高風險子癲前症孕婦服用Aspirin可以降低妊娠併發症嗎

產 房　　引言人:林靜怡 護理師
指導者:斯莉婷 護理長
日期:111/04/26

妊娠併發症

- 孕產婦的併發症：妊娠糖尿病、妊娠高血壓疾病(妊娠高血壓、先兆性子癇前症、子癲症)、靜脈血栓栓塞、感染等(余玉眉，2018)。
- 胎兒或胎盤的問題：子宮外孕、流產、胎盤早期剝離、前置胎盤、植入性胎盤等(余玉眉，2018)。

新聞

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獨家／老婆子癲前症！毛加恩痛失第二胎女兒　悲曝：盡力了

2021/11/19 18:52:00

康健

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2016/05/18 · 作者 / 楊心怡 · 出處 / Web only

大S產前癲癇發作，子癲前症是孕婦死亡的前3大原因

39歲的大S14日生下第二胎，卻傳出在生產過程中癲癇發作，出現昏迷和瞬間缺氧的癥狀，兩度急救才撿回一命。

醫生呼籲，高齡產婦、高血壓、糖尿病病史等，提早篩檢、及早預防

ETtoday新聞雲 > ETtoday星光雲　2011年12月02日 13:04

彭佳慧產後「子癲前症」送急診　輸3000c.c血撿回一命

影劇中心／綜合報導

彭佳慧28日產下一對雙胞胎女兒，她1日晚間才在臉書上報平安，她說產後當天稍晚因「子癲前症」緊急送急診室急救，輸血3000c.c.才保住一命，她發文感謝醫生當下判斷正確，也感謝其他好友替她照顧大兒子，也說大女兒Beverly和小女兒Bella都一切平安，並開心貼上兩千金照片。

她表示自己剛「救回這條小命！」「請大家給我多一些時間休息，因為只有多休息，才能讓我更快速的回到舞台上唱歌」。心存感激的她也表示將來和老公會更努力做公益，也特別感謝婦產科醫生當下的正確判斷，讓她能在如此危急的狀況之中救回小命。

彭佳慧也慶幸「子癲前症」不是在懷孕時發生，否則擔心雙胞胎女兒健康會受影響，不過她也透露產檢時都沒有發現會造成「子癲前症」的尿蛋白及高血壓問題，完全沒料到自己會在鬼門關前走一回，所幸最後母女均安。

本院現況

	108年	109年	110年
妊娠高血壓發生件數	28件	15件	20件
傷害	13位早產 5位低體重兒 10位順產	6位早產 3位低體重兒 6位順產	11位早產 4位低體重兒 6位順產

子癲前症的定義

- 子癲前症是妊娠期全身性高血壓疾病，特徵為20週後有高血壓，伴有蛋白尿等 (JT Henderson, 2021)。
- 依病情嚴重程度不同，增加孕產婦健康併發症的風險，如：子癇發作、中風、器官損傷和死亡等(JT Henderson, 2021)。
- 造成新生兒和嬰兒風險，包括子宮內生長遲滯(IUGR)、胎兒小於妊娠年齡(SGA)、早產、胎盤早剝、死產和新生兒死亡(JT Henderson, 2021)。

背景資料

- 世界衛生組織（WHO）和英國國家健康與臨床卓越機構（NICE）都建議有子癲前症風險的孕婦，可以從12 週以前開始服用Aspirin，直到35週為止，可以降低血液濃稠度，減少血管的發炎和阻塞，進而改善胎盤功能。

Aspirin藥物

- 藥理：缺血性中風、短暫性腦缺血發作、急性冠狀動脈症候群的二級預防、穩定型缺血性心臟病。
- 降低因纖維蛋白血小板栓塞而患有缺血性中風或短暫性腦缺血的死亡和非致命性中風的綜合症風險；降低疑似急性心肌梗塞 (MI)病人的血管死亡風險。
- Aspirin 作用機轉：恢復血管內皮細胞收縮與舒張平衡，促進胎盤正常形成和功能，達到抗血小板凝集的作用，可運用於預防血管栓塞。

Aspirin 100 mg/cap

藥品資訊

商品名	Bokey 100mg/cap 伯基 腸溶微粒膠囊
成分	Aspirin
劑量劑型	100 mg/cap
院內代碼	OBOK
健保代碼	AC373441G0
ATC碼	• A01AD05 • B01AC06 • N02BA01
價格	2

故藉由Aspirin提高胎盤和胎兒的血流，以達到預防子癲前症的發生率

自費：價格2元

符合先兆子癲前症高風險，健保有給付

本院現況

先兆性子癲前症篩檢
建議篩檢族群：如有子癇前症病史、懷孕伴有慢性疾病如：慢性高血壓、腎病、第1型或第2型糖尿病或自身免疫疾病；多胎妊娠、肥胖、有子癇前症家族史、年齡≥35歲、或懷孕小於胎齡(small for gestational age,SGA)、過去曾有不良妊娠結果等。
檢測週數及費用：11-13^{+6}週，自費2500元
檢測方式：抽準媽媽的血液檢測
檢測指標：胎盤生長因子(PIGF)、懷孕相關蛋白質A(PAPP-A)
評估方式：以子癲前症風險評估軟體計算風險值
處理方式：若計算風險值偏高，建議開始每日服用100毫克Aspirin，直到孕期36-37週

經由統計調查分析「早期子癲前症風險評估」篩檢人數少，約1/10，且篩檢族群無統一標準做法。

臨床問題

- Aspirin真的可以預防子癲前症的併發症嗎？

P	Pregnancy
I	Aspirin
C	nil
O	Prevent Preeclampsia

文獻搜尋過程

P	Pregnancy
I	Aspirin
C	nil
O	Prevent Preeclampsia

History and Search Details

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Search	Actions	Details	Query	Results	Time
#22	•••	›	Search: **((Pregnancy) AND (Aspirin)) AND (((Morbidity and Mortality) OR (adverse effect)) OR (Prevent Preeclampsia))** Filters: **Systematic Review, in the last 1 year**	10	02:10:50
#15	•••	›	Search: **((Pregnancy) AND (Aspirin)) AND (((Morbidity and Mortality) OR (adverse effect)) OR (Prevent Preeclampsia))**	1,607	02:10:19
#12	•••	›	Search: **((Morbidity and Mortality) OR (adverse effect)) OR (Prevent Preeclampsia)**	2,331,723	02:07:49
#3	•••	›	Search: **Pregnancy**	1,059,244	01:44:41
#1	•••	›	Search: **Aspirin**	71,244	01:42:17

PubMed.gov

((Pregnancy) AND (Aspirin)) AND (((Morbidity and Mortality) OR (adverse eff

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Page 1 of 1

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Aspirin Use to **Prevent Preeclampsia** and Related **Morbidity** and **Mortality**: Updated Evidence Report and Systematic Review for the US **Preventive** Services Task Force.

Henderson JT, Vesco KK, Senger CA, Thomas RG, Redmond N.

JAMA. 2021 Sep 28;326(12):1192-1206. doi: 10.1001/jama.2021.8551.

PMID: 34581730

Previous systematic reviews have established benefits of low-dose **aspirin** taken during **pregnancy** to **prevent preeclampsia** and its sequelae. ...Study data abstracted into prespecified forms, checked for accuracy. Random-**effects** meta-analysis. MAIN ...

★符合 PICO ★年代最新 ★符合研究設計

JAMA The Journal of the American Medical Association

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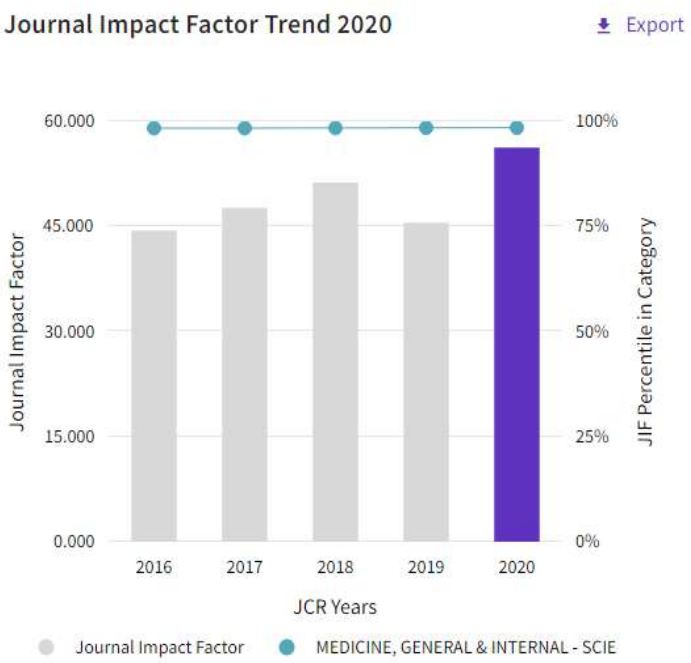
JAMA. 2021 Sep 28;326(12):1192-1206. doi: 10.1001/jama.2021.8551.

Aspirin Use to Prevent Preeclampsia and Related Morbidity and Mortality: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force

Jillian T Henderson [1], Kimberly K Vesco [1], Caitlyn A Senger [1], Rachel G Thomas [1], Nadia Redmond

Affiliations + expand

PMID: 34581730 DOI: 10.1001/jama.2021.8551



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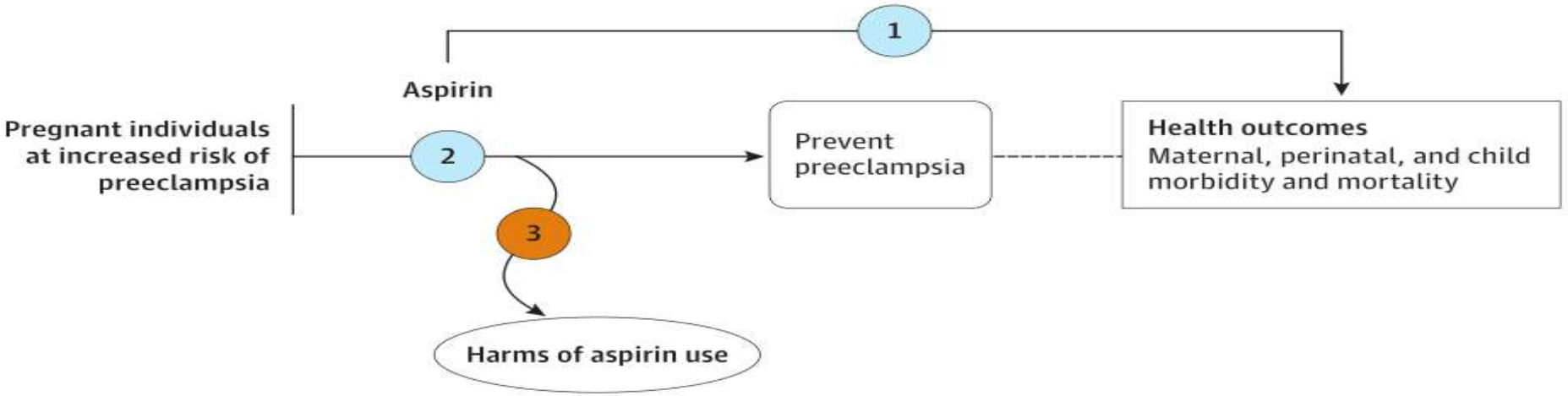
研究提問

Figure 1. Analytical Framework: Aspirin Use to Prevent Preeclampsia and Related Morbidity and Mortality



Key questions

1. Does aspirin reduce adverse maternal, perinatal, child, or combined health outcomes in pregnant persons at increased risk of preeclampsia?
   a. Does effectiveness of aspirin for reducing adverse health outcomes vary by subpopulations defined by personal characteristics or preeclampsia factors?

2. Does aspirin prevent preeclampsia in pregnant persons at increased risk for preeclampsia?
   a. Does effectiveness of aspirin for reducing preeclampsia vary by subpopulations defined by personal characteristics or preeclampsia factors?

3. What are the harms of aspirin use to prevent preeclampsia during pregnancy?
   a. Do the harms of aspirin use to prevent preeclampsia vary by subpopulations defined by personal characteristics or preeclampsia risk factors?

