Stroke

ORIGINAL CONTRIBUTION

Antihypertensive Medication Adherence, *APOE* Genotype, and Subsequent Dementia in Community-Dwelling Adults ≥50 Years

Yanan Li, PhD; Chenglong Li, PhD

BACKGROUND: We aim to examine prospective associations of longitudinal adherence to antihypertensive medication, *APOE* ε4 carrier, and subsequent dementia risk in community-dwelling middle-aged and older adults.

METHODS: A longitudinal cohort using 12-year survey data from wave 8 (2006) to wave 14 (2018) in the Health and Retirement Study, an ongoing national survey recruiting community-dwelling adults aged ≥50 years in the United States. Longitudinal adherence to antihypertensive medication was evaluated during wave 8 (2006) to wave 10 (2010), based on self-reported antihypertensive medication use at each wave. Incident dementia cases were ascertained during wave 10 (2010) to wave 14 (2018) by combining self-reported diagnosis and standardized cognitive batteries, excluding prevalent cases during the medication adherence evaluation period. Cox proportional hazard regression was utilized to assess dementia risk, with adjusted hazard ratios (HR) and 95% CIs calculated, controlling for sociodemographic characteristics, socioeconomic status indicators, lifestyle factors, and clinical conditions, as well as blood pressure measurements.

RESULTS: A total of 18 469 participants were screened, after which 11 835 participants (mean [SD] age: 66.2 [10.1] years; men: 40.6%) were included, with 1136 incident dementia cases. After controlling blood pressure and other known risk factors, hypertension participants who persistently adhered to antihypertensive medication during follow-up had a 27% lower dementia risk (HR, 0.73 [95% CI, 0.61–0.87]) than the low adherence group, which was more evident than the associations between baseline antihypertensive medication use and dementia. The difference in dementia risk was insignificant when comparing the high adherence group with the normotension group (HR, 1.03 [95% CI, 0.88–1.21]). The results were consistent in non-*APOE* ε4 carriers (HR, 0.73 [95% CI, 0.59–0.89]) versus *APOE* ε4 carriers (HR, 0.75 [95% CI, 0.55–1.02]; *P* for interaction: 0.939).

CONCLUSIONS: Persistently adhering to antihypertensive medication was consistently associated with a lower subsequent dementia risk in community-dwelling middle-aged and older adults.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: antihypertensive agents ■ blood pressure ■ dementia ■ genotype ■ hypertension

The disease burden of dementia is surging rapidly in the world.[1] It is estimated that the number of people living with dementia is expected to increase from 55 million in 2019 to 139 million in 2050 around the world.[2] Due to the lack of effective treatments, dementia prevention remains the top priority, stressing the need to identify early preventive measures.[3]

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Midlife hypertension has been identified as one modifiable risk factor of dementia. In the global range, midlife hypertension accounts for almost 1.9% of dementia cases.[1] It has also been found that elevated blood

Correspondence to: Chenglong Li, PhD, Medical School, Tianjin University, Tianjin 300072, China. Email chenglongli@tju.edu.cn
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Nonstandard Abbreviations and Acronyms

BP	blood pressure
GBTM	group-based trajectory modeling
HR	hazard ratio
HRS	Health and Retirement Study
IPW	inverse probability weighting
SBP	systolic blood pressure

pressure (BP) in midlife is significantly associated with accelerated cognitive decline or increased dementia risk in late life.[4–6] Our previous work reveals associations between elevated cumulative BP since midlife with subsequent cognitive decline and dementia onset.[6] Consequently, whether controlling hypertension can alleviate dementia risk associated with elevated BP has become an intriguing question. The Systolic Blood Pressure (SBP) Intervention Trial confirmed that the intensive SBP control (<120 mm Hg), versus 140 mm Hg, reduced the risk in the combined outcome of mild cognitive impairment or probable dementia by 15%.[7] However, no statistically significant risk reduction was observed for probable dementia alone.[7] Evidence from observational studies also suggested relationships between antihypertensive medication and reduced dementia risk.[8,9] Nevertheless, there remain unanswered questions. First, reports from interventional trials are collected in highly selected clinical populations, with limited generalizability. Moreover, the long-term time course or pattern of antihypertensive treatment has seldom been evaluated. Finally, it is well-established that the ε4 allele of the *APOE* can increase the risk of Alzheimer disease,[10,11] although little is known whether the *APOE* ε4 carrier status can interact with antihypertensive medication in relation to new-onset dementia.

Hence, our study examined the associations between the longitudinal time course of receiving antihypertensive medication, *APOE* ε4 carrier status, and dementia risk.

METHODS

Data Availability and Sharing

Original survey data sets from the HRS (Health and Retirement Study) are freely available to all bona fide researchers. Access to data can be obtained by visiting their official websites (https://hrs.isr.umich.edu/about).

Study Population and Design

The study is based on the HRS, a national longitudinal survey of community-dwelling adults aged ≥50 years in the United States. The HRS data is sponsored by the National Institute on Aging (grant number U01AG009740) and is conducted by the University of Michigan.[12] The HRS conducted biennial surveys, for example, waves, to collect longitudinal data on various aspects, including physical health. Details about the cohort's objectives, design, and methods can be found elsewhere.[13] We used the 12-year survey data for research, from wave 8 (2006) to wave 14 (2018), as the BP measurements in HRS started from wave 8. As denoted in Figure 1A, a life span approach was applied for study design, with the survey data from wave 8 (2006) to wave 10 (2010) utilized to examine antihypertensive medication time course and data from wave 10 (2010) to wave 14 (2018) utilized to evaluate dementia onset, aligning with a previous study.[6] The wave 8 (2006) was considered the baseline. The HRS was approved by the institutional review board at the University of Michigan and the National Institute on Aging (HUM00061128), with informed consent provided for all participants before enrollment. All participants' data were analyzed in an anonymous fashion, with no attempts made to identify or link sensitive person-level information to external data sources. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guideline.

Hypertension and Antihypertensive Medication

Based on standardized protocols, SBP and diastolic BP were measured 3× by trained research staff, using the Omron HEM 780 Monitor. Aligning with a previous study,[14] we used the average of the second and third BP readings for analysis. Respondents in the HRS were asked whether a doctor had told s/he had been diagnosed with high BP or hypertension. And, if a report of high BP is disputed at a certain wave, trained research staff will ask the respondents to further confirm the reported diagnosis. We defined the hypertension diagnosis at baseline, according to the 2017 American College of Cardiology/American Heart Association hypertension guidelines,[15] as either a physician-confirmed diagnosis or mean SBP/ diastolic BP ≥140/90 mm Hg or taking antihypertensive medication.

At each wave, respondents in the HRS were asked, "To lower your blood pressure, are you now taking any medication?" And those answering "yes" were categorized as using antihypertensive medication at the current wave. Only self-reported data was utilized for medication use evaluation, without incorporating external pharmacy records or healthcare utilization data for validation. We considered both baseline antihypertensive medication and the time course of antihypertensive medication during wave 8 and wave 10. We categorized baseline medication use as (1) normotension, without using medication; (2) hypertension, not using antihypertensive medication; and (3) hypertension, using antihypertensive medication.

The time course of antihypertensive medication during wave 8 and wave 10 was evaluated via 2 approaches. First, we evaluated the longitudinal adherence to antihypertensive medication, categorized as (1) normotension, without using medication; (2) hypertension with low adherence (≤1 wave reporting medication use); (3) hypertension with moderate adherence (2 waves reporting medication use); and (4) hypertension with high adherence (consistently reporting medication use). Second, based on repeated measurements, a group-based trajectory modeling (GBTM) approach was applied to identify longitudinal trajectories of medication use. The GBTM has been widely embraced to evaluate longitudinal trajectories of health-related indices,[16] with applications in evaluating long-term medication adherence.[17] Latent trajectories were identified by the estimated probability of using antihypertensive medication at each

