete-time approach, we fit pooled logistic regression with person-wave data across Waves 12-16, including wave indicators and the same covariate sets. Reverse-causation sensitivity analyses repeated fully adjusted Cox models after restricting to cognitively normal baseline (TICS-27 ≥12), excluding early events at Wave 12, or both. All analyses are conducted with Python 3 with the pandas and statsmodels libraries, and a two-sided *p*-value <0.05 was considered statistically significant.

Results

Study flow and analytic cohorts

Participant selection is summarized in the CONSORT diagram (**Figure 1**). After applying the prespecified eligibility criteria, the all-cause dementia cohort comprised 18,878 participants (no difficulty [ND], n=18,309; medication-taking difficulty [PD], n=569), and the Alzheimer's disease (AD) cohort comprised 19,348 participants (ND, n=18,590; PD, n=758). These cohorts formed the basis for all subsequent primary and sensitivity analyses, with analytic Ns varying across models due to covariate missingness, as reflected in the model-specific denominators reported in **Tables 2**-**4**.

Baseline characteristics by medication-taking difficulty

Baseline characteristics are presented in **Table 1**. Across both cohorts, participants in the PD group were older (all-cause dementia: 69.9±13.8 vs. 66.3±11.2 years; AD: 72.4±14.3 vs. 66.4±11.3 years; both P<0.001) and had lower baseline cognitive scores (TICS-27: 11.2±4.9 vs. 15.0±4.4; 10.7±5.0 vs. 15.0±4.4; both P<0.001). Functional vulnerability was striking: severe ADL limitations (≥3) were far more common in PD than ND (all-cause dementia: 41.1% vs. 3.5%; AD: 45.6% vs. 3.9%; both P<0.001). PD was also associated with higher cardiometabolic and vascular comorbidity, including hypertension, diabetes, and prior stroke (all P<0.001 in both cohorts).

Time-to-event analyses for incident dementia and AD

Kaplan-Meier curves for incident all-cause dementia and AD, stratified by medication-taking difficulty, are shown in **Figure 2**. In Cox proportional hazards models (**Table 2**), medication-

