進階臨床試驗

Meta-analysis 統合分析實務

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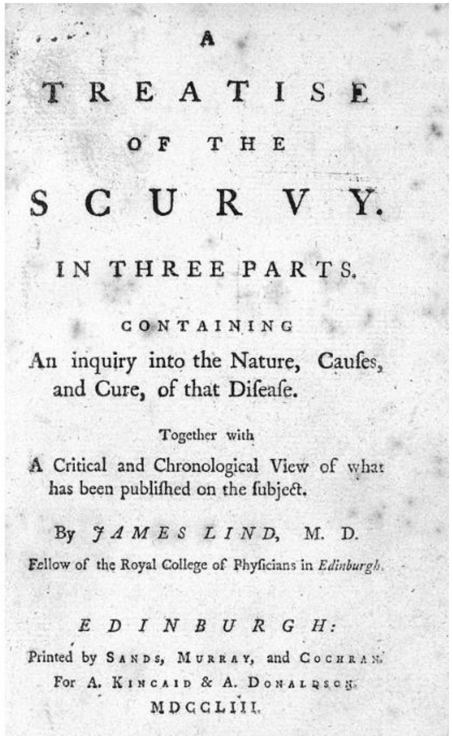
授課日期：112年7月12日

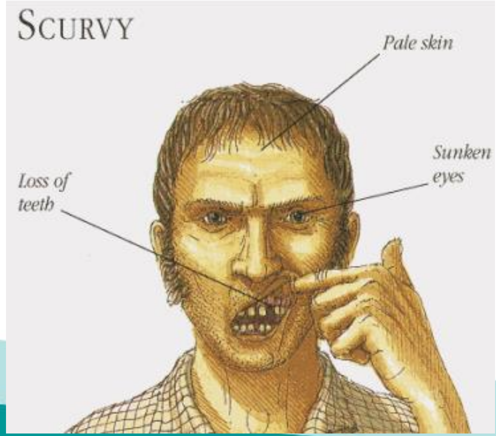
百年前的「臨床試驗」

- 詹姆斯·林德（James Lind，1716年 - 1794年 6月13日）
  - 英國皇家海軍外科醫生（1739 年 - 1748年），英格蘭衛生學的創始人
  - 發起利用柑桔類水果和新鮮蔬菜治療和預防壞血病
  - A treatise of the scurvy 壞血病論


A
TREATISE
OF THE
SCURVY.
IN THREE PARTS.
CONTAINING
An inquiry into the Nature, Caufes, and Cure, of that Difeafe.
Together with
A Critical and Chronological View of what has been publifhed on the fubject.
By JAMES LIND, M. D.
Fellow of the Royal College of Phyficians in *Edinburgh*.
EDINBURGH:
Printed by SANDS, MURRAY, and COCHRAN.
For A. KINCAID & A. DONALDSON.
MDCCLIII.

百年前的「臨床試驗」

- 百年前的歐洲，長期在海上航行的水手經常遭受壞血病的折磨，患者常常牙齦出血，甚至皮膚淤血和滲血，最後痛苦地死去，人們一直查不出病因。奇怪的是，只 要船隻靠岸，這種疾病很快就不治而癒了。
- 問題：水手們為什麼會得壞血病呢？
- 書中提到他在1747年在船上做了一個臨床試驗：
  - 出現壞血病的船員，大家都吃完全相同的食物
  - 唯一不同的是有些病人每天吃兩個橘子和一個檸檬，其他的人喝蘋果酒、稀硫酸、醋、海水。
- 實驗的結論：吃柑橘水果的兩人好轉，其它人病情依然。



TCVGH

偏差?

- 從現代的觀點看，林德的臨床試驗不夠嚴謹：
  - 病人的分派 Allocation
  - 每一組的病人數 Sample size
  - 臨床指標 Clinical indication / Outcome
  - 統計分析 Statistical analysis

TCVGH

"Bias" v.s. "Risk of Bias"

抽樣所造成測量值與真實值之間的差異，統計可處理：
通過多次測量或增加樣本數，獲得的均值儘量逼近

- Error – Systematic error v.s. Random error
- Bias – Systematic error
  - Deviation of study result from the truth，不能靠統計處理
  - 測量時即發生錯誤 (內因)：Information bias, recall bias, report bias
  - 外因：Confounding bias ~ Confounding factors
- Risk of Bias
  - In fact, we never know the truth
  - The results from a study might be unbiased despite methodological flaws
    - ✓ E.g., poor randomization or lost to follow up, but unbiased results

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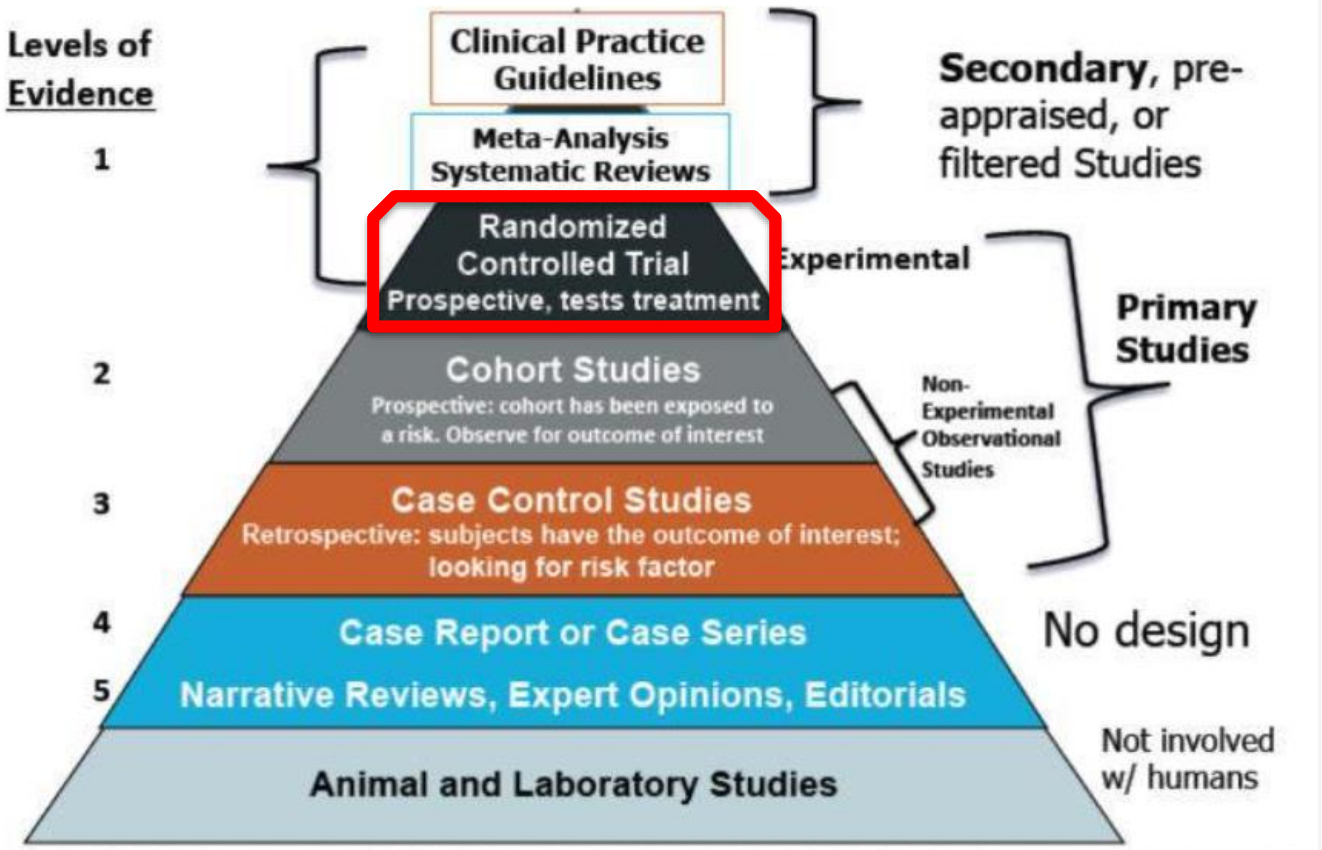
實證醫學的證據等級

- 文獻的證據等級與研究設計相關

證據金字塔 → 隨機對照試驗 (RCT)：
Level 1 (Gold Standard)



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實證醫學的證據等級

- 文獻的證據等級與研究設計相關
- 證據的等級：良好研究設計可以減少偏差的程度→**隨機對照試驗 (RCT)**

表一　Oxford證據等級與建議等級[6, 9]

建議等級	證據等級	證據的型態
〔A〕	1a	同質性隨機對照試驗的系統性回顧
	1b	單獨的隨機對照試驗
	1c	如果沒有給藥的全部病人會死，給藥後會有一些病人存活；或是如果沒有給藥會有一些病人死亡，而給藥後就不會有病人死亡。
〔B〕	2a	同質性世代研究的系統性文獻回顧
	2b	單獨的世代研究
	2c	結果研究或生態研究
	3a	同質性個案研究的系統性文獻回顧
	3b	單獨的個案對照研究
〔C〕	4	個案發現報告或是品質較差的世代研究和個案對照研究
〔D〕	5	未經清楚且嚴謹的專家意見

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為什麼要進行Meta-analysis?

統合多個臨床研究的樣本數和結果，證據力高
花費研究經費和人力相對低

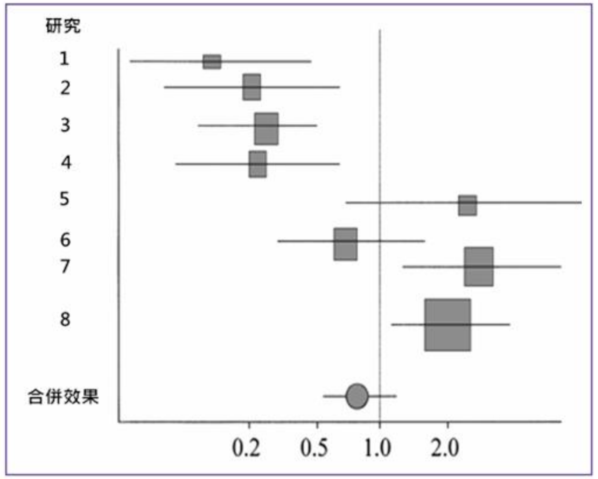


圖2　統合分析中呈現不同研究結果的明顯差異性

Meta-analysis

Major gastrointestinal bleeding risk: comparison of DOACs Radadiya *et al.* www.eurojgh.com e53

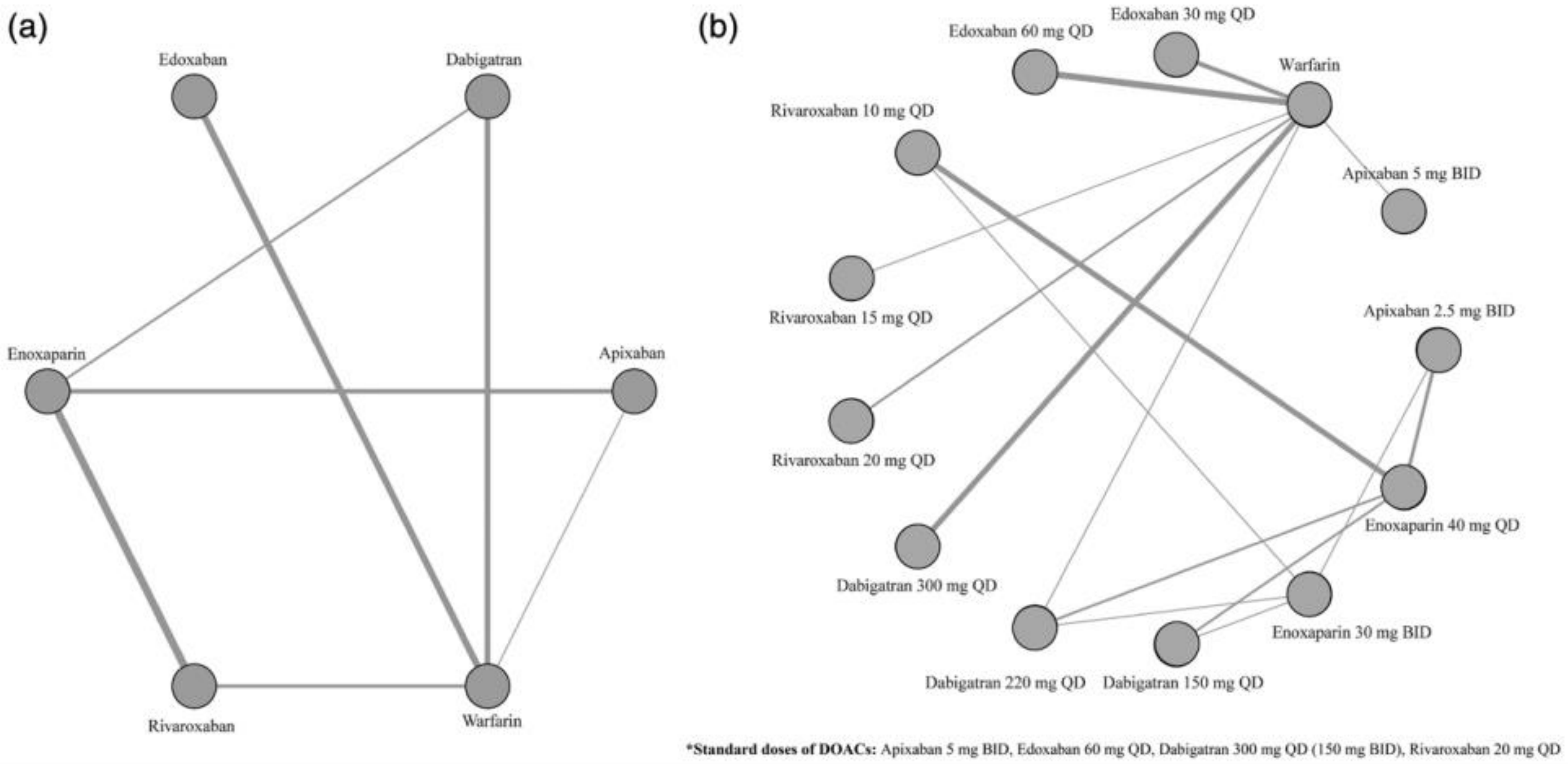


Fig. 2. Network graph showing direct comparisons available between anticoagulants (line width represents the number of trials for every pair): (a) anticoagulants grouped by type and (b) anticoagulants grouped by dosage and type.

