Meta-Analysis of Rare Events

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motivation

- recent debate on the safety of the diabetes drug *rosiglitazone*
- meta-analysis (MA) by Nissen and Wolski (2007, 2010)
- number of papers Shuster *et al.* (2007), Tian *et al.* (2009), Dahabreh (2008), Friedrich *et al.* (2009), Mannucci *et al.* (2009), Kaul and Diamond (2011)
- Böhning, Mylona, Kimber (2014) focus on existing methodology to adapt to MA of rare event trials

Table: Study data of meta–analysis on rare events in Rosiglitazone and control arm; MI refers to the myocardial infarction deaths, CV to cardiovascular deaths, *n* is the size of the respective study arm and 'duration' refers to the study period at risk (in weeks)

		treatment arm			control arm			
ID	study label	*n*	MI	CV	*n*	MI	CV	duration
1	49653/011	357	2	1	176	0	0	24
2	49653/020	391	2	0	207	1	0	52
3	49653/024	774	1	0	185	1	0	26
4	49653/093	213	0	0	109	1	0	26
...	...	...	...	...	...	...	...	...
53	49653/452	26	0	0	24	0	0	24
54	DREAM	2635	15	12	2634	9	10	156
55	ADOPT19	1456	27	2	2895	41	5	208
56	RECORD	2220	64	60	2227	56	71	260

a second example

- NiËl-Weise *et al.* (2007) did a MA on the effect of anti-infective-treated central venous catheters on catheter-related bloodstream infection (CRBSI) in the acute care setting
- meta-analysis involved 18 clinical trials
- control group is standard catheter

Table: Meta–analysis on rare evidence data on the effect of anti-infective-treated catheter in compariosn to standard catheter; CRBSI refers to catheter-related bloodstream infection events, *n* is the size of the respective study arm

	control arm		treatment arm	
study ID	CRBSI	*n*	CRBSI	*n*
1	3	117	0	116
2	3	35	1	44
3	9	195	2	208
4	7	136	0	130
5	6	157	5	151
6	4	139	1	98
7	3	177	1	174
8	2	39	1	74

	control arm		treatment arm	
study ID	CRBSI	*n*	CRBSI	*n*
9	19	103	1	97
10	2	122	1	113
11	7	64	0	66
12	1	58	0	70
13	5	175	3	188
14	11	180	6	187
15	0	105	0	118
16	1	262	0	252
17	3	362	1	345
18	1	69	4	64

a definition

MA of rare events trials deals with MA of trials which includes single-zero or double-zero trials.

A **single-zero trial** is a trial in which at least one arm are has no events. A **double-zero trial** is a trial in which both arms have no events.

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popular effect measures

- **risk difference** RD: risk in treatment arm − risk in control arm estimated by (x number of events and P is person-time)

$$\widehat{RD} = x^T/P^T - x^C/P^C$$

- **risk ratio** RR: risk in treatment arm / risk in control arm estimated by

$$\widehat{RR} = \frac{x^T/P^T}{x^C/P^C}$$

- **odds ratio** OR: odds in treatment arm / odds in control arm estimated by

$$\widehat{OR} = \frac{x^T/(P^T - x^T)}{x^C/(P^C - x^C)} = \frac{x^T(P^C - x^C)}{x^C(P^T - x^T)}$$

problems can occur on two levels with zero-studies

effect measure itself

- no problem for the risk difference

$$\widehat{RD} = x^T/P^T - x^C/P^C$$

- risk ratio and odds ratio: it might be useless (0), infinite (∞), or undefined (0/0)

$$\widehat{RR} = \frac{x^T/P^T}{x^C/P^C} \text{ and } \widehat{OR} = \frac{x^T/(P^T - x^T)}{x^C/(P^C - x^C)}$$

problems can occur on two levels with zero-studies

uncertainty assessment

- risk difference

$$var(\widehat{RD}) \approx \frac{x^T}{{P^T}^2} + \frac{x^C}{{P^C}^2}$$

- risk ratio

$$var(\widehat{\log RR}) \approx \frac{1}{x^T} + \frac{1}{x^C}$$

- odds ratio

$$var(\widehat{\log OR}) \approx \frac{1}{x^T} + \frac{1}{P^T - x^T} + \frac{1}{x^C} + \frac{1}{P^C - x^C}$$

problems can occur on two levels with zero-studies

disturbances with weighted average computation:

- $$\overline{\log RR} = \frac{\sum_i w_i \widehat{\log RR_i}}{\sum_i w_i}$$
- where
$$w_i = \frac{1}{var(\widehat{\log RR})}$$
- in a similar way for RD and OR

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strategies to cope with zero-studies

pooling all studies:

- $$\widehat{RR}_{\text{crude}} = \frac{(\sum_i x_i^T)/(\sum_i P_i^T)}{(\sum_i x_i^C)/(\sum_i P_i^C)}$$
- disadvantage: potentially strong confounding effect by ignoring `study` factor

