Update on the REGARDS Study

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

- General population study
- 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:
  - Stroke incidence
  - Case fatality (defined as death within 30 days of incident stroke)

Outline

- Insights on where to focus interventions to reduce geographic disparities
- Is control of hypertension adequate to reduce risk?

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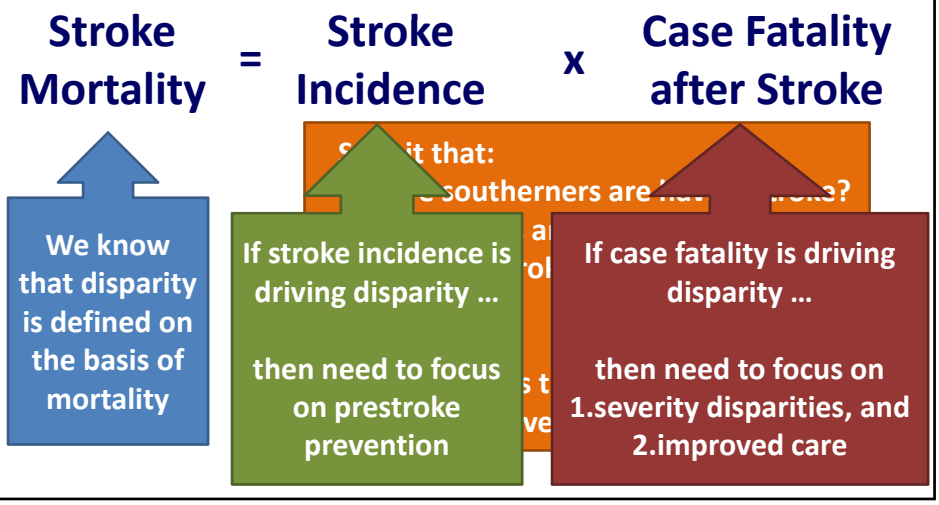
What we know … and what we don't know

- The stroke belt is documented by a higher stroke mortality in the Southeastern U.S. … that has existed for more than 60 years!
- There are two ways there could be more stroke deaths in the southern region of the US
  - More Southerners could be having strokes
  - Stroke could be more fatal in the South
    - Poorer stroke care?
    - More severe strokes?
- Stroke mortality = Stroke Incidence x Stroke Case Fatality
- But with no national stroke surveillance systems, there are no data on which is the cause!

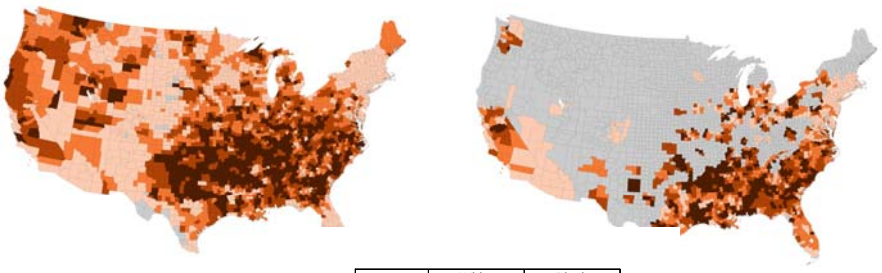
… but why do we care about this?



Methods

- **Average of NCHS smoothed stroke mortality for 2005-2007 and 2008-2010**

White **Black**



	White (n = 3,082)	Black (n = 1,547)
Q1:	27.0 – 78.9	47.3 – 115.4
Q2:	79.0 – 87.8	115.4 – 131.3
Q3:	87.8 – 98.4	131.3 – 148.8
Q4:	98.5 – 257.5	148.9 – 400.6

Statistical Methods

- **Three separate analyses**
  - **Mortality**
    - **Outcome: Incidence of fatal stroke**
    - **Proportional hazards analysis**
  - **Incidence**
    - **Outcome: Incidence of fatal or non-fatal stroke**
    - **Proportional hazards analysis**
  - **Case fatality**
    - **Outcome: Death within 30-day among those with a stroke**
    - **Logistic regression analysis**
- **In each case – assess interactions between age, race and sex, and include significant terms ($p < 0.10$)**

