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Dementia Risk and Disadvantaged Neighborhoods

Christina S. Dintica, PhD; Amber Bahorik, PhD; Feng Xia, MPH; Amy Kind, MD, PhD; Kristine Yaffe, MD

Multimedia

Supplemental content

IMPORTANCE Residence in a disadvantaged neighborhood may be associated with an increased risk for cognitive impairment and dementia but is understudied in nationally representative populations.

OBJECTIVE To investigate the association between the Area Deprivation Index (ADI) and dementia.

DESIGN, SETTING, AND PARTICIPANTS Retrospective cohort study within the US Veterans Health Administration from October 1, 1999, to September 30, 2021, with a national cohort of older veterans receiving care in the largest integrated health care system in the United States. For each fiscal year, a 5% random sample was selected from all patients (n = 2 398 659). Patients with missing ADI information (n = 492 721) or missing sex information (n = 6) and prevalent dementia cases (n = 25 379) were excluded. Participants had to have at least 1 follow-up visit (n = 1 662 863). The final analytic sample was 1 637 484.

EXPOSURE Neighborhoods were characterized with the ADI, which combines several sociodemographic indicators (eg, income, education, employment, and housing) into a census block group-level index of disadvantage. Participants were categorized into ADI rank quintiles by their census block group of residence (higher ADI rank quintile corresponds with more deprivation).

MAIN OUTCOME AND MEASURES Time to dementia diagnosis (using *International Classification of Diseases, Ninth Revision* and *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* codes) was estimated with Cox proportional hazards models with age as the time scale, and the sensitivity of the findings was evaluated with Fine-Gray proportional hazards models, accounting for competing risk of death.

RESULTS Among the 1 637 484 Veterans Health Administration patients, the mean (SD) age was 68.6 (7.7) years, and 1 604 677 (98.0%) were men. A total of 7318 patients were Asian (0.4%), 151 818 (9.3%) were Black, 10 591 were Hispanic (0.6%), 1 422 713 (86.9%) were White, and 45 044 (2.8%) were of other or unknown race and ethnicity. During a mean (SD) follow-up of 11.0 (4.8) years, 12.8% of veterans developed dementia. Compared with veterans in the least disadvantaged neighborhood quintile, those in greater disadvantage groups had an increased risk of dementia in models adjusted for sex, race and ethnicity, and psychiatric and medical comorbid conditions (first quintile = reference; second quintile adjusted hazard ratio [HR], 1.09 [95% CI, 1.07-1.10]; third quintile adjusted HR, 1.14 [95% CI, 1.12-1.15]; fourth quintile adjusted HR, 1.16 [95% CI, 1.14-1.18]; and fifth quintile adjusted HR, 1.22 [95% CI, 1.21-1.24]). Repeating the main analysis using competing risk for mortality led to similar results.

CONCLUSIONS AND RELEVANCE Results of this study suggest that residence within more disadvantaged neighborhoods was associated with higher risk of dementia among older veterans integrated in a national health care system.

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Author Affiliations: Department of Psychiatry and Behavioral Sciences, University of California, San Francisco (Dintica, Bahorik, Yaffe); Northern California Institute for Research and Education, San Francisco (Xia); University of Wisconsin Center for Health Disparities Research, Madison (Kind); Department of Medicine, University of Wisconsin School of Medicine and Public Health, Madison (Kind); San Francisco Veterans Affairs Health Care System, San Francisco, California (Yaffe).

Corresponding Author: Christina S. Dintica, PhD, Department of Psychiatry and Behavioral Sciences, University of California, San Francisco, 675 18th St, San Francisco, CA 94107 (christina.dintica@ucsf.edu).

