早期使用咖啡因治療可以改善早產兒支氣管肺發育不良及死亡率嗎?

報告日期：2019/05/28

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單位：新生兒加護病房

背景-1

- 早產兒佔新生兒加護病房百分之九十 。
- 治療呼吸暫停疾病是必須治療過程之一。
- 反覆性呼吸暫停可能導致...低氧血症和心搏過緩，甚至可能嚴重到需要使用正壓通氣。
- 臨床上使用兩種形式的甲基黃嘌呤類藥物（咖啡因和茶鹼）用於刺激呼吸，預防呼吸暫停。

背景

- 呼吸暫停是早產兒常見的問題，反覆性呼吸暫停可能導致低氧血症和心搏過緩，甚至需使用正壓通氣
- 治療：
  - 甲基黃嘌呤類藥物 (咖啡因/茶鹼) →刺激呼吸，預防呼吸暫停
    (Caffeine versus theophylline for apnea in preterm infants. CDSR. 2000;(2):CD000273)
  - 咖啡因治療安全範圍較寬，副作用較少(如:心跳過快)
  - 北部至少有兩家醫學中心開始使用咖啡因

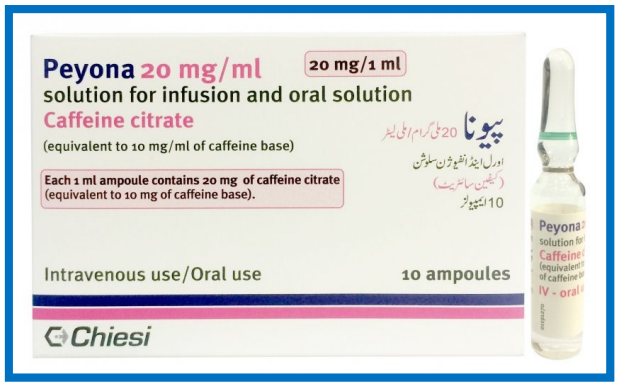
口服

針劑

Asiphylline
250mg/10mL/Amp.
心安寧注射液
250毫克/10毫升/支

單位目前使用theophylline(茶鹼)

VS



咖啡因對於改善早產兒支氣管肺發育不良有沒有效果？

Systematic review and meta-analysis of clinical outcomes of early caffeine therapy in preterm neonates (2016)

Year	Bioxbio Journal Impact*	IF
2017/2018	-	3.838
2016	-	3.493
2015	-	3.830
2014	-	3.878
2013	-	3.688
2012	-	3.578
2011	-	2.958
2010	-	3.063

步驟 1:系統性文獻回顧探討的問題為何?

Population	the use of early caffeine therapy (initiated at less than 3 days of life) in preterm infants.
Intervention	The early use of caffeine (出生三天內)
Comparison	The late use of caffeine (出生三天後)
Outcomes	Primary outcomes 1. bronchopulmonary dysplasia(支氣管肺發育不良) 2. mortality.(死亡率)

步驟 2:系統性文獻回顧的品質如何?(FAITH)

F-研究是否找到 (Find) 所有的相關證據?

良好的文獻搜尋至少應包括二個主要的資料庫(如:Medline, Cochrane 考科藍實證醫學資料庫,EMBASE 等),並且加上文獻引用檢索(參考文獻中相關研究、Web of Science, Scopus 或 Google Scholar)、試驗登錄資料等。文獻搜尋應不只限於英文,並且應同時使用 MeSH 字串及一般檢索詞彙(text words)。

