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Original Article

Mid-life antihypertensive initiation and incident dementia: a machine learning-weighted target trial emulation in the health and retirement study

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Abstract: Background: Mid-life hypertension is a treatable vascular risk for dementia, yet trial evidence on whether starting antihypertensives in middle age lowers late-life dementia remains mixed. This study aimed to emulate a randomized trial to estimate whether initiating antihypertensive therapy at mid-life reduces subsequent dementia risk. Methods: We emulated a randomized target trial of antihypertensive initiation using Health and Retirement Study data (2002-2020; 18-year follow-up). Eligible adults aged 45-65 with incident hypertension and dementia-free at baseline (n = 2,491) were classified in 2002 as antihypertensive treatment initiators or non-initiators. Inverse probability weights combined (I) a Firth-penalized logistic model for treatment initiation and (II) biennial censoring models; weighted Cox regression estimated hazard ratios (HRs) for incident dementia. To probe model dependence, we re-estimated treatment weights with a Super Learner ensemble and repeated all analyses. Results: Groups differed on several baseline covariates, but weighting brought every standardized mean difference to <0.10. During follow-up, cumulative dementia incidence reached 15% in non-initiators and 13% in initiators. The intention-to-treat risk ratio (RR) was 0.89 (95% confidence interval [CI], 0.57-1.62); biennial RRs were likewise close to the null. Re-estimating treatment weights with a Super Learner ensemble yielded comparable covariate balance and a year-18 RR of 1.05 (0.74-1.70), essentially reproducing the primary result. Analyses accounting for competing risks of death or dropout did not materially change the estimates. Conclusions: In this nationally representative cohort, starting antihypertensive therapy in mid-life did not meaningfully change dementia risk across 18 years. Agreement between conventional and machine-learning propensity approaches makes a large protective or harmful effect unlikely and underscores the need to explore additional strategies for dementia prevention beyond routine blood pressure pharmacotherapy.

Keywords: Dementia, hypertension, antihypertensive treatment, target trial emulation, causal inference, machine learning, super learner

Introduction

Dementia is primarily typified by the decline in cognition and autonomy in daily life. The neurodegenerative condition gets worse over time, with symptoms like impaired memory and reasoning becoming more severe with the advancement of the disease [1]. Cognitive impairment has been affecting over 50 million individuals globally, with predictions suggesting the number could rise to 70 million by 2030 and nearly 140 million by mid-century [2]. Age

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is still the most predictive of cognitive impairment, with no known upper age limit for the associated risk [3]. Longitudinal studies that have followed individuals over time indicate that midlife hypertension is linked to an increased risk of developing memory deficits and neurodegenerative disorders, including dementia [4-8].

Hypertension adversely affects cognitive function through both macrovascular and microvascular mechanisms [9]. Chronic elevations -in blood pressure increase the risk of clinical stroke and subclinical infarcts and induce structural and functional changes in cerebral vessels, including arterial stiffening, endothelial dysfunction, and disruption of the blood-brain barrier [10, 11]. These vascular alterations reduce cerebral perfusion, promote oxidative stress and neuroinflammation, and accelerate white-matter damage and neuronal loss [9]. A large body of epidemiologic work suggests that elevated mid-life blood pressure is more strongly associated with later-life dementia risk than comparable elevations in late life, and that vascular dementia and Alzheimer's disease often share these vascular pathways [9, 12, 13].

Of twelve randomized controlled trials investigating antihypertensive therapy and cognitive outcomes, only one reported a statistically significant reduction in dementia risk with active treatment, whereas the remaining trials did not demonstrate clear benefits for dementia prevention [14-18]. Collectively, these findings imply that blood pressure therapies initiated after midlife may have limited impact on preventing dementia, possibly because a critical window to avert vascular damage has already passed. Important evidence gaps remain regarding the potential cognitive benefits of initiating antihypertensive treatment in adults younger than 66 years, and most comparisons lack sufficient statistical power to distinguish class-specific effects due to design limitations [19]. Longitudinal analyses have suggested that agents acting on angiotensin receptors (ARBs) may confer greater cognitive protection than other drug classes, and a large 2021 review including more than 600,000 patients identified calcium channel blockers and ARBs as promising first-line options given their potential to lower dementia risk [20, 21].

Observational studies are also vulnerable to important sources of confounding, including socioeconomic determinants of medication adherence and unrecognized early-stage cognitive decline that may influence treatment decisions and follow-up patterns, which can spuriously amplify apparent protective effects [22]. Heterogeneity arises not only from differences in patient profiles (ranging from cognitively unimpaired individuals to those with mild impairment or established dementia and varying cardiovascular status) but also from potential class-specific effects of blood pressure medications on dementia risk that may be independent of their antihypertensive action [21, 23, 24].

Researchers have sought to bridge the gap between clinical trials and population-based longitudinal studies. Prior work indicates that the association between hypertension and dementia risk tends to weaken with advancing age, with the strongest correlations observed in younger and mid-life populations [25-29]. However, decades-long randomized trials of mid-life antihypertensive initiation with dementia as an outcome are practically infeasible because of time, cost, and ethical constraints. To date, no trial has directly compared long-term dementia outcomes between individuals who initiate antihypertensive therapy at the time of an incident mid-life hypertension diagnosis and those who defer treatment, leaving this clinically important question unanswered. Target trial emulation has been proposed as a way to use observational data to construct simulated hypothetical trials that adhere as closely as possible to the core principles of randomized experiments [25-29]. In this research, we therefore sought to determine whether initiation and maintenance of antihypertensive treatment in midlife among individuals with newly diagnosed hypertension reduces the risk of late-life dementia by emulating a randomized trial within a longitudinal observational cohort.

Finally, to ensure that our conclusions were not driven by a single modeling specification, we complemented conventional causal inference tools with an ensemble-based machine-learning strategy. Using Super Learner, which combines penalized logistic regression with more flexible algorithms such as random forests, we

Table 1. Specifying the emulated target trial design

Component	Definition
Target Population	HRS participants aged 45-65 at Wave 6 (2002) newly diagnosed with hypertension, free of baseline dementia, nursing home residence, and cancer.
Intervention	Initiation of antihypertensive medication at Wave 6 (2002).
Comparator	No initiation of antihypertensive medication at Wave 6 (2002).
Outcome	Incident dementia (defined as Cognition score ≤6).
Follow-up Period	Biennial follow-up from 2002 to 2020 (18 years).
Censoring Events	Death, dropout (loss to follow-up), or end of study follow-up (2020) if no event occurred.
Treatment Assignment	randomized (ITT), emulated with using inverse probability of treatment weighting (IPTW).
Causal Contrast	Risk ratio of incident dementia comparing initiators to non-initiators.

Definition of the Emulated Target Trial Components for Antihypertensive Medication Initiation and Incident Dementia

generated an alternative set of propensity weights that can capture non-linearities and interactions that traditional models may miss. This data-adaptive analysis allowed us to ask the same clinical question from a different statistical perspective and to assess the robustness of any observed signal to modeling choices.

Methods

Study design and data source

Randomized controlled trials (RCTs) are the gold standard for causal inference, but ethical and logistical barriers can limit their feasibility. Target trial emulation offers a way to approximate an RCT using observational data. The approach requires (1) specifying a hypothetical trial protocol, including eligibility criteria, treatment strategies, follow-up period, outcomes, and the causal contrast of interest, and (2) implementing that protocol in real-world data with proper alignment of time zero and maintenance of exchangeability, often via inverse probability weighting [30, 31]. Its validity is supported by multiple demonstrations in which observational emulations reproduced RCT findings [32, 33].

In this study, we emulated a target trial designed to test whether promptly initiating antihypertensive pharmacotherapy at the time of a new mid-life hypertension diagnosis reduces subsequent dementia risk. The hypothetical protocol defined eligibility (adults aged 45-65 years with incident hypertension and no baseline dementia), two treatment strategies (initiate antihypertensive medication at baseline versus defer initiation), an 18-year follow-up, incident dementia as the primary outcome, and an intention-to-treat contrast comparing initiators with non-initiators. We then operationalized this protocol in the Health and Retirement Study (HRS) by aligning time zero at the 2002 interview (Wave 6) and using inverse probability weighting to approximate random treatment assignment.

The analytic dataset was drawn from the Health and Retirement Study (HRS), a nationally representative longitudinal survey that has interviewed roughly 40,000 community-dwelling Americans aged ≥50 years every two years since 1992 [34, 35]. HRS collects rich sociodemographic, economic, behavioral, clinical, and cognitive data via harmonized questionnaires, physical measurements, and Medicare linkage. For this study, we used ten biennial waves spanning 2002 (baseline) through 2020, allowing up to 18 years of prospective follow-up per participant (**Table 1**).

Ethical oversight

All public-release HRS files are de-identified. Participants provide written informed consent at each wave, and the study protocol is continuously overseen by the University of Michigan Institutional Review Board. Because we analyzed only de-identified secondary data, no additional ethics approval was required.

