Increasing False Positive Diagnoses May Lead to Overestimation of Stroke Incidence, Particularly in the Young

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February 20, 2020 | ISC 2020 | Los Angeles, CA

MICHIGAN MEDICINE
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Presenter Disclosures:

None

Background: Strokes in young adults

Strokes are reportedly increasing:

- Hospitalizations for stroke[1,2]
- Age at first ever stroke[3]
- Increased stroke incidence in US[4] and abroad[5,6]

Proposed causes include:

Increasing CV risk factors

Increased use of advanced imaging

Changes in definition of TIA and stroke

[1]George et al. *JAMA Neurology*. 2017
[2]Tong et al. *International Journal of Stroke*. 2016
[3]Li et al. *Annals of Epidemiology*. 2018
[4]Kissela et al. *Neurology*. 2012
[5]Béjot et al. *Cerebrovascular Diseases*. 2010
[6]Medin et al. *Stroke*. 2004

Question:

Do trends in …

(1) neurologically focused emergency department visits,

(2) differential diagnostic classification of stroke and TIA over time,

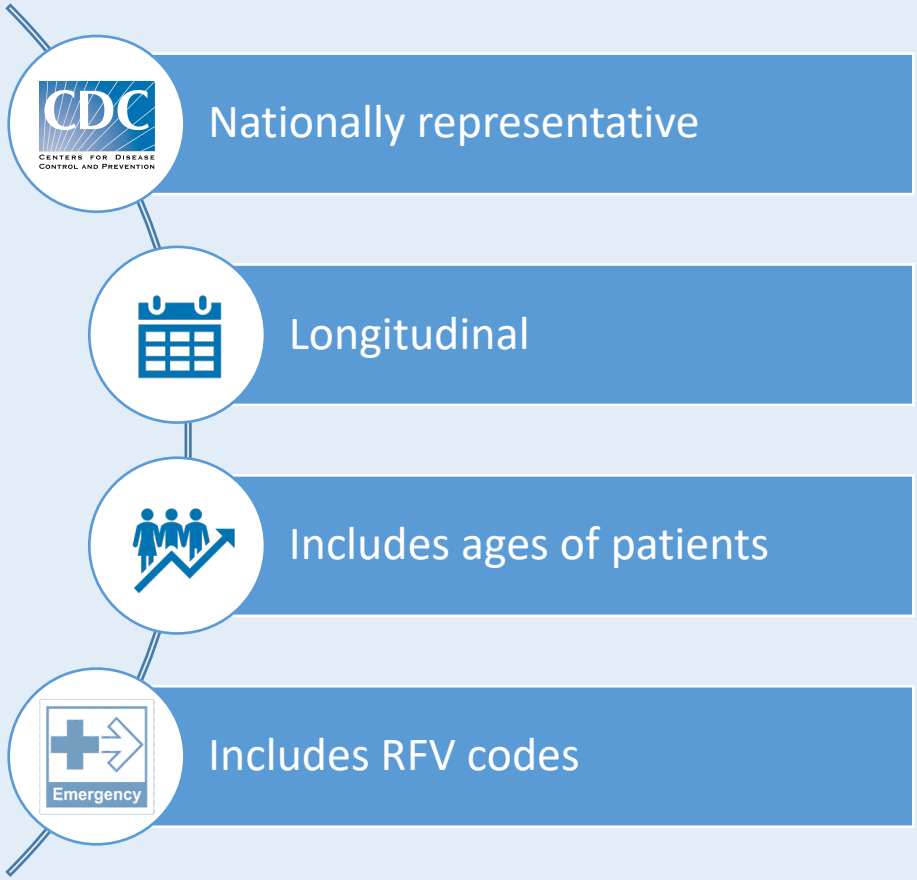
(3) changes in the use of advanced imaging

contribute to the reported increasing stroke incidence in young adults?

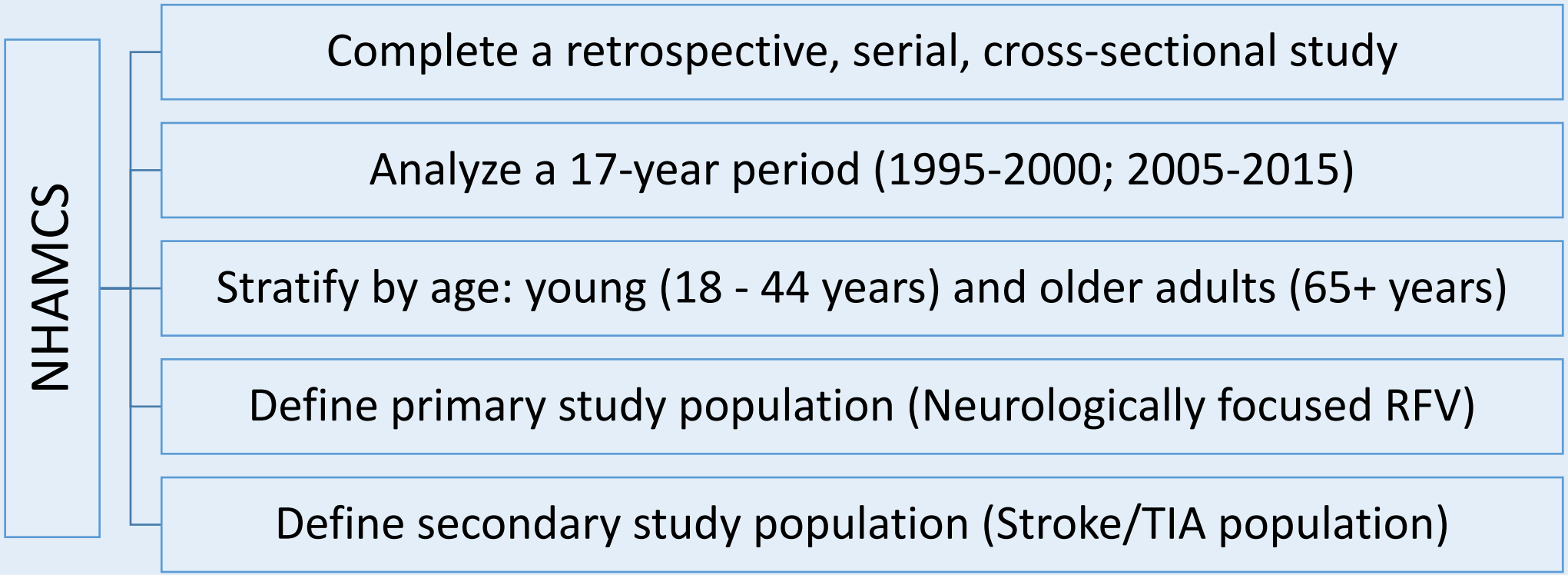
Methods: Dataset

NHAMCS

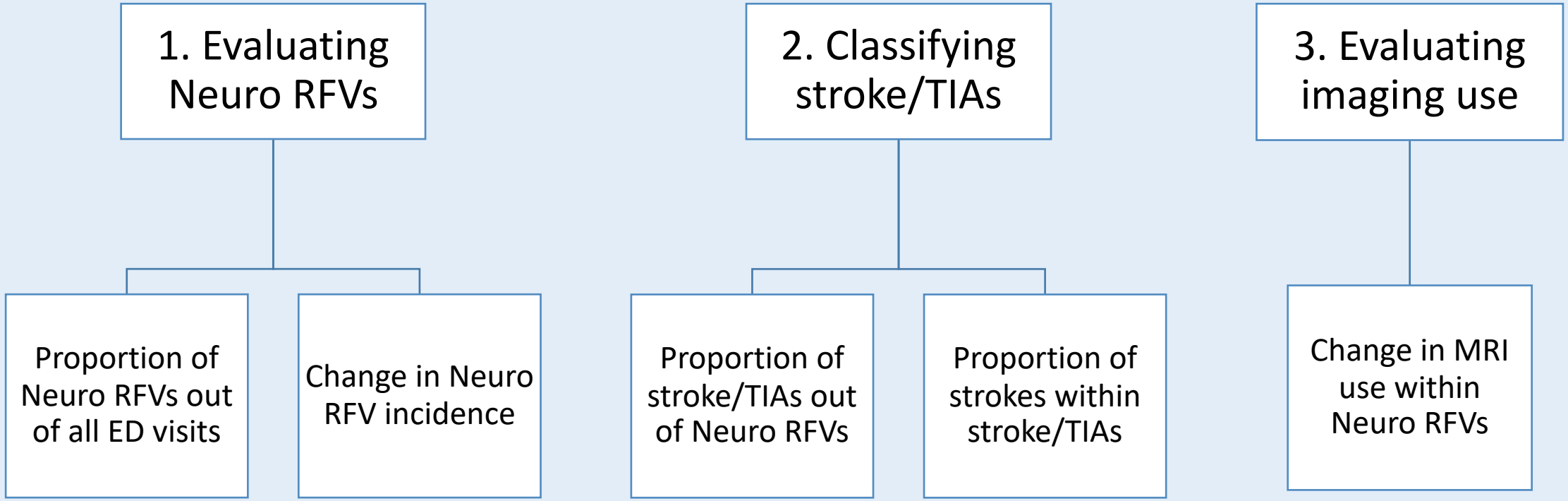
Survey data on utilization and provision of ambulatory care services in hospital EDs and outpatient departments



