2024 臺灣藥學聯合學術研討會

BMJ 經驗分享：從花果山到火焰山的研究之路

Association Between Recently Raised Anticholinergic Burden and Risk of Acute Cardiovascular Events: Nationwide Case-Case-Time-Control Study

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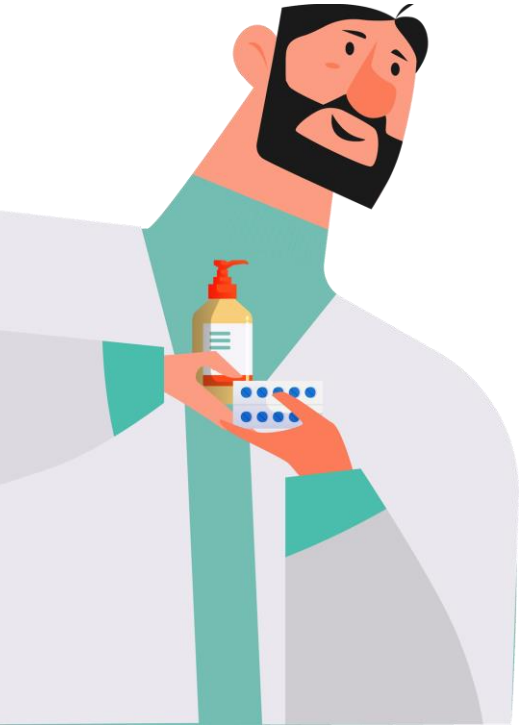
OUTLINE



1. 研究背景
   Background & Rationales
2. 方法設計
   Study Design
3. 期刊投稿及發表
   Journal Submission & Publishing

1 研究背景

Background & Rationales

Anticholinergic Burden

多種具抗膽鹼活性之藥物所累積的抗膽鹼作用

Examples of Medications with Anticholinergic Activity		
Antihistamines Chlorpheniramine, clemastine, diphenhydramine, loratadine…	**Antidepressants** Amitriptyline, clomipramine, doxepin, imipramine…	**Antispasmodics** Atropine, scopolamine, hyoscine, hyoscyamine…
Antivertigo agents/antiemetics Meclizine, cinnarizine, hydroxyzine, diphenidol…	**Antipsychotics** Chlorpromazine, clozapine, quetiapine, olanzapine…	**Bladder antimuscarinics** Oxybutynin, solifenacin, tolterodine…
Cardiovascular drugs Captopril, nifedipine, quinidine, furosemide, hydralazine…	**Benzodiazepines** Alprazolam, diazepam, lorazepam, oxazepam, midazolam…	**Skeletal muscle relaxants** Baclofen, orphenadrine, pipoxolan, tizanidine…
Antiparkinsonians Amantadine, trihexyphenidyl, benztropine, biperiden…	**Respiratory drugs** Theophylline, tiotropium, codeine, glycopyrrolate…	**Others** Analgesics, antiepileptic drugs, antiinfectives , corticosteroids…

具抗膽鹼活性藥品的藥理分類不一定是 Anticholinergics / Antimuscarinics

JAMA Intern Med. 2015 Mar;175(3):401.

老年族群 & Anticholinergic Burden

- **多重用藥 (Polypharmacy)**：約 50% 老年族群暴露過至少一種抗膽鹼藥物
- 藥品的抗膽鹼活性可能被忽略 → **病人累積的 anticholinergic burden 易被低估**
- 不良反應嚴重程度可能與劑量相關 (dose dependent)
- **年齡增加導致的 PK/PD 變化** → **老年族群更易出現抗膽鹼相關不良反應**
  - 乙醯膽鹼合成 ↓
  - CNS 膽鹼受體功能 ↓
  - BBB 通透性 ↑
  - 藥物游離態 (free fraction) ↑
  - 代謝及排除 ↓

Anticholinergic Burden
已被視為重要的老年族群用藥問題

已知可能的相關的風險：
Dementia、Delirium、Falls & Fractures

[1] *J Am Geriatr Soc.* 2011 Aug;59(8):1477. [2] *BMC Geriatr.* 2015 Mar;15:31. [3] *Clin Interv Aging.* 2009;4:225. [4] *Neurol Sci.* 2009 Apr;30(2):87.

Anticholinergic Burden 量表

各量表發展自不同年代、國家
涵蓋藥物範圍及分數定義也不同

Scales for Anticholinergic Burden Measurement		Drugs scored* (n)	Scoring levels	Reference
CrAS	Clinician-rated Anticholinergic Scale	60	0-3	Han, 2001/2008 (USA)
ADS	Anticholinergic Drug Scale	117	0-3	Carnahan, 2006 (USA)
ABC	Anticholinergic Burden Classification	27	0-3	Ancelin, 2006 (France)
ACB	Anticholinergic Cognitive Burden Scale	88	0-3	Boustani, 2008 (USA)
ARS	Anticholinergic Risk Scale	49	0-3	Rudolph, 2008 (USA)
AAS	Anticholinergic Activity Scale	99	0-4	Ehrt, 2010 (Norway)
ALS/ACL	Anticholinergic Loading Scale	49	0-3	Sittironnarit, 2011 (AUS)
AIS	Anti-cholinergic Impregnation Scale	128	1-3	Briet, 2017 (France)
AEC	Anticholinergic Effect on Cognition	165	0-3	Bishara, 2017 (UK)
GABS	German Anticholinergic Burden Scale	151	0-3	Kiesel, 2018 (Germany)
m-ACB	Modified ACB	169	0-3	An, 2018 (Korea)
KABS	Korean Anticholinergic Activity Scale	138	0-3	Jun, 2019 (Korea)

*Drugs scored > 0 point (having anticholinergic activity in any potency level)

Anticholinergic Burden 計算

ACB (Anticholinergic Cognitive Burden Scale) [Example]					
Score = 1 (Mild)		**Score = 2 (Moderate)**	**Score = 3 (Severe)**		
Atenolol	Loperamide	Amantadine	Amitriptyline	Imipramine	
Alprazolam	Metoprolol	Belladonna alkaloids	Atropine	Nortriptyline	
Captopril	Morphine	Carbamazepine	Benztropine	Olanzapine	
Codeine	Nifedipine	Cyproheptadine	Chlorphenamine	Oxybutynin	
Colchicine	Prednisolone	Meperidine	Chlorpromazine	Paroxetine	
Diazepam	Ranitidine	Oxcarbazepine	Clozapine	Promethazine	
Digoxin	Theophylline	…	Darifenacin	Solifenacin	
Haloperidol	Trazodone		Diphenhydramine	Tolterodine	
Fentanyl	Warfarin		Doxepin	Trihexyphenidyl	
Furosemide	…		Hydroxyzine	…	

Total anticholinergic burden score：將病人使用的所有藥物之分數加總

Aging Health. 2008;4(3):311.


如何決定研究題目?

Association Between Recently Raised Anticholinergic Burden and Risk of Acute Cardiovascular Events: Nationwide Case-Case-Time-Control Study