Study population

The target population included HRS participants aged 45-65 at the 2002 baseline (Wave 6) who had a new diagnosis of hypertension at that wave. We excluded individuals who were outside the 45-65 age range at Wave 6; had

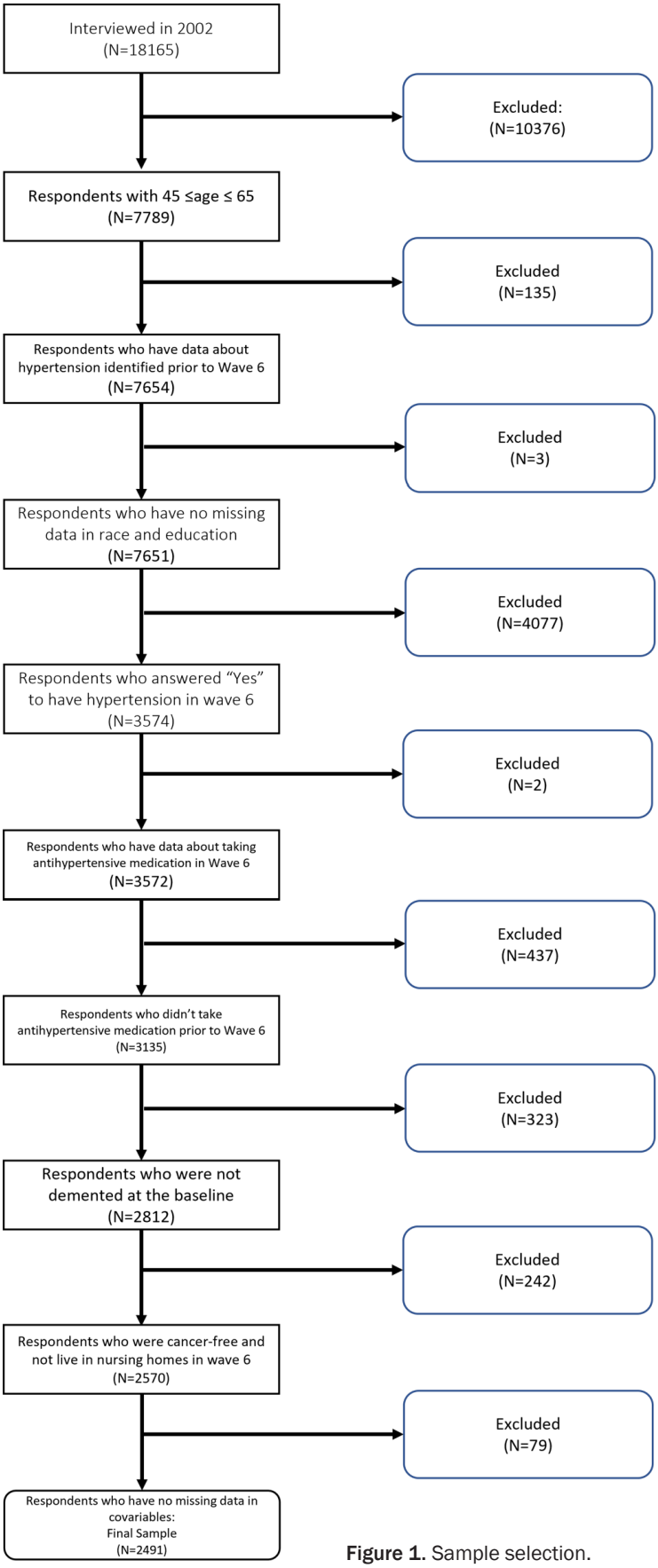

Figure 1. Sample selection.

missing information on prior hypertension diagnosis; lacked data on key demographic variables (including race and education); did not have a positive hypertension record; had unclear or missing records of antihypertensive medication use; had evidence of pre-existing hypertension before Wave 6; showed evidence of dementia at baseline; resided in nursing homes; or had a baseline history of cancer. We also excluded participants missing any other baseline covariates required for the models. These stringent criteria yielded a homogeneous, well-characterized cohort suitable for robust analysis. A CONSORT-style flow diagram (**Figure 1**) details the full selection process.

Baseline covariates

At baseline, we recorded a comprehensive set of potential confounders across four domains. Demographics: age; sex; Hispanic ethnicity; race (White/Caucasian, Black/African American, Other); education (< high-school, high-school graduate, ≥ some college); marital status. Socio-economic position: derived from earnings, pension, social security, and retirement income, categorized into five groups (including a zero-income category). Health and lifestyle: body mass index ($kg.m^{-2}$); self-rated health (excellent, very good, good, fair, poor); depressive symptoms (8-item CESD; two-level design in which scores 4-8 indicate high depressive symptoms and scores <4 indicate mild-moderate symptoms); residential setting (urban, suburban, ex-urban); limitations in activities of daily living (ADL) and instrumental ADL; ever smoking history; frequency of vigorous physical activity (≥3

time per week). Medical history: previous physician diagnoses of diabetes, lung disease, heart disease, stroke, arthritis, and unintentional weight loss attributed to hypertension. Operational definitions and coding rules are provided in Supplementary Table 1. Together, these variables capture key indicators of hypertension burden and dementia risk, including vascular comorbidities, lifestyle factors, socioeconomic position, and functional status. They were selected a priori based on prior literature linking mid-life cardiovascular and psychosocial profiles to late-life cognitive outcomes.

Exposure definition

Exposure was defined as initiation of any antihypertensive medication in 2002. Respondents reporting blood-pressure-lowering drug use in the 2002 interview were classified as initiators; those reporting no use were classified as non-initiators. Because medication data were collected at the same time as the new hypertension diagnosis, exposure status was treated as fixed at baseline.

Outcome ascertainment and follow-up

The primary outcome was incident dementia, assessed at each wave using the validated 27-point Langa-Weir Classification of Cognitive Function; scores ≤6 indicate dementia (accuracy: 87%, 95% CI: 83-91%) [36, 37]. The incidence of dementia over follow-up served as the primary indicator of cognitive outcome, allowing us to quantify the long-term impact of antihypertensive initiation on clinically relevant cognitive impairment. All included participants were dementia-free in 2002. Person-time accrued from the 2002 interview until the earliest of: (1) first recorded dementia; (2) death (ascertained through next-of-kin reports, exit interviews, or National Death Index linkage); (3) loss to follow-up (permanent withdrawal or failure to complete subsequent interviews); or (4) administrative censoring at the 2020 wave for participants alive and cognitively intact.

Statistical analysis

Baseline characteristics are presented as means and standard deviations for approximately normally distributed continuous variables, medians and interquartile ranges for skewed variables, and counts with percentages for categorical variables. Between-group differences at baseline were summarized using standardized mean differences rather than formal hypothesis tests, with absolute values ≥0.10 indicating meaningful imbalance. All confidence intervals are two-sided 95% intervals, and a *P*-value <0.05 was considered statistically significant, although interpretation focused on effect sizes and interval estimates rather than strict significance thresholds.

All analyses were conducted in R 4.4.2.

Inverse probability weighting (IPW): To approximate the exchangeability of a randomized trial, we created a pseudo-population using IPW. Treatment weights (IPTW) were estimated via Firth-penalized logistic regression of antihypertensive initiation on all baseline covariates; penalization reduces small-sample separation bias. Censoring weights (IPCW) were estimated biennially with pooled logistic regression including the same covariates plus linear and quadratic terms for time since baseline, to account for informative loss to follow-up or death. Stabilized weights were calculated as IPTW × IPCW and truncated at the 1st and 99th percentiles to limit the influence of extreme values. Full model coefficients, diagnostics, and weight distributions are reported in Supplementary Table 2.

Primary effect estimation: Weighted Cox proportional hazards models were used to estimate the hazard ratio (HR) for dementia comparing initiators with non-initiators over 18 years. The proportional hazards assumption was evaluated with Schoenfeld residuals and log-minus-log plots. We generated weighted Kaplan-Meier curves and computed cumulative incidence every two years; period-specific risk ratios (RRs) were obtained by dividing cumulative risks. Ninety-five per cent confidence intervals for HRs and RRs were derived from 200 non-parametric bootstrap samples that preserved within-person correlation.