Meta-analysis

Major gastrointestinal bleeding risk: comparison of DOACs Radadiya *et al.*

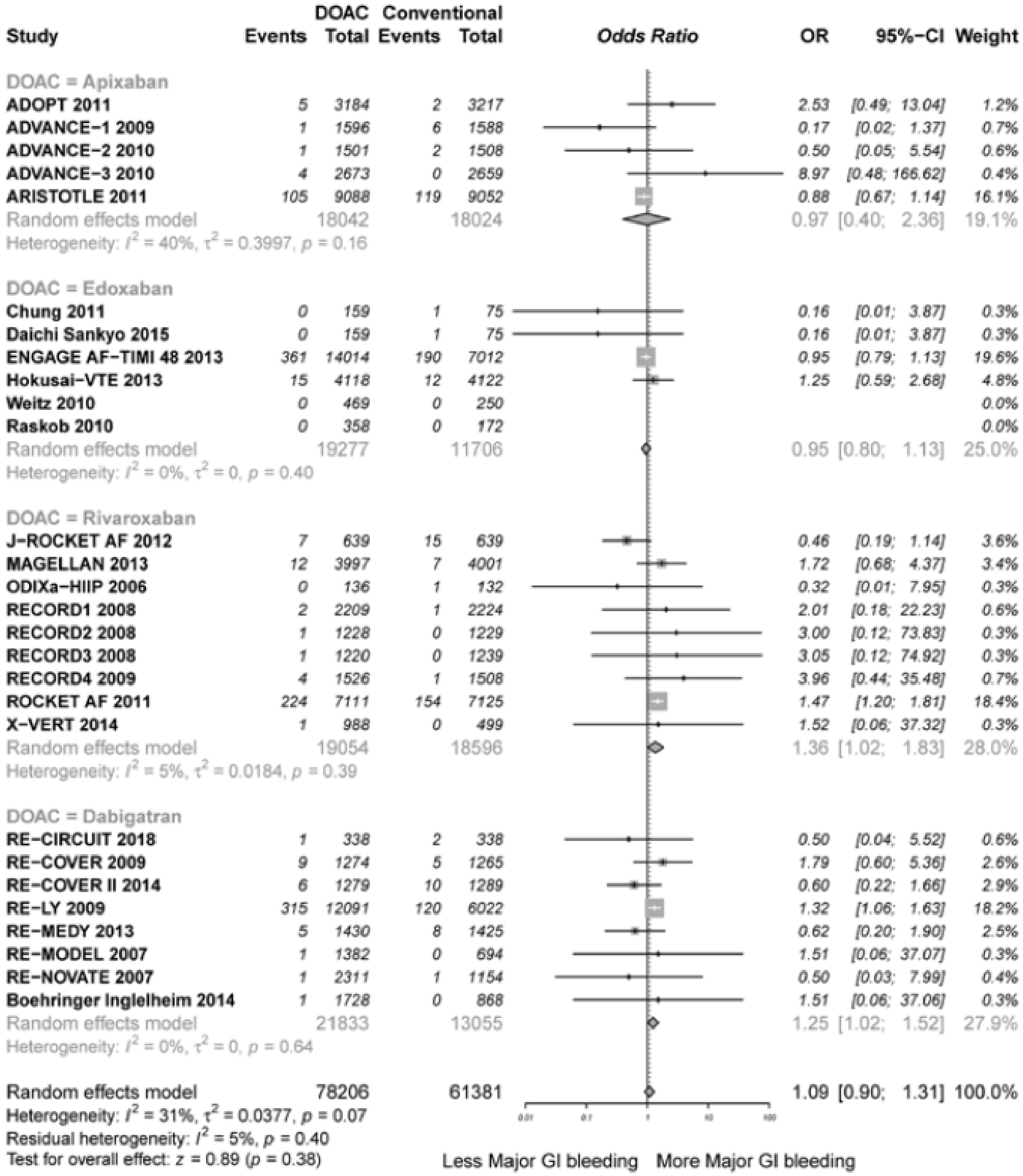


Fig. 3. Forest plots of direct pair-wise comparisons between direct oral anticoagulant (DOAC) and conventional agents: (a) subgrouped by DOAC type and (b) subgrouped by DOAC type and control type (W: warfarin, E: enoxaparin).

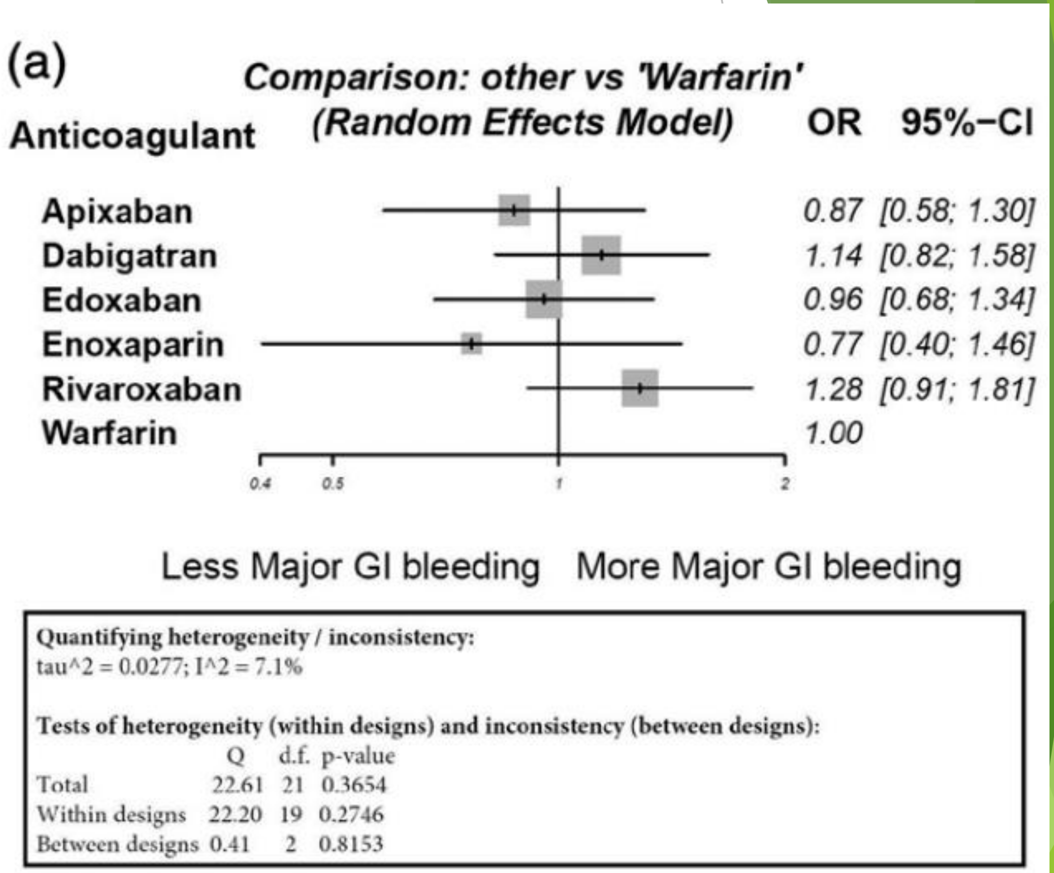


Fig. 4. Forest plots of network comparison in reference to warfarin: (a) individual direct oral anticoagulants (DOACs) as groups

Stata 統計軟體教育訓練課程

Meta-analysis

Quick Tutorial to Stata

To Install and update the metan module in Stata 9.0 ↑
(因為舊版每次都要更新)

1

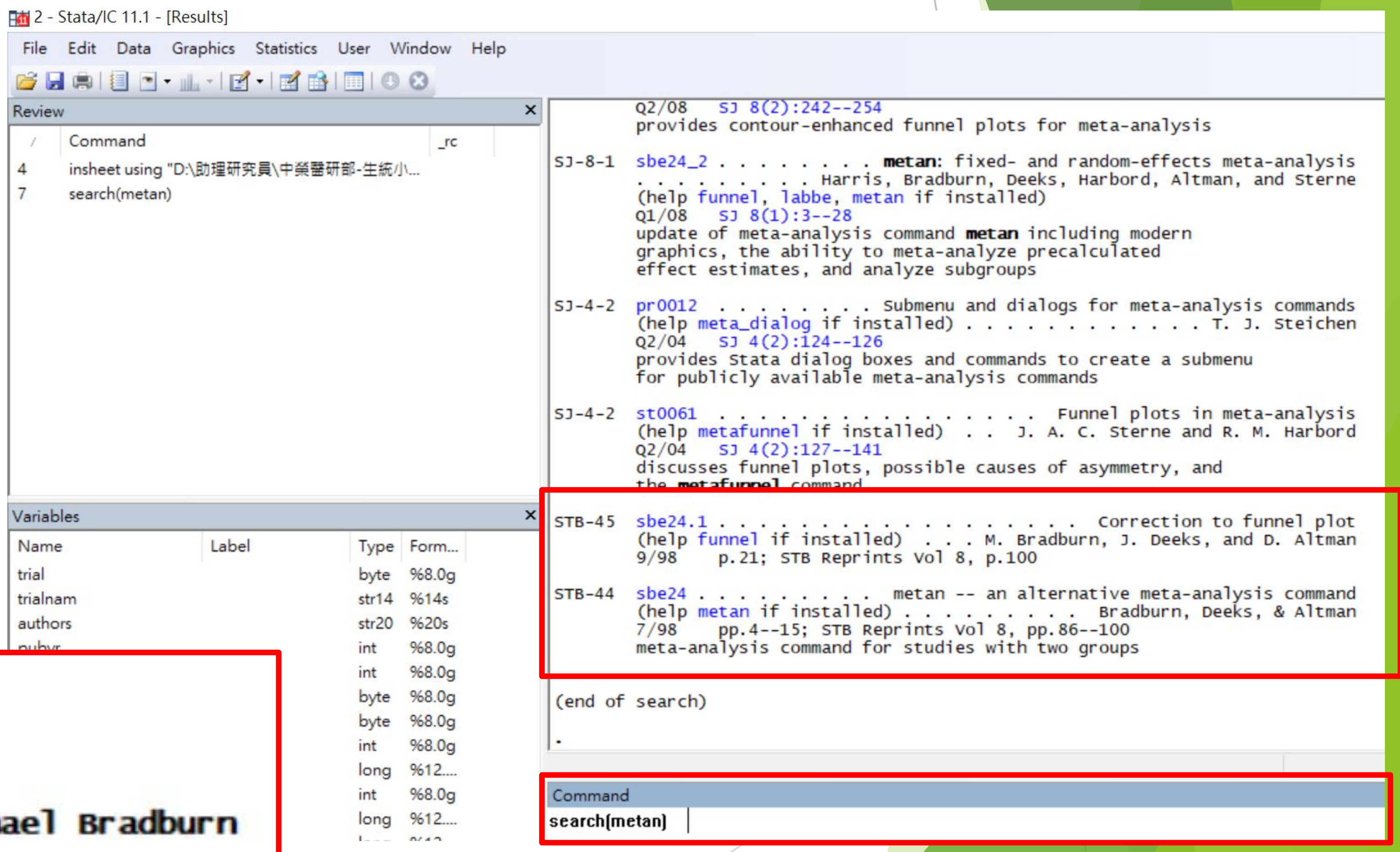
Command
search(metan)

2

Under STB-44, click on sbe24
Under STB-45, click on sbe24.1
(按—more—或空白鍵，可以到下一頁)

3 若 metan 不是最新版本，輸入指令：
which metan
ssc install metaaggr, all replace

```
. which metan
c:\ado\plus\m\metan.ado
*! version 4.06  12oct2022
*! Current version by David Fisher
*! Previous versions by Ross Harris and Michael Bradburn
```



4 若需要指令的協助： help (metan) search (metan)

Introduction to the “metan” Module

For binary (count) data:

4 variables (2*2 data)

```
insheet using "D:\助理研究員\中榮醫研部-生統小組\全院教育課程規劃-2022oct\111年第4季\20221228-初探Meta-analysis\bcg.csv", clear
```

四組數字： tcases tnoncases ccases cnoncases

```
metan tcases tnoncases ccases cnoncases
```

兩組數字： logRR, selogRR

```
gen logRR = ln( (tcases/ttotal) / (ccases/ctotal) )
gen selogRR = sqrt( 1/tcases +1/ccases -1/ttotal -1/ctotal )
```

--Two variables: metan loges seloges
metan logRR selogRR
(log, effect sizes)(standard error, log, effect sizes)

三組數字: RR, UL, LL

3組數字轉2組數字

```
gen logrr=ln(rr)
gen selogrr=(ln(ul)-ln(ll))/3.92
```

```
insheet using "D:\助理研究員\中榮醫研部-生統小組\全院教育課程規劃-2022oct\111年第4季\20221228-初探Meta-analysis\nodm.csv", clear
```

--Three variables: metan loges logll logul
metan rr ll ul
(log, effect sizes)(log, lower and upper limits)

Introduction to the “metan” Module

insheet using "D:\助理研究員\中榮醫研部-生統小組\全院教育課程規劃-2022oct\111年第4季\20221228-初探Meta-analysis\bcg.csv", clear

For binary (count) data:
4 variables (2*2 data)

1. the number of **events** in the treatment group (tcases)
2. the number of **non-events** in the treatment group (tnoncases)
3. the number of **events** in the control group (ccases)
4. the number of **non-events** in the control group (cnoncases)

1 2 3 4

In the command window type: **metan tcases tnoncases ccases cnoncases**

(1~4 順序不可以變動，名稱可隨意更改)

	trial	trialnam	authors	pubyr	startyr	latitude	alloc	tcases	tnoncases	ccases	cnoncases	ttotal	ctotal
1	2	Canada	Ferguson & Simes	1949	1933	55	1	6	300	29	274	306	303
2	1	Northern USA	Aronson	1948	1935	52	1	4	119	11	128	123	139
3	8	Chicago	Rosenthal et al	1961	1941	42	0	17	1699	65	1600	1716	1665
4	10	Georgia (Sch)	Comstock & Webster	1969	1947	33	0	5	2493	3	2338	2498	2341
5	9	Puerto Rico	Comstock et al	1974	1949	18	0	186	50448	141	27197	50634	27338
6	11	Georgia (Comm)	Comstock et al.	1976	1950	33	0	27	16886	29	17825	16913	17854
7	4	Madanapalle	Frimont-Moller et al	1973	1950	13	0	33	5036	47	5761	5069	5808
8	3	UK	Hart & Sutherland	1977	1950	53	1	62	13536	248	12619	13598	12867
9	7	South Africa	Coetzee & Berjak	1968	1965	27	1	29	7470	45	7232	7499	7277
10	5	Haiti	Vandeviere et al	1973	1965	18	1	8	2537	10	619	2545	629
11	6	Madras	TB Prevention Trial	1980	1968	13	1	505	87886	499	87892	88391	88391
12	12	Unknown	Rosenthal et al	1960	1945	42	1	3	228	11	209	231	220
13	13	Unknown	Stein and Aronson	1953	1940	52	0	180	1361	372	1079	1541	1451