Alzheimer disease and related dementias (ADRD) disproportionately affect historically underrepresented and socially disadvantaged populations.[1] Living in a socioeconomically disadvantaged neighborhood has been shown to negatively affect health (eg, higher rates of cardiovascular diseases, diabetes, and pre-mature mortality); health behaviors; stress levels; and access to food, safety, and education. This “social exposome” of social vulnerability as a result of social inequalities (characteristics of communities and the built environment, including environmental nuisance exposure)[2] has been associated with adverse health outcomes beyond individual-level factors, including social determinants of health.[3-5] Many of these conditions could affect brain health and are associated with mild cognitive impairment and ADRD risk, suggesting that a disadvantaged social exposome could be associated with late-life cognitive impairment.[6,7]

Area-level deprivation measures, such as the publicly available Area Deprivation Index (ADI),[8] encompass geographically precise area-based estimates of the socioeconomic disadvantage of neighborhoods. These composite measures integrate indicators for several social determinants of health,[1] including education, employment, housing, and poverty,[8,9] and allow the study of how living in socioeconomically disadvantaged neighborhoods may adversely affect health and disease outcomes.[8-10]

Research is still limited about the association between neighborhood socioeconomic deprivation and cognitive impairment.[8,9,11,12] A recent population-based study in Minnesota including cognitively unimpaired adults at baseline showed that the risk for progression to dementia increased for every decile increase in the ADI state ranking.[13] Another study including Asian American and non-Hispanic White members of a Northern California integrated health care delivery system reported that higher ADI quintile was associated with higher dementia incidence among non-Latino White individuals but not Asian American individuals.[14] Moreover, growing evidence has shown an association of neighborhood disadvantage with lower hippocampal volume and higher accumulation of Alzheimer disease neuropathology.[1,15] Nevertheless, these studies were conducted in populations with low ADI heterogeneity, covering a single geographic area, often with limited diversity, and did not address mortality as a competing risk. We aimed to investigate the association of ADI quintile with ADRD incidence among veterans enrolled in a Veterans Health Administration (VHA) health care system. The VHA is the largest integrated health care system in the United States, hence providing a unique opportunity to investigate the role of the ADI in dementia incidence. The VHA sample reflects more diversity in the general US population and a wider range of ADI values, particularly with more representation of populations in the most disadvantaged ADI ranks. In addition, we aimed to adjust for important demographic and health covariates that have previously been associated with higher dementia risk in veteran populations and to account for the potential competing risk of death.

Key Points

Question Is there a difference in dementia incidence among Veterans Health Administration enrollees by neighborhood disadvantage as assessed by the Area Deprivation Index?

Findings In this cohort study of 1 637 484 Veterans Health Administration patients, during a mean follow-up of 11.0 years, 12.8% of veterans developed dementia; those in greater disadvantage groups had an increased risk of dementia in models adjusted for demographic characteristics and comorbid conditions, and those residing within the most disadvantaged neighborhood quintile demonstrated the greatest risk.

Meaning Findings suggest that within a representative national cohort of older veterans who received care, significant differences in dementia incidence existed based on neighborhood deprivation.

Methods

Study Population

We identified a random sample of all patients aged 55 years or older who obtained VHA care from October 1, 1999, to September 30, 2021. For each fiscal year (2000-2021), we selected a 5% random sample from all patients and then merged these samples for all years, resulting in a random sample of 2 398 659 patients. Further details regarding the random sampling procedures have been previously reported.[16] We excluded 492 721 patients with missing ADI information and 6 patients with missing sex information.

For all participants, we obtained demographic data and ADRD diagnoses from all inpatient and outpatient visits from the National Patient Care Databases and death data from the Vital Status File database. National ADI data were linked using 9-digit address zip codes for 1 905 932 participants from the Planning Systems Support Group Geocoded Enrollee Files Database. Participants had to have at least 1 visit during a 2-year baseline period before their random selection date (baseline) and at least 1 follow-up visit (n = 1 662 863), and we excluded those with prevalent ADRD during the baseline period (n = 25 379). Our final analytic sample was 1 637 484.

