Transparent Reporting of Observational Studies Emulating a Target Trial—The TARGET Statement

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OUTLINE

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- Rationale
- Development of TARGET checklist
- Development of checklist items
- Example of an article
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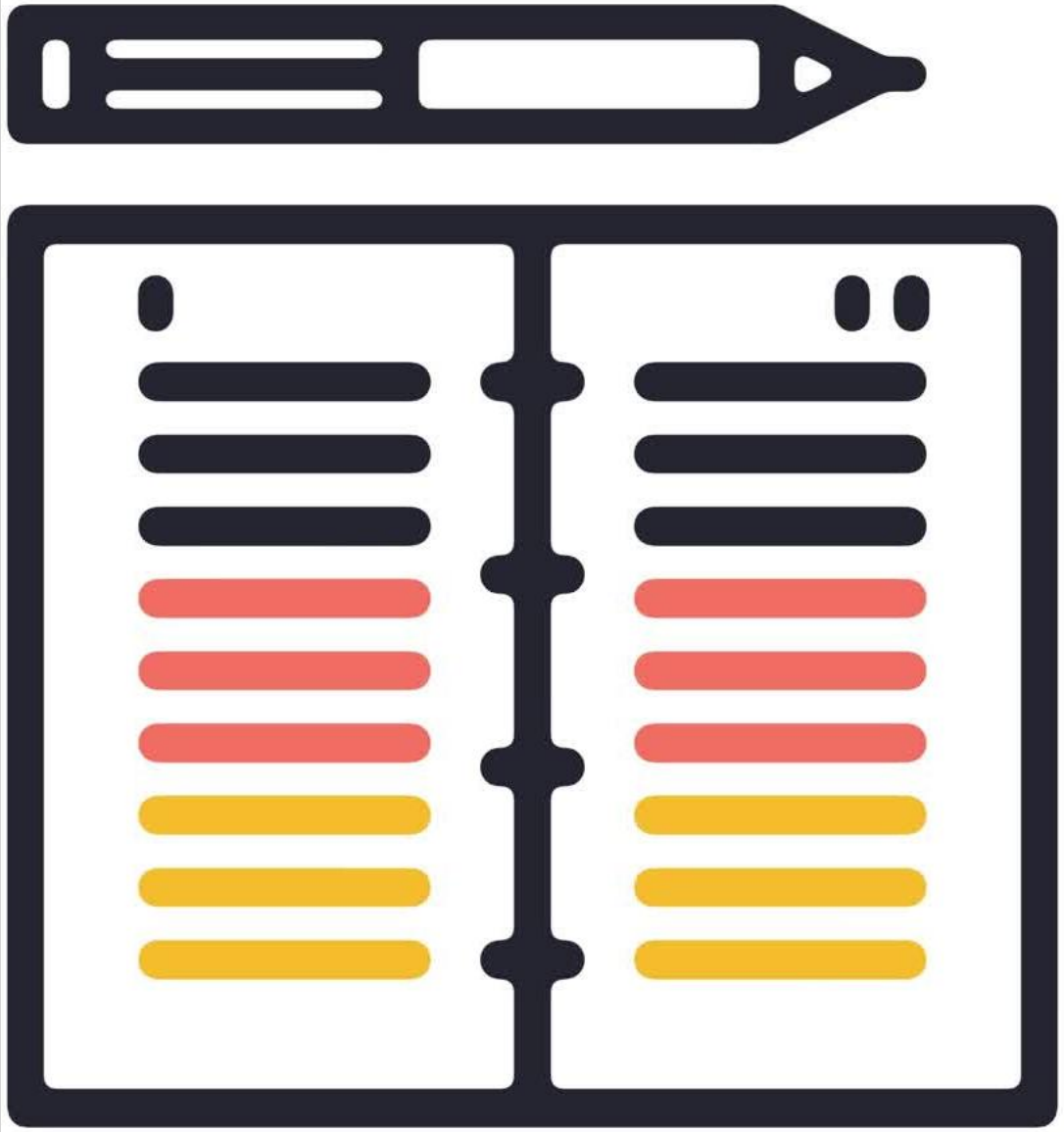
- Conclusion



Introduction

This document introduces the Transparent Reporting of Observational Studies Emulating a Target Trial (TARGET) guideline,

Which provides consensus-based recommendations for reporting observational studies designed to estimate causal effects by emulating a hypothetical randomized trial (target trial).

Rationale

The guideline addresses the lack of specific reporting standards for such studies, aiming to improve transparency, completeness, and accuracy in reporting.

Key Points:

Purpose: The Transparent Reporting of Observational Studies Emulating a Target Trial (TARGET) aims to guide researchers in reporting observational studies that emulate randomized trials, ensuring clarity and consistency in presenting causal questions, assumptions, methods, and findings.

Development of TARGET checklist

Development: The TARGET guideline was developed using the Enhancing the Quality and Transparency of Health Research (EQUATOR) framework involving,

1). Systematic reviews of reporting practices in published studies that had explicitly aimed to emulate a target trial.

2). a 2-round online expert survey

3). a 3-day expert consensus meeting

4). Piloting of the draft checklist with stakeholders

Development of Checklist

It resulted in a 21-item checklist organized into six sections:

Abstract,

Introduction,

Methods,

Results,

Discussion, and

Other information.

CHECKLIST

Table 2. TARGET Checklist of Recommended Items to Address in Reports of Studies Emulating a Target Trial[a]

Item No.	Checklist item			
Abstract				
1	a	Identify that the study attempts to emulate a target trial using observational data. State the study objectives and briefly summarize the specified target trial.		
	b	Report the data sources used for emulation.		
	c	Summarize key assumptions, statistical methods, findings and conclusions.		
Introduction				
2	Background	Describe the scientific background of the study and the gap in knowledge.		
3	Causal question	Summarize the causal question.		
4	Rationale	Describe the rationale for emulating a target trial with the available data. Cite randomized trials informing the design of the target trial if applicable.		
Methods				
5	Data sources	Cite the data sources contributing to the analyses and for each one describe the following: original purpose, type, the geographic locations, setting and time-period. If relevant, describe how the data were linked or pooled.		
	Target trial specification			**Target trial emulation**
6	Specify the components of the target trial protocol that would answer the causal question.		7	Describe how the components of the target trial protocol were emulated with the observational data, including how all variables were measured or ascertained.
	Eligibility criteria			Eligibility criteria
	a	Describe the eligibility criteria.	a	Describe how the eligibility criteria were operationalized with the data.
	Treatment strategies			Treatment strategies
	b	Describe the treatment strategies that would be compared.	b	Describe how the treatment strategies were operationalized with the data.
	Assignment procedures			Assignment procedures
	c	Report that eligible individuals would be randomly assigned to treatment strategies and may be aware of their treatment allocation.	c	Describe how assignment to treatment strategies was operationalized with the data.
	Follow-up			Follow-up
	d	Clarify that follow-up would start at time of assignment to the treatment strategies. Specify when follow-up would end.	d	Clarify that follow-up starts at the time individuals were assigned to the treatment strategies. Describe how the end of follow-up was operationalized with the data.
	Outcomes			Outcomes
	e	Describe the outcomes.	e	Describe how the outcomes were operationalized with the data.
	Causal contrasts			Causal contrasts
	f	Describe the causal contrasts of interest, including effect measures.	f	Describe how the causal contrasts were operationalized with the data, including effect measures.
	Identifying assumptions			Identifying assumptions
	g	Describe assumptions that would be made to identify each causal estimand. Describe the variables, if any, related to these assumptions.	g.i	For each causal estimand, describe assumptions made to identify it, including assumptions regarding baseline confounding due to lack of randomization.
			g.ii	Describe how the variables related to these assumptions were operationalized with the data.
	Data analysis plan			Data analysis plan
	h	For each causal estimand, describe the data analysis procedures and any associated statistical modeling assumptions, including approaches for handling missing data.	h.i	For each causal estimand, describe the data analysis procedures and any associated statistical modeling assumptions, including approaches for handling missing data.
			h.ii	For each causal estimand, describe any additional analyses conducted to assess the sensitivity of the results to the choice of operationalizations, assumptions and analysis.

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(continued)

Table 2. TARGET Checklist of Recommended Items to Address in Reports of Studies Emulating a Target Trial[a] (continued)

Item No.	Checklist Item	
Results		
8	Participant selection	Report numbers of individuals assessed for eligibility, eligible, and assigned to each treatment strategy. A flow diagram is strongly recommended.
9	Baseline data	Describe the distribution of characteristics of individuals at baseline, by treatment strategy.
10	Follow-up	Summarize length of follow-up and describe reasons for end of follow-up for each treatment strategy and causal contrast.
11	Missing data	Describe the frequency of missing data in all variables, by treatment strategy when applicable.
12	Outcomes	Describe the frequency or distribution of each outcome, by treatment strategy.
13	Effect estimates	Report the effect estimates for each causal contrast with corresponding measures of precision, including both absolute and relative measures of effect, when applicable.
14	Additional analyses	Report results of all analyses to assess the sensitivity of the estimates to choices in operationalizations, assumptions and analysis.
Discussion		
15	Interpretation	Provide an interpretation of the key findings.
16	Limitations	Discuss the limitations of the study considering differences between the target trial and its emulation and the plausibility of assumptions, including assumptions regarding baseline confounding due to lack of randomization.
Other Information		
17	Ethics	Provide the institutional research board or ethics committee that approved the study and approval numbers, if relevant.
18	Registration	State whether, when and where the study protocol was registered.
19	Sharing of study materials	Provide information on whether data, analytic code and/or other materials are accessible, and where and how they can be accessed.
20	Funding sources	Provide the sources of funding and detail the role of the funders in the design, conduct and reporting of the study.
21	Conflicts of Interest	State any conflicts of interest and financial disclosures for all authors.

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Example of an article

ORIGINAL ARTICLE

Target Trial Emulation Using Cohort Studies

Estimating the Effect of Antihypertensive Medication Initiation on Incident Dementia

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1. Abstract

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Background: Observational studies link high midlife systolic blood pressure to increased dementia risk. However, the synthesis of evidence from randomized controlled trials has not definitively demonstrated that antihypertensive medication use reduces dementia risk. Here, we emulate target trials of antihypertensive medication initiation on incident dementia using three cohort studies, with attention to potential violations of necessary assumptions.

1a

Methods: We emulated trials of antihypertensive medication initiation on incident dementia using data from the Atherosclerosis Risk in Communities study, Cardiovascular Health Study, and Health and Retirement Study. We used data-driven methods to restrict participants to initiators and noninitiators with overlap in propensity scores and positive control outcomes to look for violations of positivity and exchangeability assumptions.

1b

Results: Analyses were limited by the small number of cohort participants who met eligibility criteria. Associations between antihypertensive medication initiation and incident dementia were inconsistent and imprecise (Atherosclerosis Risk in Communities: HR = 0.30 [0.05, 1.93]; Cardiovascular Health Study: HR = 0.66 [0.27, 1.64]; Health and Retirement Study: HR = 1.09 [0.75, 1.59]). More stringent propensity score restrictions had little effect on findings. Sensitivity analyses using a positive control outcome unexpectedly suggested antihypertensive medication initiation increased the risk of coronary heart disease in all three samples.

Conclusions: Positive control outcome analyses suggested substantial residual confounding in effect estimates from our target trials, precluding conclusions about the impact of antihypertensive medication initiation on dementia risk through target trial emulation. Formalized processes for identifying violations of necessary

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Study objectives

Statistical Analysis

We characterized participants who met eligibility criteria, remained in the sample after restricting based on propensity score cutoffs, and were excluded after restricting based on propensity score cutoffs. In HRS, we weighted descriptive statistics by HRS sampling weights. Additionally, we calculated absolute standardized mean differences comparing treatment groups within each cohort after propensity score restriction to assess achieved covariate balance.

To be consistent with existing trials, we quantified the effect of antihypertensive medication initiation on incident dementia using Cox proportional hazards models adjusted for age, sex, education, race, study area (baseline study center for ARIC and CHS and census region for HRS), apolipoprotein E ε4 allele status, and each participant's propensity score. We used robust sandwich variance estimators to account for participants contributing to more than one subtrial. In analyses using HRS, participants were weighted by both their HRS sampling weight and stabilized inverse probability of attrition weights [32,33] (see Inverse probability of attrition weighting in HRS eAppendix; http://links.lww.com/EDE/C191). We then compared these findings to those reported by prior RCTs of antihypertensive medication use and dementia risk.

We also estimated the effect of antihypertensive medi-

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1a. Briefly summarize the specified target trial.

