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The rising burden of Alzheimer's disease mortality in rural America

Jessica Y. Ho *, Yujin Franco

[a] University of Southern California, United States

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ABSTRACT

Since the 1990s, there has been a striking urban-rural divergence in life expectancy within the United States, with metropolitan areas achieving strong life expectancy increases and nonmetropolitan areas experiencing stagnation or actual declines in life expectancy. While Alzheimer's disease and related dementias (ADRD) are likely to pose a particular challenge in nonmetropolitan areas, we know relatively little about the level of ADRD mortality in nonmetropolitan areas, how it has changed over time, and whether it is contributing to metropolitan/nonmetropolitan life expectancy gaps. This study finds that ADRD mortality has risen more rapidly in nonmetropolitan areas than in all other metro areas (large central metros, suburbs, and medium/small cities) between 1999 and 2019. While death rates from ADRD were nearly identical in large central metros and nonmetros in 1999, a clear metro/nonmetro gradient has emerged and widened substantially over the past two decades. Today, nonmetros now experience the highest levels of ADRD mortality, while large central metros have the lowest levels. These metro/nonmetro gaps in ADRD differ substantially by region, with the largest gaps observed in the Middle Atlantic and South Atlantic. The contribution of ADRD to metro/nonmetro differences life expectancy at age 65 is now considerable in many regions, reaching up to 30% for women and 13% for men. In several regions, ADRD's contribution to female life expectancy gaps is on par with or exceeds the contributions of other leading causes of death such as heart disease, cancer, and chronic lower respiratory diseases. The rising burden of Alzheimer's disease mortality is likely to pose a substantial challenge in rural areas of the United States which are aging rapidly, experiencing adverse mortality trends, and increasingly disadvantaged in terms of socioeconomic resources and health care infrastructure.

1. Introduction

The rise in Alzheimer's disease ranks among the many momentous changes accompanying the unprecedented aging of the American population. Over the past two decades, mortality from Alzheimer's disease and related dementias (ADRD) has more than doubled in the United States (CDC/NCHS, 2021). In 2019, ADRD accounted for nearly 10% of all deaths in the United States (Ibid.). The number of older adults with ADRD is projected to double by 2050, reaching 12.7 million Americans compared to an estimated 6.2 million Americans in 2019 (Alzheimer's Association, 2021). Prior studies have documented considerable geographic variation in Alzheimer's disease at the region, state, and county levels (Akushevich et al., 2021; Gillum et al., 2011; Taylor et al., 2017; Topping et al., 2021); however, relatively less attention has been paid to differences across the urban-rural continuum or to urban-rural differences within regions.

How rural or nonmetropolitan areas are faring in terms of ADRD mortality—on an absolute scale, compared to previous levels of ADRD mortality in these areas, and compared to their more urban or metropolitan counterparts—is of interest for several reasons. First, aging tends to be more advanced in rural parts of the country, and a rising prevalence of ADRD is likely to pose particular challenges in these areas. The health care and long-term care services needed by individuals with ADRD are much scarcer in rural than in urban areas. Difficulties in accessing care have been further exacerbated by physician shortages—including shortages of geriatricians and geriatric specialists in particular—and by increases in hospital and nursing home closures in rural areas (Gong et al., 2019; Kaufman et al., 2016; Rahman et al., 2020; Sharma et al., 2021).

Furthermore, conditions in rural areas are of increasing interest given the emergence of the rural mortality penalty in the 1990s (Cosby et al., 2019; Monnat, 2020) and the recent (post-2010) stagnation in American mortality (Arias, 2014; Arias & Xu, 2020; Ho & Hendi, 2018). The metropolitan/nonmetropolitan divergence in life expectancy has

* Corresponding author. Leonard Davis School of Gerontology and Department of Sociology, 3715 McClintock Avenue, Los Angeles, CA, 90089, United States.
E-mail address: jessica.y.ho@usc.edu (J.Y. Ho).

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been particularly striking over the past decade, during which large central metros and their suburbs achieved life expectancy increases but nonmetros experienced actual declines in life expectancy (Elo et al., 2019).

ADRD is likely to pose a substantial challenge to communities and health care infrastructure in nonmetropolitan areas of the United States given that these areas tend to be aging rapidly, experiencing adverse mortality trends, and disadvantaged in terms of socioeconomic resources and health care infrastructure. This study examines the level of ADRD mortality in nonmetros and whether differences in ADRD mortality have emerged between nonmetros and other metropolitan areas. There is considerable variation in life expectancy levels and trends across the different regions of the U.S., as well as in their degree of rurality and age distributions (Dwyer-Lindgren et al., 2016; Elo et al., 2019; Wang et al., 2013). For example, the share of the population aged 65+ residing in nonmetropolitan areas ranged from just 2.7% in the Mid-Atlantic to 36.4% in Appalachia in 2019 (National Center for Health Statistics, 2020). Prior studies have highlighted the substantial heterogeneity that exists within rural areas (Jensen et al., 2020; Monnat, 2020). Thus, this study considers metro/nonmetro differences for the nation as a whole and separately by each region.

2. Data and methods

2.1. Data

This study uses national vital statistics micro-data files and bridged-race population estimates from the National Center for Health Statistics (NCHS) (CDC/NCHS, 2021; National Center for Health Statistics, 2020). The former covers all deaths occurring in the United States between 1999 and 2019 and contains information on age, sex, underlying cause of death, and county of residence from death certificates. We subset the data to include only U.S. residents. These deaths are matched to the corresponding year-, sex-, age-, and county-specific population estimates. The main analyses focus on the total population. Additional estimates for non-Hispanic whites are provided in the Supplementary Appendix.

The counties are classified into four categories capturing the metropolitan/nonmetropolitan continuum: large central metros, large metro suburbs, small/medium metros, and nonmetro areas. These categories are based on the rural-urban continuum codes developed by the United States Department of Agriculture (USDA) Economic Research Service (ERS), which were modified and made available by the NCHS. We use the most recent (2013) classifications. The study also examines metropolitan/nonmetropolitan differences by region, where the 10 regions correspond to the nine Census Divisions (New England, Middle Atlantic, East North Central, West North Central, South Atlantic, East South Central, West South Central, Mountain, and Pacific) and Appalachia. States (and their constituent counties) are grouped into Census Divisions by the U.S. Census Bureau. Appalachia, defined by the Appalachian Regional Commission, consists of a set of counties drawn from 13 states (Appalachian Regional Commission, 2021). These counties are excluded from their overlapping Census divisions. Thus, we have a set of 40 geographic units cross-classified by region and metro/nonmetro status. These categories have been used by several prior studies of geographic inequality in mortality (Elo et al., 2019; Monnat, 2020; Vierboom et al., 2019; Vierboom & Preston, 2020).

