Received: 14 August 2024 | Revised: 21 January 2025 | Accepted: 21 January 2025

DOI: 10.1002/alz.14627

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

RESEARCH ARTICLE

Sociodemographic modifiers of effects of statin initiation on dementia incidence: An emulated trial design in a large health care member population with 10+ years of follow-up

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Funding information
National Institutes of Health; National Institute on Aging, Grant/Award Number: RF1AG069259; Research Program on Genes, Environment, and Health, Kaiser Permanente Division of Research; Wayne and Gladys Valley Foundation; Ellison Medical Foundation; Robert Wood Johnson Foundation; Kaiser Permanente Northern California, Kaiser Permanente; National and Regional Community Benefit Programs, Kaiser Permanente; Genetic Epidemiology Research on Adult Health and Aging, Kaiser Permanente Division of Research, Grant/Award Number: RC2AG036607

Abstract

INTRODUCTION: Mixed evidence on how statin use affects risk of Alzheimer's disease and related dementias (ADRD) may reflect heterogeneity across sociodemographic factors. Few studies have sufficient power to evaluate effect modifiers.

METHODS: Kaiser Permanente Northern California (KPNC) members (n = 705,061; n = 202,937 with sociodemographic surveys) who initiated statins from 2001 to 2010 were matched on age and low-density lipoprotein cholesterol (LDL-C) with non-initiators and followed through 2020 for incident ADRD. Inverse probability-weighted Cox proportional hazards models were used to evaluate effect modification by age, gender, race/ethnicity, education, marital status, income, and immigrant generation.

RESULTS: Statin initiation (vs non-initiation) was not associated with ADRD incidence in any of the 32 subgroups ($p > .05$). Hazard ratios ranged from 0.964 (95% CI: 0.923 to 1.006) among Asian-identified participants to 1.122 (95% CI: 0.995 to 1.265) in the highest income category.

DISCUSSION: Sociodemographic heterogeneity appears to have little to no influence on the relationship between statin initiation and dementia.

KEYWORDS
Alzheimer's disease and related dementias (ADRD), effect modification, emulated trial design, sociodemographic factors, statins

Highlights

- The study includes a large and diverse cohort from Kaiser Permanente ($N = 705{,}061$).
- An emulated trial design of statin initiation on dementia incidence was used.
- Effect modification by sociodemographic factors was assessed.
- There were no significant Alzheimer's disease and related dementias (ADRD) risk differences in 32 sociodemographic subgroups ($p > 0.05$).

1 | INTRODUCTION

High cholesterol level may contribute to the development of Alzheimer's disease and related dementias (ADRD),[1] with vascular pathology being a key factor in disease progression.[2,3] Such associations may occur through mechanisms involving coronary heart disease or stroke,[4] particularly during the middle-aged period.[5,6] Therefore, statins, a class of lipid-lowering medications commonly prescribed to older adults for reducing cholesterol level, are hypothesized to reduce the risk of ADRD by improving cardiovascular health.[7]

Previous studies estimating the risk of dementia associated with statin use have yielded mixed results. Randomized controlled trials (RCTs) have generally indicated no overall effect of statins on dementia or cognition.[8–14] Among large observational studies with long follow-up periods,[15–26] most studies have suggested that statins may lower the risk of dementia or cognition[15–21,25,26]; however, some studies have reported no association,[22,23] or reported protective effects only when statins were initiated at younger ages.[24] A previous systematic review[27] found that earlier studies ruled out significant short-term effects of statins on dementia and called for rigorous observational studies to avoid confounding and reverse causation. Therefore, emulated trial designs, which target the effects of initiating a medication as if conducting an intent-to-treat (ITT) analysis in an RCT, are recommended as current best practice for observational studies on pharmaceutical effects.[28] The study by Zimmerman et al.,[29] using an emulated trial design, found that statin initiation resulted in a less than 3% difference in the hazard of ADRD after the first year of follow-up. These mixed findings may reflect heterogeneity in the effects of statin use across populations,[7,30] leading to calls for evidence on effect modifiers using an emulated trial design.

Sociodemographic characteristics, including age, gender, race/ethnicity, education, income, immigration status, and social connections, have been recognized as important predictors of ADRD.[31–34] Evidence of potential effect modification by statins on dementia exists, as prior research suggests that baseline cognition significantly modifies the association between statin use and dementia.[35] However, only limited research has assessed the interaction between sociodemographic factors and statin use in relation to cognitive outcomes. This paucity of prior research is due, in part, to the need for very large samples to achieve informative estimates of effect sizes within population subgroups. In addition, few data sources have the quality of measures and diversity of inclusion to support the assessment of whether sociodemographic factors modify statin effects on dementia risk. Most research on statins and dementia or cognitive outcomes is based on relatively small cohorts or electronic health record (EHR) databases with limited linked sociodemographic information.[7,16–25] Cohort studies often have measures of key sociodemographic characteristics but are rarely adequately powered to detect effect heterogeneity.

Sociodemographic variables may modify the effects of statin treatment on ADRD via multiple mechanisms, including biological, clinical, and sociobehavioral processes. Potential age-related effects of statins on cognition have been suggested, by improving metabolic and vascular health in older adults while disrupting cholesterol homeostasis and myelination in younger adults.[36] In addition, men and women vary in response to statins due to more frequent muscle symptoms in women.[37] Black Americans experience earlier hypertension, higher ischemic stroke rates, and a greater burden of hypercholesterolemia[38–40] compared to non-Hispanic White individuals. Some Asian American subgroups have elevated levels of diabetes and are more vulnerable to cardiovascular diseases and related complications than other racial groups, conditional on body mass,[41–43] and Hispanic individuals exhibit a higher prevalence of obesity, diabetes mellitus, and dyslipidemia than non-Hispanic White individuals.[44] Finally, higher socioeconomic status (SES) is associated with better access to health care, improved health literacy, and better management of coexisting health conditions.[45–47]

In this study, we aimed to emulate a target trial to evaluate the sociodemographic modifiers of the effect of statin initiation on the incidence of dementia, using a uniquely powerful EHR database with a large, embedded survey cohort.