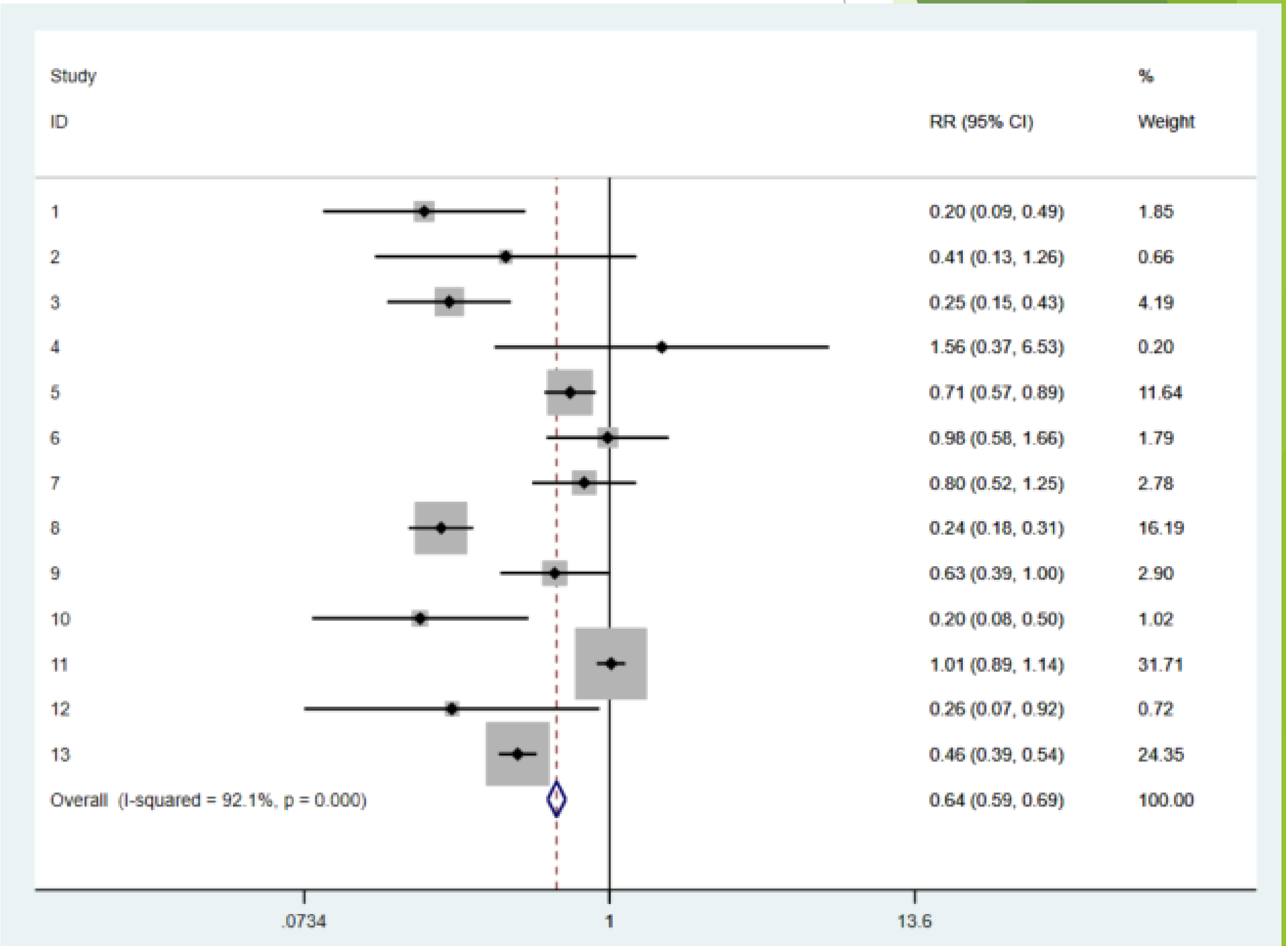
Introduction to the "metan" Module

For binary (count) data:
4 variables (2*2 data)

insheet using "D:\助理研究員\中榮醫研部-生統小組\全院教育課程規劃-2022oct\111年第4季\20221228-初探Meta-analysis\bcg.csv", clear

metan tcases tnoncases ccases cnoncases

```
. metan tcases tnoncases ccases cnoncases

           Study     |     RR   [95% Conf. Interval]     % Weight
---------------------+---------------------------------------------------
1                    |  0.205       0.086     0.486          1.85
2                    |  0.411       0.134     1.257          0.66
3                    |  0.254       0.149     0.431          4.19
4                    |  1.562       0.374     6.528          0.20
5                    |  0.712       0.573     0.886         11.64
6                    |  0.983       0.582     1.659          1.79
7                    |  0.804       0.516     1.254          2.78
8                    |  0.237       0.179     0.312         16.19
9                    |  0.625       0.393     0.996          2.90
10                   |  0.198       0.078     0.499          1.02
11                   |  1.012       0.895     1.145         31.71
12                   |  0.260       0.073     0.919          0.72
13                   |  0.456       0.387     0.536         24.35
---------------------+---------------------------------------------------
M-H pooled RR        |  0.635       0.588     0.686        100.00
---------------------+---------------------------------------------------

  Heterogeneity chi-squared = 152.57 (d.f. = 12) p = 0.000
  I-squared (variation in RR attributable to heterogeneity) =  92.1%

  Test of RR=1 : z=  11.53 p = 0.000
```



Introduction to the “metan” Module

For binary (count) data:
4 variables (2*2 data)

insheet using "D:\助理研究員\中榮醫研部-生統小組\全院教育課程規劃-2022oct\111年第4季\20221228-初探Meta-analysis\bcg.csv", clear

metan tcases tnoncases ccases cnoncases

若需要指令的協助： help (metan)

rr pools risk ratios **(the default)**.
or pools odds ratios.
rd pools risk differences.
fixed specifies a fixed effect model using the method of Mantel and Haenszel **(the default)**. For 4-variable data
fixedi specifies a fixed effect model using the inverse variance method. For 4- or 2-variable data
peto specifies that Peto's method is used to pool odds ratios. (For 4-variable data, zero cells)
random specifies a random effects model using the method of DerSimonian & Laird, with the estimate of heterogeneity being taken from the from the Mantel-Haenszel model. For 4-variable data
randomi specifies a random effects model using the method of DerSimonian & Laird, with the estimate of heterogeneity being taken from the inverse-variance fixed-effect model. For 4- or 2-variable data

Introduction to the “metan” Module

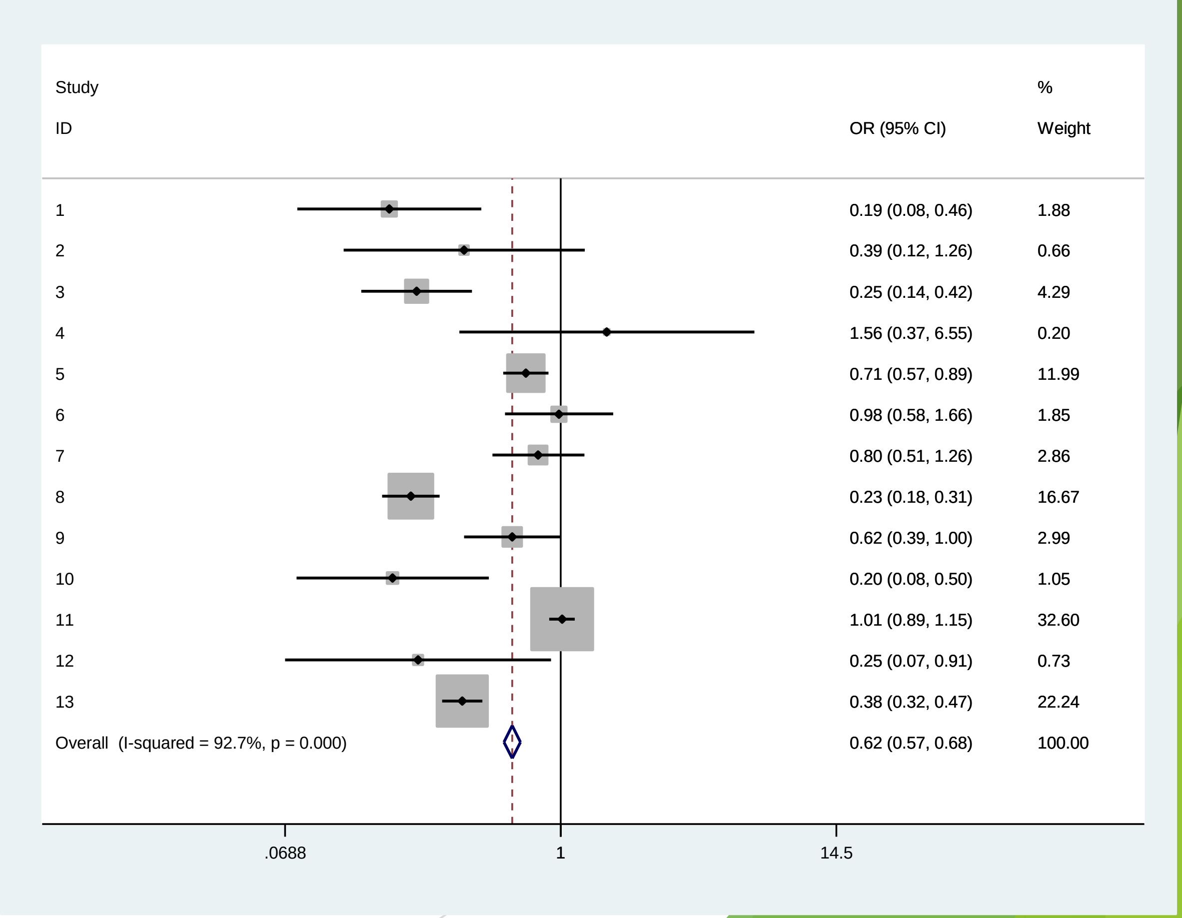
For binary (count) data:
4 variables (2*2 data)

Random effect

insheet using "D:\助理研究員\中榮醫研部-生統小組\全院教育課程規劃-2022oct\111年第4季\20221228-初探Meta-analysis\bcg.csv", clear

metan tcases tnoncases ccases cnoncases, or random

```
. metan tcases tnoncases ccases cnoncases, or random

         Study       |     OR    [95% Conf. Interval]     % Weight
---------------------+---------------------------------------------------
1                    |   0.189      0.077     0.462          6.44
2                    |   0.391      0.121     1.262          5.12
3                    |   0.246      0.144     0.422          8.37
4                    |   1.563      0.373     6.548          4.11
5                    |   0.711      0.571     0.886          9.75
6                    |   0.983      0.582     1.661          8.44
7                    |   0.803      0.514     1.256          8.83
8                    |   0.233      0.176     0.308          9.55
9                    |   0.624      0.391     0.996          8.73
10                   |   0.195      0.077     0.497          6.24
11                   |   1.012      0.894     1.146          9.97
12                   |   0.250      0.069     0.908          4.63
13                   |   0.384      0.316     0.466          9.82
---------------------+---------------------------------------------------
D+L pooled OR        |   0.474      0.325     0.691        100.00
---------------------+---------------------------------------------------

  Heterogeneity chi-squared = 163.94 (d.f. = 12) p = 0.000
  I-squared (variation in OR attributable to heterogeneity) =  92.7%
  Estimate of between-study variance Tau-squared =  0.3682

  Test of OR=1 : z=   3.88 p = 0.000
```



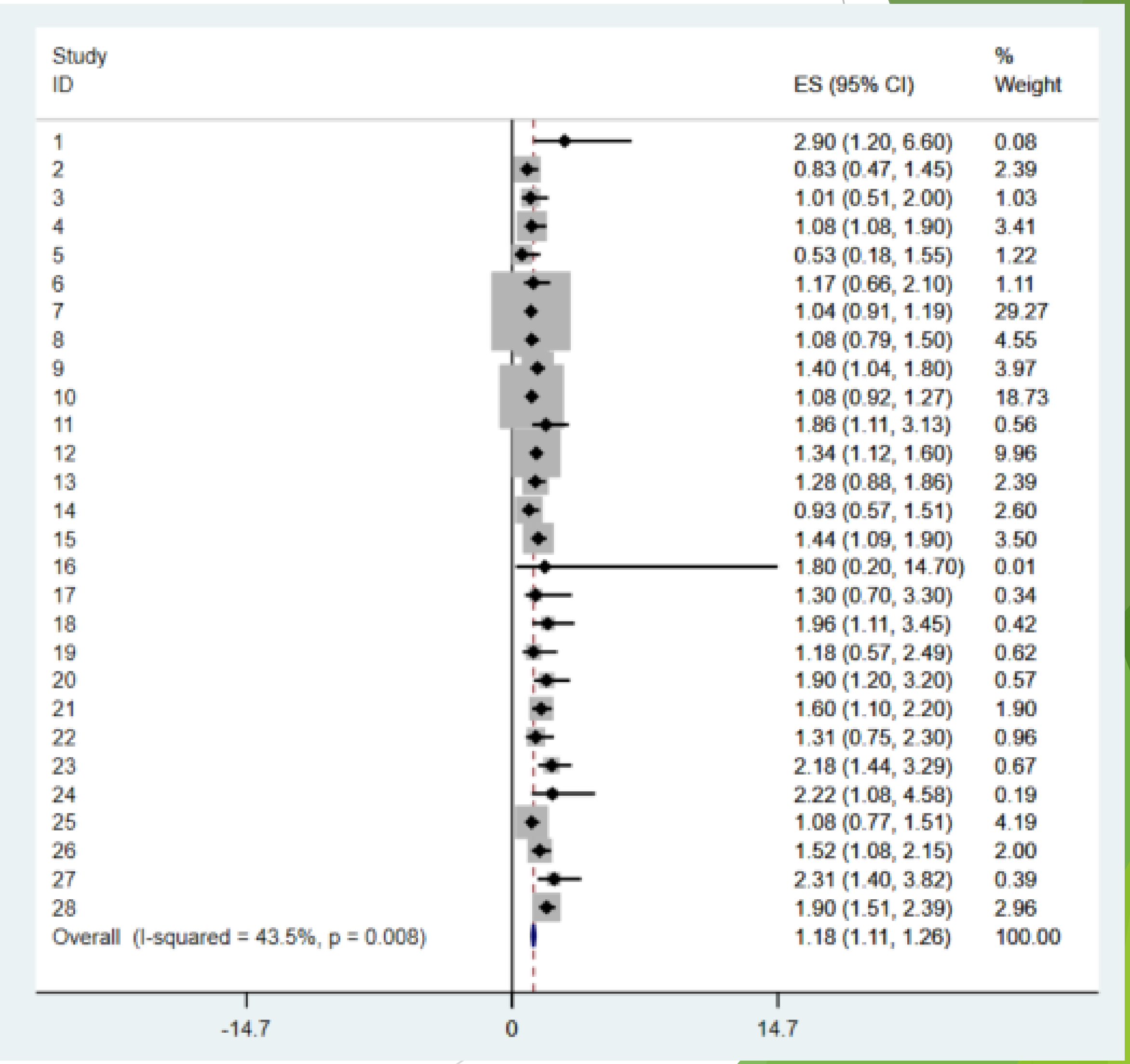
Introduction to the “metan” Module

For binary (count) data:
3 variables

insheet using "D:\助理研究員\中榮醫研部-生統小組\全院教育課程規劃-2022oct\111年第4季\20221228-初探Meta-analysis\nodm.csv", clear

