Using tools of pharmacoepidemiology to identify potential opportunities for repurposing

Joshua J Gagne

November 14, 2019

Disclosure

- I have received salary support from grants from Eli Lilly and Company and Novartis Pharmaceuticals Corporation to the Brigham and Women's Hospital and was a consultant to Aetion, Inc. and Optum, Inc., all for unrelated work.

Overview

- Examples of pharmacoepidemiology in repurposing
- Data sources
- Approaches
- Conclusion

Many examples of repurposing

Drug name	Original indication	New indication	Date of approval	Repurposing approach used	Comments on outcome of repurposing
Rituximab	Various cancers	Rheumatoid arthritis	2006	Retrospective clinical analysis (remission of coexisting rheumatoid arthritis in patients with non-Hodgkin lymphoma treated with rituximab[144])	Global sales of rituximab topped $7 billion in 2015 (REF.[145])
Raloxifene	Osteoporosis	Breast cancer	2007	Retrospective clinical analysis	Approved by the FDA for invasive breast cancer. Worldwide sales of $237 million in 2015 (see Related links)
Fingolimod	Transplant rejection	MS	2010	Pharmacological and structural analysis[146]	First oral disease-modifying therapy to be approved for MS. Global sales for fingolimod (Gilenya) reached $3.1 billion in 2017 (see Related links)
Dapoxetine	Analgesia and depression	Premature ejaculation	2012	Pharmacological analysis	Approved in the UK and a number of European countries; still awaiting approval in the US. Peak sales are projected to reach $750 million
Topiramate	Epilepsy	Obesity	2012	Pharmacological analysis	Qsymia (Vivus) contains topiramate in combination with phentermine
Ketoconazole	Fungal infections	Cushing syndrome	2014	Pharmacological analysis	Approved by the EMA for Cushing syndrome in adults and adolescents above the age of 12 years (see Related links)
Aspirin	Analgesia	Colorectal cancer	2015	Retrospective clinical and pharmacological analysis	US Preventive Services Task Force released draft recommendations in September 2015 regarding the use of aspirin to help prevent cardiovascular disease and colorectal cancer[52]

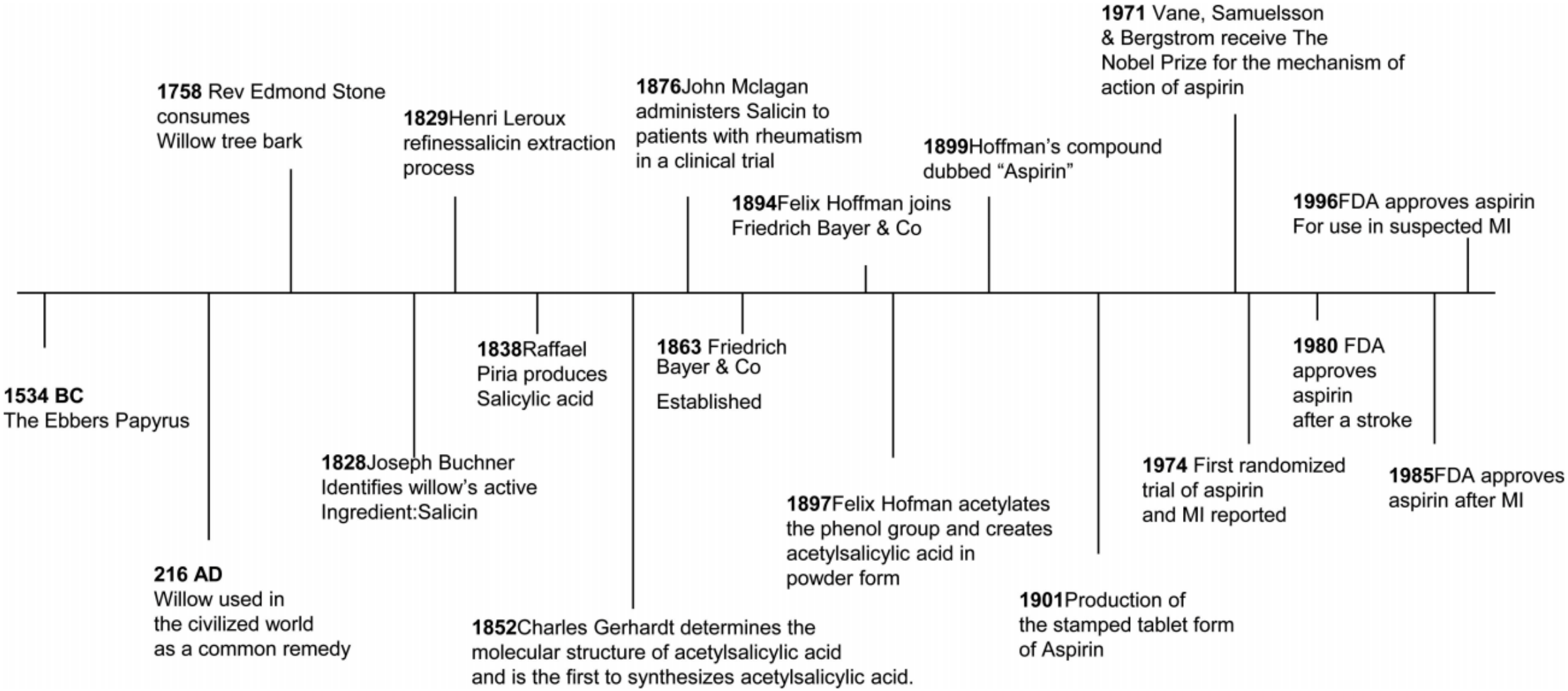
Pushpakom S et al. *Nat Rev Drug Discov* 2019;18:41-58.

