14:35 – 15:05

利用真實世界數據與因果推論方法提升臨床決策

賴嘉鎮, Edward Lai, PhD, FISPE, Professor

School of Pharmacy, Institute of Clinical Pharmacy and Pharmaceutical Sciences, College of Medicine, National Cheng Kung University, Tainan, Taiwan

NCKU National Cheng Kung University × PHDc

Disclosure

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過去發表
真實世界數據 之應用



老年衰弱族群用藥安全

BMJ 2021;374:n1925



多重用藥問題與交互作用

BMJ 2023;382:e076045


老藥新用

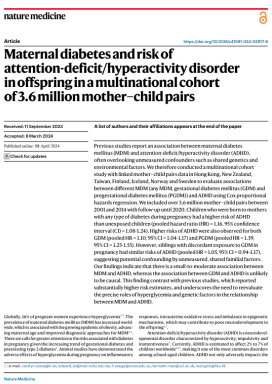
JAMA NetworkOpen. 2024;7(3):e240946.

藥物流病方法學探討

BMJ 2023;382:p2136

兒童用藥安全

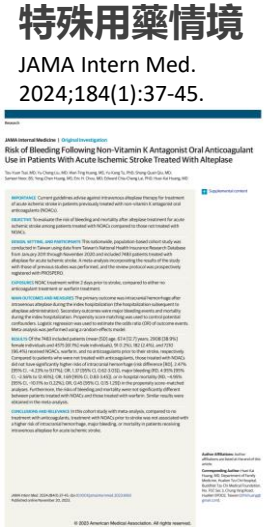
Epidemiol Psychiatr Sci. 2021 Oct 15;30:e65.



懷孕婦女用藥安全

Nat Med (2024).

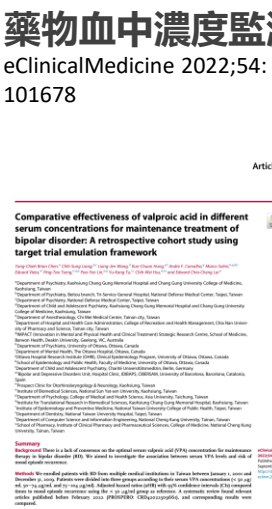




特殊用藥情境

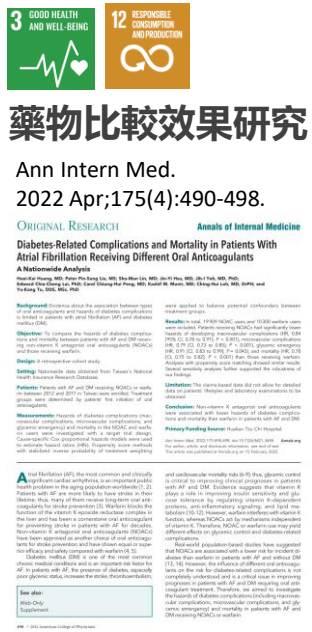
JAMA Intern Med. 2024;184(1):37-45.





藥物血中濃度監測

eClinicalMedicine 2022;54: 101678

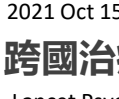
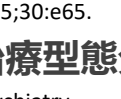


藥物比較效果研究

Ann Intern Med. 2022 Apr;175(4):490-498.

跨國治療型態分析

Lancet Psychiatry. 2018 Oct;5(10):824-835.


促進健康

產業技術革新

減少不平等

循環經濟
減少資源利用

減少碳排

夥伴關係

真實世界證據 取代 橋接性臨床試驗 （ Bridging RCT ）

臨床試驗

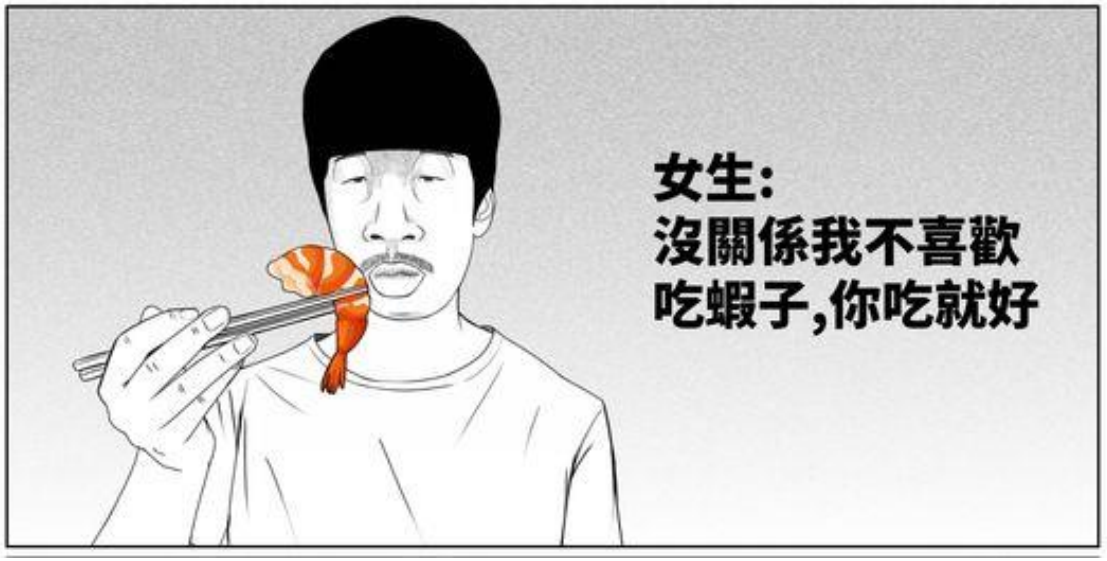
- 實驗性研究
- 理想環境
- 篩選過的族群
- 樣本小
- 觀察時間短
- 非常昂貴（A咖）
- 為了取得許可證

真實世界

Credit: 黃暐晴

- 觀察性研究
- 真實情境 (複雜且不完美)
- 真實病人 (老人小孩孕婦)
- 樣本大
- 觀察時間長
- 相對便宜有效率（小咖）
- 不是為了取得許可證

當主編收到稿件時

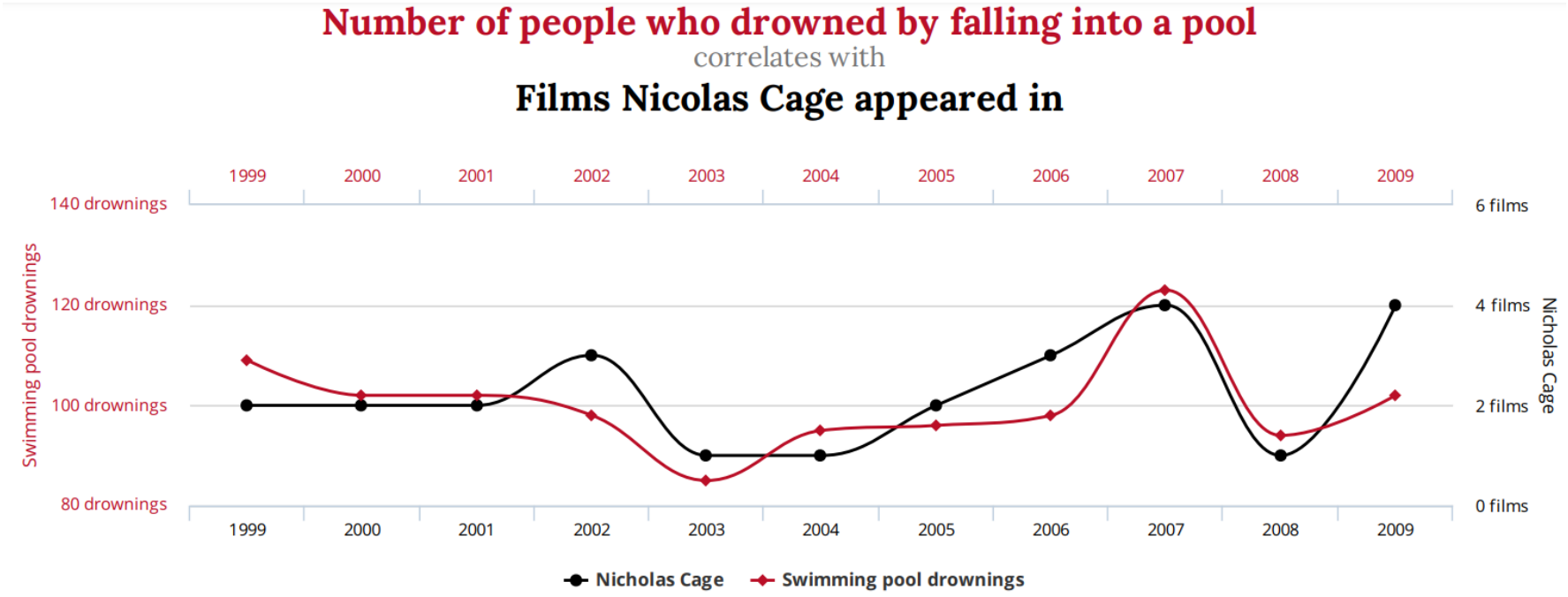


實驗性研究
(experimental study)