Anticholinergic Burden & CV Risk

文獻回顧：討論與心血管事件相關性的研究相對較少

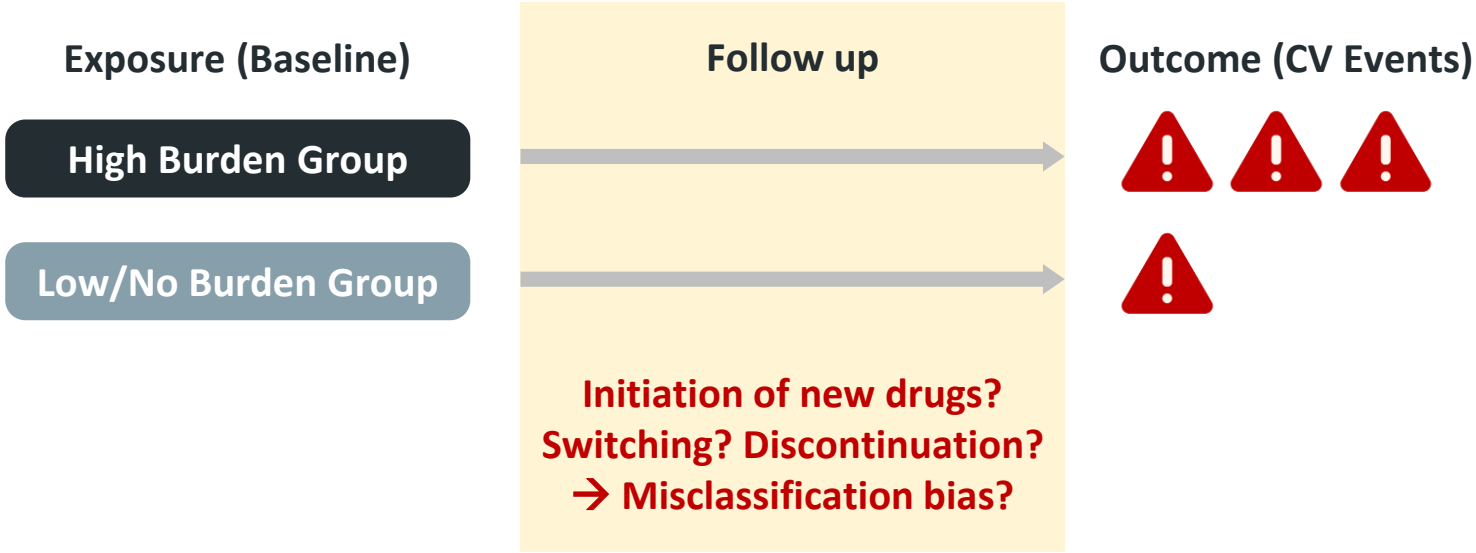
Author, year	Design	Population	Drug Use Info.	Measurement	Outcomes & Main Results (HR)
Myint, 2015 (UK)	Cohort study	40-79 y/o (n = 21,636)	Self-report	**Baseline ACB score** (>3, 2-3, 1 vs. 0)	• All-cause mortality [>3 vs.0]: 1.83 (1.53-2.20) • CVD [>3 vs.0]: 2.17 (1.87-2.52)
Gamble, 2018 (UK)	Cohort study	Avg. 58 y/o (n = 25,639)	Self-report	**Baseline ACB score** (>3, 2-3, 1 vs. 0)	• Stroke [>3 vs.0]: 1.59 (1.34-1.89) • Stroke mortality [>3 vs.0]: 1.86 (1.37-2.53)
Tan, 2018 (Sweden)	Cohort study	Avg. 80 y/o (n = 39,107)	National Database	**Annual ACB score** (≥2, 1 vs. 0)	• Stroke & all-cause mortality [≥2 vs.0]: 1.20 (1.14-1.26) • Ischemic stroke [≥2 vs.0]: 1.86 (1.37-2.53)
Hanlon, 2020 (UK)	Cohort study	37-73 y/o (n = 502,538)	Self-report & Interview	**Baseline 10 scales** (1-point increase)	• MACE: 1.01 (0.97-1.05) to 1.17 (1.14-1.2) • All-cause mortality: 1.05 (1.04-1.07) to 1.13 (1.12-1.15)
Lockery, 2021 (AUS/USA)	Cohort study	>75 y/o (n = 19,141)	Self-report & records	**Baseline ACB score** (≥3, 1-2 vs. 0)	• Ischemic stroke [≥3 vs.0]: 1.58 (1.06-2.35) • Hemorrhagic stroke [≥3 vs.0]: 0.85 (0.34-2.13)

- 過去文獻結果：**Baseline anticholinergic burden** 越高者，發生心血管事件風險越高
- 推測主要機轉：**Pro-arrhythmic & Pro-ischemic effect**

[1] *Age Ageing*. 2015 Mar;44:219. [2] *Int J Epidemiol*. 2018 Apr;47:625. [3] *J Alzheimers Dis*. 2018;65:589. [4] *Ann Fam Med*. 2020 Mar;18:148. [5] *J Gen Intern Med*. 2021 Jun;36:1629.

潛在的偏差 – 暴露可能隨時間變化

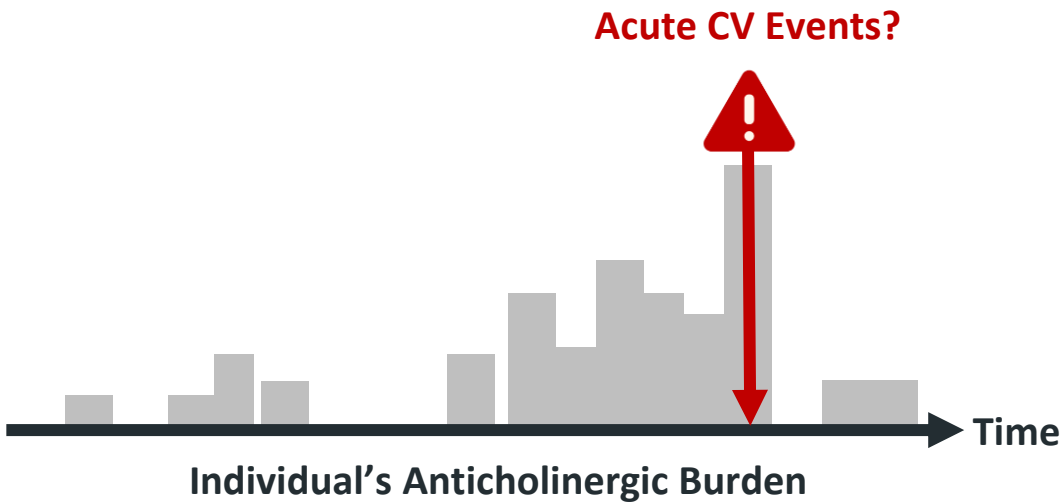
Variation of Anticholinergic Burden & Misclassification Bias



- 藥品的使用會隨時間變化，導致 **anticholinergic burden** 亦會隨著時間變化
- 忽略 **anticholinergic burden** 的高低變化可能導致 **misclassification bias** 而影響結果

未解決的疑問 – 事件發生的時間點?

The Effect of Recently Raised Anticholinergic Burden?



- 若能知道急性事件發生的時間點，更能應用於臨床實務面來預測或避免事件發生
- 疑問 & 假說：當 **anticholinergic burden** 較高時，短期內發生 **CV** 事件的風險是否較高？

Research Gap!

Association Between Recently Raised Anticholinergic Burden and Risk of Acute Cardiovascular Events: Nationwide Case-Case-Time-Control Study

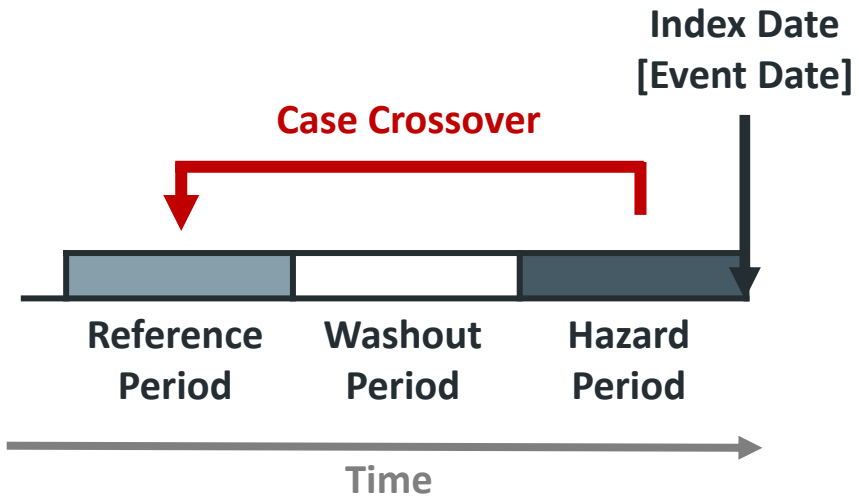
2

方法設計

Study Design

病例交叉研究 Case-Crossover Study (CCO)

"Did Anything Unusual Happen Just Before?"