Many examples of repurposing

Drug name	Original indication	New indication	Date of approval	Repurposing approach used	Comments on outcome of repurposing
Rituximab	Various cancers	Rheumatoid arthritis	2006	Retrospective clinical analysis (remission of coexisting rheumatoid arthritis in patients with non-Hodgkin lymphoma treated with rituximab[144])	Global sales of rituximab topped $7 billion in 2015 (REF.[145])
Raloxifene	Osteoporosis	Breast cancer	2007	Retrospective clinical analysis	Approved by the FDA for invasive breast cancer. Worldwide sales of $237 million in 2015 (see Related links)
Fingolimod	Transplant rejection	MS	2010	Pharmacological and structural analysis[146]	First oral disease-modifying therapy to be approved for MS. Global sales for fingolimod (Gilenya) reached $3.1 billion in 2017 (see Related links)
Dapoxetine	Analgesia and depression	Premature ejaculation	2012	Pharmacological analysis	Approved in the UK and a number of European countries; still awaiting approval in the US. Peak sales are projected to reach $750 million
Topiramate	Epilepsy	Obesity	2012	Pharmacological analysis	Qsymia (Vivus) contains topiramate in combination with phentermine
Ketoconazole	Fungal infections	Cushing syndrome	2014	Pharmacological analysis	Approved by the EMA for Cushing syndrome in adults and adolescents above the age of 12 years (see Related links)
Aspirin	Analgesia	Colorectal cancer	2015	Retrospective clinical and pharmacological analysis	US Preventive Services Task Force released draft recommendations in September 2015 regarding the use of aspirin to help prevent cardiovascular disease and colorectal cancer[52]

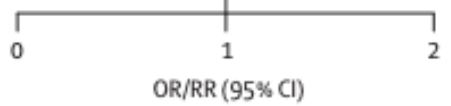
Pushpakom S et al. *Nat Rev Drug Discov* 2019;18:41-58.

A history of aspirin



Aspirin for colorectal cancer

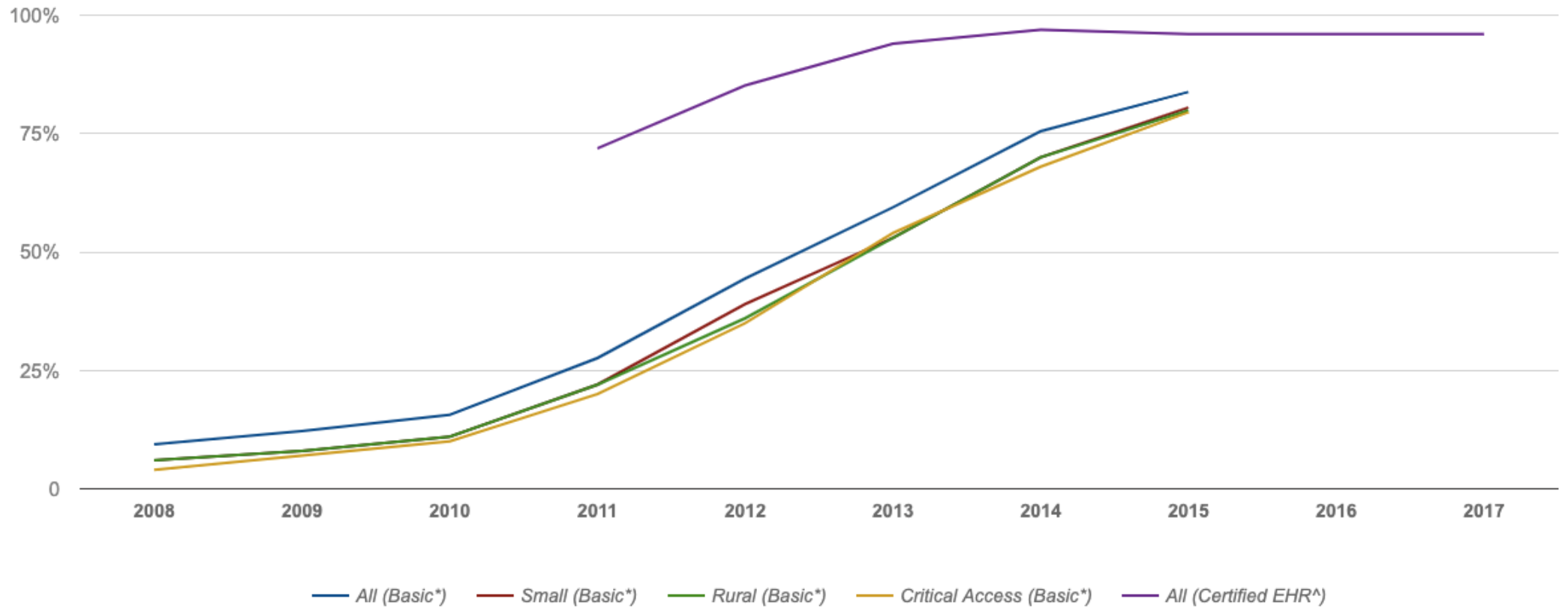
Study type	N	Aspirin	Controls	OR (95% CI)	Significance	Heterogeneity
Randomised trials						
Daily aspirin	6	91/9833	154/9859	0·58 (0·44–0·78)	p=0·0002	p=0·45
Daily aspirin ≥5 years	6	74/8034	134/8012	0·55 (0·41–0·76)	p=0·0002	p=0·26
	N	**Cases**	**Controls**	**OR (95% CI)**	**Significance**	**Heterogeneity**
Case–control						
Any aspirin	26	10 464/25 618	28 300/47 834	0·67 (0·60–0·74)	p<0·0001	p<0·0001
Maximum reported aspirin	17	1551/12 659	2664/18 153	0·62 (0·58–0·67)	p<0·0001	p=0·13
Aspirin ≥5 years	10	971/7682	1534/10 029	0·68 (0·63–0·75)	p<0·0001	p=0·82
Daily aspirin	4	165/1254	349/1523	0·49 (0·40–0·60)	p<0·0001	p=0·65
Daily aspirin ≥5 years	1	66/1668	121/1973	0·63 (0·46–0·86)	p=0·004	NA
	N	**Aspirin**	**Controls**	**RR (95% CI)**	**Significance**	**Heterogeneity**
Standard cohort						
Any aspirin	11	3791/2 764 414	3623/2 514 652	0·85 (0·82–0·89)	p<0·0001	p=0·12
Maximum reported aspirin	8	661/664 475	1858/1 374 905	0·78 (0·71–0·84)	p<0·0001	p=0·02
Aspirin ≥5 years	4	889/1 022 192	1311/1 304 760	0·76 (0·70–0·82)	p<0·0001	p=0·32
Daily aspirin	5	741/658 536	1115/819 288	0·80 (0·73–0·88)	p<0·0001	p=0·01
Daily aspirin ≥5 years	1	60/38 302	420/232 116	0·68 (0·52–0·90)	p=0·006	NA
	N	**Cases**	**Controls**	**OR (95% CI)**	**Significance**	**Heterogeneity**
Nested case–control						
Any aspirin	6	2215/8926	65 099/109 526	0·87 (0·75–1·00)	p=0·07	p=0·005
Maximum reported aspirin	5	206/4457	8302/40 948	0·67 (0·58–0·77)	p<0·0001	p=0·10
Aspirin ≥5 years	1	116/228	23 704/37 935	0·62 (0·48–0·81)	p<0·0001	NA
Daily aspirin	1	53/165	8744/22 975	0·77 (0·55–1·07)	p=0·14	NA
Daily aspirin ≥5 years	1	29/141	7274/21 505	0·51 (0·34–0·76)	p=0·012	NA



