Drug Safety in Diabetes

Work in Progress

Diabetes Research Group,
Medical Research Institute
University of Dundee
on behalf of SDRN-EPI

Danny Levin

Some Safety Questions

- TZDs and Fracture
- Insulin/analogues and cancer
- Pioglitazone and bladder cancer
- GLP-1 analogues and pancreatic cancer
- DPPIV inhibitors and respiratory infection
- Sulphonylureas and heart failure

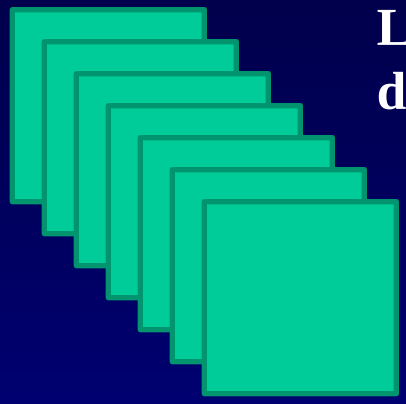
Some Methodological challenges in Pharmacoepidemiology

- **Limited data & Power**
  - rare events or short time on market
  - multi-centre collaborations using planned Meta-analysis
- **Confounding by indication (allocation bias)**
  - The drug is allocated to groups with high/low risk of getting the disease of interest e.g. frail or physically active subjects
- **Misclassification of exposure**
  - Failing to take account of periods during which exposure and/or events are unobserved e.g. can you accurately calculate cumulative exposure
  - Immortal time bias : incorrectly allocate person time that is unexposed to the exposure category
- **Reverse causation**
  - The (as yet undiagnosed) disease symptoms cause the drug to be prescribed

OMOP and Data Formats

- Many pharmacoepi studies need collaboration across several datasets/ meta analyses
- To enable this it is useful to agree a common data model
- Organising the data facilitates more rapid turnover for studies
- A necessary prequel to a national pharmacoepidemiology platform

Framework for collaboration



Local database

Person

Observation Period Events

Obs Period Drugs

Drug era

Condition occurrence

5 OMOP(ish) format files

Run Dundee R script to create survival table

"Survival"Table

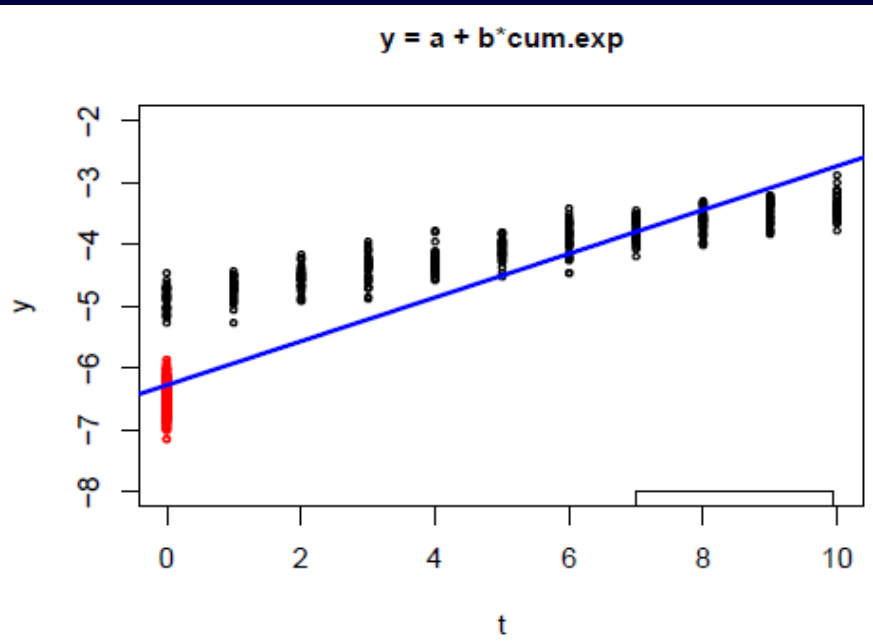
Run Dundee R script for modelling and dumping outputs as R objects

Results

Dundee to collate R objects from all models from all centres and run weighted meta-analysis