屬於自我對照研究 **(self-controlled study)**

- 回答的問題為 **"when"** 而不是 **"who"**
- 不需校正個體 **time-invariant confounder**

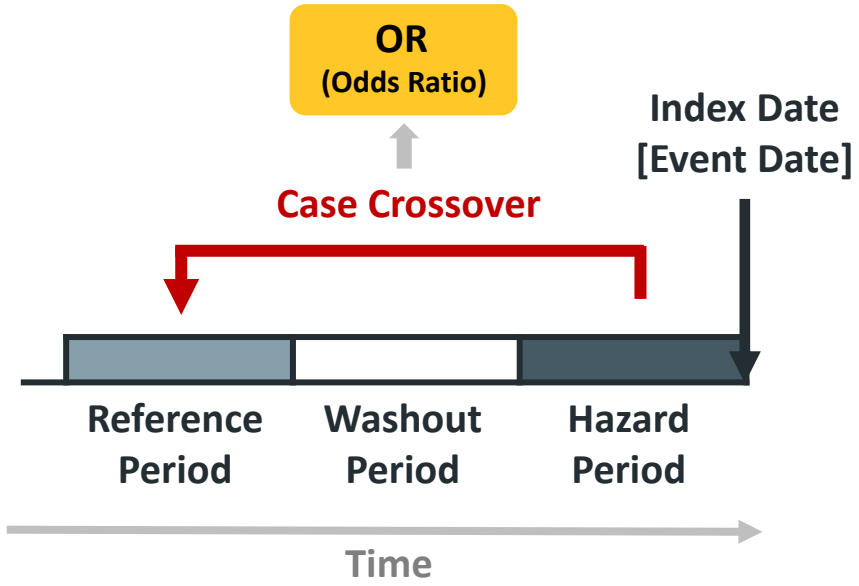
適用於研究短暫暴露 **(transient exposure)** 與急性事件 **(acute outcome)** 之相關性

事件發生時 **(hazard/case period) vs.** 前一段時間 **(reference/control period)** 兩段時間內暴露的差異性

[1] *Am J Epidemiol*. 1991;133(2):144-153. [2] *J Intern Med*. 2014;275:581-9. [3] *Pharmacoepidemiol Drug Saf*. 2021;30(6):671-684.

CCO 分析方法

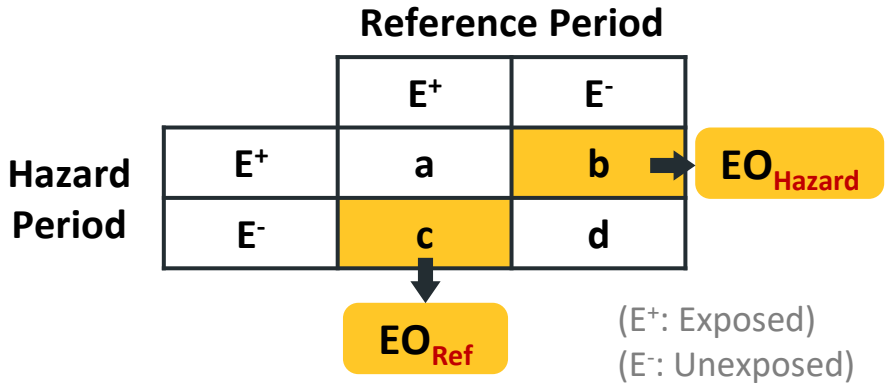
不同時間內暴露的勝算比 (Odds Ratio)



N of Discordant Pairs (EO: Exposure odds)

EO_{Hazard} = Hazard 有暴露、Ref 無暴露之人數

EO_{Ref} = Hazard 無暴露、Ref 有暴露之人數



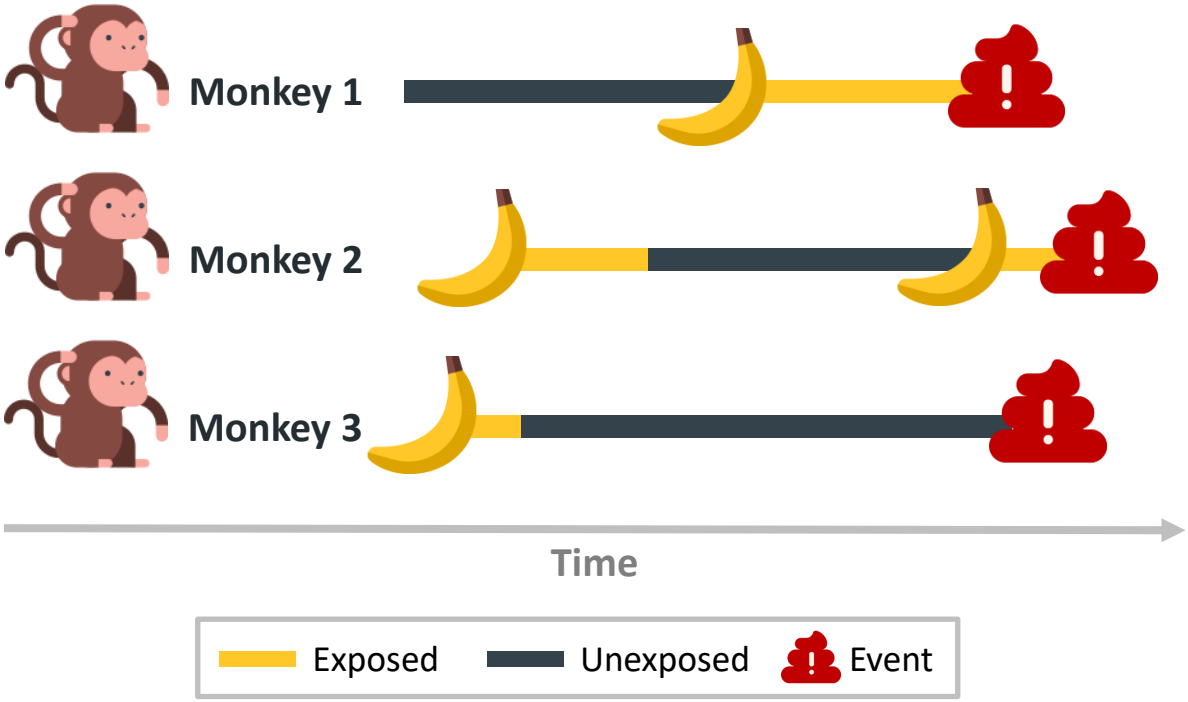
$OR = EO_{Hazard} / EO_{Ref} = b/c$

[1] *Am J Epidemiol*. 1991;133(2):144-153. [2] *J Intern Med*. 2014;275:581-9. [3] *Pharmacoepidemiol Drug Saf*. 2021;30(6):671-684.

CCO 分析方法 [Example]

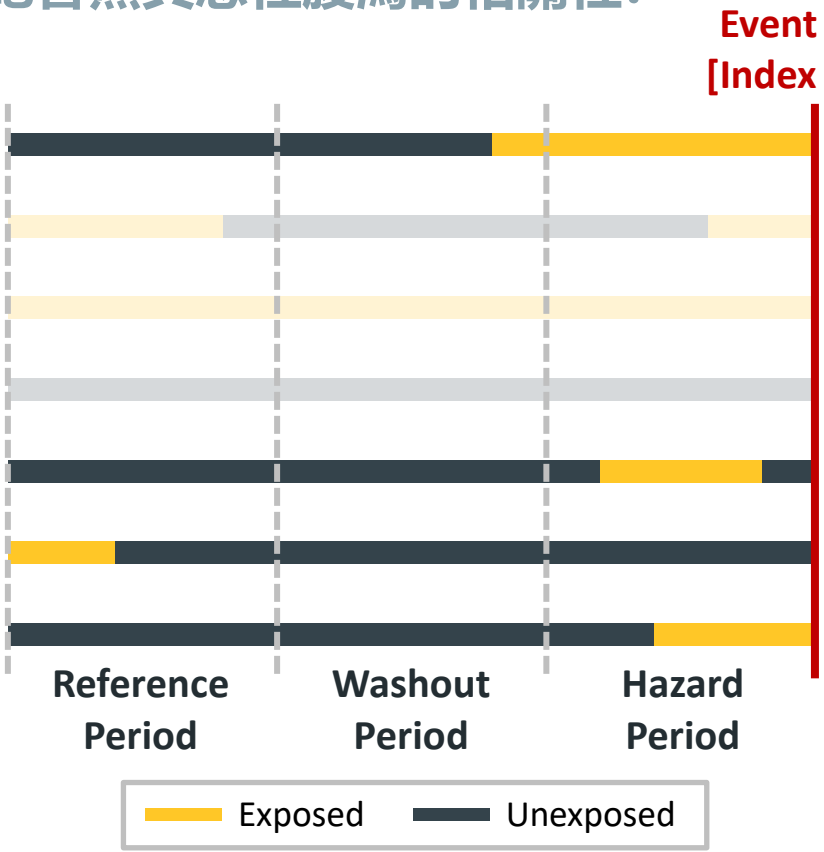
吃香蕉與急性腹瀉的相關性?

1. 找到一群有發生腹瀉的猴子
2. 定義腹瀉發生日為 **index date**
3. 觀察過去一段時間是否有吃香蕉



CCO 分析方法 [Example]

吃香蕉與急性腹瀉的相關性?