2 | METHODS

2.1 | Study population

Our study used data from members of Kaiser Permanente Northern California (KPNC), an integrated health care delivery system in Northern California. The full dataset used in these analyses included comprehensive pharmacy, laboratory, and diagnostic variables for all KPNC members from January 1, 1997 to December 31, 2020, providing a large sample size for robust statistical power. We also used survey data for a subset of KPNC members who completed one of two health surveys: the California Men's Health Survey (CMHS), fielded in 2002–2003 to men 45–69 years of age,[48] and the Research Program on Genes, Environment, and Health (RPGEH) survey, fielded to men and women in 2007.[49]

2.2 | Emulated trial design

RCTs are widely accepted as the gold standard for estimating the effect of an exposure on an outcome. However, RCTs are often ethically or practically infeasible. When RCT evidence is not available, best practice entails specifying a hypothetical target trial to guide the analysis of observational data.[28,50] The aim of a hypothetical target trial is to align sample construction in the observational data with a trial format, accounting for the absence of randomization with analytic methods. We emulated a series of hypothetical target trials using observational data, where each day a new trial is launched, and eligible participants are assigned randomly to initiate statin use or not initiate statin use and followed for incident ADRD. Table S1 shows the emulated trial framework in comparison with a theoretical RCT.

2.3 | Inclusion/exclusion criteria

KPNC members were eligible for inclusion if they were born prior to January 1, 1951, and thus were at least 45 years old during the study period. We applied a 4-year "washout period," during which individuals must have continuously been KPNC members with at least one laboratory test or prescription record and must not have been prescribed statins or diagnosed with dementia or related cognitive diseases (paralysis agitans/Parkinson's disease, dementia with Lewy bodies, alcoholic dementia, other dementia, frontotemporal dementia, amyotrophic lateral sclerosis). For the participants in the survey cohort, along with the 4 years of washout period, they must additionally not have been statin users prior to the survey completion date. We excluded individuals who enrolled in KPNC on January 1, 2007 or later to make sure participants, after 4 years of washout period, would have at least 10 years of possible follow-up prior to the end of study period (December 31, 2020). Figure S1 shows an example of eligible/ineligible subjects based on our inclusion/exclusion criteria.

RESEARCH IN CONTEXT

1. Systematic review: We searched PubMed for studies on the association between statin use and Alzheimer's disease and related dementias (ADRD). Previous research shows inconsistent results, with some studies indicating a protective effect of statins, whereas others show no effect or increased risk. Variability in findings may be due to heterogeneity across different sociodemographic factors.
2. Interpretation: Our study suggests that statin initiation is not significantly associated with ADRD incidence across various sociodemographic subgroups. This result indicates that factors such as age, gender, race/ethnicity, education, marital status, income, and immigrant generation do not substantially modify the relationship between statin initiation and ADRD risk.
3. **Future directions**: Future research should place greater emphasis on utilizing emulated trial designs to investigate the long-term effects of statins on ADRD. In addition, examining subcategories such as different doses and types of statins is crucial to determine if specific subcategories for statin use influence dementia risk differently.

2.4 | Variables

2.4.1 | Exposure: Statin initiation

The exposure of interest was initiation of statin treatment, defined as the first recorded prescription of any statin type (Table S2) during January 1, 2001~December 31, 2010 for each unique individual. At the time of each statin initiation, the individual who initiated statin use (referred to as the "statin initiator") was matched with five individuals of the same age (≤0.01 years) and low-density lipoprotein cholesterol (LDL-C) level (categorized as <70, 70–99, 100–129, 130–159, 160–189, and ≥190 mg/dL), who either never initiated statins or had not yet initiated statins, henceforth referred to as "non-initiators." Follow-up time for both the statin initiators and their matched non-initiators began on the day of the statin initiator's first filled statin prescription. Within the full cohort, there were 3651 distinct statin initiation dates (days) among 258,242 initiators, whereas in the survey cohort, there were 2920 distinct initiation dates (days) among 26,724 initiators. For each initiation date, five non-initiators were matched to each initiator. Non-initiators were required to have no prior statin use at the time of their assigned trial start date. However, after the trial start date, non-initiators could subsequently initiate statins. On each statin initiation date, both initiators and their matched non-initiators were unique subjects. However, across different initiation dates, non-initiators could be selected and matched to different initiators multiple times. Figure 1

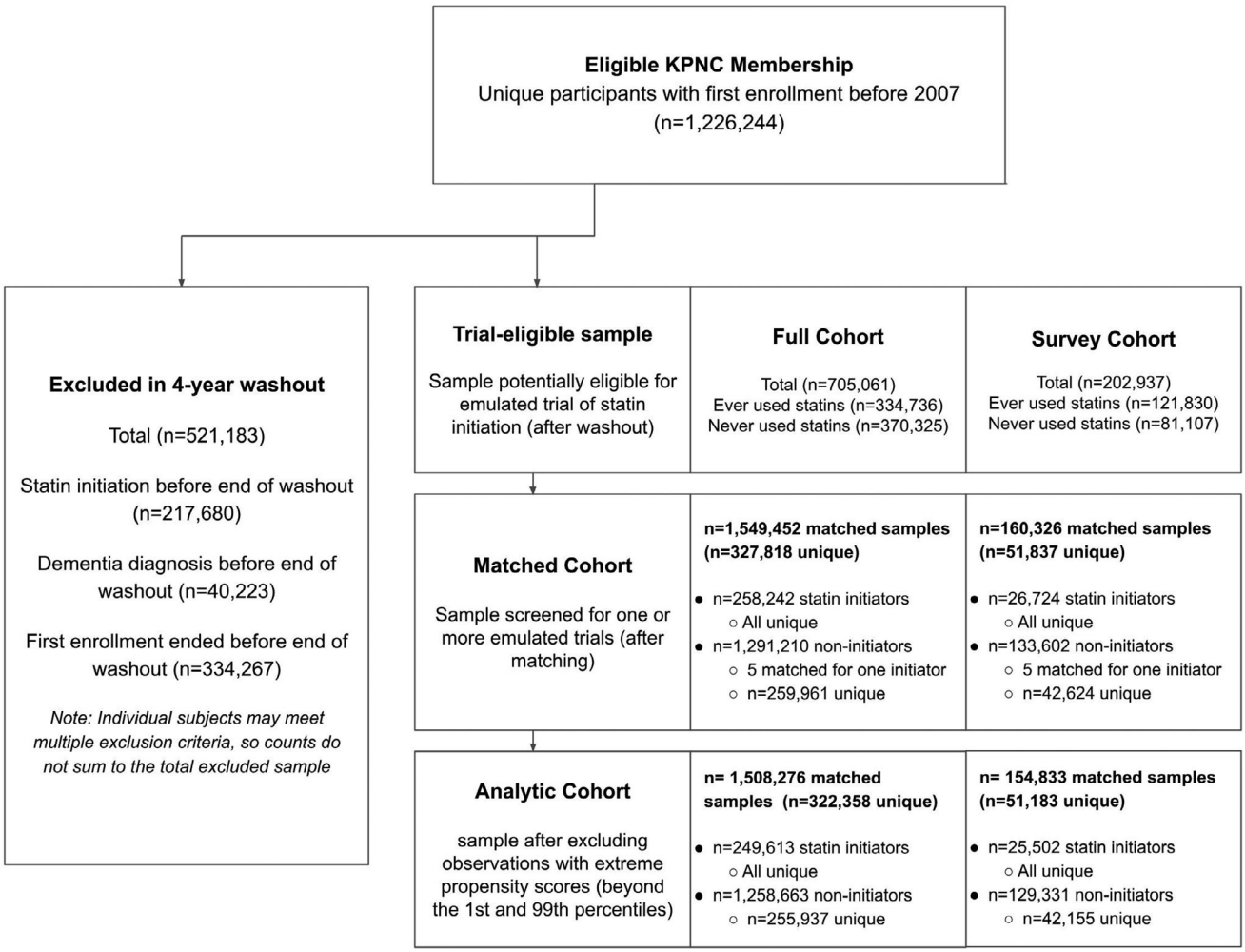

FIGURE 1 Data flowchart: Number of subjects in the cohort.