Sensitivity analysis

To evaluate robustness to model misspecification, we re-estimated IPTW using Super Learner, an ensemble machine-learning algorithm that combines generalized linear models, LASSO, gradient-boosted trees, random forests, and neural networks via 10-fold cross-

Table 2. Baseline characteristics of participants in the emulated target trial (2002 Baseline)

Characteristic	Overall (Unweighted)	Non-Initiator (Unweighted)	Initiator (Unweighted)	Unweighted SMD	Overall (Weighted)	Non-Initiator (Weighted)	Initiator (Weighted)	Weighted SMD
Number	2491	364	2127		2500.10	367.16	2132.94	
Age, M (SD)	59.95 (3.99)	59.38 (4.63)	60.04 (3.87)	0.156	60.00 (3.94)	60.27 (4.15)	59.96 (3.90)	0.079
Gender, N (%)	1502 (60.3)	191 (52.5)	1311 (61.6)	0.186	1509.3 (60.4)	220.8 (60.1)	1288.6 (60.4)	0.006
Hispanic, N (%)	235 (9.4)	53 (14.6)	182 (8.6)	0.189	231.3 (9.3)	31.4 (8.6)	199.9 (9.4)	0.028
Race, N (%)				0.219				0.016
White, Caucasian	1847 (74.1)	287 (78.8)	1560 (73.3)		1852.4 (74.1)	270.6 (73.7)	1581.8 (74.2)	
Black/African American	543 (21.8)	55 (15.1)	488 (22.9)		547.9 (21.9)	82.4 (22.4)	465.5 (21.8)	
Other	101 (4.1)	22 (6.0)	79 (3.7)		99.9 (4.0)	14.2 (3.9)	85.7 (4.0)	
Education, N (%)				0.122				0.005
Less than High School	549 (22.0)	92 (25.3)	457 (21.5)		551.8 (22.1)	81.2 (22.1)	470.6 (22.1)	
High School Graduate GED	957 (38.4)	145 (39.8)	812 (38.2)		959.0 (38.4)	141.5 (38.5)	817.6 (38.3)	
Some College. And Above	985 (39.5)	127 (34.9)	858 (40.3)		989.3 (39.6)	144.5 (39.4)	844.8 (39.6)	
Marital State, N (%)				0.068				0.013
Married Partnered	1808 (72.6)	258 (70.9)	1550 (72.9)		1817.5 (72.7)	268.6 (73.2)	1548.9 (72.6)	
Widowed	250 (10.0)	43 (11.8)	207 (9.7)		248.3 (9.9)	35.4 (9.6)	212.9 (10.0)	
Never Married Separated Divorced	433 (17.4)	63 (17.3)	370 (17.4)		434.3 (17.4)	63.2 (17.2)	371.2 (17.4)	
Income, N (%)				0.179				0.102
Zero income	399 (16.0)	77 (21.2)	322 (15.1)		397.6 (15.9)	55.8 (15.2)	341.7 (16.0)	
Q1 Lowest Income	523 (21.0)	73 (20.1)	450 (21.2)		527.8 (21.1)	80.0 (21.8)	447.8 (21.0)	
Q2	523 (21.0)	75 (20.6)	448 (21.1)		529.3 (21.2)	81.6 (22.2)	447.7 (21.0)	
Q3	523 (21.0)	77 (21.2)	446 (21.0)		510.6 (20.4)	63.9 (17.4)	446.7 (20.9)	
Q4 Highest Income	523 (21.0)	62 (17.0)	461 (21.7)		534.8 (21.4)	85.8 (23.4)	449.0 (21.0)	
Site of Living, N (%)				0.116				0.038
Urban	1162 (46.6)	168 (46.2)	994 (46.7)		1158.6 (46.3)	164.3 (44.7)	994.3 (46.6)	
Suburban	509 (20.4)	88 (24.2)	421 (19.8)		512.9 (20.5)	76.9 (21.0)	436.0 (20.4)	
Ex-urban	820 (32.9)	108 (29.7)	712 (33.5)		828.6 (33.1)	126.0 (34.3)	702.6 (32.9)	
Self-Report of Health				0.092				0.026
Excellent/Very Good	854 (34.3)	137 (37.6)	717 (33.7)		849.7 (34.0)	121.0 (33.0)	728.7 (34.2)	
Good	886 (35.6)	128 (35.2)	758 (35.6)		894.7 (35.8)	134.0 (36.5)	760.7 (35.7)	
Fair/Poor	751 (30.1)	99 (27.2)	652 (30.7)		755.7 (30.2)	112.2 (30.6)	643.5 (30.2)	
High Depressive Symptoms, N (%)	439 (17.6)	71 (19.5)	368 (17.3)	0.057	448.6 (17.9)	72.3 (19.7)	376.3 (17.6)	0.053
BMI, M (SD)	30.09 (5.95)	28.66 (5.30)	30.33 (6.03)	0.294	30.09 (5.94)	30.05 (5.94)	30.10 (5.94)	0.008

ADL Limitation, N (%)				0.076				0.005
0	2123 (85.2)	315 (86.5)	1808 (85.0)		2129.3 (85.2)	312.9 (85.2)	1816.4 (85.2)	
1	184 (7.4)	28 (7.7)	156 (7.3)		186.2 (7.4)	27.5 (7.5)	158.7 (7.4)	
≥2	184 (7.4)	21 (5.8)	163 (7.7)		184.6 (7.4)	26.7 (7.3)	157.9 (7.4)	
IADL Limitation, N (%)				0.065				0.055
0	2224 (89.3)	329 (90.4)	1895 (89.1)		2235.5 (89.4)	331.6 (90.3)	1903.9 (89.3)	
1	166 (6.7)	24 (6.6)	142 (6.7)		161.6 (6.5)	19.7 (5.4)	141.9 (6.7)	
≥2	101 (4.1)	11 (3.0)	90 (4.2)		103.0 (4.1)	15.9 (4.3)	87.1 (4.1)	
Weight loss due to HTN	1028 (41.3)	133 (36.5)	895 (42.1)	0.114	1024.7 (41.0)	145.0 (39.5)	879.7 (41.2)	0.036
Vigorous Activity (≥3 times a week)	993 (39.9)	161 (44.2)	832 (39.1)	0.104	989.4 (39.6)	142.1 (38.7)	847.3 (39.7)	0.021
Ever Smoking	1502 (60.3)	242 (66.5)	1260 (59.2)	0.150	1499.0 (60.0)	214.4 (58.4)	1284.6 (60.2)	0.037
Comorbidities, N (%)								
Diabetes	590 (23.7)	51 (14.0)	539 (25.3)	0.288	604.0 (24.2)	96.8 (26.4)	507.2 (23.8)	0.060
Lung Disease	182 (7.3)	36 (9.9)	146 (6.9)	0.109	179.2 (7.2)	23.7 (6.5)	155.5 (7.3)	0.033
Heart Disease	485 (19.5)	46 (12.6)	439 (20.6)	0.216	499.3 (20.0)	82.5 (22.5)	416.8 (19.5)	0.072
Stroke	183 (7.3)	16 (4.4)	167 (7.9)	0.145	185.0 (7.4)	27.4 (7.5)	157.7 (7.4)	0.002
Arthritis	1431 (57.4)	190 (52.2)	1241 (58.3)	0.124	1444.7 (57.8)	217.2 (59.2)	1227.5 (57.5)	0.033

Unweighted and Weighted Baseline Characteristics of Participants in the Emulated Target Trial (2002 Baseline), Showing Standardized Mean Differences (SMD) by Antihypertensive Medication Initiation Status. Values are N (%) for categorical variables and M = Mean (SD) for continuous variables.

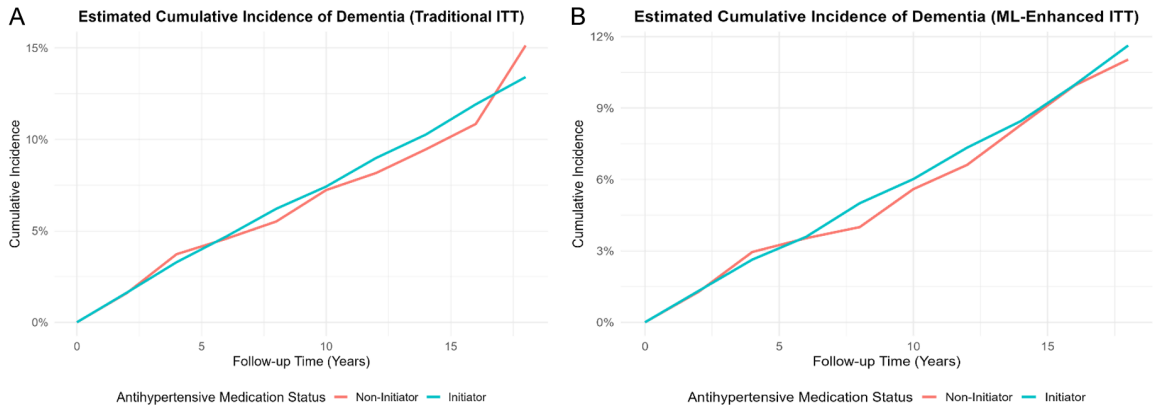

Figure 2. Estimated cumulative incidence of dementia. A. Intention-to-Treat - Traditional Analysis; B. Intention-to-Treat - ML-Enhanced Analysis.

validation. These data-driven weights were applied in the same analytic pipeline, and resulting estimates (Supplementary Table 3) were compared qualitatively and quantitatively with the primary results.

Reproducibility and data availability

All code for data construction, weighting, modelling, and figure generation is version-controlled in a Git repository and executed within a containerized RMarkdown workflow on a Linux workstation (R 4.4.2). De-identified analytic data and code are available from the corresponding author upon reasonable request, subject to HRS data-use agreements.

Supplementary material content

Supplementary Table 1 - Variable definitions and coding. Supplementary Table 2 - Full specifications and diagnostics for conventional IPW models. Supplementary Table 3 - Super Learner library, cross-validation results, and sensitivity-analysis estimates.