Hazard Period \ Reference Period	E^+	E^-
E^+	2	3 → EO_{Hazard}
E^-	1 → EO_{Ref}	1

$$OR = EO_{Hazard} / EO_{Ref} = 3/1 = 3.00$$

只有兩時間區間內暴露程度/狀態不同的
才有提供資訊用以分析

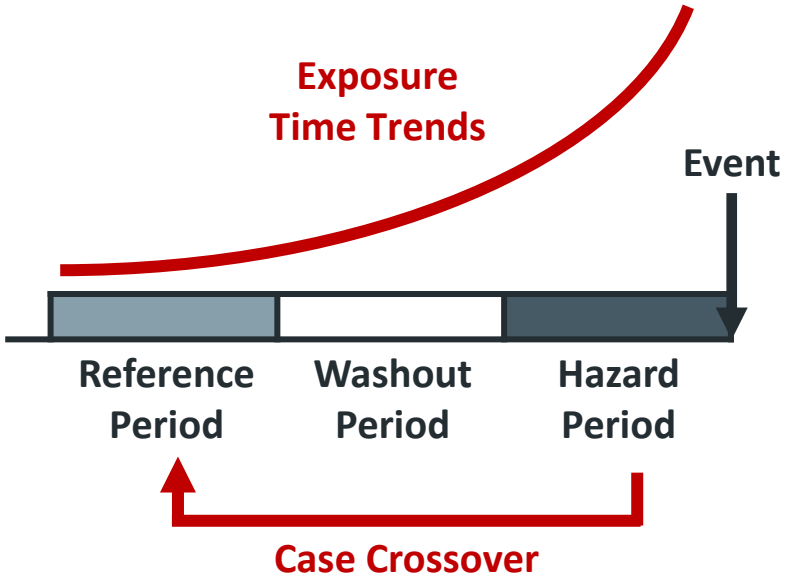
CCO 最大的限制 – Exposure Time-Trend Bias

Population-Level Exposure Time Trends

- 新藥上市 / 老藥下市
- 臨床指引更新

Individual-Level Exposure Time Trends

- 出現禁忌症導致藥品不再被使用 (如：懷孕)
- 出現新適應症而開始終生用藥
- **衰弱或病情加劇導致用藥需求增加**
- **疾病被診斷前，使用藥品治療疾病早期症狀**
  → Protopathic bias (reverse causality)

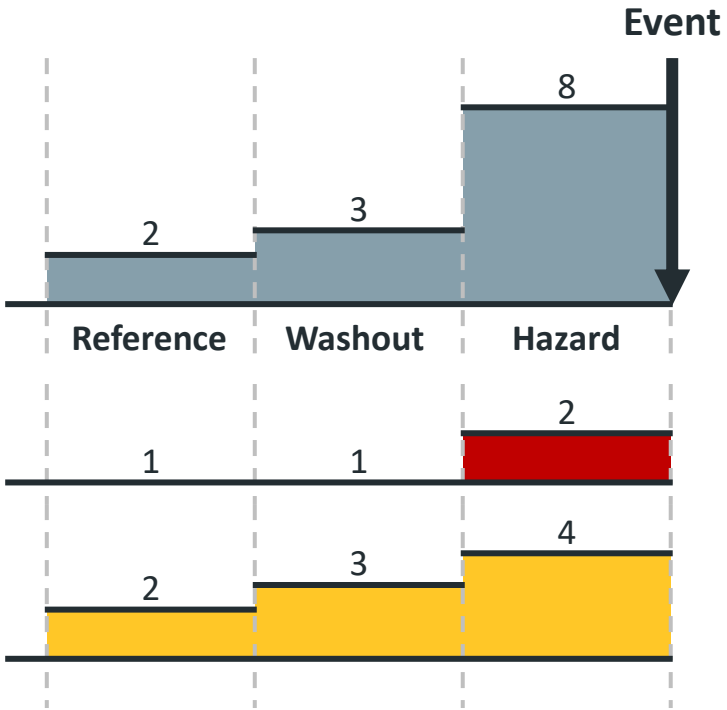


其他因素造成藥品使用增加/減少
→ 事件與暴露的相關性被高估/低估

Pharmacoepidemiol Drug Saf. 2021;30(6):671-684.

校正分析

校正 CCO 中潛在的 Exposure Time Trends



Overall Exposure ➡ $OR = OR_{causal} \times OR_{time\text{-}trend}$

觀察到的 OR 包含 causal effect 以及 time trends 貢獻的 OR

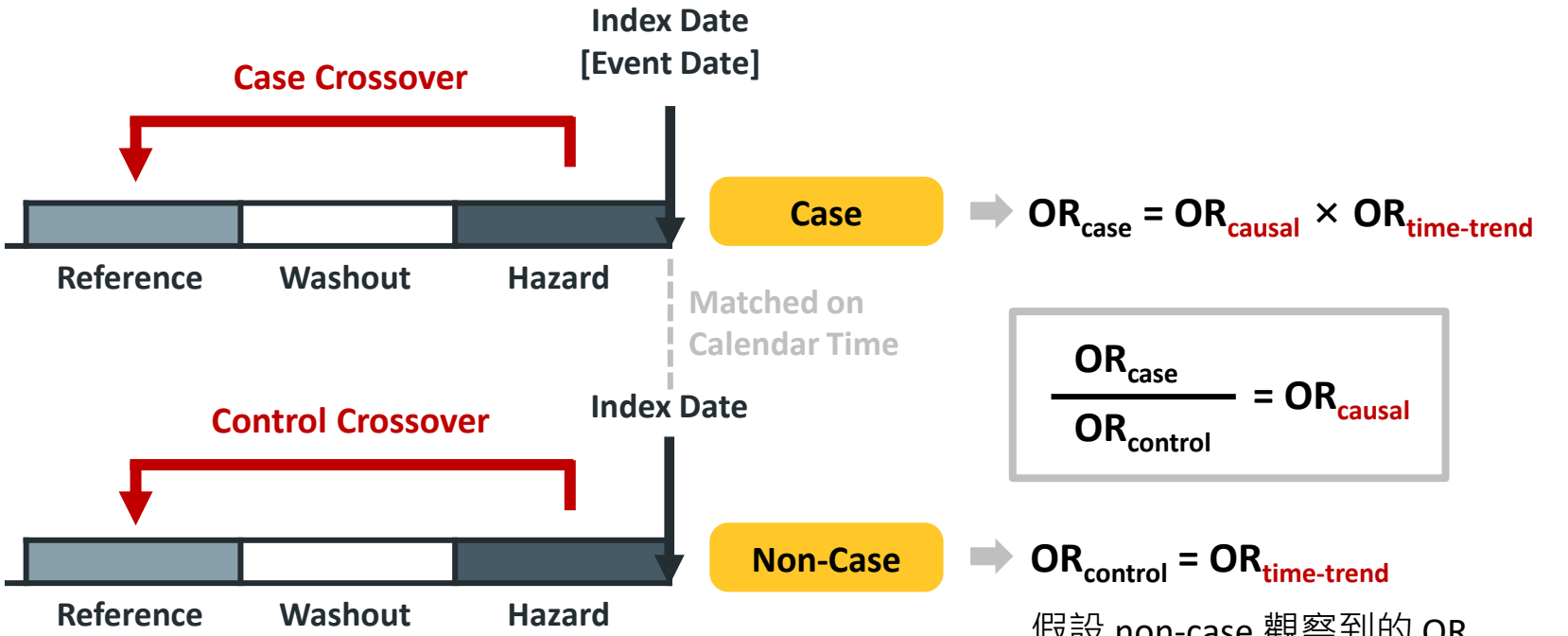
Causal Effect ➡ OR_{causal} 最終結果

Exposure Time Trends ➡ $OR_{time\text{-}trend}$ 待校正

Epidemiology 22(4):p 568-574, July 2011.

