Trends, propensity score matching and comparative safety using real world data

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Outline

- Background on real world data
- How are we using it for current research ?
- Initiatives in furthering research
- Conclusions
- Acknowledgments

Background

- Pharmacoepidemiology uses real world data to answer **effectiveness**-how does a treatment work in the real world?

- Randomised controlled trials demonstrate **efficacy**-can a treatment work under 'ideal circumstances'

Background- Why use real world data?

- No inclusion/exclusion criteria
- Treatment outcome derived from actual practice
- Estimates of treatment impact are close to reality
- Not analysed by intent-to-treat vs 'as treated'
- Provides insight to off-labelled use, prescribing behaviour
- Examine safety within the context of doses, multimorbidity in special populations (e.g. older people)

Background- Why use real world data?

"A clinical trial is the best way to assess whether an intervention works, but it is arguably the worst way to assess who will benefit from it" David Mant

Current research-How are we using real world data?

- Level A studies- prescribing trend, adherence
- Level B studies- examining adverse outcomes
- Level C studies- comparative safety

Level A studies- prescribing trend, adherence

Current research-Level A studies

Prescribing trend

Drugs Aging
DOI 10.1007/s40266-014-0205-1

ORIGINAL RESEARCH ARTICLE

Psychotropic Medicine Utilization in Older People in New Zealand from 2005 to 2013

Henry C. Ndukwe · June M. Tordoff · Ting Wang · Prasad S. Nishtala

Current research-Level A studies

Defined Daily Dose

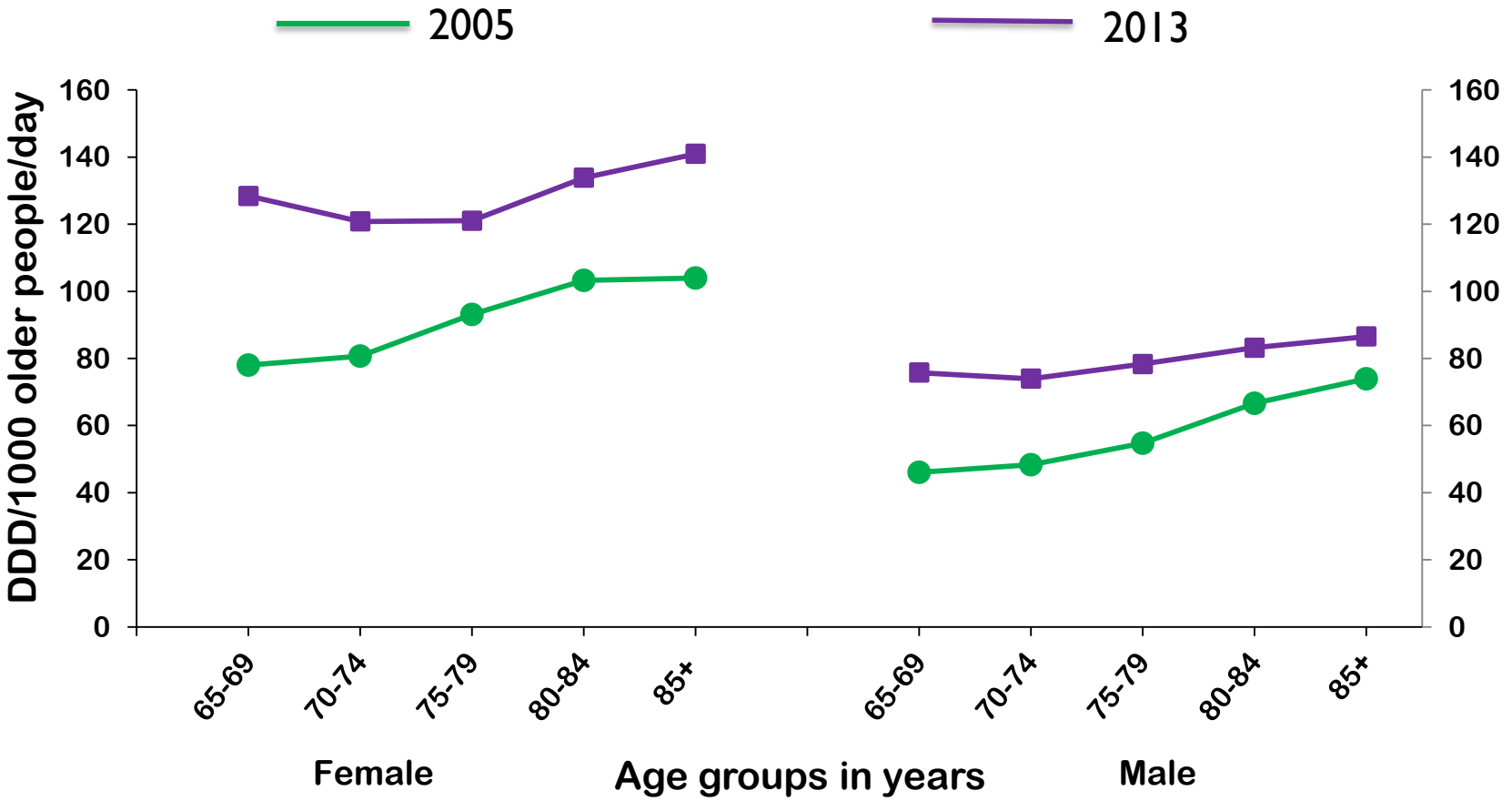
For example, Citalopram 20mg; WHO assigned (20 mg)

$$\text{DDD} = \frac{\text{Strength (20mg/tablet)} * \text{Quantity}}{\text{WHO-DDD (20mg)}}$$