Methods: Study populations



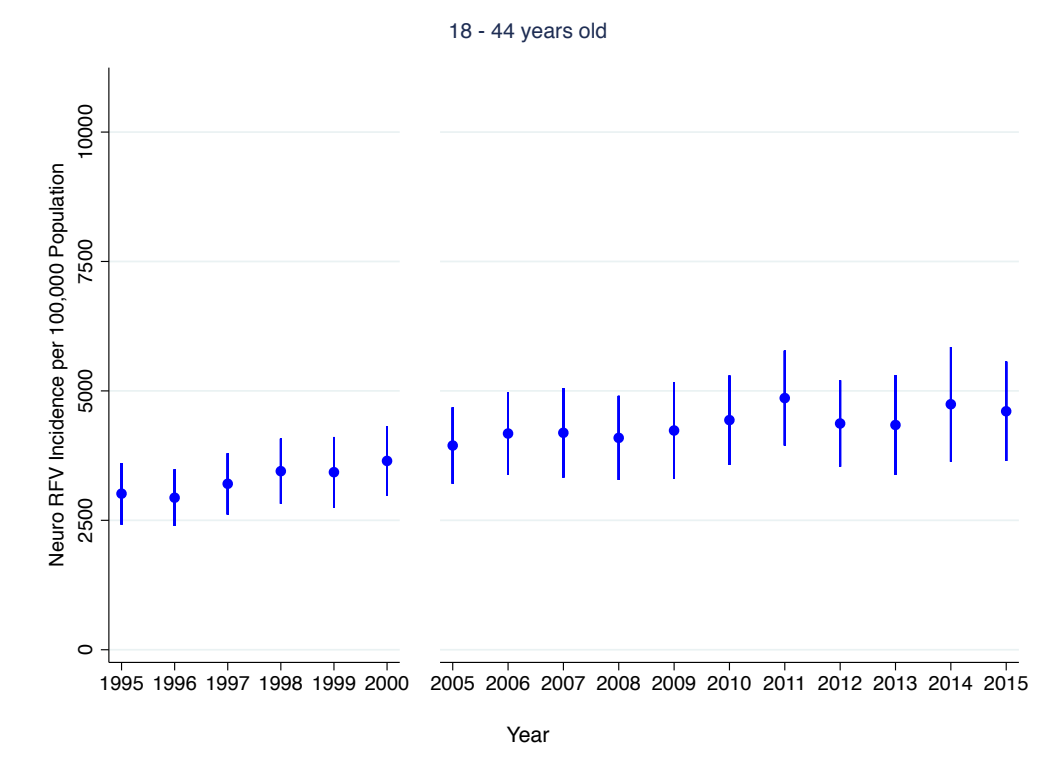
Methods: Finding trends

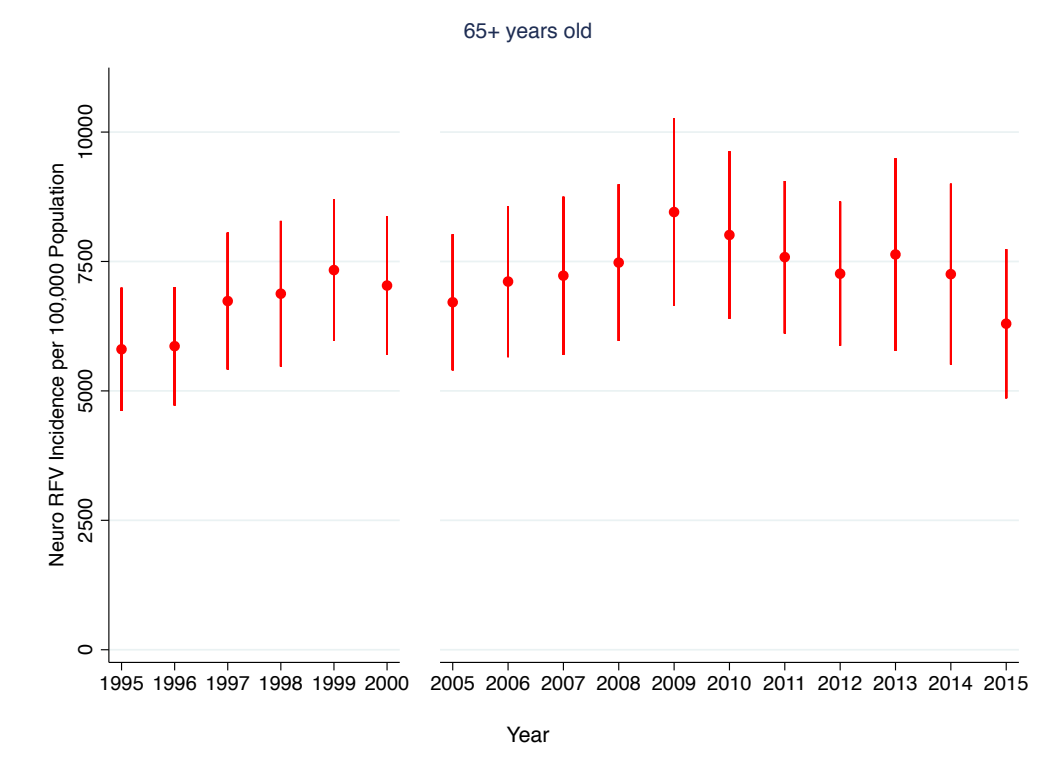


Results: Study population

Demographics	Neurological RFV, n = 189M (174M-204M)	Stroke or TIA, n = 9.6M (8.7M-10.4M)	All Subjects, n = 2.0B (1.9B-2.2B)
Age, mean yr (SD)	46 (23)	70 (15)	36 (24)
Female	59%	56%	54%
Race/ethnicity			
White	62%	73%	59%
Black	20%	13%	21%
Hispanic	11%	6%	13%
Other	7%	8%	7%
Insurance			
Private	30%	21%	32%
Medicare	26%	60%	17%
Medicaid	19%	7%	24%
Other	24%	11%	27%
MRI	2%	10%	< 1%
Age Distribution			
18 - 44	40%	6%	41%
65 +	25%	68%	15%
Comorbidities			
Hypertension	32%	66%	22%
Diabetes	13%	27%	9%
CEBVD	7%	60%	3%
Hyperlipidemia	11%	37%	7%

Results 1: Increasing Neuro RFV incidence





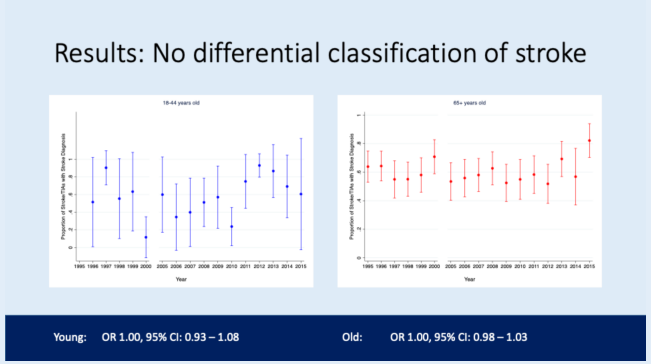
Neuro RFV incidence is rising faster in the young (p = 0.022)

Young: +111 Neuro RFVs/100,000 pop/year (95% CI: +98 – +125)

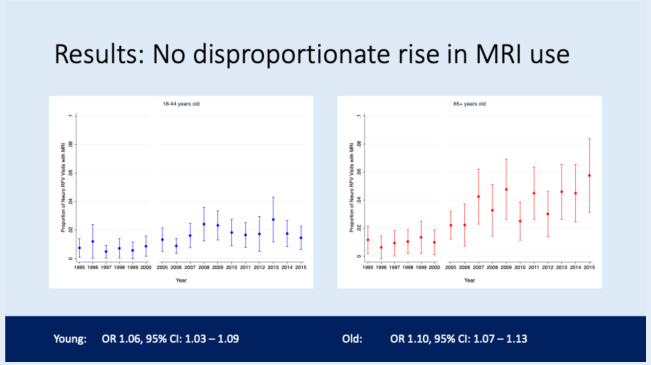
Old: +70 Neuro RFVs/100,000 pop/year (95% CI: +34 – +108)

Results 2&3: Trends of Stroke/TIAs & MRI use

2. No differential classification of TIA to stroke
   - Young: OR 1.00, 95% CI: 0.93 – 1.08
   - Old: OR 1.00, 95% CI: 0.98 – 1.03



3. No disproportionate rise in MRI use for Neuro RFVs
   - Young: OR 1.06, 95% CI: 1.03 – 1.09
   - Old: OR 1.10, 95% CI: 1.07 – 1.13



Conclusions:

If…

- **Neuro RFVs increasing faster in young compared to older adults**
- Similar specificity of stroke diagnosis for young and older adults
- Lower prior probability of stroke diagnoses in the young

Then…

- **False positive stroke diagnoses would be increasing**
- Possibly faster rise in the young compared to older adults