Allocation bias/ confounding by indication/ confounding by frailty

- Approach typically used :
- Survival analysis or Poisson regression including time-dependent binary ever-exposed variable, or cumulative dose/time exposure, with adjustment for potential confounders
- These often report an effect for any exposure versus none or for categories of cumulative exposure versus none
- BUT such analyses remain subject to fixed between person confounding by indication and reverse-causation
- Need to consider the underlying model of causality: Exposure to the drug causes an increase in risk of a disease (step-wise and/or dose-related), lagged effect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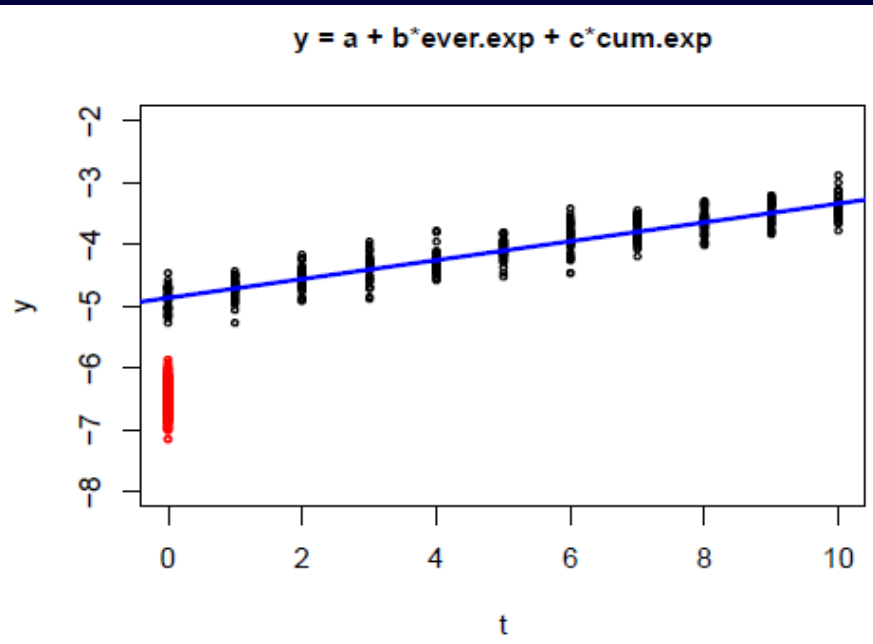
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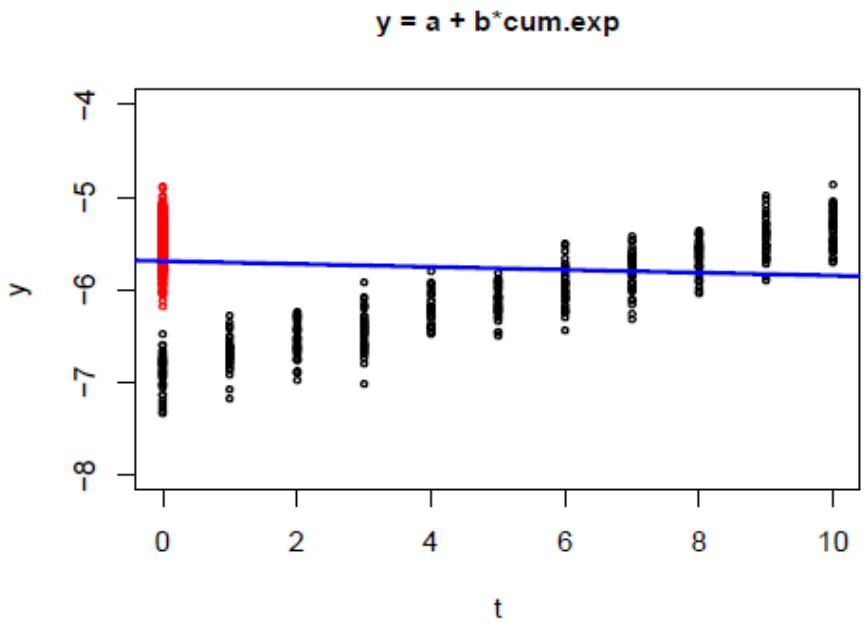
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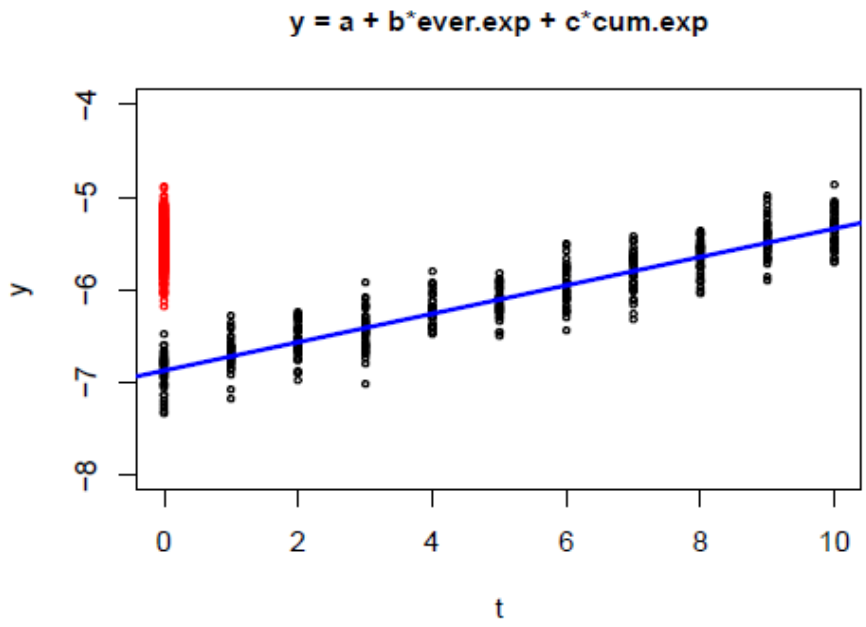
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One solution – where a cumulative effect exists