DDD per year = weighted DDD sum ($\sum DDD_i$: DDDs)

$$\text{DDD/1000 older people /day} = \frac{\text{DDD per year} * 1000}{365}$$

Current research-Level A studies



Utilization of antidepressant medicines normalized by gender and five-year age group

Current research-Level A studies

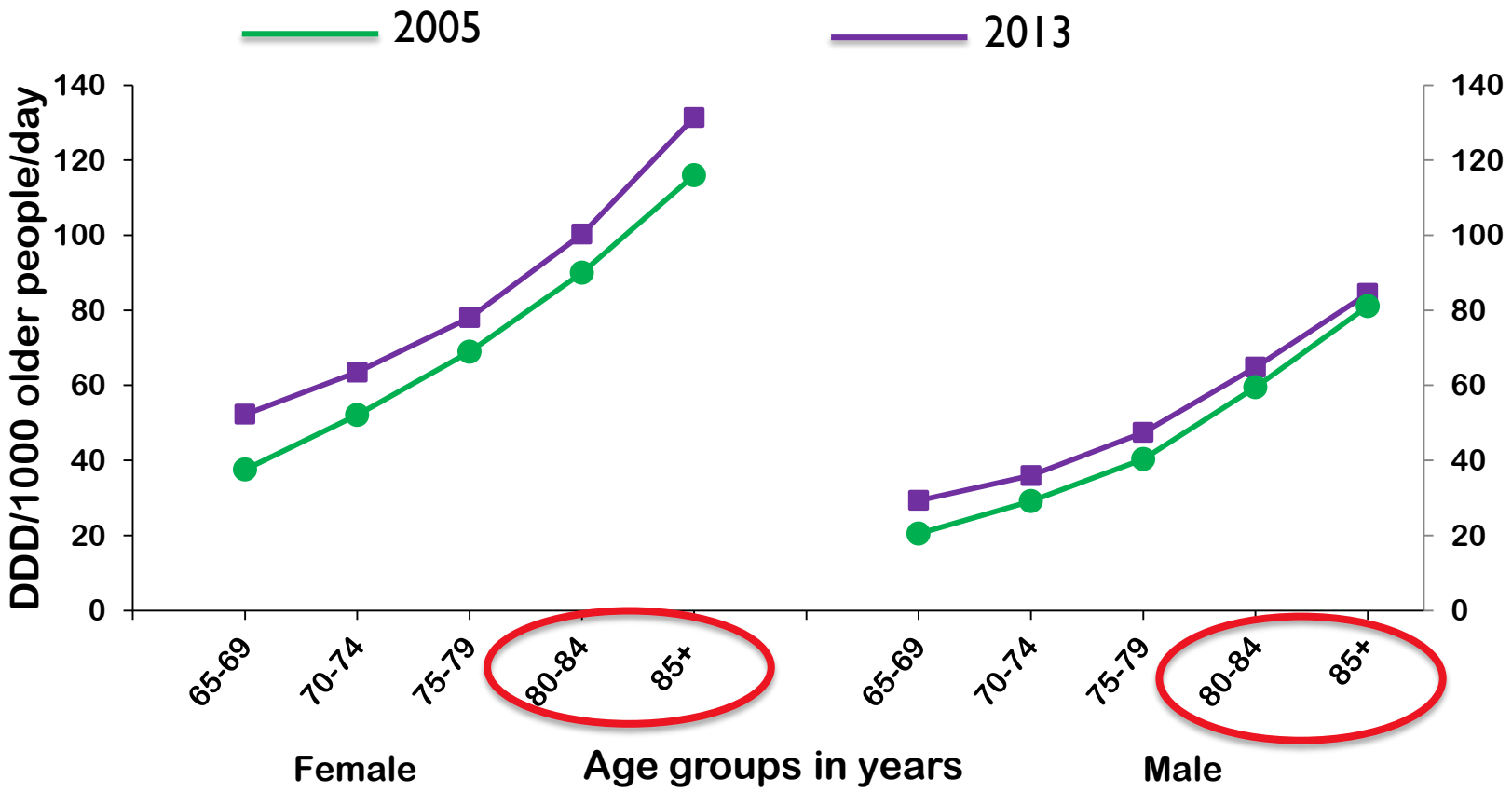
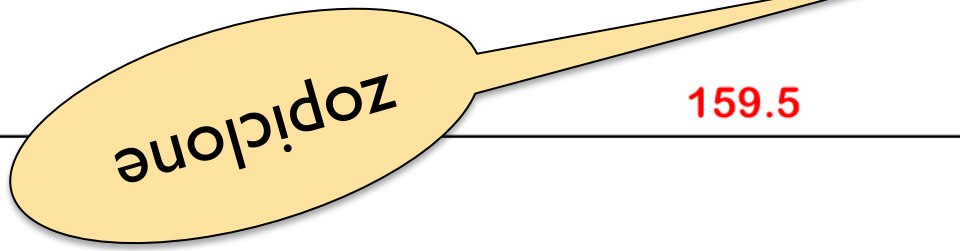


Fig 3: Utilization of hypnotic and sedative medicines normalized by gender and five-year age group