metan rr ll ul

```
. metan rr ll ul

          Study     |     ES    [95% Conf. Interval]     % Weight
---------------------+---------------------------------------------------
1                   |  2.900       1.200     6.600          0.08
2                   |  0.830       0.470     1.450          2.39
3                   |  1.010       0.510     2.000          1.03
4                   |  1.080       1.080     1.900          3.41
5                   |  0.530       0.180     1.550          1.22
6                   |  1.170       0.660     2.100          1.11
7                   |  1.040       0.910     1.190         29.27
8                   |  1.080       0.790     1.500          4.55
9                   |  1.400       1.040     1.800          3.97
10                  |  1.080       0.920     1.270         18.73
11                  |  1.860       1.110     3.130          0.56
12                  |  1.340       1.120     1.600          9.96
13                  |  1.280       0.880     1.860          2.39
14                  |  0.930       0.570     1.510          2.60
15                  |  1.440       1.090     1.900          3.50
16                  |  1.800       0.200    14.700          0.01
17                  |  1.300       0.700     3.300          0.34
18                  |  1.960       1.110     3.450          0.42
19                  |  1.180       0.570     2.490          0.62
20                  |  1.900       1.200     3.200          0.57
21                  |  1.600       1.100     2.200          1.90
22                  |  1.310       0.750     2.300          0.96
23                  |  2.180       1.440     3.290          0.67
24                  |  2.220       1.080     4.580          0.19
25                  |  1.080       0.770     1.510          4.19
26                  |  1.520       1.080     2.150          2.00
27                  |  2.310       1.400     3.820          0.39
28                  |  1.900       1.510     2.390          2.96
---------------------+---------------------------------------------------
I-V pooled ES       |  1.183       1.107     1.259        100.00
---------------------+---------------------------------------------------
 Heterogeneity calculated by formula
  Q = SIGMA_i{ (1/variance_i)*(effect_i - effect_pooled)^2 }
where variance_i = ((upper limit - lower limit)/(2*z))^2

  Heterogeneity chi-squared =  47.79 (d.f. = 27) p = 0.008
  I-squared (variation in ES attributable to heterogeneity) =  43.5%

  Test of ES=0 : z=  30.62 p = 0.000
```



Introduction to the “metan” Module

For binary (count) data:

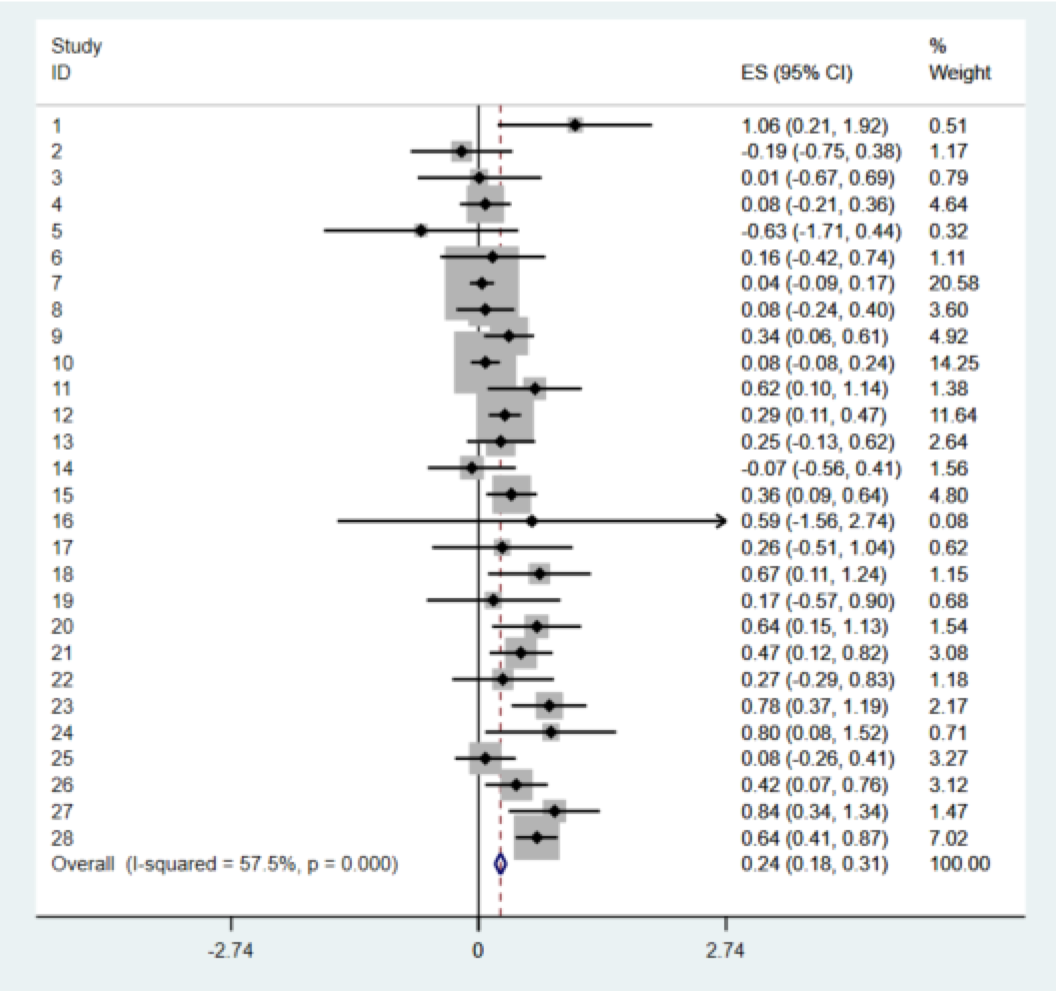
3組數字轉2組數字

gen logrr=ln(rr)

gen selogrr=(ln(ul)-ln(ll))/3.92

insheet using "D:\助理研究員\中榮醫研部-生統小組\全院教育課程規劃-2022oct\111年第4季\20221228-初探Meta-analysis\nodm.csv", clear

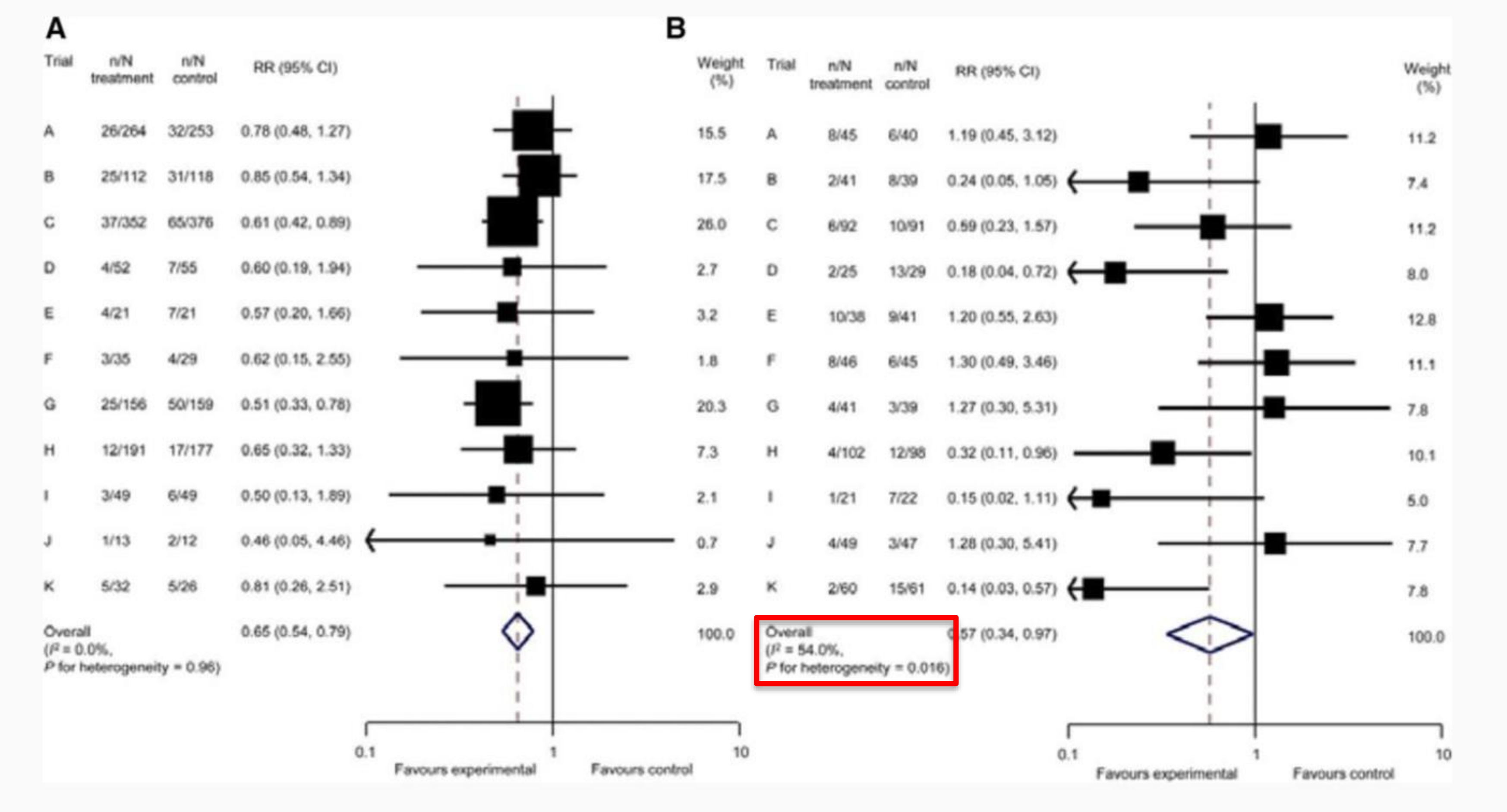
metan logrr selogrr




```
. gen logrr=ln(rr)

.
. gen selogrr=(ln(ul)-ln(ll))/3.92

. metan logrr selogrr

           Study     |     ES    [95% Conf. Interval]     % Weight
---------------------+---------------------------------------------------
1                    |  1.065      0.212     1.917          0.51
2                    | -0.186     -0.750     0.377          1.17
3                    |  0.010     -0.673     0.693          0.79
4                    |  0.077     -0.205     0.359          4.64
5                    | -0.635     -1.711     0.442          0.32
6                    |  0.157     -0.422     0.736          1.11
7                    |  0.039     -0.095     0.173         20.58
8                    |  0.077     -0.244     0.398          3.60
9                    |  0.336      0.062     0.611          4.92
10                   |  0.077     -0.084     0.238         14.25
11                   |  0.621      0.102     1.139          1.38
12                   |  0.293      0.114     0.471         11.64
13                   |  0.247     -0.127     0.621          2.64
14                   | -0.073     -0.560     0.415          1.56
15                   |  0.365      0.087     0.642          4.80
16                   |  0.588     -1.561     2.736          0.08
17                   |  0.262     -0.513     1.038          0.62
18                   |  0.673      0.106     1.240          1.15
19                   |  0.166     -0.572     0.903          0.68
20                   |  0.642      0.151     1.132          1.54
21                   |  0.470      0.123     0.817          3.08
22                   |  0.270     -0.290     0.830          1.18
23                   |  0.779      0.366     1.192          2.17
24                   |  0.798      0.075     1.520          0.71
25                   |  0.077     -0.260     0.414          3.27
26                   |  0.419      0.074     0.763          3.12
27                   |  0.837      0.335     1.339          1.47
28                   |  0.642      0.412     0.871          7.02
---------------------+---------------------------------------------------
I-V pooled ES        |  0.245      0.184     0.305        100.00
---------------------+---------------------------------------------------

  Heterogeneity chi-squared =  63.52 (d.f. = 27) p = 0.000
  I-squared (variation in ES attributable to heterogeneity) =  57.5%

  Test of ES=0 : z=   7.88 p = 0.000
```

研究出現高異質性怎麼辦?

