

# 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)

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- ▶ 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

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Martelli 1996	3	22	4	27
Martelli 2003	57	75	51	75
<b>Milpied</b>	<b>74</b>	<b>98</b>	<b>56</b>	<b>99</b>
Rodriguez 2003	39	55	30	53
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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
- ▶  $p_C$ : Control event probability

$$\hat{p}_T = a/(a + b)$$

$$\hat{p}_C = c/(c + d)$$



# Binary Data – Effect Measures

Let

- ▶  $p_T$ : Experimental event probability
- ▶  $p_C$ : Control event probability

$$\hat{p}_T = a/(a + b)$$

$$\hat{p}_C = c/(c + d)$$

Risk Ratio  $\phi$ :

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

Odds Ratio  $\psi$ :

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

Risk Difference  $\eta$ :

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

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

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

# 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")
```

# 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):

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

# Binary Effect Measures – Confidence Interval

Large sample variance estimates (Fleiss, 1993):

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

$(1 - \alpha)$ -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):

$$\widehat{\text{Var}}(\log \hat{\phi}) = \frac{1}{a + 0.5} + \frac{1}{c + 0.5} - \frac{1}{a + b + 0.5} - \frac{1}{c + d + 0.5}$$

$$\widehat{\text{Var}}(\log \hat{\psi}) = \frac{1}{a + 0.5} + \frac{1}{b + 0.5} + \frac{1}{c + 0.5} + \frac{1}{d + 0.5}$$

$$\widehat{\text{Var}}(\hat{\eta}) = \frac{(a + 0.5)(b + 0.5)}{(a + b + 1)^3} + \frac{(c + 0.5)(d + 0.5)}{(c + d + 1)^3}$$

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
```

# Binary Effect Measures – Confidence Interval

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# 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

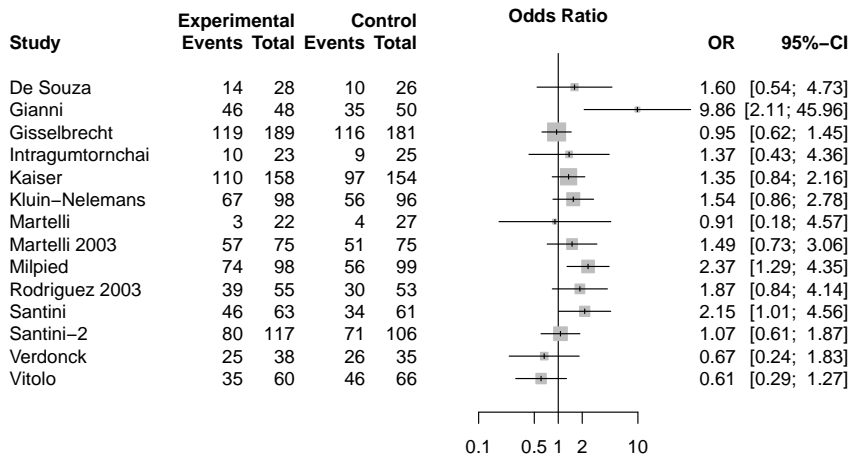
```
print(mil4, digits = 2) # log odds ratio (R package metafor)

##
## 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



# 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			

# 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			

# 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):

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

- ▶ Study index:  $k = 1, \dots, K$
- ▶ Weights:  $w_k = 1 / \widehat{\text{Var}}(\log \hat{\psi}_k)$  ( $\rightarrow$  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, nli = 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:
```

```
##
```

