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RESEARCH ARTICLE

Regional variability of the impact of cardiometabolic diseases on incident dementia in United States Medicare beneficiaries

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Abstract

INTRODUCTION: Understanding the impact of cardiometabolic diseases (CMDs) on dementia risk can inform primary preventative measures.

METHODS: We leveraged a nationwide, population-based Medicare dataset of 20,789,037 beneficiaries (756,321 with incident dementia and 20,032,716 controls) from 2017 to compute the individual and combined population attributable fractions (PAFs) of dementia attributed to eight CMDs, adjusted for age, sex, and race. We mapped PAFs at the county level to investigate the geospatial patterns of CMD burden on dementia across the United States.

RESULTS: The nationwide combined weighted PAF for the eight CMDs was 37% overall, with hypertension (9.6%), ischemic heart disease (6.7%), and chronic heart failure (5.7%) associated with the greatest attributable fractions of dementia cases. The greatest fraction of county-level dementia cases attributed to CMDs were in the Southeastern United States.

DISCUSSION: A substantial proportion of incident dementia cases in the United States can be attributed to CMDs, especially in the Southeastern United States.

KEYWORDS
Alzheimer's disease, cardiometabolic diseases, dementia, geographic information systems, geospatial analysis, population attributable risk, potential impact fraction, risk factor analysis

Highlights

- Investigated the combined effect of cardiometabolic diseases (CMDs) on dementia.
- Used novel geospatial techniques to map the burden of dementia attributed to CMDs.
- If eight CMDs are mitigated, 37% of incident dementia cases could be eliminated.
- Identified regions of the United States with high CMD burden on dementia.

1 | BACKGROUND

Dementia is a diagnosis associated with a heterogeneous set of primarily neurodegenerative pathologies and characterized clinically by progressively worsening cognitive dysfunction and behavioral impairment.[1] Dementia is the seventh leading cause of death and globally a major cause of disability and dependency among older adults.[2] Because the population of Americans 65 years of age and older is projected to increase, neurodegenerative diseases like dementia will become more common, and this will have significant economic and societal impacts.[3]

Dementia likely develops as a result of intrinsic and extrinsic risk factors.[4–7] Notable risk factors include having fewer social contacts in early and midlife,[8,9] lack of physical activity,[10–13] unhealthy dietary habits,[14,15] current cigarette smoking or heavy smoking in midlife,[16–20] and air pollution.[21–25] Cardiometabolic diseases (CMDs), specifically diabetes, hypertension, hyperlipidemia, heart disease, and stroke, have been individually identified as risk factors for dementia.[26–30] Many of these factors are likely to have cumulative effects on dementia risk; however, few studies have examined the combined effect of these multiple modifiable risk factors.[31–35] Moreover, in a culturally diverse country like the United States, regional variations in CMDs likely contribute differentially to disease risk.

Geographic information systems (GIS) provide novel and powerful approaches to investigate spatial patterns of health and disease, which can help to direct targeted prevention efforts. Use of GIS to investigate geospatial risk factors for dementia has been limited. Most dementia studies using GIS approaches have focused on investigating geographic patterns of dementia-related mortality[36–39]; yet, geographic patterns of incidence, rather than mortality, are important for understanding disease etiology. Therefore, given the importance of CMDs on dementia risk, geospatial analytic techniques elucidate the geospatial burden of dementia attributed to CMDs and can inform public health measures.

In this study, we investigated the individual and cumulative effects of CMDs on dementia burden in the Medicare population using novel GIS techniques and the geospatial patterns of the combined effect of CMDs on incident dementia to identify spatial risk clusters of dementia due to CMDs.

RESEARCH IN CONTEXT

1. **Systematic review**: We reviewed literature in PubMed and found that cardiometabolic diseases (CMDs) are critical risk factors for dementia that contribute pathology that enhances symptomatology and may contribute to disease pathophysiology. Studies investigating the combined effect of CMDs on incident dementia and identifying regions that have greater burden dementia due to CMDs are needed.
2. **Interpretation**: A substantial portion of incident dementia cases in the Medicare population could be eliminated if eight CMDs are mitigated. CMDs disproportionately affect dementia burden in the Southern United States. Interventions that reduce hypertension, ischemic heart disease, and chronic heart failure would have the greatest impact on reducing dementia rates.
3. **Future directions**: The geospatial concentration of risk of dementia attributed to CMDs in the region of the country with the highest levels of air pollution (e.g., particulate matter) suggests that some of this excess risk may be mediated by environmental risk factors.

2 | METHODS

2.1 | Standard protocol approvals, registrations, and patient consents

The St. Joseph's Hospital and Medical Center Institutional Review Board, the Human Research Protection Office at Washington University in St. Louis, and the Centers for Medicare & Medicaid Services (CMS) approved this study, which was deemed exempt, as it does not meet the definition for human subject research.

2.2 | Study design and cohort

To conduct this study, we used claims data from Medicare, the only nationwide, population-based health care program in the United States. Eligible beneficiaries were identified from the Medicare Beneficiary Annual Summary File claim data from 2017, which includes enrollment information for all Medicare beneficiaries as well as demographic information, including date of birth for calculation of age, sex, race/ethnicity, and Federal Information Processing Series for United States state and county residence. To be eligible for this study, individuals had to be 67 to 110 years of age, enrolled in Medicare Part A and/or B without Part C (Medicare Advantage/health maintenance organization) coverage, and a United States resident within the 50 states or the District of Columbia in 2017 (Figure 1).