Table 1. Characteristics of Target Trial vs. Existing Placebo-controlled Trials of Antihypertensive Medication Use and Incident Dementia[a]

	Primary Eligibility Criteria	Treatment Strategies	Follow-up	Outcome	Causal Contrast of Interest
Target trial	65 years or older at baseline, SBP ≥140 mm Hg at baseline, White or Black race, no dementia at randomization, at least one follow-up visit (in HRS), no documented use of antihypertensives at or before baseline	Initiator of any antihypertensive medication vs. noninitiator at randomization	Until incident dementia, death, loss to follow-up (in HRS), or for 6 years	Incident dementia	Emulating an intention-to-treat analysis
Existing trials					
ADVANCE[17] (N = 11,140)	55 years or older at baseline, diagnosed type 2 diabetes at the age of 30, diagnosed CVD or eligible risk factor, no definite indication or contraindication to study treatments or HbA1c target	Combined perindopril and indapamide vs. placebo	Maximum of 5.6 years mean of 4.6 years	Incident dementia	Intention-to-treat
HYVET-COG[18] (N = 3336)	80 years or older at baseline, sitting SBP of 160–200 mm Hg, standing SBP of≥140 mm Hg, sitting DBP of≥110, no ongoing nursing care, no dementia.	Indapamide with addition perindopril vs. placebo	Mean of ~2 years	Incident dementia	Intention-to-treat
PROGRESS[19] (N = 6105)	Cerebrovascular disease within past 5 years, no clear indication for or contraindication to ACE inhibitor.	Perindopril plus optional indapamide vs. placebo	Mean of 3.9 years	Incident dementia	Intention-to-treat
SCOPE[20] (N = 4937)	Age 70–89 at baseline, SBP of 160–179 mm Hg and/or DBP of 90–99 mm Hg, MMSE ≥24, no stroke or MI within 6 months of baseline, no dementia or preclusion to dementia ascertainment.	Candesartan vs. placebo	Maximum of 5 years, mean of 3.7 years	Incident dementia	Intention-to-treat

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Follow-up

Within each subtrial, time on study began at the randomization visit and ended at the first of dementia diagnosis, death, loss to follow-up (in HRS only), or elapsed follow-up of 6 years, similar to the longest follow-up of completed RCTs (see Table 1). Incident dementia was determined using hospital records in ARIC, retroactively using cognitive test scores and other cohort-collected data in CHS, and algorithmically in HRS (see eTable 1; http://links.lww.com/EDE/C191 for follow-up time until their death.

Causal Contrast of Interest

Our causal contrast of interest compared outcomes across initiators and noninitiators, regardless of adherence or contamination after randomization. This is analogous to an intention-to-treat analysis.[10]

Briefly summarize the specified target trial

Statistical Analysis

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1b. Report the data sources used for emulation.

positivity assumptions.

METHODS

Observational Data Sources

The Atherosclerosis Risk in Communities (ARIC) study began in 1987 and recruited participants aged 45–64 years from four US sites.[1] Here we use data from clinic visits that occurred every 3 years from 1987–1989 (visit 1) to 1996–1998 (visit 4), as well as data from annual follow-up telephone calls, medical record surveillance, dementia ascertainment, and death records through 2010.

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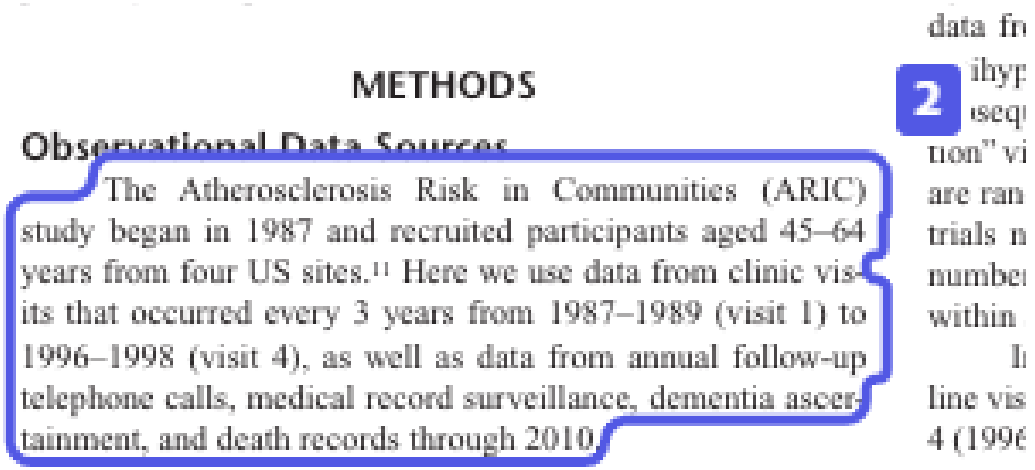

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2

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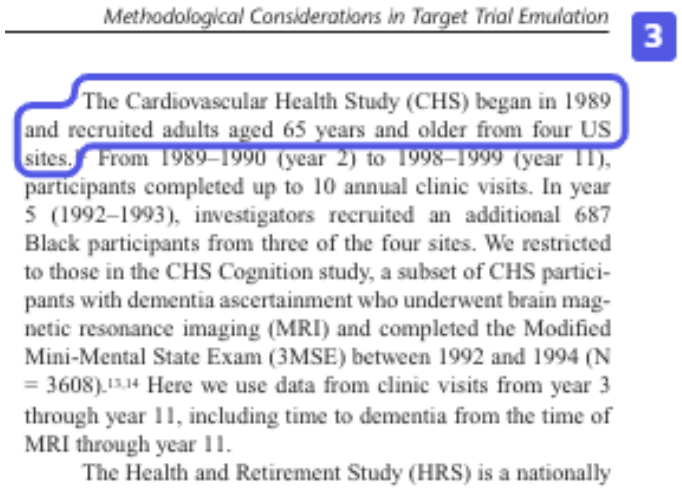

Methodological Considerations in Target Trial Emulation 3

The Cardiovascular Health Study (CHS) began in 1989 and recruited adults aged 65 years and older from four US sites.[12] From 1989–1990 (year 2) to 1998–1999 (year 11), participants completed up to 10 annual clinic visits. In year 5 (1992–1993), investigators recruited an additional 687 Black participants from three of the four sites. We restricted to those in the CHS Cognition study, a subset of CHS participants with dementia ascertainment who underwent brain magnetic resonance imaging (MRI) and completed the Modified Mini-Mental State Exam (3MSE) between 1992 and 1994 (N = 3608).[13,14] Here we use data from clinic visits from year 3 through year 11, including time to dementia from the time of MRI through year 11.

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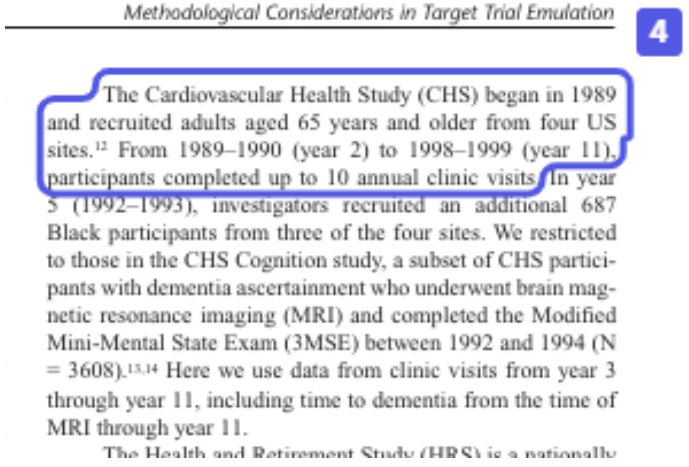

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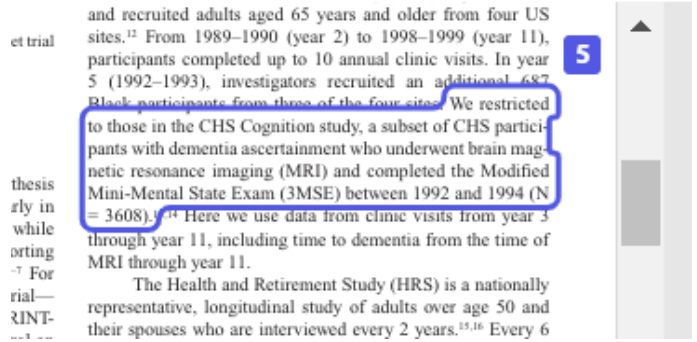

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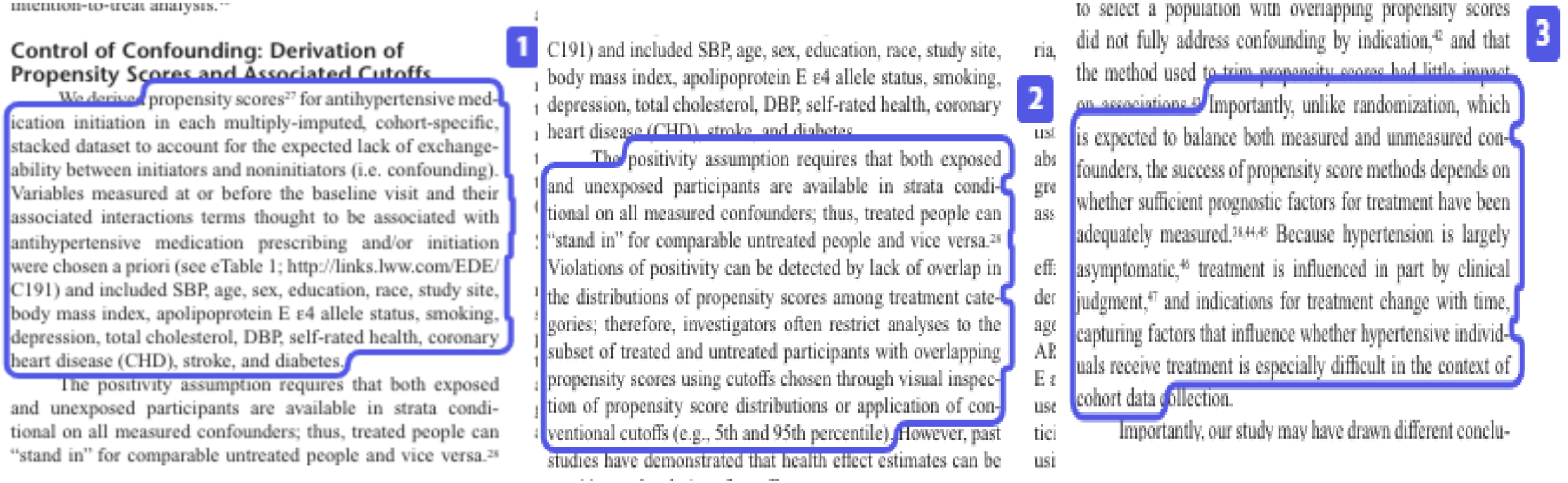
Assumptions



intention-to-treat analysis.[37]

Control of Confounding: Derivation of Propensity Scores and Associated Cutoffs

We derived propensity scores[27] for antihypertensive medication initiation in each multiply-imputed, cohort-specific, stacked dataset to account for the expected lack of exchangeability between initiators and noninitiators (i.e. confounding). Variables measured at or before the baseline visit and their associated interactions terms thought to be associated with antihypertensive medication prescribing and/or initiation were chosen a priori (see eTable 1; http://links.lww.com/EDE/C191) and included SBP, age, sex, education, race, study site, body mass index, apolipoprotein E ε4 allele status, smoking, depression, total cholesterol, DBP, self-rated health, coronary heart disease (CHD), stroke, and diabetes.

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The positivity assumption requires that both exposed and unexposed participants are available in strata conditional on all measured confounders; thus, treated people can "stand in" for comparable untreated people and vice versa.[28] Violations of positivity can be detected by lack of overlap in the distributions of propensity scores among treatment categories; therefore, investigators often restrict analyses to the subset of treated and untreated participants with overlapping propensity scores using cutoffs chosen through visual inspection of propensity score distributions or application of conventional cutoffs (e.g., 5th and 95th percentile).[29] However, past studies have demonstrated that health effect estimates can be

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to select a population with overlapping propensity scores did not fully address confounding by indication,[42] and that the method used to trim propensity scores had little impact on associations.[43] Importantly, unlike randomization, which is expected to balance both measured and unmeasured confounders, the success of propensity score methods depends on whether sufficient prognostic factors for treatment have been adequately measured.[38,44,45] Because hypertension is largely asymptomatic,[46] treatment is influenced in part by clinical judgment,[47] and indications for treatment change with time, capturing factors that influence whether hypertensive individuals receive treatment is especially difficult in the context of cohort data collection.