Example: Calculating false positives

Equations …

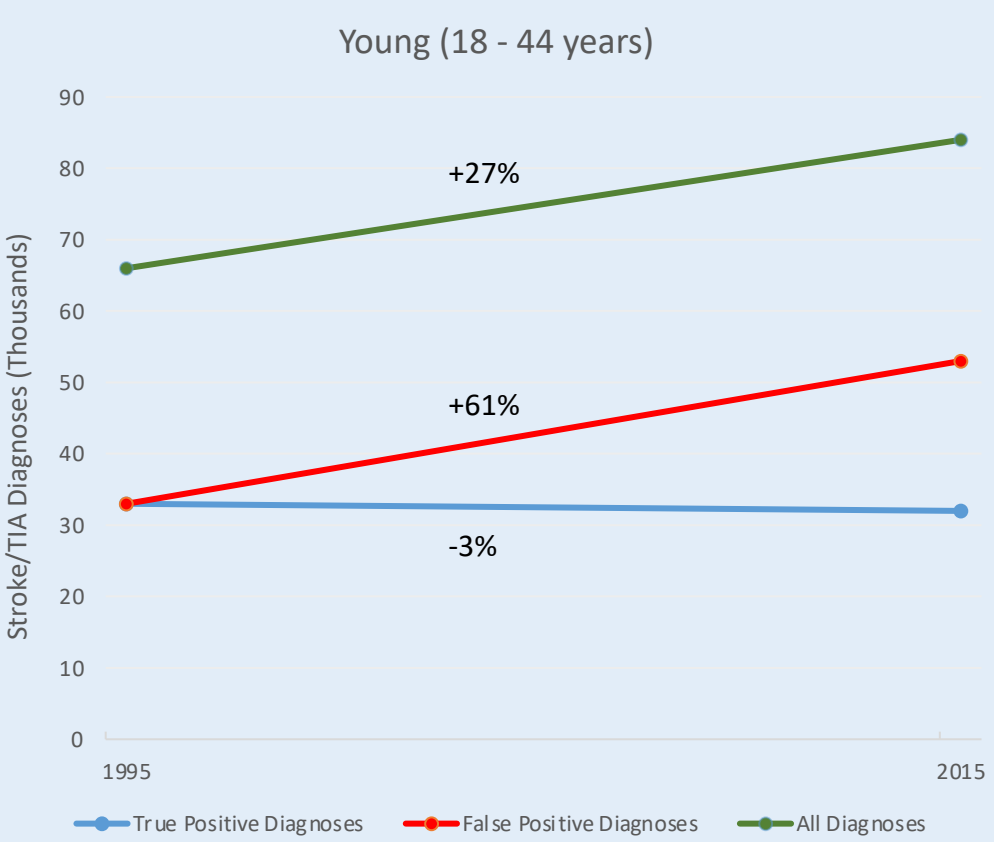
$$Stroke\ Diagnoses = True\ Positives\ (TP) + False\ Positives\ (FP)$$

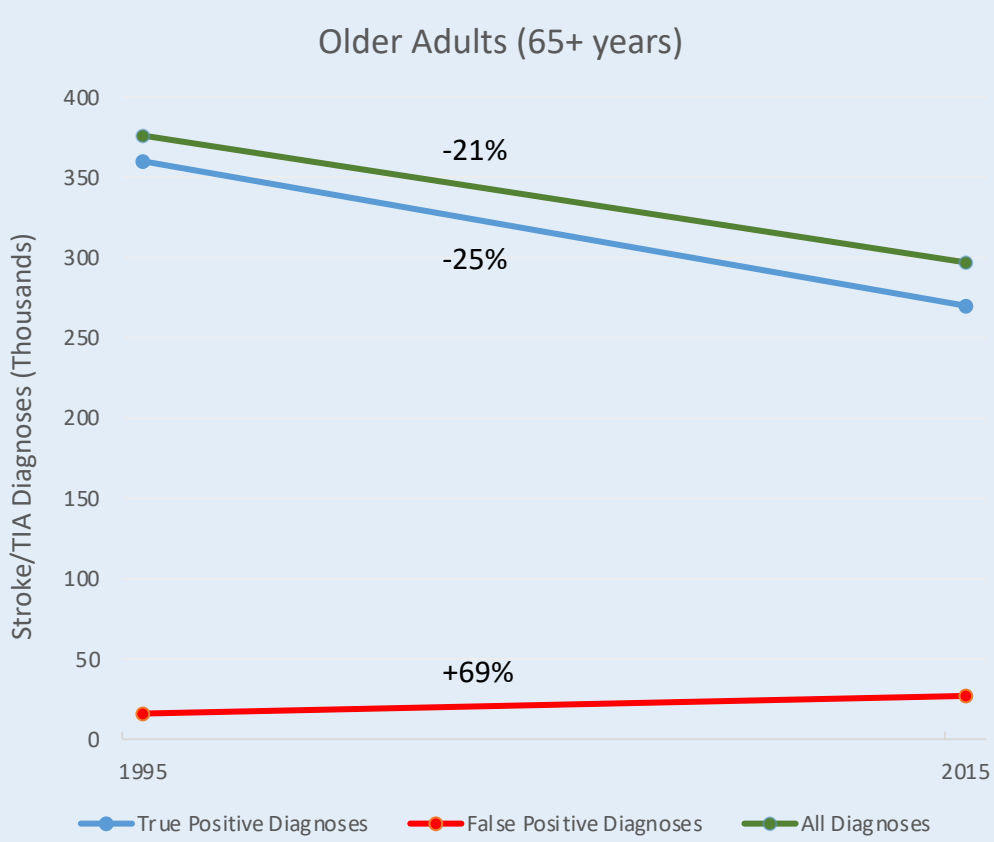
$$FP = \#\ of\ Neuro\ RFVs \times (1 - Stroke\ Prevalence) * (1 - Specificity)$$

$$TP = \#\ of\ Neuro\ RFVs \times Stroke\ Prevalence$$

* Assume specificity of stroke diagnoses $= 0.99$

Conclusions: False positives are likely rising





These data suggest a potential explanation that may contribute to higher stroke incidence in the young and merits further scrutiny.

Conclusions:

Limitations

- Reason for visit codes have not been validated
- Accuracy of stroke diagnoses may have increased over time
- Data may not account for changing hospitalization practices or strokes/TIAs diagnosed secondarily

Next Steps

- Exploring the potential of false positive diagnoses in ED
- Applying gold-standard diagnostics to all patients with Neuro RFV?

Summary:

Question:

- Do trends in neurologically focused ED visits, differential diagnostic classification of stroke and TIA over time, and changes in the use of advanced imaging contribute to the reported increasing stroke incidence in young adults?

Findings:

- In this cross-sectional study from 1995-2015, the **incidence of neurologically focused ED visits increased faster in the young compared to older adults.**
- There was no evidence of differential classification of TIA to stroke over time or disproportionate rise in MRI utilization in the young.

Meaning:

- Increasing false positive diagnoses in the young may be a contributing factor to the observed increases in stroke incidence in the young and merits further scrutiny.

- Thank You -

Supplemental Slides

Hypotheses:

1. Stroke diagnoses may be increasing in young adults due to increased use of MRI and/or due to changes in definition of TIA and stroke

2. Amongst stroke or TIA diagnoses, strokes would increase disproportionately based on changes in definition of TIA and trends in MRI use

Methods: NHAMCS

- Hospital staff or Census Bureau representatives complete a patient record form for each sampled visit based on medical record.
- Sample hospitals are randomly assigned to 16 panels that rotate across 4-week reporting periods, with each hospital surveyed approximately once every 15 months.
- On average, approximately 88% of sampled hospitals participated in the survey, and about 88% of sampled EDs provided complete information on their sample visits, for a total unweighted response rate of 75%.

Methods: Defining Neuro RFV Population

- Defined as visits by patients with a primary RFV of neurologically focused symptoms or concerns.
- From “A Reason for Visit Classification for Ambulatory Care” RFV code, we used the hierarchy of conditions listed under neurologically focused symptoms/concerns that we felt represented stroke/TIA.
- Then edited this list via manual review of the top RFVs associated with the stroke/TIA population to identify RFVs that could plausibly represent stroke visits and to nearly all cases where a primary stroke diagnosis was ultimately assigned

Methods: Defining Neuro RFV Population

Table e1. Defining Neuro RFV Population

RFV1 Code	Reason for Visit	Original Neuro RFV Definition	Top 25 RFVs from Stroke/TIA Population	RFVpop: Final Adjusted Definition
2525.0	Cerebrovascular Disease		X	✓
1230.0	Weakness (neurologic)	X	X	✓
1220.1	Loss of feeling (anesthesia)	X	X	✓
1020.0	General weakness	X	X	✓
1225.0	Vertigo - dizziness	X	X	✓
1235.2	Slurring	X	X	✓
1165.0	Other problems related to psycho…		X	✓
1240.0	Other symptoms referable to the nervo..	X	X	✓
1235.0	Disorders of speech/speech disturbance	X	X	✓
1210.0	Headache, pain in head	X	X	✓
5840.0	Unconscious on arrival		X	✓
5810.0	Accident, NOS		X	
1220.3	Abnormal sensation (paresthesia)	X	X	✓
1050.1	Chest pain, soreness		X	
1095.0	Disorders of motor function		X	✓
1415.0	Shortness of Breath		X	
2370.0	Other and unspec diseases of the nervous sys		X	✓
1945.4	Weakness of arm		X	✓
1305.2	Diminished vision	X	X	✓
5841.0	State of consciousness not specified		X	✓
1030.0	Fainting (syncope)		X	
2510.0	Hypertension		X	
5842.0	Altered level of consciousness		X	✓
1205.0	Convulsions	X	X	✓
1920.4	Weakness of leg		X	✓
1200-1259	Symptoms referable to the nervous system	X		✓
1020.0	General weakness	X		✓
1305.1-.4	Visual dysfunctions	X		✓
1340.4	Abnormal eyelid movements	X		✓
2365.0	Migraine headaches	X		✓
3345.0	Diagnostic radiological abnormalities	X		
6400.0	Radiological abnormalities	X		
6700.0	Abnormal test results	X		

Green highlight = RFV included in final definition of Neuro RFV population

Methods: Defining Stroke/TIA Population

- Defined as any patient visit to the ED that receives a primary diagnosis of stroke or TIA by the ED physician.
- We used International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) to determine visits by patients in whom the ED physician's primary diagnosis was TIA (435.XX) or ischemic stroke (433.x1, 434.x1, 436.xx)

Methods: Sensitivity analysis

- We also performed a sensitivity analysis using NHAMCS's Hospital Discharge Diagnosis flag, which was available for 2005-2015, and identified visits where the primary discharge diagnosis after hospitalization was stroke or TIA using the ICD-9-CM codes described above.
- We also all analysis (described for ED diagnoses) using the hospital discharge diagnoses.