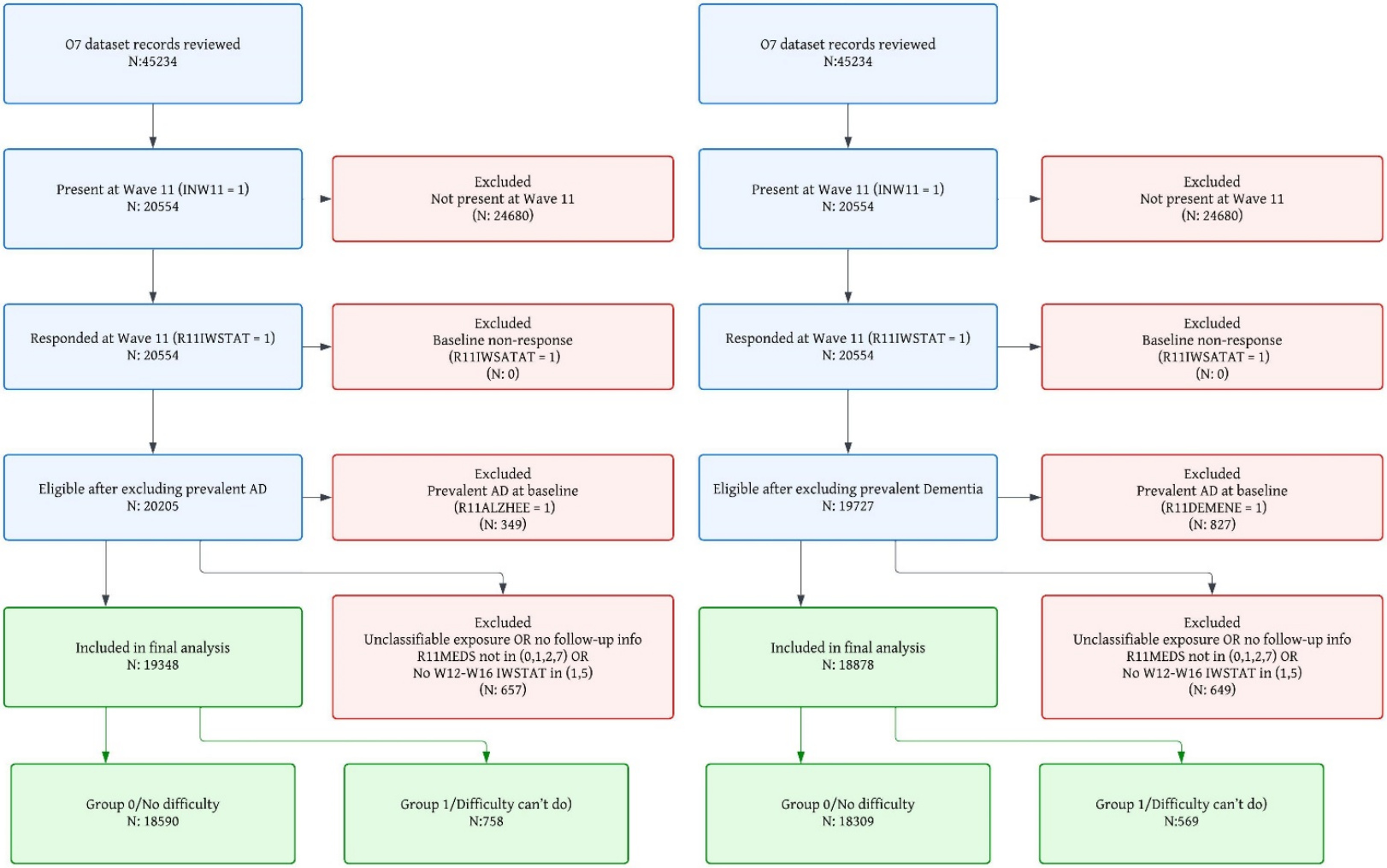

Figure 1. CONSORT flow diagram.