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Description of the Study Population by Quartile of NCHS Stroke Mortality

		Quartile of County Stroke Mortality			
		Q1 (n = 7,357)	Q2 (n = 7,468)	Q3 (n = 7,395)	Q4 (n = 7,430)
Age (mean ± SD)		65.4 ± 9.4	65.1 ± 9.5	64.8 ± 9.4	64.3 ± 9.3
Male (%)		47.9	45.3	43.2	43.3
Black (%)		41.7	40.5	41.2	41.1
Region of the Nation (%)	Buckle	4.9	16.6	28.5	33.6
	Belt	11.9	34.7	40.4	51.6
	Rest of Nation	83.2	48.7	31.1	14.8

Outcomes by Quartile of NCHS Stroke Mortality

			Quartile of County Stroke Mortality			
		All	Q1	Q2	Q3	Q4
All	Number of Participants	29,650	7,357	7,468	7,395	7,430
	Number of Stroke Events	1,317	317	320	315	365
	Number of Fatal Stroke Events	242	46	68	41	77
	Person-years exposure	205,917	52,615	51,913	50,993	50,396

Differential effect by race?

- In all analyses, there was no evidence of a differential association in African Americans and whites
- Data are pooled by race, and overall results presented

Analysis #1:

Do Stroke Deaths in REGARDS Reflect National NCHS Stroke Deaths?

County-Level Stroke Mortality Quartile	Whites + Blacks	
	Rate/100,000 (95% CI)	Relative Risk (95% CI)
Quartile 1	90 (67 – 121)	1.00 (ref)
Quartile 2	140 (110 – 178)	1.55 (1.06 – 2.25)
Quartile 3	109 (82 – 144)	1.21 (0.81 – 1.81)
Quartile 4	174 (138 – 218)	1.95 (1.35 – 2.81)
p-trend	0.0025	

Analysis #2:

Are more strokes happening in the regions with higher NCHS stroke deaths?

County-Level Stroke Mortality Quartile	Whites + Blacks	
	Rate/100,000 (95% CI)	Relative Risk (95% CI)
Quartile 1	658 (588 – 735)	1.00 (ref)
Quartile 2	690 (618 – 771)	1.06 (0.90 – 1.25)
Quartile 3	701 (627 – 784)	1.09 (0.92 – 1.29)
Quartile 4	844 (761 – 937)	1.29 (1.10 – 1.52)
p-trend	0.0023	

Analysis #3:

Is there higher stroke case-fatality in the regions with higher NCHS stroke deaths?

County-Level Stroke Mortality Quartile	Whites + Blacks	
	# Fatal / # Strokes % (95% CI)	Odds Ratio (95% CI)
Quartile 1	46/279 16.5% (12.3% - 21.4%)	1.0 (ref)
Quartile 2	68/284 23.9% (19.0% - 29.3%)	1.66 (1.08 - 2.53)
Quartile 3	51/281 18.2% (13.8% - 23.2%)	1.18 (0.76 – 1.85)
Quartile 4	77/323 23.8% (19.3% - 28.9%)	1.71 (1.13 – 2.59)
p-trend	0.058	

Summary

- REGARDS aligns with NCHS stroke deaths, implying geographic validity of the study
- In addition, stroke mortality increased 1.95 times over quartiles of NCHS mortality
- Increase in stroke incidence
  - Consistently and significantly increased in higher risk regions
  - But increase was only 1.29 times
- Increase in case fatality
  - Inconsistently and marginally significant increase in higher risk regions
  - Increase (odds) was 1.71 times
- It appears that both incidence and higher case fatality are contributing to geographic disparity

Implications

- If we are going to reduce geographic disparities, we must both:
  - Reduce excess stroke events in high risk regions
  - Improve care of stroke patients in high risk regions
- There is a role for both stroke prevention and stroke care to meet this goal

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- Insights on where to focus interventions to reduce geographic disparities
- Is control of hypertension adequate to reduce risk?