We consider eleven cause of death categories: Alzheimer's disease and related dementias, nine other leading causes of death among the population aged 65 and older—heart disease, malignant neoplasms, chronic lower respiratory diseases (CLRD), cerebrovascular diseases, diabetes, accidents (unintentional injuries), nephritis, influenza and pneumonia, and Parkinson's disease—and a residual category consisting of all remaining causes of death. We focus on ADRD as opposed to Alzheimer's disease alone to provide a more comprehensive assessment of the level of and changes in dementia mortality and its contribution to metro/nonmetro differences in life expectancy. This approach helps to address potential geographic variation in cause of death coding and captures all of the main underlying causes to which dementia deaths are attributed (Kramarow & Tejada-Vera, 2019). This is important given that it may be difficult to distinguish among various forms of dementia, and older adults may have more than one vascular and neurodegenerative disorder (e.g., the prevalence of mixed dementia, where an individual has both Alzheimer's disease and vascular dementia, may be as high as 22%) (Custodio et al., 2017). The cause of death categories are specified using the same ICD-10 codes as the NCHS (listed in Supplementary Appendix Table A1). The study period begins with 1999 since this was the first year ICD-10 was implemented and allows for a more reliable examination of trends, since significant changes can occur with ICD transitions.

2.2. Analytic strategy

First, data on deaths and population are combined to produce age-specific death rates for each year between 1999 and 2019. The age-specific death rates are then used to generate age-standardized ADRD death rates for the 4 metro categories and for the 40 geographic areas. The age groups used for age standardization and in the life table calculations are: 65–69, 70–74, 75–79, 80–84, and 85+. The 2000 U.S. Standard Population is used as the age standard (SEER, 2021). The metro/nonmetro gap is defined as the difference in the age-standardized death rate from ADRD between large central metros (the most urban category) and nonmetros (the least urban category). Next, we calculate life tables for the 4 metro categories and for the 40 geographic areas using standard life table techniques and graduation (Preston et al., 2001). We apply Arriaga's decomposition to the life table and cause of death data to determine how much of geographic differences in life expectancy at age 65 in 2019 are due to ADRD and to the other ten cause of death categories (Arriaga, 1984). The main outcome of interest is how much each cause of death contributes to the difference in life expectancy at age 65 between large central metros and nonmetropolitan areas. All of the analyses are performed separately by sex and based on the population aged 65 and older, since 98.6% of ADRD deaths occur at these ages (CDC/NCHS, 2021). We provide additional figures (Figures A1-A2) in the appendix that provide results for two age groups (60–84 and 85+). We also apply Arriaga's decomposition using death rates that have been adjusted for potential nonstationarity and age misreporting at ages 85+ (Table A4), which help account for changes over time and across areas in the open-ended age group (Elo et al., 2019; Horiuchi & Coale, 1982).

3. Results

3.1. Trends in ADRD mortality

ADRD mortality has increased substantially within the United States over the past two decades (Fig. 1). During this period, differences across metro categories have emerged and widened. Initially, levels of ADRD were very similar across all four categories. Large central metros and nonmetros had nearly identical levels of ADRD mortality (206.0 and 206.5 deaths per 100,000, respectively) in 1999. Large metro suburbs and medium/small cities had slightly higher levels (213.7 and 228.5 deaths per 100,000, respectively). While the age-standardized death rate from ADRD more than doubled in all metro areas, nonmetro areas experienced the largest increase, which drove a metro/nonmetro divergence in ADRD mortality. By 2019, the age-standardized death rate from ADRD reached 552.0 deaths per 100,000 in nonmetros—a 167% increase compared to 1999. The difference in ADRD mortality between nonmetros and large central metros increased from 0.4 deaths per 100,000 in 1999 to 83.5 deaths per 100,000 in 2019. In the most recent year, nonmetros had the highest levels of ADRD mortality, followed by medium/small metros, large metro suburbs, and large central metros.

The increase in ADRD mortality and the emergence of a clear metro/

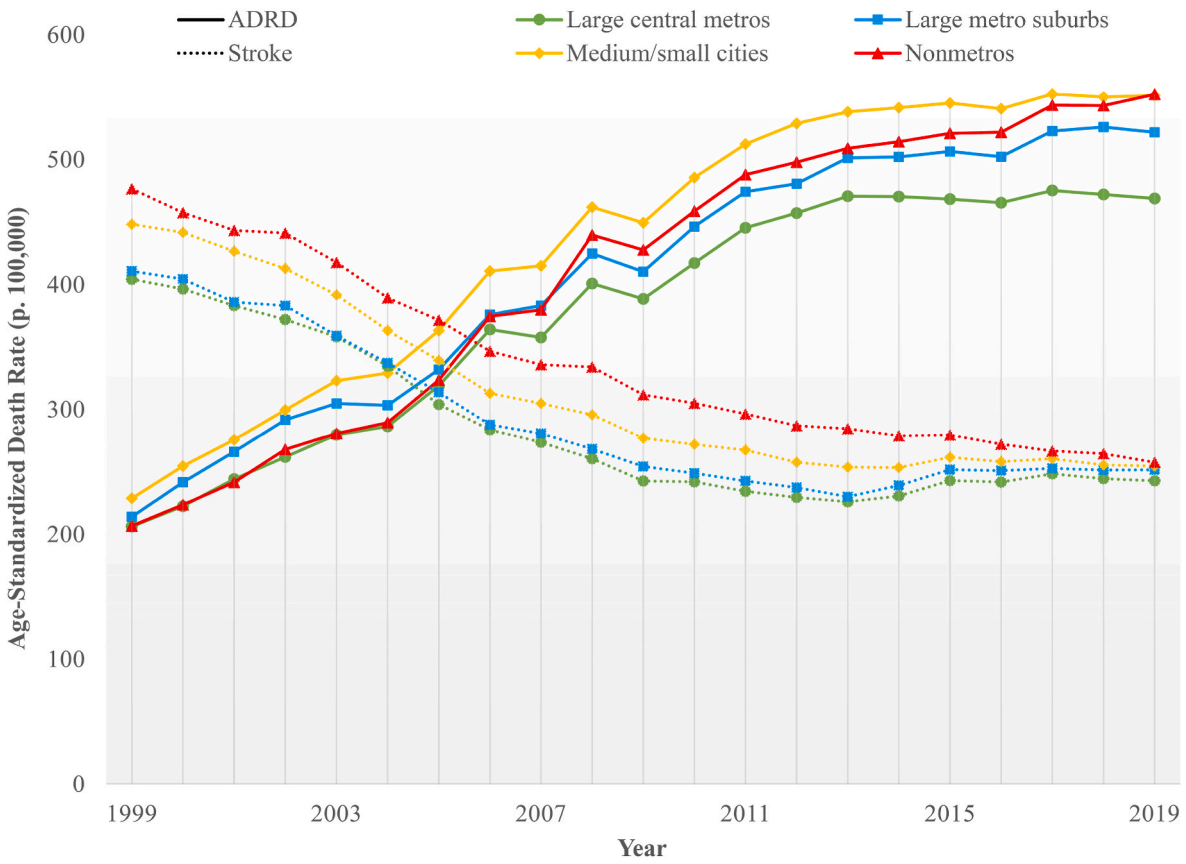

Fig. 1. Alzheimer's disease and related dementias (ADRD) and stroke mortality by metro category, total population aged 65+, 1999–2019.
Source: Authors' calculations based on NCHS data.

nonmetro gradient in ADRD mortality are particularly striking when we make the comparison to stroke, another leading cause of death. At the start of the period, levels of stroke mortality were approximately double those of ADRD in each metro category. As stroke mortality declined and ADRD mortality increased, a crossover occurred in the mid-2000s. Levels of ADRD mortality were nearly or more than double those of stroke by 2019, a complete reversal of the situation in 1999. Throughout this period, stroke mortality exhibited the same metro/nonmetro gradient that also emerged for ADRD—levels of stroke mortality were highest in nonmetros, followed by medium/small cities and large metro suburbs, and lowest in large central metros.