校正分析 – Case-Time-Control (CTC)

利用 Non-Case 進行 Control Crossover



$$OR_{case} = OR_{causal} \times OR_{time\text{-}trend}$$

$$\frac{OR_{case}}{OR_{control}} = OR_{causal}$$

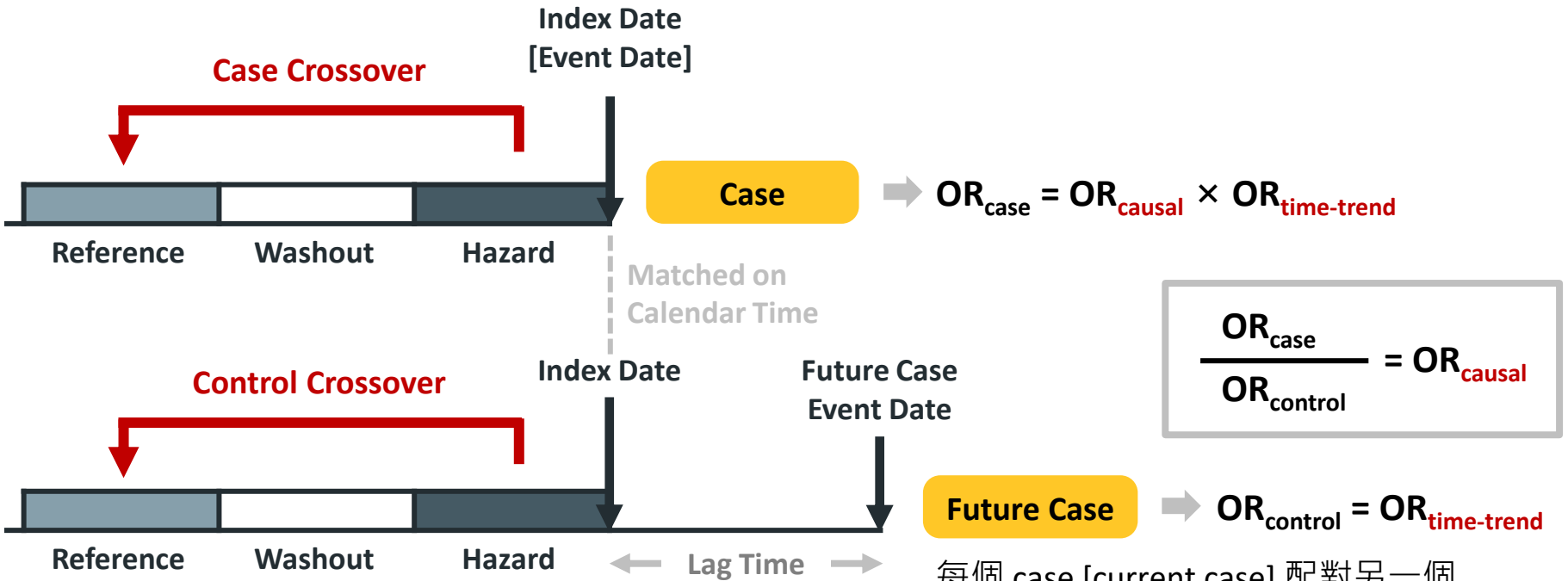
$$OR_{control} = OR_{time\text{-}trend}$$

假設 non-case 觀察到的 OR
單純為 exposure time trends 造成

Epidemiology 22(4):p 568-574, July 2011.

校正分析 – Case-Case-Time-Control (CCTC)

利用 Future Case 進行 Control Crossover



Epidemiology 22(4):p 568-574, July 2011.

校正分析 – CTC vs. CCTC

	Case-Crossover (CCO)	Case-Time-Control (CTC)	Case-Case-Time-Control (CCTC)
設計	比較事件發生時 (hazard period) 與前一段時間 (reference period) 暴露差異	校正分析；包含兩組 crossover Case crossover: Case Control crossover: **Non-case**	校正分析；包含兩組 crossover Case crossover: Case Control crossover: **Future case**
優點	• 只納入case，所需樣本少 • **不需校正 within-subject time-invariant confounder**	• **可以校正 population-level exposure time trends**	• **可以校正 population-level 及 individual-level exposure trends (可校正 protopathic bias)** • 無 non-case selection bias 疑慮
限制	• **容易受到 exposure time trends bias 影響** • 可能需進行校正分析 (CTC 或 CCTC)	• 需額外納入未發生事件者，有 **selection bias 疑慮** (可用 DRS 進行匹配以降低疑慮) • Non-case 的 exposure trends 可能與 case 的差異較大，因此僅能校正 population-level 的部分	• 若研究時長太短，future case 的匹配可能較困難 • Future case 與 current case 的相隔時間的決定無明確依據

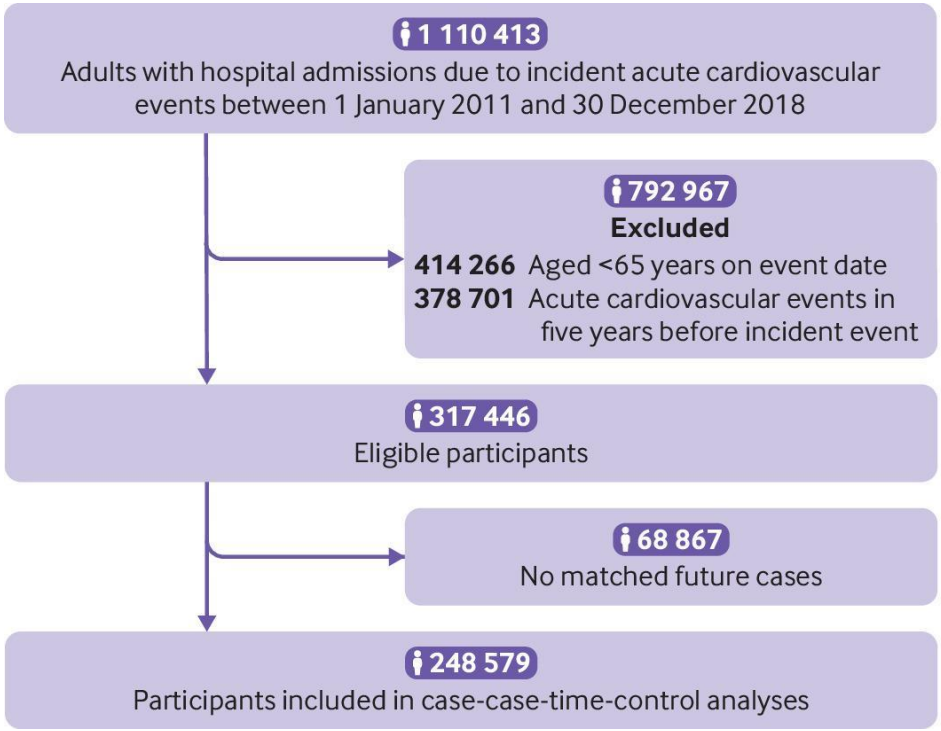
[1] *Pharmacoepidemiol Drug Saf.* 2021;30(6):671-684. [2] *J Intern Med*. 2014 Jun;275(6):581-9. (DRS: Disease risk score)

Association Between Recently Raised Anticholinergic Burden and Risk of Acute Cardiovascular Events: Nationwide Case-Case-Time-Control Study

