



Use of external data sources to evaluate the comparability of cohorts and the potential for confounding

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May 4, 2015



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Example 1: Study of AMI risk with NSAID use

- Population-based nested case-control study within Kaiser Permanente in California
- AMI risk with use of various RX NSAIDs including selective COX-2 inhibitors
- Adjusted for wide range of covariates
- What about potential unmeasured confounding:
 - Low-dose aspirin
 - OTC NSAIDs
 - Smoking history
 - Family history



Comparison of exposed controls for measured covariates

	Celecoxib (n=491)	Ibuprofen (n=2573)	Naproxen (n=1409)	Rofecoxib (n=196)	Remote use (n=18 720)
Age (years)	73.4 (8.5)	66.9 (11.3)	68.4 (10.9)	72.1 (9.9)	66.4 (11.7)
Men	245 (50%)	1591 (62%)	801 (57%)	91 (46%)	11 807 (63%)
Cardiovascular risk score	4.21 (3.24)	3.11 (3.14)	3.22 (3.15)	3.14 (3.16)	2.91 (3.16)
Cardiovascular admissions in past year	31 (6%)	59 (2%)	51 (4%)	5 (3%)	581 (3%)
Cardiovascular drug use in past year	373 (76%)	1535 (60%)	876 (62%)	129 (66%)	10 388 (55%)
Angiotensin-converting-enzyme inhibitor	140 (29%)	512 (20%)	301 (21%)	43 (22%)	3555 (19%)
Angiotensin-receptor blocker	29 (6%)	33 (1%)	28 (2%)	2 (1%)	348 (2%)
Antiarrhythmic drug	11 (2%)	29 (1%)	19 (1%)	2 (1%)	214 (1%)
Anticoagulant drug	46 (9%)	38 (1%)	27 (2%)	15 (8%)	674 (4%)
β blocker	159 (32%)	589 (23%)	318 (23%)	50 (26%)	3974 (21%)
Calcium-channel blocker	111 (23%)	351 (14%)	231 (16%)	31 (16%)	2532 (14%)
Digitalis glycoside	40 (8%)	74 (3%)	44 (3%)	9 (5%)	679 (4%)
Hypoglycaemic drug	78 (16%)	324 (13%)	182 (13%)	18 (9%)	2192 (12%)
Lipid-lowering drug	130 (26%)	489 (19%)	287 (20%)	48 (24%)	3505 (19%)
Loop diuretic	82 (17%)	165 (6%)	122 (9%)	19 (10%)	1239 (7%)
Nitrate	64 (13%)	243 (9%)	128 (9%)	23 (12%)	1463 (8%)
Platelet inhibitor	9 (2%)	27 (1%)	19 (1%)	1 (1%)	278 (1%)
Thiazide diuretic	127 (26%)	605 (24%)	352 (25%)	56 (29%)	3658 (20%)
Other medical care in past year					
Non-cardiovascular admission	49 (10%)	176 (7%)	97 (7%)	15 (8%)	1524 (8%)
Non-cardiovascular emergency room visit*	100 (20%)	532 (21%)	248 (18%)	36 (18%)	4162 (22%)
Oestrogen use by women	107 (22%)	434 (17%)	322 (23%)	52 (27%)	2779 (15%)
Smoking-related diagnoses	8 (2%)	88 (3%)	40 (3%)	2 (1%)	610 (3%)
Treated by rheumatologist	18 (4%)	39 (2%)	39 (3%)	17 (9%)	239 (1%)
Disease-modifying antirheumatic drug use	28 (6%)	60 (2%)	46 (3%)	9 (5%)	218 (1%)
Prednisone use (>1000 mg)	22 (4%)	56 (2%)	39 (3%)	12 (6%)	368 (2%)

Data are mean (SD) or number of controls (%). *Visits not resulting in admission.

Table 2: Characteristics of controls currently exposed to celecoxib, ibuprofen, naproxen or rofecoxib, or remotely exposed to an NSAID.