Mantel-Haenszel

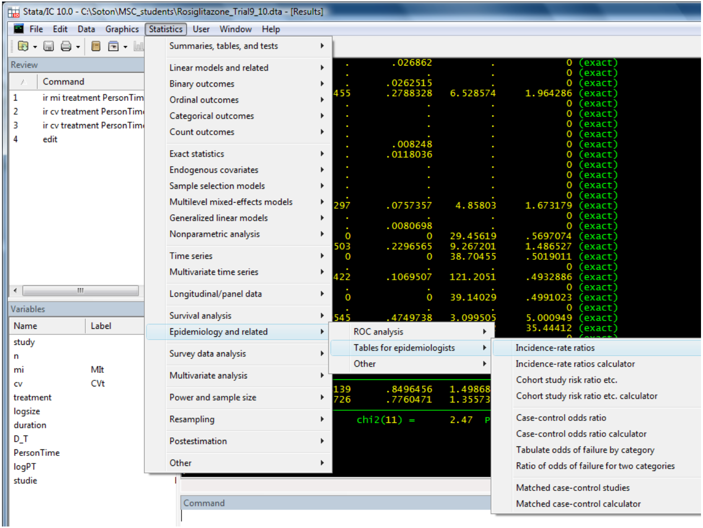
- $$\widehat{RR}_{\text{MH}} = \frac{\sum_i x_i^T P_i^C / P_i}{\sum_i x_i^C P_i^T / P_i},$$
  where $P_i = P_i^C + P_i^T$
- **advantage:** estimator is not sensitive to zero-studies
- is also a **weighted estimator**

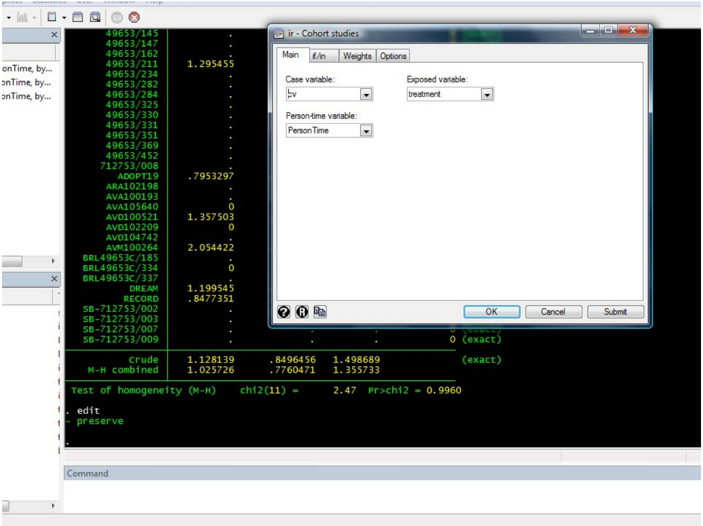
  $$\frac{\sum_i w_i \widehat{RR}_i}{\sum_i w_i}$$

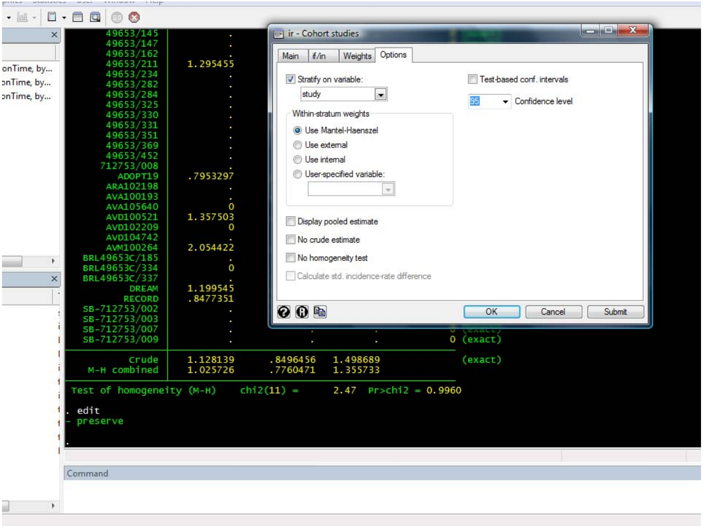
  using the weights $w_i = x_i^C P_i^T / P_i$

Table: Mantel-Haenszel estimate in the rare events meta–analysis of Rosiglitazone

method	estimate	confidence interval
MI		
crude	1.2561	0.9928 – 1.5911
MH	1.2782	1.0125 – 1.6137
CV		
crude	1.1281	0.8496 – 1.4987
MH	1.0257	0.7760 – 1.3557


Stata/IC 10.0 - C:\Soton\MSC_students\Rosiglitazone_Trial9_10.dta - [Results]
File Edit Data Graphics Statistics User Window Help
Review
Command
1 ir mi treatment PersonTim
2 ir cv treatment PersonTim
3 ir cv treatment PersonTim
4 edit
Variables
Name Label
study
n
mi MIt
cv CVt
treatment
logsize
duration
D_T
PersonTime
logPT
studie
Command
Summaries, tables, and tests
Linear models and related
Binary outcomes
Ordinal outcomes
Categorical outcomes
Count outcomes
Exact statistics
Endogenous covariates
Sample selection models
Multilevel mixed-effects models
Generalized linear models
Nonparametric analysis
Time series
Multivariate time series
Longitudinal/panel data
Survival analysis
Epidemiology and related
Survey data analysis
Multivariate analysis
Power and sample size
Resampling
Postestimation
Other
ROC analysis
Tables for epidemiologists
Other
Incidence-rate ratios
Incidence-rate ratios calculator
Cohort study risk ratio etc.
Cohort study risk ratio etc. calculator
Case-control odds ratio
Case-control odds ratio calculator
Tabulate odds of failure by category
Ratio of odds of failure for two categories
Matched case-control studies
Matched case-control calculator
chi2(11) = 2.47