Importantly, our study may have drawn different conclu-

3

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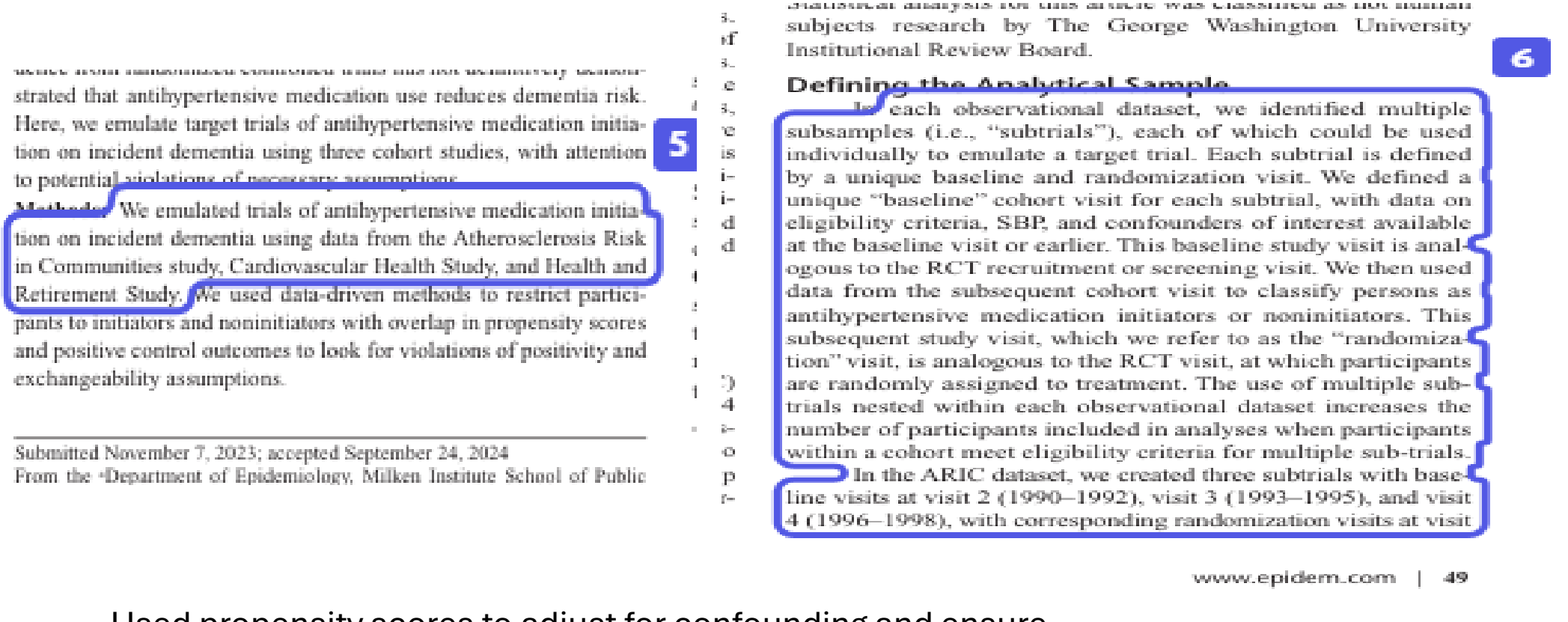
Statistical methods



strated that antihypertensive medication use reduces dementia risk. Here, we emulate target trials of antihypertensive medication initiation on incident dementia using three cohort studies, with attention to potential violations of necessary assumptions.

5

Methods: We emulated trials of antihypertensive medication initiation on incident dementia using data from the Atherosclerosis Risk in Communities study, Cardiovascular Health Study, and Health and Retirement Study. We used data-driven methods to restrict participants to initiators and noninitiators with overlap in propensity scores and positive control outcomes to look for violations of positivity and exchangeability assumptions.

Submitted November 7, 2023; accepted September 24, 2024
From the aDepartment of Epidemiology, Milken Institute School of Public

subjects research by The George Washington University Institutional Review Board.

6

Defining the Analytical Sample

In each observational dataset, we identified multiple subsamples (i.e., "subtrials"), each of which could be used individually to emulate a target trial. Each subtrial is defined by a unique baseline and randomization visit. We defined a unique "baseline" cohort visit for each subtrial, with data on eligibility criteria, SBP, and confounders of interest available at the baseline visit or earlier. This baseline study visit is analogous to the RCT recruitment or screening visit. We then used data from the subsequent cohort visit to classify persons as antihypertensive medication initiators or noninitiators. This subsequent study visit, which we refer to as the "randomization" visit, is analogous to the RCT visit, at which participants are randomly assigned to treatment. The use of multiple subtrials nested within each observational dataset increases the number of participants included in analyses when participants within a cohort meet eligibility criteria for multiple sub-trials. In the ARIC dataset, we created three subtrials with baseline visits at visit 2 (1990–1992), visit 3 (1993–1995), and visit 4 (1996–1998), with corresponding randomization visits at visit

Used propensity scores to adjust for confounding and ensure comparability between groups.

Propensity score

tistics by HRS sampling weights. Additionally, we calculated absolute standardized mean differences comparing treatment groups within each cohort after propensity score restriction to assess achieved covariate balance.

To be consistent with existing trials, we quantified the effect of antihypertensive medication initiation on incident dementia using Cox proportional hazards models adjusted for age, sex, education, race, study area (baseline study center for ARIC and CHS and census region for HRS), apolipoprotein E ε4 allele status, and each participant's propensity score. We used robust sandwich variance estimators to account for participants contributing to more than one subtrial. In analyses using HRS, participants were weighted by both their HRS sampling weight and stabilized inverse probability of attrition weights [32,33] (see Inverse probability of attrition weighting in HRS eAppendix; http://links.lww.com/EDE/C191). We then compared these findings to those reported by prior RCTs of antihypertensive medication use and dementia risk.

We also estimated the effect of antihypertensive medication initiation on another positive control outcome, incident CHD, using identical methods with the exception of restriction to those without CHD at subtrial baseline and randomization.

propensity score cutoffs based on a positive control outcome, stroke; stroke shares confounders with the primary outcome of interest, is known to be affected by antihypertensive medication initiation [20,38,51] and contributes to vascular dementia.

We created overlapping density plots of propensity scores for initiators and noninitiators within each subtrial and identified density cutoffs that would limit each subtrial to a subset of

Findings

Results: Analyses were limited by the small number of cohort participants who met eligibility criteria. Associations between antihypertensive medication initiation and incident dementia were inconsistent and imprecise (Atherosclerosis Risk in Communities: HR = 0.30 [0.05, 1.93]; Cardiovascular Health Study: HR = 0.66 [0.27, 1.64]; Health and Retirement Study: HR = 1.09 [0.75, 1.59]). More stringent propensity score restrictions had little effect on findings. Sensitivity analyses using a positive control outcome unexpectedly suggested antihypertensive medication initiation increased the risk of coronary heart disease in all three samples.

Conclusions: Positive control outcome analyses suggested sub-

Primary cutoff Primary cutoff, weighted High cutoff Low cutoff No cutoff

FIGURE 4. Hazard ratios for associations between antihypertensive medication initia 13 th incident dementia and incident CHD in each cohort within 6 years. Propensity score density cutoffs were as follows—ARIC: primary = 1.0, low = 0.5, high = 1.5; CHS: primary = 2.6, low = 1.3, high = 3.9; HRS: primary = 2.0, low = 1 0, high = 3.0.

from our positive control analysis suggested that antihypertensive medication initiation was associated with an increased risk of incident CHD in all three samples (ARIC: HR = 1.25; 95% CI = 0.48, 3.21; CHS: HR = 1.19; 95% CI = 0.70. 2.01; HRS: HR = 1.25; 95% CI = 0.71, 2.18), contrary to expectations. Altering our propensity score cutoffs, matching on or weighting by rather than adjusting for propensity scores, or omitting HRS sampling weights did not appreciably affect conclusions (Figure 4, eTable 5 and 6; http://links.lww.com/EDE/C191), although estimates for CHD in HRS were generally lower after propensity score matching or omitting HRS sampling weights.

INTRODUCTION

Introduction					
2	Background	Describe the scientific background of the study and the gap in knowledge.			
3	Causal question	Summarize the causal question.			
4	Rationale	Describe the rationale for emulating a target trial with the available data. Cite randomized trials informing the design of the target trial if applicable.			
Methods					
5	Data sources	Cite the data sources contributing to the analyses and for each one describe the following: original purpose, type, the geographic locations, setting and time-period. If relevant, describe how the data were linked or pooled.			
	Target trial specification			Target trial emulation	
6	Specify the components of the target trial protocol that would answer the causal question.		7	Describe how the components of the target trial protocol were emulated with the observational data, including how all variables were measured or ascertained.	
	Eligibility criteria			Eligibility criteria	
	a	Describe the eligibility criteria.		a	Describe how the eligibility criteria were operationalized with the data.
	Treatment strategies			Treatment strategies	
	b	Describe the treatment strategies that would be compared.		b	Describe how the treatment strategies were operationalized with the data.
	Assignment procedures			Assignment procedures	
	c	Report that eligible individuals would be randomly assigned to treatment strategies and may be aware of their treatment allocation.		c	Describe how assignment to treatment strategies was operationalized with the data.

Background

2. Introduction

(*Epidemiology* 2025;36: 49–59)

Observational studies are consistent with the hypothesis that high systolic blood pressure (SBP), particularly in midlife, adversely impacts late-life cognitive health,[1–4] while clinical trials do not provide definitive evidence supporting blood pressure management for dementia prevention.[5–7] For example, investigators from the SBP Intervention Trial—Memory and Cognition in Decreased Hypertension (SPRINT-MIND) found a benefit of intensive blood pressure control on mild cognitive impairment (MCI) and on the combined outcome of MCI and dementia, but not on the primary outcome of incident dementia alone.[8] Multiple aspects of randomized controlled trial (RCT) study design may contribute to this apparent disconnect between observational and trial evidence, including short follow-up time, highly selected samples, differences in treatment adherence, and focus on late life vs. midlife intervention.[9] On the other hand, observational studies on antihypertensive medication use and incident dementia may be limited by residual confounding.[9]

Target trial emulation, a thoughtful framework for analyzing observational data as if it came from an RCT,[10] provides an opportunity to explore factors that may contribute to discrepancies between observational and randomized studies, provided the approach generates unbiased effect estimates. Target trial emulation cannot guarantee the elimination of major sources of bias common to observational data analyses.

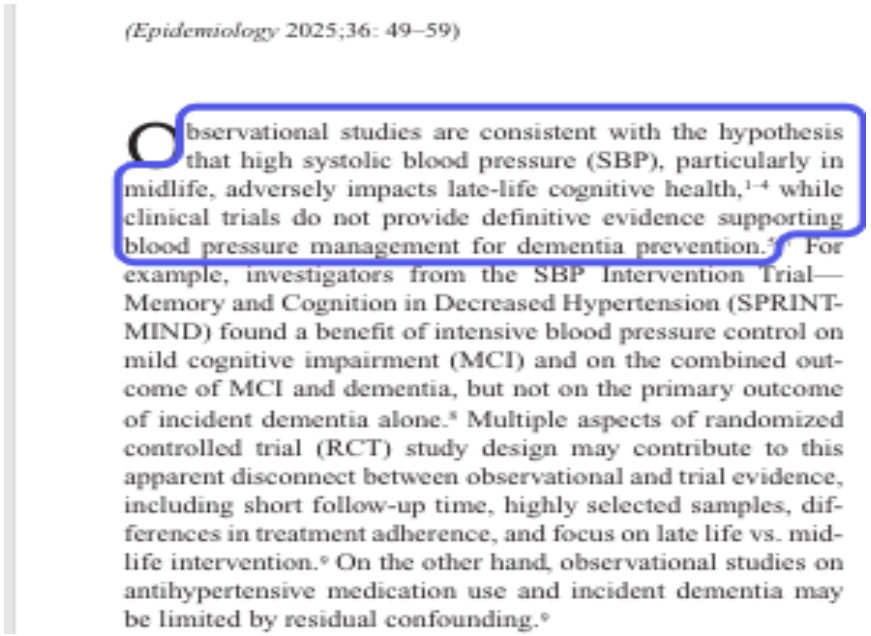
Black participants from three of the four sites. We restricted to those in the CHS Cognition study, a subset of CHS participants with dementia ascertainment who underwent brain magnetic resonance imaging (MRI) and completed the Modified Mini-Mental State Exam (3MSE) between 1992 and 1994 (N = 3608).[13,14] Here we use data from clinic visits from year 3 through year 11, including time to dementia from the time of MRI through year 11.

The Health and Retirement Study (HRS) is a nationally representative, longitudinal study of adults over age 50 and their spouses who are interviewed every 2 years.[15,16] Every 6 years, HRS enrolls new participants ages 51–56 to maintain a representative sample of adults over 50. Since 2006 (wave 8), physical measurements, including measurement of blood pressure, have been collected every 4 years on alternate halves of the sample population. Algorithmic dementia ascertainment is available from 2000 (wave 5) onwards. Here we consider data from 2006 (wave 8) through 2018 (wave 14) (Health and Retirement Study, 2021, RAND HRS Longitudinal File 2018 (V1), 2021).

Detailed information on data collection, variable definitions, and dementia ascertainment procedures are available in eTable 1; http://links.lww.com/EDE/C191. Participants of each cohort provided informed consent. Cohort procedures were approved by corresponding institutional review boards. Statistical analysis for this article was classified as not human subjects research by The George Washington University Institutional Review Board.