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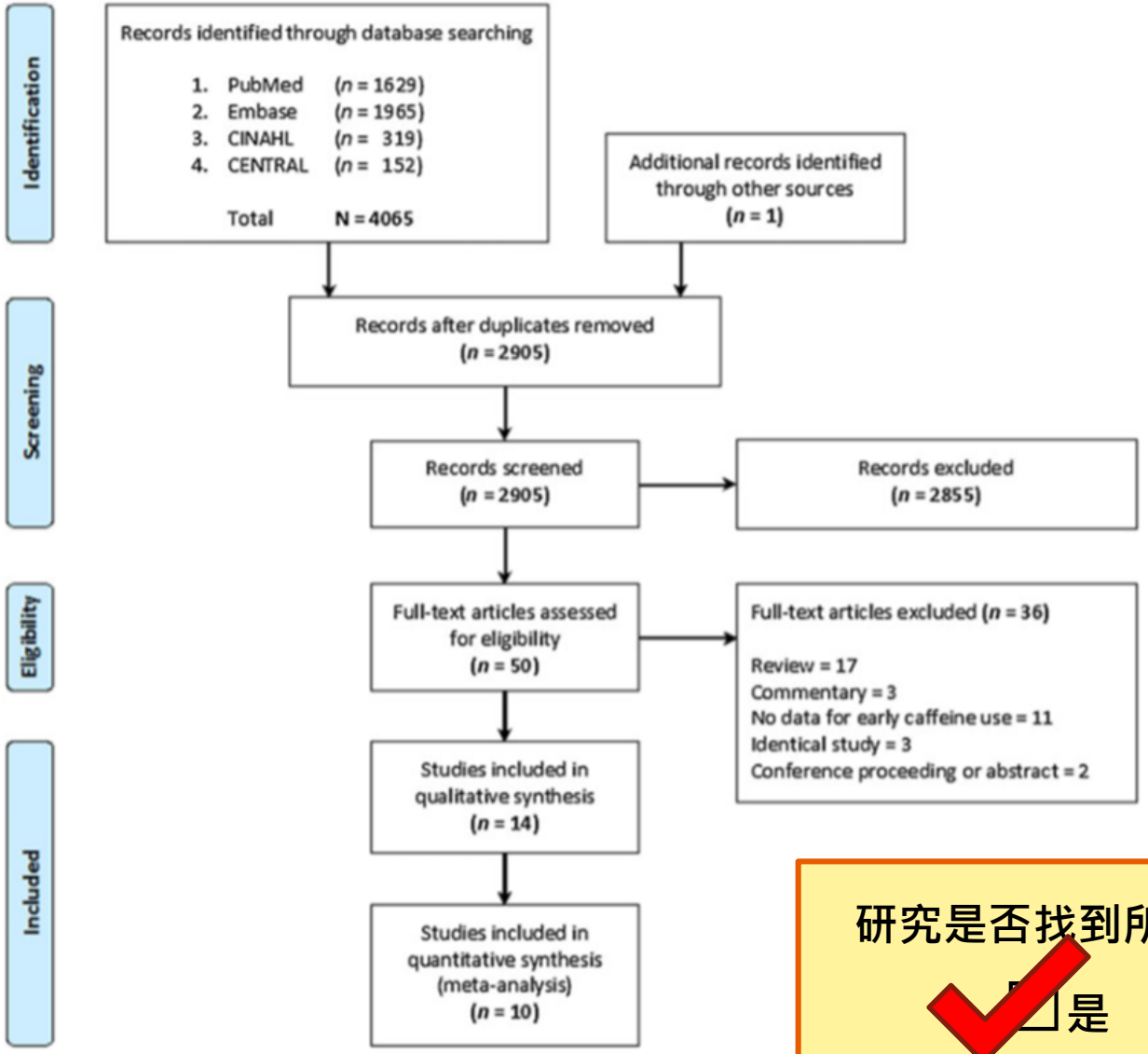
1. Included all cohort studies, case–control studies and randomized controlled.

2. Searches were performed in PubMed, Embase, CINAHL and CENTRAL from inception to 30 June 2016 without any language.

3. Keywords:' infant' , 'neonate' , 'preterm' , 'newborn' , 'premature' , 'caffeine' and 'methylxanthine' .



P3

研究是否找到所有的相關證據？

☑是 ☐否

Figure 1

Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram

步驟 2:系統性文獻回顧的品質如何?(FAITH)

A-文獻是否經過嚴格評讀 (Appraisal)?

應根據不同臨床問題的文章類型,選擇適合的評讀工具,並說明每篇研究的品質(如針對治療型的臨床問題,選用隨機分配、盲法、及完整追蹤的研究類型)。

1. Included all cohort studies, case–control studies and randomized controlled.
2. Any discrepancies were resolved through a consensus discussion.
3. The Newcastle-OttawaScale was used to evaluate the risk of bias of case–control and Cohort studies.
4. The Cochrane Collaboration’ s Tool and Jadad Scale were used to assess randomized controlled studies.

P2

研究是否找到所有的相關證據？ ☑是 ☐否

步驟 2:系統性文獻回顧的品質如何?(FAITH)

I-是否只納入 (included) 具良好效度的文章?

僅進行文獻判讀是不足夠,系統性文獻回顧需納入至少要有一項研究結果是極小偏誤的試驗。

附件檔S3

Study	Selection				Comparability of cohorts	Outcome			Total score (Range 0-9)
	Representative of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Outcome not present at beginning of study		Assessment of outcome	Sufficient follow-up duration	Adequate follow-up	
Dobson 2014 [6]	*	*	*	*	*	*	*	*	8
Gupte 2016 [20]	*	*	*	*	*	*	*	*	8
Lodha 2015 [8]	*	*	*	*	*	*	*	*	8
Patel 2013 [10]	*	*	*	*	*	*	*	*	8
Taha 2014 [9]	*	*	*	*	*	*	*	*	8
Hoecker 2002 [21]	*		*	*		*	*	*	6

A study can be awarded a maximum of one star (*) for each numbered item within the Selection and Exposure categories. A maximum of two stars (**) can be given for Comparability.

NA = Not applicable.

S3：Quality of included studies using the Newcastle-Ottawa Scale for cohort studies.

Quality of included studies using the Jadad Scale for randomised controlled trials.