Algra AM et al. *Lancet Oncol* 2012;13:518-27.

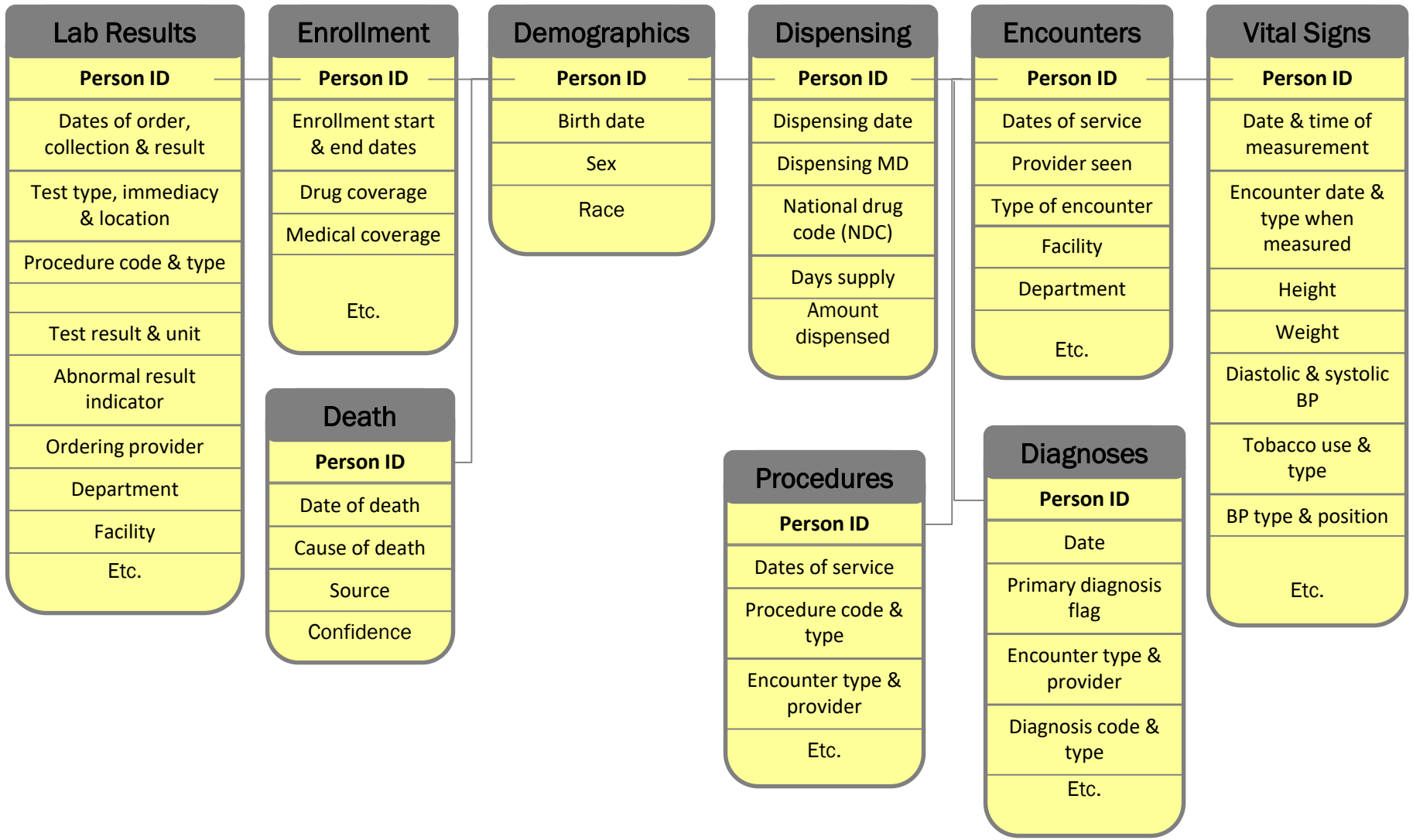
Healthcare system generates lots of data