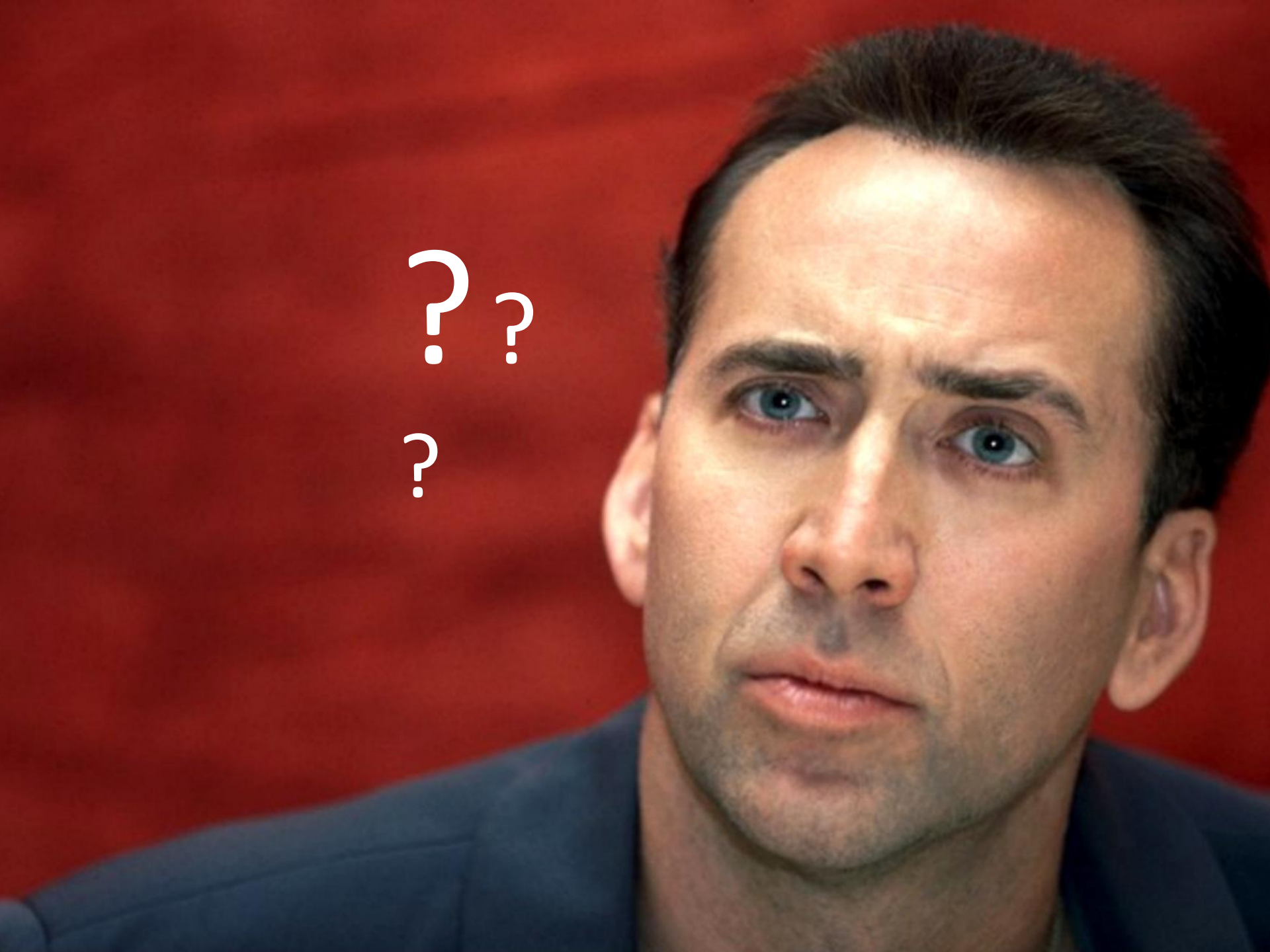
⬆⬆⬆ **因果推論**

觀察性研究
(observational study)

本圖截取自網路作家聞氫哥



Source: Spurious Correlations



Bradford Hill criteria

Strength 強度	Effect size; the larger the association, the more likely that it is causal.
Consistency 一致性	Consistent findings observed by different persons in different places with different samples.
Specificity 特異性	The more specific an association between a factor and an effect is, the bigger the probability of a causal relationship.
Temporality 時序性	The effect has to occur after the cause
Biological gradient 生物梯度	Dose-response; greater exposure should generally lead to greater incidence of the effect.
Plausibility 合理性	A plausible mechanism between cause and effect is helpful
Coherence 連貫性	Coherence between epidemiological and laboratory findings increases the likelihood of an effect.
Experiment 實驗	possible to appeal to experimental evidence.
Analogy 類比	The use of analogies or similarities between the observed association and any other associations.
Reversibility 可逆性	If the cause is deleted then the effect should attenuate as well.

Naranjo Score

	項目	是	否	不知
Plausibility	1.此不良反應是否有研究報告確定?	+1	0	0
Temporality	2.此不良反應是否發生於服藥之後?	+2	-1	0
Reversibility	3.當停藥或使用此藥之解藥，不良反應是否減輕?	+1	0	0
Consistency	4.停藥一段時間再重新使用該品項，同樣的不良反應是否再度發生?	+2	-1	0
Specificity	5.有沒有其他原因(此藥以外)可以引起同樣之不良反應?	-1	+2	0
Experiment	6.當給予安慰劑時，此項不良反應是否會再度發生?	-1	+1	0
Strength	7.此藥物的血中濃度是否達到中毒劑量?	+1	0	0
Biological gradient	8.對此病人而言，藥物劑量與不良反應的程度是否成正向關係?	+1	0	0
Analogy	9.病人過去對同樣或類似藥物是否也產生同樣的不良反應	+1	0	0
Coherence	10.此項不良反應是否有客觀的證據?	+1	0	0

總分:　分

□≧9分，確定 □ 5 - 8分，極可能 □□ 1 - 4分，可能 □≦0分，存疑

相關性 或 因果關係

Protopathic bias (倒果為因)

"If a particular treatment or exposure was started, stopped, or otherwise changed because of the baseline manifestation caused by a disease or other outcome event." – Feinstein 1985

Confounding by indication (適應症干擾)

"arises from the fact that individuals who are prescribed a medication are inherently different from those who do not take the drug, because they are taking the drug for a reason..."

Example 1

精神科藥物是否會增加跌倒風險

Use of antipsychotic drugs and cholinesterase inhibitors and risk of falls and fractures: self-controlled case series

Grace Hsin-Min Wang,[1] Kenneth K C Man,[2] Wei-Hung Chang,[3,4] Tzu-Chi Liao,[1] Edward Chia-Cheng Lai[1]

[1]School of Pharmacy, Institute of Clinical Pharmacy and Pharmaceutical Sciences, College of Medicine, National Cheng Kung University, Tainan, Taiwan
[2]Research Department of Practice and Policy, UCL School of Pharmacy, London, UK
[3]Department of Psychiatry, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan
[4]Department of Psychiatry, National Cheng Kung University Hospital, Dou-Liou Branch, Yunlin, Taiwan

Correspondence to: E C-C Lai
edward_lai@mail.ncku.edu.tw
(ORCID 0000-0002-5852-7652)

Additional material is published online only. To view please visit the journal online.