2.Describe the scientific background of the study and the gap in knowledge

Scientific background



(Epidemiology 2025;36: 49–59)

Observational studies are consistent with the hypothesis that high systolic blood pressure (SBP), particularly in midlife, adversely impacts late-life cognitive health,[1–4] while clinical trials do not provide definitive evidence supporting blood pressure management for dementia prevention.[5–7] For example, investigators from the SBP Intervention Trial—Memory and Cognition in Decreased Hypertension (SPRINT-MIND) found a benefit of intensive blood pressure control on mild cognitive impairment (MCI) and on the combined outcome of MCI and dementia, but not on the primary outcome of incident dementia alone.[8] Multiple aspects of randomized controlled trial (RCT) study design may contribute to this apparent disconnect between observational and trial evidence, including short follow-up time, highly selected samples, differences in treatment adherence, and focus on late life vs. midlife intervention.[9] On the other hand, observational studies on antihypertensive medication use and incident dementia may be limited by residual confounding.[9]

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Target trial emulation, a thoughtful framework for analyzing observational data as if it came from an RCT,[10] provides an opportunity to explore factors that may contribute to

Evidence from RCTs on the role of antihypertensive medication in dementia prevention is inconclusive.

Yes, the criteria was met

Gap in knowledge

alignment of observational analyses with RCTs, these efforts can be limited by the challenges of observational data. Here we attempted to emulate target trials of antihypertensive medication initiation and dementia risk using data from three large observational studies. Estimates for incident dementia were inconsistent and imprecise, and positive control analyses suggested they were biased.

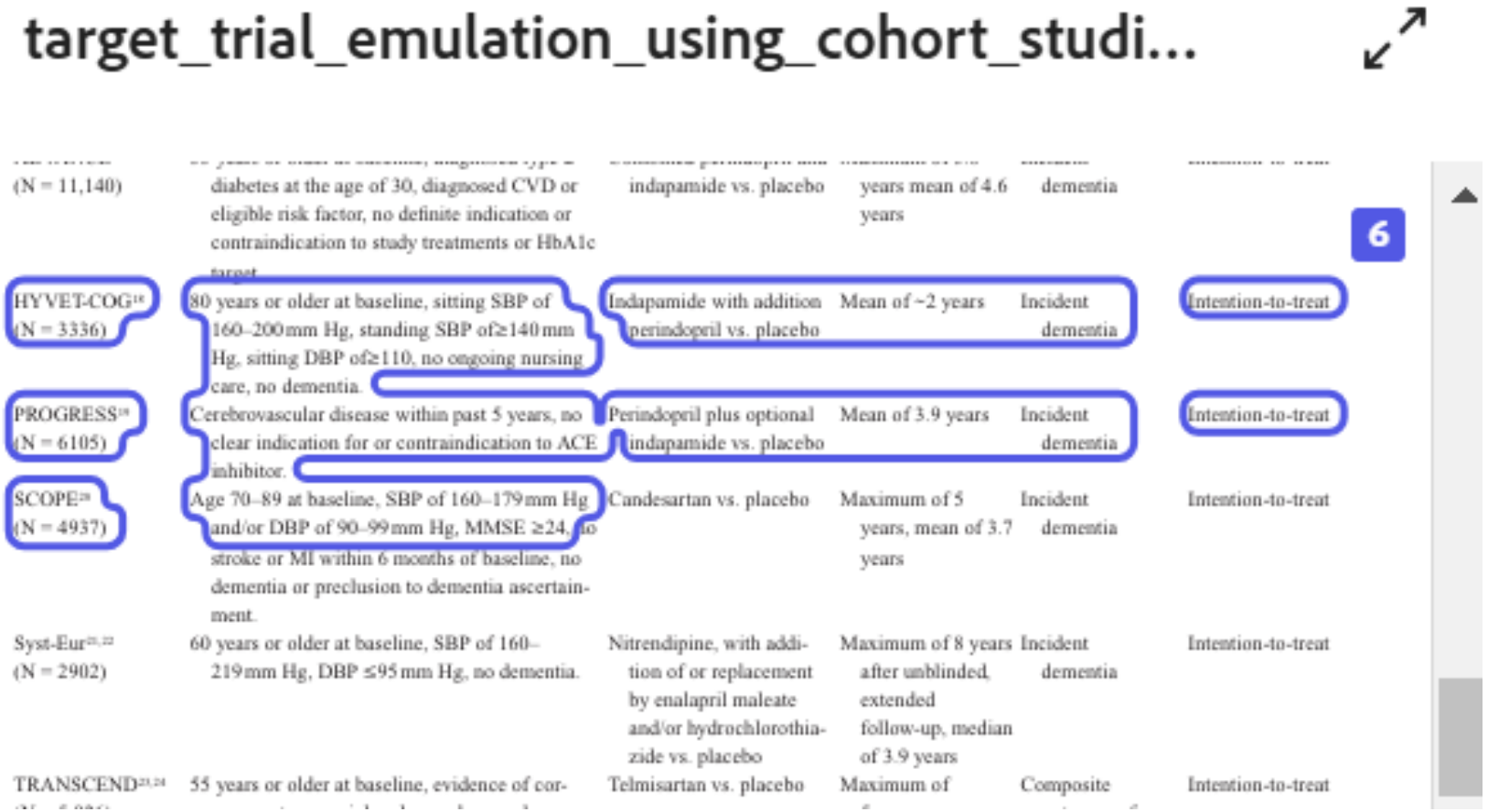
Large cohorts are an attractive observational data source for target trial emulation. They often have excellent outcome ascertainment, collect a wealth of data on potential confounders, and may be representative of a known target population. However, they often lack data on information that influences clinical decision-making.[16] Additionally, we found that few cohort participants met eligibility criteria similar to those applied in RCTs. Whether cohort studies can be used to validly emulate trials will rely on the extent to which relevant data influencing treatment is captured and the available sample size given the inclusion criteria for the desired target trial.

Other common characteristics of cohort studies may also introduce challenges for target trial emulation. For example, the time elapsed between cohort visits may raise concerns about misclassification of treatment status or misalignment of confounder measurement and treatment initiation, limiting the

3. Causal question

- *Among adults aged 65 years and older with elevated systolic blood pressure (≥140 mm Hg) and no prior antihypertensive use or dementia, what is the effect of initiating antihypertensive medication (vs. not initiating) on the 6-year risk of developing incident dementia?*
- This is framed as an **intention-to-treat contrast**, comparing outcomes between initiators and non-initiators, regardless of subsequent adherence or treatment changes.

4. Rationale



(N = 11,140)	diabetes at the age of 30, diagnosed CVD or eligible risk factor, no definite indication or contraindication to study treatments or HbA1c target	indapamide vs. placebo	years mean of 4.6 years	dementia	
HYVET-COG[18] (N = 3336)	80 years or older at baseline, sitting SBP of 160–200 mm Hg, standing SBP of≥140 mm Hg, sitting DBP of≥110, no ongoing nursing care, no dementia.	Indapamide with addition perindopril vs. placebo	Mean of ~2 years	Incident dementia	Intention-to-treat
PROGRESS[19] (N = 6105)	Cerebrovascular disease within past 5 years, no clear indication for or contraindication to ACE inhibitor.	Perindopril plus optional indapamide vs. placebo	Mean of 3.9 years	Incident dementia	Intention-to-treat
SCOPE[20] (N = 4937)	Age 70–89 at baseline, SBP of 160–179 mm Hg and/or DBP of 90–99 mm Hg, MMSE ≥24, no stroke or MI within 6 months of baseline, no dementia or preclusion to dementia ascertainment.	Candesartan vs. placebo	Maximum of 5 years, mean of 3.7 years	Incident dementia	Intention-to-treat
Syst-Eur[21,22] (N = 2902)	60 years or older at baseline, SBP of 160–219 mm Hg, DBP ≤95 mm Hg, no dementia.	Nitrendipine, with addition of or replacement by enalapril maleate and/or hydrochlorothiazide vs. placebo	Maximum of 8 years after unblinded, extended follow-up, median of 3.9 years	Incident dementia	Intention-to-treat
TRANSCEND[23,24]	55 years or older at baseline, evidence of cor-	Telmisartan vs. placebo	Maximum of	Composite	Intention-to-treat

Challenges in RCTs

Memory and Cognition in Decreased Hypertension (SPRINT-MIND) found a benefit of intensive blood pressure control on mild cognitive impairment (MCI) and on the combined outcome of MCI and dementia, but not on the primary outcome of incident dementia alone.[8] Multiple aspects of randomized controlled trial (RCT) study design may contribute to this apparent disconnect between observational and trial evidence, including short follow-up time, highly selected samples, differences in treatment adherence, and focus on late life vs. midlife intervention. On the other hand, observational studies on antihypertensive medication use and incident dementia may be limited by residual confounding.[9]

Target trial emulation, a thoughtful framework for analyzing observational data as if it came from an RCT,[10] provides an opportunity to explore factors that may contribute to

METHODS

Methods					
5	Data sources	Cite the data sources contributing to the analyses and for each one describe the following: original purpose, type, the geographic locations, setting and time-period. If relevant, describe how the data were linked or pooled.			
	Target trial specification			Target trial emulation	
6	Specify the components of the target trial protocol that would answer the causal question.		7	Describe how the components of the target trial protocol were emulated with the observational data, including how all variables were measured or ascertained.	
	Eligibility criteria			Eligibility criteria	
	a	Describe the eligibility criteria.		a	Describe how the eligibility criteria were operationalized with the data.
	Treatment strategies			Treatment strategies	
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	Assignment procedures			Assignment procedures	
	c	Report that eligible individuals would be randomly assigned to treatment strategies and may be aware of their treatment allocation.		c	Describe how assignment to treatment strategies was operationalized with the data.

Checklist item No. 5. Data Sources

- Cite the data sources contributing to the analyses and for each one describe the following: original purpose, type, the geographic locations, setting and time-period. If relevant, describe how the data were linked or pooled.
- Yes, this paper cited the data sources contributing to the analyses as shown previously in the 3 cohorts used (ARIC, CHS, HRS)

Linking and pooling data

- Data from each cohort were analysed separately, and sub trials were defined within each cohort based on baseline and randomization visit.
- Sub trial data were “stacked” into cohort-specific analytic datasets, allowing

Item 6a-h & 7a-h

	Target trial specification			Target trial emulation	
6	Specify the components of the target trial protocol that would answer the causal question.		7	Describe how the components of the target trial protocol were emulated with the observational data, including how all variables were measured or ascertained.	
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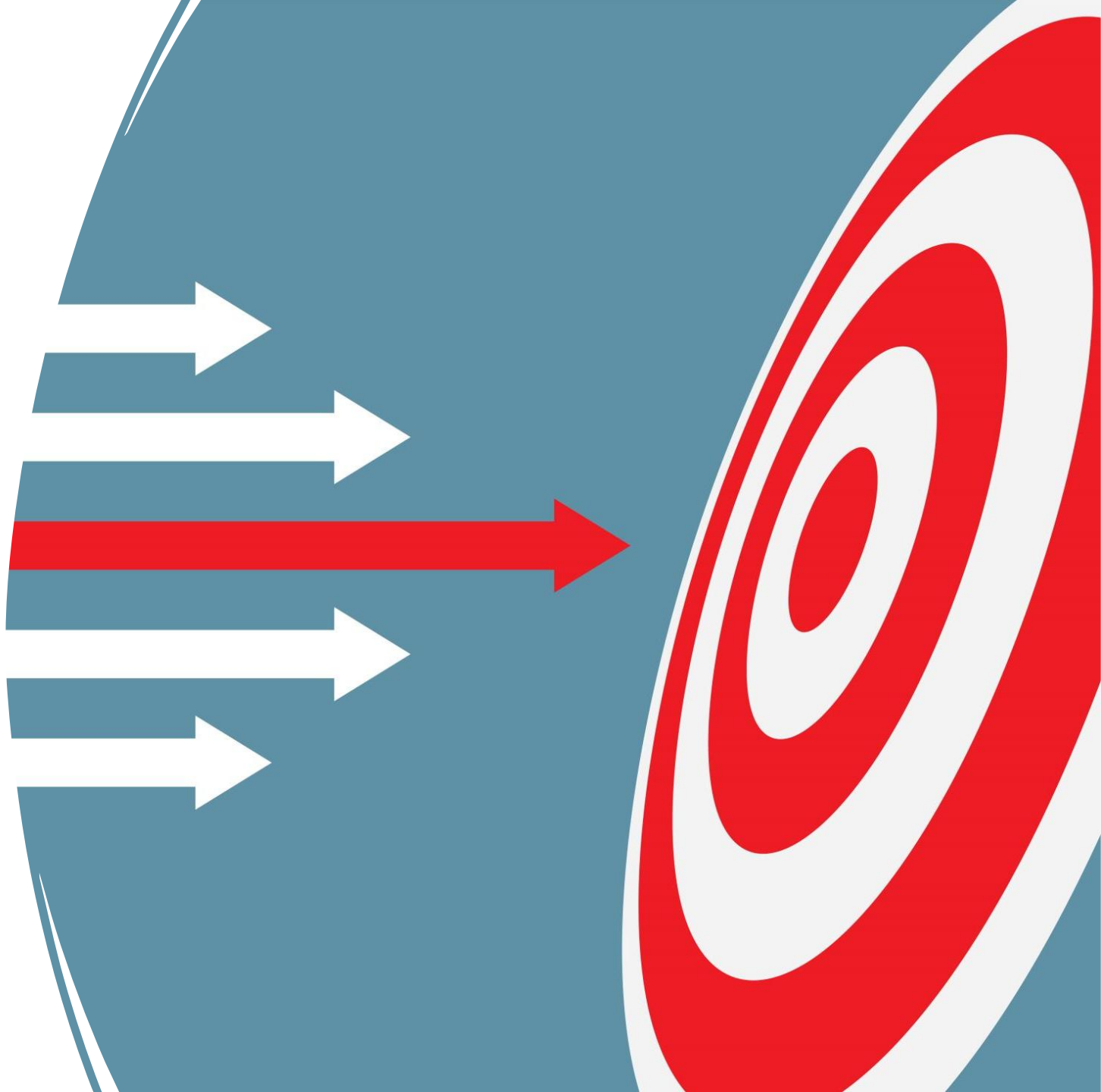
	c	Report that eligible individuals would be randomly assigned to treatment strategies and may be aware of their treatment allocation.		c	Describe how assignment to treatment strategies was operationalized with the data.
	Follow-up			Follow-up	
	d	Clarify that follow-up would start at time of assignment to the treatment strategies. Specify when follow-up would end.		d	Clarify that follow-up starts at the time individuals were assigned to the treatment strategies. Describe how the end of follow-up was operationalized with the data.
	Outcomes			Outcomes	
	e	Describe the outcomes.		e	Describe how the outcomes were operationalized with the data.
	Causal contrasts			Causal contrasts	
	f	Describe the causal contrasts of interest, including effect measures.		f	Describe how the causal contrasts were operationalized with the data, including effect measures.
	Identifying assumptions			Identifying assumptions	
	g	Describe assumptions that would be made to identify each causal estimand. Describe the variables, if any, related to these assumptions.		g.I	For each causal estimand, describe assumptions made to identify it, including assumptions regarding baseline confounding due to lack of randomization.
				g.II	Describe how the variables related to these assumptions were operationalized with the data.
	Data analysis plan			Data analysis plan	
	h	For each causal estimand, describe the data analysis procedures and any associated statistical modeling assumptions, including approaches for handling missing data.		h.I	For each causal estimand, describe the data analysis procedures and any associated statistical modeling assumptions, including approaches for handling missing data.
				h.II	For each causal estimand, describe any additional analyses conducted to assess the sensitivity of the results to the choice of operationalizations, assumptions and analysis.

