Health Disparities in Primary Stroke Prevention and Urban/Rural Differences

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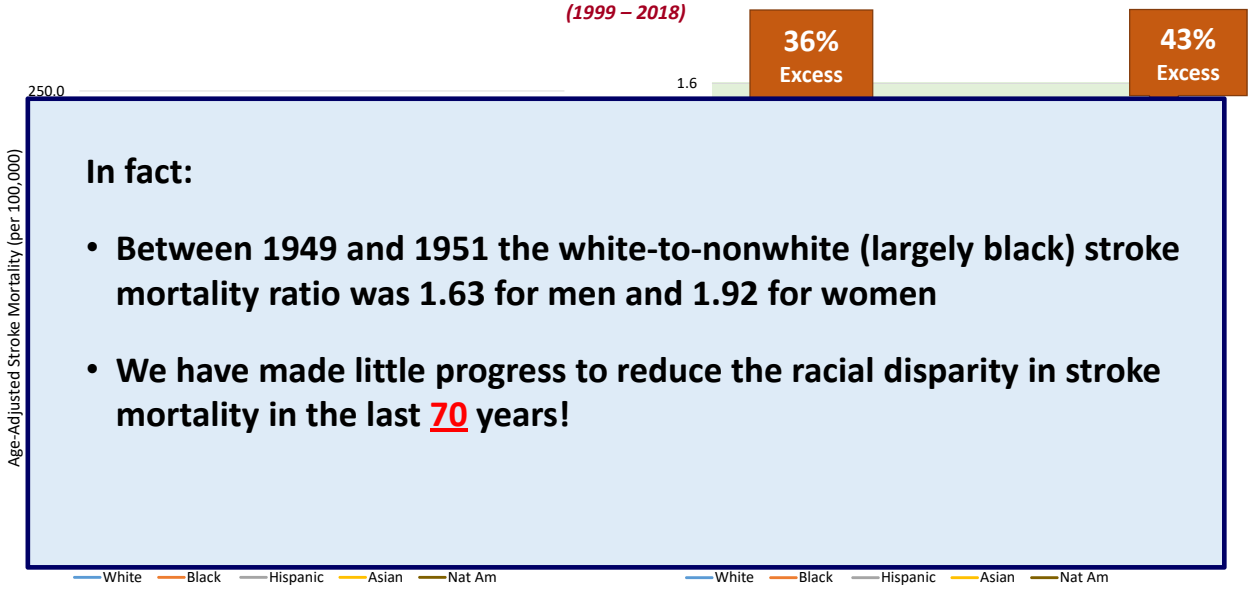
I have nothing to disclose

Recent Pattern of Racial/Ethnic Disparities in Stroke Mortality

(1999 – 2018)



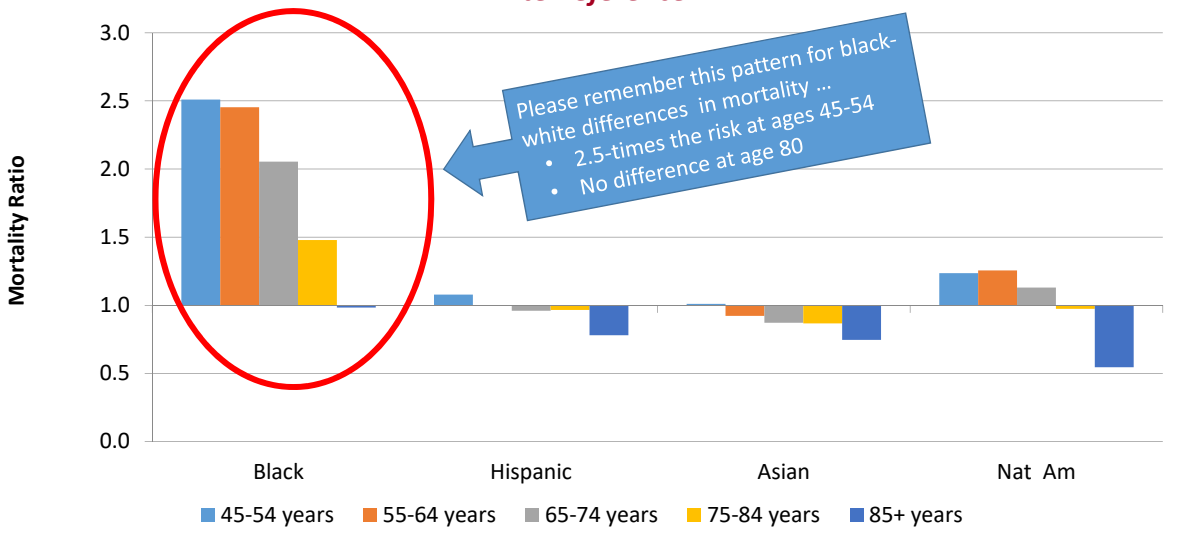
In fact:

- **Between 1949 and 1951 the white-to-nonwhite (largely black) stroke mortality ratio was 1.63 for men and 1.92 for women**
- **We have made little progress to reduce the racial disparity in stroke mortality in the last 70 years!**

Races are shown for non-Hispanic population, and Hispanic population is shown for all races.

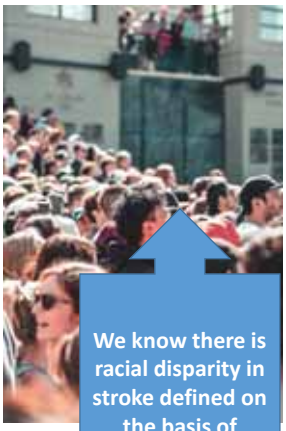
Age-Specific Race-Ethnic Stroke Mortality Disparities (2018)

White Reference



Races are shown for non-Hispanic population, and Hispanic population is shown for all races.