Methods: Statistical analysis (Stata 14)

- Created logistic regression models to determine significance of trends
- Adjusted for race, sex, and insurance status to assess other confounding factors
- Repeated using an age category-time interaction term to assess whether time trends varied by age group

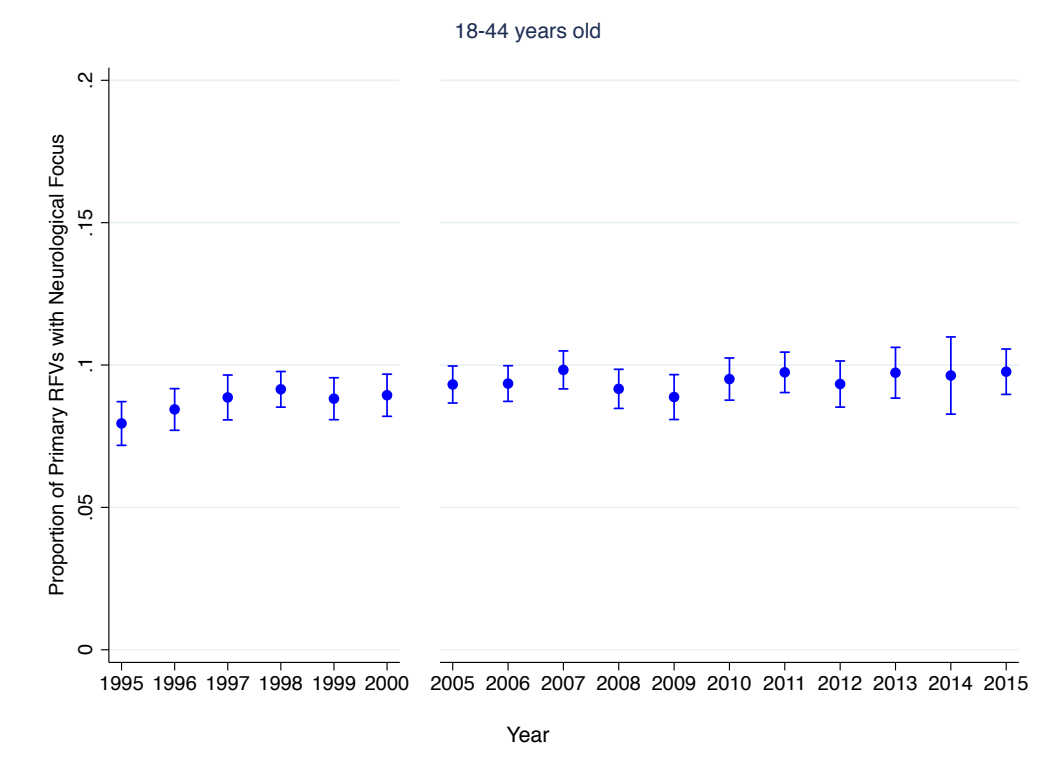
Results: Characterizing RFVs and Diagnoses

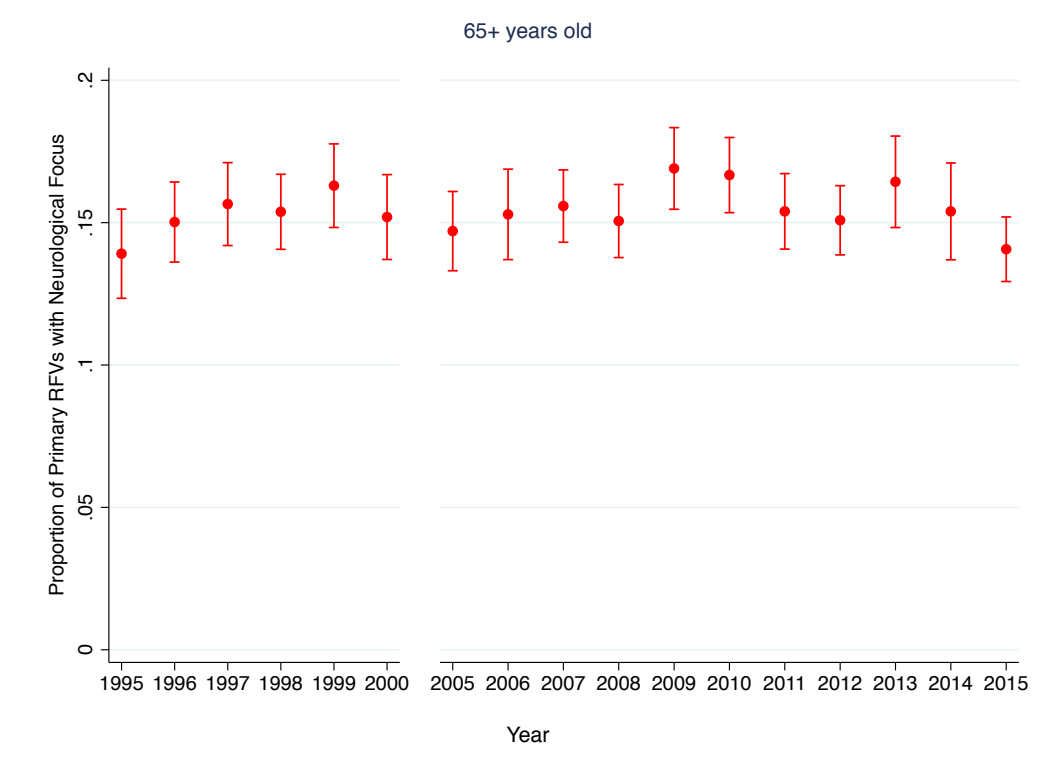
Table e3. Most Common RFVs and Primary Diagnoses by Time Period			
Time Period	**Rank**	**Top Primary RFVs within stroke/TIA pop (%)**	**Top Primary Diagnoses within Neuro RFV pop (%)**
1995 - 2000	1	Cerebrovascular disease (10%)	Headache (11%)
	2	(Anesthesia) Loss of feeling (10%)	Migraine, unspec. (9%)
	3	(Neurologic) weakness (10%)	Dizziness & giddiness (4%)
	4	General weakness (7%)	Ischemic stroke (Acute, ill-defined CVD) (3%)
	5	Vertigo - dizziness (7%)	Other convulsions (3%)
2005 - 2009	1	Cerebrovascular disease (15%)	Headache (12%)
	2	(Neurologic) weakness (12%)	Migraine, unspec. (8%)
	3	General weakness (9%)	Dizziness & giddiness (5%)
	4	(Anesthesia) Loss of feeling (9%)	Other convulsions (5%)
	5	Vertigo - dizziness (5%)	Syncope and collapse (3%)
2010 - 2015	1	Cerebrovascular disease (17%)	Headache (13%)
	2	(Neurologic) weakness (12%)	Dizziness & giddiness (6%)
	3	General weakness (10%)	Migraine, unspec. (6%)
	4	(Anesthesia) Loss of feeling (8%)	Other convulsions (4%)
	5	Slurring (5%)	Other malaise and fatigue (3%)

Results: Characterizing RFVs and Diagnoses

Table e4. Most Common RFVs and Primary Diagnoses by Age Group			
Age Group	**Rank**	**Top Primary RFVs within stroke/TIA pop (%)**	**Top Primary Diagnoses within Neuro RFV pop (%)**
< 18	1	Cerebrovascular disease (27%)	Headache (12%)
	2	Other symptoms referrable to nervous sys (16%)	Other convulsions (8%)
	3	Migraine headache (10%)	Head injury, unspecified (5%)
	4	Stiffness, site unspecified (7%)	Migraine, unspec. (3%)
	5	Other and unspec diseases of the nervous sys (7%)	Unspecified viral infection (3%)
18 - 44	1	Cerebrovascular disease (19%)	Headache (18%)
	2	(Neurologic) weakness (14%)	Migraine, unspec. (13%)
	3	(Anesthesia) Loss of feeling (11%)	Other convulsions (5%)
	4	Vertigo - dizziness (6%)	Dizziness & giddiness (4%)
	5	Headache, pain in head (5%)	Depressive disorder, not elsewhere classified (2%)
45 - 64	1	Cerebrovascular disease (15%)	Headache (11%)
	2	(Anesthesia) Loss of feeling (14%)	Migraine, unspec. (8%)
	3	(Neurologic) weakness (10%)	Dizziness & giddiness (6%)
	4	General weakness (8%)	Other convulsions (4%)
	4	Headache, pain in head (7%)	Unspecified essential hypertension (3%)
65+	1	Cerebrovascular disease (13%)	Dizziness & giddiness (7%)
	2	(Neurologic) weakness (11%)	Other malaise and fatigue (5%)
	3	General weakness (10%)	Transient cerebral ischemic attack (4%)
	4	(Anesthesia) Loss of feeling (7%)	Syncope and collapse (4%)
	5	Vertigo - dizziness (5%)	Headache (4%)