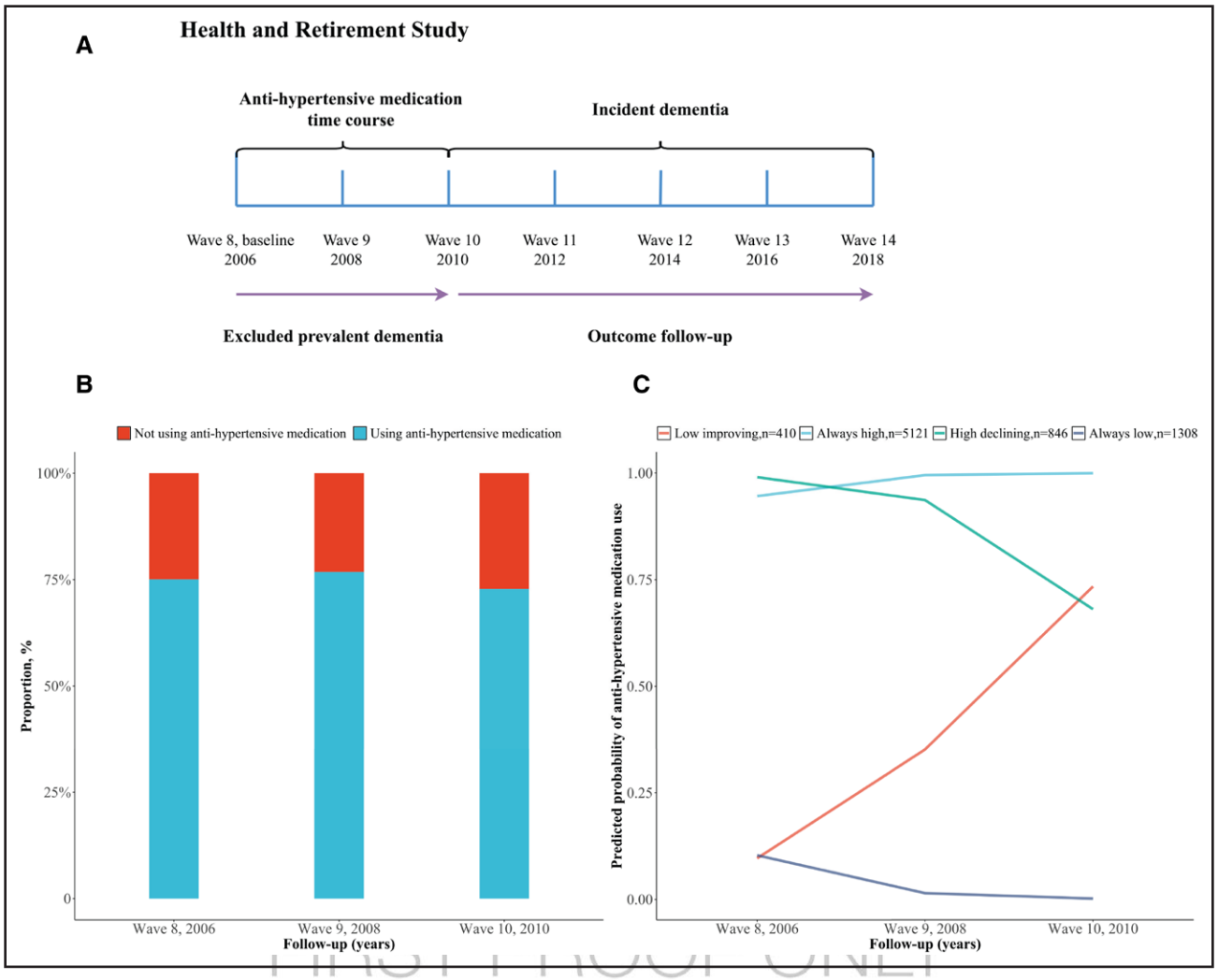

Figure 1. Study design and time course of antihypertensive medication use.
A, Study design and timeline. **B**, Proportions of antihypertensive medication use during wave 8 to wave 10, restricted to participants with hypertension at baseline (wave 8). **C**, Identified latent trajectories of antihypertensive medication use during wave 8 to wave 10, restricted to participants with hypertension at baseline (wave 8). The group-based trajectory modeling approach was applied to estimate the latent trajectories of antihypertensive medication use, based on survey data during wave 8 to wave 10.

wave, with respondents of the same trajectory sharing a similar adherence pattern.[17] The model fitting statistics of GBTM were presented in Table S1. Although the 2-group model showed the most optimal fitting statistics, we determined that the 4-group model would provide better clinical interpretability. Consequently, we used the 4-group GBTM for ascertaining medication trajectories.

APOE ε4 Carrier Status

The *APOE* genotype data were released as the *APOE* and Serotonin Transporter Alleles data product by the HRS team.[18] Participants eligible for the inclusion were those who consented and completed salivary DNA collection in 2006 (phase 1), 2008 (phase 2), 2010 (phase 3), or 2012 (phase 4). Based on 2 single-nucleotide polymorphisms, rs429358 and rs7412, 3 major isoforms (ε2, ε3, and ε4) of *APOE* were derived.[11,18] Then, with the algorithm in Table S2, we derived the status of *APOE* ε4 carrier (carrier or noncarrier). All DNA samples were genotyped and analyzed at the Center for Inherited Disease Research Genetic Resources Core Facility and Fragment Analysis Facility at Johns Hopkins University (https://cidr.jhmi.edu), with the further detailed protocol presented elsewhere.[18]

Ascertainment of Dementia Cases

Dementia cases were ascertained via 2 approaches. First, respondents were asked whether a doctor had told s/he had been diagnosed with Alzheimer disease or dementia at each wave, with additional confirmation by research staff. Second, an alternative approach was applied using standardized cognitive batteries. Based on the Aging, Demographics, and Memory Study in the HRS, Crimmins et al[19] developed an approach to defining dementia using the original HRS data. Without incorporating the proxy evaluation, 3 standard cognitive batteries were utilized for ascertaining dementia, including the word recall, the serial 7s, and backward counting tests, forming a cognitive summary score of 0 to 27. Respondents with a summary score from 0 to 6 were classified as demented,[19] aligning with previous studies.[6,20] Further details regarding administered cognitive

batteries and scoring criteria were presented in Supplemental Methods. The alternative approach based on cognitive batteries has been previously validated using the original HRS data, presenting a sensitivity of 36%, a specificity of 90%, and an overall accuracy of 84%.[21] By combining the 2 approaches, dementia cases were defined as either a reported diagnosis by physicians or dementia status by the alternative approach. For participants with dementia, years to dementia onset were calculated from the age of attending baseline survey until the age of first incident dementia diagnosis, while those without dementia were censored, with censoring time calculated from the age of attending baseline survey until death, loss-to follow-up, or end of study, whichever happened first.

Covariates

Covariates were adjusted according to previous studies and prior knowledge.[6,14] Sociodemographic characteristics included age (years), White race (yes or no), sex, and cohabitation status (living alone or not). We considered indicators of socioeconomic status, including family annual income, education, employment status, and medical insurance coverage, identical to a previous study.[22] Lifestyle factors included physical activity (engaging in vigorous or moderate activities no less than once per week), alcohol consumption (at least 3 days per week), and current smoking (yes or no).

Clinical characteristics included overweight, physical disability, and chronic diseases, including diabetes, cancer, chronic lung disease, heart disease, and stroke. Continuous measurements of SBP and diastolic BP were also adjusted in all analyses. Overweight was defined as a calculated body mass index of ≥25. Physical disability was defined as difficulties in completing ≥1 of the 5 basic activities of daily living: bathing, dressing, eating, getting in/out of bed, and walking across a room. Diabetes was defined as a physician-confirmed diagnosis or a glycated hemoglobin A1c ≥6.5% or the use of insulin. Other chronic diseases were defined as reported diagnoses.

Statistical Analysis

The mean (SD) was used for descriptive statistics of continuous variables and numbers (percentages) for categorical variables. Differences in characteristics were tested using the ANOVA or χ^2 test.

We used the Cox proportional hazard regression to examine associations between antihypertensive medication and incident dementia risk, with age as the time scale.[23] The underlying proportional hazard assumption was checked using the weighted Schoenfeld residual, with no significant violations observed (P>0.05 for variables included). We calculated adjusted hazard ratios (HRs) and 95% CIs.[24] Moreover, to evaluate the dementia incidence burden attributable to nonadherence to antihypertensive medication, we calculated the population attributable fraction of dementia onset in participants with hypertension, with details presented in Supplemental Methods. Missing rates of analyzed variables were shown in Table S3, with most missing rates below 1%. As the GBTM approach can adequately address missing adherence data,[17] no imputation procedure was utilized. The missing data in categorical covariates was addressed by single imputation,[25,26] whereas a sensitivity analysis was considered by treating the missing data as a missing indicator category.[27] No missing data in continuous covariates were identified.