2.3 | Assessment of dementia

Incident dementia cases included all study-eligible beneficiaries who were identified in the Chronic Conditions Warehouse (CCW) using their algorithm for Alzheimer's disease and Related Disorders or Senile Dementia (Dementia) in 2017, but no prior year. The CCW identified beneficiaries with chronic conditions with an algorithm that uses specific diagnosis and procedure codes found on selected types of claims within a specified lookback (reference) period.[40] For dementia, the algorithm required beneficiaries to have at least one inpatient, skilled nursing facility (SNF), home health, Part B institutional, or

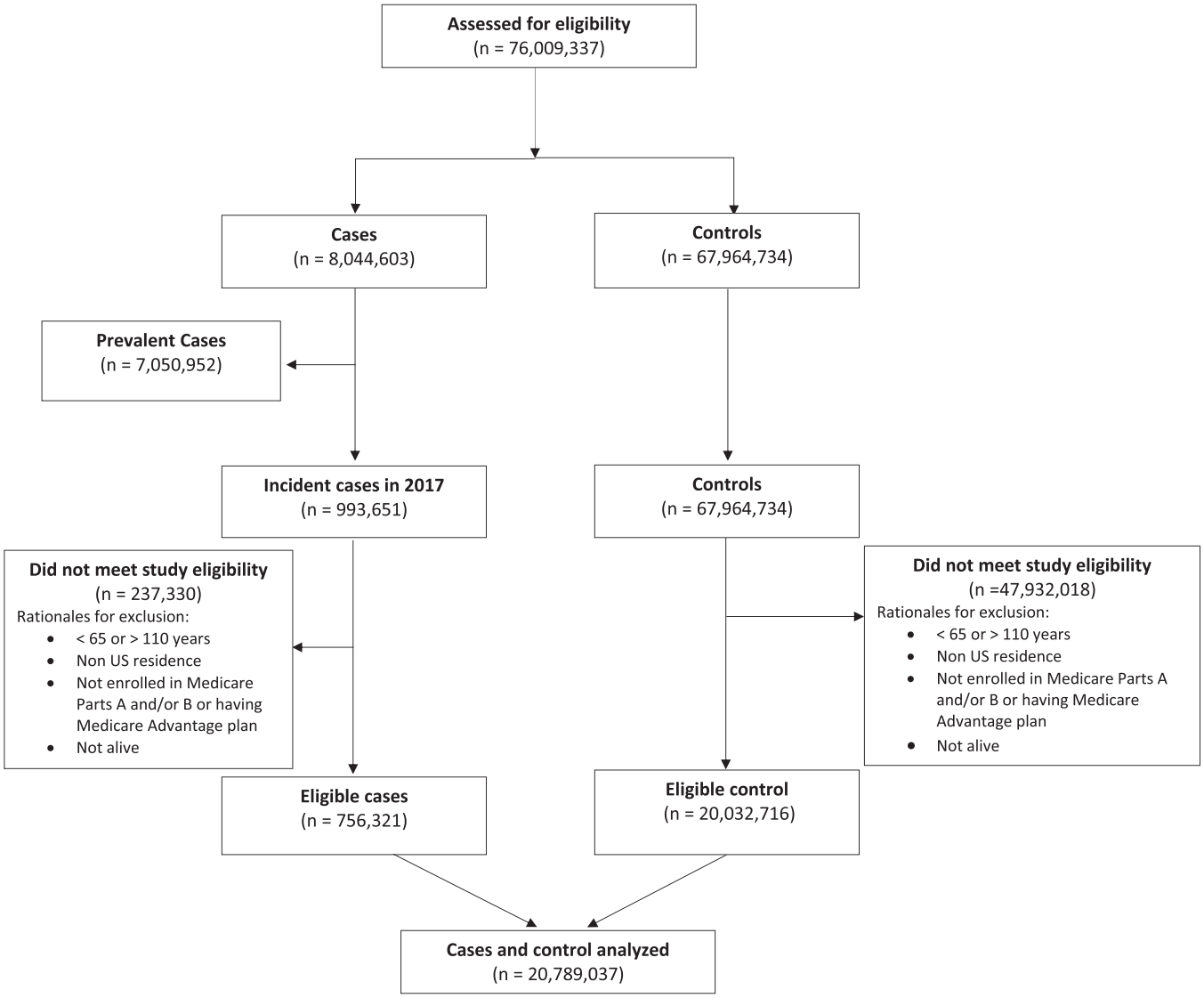

FIGURE 1 Diagram of cases and controls included for the dementia study cohort. The figure shows the size of the CCW dataset and rationale for those who were excluded from the final cohort. Eligibility was determined from the 2017 beneficiaries enrollment file. CCW, Chronic Condition Warehouse.

Part B non-institutional (carrier) claims with a related International Classification of Diseases, Ninth Revision (ICD-9) or Tenth Revision (ICD-10) code in any position during a 3-year reference period (eTable 1).[41] Controls were beneficiaries with no codes for dementia in 2017 or prior years. Beneficiaries that met the CCW algorithm for dementia before 2017 were excluded.

2.4 | Assessment of cardiometabolic diseases

We defined CMDs as diabetes, chronic heart failure, atrial fibrillation, ischemic heart disease, acute myocardial infarction, stroke/transient ischemic attack, hypertension, and hyperlipidemia.[42] Our exposure of interest was the occurrence of CMDs before incident dementia diagnosis. Using the CCW algorithm,[41] beneficiaries were identified as "exposed" if they met the CCW algorithms for a CMD diagnosis prior to meeting the criteria for dementia. For the CMD variables we included in our study, CCW used a 1-year lookback ascertainment window for diagnosis and procedure codes to identify stroke, acute myocardial infarction, atrial fibrillation, hyperlipidemia, and hypertension, and a 2-year reference period for chronic heart disease, ischemic heart disease, and diabetes (eTable 2).

2.5 | Assessment of covariates

We obtained demographic information (age, sex, and race/ethnicity) from the Medicare Beneficiary Annual Summary File. We classified race into six categories (non-Hispanic White, non-Hispanic Black, Hispanic, Asian/Pacific Islander, Native American, and other) and age into

seven age groups (67–69, 70–74, 75–79, 80–84, 85–89, 90–94, and 95 years of age or older). The seven age groups provided sufficient sample size to compute the standardized incidence ratios (SIRs) of dementia and standardized prevalence ratios (SPRs) of CMDs at the county level and allowed stratified analyses. Age was modeled as a continuous variable for our odds ratios (ORs) and population attributable fractions (PAFs) computation as described below. In addition, we used the area deprivation index (ADI),[43,44] a composite measure that uses 17 census metrics capturing education, employment, income, poverty, and housing characteristics to assess health disparities. We linked this to the beneficiaries at the census-track level.