Turning our attention from the national level to trends within regions allows us to identify which nonmetros now have the highest levels of ADRD mortality, and which nonmetros have experienced the largest growth in ADRD mortality (Table 1). Although we focus mainly on trends among nonmetros, which are of particular interest given the outsize caregiving and health care burden ADRD is likely to exert in rural areas and the recent adverse mortality trends observed in nonmetros, the age-standardized death rates and changes in these rates are also provided for the other three metro categories for comparison. Among the ten nonmetro areas, nonmetros in the East South Central region had the highest ADRD mortality in 2019 for both men and women, followed by nonmetros in Appalachia (women) and New England (men). Not only are these areas now experiencing the highest death rates from ADRD, they also tend to be the areas that have experienced the largest increases since 1999. This is the case when considering both absolute and relative changes. For example, nonmetros in the East South Central region experienced the largest increases in ADRD mortality (480.8 deaths per 100,000 for women and 394.2 deaths per 100,000 for men) over the past two decades. Today, their levels of ADRD mortality are three and a third to three and a half times higher than their levels in 1999. Nonmetros in the Mountain region had the lowest levels of ADRD mortality in 2019, followed by the Middle Atlantic region for women and the Pacific region for men. Similarly, these are also the areas which tended to have experienced the lowest absolute and relative increases in ADRD mortality. Nonmetros in the Mountain and Pacific regions reached ADRD levels in 2019 that were 65–89% higher than their 1999 levels for men and 112–124% higher than their 1999 levels for women.

3.2. *Metro/nonmetro gaps in ADRD mortality*

We have established that a metro/nonmetro gap in ADRD mortality has emerged and grown considerably at the national level. We would also like to know whether this is the case when we look across regions—do nonmetros in all regions experience a disadvantage in ADRD mortality, and do these gaps tend to be larger or smaller in certain areas? In six of the ten regions—Middle Atlantic, South Atlantic, East North Central, Appalachia, New England, and the Pacific—we observed a nonmetro disadvantage (i.e., positive metro/nonmetro gaps) in ADRD mortality among women in 2019 (Fig. 2). We also observed a nonmetro disadvantage among men in five regions. Four of the regions are the same for men and women (Middle Atlantic, South Atlantic, East North Central, and Appalachia). There was no nonmetro disadvantage in ADRD mortality for men in the Pacific, as there was for women, but there was a nonmetro disadvantage in ADRD mortality for men in the West South Central region, which was not observed for women. The largest positive metro/nonmetro gaps were observed in the Middle Atlantic. In the remaining regions, ADRD mortality was lower in nonmetros than in large central metros, with the largest difference occurring in the West North Central region. In regions where we observed a nonmetro disadvantage in ADRD mortality in 2019, these gaps have tended to increase

Table 1
Levels of and changes in ADRD mortality since 1999 by metro category and region, women and men aged 65+, 2019. The Rate in 2019 is the age-standardized death rate from ADRD in 2019. The Change since 1999 is the age-standardized death rate in 2019 minus the age-standardized death rate in 1999. The Ratio to 1999 rate is the age-standardized death rate in 2019 divided by the age-standardized death rate in 1999.

	Age-Standardized Death Rate for Alzheimer's Disease and Related Dementias (per. 100,000)					
	Women			Men		
	Rate in 2019	Change since 1999	Ratio to 1999 rate	Rate in 2019	Change since 1999	Ratio to 1999 rate
Nonmetros						
New England	634.5	364.4	2.35	497.3	276.0	2.25
Middle Atlantic	518.1	387.1	3.95	385.7	270.2	3.34
South Atlantic	651.6	429.2	2.93	477.4	281.1	2.43
Appalachia	656.9	464.8	3.42	480.4	312.3	2.86
East North Central	625.2	384.5	2.60	458.8	252.4	2.22
East South Central	666.1	480.8	3.59	563.3	394.2	3.33
West North Central	555.0	345.3	2.65	437.5	233.5	2.14
West South Central	621.8	438.3	3.39	493.3	315.3	2.77
Mountain	503.3	266.3	2.12	370.4	146.4	1.65
Pacific	527.3	291.5	2.24	379.4	178.3	1.89
National	609.2	397.4	2.88	459.5	267.5	2.39
Medium/small cities						
New England	642.6	400.7	2.66	512.8	324.1	2.72
Middle Atlantic	565.7	362.7	2.79	424.7	261.9	2.61
South Atlantic	543.2	311.4	2.34	386.9	206.0	2.14
Appalachia	699.0	451.3	2.82	530.1	323.6	2.57
East North Central	618.1	356.8	2.37	522.4	291.0	2.26
East South Central	703.1	483.8	3.21	508.2	286.8	2.30
West North Central	638.5	358.7	2.28	506.2	278.4	2.22
West South Central	644.9	421.7	2.89	482.2	289.4	2.50
Mountain	555.6	282.8	2.04	414.7	193.3	1.87
Pacific	564.8	348.7	2.61	452.8	265.6	2.42
National	606.0	366.1	2.53	461.6	261.9	2.31
Large metro suburbs						
New England	672.2	440.7	2.90	555.1	347.5	2.67
Middle Atlantic	448.7	302.7	3.07	366.9	247.3	3.07
South Atlantic	528.9	292.9	2.24	405.3	217.4	2.16
Appalachia	658.1	439.9	3.02	483.8	291.1	2.51
East North Central	609.5	371.1	2.56	465.4	265.9	2.33
East South Central	753.5	502.5	3.00	586.4	374.1	2.76
West North Central	657.6	393.3	2.49	501.2	270.3	2.17
West South Central	662.6	381.4	2.36	529.8	294.0	2.25
Mountain	552.1	170.6	1.45	423.7	124.8	1.42
Pacific	560.8	293.4	2.10	454.4	239.9	2.12
National	566.7	342.1	2.52	444.3	258.0	2.38
Large central metros						
New England	570.5	327.7	2.35	516.3	329.1	2.76
	330.8	229.9	3.28	288.2	208.6	3.62
Middle Atlantic						
South Atlantic	483.0	258.6	2.15	388.9	207.4	2.14
Appalachia	589.1	377.3	2.78	470.5	289.8	2.60
East North Central	521.6	285.5	2.21	451.9	265.8	2.43
East South Central	724.6	485.7	3.03	624.7	397.1	2.75
West North Central	654.5	339.9	2.08	564.5	294.9	2.09
West South Central	640.1	373.4	2.40	483.8	261.3	2.17
Mountain	567.8	233.1	1.70	434.3	176.0	1.68
Pacific	471.3	256.7	2.20	387.3	199.8	2.07
National	499.9	283.8	2.31	411.3	232.0	2.29