附件檔S4

Study	Randomisation	Double blinding	Description of withdrawals and dropouts	Total score (Range 0-5)
Armanian 2016 [24]	1	0	1	2
Bucher 1988 [11]	2	2	0	4
Davis 2010 [23]	2	2	1	5
Katheria 2015 [22]	2	2	1	5
Levitt 1988 [12]	2	2	0	4
McPherson 2015 [13]	2	2	1	5
Saeidi 2014 [14]	1	0	1	2
Skouroliakou 2009 [25]	1	0	1	2

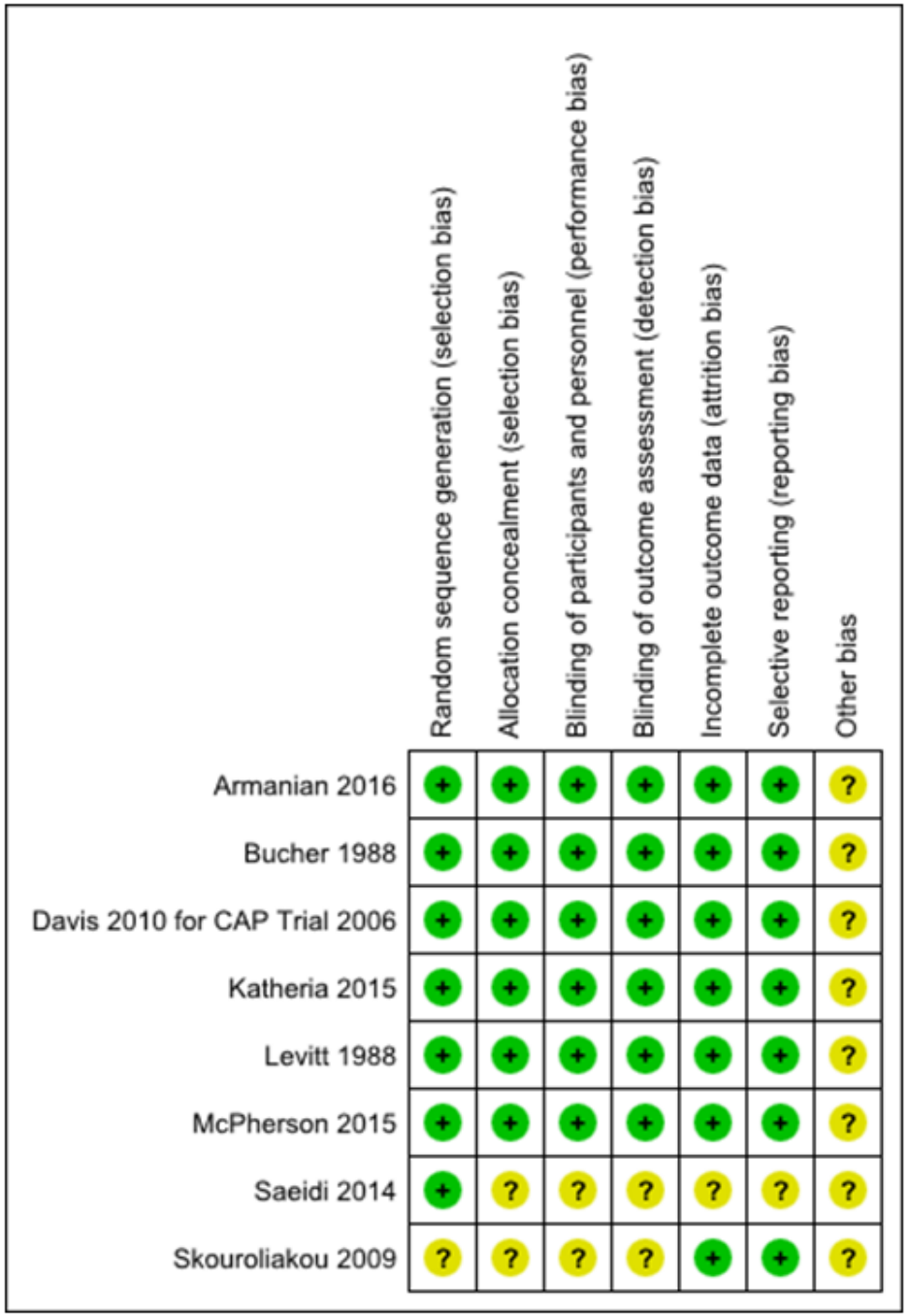


Fig. 2 Risk of bias graph: (**b**) Risk of bias summary

附件檔S1

附件檔S1

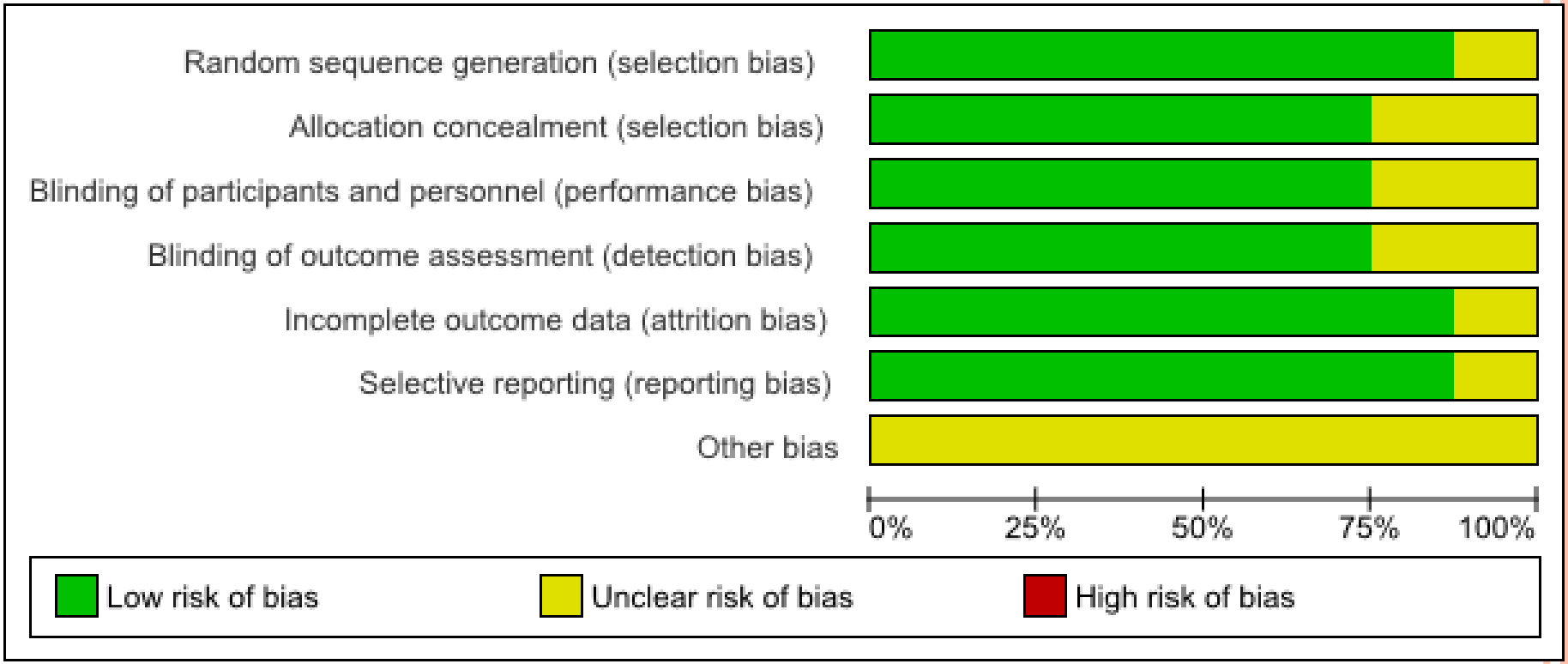


Fig. 2 Risk of bias graph: (**a**) risk of bias of all included studies

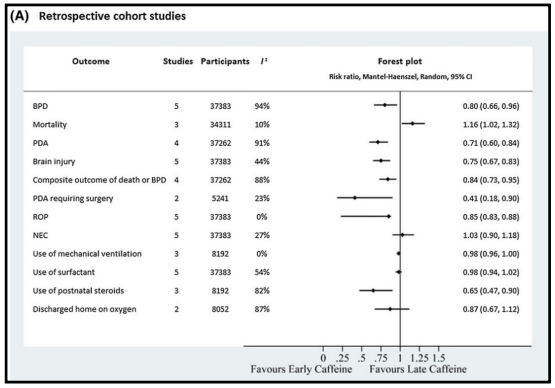