2.6 | Population attributable fractions

We used descriptive statistics to examine the univariate distribution of demographic variables and each of the eight CMDs. We conducted logistic regression to examine the association between each of the eight risk factors and dementia while adjusting for age (continuous), sex (male and female), and race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, Asian/Pacific Islander, Native American, and other). We then calculated the PAFs[31–34,45,46] and the 95% confidence intervals (CIs) for the eight individual risk factors using the graphPAF function in R, which implements the method for estimating PAFs for case-control studies.[47]

To calculate the combined contribution of the eight risk factors to the population burden of dementia, we calculated communality (clustering of risk factors) to adjust for risk factor overlap.[46] We calculated the pairwise tetrachoric correlation between all eight risk factors. Next, we conducted a principal components analysis (PCA) on the tetrachoric correlation matrix, and retained eigenvalues greater than 1 in order to maintain eigenvectors that hold the most information about the data distribution,[31] and calculated communality as the sum of the squares of these factor loadings. We then weighted each risk factor as follows:

$$\text{Weight } (W) = 1 - \text{communality}$$

Next, we calculated the combined adjusted PAF[31]:

$$\text{Combined PAF} = 1 - [(1 - W_1 * \text{PAF1})(1 - W_2 * \text{PAF2})(1 - W_3 * \text{PAF3}) \ldots]$$

Finally, we estimated the adjusted PAF for each individual risk factor (e)[31]:

$$\text{Adjusted PAF}_e = \frac{\text{PAF}_e}{\sum(\text{PAF}) * \textit{combined}\ \text{PAF}}$$

PAFs were calculated at the national and country levels.

Since a 100% reduction in CMD risk factors is unlikely, we also calculated the potential impact fraction (PIF). The PIF is an estimate of how many fewer incident dementia cases would be expected given a certain percent proportional reduction in the "exposure."[48] In our analysis, we selected a 15% proportional reduction of each risk factor to align our findings with the goal set by the Risk Reduction Subcommittee of the National Alzheimer's Project Act Advisory Council to reduce dementia risk factors 15% by 2030.[49]

Using the impact fraction function within the graphPAF package in R and estimating the PIF,[47,50] we calculated how many fewer incident dementia cases would be expected in the Medicare population given a 15% reduction in each risk factor while adjusting for age, sex, and race/ethnicity. This method uses ORs from the logistic regression, prevalence, and a counterfactual prevalence (a 15% reduction in the prevalence) to compute the adjusted PIF for each of the eight risk factors. As in previous studies, we calculated the combined adjusted PIF considering the weights from the PCA as in the following formula[31]:

$$\text{Combined PIF} = 1 - [(1 - W_1 * \text{PIF}_1)(1 - W_2 * \text{PIF}_2)(1 - W_3 * \text{PIF}_3) \ldots]$$

We conducted several sensitivity analyses. First, we stratified the PAF analyses by demographic characteristics to examine the disease-specific burden of CMDs on dementia. To ensure sufficient sample size for analyses, the disease-specific burden of CMDs on dementia was computed by sex (male and female), race/ethnicity (White and non-White), and age category (67 to 72, 73 to 78, 79 to 84, and 85 and above). Next, we categorized the eight risk factors into upstream (diabetes, hyperlipidemia, and hypertension) and downstream (stroke, chronic heart failure, ischemic heart disease, atrial fibrillation, and acute myocardial infarction) CMDs to examine the differential effect of these two categories on dementia. In addition, given that social disparities in CMDs and dementia are prominent and may arise from various regional sociodemographic factors,[44] we conducted a sensitivity analysis adjusting for ADI in addition to age, sex, and race/ethnicity. Finally, we conducted a comparable analysis of PAFs for the nationwide individual and combined CMDs using 2018 Medicare data to examine the robustness of our results.

2.7 | Computation of standardized incidence ratios of dementia and standardized prevalence ratios of CMDs

We computed county-level sex, race/ethnicity, and age SIRs of dementia in the United States Medicare population by dividing the number of observed incident dementia cases in the Medicare population in 2017 by the expected number of incident dementia cases derived from the incidence rate among the general U.S. Medicare population in 2017. We also calculated the county-level sex, race/ethnicity, and age SPRs of CMDs in the U.S. Medicare population as the number of observed prevalent CMD cases in 2017 divided by the expected number of beneficiaries with prevalent CMD in the general U.S. Medicare population in 2017. We used GeoDa and county-level mapping to create an SIR map of dementia and an SPR map of CMDs. We used spatial smoothing techniques in GeoDa[51] to smooth extreme values by taking into account neighboring values.

2.8 | Spatial correlation of CMDs and incident dementia

We used bivariate local indicators of spatial association to overlay our county-level SPR map of CMD and SIR map of dementia to assess local spatial correlation.[52] This geospatial technique identifies four clustering categories (high dementia–high CMD, low dementia–low CMD, low dementia–high CMD, and high dementia–low CMD). The high–high category represents counties where dementia risk and CMDs risk are both high relative to their means, and the low–low category represents counties where dementia risk and CMDs risk are both low relative to their means; these categories are consistent with a positive correlation between CMDs and dementia. The two discordant (low–high and high–low) categories are inconsistent with a positive correlation.

Most statistical analyses were performed using Stata software (MP 14.2; StataCorp LLC, College Station, TX, USA),[53] ArcMap, GeoDa, and R version 3.6.3 (The R Project for Statistical Computing). Several packages were used in R including graphPAF,[50] tidyverse,[54] doParallel,[55] survival,[56] and polycor.[57] We used spatial correlation analysis (GeoDa)[51] and county-level mapping (ArcMap)[58] to explore the spatial patterns of the combined weighted PAFs of CMDs on incident dementia burden at the county level across the United States. Maps of the county-level PAFs were created first in ArcMap, smoothed in GeoDa, and then finalized in ArcMap. Statistical significance was set at p value < 0.05, and all tests were two-tailed.

