Evidence Synthesis / Meta-Analysis

Session 2, Lecture 4: Meta-Analysis with Binary Outcome

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Overview Lecture 4

- Standard methods of meta-analysis with binary outcome
  - Fixed effect methods (Inverse variance, Mantel-Haenszel, Peto)
  - Random effects method (Inverse variance)
- Peculiarities of sparse binary data
- Generalised linear mixed model
  - Conditional model, exact likelihood (Hypergeometric-Normal model)
  - Conditional model, approximate likelihood (Binomial-Normal model)

Example: Aggressive Non-Hodgkin Lymphoma

Greb et al. (2008), Cochrane Database Syst Rev **1**, CD004024:

- Cochrane Review including 15 randomised controlled trials (RCTs)
- Adult patients with aggressive non-Hodgkin lymphoma
- First line treatment with high-dose chemotherapy (HDCT) versus conventional chemotherapy
- Primary outcome:
  Overall survival (14 RCTs, 2444 patients)
- **Secondary outcome:**
  Complete response (14 RCTs, 2126 patients)

Aggressive Non-Hodgkin Lymphoma – Complete Response

Study	HDCT		Control	
	Events	Total	Events	Total
De Souza	14	28	10	26
Gianni	46	48	35	50
Gisselbrecht	119	189	116	181
Intragumtornchai	10	23	9	25
Kaiser	110	158	97	154
Kluin-Nelemans	67	98	56	96
Martelli 1996	3	22	4	27
Martelli 2003	57	75	51	75
Milpied	74	98	56	99
Rodriguez 2003	39	55	30	53
Santini 1998	46	63	34	61
Santini-2	80	117	71	106
Verdonck	25	38	26	35
Vitolo	35	60	46	66

Milpied Study – Complete Response (CR)

	CR		no CR			
HDCT	74	(a)	24	(b)	98	$(a+b=n_T)$
Control	56	(c)	43	(d)	99	$(c+d=n_C)$
	130	$(a+c)$	67	$(b+d)$	197	(n)

Binary Data – Effect Measures

Let

- p_T: Experimental event probability $\hat{p}_T = a/(a+b)$
- p_C: Control event probability $\hat{p}_C = c/(c+d)$

Risk Ratio ϕ:

$$\phi = \frac{p_T}{p_C} \qquad \hat{\phi} = \frac{\hat{p}_T}{\hat{p}_C}$$

Odds Ratio ψ:

$$\psi = \frac{\left(\frac{p_T}{1-p_T}\right)}{\left(\frac{p_C}{1-p_C}\right)} = \phi \times \frac{1-p_C}{1-p_T} \qquad \hat{\psi} = \frac{a\,d}{b\,c} \tag{1}$$

Risk Difference η:

$$\eta = p_T - p_C \qquad \hat{\eta} = \hat{p}_T - \hat{p}_C$$

Binary Data – Effect Measures – R package **meta**

```
mil <- metabin(crHDCT, nHDCT, crControl, nControl,
               data = cr, subset = study == "Milpied",
               sm = "OR")
```

```
# Print odds ratio for Milpied study
round(exp(mil$TE), 2)

## [1] 2.37

# Print risk ratio
round(exp(update(mil, sm = "RR")$TE), 2)

## [1] 1.33

# Print risk difference
round(update(mil, sm = "RD")$TE, 2)

## [1] 0.19
```


Binary Data – Effect Measures – R package **metafor**

```
# Calls R function rma.uni (Random effects Meta-Analysis - UNIvariate)
mil4 <- rma(ai = crHDCT, n1i = nHDCT, ci = crControl, n2i = nControl,
            data = cr, subset = study == "Milpied",
            measure = "OR")
```

```
round(exp(mil4$b), 2)

##          [,1]
## intrcpt 2.37

round(exp(update(mil4, measure = "RR")$b), 2)

##          [,1]
## intrcpt 1.33

round(update(mil4, measure = "RD")$b, 2)

##          [,1]
## intrcpt 0.19
```