We included the main effects of antihypertensive medication adherence or trajectory, the *APOE* ε4 carrier status, and the 2-way interaction term, for example, medication×*APOE* ε4 carrier status, in Cox models to examine the interaction on the multiplicative scale, along with other covariates.[11] In addition, we evaluated the modifying role of baseline age in associations between antihypertensive medication and dementia risk by calculating the marginal effects.[28,29]

Several sensitivity analyses were conducted. First, to evaluate the potential challenge of reverse causation, we examined associations between baseline cognitive performance with the longitudinal antihypertensive medication adherence in participants with hypertension. Second, to further address the reverse causation challenge, we excluded participants who developed dementia or censoring within 3 years after wave 10 and repeated the primary analysis. Third, we excluded participants with prevalent diabetes, given the impact on dementia risk. Fourth, to further account for the impact of stroke at the baseline and during the follow-up, we repeated the primary analysis after excluding participants with prevalent stroke at baseline and new-onset stroke during follow-up, respectively. We also assessed prospective associations between antihypertensive medication and new-onset stroke risk, after excluding prevalent stroke cases recorded during waves 8 to 10. Fifth, we adopted an accelerated failure time modeling approach to estimate associations between antihypertensive medication and years to dementia onset. Sixth, we estimated the mean cognitive trajectories of antihypertensive medication groups during the follow-up. A linear mixed model was built to estimate the mean cognitive scores during the follow-up, including follow-up time, antihypertensive medication groups, and the interaction term, as well as other covariates in the model.[6] Seventh, we further assessed the modifying effects of socioeconomic status on observed associations. Stratified by indicators of socioeconomic status, we reanalyzed associations between antihypertensive medication and dementia risk in socioeconomic subgroups. Eighth, we applied an inverse probability weighting (IPW) approach to address the selection bias. The similar IPW procedure has been applied in a previous study.[22] We also conducted a nonresponse analysis to compare baseline characteristics of included and excluded participants.[22] Ninth, we treated missing data in categorical covariates as a missing indicator category and repeated the primary analysis.[27] Finally, we further accounted for clinical conditions (physical disability and chronic diseases) during follow-up by summing up the number of waves with diagnosis from waves 8 to 10 and repeated primary analysis, aligning with our previous work.[6]

Statistical analysis was conducted using SAS version 9.4 (SAS Institute) and R language 4.3.0 (R Foundation, Vienna, Austria), with a 2-tailed alpha of 0.05 considered statistically significant.

RESULTS

Baseline Characteristics

Among the 18469 participants attending the wave 8 (baseline) of HRS, we excluded 2082 participants who developed dementia at wave 8, 3559 participants without

BP measurements at wave 8, 350 participants missing follow-up visits, and 643 participants who developed dementia during wave 9 and wave 10, leaving 11 835 participants for analysis, shown in Figure S1. As shown in Table 1, among the included 11 835 participants (mean [SD] age: 66.2 [10.1] years; men: 40.6%), 4150 (35.1%) participants were categorized as normotension, and 7685 (64.9%) participants had hypertension. Among those with hypertension, 1718 (22.4%) participants had low adherence, 1221 (15.9%) participants had moderate adherence, and 4746 (61.7%) participants had high adherence, respectively. Compared with low adherence participants (Table 1), counterparts with moderate and high adherence were older in age, less likely to be of White race, less advantaged socioeconomic status, lower BP levels, a higher proportion of overweight, and more prevalent major chronic diseases (all $P<0.05$ for comparison).

Table 1. Baseline Characteristics of Participants by Longitudinal Antihypertensive Medication Adherence

Characteristics	Participants, n (%)					*P* value*
	All participants; N=11 835	With hypertension			Normotension; n=4150	
		Low adherence; n=1718	Moderate adherence; n=1221	High adherence; n=4746		
Age, y, mean (SD)	66.2 (10.1)	66.0 (10.8)	69.5 (10.8)	68.0 (8.9)	63.2 (10.2)	<0.001
Sex						<0.001
Men	4801 (40.6)	776 (45.2)	563 (46.1)	1887 (39.8)	1575 (38.0)	
Women	7034 (59.4)	942 (54.8)	658 (53.9)	2859 (60.2)	2575 (62.0)	
White race	9957 (84.1)	1458 (84.9)	986 (80.8)	3882 (81.8)	3631 (87.5)	<0.001
Education						<0.001
Less than high school	1839 (15.5)	314 (18.3)	264 (21.6)	772 (16.3)	489 (11.8)	
High school or equivalent	4380 (37.0)	613 (35.7)	467 (38.2)	1859 (39.2)	1441 (34.7)	
College or higher	5616 (47.5)	791 (46.0)	490 (40.1)	2115 (44.6)	2220 (53.5)	
Annual family income tertile						<0.001
1	3021 (25.5)	488 (28.4)	383 (31.4)	1315 (27.7)	835 (20.1)	
2	4187 (35.4)	567 (33.0)	445 (36.4)	1781 (37.5)	1394 (33.6)	
3	4627 (39.1)	663 (38.6)	393 (32.2)	1650 (34.8)	1921 (46.3)	
Medical insurance coverage						<0.001
Uninsured	674 (5.7)	157 (9.1)	56 (4.6)	171 (3.6)	290 (7.0)	
Public	3141 (26.5)	435 (25.3)	417 (34.2)	1426 (30.0)	863 (20.8)	
Private	8020 (67.8)	1126 (65.5)	748 (61.3)	3149 (66.4)	2997 (72.2)	
Employment status						0.704
Unemployed	1208 (10.2)	186 (10.8)	126 (10.3)	488 (10.3)	408 (9.8)	
Employed	10 627 (89.8)	1532 (89.2)	1095 (89.7)	4258 (89.7)	3742 (90.2)	
Living alone	3492 (29.5)	529 (30.8)	418 (34.2)	1496 (31.5)	1049 (25.3)	<0.001
Current smoking	1610 (13.6)	316 (18.4)	182 (14.9)	475 (10.0)	637 (15.3)	<0.001
Alcohol consumption	2242 (18.9)	410 (23.9)	208 (17.0)	815 (17.2)	809 (19.5)	<0.001
Physical exercise	9106 (76.9)	1364 (79.4)	840 (68.8)	3523 (74.2)	3379 (81.4)	<0.001
Systolic blood pressure, mean (SD), mm Hg	130.3 (20.2)	145.7 (17.6)	137.8 (22.3)	133.7 (20.0)	118.0 (12.2)	<0.001
Diastolic blood pressure, mean (SD), mm Hg	79.2 (11.4)	88.3 (10.7)	81.0 (13.4)	79.7 (11.4)	74.3 (8.1)	<0.001
Overweight	8722 (73.7)	1228 (71.5)	883 (72.3)	3858 (81.3)	2753 (66.3)	<0.001
Physical disability	1366 (11.5)	170 (9.9)	229 (18.8)	632 (13.3)	335 (8.1)	<0.001
Hypertension	7685 (64.9)	1718 (100.0)	1221 (100.0)	4746 (100.0)	0 (0.0)	<0.001
Diabetes	2303 (19.5)	229 (13.3)	346 (28.3)	1289 (27.2)	439 (10.6)	<0.001
Heart disease	2406 (20.3)	249 (14.5)	398 (32.6)	1194 (25.2)	565 (13.6)	<0.001
Stroke	652 (5.5)	64 (3.7)	141 (11.5)	336 (7.1)	111 (2.7)	<0.001
Cancer	1539 (13.0)	227 (13.2)	193 (15.8)	637 (13.4)	482 (11.6)	<0.001
Chronic lung disease	886 (7.5)	124 (7.2)	149 (12.2)	365 (7.7)	248 (6.0)	<0.001
APOE ε4 carrier	2852 (24.1)	405 (23.6)	291 (23.8)	1145 (24.1)	1011 (24.4)	0.927

*P value reported for differences between groups using ANOVA or χ^2 test.

The proportion of antihypertensive medication use during wave 8 and wave 10 was presented in Figure 1B. As shown in Figure 1C, 4 underlying longitudinal medication use trajectories were identified, including (1) the low improving trajectory (n=410; 5.3%), characterized by an initially low then improving medication adherence during follow-up; (2) the always high trajectory (n=5121; 66.6%), characterized by a consistently high medication adherence during follow-up; (3) the high declining trajectory (n=846; 11.0%), characterized by an initially high then declining medication adherence during follow-up; and (4) the always low trajectory (n=1308; 17.0%), characterized by a consistently low medication adherence during follow-up. Similar comparisons in baseline characteristics were observed, shown in Table S4.

Antihypertensive Medication Time Course and Dementia Risk

During a median follow-up of 8.0 (interquartile range, 4.0–8.0) years, 1136 (9.6%) participants had new-onset dementia. As shown in Table 2, the *APOE* ε4 carrier had a significantly higher dementia incidence (13.3%) than the non-*APOE* ε4 carrier (8.4%), presenting a HR of 1.75 ([95% CI, 1.54–1.98]; *P*<0.001). After controlling for BP levels and other covariates, baseline antihypertensive medication use was associated with a lower dementia onset risk.