Current research-Level A studies

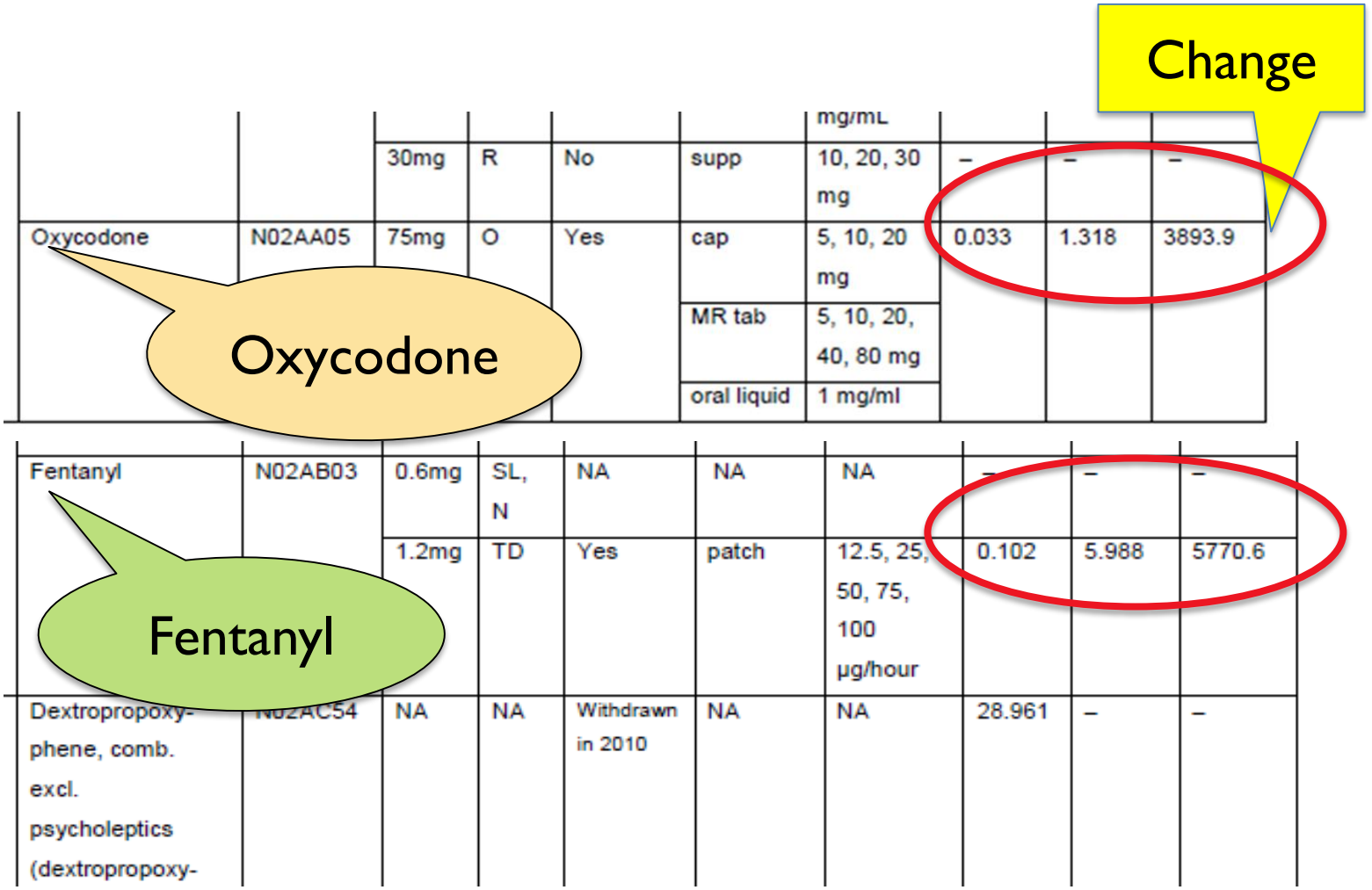
Psychotropic drug utilisation (in DDD/TOPD) compared by therapeutic class and subclass between 2005 and 2013 calendar years

Therapeutic class	Therapeutic subclass	ATC CODE	2005 DDD/TOPD	2013 DDD/TOPD
Anxiolytic	BDZ	N05BA	11.2	10.5
	Non-BDZ	N05BE	0.2	0.2
Hypnotic and Sedatives	BDZ Hypnotics	N05CD	25.5	17.5
	Zopiclone	N05CF	33.8	48.1
National Total			159.5	195.4