研究是否找到所有的相關證據？ ☑是 ☐否

步驟 2:系統性文獻回顧的品質如何?(FAITH)

T-作者是否以表格和圖表「總結」 (total up) 試驗結果?

應該用至少 1 個摘要表格呈現所納入的試驗結果。若結果相近,可針對結果進行統合分析(meta-analysis),並以「森林圖」(forest plot)呈現研究結果,最好再加上異質性分析。

P7-8



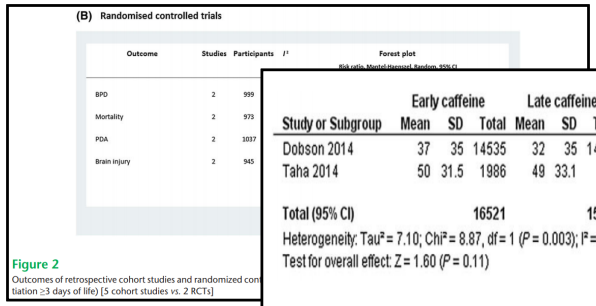


Figure 2
Outcomes of retrospective cohort studies and randomized cont
tiation ≥3 days of life) [5 cohort studies *vs.* 2 RCTs]

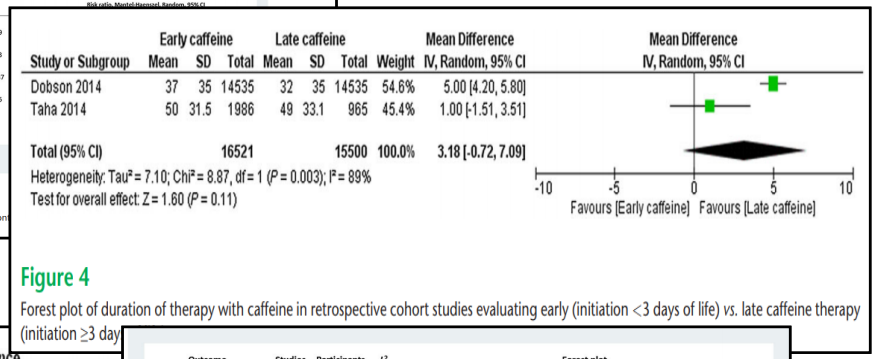


Figure 4
Forest plot of duration of therapy with caffeine in retrospective cohort studies evaluating early (initiation <3 days of life) *vs.* late caffeine therapy (initiation ≥3 day