Target trial specification and Emulation



Target trial

Specification

1. Eligibility criteria
2. Treatment strategies
3. Outcome ascertainment
4. Causal contrast of interest
5. Positive control outcomes
6. Propensity score methods
7. Follow-up and Data collection
8. Statistical analysis

Emulated (mapped onto existing cohort procedure)

1. Eligibility criteria
2. Treatment strategies
3. Outcome ascertainment
4. Causal contrast of interest
5. Positive control outcomes
6. Propensity score methods
7. Follow-up and Data collection
8. Statistical analysis

Target trial specification component

target trials (see Table 1).

Eligibility Criteria and Assignment of Treatment Strategies

For each subtrial, we included individuals with a baseline age ≥65 years, baseline SBP ≥140 mm Hg, self-identified white or Black race (given small numbers in other groups), no evidence of antihypertensive medication use at or before the baseline visit, nonmissing data on antihypertensive use at

blood pressure lowering. In ARIC and CHS, medication use was ascertained by self-report or by review and recording of medications brought to cohort visits. Use of blood pressure-lowering medications was self-reported only among those who self-reported hypertension in HRS, regardless of measured blood pressure.

Data from each subtrial within a cohort study were then "stacked" into one cohort-specific analytic dataset. Participants were included in each subtrial for which they met

Table 1. Characteristics of Target Trial vs. Existing Placebo-controlled Trials of Antihypertensive Medication Use and Incident Dementia[a]

	Primary Eligibility Criteria	Treatment Strategies	Follow-up	Outcome	Causal Contrast of Interest
Target trial	65 years or older at baseline, SBP ≥140 mm Hg at baseline, White or Black race, no dementia at randomization, at least one follow-up visit (in HRS), no documented use of antihypertensives at or before baseline	Initiator of any antihypertensive medication vs. noninitiator at randomization	Until incident dementia, death, loss to follow-up (in HRS), or for 6 years	Incident dementia	Emulating an intention-to-treat analysis

Target trial emulation

tiators (those with no record of antihypertensive medication use, including at the randomization visit), mimicking RCTs that randomize participants to either initiation or noninitiation of antihypertensive medication to investigate effects of blood pressure lowering. In ARIC and CHS, medication use was ascertained by self-report or by review and recording of medications brought to cohort visits. Use of blood pressure-lowering medications was self-reported only among those who self-reported hypertension in HRS, regardless of measured blood pressure.

Data from each subtrial within a cohort study were then "stacked" into one cohort-specific analytic dataset. Participants were included in each subtrial for which they met

6

Component of target trial

1. Eligibility criteria
2. Treatment strategies
3. Outcome ascertainment
4. Causal contrast of interest
5. Positive control outcomes
6. Propensity score methods
7. Follow-up and Data collection
8. Statistical analysis

Data analysis

CHECKLIST

	Data analysis plan		Data analysis plan
h	For each causal estimand, describe the data analysis procedures and any associated statistical modeling assumptions, including approaches for handling missing data.	h.i	For each causal estimand, describe the data analysis procedures and any associated statistical modeling assumptions, including approaches for handling missing data.
		h.ii	For each causal estimand, describe any additional analyses conducted to assess the sensitivity of the results to the choice of operationalizations, assumptions and analysis.

Defining the analytical sample

Defining the Analytical Sample

In each observational dataset, we identified multiple subsamples (i.e., "subtrials"), each of which could be used individually to emulate a target trial. Each subtrial is defined by a unique baseline and randomization visit. We defined a unique "baseline" cohort visit for each subtrial, with data on eligibility criteria, SBP, and confounders of interest available at the baseline visit or earlier. This baseline study visit is analogous to the RCT recruitment or screening visit. We then used data from the subsequent cohort visit to classify persons as antihypertensive medication initiators or noninitiators. This subsequent study visit, which we refer to as the "randomization" visit, is analogous to the RCT visit, at which participants are randomly assigned to treatment. The use of multiple subtrials nested within each observational dataset increases the number of participants included in analyses when participants within a cohort meet eligibility criteria for multiple sub-trials.

In the ARIC dataset, we created three subtrials with baseline visits at visit 2 (1990–1992), visit 3 (1993–1995), and visit 4 (1996–1998), with corresponding randomization visits at visit

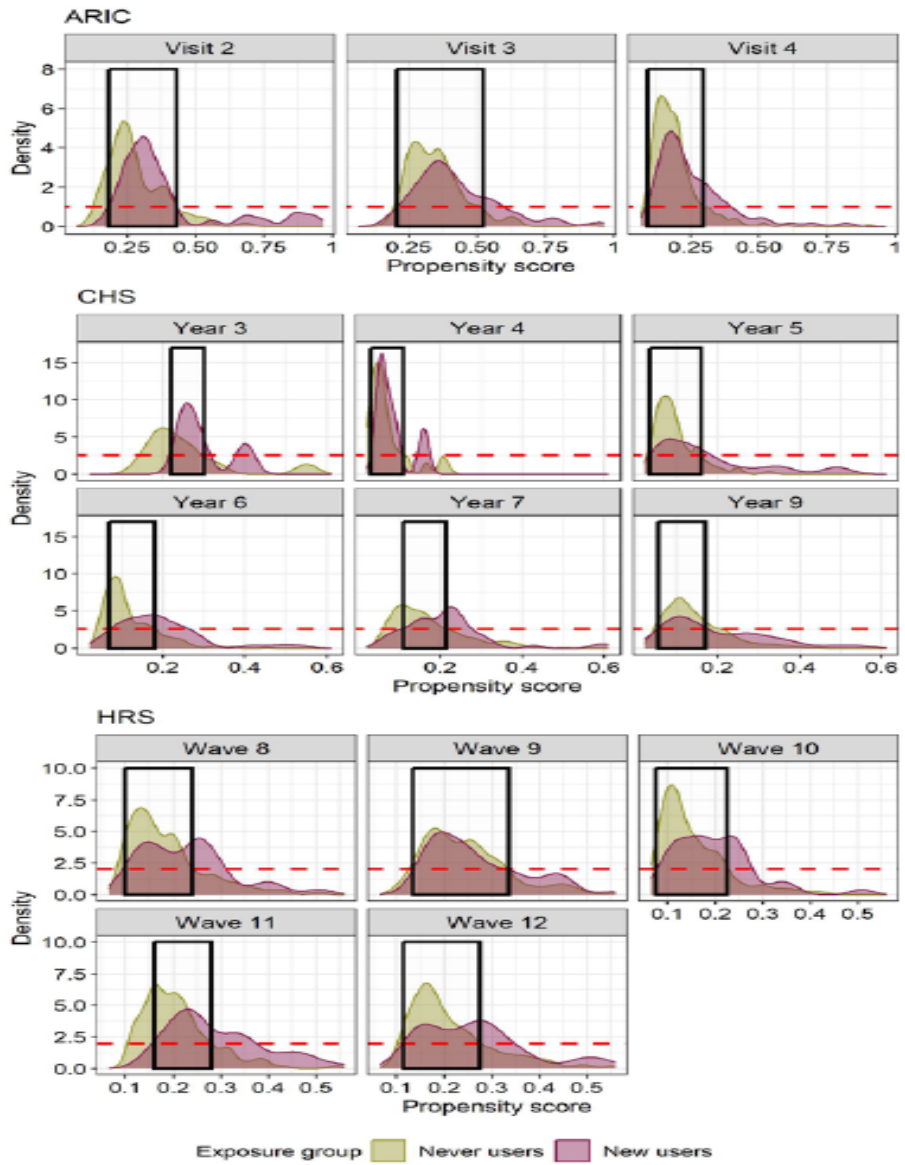
Propensity score derivation and restriction

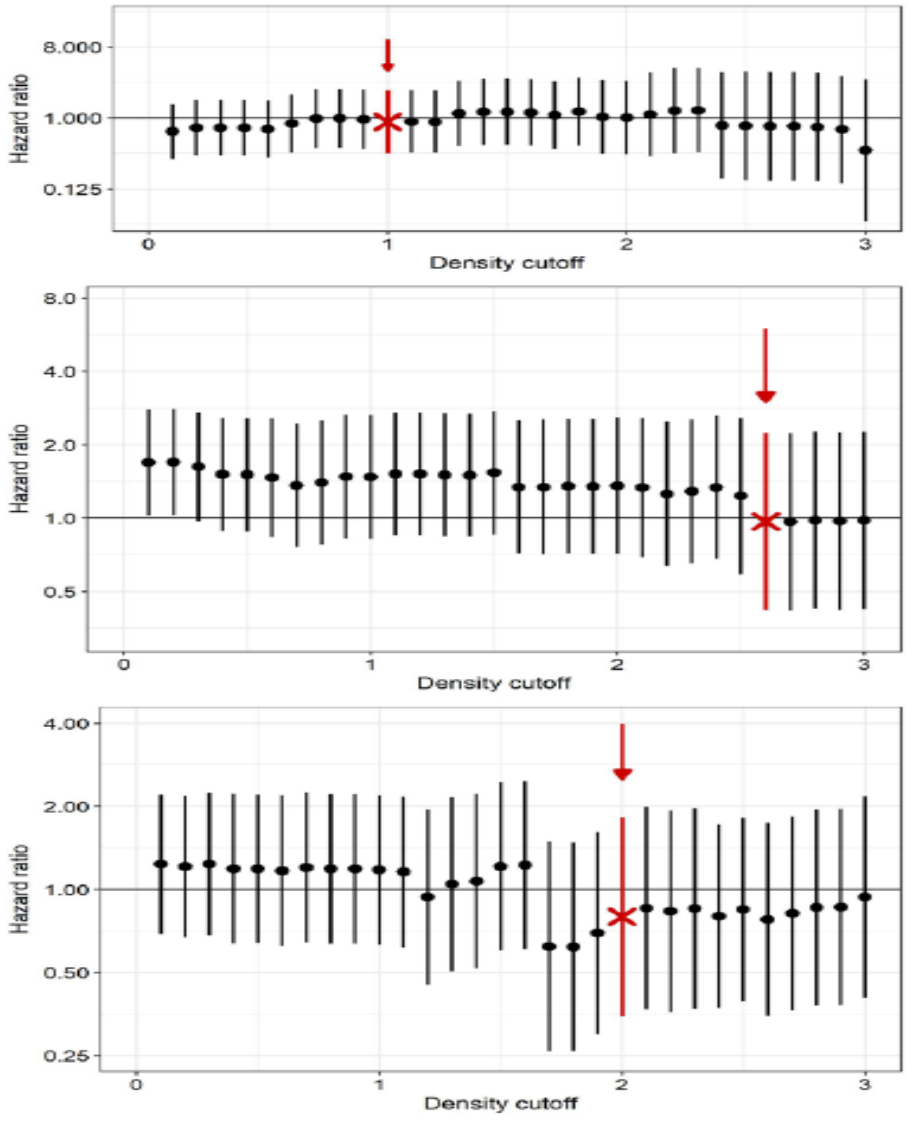
Control of Confounding: Derivation of Propensity Scores and Associated Cutoffs

We derived propensity scores[27] for antihypertensive medication initiation in each multiply-imputed, cohort-specific, stacked dataset to account for the expected lack of exchangeability between initiators and noninitiators (i.e. confounding). Variables measured at or before the baseline visit and their associated interactions terms thought to be associated with antihypertensive medication prescribing and/or initiation were chosen a priori (see eTable 1; http://links.lww.com/EDE/C191) and included SBP, age, sex, education, race, study site, body mass index, apolipoprotein E ε4 allele status, smoking, depression, total cholesterol, DBP, self-rated health, coronary heart disease (CHD), stroke, and diabetes.