研究選擇

eTable 1. Inclusion and Exclusion Criteria 納入和排除標準

	Inclusion	Exclusion
Populations	**KQs 1, 2 (Efficacy):** Pregnant persons at increased risk for preeclampsia based on: • Personal sociodemographic characteristics • Medical history • Diagnostic measurements or assays (e.g., uterine artery Doppler, biomarkers) • Risk prediction model **KQ 3 (Harms):** Pregnant persons, fetuses, infants, and children.	Nonhuman populations; nonpregnant persons; studies that only/exclusively include persons seeking fertility treatment; and other selected nongeneralizable populations
Disease/ condition	Primary prevention of preeclampsia	Trials of aspirin aimed at preventing other complications of pregnancy (e.g., stillbirth)
Setting	Countries categorized as "very high" on the 2017 Human Development Index (as defined by the United Nations Development Programme)	Countries not categorized as "very high" on the 2017 Human Development Index, as there is concern for nutritional deficiencies in developing countries
Interventions	Aspirin (≥50 mg)	Nonaspirin antiplatelet medications or aspirin combined with other potentially active interventions
Comparisons	Placebo or no treatment	Any active substance or intervention (e.g., nonaspirin medication, dietary supplements, dietary change, bed rest, or weight loss)
Outcomes	**Maternal outcomes:** • Preeclampsia; Preecalmpsia with severe features • Hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome • Eclampsia, puerperal cerebrovascular disorder, cerebrovascular hemorrhage, edema, or embolus • Renal or hepatic injury/failure • Pulmonary edema, adult respiratory distress syndrome • Disseminated intravascular coagulation • Mental health diagnoses or symptoms • Maternal mortality • Measures of well-being or quality of life **Potential treatment harms:** • Abruptio placentae • Postpartum hemorrhage • Gastrointestinal complications (e.g., bleeding ulcer) **Fetal/neonatal/child outcomes:** • Preterm birth (<37 weeks): late preterm birth (34-36 weeks), moderate perterm birth, (32-34 weeks), very preterm birth (<32 weeks), extremely preterm birth (<28 weeks) • Mean gestational age • Low birth weight • Intrauterine growth restriction/small for gestational age (<10th percentile weight for gestational age) • Stillbirth or neonatal mortality **Potential treatment harms:** • Intracranial fetal bleeding • Fetal malformations • Nonclosure of the ductus arteriosus • Chorioamnionitis • Child behavioral or developmental problems	• Length of hospital stay (without indication) • Intensive care unit admission • Neonatal intensive care unit admission
Study Designs	**KQs 1, 2 (Efficacy):** Randomized, controlled trial, individual participant data meta-analysis of trials **KQ 3 (Harms):** Randomized, controlled trial or comparative cohort studies, individual participant data meta-analysis of trials	**KQs 1, 2 (Efficacy):** Any nonrandomized controlled trial **KQ 3 (Harms):** Editorials, narrative review, commentary, postmarketing surveillance, or case reports
Study Quality	Good- and fair-quality studies	Poor-quality studies
Language	English	Languages other than English

Abbreviations: KQ = Key Question; USPSTF = U.S. Preventative Services Task Force

文獻搜尋

關鍵字(MeSH team 及同義字搜尋)	搜尋資料庫
Pregnancy Preeclamp Aspirin Acetylsalicylic acid Hellp syndrome Eclamp Fetus death Fetus mortality	Medline PubMed Cochrane Central Register of Controlled Clinical Trials Embase

- 2013 年 1 月到 2020 年 5 月 15 日，在 MEDLINE、PubMed、EMBASE 和 Cochrane Central Register of Controlled Trials
- 2020 年 5 月至 2021 年 1 月 22 日期間進行持續監測

Sources searched:

Medline

PubMed

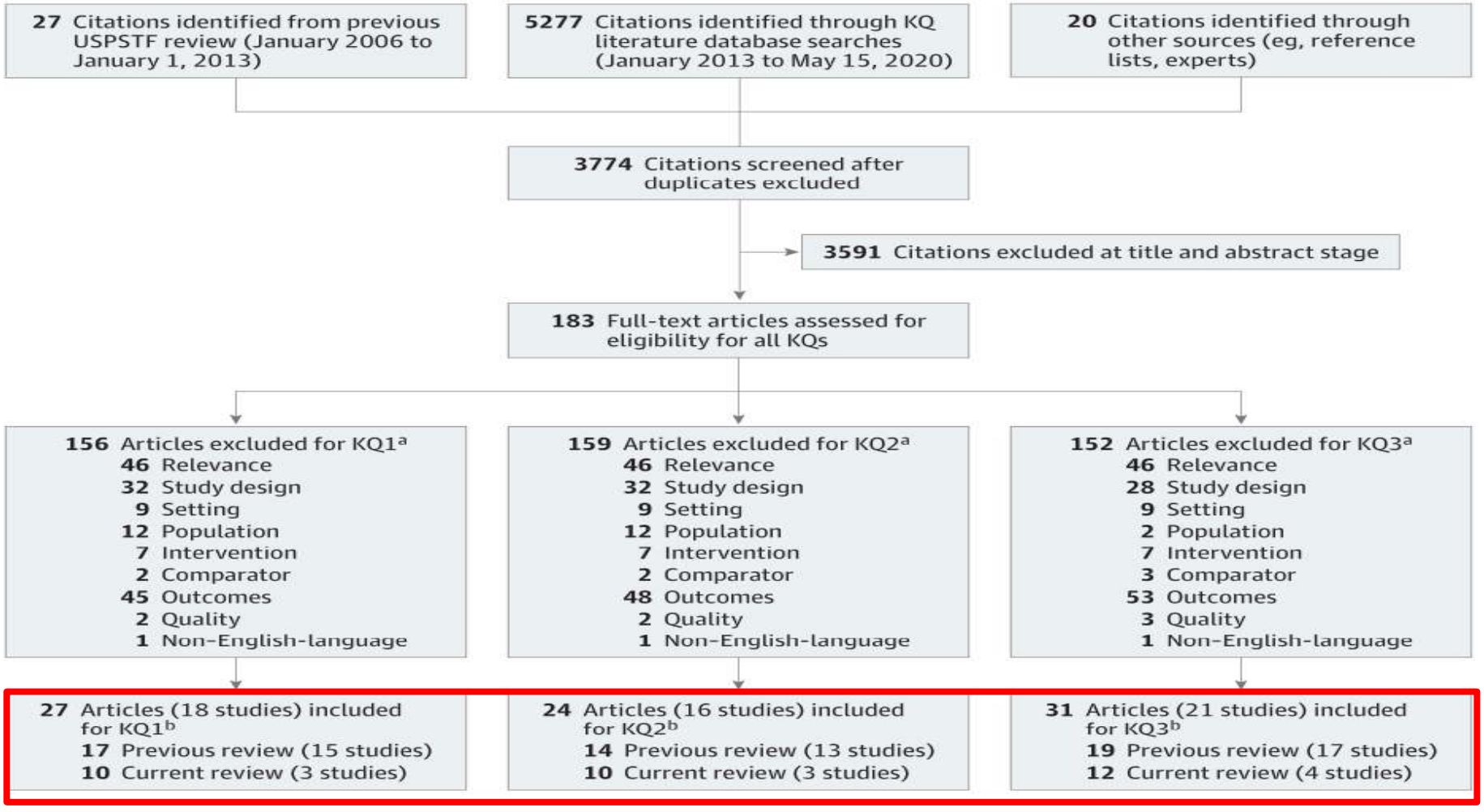
Cochrane Central Register of Controlled Clinical Trials

Embase

Key:
/ = MeSH subject heading
$ = truncation
ti = word in title
ab = word in abstract
pt = publication type
*** = truncation**
kw = keyword
lnk = subheading
de = index term
exp = explode
py = publication year

PRISMA流程圖

Figure 2. Literature Search Flow Diagram: Aspirin Use to Prevent Preeclampsia and Related Morbidity and Mortality



證據等級評估

eTable 2. Quality Assessment Criteria*

Study Design	Adapted Quality Criteria
Randomized and non-randomized controlled trials, adapted from the U.S. Preventive Services Task Force methods[1]	**Bias arising in the randomization process or due to confounding** 隨機過程混雜產生偏差 • Valid random assignment/random sequence generation method used • Allocation concealed • Balance in baseline characteristics **Bias in selecting participants into the study** 參與者的意見 • CCT only: No evidence of biased selection of sample **Bias due to departures from intended interventions** 偏離干預措施而產生偏差 • Fidelity to the intervention protocol • Low risk of contamination between groups • Participants were analyzed as originally allocated **Bias from missing data** 數據缺失的偏差 • No, or minimal, post-randomization exclusions • Outcome data are reasonably complete and comparable between groups • Reasons for missing data are similar across groups • Missing data are unlikely to bias results **Bias in measurement of outcomes** 測量結果的偏差 • Blinding of outcome assessors • Outcomes are measured using consistent and appropriate procedures and instruments across treatment groups • No evidence of inferential statistics 選擇性報告結果的偏差 **Bias in reporting results selectively**

先由兩位審查者每項研究以『good』『fair』或『poor』做為證據等級評價

再由第三位的審查者，排除『證據等級-差』的研究

研究族群

eTable 3. Patient risk Factors and Clinical Tests Used to Identify Study Populations at Increased Risk for Preeclampsia

Author, Year	%Preeclampsia incidence in control group	Hx of preeclampsia or hypertension[a] 先兆子癲	Maternal Age 產婦年齡	Nulliparity	Multifetal gestation 多胎妊娠	Renal Disease 腎病	Metabolic disease 代謝疾病	Hx of Stillbirth	Hx spontaneous abortion	Hx of SGA/IUGR	Diabetes	Prediction model[b]	Hemoglobin concentration	Positive rollover test	Angiotensin-II sensitivity	Abnormal Doppler readings 異常胎心率
Benigni, 1989[2]	NR	x						x		x						
Gallery, 1997[3]	NR	x				x										
Scazzocchio, 2017[4c]	4															x
CLASP, 1994[5]	8	x	x		x	x										
Caspi, 1994[6]	9				x											
Grab, 2000[7]	10	x						x		x						
ASPRE, 2017[8]	11	X										x				X
Viinikka, 1993[9]	11	x														
Davies, 1995[10]	12			x[d]									x			
Ayala, 2012[11]	13	x	x	x	x		x		x							
Hermida, 1997[12]	14	x	x	x	x		x		x							
Villa, 2012[13]	18	x							x	x	x					x
McParland, 1990[14]	19			x[d]												x
Yu, 2003[15a]	19															x
MFMU-HR, 1998[16]	20	x			x						x					
Morris, 1996[17]	14			x												x
Schiff, 1989[18]	23	x		x	x									x		
Wallenburg, 1986[19]	30			x[d]											x	

Abbreviations: Hx = History; SGA/IUGR = Small for gestational age/intrauterine growth restriction; NR = Not reported

[a] Includes personal history of gestational hypertension, chronic hypertension, or preeclampsia