- ~90% of Americans have health insurance
- EHR adoption continues to increase in US



https://dashboard.healthit.gov/quickstats/pages/FIG-Hospital-EHR-Adoption.php

Administrative claims data



Distributed data networks

Network	Geography	Type of data	n
AsPEN: Asian Pharmacoepidemiology Network	Asia-Pacific	Claims	220M
CNODES: Canadian Network for Observational Drug Effect Studies	Canada, US, UK	Claims, EHR	35M (Canada)
HCSRN: Health Care Systems Research Network	US and Israel	Claims, EHR	16M
PCORnet: National Patient-Centered Clinical Research Network	US	Claims, EHR	100M
PROTECT: Pharmacoepidemiological Research on Outcome of Therapeutics by a European Consortium	European Union	Claims, EHR	100M
Sentinel	US	Claims, EHR	293M
VSD: Vaccine Datalink	US	EHR	9M

Sentinel system

Lead: Harvard Pilgrim Health Care Institute

DEPARTMENT OF POPULATION MEDICINE
HARVARD MEDICAL SCHOOL
Harvard Pilgrim Health Care Institute

Data & Scientific Partners

HealthCore
Anthem
Humana
OPTUM
RTI INTERNATIONAL
veradigm
Penn Medicine
Healthagen
aetna
GDIT
OPTUM Labs
pcornet
ADVANCE Collaborative
MASSACHUSETTS
BRIGHAM HEALTH
BRIGHAM AND WOMEN'S HOSPITAL
KAISER PERMANENTE
Colorado
Hawaii
Mid-Atlantic
Northern California
Northwest
Washington
CMS CENTERS FOR MEDICARE & MEDICAID SERVICES
CAPriCORN
GPC Greater Plains Collaborative
Booz | Allen | Hamilton
Marshfield Clinic Research Institute
HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH
RUTGERS
NYC-CDRN New York City Clinical Data Research Network
UF College of Pharmacy UNIVERSITY of FLORIDA
VANDERBILT UNIVERSITY MEDICAL CENTER
The Meyers Primary Care Institute
KAISER PERMANENTE Kaiser Permanente Washington Health Research Institute
OneFlorida Clinical Research Consortium
REACHnet
IBM Watson Health
PaTH Network
PEDSnet
HealthPartners Institute
SCHOOL OF PUBLIC HEALTH UNIVERSITY of WASHINGTON
UAB
HCA Healthcare
UNC GILLINGS SCHOOL OF GLOBAL PUBLIC HEALTH
STAR Stakeholders, Technology, and Research CRN
Duke Clinical Research Institute
THE UNIVERSITY OF IOWA COLLEGE OF PUBLIC HEALTH
TriNetX

Division of Pharmacoepidemiology and Pharmacoeconomics

Sentinel distributed database

- **292.5 million** unique patient identifiers*
- **14.4 billion** prescription drug dispensings
- **13.3 billion** unique medical encounters
- **66.9 million** individuals currently contributing medical and pharmacy data

*Potential for double-counting if individuals moved between Data Partner health plans

TZDs and Parkinson Disease

- Thiazolidinediones (TZDs) – rosiglitazone, pioglitazone – are approved to treat type 2 diabetes
- Agonists for peroxisome-proliferator-activated receptor gamma
- TZDs have been found to suppress microglial activities in animals by interfering with the inflammatory feedback loop and preventing neurodegeneration
- Cohort of Medicare beneficiaries with no evidence of Parkinson disease
- New user, active comparator cohort design
- Initiators of TZDs compared to initiators of sulfonylureas
- Propensity score matching account for 81 variables
- Compared any use and increasing durations of continuous use up to 10 months

