Brief report

# Alzheimer incidence and prevalence with and without asthma: A Medicare cohort study

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**Background: International data suggest that asthma, like other inflammatory diseases, might increase Alzheimer disease (AD) risk.**

**Objective: We sought to explore risk pathways and future mitigation strategies by comparing diagnostic claims-based AD incidence and prevalence among US patients with asthma with those without asthma.**

**Methods: This cohort study included a national Medicare 20% random sample (2013-2015). Adult patients with asthma with more than 12 months continuous Medicare were compared with subjects without asthma overall and as matched. Asthma was defined by 1 inpatient or 2 outpatient codes for asthma. The main outcomes were 2-year incident or prevalent AD defined by *International Classification of Diseases, Ninth Revision* code 331.0 or *Tenth Revision* code G30.0, G30.1, G30.8, or G30.9.**

**Results: Among 5,460,732 total beneficiaries, 678,730 patients were identified with baseline asthma and more often identified as Black or Hispanic, were Medicaid eligible, or resided in a highly disadvantaged neighborhood than those without asthma. Two-year incidence of AD was 1.4% with asthma versus 1.1% without asthma; prevalence was 7.8% versus 5.4% (both $P \leq .001$). Per 100,000 patients over 2 years, 303 more incident AD diagnoses occurred in those with asthma, with 2,425 more prevalent cases ($P < .001$). Multivariable models showed that asthma had greater odds of 2-year AD incidence (adjusted odds ratio, 1.33 [95% CI, 1.29-1.36]; matched 1.2 [95% CI, 1.17-1.24]) and prevalence (adjusted odds ratio, 1.48 [95% CI, 1.47-1.50]; matched 1.25 [95% CI, 1.22-1.27]).**

**Conclusions: Asthma was associated with 20% to 33% increased 2-year incidence and 25% to 48% increased prevalence of claims-based AD in this nationally representative US sample. Future research should investigate risk pathways of underlying comorbidities and social determinants as well as whether there are potential asthma treatments that may preserve brain health. (J Allergy Clin Immunol 2024;154:498-502.)**

***Key words:*** *Asthma, Alzheimer, systemic inflammation, cohort study, claims-based data, observational study*

## INTRODUCTION

Asthma affects more than 300 million patients worldwide[1] and airway inflammation is central. Until recently, pathophysiology and treatment studies in asthma have focused on airway dysfunction, yet evidence indicates systemic effects, including metabolic and cardiovascular risks.[2] New data also suggest that changes in brain health associate with systemic inflammation in asthma.[3-5]

Research examining effects of asthma on the brain, including increased Alzheimer disease (AD) risk, is limited. A case-control study from Taiwan using nationwide claims reported increased AD risk in asthma (hazard ratio, 2.6; 95% CI, 1.7-4.0),[6] but matched only for age and sex, leaving unaddressed questions regarding other sociodemographic characteristics. Another Taiwanese study reported an asthma association with any dementia diagnoses, demonstrating amplified risk with frequent exacerbations, suggesting inflammatory dose relationships.[7] Finally, we compared brain magnetic resonance images, noting significantly greater neurodegeneration in those with asthma versus controls.[4,5]

Parallels between inflammation and AD have been reported in rheumatoid arthritis (RA).[5] Moreover, use of anti–TNF-α biologic therapies in RA has been associated with decreased risk of AD (anti-TNF and AD odds ratio [OR], 0.45, 0.23, 0.90).[8] Despite distinctions, recent evidence shows that, like RA, asthma's underlying inflammation can affect the structure and function of the central nervous system, representing potential biologic pathways that may increase AD risk.[9-13]

The possibility that asthma is a risk factor for AD has public health importance because asthma affects 10% of the US population, with greater prevalence among women, and populations identifying as Black and with low socioeconomic status. Our objective was to assess associations between

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*Abbreviations used*
AD: Alzheimer disease
ADI: Area deprivation index
*ICD-9-CM*: *International Classification of Diseases, Ninth Revision, Clinical Modification*
OR: Odds ratio
RA: Rheumatoid arthritis

diagnostic claims-based AD incidence and prevalence in Medicare patients with asthma versus without asthma while considering sociodemographic characteristics and comorbidities to begin generating hypotheses on risk pathways and potential mitigation strategies.