3 | RESULTS

There were 20,789,037 beneficiaries in the Medicare population in the United States that were included in this study: 756,321 incident dementia cases (3.6%) and 20,032,716 controls (96.4%) (Figure 1).

Dementia cases were older (mean age 81.6, SD 8.0 vs 75.2, SD 6.7) and had a higher proportion of females compared to controls (59.2% vs 55.6%) (Table 1). Dementia cases had higher proportions of non-Hispanic Black Hispanic, and Native American racial/ethnic groups compared to controls. Among the eight CMD risk factors examined, hypertension was the most common CMD seen among beneficiaries (76.5%), followed by hyperlipidemia (76.1%) and ischemic heart diseases (41.4%).

3.1 | Odds ratios and population attributable fractions

All eight CMD types were positively associated with dementia risk (Table 1). The highest ORs were for stroke at 2.23 (95% CI 2.22–2.25), followed by chronic heart failure (OR 2.12, CI 2.11–2.13) and hypertension (OR 1.78, CI 1.76–1.79). The relationship between hyperlipidemia and dementia had the lowest OR at 1.27 (95% CI 1.26–1.28). Communality, a measure of risk overlap, ranged from 31.4% for stroke to 90.8% for ischemic heart disease (Table 2). The PCA had two components with eigenvalues greater than 1 (eTable 3). The first component, with an eigenvalue of 4.31, explained 56.0% of the total variance and the second, with an eigenvalue of 1.04, explained 44.0% of the total variance. These two principal components differ in their composition, with the first driven by downstream conditions and the second reflecting the upstream conditions.

Nationwide, the combined weighted PAF for the eight CMD risk factors was 37.4% (Table 2). Hypertension, ischemic heart disease, and chronic heart failure individually had the highest PAFs (9.6%, 6.7%, and 5.7%, respectively). Nationally, a 15% proportional reduction in all eight risk factors would reduce dementia cases in the population by an estimated 6.6%. In a sensitivity analysis stratifying the disease-specific burden of CMDs on dementia based on demographics, the combined weighted PAF was slightly higher for males (38.0%, 95% CI 33.9%–42.2%) compared to females (36.8%, 33.9%–39.7%), but we observed overlapping CIs (eTable 4). Similarly, although we observed a slightly higher PAF for non-White beneficiaries (PAF = 38.4%, 95% CI 32.2%–44.7%) compared to White beneficiaries (PAF = 36.7%, 95% CI 34.1%–39.3%), the CIs overlapped. There was a lower PAF for ages 79–84 (PAF = 38.0%, 95% CI 33.6%–42.4%) and ages 85 and older (PAF = 18.6%, 95% CI 15.6%–21.6%) compared to ages 67–72 (PAF = 44.4%, 95% CI 37.9%–51.0%) or 73–78 (PAF = 42.6%, 95% CI 37.7%–47.6%).

In the sensitivity analysis examining the upstream and downstream CMDs, summarized in eTable 5, the combined weighted PAF for the upstream CMDs was 17.1% (95% CI 15.3%–19.0%) and for downstream CMDs was 25.2% (95% CI 23.9%–26.5%). When examining the upstream category independently, the weighted PAFs for diabetes (3.7%), hyperlipidemia (4.2%), and hypertension (9.2%) were similar to the PAFs when combined with the downstream category (3.8%, 4.4%, and 9.6%, respectively). The individual and combined weighted PAFs adjusting for only demographic characteristics were similar to the PAFs adjusted for ADI and demographics (eTable 6). Finally, in the comparable models with Medicare 2018 data, we observed similar PAFs with our estimates from 2017 Medicare data (eTable 7). The nationwide combined weighted PAF for the eight CMD risk factors in the 2018 dataset was 37.6%, with hypertension, ischemic heart disease, and chronic heart failure individually having the highest PAFs (9.6%, 6.7%, and 5.8%, respectively).

3.1.1 | Spatial correlation of CMDs and incident dementia

In the county-level cluster maps of dementia SIRs and CMD SPRs, we observed an overlap of the geographic pattern of risk. Notably, there was a higher incidence of dementia and higher prevalence of CMD in the Southeastern and Southcentral United States and a lower risk of dementia and CMD in the Northern and Western United States (Figure 2). We observed substantial geographic variation of the attributable fraction of CMD on dementia risk (Figure 3). The combined

TABLE 1 Demographic characteristics of incident dementia cases and population controls in Medicare beneficiaries.[a]