Binary Effect Measures – Confidence Interval

Large sample variance estimates (Fleiss, 1993):

$$\begin{aligned}\widehat{\text{Var}}(\log\hat{\phi}) &= \frac{1}{a}+\frac{1}{c}-\frac{1}{a+b}-\frac{1}{c+d}\\ \widehat{\text{Var}}(\log\hat{\psi}) &= \frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d} \qquad (2)\\ \widehat{\text{Var}}(\hat{\eta}) &= \frac{a\,b}{(a+b)^3}+\frac{c\,d}{(c+d)^3}\end{aligned}$$

$(1-\alpha)$-confidence interval (on log scale for risk ratio and odds ratio):

$$\hat{\theta} \pm z_{1-\frac{\alpha}{2}}\,\text{S.E.}(\hat{\theta})$$

with standard error $\text{S.E.}(\hat{\theta}) = \sqrt{\widehat{\text{Var}}(\hat{\theta})}$.

Binary Effect Measures – Confidence Interval

Large sample variance estimates (Fleiss, 1993):

$$\begin{aligned}\widehat{\text{Var}}(\log\hat{\phi}) &= \frac{1}{a+0.5}+\frac{1}{c+0.5}-\frac{1}{a+b+0.5}-\frac{1}{c+d+0.5}\\ \widehat{\text{Var}}(\log\hat{\psi}) &= \frac{1}{a+0.5}+\frac{1}{b+0.5}+\frac{1}{c+0.5}+\frac{1}{d+0.5}\\ \widehat{\text{Var}}(\hat{\eta}) &= \frac{(a+0.5)\,(b+0.5)}{(a+b+1)^3}+\frac{(c+0.5)\,(d+0.5)}{(c+d+1)^3}\end{aligned}$$

Add 0.5 if any cell counts are zero (Gart and Zweifel, 1967; Pettigrew et al., 1986)

Default in **metabin** (argument `incr`) and **rma** (argument `add`)

Binary Effect Measures – Confidence Interval

```
# Print confidence interval for odds ratio (R package meta)
print(mil, digits = 2)

##    OR       95%-CI    z  p-value
##  2.37 [1.29; 4.35] 2.78   0.0055
##
## Details:
## - Inverse variance method
```

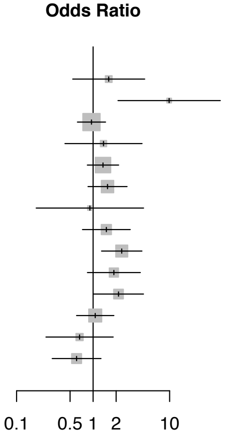
```
# Print confidence interval for log odds ratio (R package meta)
print(mil, digits = 2, backtransf = FALSE)

##  logOR       95%-CI    z  p-value
##   0.86 [0.25; 1.47] 2.78   0.0055
##
## Details:
## - Inverse variance method
```


Binary Effect Measures – Confidence Interval

```
print(mil4, digits = 2) # log odds ratio (R package metafor)

##
## Fixed-Effects Model (k = 1)
##
## Test for Heterogeneity:
## Q(df = 0) = 0.00, p-val = 1.00
##
## Model Results:
##
## estimate       se     zval     pval    ci.lb    ci.ub
##     0.86     0.31     2.78     <.01     0.25     1.47       **
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

print(predict(mil4, transf = exp), digits = 2) # odds ratio

##  pred ci.lb ci.ub
##  2.37  1.29  4.35
```

