Mechanisms of Racial/Ethnic Disparities in Cognitive Aging and Alzheimer's Disease

Jennifer Manly
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Collaborators

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### Supported by

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Overview

- Evidence for disparities in cognitive aging and AD
- Methodological challenges to AD disparities research
  - Prevalence vs. incidence
  - Intercept vs. slope
  - Neuropsychological assessment across racial/linguistic groups
  - Selection bias
  - Survival effect and possible crossover effect
- Examining potential mediators of racial disparities in AD
  - Biological
  - Environmental
  - Sociocultural

Washington Heights/Hamilton Heights/Inwood Columbia Aging Project (WHICAP)

- N = 2125 in 1992, added 2174 in 1999
- Age 65 and older
- Women (68%) outnumbered men (32%), consistent with age group
- Tested in Spanish (37%) or English (63%)
- Seen in home at 18 – 24 month intervals
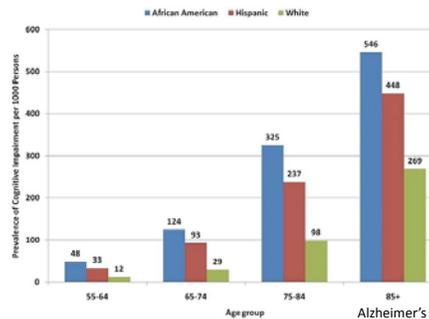- Dx based on neuropsychological test battery, medical & functional interview

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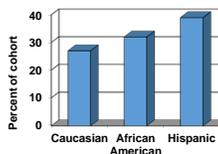
Evidence of Disparities
Incidence of AD by Age and Race/Ethnicity WHICAP 2001
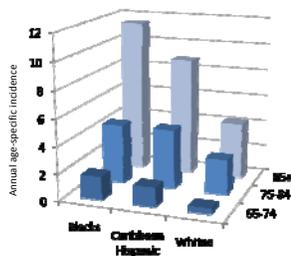
Tang et al., 2001; Neurology 56: 49-56

Evidence of Disparities
Prevalence of Cognitive Impairment by Age and Race/Ethnicity HRS 2006

Alzheimer's Association, 2010

Evidence of Disparities
Kaiser Permanente Northern California
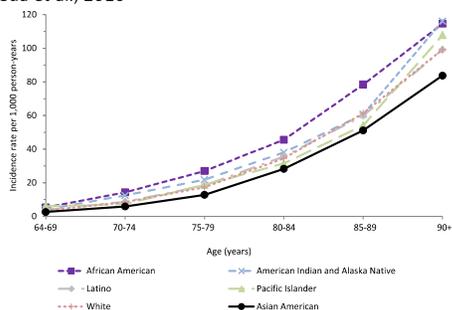Mayeda et al., 2016

Fig. 2. Dementia incidence rates per 1000 person-years by age and race-ethnicity, 2000–2013.

Societal Burden of Disparities

- Disparities populations are less likely to receive a diagnosis of dementia
- Disparities populations are typically diagnosed in later stages of the disease
  - Average per-person Medicare payments are 45 percent higher for African Americans with a dementia diagnosis and 37 percent higher for Hispanics compared with whites who have dementia.
  - Higher prevalence of neuropsychiatric symptoms among African Americans and Hispanics (Sink et al., 2004)
- Blacks and Whites born in the stroke belt states are at higher risk of dementia mortality than those born in other states, even if they moved out of stroke belt (Glymour et al., 2011)

Alzheimer's Disease and All-cause Dementia Mortality by Race and Place of Birth
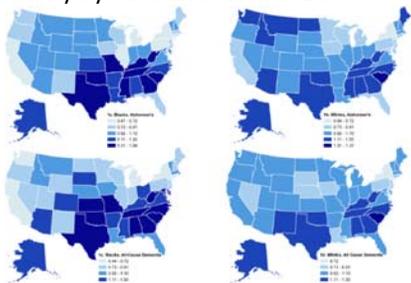
Odds ratios for Alzheimer's or all-cause dementia-related mortality in 2000, by race and state of birth, compared to the national average, based on empirical Bayes (shrinkage) random effect estimates from logistic models, US born blacks and whites ages 65–89.