Standard Protocol Approvals, Registrations, and Patient Consent

This cohort study was approved by institutional review boards at the University of California, San Francisco; the San Francisco Veterans Affairs Medical Center; and the US Army Medical Research and Material Command, Office of Research Protections, Human Research Protection Office and was granted a waiver of informed consent. The waiver was granted by the University of California, San Francisco and San Francisco Veterans Affairs Medical Center institutional review boards because this is a minimal risk study, all data used in this study have been previously extracted from the electronic health record, and any adverse effects that would stem from waiving informed consent were not anticipated. National ADI data were obtained through the Neighborhood Atlas from the University of Wisconsin–Madison School of Medicine and Public Health.[8,17] This study used the 2015 ADI. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Neighborhood Disadvantage and ADRD Diagnoses

We characterized neighborhood disadvantage with the ADI, a validated measure that combines 17 specific indicators (eg, income, education, employment, and housing) into an index of disadvantage.[8] Participants' zip codes from residential addresses were linked to the ADI via the 9-digit zip code crosswalk available on the Neighborhood Atlas. We used these data to categorize participants into ADI rank quintiles, in which higher ADI rank quintile corresponds with higher neighborhood disadvantage. Prevalent dementia during the 2-year baseline (for exclusion) and incident dementia during follow-up were identified with a comprehensive list of inpatient and outpatient *International Classification of Diseases, Ninth Revision* (*ICD-9*) and *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (*ICD-10*) codes recommended by the VHA Dementia Steering Committee.[18]

Other Measures

Demographic data, including age, sex, and race and ethnicity (categorized as Asian, Hispanic, non-Hispanic Black, non-Hispanic White, or other or unknown), were based on self-report. Participants identifying as "other" or whose race and ethnicity were unknown were categorized as other or unknown. The proportion of participants identifying as Alaska Native or American Indian was very small; therefore, this category was combined with the "other or unknown" category. We used zip codes and 2016 American Community Survey data to classify participants as living in broad educational and income strata. We categorized income by tertile of median zip code tabulation area income for participants (low, middle, and high) and reported values for the low-income group. Education was defined according to participant zip code tabulation area, in which 25% or less vs more than 25% of the adult population had completed a college education (bachelor's degree or higher). Medical and psychiatric comorbid conditions as identified by *ICD-9* and *ICD-10* codes were assessed during the 2-year baseline. Comorbid conditions included those particularly relevant for veteran populations, such as traumatic brain injury, posttraumatic stress disorder, and depression, as well as current tobacco use, diabetes, obesity, hypertension, and dyslipidemia.

Statistical Analysis

Baseline characteristics were compared across ADI quintile groups using analysis of variance for continuous variables and the χ^2 test for categorical variables. Cox proportional hazards regression was used to assess the association between ADI quintile and risk of dementia, with censoring at the date of the last medical encounter or death and age as the time scale. Models were unadjusted and adjusted for sex, race and ethnicity, traumatic brain injury, posttraumatic stress disorder, depression, current tobacco use, diabetes, obesity, hypertension, and dyslipidemia and are reported as hazard ratios (HRs) with 95% CIs. Because education and income are included in the ADI and could therefore present bias due to collinearity, we assessed correlations between education and income and ADI quintile, and we also assessed the sensitivity of the results by inclusion of education and income in the final model. We also evaluated the sensitivity of the results by repeating our main analysis with Fine-Gray proportional hazards regression, which models death as an alternate competing risk, providing a more conservative estimate of the association. Proportional hazards model assumptions were checked and met for all final models. *P* values were 2-sided, with statistical significance defined as $P < .05$. Analyses were performed with SAS, version 9.4 (SAS Institute Inc), from November 21, 2022, to May 1, 2023.