Table 1. Baseline characteristics by medication-taking difficulty group

Characteristic	All Cause Dementia Cohort			AD Cohort		
	ND	PD	*P* value	ND	PD	*P* value
N	18309	569		18590	758	
Age, years (mean [SD])	66.3 (11.2)	69.9 (13.8)	<0.001	66.4 (11.3)	72.4 (14.3)	<0.001
BMI (mean [SD])	28.7 (6.2)	28.1 (6.9)	0.054	28.6 (6.2)	27.5 (6.8)	<0.001
Cognition score TICS-27 (mean [SD])	15.0 (4.4)	11.2 (4.9)	<0.001	15.0 (4.4)	10.7 (5.0)	<0.001
Sex, n (%)			0.303			0.070
Male	7603 (41.5%)	224 (39.4%)		7727 (41.6%)	290 (38.3%)	
Female	10706 (58.5%)	345 (60.6%)		10863 (58.4%)	468 (61.7%)	
Ethnicity, n (%)			<0.001			<0.001
Non-Hispanic	15798 (86.4%)	445 (78.2%)		16050 (86.4%)	605 (79.8%)	
Hispanic	2487 (13.6%)	124 (21.8%)		2516 (13.6%)	153 (20.2%)	
Race, n (%)			<0.001			<0.001
White	13155 (72.0%)	346 (61.0%)		13367 (72.1%)	497 (65.7%)	
Black	3519 (19.3%)	153 (27.0%)		3572 (19.3%)	181 (23.9%)	
Other	1585 (8.7%)	68 (12.0%)		1601 (8.6%)	78 (10.3%)	
Education, n (%)			<0.001			<0.001
Below high school	3278 (17.9%)	225 (39.5%)		3374 (18.2%)	283 (37.3%)	
High school graduate	6232 (34.0%)	161 (28.3%)		6324 (34.0%)	230 (30.3%)	
Above high school	8796 (48.0%)	183 (32.2%)		8889 (47.8%)	245 (32.3%)	
Marital status, n (%)			<0.001			<0.001
Married/partnered	11903 (65.1%)	289 (50.8%)		12036 (64.8%)	357 (47.1%)	
Divorced/separated/widowed	5500 (30.1%)	249 (43.8%)		5630 (30.3%)	361 (47.6%)	
Never married	893 (4.9%)	31 (5.4%)		911 (4.9%)	40 (5.3%)	
Smoking, n (%)			<0.001			0.025
Never smoker	7980 (43.8%)	214 (38.0%)		8096 (43.8%)	304 (40.4%)	
Former smoker	7591 (41.7%)	230 (40.9%)		7712 (41.7%)	314 (41.8%)	
Current smoker	2635 (14.5%)	119 (21.1%)		2677 (14.5%)	134 (17.8%)	
Alcohol use, n (%)			<0.001			<0.001
0 (Non-drinker)	11258 (61.7%)	449 (79.3%)		11489 (62.0%)	618 (81.9%)	
1-2 drinks/day	5304 (29.0%)	74 (13.1%)		5350 (28.9%)	90 (11.9%)	
≥3 drinks/day	1697 (9.3%)	43 (7.6%)		1701 (9.2%)	47 (6.2%)	
Total income category, n (%)			<0.001			<0.001
0 income	2064 (11.3%)	56 (9.8%)		2079 (11.2%)	69 (9.1%)	
Q1	3887 (21.2%)	238 (41.8%)		3992 (21.5%)	294 (38.8%)	
Q2	3950 (21.6%)	151 (26.5%)		4049 (21.8%)	213 (28.1%)	
Q3	4155 (22.7%)	91 (16.0%)		4201 (22.6%)	140 (18.5%)	
Q4	4253 (23.2%)	33 (5.8%)		4269 (23.0%)	42 (5.5%)	
ADL limitations, n (%)			<0.001			<0.001
0 (No limitation)	15629 (85.4%)	167 (29.3%)		15747 (84.7%)	194 (25.6%)	
1-2 (Mild-moderate)	2040 (11.1%)	168 (29.5%)		2122 (11.4%)	218 (28.8%)	
≥3 (Severe)	640 (3.5%)	234 (41.1%)		721 (3.9%)	346 (45.6%)	
Cognition category, n (%)			<0.001			<0.001
Normal (12-27)	14071 (79.2%)	223 (47.5%)		14139 (78.7%)	242 (43.9%)	
CIND (7-11)	3063 (17.2%)	164 (35.0%)		3141 (17.5%)	194 (35.2%)	
Demented (0-6)	640 (3.6%)	82 (17.5%)		683 (3.8%)	115 (20.9%)	
Depressive symptoms (CES-D), n (%)			<0.001			<0.001
Low (0-3)	15169 (85.4%)	224 (47.9%)		15293 (85.1%)	264 (48.1%)	
High (4-8)	2603 (14.6%)	244 (52.1%)		2668 (14.9%)	285 (51.9%)	
Vigorous physical activity, n (%)			<0.001			<0.001
≥1/week	4623 (25.3%)	48 (8.4%)		4648 (25.1%)	53 (7.0%)	
≥1/month	3840 (21.0%)	58 (10.2%)		3866 (20.9%)	65 (8.6%)	
Never	9789 (53.6%)	463 (81.4%)		10019 (54.1%)	639 (84.4%)	

Moderate physical activity, n (%)			<0.001			<0.001
≥1/week	9063 (49.6%)	139 (24.4%)		9121 (49.1%)	170 (22.4%)	
≥1/month	5528 (30.2%)	134 (23.6%)		5589 (30.1%)	152 (20.1%)	
Never	3692 (20.2%)	296 (52.0%)		3853 (20.8%)	436 (57.5%)	
Light physical activity, n (%)			<0.001			<0.001
≥1/week	10047 (55.0%)	139 (24.5%)		10118 (54.5%)	160 (21.2%)	
≥1/month	6301 (34.5%)	190 (33.5%)		6379 (34.4%)	221 (29.3%)	
Never	1935 (10.6%)	239 (42.1%)		2065 (11.1%)	374 (49.5%)	
Hypertension (Yes), n (%)	10764 (58.8%)	427 (75.0%)	<0.001	10968 (59.0%)	576 (76.0%)	<0.001
Diabetes (Yes), n (%)	4174 (22.8%)	215 (37.8%)	<0.001	4261 (22.9%)	286 (37.7%)	<0.001
Cancer (Yes), n (%)	2580 (14.1%)	114 (20.0%)	<0.001	2625 (14.1%)	163 (21.5%)	<0.001
Lung disease (Yes), n (%)	1680 (9.2%)	115 (20.2%)	<0.001	1741 (9.4%)	158 (20.8%)	<0.001
Heart problems (Yes), n (%)	4066 (22.2%)	245 (43.1%)	<0.001	4202 (22.6%)	336 (44.3%)	<0.001
Stroke (Yes), n (%)	1373 (7.5%)	140 (24.6%)	<0.001	1471 (7.9%)	225 (29.7%)	<0.001