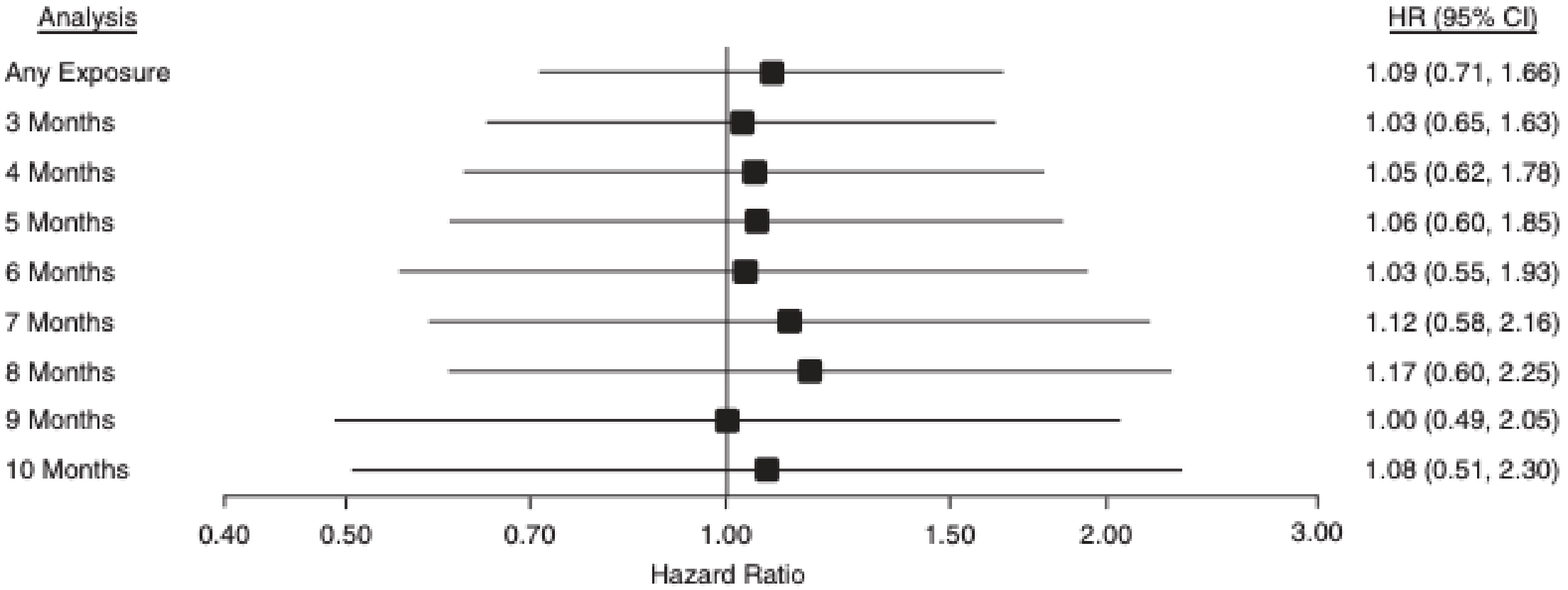
Connolly JG et al. *Am J Epidemiol* 2015;182:936-44.

TZDs and Parkinson Disease

	Unmatched		Matched	
Characteristic	Sulfonylurea users (n = 24,167)	TZD users (n = 5,230)	Sulfonylurea users (n = 5,225)	TZD users (n = 5,225)
Age, mean (sd)	78.7 (7.0)	77.6 (6.9)	77.5 (6.9)	77.6 (6.9)
Female sex, %	72.9%	72.9%	72.6%	72.9%
No. days hospitalized, mean (sd)	3.0 (6.4)	2.2 (5.4)	2.2 (5.3)	2.2 (5.4)
No. meds dispensed, mean (sd)	6.9 (4.5)	7.1 (4.4)	7.0 (4.5)	7.1 (4.4)
Combined comorbidity score, mean (sd)	1.7 (2.5)	1.4 (2.4)	1.4 (2.4)	1.4 (2.4)
Alzheimer disease, %	7.1%	6.6%	6.7%	6.6%
Cancer, %	17.2%	16.3%	16%	16.3%
Hyperlipidemia, %	41.9%	58.8%	58.8%	58.8%
Use of statins, %	24.8%	38.6%	37.4%	38.6%
Use of Parkinsonism-inducing meds, %	7.4%	5.8%	5.6%	5.8%

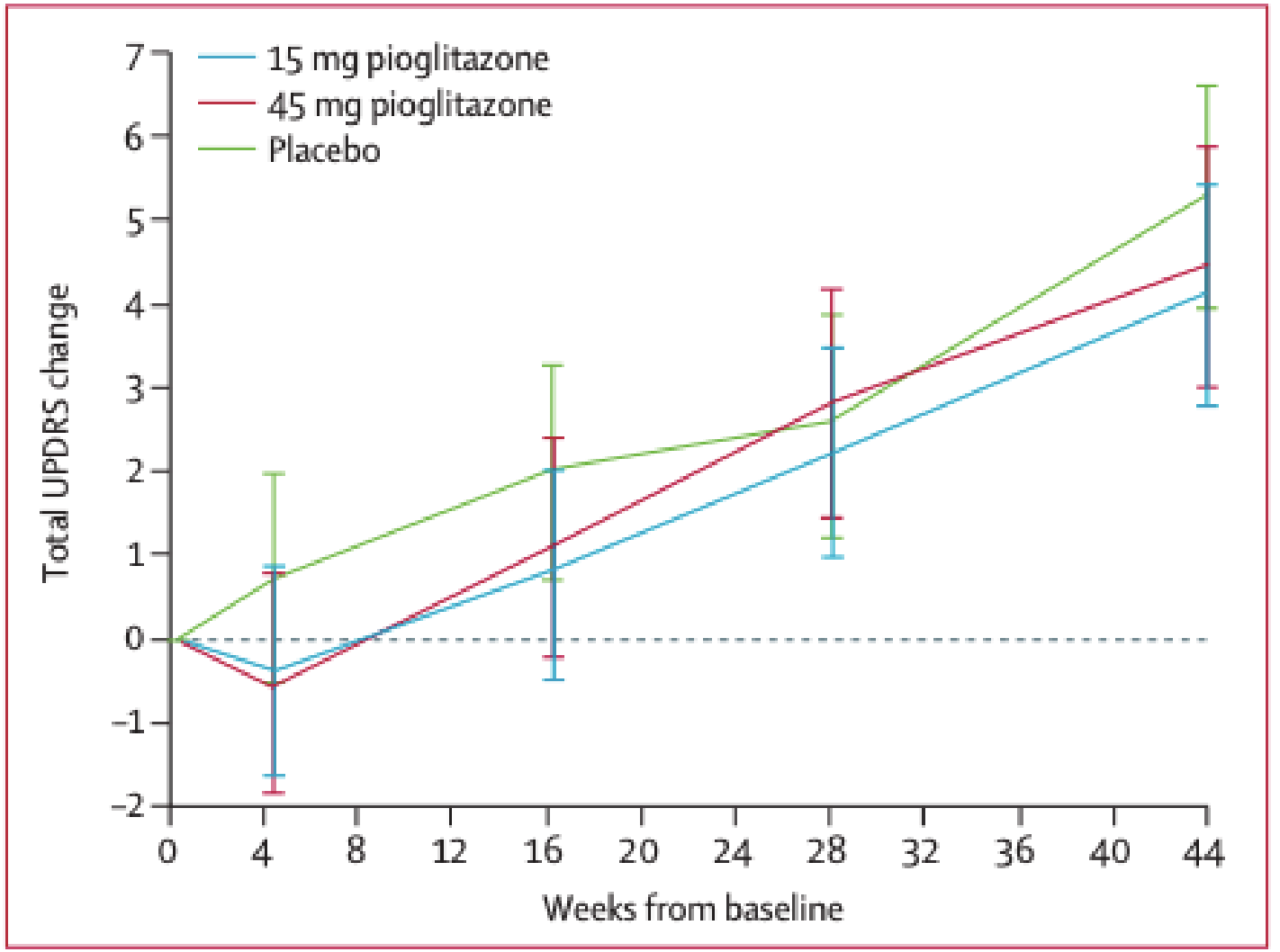
Connolly JG et al. *Am J Epidemiol* 2015;182:936-44.