ir - Cohort studies
Main
if/in
Weights
Options
Case variable:
cv
Exposed variable:
treatment
Person-time variable:
PersonTime
OK
Cancel
Submit
49653/145
49653/147
49653/162
49653/211 1.295455
49653/234
49653/282
49653/284
49653/325
49653/330
49653/331
49653/351
49653/369
49653/452
712753/008
ADOPT19 .7953297
ARA102198
AVA100193
AVA105640 0
AVD100521 1.357503
AVD102209 0
AVD104742
AVM100264 2.054422
BRL49653C/185
BRL49653C/334 0
BRL49653C/337
DREAM 1.199545
RECORD .8477351
SB-712753/002
SB-712753/003
SB-712753/007
SB-712753/009 . . . 0 (exact)
Crude 1.128139 .8496456 1.498689 (exact)
M-H combined 1.025726 .7760471 1.355733
Test of homogeneity (M-H) chi2(11) = 2.47 Pr>chi2 = 0.9960
. edit
- preserve
Command
onTime, by...
onTime, by...
onTime, by...


ir - Cohort studies
Main
if/in
Weights
Options
Stratify on variable:
study
Test-based conf. intervals
95
Confidence level
Within-stratum weights
Use Mantel-Haenszel
Use external
Use internal
User-specified variable:
Display pooled estimate
No crude estimate
No homogeneity test
Calculate std. incidence-rate difference
OK
Cancel
Submit
Crude 1.128139 .8496456 1.498689 (exact)
M-H combined 1.025726 .7760471 1.355733
Test of homogeneity (M-H) chi2(11) = 2.47 Pr>chi2 = 0.9960
. edit
- preserve
Command

Mantel-Haenszel for *OR*

- $$\widehat{OR}_{\text{MH}} = \frac{\sum_i x_i^T (P_i^C - x_i^C)/P_i}{\sum_i x_i^C (P_i^T - x_i^T)/P_i},$$

  where $P_i = P_i^C + P_i^T$
- is also a **weighted estimator**

$$\frac{\sum_i w_i \widehat{OR}_i}{\sum_i w_i}$$

using the weights $w_i = x_i^C (P_i^T - x_i^T)/P_i$

Mantel-Haenszel for *RD*

- $$\widehat{RD}_{\mathrm{MH}} = \frac{\sum_i (x_i^T P_i^C - x_i^C P_i^T)/P_i}{\sum_i (P_i^T P_i^C / P_i)},$$

  where $P_i = P_i^C + P_i^T$
- is also a **weighted estimator**

  $$\frac{\sum_i w_i \widehat{RD}_i}{\sum_i w_i}$$

  using the weights $w_i = (P_i^T P_i^C)/P_i$

testing homogeneity of effect

major difficulties with Mantel-Haenszel lies in establishing homogeneity of effect

- $$\chi^2_{k-1} = \sum_i \frac{\left(\widehat{\log RR_i} - \log \widehat{RR}_{\text{MH}}\right)^2}{var(\widehat{\log RR_i})}$$

  where k is the number of studies
- this statistic **will not work** in the case of zero-studies
- this question needs to be approached in a modelling framework

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Poisson regression

- consider number of events X as a Poisson count with mean

$$E(X) = \mu P$$

- clearly, $\mu = E(X)/P$ is the **incidence risk**
- write in study i

$$E(X_{ij}) = \mu_j P_{ij}$$

for $j = 1$ (treatment) and $j = 0$ (control)
- so that again $RR = \mu_1/\mu_0$

Poisson regression

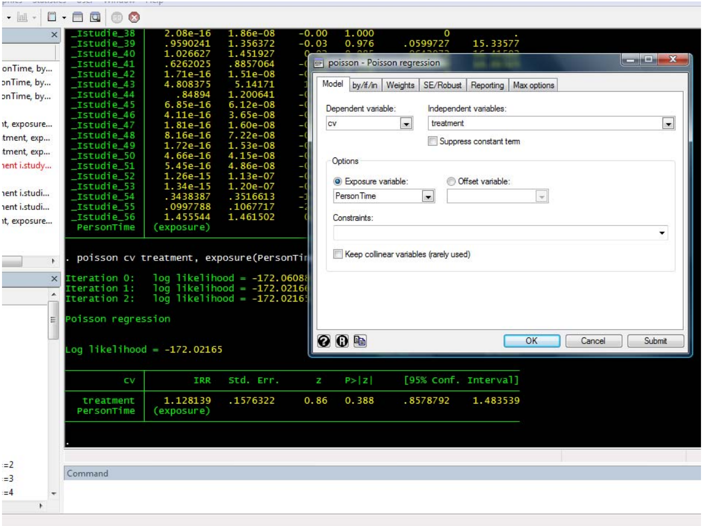
- in study i

$$E(X_{ij}) = \mu_j P_{ij}$$

- take logarithms on both sides

$$\log E(X_{ij}) = \log P_{ij} + \log \mu_j = \log P_{ij} + \alpha + \beta \times j$$