$I^2 \le 50\%$: Homogeneous (fixed effect)
$I^2 > 50\%$: Heterogeneity (random effect mode)



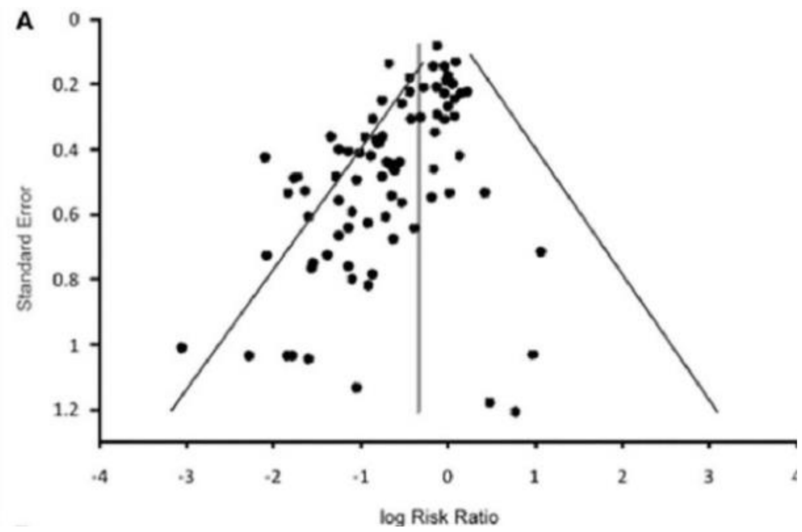
TCVGH

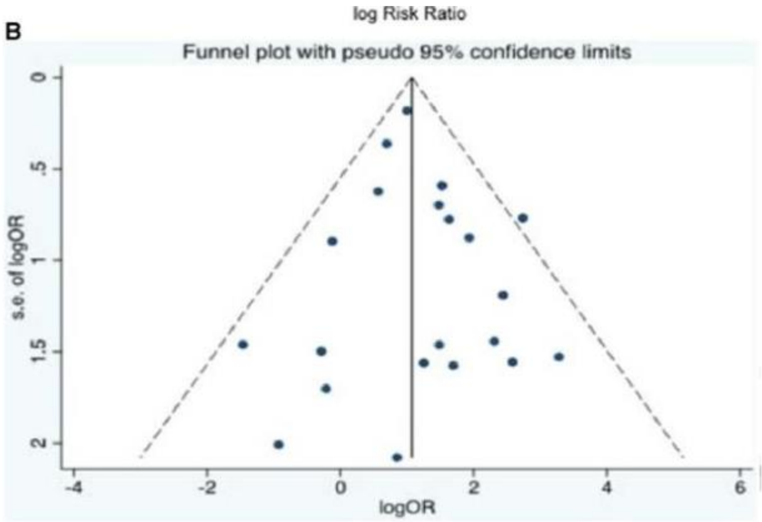
研究出現高異質性怎麼辦?

- 不要先急著作統合分析
  - 統合性迴歸分析（meta-regression）
  - 次群組分析（subgroup-analysis）：找出具有明顯的 category 差別的變項
    - 總論文數小於10篇以下，盡量不要作統合性迴歸分析 → Egger’s test
  - 敏感度分析（sensitivity analysis）：
    - 將某些不合適的論文（例如壁報或品質差的論文） 刪除
  - 使用Random effect model

圖像化評估 Publication Bias: Funnel Plot

「出版性偏差」（publication bias）：研究的質素相若，但報告較大效應值的大型研究，相比於報告較小、或沒有效應的小型研究更常被發表出版的情況。
「出版性偏差」的風險：會令綜合性的研究並不能準確地代表某主題的所有研究，而只偏重於較極端的結果。





漏斗圖：(A) 有出版性偏差、(B) 無出版性偏差

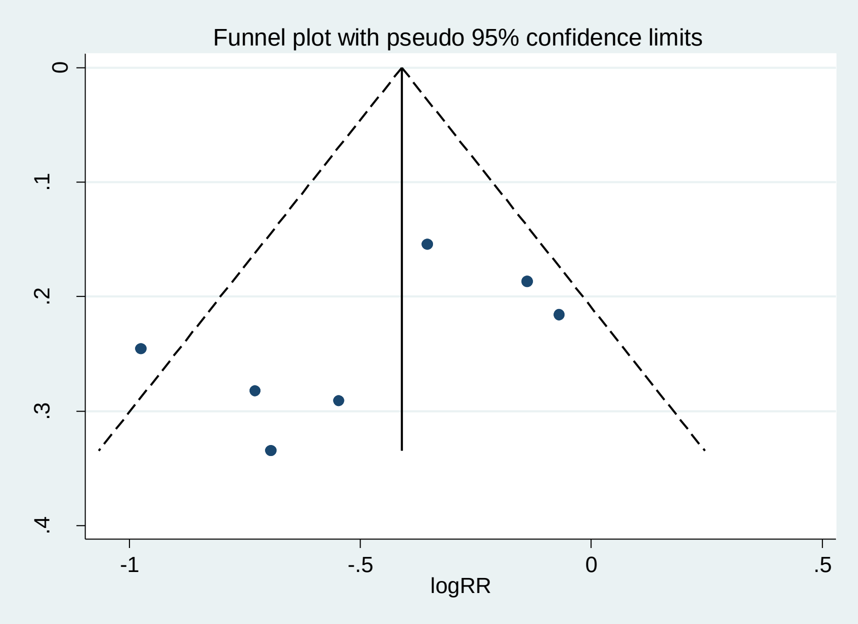
Introduction to the “metafunnel” Module

圖像化評估Publication Bias: Funnel Plot

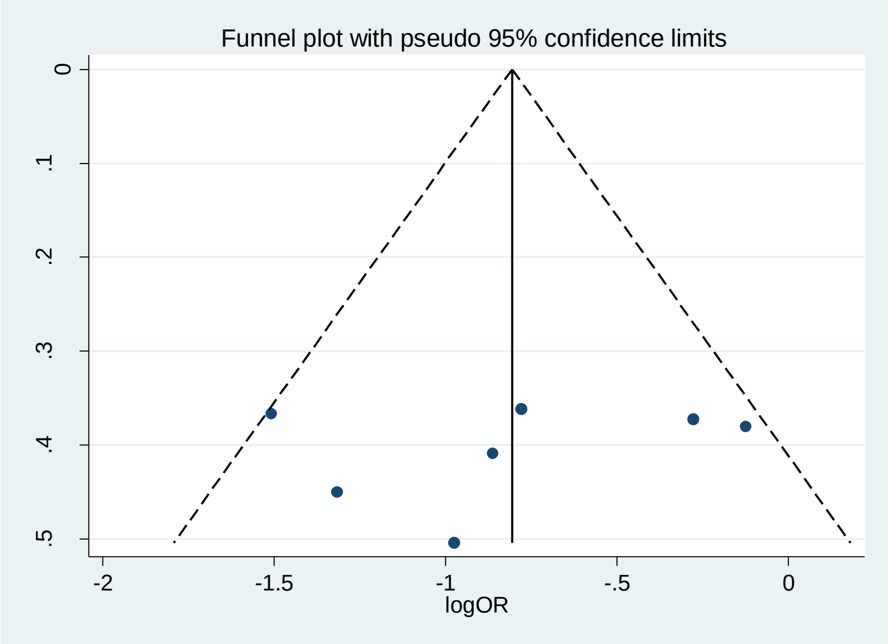
search(metafunnel)
search(metabias)

insheet using "D:\助理研究員\中榮醫研部-生統小組\全院教育課程規劃-2022oct\111年第4季\20221228-初探Meta-analysis\afreg.csv“, clear

metafunnel logrr selogrr



metafunnel logor selogor



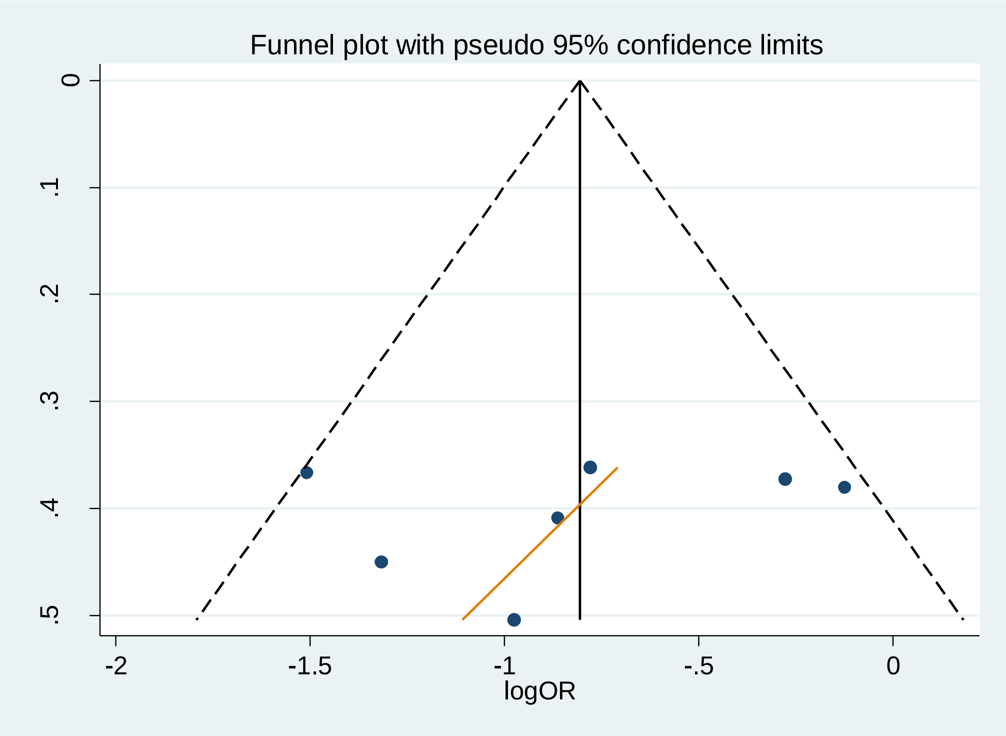
Introduction to the “metafunnel” Module

圖像化評估Publication Bias: Funnel Plot
→ Small size effect: Egger’s test

search(metafunnel)
search(metabias)

insheet using "D:\助理研究員\中榮醫研部-生統小組\全院教育課程規劃-2022oct\111年第4季\20221228-初探Meta-analysis\afreg.csv“, clear

metafunnel logor selogor, egger



metabias logor selogor, egger

```
. metabias logor selogor, egger graph

Note: default data input format (theta, se_theta) assumed.

Tests for Publication Bias

Begg's Test

  adj. Kendall's Score (P-Q) =     -12
          Std. Dev. of Score =   18.27 (corrected for ties)
           Number of Studies =      14
                           z =   -0.66
                    Pr > |z| =   0.511
                           z =    0.60 (continuity corrected)
                    Pr > |z| =   0.547 (continuity corrected)

Egger's test
------------------------------------------------------------------------------
     Std_Eff |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       slope |   .3068297   1.247459     0.25   0.810     -2.41115    3.024809
        bias |    -2.8082   3.130834    -0.90   0.387    -9.629702    4.013302
------------------------------------------------------------------------------
```

Stata 統計軟體教育訓練課程

Network Meta-analysis

安裝Network Meta-analysis相關套件

***從以下開始安裝**

*** MA/NMA**

net from "http://www.homepages.ucl.ac.uk/~rmjwiww/stata/meta/"
net install network.pkg, replace
net install mvmeta.pkg, replace

***Network plot**

ssc install netplot
net from "https://clinicalepidemio.fr/Stata"
net install network_graphs.pkg, replace
net install metamiss2.pkg, replace

help network graph

```
SJ-15-4 st0411  . Visualizing assumptions and results in network meta-analysis
        . . . . . . . . . . . . . . . . . . . . . . . A. Chaimani and G. Salanti
        (help network graphs, clusterank, ifplot, intervalplot, mdsrank,
        netfunnel, netleague, netweight, networkplot, sucra if installed)
        Q4/15   SJ 15(4):905--950
        provides a suite of commands with graphical tools to facilitate
        the understanding of data, the evaluation of assumptions, and
        the interpretation of findings from network meta-analysis
```

*** SE code**

net from "http://www.stata-journal.com/software/sj10-4/"
net install st0043_2.pkg, replace

Preparing for Analysis: 先設定長檔案

For binary (count) data:

use "D:\助理研究員\中榮醫研部-生統小組\全院教育課程規劃-2022oct\112年生統課程規劃\護理部-Stata\Stata-Network meta_new\long_data.dta ", clear

network setup d n, studyvar (study) trtvar(trt) ref(A)

Data Editor (Browse) - [long_data]

File Edit View Data Tools

study[1] Alshryda2013

	study	d	n	trt
1	Alshryda2013	10	80	C
2	Alshryda2013	26	81	A
3	Barrachina2016	8	35	E
4	Barrachina2016	4	36	B
5	Barrachina2016	14	37	A
6	Benoni2000	9	20	B
7	Benoni2000	15	19	A
8	Benoni2001	4	18	E

d: number of events
n: total sample size
studyvar → study: variable of study title
trtvar → trt: variable of treatment
ref: A or Placebo

先設定檔案 for Network Meta-analysis

network setup d n, studyvar (study) trtvar(trt) ref(A)

A	B	C	D	E
Placebo	IV_single use	IV_double use	Topical_use	Combination_IV_and_topical

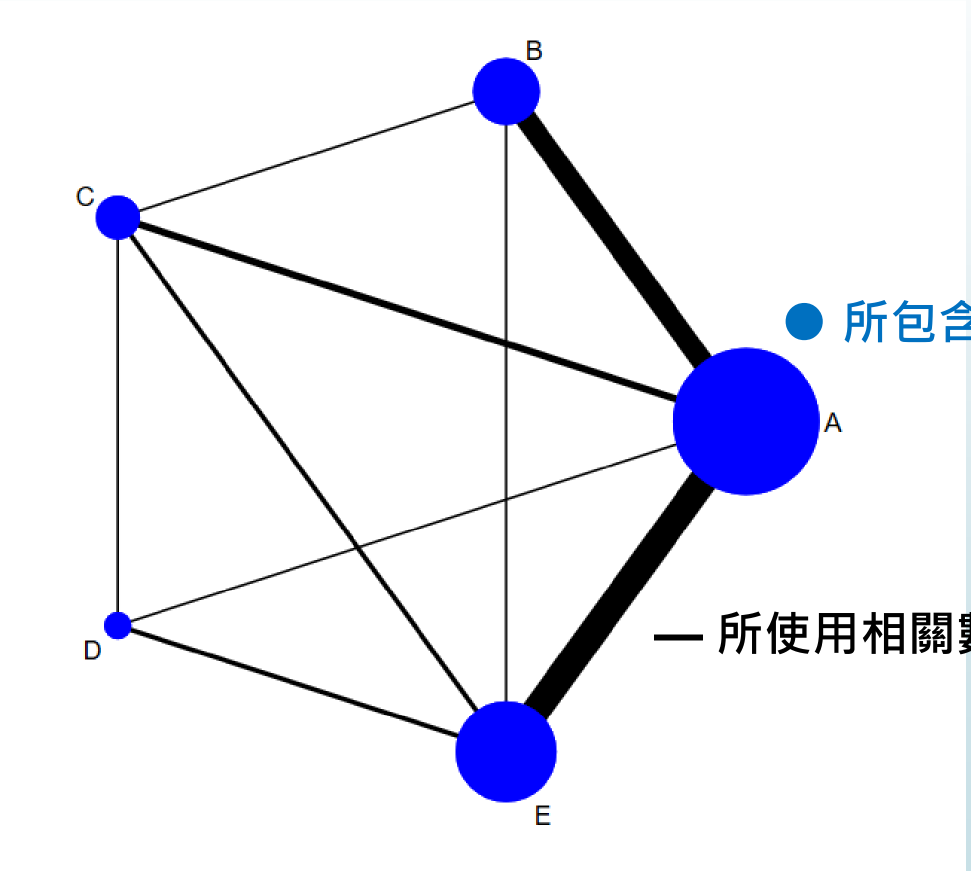
```
. network setup d n, studyvar (study) trtvar(trt) ref(A)
Treatments used
   A (reference):                    A
   B:                                B
   C:                                C
   D:                                D
   E:                                E

Measure                              Log odds ratio

Studies
   ID variable:                      study
   Number dropped:                   1
   Number used:                      24
   IDs with zero cells:              `"Xie2016"' `"Yamasaki2004"'
   - count added to all their cells: .5
   IDs with augmented reference arm: `"North2016"' `"Xie2016"'
   - observations added:             0.00001
   - mean in augmented observations: study-specific mean

Network information
   Components:                       1 (connected)
   D.f. for inconsistency:           8
   D.f. for heterogeneity:           16

Current data
   Data format:                      augmented
   Design variable:                  _design
   Estimate variables:               _y*
   Variance variables:               _S*
   Command to list the data:         list study _y* _S*, noo sepby(_design)
```