Table 2. Cox proportional hazards models

Outcome	Model	Term	HR (95% CI)	*P* value
All-cause Dementia	M0	PD (Difficulty/can't do) vs. ND (No difficulty)	3.83 (3.10-4.72)	<0.001
	M1	PD (Difficulty/can't do) vs. ND (No difficulty)	3.19 (2.58-3.95)	<0.001
	M2	PD (Difficulty/can't do) vs. ND (No difficulty)	1.59 (1.23-2.06)	<0.001
AD	M0	PD (Difficulty/can't do) vs. ND (No difficulty)	4.36 (3.30-5.74)	<0.001
	M1	PD (Difficulty/can't do) vs. ND (No difficulty)	3.00 (2.26-3.99)	<0.001
	M2	PD (Difficulty/can't do) vs. ND (No difficulty)	1.57 (1.09-2.27)	0.016

M0: undadusted, M1: age + sex adjusted, M2: fully adjusted.

Table 3. Discrete-time pooled logistic regression for incident all-cause dementia and AD by medication-taking difficulty group

Outcomes	Model	N used	Events	OR (95% CI) PD vs. ND	*P* value
All-cause dementia	M0 (Pooled logistic)	81,771	1,176	3.91 (3.14-4.86)	<0.001
	M1 (Pooled logistic)	81,771	1,176	3.41 (2.70-4.31)	<0.001
	M2 (Pooled logistic)	78,309	1,104	1.66 (1.24-2.24)	<0.001
AD	M0 (Pooled logistic)	84,180	508	4.40 (3.32-5.82)	<0.001
	M1 (Pooled logistic)	84,180	508	3.10 (2.28-4.21)	<0.001
	M2 (Pooled logistic)	80,254	451	1.61 (1.08-2.42)	0.021

Model definitions: M0 exposure + wave; M1 adds age + sex; M2 fully adjusted. Odds ratios (OR) with 95% CI and *p*-values for the exposure (medication-taking difficulty) from pooled logistic regression. Each participant contributes one row per follow-up wave (12-16) until incident outcome or censoring.

taking difficulty was strongly associated with higher risk in unadjusted analyses (all-cause dementia: HR 3.83, 95% CI 3.10-4.72; AD: HR 4.36, 95% CI 3.30-5.74; both P<0.001). Adjustment for age and sex attenuated the associations but did not eliminate them (all-cause dementia: HR 3.19, 95% CI 2.58-3.95; AD: HR 3.00, 95% CI 2.26-3.99; both P< 0.001). In fully adjusted models, PD remained independently associated with incident all-cause dementia (HR 1.59, 95% CI 1.23-2.06; P<0.001) and incident AD (HR 1.57, 95% CI 1.09-2.27; P=0.016).

Discrete-time pooled logistic regression across follow-up waves

Discrete-time pooled logistic regression results are summarized in **Table 3**. This approach leveraged repeated wave-level observations, with each participant contributing person-wave rows until incident outcome or cen-

Table 4. Reverse causation sensitivity analyses (Cox M2): All-cause dementia and AD

Outcome	Strategy	N	Events	HR_CI	*P*_value
All-cause dementia	RC0	17,975	1,104	1.59 (1.23-2.06)	<0.001
	RC1	14,128	584	2.43 (1.59-3.71)	<0.001
	RC2	17,721	850	1.62 (1.19-2.22)	0.002
	RC3	14,034	490	2.36 (1.43-3.89)	<0.001
AD	RC0	18,242	451	1.57 (1.09-2.27)	0.016
	RC1	14,214	191	2.39 (1.18-4.85)	0.016
	RC2	18,147	356	1.25 (0.78-2.00)	0.350
	RC3	14,189	166	2.40 (0.99-5.83)	0.052