## RESULTS AND DISCUSSION

### Population characteristics

Among this nationally representative cohort of 5,460,732 Medicare beneficiaries, compared with patients without asthma, the 678,730 patients with baseline asthma more often identified as Black, Hispanic, and as having prior Medicaid eligibility (Fig 1, and see Table I). Patients with asthma were also more likely to live in the most disadvantaged neighborhood quintile and had more cardiovascular disease and comorbidity.

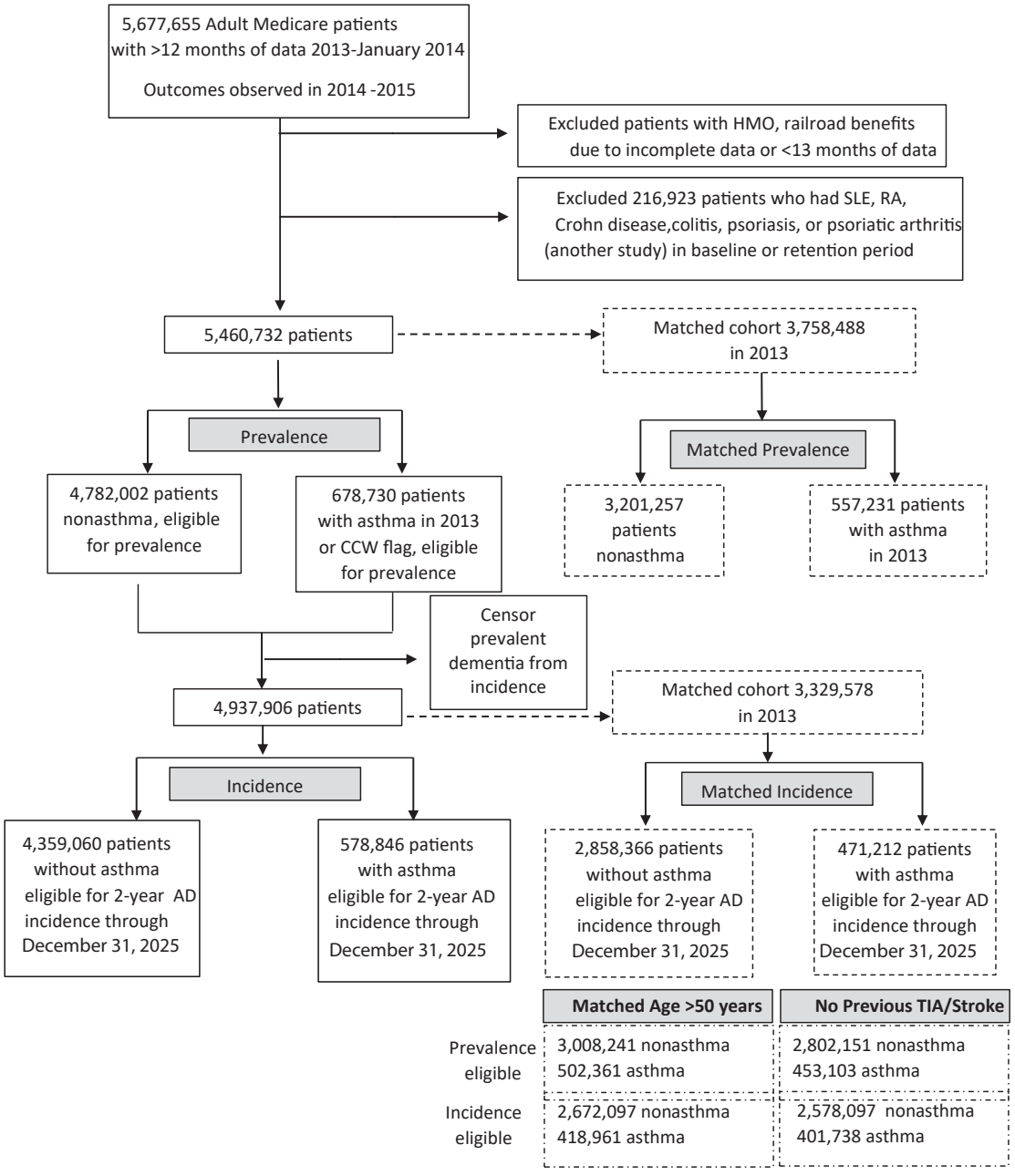


**FIG 1.** Consort diagram of Medicare study population (inclusion and exclusion). *CCW*, Chronic Conditions Data Warehouse; *HMO*, Health Maintenance Organization.