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http://dx.doi.org/10.1136/bmj.n1925

Accepted: 27 July 2021

ABSTRACT

OBJECTIVE

To evaluate the association between the use of antipsychotic drugs and cholinesterase inhibitors and the risk of falls and fractures in elderly patients with major neurocognitive disorders.

DESIGN

Self-controlled case series.

SETTING

Taiwan's National Health Insurance Database.

PARTICIPANTS

15 278 adults, aged ≥65, with newly prescribed antipsychotic drugs and cholinesterase inhibitors, who had an incident fall or fracture between 2006 and 2017. Prescription records of cholinesterase inhibitors confirmed the diagnosis of major neurocognitive disorders; all use of cholinesterase inhibitors was reviewed by experts.

MAIN OUTCOME MEASURES

Conditional Poisson regression was used to derive incidence rate ratios and 95% confidence intervals for evaluating the risk of falls and fractures for different treatment periods: use of cholinesterase inhibitors alone, antipsychotic drugs alone, and a combination of cholinesterase inhibitors and antipsychotic drugs, compared with the non-treatment period in the same individual. A 14 day pretreatment period was defined before starting the study drugs because of concerns about confounding by indication.

RESULTS

The incidence of falls and fractures per 100 person years was 8.30 (95% confidence interval 8.14 to 8.46) for the non-treatment period, 52.35 (48.46 to 56.47) for the pretreatment period, and 10.55 (9.98 to 11.14), 10.34 (9.80 to 10.89), and 9.41 (8.98 to 9.86) for use of a combination of cholinesterase inhibitors and antipsychotic drugs, antipsychotic drugs alone, and cholinesterase inhibitors alone, respectively. Compared with the non-treatment period, the highest risk of falls and fractures was during the pretreatment period (adjusted incidence rate ratio 6.17, 95% confidence interval 5.69 to 6.69), followed by treatment with the combination of cholinesterase inhibitors and antipsychotic drugs (1.35, 1.26 to 1.45), antipsychotic drugs alone (1.33, 1.24 to 1.43), and cholinesterase inhibitors alone (1.17, 1.10 to 1.24).

CONCLUSIONS

The incidence of falls and fractures was high in the pretreatment period, suggesting that factors other than the study drugs, such as underlying diseases, should be taken into consideration when evaluating the association between the risk of falls and fractures and use of cholinesterase inhibitors and antipsychotic drugs. The treatment periods were also associated with a higher risk of falls and fractures compared with the non-treatment period, although the magnitude was much lower than during the pretreatment period. Strategies for prevention and close monitoring of the risk of falls are still necessary until patients regain a more stable physical and mental state.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Antipsychotic drugs and cholinesterase inhibitors have been reported to increase the incidence of falls and fractures in patients with major neurocognitive disorders

Confounding by indication should be considered when evaluating the association between drugs and adverse reactions because cognitive impairment and neuropsychiatric symptoms of major neurocognitive disorders might lead to a high risk of falls and fractures

WHAT THIS STUDY ADDS

The risk of falls and fractures was highest before patients started treatment with cholinesterase inhibitors and antipsychotic drugs, implying that factors other than the use of drugs might have affected the incidence of falls and fractures

Although the high risk of falls and fractures in the pretreatment period was reduced after patients received treatment, the results indicated that patients might not have regained a stable condition of their major neurocognitive disorder

Introduction

Older adults with major neurocognitive disorders are often considered vulnerable and prone to falls and related fractures.[1] Falls and fractures are the most common causes for admission to hospital in older adults and are associated with substantial morbidity and mortality.[2] Cholinesterase inhibitors are typically used to improve cognition and might be linked to the risk of falls and fractures as a result of the syncope caused by parasympathomimetic effects.[3-5] Antipsychotic drugs are commonly prescribed to treat neuropsychiatric symptoms in patients with major neurocognitive disorders,[6] and concerns have been raised about falls and fractures.[7] Because of the potential adverse effects of antipsychotic drugs, including orthostatic hypotension, sedation, blurred vision, and extrapyramidal symptoms, the United States Food and Drug Administration has suggested that a complete assessment of the risk of falls should be undertaken before the start of treatment.[8] Beers criteria[9] and other studies[10-22] have also suggested that antipsychotic drugs might be associated with the risk of falls and fractures.

Although several studies and guidelines have suggested that cholinesterase inhibitors and antipsychotic drugs might be associated with the risk of falls and fractures, other studies reached different conclusions. Jin et al and Kim et al found no association

BMJ 2021;374:n1925 (IF 107.7)

研究背景 – 藥物

Major neurocognitive disorders (dementia)

- Learning and memory
- Language
- Executive function
- Complex attention
- Perceptual-motor
- Social cognition