Current research-Level A studies

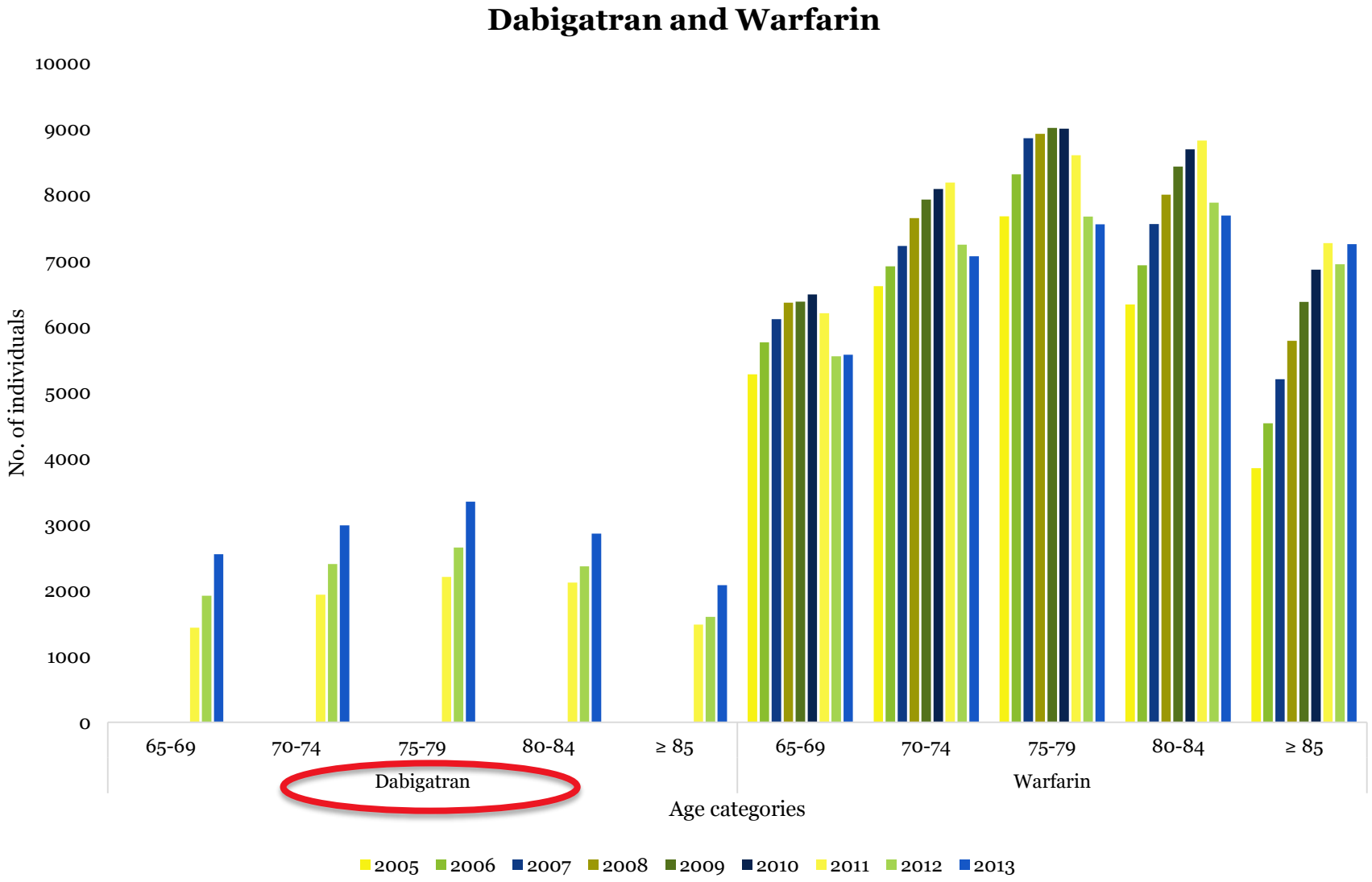
Analgesic medicine utilisation in New Zealand from 2005 to 2013 Joshua OH, Natalie CHUN, Daniel KIM, Fatimah KAMIS, Cecilia KIU (Accepted DRWO)



						mg/mL			
		30mg	R	No	supp	10, 20, 30 mg	–	–	–
Oxycodone	N02AA05	75mg	O	Yes	cap	5, 10, 20 mg	0.033	1.318	3893.9
					MR tab	5, 10, 20, 40, 80 mg			
					oral liquid	1 mg/ml			
Fentanyl	N02AB03	0.6mg	SL, N	NA	NA	NA	–	–	–
		1.2mg	TD	Yes	patch	12.5, 25, 50, 75, 100 µg/hour	0.102	5.988	5770.6
Dextropropoxy-phene, comb. excl. psycholeptics (dextropropoxy-	N02AC54	NA	NA	Withdrawn in 2010	NA	NA	28.961	–	–