- so that $\beta = \log(\mu_1/\mu_0)$ is the **log-risk ratio**
- $\log P_{ij}$ enters as a covariate with known coefficient into the model: **an offset**


_Istudie_38 2.08e-16 1.86e-08 -0.00 1.000 0 .
_Istudie_39 .9590241 1.356372 -0.03 0.976 .0599727 15.33577
_Istudie_40 1.026627 1.451927
_Istudie_41 .6262025 .8857064
_Istudie_42 1.71e-16 1.51e-08
_Istudie_43 4.808375 5.14171
_Istudie_44 .84894 1.200641
_Istudie_45 6.85e-16 6.12e-08
_Istudie_46 4.11e-16 3.65e-08
_Istudie_47 1.81e-16 1.60e-08
_Istudie_48 8.16e-16 7.22e-08
_Istudie_49 1.72e-16 1.53e-08
_Istudie_50 4.66e-16 4.15e-08
_Istudie_51 5.45e-16 4.86e-08
_Istudie_52 1.26e-15 1.13e-07
_Istudie_53 1.34e-15 1.20e-07
_Istudie_54 .3438387 .3516613
_Istudie_55 .0997788 .1067717
_Istudie_56 1.455544 1.461502
PersonTime (exposure)
. poisson cv treatment, exposure(PersonTi
Iteration 0: log likelihood = -172.0608
Iteration 1: log likelihood = -172.0216
Iteration 2: log likelihood = -172.0216
Poisson regression
Log likelihood = -172.02165
cv IRR Std. Err. z P>|z| [95% Conf. Interval]
treatment 1.128139 .1576322 0.86 0.388 .8578792 1.483539
PersonTime (exposure)
poisson - Poisson regression
Model by/if/in Weights SE/Robust Reporting Max options
Dependent variable: cv
Independent variables: treatment
Suppress constant term
Options
Exposure variable: PersonTime
Offset variable:
Constraints:
Keep collinear variables (rarely used)
OK Cancel Submit
Command

Poisson regression with random study effect

taking into account the study effect:

- the effect **homogeneity** model

$$\log E(X_{ij}) = \log P_{ij} + \alpha_i + \beta \times j$$

- the effect **heterogeneity model**

$$\log E(X_{ij}) = \log P_{ij} + \alpha_i + \beta_i \times j$$

Poisson regression with random study effect

two options:

- **fixed effects model**: α_i and β_i are treated as fixed parameters
- disadvantage: many studies $\longrightarrow$ many parameters
- **Neyman-Scott problem** (sample size and number of parameters connected)
- **random effects model**: α_i and β_i are treated as random quantities:

$$\alpha_i \sim N(\alpha, \sigma_\alpha^2) \text{ and } \beta_i \sim N(\beta, \sigma_\beta^2)$$

Poisson regression with random study effect

this leads to the following different likelihoods (in the example of the **homogeneity model**)

- **fixed effects model**:

$$\prod_i \left[Po(x_{i0}|P_{i0}\exp(\alpha_i)) \times Po(x_{i1}|P_{i1}\exp(\alpha_i+\beta)) \right], \qquad (1)$$

- **random effects model**:

$$\prod_i \int [Po(x_{i0}|P_{i0}\exp(\alpha_i))$$

$$\times Po(x_{i1}|P_{i1}\exp(\alpha_i+\beta))]\phi(\alpha_i|\alpha,\sigma_\alpha^2)d\alpha_i.$$

Poisson regression with random study effect

likelihood in the example of the **heterogeneity model**

- **random effects model**:

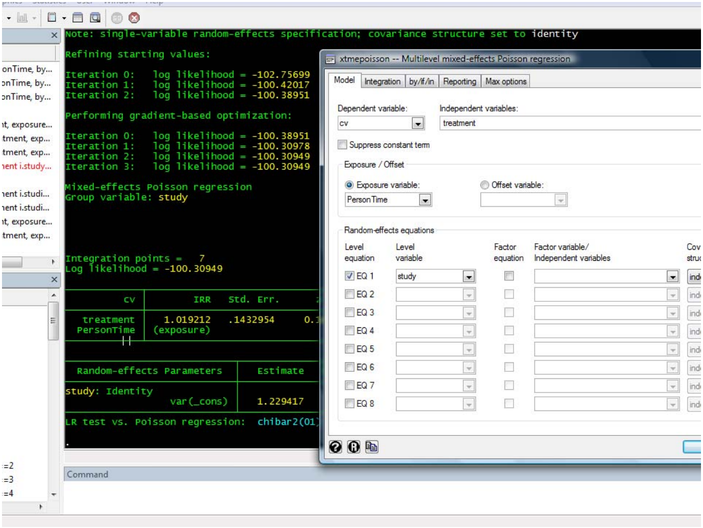
$$\prod_i \int Po(x_{i0}|P_{i0}\exp(\alpha_i))\times$$

$$\left[\int Po(x_{i1}|P_{i1}\exp(\alpha_i+\beta_i))\phi(\beta_i|0,\sigma_\beta^2)d\beta_i\right]\phi(\alpha_i|\alpha,\sigma_\alpha^2)d\alpha_i.$$