The positivity assumption requires that both exposed and unexposed participants are available in strata conditional on all measured confounders; thus, treated people can "stand in" for comparable untreated people and vice versa.[28] Violations of positivity can be detected by lack of overlap in the distributions of propensity scores among treatment categories; therefore, investigators often restrict analyses to the subset of treated and untreated participants with overlapping propensity scores using cutoffs chosen through visual inspection of propensity score distributions or application of conventional cutoffs (e.g., 5th and 95th percentile). However, past studies have demonstrated that health effect estimates can be sensitive to the choice of cutoffs.[29]

Density plot





Statistical Analysis

Statistical Analysis

We characterized participants who met eligibility criteria, remained in the sample after restricting based on propensity score cutoffs, and were excluded after restricting based on propensity score cutoffs. In HRS, we weighted descriptive statistics by HRS sampling weights. Additionally, we calculated absolute standardized mean differences comparing treatment groups within each cohort after propensity score restriction to assess achieved covariate balance.

To be consistent with existing trials, we quantified the effect of antihypertensive medication initiation on incident dementia using Cox proportional hazards models adjusted for age, sex, education, race, study area (baseline study center for ARIC and CHS and census region for HRS), apolipoprotein E ε4 allele status, and each participant's propensity score. We used robust sandwich variance estimators to account for participants contributing to more than one subtrial. In analyses using HRS, participants were weighted by both their HRS sampling weight and stabilized inverse probability of attrition weights [32,33] (see Inverse probability of attrition weighting in HRS eAppendix; http://links.lww.com/EDE/C191). We then compared these findings to those reported by prior RCTs of antihypertensive medication use and dementia risk.

We also estimated the effect of antihypertensive medication initiation on another positive control outcome, incident CHD, using identical methods with the exception of restriction to those without CHD at subtrial baseline and randomization.

Sensitivity analysis

In sensitivity analyses, rather than adjusting for participant propensity scores, we weighted analyses by inverse probability of treatment weights[32] and ran propensity score-adjusted and inverse probability of treatment weight models in HRS participants omitting HRS sampling weights. We also estimated effects using alternate density cutoffs: a "low" cutoff (half of each cohort-specific primary density cutoff), a "high" cutoff (1.5 times each cohort-specific primary density cutoff), and no density cutoff. Finally, we reran primary analyses after matching on the propensity score, using a 4:1 ratio of noninitiators to initiators (with replacement) and a caliper of 0.1, rather than restricting using density plots and positive control-based cutoffs.


Participant
selection

Item 8. Report numbers of individuals assessed for eligibility, eligible, and assigned to each treatment strategy

Item No.	Checklist item	
Results		
8	Participant selection	Report numbers of individuals assessed for eligibility, eligible, and assigned to each treatment strategy. A flow diagram is strongly recommended.

Yes, this paper reported the numbers of individuals assessed for eligibility.

Numbers at Each Stage Across all sub trials in each cohort

:

- **ARIC**
  - *Assessed for eligibility*: 809 observations (2.1% of all subtrial person-observations).
  - *Eligible after applying trial-like criteria*: 809.
  - *Included after propensity score restriction*: 660.
  - *Treatment assignment*: Initiators = 160; Non-initiators = 500.
- **CHS**
  - *Assessed for eligibility*: 1,204 observations (9.3%).
  - *Eligible*: 1,204.
  - *Included after propensity score restriction*: 762.
  - *Treatment assignment*: Initiators = 85; Non-initiators = 677.
- **HRS**
  - *Assessed for eligibility*: 1,227 observations (1.3%).
  - *Eligible*: 1,227.
  - *Included after propensity score restriction*: 811.
  - *Treatment assignment*: Initiators = 148; Non-initiators = 663.

RESULTS

Across all subtrials within a cohort, 2.1% of ARIC participant-observations (N_{obs} = 809), 9.3% of CHS substantially across cohorts (Figure 4); directionality of point estimates was protective in ARIC (HR = 0.30; 95% CI = 0.05, 1.93) and CHS (HR = 0.66; 95% CI = 0.27, 1.64) and adverse in HRS (HR = 1.09; 95% CI = 0.75, 1.59). Importantly, results

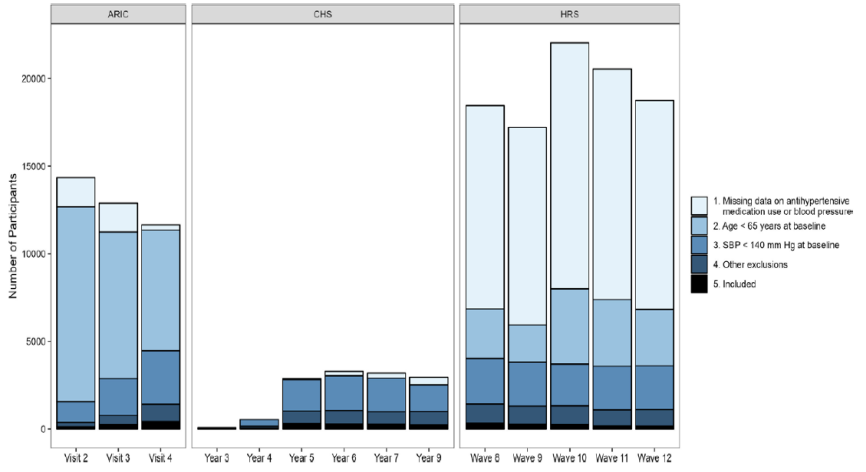


FIGURE 3. Number of participants included and excluded from each sub-trial in ARIC, CHS, and HRS. Because physical measurements are taken on alternating halves of the HRS population at each wave, blood pressure data was missing for half of the HRS

Participants

RESULTS

Across all subtrials within a cohort, 2.1% of ARIC participant-observations (N_{obs} = 809), 9.3% of CHS participant-observations (N_{obs} = 1204), and 1.3% of HRS participant-observations (N_{obs} = 1,227) met eligibility criteria before propensity score-based restriction (Figure 3). Final analytical sample sizes in primary analyses after propensity score-based restrictions were N_{obs} = 660 for ARIC, N_{obs} = 762 for CHS, and N_{obs} = 811 for HRS. Participants excluded due to high propensity scores tended to have higher SBP and were more likely to report poor self-rated health and depression compared with both included participants and those excluded with low propensity scores (eTable 2; http://links.lww.com/

substantially across cohorts (Figure 4); directionality of point estimates was protective in ARIC (HR = 0.30; 95% CI = 0.05, 1.93) and CHS (HR = 0.66; 95% CI = 0.27, 1.64) and adverse in HRS (HR = 1.09; 95% CI = 0.75, 1.59). Importantly, results

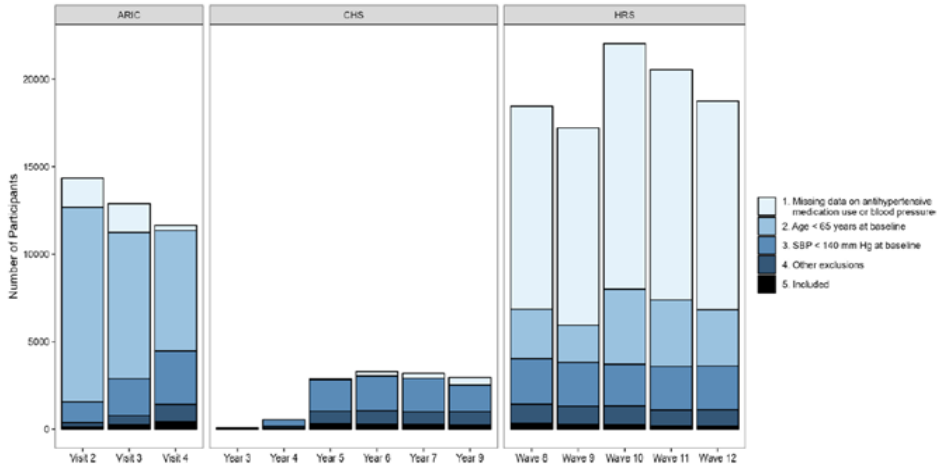


FIGURE 3. Number of participants included and excluded from each sub-trial in ARIC, CHS, and HRS. Because physical measurements are taken on alternating halves of the HRS population at each wave, blood pressure data was missing for half of the HRS

BASELINE DATA

Checklist item No.9 &10

9	Baseline data	Describe the distribution of characteristics of individuals at baseline, by treatment strategy.
10	Follow-up	Summarize length of follow-up and describe reasons for end of follow-up for each treatment strategy and causal contrast.

Yes, The study reported detailed baseline characteristics of participants who met eligibility for the target trials, and then again after propensity score (PS) restriction.

Item 9. Describe the distribution of characteristics of individuals at baseline, by treatment strategy.

TABLE 2. Baseline Characteristics of New Antihypertensive Medication Initiators and Noninitiators in First Imputed Dataset Who Met Inclusion Criteria for Target Trials Compared to Those Included in Analyses Following Propensity Score Restriction, stratified by Cohort[a]

	ARIC				CHS				HRS[b]			
	Met inclusion criteria (N_{obs} = 809)		After PS restriction (N_{obs} = 660)		Met inclusion criteria (N_{obs} = 1,204)		After PS restriction (N_{obs} = 762)		Met inclusion criteria (N_{obs} = 1,227)		After PS restriction (N_{obs} = 811)	
	Noninitiators (N_{obs} = 586)	Initiators (N_{obs} = 223)	Noninitiators (N_{obs} = 500)	Initiators (N_{obs} = 160)	Noninitiators (N_{obs} = 1,038)	Initiators (N_{obs} = 166)	Noninitiators (N_{obs} = 677)	Initiators (N_{obs} = 85)	Noninitiators (N_{obs} = 970)	Initiators (N_{obs} = 257)	Noninitiators (N_{obs} = 663)	Initiators (N_{obs} = 148)
Age, mean (SD)	68 (2)	68 (2)	68 (2)	68 (2)	76 (5)	76 (5)	76 (5)	76 (5)	73 (6)	73 (7)	73 (6)	73 (6)
Male, N (%)	46%	51%	46%	49%	39%	38%	39%	40%	50%	47%	47%	44%
Education, N (%)												
Less than high school	22%	26%	21%	23%	21%	19%	19%	21%	15%	23%	14%	16%
High school or equivalent	45%	42%	45%	43%	27%	23%	26%	29%	36%	35%	40%	36%
Greater than high school	34%	32%	34%	34%	52%	58%	55%	49%	49%	42%	46%	48%
Race, N (%)												
White	88%	86%	88%	88%	87%	90%	90%	91%	95%	92%	96%	95%
Black	12%	14%	12%	13%	13%	10%	10%	9%	5%	8%	4%	5%
At least one *APOE ε4* allele, N (%)	30%	34%	30%	35%	22%	18%	21%	21%	24%	19%	23%	23%
Smoking status, N (%)												
Current	10%	14%	9%	13%	9%	8%	8%	8%	11%	17%	4%	5%
Former	48%	45%	48%	46%	40%	35%	40%	35%	44%	41%	10%	12%
Never	43%	41%	43%	42%	52%	57%	52%	56%	45%	42%	45%	46%
SBP in mm/Hg, mean (SD)	151 (10)	155 (16)	151 (9)	151 (9)	152 (11)	158 (14)	151 (9)	153 (10)	153 (13)	159 (16)	151 (8)	151 (8)
DBP in mm/Hg, mean (SD)	76 (10)	77 (10)	75 (9)	77 (9)	75 (10)	76 (10)	74 (9)	74 (10)	88 (9)	90 (11)	87 (8)	86 (9)
Total cholesterol in mg, mean (SD)	208 (37)	220 (40)	207 (33)	216 (35)	207 (38)	204 (33)	206 (38)	208 (31)	205 (43)	210 (44)	207 (42)	206 (43)
BMI in kg/m², mean (SD)	28 (5)	28 (5)	28 (5)	28 (5)	26 (4)	26 (4)	26 (4)	26 (4)	28 (5)	28 (6)	28 (5)	29 (5)
Diabetes, N (%)	12%	16%	9%	12%	11%	14%	10%	12%	7%	8%	7%	8%
CHD, N (%)	3%	5%	2%	2%	6%	10%	6%	4%	14%	13%	15%	13%
Stroke, N (%)	1%	1%	0%	1%	3%	4%	2%	2%	3%	4%	4%	4%
Poor self-rated health, N (%)	11%	12%	10%	11%	9%	14%	8%	9%	11%	16%	11%	12%
Depression, N (%)	22%	27%	23%	25%	18%	23%	17%	14%	11%	14%	11%	13%

Abbreviations: ARIC, Atherosclerosis Risk in Communities; BMI, body mass index; CHD, coronary heart disease; CHS, Cardiovascular Health Study; DBP, diastolic blood pressure; Hg, mercury; HRS, Health and Retirement Study; mg, milligrams; mm, millimeters; PS, propensity score; SBP, systolic blood pressure; SD, standard deviation.