Glymour et al., *Alzheimer Dis Assoc Disord* 2011

Methodological challenges to AD disparities research

Selection Bias

- Differences in recruitment across racial/ethnic groups may lead to non-generalizable results
  - Ethnic minority participants may not be broadly representative of the community
  - Consider how barriers to participation may influence sample characteristics and bias results
- Racial and ethnic minorities are less likely to present to Memory Disorders Clinics, are less likely to receive a formal diagnosis of AD than non-Hispanic Whites
  - Minorities who present to clinics are more likely to have neuropsychiatric symptoms than Whites


Stigma, Fear & Shame

- Stigma - "attribute that is deeply discrediting" and causes us to change our view of the person from "a whole and usual person to a tainted and discounted one" (Goffman, 1963)
- Stigma associated with dementia causes discomfort and embarrassment, which can lead to:
  - Delay in diagnosis and care
  - Poor interactions with medical care providers
  - Increased burden on caregivers
  - Social isolation
  - Lack of participation in clinical research

Survival Bias

- Mortality is higher, at all ages, among racial/ethnic minorities and those with low education as compared to Whites/high educated
- The smaller group of people of color who live to be studied as older adults are hardier than the larger group of Whites.
- Hardiness is probably related to an unobserved characteristic.
- Even if the unmeasured factor was not initially related to race (for example, specific genes), selective survival could bias estimates of the effect of race on mortality, both exaggeration or reversal of the effect of race on mortality can occur
- This bias is not just present for mortality but for any health outcome that can occur just once (*like dementia*)

Glymour, Weuve, & Chen (2008)

Evidence for age-as-leveler effects
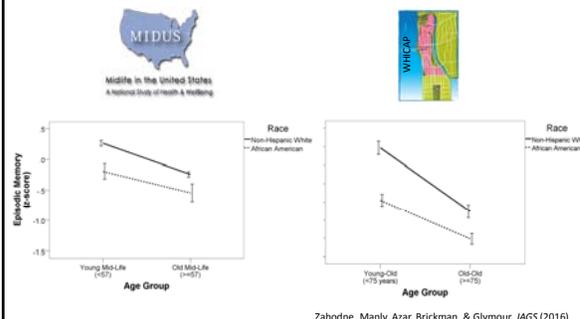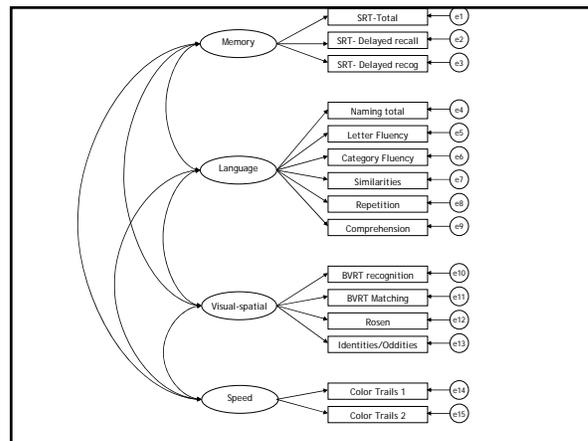

Zahodne, Manly, Azar, Brickman, & Glymour, *JAGS* (2016)

With ethnic group norms, no significant ethnic differences in prevalence of MCI
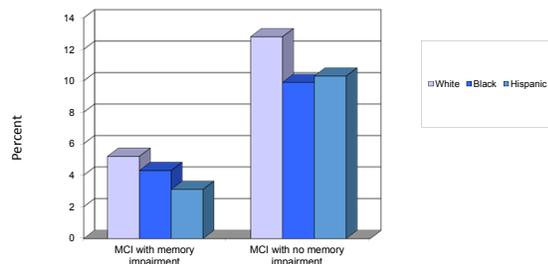
Manly et al, Arch Neurol (2005)