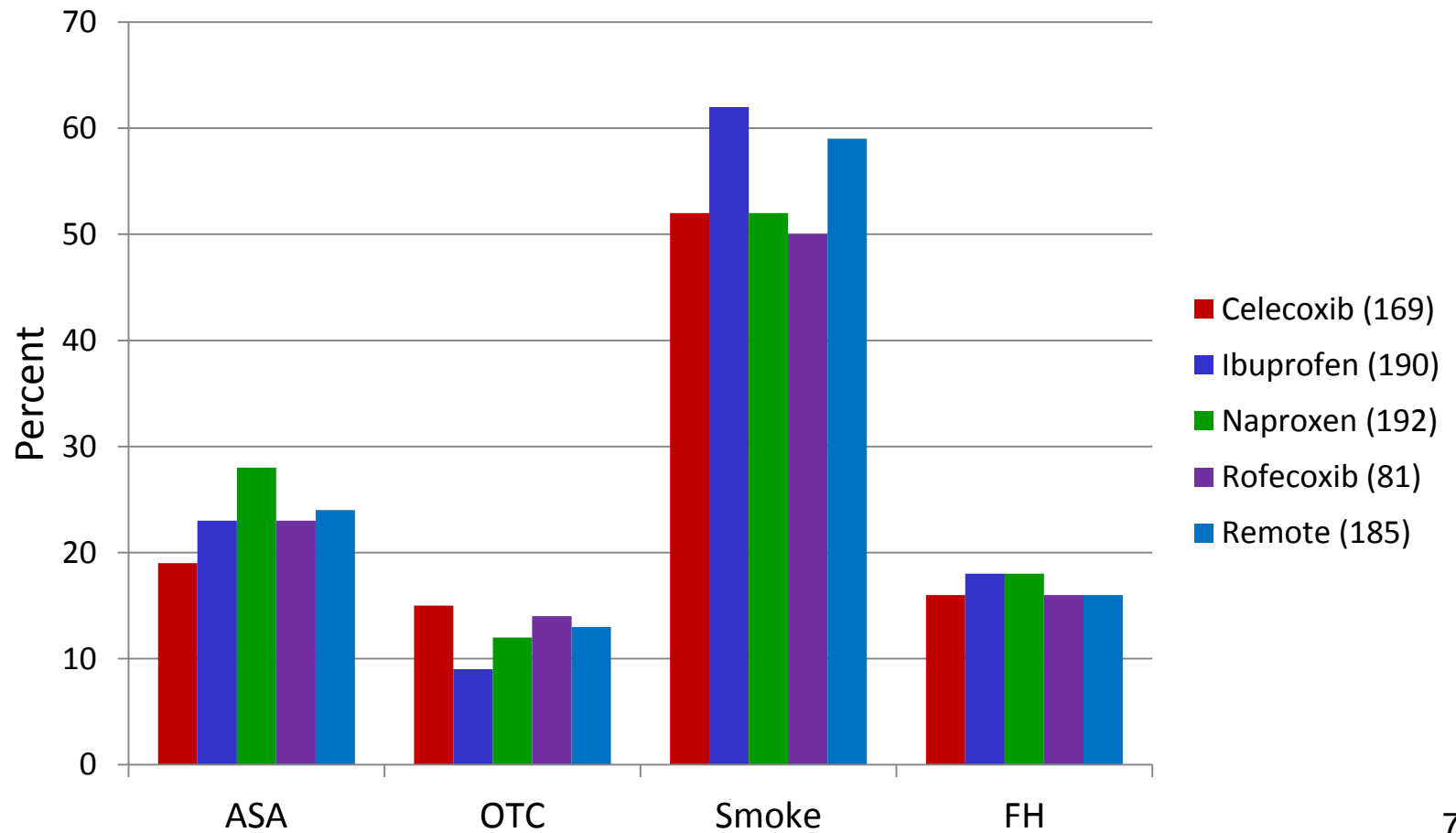


	Cases	Controls	Unadjusted odds ratio (95% CI)	Adjusted* odds ratio (95% CI)	p
Compared with remote use					
Remote use	4658	18720	1.00	1.00	
Recent use	1720	6258	1.12 (1.05–1.20)	1.11 (1.03–1.19)	0.004
Current use					
Celecoxib	126	491	1.05 (0.86–1.28)	0.84 (0.67–1.04)	0.12
Ibuprofen	670	2573	1.07 (0.98–1.18)	1.06 (0.96–1.17)	0.27
Naproxen	367	1409	1.07 (0.95–1.21)	1.14 (1.00–1.30)	0.05
Rofecoxib (all doses)	68	196	1.39 (1.05–1.83)	1.34 (0.98–1.82)	0.066
Rofecoxib ≤25 mg/day	58	188	1.23 (0.92–1.66)	1.23 (0.89–1.71)	0.21
Rofecoxib >25 mg/day	10	8	5.03 (1.98–12.76)	3.00 (1.09–8.31)	0.03
Other NSAIDs	534	1849	1.19 (1.07–1.32)	1.13 (1.01–1.27)	0.03
Compared with celecoxib use					
Celecoxib use	126	491	1.00	1.00	
Remote use	4658	18720	0.95 (0.78–1.16)	1.11 (0.96–1.48)	0.12
Recent use	1720	6258	1.07 (0.87–1.31)	1.32 (1.06–1.65)	0.015
Current use					
Ibuprofen	670	2573	1.02 (0.82–1.27)	1.26 (1.00–1.60)	0.054
Naproxen	367	1409	1.02 (0.81–1.28)	1.36 (1.06–1.75)	0.016
Rofecoxib (all doses)	68	196	1.32 (0.94–1.85)	1.59 (1.10–2.32)	0.015
Rofecoxib ≤25 mg/day	58	188	1.17 (0.82–1.67)	1.47 (0.99–2.17)	0.054
Rofecoxib >25 mg/day	10	8	4.78 (1.85–12.38)	3.58 (1.27–10.11)	0.016
Other NSAIDs	534	1849	1.13 (0.91–1.41)	1.35 (1.06–1.72)	0.015