TZDs and Parkinson Disease



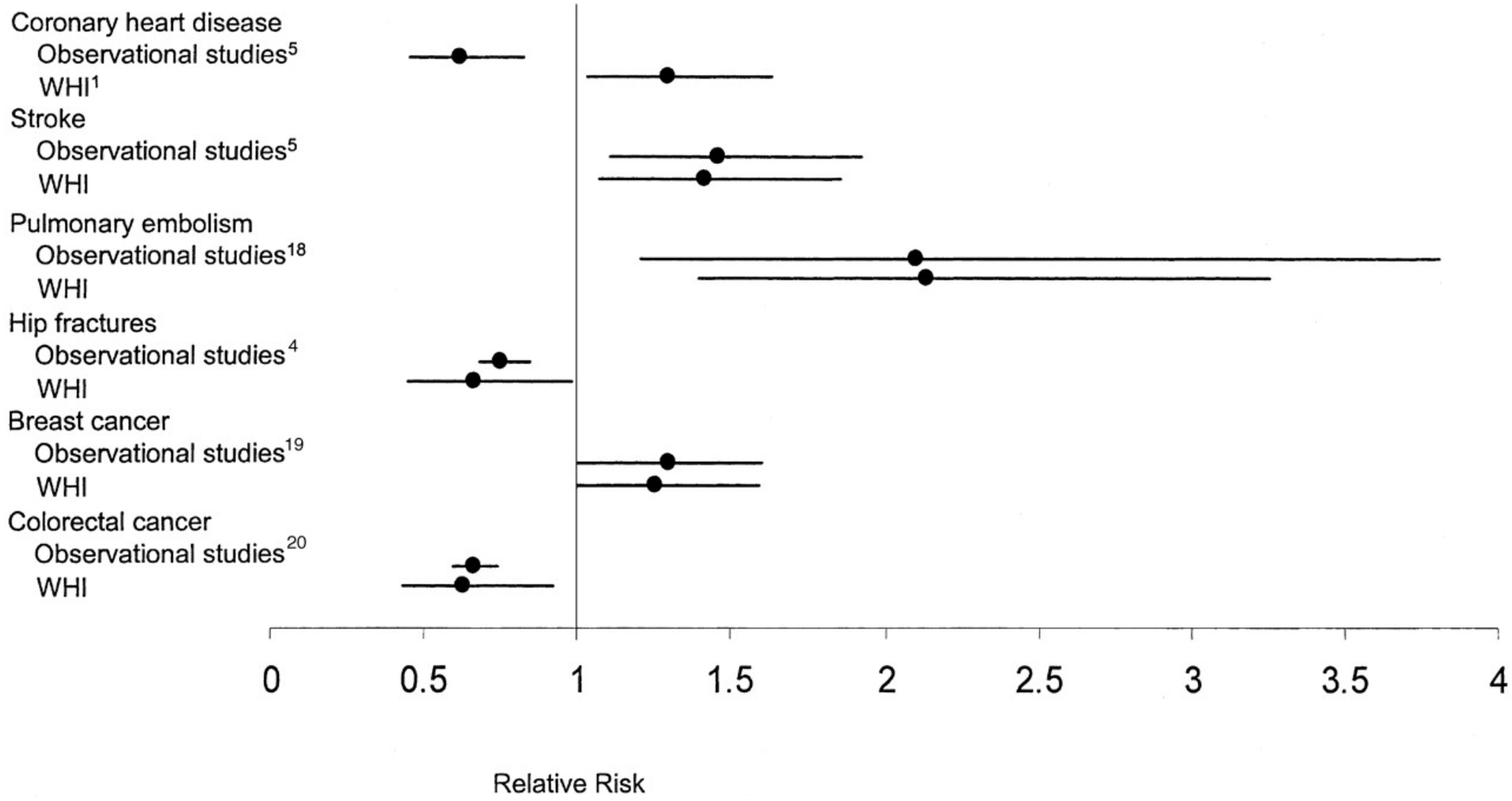
Connolly JG et al. *Am J Epidemiol* 2015;182:936-44.