Blacks and Hispanics have more rapid memory decline as compared to Whites in WHICAP
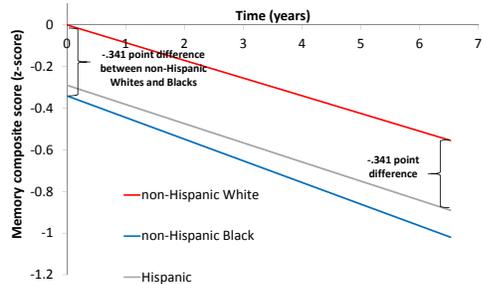
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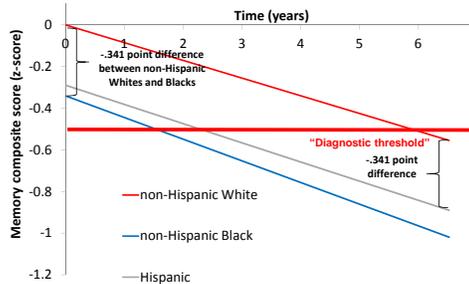
Lifecourse mechanisms or potential mediators of AD disparities
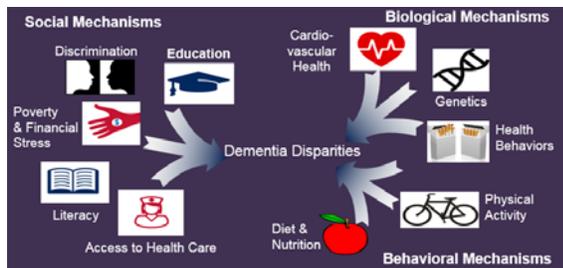
Causal pathways linking race, cognitive aging, and AD
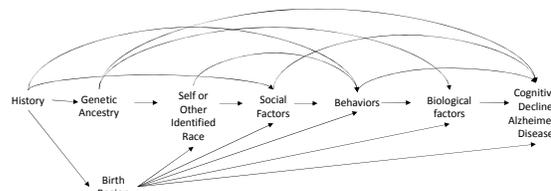
Adapted from Marden et al., 2016

Biological Mediators of AD Disparities

Biological Mediators of AD Disparities:
Age, ethnicity, and relative WMH volume
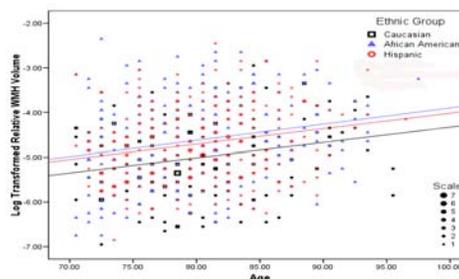
Brickman et al., Arch Neurol, 2008

WMH & language
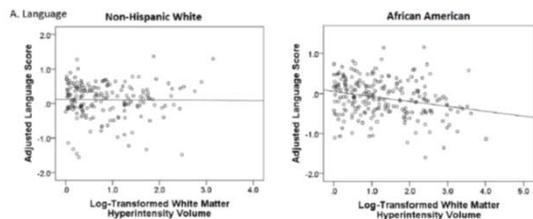
Zahodne *et al, CAR* 2015

Hippocampal vol. & incident dementia
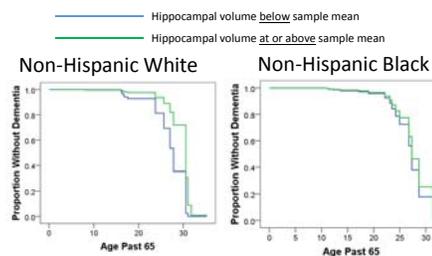
Racial differences in mixed pathology in black and white decedents with Alzheimer disease (AD) dementia

Barnes et al. Neurology 2015

Admixture mapping

- Higher levels of African ancestry (whole genome level and at specific AD-related genetic loci like ABCA7) are associated with an increased risk for AD

Hohman et al., 2015

Social factors correlate with African Ancestry and could confound relationship with AD

Marden, Walter, Kaufman, & Glymour, (2016)

- HRS non-Hispanic blacks

  Comparing highest versus lowest quartile of African Ancestry

  Higher African Ancestry is associated with
  - Less education
  - Fewer years of parental schooling
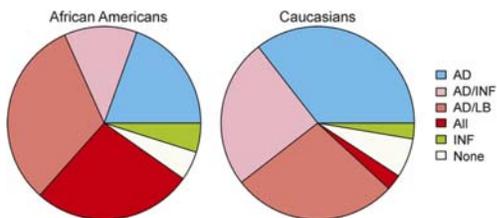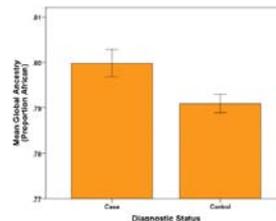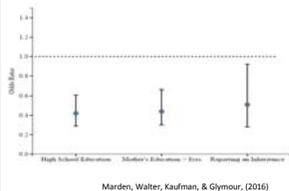 - No inheritance
  - Lower income (about $1400/year)
  - Less wealth (about $12,000)

  Ancestry doesn't biologically mediate or influence these factors
- African ancestry is a marker for social experiences of individual, parents and grandparents

Accounting for socioeconomic status eliminated the association of European ancestry with lower risk of diabetes Colombia and attenuated the association in Mexicans (Flores et al., 2009)

Potential Biological Mechanisms of AD Disparities

- Epigenome and miRNA expression
  - Need brain tissue?
- Telomere Shortening
  - Need rate?
- Systemic inflammation
  - Mid-life critical period?