➢ Cholinesterase inhibitor

➢ **Donepezil, rivastigmine, galantamine**

Neuropsychiatric symptoms **(BPSD)**

- Perception
- Thought content
- Mood
- Behavior

➢ **Antipsychotics**

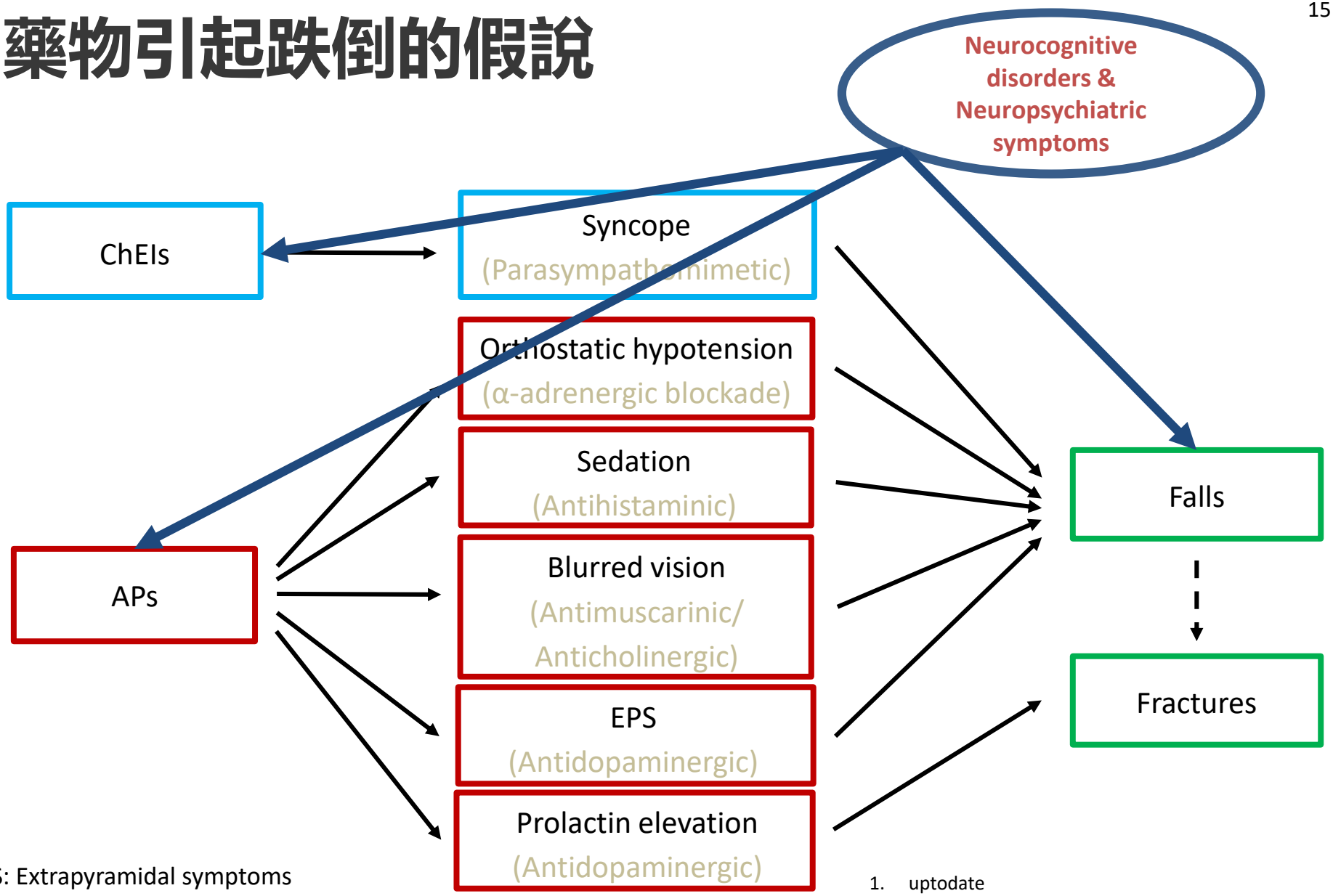
haloperidol

risperidone, aripiprazole, quetiapine

BMJ. 2015 Mar 2;350:h369.; Ther Adv Neurol Disord. 2017 Aug; 10(8): 297–309.

學生 王馨敏的投影片

藥物引起跌倒的假說



EPS: Extrapyramidal symptoms

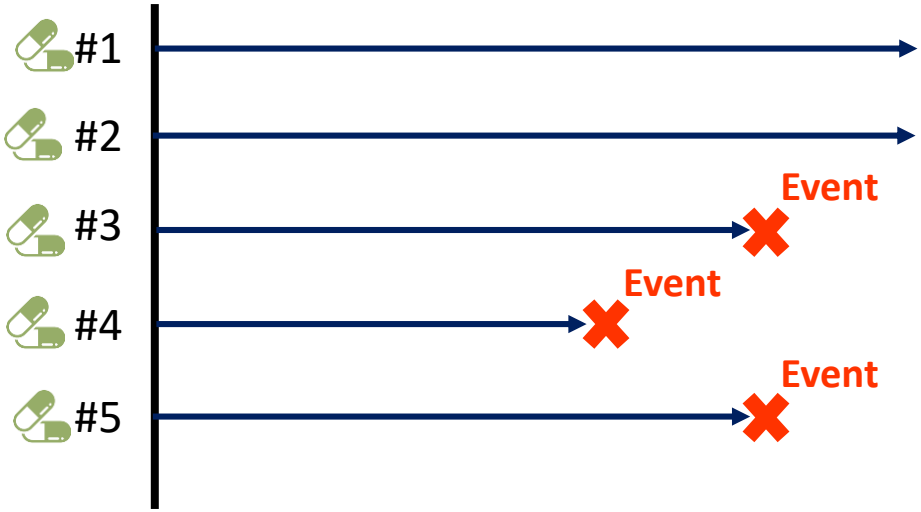
1. uptodate
2. J Am Geriatr Soc. 2011 Jun; 59(6): 1019–1031.
3. http://www.accessdata.fda.gov/drugsatfda_docs/label/2017/020639s065lbl.pdf

用時序來證明適應症干擾

Self-controlled case series (SCCS)

Cohort study

Treatment group



Population at risk:

#1: 5 person-years

#2: 5 person-years

#3: 4 person-years

#4: 3 person-years

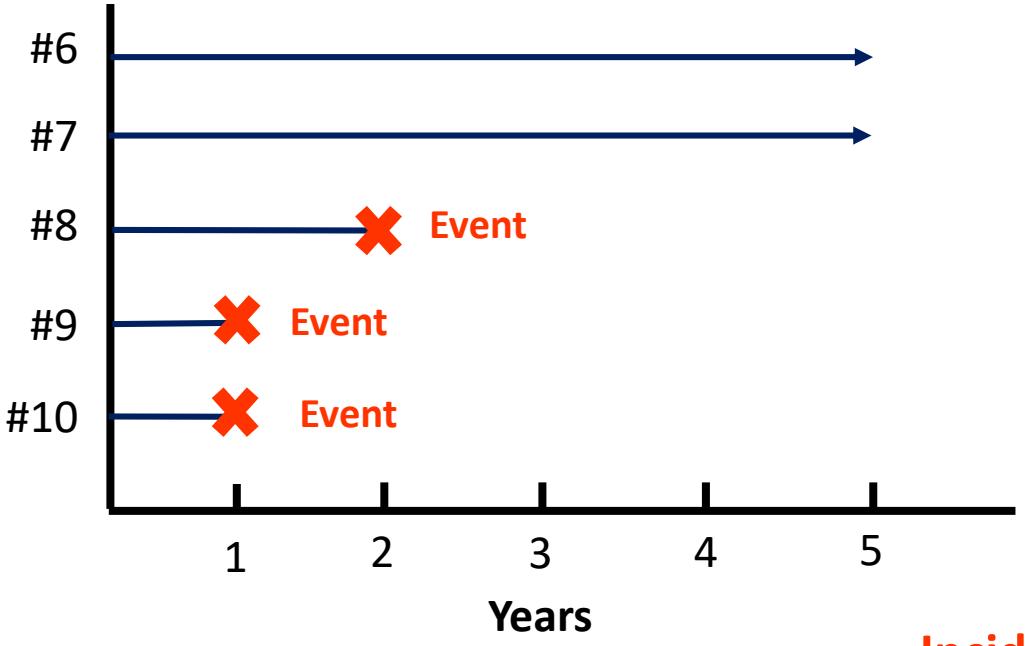
#5: 4 person-years

Total= 5+5+4+3+4 =21 person-years

Events = 3

Incidence rate=3/21*1,000 = 142 per 1,000 person-years

Non-treatment group



Population at risk:

#1: 5 person-years

#2: 5 person-years

#3: 2 person-years

#4: 1 person-years

#5: 1 person-years

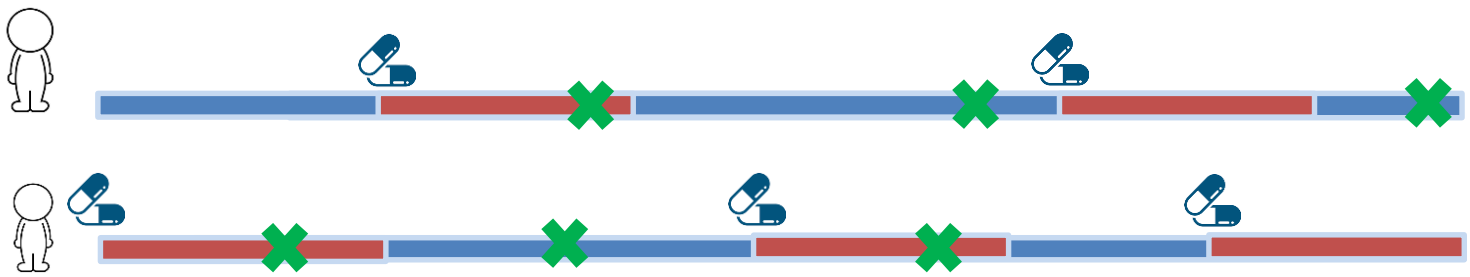
Total= 5+5+2+1+1 =14 person-years

Events = 3

Incidence rate=3/14*1,000 = 214 per 1,000 person-years

Incidence rate ratio =142/214 = 0.66

Self-controlled case series (SCCS)



Exposed period:

#1: 3 person-days

#2: 3 person-days

#3: 3 person-days

#4: 3 person-days

#5: 3 person-days

Total= 3+3+3+3+3
=15 person-days **Events = 3**

Incidence rate=3/15*1,000 = 200 per 1,000 person-days

Unexposed period:

#1: 3 person-days

#2: 6 person-days

#3: 2 person-days

#4: 5 person-days

#5: 3 person-days

Total= 3+6+2+5+3
=19 person-days **Events = 3**

Incidence rate=3/19*1,000 = 158 per 1,000 person-days

Incidence rate ratio =200/158 = 1.27

病人在吃藥之前的風險已經很高了?