Study Population

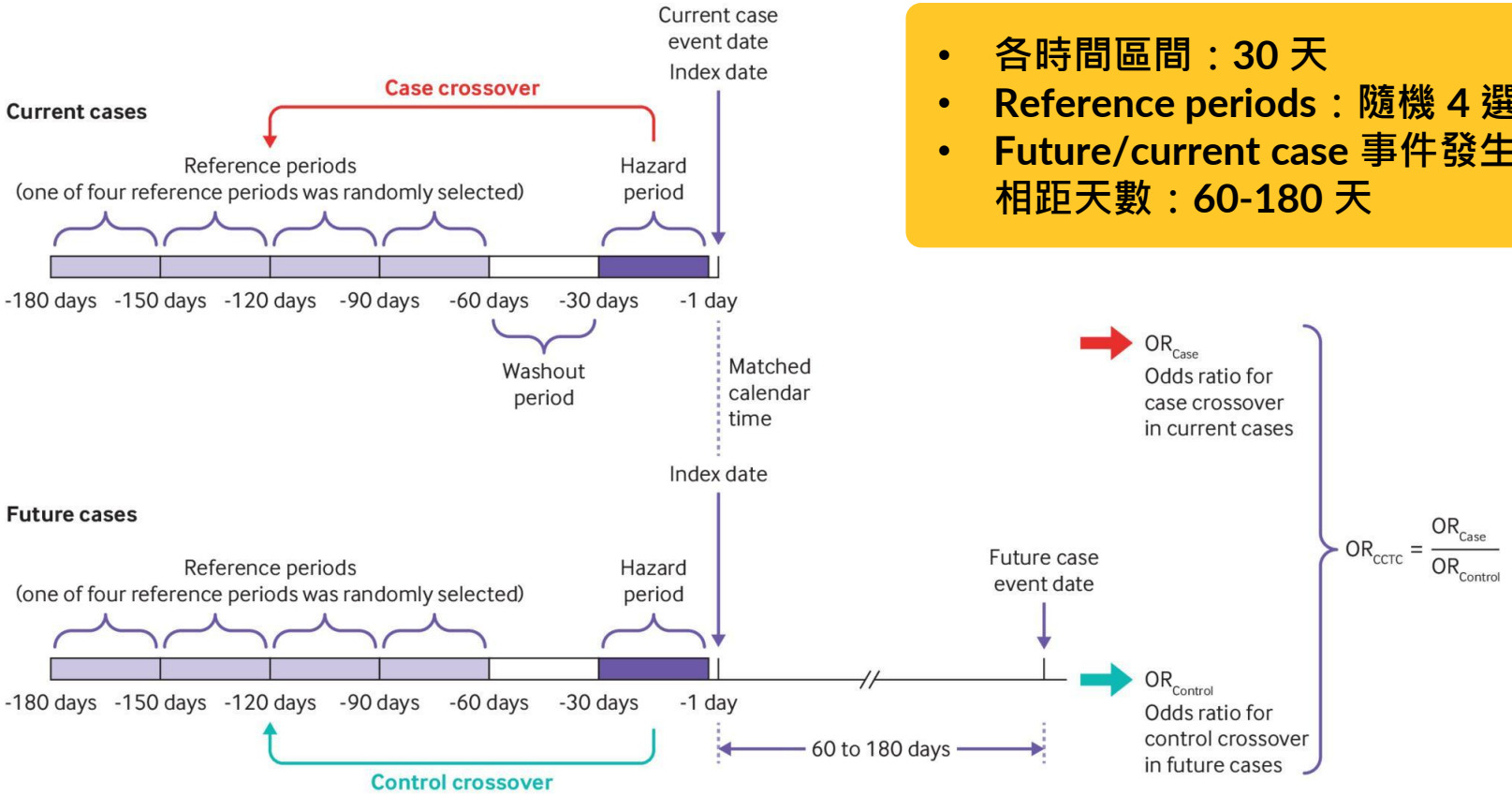
Data Source: Taiwan NHIRD 台灣健保資料庫 (2006-2018)

- 在 2011-2018 年間，因急性心血管事件入院者
  - Myocardial infarction
  - Strokes
  - Arrhythmias
  - Conduction disorders
  - CV death
    [ICD-9-CM & ICD-10-CM]
- 年齡 ≥65 歲
- 過去五年無心血管事件病史



NHIRD: National Health Insurance Research Database

Case-Case-Time-Control (CCTC) 研究設計



- 各時間區間：30 天
- Reference periods：隨機 4 選 1
- Future/current case 事件發生日之相距天數：60-180 天

Anticholinergic Burden 測量 & 統計分析

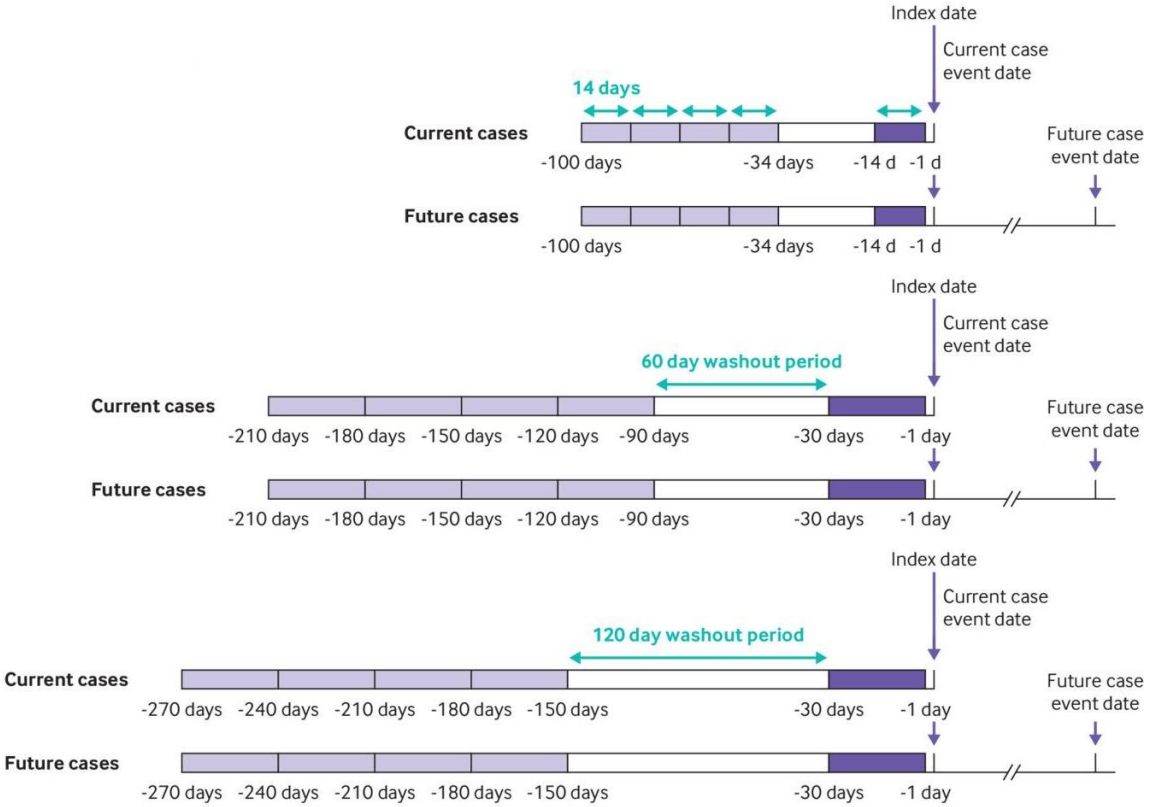
- **量表選擇：ACB (Anticholinergic Cognitive Burden Scale)**[1]
- 將每位病人在各時間區間所有使用的**藥物的 ACB 分數加總**
  - 排除外用製劑 (例外：吸入劑；因先前研究發現具相關性)[2]
  - ATC code 抓取藥物使用資料
  - 複方製劑以成分中最高分之藥物的分數做計算
- **暴露程度分組：≥3、1-2、0**
- **Conditional logistic regression**

Exposure Category	Total Anticholinergic Burden		Analysis
	Hazard period	Reference period	
A	1-2	0	→ 1-2 vs. 0
B	0	1-2	
C	≥3	0	→ ≥3 vs. 0
D	0	≥3	
E	≥3	1-2	→ ≥3 vs. 1-2
F	1-2	≥3	
G	0	0	Provide no information
H	1-2	1-2	
I	≥3	≥3	

[1] *Aging health* 4.3 (2008): 311-320. [2] *Thorax* 2013;68:114-6.

Sensitivity Analyses - 1

對於沒有明確標準的假設



CCTC design 各時間區間長度

- Hazard/reference period
- Washout period
- Future/current case 距離天數

Anticholinergic burden 分數切點

- ≥5、1-4、0
- ≥10、1-9、0

Sensitivity Analyses - 2

考量可能影響研究結果的 Bias

- **考量藥物劑量**：使用 WHO defined daily dose (DDD) 校正
- **考量使用藥物時間**：排除使用天數少於 3 天、7 天的藥品
- **考量 time-varying confounders**：急性感染*、心內膜炎、心肌炎、AKI
- **降低 OTC 疑慮**：只納入有慢性病者 (DM、HTN、Dyslipidemia)
- **使用不同量表計算 anticholinergic burden**

Scale		Drugs scored (N)	Scoring levels	Reference
ACB	Anticholinergic Cognitive Burden Scale	105	0-3	Boustani, 2008 (USA)
ADS	Anticholinergic Drug Scale	117	0-3	Carnahan, 2006 (USA)
GABS	German Anticholinergic Burden Scale	151	0-3	Kiesel, 2018 (Germany)
m-ACB	Modified ACB	169	0-3	An, 2018 (Korea)
KABS	Korean Anticholinergic Burden Scale	138	0-3	Jun, 2019 (Korea)

*Upper respiratory tract infection, pneumonia, influenza, urinary tract infection, bloodstream infection