For the longitudinal adherence, hypertensive participants with high medication adherence had a 27% lower dementia risk (HR, 0.73 [95% CI, 0.61–0.87]; *P*<0.001) than the low adherence group. When compared with the normotension group, no significant difference was observed in dementia risk among those with high medication adherence (HR, 1.03 [95% CI, 0.88–1.21]; *P*=0.694). When comparing dementia risk according to longitudinal antihypertensive medication use trajectories, similar findings were observed. As shown in Table 2, compared with the always low trajectory, hypertensive participants with an always high trajectory had a 27% lower dementia risk (HR, 0.73 [95% CI, 0.60–0.89]; *P*=0.001), similar to the normotension group (HR, 0.70 [95% CI, 0.56–0.88]; *P*=0.002). Moreover, compared with the normotension group, no significantly higher dementia risk was observed for the always high trajectory of medication use (HR, 1.04 [95% CI, 0.89–1.21]; *P*=0.616).

Dementia Incidence Burden Attributable to Antihypertensive Medication Nonadherence

As shown in Figure 2, in participants with hypertension, nonadherence to antihypertensive medication, no matter at baseline or during follow-up, considerably contributed to the dementia incidence burden. At age 55 years, 7.9% of incident dementia cases can be attributable to not using antihypertensive medication at baseline, 9.0% of dementia cases can be attributable to the always low trajectory of antihypertensive medication use, and 10.2% of dementia cases can be attributable to the low antihypertensive medication adherence (Figure 2). By contrast, physical disability and major chronic diseases (diabetes, stroke, and heart disease) all contributed to <5% of dementia incidence (Figure 2). The dementia incidence burden attributable to antihypertensive medication adherence was slightly lower than the *APOE* ε4 carrier in hypertensive participants (Figure 2).

Interactions Between the Antihypertensive Medication Time Course and *APOE* ε4 Carrier

In the non-*APOE* ε4 carrier subgroup, hypertensive participants with high medication adherence, compared with the low adherence group, had a 27% lower dementia risk (HR, 0.73 [95% CI, 0.59–0.89]). In the *APOE* ε4 carrier subgroup, the corresponding HR was 0.75 (95% CI, 0.56–1.02), without identifying a significant multiplicative interaction (*P* for interaction=0.939; Figure 3A). Similarly, hypertensive participants of the always high trajectory, compared with the always low trajectory, had a 31% lower dementia risk (HR, 0.69 [95% CI, 0.55–0.87]) in the non-*APOE* ε4 carrier subgroup. In the *APOE* ε4 carrier subgroup, the corresponding HR was 0.83 ([95% CI, 0.59–1.19]), without identifying a significant multiplicative interaction (*P* for interaction=0.642; Figure 3B).

Modifying Role of Age in Associations of Antihypertensive Medication Time Course With Dementia Risk

As presented in Figure 4, age significantly modified observed associations between antihypertensive medication adherence and dementia risk (all *P* for interaction <0.05). Compared with low medication adherence or persistently low trajectory, the lower dementia risk associated with high medication adherence or persistently high trajectory was less evident with the increased age and became statistically insignificant for age >78 years. Similar findings were presented in the age-stratified analysis, with more pronounced associations observed in participants aged <65 years, compared with counterparts aged ≥65 years (Figure 5).

Sensitivity Analyses

As shown in Table S5, better baseline global cognition was consistently associated with higher antihypertensive medication adherence during the follow-up, independent of baseline characteristics. Further excluding participants who developed dementia or censoring within 3 years since wave 10 also did not alter the

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Table 2. Associations Between *APOE* ε4 Carrier Status, Antihypertensive Medication Use, and Dementia Onset Risk

Exposures	Events/total	Incidence, %	Incident dementia	
			HR (95% CI)*	*P* value
APOE ε4 carrier status				
Non-*APOE* ε4 carrier	758/8983	8.4	1 [Reference]	NA
APOE ε4 carrier	378/2852	13.3	1.75 (1.54–1.98)	<0.001
Baseline antihypertensive medication use				
Hypertension not using medication	207/1917	10.8	1 [Reference]	NA
Hypertension using medication	639/5768	11.1	0.84 (0.71–1.00)	0.048
Normotension	290/4150	7.0	0.78 (0.64–0.96)	0.017
Compared with normotension				
Normotension	290/4150	7.0	1 [Reference]	NA
Hypertension not using medication	207/1917	10.8	1.28 (1.05–1.57)	0.017
Hypertension using medication	639/5768	11.1	1.08 (0.93–1.26)	0.319
Longitudinal adherence to antihypertensive medication				
Hypertension, low adherence	189/1718	11.0	1 [Reference]	NA
Hypertension, moderate adherence	104/1221	8.5	0.96 (0.75–1.22)	0.714
Hypertension, high adherence	553/4746	11.7	0.73 (0.61–0.87)	<0.001
Normotension	290/4150	7.0	0.71 (0.58–0.87)	0.001
Compared with normotension				
Normotension	290/4150	7.0	1 [Reference]	NA
Hypertension, low adherence	189/1718	11.0	1.41 (1.15–1.73)	0.001
Hypertension, moderate adherence	104/1221	8.5	1.35 (1.06–1.71)	0.014
Hypertension, high adherence	553/4746	11.7	1.03 (0.88–1.21)	0.694
Trajectories of antihypertensive medication use				
Hypertension, always low trajectory	136/1308	10.4	1 [Reference]	NA
Hypertension, low improving trajectory	53/410	12.9	0.93 (0.68–1.29)	0.678
Hypertension, always high trajectory	597/5121	11.7	0.73 (0.60–0.89)	0.001
Hypertension, high declining trajectory	60/846	7.1	1.03 (0.76–1.41)	0.838
Normotension	290/4150	7.0	0.70 (0.56–0.88)	0.002
Compared with normotension				
Normotension	290/4150	7.0	1 [Reference]	NA
Hypertension, always low trajectory	136/1308	10.4	1.43 (1.14–1.78)	0.002
Hypertension, low improving trajectory	53/410	12.9	1.33 (0.97–1.82)	0.072
Hypertension, always high trajectory	597/5121	11.7	1.04 (0.89–1.21)	0.616
Hypertension, high declining trajectory	60/846	7.1	1.47 (1.10–1.97)	0.009

HR indicates hazard ratio; and NA, not applicable.

*HR was estimated using Cox proportional hazard regression models. Adjusted covariates included age, sex, race, education, income, medical insurance, employment status, cohabitation status, physical activity, alcohol consumption, current smoking, overweight, physical disability, hypertension, diabetes, cancer, chronic lung disease, heart disease, stroke, and baseline measurements of blood pressure (systolic and diastolic blood pressure).

analysis results, shown in Table S6. The observed associations were not materially changed after excluding prevalent diabetes (Table S7) and stroke at the baseline (Table S8). After excluding prevalent stroke cases during waves 8 to 10, no significant associations were observed between antihypertensive medication use and new-onset stroke risk, shown in Table S9. Observed associations were not materially altered after excluding both prevalent stroke and new-onset stroke cases (Table S10). The hypertensive participants with high antihypertensive medication adherence had significantly prolonged years to dementia onset (time ratio, 1.09 [95% CI, 1.04–1.13]; $P<0.001$; Table S11). As shown in Figure S2, participants who persistently adhered to antihypertensive medication had flat cognitive trajectories. As shown in Figures S3 and S4, adhering to antihypertensive medication was significantly associated with lower dementia risk among lower-income, lower-education, and unemployed status participants. However, more evident associations were observed among participants