Characteristic[b]	Total *N* = 20,789,037	Dementia *N* = 756,321	Control *N* = 20,032,716	OR (95% CI)
Female, *n* (%)	11,581,374 (55.7)	448,037 (59.2)	11,133,337 (55.6)	1.02 (1.01–1.02)
Race/ethnicity, *n* (%)				
White	17,479,631 (84.1)	627,334 (83.0)	16,852,297 (84.1)	1.0 (reference)
Black	1,442,499 (6.9)	63,275 (8.4)	1,379,224 (6.9)	1.42 (1.41–1.43)
Hispanic	1,006,644 (4.8)	38,455 (5.1)	968,189 (4.8)	1.23 (1.21–1.24)
Asian/Pacific Islander	591,363 (2.8)	18,709 (2.5)	572,654 (2.9)	0.91 (0.89–0.92)
Other	173,352 (0.8)	4,870 (0.6)	168,482 (0.8)	0.93 (0.90–0.96)
Native American	95,548 (0.5)	3,678 (0.5)	91,870 (0.5)	1.26 (1.21–1.30)
Age				
Mean (SD)	75.5 (6.9)	81.6 (8.0)	75.2 (6.7)	1.12 (1.12–1.12)
Category, *n* (%)				
65–69	4,680,020 (22.5)	54,752 (7.2)	4,625,268 (23.1)	1.0 (reference)
70–74	6,407,676 (30.8)	116,583 (15.4)	6,291,093 (31.4)	1.06 (1.05–1.07)
75–79	4,356,637 (21.0)	140,048 (18.5)	4,216,589 (21.1)	1.15 (1.13–1.17)
80–84	2,782,191 (13.4)	155,612 (20.6)	2,626,579 (13.1)	1.24 (1.21–1.27)
85–89	1,649,847 (7.9)	151,441 (20.0)	1,498,406 (7.5)	1.29 (1.25–1.33)
90–94	716,221 (3.5)	99,710 (13.2)	616,511 (3.1)	1.27 (1.22–1.32)
95+	196,445 (0.9)	38,175 (5.1)	158,270 (0.8)	1.09 (1.04–1.14)
CMD type, *n* (%)				
Acute myocardial infarction	871,168 (4.2)	64,587 (8.5)	806,581 (4.0)	1.55 (1.53–1.56)
Ischemic heart disease	8,597,509 (41.4)	483,774 (64.0)	8,113,735 (40.5)	1.75 (1.75–1.76)
Atrial fibrillation	2,840,450 (13.7)	207,970 (27.5)	2,632,480 (13.1)	1.66 (1.65–1.67)
Chronic heart failure	4,171,806 (20.1)	334,550 (44.2)	3,837,256 (19.2)	2.12 (2.11–2.13)
Diabetes	6,991,041 (33.6)	346,224 (45.8)	6,644,817 (33.2)	1.52 (1.51–1.52)
Hypertension	15,897,584 (76.5)	680,824 (90.0)	15,216,760 (76.0)	1.78 (1.76–1.79)
Hyperlipidemia	15,828,605 (76.1)	641,292 (84.8)	15,187,313 (75.8)	1.27 (1.26–1.28)
Stroke/transient ischemic attack	2,256,228 (10.9)	208,656 (27.6)	2,047,572 (10.2)	2.23 (2.22–2.25)

Note: The OR is the association between dementia and demographic characteristics, and dementia and each of the eight risk factors while adjusting for age, sex, and race/ethnicity.
Abbreviations: CI, confidence interval; CMD, cardiometabolic disease; OR, odds ratio; SD, standard deviation.
[a]2017 Medicare data.
[b]Percentages may not sum to 100 due to rounding.

effects of CMD on dementia varied by county, ranging from 0% to 63%, with the greatest PAFs in southeastern Texas, Louisiana, Northern Florida, New Jersey, and Michigan (excluding the upper peninsula), and in parts of the Stroke and Rust Belt. CMD attributed far less to dementia risk in the Pacific Northwest, Great Plains, and the Rocky Mountains compared to the rest of the United States. This pattern was also apparent in the bivariate local indicators of spatial association correlation map (based on maps of CMD SPR and dementia SIR), which demonstrated local spatial correlation characterized by high–high clustering (counties with above average dementia and above average CMDs) in the Southeastern and Southcentral United States and low–low clustering (counties with below average dementia and below average CMDs) in the Northern and Western United States (Figure 4).

4 | DISCUSSION

This population-based, case–control, geographic study investigating the individual and cumulative effect of eight modifiable CMD risk factors on dementia burden revealed that a substantial portion of the dementia cases in the Medicare population could be eliminated by reducing the burden of CMD. Eliminating eight CMD risk factors from the population would reduce incident dementia cases among Medicare beneficiaries nationally by 37%. More realistically, a 15% proportional reduction in these risk factors would reduce incident dementia cases in the population by an estimated 6.6%. Among these eight CMD risk factors, hypertension, ischemic heart disease, and chronic heart failure were individually associated with the greatest PAFs for dementia.

TABLE 2 Unweighted and weighted population attributable risk and 95% confidence intervals for the individual and combined cardiometabolic diseases in Medicare beneficiaries.[a]

CMD Type	Unweighted PAF[b] (95% CI)	Communality[c] (%)	Weighted PAF[d] (95% CI)	Weighted PIF[e] (%)
Stroke	15.2 (14.0–16.5)	31.4	3.7 (2.5–4.9)	0.7
Chronic heart failure	23.4 (22.4–24.5)	65.4	5.7 (4.7–6.8)	1.0
Hypertension	39.3 (37.9–40.7)	78.3	9.6 (8.2–11.0)	1.7
Ischemic heart disease	27.5 (26.6–28.4)	90.8	6.7 (5.8–7.6)	1.2
Atrial fibrillation	10.9 (10.0–11.8)	47.2	2.7 (1.8–3.6)	0.5
Acute myocardial infarction	3.0 (1.7–4.3)	75.2	0.7 (0.0[f]-2.1)	0.1
Diabetes	15.6 (14.9–16.3)	77.0	3.8 (3.1–4.5)	0.7
Hyperlipidemia	18.1 (17.3–18.9)	69.5	4.4 (3.6–5.3)	0.8
Overall	82.9 (80.5–85.4)		37.4 (35.0–39.8)	6.6

Abbreviations: CI, confidence interval; CMD, cardiometabolic disease; PAF, population attributable fraction; PIF, population impact fraction.
[a]2017 Medicare data.
[b]Unweighted PAF does not account for overlap with the other risk factors examined.
[c]Communality is the clustering of factors (higher communality indicates greater correlation with other risk factors).
[d]Weighted PAF accounts for the communality across the eight risk factors.
[e]PIF is a counterfactual situation with a 15% proportional reduction in each risk factor.
[f]PAF is zero if a condition has no burden on incident dementia in the population (i.e., PAF ≤ 0).

Of course, these specific risk factors are highly correlated and reducing hypertension would likely yield the greatest reduction in dementia case burden. Another important finding is the strong geospatial variability in the proportion of incident dementia cases attributed to CMD, which was as high as 63% in the Southeastern and Southcentral United States. In combination, our study demonstrates the important burden of CMD on all-cause dementia and provides critical regional data to inform public health interventions.

