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Influenza vaccination and pneumococcal vaccination and risk of stroke/transient ischaemic attack (IPVASTIA): matched case-control study

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Background

- Stroke is a major cause of death and long term illness
- 5% of UK population are affected, around 130 thousand suffer a new or recurrent stroke each year
- Common risk factors such as **age, gender, smoking, diabetes** .., don't account for all the stroke cases
- Emerging evidence shows that respiratory infections and incidence of strokes may be related

Previous studies

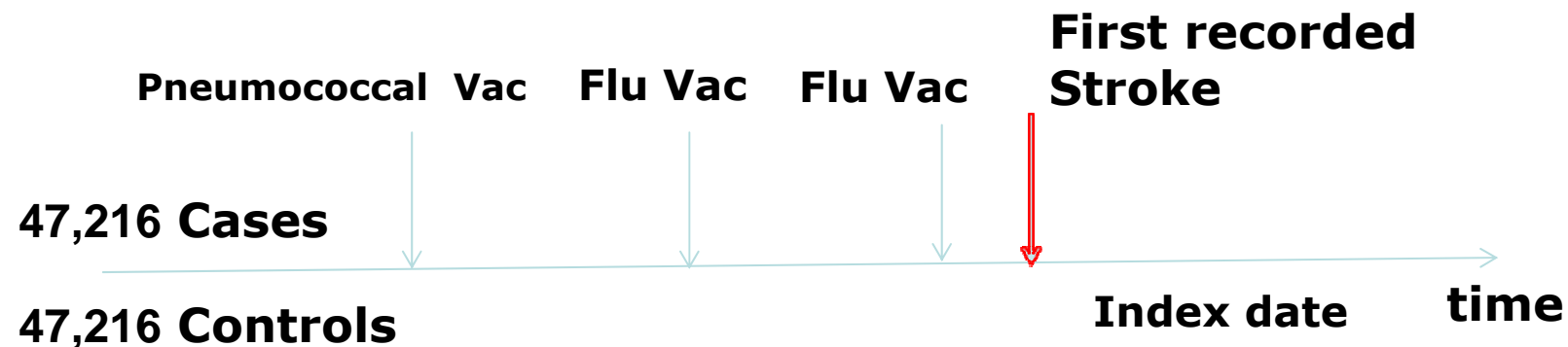
- ❑ Contradictory evidence: Small study size
- ❑ Design Bias: recall, therapeutic
- ❑ Confounding: 'healthy user effect', missing different treatments and differences in health behaviours in vaccinees

Study aim

To investigate association of influenza & pneumococcal vaccination with Stroke/TIA using General Practice Research Database (**GPRD**) to account for known confounders

Method

- Vaccination season from 01 Sept 2001-31 Aug 2009



- Matched for age, sex, calendar time and practice
- Data is up-to-standard: patients are registered with the same practice for the study period.

Method

- ❑ 'Case': medical diagnostic Read/OXMIS codes for first stroke entered by GP
- ❑ 'Index date': first date when GP recorded stroke/TIA code (fatal/non-fatal) in clinical/referral record
- ❑ 'Control': age/sex/ calendar time/practice matched controls per case with index date corresponding to date of matched case

Analysis

- ❑ STATA: conditional logistic regression
- ❑ Outcomes: unadjusted and adjusted odds ratios
- ❑ Factors considered for adjusted OR included
 - Vaccine risk groups: chronic heart (and other cardiovascular diseases); diabetes, asthma/COPD; chronic renal and liver disease; splenectomy; chronic neurological disease
 - Other CHD risk factors: smoking status; hyperlipidaemia; BMI; family history of AMI; family history of stroke; hypertension; SBP; total cholesterol

Descriptive statistics

		Cases (those with stroke/TIA) N= 47,216 (%)	Controls N= 47,216 (%)
Age (years):	Mean (SD)	79.8 (13.4)	79.8 (13.4)
	95% CI	79.7 – 80.0	79.7 – 80.0
Aged under 65 years		23.2	23.2
Aged over 65 years		76.8	76.8
Gender:	Male	48.0	48.0
Index period:	Sep – Nov	24.6	
	Dec – Mar	33.9	--
	April – Aug	41.5	

Vaccine risk groups	Cases (those with stroke/TIA) N= 47,216 (%)	Controls N= 47,216 (%)	p
Asthma/COPD attack ever	7,666 (16.2)	6,878 (14.6)	<0.001
Chronic heart disease	11,778 (24.9)	8,121 (17.2)	<0.001
Diabetes	5,787 (12.3)	4,133 (8.8)	<0.001
Splenectomy	145 (0.3)	76 (0.2)	<0.001
Chronic liver disease	179 (0.4)	90 (0.2)	<0.001
Chronic renal disease	4,132 (8.8)	3,428 (7.3)	<0.001
Chronic neurological disease	300 (0.6)	185 (0.4)	<0.001