M2 (fully adjusted) hazard ratios (HR) for the exposure across reverse-causation strategies. RC1 restricts baseline cognition to normal (TICS-27 ≥12). RC2 excludes early incident events occurring at Wave 12. RC3 applies both restrictions. Each model reports the effective N and number of events used by Cox after automatic omission of missing covariates.

soring. Consistent with the Cox findings, PD was associated with substantially higher odds of incident all-cause dementia in minimally adjusted models (M0 OR 3.91, 95% CI 3.14-4.86; P<0.001), with attenuation after covariate adjustment. In the fully adjusted model, PD remained associated with increased odds of all-cause dementia (OR 1.66, 95% CI 1.24-2.24; P<0.001; 78,309 person-wave rows; 1,104 events). A similar pattern was observed for AD, where the fully adjusted association persisted (OR 1.61, 95% CI 1.08-2.42; P=0.021; 80,254 person-wave rows; 451 events).

Reverse-causation sensitivity analyses

Reverse-causation analyses are shown in **Table 4**, using fully adjusted Cox models under progressively stricter strategies. The primary fully adjusted estimate (RC0) mirrored the main Cox results for both outcomes (all-cause dementia: HR 1.59, 95% CI 1.23-2.06; P<0.001; AD: HR 1.57, 95% CI 1.09-2.27; P=0.016). When restricting to participants with normal baseline cognition (RC1), effect estimates strengthened for all-cause dementia (HR 2.43, 95% CI 1.59-3.71; P<0.001) and AD (HR 2.39, 95% CI 1.18-4.85; P=0.016), suggesting that medication-taking difficulty may capture early vulnerability even before measurable impairment. Excluding early incident events (RC2) yielded a comparable estimate for all-cause dementia (HR 1.62; P=0.002) but attenuated the AD association (HR 1.25; P=0.350). Under the combined restriction (RC3), associations remained elevated yet less precise, particularly for AD (HR 2.40; P=0.052).

Discussion

One fundamental principle of geriatric practice emphasizes that medical illnesses and social determinants of health that undermine well-being and functional capacity often co-occur and interact [42]. Chronic conditions, such as hypertension, osteoarthritis/rheumatoid arthritis and diabetes, which many older people suffer from, must be studied by going beyond reductionist models: single-disease models are not adequate, and dichotomous multimorbidity variables may mask differential disease effects [43, 44]. People with diabetes who suffer from cognitive impairment struggle with managing their diabetes, resulting in complications affecting the blood vessels and other organs. These complications further increase the risk of cerebrovascular damage and cognitive decline. The combination of diabetes and cognitive impairment creates a situation where a person experiences multiple physical disabilities that create more difficulties in managing their diabetes. While caregivers may help manage the effects of cognitive impairment on diabetes self-management, they often face insurmountable challenges when attempting to help manage the behaviors associated with dementia [45-47]. Cognitive decline associated with diabetes is caused by metabolic disorders that produce an inflammatory response, produce insulin resistance, cause oxidative stress, and create cerebrovascular disease; all of which adversely affect the functioning of the frontal and subcortical regions of the brain, increasing future risk for developing vascular dementia. Diabetes has also been linked to Alzheimer's disease through alterations to insulin regulation, fluctu-