What we know … and what we need to know



= Stroke Incidence x Case Fatality after Stroke

We know there is racial disparity in stroke defined on the basis of mortality

If stroke incidence is driving disparity …

then need to focus on prestroke prevention in the general population

If case fatality is driving disparity …

then need to focus on
1. severity disparities, and
2. improved care in the hospital

REasons for Geographic And Racial Differences in Stroke (REGARDS) Study

- General population study with diverse aims … but for today …
- Central participant recruitment and telephone interview
  - 30,239 white and black participants aged 45+
  - 56% from the Stroke Belt
  - 42% black
- In-home evaluation for physical, venipuncture and ECG
- Central follow-up at 6-month intervals for detection of suspected stroke events (and other outcomes)
- Physician adjudication of new stroke events
- Provides both measures of stroke incidence and case fatality

Statistical Methods for Part 1

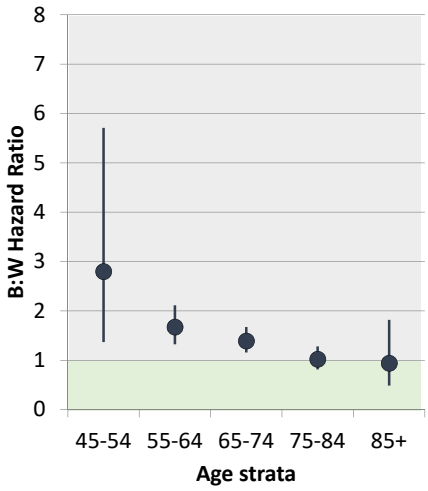
(Is it incidence or case fatality?)

- **Two separate analyses**
  - **Incidence**
    - **Outcome: Incidence of stroke**
    - **Proportional hazards analysis**
  - **Case fatality**
    - **Outcome: Death within 30-day among those with a stroke**
    - **Logistic regression analysis**
- **In both cases – assess interactions between age, race and sex, and include significant terms (p < 0.10)**

Howard G, et al. Stroke 2016;47:1893-1898

Black-White Disparities in Stroke Incidence in REGARDS

(Incidence of Strokes)



… and the pattern of stroke incidence nearly perfectly mirrors the previously shown pattern of stroke mortality

- **2.5-times the risk at ages 45-54**
- **No difference at age 80**

Howard G, et al. Stroke 2016;47:1893-1898

Black-White Disparities in Stroke Case-Fatality In REGARDS

- Examined case-fatality in the 30-days after stroke
- There were no interactions between age, race and sex ($p > 0.10$)
- Predictors of case-fatality

Howard G, et al. Stroke 2016;47:1893-1898

Implications

- These findings were mirrored in the GCNKSS
- If black-white disparities are to be reduced:
  - Focus MUST be on stroke prevention in blacks
  - As the disparity is nearly all in ages less than 75 years, the focus must be in younger blacks
  - Suggestion of only minor gains through improved stroke treatment in blacks
- So … what is it that places African Americans at higher stroke risk?

Looking under the street light?

- So … there is approximately a 300% increased stroke risk in "young" blacks
- Everyone knows the prevalence of hypertension and diabetes in blacks is hugely higher than whites
- For example, in REGARDS
  - 71% of blacks are hypertensive - 51% of whites
  - 29% of blacks of diabetic - 15% of whites
- Framingham and CHS have shown hypertension and diabetes approximately double the risk of stroke
- But the disparity in prevalence of hypertension only differentially affects 71% - 51% = 20% of the black population, and diabetes 29% - 15% = 14%
- … but difference in the prevalences should be expected to be only a 71% increased risk

  1.0 + (0.2 x 2.0) + (0.15 x 2.0) = 1.7

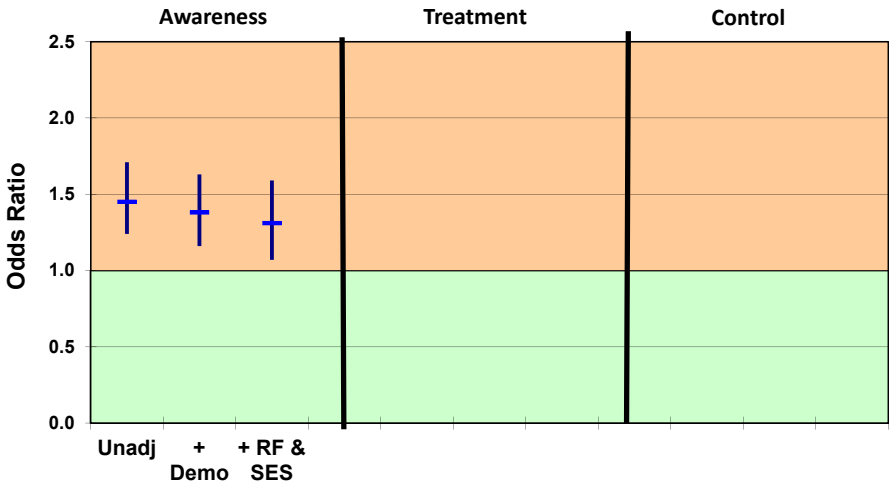
But what accounts for the rest of the disparity????