study[1] Alshryda2013

	study	dA	nA	dB	nB	dC	nC	dD	nD	dE	nE	_design	_y_B	_y_C	_y_D	_y_E	_S_B_B
1	Alshryda2013	26	81	.	.	10	80	.	.	.	.	A C	.	-1.1966735	.	.	.
2	Barrachina2016	14	37	4	36	.	.	.	.	8	35	A B E	-1.5830047	.	.	-.71995844	.39615683
3	Benoni2000	15	19	9	20	.	.	.	.	.	.	A B	-1.5224265	.	.	.	.51868687
4	Benoni2001	8	20	.	.	.	.	.	.	4	18	A E	.	.	.	-.84729786	.
5	Claeys2007	6	20	.	.	.	.	.	.	1	20	A E	.	.	.	-2.0971411	.
6	Ekb2000	1	20	1	20	.	.	.	.	.	.	A B	0	.	.	.	2.1052632
7	Fraval2017	6	51	1	50	.	.	.	.	.	.	A B	-1.8769173	.	.	.	1.2092971
8	Garneti2004	14	25	.	.	.	.	.	.	16	25	A E	.	.	.	.33420209	.
9	Hsu2015	9	30	2	30	.	.	.	.	.	.	A B	-1.7917595	.	.	.	.69444444
10	Husted2003	7	20	2	20	.	.	.	.	.	.	A B	-1.5781854	.	.	.	.77533578
11	Johansson2005	23	53	.	.	.	.	.	.	8	47	A E	.	.	.	-1.3184169	.

Step 1: Generating Network Geometry

- Network plot:　輸入指令　**network map**



● 所包含研究的數量

— 所使用相關數據的數量

Step 2: Testing for Inconsistency

- Global inconsistency Test 輸入指令 **network meta inconsistency**

```
Multivariate meta-analysis
Variance-covariance matrix = proportional .5*I(4)+.5*J(4,4,1)
Method = reml                                  Number of dimensions    =      4
Restricted log likelihood = -34.684006         Number of observations  =     24

------------------------------------------------------------------------------
             | Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
-------------+----------------------------------------------------------------
_y_B         |
     des_ABE |  -.2177834      .6846    -0.32   0.750    -1.559575    1.124008
       _cons |  -1.365221    .269296    -5.07   0.000    -1.893032   -.8374108
-------------+----------------------------------------------------------------
_y_C         |
     des_ACE |  -.6561662   .6028711    -1.09   0.276    -1.837772    .5254395
      des_BC |   .1947812   .6700162     0.29   0.771    -1.118426    1.507989
     des_CDE |   .6167358    .974232     0.63   0.527    -1.292724    2.526195
       _cons |  -1.070454   .3665995    -2.92   0.004    -1.788976   -.3519321
-------------+----------------------------------------------------------------
_y_D         |
     des_CDE |   .6929186   1.922747     0.36   0.719    -3.075596    4.461433
       _cons |  -3.402272   1.051331    -3.24   0.001    -5.462844     -1.3417
-------------+----------------------------------------------------------------
_y_E         |
     des_ACE |  -.9961905   .7114154    -1.40   0.161    -2.390539    .3981581
     des_ADE |  -.4487215   .7145929    -0.63   0.530    -1.849298    .9518549
      des_AE |  -.2528214   .5704532    -0.44   0.658    -1.370889    .8652463
       _cons |  -.7199583   .5262546    -1.37   0.171    -1.751398    .3114817
------------------------------------------------------------------------------

Estimated between-studies SDs and correlation matrix
--------------------------------------------------------
              SD        _y_B       _y_C       _y_D       _y_E
_y_B   3.083e-07           1          .          .          .
_y_C   3.083e-07          .5          1          .          .
_y_D   3.083e-07          .5         .5          1          .
_y_E   3.083e-07          .5         .5         .5          1
--------------------------------------------------------
```

```
Estimated between-studies SDs and correlation matrix
--------------------------------------------------------
              SD        _y_B       _y_C       _y_D       _y_E
_y_B   3.083e-07           1          .          .          .
_y_C   3.083e-07          .5          1          .          .
_y_D   3.083e-07          .5         .5          1          .
_y_E   3.083e-07          .5         .5         .5          1
--------------------------------------------------------

Testing for inconsistency:
 ( 1)  [_y_B]des_ABE = 0
 ( 2)  [_y_E]des_ACE = 0
 ( 3)  [_y_C]des_ACE = 0
 ( 4)  [_y_E]des_ADE = 0
 ( 5)  [_y_E]des_AE = 0
 ( 6)  [_y_C]des_BC = 0
 ( 7)  [_y_C]des_CDE = 0
 ( 8)  [_y_D]des_CDE = 0

           chi2(  8) =    4.09
         Prob > chi2 =    0.8492
```

無法拒絕虛無假說
一致性 consistency 的水準可接受

Step 2: Testing for Inconsistency

- Local inconsistency Test 輸入指令 **network sidesplit all**

```
. network sidesplit all
```

無法拒絕虛無假說
一致性 consistency 的水準可

Side	Direct Coef.	Direct Std. Err.	Indirect Coef.	Indirect Std. Err.	Difference Coef.	Difference Std. Err.	P>|z|
A B	-1.387832	.246631	-1.834588	.5000808	.4467555	.5475861	0.415
A C	-1.346768	.2878734	-.7355726	.4132222	-.6111958	.4901931	0.212
A D	-3.420298	.939617	-3.203182	1.005883	-.2171159	.9367965	0.817
A E	-1.08404	.1738511	-.7891631	.6352852	-.2948771	.6513169	0.651
B C	.4895483	.4919413	.2233391	.3632928	.2662092	.6115455	0.663
B E	.8919491	.655003	.3065194	.2968191	.5854297	.7146861	0.413
C D	-2.534345	1.25485	-2.009367	.9639263	-.5249778	1.320922	0.691
C E	-.0989284	.4620928	.1914716	.3474008	-.2904	.5783735	0.616
D E *	2.152297	.8813737	2.593058	1.087671	-.4407617	.8966076	0.623

Because inconsistency was found to be absent in both global and local tests, the consistency assumption was accepted

Step 3: Creating Plots and League Table of Effect Size by Treatment

- 先設定 **network meta consistency**

For network forest

```
. network meta consistency
Command is: mvmeta _y _S  , bscovariance(exch 0.5) longparm suppress(uv mm)  vars(_y_B _y_C _y_D _y_E)
Note: using method reml
Note: using variables _y_B _y_C _y_D _y_E
Note: 24 observations on 4 variables
Note: variance-covariance matrix is proportional to .5*I(4)+.5*J(4,4,1)

initial:       log likelihood = -49.494181
rescale:       log likelihood = -49.494181
rescale eq:    log likelihood = -41.242314
Iteration 0:   log likelihood = -41.242314
Iteration 1:   log likelihood = -41.138072
Iteration 2:   log likelihood =  -41.13807

Multivariate meta-analysis
Variance-covariance matrix = proportional .5*I(4)+.5*J(4,4,1)
Method = reml                                Number of dimensions     =      4
Restricted log likelihood = -41.13807        Number of observations   =     24
```

	Coefficient	Std. err.	z	P>|z|	[95% conf. interval]	
_y_B						
_cons	-1.470223	.2250083	-6.53	0.000	-1.911231	-1.029215
_y_C						
_cons	-1.152938	.2422897	-4.76	0.000	-1.627817	-.6780585
_y_D						
_cons	-3.327687	.8504168	-3.91	0.000	-4.994473	-1.660901
_y_E						
_cons	-1.066367	.1694118	-6.29	0.000	-1.398408	-.7343258

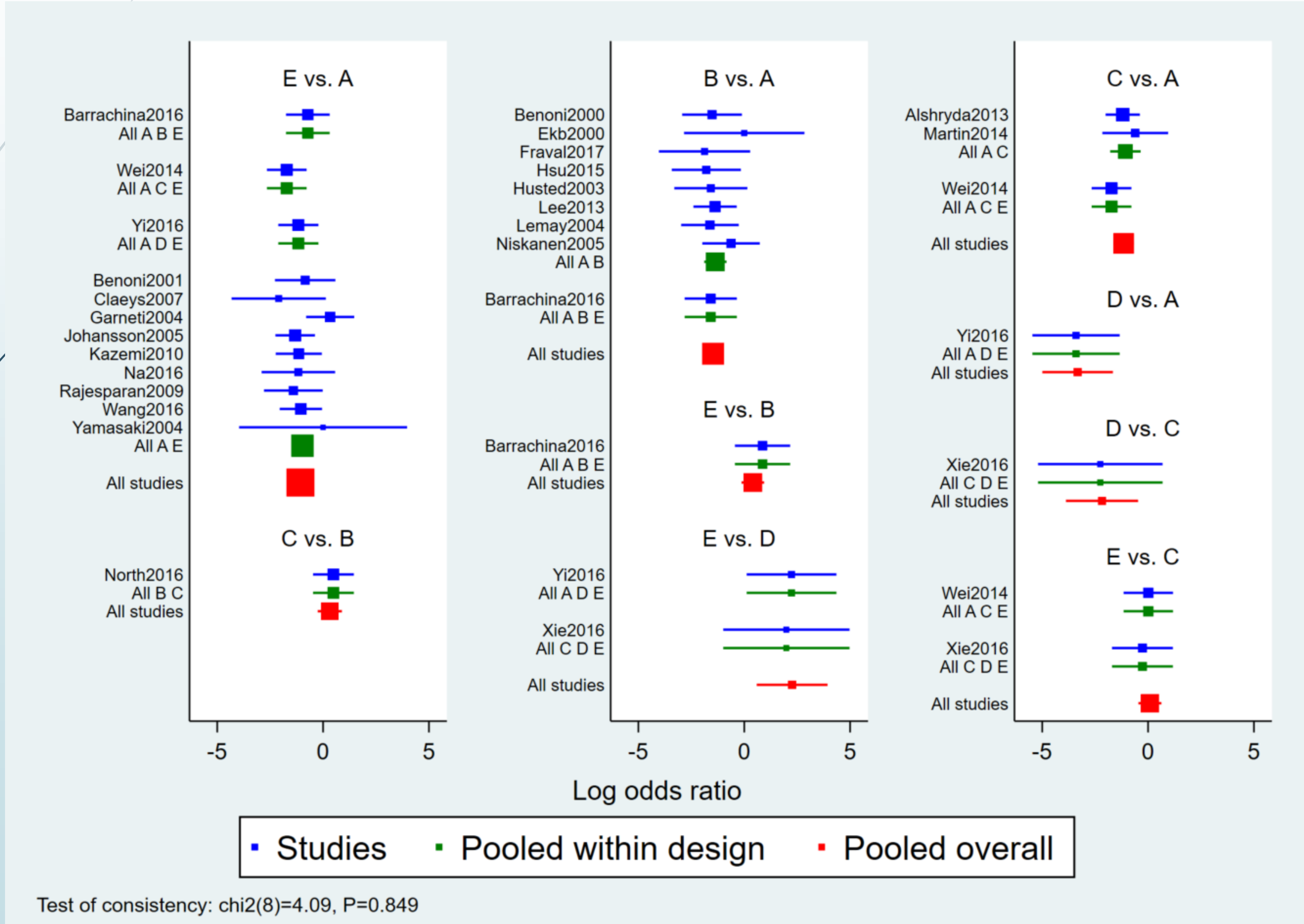
Estimated between-studies SDs and correlation matrix

	SD	_y_B	_y_C	_y_D	_y_E
_y_B	2.246e-07	1	.	.	.
_y_C	2.246e-07	.5	1	.	.
_y_D	2.246e-07	.5	.5	1	.
_y_E	2.246e-07	.5	.5	.5	1

