Birth in High Infant Mortality States and Dementia Risk in a Cohort of Elderly African American and White Health Care Members

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Abstract

Importance: Birth in areas with high infant mortality rates (IMRs) has been linked to worse long-term health outcomes, yet it is completely unknown if it impacts dementia risk.

Methods: 6,268 healthcare members were followed for dementia diagnosis from 1996–2015. Birth state IMRs from 1928 were ranked into quartile (worst IMRs quartile range: Whites: 69–129 deaths/1,000 live births, Non-Whites: 129–277 deaths/1,000 live births). Cox proportional hazard models estimated the dementia risk associated with birth state IMR quartile adjusting for demographics and lifecourse health indicators.

Results: Compared with Whites born outside of states in the worst IMR quartile, African Americans born in states in the worst IMR quartile had 92% increased dementia risk (HR=1.92; 95% CI: 1.42, 2.59), and African Americans born outside those states had 36% increased risk (HR=1.36; 95% CI: 1.20, 1.53). There was no association between birth state IMR and dementia risk among Whites.

Conclusions: Birth in states with the highest rates of infant mortality was associated with elevated dementia risk among African Americans but not Whites. The large absolute difference in IMRs likely reflects harsher early-childhood conditions experienced by African Americans. These findings suggest that childhood conditions may play a role in racial disparities in dementia rates.

Keywords

dementia; lifecourse; longitudinal; disparities; early life; infant mortality

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BACKGROUND

African Americans have 50–100% greater risk of dementia compared to Whites[1] and reducing such disparities was identified as a national priority by the National Alzheimer's Project Act[2]. However, the drivers of these differences are unclear, impeding the development of effective interventions. Identifying the primary drivers is a critical next step in identifying targets for interventions to diminishing these inequalities.

Infant mortality rates (i.e. the number of deaths among children under 1 year of age per 1,000 live births in the same year; IMR) are a powerful indicator of general population health and reflect the social and physical conditions of the environment in which the births occurred. Studies have linked infant mortality rates to area-level measures of income[3,4], unemployment rate[4,5], and educational attainment[4,6]. The effects of adverse early childhood conditions on health can persist into adult years through possible pathways such as health behaviors (e.g. smoking, alcohol consumption), educational opportunities, and later socioeconomic status.[7,8] Individuals born in areas with high IMRs have been shown to experience elevated mortality due to heart disease[9,10], stroke[11,12], stomach cancer[11], and tuberculosis[11], as well as increased all cause adult mortality[10,13]. Yet it remains unclear if IMRs are associated with worse brain health in late life and if this association may partially explain racial inequalities in rates of dementia. In this study, we examined whether birth in states with high IMRs is associated with elevated dementia risk in a large, diverse cohort of health plan members who all resided in Northern California by midlife.

METHODS

Study Participants.

Kaiser Permanente Northern California (KPNC) is a large integrated health care delivery system. KPNC has over 3 million members in Northern California and provides care to approximately 30% of the population in the catchment area. Its member population is generally representative of the overall population of the region, except with respect to the extremes of the income distribution[14–16]. Starting in 1964, all KPNC members in the San Francisco Bay Area were offered optional check-ups called Multiphasic Health Checkups (MHCs) that collected information on demographics, lifestyle, and health.[17] In these analyses, we included members who participated in the Multiphasic Health Checkups (MHC) during the 1960s-1970s. This study was approved by the KPNC Institutional Review Board.

Study Design.

A total of 10,862 members of KPNC met the following eligibility criteria: 1) participated in at least one MHC visit between 1964 and 1973, 2) were between 40–45 at the time of MHC participation, 3) and were KPNC members in 1996, when electronic medical records were implemented in the KPNC system. We excluded 1,624 individuals without information on birth place, 1,815 individuals born outside of the US, 696 individuals born in states that were not part of the US birth registry as of 1928 (Nevada, New Mexico, South Dakota, Texas,

Hawaii, District of Columbia, and Alaska), and 459 individuals who did not identify as African American or White. Our final sample included 6,268 people.

Birth state IMR.