Poisson regression with random study effect

integrals have no closed form solution:

- Laplace approximation
- Gauss-Hermite quadrature


Note: single-variable random-effects specification; covariance structure set to identity
Refining starting values:
Iteration 0: log likelihood = -102.75699
Iteration 1: log likelihood = -100.42017
Iteration 2: log likelihood = -100.38951
Performing gradient-based optimization:
Iteration 0: log likelihood = -100.38951
Iteration 1: log likelihood = -100.30978
Iteration 2: log likelihood = -100.30949
Iteration 3: log likelihood = -100.30949
Mixed-effects Poisson regression
Group variable: study
Integration points = 7
Log likelihood = -100.30949
cv IRR Std. Err.
treatment 1.019212 .1432954
PersonTime (exposure)
Random-effects Parameters Estimate
study: Identity
var(_cons) 1.229417
LR test vs. Poisson regression: chibar2(01)
Command
xtmepoisson -- Multilevel mixed-effects Poisson regression
Model
Integration
by/if/in
Reporting
Max options
Dependent variable:
cv
Independent variables:
treatment
Suppress constant term
Exposure / Offset
Exposure variable:
PersonTime
Offset variable:
Random-effects equations
Level equation
Level variable
Factor equation
Factor variable/ Independent variables
EQ 1
study
EQ 2
EQ 3
EQ 4
EQ 5
EQ 6
EQ 7
EQ 8

Testing homogeneity with the likelihood ratio test

- **random effects model** M_1:

$$L_1 = \prod_i \int Po(x_{i0}|P_{i0}\exp(\alpha_i))Po(x_{i1}|P_{i1}\exp(\alpha_i+\beta))\phi(\alpha_i|0,\sigma_\alpha^2)d\alpha_i$$

- **NO random effects** M_0:

$$L_0 = \prod_i [Po(x_{i0}|P_{i0}\exp(\alpha)) \times Po(x_{i1}|P_{i1}\exp(\alpha+\beta))]$$

likelihood ratio

$$\log\lambda = 2\log L_1/L_0$$

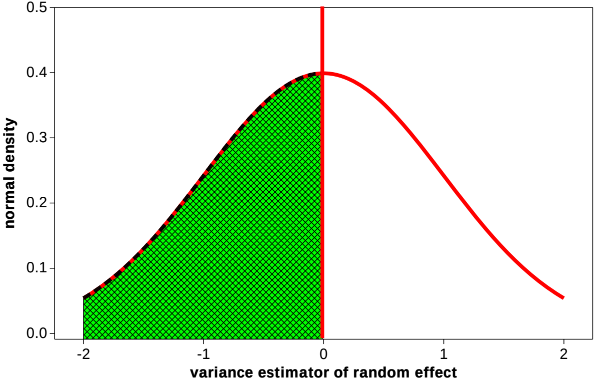
is χ^2 with 1 df under the M_0

Testing homogeneity with the likelihood ratio test

- variance estimates cannot be negative :

$$\hat{\sigma}_{\alpha}^{2} \geq 0$$

- hence: distribution of $\hat{\sigma}_{\alpha}^{2}$ cannot be normal


0.5
0.4
0.3
0.2
0.1
0.0
normal density
-2
-1
0
1
2
variance estimator of random effect

Testing homogeneity with the likelihood ratio test

- asymptotic distribution:

$$P(\hat{\sigma}^2_\alpha / s.e.(\hat{\sigma}^2_\alpha) < x) = 0.5 + 0.5\Phi(x)$$

  where $\Phi(x)$ is the CDF of a standard normal distribution
- similarly for the asymptotic distribution of the likelihood ratio

$$\log \lambda = 2 \log L_1/L_0 \sim 0.5 + 0.5\chi^2_{(1)}$$

- in practice, conventionally computed P-values need only be divided by 2 since:

$$P(\log \lambda > \log \lambda_{\text{obs}}) = 1 - [0.5 + 0.5\{1 - P(\log \lambda > \log \lambda_{\text{obs,old}})\}]$$

$$= 0.5 P(\log \lambda > \log \lambda_{\text{obs,old}})$$

Table: Poisson regression estimates in the rare events meta–analysis of Rosiglitazone; Log-L stands for the maximised log-likelihood

Poisson model	estimate	confidence interval	Log-L
MI			
treatment	1.2561	0.9991 – 1.5793	-174.2054
treatment	1.2634	1.0006 – 1.5952	-137.9558
σ_α^2	0.6346		
treatment	1.2634	1.0006 – 1.5952	-137.9558
σ_α^2	0.6346		
σ_β^2	0.		