- survival model : eg Cox or Poisson
- Include ever term and cumulative term in the model
- Focus inference on the cumulative term not the ever term
- Ever exposed term is the sum of allocation bias and any immediate stepwise effect of drug
- Cumulative terms can be shown algebraically to be independent of the event rate in non exposed periods i.e. free of allocation bias.

Pioglitazone and Bladder Cancer
Methods

- survival analysis using Poisson and Cox regression with time dependent covariates
- time in: latest of diabetes diagnosis date, observability for drug data, 1/1/2000
- time out – earliest of date of first adverse event, cessation of observability for exposure or events, or 31/12/2008
- divide person time into regular intervals: discrete time units
- term for ever exposure to a given drug prior to start of each interval 0/1
- term for cumulative exposure in days at start of time interval
- covariate status either for baseline or at start of each interval if time dependent adjustment warranted

SCI-DC Data: Bladder cancer

223,572 subjects with Type 2 DM	
Male/Female	54% / 46%
Age at entry (median, IQR)	63.5, 54.6-71.9
DM duration at entry (med, IQR)	0.15, 0-4
events / p.years (rate per 100,000 pyrs)	748 / 1.283 Mpyrs (58)
Male	544 / 688,280 pyrs (79)
Female	204 / 595,060 (34)
pre-pio exposure	715 / 1.231 M (58)
post-pio exposure	33 / 52,740 (62)
pre-pio exp - M	521 / 659,980 (79)
post-pio exp - M	23 / 28,300 (81)
pre-pio exp - F	194 / 570,620 (34)
post-pio exp - F	10 / 24,440 (41)

Effect of Cumulative Pioglitazone on Bladder Cancer

covariate	HR	95% CI
Female	0.36	(0.30,0.42) ***
Age at entry 55-65	4.6	(3.2,6.6) ***
Age at entry 65-75	10	(7.0,14.2) ***
Age at entry >75	16.7	(11.6,24.0) ***
DM duration	0.99	(0.98,1.01)
Ever-exposed Pio	1.48	(0.90,2.4)
Cum. Exposure Pio	0.98	(0.77,1.25)

Summary

- Challenging problems & methods
- Sources of bias reduced through proper use of person time and its correct classification wrt exposure
- Allocation bias much less tractable
- Use of separate ever- and cumulative-exposure terms useful
- Does not allow for immediate stepwise effects
- Using standard data formats essential for national platform

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