Looking Just a Little Further From the Street Light …

- Could lower average SES of blacks contribute to less awareness and lower treatment levels?
- The hypothesis of contributions of awareness-treatment-control have been examined in REGARDS and NHANES … with nearly identical findings

Black/White Differences in REGARDS Awareness-Treatment-Control of Hypertension

Estimated Odds Ratios in Incremental Models



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Black/White Differences in REGARDS Awareness-Treatment-Control of Hypertension

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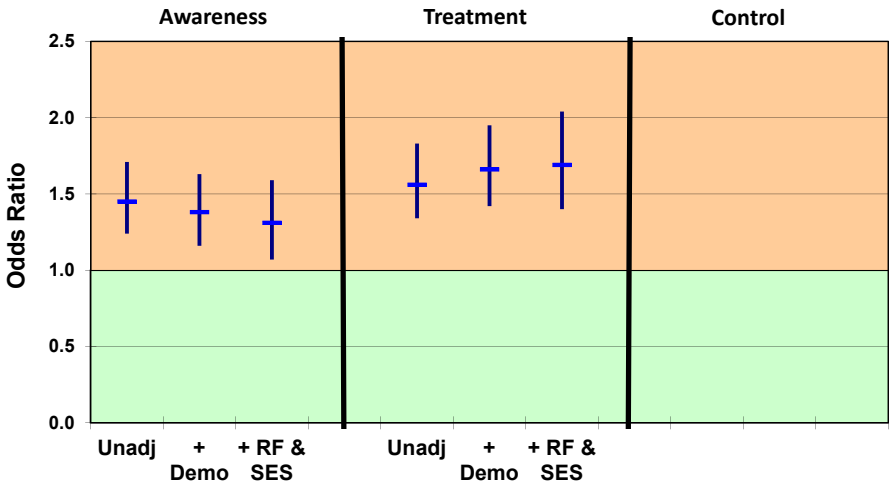

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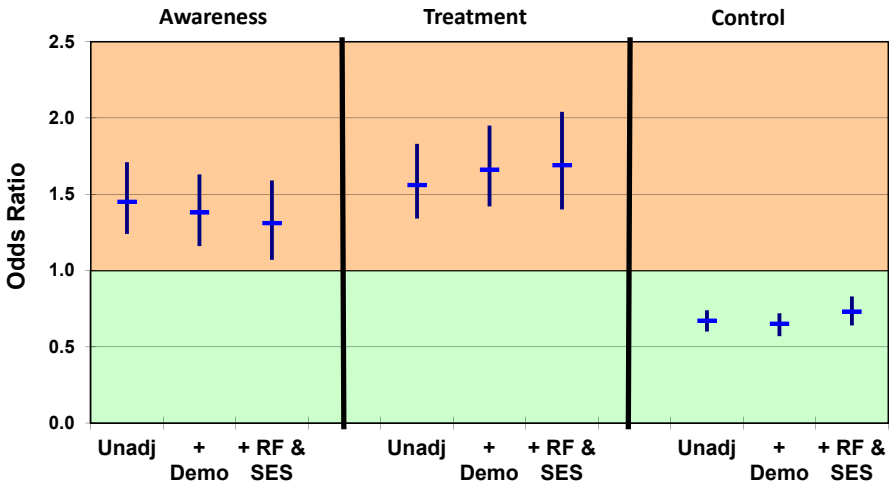

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So does this lack of control explain the difference in stroke mortality?

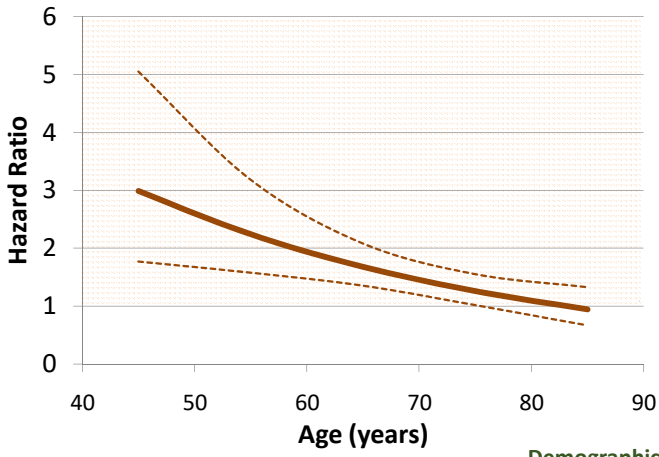
- So … even among <u>treated</u> hypertensives, blacks have average SBP levels about 5 mmHg greater than whites.
- Could this (or other "traditional" risk factors) account for differences in stroke incidence?
- Both NHANES and REGARDS have examined this question … again with very similar findings
  - Remember at age 45 blacks have 3x risk of ***<u>stroke mortality</u>***, reduced to no difference at age 85
  - How about ***<u>stroke incidence?</u>***

Potential for Mediation?

			Race		Incident Stroke During Follow-up	
			White	Black	No	Yes*
N			15464	10254	25291	427
Demographic Factors	Age (mean + SD)		65.2 ± 9.4	63.8 ± 9.2	64.5 ± 9.3	70.2 ± 8.7
	Black (%)		0.0	100.0	39.8	42.4
	Male (%)		49.9	37.6	44.9	54.3
Risk Factors	Atrial Fibrillation (%)		8.8	7.2	8.0	15.0
	Diabetes (%)		15.0	29.3	20.6	25.8
	Systolic blood pressure (mean + SD)		125.1 ± 15.7	130.5 ± 17.2	127.2 ± 16.4	134.9 ± 18.2
	Antihypertensive Medications (%)		41.8	62.0	49.6	61.8
	Heart Disease (%)		18.1	13.8	16.1	30.7
	Current Smoking (%)		12.2	16.7	13.9	20.8
	Left Ventricular Hypertrophy (%)		3.4	9.0	5.5	11.2
SES Factors	Education (%)	Less than High School	6.9	18.3	11.5	15.0
		High School Graduate	24.2	27.9	25.6	29.7
		Some College	26.7	26.9	26.9	23.4
		College Graduate +	42.2	26.9	36.0	31.9
	Income (%)	Less than $20K	11.2	25.5	16.7	22.5
		$20K - $34K	22.3	26.4	23.9	28.8
		$35K – $74K	33.2	26.8	30.7	28.1
		$75K+	21.5	9.5	16.9	8.2
		Refused	11.8	11.8	11.8	12.4

So, how much of the black-white disparity in stroke risk is <u>collectively</u> explained by risk factors and socio-economic status disparities?