Results: Prop of Neuro RFVs from all ED RFVS

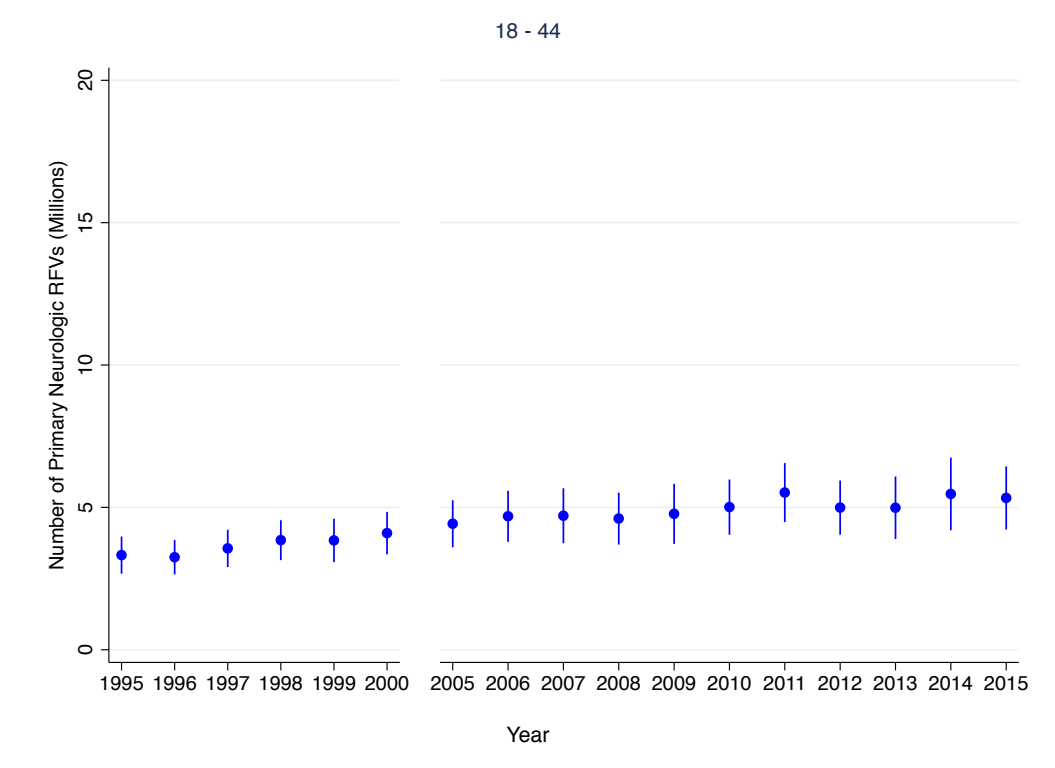


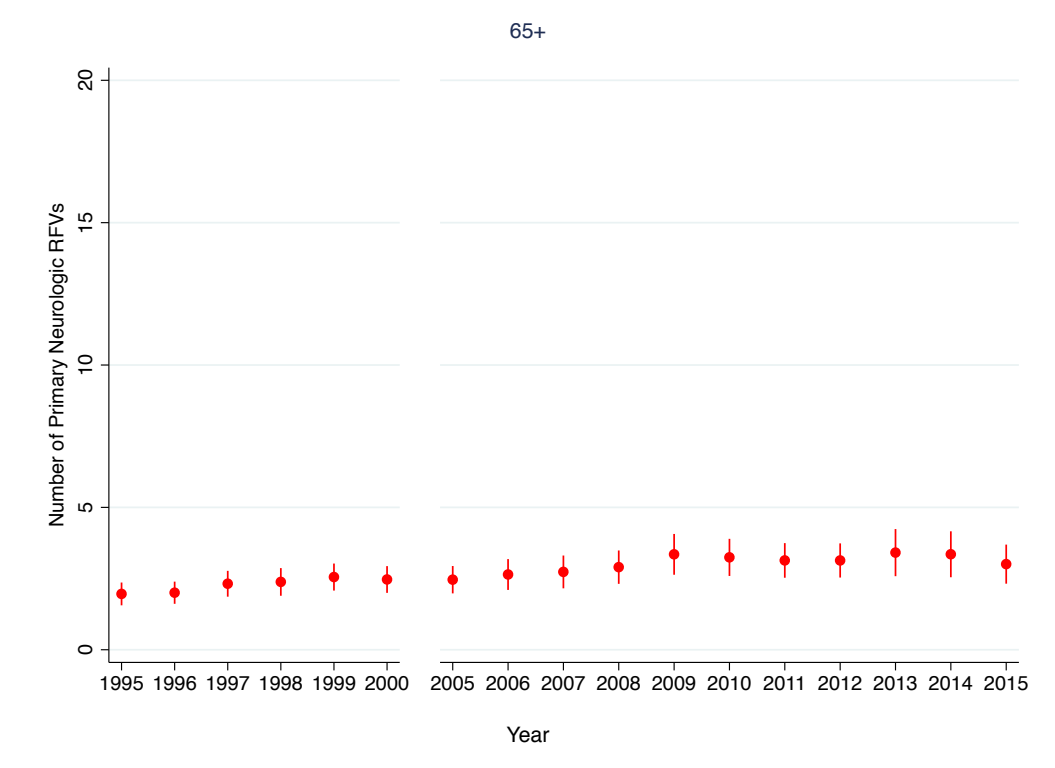


Young: OR 1.007 per year
95% CI: 1.003 – 1.011; p = 0.001

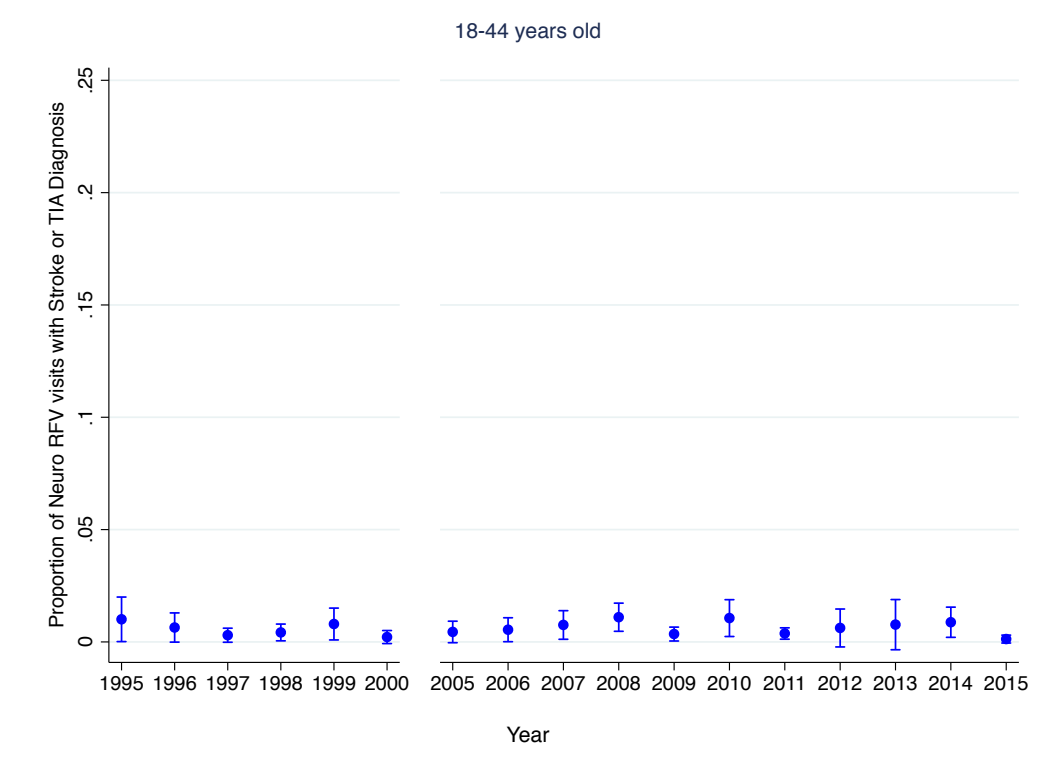
Old: OR 1.001 per year
95% CI: 0.998 – 1.005; p = 0.504