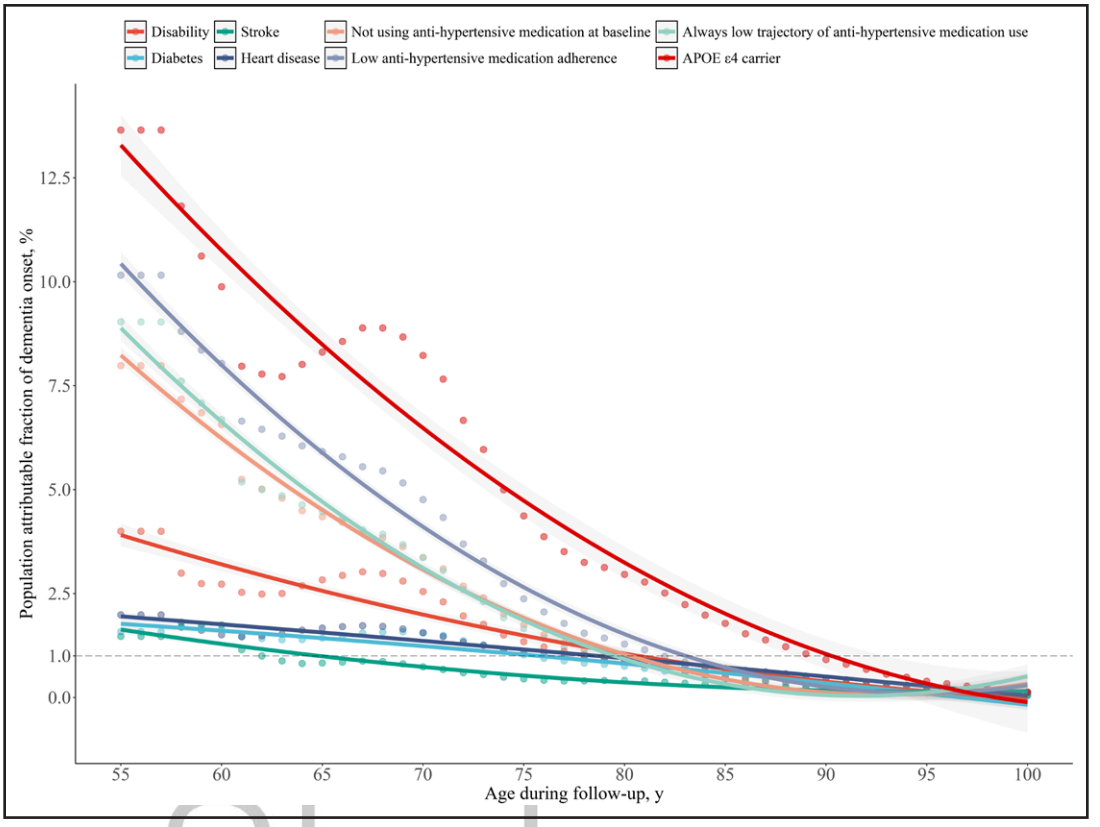

Figure 2. Population attributable fraction of incident dementia cases in participants with hypertension.
Fitted Cox proportional hazard regression models with age as the time scale were used to estimate the attributable fraction for each exposure. Identical covariates in Table 2 were adjusted for the analysis. Dots represent point estimates, whereas lines and shadows represent fitted smooth splines.

covered by private medical insurance, compared with public insurance or the uninsured. As shown in Figure S5, after the IPW procedure, all baseline characteristics were balanced between included and excluded participants. Then, based on the IPW-weighted samples, all primary results were not materially altered (Table S12). A total of 6634 participants were excluded from the analysis, who were generally older, less likely to be of White race, less advantaged socioeconomic status, and more prevalent major chronic diseases, compared with included participants (Table S13). Addressing missing categorical covariates and accounting for clinical conditions during follow-up also did not alter the results (Tables S14 and S15).

DISCUSSION

In this longitudinal cohort study, hypertension participants persistently adhering to antihypertensive medication during follow-up had a significantly lower risk of subsequent dementia onset, compared with counterparts with low medication adherence. Moreover, participants with hypertension high long-term medication adherence did not have higher dementia risks, compared with those with normotension. The observed associations were independent of BP levels and several known risk factors of dementia. Intriguingly, in participants with hypertension, 9% to 10% of incident dementia cases can be attributed to nonadherence to antihypertensive medication during follow-up, approximating the impact of *APOE* ε4 carriage and surpassing the impact of major chronic diseases. No significant interactions were found between antihypertensive medication and *APOE* ε4 carrier status. To the best of our current knowledge, this is the first study to evaluate prospective associations of long-term antihypertensive medication time course, *APOE* ε4 carrier status, and subsequent dementia risk.

The associations between antihypertensive medication or BP control and neurocognitive outcomes have been an appealing topic for years, with heterogeneous findings. The well-known SBP Intervention Trial confirmed that intensive SBP control could reduce the risk of mild cognitive impairment by 19% among adults aged 50 years or older with hypertension but without diabetes or a history of stroke.[7] Another meta-analysis of 5 randomized trials showed the efficacy of antihypertensive treatment use in reducing dementia risk by 13% in hypertensive patients aged >65 years.[30] A meta-analysis of 6 prospective cohort studies found in individuals with SBP/diastolic BP ≥140/90 mm Hg,

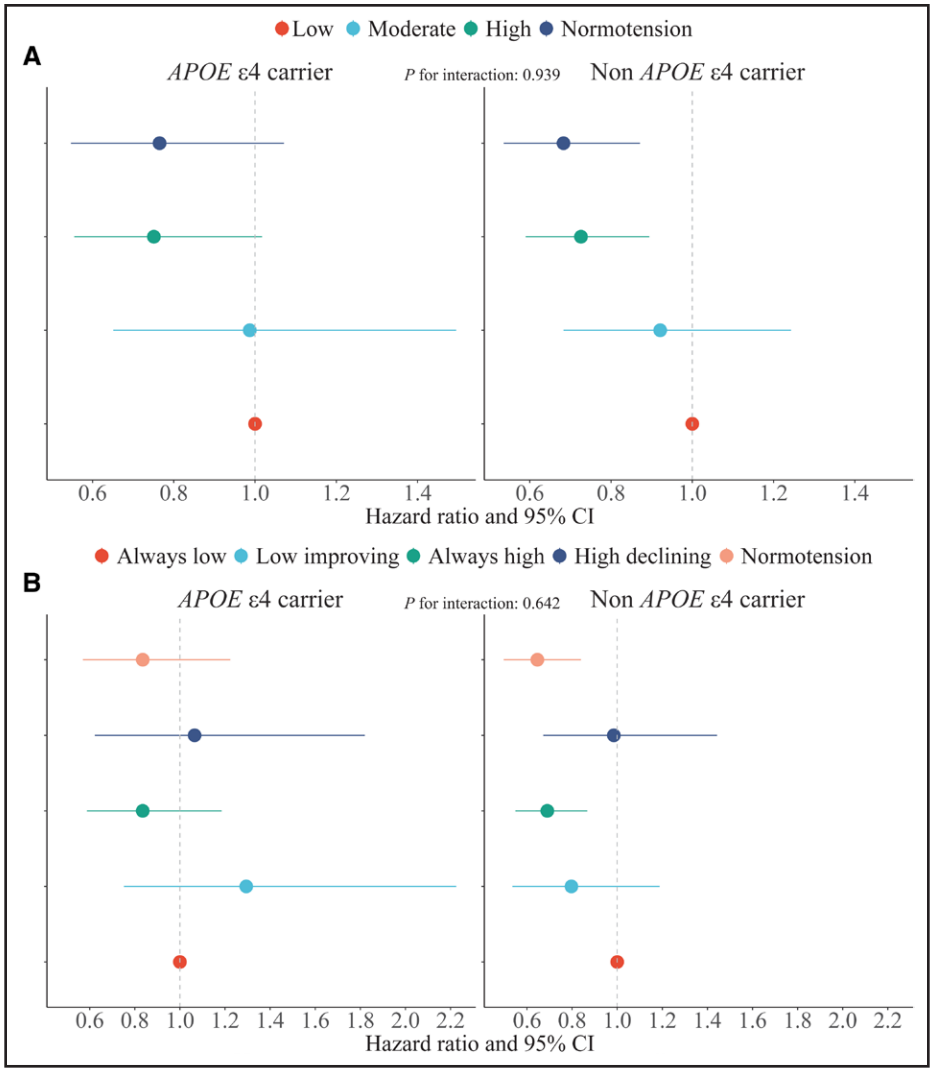

Figure 3. Associations between antihypertensive medication time course and incident dementia risk, according to *APOE* ε4 carrier status.

A, Associations of longitudinal medication adherence with dementia risk, by *APOE* ε4 carrier status. **B**, Associations of trajectories of medication use with dementia risk, by *APOE* ε4 carrier status. Cox proportional hazard regression models were built to estimate hazard ratios and 95% CIs. Identical covariates in Table 2 were adjusted for the analysis. The multiplicative interaction was examined by including the main effects of antihypertensive medication adherence or trajectory, the APOE ε4 carrier status, and the 2-way interaction term in the Cox regression model, along with other covariates.

using antihypertensive medication was associated with a 12% reduced dementia risk, whereas no significant associations were found in the normal BP stratum.[8] However, most previous investigations have focused on the temporal status of antihypertensive medication at the baseline. Recently, a large-scale nested case-control study found that participants with high adherence to antihypertensive medication during follow-up had a 24% lower dementia risk, compared with the very low adherence group.[31] Similarly, we also observed significant associations between higher longitudinal antihypertensive medication adherence and lower subsequent dementia risk. And we demonstrated that such associations were more evident than baseline antihypertensive medication status and independent of conventional risk factors, including BP levels and socioeconomic status.