Results: Main Analysis

Groups for comparing total anticholinergic burden score	No. of patients			Odds ratio (95% CI)
	Total	Higher burden in hazard period	Higher burden in referent period	
1-2 vs. 0				
Case crossover	26,110	17,603	8,507	1.86 (1.83 to 1.90)
Control crossover	24,683	14,247	10,436	1.35 (1.33 to 1.38)
CCTC	-	-	-	**1.38 (1.34 to 1.42)**
≥3 vs. 0				
Case crossover	45,384	33,174	12,210	2.91 (2.86 to 2.96)
Control crossover	36,368	21,363	15,005	1.43 (1.41 to 1.46)
CCTC	-	-	-	**2.03 (1.98 to 2.09)**
≥3 vs. 1-2				
Case crossover	30,880	19,432	11,448	1.56 (1.53 to 1.59)
Control crossover	24,627	12,703	11,924	1.06 (1.04 to 1.08)
CCTC	-	-	-	**1.48 (1.44 to 1.52)**

發生心血管事件的病人，在事件前 **30** 天內的 **anticholinergic burden** 比先前高
→ 當病人有較高 **anticholinergic burden** 時，短期內可能有較高心血管風險

Results: Sensitivity Analyses

就算調整定義或進行各種校正結果皆與主分析方向性一致

Analyses	Odds ratio (95% CI)		
	1-2 vs. 0	≥3 vs. 0	≥3 vs. 1-2
Cut-off point for exposure category			
0, 1-4, ≥5	1.54 (1.51 to 1.58)	2.46 (2.38 to 2.53)	-
0, 1-9, ≥10	1.70 (1.67 to 1.74)	2.90 (2.75 to 3.06)	-
Hazard/reference periods: 14 days	1.46 (1.43 to 1.50)	1.94 (1.89 to 1.99)	1.33 (1.28 to 1.37)
Washout periods			
60 days	1.34 (1.31 to 1.38)	2.02 (1.98 to 2.07)	1.51 (1.47 to 1.55)
120 days	1.30 (1.27 to 1.34)	1.97 (1.93 to 2.02)	1.51 (1.47 to 1.55)
Interval between event dates of future/current cases: 120-240 days	1.40 (1.36 to 1.45)	2.23 (2.16 to 2.30)	1.59 (1.54 to 1.64)
Adjusted by medication dosing	2.81 (2.74 to 2.88)	5.43 (5.26 to 5.62)	1.93 (1.88 to 1.99)
Adjusted by the duration of drugs used			
Used >3 days within 30 days	1.74 (1.69 to 1.79)	2.15 (2.09 to 2.22)	1.24 (1.20 to 1.28)
Used >7 days within 30 days	1.25 (1.21 to 1.28)	1.32 (1.27 to 1.36)	1.06 (1.02 to 1.10)
Adjusted by time-varying covariates	1.34 (1.31 to 1.38)	1.86 (1.81 to 1.91)	1.38 (1.34 to 1.42)
Lag-time inserted			
3 days	1.23 (1.20 to 1.27)	1.70 (1.66 to 1.75)	1.38 (1.34 to 1.42)
7 days	1.14 (1.11 to 1.17)	1.44 (1.40 to 1.48)	1.26 (1.23 to 1.30)
Exclusion of patients with CV drugs	1.48 (1.40 to 1.55)	1.99 (1.91 to 2.06)	1.35 (1.28 to 1.42)
Selecting patients with chronic conditions	1.34 (1.30 to 1.39)	2.02 (1.96 to 2.08)	1.51 (1.46 to 1.55)

Conclusions

- 當年長者有較高 anticholinergic burden 時，短期內可能有較高心血管風險
- 就算考量 protopathic bias 的影響，仍有觀察到相關性

Clinical Relevance

- 並非針對特定藥物，而是整體 anticholinergic burden 的影響
- 當藥品為必須使用時，需考量病人 anticholinergic burden 並監測相關不良反應

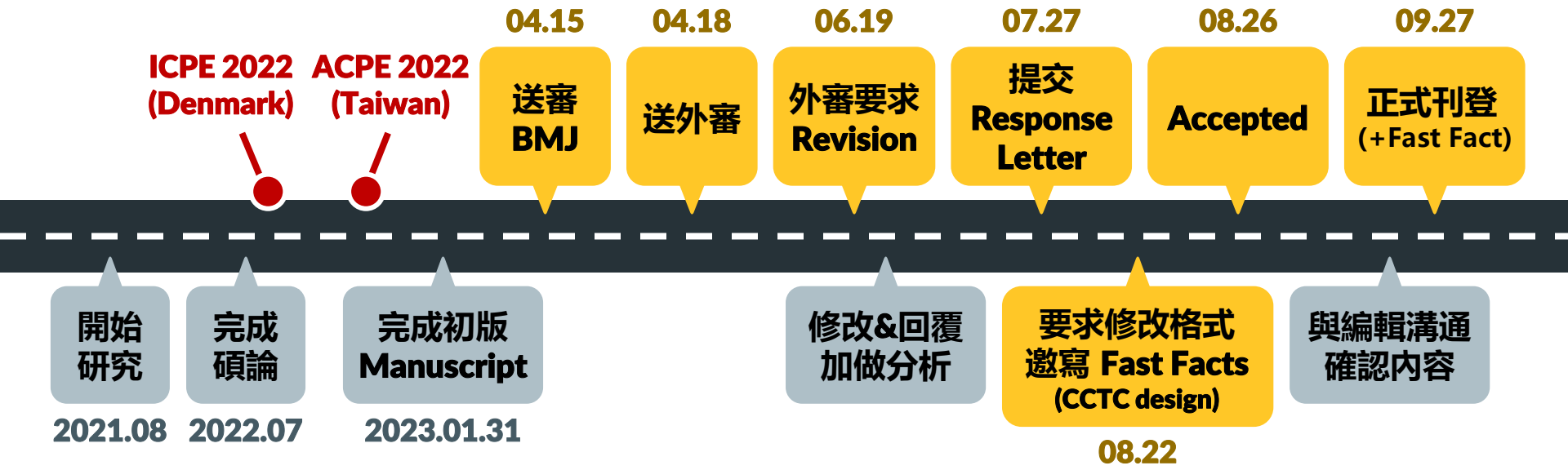
Future Work

- Threshold of anticholinergic burden：高低風險的切點
- 方法學：Protopathic bias 的校正方法、CCTC 發展與改良

期刊投稿及發表

Journal Submission & Publishing

研究進行 & 投稿過程 Timeline



ICPE: International Conference on Pharmacoepidemiology and Therapeutic Risk Management
ACPE: ISPE's Asian Conference on Pharmacoepidemiology