Forest Plot – CR

Study	Experimental Events	Experimental Total	Control Events	Control Total	OR	95%–CI
De Souza	14	28	10	26	1.60	[0.54; 4.73]
Gianni	46	48	35	50	9.86	[2.11; 45.96]
Gisselbrecht	119	189	116	181	0.95	[0.62; 1.45]
Intragumtornchai	10	23	9	25	1.37	[0.43; 4.36]
Kaiser	110	158	97	154	1.35	[0.84; 2.16]
Kluin–Nelemans	67	98	56	96	1.54	[0.86; 2.78]
Martelli	3	22	4	27	0.91	[0.18; 4.57]
Martelli 2003	57	75	51	75	1.49	[0.73; 3.06]
Milpied	74	98	56	99	2.37	[1.29; 4.35]
Rodriguez 2003	39	55	30	53	1.87	[0.84; 4.14]
Santini	46	63	34	61	2.15	[1.01; 4.56]
Santini–2	80	117	71	106	1.07	[0.61; 1.87]
Verdonck	25	38	26	35	0.67	[0.24; 1.83]
Vitolo	35	60	46	66	0.61	[0.29; 1.27]



Naive Pooling – Fictitious Example

		CR	no CR	$\hat{p}_T$	$\hat{p}_C$	$\widehat{RR}$ [95%-CI]
Study 1	HDCT	4	56	6.7%	7.3%	0.91 [0.30; 2.74]
	Control	11	139			
Study 2	HDCT	40	140	22.2%	24.0%	0.93 [0.53; 1.63]
	Control	12	38			
Study 1&2	HDCT	44	196	18.3%	11.5%	1.59 [1.00; 2.55]
	Control	23	177			
Appropriate meta-analysis						0.92 [0.56; 1.52]

Inverse Variance Method – Odds ratio – Definition

Overall odds ratio $\hat{\psi}_{IV}$ (Fleiss, 1993):

$$\hat{\psi}_{IV} = \exp\left(\frac{\sum_{k=1}^{K} w_k \cdot \log \hat{\psi}_k}{\sum_{k=1}^{K} w_k}\right) \tag{3}$$

- Study index: $k = 1, ..., K$
- Weights: $w_k = 1 \big/ \widehat{\text{Var}}(\log \hat{\psi}_k)$ ($\rightarrow$ fixed effect model)
- See formulae (1) and (2) for definition of $\hat{\psi}_k$ and $\widehat{\text{Var}}(\log \hat{\psi}_k)$
- Analogous for risk ratio as effect measure: $\log \hat{\phi}_k$
- For risk difference: $\hat{\eta}_k$ (without exp function in equation (3))

Meta-Analysis of CR – Inverse Variance Method

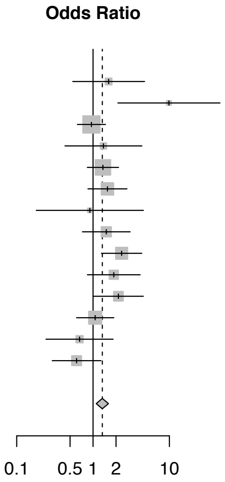
```
m <- metabin(crHDCT, nHDCT, crControl, nControl,
             data = cr, studlab = study,
             sm = "OR", method = "Inverse", comb.random = FALSE)
summary(m)

## Number of studies combined: k=14
##
##                         OR           95%-CI      z p-value
## Fixed effect model 1.3228 [1.0999; 1.5909] 2.9713   0.003
##
## Quantifying heterogeneity:
## tau^2 = 0.0897; H = 1.3 [1; 1.78]; I^2 = 41% [0%; 68.6%]
##
## Test of heterogeneity:
##      Q d.f.  p-value
##  22.03   13   0.0549
##
## Details on meta-analytical method:
## - Inverse variance method
```