Compared with previous studies, our study was additive mainly by identifying prospective associations between longitudinal antihypertensive medication adherence and subsequent lower dementia risk. Notably, we observed that individuals persistently adhering to antihypertensive medication in the long-term did not have higher dementia risk, compared with their counterparts with normotension. In comparison, hypertensive patients who persistently did not adhere to medication or with declining adherence consistently had higher subsequent dementia risks. Collectively, these findings extend the available evidence regarding the protective role of antihypertensive medication against dementia, showing

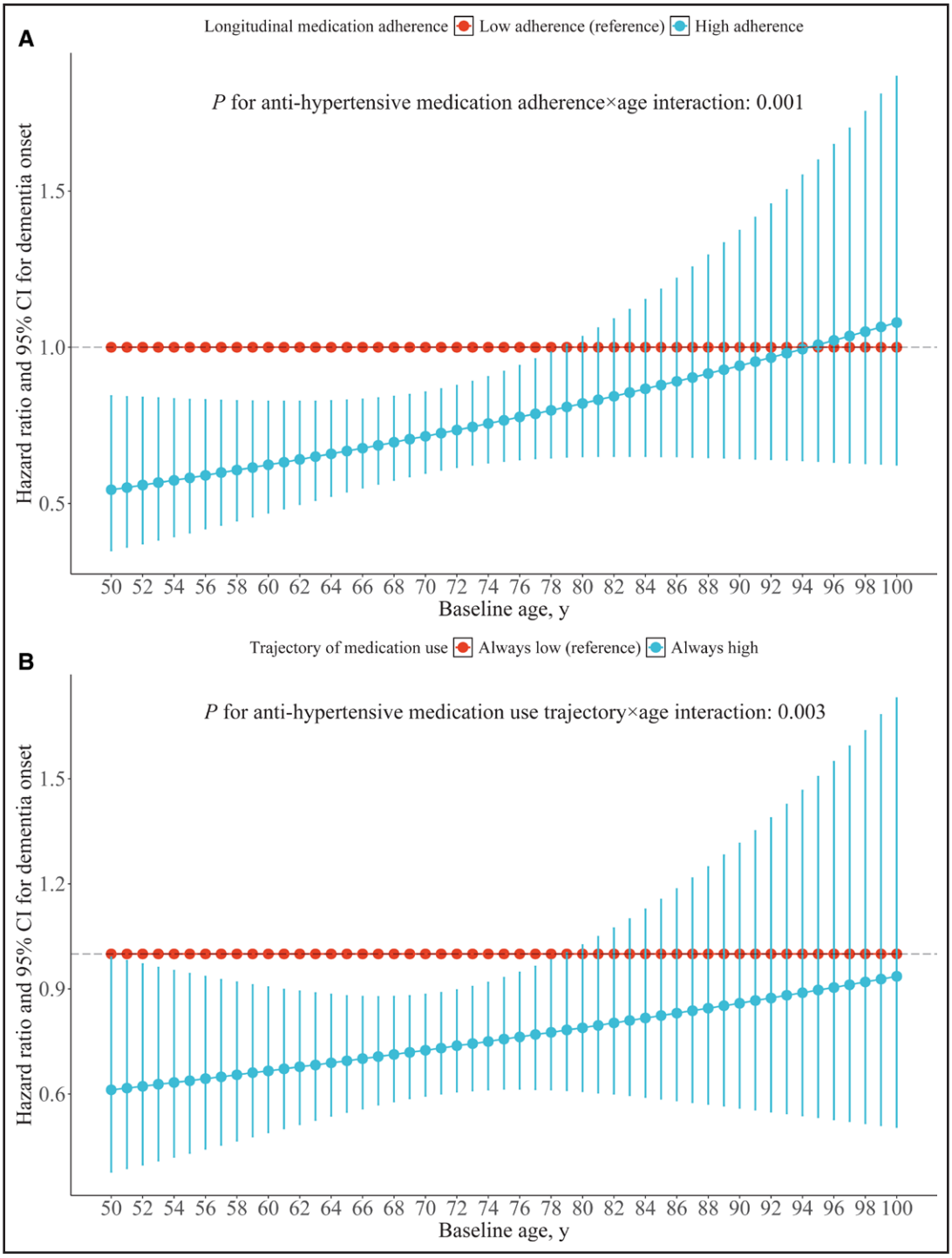

Figure 4. Marginal effects of longitudinal antihypertensive medication adherence and antihypertensive medication use trajectories on incident dementia risk, by baseline age.

A, Marginal effects of longitudinal medication adherence on dementia onset risk by baseline age. **B**, Marginal effects of trajectories of medication use on dementia onset risk by baseline age. Cox proportional hazard regression models were built to estimate hazard ratios and 95% CIs. Identical covariates in Table 2 were adjusted for the analysis. Marginal effects were calculated by including the interaction term between antihypertensive medication adherence/trajectories and baseline age (years) in Cox models.

that persistently adhering to antihypertensive medication could be beneficial in preventing dementia onset in general middle-aged and older adults. Despite the implications, cautions should be taken when interpreting our findings, mainly due to the potential reverse causation challenge. We found that the better baseline cognition was consistently associated with higher adherence to antihypertensive medication during follow-up. Likewise, it

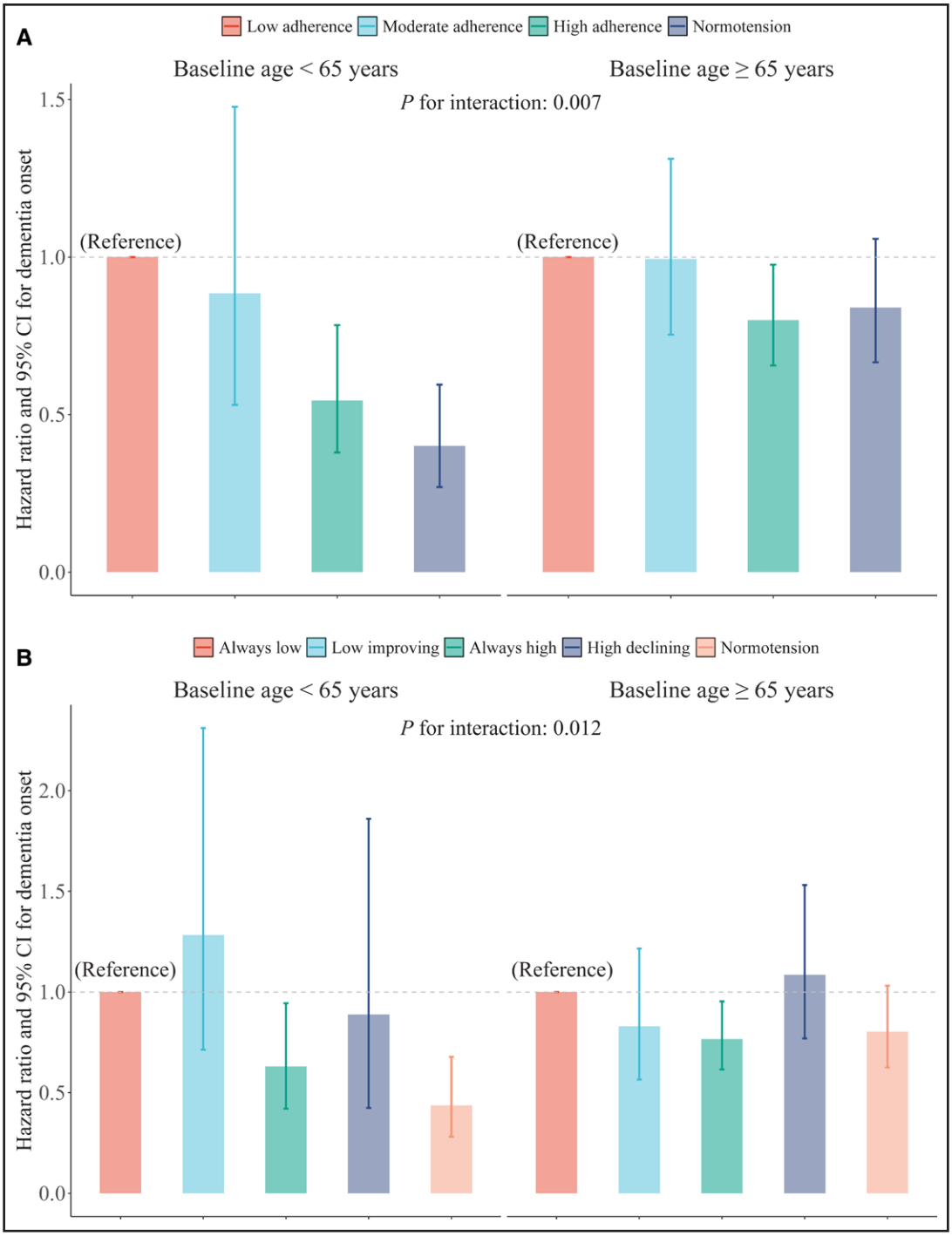

Figure 5. Age-stratified analysis of associations between longitudinal antihypertensive medication adherence and antihypertensive medication use trajectories with dementia risk.