State-level IMRs were obtained from a historical report issued by the US Census Bureau, which included IMRs from 1926–1931 for Whites and "Colored" (Non-White) groups separately.[18] IMRs from 1928 were used to best balance data completeness and proximity to the median sample birth year (1924). Race-specific infant mortality rates were linked to individual's place of birth, which was captured by an open-ended MHC questionnaire item asking "Where were you born?" IMRs for Non-Whites were used as a proxy for African American IMRs; African Americans comprised 96% of the Non-White population of the US in 1920.[19] In 1928 state-level IMRs ranged from 45 to 129 deaths per 1,000 live births (mean=65 deaths per 1,000 live births) for Whites and from 65 to 277 deaths per 1,000 live births (mean=126 deaths per 1,000 live births) for Non-Whites. In order to not impose a linear association between state-level IMRs and dementia, IMRs for were divided into quartiles for Whites and Non-Whites separately.

States with IMRs in the top quartile were classified as high IMR states (see Supplemental Table 1 for list of high IMR states by race). IMRs in those states ranged from 69 to 129 deaths per 1000 live births for Whites (mean=79 deaths per 1,000 live births) and 129 to 277 deaths per 1,000 live births for Non-White (mean=183 deaths per 1,000 live births). Of the eleven states in the top quartile of Non-White state-level IMRs, African Americans in our sample were only born in the following four: Oklahoma (88 people), Arizona (9 people), Montana (1 person), and Utah (1 person). Our sample included at least one White individual born in each of the ten states in the top quartile of White state-level IMRs.

Dementia Diagnosis.

Dementia diagnoses were ascertained from KPNC electronic records between January 1, 1996 and October 1, 2015 using the following International Classification of Diseases, Ninth Revision (ICD-9) diagnosis codes: Alzheimer's disease (331.0), vascular dementia (290.4x), and other/nonspecific dementia (290.0, 290.1x, 290.2x, 290.3, 294.2x, and 294.8). This method of identifying dementia cases is consistent with previous publications in this population.[20–23] A similar set of ICD-9 codes was found to have a sensitivity of 77% and a specificity of 95% compared with a consensus diagnosis of dementia utilizing medical records review, physical examination, neuropsychiatric battery, and structured interviews.[24]

Mortality.

Death between January 1, 1996 and October 1, 2015 was captured through electronic medical records, the California State Mortality File, and Social Security Death records.

Survey Health Data and Midlife and Late-life Risk Factors.

The 1964–1973 MHC questionnaire included questions about age, sex, race, and level of educational attainment. Educational attainment was operationalized as high school education or less versus greater than high school education. The 1964–1973 MHC visit also included several clinical measures of midlife vascular risk factors, including height and weight used

to calculate body mass index (BMI), systolic blood pressure, and diastolic blood pressure. Midlife high blood pressure was defined as systolic blood pressure 140 mm Hg and diastolic pressure 90 mm Hg.

Late-life diabetes and stroke were collected from electronic medical record diagnoses between January 1st, 1996 and October 1th, 2015. Diabetes status was collected from the KPNC Diabetes Registry which incorporates information from ICD-9 diagnoses, diabetes medication, and clinical measurements of hemoglobin A1c. Strokes were identified using ICD-9 codes for hemorrhagic stroke (430, 431), ischemic stroke (433.01–435.9), acute ill-defined cerebrovascular disease (436), and iatrogenic cerebrovascular infarction or hemorrhage (997.02). Missing indicators were used for 358 people without information on weight or height. There were no other missing data.

Statistical analysis.

We examined the distribution of demographic variables, and lifecourse vascular risk factors by birth in high IMR states and race. Next, we estimated age-adjusted dementia incidence rates (by standardizing to the 2000 US Census population) for African Americans and Whites by birth in high IMR state.

For African Americans and Whites separately, we estimated the risk of dementia associated with IMRs through two series of Cox proportional hazards models with age as the timescale. The first series of models examined quartiles of IMRs to allow for a non-linear association between IMRs and dementia adjusting for covariates in groups. Since mid- and late-life risk factors may be partial mediators of the association between IMR and dementia risk, we first adjusted for demographic variables, followed by further adjustment for midlife vascular risk factors, and lastly, further adjustment for late-life vascular risk factors.

Next, a series of models examined the association between dementia and birth in high IMR states (i.e. the top quartile of state-level IMRs) also sequentially adjusting for demographics, midlife vascular risk factors, and then late-life vascular risk factors. Individuals were censored at the first diagnosis of dementia, lapse in health plan membership 90 days or more, death, or at the end of study follow-up on October 1, 2015.

Next we concurrently examined the effects of birth state IMRs and race by grouping people into four categories: 1) Whites born outside high IMR states, 2) African Americans born outside high IMR states, 3) Whites born in high IMR states, and 4) African Americans born in high IMR states. We implemented Cox proportional hazards models examining the association between these four groups and dementia risk with Whites born outside high IMR states as the reference category. These models were adjusted for demographics, followed by additional adjustment for midlife vascular risk factors and then late-life vascular risk factors.