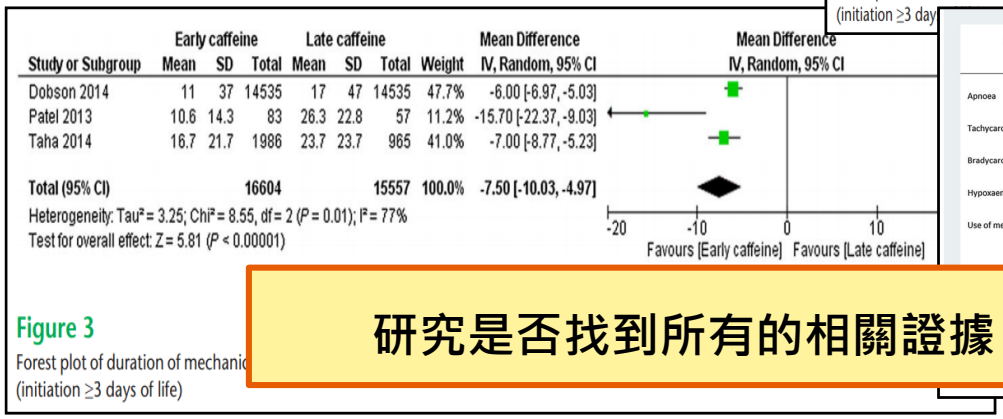
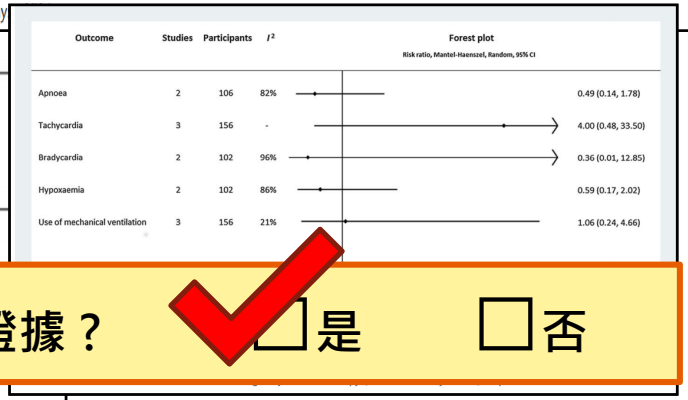


Figure 3
Forest plot of duration of mechanic
(initiation ≥3 days of life)



研究是否找到所有的相關證據？ ☑是 ☐否

步驟 2:系統性文獻回顧的品質如何?(FAITH)

H-試驗的結果是否相近-異質性 (Heterogeneity)?

在理想情況下,各個試驗的結果應相近或具同質性,若具有異質性,作者應評估差異是否顯著(卡方檢定)。根據每篇個別研究中不同的 PICO 及研究方法,探討造成異質性的原因。

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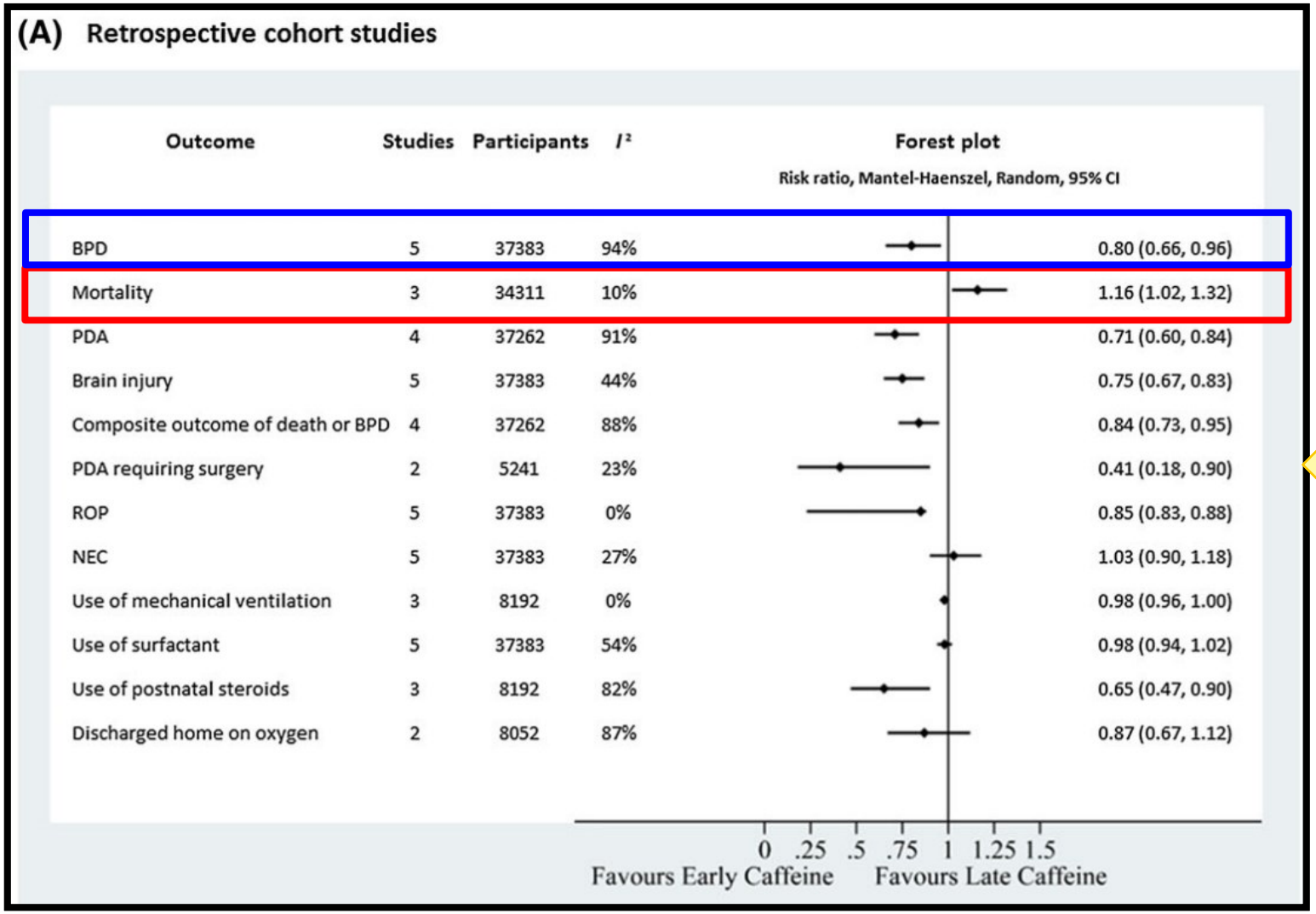
Table 2