Results

Cohort assembly and baseline balance

Of the 18,165 respondents interviewed in the 2002 Health and Retirement Study wave, 2,491 met every eligibility criterion for the emulated trial (**Figure 1**). This step-wise reduction, detailed in **Figure 1** and **Table 2**, yielded a final cohort composed solely of middle-aged adults with an incident hypertension diagnosis, no baseline dementia, and complete covariate data. Before weighting, antihypertensive initiators differed from non-initiators on several attributes (**Table 2**). Initiators were slightly older, more often female, and had higher prevalences of diabetes and heart disease; corresponding unweighted standardized mean differences (SMDs) often exceeded the conventional 0.10 threshold. After applying inverse-probability-of-treatment weights (IPTW), these imbalances were largely eliminated: nearly all covariates showed SMDs <0.10 and many <0.05 (**Table 2**). This successful re-weighting produced a pseudo-population in which treatment groups were virtually indistinguishable on observed baseline factors, strengthening the internal validity of subsequent risk estimates.

Incident dementia: traditional weighted analysis

Over the follow-up period (2002-2020), the dementia weighted cumulative incidence rose constantly in both groups (**Figure 2A**). Point estimates for the two-year risk first observed at 2% in each group and reached 15% for non-initiators and 13% for initiators at year 18 (**Table 3**). At every wave, the risk ratio (RR) was near the null, and all 95% confidence intervals (CIs) included 1.0; for example, the RR at year 10 was 1.03 (95% CI 0.69-1.87) and at year 18 was 0.89 (0.57-1.62). These results suggest that no material difference in dementia risk between those who started medication promptly and those who deferred.

Machine-learning-enhanced sensitivity analysis

Because traditional logistic models may miss subtle non-linear structure, we re-estimated

Table 3. Estimated cumulative incidence and risk ratios for incident dementia (intention-to-treat - traditional analysis)

Time	Cumulative Incidence Non-Initiator	Cumulative Incidence Initiator	Risk Ratio 95% CI	*P*-value
2 Years	0.02	0.02	1.02 (0.45, 5.70)	0.824
4 Years	0.04	0.03	0.88 (0.49, 2.54)	0.900
6 Years	0.05	0.05	1.03 (0.64, 2.30)	0.730
8 Years	0.06	0.06	1.13 (0.74, 2.54)	0.550
10 Years	0.07	0.07	1.03 (0.69, 1.87)	0.780
12 Years	0.08	0.09	1.10 (0.78, 1.89)	0.560
14 Years	0.09	0.10	1.09 (0.80, 1.81)	0.600
16 Years	0.11	0.12	1.10 (0.81, 1.74)	0.540
18 Years	0.15	0.13	0.89 (0.57, 1.62)	0.680

Estimated Cumulative Incidence of Incident Dementia and Risk Ratios for Initiating Antihypertensive Medication at Biennial Follow-up Points (Traditional Intention-to-Treat Analysis). Cumulative incidence values are point estimates. Risk Ratios (RR) and their 95% Confidence Intervals (CI) and *P*-values were estimated using 200 bootstrap replicates (percentile method for CI; proportion of bootstrapped RRs relative to 1 for *P*-value).

Table 4. Detailed results of ML-enhanced intention-to-treat analysis

Time	Cumulative Incidence Non-Initiator	Cumulative Incidence Initiator	Risk Ratio 95% CI	*P*-value
2 Years	0.01	0.01	1.03 (0.45, 2.87)	0.975
4 Years	0.03	0.03	0.89 (0.46, 2.10)	0.750
6 Years	0.04	0.04	1.02 (0.60, 2.08)	0.910
8 Years	0.04	0.05	1.25 (0.78, 2.43)	0.380
10 Years	0.06	0.06	1.08 (0.73, 1.63)	0.790
12 Years	0.07	0.07	1.11 (0.77, 1.65)	0.690
14 Years	0.08	0.08	1.02 (0.70, 1.58)	0.960
16 Years	0.10	0.10	1.00 (0.66, 1.62)	0.940
18 Years	0.11	0.12	1.05 (0.74, 1.70)	0.830

Detailed Estimated Cumulative Incidence of Incident Dementia and Risk Ratios for Initiating Antihypertensive Medication at Biennial Follow-up Points (ML-Enhanced Intention-to-Treat Analysis). Cumulative incidence values are point estimates. Risk Ratios (RR) and their 95% Confidence Intervals (CI) and *P*-values were estimated using 200 bootstrap replicates (percentile method for CI; proportion of boots trapped RRs relative to 1 for *p*-value).

treatment weights using a Super Learner ensemble that combined penalized regression, random forests, and standard generalized linear models (details in Supplementary Table 3). This data-adaptive approach flexibly fits the propensity score without the strong functional-form constraints of classical models while retaining the transparency of a pre-specified library. The resulting ML-derived weights reproduced the excellent covariate balance seen in the primary analysis (**Table 2**) and generated cumulative incidence curves (**Figure 2B**) and RRs (**Table 4**) closely aligned with the traditional estimates. For example, the ML-enhanced RR at year 10 was 1.08 (95% CI 0.73-1.63), and at year 18 was 1.05 (0.74-1.70), virtually indistinguishable from the corresponding traditional figures. A side-by-side comparison in **Table 5** shows overlapping CIs at every wave with no systematic drift toward stronger or weaker effects. This concordance indicates that our inference is not an artifact of parametric model choice; it is robust to a modern ensemble-based alternative that can capture complex relationships automatically. We present the ML analysis as a complementary check that reaches the same substantive conclusion and reinforces confidence in the null association.

Competing events

Death and permanent study dropout were treated as competing risks. Cause-specific hazards for death (HR 1.05, 95% CI 0.78-1.41) and for dropout (HR 0.91, 0.70-1.19) did not differ meaningfully by treatment status (**Table 5**), suggesting that differential censoring is unlikely to account for the dementia results.

Discussion

This emulated 18-year target trial in the Health and Retirement Study found no evidence that starting antihypertensive medication in mid-life alters the long-term risk of dementia. After extensive weighting to recreate randomization, the intention-to-treat hazard ratio was 0.97 (95% CI 0.75-1.25) and biennial risk ratios consistently centered on the null. Cumulative incidence by 2020 was 15% among non-initia-

Table 5. Comparison of key effect estimates for incident dementia: traditional vs. ML-enhanced analyses across waves

Time Years	Traditional ITT RR 95% CI	ML Enhanced ITT RR 95% CI
2 Years	1.02 (0.45, 5.70)	1.03 (0.45, 2.87)
4 Years	0.88 (0.49, 2.54)	0.89 (0.46, 2.10)
6 Years	1.03 (0.64, 2.30)	1.02 (0.60, 2.08)
8 Years	1.13 (0.74, 2.54)	1.25 (0.78, 2.43)
10 Years	1.03 (0.69, 1.87)	1.08 (0.73, 1.63)
12 Years	1.10 (0.78, 1.89)	1.11 (0.77, 1.65)
14 Years	1.09 (0.80, 1.81)	1.02 (0.70, 1.58)
16 Years	1.10 (0.81, 1.74)	1.00 (0.66, 1.62)
18 Years	0.89 (0.57, 1.62)	1.05 (0.74, 1.70)
Traditional CSH (Death)	1.05 (0.78, 1.41)	
Traditional CSH (Dropout)	0.91 (0.70, 1.19)	

Comparison of Risk Ratios (RR) for Incident Dementia between Traditional Intention-to-Treat (ITT) Analysis and ML-Enhanced ITT Analysis at Biennial Follow-up Points. RRs and 95% Confidence Intervals (CI) were estimated using 200 bootstrap replicates (percentile method). Competing Events Hazard Ratios are also Reported.

tors versus 13% among initiators, an absolute difference of only two percentage points. Cause-specific analyses for both death and dropout were neutral, showing that competing events did not mask a hidden benefit. Taken together, these findings indicate that, while pharmacological control of mid-life hypertension remains essential for cardiovascular health, initiating antihypertensive therapy at the time of an incident mid-life hypertension diagnosis is unlikely to confer a substantial additional protective effect against late-life dementia in the general U.S. population.

Hypertension can cause cognitive impairment through vascular and cellular mechanisms. Chronic hypertension injures vessel walls, interferes with brain blood flow, and triggers atherosclerosis, oxidative stress, and reduced nitric oxide, mechanisms that provoke inflammation and neuronal death [38, 39]. It also hastens comorbid diseases such as kidney disease and cardiovascular disorders, which themselves heighten the risk of dementia [40]. A decade-long research project tracked vascular risk factors for dementia across life stages (mid-life: 55 years; late-life: 65-70; later-life: 70-80). Results showed shifting priorities: systolic hypertension (>130 mmHg) and diabetes predominated in mid-life, whereas non-stroke cardiovascular disease became more important by age 65. By ages 70-75, stroke and diabetes emerged as key predictors, and antihypertensive medication use gained relevance at age 80 [41]. Emerging research continues to show a significant association between hypertension in mid-life and higher dementia risks, though the association can vary by type and severity. Notably, the relationship between high systolic blood pressure in mid-life and dementia persisted regardless of late-life blood pressure levels. Walker et al. (2019), in a diverse sample (59% women, 21% Black participants) broadly reflecting the U.S. population, confirmed similar patterns [25]. A meta-analysis of more than 100 studies found that systolic blood pressure >130 mmHg in mid-life is associated with a 34% higher risk of cognitive impairment and dementia in later life. For Alzheimer's disease (AD) specifically, diastolic blood pressure >90 mmHg raises risk by 51%, although this relationship appears less consistent across studies. Moderate hypertension (140-159/90-99 mmHg) and more severe cases (>160/95 mmHg) both elevate the risk of AD, suggesting that systolic readings are more predictive [13, 42].