Interesting Story

- I have the honor to work with the ADPH on the Million Hearts Initiative
- Focus is on hypertension control (although I have convinced the ADPH that hypertension prevention is a key)
- Work is with several other state health departments
- One of the other state health officers stated that with efficacy of pharmacological treatment of hypertension … prevention is not important
- Should our approach be to just effectively treat hypertension????

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

Conclusions (part 2)

- I am not saying that pharmacologic treatment of hypertension is not beneficial!
- Rather, I am saying that:
  - It is only partially effective, and does not return risk to hypertension-free levels
  - The only way to get the maximum risk reduction is to prevent the development of hypertension
- There are at least 6 proven approaches for hypertension prevention (Level 1A evidence)
- We need to extend primordial risk factor prevention into adulthood!

Overall Conclusions

- Both higher stroke incidence and higher case fatality appear to contribute to regions of higher stroke mortality
- Important to focus on both efforts to
  - Prevent stroke in the regions
  - Improve care once stroke occurs
- Primary prevention is important for stroke prevention, but real success will also require primordial prevention

Acknowledgments

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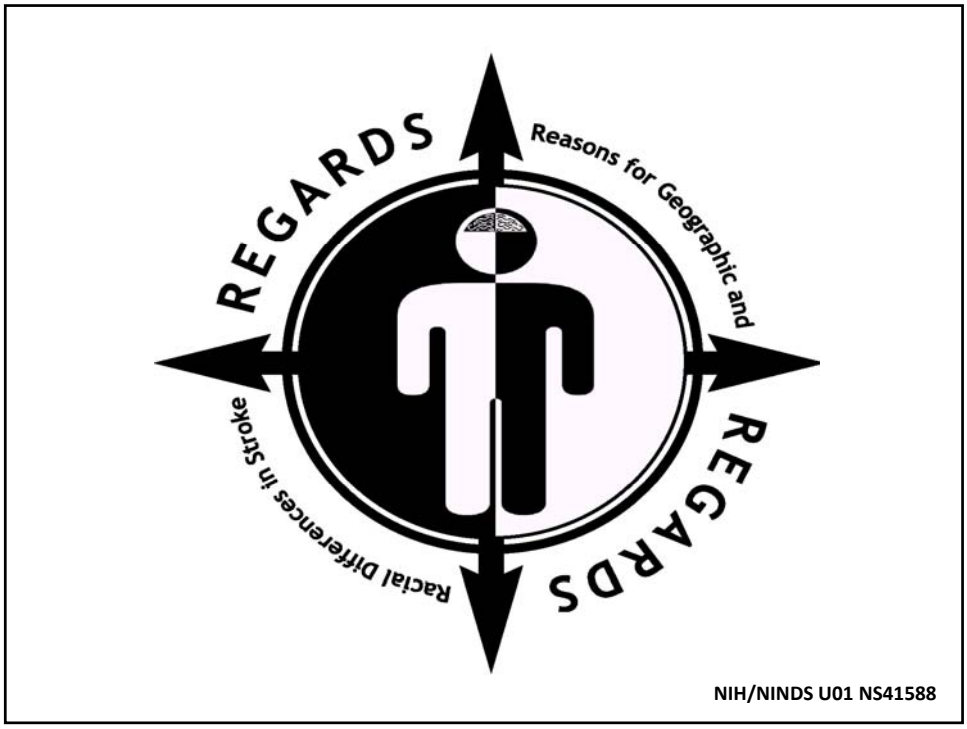
- We thank the investigators, staff, and most of all the participants of the REGARDS study for their valuable contributions. A full list of participating investigators and institutions can be found at http://www.regardsstudy.org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