Previous United States population-based studies assessing the burden of different risk factors on dementia including lifestyle and environmental factors reported PAF estimates ranging from 30% to 41%.[34,35,45,46] A 2014 study found that 30% of the dementia cases in the United States could be reduced by eliminating diabetes, midlife hypertension, midlife obesity, physical inactivity, depression, smoking, and low educational attainment.[46] Another study found that 36.9% of dementia cases could be reduced by removing diabetes, midlife hypertension, midlife obesity, physical inactivity, depression, smoking, low educational attainment, and hearing loss from the U.S. population.[35,45] Based upon the Lancet Commission report on risk factors for worldwide dementia, a recent study estimated that 41.0% of United States dementia cases could be reduced by eliminating low education, hearing loss, traumatic brain injury, hypertension, excessive alcohol consumption, obesity, smoking, depression, social isolation, physical inactivity, diabetes, and air pollution.[34] Our work adds to this literature by expanding the CMDs studied and by incorporating geospatial analytic techniques to inform the understanding of regional variations in the impact of CMD on dementia risk. When we calculated the PAFs for upstream versus downstream CMDs, our results for diabetes and hypertension were consistent with previous studies.[35,45,46] We were unable to compare the PAF for hyperlipidemia with the literature as there is no United States population-based study on the burden of this condition on dementia.

Previous studies have demonstrated geographic variability of dementia prevalence and mortality in the United States. In 2008, the prevalence of diagnosed dementia among older United States adults was lowest in the Central North and West and highest in the South and East.[59] A population-based survey of older United States adults from 2006 to 2016 identified higher standardized prevalence of dementia in the Southern United States as compared to the Northeast and Midwest, and that being born in the South was associated with a significantly higher risk of dementia.[60] From 2000 to 2012, dementia prevalence declined over time across all regions of the United States except the South.[61] Regional variation in dementia burden likely can be explained by the disproportionate concentration of obesity, lack of physical activity, and unhealthy diet among those living in the Southern states.[62–65] Physical inactivity is associated with an increased risk

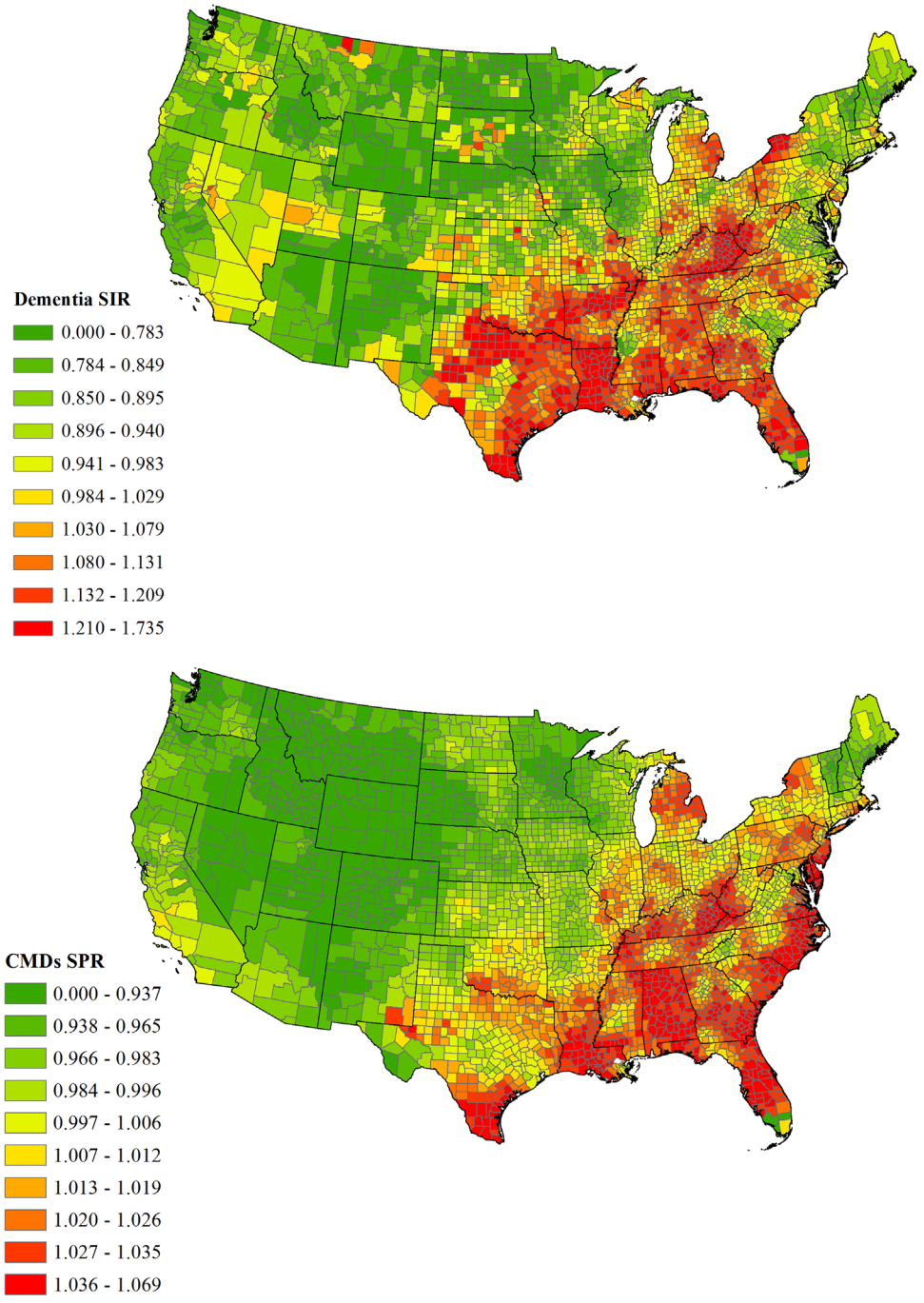

FIGURE 2 County-level SPRs for CMDs from the CCW in 2017 and SIRs for 2017 for dementia using deciles. The eight CMDs included stroke, diabetes, hypertension, hyperlipidemia, and major heart diseases (including chronic heart failure, atrial fibrillation, ischemic heart disease, and acute myocardial infarction). Both SPR and SIRs were classified in deciles. CCW, Chronic Condition Warehouse; CMD, cardiometabolic disease; SIR, standardized incidence ratio; SPR, standardized prevalence ratio.