Black-to-White Stroke Incidence Rate Ratio in REGARDS (by Age)

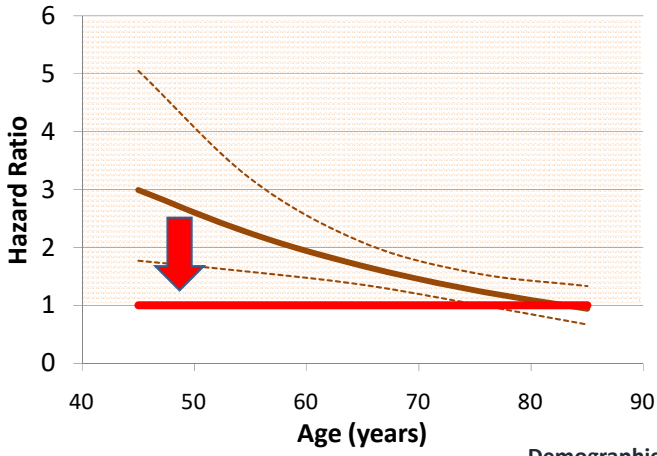


Demographic Model

So do the "Framingham" risk factors and SES explain the racial disparities in stroke?

Howard et al. Stroke 2011;42:3369-3375.

Black-to-White Stroke Incidence Rate Ratio in REGARDS (by Age)

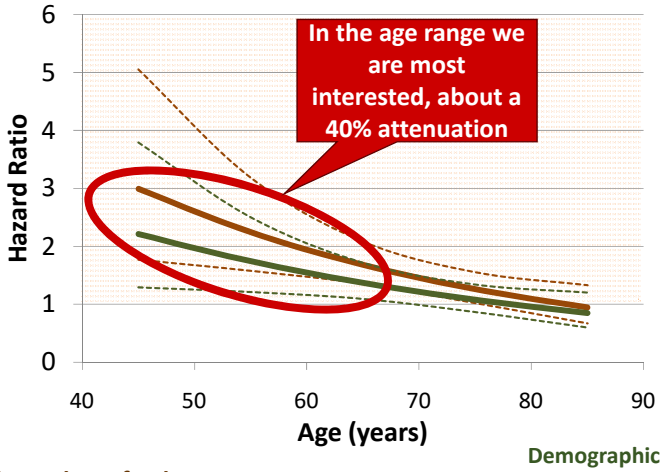


Demographic Model

So what is happening when we adjust for just the traditional risk factors?

Howard et al. Stroke 2011;42:3369-3375.

Black-to-White Stroke Incidence Rate Ratio in REGARDS (by Age)

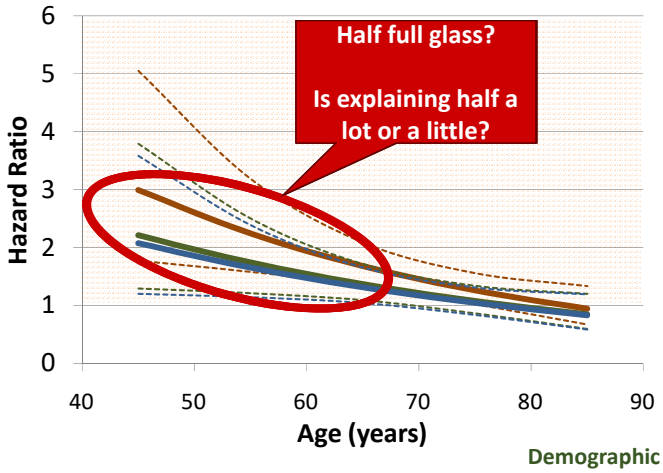


… and how about further adjustment for SES?

Demographic Model
Risk Factor Model

Howard et al. Stroke 2011;42:3369-3375.

Black-to-White Stroke Incidence Rate Ratio in REGARDS (by Age)



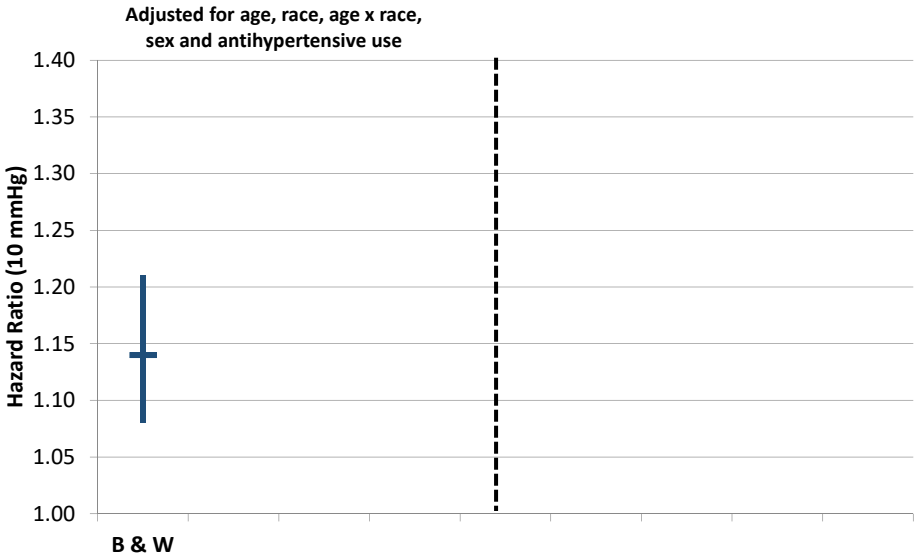
Demographic Model
Risk Factor Model
SES Model

Howard et al. Stroke 2011;42:3369-3375.