shows the flowchart of the study datasets with numbers of unique participants/trial subjects for each step. Prescription data were coded in KPNC using the American Hospital Formulary Service Drug Information classification 2020[51] and extracted by generic drug name (Table S2).

2.4.2 | Outcomes: All-cause dementia and AD

The study has two primary outcomes: ADRD and AD alone. Both outcomes were ascertained through EHRs from any encounter type (e.g., inpatient, outpatient, ambulatory) other than lab-only or radiology-only encounters. We considered all encounters occurring after the start of the emulated trial and before the end of the study period (December 31, 2020). ADRD was defined as AD, vascular dementia, and nonspecific dementia. Specific International Classification of Diseases (ICD) codes used in outcome definitions can be found in Table S3. Diagnosis of other types of dementia (paralysis agitans/Parkinson's disease, dementia with Lewy bodies, alcoholic dementia, other dementia, frontotemporal dementia, and amyotrophic lateral sclerosis) were considered censoring events because they may reduce the likelihood that the individual subsequently receives an ADRD diagnosis. In analyses using only AD as the outcome, vascular dementia and nonspecific dementia were also included as censoring variables. To account for possible misclassification of the first diagnosis of the outcome (ADRD or AD), all first occurrences of censoring dementias were re-coded as ADRD or AD if a diagnosis of an outcome of interest—either ADRD or AD respectively—occurred within 1 year of the initial outcome diagnosis.

2.4.3 | Possible modifiers: Sociodemographics

Age and gender were obtained from the KPNC EHR. Age was operationalized into the following categories: "below 60," "60 to <65," "65 to <75," and "75 or older." Race and ethnicity were obtained from self-report and administrative records and categorized as non-Hispanic Black, Hispanic, non-Hispanic Asian, non-Hispanic White, other racial/ethnic identity, or unknown. The survey subsample included self-reported educational attainment (grade school [grades 1–8], some high school [grades 9–11], high school or GED, technical/trade school, some college, college, graduate school, other, or as a

binary variable: lower education [grade school, some high school, high school or GED, other] and higher education [technical/trade school, some college, college, graduate school]), income (less than $20,000, $20,000–$39,999, $40,000–$59,999, $60,000–$99,999, $100,000 or more), marital status (never married, married or living as married, separated/divorced, widowed, or as a binary variable: not married [never married, separated/divorced, widowed] and married [married or living as married]), and participant and parental U.S. nativity (yes, no, unknown) (Table S4).

2.4.4 | Covariates

For each participant who initiated statins and their matched non-initiators, covariates were obtained from the EHR at the date of the statin initiator's first recorded prescription of statins. Covariates included comorbidities, lab measures, and health care utilization. Comorbidities included stroke, cardiovascular disease, hypertension, diabetes of any type, major depressive disorder, and head injury (refer to Table S3 for corresponding ICD codes). Lab measures included LDL-C, high-density lipoprotein cholesterol (HDL-C), and glycated hemoglobin (HbA1c), which represent the most recent values documented before the initiation of the trial. Lab values for individuals with no recorded values before the date of emulated trial initiation were imputed based on the conditional mean of lab values (HbA1c by diabetes status, and LDL-C and HDL-C by cardiovascular disease [CVD] status). Health care utilization was operationalized as four variables defined as the natural log-transformed, that is, log(1+count), yearly count of visits (inpatient, outpatient, and telehealth), or prescriptions (pharmacy) 1 year before trial initiation.

2.4.5 | Censoring variables

Individuals were censored at the earliest of the first occurrence of the outcome of interest, the first occurrence of another type of dementia likely to reduce the chance of later diagnosis of ADRD or AD, the end of their KPNC membership, death, or the end of the study period (December 31, 2020). For participants with multiple periods of KPNC membership, we restricted the sample to data from their first enrollment of KPNC membership. Mortality data from the KPNC mortality database was combined with clinical and administrative records, the National Death Index, California State death records, and Social Security Administration records.

2.5 | Analysis

We conducted descriptive analyses comparing baseline characteristics of statin initiators to non-initiators for the full and survey cohort. In addition, we summarized the baseline characteristics of the original population of eligible individuals, that is, prior to selecting statin initiators and matching non-initiators for the emulated trials.

2.5.1 | Estimation of inverse probability of treatment weighting

We used stabilized inverse probability of treatment weighting (IPTW) in all outcome models, developed from a statin initiation model. Logistic regression models estimated the probability of statin initiation given race, gender, year of initiation, depression, hypertension, stroke, head injury, diabetes, and, among the survey cohort—the survey in which individuals participated (Figure S2). Stabilized IPTW was calculated as the proportion of the exposed over the inverse of the propensity score for statin initiators, or the proportion of the unexposed over the inverse of 1 minus the propensity score for non-initiators. We excluded individuals with extreme propensity scores (below the 1st or above the 99th percentile of all propensity scores) to meet the positivity assumption.

We also evaluated the feasibility of developing time-updated weights to account for treatment switching, that is, individuals who were randomized to the initiator group ceasing use over the course of follow-up or individuals randomized to the non-initiator group beginning statins over the course of the follow-up. Such weights would allow us to estimate a per-protocol estimand corresponding with the effects of consistent statin use. However, the treatment censoring weighting model for the time-varying analysis did not achieve a good statistical fit (Table S5), and there was evidence that cessation of statin use was likely influenced by unmeasured predictors of dementia (Table S6). We therefore did not pursue per-protocol estimates.

2.5.2 | First-year indicators

Initiation of statins may coincide with an increase in medical utilization and thus is likely to result in a higher possibility of detection of prevalent dementia regardless of whether there is a biological effect of statins on dementia. Our result showed an exceptionally higher association of statin initiation with dementia diagnoses within the first year after statin initiation (Figure S3). We believe that this short-term elevation reflects that statin initiators have a higher probability of being diagnosed with dementia due to their more frequent medical care utilization compared to non-initiators. Furthermore, statins may lead to short-term memory complaints that later resolve but may be recorded using dementia codes in the medical record. Therefore we divided follow-up time into periods before and after 1 year of follow-up, by creating an indicator variable for the first year of follow-up in the analysis models to capture the effect only "after each subject's first year of follow-up."