Environmental Mediators of AD Disparities

SES Disparities and Incident Dementia
Yaffe et al., 2013

Associations between socioeconomic factors and dementia risk among black and white older adults participating in Health ABC study

Factors	Hazard ratio (95% CI)		
	All combined	White	Black
Education:			
<High school	1.47 (1.17 to 1.86)	0.99 (0.66 to 1.47)	1.75 (1.26 to 2.43)
High school or technical school	1.00 (reference)	1.00 (reference)	1.00 (reference)
≥Some college	0.80 (0.64 to 1.00)	0.72 (0.55 to 0.96)	0.99 (0.67 to 1.47)
Literacy:			
<9th grade	1.70 (1.41 to 2.05)	1.42 (1.05 to 1.93)	1.67 (1.25 to 2.21)
≥9th grade	1.00 (reference)	1.00 (reference)	1.00 (reference)
Family income:			
<$10 000	1.66 (1.29 to 2.15)	1.49 (0.80 to 2.77)	1.45 (1.07 to 1.96)
$10 000-49 000	1.00 (reference)	1.00 (reference)	1.00 (reference)
≥$50 000	0.92 (0.71 to 1.20)	1.01 (0.75 to 1.36)	1.00 (0.54 to 1.87)
Financial inadequacy	1.46 (1.13 to 1.90)	1.40 (0.88 to 2.21)	1.29 (0.93 to 1.79)
Sum of worst case levels of above variables (range 0-4)	1.32 (1.22 to 1.42)	1.25 (1.06 to 1.47)	1.31 (1.18 to 1.46)

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SES Disparities and Incident Dementia
Yaffe et al., 2013
Cox proportional hazard ratios for time to dementia by race* (n=2457)

Model	Cox proportional hazard ratio (95% CI)
Unadjusted	1.44 (1.20 to 1.74)
Model 1: Demographics and apolipoprotein E e4 status	1.36 (1.12 to 1.64)
Model 2: Demographics, apolipoprotein E e4, and comorbidities	1.38 (1.14 to 1.67)
Model 3: Demographics, apolipoprotein E e4, comorbidities, and lifestyle	1.37 (1.12 to 1.67)
Model 4: Demographics, apolipoprotein E e4, comorbidities, lifestyle, and socioeconomic measures	1.09 (0.87 to 1.37)

Education and Cognitive Decline

- More years of education predicted higher cognitive level and attenuated cognitive decline in individuals with low or high educational attainment
- The protective effect of education among those with >8 yrs of school was fully mediated by income
- The protective effect of early education (i.e., additional years up to 8) was independent of income

Zahodne et al., 2014
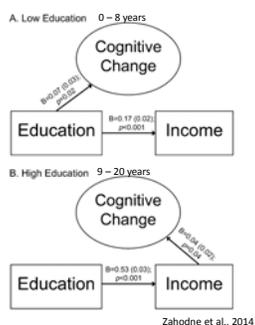
Environmental Mediators of AD Disparities: School Quality

- Educational attainment (years or credential) ignores tremendous variability in quality of schooling
  - Race/ethnicity
  - Geographic region
  - Secular trends

Length of School Year

Student Teacher Ratio

Slide 1

Alabama counties of residence during participants' childhood schooling

- Student–teacher ratio and school year length, not expenditures, were associated with baseline cognitive function
- Independent of education level, age, race, gender, income, reading ability, vascular risk factors, and health behaviors
- Associations were stronger in those with lower levels of education (≤12 years)
- Not related to 4-year change in cognitive function

Michael Crowe et al. J Gerontol A Biol Sci Med Sci 2012

Slide 2

Determinants of cross-sectional language test performance

Legend: Race, Yrs ed, State, Reading

All models are adjusted for age and sex

Slide 3

Racial disparities by US region of primary school education in HRS

Liu, Glymour, Zahodne, Weiss, & Manly, *JINS* (2015)