Approaches to reduce racial disparities in stroke?

- So what can be done to address the half-full portion?
  - For most risk factors (for example, hypertension and diabetes) we are examining prevalent disease (present/absent) … not effectiveness of treatment
  - This implies that risk factor treatment is not the key … but risk factor prevention
  - Suggesting that focus of "racial disparities in stroke" research should shift to "racial disparities in risk factor prevention" research
- … and what is happening with the half empty portion?
  - Differential susceptibility to risk factors?
  - Residual confounding?
  - Impact of "non-traditional" risk factors?
  - Measurement error?

Potential Differential Impact of SBP?



Howard G, et al. JAMA Int Med 2013;173:46-51

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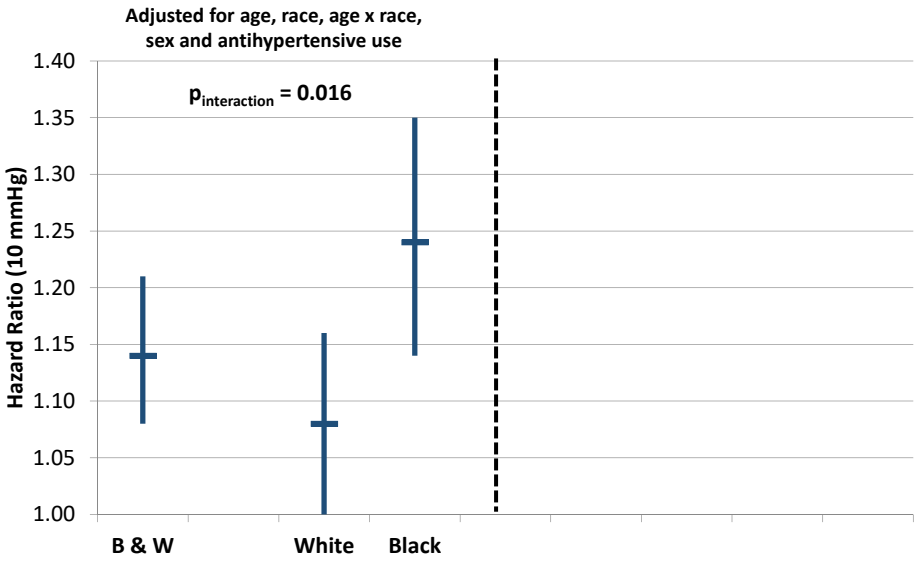

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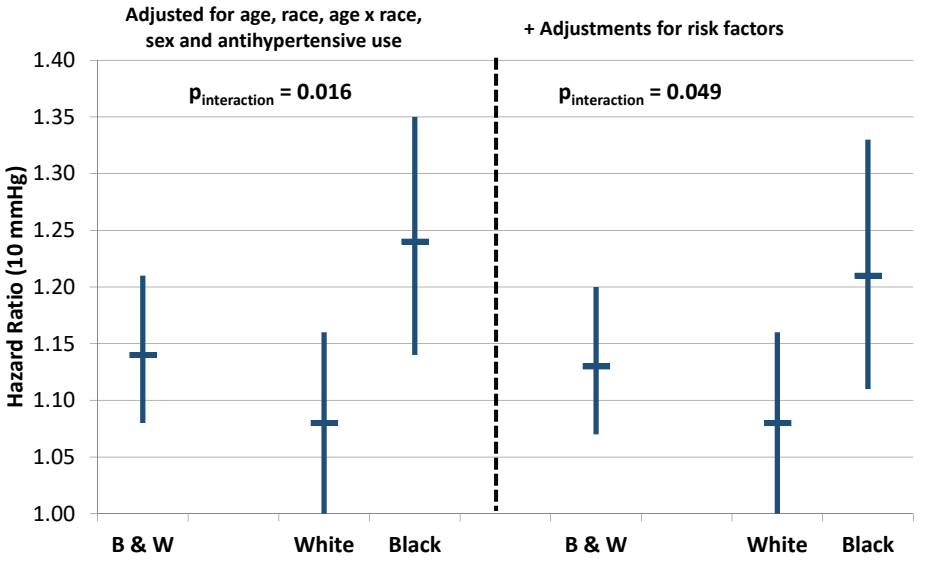

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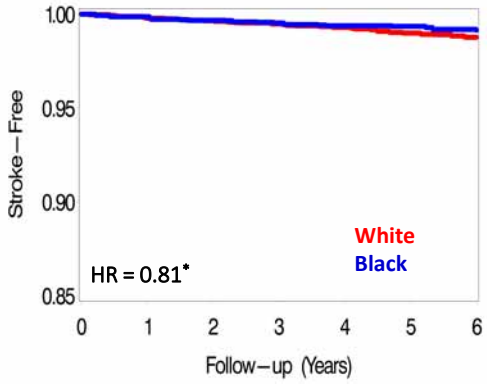
Implications of Differential Susceptibility?