2.5.3 | Outcome models

In the full cohort and then the survey cohort, we estimated two types of Cox proportional hazard models for each of our outcomes (ADRD, AD): (1) initial models including a binary variable of statin initiation, an interaction between statin initiation and an indicator for the first year of follow-up, an interaction between statin initiation and the

hypothesized sociodemographic modifier of interest, age categories, and the quartile of LDL values; (2) models additionally adjusted for the decile of propensity score along with all the variables in (1). All outcome models were weighted for the stabilized IPTW.

2.5.4 | Interaction

Our analysis examined the multiplicative interaction between statin initiation and various sociodemographic factors on the risk of ADRD/AD. For the full cohort, we evaluated age categories, gender, and race/ethnicity as possible modifiers. Using the survey cohort data, we evaluated age categories, gender, race/ethnicity, and additional survey variables including education (both as categorical or binary), marital status (both as categorical or binary), income level, U.S. nativity, and mother's U.S. nativity (Table S4). Equation 1 summarizes a typical model:

$$\begin{aligned}(_{ADRD/AD}(t) = h_0(t) * \exp(&\beta_1 * Statin\_initiation \\ &+ \beta_2 * Statin\_initiation * first\_year \\ &+ \cdots \beta_3 * sociodemographic\_factor \\ &+ \beta_4 * Statin\_initiation * sociodemographic\_factor \\ &+ \cdots \beta_5 * deciles\_of\_propensity\_scores \\ &+ \beta_6 * categories\_of\_age + \beta_7 * quartiles\_of\_LDL) \quad (1)\end{aligned}$$

Equation 1: Hazard Function for ADRD/AD Risk with Statin Initiation and Sociodemographic Factors

Our primary coefficients of interest were the interaction terms between statin initiation and the sociodemographic modifier (β_4), corresponding to the hazard of ADRD/AD among statin initiators compared to statin non-initiators within a certain stratum of a sociodemographic variable after the first year of follow-up. Analysis of the survey cohort used the same initial and adjusted models, but to avoid immortal person-time, follow-up time for analyses in the survey cohort was restricted to begin no earlier than the survey completion date.

This study follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cohort studies.[52] Human subjects approval for this study was granted by the University of California San Francisco Institutional Review Board (IRB), the Boston University IRB, and the KPNC and Mid-Atlantic States IRBs. All analyses were conducted using R version 4.1.3.[53] Statistical significance was set at $p < 0.05$; since no results met this threshold, we did not implement any multiple comparison corrections.

3 | RESULTS

Our full analytic cohort sample included 258,242 individuals who received a first statin prescription between January 2001 and December 2010, matched to 1,291,210 individuals who either never initiated statins or had not initiated statins at the first statin prescription date of their matched statin initiator (Figure 1). The survey analytic cohort included 26,724 individuals who received a first statin prescription after completing the survey and before December 2010, matched to 133,602 individuals (Figure 1). The average age at statin initiation was 67.40 (SD = 9.14) years for the full cohort and 69.09 (SD = 8.56) years for the survey cohort (Table 1). Statin initiators in the full cohort were more likely to have prior diagnoses of major depressive disorder, hypertension, cardiovascular disease, stroke, and diabetes. The demographics and mean follow-up time in the full cohort were similar to the those in the survey cohort (11.79 years [SD = 5.21] vs 10.67 years [SD = 4.04]). In the survey cohort, the social characteristics of statin initiators were generally similar to those of non-initiators (Table 2). The description for the full and the survey cohort when excluding individuals with extreme propensity scores (below the 1st or above the 99th percentile of all propensity scores) can be found in Tables S7 and S8.

Average propensity scores for statin initiation were higher among statin initiators than their matched non-initiators (0.22 [SD = 0.11] vs 0.16 [SD = 0.08]) but substantial overlap in propensity score distributions for initiators and non-initiators was attained (Figure S2). After applying IPTW, the distributions of most covariates were similar for statin initiators and their matched non-initiators, except for LDL-C, which showed a larger standardized difference in the weighted sample compared to the crude sample (Tables S9–S12, Figures S4–S7).

Using the full cohort, adjusted hazard ratios (HRs) for dementia were close to the null and statistically indistinguishable from the null for all gender, age, and race/ethnicity groups examined ($p > 0.05$; Figure 2, left, Table S13, left). Estimated effects of statin initiation were lowest—but still nearly null—for Asian-identified individuals (HR = 0.964, CI: 0.923–1.006), Black individuals (HR = 0.966, CI: 0.927–1.006) and the youngest age (below 60 years; HR = 0.966, CI: 0.915–1.02). Trend tests for age suggested no significant effect modification by age category for the full cohort ($p = 0.766$). The patterns for AD were generally similar to those for ADRD and showed no clinically meaningful difference from the null for the overall samples as well as across age, gender, and race/ethnicity (Figure S8, left, Table S13, left).

In the survey cohort, adjusted HRs for dementia were within 12% of the null (i.e., HR 0.95 to 1.12) in every subgroup examined, with no significant difference from the null across age, gender, race/ethnicity (Figure 2, right, Table S13, right) or education, income, nativity, or maternal nativity (Figure 3, Table S14). The estimated effects of statin initiation were lowest—but again close to null—for Asian (HR = 0.955, 95% CI: 0.816–1.119) and Black (HR = 0.967, 95% CI: 0.812–1.151) individuals. Trend tests for age indicated no significant effect modification by age category ($p = 0.206$). The estimated effects were highest for the highest income group (HR = 1.122, 95% CI: 0.995–1.265), but there was no trend across levels of income ($p = 0.912$). The patterns for AD were similar to those for ADRD and showed no clinically meaningful difference from the null across age, gender, and race/ethnicity subgroups (Figure S8, right, Table S13, right), and for other sociodemographic variables in the survey cohort (Figure S9, Table S14).

TABLE 1 Demographic characteristics of subjects in the full and survey-matched cohorts.