Lastly, we estimated the cumulative risk of dementia (in 5-year increments from 10 to 25 years) conditional on survival free of dementia to age 65 for each group using the Practical Incidence Estimator macro.[25] This macro incorporates death rates and assumes that individuals who die without a dementia diagnosis never develop dementia.

RESULTS

The sample eligible for the current study included 1,058 African Americans and 5,210 Whites, of which 29% and 38% respectively developed dementia during follow-up (Table 1). A slightly larger percent of African Americans were born in high IMR states than Whites (9.4% vs 7.7%; p= 0.08). By the end of follow up, 30% of the sample developed dementia, 33% died without a dementia diagnosis, and 18% were censored due to lapse in membership. The mean follow-up time was 11.6 years (range: 0.07 to 19.7 years).

The age-adjusted dementia incidence rate for African Americans born in high IMR states was 26 cases per 1,000 person-years compared to 23 cases per 1,000 person-years among African Americans born outside those states (Supplemental Table 2). The age-adjusted dementia incidence rate for Whites born in high IMR states was 17 cases per 1,000 person-years compared to 15 cases per 1,000 person-years among Whites born outside those states.

Compared to those born in the lowest quartile of state-level IMR, Whites born in the highest quartile were not at elevated risk of dementia in models adjusting for demographics and vascular lifecourse risk factors (HR=1.07; 95% CI: 0.86, 1.34; Table 2). African Americans born in the worst quartile of IMRs had 44% greater risk of dementia compared to African Americans born in the best quartile of IMRs (HR=1.44; 95% CI: 1.03, 2.01). The effect estimates remained similar in fully adjusted models for both racial groups.

Compared to all African Americans born outside of states in the top quartile of IMRs, African Americans born in high IMR states had a 40% increased risk of dementia after adjusting for demographics and lifecourse vascular risk factors (HR=1.40; 95% CI: 1.02, 1.91; Table 3). There was no evidence of an association between birth in high IMR states and dementia risk among Whites in minimally or fully adjusted models (minimally adjusted HR=1.01; 95% CI: 0.84, 1.22; fully adjusted HR=1.03; 95% CI: 0.85, 1.25).

Compared with Whites born outside high IMR states, African Americans born in high IMR states had 92% increased risk of dementia (HR=1.92; 95% CI: 1.42, 2.59), and African Americans born outside high IMR states had 36% higher risk of dementia (HR=1.36; 95% CI: 1.20, 1.53) adjusting for demographics and lifecourse vascular risk factors (Table 4). There was no evidence that Whites born in high IMR states were at elevated risk of dementia (HR=1.03; 95% CI: 0.85, 1.25).

The same pattern was found when estimating cumulative risk of dementia across the four categories of race and birth state IMRs (Figure 1, Supplemental Table 3): African Americans born in high IMRs states consistently had the highest risk followed by African Americans born outside high IMR states and Whites born in high IMRs states did not differ from those born in outside those states. The estimated 25-year cumulative risk of dementia for African Americans born in high IMR states was 47% (95% CI: 34%, 58%) compared to 41% (95% CI: 37%, 45%) for African Americans born outside those states. For Whites the estimated 25-year cumulative risk of dementia was 31% or 32% depending on birth state IMR (born in high IMR states: 95% CI: 25%, 37%; born outside high IMR states: 95% CI: 30%, 33%).

DISCUSSION

This is the first paper examining birth state IMRs and dementia risk. In this large cohort of men and women born across the US, birth in states with high levels of IMRs was associated with elevated dementia risk among African Americans. IMRs are a sensitive marker of early-life living conditions. The leading causes of infant mortality in the 1920s were premature birth, respiratory infections, and diarrheal diseases[18,26], all of which have been associated with poverty, access to health care, prenatal care, nutrition, and sanitation. In 1928, the national IMR in Non-White populations was 66% greater than among Whites (106 vs 64 death per 1,000 live births)[18], indicating that African Americans likely faced much harsher environments in early life than Whites. Among African-Americans, those born in states in the top quartile of IMRs had 40% increased risk of dementia compared to those born outside these states after taking into account demographics and vascular comorbidities. Consistent with multiple studies, our study also shows that race is also a risk factor for dementia[20,27]. Among individuals born outside of high IMR states, African Americans had 36% greater dementia risk than Whites. However, African Americans born in high IMR states had the largest relative and absolute risk of dementia. Compared with Whites born outside high IMR states, African Americans born in high IMR states had 92% increased risk of dementia and 47.9% greater estimated 25-year cumulative risk of dementia. These results suggest that childhood conditions may partially explain racial disparities in dementia risk.