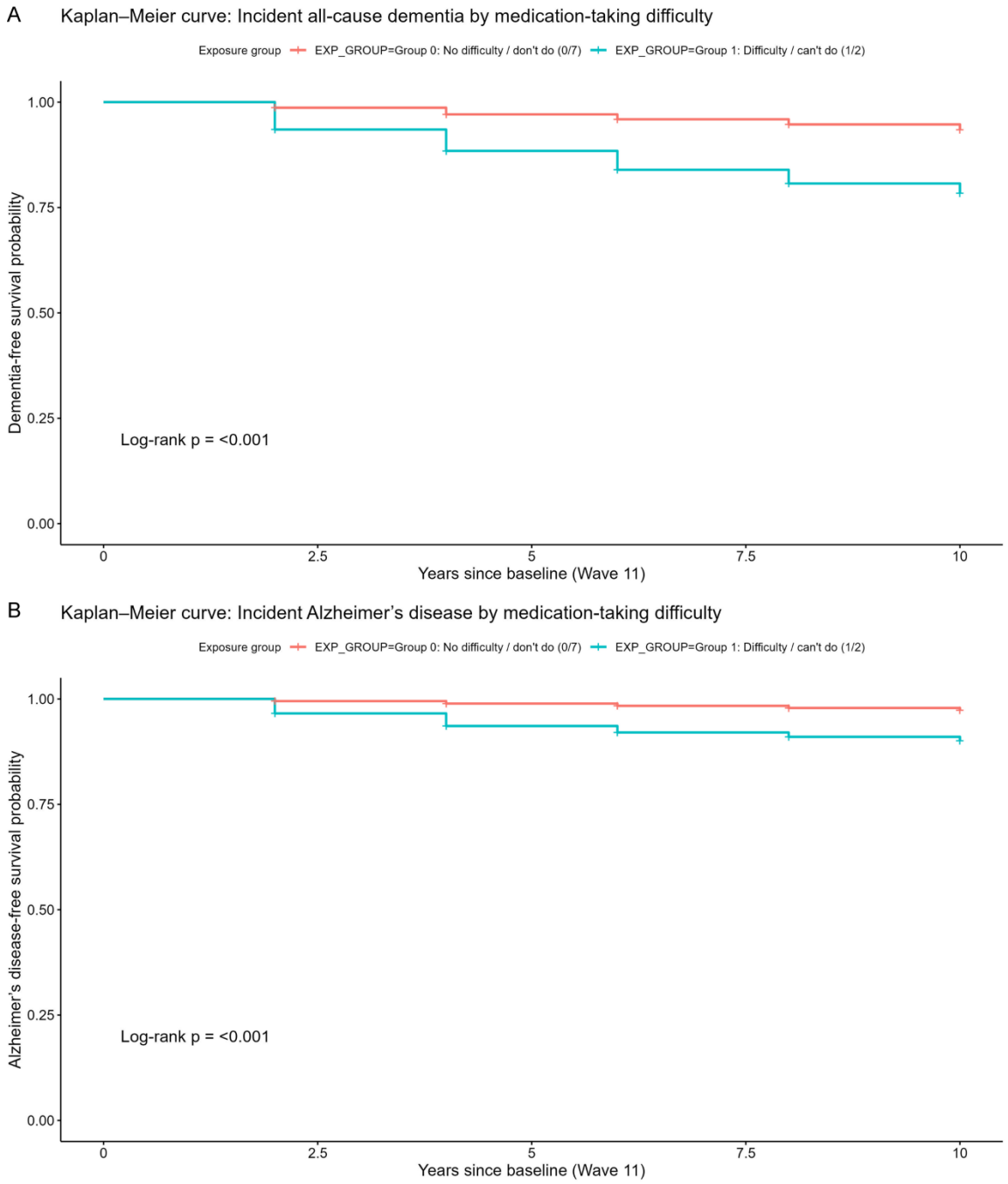

Figure 2. Kaplan-Meier curve for incident (A) all-cause dementia and (B) AD, by medication-taking difficulty group. Log-rank *p*-value compares survival curves between exposure groups.

ations in glucose levels associated with ApoE ε4, and toxic glucose levels in the brain leading to accelerating age-related neurocognitive decline [48, 49].

Long-term prescribing through various pill combinations and frequent daily doses of the same medication can lead to significantly lower levels of medication adherence among patients with multiple chronic medical problems, resulting in substantially greater medication non-compliance [41]. In addition to causing significant problems for chronic disease management, medication non-compliance is due to the com-

plex interplay between innumerable factors, including the individual characteristics of a patient (e.g., concurrent psychiatric disorders, health-disbeliefs), dire social and economic barriers (underserved healthcare access - absence of support from the healthcare system), clinical factors (length of treatment, side effects), and systemic barriers (clinician/patient relationships). Neuro-cognitive impairment is clearly a significant risk factor for non-compliance in medicated patients, and neuro-cognitive impairment can impede the patients' ability to properly plan and take their medications because of the impact of comorbid conditions on their executive functions [50, 51]. Older adult patients, in particular, have additional risk factors that can lead to decreased medication adherence; normal age-related declines in sensory and motor function (vision, hearing, manual dexterity) are frequently compounded by their cognitive impairments [52, 53].