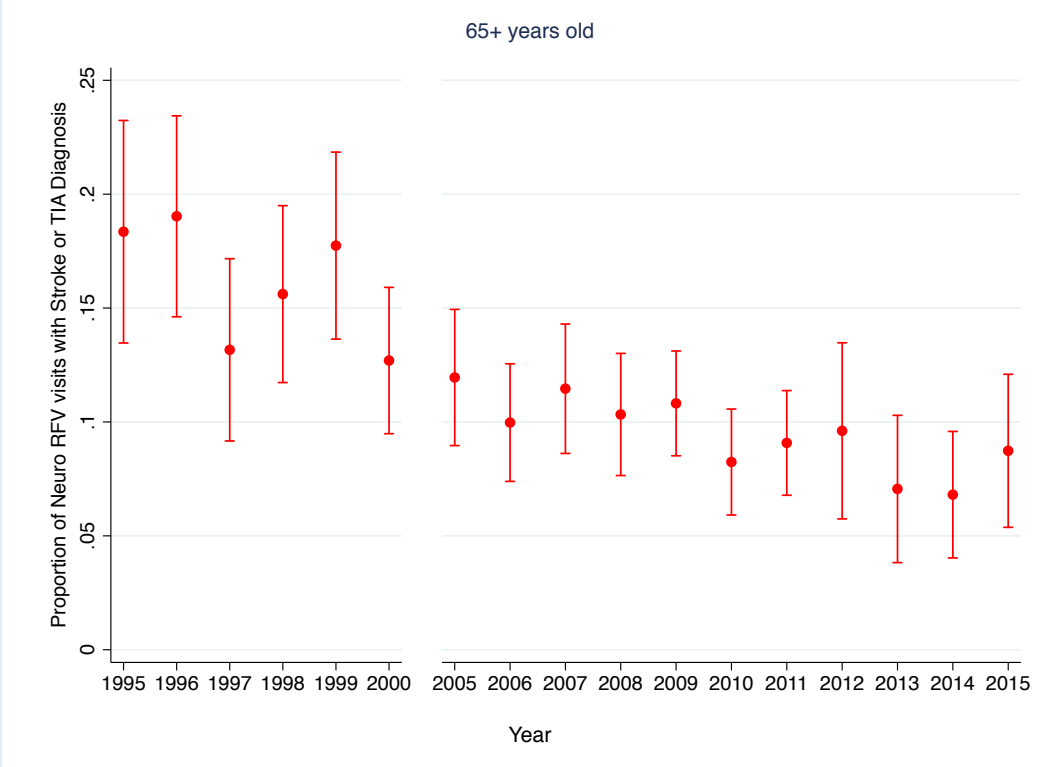
Results: Increasing Neuro RFVs numbers





Results: Stroke/TIAs from Neuro RFVs

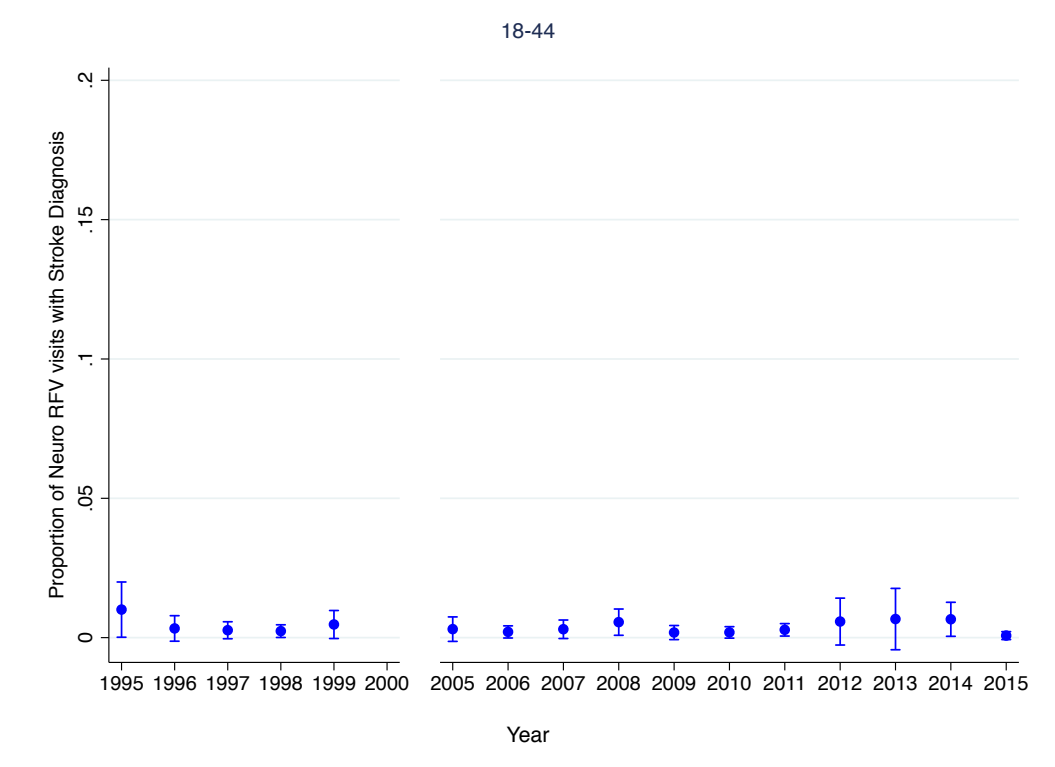


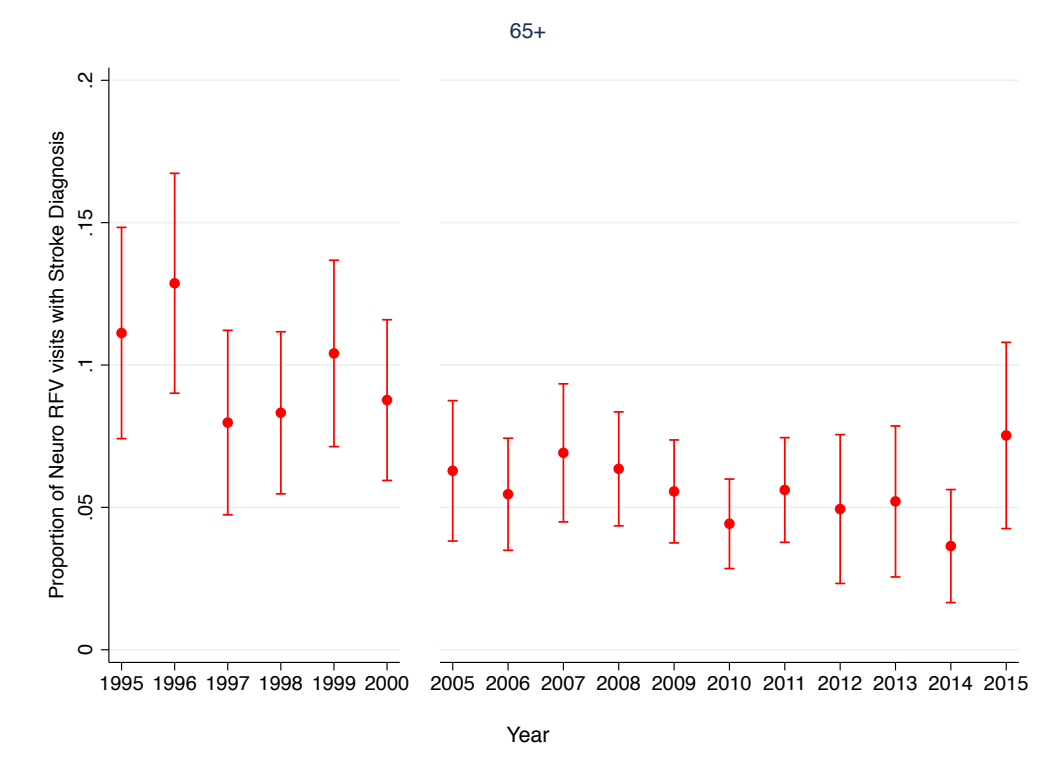


Young: OR 1.00, 95% CI: 0.96 – 1.04, p = 0.92

Old: OR 0.95, 95% CI: 0.94 – 0.96, p < 0.01

Results: Strokes from Neuro RFVs

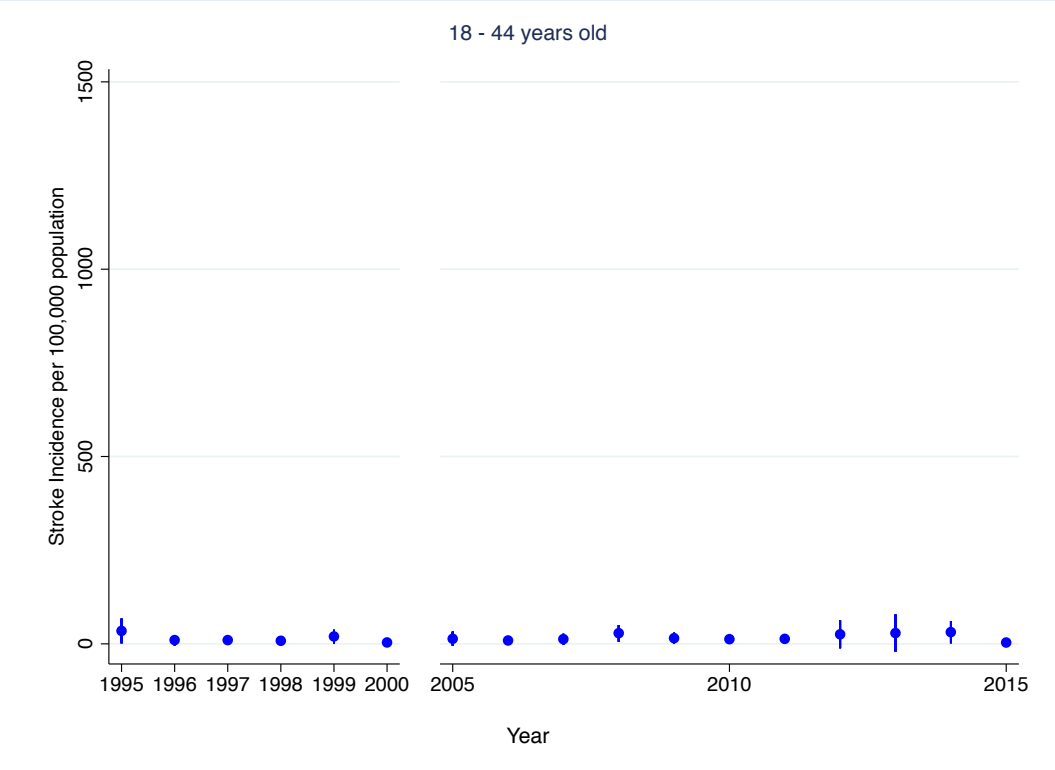