One limitation of our study is that we were unable to find IMRs for African American's in the 1920s (mean/median birth year=1924), requiring us to use the IMR for Non-Whites as a proxy. However, African Americans comprised 96% of the Non-White population of the US in 1920.[19] In our sample, 89% of African Americans born in high IMR states were born in Oklahoma, which had a minority population predominantly comprised by African Americans (73% of the state's minority population in 1920)[28]. On the other hand, 9% of African Americans born in high IMR states in our sample were born in Arizona, where African Americans were only 19% of the minority population[28]. The use of IMRs estimated mostly on Native Americans is appropriate to the extent that African Americans and Native Americans both experienced harsh early-life living conditions.

In our sample, 98% of African Americans born in high IMR states were born in Oklahoma or Arizona, both of which enforced Jim Crow laws.[29] In 21 states, Jim Crow laws legalized racial discrimination in education, medical access, transportation, employment, and other domains of life.[29] The effects of structural racism are evident in the extreme absolute difference in the IMRs between Whites and Non-Whites. The range of IMRs in the top quartile for Non-Whites and Whites barely overlap: the lowest IMR in the top quartile for Non-Whites was 129 deaths per 1,000 live births which was the highest IMR among Whites. Thus it is unknown if Whites born in states with IMRs above 131 deaths per 1,000 live births would also have increased dementia risk. IMRs at this level may indicate a threshold of profound disadvantage which could increase dementia risk in Whites as well.

Our work is consistent with prior literature demonstrating a strong association between high IMRs and worse adult health. Initial studies in the 1970s and 1980s demonstrated associations between IMRs and mortality due to ischemic heart disease in Norway, England,

and Wales.[9,10,30] A study in the US showed an association between infant mortality due to diarrheal diseases in the 1917–1921 birth cohorts and ischemic heart disease mortality even after adjusting for contemporaneous IMRs in later life as a proxy for adult living conditions. [31] High IMRs have also been associated with increased risk of deaths due to stroke[11,12], tuberculosis[11], and stomach cancer[9,11]. These studies conceptualize high levels of infant mortality as markers of a range of poor early-life living conditions and are part of a larger body of research demonstrating a link between childhood exposures and late-life health.[32]

It is increasingly accepted that health and conditions in early-life can have lasting effects on brain health and dementia risk[23,33–35]. Exposure to adverse conditions in early life may have physiological consequences on the developing brain. For example, malnutrition during the first two years of life may lead to reduced synaptogenesis and stunted dendrite growth[36]. Other early-life exposures that may impact brain health include lead, infection, and chronic stress[34,37,38]. Separately or in conjunction, adverse childhood environments could also elevate dementia risk by impacting educational opportunities, income, health behaviors, and risk of other health conditions later in life.

Strengths of this study include a well-characterized, diverse sample from members of an integrated healthcare delivery system with equal access to health care beginning in the 1960s enabling us to follow them across many decades. We are able to link birth state IMRs to medical records, providing information on dementia incidence as well as other medical conditions. Our cohort only includes individuals who migrated to California by their early 40s and the majority of African Americans born in high IMR states in our sample were born in Oklahoma or Arizona. This limits our understanding of the impact of birth in a state with high IMRs other than Oklahoma or Arizona and among people who continue to reside in those states past midlife. Since people who migrated to California may be healthier or more advantaged than those who stayed in states with high IMRs, we likely underestimated the effect of high IMRs on dementia risk for those who did not migrate to California. We do not have information on when members migrated, so we are unable to examine the effects of duration or the possibility of a sensitive period. We were unable to adjust for education quality which may vary by race/ethnicity and partially explain differences in cognitive outcomes in Whites compared to African Americans.[39] Since we do not have cognitive or neuroimaging data we cannot determine if birth in a high IMR was associated with a different trajectory of cognitive change and/or differences in imaging markers of brain function.