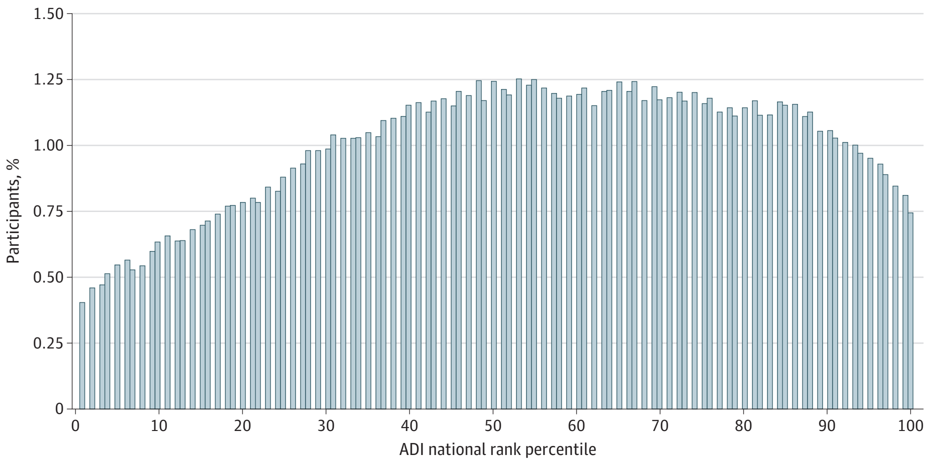
Results

Of the 1 637 484 VHA patients without dementia at baseline, the mean (SD) age was 68.6 (7.7) years, 1 604 677 were men (98.0%), and 32 807 were women (2.0%). A total of 7318 patients were Asian (0.4%), 151 818 were Black (9.3%), 10 591 were Hispanic (0.6%), 1 422 713 were White (86.9%), and 45 044 were of other or unknown race and ethnicity (2.8%). There was a wide range of ADI values in the sample, with most in the middle or more disadvantaged ranks and a lower proportion in the least disadvantaged ranks (**Figure 1**). Participants were followed up for a mean (SD) of 11.0 (4.8) years (median, 11.2 years; range, 7.4-14.9 years) until they developed dementia, died, or had their last medical encounter, whichever occurred first.

Baseline characteristics of the participants according to ADI quintile groups are shown in **Table 1**. Most demographic characteristics and comorbid conditions varied by ADI quintile groups, with Black and Hispanic participants more likely to live in the most disadvantaged neighborhood quintile (Black participants, 14 714 in first quintile vs 55 365 in fifth quintile; Hispanic participants, 1558 in first quintile vs 2884 in fifth quintile). All ADI groups had a high prevalence of cardiovascular risk factors, with those living in the most disadvantaged neighborhood quintile having a higher prevalence of most conditions (except for dyslipidemia) than those in other quintiles. The prevalence of depression was similar across all groups, with a slightly higher prevalence among the most disadvantaged quintile (first quintile, 23 862 [11.8%]; second quintile, 39 208 [12.2%]; third quintile, 48 409 [12.3%]; fourth quintile, 48 591 [12.5%]; and fifth quintile, 43 049 [12.9%]). Prevalence of posttraumatic stress disorder and traumatic brain injury ranged from 0.2% (776 of 334 268 patients in the fifth quintile for traumatic brain injury) to 6.7% (13 586 of 202 247 patients in the first quintile for posttraumatic stress disorder), with a lower prevalence among the most disadvantaged quintile group (5.5% [18 507 of 334 268 patients] for posttraumatic stress disorder and 0.2% [776 of 334 268 patients] for traumatic brain injury).

Overall, 208 909 of the 1 637 484 participants (12.8%) developed dementia during follow-up. Kaplan-Meier survival curves (**Figure 2**) by ADI quintile groups indicated that the groups significantly differed by dementia risk. The unadjusted and adjusted risk of dementia by ADI quintile groups is

Figure 1. Histogram of Area Deprivation Index (ADI) National Rank



In this veteran population, the proportion of participants living in the most disadvantaged neighborhoods was higher than in the least disadvantaged neighborhoods across the United States. Data are categorized in percentiles from 1 to 100 (lower ADI values = less disadvantaged).