- **Many interactions between race, age, and SBP**
- **Consider black-white stroke risk differences within strata by age and SBP**
  - **Age: <65, 65-74, 75+**
  - **SBP:**
    - **Normotensive (<120 mmHg)**
    - **Prehypertension (120 – 139 mmHg)**
    - **Stage 1 hypertension (140 - 159 mmHg)**
    - **Stage 2 hypertension (160+ mmHg) too few white participants, not presented**
- **Remember … the excess black stroke risk is at young ages (< 65 years mainly)**

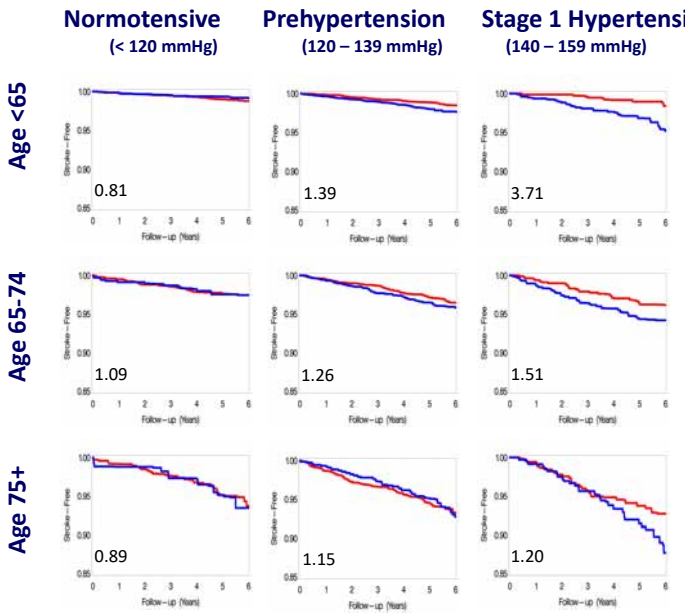
Black-white stroke risk in young (<65) normotensive (< 120 mmHg)



* Black-to-white hazard ratio after adjustment for sex and hypertension medications

Howard G, et al. JAMA Int Med 2013;173:46-51

Black-white stroke risk within age-SBP strata



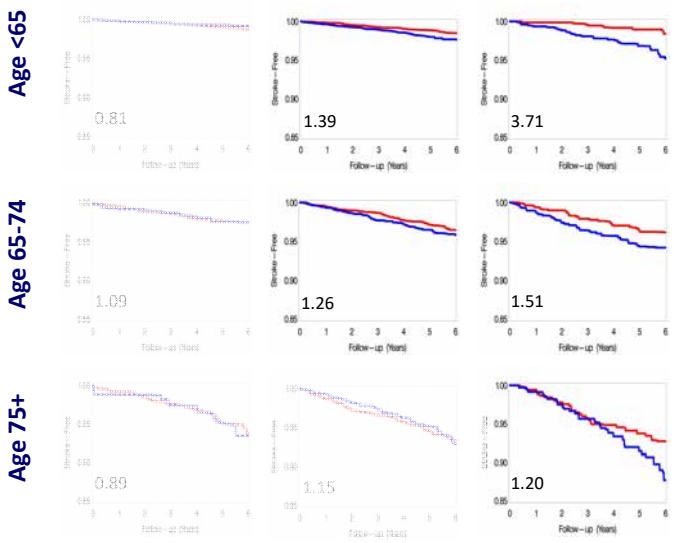
Suggests differential susceptibility could be a key to racial disparities in stroke

White
Black

All hazard ratios are risk factor adjusted

Howard G, et al. JAMA Int Med 2013;173:46-51

Black-white stroke risk within age-SBP strata



Suggests differential susceptibility could be a key to racial disparities in stroke

Most importantly … we are getting closer to identifying targets for intervention

White
Black

All hazard ratios are risk factor adjusted

Howard G, et al. JAMA Int Med 2013;173:46-51

… so SBP and Racial Disparities in Stroke

- **Strike 1: African Americans are more likely to be hypertensive**
  - 51% of whites versus 71% of AAs in REGARDS
  - Everyone knows this
- **Strike 2: African Americans are more likely to know they are hypertensive, more likely to be treated, but less likely to be controlled**
  - B/W odds ratio for control ≈ 0.70
  - Fewer people know this
- **Strike 3: Once blood pressure is not controlled, it is much worse for AAs than whites**
  - Three times as bad!

But Will Control of Blood Pressure Really Solve the Problem?

Risk of incident stroke by SBP level achieved and number of antihypertensive medications

	Normotensive (< 120 mmHg)	Prehypertension (120 mmHg – 139 mmHg)	Stage 1 Hypertension (140 mmHg – 159 mmHg)	Stage 2 Hypertension (160+ mmHg)	Tests for Trend	
No Meds	1.0 (ref)	1.44 (1.04 – 2.01)	2.19 (1.45 – 3.31)	3.35 (1.78 – 6.28)	1.49 (1.26 - 1.76)	
1 Med	1.42 (0.94 – 2.15)	2.00 (1.44 – 2.77)	1.67 (1.09 – 2.54)	3.00 (1.71 – 5.26)	1.16 (0.98 - 1.37)	$p_{interaction}$ = 0.13
2 Meds	1.60 (1.06 - 2.42)	1.88 (1.35 - 2.62)	2.84 (1.95 – 4.13)	1.42 (0.67 – 2.99)	1.16 (0.98 - 1.37)	
3+ Meds	2.48 (1.63 - 3.77)	2.34 (1.66 - 3.32)	3.35 (2.28 – 4.92)	4.62 (2.84 - 7.51)	1.26 (1.07 - 1.48)	
Tests for Trend	1.33 (1.16 - 1.52)	1.15 (1.05 - 1.26)	1.22 (1.06 - 1.39)	1.10 (0.86 - 1.40)		

$p_{interaction}$ = 0.29

Table 2: Hazard ratio for incident stroke (95% CI) after adjustment for age, race, age-by-race interaction, sex and the deviation from the mean SBP level for the category. Tests for trend represent the estimated increase in the hazard ratio per category for number of medications and SBP category (and test for interaction across strata).