Slide 4

Reading Level

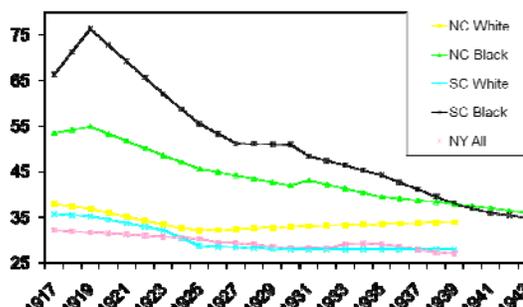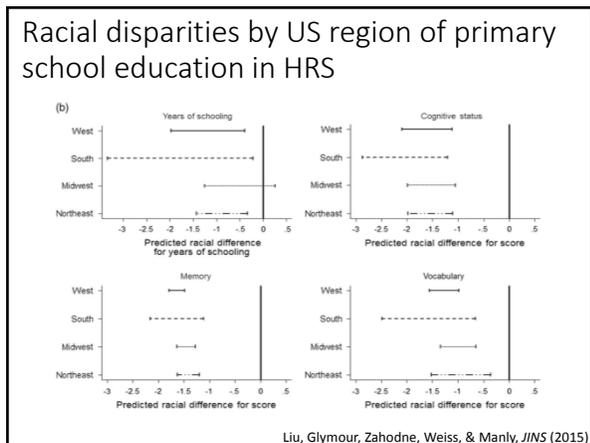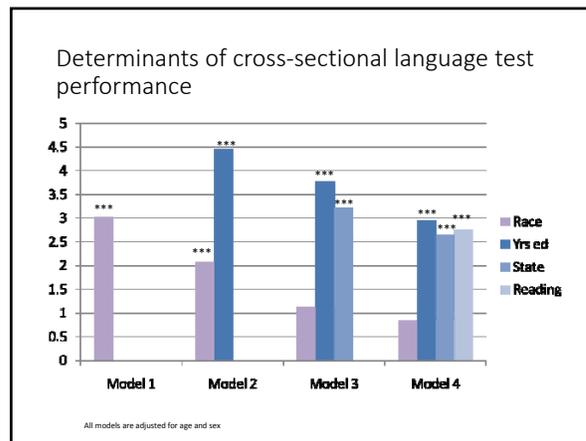| English				Spanish
Wide Range Achievement Test - reading subtest				**Word Accentuation Test**
	I V Z J Q			ACULLA ABOGACIA ANOMALO CELIBE
see	red	milk	was	ALELI RABI APATRIDA HUSAR LEGORIA
between	cliff	stalk	grunt	MANCHU DIAMETRO MOARE CONCAVO
clarify	residence	urge	rancid	AMBAR PUGIL POLIGAMO ACME SILICE
conspiracy	deny	quarantine		GRISU ALBEDRIO CANON PIFANO
deteriorate	regime	beatify		TACTIL VOLATIL DESCORTES DISCOLO
internecine	regicidal	puerile		BULGARO BALADI ACOLITO CUPULA
factitious	lucubration			
epithalamion	inefficacious	synecdoche		**Identificacion de letras y palabras**

de	ciudad
la	página
es	vertical
uno	zaramugullón
por	medicoquirúrgico
niño	corpóreo

Slide 5

Reading level and Memory

Manly et al., JCEN 2003

Slide 6

Disparities in WHICAP

Figure 1. Unadjusted Cox regression plot for dementia incidence associated with race and ethnicity

Watson et al., in preparation
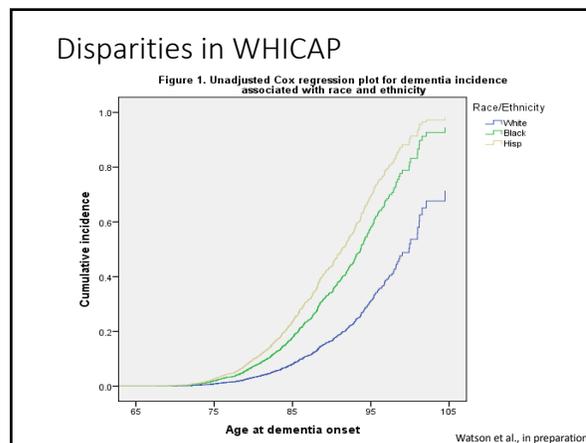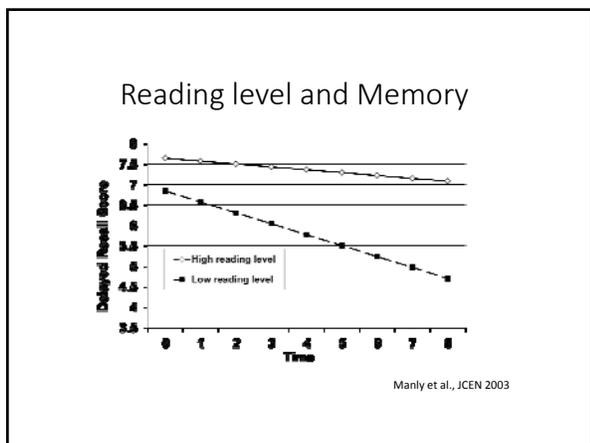
Mechanisms of AD Disparities in WHICAP