**TABLE I.** Characteristics of Medicare beneficiaries with and without asthma (full cohort: N = 5,460,732; matched: N = 3,758,488)

| Characteristics | Without asthma full cohort (n = 4,782,002) | Asthma full cohort (n = 678,730) | Without asthma matched (n = 3,201,257) | Asthma matched (n = 557,231) |
|---|---|---|---|---|
| Age (y), mean ± SD | 70.65 ± 12.4 | 69.60 ± 13.7 | 71.42 ± 12.3 | 69.53 ± 13.8 |
| Sex | | | | |
| Female | 2,555,483 (53.4) | 459,248 (67.7) | 1,829,607 (57.2) | 385,005 (69.1) |
| Male | 2,226,519 (46.6) | 219,482 (32.3) | 1,371,650 (42.9) | 172,226 (30.9) |
| Race/ethnicity* | | | | |
| White | 4,064,418 (85.0) | 563,364 (83.0) | 2,770,891 (86.6) | 465,099 (83.5) |
| Black | 428,271 (9.0) | 74,456 (11.0) | 278,234 (8.7) | 62,088 (11.1) |
| Asian | 76,590 (1.6) | 10,886 (1.6) | 37,066 (1.2) | 7,144 (1.3) |
| American Indian | 25,169 (0.5) | 4,958 (0.7) | 13,844 (0.4) | 3,648 (0.7) |
| Unknown | 105,914 (2.2) | 11,090 (1.6) | 55,769 (1.7) | 8,148 (1.5) |
| Hispanic | 81,640 (1.7) | 81,640 (1.7) | 45,453 (1.4) | 11,104 (2.0) |
| Medicaid ever | 845,906 (17.7) | 201,020 (29.6) | 614,971 (19.2) | 170,192 (30.5) |
| Medicare disability | 1,095,203 (22.9) | 244,574 (36.0) | 725,502 (22.7) | 204,828 (36.8) |
| ADI disadvantage | | | | |
| Most disadvantage 81-100 | 635,338 (14.0) | 107,748 (16.7) | 462,238 (14.4) | 95,943 (17.2) |
| Baseline visits, mean ± SD | 8.34 ± 8.9 | 14.14 ± 12.6 | 10.04 ± 9.3 | 14.95 ± 12.8 |
| Elixhauser score, mean ± SD | 2.11 ± 6.7 | 3.25 ± 7.9 | 2.11 ± 6.7 | 3.26 ± 7.9 |
| Chronic kidney disease | 835,833 (17.5) | 205,717 (30.3) | 670,023 (20.9) | 179,128 (32.2) |
| COPD | 753,133 (15.8) | 8.34 [8.9] | 596,643 (18.6) | 336,524 (60.4) |
| Diabetes mellitus (baseline) | 1,393,197 (29.1) | 310,699 (45.8) | 1,039,755 (32.5) | 260,836 (46.8) |
| AMI/IHD/CHF | 1,704,736 (35.7) | 391,603 (57.7) | 1,314,016 (41.1) | 331,693 (59.5) |
| Baseline AD | 173,015 (3.6) | 37,498 (5.5) | 139,957 (4.4) | 32,132 (5.8) |
| Baseline any dementia | 422,942 (8.8) | 99,884 (14.7) | 340,242 (10.6) | 85,935 (15.4) |

Data are presented as n (%) unless indicated otherwise. Asthma *ICD-9-CM* codes: 493.00, 493.01, 493.02, 493.10, 493.11, 493.12, 493.20, 493.21, 493.22, 493.81, 493.82, 493.90, 493.91, and 493.92.In the full cohort, there are missing values for some matching covariates and the cohort with complete data totaled 3,774,626 (without asthma, n = 3,216,991; asthma, n = 557,635). Using complete data for all matching covariates resulted in the numbers shown. Numbers of unmatched case patients were small compared with the overall sample size.