of several cardiovascular risk factors that in turn are associated with an increased risk of dementia.[66] Obesity is linked to comorbid conditions including cardiovascular disease, hypertension, stroke, and diabetes, which contribute to a higher risk of dementia.[67] Other factors including economic, social, and health inequalities, which are exacerbated by structural racism, residential segregation, acculturation, and socioeconomic deprivation, may also contribute to the regional variation in CMD burden on dementia.[68–71]These findings might explain why the burden of dementia attributed to CMD is higher in the South compared to other regions of the United States.

Our study has several important strengths. We used nationwide, population-based data and innovative epidemiologic and geographic methods to explore the association between CMDs and dementia. The use of GIS permits smoothing of extreme values within the maps by considering neighboring values, and it provides the ability to go beyond regression or simple distribution analysis of data. Our weighted

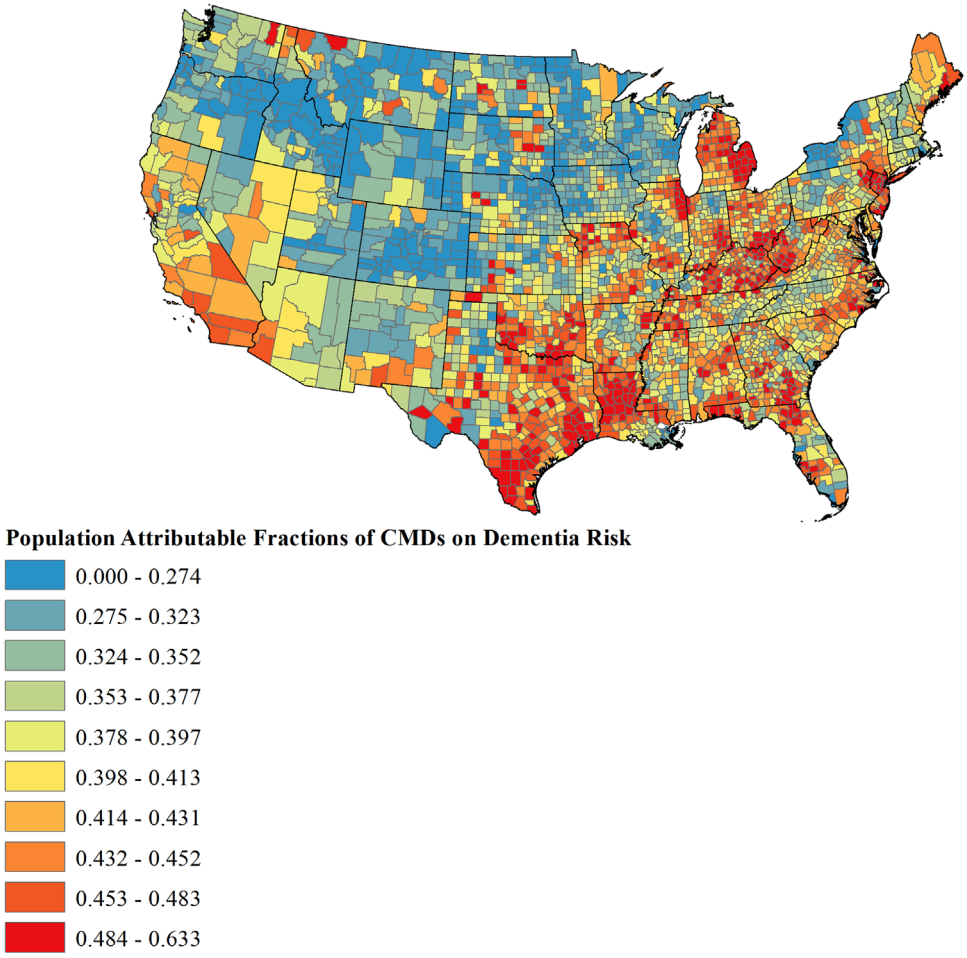

FIGURE 3 Spatial pattern of combined weighted PAFs of eight CMDs on dementia burden across the United States using 2017 data from the CCW. The eight CMDs included stroke, diabetes, hypertension, hyperlipidemia, and major heart diseases (including chronic heart failure, atrial fibrillation, ischemic heart disease, and acute myocardial infarction). PAFs were classified and mapped in deciles. CCW, Chronic Condition Warehouse; CMD, cardiometabolic disease; PAF, population attributable fraction.

calculation of PAFs allowed us to account for risk overlap across the eight risk factors, thereby avoiding an inflated estimate of the combined contribution of the risk factors on dementia due to the strong correlation between CMD variables. In addition, we used individual-level data to directly estimate the PAFs, adjusted for confounding based on the prevalence of risk factors and the strength of their association with incident dementia both nationally and at the county level. By contrast, the other population-based studies[31–35] adopted relative risks from meta-analysis for PAF calculation due to the lack of raw data to adjust for confounders. Furthermore, the use of GIS allowed us to identify the geospatial differences in our results and highlight regions of the country where both the burden of CMD is higher than expected and incident dementia is higher than expected, a crucial precursor to crafting policies with an equitable health impact. Our use of Medicare data allowed us to focus on the portion of the population that is at highest risk for both CMD multimorbidity and dementia.