Higher levels of IMRs among African Americans likely reflect higher levels of early childhood adversity which was associated with a higher risk of dementia. Even among people who subsequently moved to California, birth in states with the highest IMR was associated with elevated dementia risk for African Americans. Although IMRs have drastically decreased since the 1920s, the national IMR for African American is still twice as high as for Whites (11.0 versus 4.9 deaths per 1,000 live births)[40]. Further research is needed to identify the role of early childhood conditions on racial disparities in dementia risk. Identifying modifiable pathways through which early childhood exposures may underlie racial disparities is a critical step in redressing inequities in dementia risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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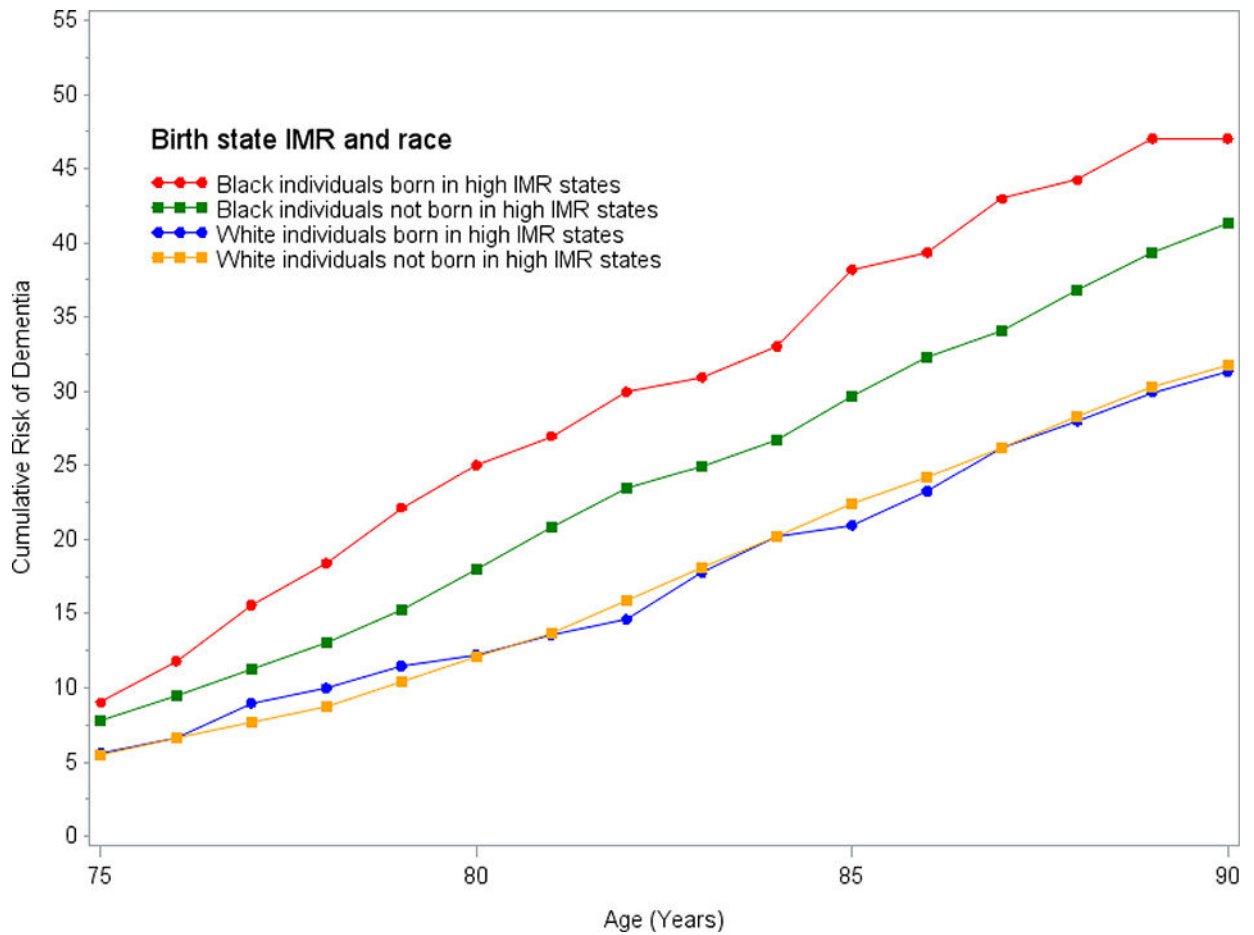
Figure 1. Cumulative risk of dementia conditional on survival free of dementia until age 65 by race and birth in a high infant mortality rate (IMR) state

High IMR state defined as defined as states with the highest quartile of state-level infant mortality rate in 1928.

Table 1.