Some research claims antihypertensives reduce dementia risk by 21%, regardless of drug type, but RCTs are mixed: a few shows clear cognitive benefits, while others report no significant link [13]. However, using any proven medication to lower blood pressure may still help mitigate dementia risk, emphasizing the importance of blood pressure control itself rather than drug choice [43, 44]. One investigation compared the incidence of dementia in subjects who were treated with antihypertensive drugs for varying durations and untreated cohorts. Surprisingly, dementia risk reduction that was statistically significant was found in participants who had taken these medications for 12+ years [45]. Another investigation that followed heterogeneous racial/ethnic cohorts for ~4 years found untreated increased BP raised the risk of AD by 36% relative to controls and 42% relative to treated hypertension.

Treated and untreated groups both had greater risk of non-AD dementia than controls, but with no difference between the two and race being non-significant [46].

In one of the most recent research studies, a cohort study tracking over 215,500 patients (mean age = 77.5, 40% male) for over seven years developed 13,812 cases of dementia/AD. Most initiated-on monotherapy (e.g., ACE inhibitors), with common combinations involving diuretics. A greater reduction in dementia risk was seen with higher doses: modest (2%) with low doses, rising to 24% with high doses versus very low drug exposure. Benefits extended even beyond age 85, although protection decreased relative to 65-74-year-olds [47].

However, many of these studies focus on older populations, specific drug classes, or long-term cumulative exposure, and several are vulnerable to residual confounding, which may partly explain why their reported risk reductions appear stronger than the essentially null association observed in our mid-life initiation trial emulation.

Specifically, potassium-sparing diuretics performed better than other antihypertensive classes in reducing AD risk by >70%. Dihydropyridine calcium channel blockers (CCBs) were also more effective at reducing AD risk compared to non-dihydropyridine agents, particularly in the 2-4 years before diagnosis [48, 49]. The lipophilicity of the latter allows them to cross the blood brain barrier with relative ease, an attribute that accounts for their potential brain-protective action [50, 51]. Given that calcium plays vital roles in memory formation and learning, aging and reduced blood flow impair calcium regulation, leading to excess calcium inside brain cells [52]. This calcium overload triggers blood vessel narrowing, restricting oxygen delivery to neural areas but dihydropyridines counteract this by relaxing blood vessels [53]. Persistent low blood flow raises calcium levels, potentially accelerating amyloid plaque formation through specific enzyme activation [54]. A decade-long longitudinal study of hypertensive patients uncovered that therapy reduced their risk of dementia by approximately one-fifth, giving robust evidence to the above hypotheses [55]. Another systematic review gave further evidence in support of the protective effects of CCBs and ARBs, in terms of reducing the risk of dementia [21].

Furthermore, unlike other diuretics, potassium-sparing types enhance cerebral activity independent of hypertension management. These drugs maintain potassium levels, which are linked to better memory and reduced risk of dementia. Studies report enhanced cognitive status in patients taking these drugs [56, 57]. Proper levels of potassium might protect against AD by reducing vascular dysfunction and cellular stress pathways [58, 59]. Elevated calcium levels affect the calcium-activated enzyme that regulates tau protein phosphorylation, paving the way for pathological tau accumulation [60, 61]. Overall, this heterogeneous literature suggests that specific antihypertensive classes - particularly ARBs, calcium channel blockers, and possibly potassium-sparing diuretics - may influence dementia risk through mechanisms beyond blood pressure lowering alone, but definitive class-specific causal estimates remain elusive.

A follow-up period of 7.6 years for 133,355 patients who were prescribed blood pressure drugs found that roughly 4 in 100 developed dementia, reported that ARB users had improved survival, beta blockers and diuretics were linked to a higher risk of death, and CCBs had no influence. Intriguingly, medications that activate angiotensin II pathways, rather than suppress them, correlated with both reduced dementia incidence and better survival. These patterns held true regardless of gender, preexisting diabetes, cardiovascular conditions, or combinations of medications [62]. Moreover, a large-scale analysis found that patients taking CCBs or ARBs had a 12-17% reduced risk of dementia compared to those on ACE inhibitors or beta blockers. In comparison with diuretics, risk reduction was smaller (7-11%) and was not significant statistically [21]. Some studies claim ARBs and ACE inhibitors both promote brain health [63-65]. Other studies warn that ACEIs can raise the risk of dementia [66, 67], or have no effect [68, 69]. ARBs inhibit AT1 receptors and activate AT2/AT4 receptor function, which enhances brain blood vessel integrity, reduces vascular inflammation, and limits amyloid-β deposition, all crucial in dementia development [23, 70, 71]. Orchard et al. (2024), in a preprint (not reviewed by a journal), report-

ed that individuals treated with ARBs had a 25-30% reduction in dementia compared with those who were untreated or received ACE inhibitors, aligning with previous reports of a 20-22% risk reduction [72]. There is some evidence that ACE inhibitors may enhance dementia risk by increasing bradykinin, a compound associated with impaired blood vessels, inflammatory processes, and oxidative stress. Such mechanisms may hasten neuronal damage and amyloid accumulation [73, 74]. Comparative studies show that ACE inhibitors are linked with greater cortical amyloid burden in cognitively normal individuals, in line with their higher apparent risk for dementia when compared with ARBs [75]. Another study, more recently published, showed that not only were ACE inhibitors no more protective against dementia than no treatment, but ACE inhibitors actually increased the risk of dementia by 37-45% relative to ARBs when utilized alone or in combination with other agents [72]. Importantly, most of these investigations did not isolate the effect of initiating treatment at the exact time of incident mid-life hypertension, and many combined heterogeneous drug regimens over long periods. Our emulated trial instead asks a narrower question about the impact of starting any antihypertensive therapy at mid-life onset, which may partly account for the contrast between our null estimates and some class-specific findings in the literature.

Our primary and machine-learning-enhanced analyses therefore tell a consistent story, that across multiple modeling strategies, we did not detect a clinically meaningful protective or harmful effect of mid-life antihypertensive initiation on dementia risk. Recognizing that conventional logistic models may overlook subtle non-linearities, we repeated the entire weighting procedure with Super Learner, an ensemble that optimally combines penalized regression, random forests, gradient-boosted trees and other algorithms. The machine-learning weights achieved the same excellent covariate balance (all stabilized SMDs <0.05) and produced effect estimates that were practically indistinguishable from the primary analysis (year-18 RR = 1.05, 95% CI 0.74-1.70). This convergence across two analytically divergent frameworks reinforces the credibility of a null association and demonstrates how modern, data-adaptive weighting can serve as a transparent robustness check rather than a black-box replacement for classical causal tools. By showing that more flexible models do not unearth a hidden protective signal, our study strengthens confidence that any true medication effect on dementia, if present, is likely to be small.

This study has several limitations that should be considered when interpreting the findings. First, dementia status was ascertained algorithmically rather than through comprehensive clinical evaluations, which may have led to some misclassification of cases. Second, hypertension and antihypertensive medication use were based on self-report, introducing the possibility of exposure misclassification between initiators and non-initiators. Third, we did not capture specific antihypertensive drug classes or detailed treatment trajectories, so we could not distinguish whether particular regimens might differentially affect dementia risk. Finally, important factors such as dietary patterns, genetic markers, and subclinical vascular brain injury were not measured, which means that residual confounding and unmeasured pathways may have attenuated or obscured small true effects.

Conclusion

In a large, nationally representative cohort followed for nearly two decades, we found that starting to take antihypertensive medication at the time of a new mid-life hypertension diagnosis did not considerably change the risk of getting dementia. Traditional inverse-probability-weighted Cox models and a complementary Super Learner-based analysis showed virtually identical null estimates, attesting to the robustness of the finding across modeling assumptions. These results do not diminish the cardiovascular benefits of timely blood pressure control, but they do suggest that pharmacological treatment alone is unlikely to confer substantial neuroprotection. Future studies should (I) disentangle drug-class-specific effects, (II) incorporate granular blood pressure trajectories and vascular imaging, and (III) explore multifactorial prevention strategies that combine vascular risk management with lifestyle and neurocognitive interventions. Until such evidence emerges, clinicians should continue to treat hypertension for proven cardio-renal benefits while maintaining realistic expectations about its role in dementia prevention.

Disclosure of conflict of interest

None.

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References

[1] van der Flier WM and Scheltens P. Epidemiology and risk factors of dementia. J Neurol Neurosurg Psychiatry 2005; 76 Suppl 5: v2-7.

[2] Dementia. www.who.int: World Health Organization; [updated 31 March 2025. Available from: https://www.who.int/news-room/fact-sheets/detail/dementia.

[3] Lucca U, Tettamanti M, Tiraboschi P, Logroscino G, Landi C, Sacco L, Garrì M, Ammesso S, Biotti A, Gargantini E, Piedicorcia A, Mandelli S, Riva E, Galbussera AA and Recchia A. Incidence of dementia in the oldest-old and its relationship with age: the monzino 80-plus population-based study. Alzheimers Dement 2020; 16: 472-481.