Table: Poisson regression estimates in the rare events meta–analysis of Rosiglitazone; Log-L stands for the maximised log-likelihood

Poisson model	estimate	confidence interval	Log-L
CV			
treatment	1.1281	0.8579 – 1.4835	-172.0216
treatment	1.0192	0.7737 – 1.3426	-100.3095
σ_α^2	1.2294		
treatment	1.0192	0.7737 – 1.3426	-100.3095
σ_α^2	1.12294		
σ_β^2	0.		

model evaluation

- for model assessment we will use criteria that compromise between **model fit** and **model complexity**
- Akaike information criterion

$$AIC = -2 \log L + 2p$$

- Bayesian Information criterion

$$BIC = -2 \log L + p \log k$$

- where p is the number of parameters in the model
- and k is the number of trials in the meta-analysis
- we seek a model for which AIC and/or BIC are **small**

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sensitivity analysis:

how does the effect estimate of the risk ratio depend on the **exclusion/inclusion** of

- double-zero (DZ)
- single-zero (SZ)

studies?

Table: Poisson random effects regression estimates of the risk ratio: the effect of excluding double-zero (DZ) and single-zero (SZ) studies and none excluded (NONE); number of studies included is given in brackets in the first column

excluding (k)	RR	SE	Z	P-value	95% CI
MI					
NONE(56)	1.2633	0.1503	1.96	0.049	1.0006 – 1.5952
DZ(41)	1.2634	0.1503	1.97	0.049	1.0008 – 1.5955
SZ(15)	1.2101	0.1512	1.53	0.127	0.9473 – 1.5458
CV					
NONE(56)	1.0193	0.1433	0.14	0.892	0.7738 – 1.3426
DZ(27)	1.0246	0.1441	0.17	0.863	0.7778 – 1.3497
SZ(8)	0.9427	0.1395	-0.40	0.690	0.7054 – 1.2599

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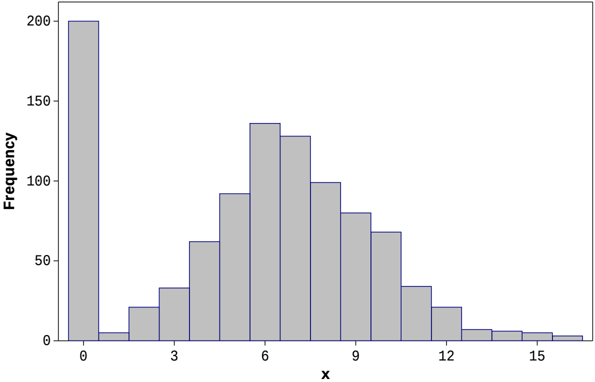
Zero-inflation models

count data with many zeros lead to the question:

- is there an excess of zero counts relative to the Poisson model
- an excess in zero-counts is called **zero-inflation**

$$Pr[X = 0] = \pi + (1 - \pi)Po(0|\mu) \quad (2)$$

$$Pr[X = x] = (1 - \pi)Po(x|\mu) \text{ for } x = 1, 2, \ldots \quad (3)$$

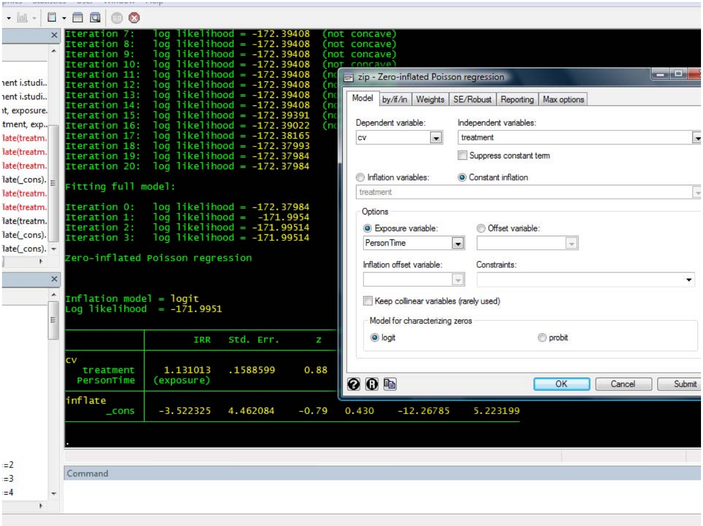

Frequency
x
0
50
100
150
200
0
3
6
9
12
15

Zero-inflation models

Lambert (1992) extended the simple ZIP-model to covariates:

$$\log \mu_{ij} = \log P_{ij} + \alpha + \beta \times j \tag{4}$$

$$\text{logit } \pi_{ij} = \log \frac{\pi_{ij}}{1-\pi_{ij}} = \alpha' + \beta' \times j. \tag{5}$$