*AMI*, Acute myocardial infarction; *CHF*, chronic heart failure; *COPD*, chronic obstructive pulmonary disease; *IHD*, ischemic heart disease.

*Race/ethnicity defined by Research Triangle Institute variables.

## Relationship of asthma to AD

Two-year unadjusted incidence of AD was 1.4% with asthma versus 1.1% without asthma ($P \leq .001$; Table II). Per 100,000 patients over 2 years, 303 more incident AD cases occurred in those with asthma (1,408 asthma vs 1,105 without asthma; $P < .001$). Two-year unadjusted incidence of any dementia was 6.5% with asthma and 4.4% without asthma ($P \leq .001$; Table II). Per 100,000 patients over 2 years, 2,060 more incident dementia cases occurred in those with asthma.

The overall prevalence of AD was 7.8% with asthma versus 5.4% without asthma ($P \leq .001$) and 2425 more prevalent cases were found in those with asthma (7,834 asthma vs 5,409 without asthma; $P < .001$).

Prevalence of any dementia was 20.3% with asthma versus 12.9% without asthma (both $P \leq .001$; Table II). Prevalence per 100,000 showed an excess of 7,368 dementia cases in those with asthma ($P < .001$).

In multivariable models including age, sex, race, and ethnicity, those with asthma had greater odds of 2-year AD incidence (adjusted OR, 1.33 [95% CI, 1.29-1.36], full Model 1; Table III). Likewise, asthma associated with higher AD prevalence (adjusted OR, 1.44 [95% CI, 1.42-1.46], Model 1).

Mediation testing showed that indirect effects were statistically significant, and proportions mediated were the highest in chronic obstructive pulmonary disease and cardiac disease. Thus, we treated them as mediators, not adjusted in analyses. Chronic kidney disease, diabetes, and Elixhauser score mediated less than 30% and were considered covariates. Exact matching balanced covariates: age, sex, race/ethnicity, Medicare disability, area deprivation index (ADI) disadvantage quintiles, baseline visits versus median, Medicaid ever, chronic kidney disease, diabetes, and Elixhauser score[14] versus median. Differences pre- and post-matching were small for each covariate. Therefore, matched cohorts were representative. In addition, standardized mean differences for all covariates and 2-way interactions were 0, indicating covariate balancing. The asthma marginal OR for 2-year AD incidence was 1.20 (95% CI, 1.17-1.24) (Table III, Model 2). AD prevalence was 1.25 (95% CI, 1.22-1.27), suggesting that asthma increases the risk of AD. Sensitivity analyses excluding for those younger than 50 years or baseline transient ischemic attack/stroke were similar (Table III, *right*).

Our analysis of the Medicare cohort suggests that asthma is associated with significantly increased population risk of AD. We found a 20% to 33% higher AD incidence and 25% to 48% higher AD prevalence.

These data from a large, nationally representative US sample support previous international observations that AD occurs more frequently in asthma.[6] Findings parallel previous RA studies showing links to AD, pointing to potential biologic pathways that may be modifiable sequelae of systemic inflammation.[8] Our

**TABLE II.** Observed incidence and prevalence of AD and any dementia in patients with asthma vs patients without (n = 5,406,732)

| Incidence/prevalence | Nonasthma, n = 4,782,002 (4,359,060), n (%) | Cases/100,000 non-asthma, n (95% CI*) | Asthma, n = 678,730 (578,846), n (%) | Cases/100,000 asthma, n (95% CI*) | *P* |
|---|---|---|---|---|---|
| 2-y Alzheimer incidence | 48,186 (1.1) | 1,105 (1,096-1,115) | 8,153 (1.4) | 1,408 (1,378-1,439) | † |
| Ever Alzheimer prevalence | 258,635 (5.4) | 5,409 (5,388-5,429) | 53,175 (7.8) | 7,834 (7,771-7,899) | † |
| 2-y any dementia incidence | 193,314 (4.4) | 4,435 (4,415-4,454) | 37,594 (6.5) | 6,495 (6,431-6,558) | † |
| Ever dementia prevalence | 616,256 (12.9) | 12,887 (12,857-12,917) | 137,478 (20.3) | 20,255 (20,160-20,351) | † |

*Case/100,000 CIs by the Clopper-Pearson test.
†The $\chi^2$ test ($P < .001$).