Reported medication adherence difficulties should prompt a careful search for a wide array of other problems that may impact an individual's functional capabilities [30]. Difficulties in medication management indicate the need for a broad evaluation of their functional capacities and cognitive status. Although such problems are appropriately noted as a risk factor for ADRD, the underlying relationship is usually more complicated. Many ADRD, or even mild cognitive impairment (MCI), a condition of cognitive deficits not yet significantly impairing independent functioning, go undiagnosed for years. Studies document impaired medication management decision-making in individuals with MCI. Thus, many reporting trouble managing their prescriptions are likely to be already experiencing undiagnosed cognitive impairment [40, 54-56].

Challenges with managing medications can signal more global IADL impairment, especially financial skills. In assessing medication nonadherence or financial difficulty, providers should take into account anosognosia, diminished awareness of functional loss, prevalent in cognitive decline from MCI to dementia. Therefore, combining the caregiver report with the patient report guarantees a trustworthy assessment of functional capacities [30]. Wang et al. posited that although declining cognition (cognitive impairment no dementia to dementia) predicted increasing medication management difficulty, also demonstrated by Kuzuya et al., cost-related nonadherence was not similarly associated. Substantial cost increase arises chiefly in moderate/severe dementia stages, wherein cognitive decline requires resource-intensive, prolonged care support. This discrepancy may be due to their sample's functional independence: self-responding HRS participants were likely not sufficiently impaired to trigger the astronomical care costs that magnify socioeconomic barriers in late dementia [57-60].

Whereas Kuzuya et al. and Sokol et al. implied that medication management difficulty and nonadherence both uniformly increase the risk of hospitalization, Wang et al. indicated that dementia patients are especially susceptible. Progressive ADRD erodes medication self-administration aptitude just as complicated multi-drug regimens become essential, setting the stage for a perfect storm for chronic disease exacerbations necessitating hospitalization. Hospitalization risk demonstrated cognitive-stratified relationships: cost-driven nonadherence mattered most for intact cognition, whereas medication management challenges dominated in dementia, and neither impacted the cognitive impairment/no dementia cohort [57, 58, 61-63].

In keeping with extant literature on presymptomatic functional decline in ADRD, our results confirm medication management difficulties as precursors of cognitive decline, pointing to their usefulness in early-intervention models [41, 57, 64]. Both our research and Barthold et al. (2020) demonstrate that medication problems strongly predict incipient ADRD, with French studies corroborating IADL-based predictions. Whereas previous studies employed planned specialist diagnoses, our real-world clinical data demonstrated an incremental risk increase near diagnosis, adding to the evidence for medication difficulties as precursors of cognitive decline. AD's more robust association is due to its unique cognitive pathology, a confluence of deficits in episodic memory, executive function, working memory, information processing speed and prospective planning that singularly undermines medication management earlier and more severely than non-AD dementias [50].

Senior citizens who neglect themselves greatly struggle with taking their medicine as prescribed, especially if they take multiple drugs or have some limitation with their physical ability to take these medicines. If a physician identifies noncompliance, they should assess barriers [65]. Some research indicates for patients with ADRD, there are four factors related to greater compliance with oral medications: being male gender, being at least 86 years old, having more polysychopharmacy, and taking AD medications from the lower tier formulary [8]. The chronicity of lack of manual dexterity affects the ability of patients with physical impairment to be compliant with their medications, especially things like showing up to an appointment, using an inhaler, putting eye drops in their eyes, and opening medication containers. All of these individuals need to have access to tailored support systems, such as dose pack systems, modified MDIs, and devices to assist in receiving eye drops, etc., and therefore researching the root causes of medication nonadherence will assist with developing successful intervention strategies for people in this population [65, 66].