Iteration 7: log likelihood = -172.39408 (not concave)
Iteration 8: log likelihood = -172.39408 (not concave)
Iteration 9: log likelihood = -172.39408 (not concave)
Iteration 10: log likelihood = -172.39408
Iteration 11: log likelihood = -172.39408
Iteration 12: log likelihood = -172.39408
Iteration 13: log likelihood = -172.39408
Iteration 14: log likelihood = -172.39408
Iteration 15: log likelihood = -172.39391
Iteration 16: log likelihood = -172.39022
Iteration 17: log likelihood = -172.38165
Iteration 18: log likelihood = -172.37993
Iteration 19: log likelihood = -172.37984
Iteration 20: log likelihood = -172.37984
Fitting full model:
Iteration 0: log likelihood = -172.37984
Iteration 1: log likelihood = -171.9954
Iteration 2: log likelihood = -171.99514
Iteration 3: log likelihood = -171.99514
Zero-inflated Poisson regression
Inflation model = logit
Log likelihood = -171.9951
IRR Std. Err. z
cv
treatment 1.131013 .1588599 0.88
PersonTime (exposure)
inflate
_cons -3.522325 4.462084 -0.79 0.430 -12.26785 5.223199
zip - Zero-inflated Poisson regression
Model
by/if/in
Weights
SE/Robust
Reporting
Max options
Dependent variable:
cv
Independent variables:
treatment
Suppress constant term
Inflation variables:
Constant inflation
treatment
Options
Exposure variable:
PersonTime
Offset variable:
Inflation offset variable:
Constraints:
Keep collinear variables (rarely used)
Model for characterizing zeros
logit
probit
OK
Cancel
Submit
Command

Contents

Logistic regression

let Y_{ij} denote the binary outcome for an event ($Y_{ij} = 1$) in study i and treatment arm j ($j = 0, 1$)

- $$\pi_{ij} = P(Y_{ij} = 1) \text{ probability of an event}$$
- logistic transformation
$$\log \frac{\pi_{ij}}{1 - \pi_{ij}} = \alpha + \beta \times j$$
- so that β is the **log-odds ratio**

Logistic regression model

- each trial arm within each study contributes a binomial likelihood
- $$\binom{n_{ij}}{x_{ij}} \pi_{ij}^{x_{ij}} (1-\pi_{ij})^{n_{ij}-x_{ij}}$$
- where
$$\log \frac{\pi_{ij}}{1-\pi_{ij}} = \alpha + \beta \times j$$

Logistic likelihood

- $$L = \prod_i \prod_j \binom{n_{ij}}{x_{ij}} \pi_{ij}^{x_{ij}} (1 - \pi_{ij})^{n_{ij} - x_{ij}}$$
- where
$$\log \frac{\pi_{ij}}{1 - \pi_{ij}} = \alpha + \beta \times j$$

Logistic regression with random intercept effect for study

- $$\log \frac{\pi_{ij}}{1 - \pi_{ij}} = \alpha_i + \beta \times j$$
- where $\alpha_i \sim N(\alpha, \sigma_\alpha^2)$ is a random intercept effect

Mixed Logistic Likelihood

- $$L = \prod_i \int_{\alpha_i} \prod_j \binom{n_{ij}}{x_{ij}} \pi_{ij}^{x_{ij}} (1 - \pi_{ij})^{n_{ij} - x_{ij}} \phi(\alpha_i) d\alpha_i$$
- where $\phi(\alpha_i)$ is a normal density with mean α and variance σ_α^2
- and
$$\log \frac{\pi_{ij}}{1 - \pi_{ij}} = \alpha_i + \beta \times j$$

Logistic regression with random intercept effect for study

- $$\log \frac{\pi_{ij}}{1-\pi_{ij}} = \alpha_i + \beta_i \times j$$
- where $\alpha_i \sim N(\alpha, \sigma_\alpha^2)$ is a random intercept effect
- and $\beta_i \sim N(\beta, \sigma_\beta^2)$ is a random slope (treatment) effect

Mixed Logistic Likelihood

- $$L = \prod_i \int_{\alpha_i} \left(\int_{\beta_i} \prod_j \binom{n_{ij}}{x_{ij}} \pi_{ij}^{x_{ij}} (1-\pi_{ij})^{n_{ij}-x_{ij}} \phi(\beta_i) d\beta_i \right) \phi(\alpha_i) d\alpha_i$$
- where $\phi(\alpha_i)$ is a normal density with mean α and variance σ_α^2
- where $\phi(\beta_i)$ is a normal density with mean β and variance σ_β^2
- and
$$\log \frac{\pi_{ij}}{1-\pi_{ij}} = \alpha_i + \beta_i \times j$$

```
Mixed-effects logistic regression               Number of obs      =        36
Binomial variable:            n
Group variable:         study_02                Number of groups   =        18

                                                Obs per group: min =         2
                                                               avg =       2.0
                                                               max =         2

Integration method: mvaghermite                 Integration points =         7

                                                Wald chi2(1)       =     16.16
Log likelihood = -78.215149                     Prob > chi2        =    0.0001
```

x	Odds Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Treat_bin	.2458528	.0857953	-4.02	0.000	.1240598	.4872135
_cons	.0310596	.0077302	-13.95	0.000	.0190698	.0505877
study_02						
var(Treat_~n)	.6187426	.5829695			.0976161	3.921919
var(_cons)	.7717062	.3642633			.3059603	1.946431