Manuscript - 期刊規範

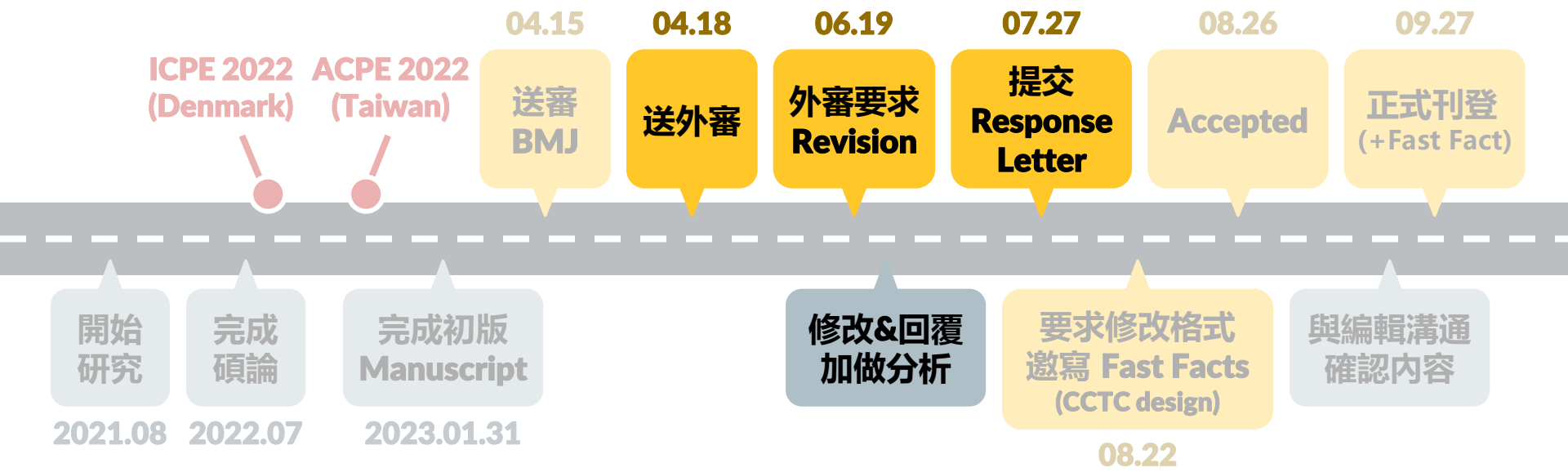
以 BMJ 寫作格式為例

- **字數限制**：Abstracts 250 - 300 字 (≤ 400 字)，內文不限
- **特殊架構**：Structured abstract、structured discussion、summary box…
- **數字標示**：
  - 小於 10 的數字須以英文拼寫 (除非有附單位如 8 mmol/L)
  - 95% CI 上下限須以 “to” 而非 “hyphen (-)” 連接
- **表格**：置於 Word 檔內，最多橫跨兩頁，內容不與內文重複
- **圖片**：獨立檔案，但 Word 檔內可附縮圖
- **資料來源格式**：Vancouver style
- **文法建議**：減少縮寫使用、避免名詞堆疊
- **額外考量**：British/American English spelling、期刊主題色…

等待審核過程

- 每週五等開獎 (?)
- 同步準備投稿至下一個期刊

研究進行 & 投稿過程 Timeline



Response Letter - 回答問題 & 修正

6 Reviewers & 43 Comments

- **問題與建議類別：**
  - 內文說明不足之處 (結果闡釋、分析方法、名詞解釋...)
  - 建議加做分析、補足 data
  - 潛在的 bias 或 limitations
- **逐條列出並個別回應每位 reviewer 的每一個問題**
- **回覆問題：理解 reviewer 真正想知道的是什麼**
  1. 認同並感謝建議、點出重要的問題、提出新觀點
  2. 接受建議 → 已於文章修改、已加做分析、已補上說明
  3. 各種疑問或難執行的建議 → **Justify**、替代的方案
- **標示出文章內相應的修改內容，以便 reviewer 檢視**

Response Letter - 回答問題 & 修正

Example: Potential Limitations

Reviewer 4, Comment 4:

Finally, among the limitations one should also consider that data are about prescribed medications however with no information regarding **adherence/compliance**.

Response

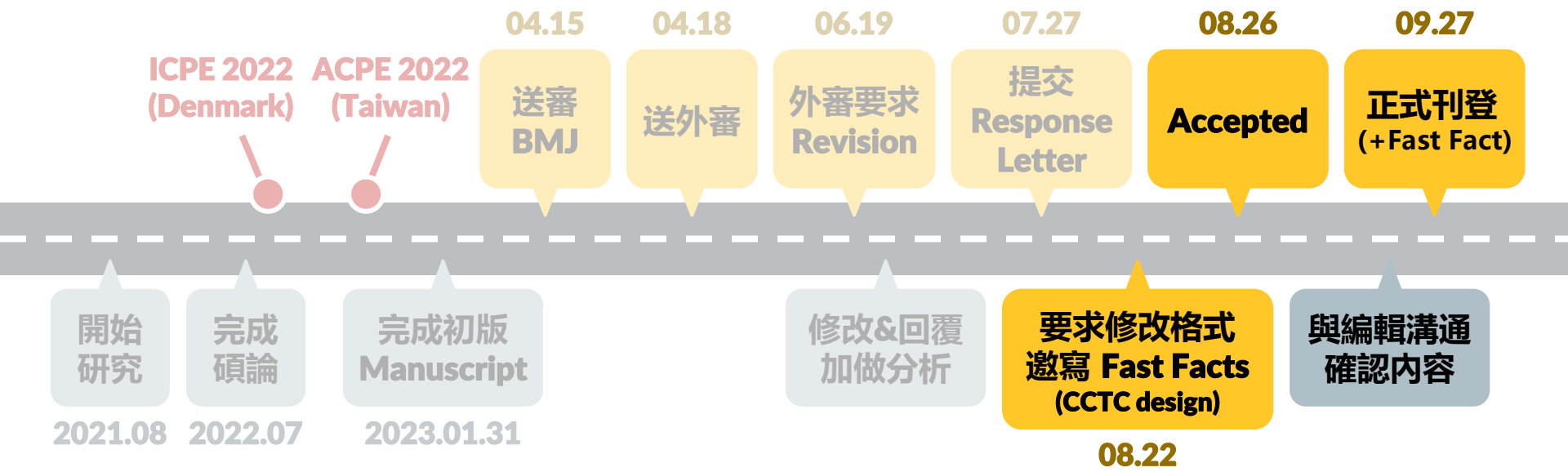
Thank you very much for your comment. We have revised the manuscript and added a discussion on treatment adherence.

Revision

(DISCUSSION, Strengths and Weaknesses of This Study, 2nd paragraph)

Finally, although the claims database provided complete records of prescriptions, the lack of information on drug adherence prevented us from confirming whether the patients actually took their drugs, leading to possible misclassification bias. However, this bias did not affect our conclusion because we could expect the effects of drug adherence to be consistent across the hazard and reference windows, resulting in a similar impact on estimates.

研究進行 & 投稿過程 Timeline



Research

Association between recently raised anticholinergic burden and risk of acute cardiovascular events: nationwide case-case-time-control study

BMJ 2023 ; 382 doi: https://doi.org/10.1136/bmj-2023-076045 (Published 27 September 2023)
Cite this as: *BMJ* 2023;382:e076045

Linked research

Future-case control crossover analysis for adjusting bias in case crossover studies

Fast Facts

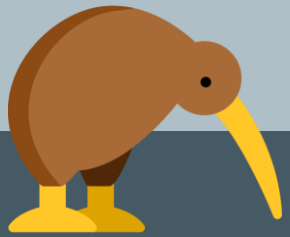
Linked editorial

Anticholinergic medicines linked to cardiovascular events in older adults

Article | Related content | Metrics | Responses | Peer review

Wei-Ching Huang, *masters student* [1], *Avery Shuei-He Yang*, *doctoral student* [1], *Daniel Hsiang-Te Tsai*, *doctoral student* [1], *Shih-Chieh Shao*, *pharmacist* [1 2], *Swu-Jane Lin*, *adjunct associate professor* [3], *Edward Chia-Cheng Lai*, *professor* [1]

研究菜鳥的研究之路
小小心得分享



研究興趣與熱情

堅持下去的動力!

- 老師與學長姐的引導鼓勵
- 集思廣益解決問題
- 一起為研究結果歡呼

分享想法與交流

參與各種研討會

找到盲點 & 新方法

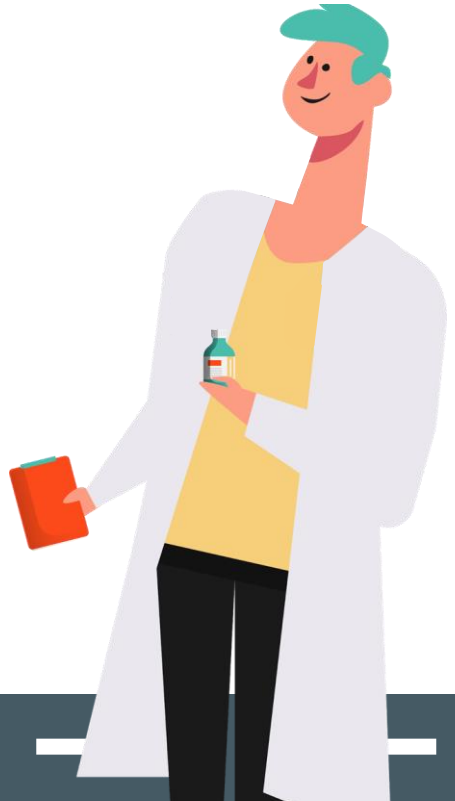
The Grandma Test!

任何結果與偏差都有意義！

來自老師的一封信

Embrace it!

- “The purpose of a research is to **find out the truth**, not to prove the hypothesis or the assumed relationship between factors are true.”
- “I wouldn't worry even if a hypothesis was refuted, as long as it is a high-quality study.”
- “You don't need to think of protopathic bias or other sensitivity analyses results as 'biased'. **On the contrary, I think you should 'embrace' it, and proudly present the results as an improvement in research methods for future researchers**.“



THANK YOU FOR LISTENING

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