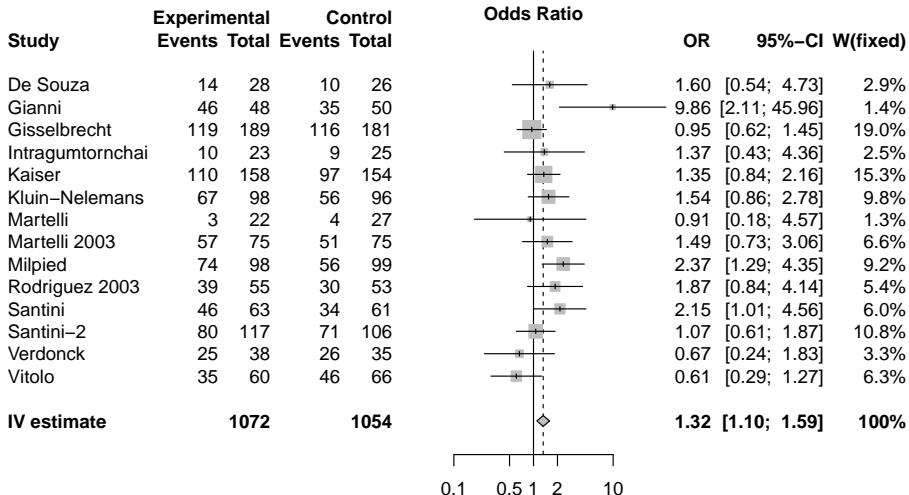
## estimate	se	zval	pval	ci.lb	ci.ub	
## 0.2798	0.0942	2.9713	0.0030	0.0952	0.4643	**

```
##
```

```
## ---
```

```
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

# Forest Plot – CR – Inverse Variance Method



# 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 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  $\hat{\psi}_{MH}$ :

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

- ▶ 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):
```

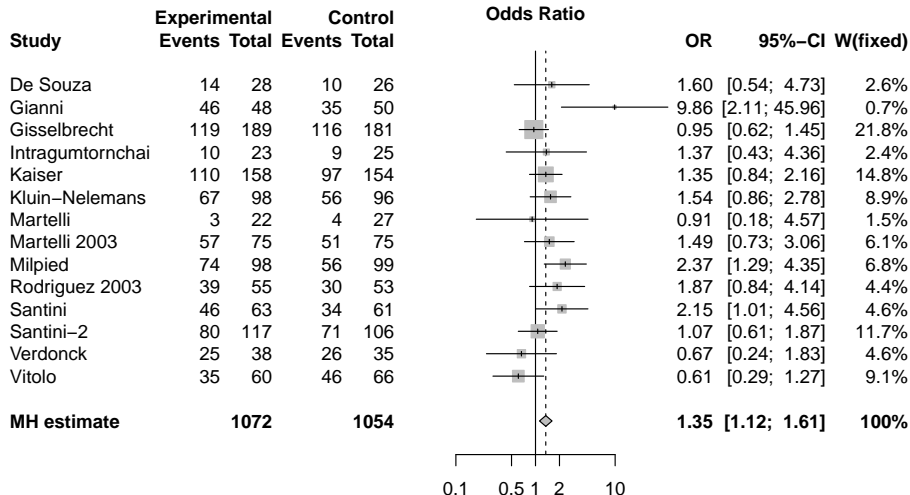
```
##
## estimate      se      zval      pval      ci.lb      ci.ub
##    0.2971    0.0926    3.2093    0.0013    0.1157    0.4785
```

```
##
## Model Results (OR scale):
```

```
##
## estimate      ci.lb      ci.ub
##    1.3459    1.1226    1.6137
```

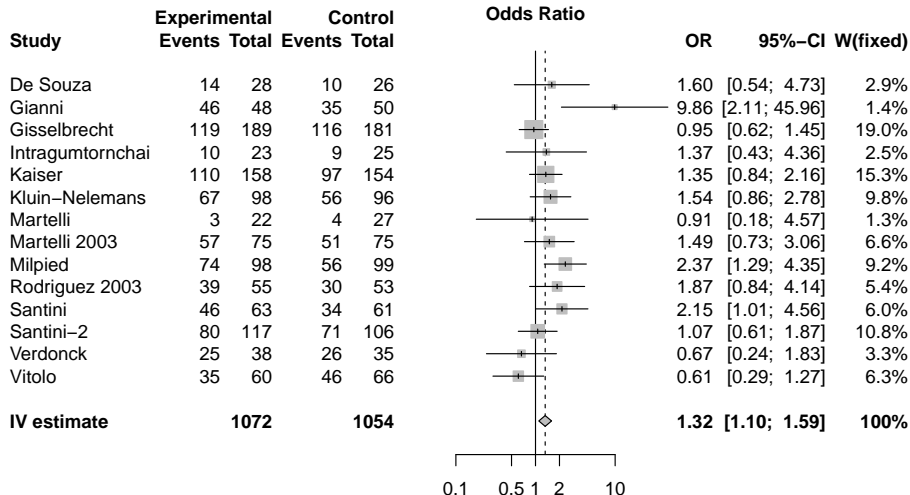
```
## Cochran-Mantel-Haenszel Test:      CMH = 10.0612, df = 1, p-val = 0.0015
```