Table 1. Baseline Characteristics of 1 637 484 Older Veterans by Area Deprivation Index Quintile of Their Neighborhood of Residence[a]

Characteristic	Quintile, No. (%) First (1-20) (n = 202 247)	Second (21-40) (n = 320 934)	Third (41-60) (n = 392 438)	Fourth (61-80) (n = 387 597)	Fifth (81-100) (n = 334 268)	*P* value
Age, mean (SD), y	69.8 (8.0)	68.9 (7.7)	68.5 (7.7)	68.3 (7.7)	68.0 (7.7)	<.001
Sex						
Male	198 247 (98.0)	314 457 (98.0)	384 506 (98.0)	379 928 (98.0)	327 539 (98.0)	.55
Female	4000 (2.0)	6477 (2.0)	7932 (2.0)	7669 (2.0)	6729 (2.0)	
Race and ethnicity						
Asian	3573 (1.8)	1732 (0.5)	944 (0.2)	641 (0.2)	428 (0.1)	<.001
Hispanic	1558 (0.8)	1847 (0.6)	2002 (0.5)	2300 (0.6)	2884 (0.9)	
Non-Hispanic Black	14 714 (7.3)	22 189 (6.9)	27 064 (6.9)	32 486 (8.4)	55 365 (16.6)	
Non-Hispanic White	174 760 (86.4)	285 932 (89.1)	352 543 (89.8)	342 574 (88.4)	266 904 (79.8)	
Other or unknown[b]	7642 (3.8)	9234 (2.9)	9885 (2.5)	9596 (2.5)	8687 (2.6)	
Education >25% college educated in zip code[c]	169 424 (85.5)	211 628 (67.1)	167 650 (43.5)	97 258 (25.6)	50 879 (15.6)	<.001
Low median income tertile in zip code[d]	13 095 (6.6)	41 343 (13.1)	94 749 (24.6)	162 125 (42.8)	221 695 (68.3)	<.001
TBI	639 (0.3)	847 (0.3)	915 (0.2)	934 (0.2)	776 (0.2)	<.001
PTSD	13 586 (6.7)	19 847 (6.2)	21 969 (5.6)	21 014 (5.4)	18 507 (5.5)	<.001
Depression	23 862 (11.8)	39 208 (12.2)	48 409 (12.3)	48 591 (12.5)	43 049 (12.9)	<.001
Current tobacco use	17 159 (8.5)	35 797 (11.2)	51 586 (13.1)	58 172 (15.0)	57 350 (17.2)	<.001
Diabetes	42 339 (20.9)	73 621 (22.9)	95 239 (24.3)	97 750 (25.2)	88 457 (26.5)	<.001
Obesity	29 047 (14.4)	50 592 (15.8)	64 686 (16.5)	65 402 (16.9)	57 605 (17.2)	<.001
Hypertension	123 574 (61.1)	202 274 (63.0)	254 231 (64.8)	257 737 (66.5)	228 508 (68.4)	<.001
Dyslipidemia	115 094 (56.9)	187 896 (58.5)	232 974 (59.4)	228 984 (59.1)	191 262 (57.2)	<.001

Abbreviations: PTSD, posttraumatic stress disorder; TBI, traumatic brain injury.

[a] Area Deprivation Index national rank: first equals least disadvantaged neighborhoods and fifth equals most disadvantaged neighborhoods.

[b] Participants identifying as "other" or whose race and ethnicity were unknown were categorized as other or unknown. The proportion of participants identifying as Alaska Native or American Indian was very small; therefore, this category was combined with the "other or unknown" category.

[c] Education had 32 410 (2.0%) missing values.

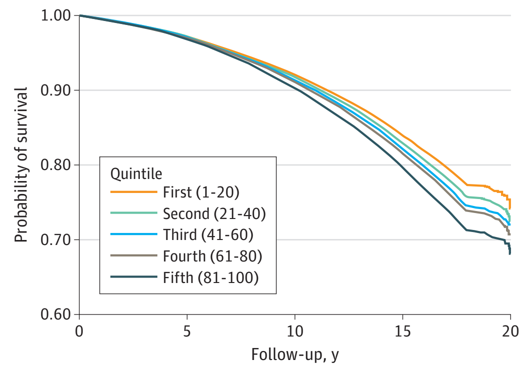
[d] Income had 37 475 (2.3%) missing values.