[a] Participants may contribute multiple times to each cohort if they are represented in more than one sub-trial. Sample sizes represent participant-observations.

[b] All summary statistics for HRS are weighted by participants' HRS sampling weights.

Yes, to all the Target checklist item No.8 -21

Table 2. TARGET Checklist of Recommended Items to Address in Reports of Studies Emulating a Target Trial[a] (continued)

Item No.	Checklist item	
Results		
8	Participant selection	Report numbers of individuals assessed for eligibility, eligible, and assigned to each treatment strategy. A flow diagram is strongly recommended.
9	Baseline data	Describe the distribution of characteristics of individuals at baseline, by treatment strategy.
10	Follow-up	Summarize length of follow-up and describe reasons for end of follow-up for each treatment strategy and causal contrast.
11	Missing data	Describe the frequency of missing data in all variables, by treatment strategy when applicable.
12	Outcomes	Describe the frequency or distribution of each outcome, by treatment strategy.
13	Effect estimates	Report the effect estimates for each causal contrast with corresponding measures of precision, including both absolute and relative measures of effect, when applicable.
14	Additional analyses	Report results of all analyses to assess the sensitivity of the estimates to choices in operationalizations, assumptions and analysis.
Discussion		
15	Interpretation	Provide an interpretation of the key findings.
16	Limitations	Discuss the limitations of the study considering differences between the target trial and its emulation and the plausibility of assumptions, including assumptions regarding baseline confounding due to lack of randomization.
Other information		
17	Ethics	Provide the institutional research board or ethics committee that approved the study and approval numbers, if relevant.
18	Registration	State whether, when and where the study protocol was registered.
19	Sharing of study materials	Provide information on whether data, analytic code and/or other materials are accessible, and where and how they can be accessed.
20	Funding sources	Provide the sources of funding and detail the role of the funders in the design, conduct and reporting of the study.
21	Conflicts of interest	State any conflicts of interest and financial disclosures for all authors.

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FOLLOW UP

Item 10. Summarize length of follow-up and describe reasons for end of follow-up for each treatment strategy and causal contrast

Follow-up

Within each subtrial, time on study began at the randomization visit and ended at the first of dementia diagnosis, death, loss to follow-up (in HRS only), or elapsed follow-up of 6 years, similar to the longest follow-up of completed RCTs (see Table 1). Incident dementia was determined using hospital records in ARIC, retroactively using cognitive test scores and other cohort-collected data in CHS, and algorithmically in HRS (see eTable 1; http://links.lww.com/EDE/C191 for

more details). Because cohort procedures for ARIC and CHS included the collection of proxy interviews, medical records, administrative data, and/or death records to identify incident dementia cases among all participants, including those who stopped attending study visits, there was no loss to follow-up among ARIC and CHS participants. On the contrary, dementia status is unknown for HRS participants who did not return for follow-up visits. Thus, we only address loss to follow-up using inverse probability of attrition weights in HRS. As in clinical trials, participants who died during follow-up and before developing dementia were allowed to contribute follow-up time until their death.

MISSING DATA

Missing data

eligibility criteria; thus, participants who met inclusion criteria for multiple subtrials were represented more than once in each cohort-specific stacked dataset. Participants were not eligible to be included in subsequent subtrials after being included in a subtrial as an initiator. Within each cohort-specific stacked dataset, we imputed missing covariate data using multiple imputation by chained equations (MICE) models to avoid loss of sample size due to missing data (see Imputation methods eAppendix; http://links.lww.com/EDE/C191).

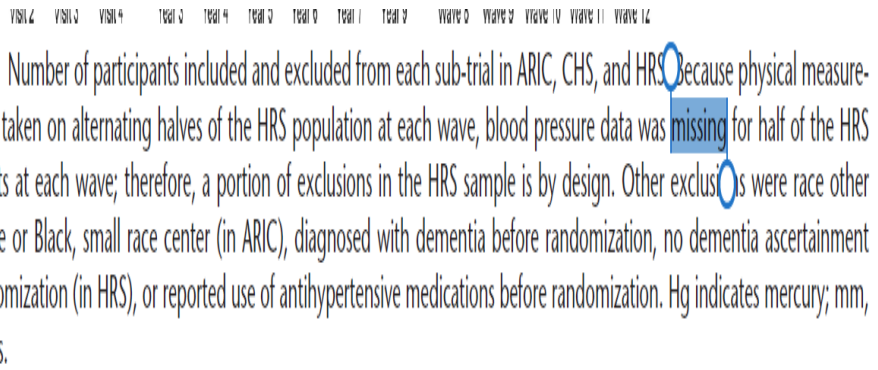
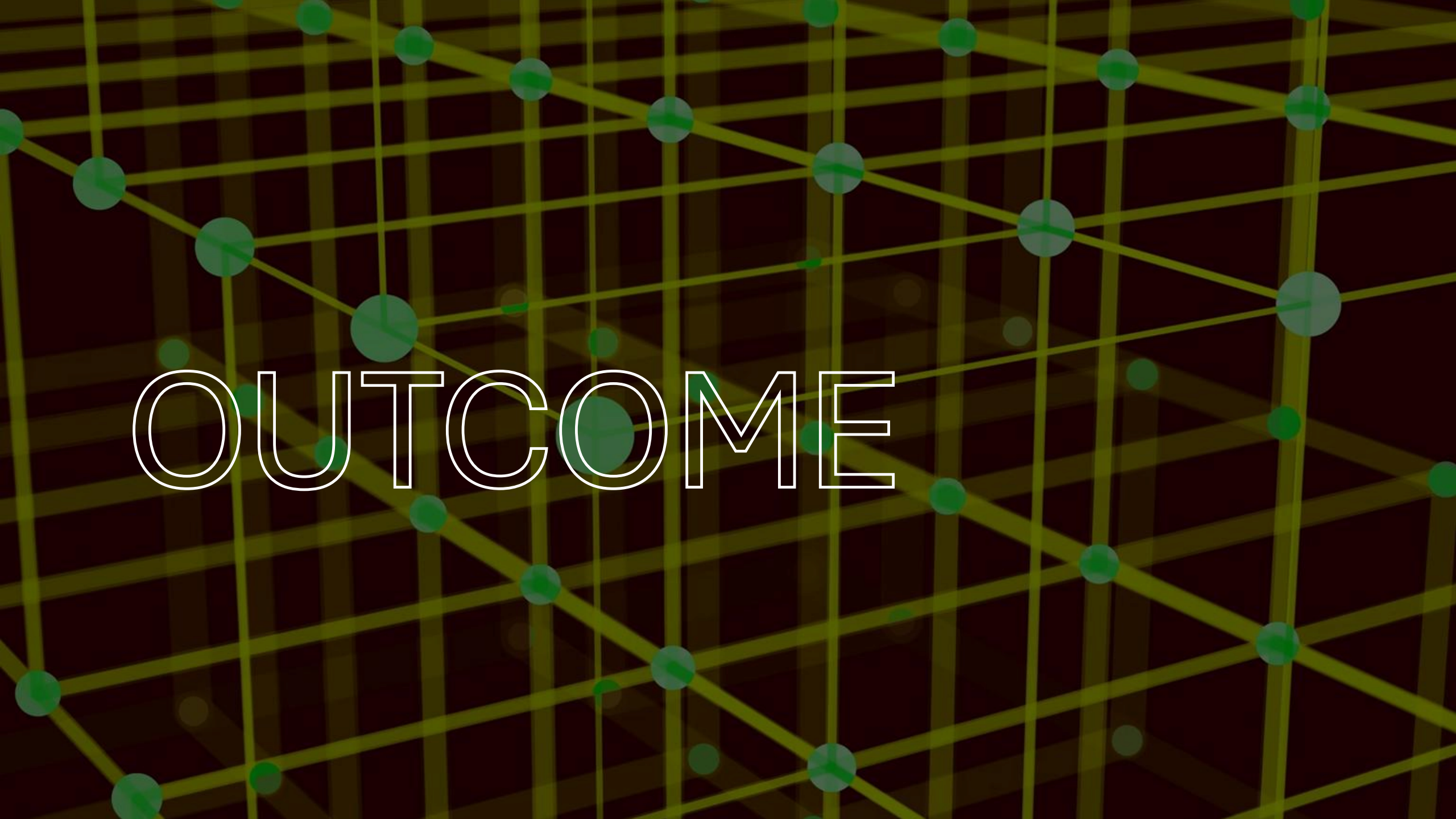


FIGURE 3. Number of participants included and excluded from each sub-trial in ARIC, CHS, and HRS. Because physical measurements are taken on alternating halves of the HRS population at each wave, blood pressure data was missing for half of the HRS participants at each wave; therefore, a portion of exclusions in the HRS sample is by design. Other exclusions were race other than White or Black, small race center (in ARIC), diagnosed with dementia before randomization, no dementia ascertainment after randomization (in HRS), or reported use of antihypertensive medications before randomization. Hg indicates mercury; mm, millimeters.


OUTCOME

Outcomes

- Describe the frequency or distribution of each outcome, by treatment strategy
- Yes, they did

Results: Analyses were limited by the small number of cohort participants who met eligibility criteria. Associations between antihypertensive medication initiation and incident dementia were inconsistent and imprecise (Atherosclerosis Risk in Communities: HR = 0.30 [0.05, 1.93]; Cardiovascular Health Study: HR = 0.66 [0.27, 1.64]; Health and Retirement Study: HR = 1.09 [0.75, 1.59]). More stringent propensity score restrictions had little effect on findings. Sensitivity analyses using a positive control outcome unexpectedly suggested antihypertensive medication initiation increased the risk of coronary heart disease in all three samples.

Effect estimate

Incident dementia

of noninitiators to initiators (with replacement) and a caliper of 0.1, rather than restricting using density plots and positive control-based cutoffs.

We conducted analyses using SAS version 9.4 and RStudio version 4.1.0. Analytic code may be made available upon request.

RESULTS

Across all subtrials within a cohort, 2.1% of ARIC participant-observations (N_{obs} = 809), 9.3% of CHS balance of confounders between treatment groups (eTable 3; http://links.lww.com/EDE/C191). Few ARIC or CHS participants eligible for our target trials developed dementia (eTable 4; http://links.lww.com/EDE/C191).