	Full cohort			Survey cohort		
Baseline sample characteristics	Total (n = 1,549,452)	Statin initiators (n = 258,242)	Statin non-initiators (n = 1,291,210)	Total (n = 160,326)	Statin initiators (n = 26,724)	Statin non-initiators (n = 133,602)
Age, years, mean (SD)	67.40 (9.14)	67.40 (9.14)	67.40 (9.14)	69.09 (8.56)	69.09 (8.56)	69.09 (8.56)
Propensity score for statin initiation, mean (SD)	0.17 (0.09)	0.22 (0.11)	0.16 (0.08)	0.17 (0.07)	0.20 (0.10)	0.16 (0.06)
Gender (Male), *n* (%)	687,918 (44.4)	11,9181 (46.2)	568,737 (44.0)	94,304 (58.8)	15,223 (57.0)	79,081 (59.2)
Race, *n* (%)						
Non-Hispanic White	1,013,405 (65.4)	160,580 (62.2)	852,825 (66.0)	116,334 (72.6)	18,861 (70.6)	97,473 (73.0)
Non-Hispanic Asian	159,878 (10.3)	28,144 (10.9)	131,734 (10.2)	14,337 (8.9)	2462 (9.2)	11,875 (8.9)
Non-Hispanic Black	104,330 (6.7)	19,513 (7.6)	84,817 (6.6)	6767 (4.2)	1235 (4.6)	5532 (4.1)
Hispanic	164,519 (10.6)	30,201 (11.7)	134,318 (10.4)	13,865 (8.6)	2515 (9.4)	11,350 (8.5)
Other	91,367 (5.9)	15,984 (6.2)	75,383 (5.8)	8220 (5.1)	1474 (5.5)	6746 (5.0)
Unknown	15,953 (1.0)	3820 (1.5)	12,133 (0.9)	803 (0.5)	177 (0.7)	626 (0.5)
Major depressive disorder, *n* (%)	241,857 (15.6)	43,833 (17.0)	198,024 (15.3)	25,899 (16.2)	4566 (17.1)	21,333 (16.0)
Hypertension, *n* (%)	890,932 (57.5)	178,755 (69.2)	712,177 (55.2)	95,473 (59.5)	17,936 (67.1)	77,537 (58.0)
Cardiovascular disease, *n* (%)	212,632 (13.7)	56,773 (22.0)	155,859 (12.1)	33,287 (20.8)	5594 (20.9)	27,693 (20.7)
Stroke, *n* (%)	36,475 (2.4)	12,601 (4.9)	23,874 (1.8)	3117 (1.9)	1181 (4.4)	1936 (1.4)
Head injury, *nN* (%)	11,356 (0.7)	1975 (0.8)	9381 (0.7)	1540 (1.0)	276 (1.0)	1264 (0.9)
Diabetes, *n* (%)	197,674 (12.8)	69,347 (26.9)	128,327 (9.9)	14,250 (8.9)	4590 (17.2)	9660 (7.2)
Low-density lipoprotein (mg/dL), mean (SD)	137.92 (36.72)	147.82 (38.20)	135.95 (36.09)	125.34 (31.13)	139.48 (35.55)	122.51 (29.36)
Imputed low-density lipoprotein, *n* (%)	159,389 (10.3)	4090 (1.6)	155,299 (12.0)	6621 (4.1)	148 (0.6)	6473 (4.8)
High-density lipoprotein (mg/dL), mean (SD)	53.29 (14.84)	51.06 (14.28)	53.73 (14.91)	52.50 (15.22)	51.44 (14.73)	52.71 (15.31)
Imputed high-density lipoprotein, *n* (%)	101,872 (6.6)	2605 (1.0)	99,267 (7.7)	4327 (2.7)	114 (0.4)	4213 (3.2)
HbA1c (mg/dL), mean (SD)	5.99 (0.85)	6.27 (1.25)	5.93 (0.73)	5.85 (0.57)	5.98 (0.86)	5.82 (0.49)
Imputed HbA1c, *n* (%)	980,909 (63.3)	124,194 (48.1)	856,715 (66.3)	95,267 (59.4)	13,389 (50.1)	81,878 (61.3)
Outpatient visits, mean (SD)	8.21 (10.19)	8.98 (10.74)	8.06 (10.07)	9.02 (10.56)	9.22 (10.85)	8.97 (10.50)
Inpatient visits, mean (SD)	0.09 (0.38)	0.11 (0.45)	0.08 (0.36)	0.09 (0.39)	0.10 (0.41)	0.09 (0.39)
Telehealth visits, mean (SD)	0.19 (1.04)	0.23 (1.21)	0.19 (1.01)	0.64 (1.81)	0.67 (1.88)	0.63 (1.79)
Prescription visits, mean (SD)	8.72 (8.09)	10.00 (8.61)	8.46 (7.96)	9.25 (8.15)	9.72 (8.29)	9.15 (8.12)
Outcomes accrued during follow-up						
ADRD, *n* (%)	254,910 (16.5)	39,245 (15.2)	215,665 (16.7)	20,442 (12.8)	3193 (11.9)	17,249 (12.9)
AD, *n* (%)	66,636 (4.3)	9847 (3.8)	56,789 (4.4)	5780 (3.6)	934 (3.5)	4846 (3.6)
Years followed, mean (SD)	11.79 (5.21)	10.16 (5.82)	12.11 (5.02)	10.67 (4.04)	9.66 (4.63)	10.87 (3.88)

Abbreviation: ADRD, Alzheimer's disease and related dementias; HbA1c, hemoglobin A1c; SD, standard variation.

4 | DISCUSSION

In this study, we aimed to emulate a target trial to evaluate sociodemographic modifiers of the effect of statin initiation on the incidence of dementia, leveraging a uniquely robust EHR database that includes up to 20 years of follow-up and a large, embedded survey cohort. Our findings suggested that the association of statin initiation with ADRD/AD incidence was close to null across all sociodemographic groups evaluated, including by age, sex, racial/ethnic identity, education, marital status, income, U.S. nativity, and maternal U.S. nativity.

Our findings suggest that statin initiation does not significantly impact ADRD/AD incidence across various sociodemographic groups. This inference is bolstered by the observation of no significant effects for statin initiation on ADRD/AD overall,[29] and no statistically or clinically significant estimated associations within any of the evaluated sociodemographic groups, with results consistent in both the full and the survey cohorts. This lack of association suggests that the protective cardiovascular effects of statins may not extend to reducing dementia risk.

Previous studies on the risk of dementia associated with statin use have produced inconsistent results. RCTs with short follow-up

TABLE 2 Survey characteristics of subjects in the survey-matched cohort.