研究結果

18

23篇

Table 1. Characteristics of Included Studies

文獻年代 | 證據等級 | 人數 | 使用劑量 | 開始及停止時間 | 年齡

Source, country/countries	Study quality	No. randomized	Increased risk criteria	Aspirin dosage, mg[a]	Timing of aspirin initiation; discontinuation	Age, mean (range), y	White, %	Nulliparous, %	Previous preeclampsia, %	Chronic hypertension, %
Increased-risk population										
ASPRE Rolnik et al,[48] 2017 Spain, Italy, UK, Israel, Belgium, Greece	Good	1776	Risk prediction model findings at 11-13 wk gestation	150	11-14 wk; 36 wk	31.5[b]	67.1	67.3	10.5	6.8
Ayala et al,[45] 2013 Spain	Good	350	Receiving pregnancy care at high-risk obstetric unit owing to range of factors	100	12-16 wk; delivery[c]	30.7	NR	52.2	NR	NR
Benigni et al,[29] 1989 Italy	Fair	33	Presence of hypertension or previous history of fetal death due to placental insufficiency, severe IUGR, early-onset preeclampsia [<32 wk]	60	12 wk; delivery	31.5	NR	NR	42.7	33.3
Caspi et al,[35] 1994 Ireland	Good	48	Uncomplicated twin pregnancies	100	Start of the second trimester; delivery[d]	28.3				
CLASP,[36] 1994 US, Australia, Canada, Germany, Spain, Hong Kong, Ireland, The Netherlands, New Zealand, Sweden, UK, Argentina, Belgium, Malaysia, Russia, United Arab Emirates	Good	9364	Increased risk determined by clinician based on range of factors including obstetric history, family history, patient and pregnancy characteristics	60	12 to 32 wk; delivery	28.5				
Davies et al,[37] 1995 UK	Fair	122	Hemoglobin concentration greater than 13.2 g/dL	75	18 wk; delivery	25.0				
Gallery et al,[38] 1997 Australia	Fair	108	Chronic hypertension or previous early, severe preeclampsia	100	17 to 19 wk; 2 wk before planned delivery	28.5 (22-38)	95.5	42.5	19.3	54.7
Grab et al,[42] 2000 Germany	Fair	43	Early IUGR, impaired uteroplacental blood, chronic hypertension or previous stillbirth, growth restriction or preeclampsia	100	18 wk; 38 wk	NR				
Hermida et al,[39] 1997 Spain	Good	100	Receiving pregnancy care at high-risk hospital unit owing to broad range of preeclampsia factors	100	12 to 16 wk; delivery[c]	30.2	100	NR	NR	NR
McParland et al,[31] 1990 UK	Fair	106	Nulliparous with persistent abnormal Doppler flow-velocity waveforms at 24 wk gestation	75	24 wk; delivery	26.1	69.0	100	NR	NR
MFMU-HR Caritis et al,[40] 1998 US	Good	2539	Presence of diabetes, chronic hypertension, multifetal gestation, previous preeclampsia	60	13 to 26 wk; delivery or if preeclampsia developed	26.5	32.7	NR	NR	NR

(continued)

Aspirin使用劑量範圍為
50 mg/d 至 150 mg/d
6項研究劑量為60 mg/d
9項研究劑量為100 mg/d
2項研究劑量150 mg/d

15項研究於分娩時同時停藥，
8項研究於分娩前即停止服用

研究結果

Table 1. Characteristics of Included Studies (continued)

文獻年代 證據等級 人數 使用劑量 開始及停止時間 年齡

Source, country/countries	Study quality	No. randomized	Increased risk criteria	Aspirin dosage, mg[a]	Timing of aspirin initiation; discontinuation	Age, mean (range), y	White, %	Nulliparous, %	Previous preeclampsia, %	Chronic hypertension, %
Morris et al,[50] 1996 Australia	Fair	102	Nulliparous with abnormal Doppler ultrasound findings at 17-19 wk gestation	100	18 wk; NR	23.8	NR	100	NR	NR
Scazzocchio et al,[49] 2017 Spain	Good	186	Abnormal Doppler ultrasound findings at 11-14 wk gestation	150	11 to 14 wk; delivery[e]	32.9	NR	63.2	0	0
Schiff et al,[30] 1989 Israel	Good	65	Nulliparity, twin gestation, history of preeclampsia, or positive rollover test	100	28 or 29 wk to 38 wk	27.4	100	NR	16.9	0
Viinikka et al,[34] 1993 Finland	Fair	208	Presence of hypertension or previous severe preeclampsia	50	16 wk; delivery	33.0	NR	24.5	11.1	88.9
Villa et al,[46] 2013 Finland	Fair	152	Range of preeclampsia risk factors accompanied by abnormal Doppler ultrasound findings at 12-14 wk gestation	100	12 to 14 wk; 35 wk or delivery (whichever came first)	30.9 (20-40)	NR	20.7	30.6	16.5
Wallenburg et al,[28] 1986 The Netherlands	Good	46	Angiotensin-II sensitivity infusion and blood pressure test	60	28 wk; delivery[d]	24 (17-38)	NR	100	0	0
Yu et al,[44] 2003 UK, Chile, South Africa, Brazil	Good	560	Abnormal Doppler ultrasound findings at 22-24 wk gestation	150	22 to 24 wk; 36 wk	29 (23-33)[b]	62.3	25.1	9.9	0
General population (included for harms only)										
Hauth et al,[32] 1993 US	Good	606	NA	60	No later than 22 wk; delivery	20.4	28.5	100	NR	0
MFMU-LR Sibai et al,[33] 1993 US	Good	3135	NA	60	13 to 25 wk; delivery	20.5	17.9	100	NR	0
Mone et al,[47] 2018 Ireland	Fair	362	NA	75	11 to 13 wk; 36 wk[e]	33.5 (19-44)	96.8	100	NR	0
Rotchell et al,[41] 1998 Barbados	Good	3647	NA	75	12 to 32 wk; delivery	NR	NR	44	NR	0.4
Subtil et al,[43] 2003 France, Belgium	Good	3294	NA	100	14 to 20 wk; 34 wk	24.7	NR	100	NR	0

Abbreviations: ASPRE, Combined Multimarker Screening and Randomized Treatment With Aspirin for Evidence-based Preeclampsia Prevention; CLASP, Collaborative Low-dose Aspirin Study in Pregnancy; IUGR, intrauterine growth restriction; MFMU-LR, Maternal Fetal Medicine Unit Network Trial enrolling low- and average-risk participants; NA, not applicable; NR, not reported.

[a] All studies placebo-controlled except for Mone et al,[47] which had a usual-care control.

[b] Median (range).

[c] Treatment time of day randomly assigned (morning, afternoon, or evening).

[d] Treatment time of day, morning. [e] Treatment time of day, evening.

結果

Table 2. Summary of Meta-analysis Results

	No. of studies reporting outcome (No. of observations randomized)	Pooled analysis, No. of studies (No. analyzed)[a]	Pooled RR, random-effects model (95% CI)[b]	I^2, %	τ^2	Relative risk, range	ARD	Relative risk, median (IQR)	ARD (range)
Perinatal mortality	15 (15 527)	11 (13 860)	0.79 (0.66-0.96)	0.0	0.0	0.31-5.15	−6.3 to 2.9	0.96 (0.59-1.10)	0.0 (−1.1 to 0.5)
Preterm birth	13 (15 213)	13 (13 619)	0.80 (0.67-0.95)	48.7	0.02	0.12-1.03	−19.5 to 0	0.65 (0.35-0.90)	−5.7 (−12.9 to −3.0)
SGA/IUGR	16 (15 767)	16 (14 385)	0.82 (0.68-0.99)	41.2	0.04	0.30-1.22	−25.7 to 4.9	0.63 (0.48-0.97)	−4.6 (−8.9 to −0.2)
Preeclampsia	16 (15 767)	16 (14 093)	0.85 (0.75-0.95)	0.0	0.0	0.07-1.43	−30.4 to 4.1	0.72 (0.31-0.89)	−4.1 (−8.4 to −1.3)
								2 94-1.23)	0.2 (−0.4 to 0.9)
Placental abruption	13 (25 761)	10 (24 970)	1.15 (0.76-1.72)	25.3	0.07	0.64-5.56	−0.6 to 1.8	1.21 (0.96-2.07)	0.3 (0 to 0.6)
bleeding					0.06	0.17-2.06	−0.3 to 0.6	0.94 (0.74-1.08)	0.0 (−0.1 to 0.0)

KQ1：Aspirin與周產期死亡率、早產和 SGA/IUGR 風險降低相關

KQ2：Aspirin與先兆子癇風險顯著降低相關

Abbreviations: ARD, absolute risk difference; RR, risk ratio; SGA/IUGR, small for gestational age/intrauterine growth restriction.

[a] Studies that reported no events in both study groups were excluded from the pooled analysis.

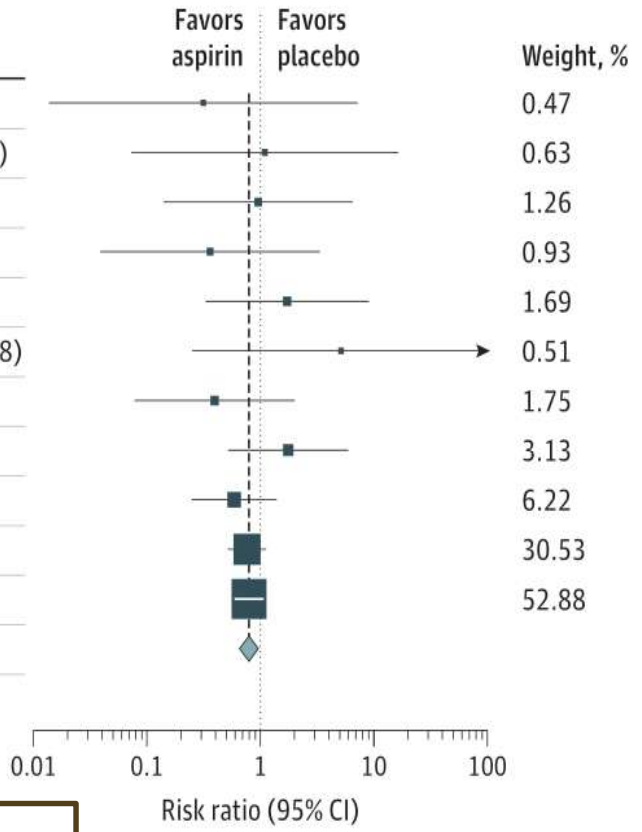
[b] Restricted maximum likelihood model with Knapp-Hartung confidence intervals.

結果

Figure 3. Perinatal Mortality, Sorted by Study Size

Source	Preeclampsia incidence with placebo, %	Aspirin dose, mg	Events, No./total		Risk ratio (95% CI)	Weight, %
			Aspirin	Placebo		
Benigni et al,[29] 1989	NR	60	0/17	1/16	0.31 (0.01-7.21)	0.47
Wallenburg et al,[28] 1986	30	60	1/21	1/23	1.10 (0.07-16.43)	0.63
Caspi et al,[35] 1994	9	100	2/48	2/46	0.96 (0.14-6.52)	1.26
McParland et al,[31] 1990	19	75	1/48	3/52	0.36 (0.04-3.35)	0.93
Gallery et al,[38] 1997	NR	100	4/58	2/50	1.72 (0.33-9.02)	1.69
Viinikka et al,[34] 1993	11	50	2/97	0/100	5.15 (0.25-105.98)	0.51
Ayala et al,[45] 2013	13	100	2/176	5/174	0.40 (0.08-2.01)	1.75
Yu et al,[44] 2003	19	150	7/276	4/278	1.76 (0.52-5.95)	3.13
ASPRE,[48] 2017	11	150	8/798	14/822	0.59 (0.25-1.40)	6.22
MFMU-HR,[40] 1998	20	60	43/1254	56/1249	0.76 (0.52-1.13)	30.53
CLASP,[36] 1994	8	60	77/4123	97/4134	0.80 (0.59-1.07)	52.88
Overall					0.79 (0.66-0.96)	

Heterogeneity: $\tau^2 = 0.00$; $I^2 = 0.00\%$
Test of $\theta = 1$; $t(10) = -2.70$; $P = .02$



周產期死亡率:風險降低21%

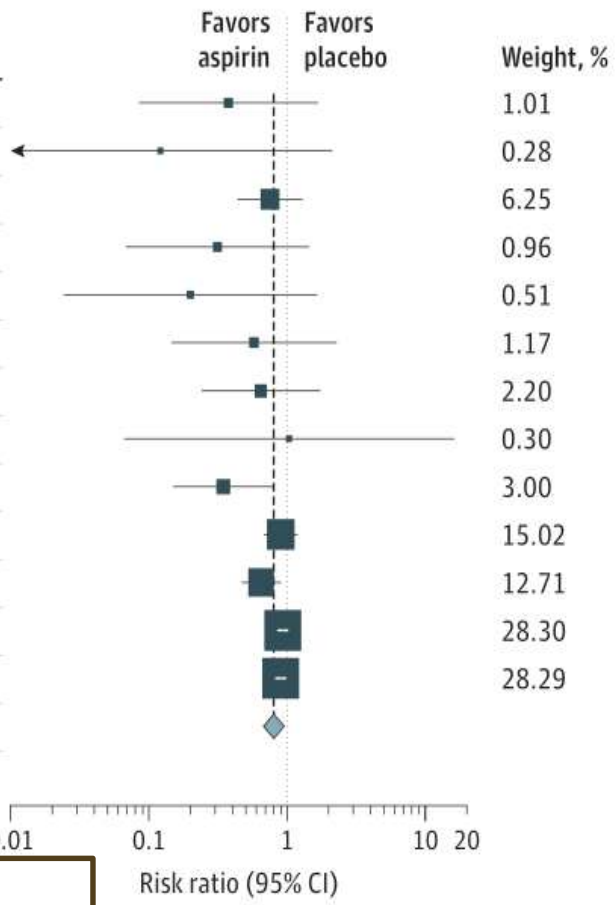
周產期死亡率：
15 studies 15,527 women RR 0.79, 95% CI 0.66 to 0.96 11 RCT 13, 860, I^2=0%