The estimated effects of antihypertensive medication initiation on incident dementia were imprecise and varied substantially across cohorts (Figure 4); directionality of point estimates was protective in ARIC (HR = 0.30; 95% CI = 0.05, 1.93) and CHS (HR = 0.66; 95% CI = 0.27, 1.64) and adverse in HRS (HR = 1.09; 95% CI = 0.75, 1.59). Importantly, results

Positive control outcome

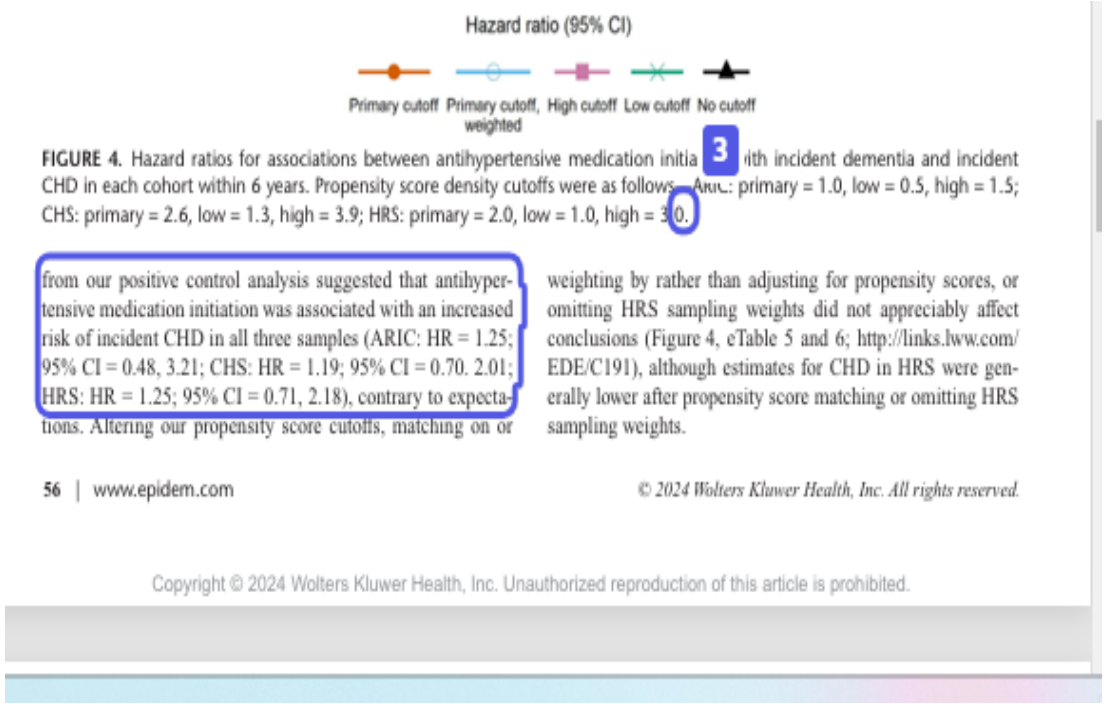


FIGURE 4. Hazard ratios for associations between antihypertensive medication initia 3 ith incident dementia and incident CHD in each cohort within 6 years. Propensity score density cutoffs were as follows: ARIC: primary = 1.0, low = 0.5, high = 1.5; CHS: primary = 2.6, low = 1.3, high = 3.9; HRS: primary = 2.0, low = 1.0, high = 3.0.

from our positive control analysis suggested that antihypertensive medication initiation was associated with an increased risk of incident CHD in all three samples (ARIC: HR = 1.25; 95% CI = 0.48, 3.21; CHS: HR = 1.19; 95% CI = 0.70. 2.01; HRS: HR = 1.25; 95% CI = 0.71, 2.18), contrary to expectations. Altering our propensity score cutoffs, matching on or weighting by rather than adjusting for propensity scores, or omitting HRS sampling weights did not appreciably affect conclusions (Figure 4, eTable 5 and 6; http://links.lww.com/EDE/C191), although estimates for CHD in HRS were generally lower after propensity score matching or omitting HRS sampling weights.

Additional analyses

Sensitivity analyses

potential violations of the exchangeability assumption, or no unmeasured confounding, as CHD shares many of the same risk factors as dementia and stroke, and RCTs demonstrate that antihypertensive medication use reduces CHD risk.[33,34,35]

In sensitivity analyses, rather than adjusting for participant propensity scores, we weighted analyses by inverse probability of treatment weights[32] and ran propensity score–adjusted and inverse probability of treatment weight models in HRS participants omitting HRS sampling weights. We also estimated effects using alternate density cutoffs: a "low" cutoff (half of each cohort-specific primary density cutoff), a "high" cutoff (1.5 times each cohort-specific primary density cutoff), and no density cutoff. Finally, we reran primary analyses after matching on the propensity score, using a 4:1 ratio of noninitiators to initiators (with replacement) and a caliper of 0.1, rather than restricting using density plots and positive control–based cutoffs.

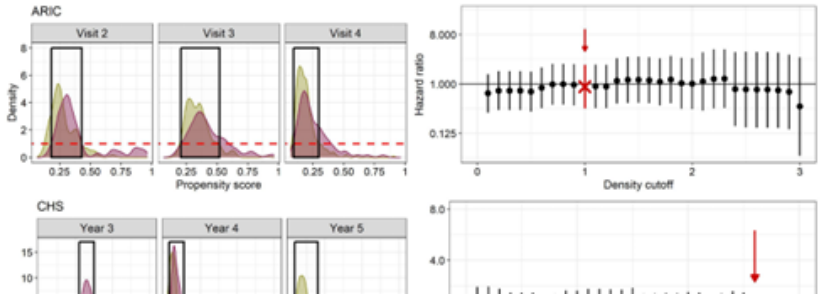
We conducted analyses using SAS version 9.4 and RStudio version 4.1.0. Analytic code may be made available upon request.

RESULTS

Across all subtrials within a cohort, 2.1% of ARIC participant-observations (N_{obs} = 809), 9.3% of CHS

propensity score cutoffs based on a positive control outcome, stroke; stroke shares confounders with the primary outcome of interest, is known to be affected by antihypertensive medication initiation[20,21] and contributes to vascular dementia. We created overlapping density plots of propensity scores for initiators and noninitiators within each subtrial and identified density cutoffs that would limit each subtrial to a subset of HRS eAppendix; http://links.lww.com/EDE/C191). We then compared these findings to those reported by prior RCTs of antihypertensive medication use and dementia risk.

We also estimated the effect of antihypertensive medication initiation on another positive control outcome, incident CHD, using identical methods with the exception of restriction to those without CHD at subtrial baseline and randomization.



Discussion		
15	Interpretation	Provide an interpretation of the key findings.
16	Limitations	Discuss the limitations of the study considering differences between the target trial and its emulation and the plausibility of assumptions, including assumptions regarding baseline confounding due to lack of randomization.
Other information		
17	Ethics	Provide the institutional research board or ethics committee that approved the study and approval numbers, if relevant.
18	Registration	State whether, when and where the study protocol was registered.
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20	Funding sources	Provide the sources of funding and detail the role of the funders in the design, conduct and reporting of the study.
21	Conflicts of interest	State any conflicts of interest and financial disclosures for all authors.

Discussion

DISCUSSION

While target trial emulation improves the conceptual alignment of observational analyses with RCTs, these efforts can be limited by the challenges of observational data. Here we attempted to emulate target trials of antihypertensive medication initiation and dementia risk using data from three large, observational studies. Estimates for incident dementia were inconsistent and imprecise, and positive control analyses suggested they were biased.

Large cohorts are an attractive observational data source for target trial emulation. They often have excellent outcome ascertainment, collect a wealth of data on potential confounders, and may be representative of a known target population. However, they often lack data on information that influences clinical decision-making.[36] Additionally, we found that few cohort participants met eligibility criteria similar to those applied in RCTs. Whether cohort studies can be used to validly emulate trials will rely on the extent to which relevant data influencing treatment is captured and the available sample size given the inclusion criteria for the desired target trial.

Other common characteristics of cohort studies may also introduce challenges for target trial emulation. For example, the time elapsed between cohort visits may raise concerns about misclassification of treatment status or misalignment of subtrials (e.g., because clinical guidelines or prescribing practices change over time). Where propensity score overlap is achieved, it can be difficult to determine whether there are sufficient numbers of participants across the entire range of propensity scores. Using density-based cutoffs chosen using a positive control outcome ensures a minimum density of participants across the range of propensity scores where there is support for positivity while allowing propensity score ranges to vary across subcohorts and maximizing sample size.

Interestingly, after the restriction of the sample to those with indications for treatment, further restricting our sample population to subsets with more homogenous propensity scores did not materially change findings. This is consistent with pharmacoepidemiology reports reporting that trimming to select a population with overlapping propensity scores did not fully address confounding by indication,[42] and that the method used to trim propensity scores had little impact on associations.[43] Importantly, unlike randomization, which is expected to balance both measured and unmeasured confounders, the success of propensity score methods depends on whether sufficient prognostic factors for treatment have been adequately measured.[38,44,45] Because hypertension is largely asymptomatic,[46] treatment is influenced in part by clinical judgment,[47] and indications for treatment change with time,

Ethics

Detailed information on data collection, variable definitions, and dementia ascertainment procedures are available in eTable 1; http://links.lww.com/EDE/C191. Participants of each cohort provided informed consent. Cohort procedures were approved by corresponding institutional review boards. Statistical analysis for this article was classified as not human subjects research by The George Washington University Institutional Review Board.

Institutional review boards

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E.E.B.: reports receiving consulting fees from Massachusetts General Hospital. K.Z.G.: currently reports funding from NIA, CMS, and HRSA. S.C.Z.: reports recently owning stock in AbbVie Inc., Gilead Sciences LLC, CRISPR Therapeutics, Abbott Laboratories, and Eli Lilly and Co. A.L.F.: reports receiving funding from NIH, serving on a Data Safety and Monitoring Board, and consulting on a project involving MESA genetics. M.C.P.: reports grant funding from NIH and DOD, participation in the Health and Aging Policy Fellowship, and prior service as a paid member of the Biogen Healthy Lives, Healthy Climate Scientific Advisory Panel. The other authors report no conflicts of interest.

The HRS data used in this study are available on the Health and Retirement Study website (http://hrsonline.isr.umich.edu/). ARIC data can be made available to interested researchers through established study protocols (https://sites.cscc.unc.edu/aric/). CHS data and study materials may be requested from the CHS Coordinating Center at https://chs-nhlbi.org/. Code can be made available to interested researchers by contacting the corresponding author.

SDC Supplemental digital content is available through direct URL citations in the HTML and PDF versions of this article (www.epidem.com).

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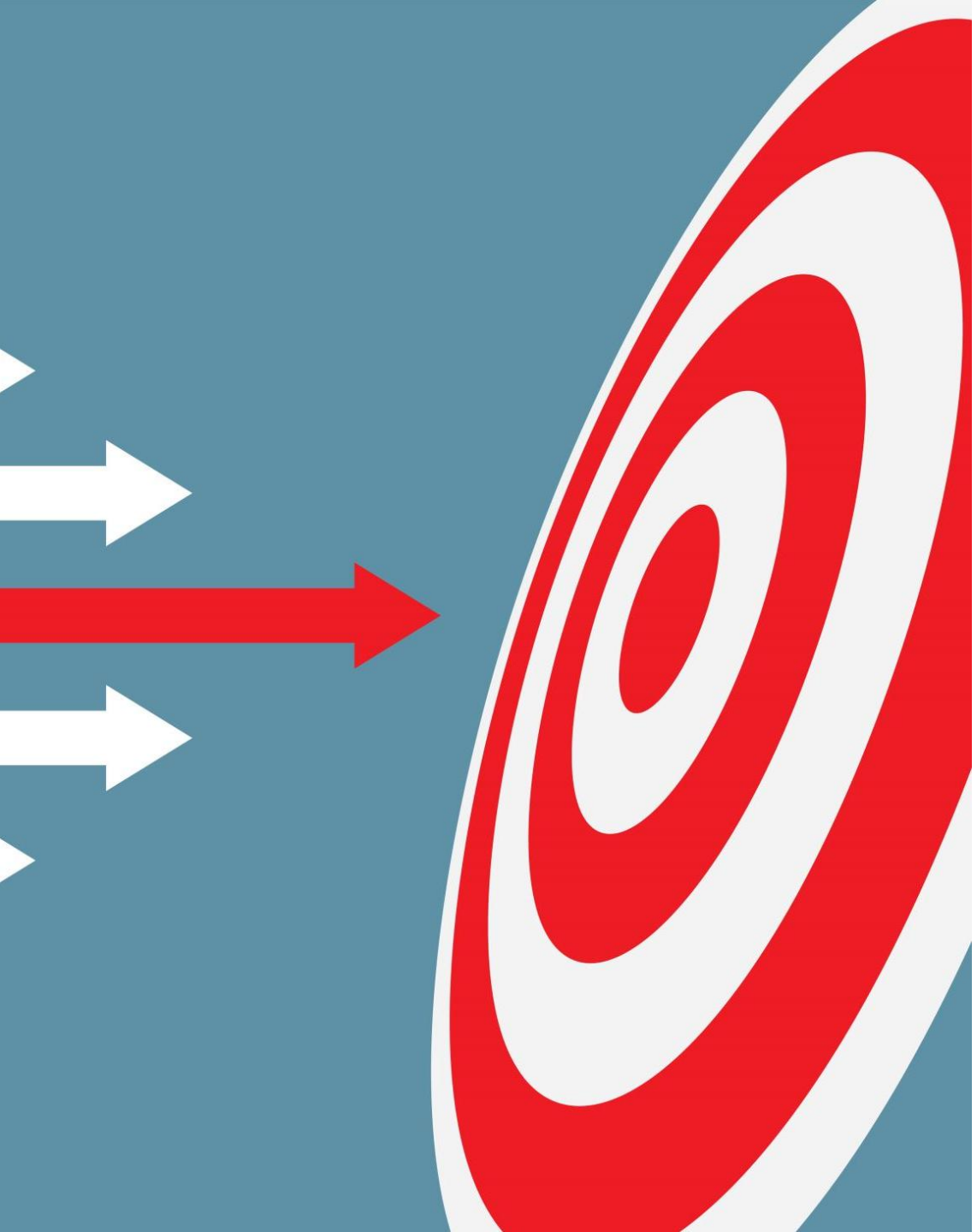

Conclusion

- TARGET provides guidance for reporting analyses of observational data that aim to estimate causal effects by explicitly emulating a target trial.