Source: Authors' calculations based on NCHS data.

dramatically over time. For most of these cases, a nonmetro disadvantage existed in 1999 but was considerably smaller than in 2019. For example, the gaps in the Middle Atlantic region increased from 30.2 to 187.4 deaths per 100,000 among women and from 35.9 to 97.5 deaths per 100,000 among men. In a few cases, there was a negative gap (i.e., nonmetros had lower levels of ADRD mortality than large central metros) in 1999 that reversed by 2019. In one case—men in the East North Central region—the gap was smaller in 2019 than in 1999.

Fig. 3 may shed some light on why we observe these patterns. There is a negative association between the size of the metro/nonmetro gap in ADRD mortality and the share of the population living in nonmetros (panels A and B). In other words, regions with smaller shares of their population living in nonmetros tend to have larger metro/nonmetro gaps in ADRD mortality, while regions with larger shares of their population living in nonmetros tend to have smaller or even negative gaps. One possible interpretation of this association is that regions with larger nonmetro populations may have a more equitable metro/nonmetro distribution of resources that can improve overall levels of health and reduce gaps in ADRD mortality. In other regions with very small nonmetro populations, it is possible that these nonmetro populations are highly negatively select and/or that nonmetro areas within these regions have fewer resources for promotion of good health. That being said, these estimates are only suggestive, not causal, and should be taken with a grain of salt since the associations are based on only 10 data points.

3.3. Contribution of ADRD to metro/nonmetro gaps in life expectancy at age 65

Finally, we investigate how much ADRD mortality now contributes to life expectancy differences between large central metros and nonmetros and how these contributions compare to those of nine other leading causes of death. We decompose the gap in life expectancy at age 65 in 2019 between large central metros and nonmetros in each of the 10 regions separately for men and women.

Starting with women, we see that the gap in e_{65} between large central metros and nonmetros ranged from 0.41 years in the Mountain region to 2.52 years in the Middle Atlantic region (Table 2). In the regions where we observed a positive metro/nonmetro gap in ADRD mortality, ADRD is a key contributor to the nonmetro life expectancy disadvantage, accounting for between 10.6% and 27.9% of the gap in these areas. ADRD accounts for the largest percent share—27.9%—of the gap in the East North Central region. It makes the largest absolute contribution to

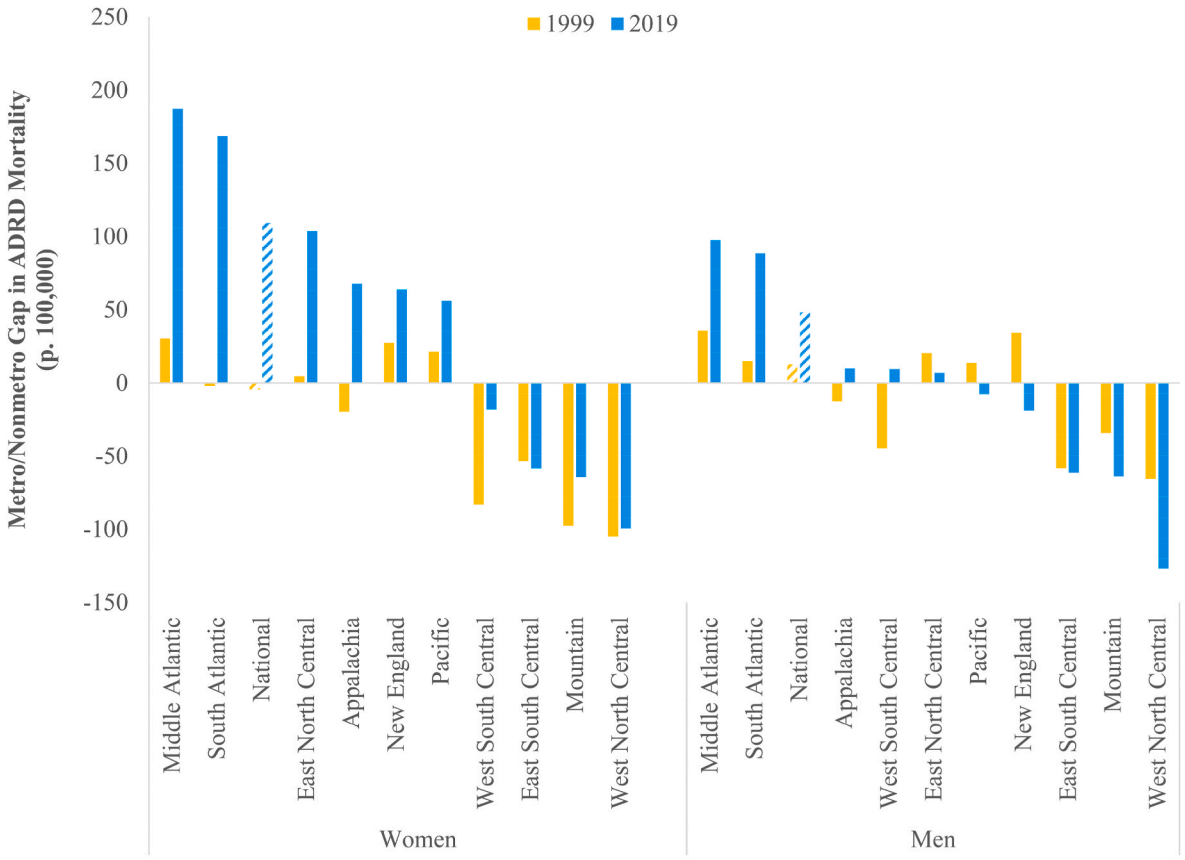

Fig. 2. Gap in ADRD mortality between nonmetros and large central metros by region, women and men aged 65+, 1999 and 2019. The metro/nonmetro gap in ADRD mortality is defined as the age-standardized death rate from ADRD in nonmetros minus the age-standardized death rate from ADRD in large central metros. Solid bars are used for the 10 regions and striped bars are used for the nation as a whole.
Source: Authors' calculations based on NCHS data.