TZDs and Parkinson Disease



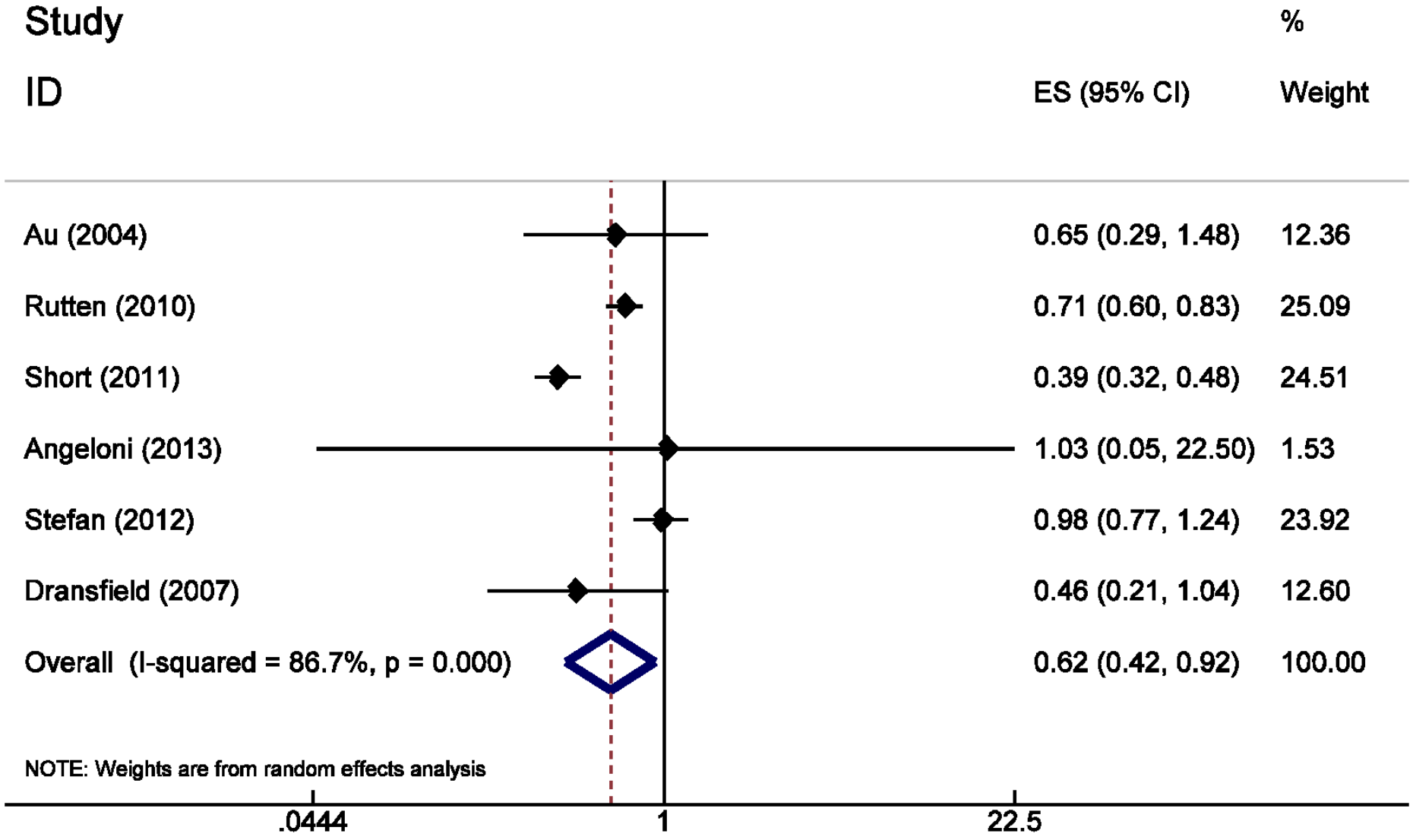
NET-PD FS-Zone Investigators. *Lancet Neurol* 2015;14:795-803.

Observational studies can also get it wrong



Michels KB et al. *Circulation* 2003;107:1830-33.

Beta-blockers for treatment of COPD?



Du Q et al. *PLoS One* 2014;9:e113048.

We are getting better at detecting when we are wrong

	Total study cohort (n=22 985)	
	Cardioselective BBs (n=18 406)	Non-DHP CCBs (n=4579)
Age, mean (SD)	70.4 (9.9)	73.8 (10.2)
Male, %	59.6	55.4
Resource utilisation		
Number of hospitalisation due to any episodes, mean (SD)	1.4 (0.8)	1.6 (1.0)
Number of outpatient visits due to any episodes, mean (SD)	8.2 (6.2)	14.5 (9.6)
Number of outpatient visits due to CV episodes,‡ mean (SD)	3.9 (4.3)	5.2 (4.9)
Number of outpatient visits due to pulmonary-related episodes,§ mean (SD)	1.2 (2.6)	2.7 (3.9)
Number of drugs, mean (SD)	14.4 (6.7)	21.0 (9.4)

Dong YH et al. *BMJ Open* 2017;7:e012997.