Results of subgroup and sensitivity analysis for primary outcomes

	Number of studies	Fixed-effects model		Random-effects model	
		Effect measure (95% CI)	Heterogeneity, I^2	Effect measure (95% CI)	Heterogeneity, I^2
All studies					
BPD					
Odds ratio	5	0.71 (0.68–0.74)	92%	0.70 (0.53–0.93)	92%
Risk ratio		0.78 (0.76–0.81)	94%	0.80 (0.66–0.96)	94%
Mortality					
Odds ratio	3	1.18 (1.07–1.32)	7%	1.17 (1.03–1.33)	7%
Risk ratio		1.18 (1.06–1.30)	10%	1.16 (1.02–1.32)	10%
Subgroup analysis (Risk ratio)					
BPD					
Studies conducted in US	4	0.74 (0.72–0.77)	51%	0.75 (0.68–0.82)	51%
Studies conducted in Canada	1	1.04 (0.96–1.13)[a]	NA	1.04 (0.96–1.13)[a]	NA
Mortality					
Studies conducted in US	2	1.22			
Studies conducted in Canada	1	0.98			

試驗的結果是否相近-異質性？□是 □否

RESULTS-1


(A) Retrospective cohort studies
Outcome
Studies
Participants
I²
Forest plot
Risk ratio, Mantel-Haenszel, Random, 95% CI
BPD 5 37383 94% 0.80 (0.66, 0.96)
Mortality 3 34311 10% 1.16 (1.02, 1.32)
PDA 4 37262 91% 0.71 (0.60, 0.84)
Brain injury 5 37383 44% 0.75 (0.67, 0.83)
Composite outcome of death or BPD 4 37262 88% 0.84 (0.73, 0.95)
PDA requiring surgery 2 5241 23% 0.41 (0.18, 0.90)
ROP 5 37383 0% 0.85 (0.83, 0.88)
NEC 5 37383 27% 1.03 (0.90, 1.18)
Use of mechanical ventilation 3 8192 0% 0.98 (0.96, 1.00)
Use of surfactant 5 37383 54% 0.98 (0.94, 1.02)
Use of postnatal steroids 3 8192 82% 0.65 (0.47, 0.90)
Discharged home on oxygen 2 8052 87% 0.87 (0.67, 1.12)
0 .25 .5 .75 1 1.25 1.5
Favours Early Caffeine
Favours Late Caffeine