Patient survey for collection of data on unmeasured factors

- Brief, targeted questions
- ASA use, OTC NSAID use, +FH, smoking history
- Sampling frame: all controls with current exposure to celecoxib, ibuprofen, naproxen, rofecoxib, or remote exposure to any NSAID
- Target sample n=900, estimated cost of \$50/survey
- Telephone survey of random sample from each exposure group
- Conducted by professional survey organization
- De-identified dataset provided to study investigators

Survey findings (n=817)



Example 2: ACEI or ARB use and lung cancer risk

- Long-term interest in cancer risk with antihypertensive meds
- Conflicting study results for lung cancer risk with ARB use
- Could a valid study comparing ACEI vs. ARB users be conducted using Medicare claims data?
 - Same indications; presumed similar patients
- A very complex issue
- Smoking history an essential consideration
- Smoking history and status poorly captured in claims data
- If smoking history very similar between ACEI and ARB users...
- Medicare Current Beneficiary Survey (MCBS)

Overview of MCBS

- Continuous survey of nationally representative sample of Medicare beneficiaries
- Rotating panel design with 4 panels active at any time, each with ~4,000 participants
- Collects information on health status and functioning, health care use and expenditures, and insurance coverage
- Data from survey participants linked to other Medicare claims data
- We looked at MCBS from 2006-2010, comparing ACEI with ARB users

Comparison of ACEI and ARB users in MCBS 2006-10

Characteristic (%)	ACEI (n=4675)	ARB (n=1625)
Age		
65-74	40	37
75-84	42	44
85+	17	19
Male	51	39
Health status ≥ “Good”	74	75
BMI ≥ 25 (overweight+)	65	66
Smoking history		
Ever	61.6	54.9
Current	9.7	6.2

Drill-down on “ever” smoker by age/gender

(% smoker)	ACEI (n=4675)	ARB (n=1625)	Standardized mean difference
Male			
65-74	77.7	75.3	0.06
75-84	79.2	79.9	0.02
85+	72.7	75.2	0.00
Female			
65-74	53.5	46.1	0.15
75-84	44.2	41.4	0.06
85+	31.7	32.6	0.02

Drill-down on “current” smoker by age/gender

(% smoker)	ACEI (n=4675)	ARB (n=1625)	Standardized mean difference
Male			
65-74	14.2	13.3	0.02
75-84	9.9	5.9	0.15
85+	4.5	1.1	0.21
Female			
65-74	13.8	7.5	0.21
75-84	6.7	4.7	0.09
85+	2.4	1.4	0.07

Risk of “positive” smoking history in MCBS, odds ratio (95% confidence interval)

Smoking history	ACEI vs. ARB	Men vs. Women
Current	1.53 (1.22-1.92)	1.29 (1.08-1.55)
Former	0.98 (0.87-1.10)	3.55 (3.20-3.95)
Ever	1.12 (0.99-1.27)	4.26 (3.81-4.76)

Potential impact of confounding by smoking history if claims data were used*

- Published data on lung cancer risks in former and current smokers (Lee et al., BMC Cancer 2012)
- Distribution of former and current smokers in ACEI and ARB from MCBS
- Net bias calculation assuming no difference in lung cancer risk
 - MCBS 2006-10: -11%
- ARB users would appear to have 11% lower risk than ACEI, based solely on differences in smoking history
 - Relatively large bias due mainly to strong association between smoking history and lung cancer risk

Ascertainment of smoking history using claims

- Poorly done overall
- Current probably much better than former

	ACEI	ARB
MCBS Former	51.9%	48.7%
Current	9.7%	6.2%

Recent study		
Smoking hx	9.1%	6.6%

- Current probably also poor
 - Study in varenicline users: “Smoking” = 1 in 50%