Cox proportional hazard regression models were built to estimate hazard ratios and 95% CIs. Identical covariates in Table 2 were adjusted for the analysis. Analysis was conducted by including the interaction term between antihypertensive medication adherence/trajectories and baseline age (<65 years or ≥65 years) in Cox models.

has been reported that the worst cognitive performance was related to poor adherence to antihypertensive medication.[32,33] Consequently, the lower dementia risk associated with high medication adherence could represent the potential bias of reverse causality and should be interpreted cautiously. Although we have done several sensitivity analyses to address the challenge, including further excluding individuals developing dementia at the early stage, the bias cannot be eliminated. And investigations overcoming the limitation, especially high-quality randomized controlled trials, are still required to validate our findings.

There are other notable findings of the study that can provide novel insights for the current practice. First, we quantified the dementia incidence burden attributable to nonadherence to antihypertensive medication in the long term. We found that, in participants with hypertension, almost 10% of new-onset dementia cases can be attributable to long-term nonadherence to antihypertensive medication, highlighting its role as an important modifiable risk factor. As dementia has been increasingly recognized as a global public health challenge,[34] together with hypertension,[35] our findings provide implications by showing the crucial significance of tackling the nonadherence to antihypertensive medication and promoting accessible BP-lowering interventions for timely dementia prevention.

Second, we found age significantly modified observed associations. The lower dementia risk associated with high antihypertensive medication adherence became less evident with increased age, aligning with previous investigations.[30,31] These findings indicate that the protective role of antihypertensive medication against dementia onset could be age-dependent, highlighting the significance of promoting medication adherence in younger hypertensive patients to achieve early prevention.

Our study possesses several strengths. First, based on a large longitudinal cohort of national representativeness, we were able to apply a prospective study design and assess prospective associations between longitudinal adherence and subsequent dementia risk. Second, distinguished from most previous studies, the current study focused on long-term adherence during follow-up. Third, our study was based on the general community-dwelling middle-aged and older adults, with both a high prevalence of hypertension and an increased risk of dementia.[36] Consequently, our findings can provide more enriched insights for the current practice by highlighting the significance of promoting antihypertensive treatment adherence in general settings. Fourth, we additionally examined interactions between antihypertensive treatment with dementia genetic susceptibility and age, providing more enriched findings. Finally, our findings are relevant for the current practice, providing implications from both clinical and public health perspectives. Several sensitivity analyses also yielded robust findings.

Limitations

There also exist important limitations that should be acknowledged. First, only self-reported data were collected for categorizing antihypertensive medication status and evaluating long-term adherence. Due to the lack of pharmacy filling records or electronic monitoring, the antihypertensive medication adherence ascertaining procedure in our study could be subject to recall bias and potential misclassification. Moreover, unlike previous studies with objective medication exposure assessments or randomized controlled trials design,[7,31,37] we also could not differentiate between antihypertensive medication classes, or compare the subsequent dementia risk associated with antihypertensive medication classes, preventing us from presenting more enriched findings. Second, the dementia ascertaining procedure could underestimate the true number of cases. Although we have adopted an alternative approach for ascertaining dementia cases based on standard cognitive batteries, with performance previously validated, the possibility of undiagnosed dementia persists. Moreover, as the approach only accounted for limited cognitive domains, severe impairments in other cognitive domains could have been missed, further leading to outcome misclassification bias. Third, despite the prospective design, the challenge of reverse causation persisted. We found that hypertension participants with better cognition were more likely to adhere to antihypertensive medication in the long term, further indicating the potential reverse causation. Although we have excluded prevalent dementia cases when evaluating medication adherence and conducted sensitivity analyses by further excluding participants developing dementia at the early stage of follow-up, the potential challenge of reverse causation still cannot be entirely precluded. Consequently, caution should be taken when interpreting our findings, and further investigations are warranted to confirm our findings. Fourth, we excluded a considerable number of participants, leading to potential selection bias. Despite the similar findings observed in IPW analysis, our findings could still be subject to the influence. Fifth, as the HRS only enrolled participants in the United States, the generalizability of our findings to other diverse or non-US populations can be limited. Finally, owing to the observational investigation design, we could not eliminate the impact of residual confounding.[38] Consequently, no formal conclusions regarding the causal relationships between antihypertensive medication adherence and dementia risk can be drawn.

Conclusions

Persistently adhering to antihypertensive medication was consistently associated with a lower subsequent dementia risk in community-dwelling middle-aged and older adults, which did not vary by *APOE* genotype. No significant differences were observed in dementia risk between hypertension participants persistently adhering to antihypertensive medication and their counterparts with normotension. These findings highlight the significance of taking measures, such as utilizing primary care–based adherence interventions or applying digital monitoring tools of medication adherence, to promote long-term antihypertensive medication adherence in general middle-aged and older adults living with

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hypertension, to address the excess dementia risk and heavy disease burden in the population.

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Affiliations

Central Hospital, Tianjin University/Tianjin Third Central Hospital, China (Y.L.). Medical School, Tianjin University, China (C.L.).

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Author Contributions

Y. Li contributed to the study design and wrote the original draft. C. Li contributed to data curation and funding acquisition, had full access to the data in the study, and takes responsibility for the integrity of the data and the accuracy of the data analysis. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Disclosures

None.