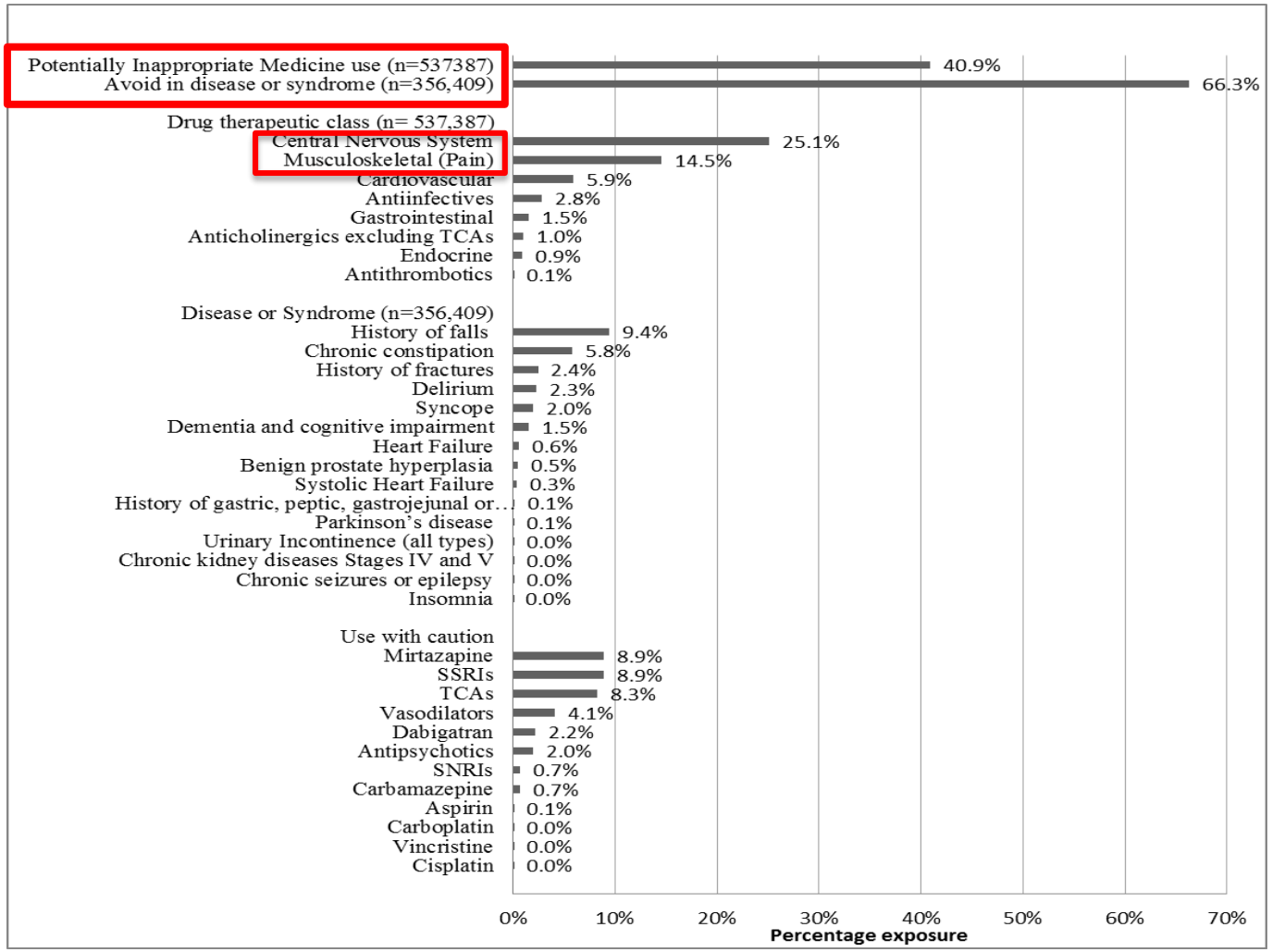
Current research-Level A studies

Preventive medicine utilisation in New Zealand from 2005 to 2013 Narayan et al



Current research-Level A studies

Prevalence of Potentially Inappropriate Medicine use in older New Zealanders: A population-level study (>half a million) using the updated 2012 Beers criteria Narayan et al



The updated Beers 2012 criteria uncovered that a number of older New Zealanders were prescribed NSAIDs, amitriptyline and zopiclone.

Level B studies- examining drug exposures and adverse outcomes

Current research-Level B studies

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY (2014)
Published online in Wiley Online Library (wileyonlinelibrary.com) **DOI**: 10.1002/pds.3624

ORIGINAL REPORT

Associations of drug burden index with falls, general practitioner visits, and mortality in older people

Prasad S. Nishtala[1]*, Sujita W. Narayan[1], Ting Wang[2] and Sarah N. Hilmer[3]

Current research-Level B studies

- The drug burden attributable to each anticholinergic or sedative medication was calculated using the equation,

$$Drug\ burden = D \div (\partial + D)$$

where *D* is the daily dose taken by the patient, and δ is the minimum efficacious dose.

- The total drug burden for an individual was calculated as the sum of the drug burden using a linear additive model.

Current research-Level B studies

Characteristic (n=537,387)	Value (95% CI)
Age (yrs) mean	74.72 (74.70-74.74)
Sex (% female)	54.90 (54.77-55.03)
DBI group (%)	43.22 (43.09-43.35)
DBI exposure	0.177 (0.176-0.178)
Polypharmacy (%)	55.58 (55.45-55.72)
Medicines	5.64 (5.63-5.65)
Chronic Disease Score	6.04 (6.03-6.05)

Current research-Level B studies

N=537,387	DBI group (n = 232,291)	Control (n = 305,096)
Sex		
Male n(%)	103,031(44.4%)	139,295(55.6%)
Female n(%)	129,260(55.7%)	165,801(54.3%)
Ethnicity		
NZ-European n(%)	192,488(50%)	232,690(76.2%)
Māori n(%)	9,903(4.2%)	15,386(5.0%)
Age groups		
Group A n(%)	115,415(49.7%)	180,613(55.1%)
Group B n(%)	81,057(34.9%)	91,404(27.9%)
Group C n(%)	35,819(15.4%)	33,079(10.9%)
Polypharmacy		
Value = 1 n(%)	54,742(23.6%)	183,925(60.3%)
Value = 2 n(%)	177,549(76.4%)	121,171(39.7%)
CDS scores		
0-5 n(%)	104,005(33.0%)	178,365(58.4%)
6-10 n(%)	73,741(25.9%)	89,004(29.1%)

IMBALANCE

Current research-Level B studies

$$y \sim Negbin\ (\mu_i, k)$$

$$\log \mu_i = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \cdots \ldots .$$

Current research-Level B studies

Negative binomial regression model

	Falls	**GP visits**
	NB Model	NB Model
	IRR (95% CI)	IRR (95% CI)
Age (linear)	1.366 (1.289-1.447)	1.021 (1.016-1.025)
Age (quadratic)	0.998 (0.998-0.998)	0.999 (0.999-0.999)
Female	1.197 (1.135-1.263)	1.042 (1.038-1.046)
Ethnicity		
*European		
Māori	0.852 (0.738-0.983)	0.972 (0.963-0.980)
CDS scores	1.043 (1.037-1.048)	1.021 (1.020- 1.021)
Polypharmacy	1.792 (1.659-1.936)	1.238 (1.232-1.244)
DBI>0	1.561 (1.476-1.651)	1.125 (1.121-1.129)