結果

Figure 4. Preterm Birth Before 37 Weeks' Gestation, Sorted by Study Size

Source	Preeclampsia incidence with placebo, %	Aspirin dose, mg	Events, No./total		Risk ratio (95% CI)	Weight, %
			Aspirin	Placebo		
Benigni et al,[29] 1989	NR	60	2/17	5/16	0.38 (0.08-1.67)	1.01
Wallenburg et al,[28] 1986	30	60	0/21	4/23	0.12 (0.01-2.12)	0.28
Caspi et al,[35] 1994	9	100	11/24	14/23	0.75 (0.44-1.30)	6.25
Schiff et al,[30] 1989	23	100	2/34	6/32	0.31 (0.07-1.44)	0.96
Hermida et al,[39] 1997	14	100	1/50	5/50	0.20 (0.02-1.65)	0.51
Morris et al,[50] 1996	14	100	3/52	5/50	0.58 (0.15-2.29)	1.17
Gallery et al,[38] 1997	NR	100	6/58	8/50	0.65 (0.24-1.74)	2.20
Davies et al,[37] 1995	12	75	1/58	1/60	1.03 (0.07-16.15)	0.30
Ayala et al,[45] 2013	13	100	7/176	20/174	0.35 (0.15-0.80)	3.00
Yu et al,[44] 2003	19	150	67/276	75/278	0.90 (0.68-1.20)	15.02
ASPRE,[48] 2017	11	150	53/798	84/822	0.65 (0.47-0.90)	12.71
HFMU-HR,[40] 1998	20	60	502/1254	537/1249	0.93 (0.85-1.02)	28.30
CLASP,[36] 1994	8	60	686/3992	761/3982	0.90 (0.82-0.99)	28.29
Overall					0.80 (0.67-0.95)	

Heterogeneity: $\tau^2 = 0.02$; $I^2 = 48.71\%$
Test of $\theta = 1$; $t(12) = -2.79$; $P = .02$



早產(<37孕週)風險:降低20%

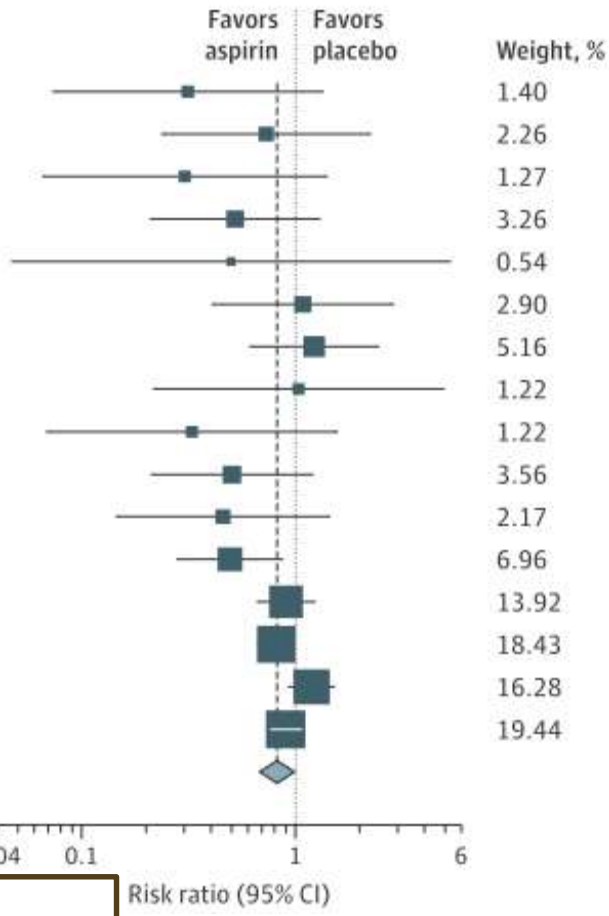
早產(<37孕週)：
13 studies 15,213 women RR 0.80, 95% CI, 0.67 to 0.95 13 RCT 13,619 , I^2=49%

結果

Figure 5. Small for Gestational Age or Intrauterine Growth Restriction, Sorted by Study Size

Source	Preeclampsia incidence with placebo, %	Aspirin dose, mg	Events, No./total		Risk ratio (95% CI)
			Aspirin	Placebo	
Benigni et al,[29] 1989	NR	60	2/17	6/16	0.31 (0.07-1.33)
Wallenburg et al,[28] 1986	30	60	4/21	6/23	0.73 (0.24-2.23)
Schiff et al,[30] 1989	23	100	2/34	6/31	0.30 (0.07-1.40)
Caspi et al,[35] 1994	9	100	6/48	11/46	0.52 (0.21-1.30)
Hermida et al,[39] 1997	14	100	1/50	2/50	0.50 (0.05-5.34)
McParland et al,[31] 1990	19	75	7/48	7/52	1.08 (0.41-2.86)
Morris et al,[50] 1996	14	100	14/52	11/50	1.22 (0.62-2.43)
Davies et al,[37] 1995	12	75	3/58	3/60	1.03 (0.22-4.92)
Villa et al,[46] 2013	18	100	2/61	6/60	0.33 (0.07-1.56)
Scazzochio et al,[49] 2017	4	150	7/80	13/75	0.50 (0.21-1.20)
Viinikka et al,[34] 1993	11	50	4/97	9/100	0.46 (0.15-1.44)
Ayala et al,[45] 2013	13	100	16/176	32/174	0.49 (0.28-0.87)
Yu et al,[44] 2003	19	150	61/276	68/278	0.90 (0.67-1.22)
ASPRE,[48] 2017	11	150	148/785	187/807	0.81 (0.67-0.99)
HFMU-HR,[40] 1998	20	60	129/1254	108/1249	1.19 (0.93-1.52)
CLASP,[36] 1994	8	60	244/4123	272/4134	0.90 (0.76-1.06)
Overall					0.82 (0.68-0.99)

Heterogeneity: $\tau^2 = 0.03$; $I^2 = 41.24\%$
Test of $\theta = 1$; $t(15) = -2.28$; $P = .04$



SGA/IUGR：風險降低18%

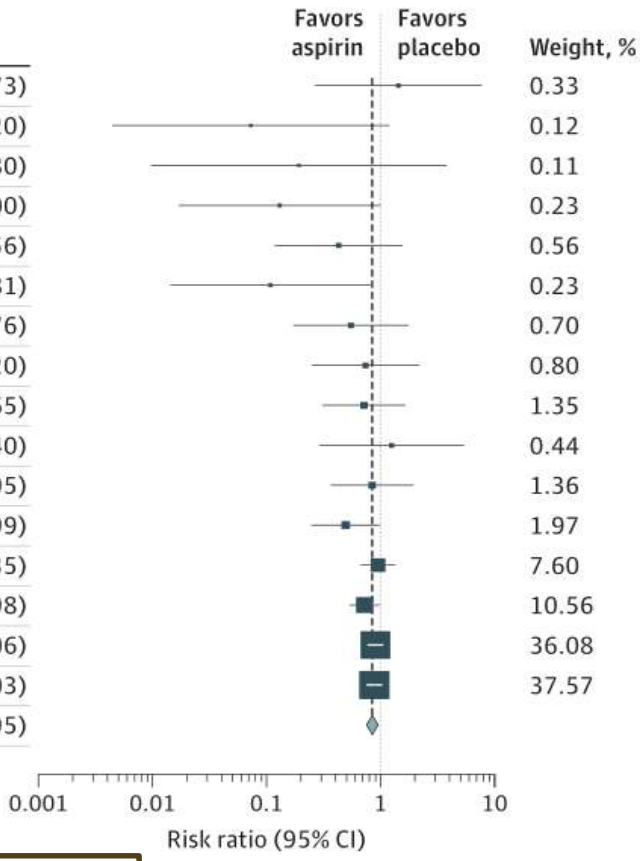
胎兒小於妊娠年齡(SGA)、子宮內生長遲滯(IUGR)
16 studies 15,767 women RR 0.82, 95% CI 0.68 to 0.99 16 RCT 14,385, I^2=41%

結果

Figure 6. Preeclampsia, Sorted by Study Size

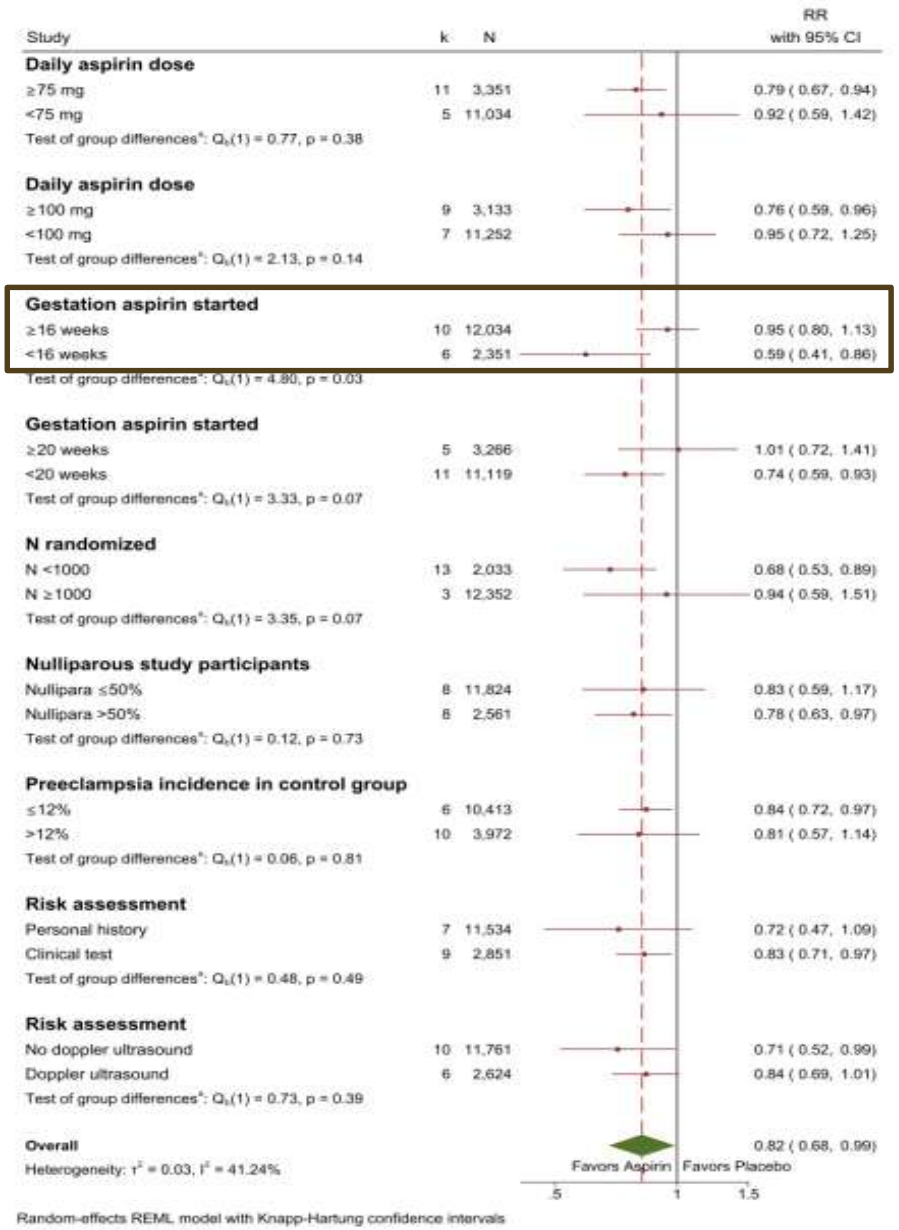
Source	Preeclampsia incidence with placebo, %	Aspirin dose, mg	Events, No./total		Risk ratio (95% CI)
			Aspirin	Placebo	
Grab et al,[42] 2000	10	100	3/22	2/21	1.43 (0.27-7.73)
Wallenburg et al,[28] 1986	30	60	0/21	7/23	0.07 (0.00-1.20)
Caspi et al,[35] 1994	9	100	0/24	2/23	0.19 (0.01-3.80)
Schiff et al,[30] 1989	23	100	1/34	7/31	0.13 (0.02-1.00)
Hermida et al,[39] 1997	14	100	3/50	7/50	0.43 (0.12-1.56)
McParland et al,[31] 1990	19	75	1/48	10/52	0.11 (0.01-0.81)
Morris et al,[50] 1996	14	100	4/52	7/50	0.55 (0.17-1.76)
Davies et al,[37] 1995	12	75	5/58	7/60	0.74 (0.25-2.20)
Villa et al,[46] 2013	18	100	8/61	11/60	0.72 (0.31-1.65)
Scazzochio et al,[49] 2017	4	150	4/80	3/75	1.25 (0.29-5.40)
Viinikka et al,[34] 1993	11	50	9/97	11/100	0.84 (0.37-1.95)
Ayala et al,[45] 2013	13	100	11/176	22/174	0.49 (0.25-0.99)
Yu et al,[44] 2003	19	150	49/276	52/278	0.95 (0.67-1.35)
ASPRE,[48] 2017	11	150	66/798	94/822	0.72 (0.54-0.98)
HFMU-HR,[40] 1998	20	60	226/1254	250/1249	0.90 (0.77-1.06)
CLASP,[36] 1994	8	60	267/3992	302/3982	0.88 (0.75-1.03)
Overall					0.85 (0.75-0.95)