Meta-Analysis of CR – Inverse Variance Method

```
m4 <- rma(ai = crHDCT, n1i = nHDCT, ci = crControl, n2i = nControl,
          data = cr, measure = "OR", method = "FE")

m4

##
## Fixed-Effects Model (k = 14)
##
## Test for Heterogeneity:
## Q(df = 13) = 22.0277, p-val = 0.0549
##
## Model Results:
##
## estimate      se    zval    pval   ci.lb   ci.ub
##   0.2798  0.0942  2.9713  0.0030  0.0952  0.4643      **
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```


Forest Plot – CR – Inverse Variance Method

Study	Experimental Events	Experimental Total	Control Events	Control Total	OR	95%–CI	W(fixed)
De Souza	14	28	10	26	1.60	[0.54; 4.73]	2.9%
Gianni	46	48	35	50	9.86	[2.11; 45.96]	1.4%
Gisselbrecht	119	189	116	181	0.95	[0.62; 1.45]	19.0%
Intragumtornchai	10	23	9	25	1.37	[0.43; 4.36]	2.5%
Kaiser	110	158	97	154	1.35	[0.84; 2.16]	15.3%
Kluin–Nelemans	67	98	56	96	1.54	[0.86; 2.78]	9.8%
Martelli	3	22	4	27	0.91	[0.18; 4.57]	1.3%
Martelli 2003	57	75	51	75	1.49	[0.73; 3.06]	6.6%
Milpied	74	98	56	99	2.37	[1.29; 4.35]	9.2%
Rodriguez 2003	39	55	30	53	1.87	[0.84; 4.14]	5.4%
Santini	46	63	34	61	2.15	[1.01; 4.56]	6.0%
Santini–2	80	117	71	106	1.07	[0.61; 1.87]	10.8%
Verdonck	25	38	26	35	0.67	[0.24; 1.83]	3.3%
Vitolo	35	60	46	66	0.61	[0.29; 1.27]	6.3%
IV estimate		**1072**		**1054**	**1.32**	**[1.10; 1.59]**	**100%**



Mantel-Haenszel Method – Odds ratio – Definition

Mantel and Haenszel (1959), JNCI:

- Estimator for common odds ratio in stratified case-control study
- Can be used in meta-analysis of RCTs
- Fixed effect method

Mantel-Haenszel odds ratio $\hat{\psi}_{MH}$:

$$\hat{\psi}_{MH} = \frac{\sum_{k=1}^{k} w_k \cdot \hat{\psi}_k}{\sum_{k=1}^{k} w_k} \qquad (4)$$

- Weights: $w_k = \frac{b_k c_k}{n_k}$

Meta-Analysis of CR – Mantel-Haenszel Method

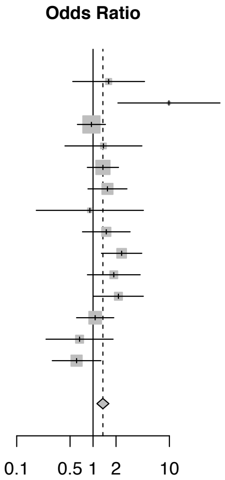
```
m.mh <- update(m, method = "MH")
summary(m.mh)

## Number of studies combined: k=14
##
##                         OR           95%-CI      z  p-value
## Fixed effect model 1.3459 [1.1226; 1.6137] 3.2093   0.0013
##
## Quantifying heterogeneity:
## tau^2 = 0.0897; H = 1.3 [1; 1.78]; I^2 = 41% [0%; 68.6%]
##
## Test of heterogeneity:
##      Q d.f.  p-value
##  22.03   13   0.0549
##
## Details on meta-analytical method:
## - Mantel-Haenszel method
```

Meta-Analysis of CR – Mantel-Haenszel Method

```
rma.mh(ai = crHDCT, n1i = nHDCT, ci = crControl, n2i = nControl,
       data = cr, measure = "OR")