Current research-Level B studies

	Mortality
	Cox Model
	HR (95% CI)
Age (linear)	1.816 (1.755-1.880)
Age (quadratic)	0.997 (0.996-0.997)
Female	0.759 (0.737-0.781)
Ethnicity	
*European	
Māori	1.798 (1.689-1.916)
CDS scores	1.044 (1.041-1.047)
Polypharmacy	1.661 (1.592-1.732)
DBI >0	1.287 (1.249-1.326)

Current research-Level B studies

Using apposite regression models, we found that higher DBI was associated with greater primary care visits, falls and mortality

Associations of drug burden index……*revisited*

Propensity score matching

	DBI group (n = 172,714)	Control (n = 172,714)
Sex		
Male n(%)	94,258	94,258
Female n(%)	78,456	78,456
Ethnicity		
NZ-European n(%)	137,393	137,393
Māori n(%)	9,116	9,116
Age groups		
Group A n(%)	92,929	92,929
Group B n(%)	57,226	57,226
Group C n(%)	22,559	22,559
Polypharmacy		
Value = 1 n(%)	54,741	54,741
Value = 2 n(%)	117,973	117,973
CDS scores		
0-5 n(%)	76,761	76,761
6-10 n(%)	60,256	60,256

BALANCE

Propensity Score Matching

- Propensity score is the conditional probability of receiving treatment given a set of pre-treatment characteristics.

- Propensity scores are computed using Probit/Logit models.

- Individuals in the treatment group are matched with control group that have similar (or close) propensity scores.