Survey cohort			
Sample characteristics	**Total (*n* = 160,326)**	**Statin initiators (*n* = 26,724)**	**Statin non-initiators (*n* = 133,602)**
Education level, *n* (%)			
Grade school (grades 1–8)	3383 (2.1)	617 (2.3)	2766 (2.1)
Some high school (grades 9–11)	6421 (4.0)	1191 (4.5)	5230 (3.9)
High school or GED	23,125 (14.4)	4189 (15.7)	18,936 (14.2)
Technical/trade school	5158 (3.2)	936 (3.5)	4222 (3.2)
Some college	41,114 (25.6)	6964 (26.1)	34,150 (25.6)
College	34,667 (21.6)	5573 (20.9)	29,094 (21.8)
Graduate school	36,346 (22.7)	5452 (20.4)	30,894 (23.1)
Other	696 (0.4)	120 (0.4)	576 (0.4)
Missing	9416 (5.9)	1682 (6.3)	7734 (5.8)
[a]Education (Higher, binary), *n* (%)	11,7285 (73.2)	18,925 (70.8)	98,360 (73.6)
Missing	9416 (5.9)	1682 (6.3)	7734 (5.8)
Marital status, (*N* (%)			
Never married	6861 (4.3)	1114 (4.2)	5747 (4.3)
Married or living as married	11,2957 (70.5)	18,599 (69.6)	94,358 (70.6)
Separated/divorced	19,285 (12.0)	3255 (12.2)	16,030 (12.0)
Widowed	17,604 (11.0)	3141 (11.8)	14,463 (10.8)
Missing	3619 (2.3)	615 (2.3)	3004 (2.2)
[b]Marital status (Married, binary), *n* (%)	112,957 (70.5)	18,599 (69.6)	94,358 (70.6)
Missing	3619 (2.3)	615 (2.3)	3004 (2.2)
Income level, *n* (%)			
<$20,000	11,559 (7.2)	2140 (8.0)	9419 (7.1)
$20,000–$39,999	24,627 (15.4)	4395 (16.4)	20,232 (15.1)
$40,000–$59,999	28,796 (18.0)	4851 (18.2)	23,945 (17.9)
$60,000-–$99,999	41,986 (26.2)	6751 (25.3)	35,235 (26.4)
$100,000+	35,945 (22.4)	5600 (21.0)	30,345 (22.7)
Missing	17,413 (10.9)	2987 (11.2)	14,426 (10.8)
Born in USA, *n* (%)			
No	25,479 (15.9)	4461 (16.7)	21,018 (15.7)
Yes	129,126 (80.5)	21,294 (79.7)	107,832 (80.7)
Unknown	592 (0.4)	104 (0.4)	488 (0.4)
Missing	5129 (3.2)	865 (3.2)	4264 (3.2)
Born in USA (mother), *n* (%)			
No	40,771 (25.4)	6970 (26.1)	33801 (25.3)
Yes	114468 (71.4)	18883 (70.7)	95585 (71.5)
Unknown	1124 (0.7)	200 (0.7)	924 (0.7)
Missing	3963 (2.5)	671 (2.5)	3292 (2.5)

[a]Education "lower" category includes "grade school (grades 1–8), some high school (grades 9–11), high school or GED; other," "higher" category includes "technical/trade school, some college, college, graduate school."
[b]Marital status "currently not married" category includes "never married, separated/divorced, widowed"; "currently married" category includes "married or living as married."

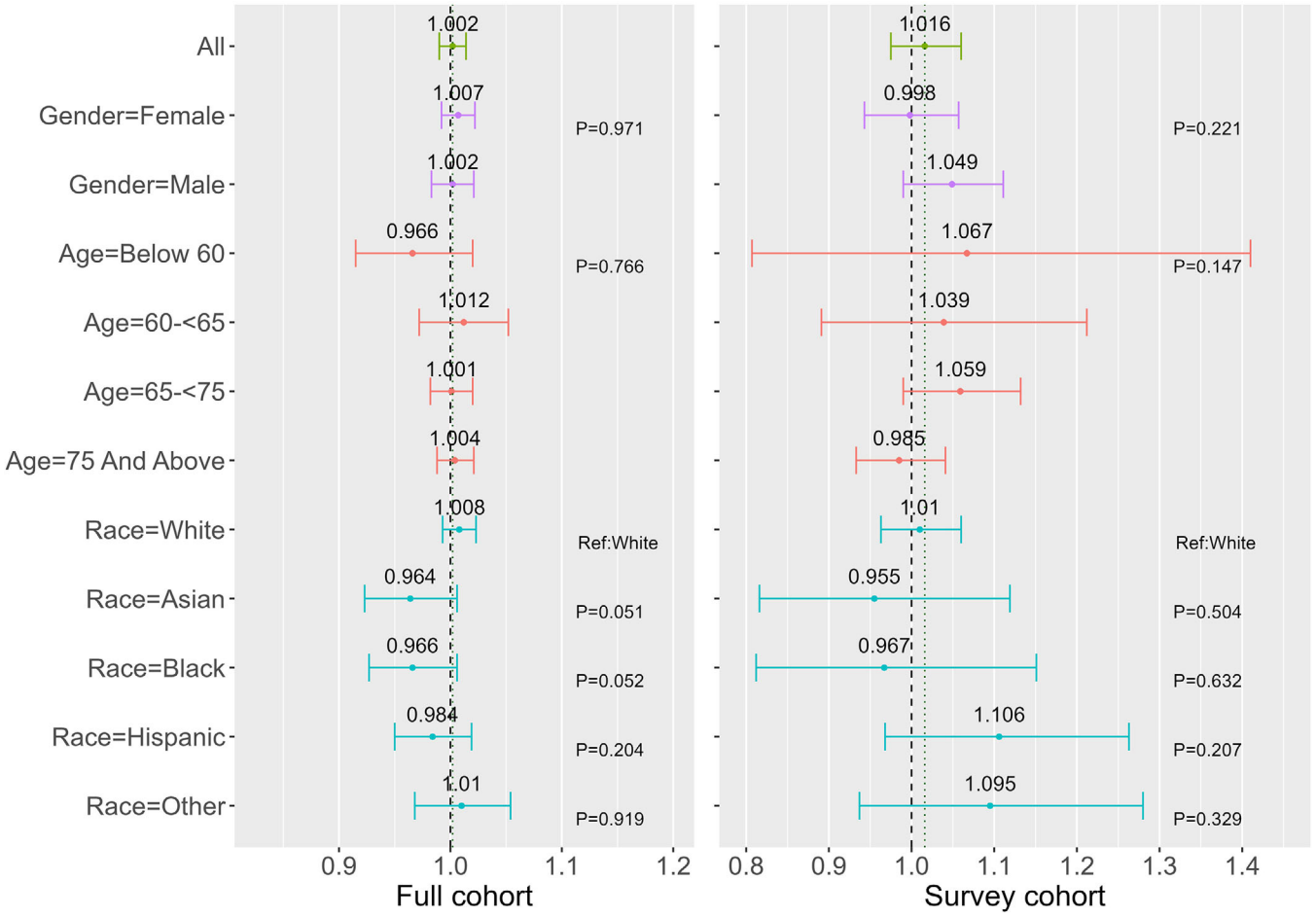

FIGURE 2 HR (hazard ratio) estimates of statins on ADRD by demographic subgroups in the full (left) and survey (right) cohort. The estimates show the HR of statins on dementia for the corresponding reference groups, after each subject's first year of follow-up. The estimates are from the adjusted model that controls for deciles of propensity score, age categories, and quartiles of LDL-C. Stabilized IPTW has been applied. The age category was set based on "below 60," "60 to <65," "65 to <75," and "75 or older." for both the full and the survey cohort. *p*-Values represent the significance of heterogeneous effects across different levels. Specifically: for gender, comparing female versus male; for age, the significance of a linear trend across four levels on an ordinal scale; and for race, comparing each racial group against the reference group, non-Hispanic White. The effects for Race = Unknown were excluded. ADRD, Alzheimer's disease and related dementias; HR, hazard ratio; IPTW, inverse probability of treatment weighting; LDL-C, low-density lipoprotein cholesterol.