LR test vs. logistic regression: chi2(2) = 50.11 Prob > chi2 = 0.0000

Table: Logistic regression estimates in the rare evidence meta–analysis of CRBSI; Log-L stands for the maximised log-likelihood

logistic model	estimate	confidence interval	Log-L
treatment	0.30	0.20 – 0.47	-103.27
treatment	0.29	0.19 – 0.46	-79.70
σ_α^2	0.74	0.30 – 1.87	
treatment	0.25	0.12 – 0.49	-78.22
σ_α^2	0.77	0.31 – 1.95	
σ_β^2	0.62	0.10 – 3.92	

Contents

recall:

let $RR = \mu_1/\mu_0$ and $X_i = X_{i1} + X_{i0}$

- in study i, for treatment

$$E(X_{i1}) = \mu_1 P_{i1}$$

for control

$$E(X_{i0}) = \mu_0 P_{i0}$$

it follows:

- then $E(X_{i1} + X_{i0}) = \mu_1 P_{i1} + \mu_0 P_{i0}$ so that

$$E(X_{i1}|X_i) = X_i \frac{\mu_1 P_{i1}}{\mu_1 P_{i1} + \mu_0 P_{i0}} = X_i \frac{RR \frac{P_{i1}}{P_{i0}}}{1 + RR \frac{P_{i1}}{P_{i0}}}$$

depends only on RR, the parameter of interest

Table: Layout for conditional logistic regression in study i

	treatment	control	margin
events	X_{i1}	X_{i0}	X_i
person time	P_{i1}	P_{i0}	P_i

- $$X_{i1}|X_i \sim Bin(q_i, X_i) \text{ with } q_i = \frac{\mu_1 P_{i1}}{\mu_1 P_{i1} + \mu_0 P_{i0}} = \frac{RR\frac{P_{i1}}{P_{i0}}}{1 + RR\frac{P_{i1}}{P_{i0}}}$$

furthermore:

- let $RR = \exp(\beta)$

$$q_i = \frac{RR\frac{P_{i1}}{P_{i0}}}{1 + RR\frac{P_{i1}}{P_{i0}}}$$

-

$$= \frac{\exp[\beta + \log(\frac{P_{i1}}{P_{i0}})]}{1 + \exp[\beta + \log(\frac{P_{i1}}{P_{i0}})]}$$

$$\frac{q_i}{1 - q_i} = \exp[\beta + \log(\frac{P_{i1}}{P_{i0}})]$$

$$\log\left(\frac{q_i}{1 - q_i}\right) = \beta + \log(\frac{P_{i1}}{P_{i0}})$$

hence:

- $$\log\left(\frac{q_i}{1-q_i}\right) = \beta + \log\left(\frac{P_{i1}}{P_{i0}}\right)$$
- we find $\widehat{RR}$ as **logistic regression with intercept only and offset** $\log(\frac{P_{i1}}{P_{i0}})$
- note that β is a **log-risk ratio**

Table: Meta–analysis on rare evidence data on the effect of anti-infective-treated catheter in compariosn to standard catheter; CRBSI (X_{i1}, X_{i0}) refers to catheter-related bloodstream infection events, n_{i1}, n_{i0} is the size of the respective study arm

	control arm		treatment arm		conditional	
study ID	X_{i0}	n_{i0}	X_{i1}	n_{i1}	X_i	n_{i1}/n_{i0}
1	3	117	0	116	3	116/117
2	3	35	1	44	4	44/35
3	9	195	2	208	11	208/195
4	7	136	0	130	7	130/136
5	6	157	5	151	11	151/157
6	4	139	1	98	5	98/139
7	3	177	1	174	4	174/177
8	2	39	1	74	3	74/39

```
. melogit xt, offset(log_ratio) binomial(xsum) or

Iteration 0:   log likelihood = -26.454133
Iteration 1:   log likelihood = -26.199518
Iteration 2:   log likelihood = -26.199183
Iteration 3:   log likelihood = -26.199183

Logistic regression                             Number of obs     =         18
Binomial variable:          xsum

                                                Wald chi2(0)      =          .
Log likelihood = -26.199183                     Prob > chi2       =          .
------------------------------------------------------------------------------
          xt | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       _cons |   .3072359   .0678268    -5.35   0.000     .1993228    .4735732
   log_ratio |          1  (offset)
------------------------------------------------------------------------------
```

can be easily extend to **random effects model**

$$\log\left(\frac{q_i}{1-q_i}\right) = \beta_i + \log(\frac{P_{i1}}{P_{i0}})$$

with $\beta_i \sim N(\beta, \sigma^2_\beta)$

```
Mixed-effects logistic regression               Number of obs      =        18
Binomial variable:          xsum
Group variable:      study_short                Number of groups   =        18

                                                Obs per group: min =         1
                                                               avg =       1.0
                                                               max =         1

Integration method: mvaghermite                 Integration points =         7

                                                Wald chi2(0)       =         .
Log likelihood = -24.794429                     Prob > chi2        =         .
------------------------------------------------------------------------------
          xt | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       _cons |   .2718073   .0920478    -3.85   0.000     .1399591     .527863
   log_ratio |          1  (offset)
-------------+----------------------------------------------------------------
study_short  |
   var(_cons)|   .6007426   .5915841                      .0871894    4.139168
------------------------------------------------------------------------------
LR test vs. logistic regression: chibar2(01) =      2.81 Prob>=chibar2 = 0.0469
```