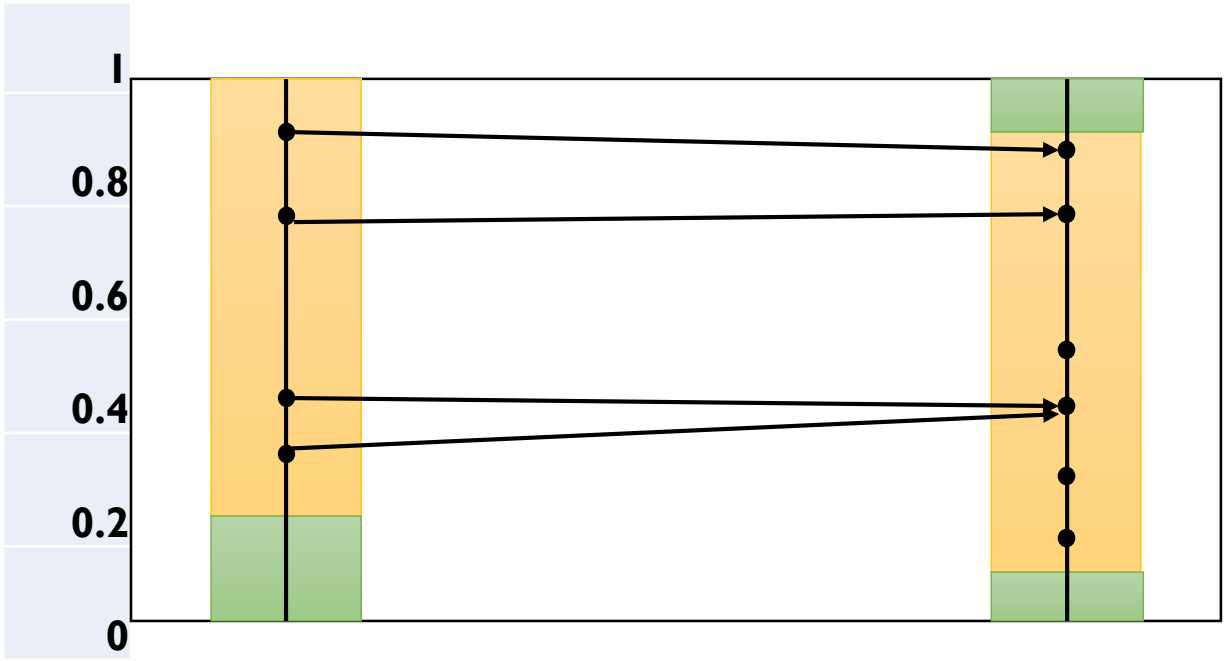
Propensity score matching

$$\acute{p}_i = \frac{\exp(\beta \hat{} X_i)}{1+\exp(\beta \hat{} X_i)}$$

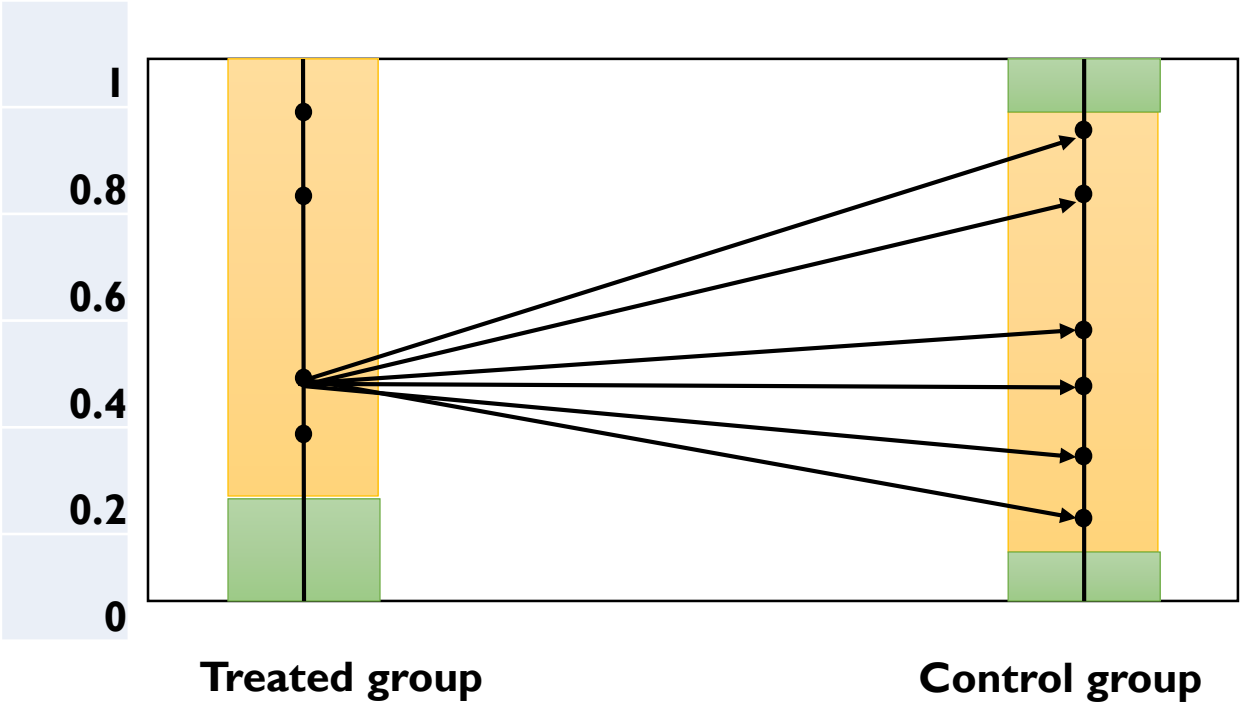
Propensity score matching

Individuals	Exposure	Predicted Probabilities
1	DBI=Y	0.9876
2	DBI=Y	0.7564
3	DBI=N	0.9778
4	DBI=Y	0.7865
5	DBI=N	0.2101
6	DBI=Y	0.2000
7	DBI=N	0.3390
8	DBI=Y	0.3387
9	DBI=N	0.7729
10	DBI=Y	0.6988

Nearest neighbour matching



Kernel matching



Propensity score matching assumptions

Eq1 $Y_1=\bar{u}_1(X) + Z_1$ $\bar{u}$ = Mean effect

Eq2 $Y_0=\bar{u}_0(X) + Z_0$ Z=error term

$\blacktriangle=(Y_1-Y_0)=\{\bar{u}_1(X) - \bar{u}_0(X)\} + \bar{u}_1-\bar{u}_0$ Heterogeneity

ATE

Eq3 $Y=T*Y_1 + (1-T)*Y_0$

if T=1, then $Y=Y_1$, if T=0 then $Y=Y_0$

Eq4 $Y=Z_0(X) + \blacktriangle ATE*T + \{T(Z_1-Z_0)+Z_0\}$

1. All confounders (X) have been accounted
2. No/minimal error terms

Current research-Level B studies

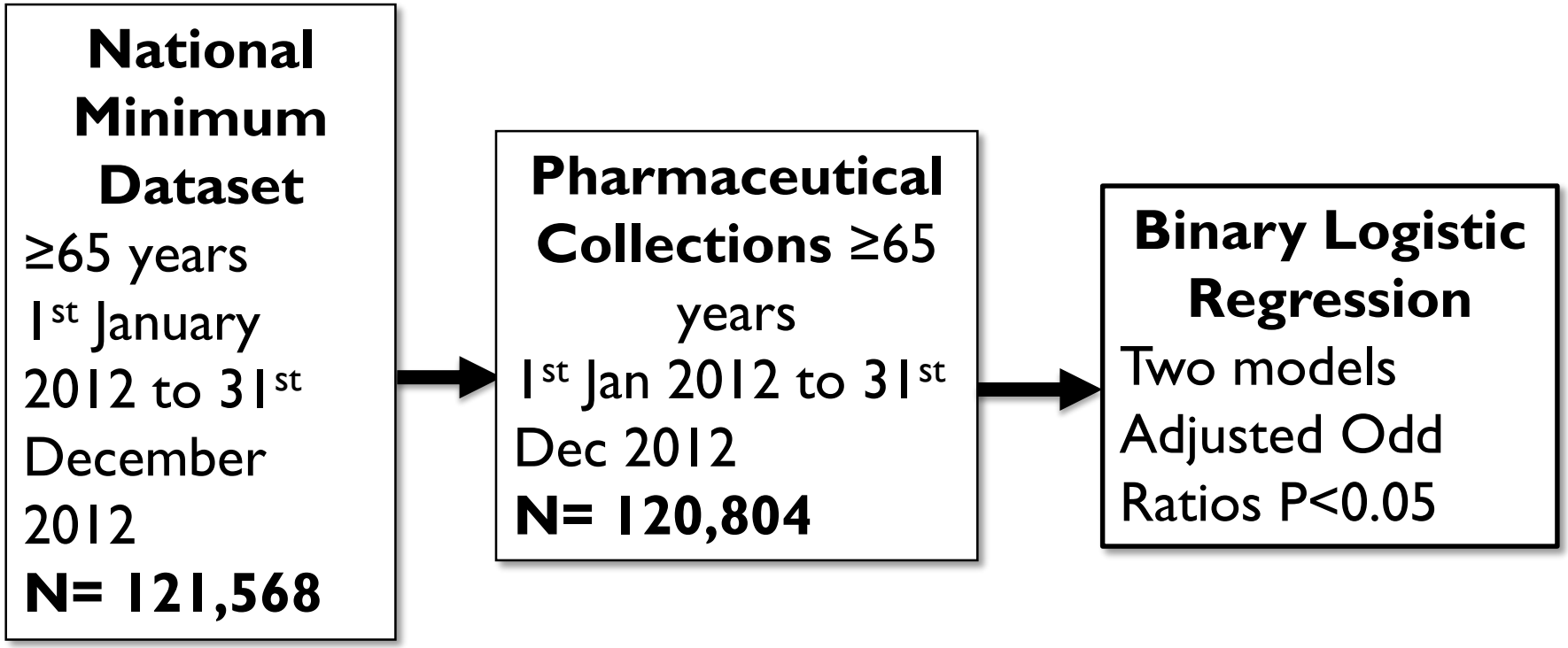
	Falls		GP visits		Mortality	
	Before Matching IRR	After Matching IRR	Before Matching IRR	After Matching IRR	Before Matching HR	After Matching HR
PP	1.79 (1.65-1.93)	1.99 (1.79-2.21)	1.23 (1.23-1.24)	1.31 (1.30-1.31)	1.66 (1.59-1.73)	1.10 (1.04-1.17)
DB I	1.56 (1.47-1.65)	1.56 (1.47-1.67)	1.12 (1.12-1.12)	1.12 (1.11-1.12)	1.28 (1.24-1.32)	1.08 (1.04-1.11)