shown in **Table 2**. Compared with individuals residing in the least disadvantaged neighborhood quintile (first quintile), the HR of dementia was higher for those residing in greater disadvantage neighborhood groups (second quintile HR, 1.08 [95% CI, 1.06-1.10]; third quintile HR, 1.13 [95% CI, 1.11-1.15]; fourth quintile HR, 1.17 [95% CI, 1.15-1.19]; and fifth quintile HR, 1.31 [95% CI, 1.29-1.33]). In the adjusted model (including further adjustment for sex, race and ethnicity, and psychiatric and medical comorbid conditions), compared with individuals residing in the least disadvantaged neighborhood quintile (first quintile), the adjusted HR (AHR) of dementia remained higher for those residing in greater disadvantage neighborhood groups (second quintile AHR, 1.09 [95% CI, 1.07-1.10]; third quintile AHR, 1.14 [95% CI, 1.12-1.15]; fourth quintile AHR, 1.16 [95%

CI, 1.14-1.18]; and fifth quintile AHR, 1.22 [95% CI, 1.21-1.24]). The association was linear (HR, 1.05; 95% CI, 1.04-1.05; $P < .001$ for trend), with individuals residing within the most disadvantaged neighborhood quintile demonstrating the greatest risk.

Collinearity was not demonstrated between education and ADI quintile (φ = 0.48) or between income and ADI quintile (Cramer V = 0.42). Results were similar after inclusion of education and income in the fully adjusted model. Moreover, repeating our main analysis (eg, unadjusted model with age as time scale and adjusted model) using competing risks regression led to similar results.

Figure 2. Kaplan-Meier Dementia-Free Survival by Area Deprivation Index Quintile Groups



No. at risk					
First (1-20)	202 247	175 235	116 360	50 353	2
Second (21-40)	320 934	277 464	183 211	76 538	3
Third (41-60)	392 438	340 933	226 823	93 972	3
Fourth (61-80)	387 597	339 419	227 481	95 509	5
Fifth (81-100)	334 268	293 619	197 342	84 579	7

Area Deprivation Index groups differed significantly in dementia risk ($P < .001$ for trend by log-rank test).

Discussion

Our study of 1 637 484 older veterans investigated the association between neighborhood disadvantage assessed with the ADI and dementia incidence in a nationwide sample with large representation across ADI strata, particularly in the most advantaged ADI ranks. We found a linear association between living in neighborhoods with greater disadvantage by ADI quintile and risk of developing dementia, even after adjustment for important covariates and accounting for competing risk of death. This finding underscores the importance of the social exposome and social vulnerability for dementia risk, even in a population enrolled in the largest national, integrated health care system in the United States.

Research suggests that aspects of the social exposome such as neighborhood disadvantage can affect a person's health through various physical and social characteristics, such as access to healthy food and recreation opportunities.[15,19,20] Socioeconomically disadvantaged neighborhoods may have more stressors and fewer resources, which can hinder cognitively and physically beneficial activities.[21] The social exposome may also be associated with differential vulnerability and exposure to negative external factors. Most studies suggest that vulnerability is increased for individuals or groups with the lowest socioeconomic status, and this is associated with their health outcomes and their capacity to respond.[22] For example, the health consequences of exposure to air pollutants during pregnancy can be modified by the mother's socioeconomic status, which is associated with the ability to afford and access health care.[23] Indeed, evidence suggests that social and built neighborhood characteristics can affect health either through health promotion or by serving as a barrier to health promotion.[24] Previous studies on the association between area-based socioeconomic status and ADRD risk have yielded mixed results, with some studies not finding a significant association.[25] Individual-level socioeconomic status factors (eg, wealth) also play a role, which may partly explain this discrepancy.[25] There may also have been a lack of representation of individuals in the most disadvantaged neighborhoods. Additionally, the socioeconomic status of a neighborhood during middle or later adulthood may not reflect a person's early-life socioeconomic status experiences. More work is needed to study the life span repercussions of the social exposome. For instance, disadvantage as measured by the ADI has been associatd with children's brain development independently of other factors.[26,27] Hence, future studies should aim to implement a life course approach to understand how early-life, midlife, and late-life social and environmental vulnerability affects brain health and eventual risk of ADRD.