We are getting better at detecting when we are wrong

Table 5 Results of sensitivity analyses comparing cardioselective BB versus non-DHP CCB initiators in three US databases*

Type of analysis	Main analysis†	Sensitivity analysis			
		PS matching caliper of 0.005	Asymmetric PS trimming	hd-PS with additional 100 empirical covariates	Restricting to high-risk patients
Database	HR after PS matching (95% CI)				
COPD hospitalisations					
US Optum	0.54 (0.37 to 0.87)	0.59 (0.35 to 0.97)	0.67 (0.37 to 1.23)	0.77 (0.44 to 1.34)	0.61 (0.30 to 1.22)
US PACE	0.51 (0.39 to 0.67)	0.52 (0.40 to 0.67)	0.50 (0.37 to 0.66)	0.61 (0.46–0.80)	0.56 (0.39 to 0.81)
US PAAD	0.45 (0.32 to 0.62)	0.46 (0.33 to 0.64)	0.36 (0.25 to 0.51)	0.59 (0.41 to 0.84)	0.52 (0.31 to 0.88)
Summary estimate	0.50 (0.41 to 0.69)	0.51 (0.42 to 0.61)	0.47 (0.35 to 0.64)	0.62 (0.51 to 0.76)	0.56 (0.42 to 0.73)

Dong YH et al. *BMJ Open* 2017;7:e012997.

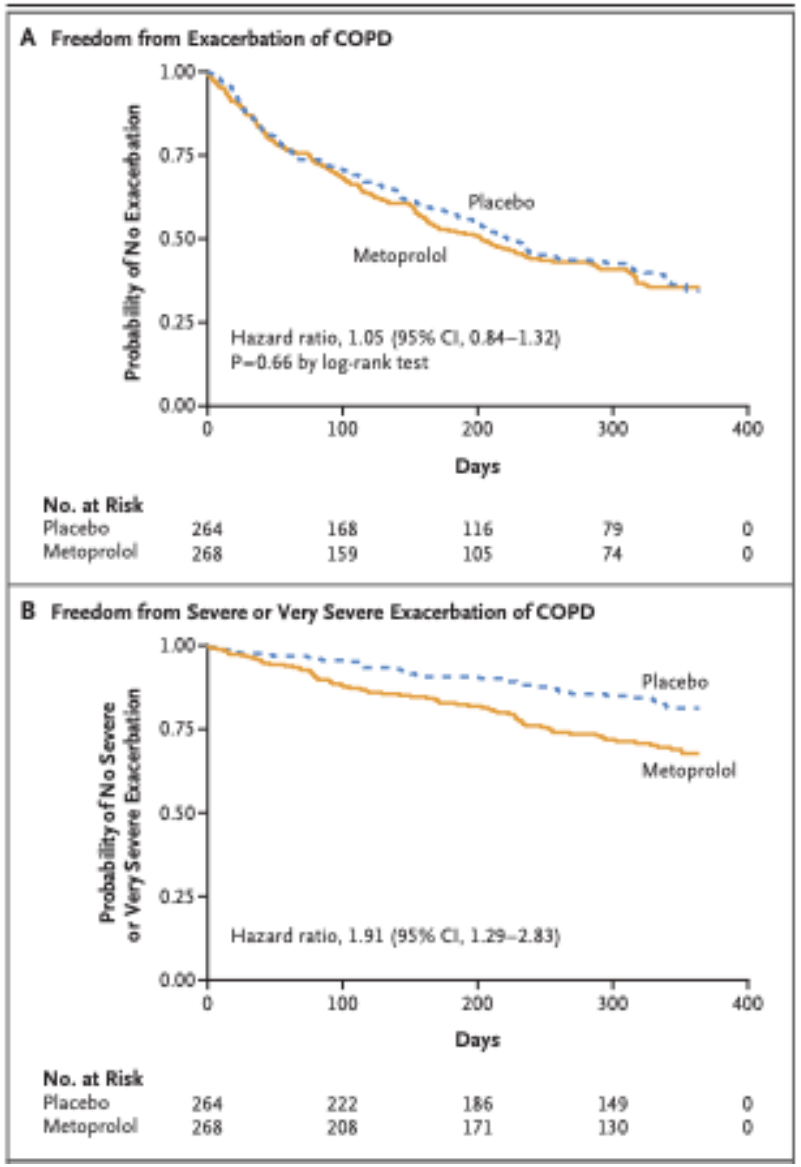
We are getting better at detecting when we are wrong

Table 4 Results for 30-day COPD hospitalisations comparing cardioselective BB versus non-DHP CCB initiators*

Database	Crude HR (95% CI)	HR after PS matching (95% CI)
US Optum	0.28 (0.06 to 1.23)	1.33 (0.17 to 10.70)
US PACE	0.27 (0.15 to 0.47)	0.70 (0.31 to 1.54)
US PAAD	0.19 (0.09 to 0.37)	0.43 (0.18 to 0.99)
Italy RER	0.22 (0.10 to 0.48)	0.37 (0.16 to 0.84)
Taiwan NHI	0.28 (0.15 to 0.51)	0.67 (0.32 to 1.38)
Summary estimate	0.25 (0.18 to 0.34)	0.55 (0.37 to 0.82)

Dong YH et al. *BMJ Open* 2017;7:e012997.

We are getting better at detecting when we are wrong



Dransfield MT et al. *N Engl J Med* 2019 Oct 20 [Epub ahead of print]

Conclusions

- Great care (and epidemiological thinking) is needed when conducting observational studies of therapeutics
- Secondary data sources do not always include information on every variable (exposures, confounders, outcomes) of interest and follow-up can be short in many databases
- However, we are constantly improving the data and the methods for analyzing the data for meaningful inference
- Large healthcare data and networks of databases provide unprecedented opportunity for identifying and evaluating targets for repurposing