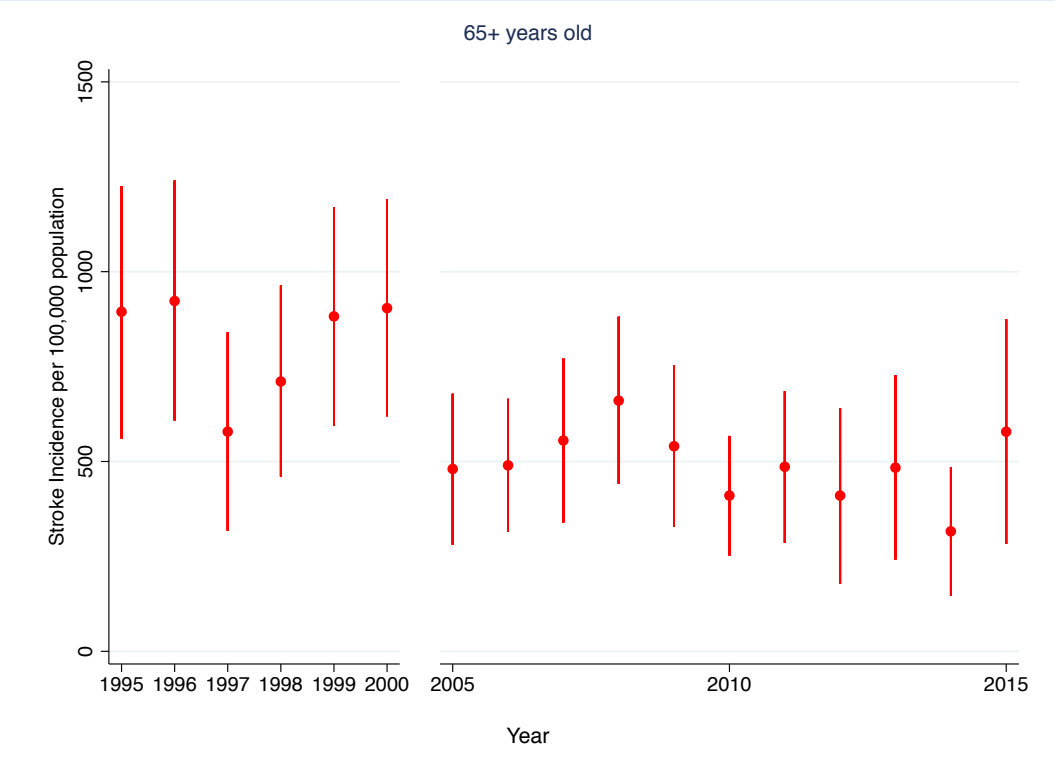


Young: OR 1.00, 95% CI: 0.94 – 1.06, p = 0.99

Old: OR 0.96, 95% CI: 0.94 – 0.97, p < 0.01

Results: Incidence of Stroke

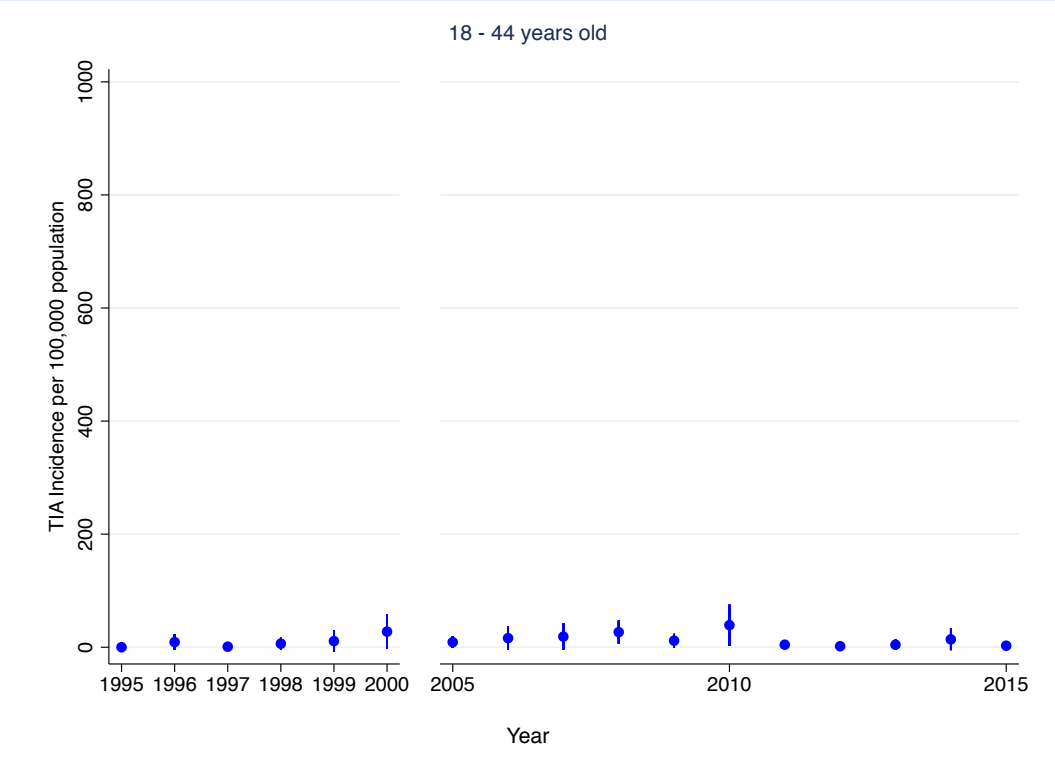


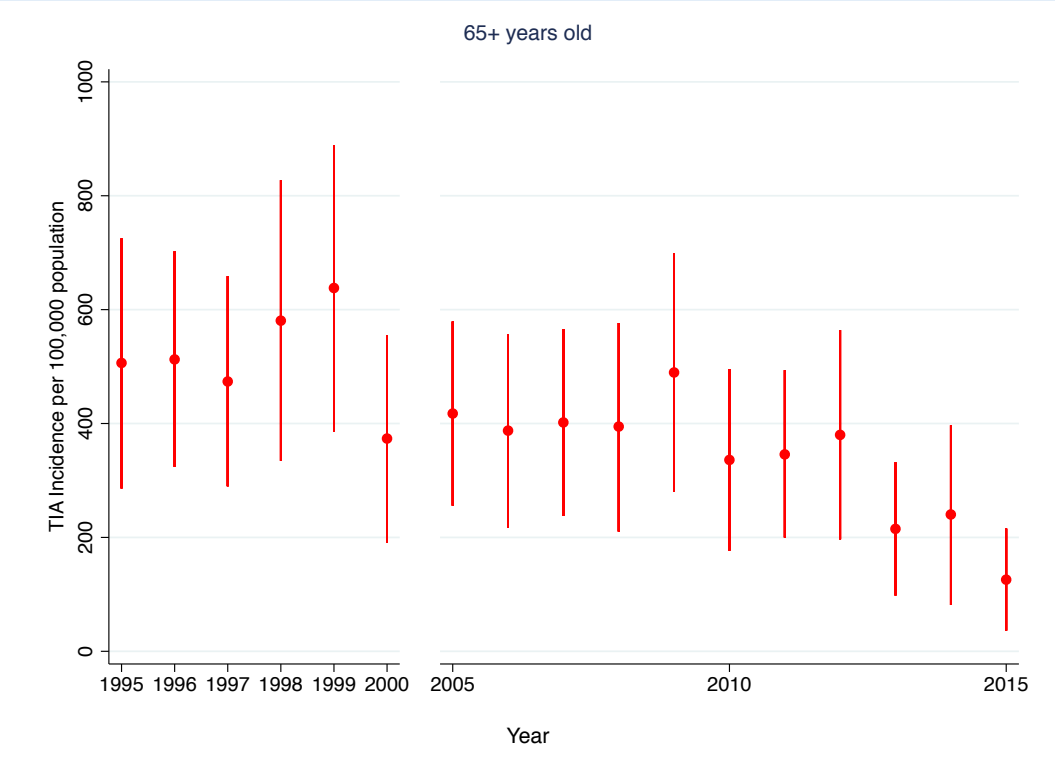


Young: +0 stroke diagnoses/100,000 pop/year (95% CI: -1 – +2)

Old: -29 stroke diagnoses/100,000 pop/year (95% CI: -40 – -18)