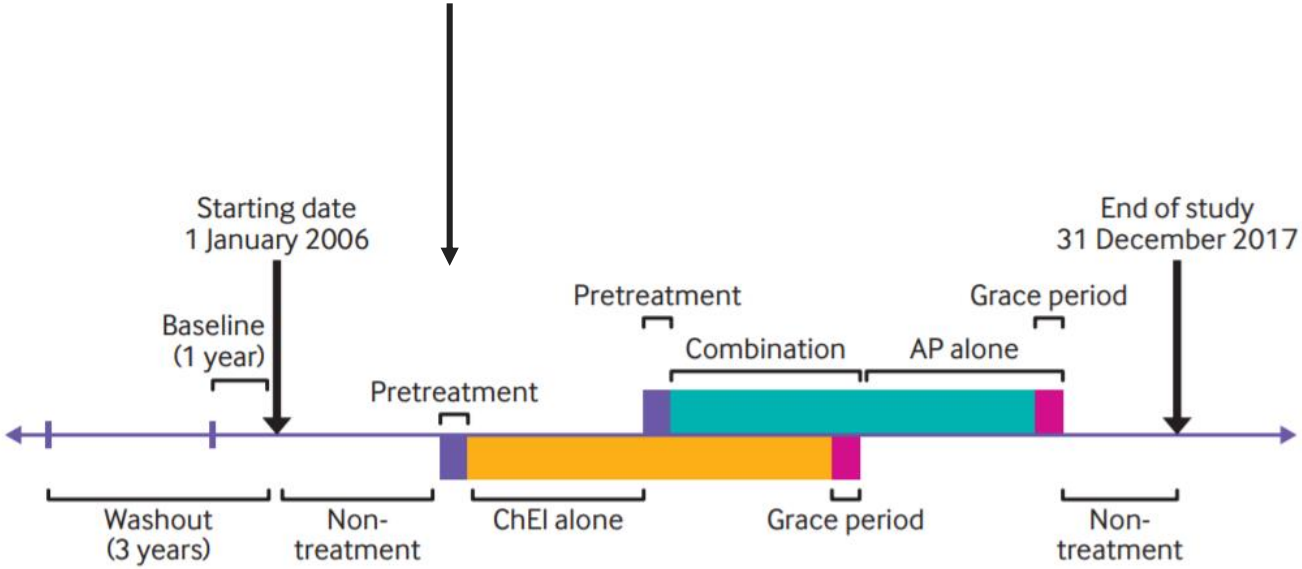
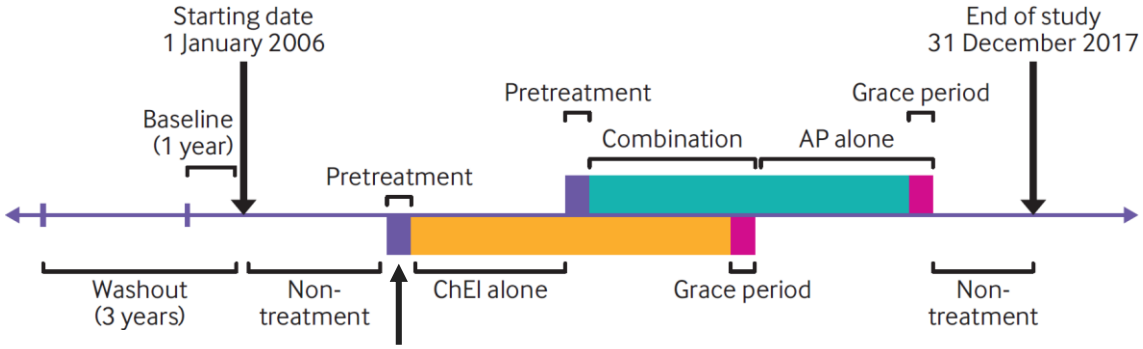


Fig 2 | Study scheme and definitions of treatment periods. A three year washout period before the start date was used to exclude patients with a history of falls and fractures. A one year baseline period was defined to assess patients' baseline covariates. The study was divided into five separate periods: 14 day pretreatment period before the use of drugs, use of cholinesterase inhibitors alone, use of antipsychotic drugs alone, use of a combination of cholinesterase inhibitors and antipsychotic drugs, and non-treatment period, when cholinesterase inhibitors and antipsychotic drugs were not used. A refill noted within 14 days after the end date of the last prescription (that is, 14 day grace period) was considered as a continuation of a previous prescription. ChEI=cholinesterase inhibitor; AP=antipsychotic drug

Risk of fall and fractures in different study periods

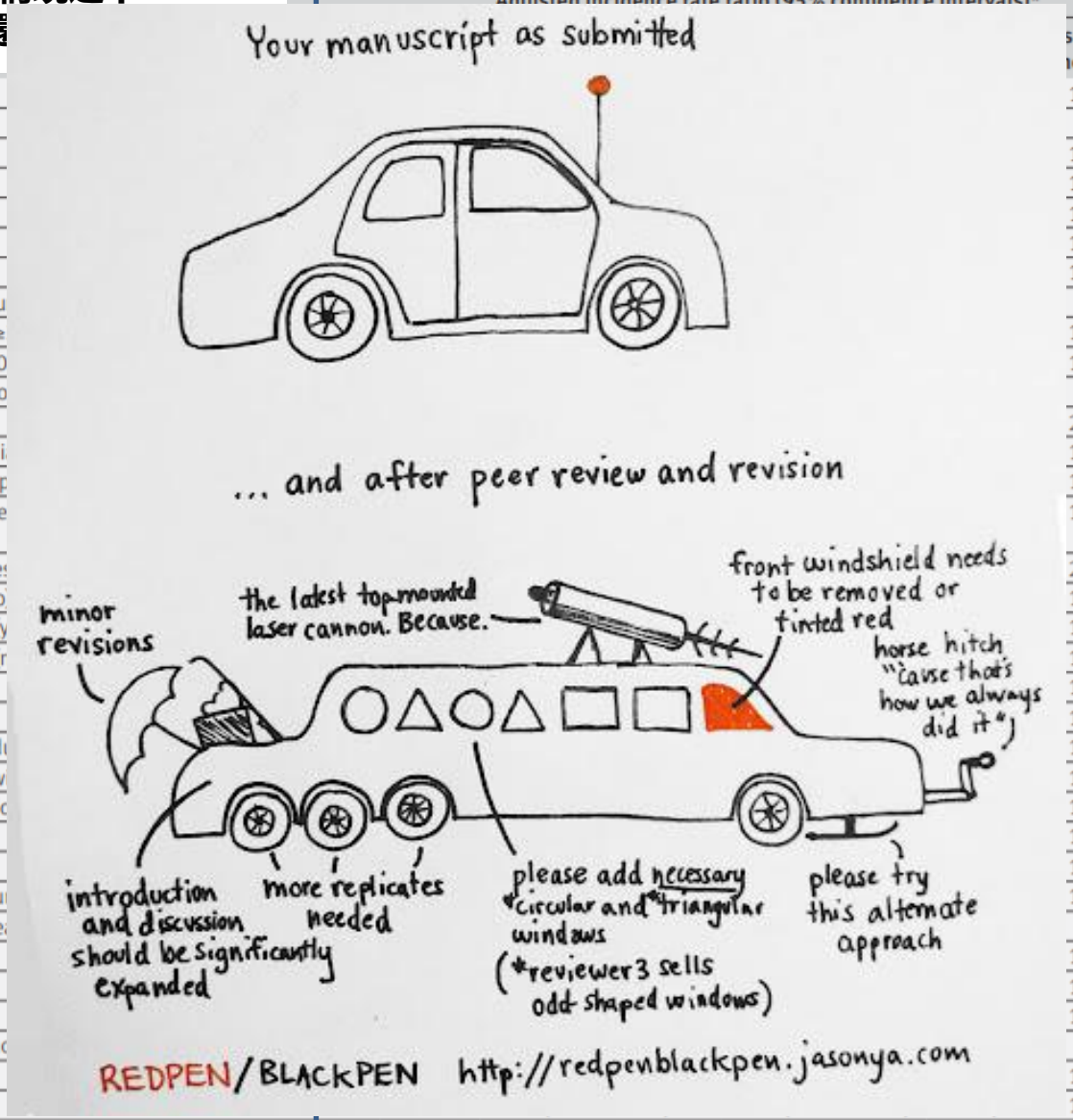
	No of events	Follow-up time (years; median (IQR))	Incidence rate (95% CI)/100 person years	Adjusted incidence rate ratio (95% CI) compared with non-treatment period
All events (n=15 278):				
Non-treatment	10 208	8.55 (4.01)	8.30 (8.14 to 8.46)	Reference
Pretreatment	657	0.07 (0.03)	52.35 (48.46 to 56.47)	6.17 (5.69 to 6.69)
Cholinesterase inhibitor alone	1790	0.96 (1.92)	9.41 (8.98 to 9.86)	1.17 (1.10 to 1.24)
Antipsychotic drug alone	1353	0.35 (1.21)	10.34 (9.80 to 10.89)	1.33 (1.24 to 1.43)
Combination	1270	0.56 (1.31)	10.55 (9.98 to 11.14)	1.35 (1.26 to 1.45)