Supplemental Material

Supplemental Methods
Tables S1–S15
Figures S1–S5
STROBE Checklist

REFERENCES

1. Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, Brayne C, Burns A, Cohen-Mansfield J, Cooper C, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet*. 2020;396:413–446. doi: 10.1016/S0140-6736(20)30367-6
2. Alzheimer's Disease International. World Alzheimer Report 2023 Reducing dementia risk: never too early, never too late. Accessed June 25, 2025. https://www.alzint.org/resource/world-alzheimer-report-2023/
3. Reuben DB, Kremen S, Maust DT. Dementia prevention and treatment: a narrative review. *JAMA Intern Med*. 2024;184:563–572. doi: 10.1001/jamainternmed.2023.8522
4. Levine DA, Gross AL, Briceño EM, Tilton N, Kabeto MU, Hingtgen SM, Giordani BJ, Sussman JB, Hayward RA, Burke JF, et al. Association between blood pressure and later-life cognition among black and white individuals. *JAMA Neurol*. 2020;77:810–819. doi: 10.1001/jamaneurol.2020.0568
5. Daugherty AM. Hypertension-related risk for dementia: a summary review with future directions. *Semin Cell Dev Biol*. 2021;116:82–89. doi: 10.1016/j.semcdb.2021.03.002
6. Li C, Zhu Y, Ma Y, Hua R, Zhong B, Xie W. Association of cumulative blood pressure with cognitive decline, dementia, and mortality. *J Am Coll Cardiol*. 2022;79:1321–1335. doi: 10.1016/j.jacc.2022.01.045
7. Williamson JD, Pajewski NM, Auchus AP, Bryan RN, Chelune G, Cheung AK, Cleveland ML, Coker LH, Crowe MG, Cushman WC, et al; SPRINT MIND Investigators for the SPRINT Research Group. Effect of intensive vs standard blood pressure control on probable dementia: a randomized clinical trial. *JAMA*. 2019;321:553–561. doi: 10.1001/jama.2018.21442
8. Ding J, Davis-Plourde KL, Sedaghat S, Tully PJ, Wang W, Phillips C, Pase MP, Himali JJ, Gwen Windham B, Griswold M, et al. Antihypertensive medications and risk for incident dementia and Alzheimer's disease: a meta-analysis of individual participant data from prospective cohort studies. *Lancet Neurol*. 2020;19:61–70. doi: 10.1016/S1474-4422(19)30393-X
9. Peters R, Yasar S, Anderson CS, Andrews S, Antikainen R, Arima H, Beckett N, Beer JC, Bertens AS, Booth A, et al. Investigation of antihypertensive class, dementia, and cognitive decline: A meta-analysis. *Neurology*. 2020;94:e267–e281. doi: 10.1212/WNL.0000000000008732
10. Lourida I, Hannon E, Littlejohns TJ, Langa KM, Hyppönen E, Kuzma E, Llewellyn DJ. Association of lifestyle and genetic risk with incidence of dementia. *JAMA*. 2019;322:430–437. doi: 10.1001/jama.2019.9879
11. Littlejohns TJ, Collister JA, Liu X, Clifton L, Tapela NM, Hunter DJ. Hypertension, a dementia polygenic risk score, APOE genotype, and incident dementia. *Alzheimers Dement*. 2022;19:467–476. doi: 10.1002/alz.12680
12. Institute for Social Research, University of Michigan. Health and Retirement Study.
13. Sonnega A, Faul JD, Ofstedal MB, Langa KM, Phillips JWR, Weir DR. Cohort profile: the Health and Retirement Study (HRS). *Int J Epidemiol*. 2014;43:576–585. doi: 10.1093/ije/dyu067
14. Li H, Wang M, Qian F, Wu Z, Liu W, Wang A, Guo X. Association between untreated and treated blood pressure levels and cognitive decline in community-dwelling middle-aged and older adults in China: a longitudinal study. *Alzheimers Res Ther*. 2024;16:104. doi: 10.1186/s13195-024-01467-y
15. Whelton PK, Carey RM, Aronow WS, Casey DEJ, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension*. 2018;71:1269–1324. doi: 10.1161/HYP.0000000000000066
16. Allen NB, Siddique J, Wilkins JT, Shay C, Lewis CE, Goff DC, Jacobs DR, Liu K, Lloyd-Jones D. Blood pressure trajectories in early adulthood and subclinical atherosclerosis in middle age. *JAMA*. 2014;311:490–497. doi: 10.1001/jama.2013.285122
17. Franklin JM, Shrank WH, Pakes J, Sanfélix-Gimeno G, Matlin OS, Brennan TA, Choudhry NK. Group-based trajectory models: a new approach to classifying and predicting long-term medication adherence. *Med Care*. 2013;51:789–796. doi: 10.1097/MLR.0b013e3182984c1f
18. Faul J, Collins S, Smith J, Zhao W, Kardia S, Weir D. Health and Retirement Study: APOE and serotonin transporter alleles—early release. Accessed July 15, 2024. https://hrsdata.isr.umich.edu/data-products/apoe-and-serotonin-transporter-alleles
19. Crimmins EM, Kim JK, Langa KM, Weir DR. Assessment of cognition using surveys and neuropsychological assessment: the Health and Retirement Study and the Aging, Demographics, and Memory Study. *J Gerontol B Psychol Sci Soc Sci*. 2011;66:i162–i171. doi: 10.1093/geronb/gbr048
20. Grasset L, Glymour MM, Yaffe K, Swift SL, Gianattasio KZ, Power MC, Zeki Al Hazzouri A. Association of traumatic brain injury with dementia and memory decline in older adults in the United States. *Alzheimers Dement*. 2020;16:853–861. doi: 10.1002/alz.12080
21. Gianattasio KZ, Wu Q, Glymour MM, Power MC. Comparison of methods for algorithmic classification of dementia status in the health and retirement study. *Epidemiology*. 2019;30:291–302. doi: 10.1097/EDE.0000000000000945
22. Li C, Ma Y, Yang C, Hua R, Xie W, Zhang L. Association of cystatin C kidney function measures with long-term deficit-accumulation frailty trajectories and physical function decline. *JAMA Netw Open*. 2022;5:e2234208. doi: 10.1001/jamanetworkopen.2022.34208
23. Yates T, Zaccardi F, Dhalwani NN, Davies MJ, Bakrania K, Celis-Morales CA, Gill JMR, Franks PW, Khunti K. Association of walking pace and handgrip strength with all-cause, cardiovascular, and cancer mortality: a UK Biobank observational study. *Eur Heart J*. 2017;38:3232–3240. doi: 10.1093/eurheartj/ehx449
24. Wen F, Zhang Y, Yang C, Li P, Wang Q, Zhang L. Survival disparities among cancer patients based on mobility patterns: a population-based study. *Heal Data Sci*. 2024;4:0. doi: 10.34133/hds.0198
25. Johansson AM, Karlsson MO. Comparison of methods for handling missing covariate data. *AAPS J*. 2013;15:1232–1241. doi: 10.1208/s12248-013-9526-y
26. Ren W, Liu Z, Wu Y, Zhang Z, Hong S, Liu H; Missing Data in Electronic Health Records (MINDER) Group. Moving beyond medical statistics: a systematic review on missing data handling in electronic health records. *Health Data Sci*. 2024;4:0176. doi: 10.34133/hds.0176
27. Ma H, Wang X, Xue Q, Li X, Liang Z, Heianza Y, Franco OH, Qi L. Cardiovascular health and life expectancy among adults in the United States. *Circulation*. 2023;147:1137–1146. doi: 10.1161/CIRCULATIONAHA.122.062457
28. Chou A, Beach SR, Lutz BJ, Rodakowski J, Terhorst L, Freburger JK. Moderating effects of informal care on the relationship between ADL limitations

and adverse outcomes in stroke survivors. *Stroke*. 2024;55:1554–1561. doi: 10.1161/STROKEAHA.123.045427
29. Koo AB, Reeves BC, Renedo D, Maier IL, Al Kasab S, Jabbour P, Kim JT, Wolfe SQ, Rai A, Starke RM, et al. Impact of procedure time on first pass effect in mechanical thrombectomy for anterior circulation acute ischemic stroke. *Neurosurgery*. 2024. doi: 10.1227/neu.0000000000002900
30. Peters R, Xu Y, Fitzgerald O, Aung HL, Beckett N, Bulpitt C, Chalmers J, Forette F, Gong J, Harris K, et al; Dementia rIsk REduCTion (DIRECT) Collaboration. Blood pressure lowering and prevention of dementia: an individual patient data meta-analysis. *Eur Heart J*. 2022;43:4980–4990. doi: 10.1093/eurheartj/ehac584
31. Rea F, Corrao G, Mancia G. Risk of dementia during antihypertensive drug therapy in the elderly. *J Am Coll Cardiol*. 2024;83:1194–1203. doi: 10.1016/j.jacc.2024.01.030
32. Cho MH, Shin DW, Chang S-A, Lee JE, Jeong S-M, Kim SH, Yun JM, Son K. Association between cognitive impairment and poor antihypertensive medication adherence in elderly hypertensive patients without dementia. *Sci Rep*. 2018;8:11688. doi: 10.1038/s41598-018-29974-7
33. Chou CC, Chien LY, Liaw JJ, Wang CJ, Liu PY. Association between cognitive function and self-reported antihypertensive medication adherence among middle-aged and older hypertensive women. *J Clin Nurs*. 2022;31:2839–2849. doi: 10.1111/jocn.16106
34. Olivari BS, French ME, McGuire LC. The public health road map to respond to the growing dementia crisis. *Innov Aging*. 2020;4:igz043. doi: 10.1093/geroni/igz043
35. Fisher NDL, Curfman G. Hypertension—a public health challenge of global proportions. *JAMA*. 2018;320:1757–1759. doi: 10.1001/jama.2018.16760
36. Lv H, Zeng N, Li M, Sun J, Wu N, Xu M, Chen Q, Zhao X, Chen S, Liu W, et al. Association between body mass index and brain health in adults: a 16-year population-based cohort and Mendelian randomization study. *Heal Data Sci*. 2024;4:87. doi: 10.34133/hds.0087
37. Peters R, Beckett N, Forette F, Tuomilehto J, Clarke R, Ritchie C, Waldman A, Walton I, Poulter R, Ma S, et al; HYVET Investigators. Incident dementia and blood pressure lowering in the Hypertension in the Very Elderly Trial cognitive function assessment (HYVET-COG): a double-blind, placebo controlled trial. *Lancet Neurol*. 2008;7:683–689. doi: 10.1016/S1474-4422(08)70143-1
38. Streeter AJ, Lin NX, Crathorne L, Haasova M, Hyde C, Melzer D, Henley WE. Adjusting for unmeasured confounding in non-randomised longitudinal studies: a methodological review. *J Clin Epidemiol*. 2017;87:23–34. doi: 10.1016/j.jclinepi.2017.04.022