Heterogeneity: $\tau^2 = 0.00$; $I^2 = 0.00\%$
Test of $\theta = 1$; $t(15) = -3.07$; $P = .01$



子癲前症：
16 studies 15,767 women RR 0.85, 95% CI, 0.75 to 0.95 16RCT 14,093, I^2=0%

eFigure 5. Subgroup Analyses of Aspirin Effectiveness Comparisons for Dosage, Timing, Study Design, and Population Characteristics on Small For Gestational Age or Intrauterine Growth Restriction



Random-effects REML model with Knapp-Hartung confidence intervals

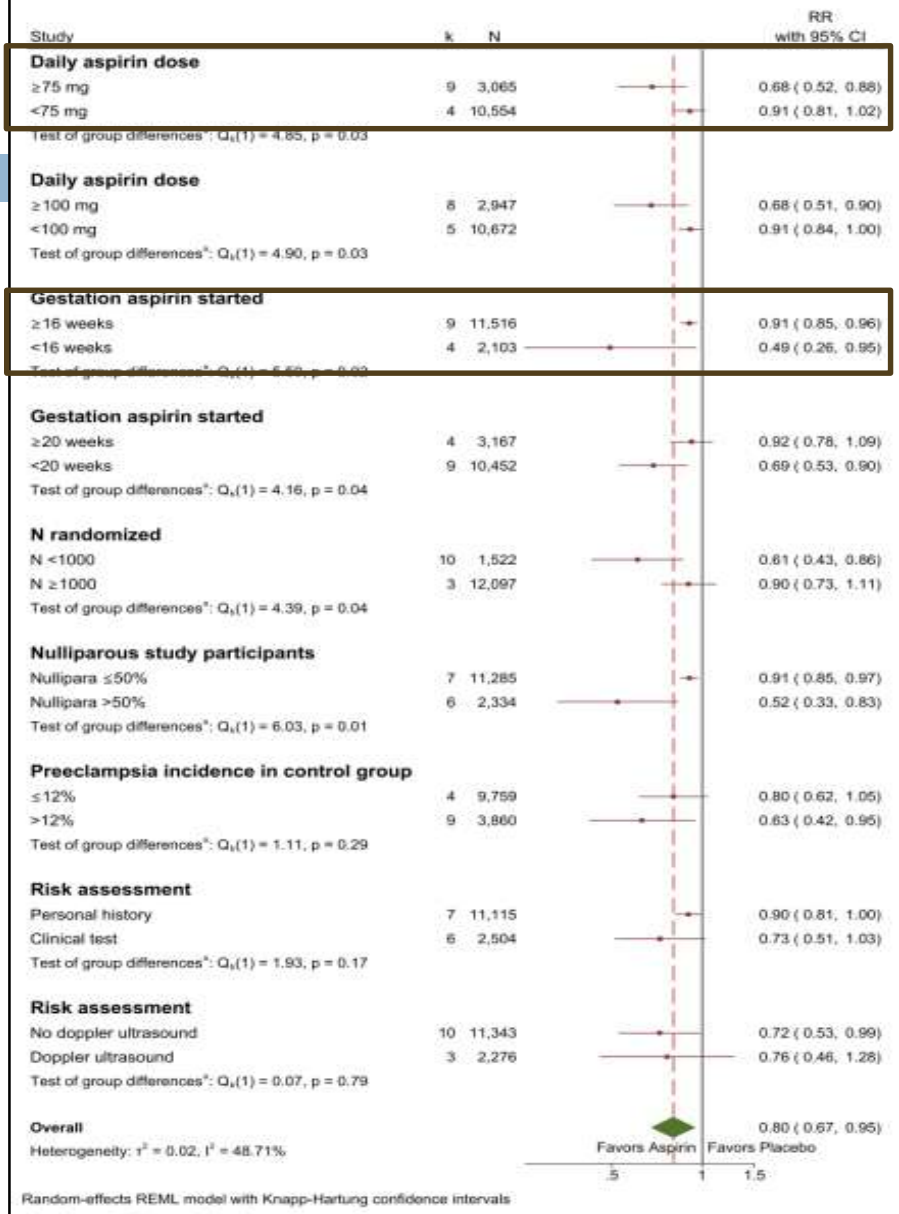
[a]Cochran's Q statistical test

Abbreviations: CI = Confidence interval; K = Number of studies; mg = milligrams; N = Number of observations; RR= Relative Risk

- **SGA/IUGR進行次族群分析結果:**

1.早期(妊娠20週之前)開始使用Aspirin和預防SGA/IUGR有顯著相關

eFigure 6. Subgroup Analyses of Aspirin Effectiveness Comparisons for Dosage, Timing, Study Design, and Population Characteristics on Preterm Delivery



*Cochran's Q statistical test

Abbreviations: CI = Confidence interval; K = Number of studies; mg = milligrams; N = Nu

RR= Relative Risk

- 早產的結果進行次族群分析

結果:

1.早期(妊娠20週之前)開始使用Aspirin與預防早產有顯著相關

2.服用Aspirin劑量>75mg/d與顯著預防早產有關

結論

Table 3. Summary of Evidence

No. of studies (study designs [No. of observations])	Summary of findings	Consistency and precision	Other limitations	Strength of evidence	Applicability
KQ1: Benefits of aspirin use on health outcomes					
18 RCTs (10 good quality, 8 fair quality [n = 15 908])	Aspirin was associated with a reduced risk of perinatal mortality (pooled RR, 0.79 [95% CI, 0.66-0.96]; I^2 = 0%), preterm birth (pooled RR, 0.80 [95% CI, 0.67-0.95]; I^2 = 49%), and SGA/IUGR (pooled RR, 0.82 [95% CI, 0.68-0.99]; I^2 = 41%)	Reasonably consistent[a]; reasonably precise[b]	Small-study effects could not be ruled out for SGA/IUGR and preterm delivery Rare maternal health outcomes, such as eclampsia and maternal mortality, occurred too infrequently to estimate preventive	Moderate for perinatal health benefits	Studies in prenatal care settings in US or comparable settings; however, mostly White participants Different criteria for
KQ2: Benefits of aspirin use on preeclampsia prevention					
16 RCTs (10 good quality, 6 fair quality [n = 15 767])	Aspirin was associated with a statistically significant reduction in the risk of preeclampsia compared with placebo (pooled RR, 0.85 [95% CI, 0.75-0.95]; I^2 = 0%) No evidence of statistical difference in the magnitude of	Reasonably consistent evidence for aspirin benefit Reasonably precise 15% reduced risk of preeclampsia associated	Small-study effects could not be ruled out and might lead to some overestimation of pooled risk estimate Confounding of study size with other study	Moderate	Studies in prenatal care settings in US or comparable settings; however, mostly White participants
			of included studies and few within-trial subgroup analyses reported		

Q1：Aspirin與周產期死亡風險降低21%（RR 0.79, 95% CI,0.66-0.96, I^2 = 0%），早產風險降低20%（RR 0.80, 95% CI,0.67-0.95, I^2 = 49%）SGA/IUGR風險降低18%（RR 0.82 , 95% CI,0.68-0.99,I^2 = 41%）

Q2：使用Aspirin與安慰劑相比，先兆子癲風險顯著降低（RR 0.85, 95% CI, 0.75-0.95, I^2 = 0%）

結論

KQ3: Harms of aspirin use					
21 RCTs (16 increased-risk and 5 average-risk populations; 14 good quality, 7 fair quality [n = 26 757]	Studies conducted among average-risk and increased-risk populations did not find any clear evidence of harms associated with daily aspirin use (<150 mg) taken during the second or third trimester of pregnancy No difference in harms by the dosage or timing of aspirin or for specific populations were identified in limited subgroup comparisons Bleeding harms were uncommon and showed null effects for differences in risk of postpartum hemorrhage (pooled RR, 1.03 [95% CI, 0.94-1.12]; I^2 = 0%; 11 studies) or fetal intracranial bleeding (pooled RR, 0.90 [95% CI, 0.51-1.57]; I^2 = 19%; 9 studies) were found The result for placental abruption (pooled RR, 1.15 [95% CI, 0.76-1.72]; I^2 = 25%; 13 studies) was also null Longer-term follow-up from 1 large trial found no difference in child developmental outcomes for aspirin-exposed vs placebo-exposed groups No differences were found within a limited set of studies reporting other rare perinatal harms	Reasonably consistent evidence of null effects for bleeding harms of daily aspirin, especially among pregnant individuals at increased preeclampsia risk Reasonably precise evidence for null effects, but less precise for especially rare harms	Reported harms were rare and not consistently reported across studies	Moderate for no difference in bleeding harms between groups, low for very rare or inconsistently reported harms[c]	Studies in prenatal care settings in US or comparable settings; however, mostly White participants Different criteria for identifying at-risk populations Aspirin dose, 50-150 mg/d Harms from trials in average-risk and increased-risk populations