Increased risk?
Reduced risk?



病人在吃藥之前的風險已經很高 (約6.17倍)

假設不同情境之下
這些證據都還



			Adjusted incidence rate ratio (95% confidence intervals)*		
					Combination
Main analysis					1.35 (1.26 to 1.45)
Grouped by sex and age:					
Men					1.48 (1.31 to 1.67)
Women					1.29 (1.18 to 1.41)
Age group 65-74					1.67 (1.29 to 2.16)
Age group 75-84					1.25 (1.14 to 1.37)
Age group ≥85					1.51 (1.33 to 1.72)
Grouped by anticholinergic bu					
Anticholinergic drug scale ≥					1.67 (1.51 to 1.85)
Anticholinergic drug scale 0					1.11 (1.01 to 1.23)
Grouped by cumulative dose o					
Higher than median value					5.38 (4.79 to 6.05)
Equal to or lower than medi					2.12 (1.82 to 2.47)
Restricted to outcomes at outp					1.02 (0.91 to 1.13)
Re-selected patients without e disorder					1.33 (1.24 to 1.43)
Grouped by schizophrenia (yes					1.79 (0.75 to 4.28)
Grouped by schizophrenia (no					1.33 (1.24 to 1.43)
Grouped by bipolar disorder (y					0.84 (0.55 to 1.30)
Grouped by bipolar disorder (r					1.35 (1.26 to 1.45)
Grouped by depression (yes)					1.06 (0.93 to 1.20)
Grouped by depression (no)					1.48 (1.37 to 1.61)
Removed patients who died d					1.18 (1.08 to 1.30)
Removed patients who died w					1.31 (1.22 to 1.41)
Redefined outcome by specific					1.67 (1.49 to 1.87)
Falls					1.49 (1.09 to 2.04)
Fractures					1.70 (1.51 to 1.91)
All episodes of falls and fractu					1.31 (1.25 to 1.38)
Redefined the length of pretre					
7 days before treatment					1.32 (1.23 to 1.42)
21 days before treatment					1.37 (1.27 to 1.47)
28 days before treatment					1.39 (1.29 to 1.49)
Focus on individual antipsych					
Haloperidol					4.26 (3.37 to 5.37)
Risperidone					1.32 (1.13 to 1.54)
Olanzapine	1314	3.72 (2.57 to 5.37)	1.35 (1.00 to 1.82)	1.31 (1.09 to 1.56)	1.77 (1.31 to 2.39)
Quetiapine	12851	5.40 (4.91 to 5.93)	1.16 (1.07 to 1.26)	1.18 (1.11 to 1.26)	1.16 (1.07 to 1.26)

Conclusion

The incidence of falls and fractures was especially high in the pretreatment period, suggesting that factors other than drugs, such as underlying diseases, should be taken into consideration when evaluating the association between the risk of falls and fractures and the use of cholinesterase inhibitors and antipsychotic drugs. The treatment periods were also associated with a higher risk of falls and fractures compared with the non-treatment period although the magnitude was much lower than during the pretreatment period. Strategies for prevention and close monitoring of the risk of falls are still necessary until there is evidence that patients have regained a more stable physical and mental state.

Example 2

高齡族群多重用藥問題

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

Wei-Ching Huang,[1] Avery Shuei-He Yang,[1] Daniel Hsiang-Te Tsai,[1] Shih-Chieh Shao,[1,2] Swu-Jane Lin,[3] Edward Chia-Cheng Lai[1]

[1]School of Pharmacy, Institute of Clinical Pharmacy and Pharmaceutical Sciences, College of Medicine, National Cheng Kung University, Tainan, Taiwan
[2]Department of Pharmacy, Keelung Chang Gung Memorial Hospital, Keelung, Taiwan
[3]Department of Pharmacy Systems, Outcomes & Policy, College of Pharmacy, University of Illinois at Chicago, Chicago, IL, USA

Correspondence to: EC-C Lai
edward_lai@mail.ncku.edu.tw
(or @Lai_Edw on Twitter;
ORCID 0000-0002-5852-7652)

Additional material is published online only. To view please visit the journal online.

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http://dx.doi.org/10.1136/bmj-2023-076045

Accepted: 26 August 2023

ABSTRACT

OBJECTIVE

To evaluate the association between recently raised anticholinergic burden and risk of acute cardiovascular events in older adults.

DESIGN

Case-case-time-control study (ie, incorporating a case crossover design and a control crossover design consisting of future cases).

SETTING

Taiwan's National Health Insurance Research Database.

PARTICIPANTS

317 446 adults aged ≥65 who were admitted to hospital because of an incident acute cardiovascular event between 2011 and 2018. Acute cardiovascular events included myocardial infarction, strokes, arrhythmias, conduction disorders, and cardiovascular death.

MAIN OUTCOME MEASURES

The anticholinergic burden was measured for each participant by adding up the anticholinergic scores for individual drugs using the Anticholinergic Cognitive Burden Scale. Scores were classified into three levels (0 points, 1-2 points, and ≥3 points). For each participant, anticholinergic burden levels during hazard periods (day −1 to −30 before the cardiovascular event) were compared with randomly selected 30 day reference periods (ie, periods between days −61 and −180). Conditional logistic regression determined odds ratios with 95% confidence intervals to evaluate the association between acute cardiovascular events and recently raised anticholinergic burden.

RESULTS

The crossover analyses included 248 579 current cases. Participants' average age on the index date was 78.4 years (standard deviation 0.01), and 53.4% were men. The most frequently prescribed drugs with anticholinergic activity were antihistamines (68.9%), gastrointestinal antispasmodics (40.9%), and diuretics (33.8%). Among patients with varying levels of anticholinergic burden in different periods, more patients carried higher levels of anticholinergic burden during hazard periods than during reference periods. For example, 17 603 current cases had 1-2 points of anticholinergic burden in the hazard period with 0 points in the reference period, while 8507 current cases had 0 points in the hazard period and 1-2 points in the reference period. In the comparison of 1-2 points versus 0 points of anticholinergic burden, the odds ratio was 1.86 (95% confidence interval 1.83 to 1.90) in the case crossover analysis and 1.35 (1.33 to 1.38) in the control crossover analysis, which yielded a case-case-time-control odds ratio of 1.38 (1.34 to 1.42). Similar results were found in the comparison of ≥3 versus 0 points (2.03, 1.98 to 2.09) and ≥3 versus 1-2 points (1.48, 1.44 to 1.52). The findings remained consistent throughout a series of sensitivity analyses (eg, cut-off points for anticholinergic burden categories were redefined and different scales were used to measure anticholinergic burden).