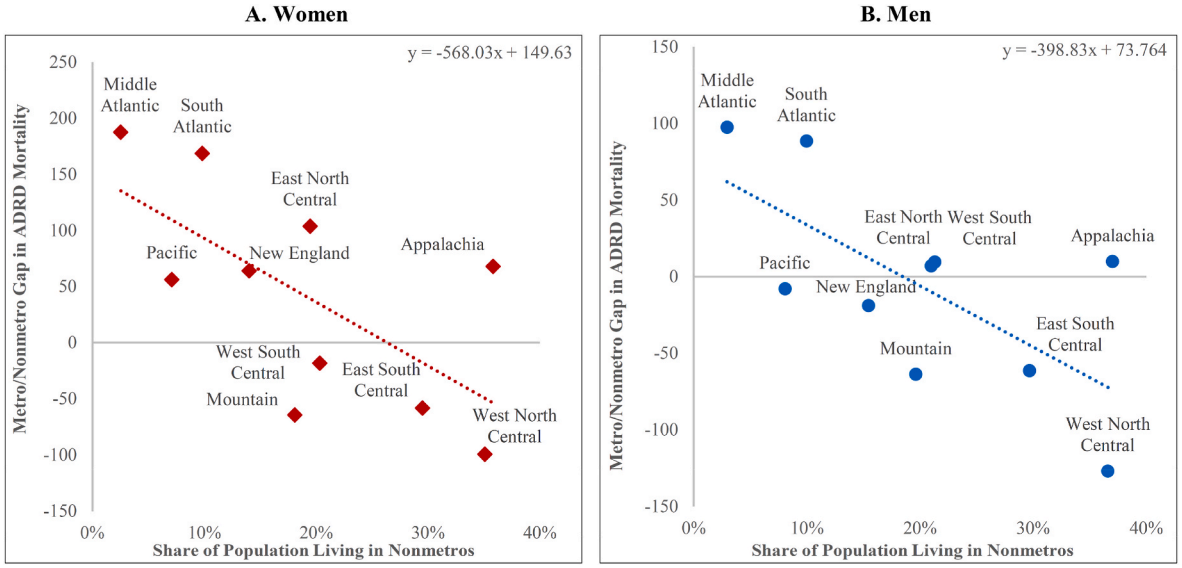

Fig. 3. Metro/nonmetro gap in ADRD mortality and share of population living in metros by region, women (panel A) and men (panel B) aged 65+, 2019. Regression lines and corresponding equations are displayed for each panel. The slopes are significant at $p < 0.05$ for women and men.
Source: Authors' calculations based on NCHS data.

the gap in the Middle Atlantic region, accounting a substantial 0.55 years of the 2.52-year gap. In these two regions, ADRD is the largest contributor to the metro/nonmetro life expectancy gap among the ten leading causes of death. In other words, in these regions, the contribution of ADRD is larger than that of heart disease, cancer, CLRD, stroke, diabetes, or accidents. In the East North Central region, chronic lower respiratory diseases (CLRD) account for 25.1% of the gap, while heart disease and cancer account for only 7.2% and 1.1% of the gap,

Table 2
Contribution of ADRD and nine other leading causes of death to the difference in life expectancy at age 65 (e_{65}) between nonmetros and large central metros by region, women and men aged 65+, 2019. The e_{65} gap is defined as life expectancy at age 65 for large central metros minus life expectancy at age 65 for nonmetros. For the cause of death contributions, positive (negative) values indicate that a particular cause of death increases (narrows) the e_{65} gap between nonmetros and large central metros. Regions are ordered from the largest to smallest percent contribution of ADRD to the metro/nonmetro gap. The causes of death are mutually exclusive and exhaustive such that for each row, the absolute contributions (in years) sum to the e_{65} gap and the percentages contributions sum to 100%. ADRD = Alzheimer's disease and related dementias, CLRD = chronic lower respiratory diseases.

Women		Contribution to e_{65} gap (in years and % contribution)										
Region	e_{65} gap	ADRD	Heart disease	Cancer	CLRD	Stroke	Diabetes	Accidents	Nephritis	Influenza and pneumonia	Parkinson's disease	All other
East North Central	0.90	0.25	0.06	0.01	0.23	0.01	0.04	0.08	0.00	0.02	0.02	0.17
		27.9%	7.2%	1.1%	25.1%	1.6%	4.9%	9.3%	0.0%	1.7%	2.0%	19.1%
Middle Atlantic	2.52	0.55	−0.08	0.49	0.46	0.07	0.06	0.03	0.10	0.08	0.03	0.73
		21.9%	−3.3%	19.5%	18.3%	2.7%	2.5%	1.1%	3.8%	3.1%	1.3%	29.1%
South Atlantic	2.10	0.46	0.48	0.13	0.25	−0.03	0.11	0.04	0.11	0.08	0.00	0.48
		21.7%	22.7%	6.0%	11.9%	−1.5%	5.3%	2.1%	5.3%	3.8%	−0.2%	22.9%
New England	0.82	0.16	−0.07	0.26	0.22	0.18	0.04	0.07	−0.08	0.03	0.02	0.00
		19.9%	−9.1%	31.5%	26.4%	21.7%	4.7%	9.0%	−10.2%	3.2%	2.8%	−0.1%
Appalachia	0.78	0.14	0.15	−0.01	0.27	−0.02	0.13	0.04	0.02	0.02	−0.01	0.07
		17.5%	18.6%	−1.6%	34.1%	−3.1%	16.7%	4.8%	1.9%	2.7%	−0.8%	9.1%
Pacific	1.67	0.18	0.11	0.30	0.31	0.05	−0.04	0.11	0.01	−0.03	−0.03	0.68
		10.6%	6.9%	18.3%	18.5%	3.0%	−2.2%	6.9%	0.8%	−1.7%	−1.9%	40.9%
West South Central	1.57	−0.05	0.68	0.21	0.34	0.03	0.07	0.00	0.03	0.07	0.01	0.18
		−3.0%	43.5%	13.5%	21.9%	2.0%	4.3%	0.0%	1.8%	4.3%	0.5%	11.2%
East South Central	1.06	−0.12	0.54	0.10	0.18	0.10	0.08	0.00	0.04	0.07	0.03	0.03
		−11.7%	51.4%	9.9%	17.2%	9.6%	7.9%	0.3%	3.4%	6.3%	2.6%	3.1%
West North Central	0.67	−0.26	0.59	−0.05	0.20	−0.03	0.10	−0.08	0.04	0.09	−0.02	0.09
		−38.6%	87.7%	−7.4%	29.2%	−4.0%	14.8%	−11.5%	5.4%	13.4%	−2.5%	13.5%
Mountain	0.41	−0.18	0.08	−0.02	0.11	−0.04	0.04	0.08	0.06	0.06	0.00	0.24
		−44.1%	18.9%	−5.7%	25.8%	−10.6%	9.2%	19.9%	14.9%	13.6%	−0.9%	58.9%
Men		Contribution to e_{65} gap (in years and % contribution)										
Region	e_{65} gap	ADRD	Heart disease	Cancer	CLRD	Stroke	Diabetes	Accidents	Nephritis	Influenza and pneumonia	Parkinson's disease	All other
Middle Atlantic	1.66	0.21	−0.16	0.39	0.30	0.03	0.04	0.07	0.09	−0.04	0.03	0.71
		12.6%	−9.5%	23.5%	18.1%	1.7%	2.3%	4.1%	5.3%	−2.3%	1.5%	42.6%
South Atlantic	1.96	0.16	0.43	0.39	0.25	0.01	0.10	0.04	0.10	0.06	−0.01	0.42
		8.1%	21.9%	20.1%	12.7%	0.6%	5.0%	2.1%	5.3%	3.2%	−0.3%	21.3%
Appalachia	0.36	0.01	0.02	0.06	0.24	−0.08	0.10	0.01	0.00	0.01	0.00	0.01
		3.1%	5.0%	16.8%	67.2%	−22.7%	26.2%	1.8%	−1.0%	2.5%	−1.3%	2.3%
West South Central	1.73	0.02	0.63	0.42	0.41	−0.02	0.07	0.02	0.00	0.06	−0.02	0.14
		1.0%	36.6%	24.2%	23.4%	−1.3%	4.1%	1.1%	0.3%	3.6%	−1.3%	8.2%
East North Central	0.49	0.00	0.03	0.09	0.30	−0.02	0.06	0.04	−0.03	−0.01	0.01	0.03
		0.4%	5.2%	17.9%	60.4%	−4.5%	12.4%	8.0%	−5.7%	−2.6%	3.0%	5.4%
Pacific	1.15	−0.02	0.11	0.23	0.22	0.02	−0.01	0.13	0.00	−0.03	−0.05	0.56
		−1.6%	9.4%	20.3%	19.2%	1.4%	−1.3%	11.7%	−0.4%	−2.9%	−4.7%	49.0%
East South Central	1.24	−0.08	0.50	0.24	0.33	0.06	0.10	0.03	0.03	0.07	0.00	−0.04
		−6.2%	40.2%	19.1%	26.4%	5.1%	8.4%	2.5%	2.6%	5.6%	−0.1%	−3.5%
West North Central	0.74	−0.22	0.62	0.11	0.24	−0.02	0.06	−0.05	−0.01	0.09	−0.05	−0.03
		−30.1%	83.6%	15.4%	32.4%	−2.8%	8.7%	−7.1%	−1.3%	12.3%	−7.3%	−3.8%
Mountain	0.30	−0.14	−0.02	−0.02	0.14	−0.03	−0.01	0.10	0.04	0.04	−0.05	0.23
		−46.7%	−6.9%	−6.5%	48.5%	−10.0%	−4.2%	34.6%	14.6%	14.8%	−16.2%	78.0%
New England	0.02	−0.03	0.01	0.03	0.17	0.03	0.00	0.05	−0.06	0.02	0.02	−0.22
		−139.3%	40.7%	135.6%	909.4%	178.8%	5.2%	238.4%	−300.0%	79.8%	95.4%	−1144.0%