	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)	Model 4 HR (95% CI)	Model 5 HR (95% CI)
African-American	2.25 (1.75–2.90)	1.99 (1.47–2.68)	1.70 (1.26–2.30)	1.57 (1.11–2.22)	1.10 (0.76–1.60)
Latino	3.11 (2.47–3.93)	3.09 (2.36–4.03)	1.59 (1.16–2.16)	1.41 (0.98–2.03)	1.47 (1.00–2.16)
White	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
Characteristics					
Age	1.11 (1.10–1.13)	1.11 (1.10–1.13)	1.11 (1.10–1.13)	1.09 (1.09–1.12)	1.11 (1.10–1.13)
Gender	0.99 (0.84–1.17)	1.05 (0.85–1.30)	1.02 (0.82–1.26)	0.96 (0.76–1.21)	0.99 (0.77–1.27)
APOE e4 carrier		1.47 (1.21–1.78)	1.43 (1.18–1.73)	1.45 (1.18–1.77)	1.58 (1.27–1.96)
Stroke		1.64 (1.24–2.16)	1.70 (1.28–2.24)	1.63 (1.21–2.21)	1.69 (1.22–2.34)
Diabetes		1.43 (1.16–1.77)	1.35 (1.09–1.66)	1.31 (1.05–1.64)	1.23 (0.96–1.58)
Heart Disease		0.93 (0.75–1.15)	0.98 (0.78–1.22)	0.96 (0.76–1.22)	1.01 (0.78–1.30)
Hypertension		0.92 (0.76–1.10)	0.90 (0.75–1.08)	0.94 (0.77–1.15)	1.02 (0.82–1.26)
Depression		1.55 (1.27–1.90)	1.48 (1.21–1.81)	1.44 (1.16–1.78)	1.39 (1.10–1.76)
Arthritis		1.14 (0.93–1.37)	1.10 (0.91–1.31)	1.09 (0.90–1.32)	1.15 (0.93–1.42)
History of Smoking		1.11 (0.93–1.33)	1.07 (0.90–1.28)	1.12 (0.92–1.35)	1.19 (0.97–1.47)
History of Drinking		1.16 (0.84–1.62)	1.19 (0.85–1.66)	1.17 (0.82–1.67)	1.21 (0.82–1.78)
Years of Education			0.90 (0.88–0.92)	0.92 (0.90–0.95)	0.95 (0.92–1.47)
Occupation				0.88 (0.73–1.06)	0.90 (0.74–1.10)
Income				0.72 (0.59–0.88)	0.76 (0.62–0.94)
Reading Level					0.53 (0.42–0.67)

Watson et al., in preparation

Cohort Characteristics

Characteristic	Total Cohort	1992	1999
N	2857	1129	1728
Baseline Age (M,SD)	75.0 (5.0)	75.4 (4.8)	74.8 (5.2)*
Follow-up (M, SD)	5.3 (4.6)	4.9 (4.4)	5.5 (4.7)
Female (N,%)	1890 (66.2)	754 (66.8)	1136 (65.7)
Education (M, SD)	9.9 (4.8)	8.7 (4.6)	10.6 (4.8)*
White (N, %)	773 (27.1)	245 (21.7)	528 (30.6)*
African-American (N, %)	962 (33.7)	393 (34.8)	569 (32.9)*
Hispanic (N, %)	1122 (39.3)	491 (43.5)	631 (36.5)*
Dead (N, %)	1514 (53.0)	827 (73.3)	687 (39.8)*

Race and incident dementia by recruitment cohort

	White	Black	Hispanic	Total
1992 total	245	393	491	1129
1992 incident AD	20	76	126	222
1992 %	8.2	19.3	25.7	19.7
Person years	1080.02	1695.45	2203.22	
1999 total	528	569	631	1728
1999 incident AD	30	57	107	194
1999 %	5.7	10	17	11.2
Person years	3126.82	2899.16	3190.37	