CONCLUSIONS

An association was found between recently raised anticholinergic burden and increased risk of acute cardiovascular events. Furthermore, a greater increase in anticholinergic burden was associated with a higher risk of acute cardiovascular events.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Previous studies have reported an association between anticholinergic burden and increased cardiovascular risk, but have not considered the potential issue of protopathic bias

Research has investigated the relation between anticholinergic burden and long term cardiovascular events, but variations in anticholinergic burden over time require investigation

Studies examining the effect of a recently raised anticholinergic burden on the risk of cardiovascular events are lacking

WHAT THIS STUDY ADDS

A recently raised anticholinergic burden was associated with an increased risk of acute cardiovascular events, even after addressing the issue of protopathic bias

A dose-response relation was found between anticholinergic burden and risk of acute cardiovascular events

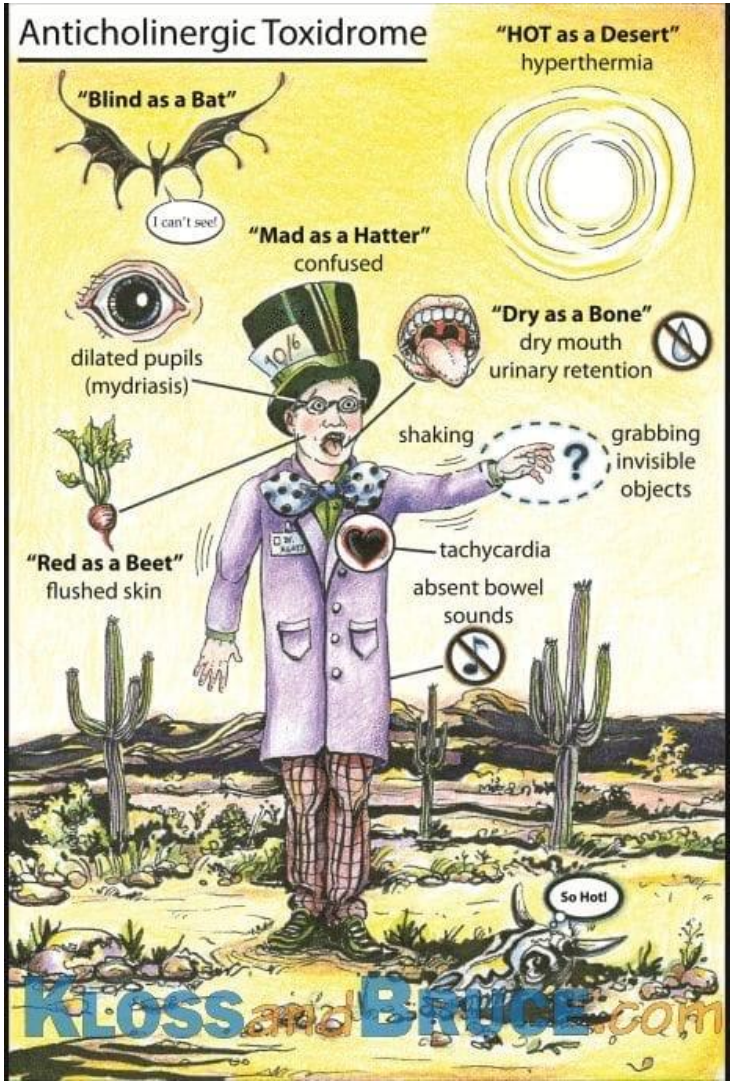
The findings highlight the need to consider protopathic bias when interpreting the results from observational studies

Introduction

Ageing populations present various challenges for healthcare worldwide, including increases in multimorbidity rates and subsequent polypharmacy issues. Polypharmacy has been associated with various unintended clinical consequences, with a prevalence reported to be as high as 90% in older adults.[1-3] Drugs with anticholinergic activity are among the most commonly prescribed drugs in older adults with polypharmacy.[4-6] However, for most of these drugs, anticholinergic activity is not the main intended effect and is often considered a side effect. As a result, clinicians might prescribe these drugs without

BMJ 2023;382:e076045

抗膽鹼作用:



Hot as a hare

(像野兔一樣高熱)→體溫上升

Red as a beet

(像甜菜一樣泛紅)→皮下微血管擴張

Dry as a bone

(像骨頭一樣乾燥)→口乾、皮膚乾燥

Blind as a bat

(像蝙蝠一樣盲目)→視力模糊

Mad as a hatter

(像帽匠一樣瘋狂)→譫妄

Bloated as a toad

(像蟾蜍一樣腹脹)→便祕

Full as a flask

(像燒瓶一樣填滿)→尿滯留

The heart runs alone

(心臟自己在奔跑)→心跳過速

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

Wei-Ching Huang,[1] Avery Shuei-He Yang,[1] Daniel Hsiang-Te Tsai,[1] Shih-Chieh Shao,[1,2] Swu-Jane Lin,[3] Edward Chia-Cheng Lai[1]

- **Polypharmacy** has been associated with various unintended clinical consequences, with a prevalence reported to be as high as 90% in older adults.
- Drugs with **anticholinergic activity** are among the most commonly prescribed drugs in older adults with polypharmacy.
- Anticholinergic activity **is not the main intended effect** and is often considered a side effect. As a result, clinicians might prescribe these drugs without taking into account their anticholinergic activity.
- Anticholinergic burden refers to the **cumulative adverse effect** of several drugs with anticholinergic activity.

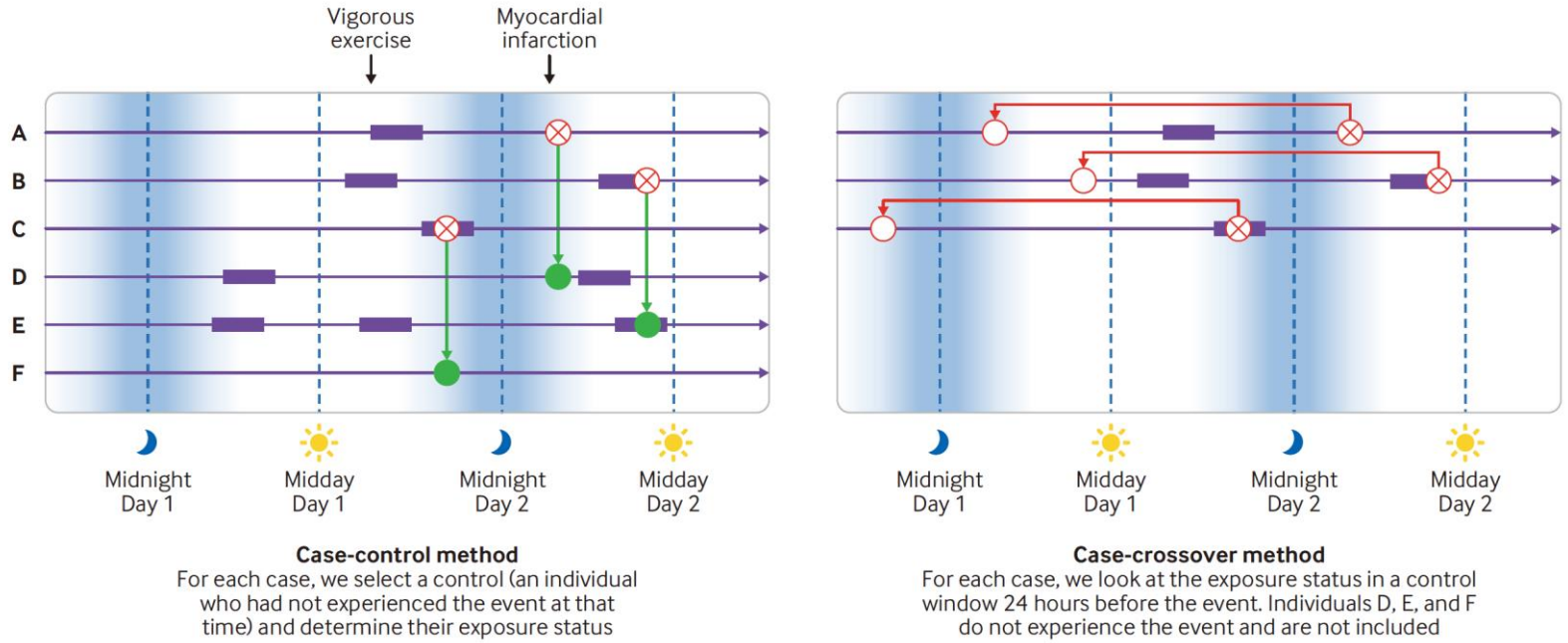
Anticholinergic burden and acute cardiovascular events

- **Biological plausibility:** anticholinergic activity has pro-arrhythmic and pro-ischaemic effects that can lead to **tachyarrhythmias** and increased oxygen requirements.
- The onset of anticholinergic effects can be **rapid** after taking a drug, which increases the likelihood of acute cardiovascular events.
- Research is needed examining the risk of **acute cardiovascular events** in the light of **recently increased** anticholinergic burden.