respectively. ADRD accounts for about a fifth (21.9%) of the gap in the Middle Atlantic region, which has the largest metro/nonmetro gap among these regions. In the Middle Atlantic, life expectancy at age 65 is 2.52 years higher for women residing in large central metros than for women in nonmetros. Cancer makes the next largest contribution (19.5%), followed by CLRD (18.3%), in this region. In South Atlantic, New England, Appalachia, and Pacific regions, ADRD is either the second or third largest contributor to e_{65} gaps, accounting for more of these gaps than stroke, diabetes, or accidents. In the remaining regions, differences in ADRD do not contribute to the metro/nonmetro life expectancy gap but instead act to narrow the gap. In these regions, the largest contributors to life expectancy gaps tend to be heart disease, CLRD, and either cancer (West South Central, East South Central, West North Central) or accidents (Mountain).

The e_{65} gaps tend to be smaller for men than for women, ranging from 0.02 years in New England to 1.96 years in the South Atlantic. The share of these gaps accounted for by ADRD also tends to be smaller for men than for women, ranging from 1.0% to 12.6% in the five regions

where we observed a metro/nonmetro gap in ADRD mortality. ADRD is the largest contributor to the nonmetro life expectancy disadvantage for men in the Middle Atlantic region, where it accounts for 0.21 years or 12.6% of the 1.66-year gap. In this region, ADRD is the third largest contributor to the metro/nonmetro gap after cancer (23.5%) and CLRD (18.1%). ADRD accounted for 8.1% (0.16 years of the 1.96-year gap) in the South Atlantic region. Its contribution ranks fourth after heart disease, cancer, and CLRD. In the remaining regions, ADRD does not make significant contributions to the metro/nonmetro life expectancy gaps.

4. Discussion

ADRD is an increasingly important cause of morbidity and mortality in the United States. It was the third leading cause of death among adults aged 65 and older in 2019 (CDC/NCHS, 2021). Levels of ADRD mortality are now roughly or over twice as high as stroke mortality. Although rural areas tend to be older than other parts of the country, have experienced particularly adverse mortality trends over the past decade, and are expected to find it particularly challenging to cope with the rising prevalence of ADRD, we are not aware of prior studies that have documented the increases in ADRD mortality in nonmetro areas. This study also establishes that differences in ADRD mortality between metro/nonmetro areas have grown substantially. Death rates from ADRD were nearly identical in large central metros and nonmetros in 1999, but a clear metro/nonmetro gradient has emerged over the past two decades. Today, the highest levels of ADRD mortality are observed in the most rural areas (nonmetros) and the lowest levels of ADRD mortality are observed in the most urban areas (large central metros). Few prior studies have examined whether the nonmetro disadvantage differs across regions, which is especially salient given the considerable heterogeneity among nonmetro areas.

We find that metro/nonmetro gaps in ADRD mortality exist in six regions for women and five regions for men, with the largest gaps observed in the Middle Atlantic, South Atlantic, and East North Central regions. ADRD now makes a substantial contribution to the difference in life expectancy at age 65 between large central metros and nonmetros within these regions. Among women, ADRD's contribution is on par with the contributions of top leading causes of death such as heart disease, cancer, and chronic lower respiratory diseases. In most cases, ADRD's contribution is far larger than the contributions of the remaining leading causes of death, which include stroke, diabetes, and accidents. ADRD accounted for 11–30% of the nonmetro life expectancy disadvantage among women in 2019. Among men, ADRD made smaller contributions than for women, but these contributions may be expected to rise in the coming decades. ADRD tends to make the largest contributions to metro/nonmetro life expectancy gaps in regions located in the Northeast and along the east coast of the United States, as well as the Pacific (among women). What are some factors shared by these regions? The Middle Atlantic and South Atlantic have fairly sizeable metro/nonmetro life expectancy gaps compared to the other regions. The same factors that contribute to higher overall life expectancy in large central metros compared to nonmetros may also contribute to lower levels of ADRD mortality in the former areas and elevated levels of ADRD mortality in the latter areas. These regions also have among the largest differences in population density between metro and nonmetro areas. It could be that metro/nonmetro areas are more differentiated within these regions, leading to more selective out-migration from nonmetros or more selective in-migration into metros. Another possibility is that the relatively small nonmetro populations in places like the Middle Atlantic may confer greater within-region/within-state political power on metropolitan areas, leading to sharper distinctions in resource distribution between metro and nonmetro areas within these regions. Future research further unpacking these differences is needed.