Cardiovascular risk factors	Cases (those with stroke/TIA) N= 47,216 (%)	Controls N= 47,216 (%)	P
Hyperlipidaemia	6,217(13.2)	5,180 (11.0)	<0.001
Family history of myocardial infarction	8,085 (17.1)	7,234 (15.3)	<0.001
Family history of stroke	4,238 (9.0)	3,582 (7.6)	<0.001
Body mass index recorded within past 5 years†	19097 (40.4)	17536 (37.1)	<0.001
Body mass index kg/m2 (mean [SD])	27.8 [5.0]	27.4 [4.8]	<0.001
Peripheral vascular diseases	1,677 (3.6)	1,049 (2.2)	<0.001
Hypertension	23,053 (48.8)	18,407 (39.0)	<0.001

Cardiovascular risk factors	Cases (those with stroke/TIA) N= 47,216 (%)	Controls N= 47,216 (%)	P
Latest Smoking history			
Never smoked	18,508 (45.0)	19,878 (49.5)	
Ex-smoker	18,556 (45.0)	16,037 (40.0)	<0.001
Current smoker	3,361 (8.2)	2,646 (6.6)	
Not recorded	684 (1.2)	1,574 (3.9)	
Aspirin uptake (≥ 2 prescriptions in previous 6 months)			
	5,112 (10.8)	2,151 (4.6)	<0.001
Statin uptake (≥ 1 prescription in previous year)			
	7,714 (16.3)	3,814(8.1)	<0.001
Antihypertensive treatment (≥ 1 prescription in previous year)			
	7,034 (14.9)	5,313 (11.3)	<0.001
Oral anticoagulant (≥ 1 prescription in previous year)			
	1,308 (2.8)	630 (1.3)	<0.001

Cardiovascular risk factors	Cases (those with stroke/TIA) N= 47,216 (%)	Controls N= 47,216 (%)	P
GP surgery Consultations			
≤12	12278 (26.0)	16241 (34.4)	<0.001
13-26	11692 (24.8)	12249 (25.9)	
27-44	11126 (23.6)	9717 (20.6)	
≥45	12120 (25.7)	9009 (19.1)	
Charlson index			
0	16258 (34.4)	25414 (53.8)	<0.001
1	8985 (19.0)	7085 (15.0)	
2	6981 (14.8)	5640 (12.0)	
3	4680 (9.9)	2989 (6.3)	
4	3201 (6.8)	2166 (4.6)	
≥5			

Main results

Timing of Vaccination	Cases N(%)	Controls N(%)	Adjusted	
			OR	95% CI
Same season as index date	24,819 (52.6)	23,974 (50.8)	0.90	0.87 – 0.93
Early within-season (Sept. to mid-Nov.)	21,880 (46.3)	21,383 (45.3)	0.88	0.85 – 0.92
Late within-season (mid-Nov. to Feb.)	2,939 (6.2)	2,591 (5.5)	1.04	0.97 – 1.11

Main results

Timing of Vaccination	Age (yrs)	Cases N(%)	Controls N(%)	Adjusted	
				OR	95% CI
Within season	≤64	2,239 (20.5)	1,472 (13.5)	0.92	0.83 – 1.01
	≥65	22,580 (62.3)	22,502 (62.0)	0.89	0.85 – 0.92
Early within-season	≤64	1,813 (16.6)	1,182 (10.8)	0.93	0.84 – 1.03
	≥65	20,201 (55.7)	20,067 (55.3)	0.87	0.83 – 0.91

Main results

Timing of Vaccination	Age (yrs)	Cases N(%)	Controls N(%)	Adjusted	
				OR	95% CI
Late within-season	≤64	426 (3.9)	290 (2.7)	0.87	0.73 – 1.05
	≥ 65	12,513 (6.9)	2,301 (6.3)	1.02	0.95 – 1.09

Main results: pneumococcal vaccine

* Adjusted for influenza vaccination as well

Age (yrs)	Cases N(%)	Controls N(%)	Adjusted*	
			OR	95% CI
All ages	23,306 (49.4)	21,856 (46.3)	0.98	0.94 – 1.02
<65 years	1,782 (16.3)	1,013 (9.3)	0.96	0.95 – 1.07**
≥ 65 years	21,524 (59.3)	20,843 (57.5)	1.00	0.95 – 1.03

** After sensitivity analysis for unmeasured confounder

Study strengths and limitations

- ❑ Large GPRD dataset, no problems with recall bias.
- ❑ Charlson index, GP home visits (frailty) with many more confounders accounted for.
- ❑ Sensitivity analysis done to complement the findings.
- ❑ Residual confounding (unknown factors)
- ❑ 'Healthy vaccination' bias
- ❑ Inadequate patient data on GPRD due to practice transfers
- ❑ Incomplete recording of blood pressure, cholesterol levels, BMI, etc. on the GPRD

Conclusions

- ❑ **Influenza vaccination is associated with reduced risk of stroke/TIA**
 - 10% reduction in risk of over all stroke/TIA
 - adjusted OR 0.90; 95% CI 0.87 to 0.93
- ❑ **Early influenza seasonal vaccination (September to mid-November) associated with lower risk of stroke/TIA than later vaccination (mid-November to January):**
 - Early Over 65's: 13% reduction in risk of stroke/TIA
 - adjusted OR 0.87; 95% CI 0.83 to 0.91
 - This was significant after sensitivity analysis.
- ❑ **Pneumococcal vaccination was not associated with a reduction in risk of stroke after sensitivity analysis for unmeasured confounding (frailty)**
 - OR 0.96; 95% CI (0.95 – 1.07)

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