periods have generally suggested no overall effect of statins on dementia or cognitive outcomes.[8–14] RCTs are often limited by small sample size, short follow-up periods, and participant characteristics that differ significantly from the typical clinical populations. High-quality observational studies have achieved much larger samples than RCTs,[15–26] and generally have suggested protective effects[15–21,25,26] of statins for cognition and dementia, although results have been mixed, supporting no association,[22,23] or protective effects only when initiated at younger ages.[24] A previous emulated trial of statin initiation on dementia risk found no ITT effect of statin initiation on dementia incidence using pooled logistic regression in a sample of 6373 participants with up to 10 years of follow-up. However, with only 622 statin initiators and 63 dementia cases among those initiators, the sample in the previous emulated trial was too small to rule out important effects or evaluate heterogeneity.[54] Our emulated trial design included over 400 times more statin initiators in the full cohort and 43 times as many statin initiators in the survey cohort, with slightly longer average follow-up, allowing for precise effect estimates even in subgroups.

Several studies have investigated demographic modifiers of the effect of statins on dementia or cognition, including age, gender, and race/ethnicity with mixed findings.[30] Although some studies showed insignificant evidence of age as an effect modifier of the relationship between statins and dementia/cognitive outcomes,[55,56] others suggested potential interactions, where higher age would result in a reduced hazard of statins on dementia or cognitive outcomes compared to lower age.[36,57,58] However, many these of studies focused on different cognitive test scores rather than time-to-diagnosis of dementia or AD,[36] evaluated the efficacy of statins in delaying the progression of AD in already diagnosed individuals,[57] or included only high-risk patients ≥65 years of age with preexisting ischemic heart disease.[58] Fairly few prior studies include both large samples and high-quality data on both lab values and social determinants of health. Previous

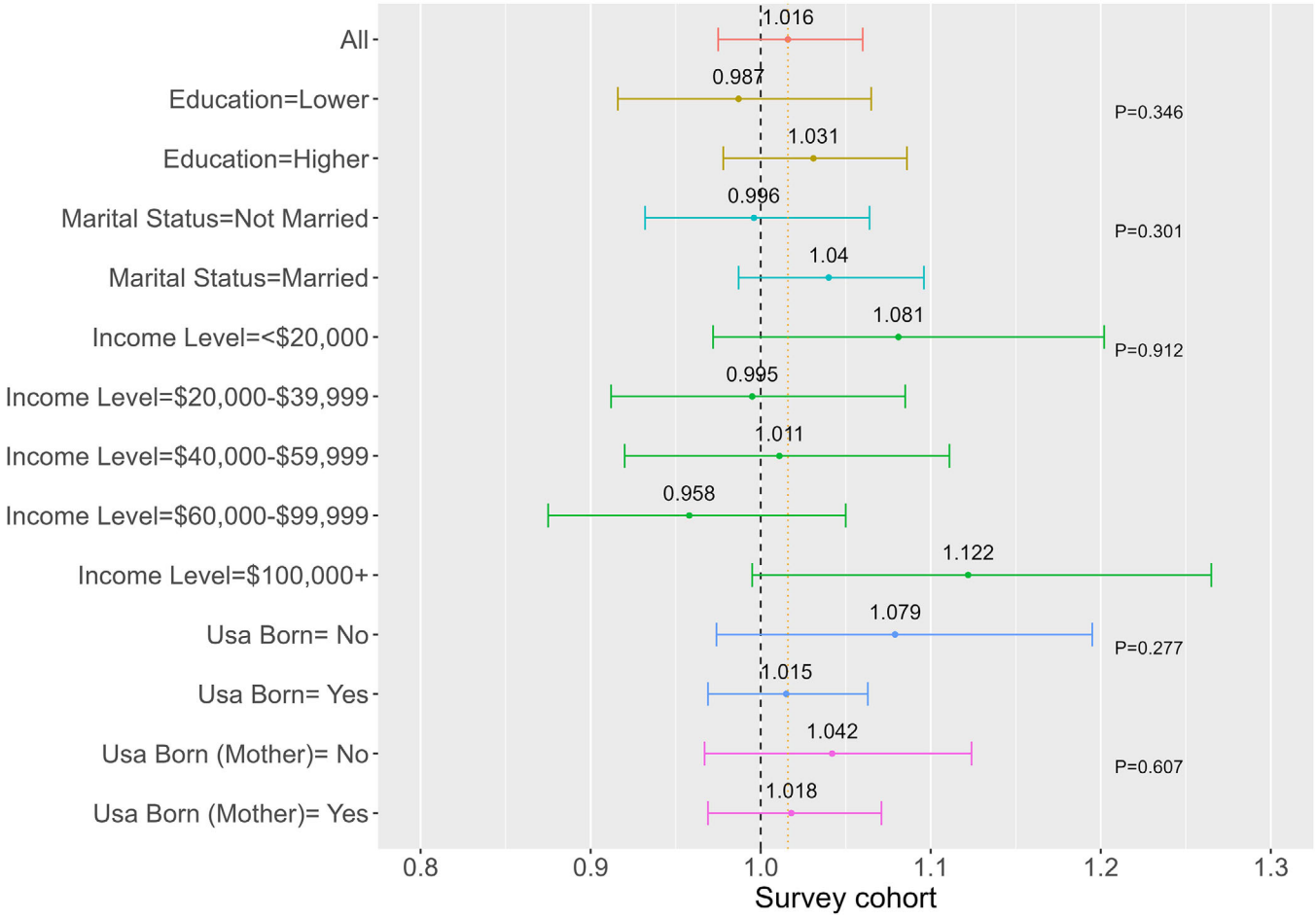

FIGURE 3 HR estimates of statins on ADRD by demographic subgroups as reported in the survey cohort. The estimates show the HR of statins on dementia for the corresponding reference groups, after each subject's first year of follow up. The estimates are from the adjusted model that controls for deciles of propensity score, age categories, and quartiles of LDL-C. Stabilized IPTW has been applied. *p*-values represent the significance of heterogeneous effects across different levels. Specifically: for education, comparing lower versus higher education; for marital status, comparing not married versus married; for income level, the significance of a linear trend across five levels on an ordinal scale; for born in USA and born in USA (Mother), comparing Yes versus No. The effects for born in the USA and born in USA (Mother) = unknown were not included. ADRD, Alzheimer's disease and related dementias; HR, hazard ratio; IPTW, inverse probability of treatment weighting; LDL-C, low-density lipoprotein cholesterol.