We have also identified the rural areas experiencing the highest levels of ADRD mortality. In some cases, these areas may not overlap with those exhibiting the largest metro/nonmetro gaps because ADRD mortality is more uniformly distributed across metro/nonmetro areas within some regions than others. The nonmetro areas with the highest levels of ADRD mortality are the East South Central region followed by Appalachia (for women) and New England (for men). It is notable that several of these regions have historically been disadvantaged; the East South Central region has the lowest life expectancy among all ten regions, and Appalachia has the second lowest life expectancy (Elo et al., 2019; Monnat, 2020; Singh et al., 2017). These areas have also experienced the largest increases in ADRD mortality over the past two decades—the levels of ADRD mortality in these areas were more than triple the levels observed in 1999. These nonmetro areas not only have the highest levels of ADRD mortality today, but they have also experienced dramatic increases in a fairly short period of time. These very rapid increases may be particularly difficult for families, communities, and health and long-term care systems to address.

The limitations of this study include the possibilities that reporting of Alzheimer's disease on death certificates has changed over time, that it is underreported on death certificates, or that it may be differentially reported across geographic areas (James et al., 2014; Stokes et al., 2020). These concerns are partly addressed by the use of the broader ADRD category rather than AD alone, and the fact that the NCHS provides specific guidance for coding the underlying cause of death where dementia is mentioned on the death certificate and conducts consistency checks of the information provided on death certificates (Kramarow & Tejada-Vera, 2019).

Alzheimer's disease mortality has been increasing over time. These increases may reflect improvements in survival (i.e., as more individuals survive to older ages, rather than dying of causes that predominate at younger ages, they become more susceptible to dying of causes that prevail at the older ages like ADRD), improved diagnosis of AD, and greater awareness and recognition among physicians and the public about AD as a cause of death (Hoyert, 1996; Hoyert & Rosenberg, 1997). A report by the NCHS concluded that factors like attributing AD deaths to other types of dementia or changes over time in the propensity for AD to be listed as an underlying versus a multiple cause of death could not account for the entirety of increases in AD mortality (Hoyert, 1996). This set of studies considering changes over time in AD reporting are based on earlier data which predate the present analysis. More recent studies (discussed in the following paragraphs) have largely focused on how reporting changed in response to changes in ICD coding and on producing estimates of the underreporting of AD.

The most significant change in the reporting of AD deaths occurred with the transition from ICD-9 to ICD-10 in 1999. In ICD-9, deaths classified as Alzheimer's disease deaths required a definitive diagnosis, while probable cases without a definitive diagnosis were classified separately as presenile dementia (Anderson et al., 2001; Moschetti et al., 2012). With the change to ICD-10, both definitive and probable cases of AD were consolidated into a single code, which meant that the majority of presenile dementia deaths became classified as AD deaths (Anderson et al., 2001; Moschetti et al., 2012). In this study, we use data from 1999 onwards—only after the transition to ICD-10 occurred—and we examine the broader category of ADRD deaths rather than AD alone. The use of this combined category is recommended by several studies (Akushevich et al., 2021; Hoyert & Rosenberg, 1997; Kramarow & Tejada-Vera, 2019). It also accounts for changing patterns in attribution of ADRD deaths[1] and in part addresses the difficulty of assigning deaths to a single cause (Kramarow & Tejada-Vera, 2019).

[1] Using the broader ADRD category will be more consistent in the following two examples: (1) if AD-related deaths were initially more likely to be attributed to unspecified dementia but are increasingly likely to be attributed to Alzheimer's disease, or (2) if the introduction of new screening methods indicating evidence of AD in the absence of clinical symptoms of cognitive decline make it more likely for deaths to be classified as AD deaths rather than other forms of dementia.

A variety of approaches have been used to generate estimates of underreporting, including comparing Medicare claims data to death certificates, using surveys with diagnostic assessments of dementia and examining the proportion of cases where AD appears on death certificates, and comparing estimates based on when AD is listed as the lone underlying cause versus when AD is listed elsewhere on the death certificate (Ganguli & Rodriguez, 1999; Hoyert, 1996; Hoyert & Rosenberg, 1997; Ives et al., 2009; James et al., 2014; Macera et al., 1992; Steenland et al., 2009; Stokes et al., 2020; Weuve et al., 2014). The majority of these studies face some limitations—for example, they are restricted to a single city (Weuve et al., 2014), a single study or dementia registry based within selected states (Ganguli & Rodriguez, 1999; Ives et al., 2009; James et al., 2014; Macera et al., 1992), or to members of a specific religious order (James et al., 2014). Most studies find underreporting in the range of 1.5–3.0, although some find an adjustment factor as high as 6.0 (Ganguli & Rodriguez, 1999; Hoyert & Rosenberg, 1997; Ives et al., 2009; James et al., 2014; Macera et al., 1992; Stokes et al., 2020; Weuve et al., 2014). The estimates on the higher end (i.e., upwards of an adjustment factor of 3) take a fairly extreme approach of assuming that all deaths occurring among people with AD should be attributed to ADRD.

Prior studies have found that differences in cause of death coding were not major contributors to geographic variation in ADRD mortality (Akushevich et al., 2021). They found that differences across states did not change when they used multiple cause of death data instead of only underlying cause data, nor did these patterns change when they consolidated causes of death with symptomology similar to ADRD into a single combined category (Akushevich et al., 2021). To the best of our knowledge, studies have not examined differences in underreporting of ADRD across the urban-rural continuum. The most likely scenario is that the degree to which ADRD is underreported on death certificates would be higher in rural than urban areas given their lower diagnostic capacity (Abner et al., 2016). This would imply that rural areas may in fact be experiencing even higher levels of ADRD mortality and that metro/-nonmetro gaps in ADRD mortality may be even larger than those documented in this study. Despite these limitations, ADRD mortality based on death certificate data is likely among the most accurate markers of the mortality impact of ADRD available to researchers. Other measures, such as the case fatality rate based on survey data, are likely more affected by differentials in the quality of health care across regions and metro categories.

In order to examine how differential trajectories of misreporting may influence the findings reported in this study, we calculate a series of counterfactual scenarios reported in Appendix Figures A7-A11. These simulations use underreporting factors consistent with the prior literature and explore several alternative scenarios (e.g., what the metro/nonmetro gaps in ADRD mortality would look like with adjustment for underreporting, if underreporting differed across time, and if the accuracy of reporting differentially increased over time). Although the absolute levels of ADRD mortality differ in each of these scenarios, they indicate that we would consistently observe a large and widening metro/nonmetro gap in ADRD mortality across a range of misreporting trajectories.