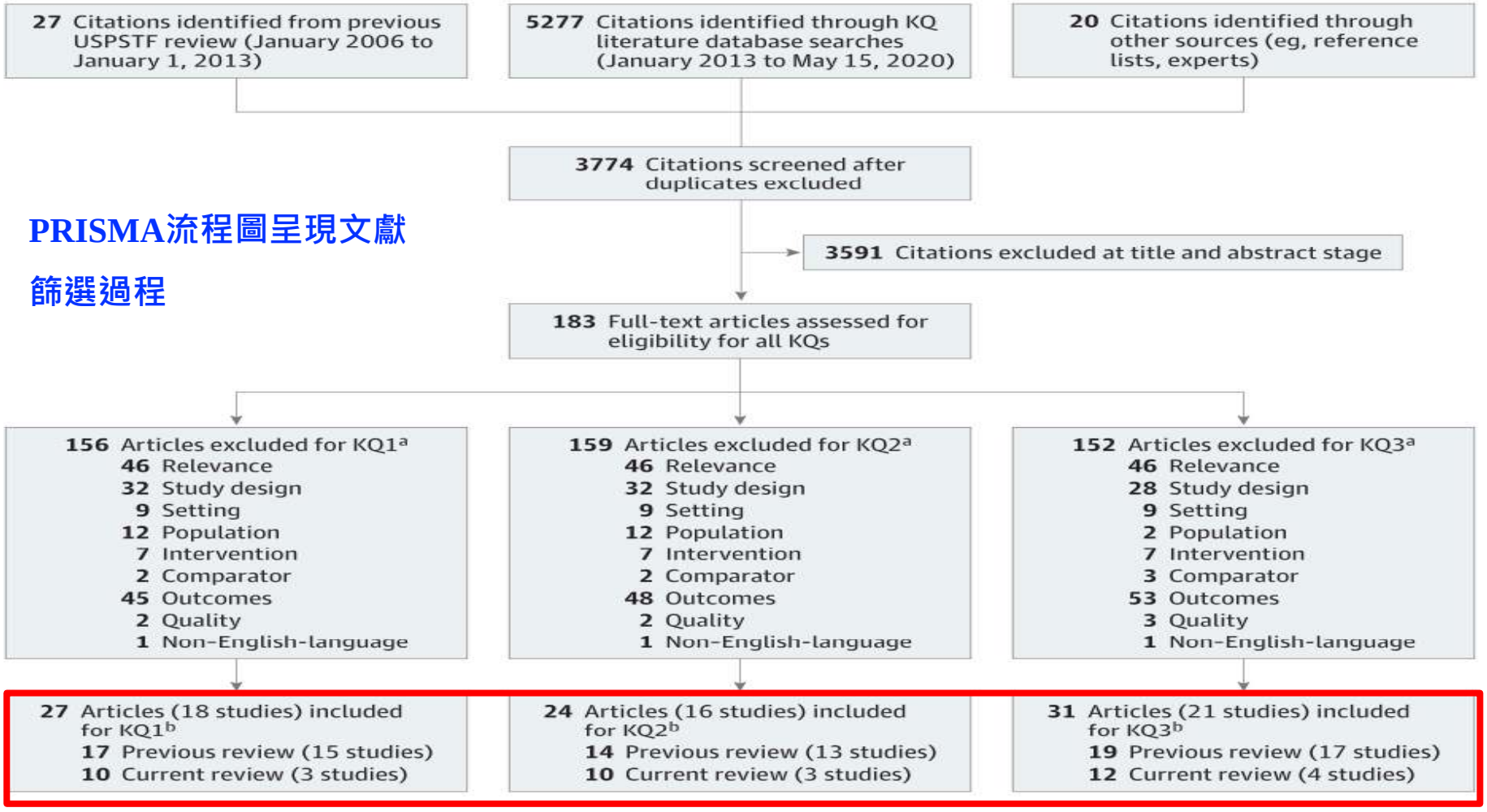
Q3：研究沒有明確發現，在妊娠孕期，每天服用阿司匹林(<150mg)會造成傷害

步驟 1：系統性文獻回顧探討的問題未何？

研究族群 / 問題 (Population/ Problem)	**先兆性子癲風險的孕婦**
介入措施 (Intervention)	**使用Aspirin**
比較 (Comparison)	**無使用Aspirin**
結果 (Outcomes)	• 周產期死亡率 • 早產 • 子宮內生長遲滯 • 先兆子癲症

步驟 2：系統性文獻回顧的品質如何？(FAITH)

Figure 2. Literature Search Flow Diagram: Aspirin Use to Prevent Preeclampsia and Related Morbidity and Mortality



PRISMA流程圖呈現文獻篩選過程

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？

最好的狀況是？

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)。

Data Sources and Searches

To identify studies published since the previous review,[18] literature searches were conducted from January 2013 through May 15, 2020, in MEDLINE, PubMed (for publisher-supplied records only), EMBASE, and the Cochrane Central Register of Controlled Trials . Additional studies were sought by reviewing reference lists of other systematic reviews. Ongoing sur- veillance was conducted after May 2020 through January 22, 2021, to identify newly published studies that might affect the findings of the review. This was accomplished through article alerts and tar- geted searches of journals with a high impact factor and journals relevant to the topic. The last surveillance on January 22, 2021, identified no new studies.

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？

最好的狀況是？

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)。

Limitations

The evidence review has several limitations. First, the search was limited to English-language literature, and only trials conducted in settings with very high Human Development Index scores were included. Studies rated as poor quality were also excluded from analysis. However, other reviews without these exclusions have not found substantively different results.[57,58]

評讀結果：□是 ☑否 □不清楚

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) ？

最好的狀況是？

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) 。

- Two reviewers applied USPSTF design-specific criteria to assess the methodological quality of all eligible studies, and each study was assigned a quality rating of “good,” “fair,” or “poor” (eTable 2 in the Supplement). Discordant quality ratings were resolved by discussion and adjudicated by a third reviewer as needed. Studies rated as poor quality were excluded from the review. Good-quality RCTs were those that met all or nearly all prespecified quality criteria. Fair-quality studies did not meet all criteria but did not have serious threats to their internal validity related to design, execution, or reporting.

評讀結果：☑是 ☐否 ☐不清楚

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) ？

最好的狀況是？

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) 。

eTable 2. Quality Assessment Criteria*

Study Design	Adapted Quality Criteria
Randomized and non-randomized controlled trials, adapted from the U.S. Preventive Services Task Force methods[1]	**Bias arising in the randomization process or due to confounding** • Valid random assignment/random sequence generation method used • Allocation concealed • Balance in baseline characteristics **Bias in selecting participants into the study** • CCT only: No evidence of biased selection of sample **Bias due to departures from intended interventions** • Fidelity to the intervention protocol • Low risk of contamination between groups • Participants were analyzed as originally allocated **Bias from missing data** • No, or minimal, post-randomization exclusions • Outcome data are reasonably complete and comparable between groups • Reasons for missing data are similar across groups • Missing data are unlikely to bias results **Bias in measurement of outcomes** • Blinding of outcome assessors • Outcomes are measured using consistent and appropriate procedures and instruments across treatment groups • No evidence of inferential statistics **Bias in reporting results selectively** • No evidence that the measures, analyses, or subgroup analyses are selectively reported

* Good quality studies generally meet all quality criteria. Fair quality studies do not meet all the criteria but do not have critical limit… …tions that coul… …by at least two … … third independent reviewer

每項研究以“good”、“fair”、“poor”分配證據等級

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 ？

最好的狀況是？

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

Table 1. Characteristics of Included Studies

Source, country/countries	Study quality	No. randomized	Increased risk criteria	Aspirin dosage, mg[a]	Timing of aspirin initiation; discontinuation	Age, mean (range), y	White, %	Nulliparous, %	Previous preeclampsia, %	Chronic hypertension, %
Increased-risk population										
ASPRE Rolnik et al,[48] 2017 Spain, Italy, UK, Israel, Belgium, Greece	Good	1776	Risk prediction model findings at 11-13 wk gestation	150	11-14 wk; 36 wk					
Ayala et al,[45] 2013 Spain	Good	350	Receiving pregnancy care at high-risk obstetric unit owing to range of factors	100	12-16 wk; delivery[c]					
Benigni et al,[29] 1989 Italy	Fair	33	Presence of hypertension or previous history of fetal death due to placental insufficiency, severe IUGR, early-onset preeclampsia [<32 wk]	60	12 wk; delivery					
Caspi et al,[35] 1994 Ireland	Good	48	Uncomplicated twin pregnancies	100	Start of the second trimester; delivery[d]					
CLASP,[36] 1994 US, Australia, Canada, Germany, Spain, Hong Kong, Ireland, The Netherlands, New Zealand, Sweden, UK, Argentina, Belgium, Malaysia, Russia, United Arab Emirates	Good	9364	Increased risk determined by clinician based on range of factors including obstetric history, family history, patient and pregnancy characteristics	60	12 to 32 wk; delivery					
Davies et al,[37] 1995 UK	Fair	122	Hemoglobin concentration greater than 13.2 g/dL	75	18 wk; delivery	25.0	95.8	100	0	0
Gallery et al,[38] 1997 Australia	Fair	108	Chronic hypertension or previous early, severe preeclampsia	100	17 to 19 wk; 2 wk before planned delivery	28.5 (22-38)	95.5	42.5	19.3	54.7
Grab et al,[42] 2000 Germany	Fair	43	Early IUGR, impaired uteroplacental blood, chronic hypertension or previous stillbirth, growth restriction, or preeclampsia	100	18 wk; 38 wk	NR	NR	NR	41.9	44.2
Hermida et al,[39] 1997 Spain	Good	100	Receiving pregnancy care at high-risk hospital unit owing to broad range of preeclampsia factors	100	12 to 16 wk; delivery[c]	30.2	100	NR	NR	NR
McParland et al,[31] 1990 UK	Fair	106	Nulliparous with persistent abnormal Doppler flow-velocity waveforms at 24 wk gestation	75	24 wk; delivery	26.1	69.0	100	NR	NR
MFMU-HR Caritis et al,[40] 1998 US	Good	2539	Presence of diabetes, chronic hypertension, multifetal gestation, previous preeclampsia	60	13 to 26 wk; delivery or if preeclampsia developed					

- 所有納入文獻都是 **RCT**
- 先由兩位審查者每項研究以『good』『fair』或『poor』做為證據等級評價
- 再由第三位的審查者，排除『證據等級-差』的研究

評讀結果：☑是　☐否　☐不清楚

步驟 2：系統性文獻回顧的品質如何？(FAITH)

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Table 1. Characteristics of Included Studies (continued)

Source, country/countries	Study quality	No. randomized	Increased risk criteria	Aspirin dosage, mg[a]	Timing of aspirin initiation; discontinuation	Age, mean (range), y	White, %	Nulliparous, %	Previous preeclampsia, %	Chronic hypertension, %
Morris et al,[50] 1996 Australia	Fair	102	Nulliparous with abnormal Doppler ultrasound findings at 17-19 wk gestation	100	18 wk; NR	23.8	NR	100	NR	NR
Scazzocchio et al,[49] 2017 Spain	Good	186	Abnormal Doppler ultrasound findings at 11-14 wk gestation	150	11 to 14 wk; delivery[c]	32.9	NR	63.2	0	0
Schiff et al,[30] 1989 Israel	Good	65	Nulliparity, twin gestation, history of preeclampsia, or positive rollover test	100	28 or 29 wk to 38 wk	27.4	100	NR	16.9	0
Viinikka et al,[34] 1993 Finland	Fair	208	Presence of hypertension or previous severe preeclampsia	50	16 wk; delivery	33.0	NR	24.5	11.1	88.9
Villa et al,[46] 2013 Finland	Fair	152	Range of preeclampsia risk factors accompanied by abnormal Doppler ultrasound findings at 12-14 wk gestation	100	12 to 14 wk; 35 wk or delivery (whichever came first)	30.9 (20-40)	NR	20.7	30.6	16.5
Wallenburg et al,[28] 1986 The Netherlands	Good	46	Angiotensin-II sensitivity infusion and blood pressure test	60	28 wk; delivery[d]	24 (17-38)	NR	100	0	0
Yu et al,[44] 2003 UK, Chile, South Africa, Brazil	Good	560	Abnormal Doppler ultrasound findings at 22-24 wk gestation	150	22 to 24 wk; 36 wk	29 (23-33)[b]	62.3	25.1	9.9	0
General population (included for harms only)										
Hauth et al,[32] 1993 US	Good	606	NA	60	No later than 22 wk; delivery	20.4	28.5	100	NR	0
MFMU-LR Sibai et al,[33] 1993 US	Good	3135	NA	60	13 to 25 wk; delivery	20.5	17.9	100	NR	0
Mone et al,[47] 2018 Ireland	Fair	362	NA	75	11 to 13 wk; 36 wk[e]	33.5 (19-44)	96.8	100	NR	0
Rotchell et al,[41] 1998 Barbados	Good	3647	NA	75	12 to 32 wk; delivery	NR	NR	44	NR	0.4
Subtil et al,[43] 2003 France, Belgium	Good	3294	NA	100	14 to 20 wk; 34 wk	24.7	NR	100	NR	0

Abbreviations: ASPRE, Combined Multimarker Screening and Randomized Treatment With Aspirin for Evidence-based Preeclampsia Prevention; CLASP, Collaborative Low-dose Aspirin Study in Pregnancy; IUGR, intrauterine growth restriction; MFMU-LR, Maternal Fetal Medicine Unit Network Trial enrolling low- and average-risk participants; NA, not applicable; NR, not reported.

[a] All studies placebo-controlled except for Mone et al,[47] which had a usual-care control.