In addition to interventions at the individual level, those at neighborhood, community, state, or federal levels play a key role in promoting cognitive health and reducing disparities.[28,29] The social exposome should be addressed when interventions are developed because it is an essential factor associated with health disparities, reflecting systemic inequities within any society.[30] The findings of this study highlight the significance and value of taking the social exposome into account in research, outreach, community-based care management, and policy.[31] Social exposome measures such as the ADI can aid in identifying individuals at a higher risk of developing ADRD and informing clinical practices, as well as research design, recruitment, and retention strategies that ensure the inclusion of participants from areas with high ADI values. These practices are particularly important considering that veterans enrolled in the VHA theoretically have equal access to care; however, this study shows that health inequalities persist in disadvantaged areas.

Strengths and Limitations

A considerable strength of this study is the use of a large, representative, national sample of older adults, allowing for testing inferences about ADI differences in ADRD risk across the United States. Most prior studies have used samples with poor representation of individuals residing in contexts with high ADI values. This study used national data from the VHA, the largest integrated health care system in the United States, thus allowing for higher representation across ADI strata, geographic areas, and demographic characteristics. Moreover, we adjusted our analyses for important health and demographic

Table 2. Unadjusted and Adjusted Risk of Dementia by ADI Quintile of Participant Residence

	ADI national rank: quintile, HR (95% CI)[a]				
Model	First (1-20)	Second (21-40)	Third (41-60)	Fourth (61-80)	Fifth (81-100)
Unadjusted	1 [Reference]	1.08 (1.06-1.10)	1.13 (1.11-1.15)	1.17 (1.15-1.19)	1.31 (1.29-1.33)
Model 1[b]	1 [Reference]	1.09 (1.07-1.10)	1.14 (1.12-1.15)	1.16 (1.14-1.18)	1.22 (1.21-1.24)
Model 2[c]	1 [Reference]	1.08 (1.06-1.09)	1.12 (1.10-1.14)	1.13 (1.11-1.15)	1.17 (1.15-1.20)

Abbreviations: ADI, Area Deprivation Index; HR, hazard ratio; reference, ADI first (lowest) quintile, corresponding with the lowest level of neighborhood disadvantage.

[a] Hazard ratios and 95% CIs are from Cox proportional hazards regression, with age as the time scale. Unadjusted model has age as the time scale.

[b] Sex, race and ethnicity, traumatic brain injury, posttraumatic stress disorder, depression, current tobacco use, diabetes, obesity, hypertension, and dyslipidemia.

[c] Model 1 plus education and income.

variables and accounted for the competing risk of mortality, which is essential when assessing the differential risk of ADRD.

There are certain limitations to this study that may affect the interpretation and generalizability of its findings, particularly the use of *ICD-9* and *ICD-10* codes to establish diagnoses. Using administrative diagnostic codes for dementia may not be as sensitive as structured interviews and may have lower sensitivity. Moreover, the study was unable to examine ADRD diagnosis by subtype, which is not well defined in claims-based diagnostic codes. Although the cohort of veterans in this study represents a sample of patients throughout the US population, it did not include veterans who did not receive care through the VHA health care system and nonveterans. Therefore, the results may not be fully generalizable to those populations. In addition, veterans are not representative of the general population, particularly with only 2% of the participants being women and most being non-Hispanic White. Finally, we used 1 measurement of the ADI (2015) on the census block group level of the place of residence, and we cannot account for years of exposure at this ADI level. Moreover, neighborhoods are subject to change through forces such as gentrification that alter the individual sociodemographic profiles of the residents, as well as aspects of the neighborhood, including health care facility prevalence and crime rates; therefore, a limitation of this study was that such changes were not possible to address.

Conclusions

This study demonstrated that neighborhood disadvantage was negatively associated with brain health beyond individual-level factors, even in a population that theoretically has equal access to care. Continued research is needed on the association of neighborhood socioeconomic disadvantage and ADRD to understand the potential pathways involved and provide further valuable insight for public policies, community interventions, and social and health care to prevent and treat ADRD.

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Concept and design: Dintica, Kind, Yaffe.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Dintica, Bahorik, Xia.
Critical revision of the manuscript for important intellectual content: Dintica, Kind, Yaffe.
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