studies investigating gender as a modifier of the relationship between statin use and dementia or cognitive outcomes have also produced varied results.[14,58–60] Among studies that focused on dementia, estimated interactions with gender were inconsistent across statin types dementia,[58] or were observed only for vascular dementia.[59] A study examining race/ethnicity as an effect modifier found that simvastatin was associated with lower AD risk for White men and women, Hispanic men and women, and Black women, whereas pravastatin and rosuvastatin were associated with reduced AD risk for White women.[26] Our study found no heterogeneity in the effects of statin initiation on dementia by race/ethnicity.

Several strengths of this study contribute to the reliability and generalizability of our findings. First, we used a large and diverse database, with the unusual strength of detailed measures on a wide range of sociodemographic characteristics in a routine clinical care setting. This allows for better representation of the population, which increases the external validity of our results and allows us to evaluate confounding and heterogeneity by covariates that are rarely available in EHR databases. Second, we employed the emulated trial design, which simulates an RCT setting. This approach helps mitigate confounding, avoids the potential for immortal time-bias, and provides the best feasible support for causal inference in the absence of actual randomization. Finally, we employed rigorous statistical models, including restricting follow-up to after the first year, applying stabilized inverse probability of treatment weighting, and additionally adjusting for propensity score deciles in the outcome modeling. These methodological choices strengthen the internal validity of our study.

However, several limitations should be acknowledged. The ITT analysis likely attenuates the true effect of remaining on statins because some participants who initiated treatment subsequently stopped using statins, whereas some participants classified as non-initiators at baseline subsequently began statin treatment. Such changes in treatment

would dilute the observed effect of initiating status compared to the effect of using statins, potentially leading to estimates closer to the null.[61–63] In our full matched cohort, nonadherence is present in both the initiator and non-initiator groups during follow-up (Figure S10). However, the two groups showed a substantial difference in cumulative exposure, with an average difference of ≈5 statin years over a 20-year follow-up period. Although the emulated trial method is a powerful tool, it depends on assumptions of exchangeability that are conditional on observed covariates. Although our list of covariates is more comprehensive than that of most studies, some factors such as personality or undocumented health concerns, may nonetheless contribute to unmeasured confounding. Per-protocol analysis was not conducted due to the models' poor fit for predicting treatment switching and the lack of necessary variables needed to accurately capture the complexity of the treatment switching mechanism. Finally, we did not evaluate different statin types, dose variations, or duration of statin use in this analysis due to complexities arising from changing prescribing trends and adherence patterns over time.

Future studies should implement emulated trial designs on large-scale datasets with extended follow-up periods, employing rigorous methodologies to investigate the impact of statins on dementia. Identifying both the neuropsychological and sociodemographic mechanisms underlying treatment censoring will enable the application of per-protocol analyses using IPCW, providing insights into the causal relationship between continued statin use and dementia outcomes. In addition, it is essential to explore distinct subcategories, such as the dosage and type of statins, to determine if these factors differentially affect the risk of developing dementia.

In conclusion, this study is the first emulated trial design that aimed to assess the potential effect modification of sociodemographic factors on the association of statin initiation on dementia incidence. No significant effect modification of sociodemographic factors on the association between statin initiation and dementia was observed.

ACKNOWLEDGMENTS

We extend our gratitude to the Kaiser Permanente members, whose participation in the research program has made this project possible. This study was supported by the National Institutes of Health–National Institute on Aging (NIH-NIA) grant RF1AG069259. The Research Program on Genes, Environment, and Health (RPGEH) cohort was funded by the Wayne and Gladys Valley Foundation, the Ellison Medical Foundation, the Robert Wood Johnson Foundation, Kaiser Permanente Northern California, and the Kaiser Permanente National and Regional Community Benefit Programs. The Genetic Epidemiology Research on Adult Health and Aging (GERA) cohort was funded by NIH-NIA grant RC2AG036607.

CONFLICT OF INTEREST STATEMENT

S.Z. has received support for the present work through the National Institutes of Health–National Institute on Aging (NIH-NIA) grant RF1AG069259 and holds personal stock in Eli Lilly and Company, Abbvie, Inc., Abbott Laboratories, CRISPR Therapeutics, and Gilead Sciences LLC. J.W. has received support through funding from the NIH-NIA. E.L.F. has received funding from the NIH-NIA (F31AG085965 and T32AG049663) and travel support from the Society for Epidemiologic Research (SER). T.J.M. works as a staff scientist for an institution supported by NIH-NIA grant RF1AG069259. R.W. has received funding from NIH grants and the Alzheimer's Association, consulted for Genentech, and serves on advisory boards for MIDUS, ADD Health, EDIC Observational Safety Monitoring Board, and DPPOS Observational Safety Monitoring Board. N.R. has received funding from NIH grants. R.K. has received funding from the NIA through grant support to his institution. C.S. has received support through funding from the NIA (NIH-NIA grant RF1AG069259) paid to her institution. M.M.G. has received funding from NIH-NIA and the Robert Wood Johnson Foundation, royalties from Oxford University Press, honoraria for lectures from Harvard University and the University of Wisconsin, and serves on the advisory board for the Study of Women Across the Nation OSMB. P.G. receives funding from NIH-NIA, with payments made to her institution, and serves as an unpaid Associate Editor of *Alzheimer's & Dementia*. Author disclosures are available in the Supporting Information.

ROLE OF THE FUNDER/SPONSOR

The National Institutes of Health (NIH) had no role in the conduct of the study; collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

CONSENT STATEMENT

All human subjects provided written informed consent. Human subjects approval for this study was granted by the University of California San Francisco Institutional Review Board (IRB), the Boston University IRB, and the Kaiser Permanente Northern California and Mid-Atlantic States IRBs.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Choi M, Zimmerman SC, Jiang C, et al. Sociodemographic modifiers of effects of statin initiation on dementia incidence: An emulated trial design in a large health care member population with 10+ years of follow-up. *Alzheimer's Dement*. 2025;21:e14627. https://doi.org/10.1002/alz.14627