[b] Median (range).

[c] Treatment time of day

[d] Treatment time of day.

評讀結果：☑是 ☐否 ☐不清楚

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？

最好的狀況是？

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

Figure 3. Perinatal Mortality, Sorted by Study Size

Source	Preeclampsia incidence with placebo, %	Aspirin dose, mg	Events, No./total		Risk ratio (95% CI)	Weight, %
			Aspirin	Placebo		
Benigni et al,[29] 1989	NR	60	0/17	1/16	0.31 (0.01-7.21)	0.47
Wallenburg et al,[28] 1986	30	60	1/21	1/23	1.10 (0.07-16.43)	0.63
Caspi et al,[35] 1994	9	100	2/48	2/46	0.96 (0.14-6.52)	1.26
McParland et al,[31] 1990	19	75	1/48	3/52	0.36 (0.04-3.35)	0.93
Gallery et al,[38] 1997	NR	100	4/58	2/50	1.72 (0.33-9.02)	1.69
Viinikka et al,[34] 1993	11	50	2/97	0/100	5.15 (0.25-105.98)	0.51
Ayala et al,[45] 2013	13	100	2/176	5/174	0.40 (0.08-2.01)	1.75
Yu et al,[44] 2003	19	150	7/276	4/278	1.76 (0.52-5.95)	3.13
ASPRE,[48] 2017	11	150	8/798	14/822	0.59 (0.25-1.40)	6.22
MFMU-HR,[40] 1998	20	60	43/1254	56/1249	0.76 (0.52-1.13)	30.53
CLASP,[36] 1994	8	60	77/4123	97/4134	0.80 (0.59-1.07)	52.88
Overall					0.79 (0.66-0.96)	

Heterogeneity: $\tau^2 = 0.00$; $I^2 = 0.00\%$
Test of $\theta = 1$; $t(10) = -2.70$; $P = .02$

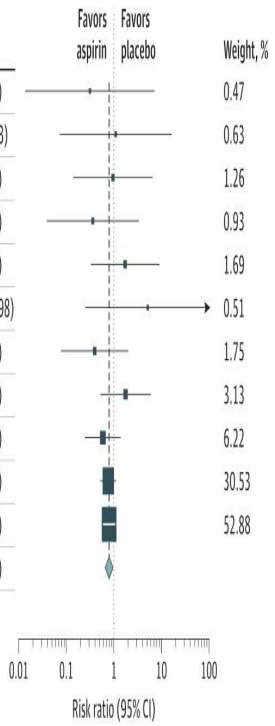
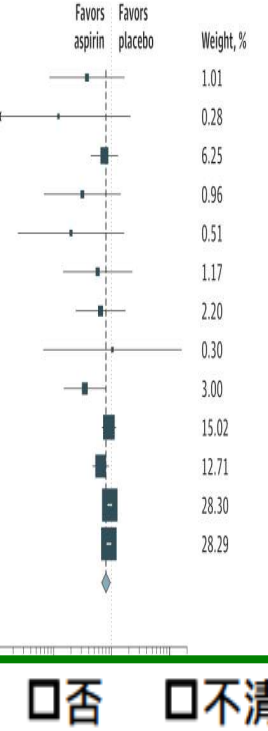


Figure 4. Preterm Birth Before 37 Weeks' Gestation, Sorted by Study Size

Source	Preeclampsia incidence with placebo, %	Aspirin dose, mg	Events, No./total		Risk ratio (95% CI)	Weight, %
			Aspirin	Placebo		
Benigni et al,[29] 1989	NR	60	2/17	5/16	0.38 (0.08-1.67)	1.01
Wallenburg et al,[28] 1986	30	60	0/21	4/23	0.12 (0.01-2.12)	0.28
Caspi et al,[35] 1994	9	100	11/24	14/23	0.75 (0.44-1.30)	6.25
Schiff et al,[30] 1989	23	100	2/34	6/32	0.31 (0.07-1.44)	0.96
Hermida et al,[39] 1997	14	100	1/50	5/50	0.20 (0.02-1.65)	0.51
Morris et al,[50] 1996	14	100	3/52	5/50	0.58 (0.15-2.29)	1.17
Gallery et al,[38] 1997	NR	100	6/58	8/50	0.65 (0.24-1.74)	2.20
Davies et al,[37] 1995	12	75	1/58	1/60	1.03 (0.07-16.15)	0.30
Ayala et al,[45] 2013	13	100	7/176	20/174	0.35 (0.15-0.80)	3.00
Yu et al,[44] 2003	19	150	67/276	75/278	0.90 (0.68-1.20)	15.02
ASPRE,[48] 2017	11	150	53/798	84/822	0.65 (0.47-0.90)	12.71
HFMU-HR,[40] 1998	20	60	502/1254	537/1249	0.93 (0.85-1.02)	28.30
CLASP,[36] 1994	8	60	686/3992	761/3982	0.90 (0.82-0.99)	28.29
Overall					0.80 (0.67-0.95)	

Heterogeneity: $\tau^2 = 0.02$; $I^2 = 48.71\%$
Test of $\theta = 1$; $t(12) = -2.79$; $P = .02$



評讀結果：☑是　☐否　☐不清楚

步驟 2：系統性文獻回顧的品質如何？(FAITH)

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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

Figure 6. Preeclampsia, Sorted by Study Size

Source	Preeclampsia incidence with placebo, %	Aspirin dose, mg	Events, No./total		Risk ratio (95% CI)	Weight, %
			Aspirin	Placebo		
Grab et al,[42] 2000	10	100	3/22	2/21	1.43 (0.27-7.73)	0.33
Wallenburg et al,[28] 1986	30	60	0/21	7/23	0.07 (0.00-1.20)	0.12
Caspi et al,[35] 1994	9	100	0/24	2/23	0.19 (0.01-3.80)	0.11
Schiff et al,[30] 1989	23	100	1/34	7/31	0.13 (0.02-1.00)	0.23
Hermida et al,[39] 1997	14	100	3/50	7/50	0.43 (0.12-1.56)	0.56
McParland et al,[31] 1990	19	75	1/48	10/52	0.11 (0.01-0.81)	0.23
Morris et al,[50] 1996	14	100	4/52	7/50	0.55 (0.17-1.76)	0.70
Davies et al,[37] 1995	12	75	5/58	7/60	0.74 (0.25-2.20)	0.80
Villa et al,[46] 2013	18	100	8/61	11/60	0.72 (0.31-1.65)	1.35
Scazzochio et al,[49] 2017	4	150	4/80	3/75	1.25 (0.29-5.40)	0.44
Viinikka et al,[34] 1993	11	50	9/97	11/100	0.84 (0.37-1.95)	1.36
Ayala et al,[45] 2013	13	100	11/176	22/174	0.49 (0.25-0.99)	1.97
Yu et al,[44] 2003	19	150	49/276	52/278	0.95 (0.67-1.35)	7.60
ASPRE,[48] 2017	11	150	66/798	94/822	0.72 (0.54-0.98)	10.56
HFMU-HR,[40] 1998	20	60	226/1254	250/1249	0.90 (0.77-1.06)	36.08
CLASP,[36] 1994	8	60	267/3992	302/3982	0.88 (0.75-1.03)	37.57
Overall					0.85 (0.75-0.95)	

Heterogeneity: $\tau^2 = 0.00$; $I^2 = 0.00\%$
Test of $\theta = 1$; $t(15) = -3.07$; $P = .01$

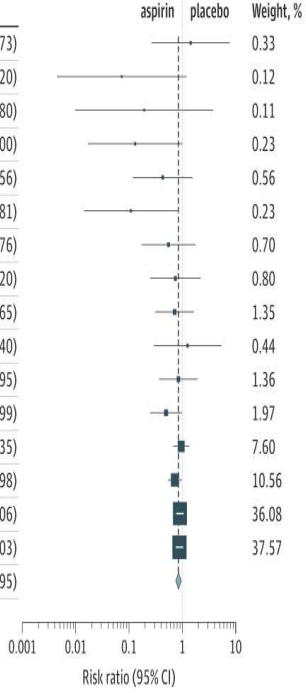
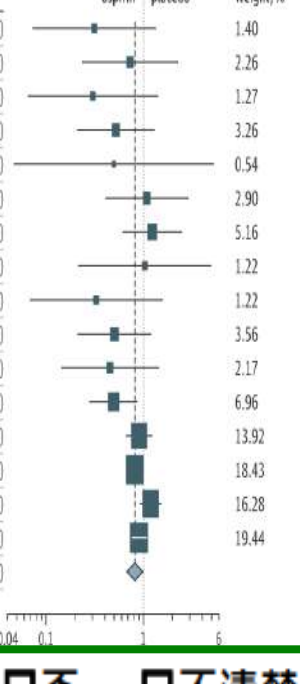


Figure 5. Small for Gestational Age or Intrauterine Growth Restriction, Sorted by Study Size

Source	Preeclampsia incidence with placebo, %	Aspirin dose, mg	Events, No./total		Risk ratio (95% CI)	Weight, %
			Aspirin	Placebo		
Benigni et al,[29] 1989	NR	60	2/17	6/16	0.31 (0.07-1.33)	1.40
Wallenburg et al,[28] 1986	30	60	4/21	6/23	0.73 (0.24-2.23)	2.26
Schiff et al,[30] 1989	23	100	2/34	6/31	0.30 (0.07-1.40)	1.27
Caspi et al,[35] 1994	9	100	6/48	11/46	0.52 (0.21-1.30)	3.26
Hermida et al,[39] 1997	14	100	1/50	2/50	0.50 (0.05-5.34)	0.54
McParland et al,[31] 1990	19	75	7/48	7/52	1.08 (0.41-2.86)	2.90
Morris et al,[50] 1996	14	100	14/52	11/50	1.22 (0.62-2.43)	5.16
Davies et al,[37] 1995	12	75	3/58	3/60	1.03 (0.22-4.92)	1.22
Villa et al,[46] 2013	18	100	2/61	6/60	0.33 (0.07-1.56)	1.22
Scazzochio et al,[49] 2017	4	150	7/80	13/75	0.50 (0.21-1.20)	3.56
Viinikka et al,[34] 1993	11	50	4/97	9/100	0.46 (0.15-1.44)	2.17
Ayala et al,[45] 2013	13	100	16/176	32/174	0.49 (0.28-0.87)	6.96
Yu et al,[44] 2003	19	150	61/276	68/278	0.90 (0.67-1.22)	13.92
ASPRE,[48] 2017	11	150	148/785	187/807	0.81 (0.67-0.99)	18.43
HFMU-HR,[40] 1998	20	60	129/1254	108/1249	1.19 (0.93-1.52)	16.28
CLASP,[36] 1994	8	60	244/4123	272/4134	0.90 (0.76-1.06)	19.44
Overall					0.82 (0.68-0.99)	

Heterogeneity: $\tau^2 = 0.03$; $I^2 = 41.24\%$
Test of $\theta = 1$; $t(15) = -2.28$; $P = .04$