##
## Fixed-Effects Model (k = 14)
##
## Test for Heterogeneity:
## Q(df = 13) = 22.0615, p-val = 0.0544
##
## Model Results (log scale):
##
## estimate      se     zval     pval    ci.lb    ci.ub
##   0.2971  0.0926   3.2093   0.0013   0.1157   0.4785
##
## Model Results (OR scale):
##
## estimate   ci.lb   ci.ub
##   1.3459  1.1226  1.6137
##
## Cochran-Mantel-Haenszel Test:    CMH = 10.0612, df = 1,  p-val = 0.0015
```


Forest Plot – CR – Mantel-Haenszel Method

Study	Experimental Events	Experimental Total	Control Events	Control Total	OR	95%–CI	W(fixed)
De Souza	14	28	10	26	1.60	[0.54; 4.73]	2.6%
Gianni	46	48	35	50	9.86	[2.11; 45.96]	0.7%
Gisselbrecht	119	189	116	181	0.95	[0.62; 1.45]	21.8%
Intragumtornchai	10	23	9	25	1.37	[0.43; 4.36]	2.4%
Kaiser	110	158	97	154	1.35	[0.84; 2.16]	14.8%
Kluin–Nelemans	67	98	56	96	1.54	[0.86; 2.78]	8.9%
Martelli	3	22	4	27	0.91	[0.18; 4.57]	1.5%
Martelli 2003	57	75	51	75	1.49	[0.73; 3.06]	6.1%
Milpied	74	98	56	99	2.37	[1.29; 4.35]	6.8%
Rodriguez 2003	39	55	30	53	1.87	[0.84; 4.14]	4.4%
Santini	46	63	34	61	2.15	[1.01; 4.56]	4.6%
Santini–2	80	117	71	106	1.07	[0.61; 1.87]	11.7%
Verdonck	25	38	26	35	0.67	[0.24; 1.83]	4.6%
Vitolo	35	60	46	66	0.61	[0.29; 1.27]	9.1%
MH estimate		**1072**		**1054**	**1.35**	**[1.12; 1.61]**	**100%**



Peto Odds Ratio (Yusuf et al., 1985)

Peto Odds Ratio ψ^*:

$$\hat{\psi}^* = \exp\left(\frac{a - \mathrm{E}(a|\ldots;\psi = 1)}{\mathrm{Var}(a|\ldots;\psi = 1)}\right) \tag{5}$$

with

- Four fixed marginal totals: '...'
- Expected cell count:

$$\mathrm{E}(a|\ldots;\psi = 1) = \frac{(a+b)(a+c)}{n}$$

- Hypergeometric variance of cell count a:

$$\mathrm{Var}(a|\ldots;\psi = 1) = (a+b)(c+d)(a+c)(b+d)/(n^2(n-1)) \tag{6}$$

Peto Method – Definition

Yusuf et al. (1985):

- Variant of the inverse variance method using Peto odds ratio and its variance
  → Dedicated method for odds ratio as summary measure
- Fixed effect method

Overall Peto odds ratio $\hat{\psi}_{Peto}$:

$$\hat{\psi}_{Peto} = \exp\left(\frac{\sum_{i=1}^{k} w_i^* \cdot \log \hat{\psi}_i^*}{\sum_{i=1}^{k} w_i^*}\right) \tag{7}$$

- Weights: $w_i^* = 1/\widehat{\mathrm{Var}}(\log \hat{\psi}_i^*)$
- See formulae (5) and (6) for definition of $\hat{\psi}_i^*$ and $\widehat{\mathrm{Var}}(\log \hat{\psi}_i^*) = 1\,/\mathrm{Var}\,(a|\ldots;\psi = 1)$

Example: Aggressive Non-Hodgkin Lymphoma

Effect measure	Estimate	95%-CI
Risk ratio $\hat{\psi}_{IV}$	1.1157	[1.0493; 1.1864]
Risk ratio $\hat{\psi}_{MH}$	1.1076	[1.0404; 1.1791]
Odds ratio $\hat{\phi}_{IV}$	1.3228	[1.0999; 1.5909]
Odds ratio $\hat{\phi}_{MH}$	1.3459	[1.1226; 1.6137]
Odds ratio $\hat{\phi}_{Peto}$	1.3462	[1.1233; 1.6134]
Risk difference $\hat{\eta}_{IV}$	0.0715	[0.0325; 0.1105]
Risk difference $\hat{\eta}_{MH}$	0.0656	[0.0261; 0.1051]

Peto method:

- R function `metabin`, argument `method = "Peto"`
- R function `rma.peto`

Fixed Effect Model – Comparison of Methods

Availability of methods:

Method	OR	RR	RD	other