PP-Polypharmacy

Current research-Level B studies-

A Data linkage study:

Nishtala PS, Soo L. Proton pump inhibitors utilisation in older people in New Zealand from 2005 to 2013. Intern Med J 2015.



Current research-Level B studies

Nishtala PS, Soo L. Proton pump inhibitors utilisation in older people in New Zealand from 2005 to 2013. Intern Med J 2015.

- Short-term PPI (30-60 days) use associated with aspirin and NSAID exposures
- Long-term (>180 days) PPI use associated with aspirin exposure, NSAID exposure, gastritis/duodenitis, GORD and increasing age

Level C studies- comparative safety

Current research-Level C studies

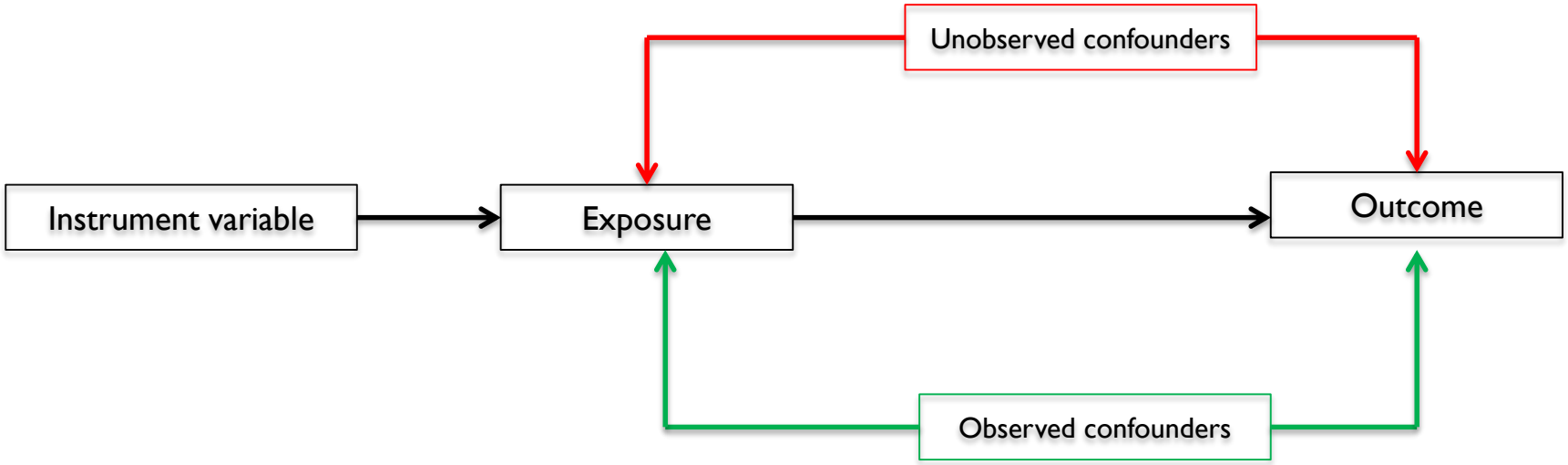
'Real-world' haemorrhagic rates for warfarin and dabigatran using population level data

- New user design: Followed inception cohort using warfarin or dabigatran for the first time
- Followed cohort for period of 18 months
- Estimated incidence rate (person years), incidence rate for 30 days and hazard ratios
- Propensity score matching

Initiatives for advanced research

- Marginal structural models: when you have a time varying covariate

- Instrumental variables



Conclusions

- Real world data can provide evidence in special populations (e.g. older people) often excluded in RCTs
- Real world data can account for comorbidity
- Support policy decisions
- Detect off-labelled & inappropriate medicine use

Acknowledgements

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