Sample characteristics by category of race and birth in high infant mortality rate (IMR) states

	Whites			African Americans		
	Born outside high IMR state n (%) or mean (SD)	Born in high IMR state n (%) or mean (SD)		Born outside high IMR state n (%) or mean (SD)	Born in high IMR state n (%) or mean (SD)	
n	4807	403		959	99	
Dementia cases	1373	116		362	45	
Age in 1996 (yrs)	71.2 (2.7)	71.5 (2.8)		70.9 (2.8)	71.4 (2.8)	
Female	2581 (54%)	197 (49%)		560 (58%)	61 (62%)	
High school education	2023 (42%)	168 (42%)		664 (69%)	69 (70%)	
Midlife BMI	24.7 (3.7)	24.6 (3.7)		26.7 (4.5)	26.9 (4.2)	
Midlife high blood pressure	447 (10%)	45 (11%)		217 (23%)	26 (26%)	
Late-life stroke	1330 (28%)	110 (27%)		282 (29%)	33 (33%)	
Late-life diabetes	1151 (24%)	109 (27%)		379 (40%)	44 (44%)	

Notes: High IMR state defined as states with the highest quartile of state-level infant mortality rate in 1928. BMI=body mass index

Table 2.

Cox proportional hazard models of quartiles of birth state infant mortality rates (IMR) and risk of dementia stratified by race

IMR quartile	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)
Whites			
Q1 (best quartile)	ref	ref	ref
Q2	1.03 (0.89, 1.19)	1.02 (0.88, 1.18)	1.03 (0.89, 1.18)
Q3	1.20 (1.00, 1.45)	1.20 (0.99, 1.45)	1.20 (1.00, 1.45)
Q4 (worst quartile)	1.06 (0.85, 1.32)	1.06 (0.85, 1.33)	1.07 (0.86, 1.34)
African Americans			
Q1 (best quartile)	ref	ref	ref
Q2	1.03 (0.83, 1.28)	1.05 (0.85, 1.31)	1.08 (0.87, 1.35)
Q3	0.92 (0.64, 1.33)	0.95 (0.66, 1.37)	0.96 (0.67, 1.40)
Q4 (worst quartile)	1.35 (0.97, 1.88)	1.40 (1.00, 1.95)	1.44 (1.03, 2.01)

Notes: Model 1 adjusts for age, sex, and education. Model 2 further adjust for midlife vascular risk factors (body mass index and high blood pressure). Model 3 further adjust for late-life vascular risk factors (stroke and diabetes).

Table 3.

Cox proportional hazard models of birth in a high infant mortality rate (IMR) state and risk of dementia stratified by race

	Whites		African Americans	
Adjusting for:	**Born outside high IMR state HR (95% CI)**	**Born in high IMR state HR (95% CI)**	**Born outside high IMR state HR (95% CI)**	**Born in high IMR state HR (95% CI)**
Age, sex, education	ref	1.01 (0.84, 1.22)	ref	1.35 (0.99, 1.84)
Age, sex, education, midlife vascular risk factors	ref	1.02 (0.85, 1.24)	ref	1.37 (1.01, 1.87)
Age, sex, education, midlife and late-life vascular risk factors	ref	1.03 (0.85, 1.24)	ref	1.40 (1.02, 1.91)

Notes: High IMR state defined as states with the highest quartile of state-level infant mortality rate in 1928. Midlife vascular risk factors are body mass index and high blood pressure. Late-life vascular risk factors are stroke and diabetes.

Table 4.

Cox proportional hazard models of birth in a high infant mortality rate (IMR) state by race and dementia risk

Adjusting for:	Whites		African Americans	
	Born outside high IMR state HR (95% CI)	Born in high IMR state HR (95% CI)	Born outside high IMR state HR (95% CI)	Born in high IMR state HR (95% CI)
Age, sex, education	ref	1.01 (0.84, 1.22)	1.43 (1.27, 1.61)	1.93 (1.44, 2.61)
Age, sex, education, midlife vascular risk factors	ref	1.02 (0.85, 1.24)	1.34 (1.19, 1.51)	1.84 (1.37, 2.49)
Age, sex, education, midlife and late-life vascular risk factors	ref	1.03 (0.85, 1.25)	1.36 (1.20, 1.53)	1.92 (1.42, 2.59)

Notes: High IMR state defined as defined as states with the highest quartile of state-level infant mortality rate in 1928. Midlife vascular risk factors are body mass index and high blood pressure. Late-life vascular risk factors are stroke and diabetes.