There were some limitations to our study. Medicare is national health insurance for those 65 years of age and older, but we had to exclude those with Medicare Advantage plans from analyses because those plans do not report detailed claims to CMS. Unfortunately, excluding those beneficiaries is necessary to ensure that we used population-based data. Although we were limited to studying individuals 67 years of age and older, those patients represent the majority of people who develop dementia.[3] In addition, dementia and CMDs were defined based on the CCW algorithms. Other factors including the intersection of disease etiology and health care utilization may influence the accuracy of the CCW algorithm to detect a chronic condition.[40] As a result, patients with conditions who do not require health care for extended periods may be missed by the algorithm.[40] Beneficiaries who underutilize health care due to limited access to care (e.g., in rural areas) or those who utilize services not covered by Medicare may also be missed.[40] The lookback period (the number of years of claims data necessary to detect a condition) also affects the accuracy of the CCW algorithms. Although the fixed lookback period of the CCW algorithms allows uniformity in dementia ascertainment across studies, it may not be sufficient for all analyses. The CCW algorithm is also based on ICD codes. ICD-based diagnostic codes are a

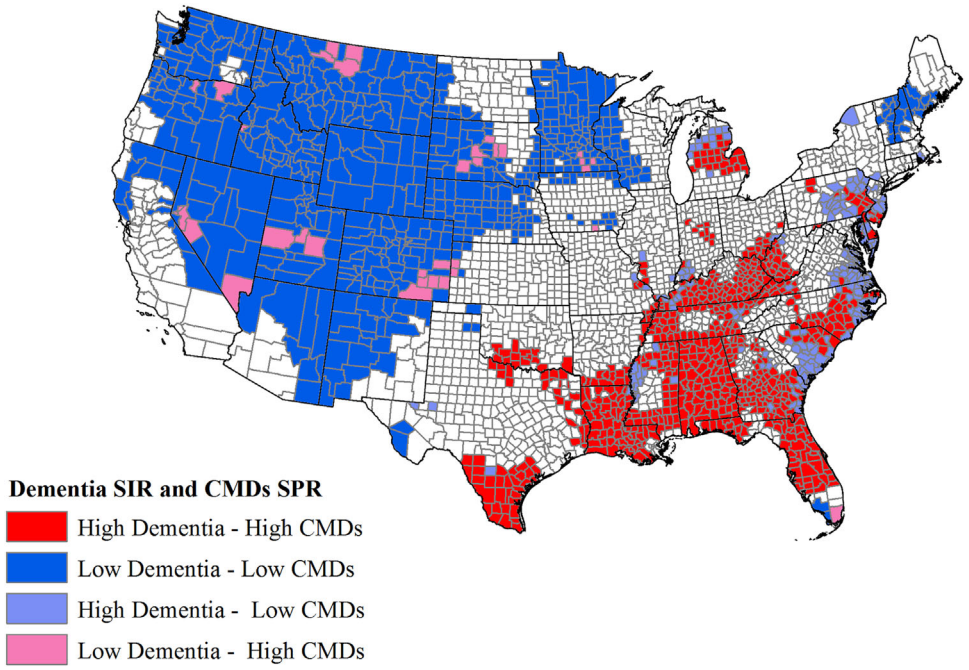

FIGURE 4 Spatial correlation between dementia SIRs and CMD SPRs across the United States using bivariate local indicators of spatial association. CMDs were defined from the CCW in 2017. The eight CMDs included stroke, diabetes, hypertension, hyperlipidemia, and major heart diseases (including chronic heart failure, atrial fibrillation, ischemic heart disease, and acute myocardial infarction). CCW, Chronic Condition Warehouse; CMD, cardiometabolic disease; SIR, standardized incidence ratio; SPR, standardized prevalence ratio.

useful tool for identifying Medicare beneficiaries with dementia, and perhaps the only feasible way to obtain national estimates of dementia; however, misclassification of case and control status can result from diagnostic or coding errors and possibly lead to an overestimation of the true dementia prevalence.[71,75] Despite these limitations, Medicare claims have the highest sensitivity (89%) and specificity (85%–89%) for identifying dementia compared to other administrative datasets, and the overall accuracy of dementia cases ascertained in administrative claims has improved over time.[72–75] Another limitation is that PAFs assume a causal relationship between each risk factor and dementia, and if this assumption is not met, the PAF estimates could be biased away from the true value. This assumption of a causal relationship is likely met in our study as many previous studies have established causal relationships between each of the eight risk factors investigated and dementia.[26–31,45] The burden of CMDs on dementia is likely influenced by the management of the individual CMDs and the underlying socioeconomic context of the population. While adjusting for ADI, a proxy for the latter, in our sensitivity analysis yielded similar results to models adjusted for demographics, we were unable to account for the former in our analysis due to the nature of our dataset. Furthermore, we could not account for mediation pathways in our dataset, but we were able to consider overlap among the risk factors in our analysis. Finally, our county-level analysis assumes that beneficiaries are nonmobile during the 3 years before diagnosis, which is largely accurate, since the overwhelming majority of this Medicare population are relatively nonmobile for up to 5 years.[52]

4.1 | Conclusion

Reducing dementia risk by targeting modifiable risk factors is currently the best tool to manage the projected increase in dementia cases in the United States. A substantial number of incident dementia cases could be eliminated by mitigating modifiable cardiometabolic risk factors, especially in United States counties with a high risk of dementia attributed to these risk factors.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest. Author disclosures are available in Supporting Information.

DATA AVAILABILITY STATEMENT

The data and associated materials used in this study cannot be made publicly available due to contracting requirements with Centers for Medicare & Medicaid Services (CMS). These de-identified individual

level research data were obtained through a formal Data Use Agreement with CMS via a secure, CMS-approved data access method. The data we used was a custom dataset, as detailed in the methods. All summary data that we were able to share are contained in the manuscript. Information and inquiries on how to obtain CMS data, with specific details about the process for requesting and contact information for initiating the process through the Research Data Assistance Center, can be found at https://resdac.org.

CONSENT STATEMENT

Informed consent was not obtained, as this study does not meet the definition of human subject research.

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SUPPORTING INFORMATION

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

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