Inverse Variance	×	×	×	×
Mantel-Haenszel	×	×	×	–
Peto	×	–	–	–

Properties for binary outcomes:

- Inverse variance method performs poor in meta-analyses with small studies
- Peto method performs poor in unbalanced designs and nearly balanced designs if odds ratio differs substantially from 1.00 (Greenland and Salvan, 1990)
- Peto method performs well in meta-analysis with very sparse data (Bradburn et al., 2007)
- MH approach recommended as method of choice (Emerson, 1994)

Random Effects Method – Odds ratio – Definition

Random effects estimate $\hat{\psi}_{RE}$ (Fleiss, 1993):

$$\hat{\psi}_{RE} = \exp\left(\frac{\sum_{k=1}^{K} w_k^{\star} \cdot \log \hat{\psi}_k}{\sum_{k=1}^{K} w_k^{\star}}\right)$$

- Study index: $k = 1, ..., K$
- Weights: $w_k^{\star} = 1 \Big/ \left(\widehat{\text{Var}}(\log \hat{\psi}_k) + \hat{\tau}^2\right)$ $\quad$ (→ random effects model)
- See Session 1 for estimation of between-study variance τ^2
- Calculated in addition to fixed effect estimate by default in R function `metabin` (see arguments `comb.random` and `method.tau`)
- Default in R function `rma.uni` (see argument `method`)

Drawbacks of classic random effects model

- Fixed effect model:
  Inverse variance method inferior to Mantel-Haenszel and Peto method
- Fixed effect model often not reasonable
  → Random effects model (based on inverse variance method)
- Problems of inverse variance method (Stijnen et al., 2010):
  1. Variance estimate $\widehat{\text{Var}}(\log \hat{\psi}_k)$ assumed to be known (uncertainty not taken in account)
  2. Normal distribution assumption for $\log \hat{\psi}_k$ might not be justified
  3. **(!)** $\log \hat{\psi}_k$ and $\widehat{\text{Var}}(\log \hat{\psi}_k)$ are typically correlated (not taken into account)
  4. Additional difficulties in sparse binary data
- Stijnen et al. (2010): Use of generalised linear mixed models

Generalised Linear Mixed Models (GLMM)

Classic random effects model (Normal-Normal model):

$$\theta_k \sim N(\theta, \tau^2)$$

$$\hat{\theta}_k \sim N(\theta_k,\ \mathrm{Var}(\hat{\theta}_k))$$

GLLM – Hypergeometric-Normal model:

- Model for odds ratio as effect measure
- Conditional on total number of events

$$\theta_k \sim N(\theta, \tau^2)$$

$$\hat{\theta}_k \sim \text{Non-central Hypergeometric (with argument } \theta_k)$$

Generalised Linear Mixed Models (GLMM)

GLLM – Binomial-Normal model:

- Approximation to Hypergeometric-Normal model
- Applicable if total number of events is small relative to group sizes
- Number of events in experimental group a_{Tk} and control group c_{Tk}:

$$a_{Tk} \sim \mathrm{Binomial}(a_{Tk} + c_{Tk},\ p_k)$$

$$p_k = \frac{\exp(\log(n_{Tk}/n_{Ck}) + \theta_k)}{1 + \exp(\log(n_{Tk}/n_{Ck}) + \theta_k)}$$

with n_{Tk}, n_{Ck} number of patients in treatment groups

- Random intercept logistic regression model with offset $\log(n_{Tk}/n_{Ck})$

GLMM - Estimation - R package **metafor**

GLLM – Hypergeometric-Normal model:

```
glmm1 <- rma.glmm(ai = crHDCT, n1i = nHDCT,
                  ci = crControl, n2i = nControl,
                  data = cr, measure = "OR",
                  model = "CM.EL")
```

`model = "CM.EL"`: conditional model with exact likelihood

GLLM – Binomial-Normal model:

```
glmm2 <- update(glmm1, model = "CM.AL")
```

`model = "CM.AL"`: conditional model with approximate likelihood

GLMM - Results - Exact Model

```
glmm1

##
## Random-Effects Model (k = 14; tau^2 estimator: ML)
## Model Type: Conditional Model with Exact Likelihood
##
## tau^2 (estimated amount of total heterogeneity): 0.0791 (SE = 0.0910)
## tau (square root of estimated tau^2 value):      0.2812
## I^2 (total heterogeneity / total variability):   37.99%
## H^2 (total variability / sampling variability):  1.61
##
## Tests for Heterogeneity:
## Wld(df = 13) = 21.8322, p-val = 0.0580
## LRT(df = 13) = 24.8475, p-val = 0.0242
##
## Model Results:
##
## estimate      se    zval    pval   ci.lb   ci.ub
##   0.3312  0.1274  2.5998  0.0093  0.0815  0.5810      **
##
```

GLMM - Results - Approximate Model

```
glmm2

##
## Random-Effects Model (k = 14; tau^2 estimator: ML)
## Model Type: Conditional Model with Approximate Likelihood
##
## tau^2 (estimated amount of total heterogeneity): 0
## tau (square root of estimated tau^2 value):      0
## I^2 (total heterogeneity / total variability):   0.00%
## H^2 (total variability / sampling variability):  1.00
##
## Tests for Heterogeneity:
## Wld(df = 13) = 6.4477, p-val = 0.9283
## LRT(df = 13) = 6.4827, p-val = 0.9268
##
## Model Results:
##
## estimate       se     zval     pval    ci.lb    ci.ub
##   0.1022   0.0542   1.8850   0.0594  -0.0041   0.2085        .
##
```


Comparison of results

```
# Classic random effects model (Normal-Normal model)
predict(update(m4, method = "ML"), transf = exp)