The focus of this paper is on the growing gap between large central metros and nonmetros because these two groups lie at the extremes of the urban-rural continuum, constituting the most and least metropolitan areas. However, it is also important to note that in some regions, medium/small metros or large metro suburbs have higher ADRD mortality rates than even nonmetros. For example, in the Middle Atlantic region, nonmetros have higher ADRD mortality rates than large central metros, but lower ADRD mortality rates than medium/small cities. The rate of increase in ADRD mortality in nonmetros outstripped the corresponding rates of increase for large central metros in eight regions, for large metro suburbs in six regions, and for medium/small cities in six regions (Appendix Table A3). Future studies should examine the sources of this variation.

Another fruitful avenue for future research is further investigation of how social, economic, and health care system factors contribute to metro/nonmetro differences in ADRD mortality. To provide some initial insights, we conducted supplemental analyses examining the associations between ADRD mortality and socioeconomic status, population characteristics, health care system variables, and mortality from other causes at the county level (Appendix Figure A6 and Table A6). These are purely point-in-time associations and do not have any casual interpretation. We find that higher population density, education, income, and physician and specialist density are all significantly associated with lower ADRD mortality, while mortality from other causes is significantly associated with higher ADRD mortality. Higher levels of socioeconomic resources—higher shares of the population with a college degree or more and higher median household income—are associated with lower ADRD mortality. Prior studies have identified the fundamental role of SES in determining health outcomes in part due to its influence on the uptake of healthy behaviors, the more rapid adoption of new health technologies, greater access to high quality health care, and greater access to high quality housing and lower exposure to unhealthy environments (Link & Phelan, 1995). While these estimates suggest that similar mechanisms may be operating for ADRD mortality, more research is needed to identify the precise pathways leading to this association. Higher population density is significantly associated with lower ADRD mortality. This may reflect greater ease of access to health care and socioeconomic resources, which tend to be concentrated in population centers. The health care access pathway is further supported by the result that counties with a greater number of doctors per capita, a higher share of specialists, and a greater number of neurologists per capita also tend to have lower mortality from ADRD. Being in poor health in general and having more chronic conditions may increase ADRD mortality risk (James et al., 2014). A greater presence of doctors and specialists may be helpful in preventing the initial development of chronic disease and providing more effective management of chronic diseases, which could reduce the risk of developing or dying from ADRD. Health care personnel seem to be the salient factor rather than hospitals or other physical infrastructure in general, since the number of hospital beds per capita is not significantly associated with ADRD mortality. Selective migration has been suggested as one potential explanation for geographic variation in all-cause mortality and mortality from other causes. Considering the metro/nonmetro gap in particular, it is possible that populations in nonmetro areas may be becoming more negatively select on characteristics that are associated with increased mortality risk. While this selective effect is difficult to precisely identify, we find no significant association between population loss and ADRD mortality, though it remains an open question worthy of further examination. Finally, mortality from all other causes besides ADRD, which may be an indicator of overall levels of health and chronic disease in the population, is significantly and positively associated with ADRD mortality. One potential explanation is that areas with higher ADRD mortality may include a larger share of the population arriving at the older ages in poor health, which is itself a risk factor for ADRD mortality.

Understanding the high and increasing level of ADRD mortality, particularly in nonmetro areas, is critical. Populations in rural areas tend to have a higher prevalence of behavioral risk factors including smoking, obesity, and sedentary lifestyles (Dwyer-Lindgren et al., 2017; Hendi et al., 2021; Matthews et al., 2017). As a result, rural populations also experience high prevalences of chronic diseases including hypertension, diabetes, hyperlipidemia, and depression, as well as high comorbidity rates (Abner et al., 2016; Jensen et al., 2020; Rahman et al., 2020). These chronic conditions may be more poorly managed due to barriers to health care access and weaker health care infrastructure in rural areas. Individuals living in rural areas may also be more exposed to environmental pollutants and occupation-based exposures to toxins. All of these factors tend to elevate the risks of developing ADRD and overall mortality. Poor health care infrastructure and barriers to timely diagnosis may restrict access to treatments that can slow the progression of

or help manage symptoms associated with ADRD (Rahman et al., 2020, 2021). This may contribute to shorter survival and higher mortality among individuals with ADRD in rural versus urban areas. Compositional factors may also play a role. For example, education levels are lower in rural than urban areas. Low education is a risk factor for ADRD (Langa et al., 2017), and there are steep educational gradients in life expectancy and particularly adverse mortality trends among the least educated (Hendi, 2015, 2017). However, given that prior studies have found a persistent rural disadvantage in cognitive functioning even after accounting for sociodemographic characteristics including age, education, and household assets (Weden et al., 2018), it is unlikely that the higher prevalence of adults with low education alone can account for the nonmetro disadvantage observed in this study. Selective outmigration from rural to urban areas may contribute to both population decline and higher levels of ADRD mortality in rural areas if less educated and unhealthier individuals are left behind.

This process has contributed to a sharp decline in services, particularly health and long-term care services, in nonmetropolitan areas. Hospital and nursing home closures are accelerating in rural areas, generating both acute and long-term care access problems (Kaufman et al., 2016). Between 2008 and 2018, 472 nursing homes in 400 nonmetropolitan counties closed, and in 2018, around a tenth (10.1%) of nonmetro counties had no nursing homes compared to only 3.7% of metro counties (Sharma et al., 2021). The declining availability of services in rural areas is alarming given the aging of rural populations, the dramatic increase in ADRD mortality documented in this study, and the high use of services among individuals with ADRD. Nearly half of nursing home residents (47.8%) and hospice patients (44.5%) have been diagnosed with Alzheimer's disease or other dementias, and it is estimated that at least three-quarters of people with dementia will spend time in a nursing home (Bynum, 2014; Harris-Kojetin et al., 2019). The majority of deaths due to dementia occur in nursing homes or other long-term care facilities (Kramarow & Tejada-Vera, 2019). In the absence of sufficient formal care options, it is likely that family members and other unpaid caregivers will be called upon to fill these gaps. The burden on families and informal caregivers is already substantial, amounting to an estimated 18.6 billion hours of care worth $244 billion in 2019, and may occur disproportionately in rural areas (Alzheimer's Association, 2020).

Author statement

Jessica Y. Ho: Conceptualization, Methodology, Data Curation, Formal Analysis, Investigation, Writing – Original Draft, Writing – Review & Editing, Visualization. Yujin Franco: Formal Analysis, Writing – Original Draft, Writing – Review & Editing.

Ethical statement

The authors declare no competing interests and certify that the material in this manuscript is not published or under consideration for publication elsewhere.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ssmph.2022.101052.

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