It is vital to identify cognitive decline as soon as possible, as most treatments do not reverse the process of cognitive decline [9]. Early diagnosis enables individuals, their families, and caregivers to receive the appropriate care. An accurate diagnosis gives patients and their families access to community resources and the support needed to remain independent, and it allows families to organize finances, make legal arrangements, and plan for the future [67]. Traditional cognitive assessments are expensive, complex, and take place over an extended period of time. Continuous tracking of adherence to a prescribed medication regimen allows for the early identification of proven prodromal cognitive impairment. Continuous tracking offers an effective method of identifying the prodromal stage of decline during the ideal timeframe for therapeutic or behavioral intervention [9]. A number of strategies can alleviate common delays in ADRD diagnosis and management. Firstly, primary care clinicians can involve neuropsychologists as consultants through in-person/virtual visits and the Project ECHO® tele-mentoring model [68]. Secondly, they can seek out specialist dementia training through programs that engage academic geriatricians with community practices to create Age-Friendly Health Systems and augment interprofessional dementia care. Thirdly, clinical training programs must curricula address diagnostic hurdles by instituting longitudinal geriatric rotations, memory clinic experiences, and heterogeneous patient panels, including assisted living populations [67].

The direction of future research planning in this field should focus on improving the early and accurate detection of functional decline, particularly through low-burden methods such as identifying medication-taking difficulties, so that healthcare providers can deliver more effective and timely care than ever before. During clinic appointments, primary care providers and pharmacists should regularly gauge medication comprehension and social barriers (e.g., financial constraints) among patients and their caregivers. Separately, home healthcare nurses performing visits provide essential medication education at the point of care. In addition to the fact that patient education and behavior modification can improve compliance, identifying innovative cognitive predictors of adherence could enhance clinical decision-making. Emerging evidence positions prospective memory - the neurocognitive ability to form, retain, and implement future intentions upon encountering cues (i.e., remembering planned actions) - as a significant adherence determinant [50, 57, 69].

Implications for practice and research

Our research finds that asking one simple question about difficulty managing your medication could provide an early warning of having ADRD (Alzheimer's Disease and Related Diseases) years prior to being diagnosed. In contrast to many cognitive batteries that require complex assessment, dysfunction in managing medications is a functional marker that clinicians will easily be able to determine during routine primary care or pharmacy appointments. Medications with difficulty managing should not only be interpreted by clinicians as adherence, and that pillboxes solve the problem, but it should also be considered as a potential indicator of underlying cognitive decline and therefore warrant an assessment of cognitive function. Future studies will be able to establish a causative relationship between these medications

and different cognitive domains (for example, prospective memory vs. executive function) that are causing these problems. It will also be of great interest to discover whether assisting individuals with medication management in early interventions can delay more extensive disability.

Limitations

This research is supported by data from a substantial and nationally representative cohort and takes into consideration several key demographic variables when looking at the study sample size; however, as is common with secondary data analysis, this research has some limitations. The primary limitation is that we did not assess quality of life or behavioural symptoms using standardised measures, which are important as complementary variables when assessing dementia-related functional decline. Other limitations include that we have not considered medication cost as a determinant of medication adherence; therefore, future studies regarding medication adherence should include this variable as an important factor. Additional limitations of the current study include reliance on self-reported measures, potential misclassification of medication difficulty due to participant perception, and no clinical confirmation of the ADRD diagnosis (the diagnosis was based solely on claims and participant reports). Although the HRS cognitive impairment no dementia/dementia evaluations are clinically standardised, there is very little granularity to the ADRD longitudinal classifications. Furthermore, the use of telephone survey methods restricts the ability to generalise the results across a wider population. Lastly, differences in sample composition for both time lag analyses do not allow comparisons of odds ratios. Despite these limitations, the consistent relationships observed throughout the sensitivity analyses support the credibility of the findings and highlight the importance of medication difficulty as an early predictor of cognitive impairment.

Conclusion

The forecast of future cognitive impairment and diagnosis of ADRD is a strong, independent predictor of how effectively the patient manages their medications. The result of our research indicates that older adults who have reported difficulty managing their medications face an increased chance of developing Alzheimer's disease or dementia when adjusted for age, education and various other factors in the patient's life. Additionally, because most patients are diagnosed with ADRD long after they have shown signs of cognition problems, medical professionals must develop methods for identifying early warning signs of cognitive impairment. We recommend that health-care providers routinely ask patients if they have difficulty managing their medications; by incorporating this assessment into their regular care practices, they can determine the level of cognitive function in the patient and offer them assistance sooner so that they and their family members can effectively prepare for the gradual deterioration associated with ADRD.

Disclosure of conflict of interest

None.

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