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RESULTS-2

(B) Randomised controlled trials

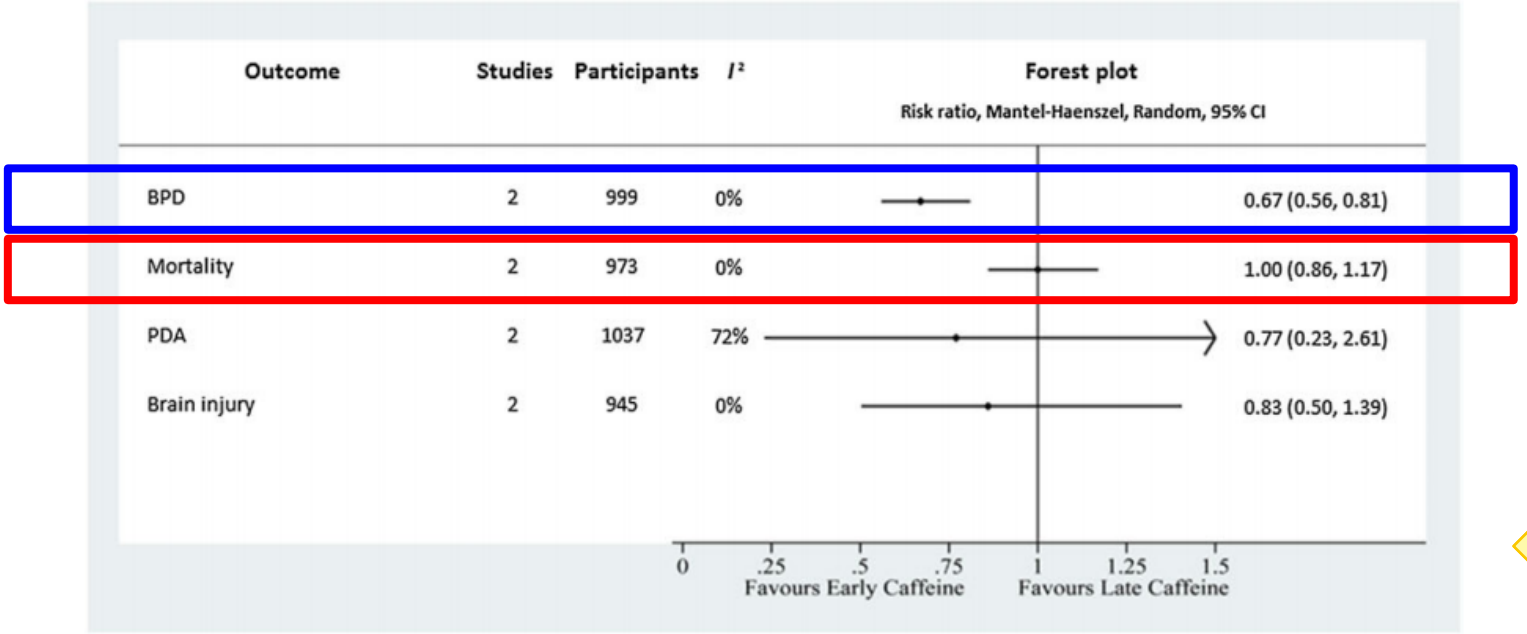

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Figure 2

Outcomes of retrospective cohort studies and randomized controlled trials evaluating early (initiation <3 days of life) *vs.* late caffeine therapy (initiation ≥3 days of life) [5 cohort studies *vs.* 2 RCTs]

RESULTS-3

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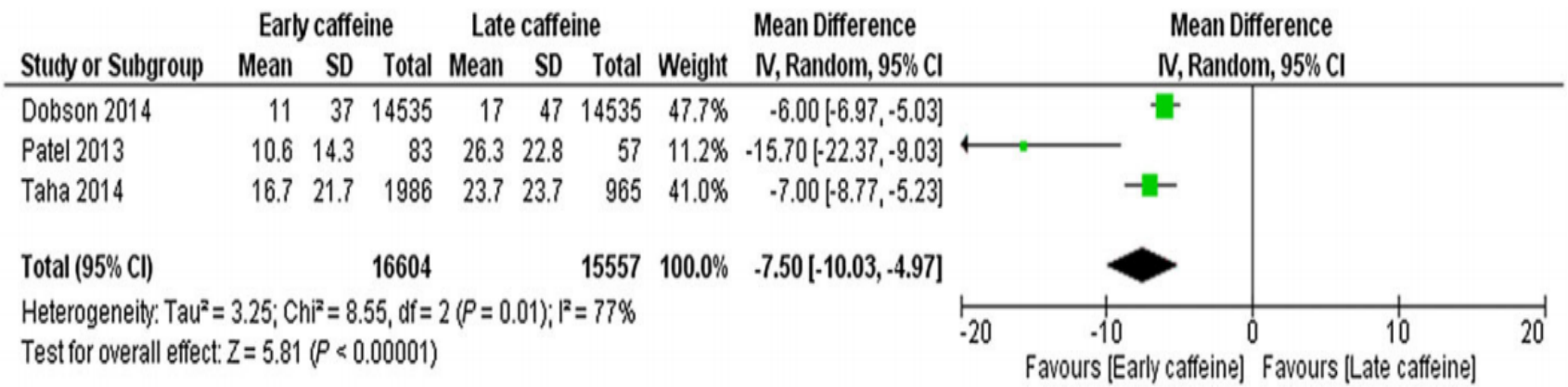

Figure 3

Forest plot of duration of mechanical ventilation in retrospective cohort studies evaluating early (initiation <3 days of life) *vs.* late caffeine therapy (initiation ≥3 days of life)

RESULTS-4

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Study or Subgroup	Early caffeine Mean	SD	Total	Late caffeine Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Dobson 2014	37	35	14535	32	35	14535	54.6%	5.00 [4.20, 5.80]
Taha 2014	50	31.5	1986	49	33.1	965	45.4%	1.00 [-1.51, 3.51]
Total (95% CI)			**16521**			**15500**	**100.0%**	**3.18 [-0.72, 7.09]**

Heterogeneity: Tau² = 7.10; Chi² = 8.87, df = 1 (*P* = 0.003); I² = 89%

Test for overall effect: Z = 1.60 (*P* = 0.11)

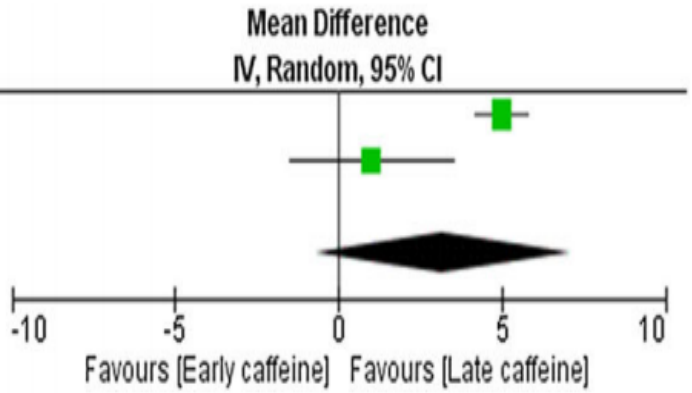

Figure 4

Forest plot of duration of therapy with caffeine in retrospective cohort studies evaluating early (initiation <3 days of life) *vs.* late caffeine therapy (initiation ≥3 days of life)