**TABLE III.** OR of AD 2-y incidence and prevalence in asthma vs without asthma

| Incidence/prevalence | Unadjusted asthma | Model 1: Full cohort age, sex, race/ethnicity controls | Model 2: Matched* cohort plus SES, visits, disability, comorbidity | Model 2S: Matched sensitivity ≥50 y† and excluding baseline TIA/stroke‡ |
|---|---|---|---|---|
| AD 2-y incidence OR asthma vs without asthma, OR (95% CI) | 1.28 (1.25-1.31) | 1.33 (1.29-1.36) | 1.2 (1.17-1.24) | 1.2 (1.17-1.24) [1.23 (1.19-1.28)] |
| AD prevalence OR asthma vs without asthma, OR (95% CI) | 1.49 (1.47-1.50) | 1.48 (1.47-1.50) | 1.25 (1.22-1.27) | 1.25 (1.23-1.27) [1.25 (1.22-1.28)] |

Generalized linear models: Model 1 multivariable logistic regression analyses adjusted for age categories (18-33, 34-49, 50-64, 65-79, 80+ y), sex, race, ethnicity by Research Triangle Institute definition in the full cohort; Model 2 used a matched cohort matching on all Model 1 Plus: Medicare disability indicator, ADI disadvantage ranking quintiles, Medicaid ever status (SES proxy), baseline visits above or below median, chronic kidney disease, diabetes, and composite Elixhauser comorbidity score above or below median. Model 2S sensitivity analyses used matched cohort and Model 2 restricted to age ≥50 y and absence of baseline TIA/stroke.
*SES*, Socioeconomic status; *TIA*, transient ischemic attack.
*Incidence model: 16,891 and 424 units were unmatched and discarded in without asthma and asthma cohorts after exact matching. Prevalence model: 15,734 and 404 units were unmatched.
†Incidence model: 12,627 and 238 units were unmatched. Prevalence model: 11,461 and 214 units were unmatched.
‡Incidence model: 17,579 and 423 units were unmatched. Prevalence model: 16,751 and 400 units were unmatched.

analyses do not indicate, nor do we propose, that asthma alone causes AD, but rather that asthma may contribute to elevated AD risk, together with other factors such as vascular dysfunction, hypoxia, medications, and genetics. Because the systemic inflammation of asthma is modifiable, our findings suggest that early steps toward risk reduction may include aggressively treating asthma airway inflammation to diminish systemic effects.

We previously showed that airway inflammation affects brain structure and function. We reported extensive changes in white matter microstructure in asthma, characteristic of neurodegeneration that correlated with biomarkers of reactive glia. Although precise mechanisms are undefined, findings raise the possibility that systemic asthmatic inflammation may be a treatable cofactor to potentially mitigate some AD risk.

Despite strengths of a nationally representative sample to examine relationships between asthma and AD, there are limitations. First, Medicare populations, including fee-for-service Medicare, may not be generalizable, because they may overrepresent disability, low socioeconomic status, and age 65 years or more. Given older age in Medicare, findings may not represent all populations. Second, claims-based studies may misclassify, although validated algorithms were used to minimize misclassification.[15,16] Third, we acknowledge that patients may disenroll, die, or be lost to follow-up (4%-9% annually in fee-for-service Medicare).[17] Nonetheless, analyses provide meaningful estimates suggesting elevated AD risk and generating hypotheses for future inflammation-focused research.

Adjusted for age, sex, race, and ethnicity, asthma was associated with 20% to 33% increased 2-year AD incidence. AD prevalence was 25% to 48% higher in patients with asthma than in those without. Future research should investigate timing, and pathway analysis of risk pathways including comorbidities and adverse social determinants, as well as potential protective anti-inflammatory asthma treatments to preserve brain health.