[4] Abell JG, Kivimäki M, Dugravot A, Tabak AG, Fayosse A, Shipley M, Sabia S and Singh-Manoux A. Association between systolic blood pressure and dementia in the Whitehall II cohort study: role of age, duration, and threshold used to define hypertension. Eur Heart J 2018; 39: 3119-3125.

[5] Cheng W, Du Y, Zhang Q, Wang X, He C, He J, Jing F, Ren H, Guo M, Tian J and Xu Z. Age-related changes in the risk of high blood pressure. Front Cardiovasc Med 2022; 9: 939103.

[6] Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, de Ferranti S, Després JP, Fullerton HJ, Howard VJ, Huffman MD, Judd SE, Kissela BM, Lackland DT, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Matchar DB, McGuire DK, Mohler ER 3rd, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Willey JZ, Woo D, Yeh RW and Turner MB. Heart disease and stroke statistics--2015 update: a report from the American heart association. Circulation 2015; 131: e29-322.

[7] Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, Brayne C, Burns A, Cohen-Mansfield J, Cooper C, Costafreda SG, Dias A, Fox N, Gitlin LN, Howard R, Kales HC, Kivimäki M, Larson EB, Ogunniyi A, Orgeta V, Ritchie K, Rockwood K, Sampson EL, Samus Q, Schneider LS, Selbæk G, Teri L and Mukadam N. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. Lancet 2020; 396: 413-446.

[8] Levine DA, Galecki AT, Langa KM, Unverzagt FW, Kabeto MU, Giordani B, Cushman M, McClure LA, Safford MM and Wadley VG. Blood pressure and cognitive decline over 8 years in middle-aged and older black and white Americans. Hypertension 2019; 73: 310-318.

[9] Santisteban MM, Iadecola C and Carnevale D. Hypertension, neurovascular dysfunction, and cognitive impairment. Hypertension 2023; 80: 22-34.

[10] Ihle-Hansen H, Thommessen B, Fagerland MW, Øksengård AR, Wyller TB, Engedal K and Fure B. Blood pressure control to prevent decline in cognition after stroke. Vasc Health Risk Manag 2015; 11: 311-316.

[11] McEvoy LK, Fennema-Notestine C, Eyler LT, Franz CE, Hagler DJ Jr, Lyons MJ, Panizzon MS, Rinker DA, Dale AM and Kremen WS. Hypertension-related alterations in white matter microstructure detectable in middle age. Hypertension 2015; 66: 317-323.

[12] Jochemsen HM, Muller M, Visseren FL, Scheltens P, Vincken KL, Mali WP, van der Graaf Y and Geerlings MI. Blood pressure and progression of brain atrophy: the SMART-MR Study. JAMA Neurol 2013; 70: 1046-1053.

[13] Ou YN, Tan CC, Shen XN, Xu W, Hou XH, Dong Q, Tan L and Yu JT. Blood pressure and risks of cognitive impairment and dementia: a systematic review and meta-analysis of 209 prospective studies. Hypertension 2020; 76: 217-225.

[14] Forette F, Seux ML, Staessen JA, Thijs L, Babarskiene MR, Babeanu S, Bossini A, Fagard R, Gil-Extremera B, Laks T, Kobalava Z, Sarti C, Tuomilehto J, Vanhanen H, Webster J, Yodfat Y and Birkenhäger WH. The prevention of dementia with antihypertensive treatment: new evidence from the Systolic Hypertension in Europe (Syst-Eur) study. Arch Intern Med 2002; 162: 2046-2052.

[15] Tzourio C, Anderson C, Chapman N, Woodward M, Neal B, MacMahon S and Chalmers J; PROGRESS Collaborative Group. Effects of blood pressure lowering with perindopril and indapamide therapy on dementia and cognitive decline in patients with cerebrovascular disease. Arch Intern Med 2003; 163: 1069-1075.

[16] Lithell H, Hansson L, Skoog I, Elmfeldt D, Hofman A, Olofsson B, Trenkwalder P and Zanchetti A. The study on cognition and prognosis in the elderly (scope): principal results of

a randomized double-blind intervention trial. J Hypertens 2003; 21: 875-886.
[17] de Galan BE, Zoungas S, Chalmers J, Anderson C, Dufouil C, Pillai A, Cooper M, Grobbee DE, Hackett M, Hamet P, Heller SR, Lisheng L, MacMahon S, Mancia G, Neal B, Pan CY, Patel A, Poulter N, Travert F and Woodward M. Cognitive function and risks of cardiovascular disease and hypoglycaemia in patients with type 2 diabetes: the action in diabetes and vascular disease: preterax and diamicron modified release controlled evaluation (ADVANCE) trial. Diabetologia 2009; 52: 2328-2336.
[18] SPRINT MIND Investigators for the SPRINT Research Group; Williamson JD, Pajewski NM, Auchus AP, Bryan RN, Chelune G, Cheung AK, Cleveland ML, Coker LH, Crowe MG, Cushman WC, Cutler JA, Davatzikos C, Desiderio L, Erus G, Fine LJ, Gaussoin SA, Harris D, Hsieh MK, Johnson KC, Kimmel PL, Tamura MK, Launer LJ, Lerner AJ, Lewis CE, Martindale-Adams J, Moy CS, Nasrallah IM, Nichols LO, Oparil S, Ogrocki PK, Rahman M, Rapp SR, Reboussin DM, Rocco MV, Sachs BC, Sink KM, Still CH, Supiano MA, Snyder JK, Wadley VG, Walker J, Weiner DE, Whelton PK, Wilson VM, Woolard N, Wright JT Jr and Wright CB. Effect of intensive vs standard blood pressure control on probable dementia: a randomized clinical trial. JAMA 2019; 321: 553-561.
[19] Peters R, Yasar S, Anderson CS, Andrews S, Antikainen R, Arima H, Beckett N, Beer JC, Bertens AS, Booth A, van Boxtel M, Brayne C, Brodaty H, Carlson MC, Chalmers J, Corrada M, DeKosky S, Derby C, Dixon RA, Forette F, Ganguli M, van Gool WA, Guaita A, Hever AM, Hogan DB, Jagger C, Katz M, Kawas C, Kehoe PG, Keinanen-Kiukaanniemi S, Kenny RA, Köhler S, Kunutsor SK, Laukkanen J, Maxwell C, McFall GP, van Middelaar T, Moll van Charante EP, Ng TP, Peters J, Rawtaer I, Richard E, Rockwood K, Rydén L, Sachdev PS, Skoog I, Skoog J, Staessen JA, Stephan BCM, Sebert S, Thijs L, Trompet S, Tully PJ, Tzourio C, Vaccaro R, Vaaramo E, Walsh E, Warwick J and Anstey KJ. Investigation of antihypertensive class, dementia, and cognitive decline: a meta-analysis. Neurology 2020; 94: e267-e281.
[20] Liampas I, Hatzimanolis A, Siokas V, Yannakoulia M, Kosmidis MH, Sakka P, Hadjigeorgiou GM, Scarmeas N and Dardiotis E. Antihypertensive medication class and the risk of dementia and cognitive decline in older adults: a secondary analysis of the prospective HELIAD cohort. J Alzheimers Dis 2022; 89: 709-719.
[21] den Brok M, van Dalen JW, Abdulrahman H, Larson EB, van Middelaar T, van Gool WA, Moll van Charante EP and Richard E. Antihypertensive medication classes and the risk of dementia: a systematic review and network meta-analysis. J Am Med Dir Assoc 2021; 22: 1386-1395, e1315.
[22] Wei J, Xu H, Zhang D, Tang H, Wang T, Steck SE, Divers J, Zhang J and Merchant AT. Initiation of antihypertensive medication from midlife on incident dementia: the health and retirement study. J Alzheimers Dis 2023; 94: 1431-1441.
[23] Kehoe PG. The coming of age of the angiotensin hypothesis in alzheimer's disease: progress toward disease prevention and treatment? J Alzheimers Dis 2018; 62: 1443-1466.
[24] Hajjar I, Okafor M, McDaniel D, Obideen M, Dee E, Shokouhi M, Quyyumi AA, Levey A and Goldstein F. Effects of candesartan vs lisinopril on neurocognitive function in older adults with executive mild cognitive impairment: a randomized clinical trial. JAMA Netw Open 2020; 3: e2012252.
[25] Walker KA, Sharrett AR, Wu A, Schneider ALC, Albert M, Lutsey PL, Bandeen-Roche K, Coresh J, Gross AL, Windham BG, Knopman DS, Power MC, Rawlings AM, Mosley TH and Gottesman RF. Association of midlife to late-life blood pressure patterns with incident dementia. JAMA 2019; 322: 535-545.
[26] Cheng G, He S, He Q, Xie X, Tang C, Xie Q, Wu X, Jiang N, Li C, Min X and Yan Y. Trajectory patterns of blood pressure change up to six years and the risk of dementia: a nationwide cohort study. Aging (Albany NY) 2021; 13: 17380-17406.
[27] Shang X, Hill E, Zhu Z, Liu J, Ge BZ, Wang W and He M. The association of age at diagnosis of hypertension with brain structure and incident dementia in the UK biobank. Hypertension 2021; 78: 1463-1474.
[28] van Dalen JW, Brayne C, Crane PK, Fratiglioni L, Larson EB, Lobo A, Lobo E, Marcum ZA, Moll van Charante EP, Qiu C, Riedel-Heller SG, Röhr S, Rydén L, Skoog I, van Gool WA and Richard E. Association of systolic blood pressure with dementia risk and the role of age, U-shaped associations, and mortality. JAMA Intern Med 2022; 182: 142-152.
[29] Jung H, Yang PS, Kim D, Jang E, Yu HT, Kim TH, Sung JH, Pak HN, Lee MH, Lip GYH and Joung B. Associations of hypertension burden on subsequent dementia: a population-based cohort study. Sci Rep 2021; 11: 12291.
[30] Hernán MA and Robins JM. Using big data to emulate a target trial when a randomized trial is not available. Am J Epidemiol 2016; 183: 758-764.
[31] Hernán MA, Wang W and Leaf DE. Target trial emulation: a framework for causal inference