RESULTS-5

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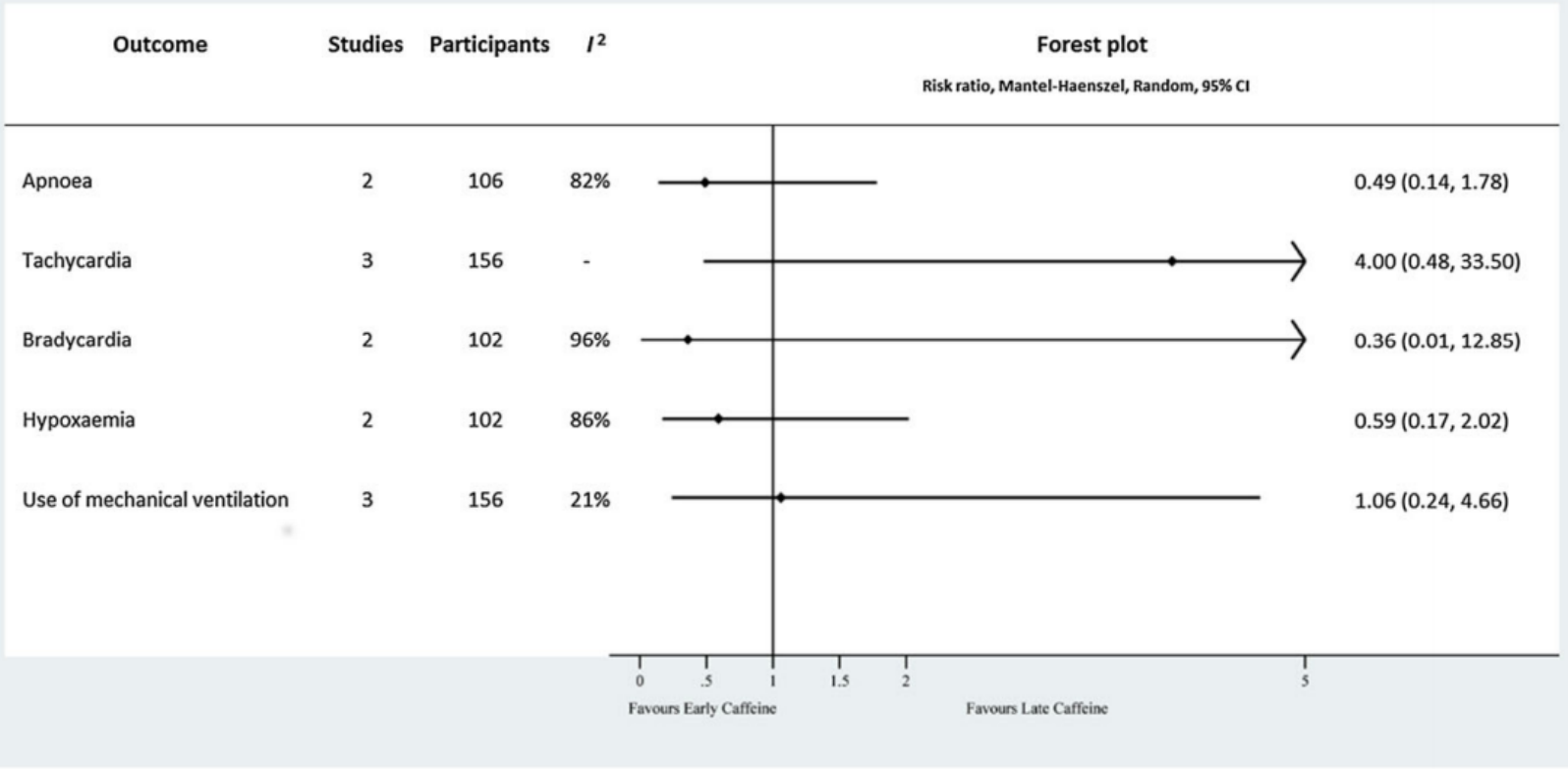

Figure 5

Outcomes of randomized controlled trials evaluating early caffeine therapy (initiation <3 days of life) *vs.* placebo

Conclusions

- ✓ Early caffeine therapy is associated with reduced incidence of bronchopulmonary dysplasia and may help decrease the burden of morbidities in preterm infants.
- ✓ <u>Limitations</u>
  - In most of the RCTs included in the current study, the sample sizes were small.
  - The effect of observational studies?
- ✓ 延伸討論： Caffeine 自費 $1060

DISCUSSION

早期使用咖啡因治療可以改善早產兒支氣管肺發育不良及死亡率嗎?

* 綠牌(同意)：9位
* 黃牌(需要更多文獻支持)：15位
* 紅牌(不同意)：1位

Thank you