# Forest Plot – CR – Mantel-Haenszel Method





# Forest Plot – CR – Inverse Variance Method



# Peto Odds Ratio (Yusuf et al., 1985)

Peto Odds Ratio  $\psi^*$ :

$$\hat{\psi}^* = \exp\left(\frac{a - E(a|\dots; \psi = 1)}{\text{Var}(a|\dots; \psi = 1)}\right) \quad (5)$$

with

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

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

- ▶ Hypergeometric variance of cell count  $a$ :

$$\text{Var}(a|\dots; \psi = 1) = (a+b)(c+d)(a+c)(b+d)/(n^2(n-1)) \quad (6)$$

# 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

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- ▶ 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  $\hat{\psi}_{Peto}$ :

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

- ▶ Weights:  $\mathbf{w}_i^* = 1 / \widehat{\text{Var}}(\log \hat{\psi}_i^*)$
- ▶ See formulae (5) and (6) for definition of  $\hat{\psi}_i^*$  and  $\widehat{\text{Var}}(\log \hat{\psi}_i^*) = 1 / \widehat{\text{Var}}(a | \dots; \psi = 1)$

## 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]

## Example: Aggressive Non-Hodgkin Lymphoma

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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]

# Example: Aggressive Non-Hodgkin Lymphoma

Effect measure	Estimate	95%-CI
Risk ratio $\hat{\psi}_{IV}$	1.1157	[1.0493; 1.1864]
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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]

# 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	×	–	–	–

# Fixed Effect Model – Comparison of Methods

Availability of methods:

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Peto	×	–	–	–

Properties for binary outcomes:

- ▶ Inverse variance method performs poor in meta-analyses with small studies

# Fixed Effect Model – Comparison of Methods

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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)

# Fixed Effect Model – Comparison of Methods

Availability of methods:

Method	OR	RR	RD	other
Inverse Variance	×	×	×	×
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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)

# 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):

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

- ▶ Study index:  $k = 1, \dots, K$
- ▶ Weights:  $w_k^* = 1 / \left( \widehat{\text{Var}}(\log \hat{\psi}_k) + \hat{\tau}^2 \right)$  ( $\rightarrow$  random effects model)
- ▶ See Session 1 for estimation of between-study variance  $\tau^2$

# Random Effects Method – Odds ratio – Definition

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

- ▶ Study index:  $k = 1, \dots, K$
- ▶ Weights:  $w_k^* = 1 / (\widehat{\text{Var}}(\log \hat{\psi}_k) + \hat{\tau}^2)$  ( $\rightarrow$  random effects model)
- ▶ See Session 1 for estimation of between-study variance  $\tau^2$
- ▶ 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)



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- ▶ 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

# 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  
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  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):

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

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

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GLLM – Hypergeometric-Normal model:

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

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

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

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# Generalised Linear Mixed Models (GLMM)

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- ▶ 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  $c_{Tk}$ :

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

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

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

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# Mantel-Haenszel Method – Odds ratio – Confidence int.

Robins et al. (1986a,b):

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

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

- Variance estimator robust both in sparse data and large strata models

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- ▶ 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:  $w_k = \frac{(a_k + b_k)c_k}{n_k}$

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

Greenland and Robins (1985):

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

- Robust variance estimator

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

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

Greenland and Robins (1985):

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

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- ▶ 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  $\hat{\psi}_{Peto}$ :

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

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