from observational data. JAMA 2022; 328: 2446-2447.
[32] Hernán MA, Alonso A, Logan R, Grodstein F, Michels KB, Willett WC, Manson JE and Robins JM. Observational studies analyzed like randomized experiments: an application to postmenopausal hormone therapy and coronary heart disease. Epidemiology 2008; 19: 766-779.
[33] Magliano DJ, Rogers SL, Abramson MJ and Tonkin AM. Hormone therapy and cardiovascular disease: a systematic review and meta-analysis. BJOG 2006; 113: 5-14.
[34] Bugliari D, Carroll J, Hayden O, Hayes J, Hurd MD, Lee S, et al. RAND HRS longitudinal file 2020 (V1) documentation. Aging 2023.
[35] Sonnega A, Faul JD, Ofstedal MB, Langa KM, Phillips JW and Weir DR. Cohort profile: the health and retirement study (HRS). Int J Epidemiol 2014; 43: 576-585.
[36] Crimmins EM, Kim JK, Langa KM and 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 Suppl 1: i162-171.
[37] Gianattasio KZ, Wu Q, Glymour MM and Power MC. Comparison of methods for algorithmic classification of dementia status in the health and retirement study. Epidemiology 2019; 30: 291-302.
[38] Iadecola C, Yaffe K, Biller J, Bratzke LC, Faraci FM, Gorelick PB, Gulati M, Kamel H, Knopman DS, Launer LJ, Saczynski JS, Seshadri S and Zeki Al Hazzouri A. Impact of hypertension on cognitive function: a scientific statement from the American heart association. Hypertension 2016; 68: e67-e94.
[39] Katusic ZS and Austin SA. Endothelial nitric oxide: protector of a healthy mind. Eur Heart J 2014; 35: 888-894.
[40] Canavan M and O'Donnell MJ. Hypertension and cognitive impairment: a review of mechanisms and key concepts. Front Neurol 2022; 13: 821135.
[41] McGrath ER, Beiser AS, O'Donnell A, Himali JJ, Pase MP, Satizabal CL and Seshadri S. Determining vascular risk factors for dementia and dementia risk prediction across mid- to later life: the framingham heart study. Neurology 2022; 99: e142-e153.
[42] Lennon MJ, Makkar SR, Crawford JD and Sachdev PS. Midlife hypertension and Alzheimer's disease: a systematic review and meta-analysis. J Alzheimers Dis 2019; 71: 307-316.
[43] Ding J, Davis-Plourde KL, Sedaghat S, Tully PJ, Wang W, Phillips C, Pase MP, Himali JJ, Gwen Windham B, Griswold M, Gottesman R, Mosley TH, White L, Guðnason V, Debette S, Beiser AS, Seshadri S, Ikram MA, Meirelles O, Tzourio C and Launer LJ. 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.
[44] Lin CY, Chen PH, Tsai CL, Hsieh YW, Hu KC, Tsai FJ, Cho DY and Liao HY. Antihypertensive medication and dementia risk in patients with hypertension: a nationwide population-based study. J Clin Neurosci 2024; 125: 83-94.
[45] Peila R, White LR, Masaki K, Petrovitch H and Launer LJ. Reducing the risk of dementia: efficacy of long-term treatment of hypertension. Stroke 2006; 37: 1165-1170.
[46] Lennon MJ, Lipnicki DM, Lam BCP, Crawford JD, Schutte AE, Peters R, Rydberg-Sterner T, Najar J, Skoog I, Riedel-Heller SG, Röhr S, Pabst A, Lobo A, De-la-Cámara C, Lobo E, Lipton RB, Katz MJ, Derby CA, Kim KW, Han JW, Oh DJ, Rolandi E, Davin A, Rossi M, Scarmeas N, Yannakoulia M, Dardiotis T, Hendrie HC, Gao S, Carriere I, Ritchie K, Anstey KJ, Cherbuin N, Xiao S, Yue L, Li W, Guerchet M, Preux PM, Aboyans V, Haan MN, Aiello A, Scazufca M and Sachdev PS. Blood pressure, antihypertensive use, and late-life alzheimer and non-alzheimer dementia risk: an individual participant data meta-analysis. Neurology 2024; 103: e209715.
[47] Rea F, Corrao G and Mancia G. Risk of dementia during antihypertensive drug therapy in the elderly. J Am Coll Cardiol 2024; 83: 1194-1203.
[48] Khachaturian AS, Zandi PP, Lyketsos CG, Hayden KM, Skoog I, Norton MC, Tschanz JT, Mayer LS, Welsh-Bohmer KA and Breitner JC. Antihypertensive medication use and incident alzheimer disease: the cache county study. Arch Neurol 2006; 63: 686-692.
[49] Yasar S, Corrada M, Brookmeyer R and Kawas C. Calcium channel blockers and risk of AD: the baltimore longitudinal study of aging. Neurobiol Aging 2005; 26: 157-163.
[50] Welsh TJ, Gladman JR and Gordon AL. The treatment of hypertension in people with dementia: a systematic review of observational studies. BMC Geriatr 2014; 14: 19.
[51] da Costa Cabrera D, Santa-Helena E, Leal HP, de Moura RR, Nery LEM, Gonçalves CAN, Russowsky D and Montes D'Oca MG. Synthesis and antioxidant activity of new lipophilic dihydropyridines. Bioorg Chem 2019; 84: 1-16.
[52] Wu QJ and Tymianski M. Targeting NMDA receptors in stroke: new hope in neuroprotection. Mol Brain 2018; 11: 15.
[53] Hanyu H, Hirao K, Shimizu S, Iwamoto T, Koizumi K and Abe K. Favourable effects of nilvadipine on cognitive function and regional cere-