Step 3: Creating Plots and League Table of Effect Size by Treatment

- Network forest plot (NFP) 輸入：

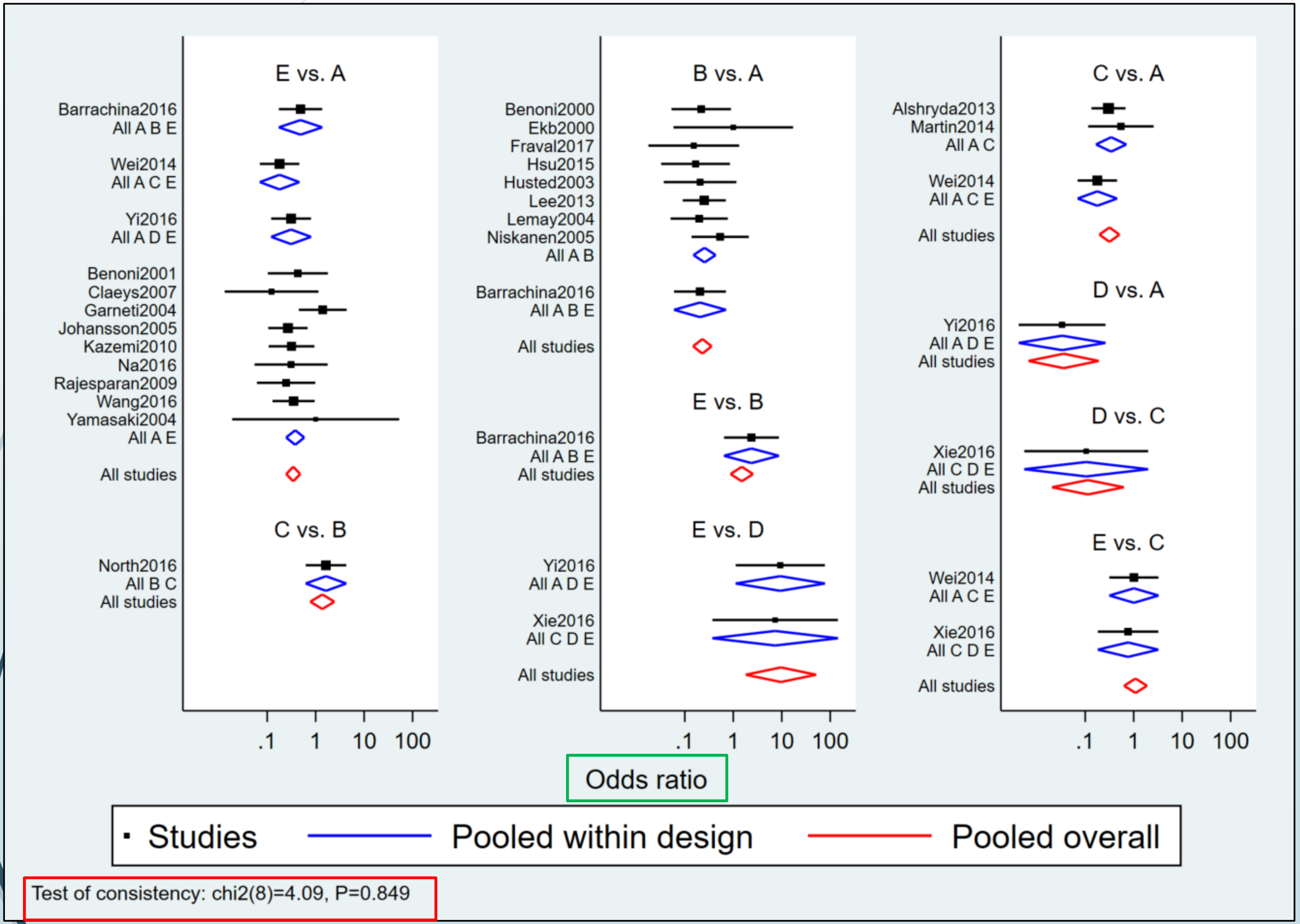
network forest



Step 3: Creating Plots and League Table of Effect Size by Treatment

- Network forest plot (NFP) 輸入：

network forest, msize (*0.15) diamond eform xlabel (0.1 1 10 100) colors (black blue red) list



Global test on inconsistency

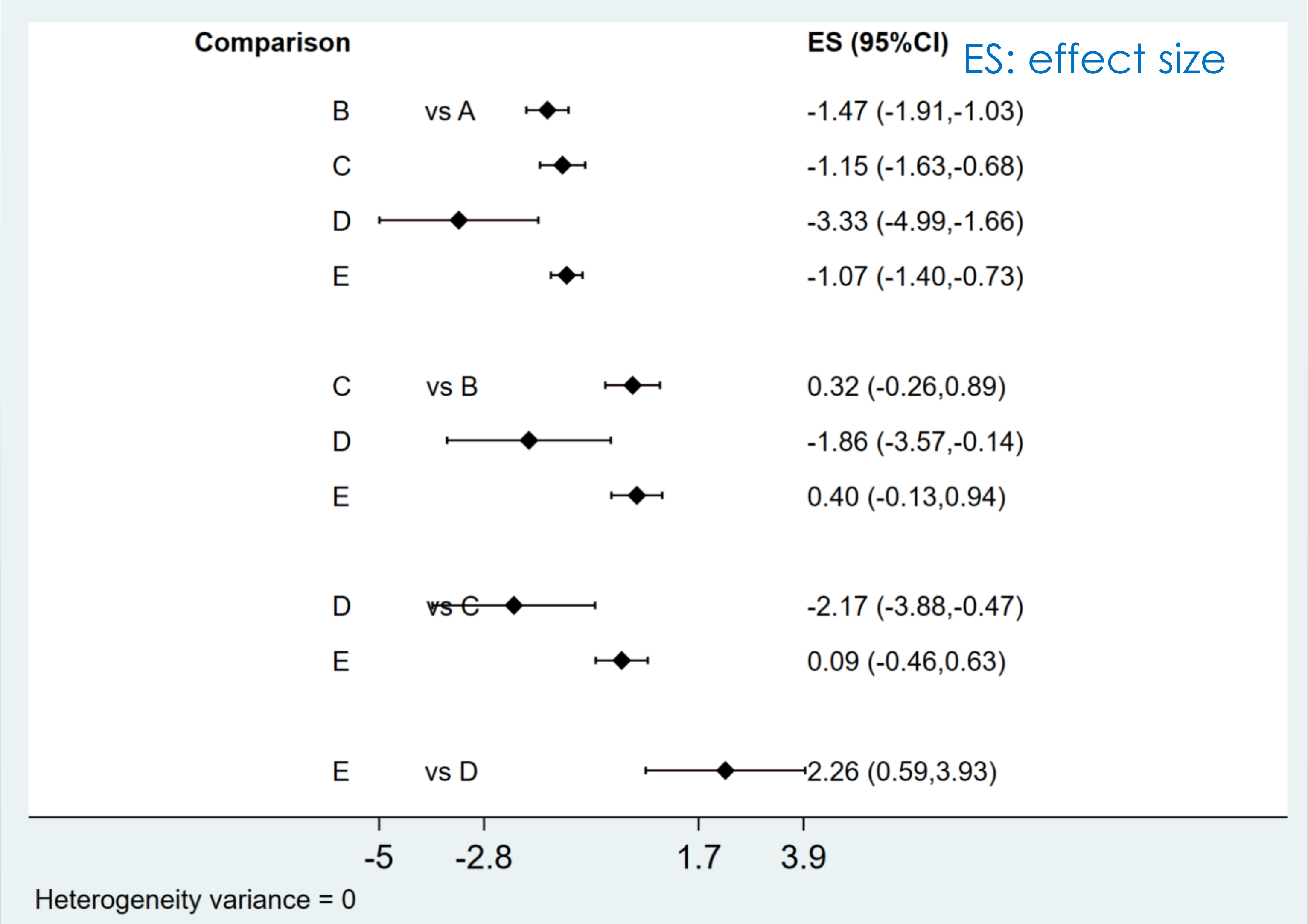
<diamond> uses a diamond shape to show summary effect sizes

<eform> generates transformed indices to make it easy to interpret the forest plot

Step 3: Creating Plots and League Table of Effect Size by Treatment

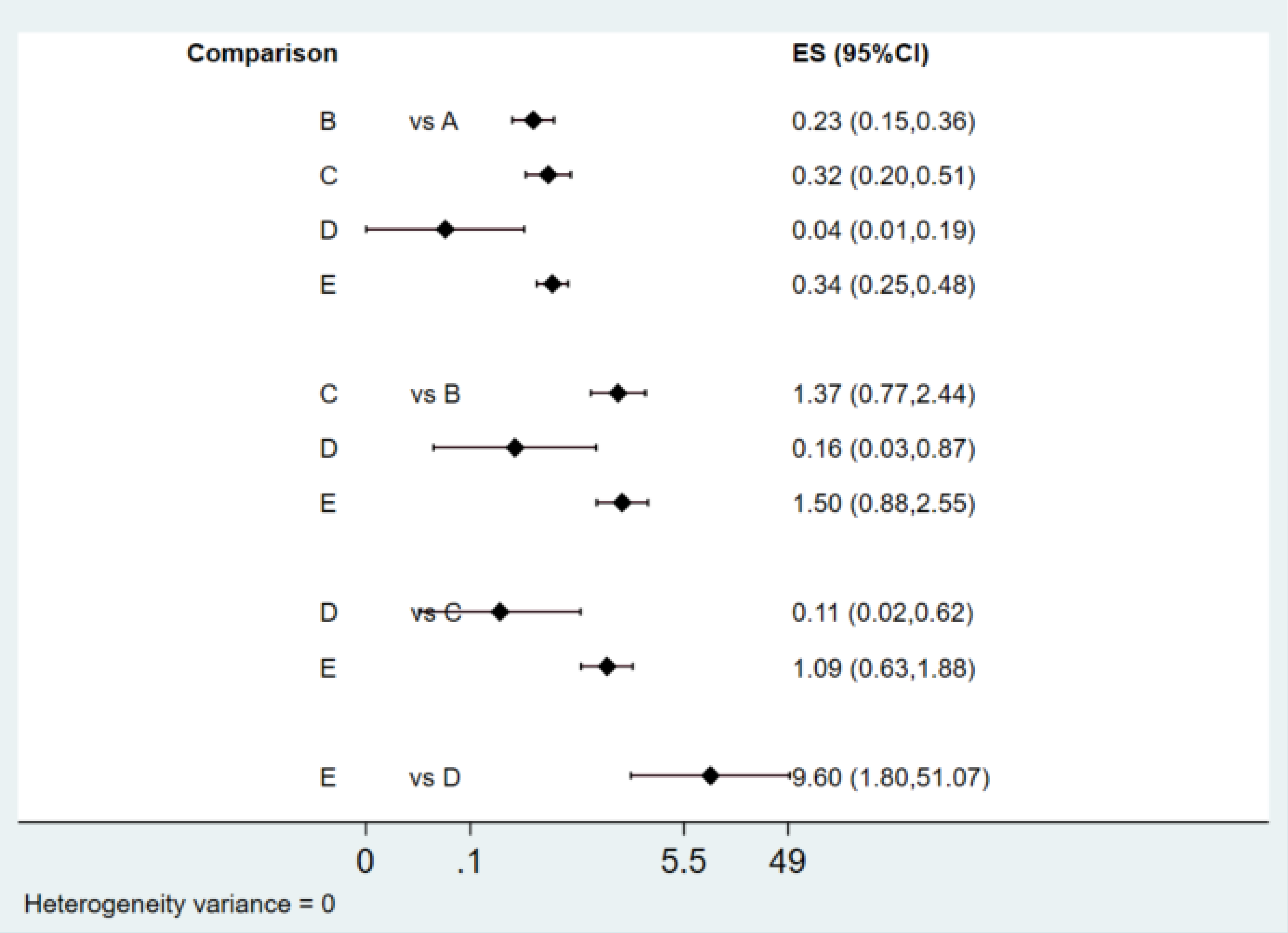
- Network forest plot (NFP) 輸入：

  intervalplot



Step 3: Creating Plots and League Table of Effect Size by Treatment

- Network forest plot (NFP) and interval plot 輸入：
  intervalplot, eform



ES: effect size

<eform> generates transformed indices to make it easy to interpret the forest plot

Step 3: Creating Plots and League Table of Effect Size by Treatment

- Network forest plot (NFP) and interval plot 輸入：

intervalplot, eform null (1) labels (Placebo IV_single IV_double Topical Combination)   margin (10 8 5 10) textsize (2) xlabel (0.01 0.1 1 10)

intervalplot, eform null (1) labels (Placebo IV_single IV_double Topical Combination) separate margin (10 8 5 10) textsize (2) xlabel (0.01 0.1 1 10)

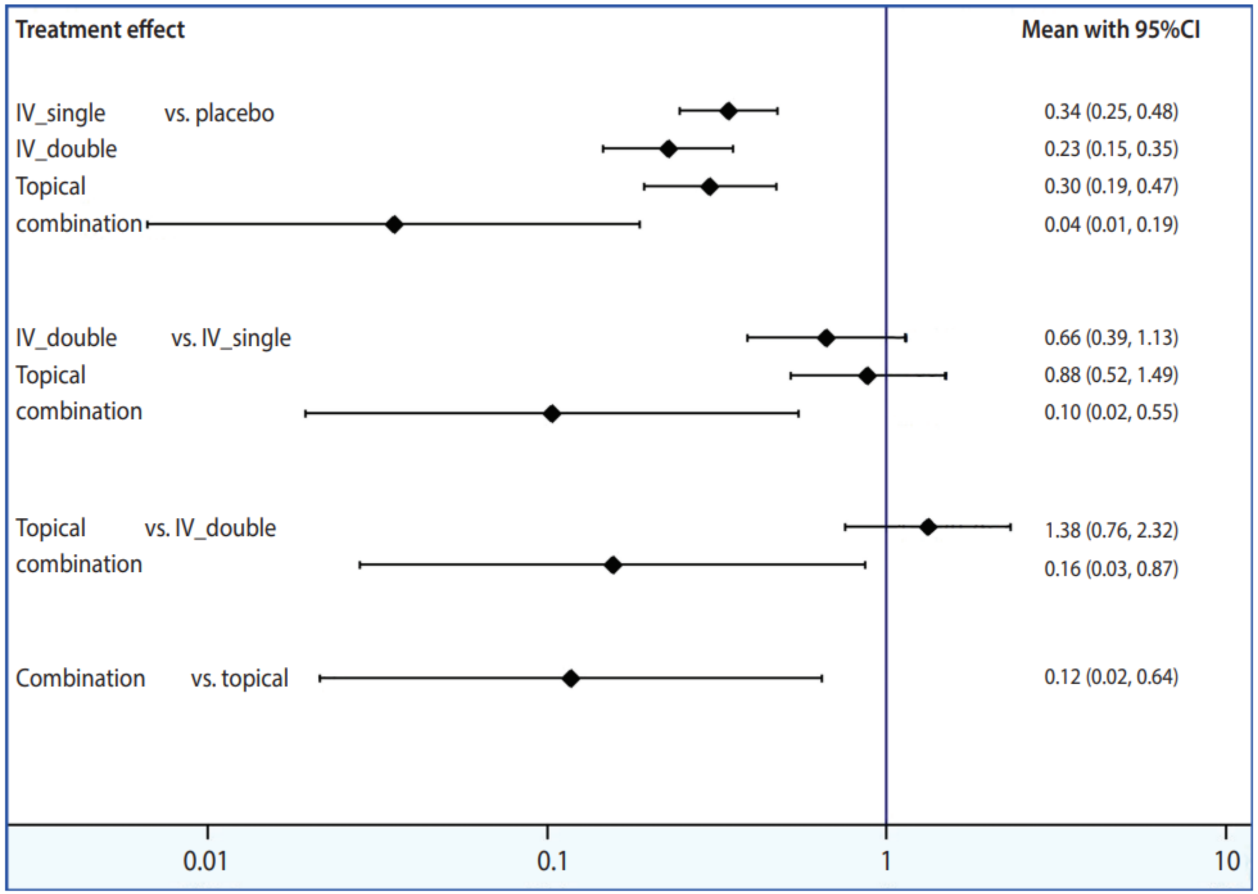


Figure 5. Interval plot. CI, confidence interval.