Secular Trends in AD incidence by race
Schupf et al., under review

	Model 1 HR (95%CI)	Model 2 HR (95%CI)	Model 3 HR (95%CI)
All Participants			
1999	0.59 (0.49-0.72)	0.62 (0.50-0.77)	0.69 (0.55-0.86)
1992	1.0 (ref)	1.0 (ref)	1.0 (ref)
Non-Hispanic White			
1999	0.60 (0.34-1.05)	0.72 (0.35-1.47)	0.80 (0.37-1.71)
1992	1.0 (ref)	1.0 (ref)	1.0 (ref)
African-American			
1999	0.52 (0.36-0.73)	0.65 (0.44-0.97)	0.87 (0.57-1.34)
1992	1.0 (ref)	1.0 (ref)	1.0 (ref)
Hispanic			
1999	0.64 (0.49-0.83)	0.60 (0.45-0.79)	0.62 (0.47-0.83)
1992	1.0 (ref)	1.00 (ref)	1.00 (ref)

Model 1 Including cohort as predictor, adjusted for age, sex, race/ethnicity, baseline memory complaints
Model 2: Model 1 plus diabetes, heart disease, stroke, hypertension, current smoking, and BMI
Model 3: Model 2 plus education

Secular trends summary

- Overall decline in AD incidence among Blacks, Whites, and Hispanics (Schupf et al.)
  - Vascular risk factors attenuated decline among Whites
  - Years of school explained lower incidence in Blacks
  - None of these variables explained lower rates in Hispanics
- Absolute racial/ethnic disparities in AD incidence narrowed over time
  - Years of school and a proxy for school quality (reading level), but not geographic location of education, accounted for decreases in racial disparities

Sociocultural Mediators of AD Disparities

Racial difference in benefit from cognitive intervention is mediated by psychosocial factors: ACTIVE trial
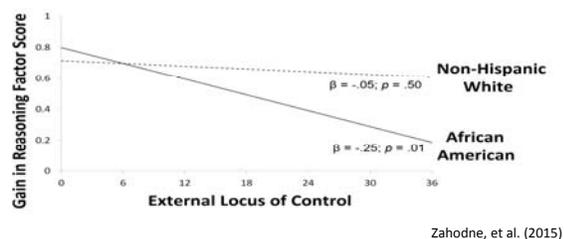
Zahodne, et al. (2015)

Conclusions

- There are racial disparities in cognitive aging and AD
  - Not attributable to assessment bias, although this is a major factor in some studies
  - The independent effect of race on cognitive function is larger on intercept (cross-sectional) than on slope or change over time (longitudinal)
  - Differences across studies may be attributable to differential recruitment, selection, and survival bias
  - Declining trend of dementia incidence among African Americans is explained by secular increases in years of school
  - Clinic-based cohorts are not appropriate for research on AD disparities

Conclusions

- Biological, environmental, and sociocultural mediators of disparities have been examined
  - Indicators of school quality explain racial disparities in cognitive function cross-sectionally and longitudinally, and AD incidence
  - Intervening on psychosocial factors may narrow disparities in cognitive decline and improve response to interventions
  - Sociocultural factors correlate with African Ancestry and may confound relationship of African Ancestry with AD risk or age at onset

Understanding the mechanisms of dementia disparities

- Conduct studies designed to elucidate causal mechanisms
- Longitudinal studies
  - baseline prior to development of dementia (midlife or prior)
  - repeat cognitive assessment
  - importance of incidence and trajectory data
- Measure educational experience, not just years attended or credential
- Measure burden of neuropathology

Understanding the mechanisms of dementia disparities

- Follow up into mid-life and later life needed for school, twin, and birth cohorts
- Investigate potential critical periods (elementary vs. secondary; later life learning)
- Evaluate natural experiments using instrumental variables
- ADRD outcomes incorporated within planned interventions
  - Increased income
  - Improving neighborhood and household
  - Values affirmation reduces stereotype threat/perceived racism

Practice Implications

- Culturally competent practice
- Equitable community partnerships to increase early diagnosis
- Evidence for early life social determinants of disparities shifts strategies for prevention even earlier upstream
- Social determinants may drive course of disease more than clinical care
- Advocate for public policies that address social determinants of health