bral blood flow on SPECT in hypertensive patients with mild cognitive impairment. Nucl Med Commun 2007; 28: 281-287.
[54] Kawahara M and Kuroda Y. Intracellular calcium changes in neuronal cells induced by Alzheimer's beta-amyloid protein are blocked by estradiol and cholesterol. Cell Mol Neurobiol 2001; 21: 1-13.
[55] Hwang D, Kim S, Choi H, Oh IH, Kim BS, Choi HR, Kim SY and Won CW. Calcium-channel blockers and dementia risk in older adults - national health insurance service - senior cohort (2002-2013). Circ J 2016; 80: 2336-2342.
[56] Ozawa M, Ninomiya T, Ohara T, Hirakawa Y, Doi Y, Hata J, Uchida K, Shirota T, Kitazono T and Kiyohara Y. Self-reported dietary intake of potassium, calcium, and magnesium and risk of dementia in the Japanese: the hisayama study. J Am Geriatr Soc 2012; 60: 1515-1520.
[57] Zhao H, Liu P, Wang R, Liu X, Wu X, Xu C, Ji X, Gao L and Luo Y. Expression profile of microRNAs in the peripheral lymphocyte of acute stroke patients. J Neurol Sci 2013; 333: e202.
[58] Chang CH, Chang YC, Wu LC, Lin JW, Chuang LM and Lai MS. Different angiotensin receptor blockers and incidence of diabetes: a nationwide population-based cohort study. Cardiovasc Diabetol 2014; 13: 91.
[59] Udensi UK and Tchounwou PB. Potassium homeostasis, oxidative stress, and human disease. Int J Clin Exp Physiol 2017; 4: 111-122.
[60] Cao LL, Guan PP, Liang YY, Huang XS and Wang P. Calcium Ions stimulate the hyperphosphorylation of tau by activating microsomal prostaglandin E synthase 1. Front Aging Neurosci 2019; 11: 108.
[61] Wang Y, Zhang R, Tao C, Xu Z, Chen W, Wang C, Song L, Zheng J and Gao F. Blood-brain barrier disruption and perivascular beta-amyloid accumulation in the brain of aged rats with spontaneous hypertension: evaluation with dynamic contrast-enhanced magnetic resonance imaging. Korean J Radiol 2018; 19: 498-507.
[62] Schroevers JL, Hoevenaar-Blom MP, Busschers WB, Hollander M, Van Gool WA, Richard E, Van Dalen JW and Moll van Charante EP. Antihypertensive medication classes and risk of incident dementia in primary care patients: a longitudinal cohort study in the Netherlands. Lancet Reg Health Eur 2024; 42: 100927.
[63] Johnson ML, Parikh N, Kunik ME, Schulz PE, Patel JG, Chen H, Aparasu RR and Morgan RO. Antihypertensive drug use and the risk of dementia in patients with diabetes mellitus. Alzheimers Dement 2012; 8: 437-444.
[64] Hajjar I, Hart M, Mack W and Lipsitz LA. Aldosterone, cognitive function, and cerebral hemodynamics in hypertension and antihypertensive therapy. Am J Hypertens 2015; 28: 319-325.
[65] Tully PJ, Helmer C, Peters R and Tzourio C. Exploiting drug-apolipoprotein E gene interactions in hypertension to preserve cognitive function: the 3-city cohort study. J Am Med Dir Assoc 2019; 20: 188-194, e184.
[66] Sink KM, Leng X, Williamson J, Kritchevsky SB, Yaffe K, Kuller L, Yasar S, Atkinson H, Robbins M, Psaty B and Goff DC Jr. Angiotensin-converting enzyme inhibitors and cognitive decline in older adults with hypertension: results from the cardiovascular health study. Arch Intern Med 2009; 169: 1195-1202.
[67] Gao Y, O'Caoimh R, Healy L, Kerins DM, Eustace J, Guyatt G, Sammon D and Molloy DW. Effects of centrally acting ACE inhibitors on the rate of cognitive decline in dementia. BMJ Open 2013; 3: e002881.
[68] Fazal K, Perera G, Khondoker M, Howard R and Stewart R. Associations of centrally acting ACE inhibitors with cognitive decline and survival in Alzheimer's disease. BJPsych Open 2017; 3: 158-164.
[69] Scotti L, Bassi L, Soranna D, Verde F, Silani V, Torsello A, Parati G and Zambon A. Association between renin-angiotensin-aldosterone system inhibitors and risk of dementia: a meta-analysis. Pharmacol Res 2021; 166: 105515.
[70] Ho JK and Nation DA. Cognitive benefits of angiotensin IV and angiotensin-(1-7): a systematic review of experimental studies. Neurosci Biobehav Rev 2018; 92: 209-225.
[71] Forrester SJ, Booz GW, Sigmund CD, Coffman TM, Kawai T, Rizzo V, Scalia R and Eguchi S. Angiotensin II signal transduction: an update on mechanisms of physiology and pathophysiology. Physiol Rev 2018; 98: 1627-1738.
[72] Orchard SG, Zhou Z, Fravel M, Ryan J, Woods RL, Wolfe R, Shah RC, Murray A, Sood A, Reid CM, Nelson MR, Bellin L, Polkinghorne KR, Stocks N and Ernst ME. Antihypertensive medications and dementia in older adults with hypertension. medRxiv 2024.
[73] Singh PK, Chen ZL, Ghosh D, Strickland S and Norris EH. Increased plasma bradykinin level is associated with cognitive impairment in Alzheimer's patients. Neurobiol Dis 2020; 139: 104833.
[74] Ionescu-Tucker A and Cotman CW. Emerging roles of oxidative stress in brain aging and Alzheimer's disease. Neurobiol Aging 2021; 107: 86-95.
[75] Ouk M, Wu CY, Rabin JS, Edwards JD, Ramirez J, Masellis M, Swartz RH, Herrmann N, Lanctôt KL, Black SE and Swardfager W. Associations between brain amyloid accumulation and the use of angiotensin-converting enzyme inhibitors versus angiotensin receptor blockers. Neurobiol Aging 2021; 100: 22-31.

Supplementary Table 1. Variable's codebook

No.	Variable Name[a]	Description[b]
	HHIDPN	HHIDPN: HHold ID + Person Number/Num
	R6AGE	R6AGEY_M:W6 R Age (years) at Ivw MidMon
	R6HTN	hc005:high blood pressure
	R6HTNDRUG	hc006:blood pressure medication
	R6HTNWTLOS	hc007:lost weight high blood pressure
	R6IWSTAT	R6IWSTAT:W6 R Interview Status
	R7IWSTAT	R7IWSTAT:W7 R Interview Status
	R8IWSTAT	R8IWSTAT:W8 R Interview Status
	R9IWSTAT	R9IWSTAT:W9 R Interview Status
	R10IWSTAT	R10IWSTAT:W10 R Interview Status
	R11IWSTAT	R11IWSTAT:W11 R Interview Status
	R12IWSTAT	R12IWSTAT:W12 R Interview Status
	R13IWSTAT	R13IWSTAT:W13 R Interview Status
	R14IWSTAT	R14IWSTAT:W14 R Interview Status
	R15IWSTAT	R15IWSTAT:W15 R Interview Status
	RAEDUC	RAEDUC: R education (categ)
	R6URBRUR	R6URBRUR:W6 Urban-Suburban-Rural
	R6SHLT	R6SHLT:W6 Self-report of health
	R6CESD	R6CESD:W6 CESD score
	R6VIGACT	R6VIGACT:W6 R Wtr vigorus phys act 3+/wk
	R6BMI	R6BMI:W6 Self-reported body mass index=kg/m^2
	R6SMOKEV	R6SMOKEV:W6 R smoke ever
	R6HIBPE	R6HIBPE:W6 R ever had high blood pressure
	R6HIBPS	R6HIBPS:W6 R had hi BP since last IW
	R6DIABE	R6DIABE:W6 R ever had diabetes
	R6CANCRE	R6CANCRE:W6 R ever had cancer
	R6LUNGE	R6LUNGE:W6 R ever had lung disease
	R6HEARTE	R6HEARTE:W6 R ever had heart problems
	R6STROKE	R6STROKE:W6 R ever had stroke
	R6ARTHRE	R6ARTHRE:W6 R ever had arthritis
	R6COG27	R6COG27:W6 27-POINT COGNITION SUMMARY SCORE
	R7COG27	R7COG27:W7 27-POINT COGNITION SUMMARY SCORE
	R8COG27	R8COG27:W8 27-POINT COGNITION SUMMARY SCORE
	R9COG27	R9COG27:W9 27-POINT COGNITION SUMMARY SCORE
	R10COG27	R10COG27:W10 27-POINT COGNITION SUMMARY SCORE
	R11COG27	R11COG27:W11 27-POINT COGNITION SUMMARY SCORE
	R12COG27	R12COG27:W12 27-POINT COGNITION SUMMARY SCORE
	R13COG27	R13COG27:W13 27-POINT COGNITION SUMMARY SCORE
	R14COG27	R14COG27:W14 27-POINT MODE-ADJUSTED COGNITION SUMMARY SCORE
	R15COG27	R15COG27:W15 27-POINT MODE-ADJUSTED COGNITION SUMMARY SCORE
	R6NHMLIV	R6NHMLIV:W6 Live in Nurs home at Ivw
	R6IEARN	R6IEARN:W6 Income:R Earnings
	R6IPENA	R6IPENA:W6 Income:R Pension + Annuity
	R6ISSDI	R6ISSDI:W6 Income:R SSI + SS Disability
	R6ISRET	R6ISRET:W6 Income:R SocSec Retirement
	RAGENDER	RAGENDER:R Gender
	RAHISPAN	RAHISPAN:R Hispanic

RARACEM	RARACEM:R Race-masked
R6MSTAT	R6MSTAT:W6 R Marital Status
R6ADL5A	R6ADL5A:W6 Any Diff-sum of ADLs/0-5
R6IADL5A	R6IADL5A:W6 Any Diff-sum of IADLs/0-5

Details of variables are used for analysis. [a]The names of variables that are used in the analysis script; [b]Original name of each variable and its description, some of the variable names are changed in the analysis script owing to more clear code lines.

Supplementary Table 2. Full specifications of traditional models

Model	Formula	Method	Purpose
Propensity Score Model (IPTW)	exposure ~ AGE + BMI + Gender + Hispanic + Race + Education + Marital State + Income + Site of Living + Self Report of Health + CESD Score (Depression) + ADL limitation + IADL limitation+ Weight loss due to Hypertension + Vigorous Activity + Smoking + Diabetes + Lung Disease + Heart Disease + Stroke + Arthritis	Logistic Regression (Firth's penalized)	Estimate probability of exposure (Initiator vs. Non-Initiator) at baseline.
Censoring Model (IPCW)	Current censored ~ exposure + time point + AGE + BMI + Gender + Hispanic + Race + Education + Marital State + Income + Site of Living + Self Report of Health + CESD Score (Depression) + ADL limitation + IADL limitation+ Weight loss due to Hypertension + Vigorous Activity + Smoking + Diabetes + Lung Disease + Heart Disease + Stroke + Arthritis	Logistic Regression (Firth's penalized)	Estimate probability of not being censored (death or dropout) at each follow-up wave.

Full Specifications of Traditional Propensity Score and Censoring Models.

Supplementary Table 3. Full details of ML-enhanced model implementation

Component	Details
ML Algorithm	Super Learner (ensemble learning)
Super Learner Library	SL.glm, SL.glmnet, SL.randomForest
Hyperparameters	Default hyperparameters for chosen learners (e.g., glm, glmnet, randomForest) with cross-validation for ensemble weights.
Software/Packages	SuperLearner, glm, glmnet, randomForest packages in R.

Full Details of ML-Enhanced Model Implementation for Propensity Score Estimation.