##    pred  ci.lb  ci.ub  cr.lb  cr.ub
##  1.3550 1.0788 1.7019 0.8337 2.2023

# GLLM - exact model (Hypergeometric-Normal model)
predict(glmm1, transf = exp)

##    pred  ci.lb  ci.ub  cr.lb  cr.ub
##  1.3927 1.0849 1.7877 0.7604 2.5507

# GLLM - approximate model (Binomial-Normal model)
predict(glmm2, transf = exp)

##    pred  ci.lb  ci.ub  cr.lb  cr.ub
##  1.1076 0.9959 1.2319 0.9959 1.2319
```


Summary

Meta-analysis with binary outcome

- Fixed effect model
  - Well established methods long available
- Random effects model:
  - Generalised linear mixed model preferable over inverse variance method
  - Exact method (Hypergeometric-Normal model) typically computational feasible in meta-analysis setting
  - Disadvantage of GLMMs: no forest plot

References

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Mantel-Haenszel Method – Odds ratio – Confidence int.

Robins et al. (1986a,b):

$$\widehat{\text{Var}}(\log \hat{\psi}_{MH}) = \frac{\sum_{k=1}^{K} P_k R_k}{2\left(\sum_{k=1}^{K} R_k\right)^2} + \frac{\sum_{k=1}^{K} (P_k S_k + Q_k R_k)}{2 \sum_{k=1}^{K} R_k \sum_{k=1}^{K} S_k} + \frac{\sum_{k=1}^{K} Q_k S_k}{2\left(\sum_{k=1}^{K} S_k\right)^2}$$

with $P_k = \dfrac{a_k + d_k}{n_k}$, $Q_k = \dfrac{b_k + c_k}{n_k}$, $R_k = \dfrac{a_k\, d_k}{n_k}$, and $S_k = \dfrac{b_k\, c_k}{n_k}$

- Variance estimator robust both in sparse data and large strata models
- $(1 - \alpha)$-confidence interval:

$$\exp\left(\log \hat{\psi}_{MH} \;\pm\; z_{1-\frac{\alpha}{2}} \text{ S.E.}(\log \hat{\psi}_{MH})\right)$$

- Standard error $\text{S.E.}(\log \hat{\psi}_{MH}) = \sqrt{\widehat{\text{Var}}(\log \hat{\psi}_{MH})}$

Mantel-Haenszel Method – Risk ratio – Definition

Mantel-Haenszel risk ratio $\hat{\phi}_{MH}$:

$$\hat{\phi}_{MH} = \frac{\sum_{k=1}^{K} w_k \cdot \hat{\phi}_k}{\sum_{k=1}^{K} w_k}$$

- Weights: $w_k = \dfrac{(a_k + b_k)c_k}{n_k}$

Mantel-Haenszel Method – Risk ratio – Conf. int.

Greenland and Robins (1985):

$$\widehat{\text{Var}}(\log \hat{\phi}_{MH}) = \frac{\sum_{k=1}^{K} \dfrac{(a_k + b_k)(c_k + d_k)(a_k + c_k) - a_k c_k n_k}{n_k^2}}{\sum_{k=1}^{K} \dfrac{a_k(c_k + d_k)}{n_k} \sum_{k=1}^{K} \dfrac{c_k(a_k + b_k)}{n_k}}$$

- Robust variance estimator
- $(1 - \alpha)$-confidence interval:

$$\exp\left(\log \hat{\phi}_{MH} \;\pm\; z_{1-\frac{\alpha}{2}} \text{ S.E.}(\log \hat{\phi}_{MH})\right)$$

- Standard error $\text{S.E.}(\log \hat{\phi}_{MH}) = \sqrt{\widehat{\text{Var}}(\log \hat{\phi}_{MH})}$

Mantel-Haenszel Method – Risk difference – Definition

Mantel-Haenszel risk difference $\hat{\eta}_{MH}$:

$$\hat{\eta}_{MH} = \frac{\sum_{k=1}^{K} w_k \cdot \hat{\eta}_k}{\sum_{k=1}^{K} w_k}$$

- Weights: $w_k = \dfrac{(a_k + b_k)(c_k + d_k)}{n_k}$

Mantel-Haenszel Method – Risk difference – Conf. int.

Greenland and Robins (1985):

$$\widehat{\text{Var}}(\hat{\eta}_{MH}) = \frac{\displaystyle\sum_{k=1}^{K} \frac{(a_k b_k n_{Ck})^3 + (c_k d_k n_{Tk})^3}{(n_{Tk} n_{Ck}(n_{Tk} + n_{Ck}))^2}}{\left(\displaystyle\sum_{k=1}^{K} \frac{(a_k + b_k)(c_k + d_k)}{n_k}\right)^2} .$$

- Robust variance estimator
- $(1 - \alpha)$-confidence interval:

$$\hat{\eta}_{MH} \;\pm\; z_{1-\frac{\alpha}{2}} \text{ S.E.}(\hat{\eta}_{MH})$$

- Standard error $\text{S.E.}(\hat{\eta}_{MH}) = \sqrt{\widehat{\text{Var}}(\hat{\eta}_{MH})}$

Peto Method – Confidence interval

- Large sample variance estimate for logarithm of $\hat{\psi}_{Peto}$:

$$\widehat{\text{Var}}(\log \hat{\psi}_{Peto}) = \frac{1}{1/\sum_{k=1}^{K} \widehat{\text{Var}}(\log \hat{\psi}^*_k)}$$

- $(1 - \alpha)$-confidence interval:

$$\exp\left(\log \hat{\psi}_{Peto} \;\pm\; z_{1-\frac{\alpha}{2}} \text{ S.E.}(\log \hat{\psi}_{Peto})\right)$$

- Standard error $\text{S.E.}(\log \hat{\psi}_{Peto}) = \sqrt{\widehat{\text{Var}}(\log \hat{\psi}_{Peto})}$