Results: Incidence of TIA

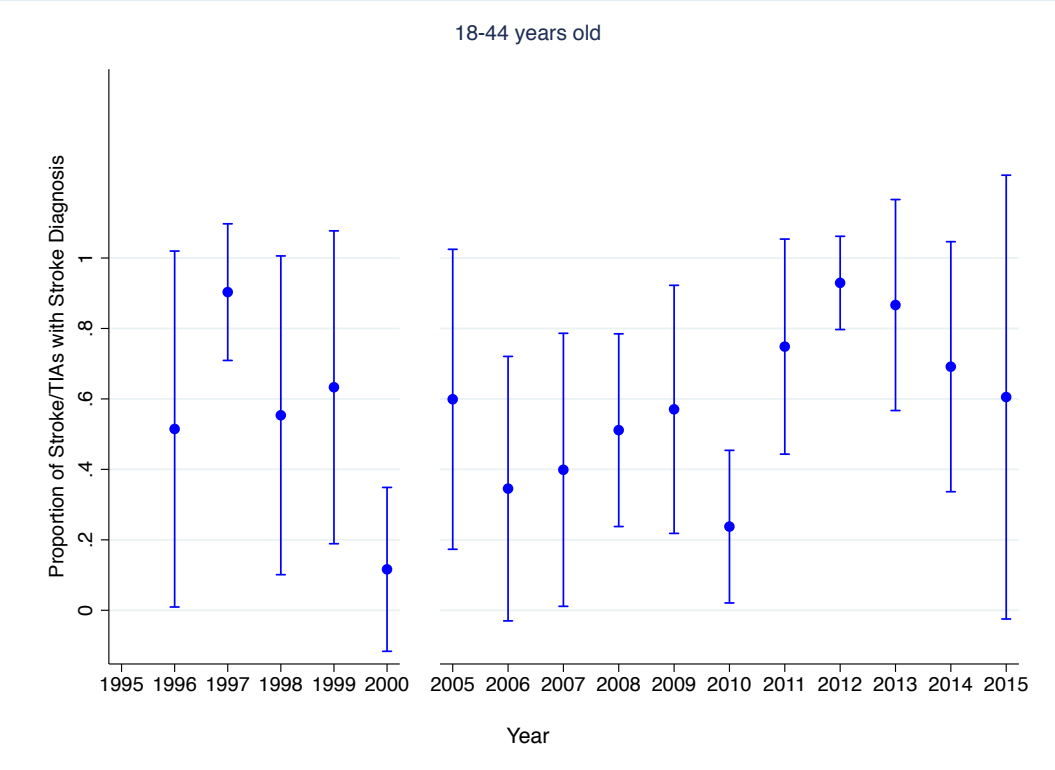


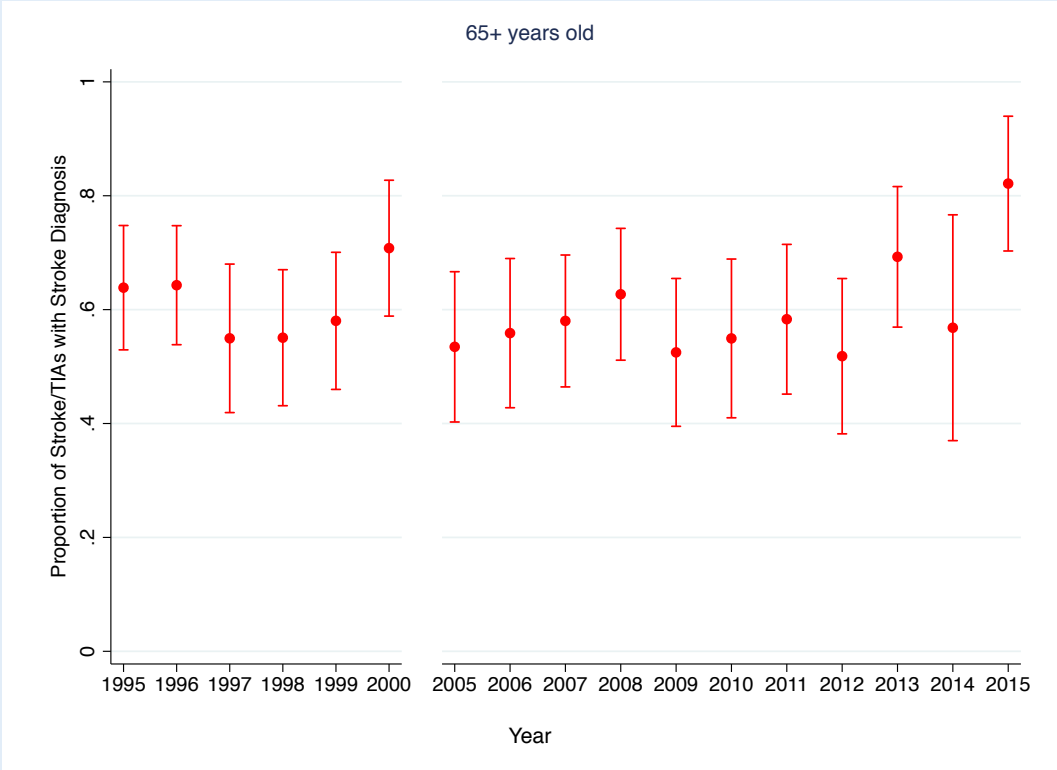


Young: +0 TIA diagnoses/100,000 pop/year (95% CI: +0 – +1)

Old: -21 TIA diagnoses/100,000 pop/year (95% CI: -30 – -12)

Results: No differential classification of stroke

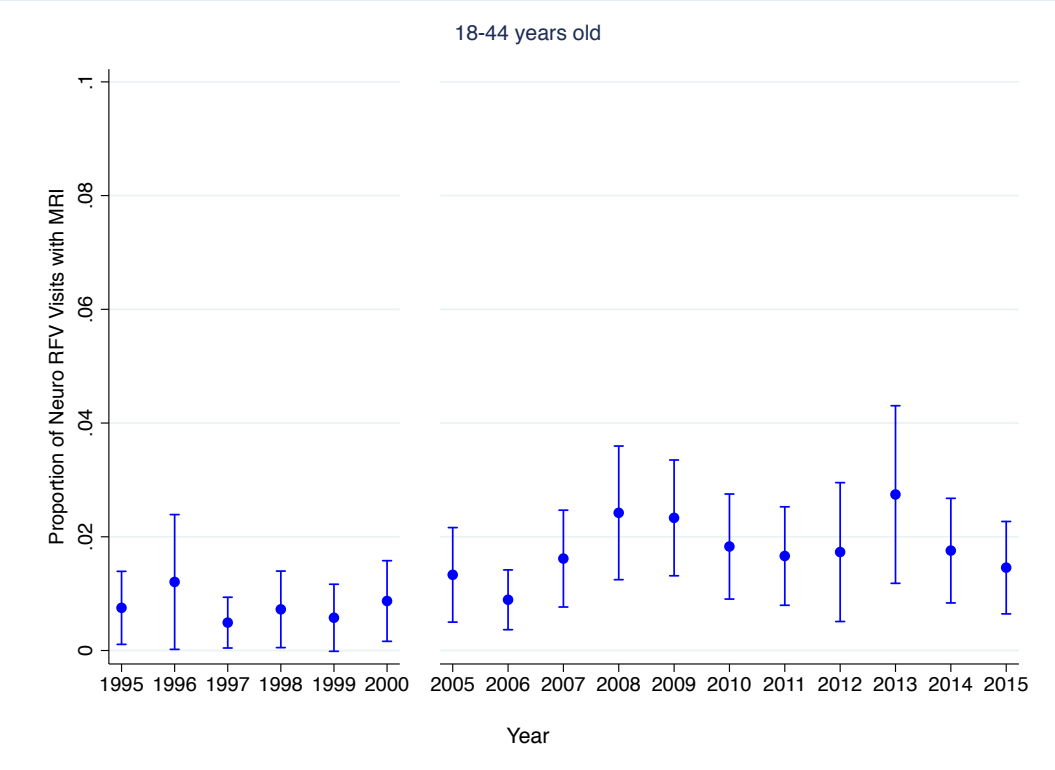


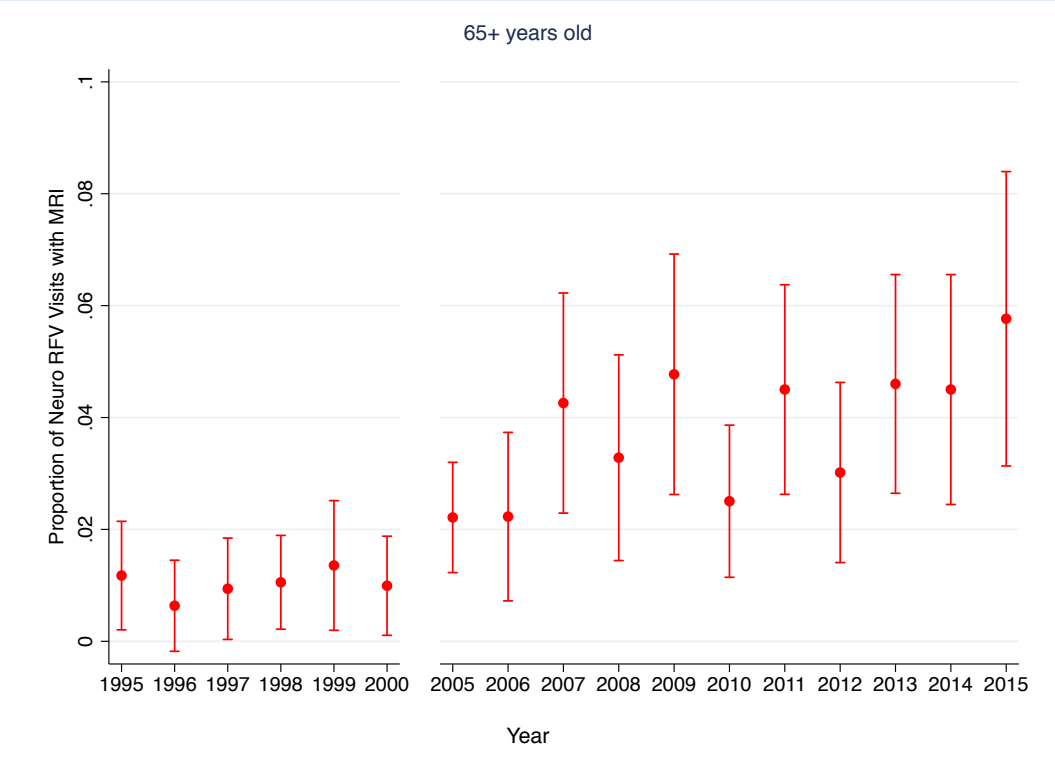


Young: OR 1.00, 95% CI: 0.93 – 1.08

Old: OR 1.00, 95% CI: 0.98 – 1.03

Results: No disproportionate rise in MRI use





Young: OR 1.06, 95% CI: 1.03 – 1.09

Old: OR 1.10, 95% CI: 1.07 – 1.13

Results: Using Hospital Discharge Diagnoses

Compared to primary ED diagnosis, all trends with hospital discharge diagnosis…

- Showed no major shifts in direction of trends
- Had wider confidence intervals
- And all effect sizes were attenuated

Example: Calculating false positives

Equations …

$$Stroke\ Diagnoses = True\ Positives\ (TP) + False\ Positives\ (FP)$$

$$FP = \#\ of\ Neuro\ RFVs \times (1 - Stroke\ Prevalence) * (1 - Spec)$$

$$TP = \#\ of\ Neuro\ RFVs \times Stroke\ Prevalence$$

$*$ *Assume specificity of stroke diagnoses* $= 0.99$

ɬ *Values estimated from range of CIs*

	Neuro RFVs		**Stroke/TIA Prevalence in Neuro RFV Popɬ**	
	Young	Older	Young	Older
1995	3.3M	2M	1%	18%
2015	5.3M	3M	0.6%	9%