Howard G, et al . Stroke 2015;46:1595-1600

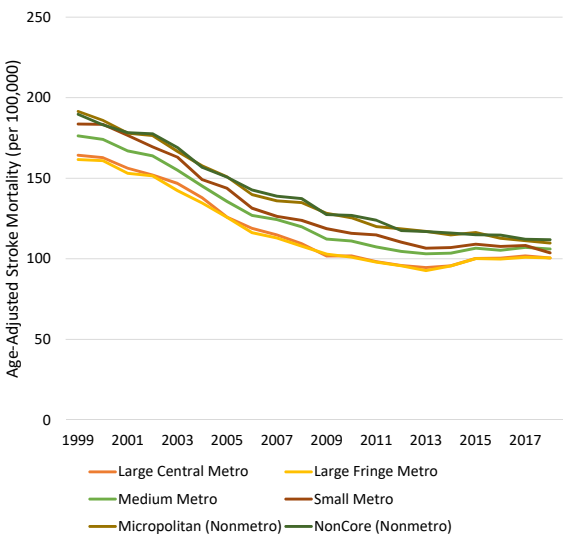
Concluding thoughts on B/W disparity in stroke risk

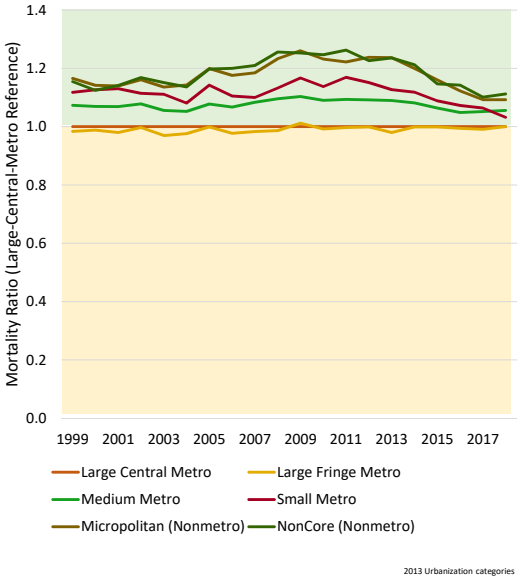
- Excess risk of stroke mortality in African Americans is concentrated below age 75, where the risk of stroke death is 2-3 times higher
- The B/W disparity in stroke mortality is nearly perfectly reflected in a B/W disparity in stroke incidence; however, there is no apparent disparity in case fatality
- This suggests that community-based interventions reducing stroke risk in AAs will be the key to reducing the B/W disparity in stroke
- A higher prevalence of "traditional" risk factors and poorer SES profile explain about half of the disparity; however, but affecting this contributor will require risk factor prevention (rather than control)
- A wide spectrum of other factors are likely to be contributing to the other half of the disparity, including differential susceptibility, residual confounding, and non-traditional risk factors

Changing Gears … how about rural disparities in stroke risk

Recent Pattern of Urban-Rural Disparities in Stroke Mortality

CDC WONDER: 1999 – 2018





… and using these data, let's focus on two similar questions for rurality disparities

1. **Is it that rural people are having more strokes, or is it that a person living in rural area is more likely to die after having a stroke?**
2. **… and cheating and looking ahead, what is it that makes rural people more likely to have a stroke?**

Question #1: Incidence vs Case Fatality as the Contributor to Urban-Rural Differences in Mortality

			Age-Race-Sex and Region
Hazard Ratio for Incident Stroke	County Urban / Rural Status	Urban	1.00 (ref)
		Large Rural	1.23 (1.01 – 1.51)
		Small Rural City/Town or Isolated Area	1.30 (1.03 – 1.62)
		P-value for trend	0.0073

- Urban-rural disparities seem driven by higher incidence, with case fatality playing minor role
- Again … this implies that reduction of the disparities needs to focus on reduction of stroke risk in rural areas *(more than improved stroke care in rural areas)*
- But what seem to be the contributors to the higher incidence (a.k.a., question #2)?

Howard G, et al. Stroke 2017;48:1773-1778

Step 1: Are Stroke Risk Factors and SES more Adverse in Rural Areas?

Risk factors	Hypertension, %
	Diabetes mellitus, %
	Smoking, %
	Atrial fibrillation, %
	Left ventricular hypertrophy, %
	Heart disease, %

We already know that these risk factors and SES measures are related to stroke/CHD in general … so now let's see how much of the *rurality → stroke risk* relationship is mediated by adjustment for them?

Calculate the odds of prevalent condition after adjustment for age, sex, race and geographic region … looking for a "dose-response" relationship with rurality

2 SES measures promising for SES measures

Why is the incidence of stroke higher in rural areas?