## DISCLOSURE STATEMENT

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**Key messages**

- **Recognizing links between inflammation and neurodegeneration, and work by our group showing greater neurodegeneration in asthma, we aimed to examine epidemiologic associations between asthma and AD in a representative US population.**
- **Findings highlight increased incidence (adjusted OR, 1.33 [95% CI, 1.29-1.36]) and prevalence (adjusted OR, 1.48 [95% CI, 1.47-1.50]) of AD in asthma among 5 million US Medicare patients.**
- **Asthma may associate with AD risk. Future studies will be needed to investigate biologic pathways of vascular dysfunction, hypoxia, and immune, genetic, or treatment factors that may be modifiable in systemic asthmatic inflammation.**

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## METHODS

### Study sample

This cohort study examined a nationwide 20% US sample of Medicare adults with or without asthma to compare the 2-year AD incidence from 2014 to 2015 (events occurring in a population [numerator] divided by a population at risk over that time [denominator][E1] without baseline AD or dementia). Prevalence of AD and dementia (existing cases in a given population at a certain time)[E1] were assessed through December 31, 2015. Inclusion required patients to be 18 years or older, have more than 12 months of continuous Medicare parts A and B (2013) coverage, and being alive from January 1, 2014, through the end of data or December 31, 2015, to calculate 2-year incidence. Those with health maintenance organization or railroad benefits were excluded (incomplete claims).

Asthma was defined as 1 inpatient or 2 outpatient claims in 2013 using the *International Classification of Diseases, Clinical Modification* (*ICD-9-CM*) codes per Medicare Chronic Conditions Data Warehouse algorithms (asthma *ICD-9-CM* codes: 493.00, 493.01, 493.02, 493.10, 493.11, 493.12, 493.20, 493.21, 493.22, 493.81, 493.82, 493.90, 493.91, and 493.92.).[E2,E3] The without asthma cohort included all patients without asthma or well-recognized inflammatory diseases under investigation elsewhere: RA, lupus, psoriasis/psoriatic arthritis, or inflammatory bowel disease. The Institutional Review Board approved this study with a waiver of consent.

### Outcome measures

Our primary outcome was 2-year incident or prevalent AD by *ICD-9-CM* code 331.0 or *ICD-10* code G30.0, G30.1, G30.8, or G30.9. As a secondary outcome, we report incidence and prevalence of any dementia as per Chronic Conditions Data Warehouse algorithms.[E3]

### Additional variables

We examined baseline age, sex, race, ethnicity, comorbidities, and sociodemographic characteristics as per AD literature.[E4] Race and ethnicity categories used the Research Triangle definitions[E5]: White, Black, Asian, Native American, Unknown, and separate Hispanic ethnicity. We used the ADI,[E6] a validated composite of 17 neighborhood-level factors (eg, income, education, employment, and housing quality)[E7] across 9-digit ZIP codes, to define social and neighborhood-level disparities. Higher ADI predicts adverse health outcomes.[E7,E8] Baseline comorbidities related to asthma and vascular health were examined as potential mediators, hypothesizing that inflammation drives relationships between asthma and AD mediated by comorbidities. Our analysis data set had indicators but lacked AD or death dates.

### Statistical analysis

Beyond descriptive statistics, 2-year incidence and prevalence were calculated as observed and as cases per 100,000 (Clopper-Pearson CIs). Patients with codes for AD or dementia before 2014 were excluded from incidence analyses. Age, sex, race, ethnicity, disability status, neighborhood ADI quintile, baseline visit utilization, and socioeconomic status by Medicaid eligibility were considered important confounders or prognostics on the basis of AD literature.[E4] We tested mediation effects of each comorbidity.[E9] Comorbidities with significant indirect effects and proportions mediated by more than 30% were considered mediators.[E10]

To test our hypothesis that AD increases in asthma, we performed logistic regression adjusting age, sex, and race/ethnicity, reporting OR and 95% CIs given AD is a rare outcome. Next, we used exact matching on known confounding and prognostic covariates, which requires few assumptions. Multivariable logistic regression modeled 2-year AD incidence and prevalence through December 31, 2015, including matching covariates and exact matching weights. G-computation with cluster-robust variance estimated the marginal asthma OR and 95% CIs. Sensitivity and subgroup analyses examined asthma's effect excluding for those younger than 50 years, previous baseline ischemic transient ischemic attack/stroke, and tested interactions with asthma. Secondary mediation analyses were exploratory and hypothesis-generating. All analyses used the R software including mediation, MatchIt, and marginal effects packages (version 4.1.3; Vienna, Austria).

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