<eform> generates transformed indices to make it easy to interpret the forest plot

<separate> and < margin> set the ranges to generate easy-to-read plots, the values of which should be appropriately determined by the user

Step 4: Determining Relative Rankings of Treatments

- Identify superiority 輸入：

network rank min

```
. network rank min
Command is: mvmeta, noest pbest(min  in 1, zero id(study)  stripprefix(_y_) zeroname(A) rename(A = A, B = B, C = C, D = D, E = E))

Estimated probabilities (%) of each treatment having each rank
- assuming the minimum parameter is the best
- using 1000 draws
- allowing for parameter uncertainty
```

Rank	Treatment A	B	C	D	E
Best	0.0	1.4	0.4	98.1	0.1
2nd	0.0	81.2	12.5	1.1	5.2
3rd	0.0	13.4	51.3	0.2	35.1
4th	0.0	4.0	35.8	0.6	59.6
Worst	100.0	0.0	0.0	0.0	0.0

network rank max

```
. network rank max
Command is: mvmeta, noest pbest(max  in 1, zero id(study)  stripprefix(_y_) zeroname(A) rename(A = A, B = B, C = C, D = D, E = E))

Estimated probabilities (%) of each treatment having each rank
- assuming the maximum parameter is the best
- using 1000 draws
- allowing for parameter uncertainty
```

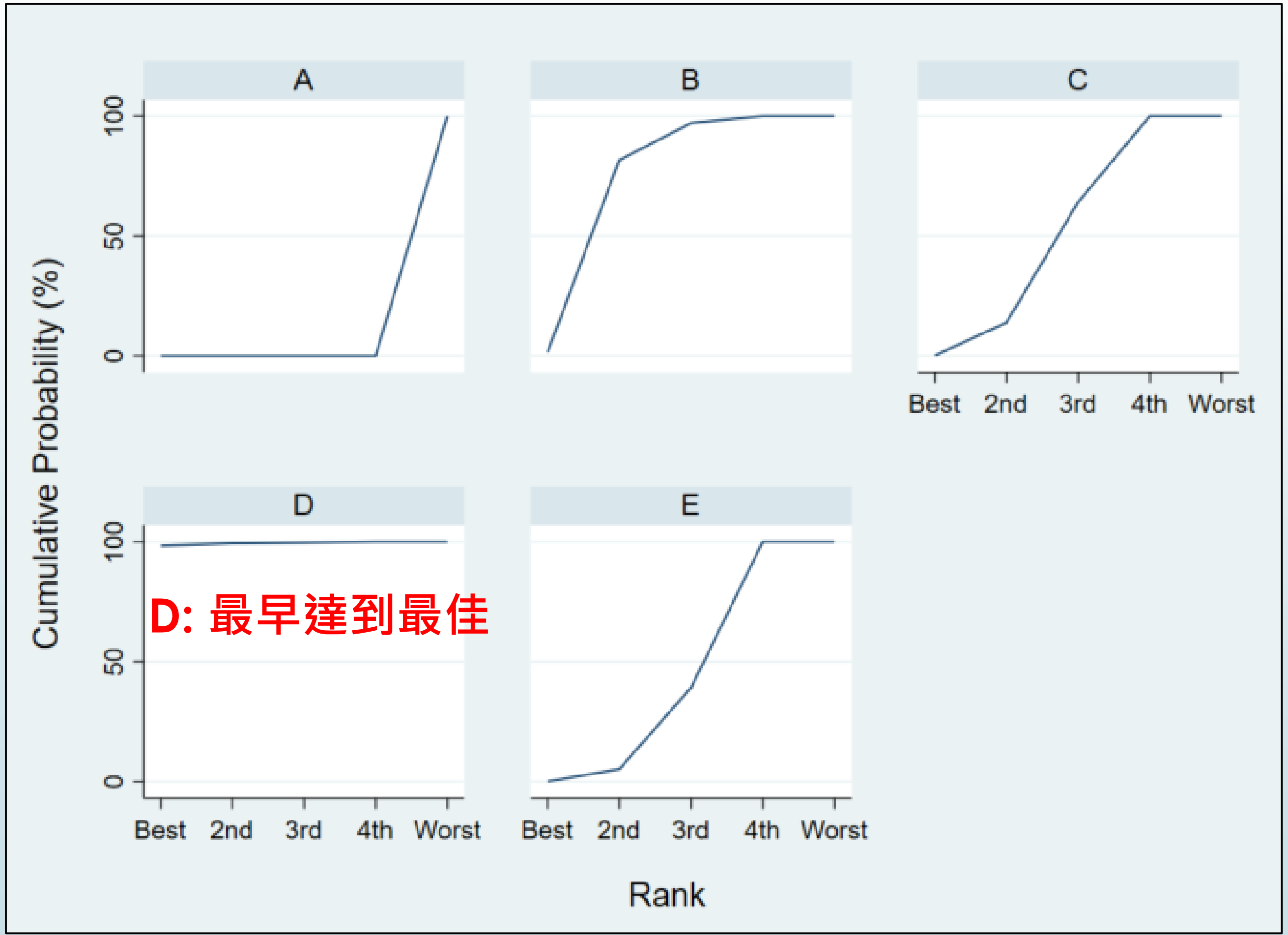
Rank	Treatment A	B	C	D	E
Best	100.0	0.0	0.0	0.0	0.0
2nd	0.0	3.0	33.7	0.3	63.0
3rd	0.0	13.3	54.2	0.3	32.2
4th	0.0	82.0	12.0	1.2	4.8
Worst	0.0	1.7	0.1	98.2	0.0

Step 4: Determining Relative Rankings of Treatments

- Identify superiority 輸入：
  network rank min, line cumulative xlabel (1/5) seed (10000) reps (10000) meanrank

```
Estimated probabilities (%) of each treatment hav
- assuming the minimum parameter is the best
- using 10000 draws
- allowing for parameter uncertainty
```

Rank	A	B	C	D	E
	Treatment				
Best	0.0	1.5	0.2	98.3	0.0
2nd	0.0	80.1	13.7	1.0	5.2
3rd	0.0	15.4	50.3	0.3	34.0
4th	0.0	3.0	35.8	0.4	60.8
Worst	100.0	0.0	0.0	0.0	0.0
MEAN RANK	5.0	2.2	3.2	1.0	3.6
SUCRA	0.0	0.7	0.4	1.0	0.4



SUCRA: Surface under the cumulative ranking →
more precise estimation of cumulative ranking probabilities

Step 3: Creating Plots and League Table of Effect Size by Treatment
Step 5: Checking for Publication Bias

use "D:\助理研究員\中榮醫研部-生統小組\全院教育課程規劃-2022oct\112年生統課程規劃\護理部-Stata\Stata-Network meta_new\funnel plot.dta ", clear

- Comparative effect size (diff) and standard error (se) for each pair of treatment 輸入：

network forest, msize (*0.15) diamond eform xlabel (0.1 1 10 100) colors (black blue red) list

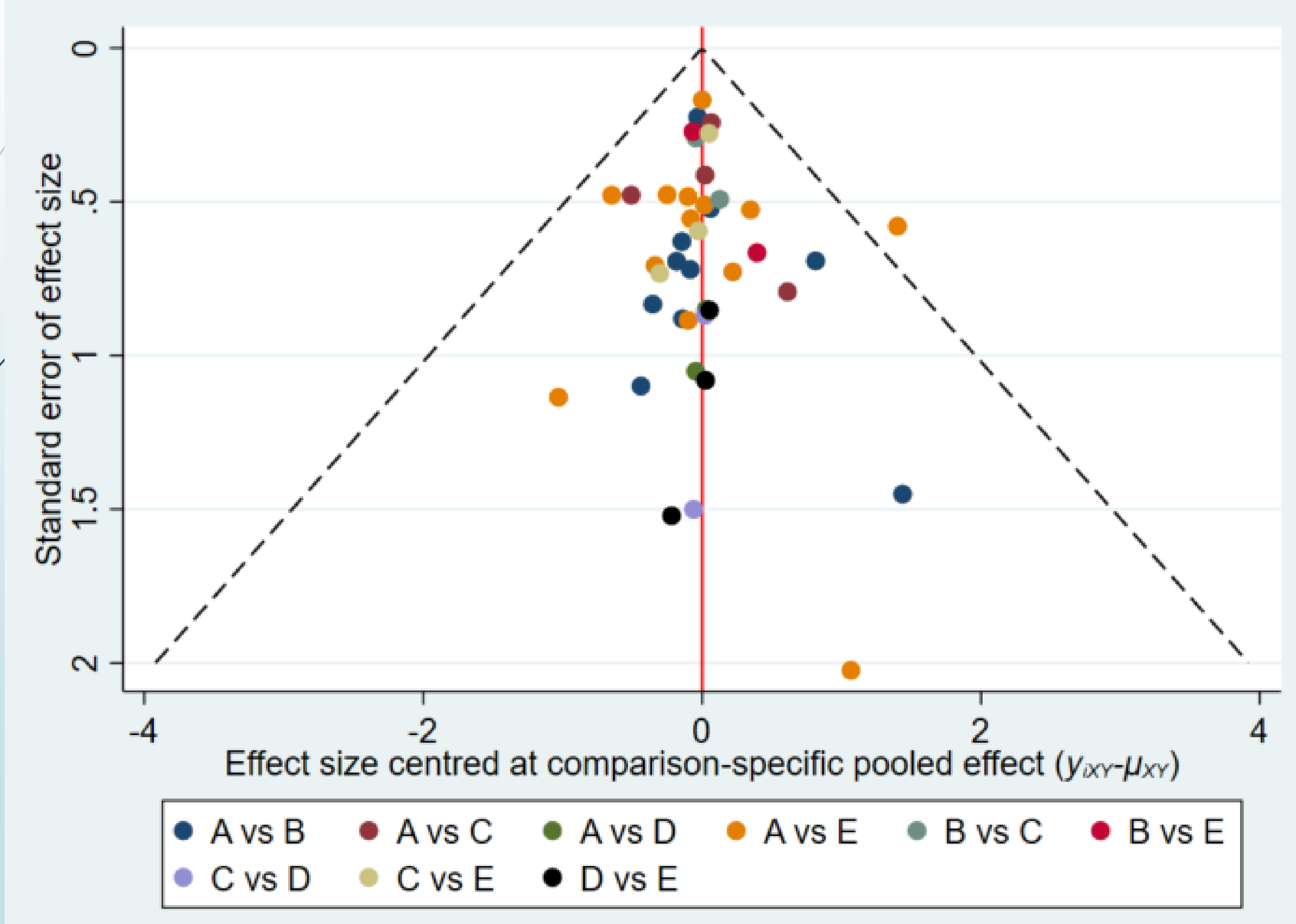
```
. network forest, msize (*0.15) diamond eform xlabel (0.1 1 10 100) colors (black blue red) list
Warning: inconsistency matrix of fitted values not found - forest plot will be incomplete
Listing of results extracted from current data and saved network meta-analyses:
```

	t1	t2	design	type	studyvar	diff	se
1.	A	B	A B E	study	Barrachina2016	-1.5830047	.62940991
2.	A	B	A B	study	Benoni2000	-1.5224265	.72019919
3.	A	B	A B	study	Ekb2000	0	1.4509525
4.	A	B	A B	study	Fraval2017	-1.8769173	1.0996804
5.	A	B	A B	study	Hsu2015	-1.7917595	.83333333
6.	A	B	A B	study	Husted2003	-1.5781854	.88053153
7.	A	B	A B	study	Lee2013	-1.3783262	.52205333
8.	A	B	A B	study	Lemay2004	-1.6204877	.69403529
9.	A	B	A B	study	Niskanen2005	-.62415431	.69264847
10.	A	B		cons		-1.4702229	.22500835
11.	A	C	A C	study	Alshryda2013	-1.1966735	.41343569
12.	A	C	A C	study	Martin2014	-.6061358	.79296146
13.	A	C	A C E	study	Wei2014	-1.7266202	.47860044
14.	A	C		cons		-1.1529375	.24228968
15.	A	D	A D E	study	Yi2016	-3.4022721	1.0513314
16.	A	D		cons		-3.327687	.85041684
17.	A	E	A B E	study	Barrachina2016	-.71995844	.52625457
18.	A	E	A E	study	Benoni2001	-.84729786	.72784745
19.	A	E	A E	study	Claeys2007	-2.0971411	1.1361016
20.	A	E	A E	study	Garneti2004	.33420209	.57961088

Step 3: Creating Plots and League Table of Effect Size by Treatment
Step 5: Checking for Publication Bias

- **Network Funnel Plot 輸入：**

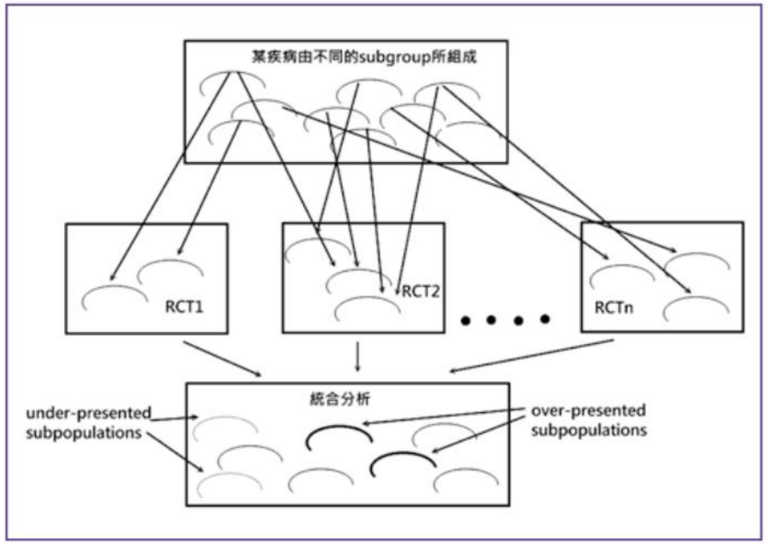
netfunnel diff se t1 t2, random bycomparison



總結

- 僅由單一個隨機分派研究的結果來下結論是一種比較危險的行為，萬一這個結果有隨機錯誤時（error by chance），我們就有可能對某個醫學議題造成誤判。
- 統合分析可以提供較客觀的整合分析結果，對於不合適的研究我們也可藉由敏感性分析將其剔除，而使分析結果更正確。
- 隨機分派研究與觀察性研究的證據強度（level of evidence）是不同的，我們在看一篇統合分析的論文時一定要注意所選取論文的研究種類、品質、和訊息強度。

統合分析和隨機分派研究論文結果牴觸的可能原因:
某些特定族群被過度呈現



生統小組：統計方法教育訓練

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臨床試驗與統合分析實務

Thank you for listening