			Age-Race-Sex and Region
Hazard Ratio for Incident Stroke	County Urban / Rural Status	Urban	1.00 (ref)
		Large Rural	1.23 (1.01 – 1.51)
		Small Rural City/Town or Isolated Area	1.30 (1.03 – 1.62)
	P-value for trend		0.0073

So here is that relationship we had with incidence

→ 18% = 22% attenuation

→ 19% = 37% attenuation

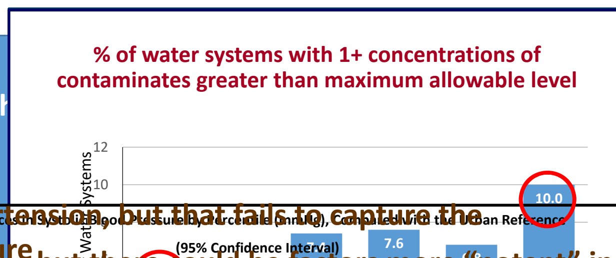
- What does adjustment for risk factors and SES do to the relationship?
- So adjustment for risk factors and SES does partially mediates association … it even becomes non-significant
- Most of this attenuation seems tied to SES measures
- Suggests that risk factors and SES are contributors to excess rural stroke mortality … and are targets for intervention
- However, (while no longer significant), over half the association remains
- Gee … we need to understand what else is contributing

HG1

What else could be going on?

Well … lots!

- Other factors could be playing a role, including:
  - Psychosocial
  - Structural
  - Environmental
  - Of course, others!
- Residual confounding
- Effect modification
  - Don't have a good example … but there could be factors more "potent" in rural areas
- Measurement error
- No good talk neglects to state that a lot more work is needed to understand these effects!



We have adjusted for hypertension, but that fails to capture the distribution of blood pressure

In unpublished work by Dr. Brittain Heindl, he examined the percentiles of SBP after adjustment for age, race, sex, state, and use of antihypertensive medications

Differences in Systolic Blood Pressure by Percentile (mmHg), Compared with the Urban Reference (95% Confidence Interval)

RUCA Classification	5	10	25	50	75	90	95
Urban	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Large Rural	2.00 (1.11 to 2.89) *P* < .0001	1.88 (1.20 to 2.57) *P* < .0001	1.25 (0.68 to 1.81) *P* < .0001	0.92 (0.33 to 1.52) *P* = .002	1.73 (0.97 to 2.49) *P* < .0001	1.92 (0.63 to 3.20) *P* = .004	3.23 (1.39 to 5.06) *P* = .0006
Small-Isolated Rural	0.50 (-0.66 to 1.66) *P* = .39	0.07 (-0.81 to 0.95) *P* = .88	0.06 (-0.62 to 0.74) *P* = .86	0.23 (-0.51 to 0.97) *P* = .54	1.45 (0.44 to 2.46) *P* = .005	3.08 (1.43 to 4.73) *P* = .0002	3.23 (1.41 to 5.05) *P* = .0005

Slide 38

HG1 Howard, George, 10/1/2020

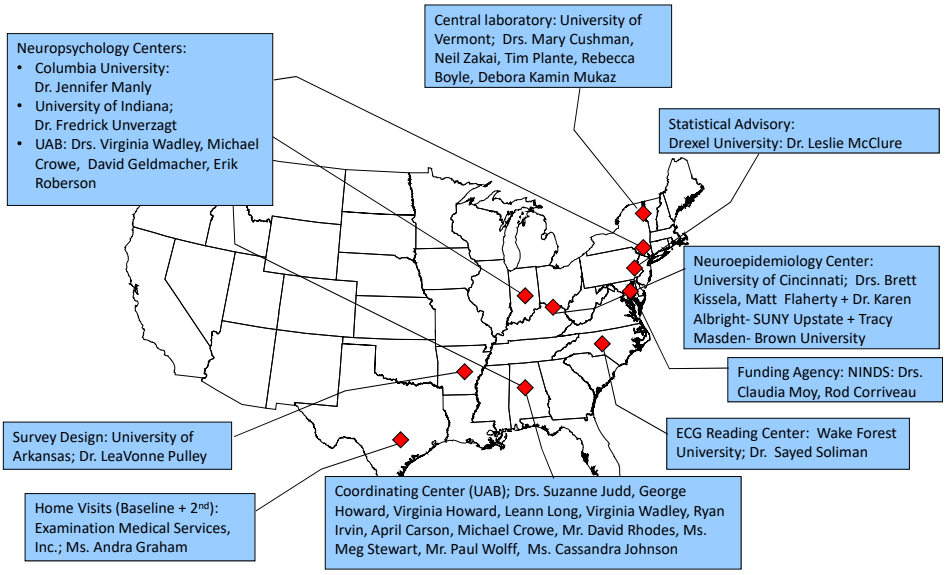
Conclusions

- Data from Vital Statistics shows a nearly monotonically higher risk of stroke death with increasing rurality
  - This disparity increased from ≈16% in 1999 → ≈25% in 2009
  - Has been fairly rapidly decreasing to ≈11% in 2018
- Data from REGARDS shows:
  - The higher risk in rural areas appears to be nearly completely related to higher stroke incidence in rural areas (with higher case-fatality playing a minor role)
  - This suggests the focus of interventions needs to be community-based efforts to reduce risk of incident stroke in rural areas
  - A heavier risk factor burden and poorer SES profile contribute about 25% to 35% of this excess, and are clearly targets for intervention
  - This implies that the factors driving 65% to 75% of the excess are not understood (… yes … the more work is needed statement)
- I really, really, really wish we had time to discuss geographic disparities (a.k.a., the stroke belt … invite me back!)
- We welcome others to join in analysis of REGARDS data to better understand this disparity

Acknowledgments

- REGARDS is supported by cooperative agreement U01 NS041588 from NINDS/NIH-NIA
- We thank the investigators, staff, and participants of the REGARDS study for their valuable contributions. A full list of participating investigators and institutions can be found at http://www.regardsstudy.org

REGARDS Functional Units



Questions?

NIH/NINDS U01 NS41588

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