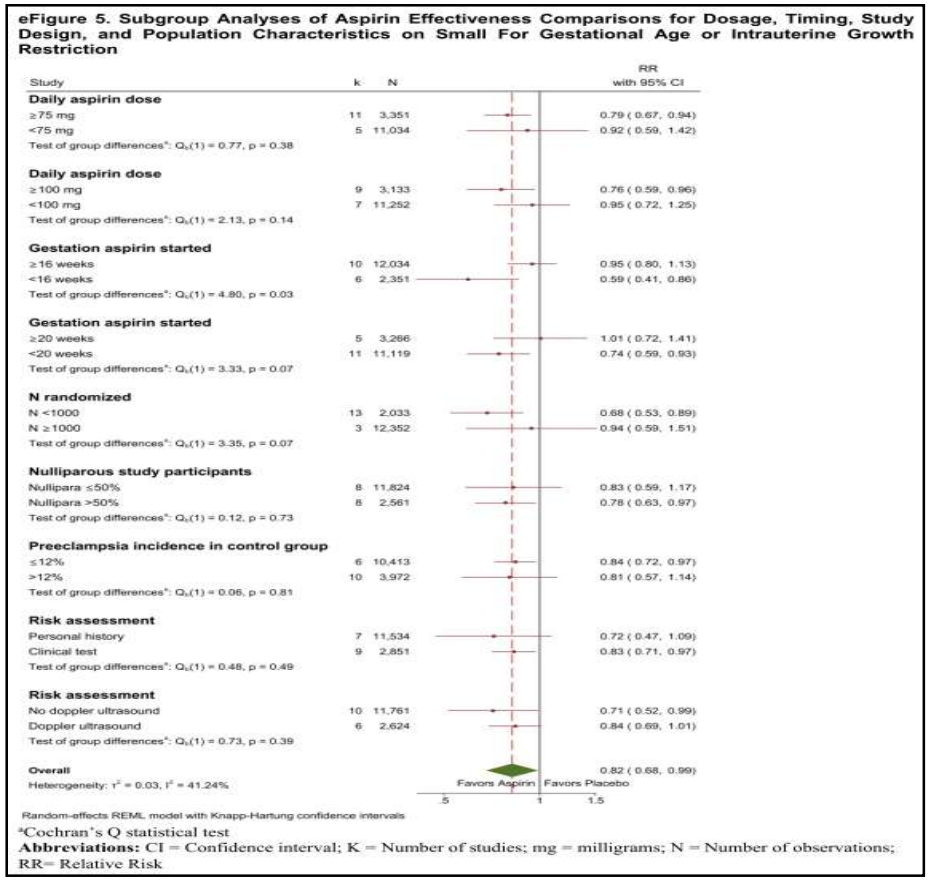
評讀結果：☑是　☐否　☐不清楚

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)？

最好的狀況是？

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。



eFigure 5. Subgroup Analyses of Aspirin Effectiveness Comparisons for Dosage, Timing, Study Design, and Population Characteristics on Small For Gestational Age or Intrauterine Growth Restriction

Study	k	N	RR with 95% CI
Daily aspirin dose			
≥75 mg	11	3,351	0.79 (0.67, 0.94)
<75 mg	5	11,034	0.92 (0.59, 1.42)
Test of group differences[a]: $Q_1(1) = 0.77$, p = 0.38			
Daily aspirin dose			
≥100 mg	9	3,133	0.76 (0.59, 0.96)
<100 mg	7	11,252	0.95 (0.72, 1.25)
Test of group differences[a]: $Q_1(1) = 2.13$, p = 0.14			
Gestation aspirin started			
≥16 weeks	10	12,034	0.95 (0.80, 1.13)
<16 weeks	6	2,351	0.59 (0.41, 0.86)
Test of group differences[a]: $Q_1(1) = 4.80$, p = 0.03			
Gestation aspirin started			
≥20 weeks	5	3,266	1.01 (0.72, 1.41)
<20 weeks	11	11,119	0.74 (0.59, 0.93)
Test of group differences[a]: $Q_1(1) = 3.33$, p = 0.07			
N randomized			
N <1000	13	2,033	0.68 (0.53, 0.89)
N ≥1000	3	12,352	0.94 (0.59, 1.51)
Test of group differences[a]: $Q_1(1) = 3.35$, p = 0.07			
Nulliparous study participants			
Nullipara ≤50%	8	11,824	0.83 (0.59, 1.17)
Nullipara >50%	8	2,561	0.78 (0.63, 0.97)
Test of group differences[a]: $Q_1(1) = 0.12$, p = 0.73			
Preeclampsia incidence in control group			
≤12%	6	10,413	0.84 (0.72, 0.97)
>12%	10	3,972	0.81 (0.57, 1.14)
Test of group differences[a]: $Q_1(1) = 0.06$, p = 0.81			
Risk assessment			
Personal history	7	11,534	0.72 (0.47, 1.09)
Clinical test	9	2,851	0.83 (0.71, 0.97)
Test of group differences[a]: $Q_1(1) = 0.48$, p = 0.49			
Risk assessment			
No doppler ultrasound	10	11,761	0.71 (0.52, 0.99)
Doppler ultrasound	6	2,624	0.84 (0.69, 1.01)
Test of group differences[a]: $Q_1(1) = 0.73$, p = 0.39			
Overall			0.82 (0.68, 0.99)
Heterogeneity: $\tau^2 = 0.03$, $I^2 = 41.24\%$			

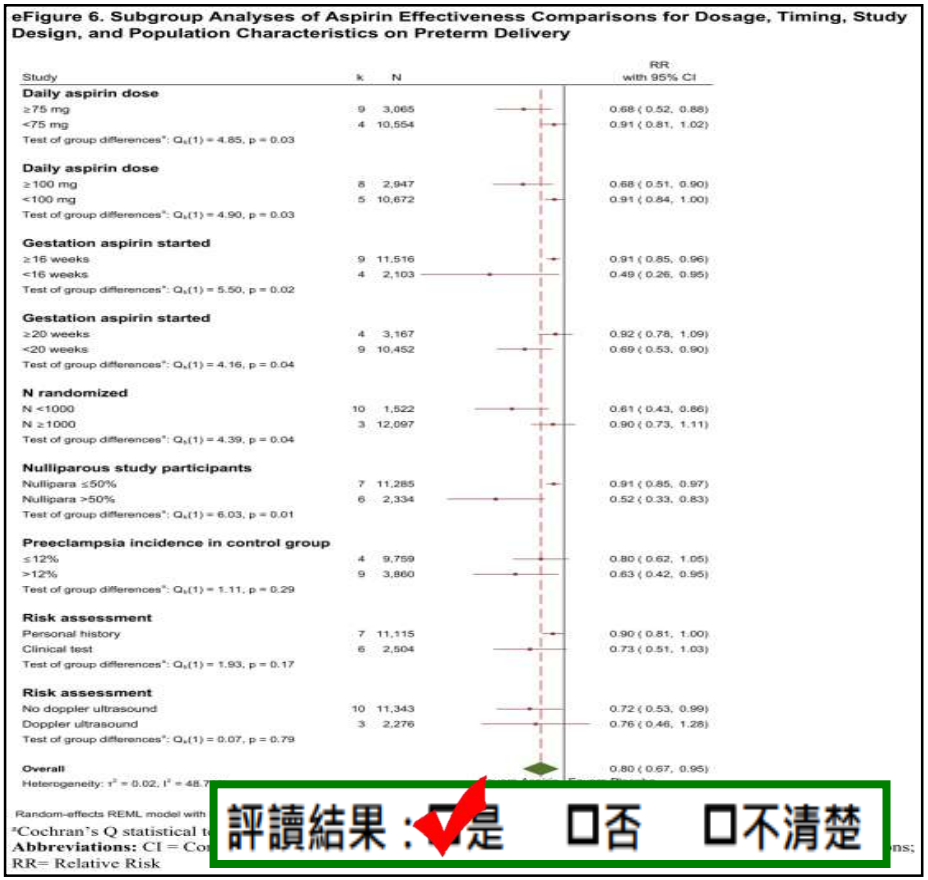
Favors Aspirin | Favors Placebo

.5 1 1.5

Random-effects REML model with Knapp-Hartung confidence intervals

[a]Cochran's Q statistical test

Abbreviations: CI = Confidence interval; K = Number of studies; mg = milligrams; N = Number of observations; RR= Relative Risk



eFigure 6. Subgroup Analyses of Aspirin Effectiveness Comparisons for Dosage, Timing, Study Design, and Population Characteristics on Preterm Delivery

Study	k	N	RR with 95% CI
Daily aspirin dose			
≥75 mg	9	3,065	0.68 (0.52, 0.88)
<75 mg	4	10,554	0.91 (0.81, 1.02)
Test of group differences[a]: $Q_1(1) = 4.85$, p = 0.03			
Daily aspirin dose			
≥100 mg	8	2,947	0.68 (0.51, 0.90)
<100 mg	5	10,672	0.91 (0.84, 1.00)
Test of group differences[a]: $Q_1(1) = 4.90$, p = 0.03			
Gestation aspirin started			
≥16 weeks	9	11,516	0.91 (0.85, 0.96)
<16 weeks	4	2,103	0.49 (0.26, 0.95)
Test of group differences[a]: $Q_1(1) = 5.50$, p = 0.02			
Gestation aspirin started			
≥20 weeks	4	3,167	0.92 (0.78, 1.09)
<20 weeks	9	10,452	0.69 (0.53, 0.90)
Test of group differences[a]: $Q_1(1) = 4.16$, p = 0.04			
N randomized			
N <1000	10	1,522	0.61 (0.43, 0.86)
N ≥1000	3	12,097	0.90 (0.73, 1.11)
Test of group differences[a]: $Q_1(1) = 4.39$, p = 0.04			
Nulliparous study participants			
Nullipara ≤50%	7	11,285	0.91 (0.85, 0.97)
Nullipara >50%	6	2,334	0.52 (0.33, 0.83)
Test of group differences[a]: $Q_1(1) = 6.03$, p = 0.01			
Preeclampsia incidence in control group			
≤12%	4	9,759	0.80 (0.62, 1.05)
>12%	9	3,860	0.63 (0.42, 0.95)
Test of group differences[a]: $Q_1(1) = 1.11$, p = 0.29			
Risk assessment			
Personal history	7	11,115	0.90 (0.81, 1.00)
Clinical test	6	2,504	0.73 (0.51, 1.03)
Test of group differences[a]: $Q_1(1) = 1.93$, p = 0.17			
Risk assessment			
No doppler ultrasound	10	11,343	0.72 (0.53, 0.99)
Doppler ultrasound	3	2,276	0.76 (0.46, 1.28)
Test of group differences[a]: $Q_1(1) = 0.07$, p = 0.79			
Overall			0.80 (0.67, 0.95)
Heterogeneity: $\tau^2 = 0.02$, $I^2 = 48.7$			

Random-effects REML model with

[a]Cochran's Q statistical t

Abbreviations: CI = Co ns;

RR= Relative Risk

評讀結果：☑是 ☐否 ☐不清楚

結果

A total of 23 randomized clinical trials (RCTs) (N = 26 952) were included; 18 were conducted among participants at increased preeclampsia risk. Aspirin dosages ranged from 50 mg/d to 150 mg/d. Most trials enrolled majority White populations selected based on a range of risk factors. The incidence of preeclampsia among the trials of participants at increased risk ranged from 4% to 30%. Aspirin use was significantly associated with lower risk of preeclampsia (pooled relative risk [RR], 0.85 [95% CI, 0.75-0.95]; 16 RCTs [n = 14 093]; $I^2 = 0\%$), perinatal mortality (pooled RR, 0.79 [95% CI, 0.66-0.96]; 11 RCTs [n = 13 860]; $I^2 = 0\%$) preterm birth (pooled RR, 0.80 [95% CI, 0.67-0.95]; 13 RCTs [n = 13 619]; I^2 growth restriction (pooled RR, 0.82 [95% CI, 0.68-0. $I^2 = 41\%$). There were no significant associations of aspi rtum hemorrhage (pooled RR, 1.03 [95% CI, 0.94- ; $I^2 = 0\%$) and other bleeding-related harms, or with rare peri s. Absolute risk reductions for preeclampsia associated wi −1% to −6% across larger trials (n >300) and were greater in smaller trials. For perinatal mortality, absolute risk reductions ranged from 0.5% to 1.1% in the 3 largest trials.

- 使用Aspirin效益:
  顯著降低
1. 先兆子癲症風險
2. 周產期死亡率
3. 早產發生率
4. 子宮內生長遲滯率

結論

- Daily low-dose aspirin during pregnancy was associated with lower risks of serious perinatal outcomes for individuals at increased risk for preeclampsia, without evident harms.

先兆子癇風險的孕產婦，於妊娠期間每日服用低劑量Aspirin，發生嚴重周產期併發症結果的風險降低，且無明顯危害。

評讀總表

研究的品質有多好(內在效度)	評讀結果
研究是否找到 (Find) 所有的相關證據？	否
文獻是否經過嚴格評讀 (Appraisal)？	是
是否只納入 (included) 具良好效度的文章？	是
作者是否以表格和圖表「總結」(total up) 試驗結果？	是
試驗的結果是否相近 - 異質性 (Heterogeneity)	是

敬請指導 感謝聆聽

臨床應用

是否贊成高風險子癲前症孕婦每日服用Aspirin嗎?

同意：23票

需更多文獻支持：3票

不同意：0票