Introduction

The onset of anticholinergic effects can be rapid after taking a drug, which increases the likelihood of acute cardiovascular events. Research is needed examining the risk of acute cardiovascular events in the light of recently increased anticholinergic burden. Therefore, this study aimed to evaluate the association between recently raised anticholinergic burden and the risk of acute cardiovascular events. Additionally, patients receiving anticholinergic drugs might have several morbidities, leading to possible confounding by indications compared with those not receiving anticholinergic drugs.

Case-control vs Case-Crossover (CCO) (outcome anchored)



Case-control method
For each case, we select a control (an individual who had not experienced the event at that time) and determine their exposure status

Case-crossover method
For each case, we look at the exposure status in a control window 24 hours before the event. Individuals D, E, and F do not experience the event and are not included

Figure 1 | Illustrative study of the association between vigorous exercise and myocardial infarction, using case-crossover and case-control study designs. Figure shows timelines for six individuals (A to F). In a case-control study (left), individuals A, B, and C had myocardial infarctions (crossed red circles); individuals D, E, and F are controls selected at the same times (green circles); and the exposure of interest was vigorous exertion (occurring at the left edge of rectangles). A case-crossover design (right) compares the probability of exertion in the hour before myocardial infarction to the same time the previous day in the same individual (empty red circles); non-cases (individuals D, E, and F) do not contribute to the case-crossover analysis

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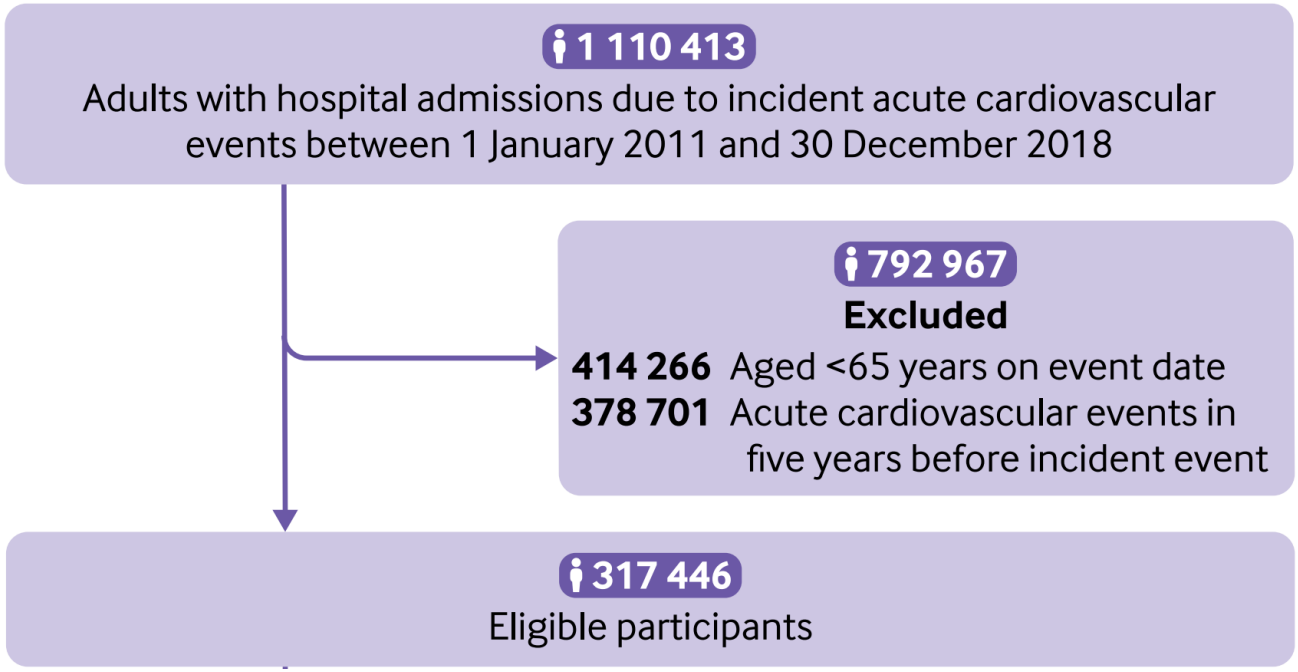


Fig 3 | Flowchart of study population and selection of eligible patients

Scales for Anticholinergic Burden Measuring

Quantification & Calculation

Scales		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)

7

Analyses	Odds ratio (95% CI)		
	1-2 vs. 0	≥3 vs. 0	≥3 vs. 1-2
Case crossover analysis	1.83 (1.80 to 1.86)	2.93 (2.89 to 2.98)	1.60 (1.57 to 1.63)

Protopathic bias

A clinician might prescribe drugs (such as antivertigo drugs for dizziness) symptoms of cardiovascular events before a confirmed diagnosis, making challenging to infer a causal relation or even leading to reverse causality drug use and outcomes (that is, protopathic bias).

黃暐晴——和 **Shih-Chieh Shao** 及**其他 3 人**。

9月28日下午10:21 ·

#BMJ #accepted (IF=105.7)

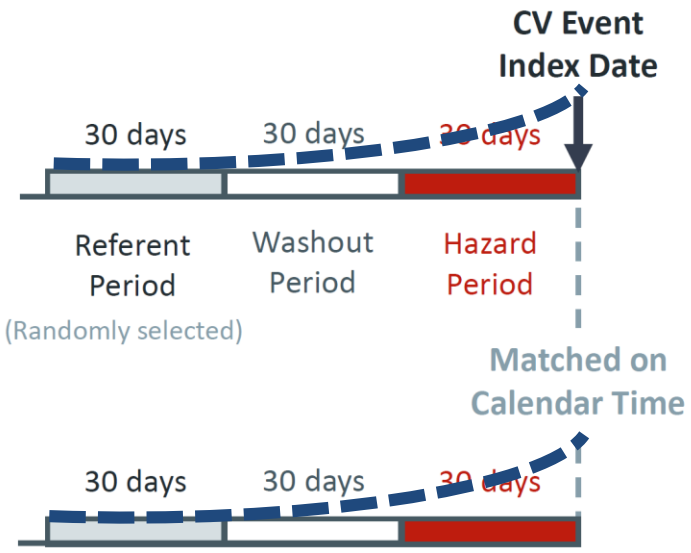
人生第一篇研究總算發表了！！！
能夠登上BMJ、達成這兩年最大的夢想
已經覺得此生無憾了🥹

從兩年前開始做研究到現在
曾經因為看見漂亮的data而一起興奮過
曾經為了難以解決的bias而苦惱卡關過
曾經在口試前三天崩潰大哭過
曾經在下班後寫manuscript 寫到睡著過
也曾經回reviewer刁鑽問題回到精神耗弱過
一路走來那些難忘的瞬間與無價的經驗
比什麼都珍貴

問題一: 群體趨勢

DRS-Matched Case-Time-Control

Control of Population Exposure Trend Bias



Case → **Case-crossover**

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

Control → **Control-crossover**

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

DRS-Matched Non-Case

DRS: Disease risk score

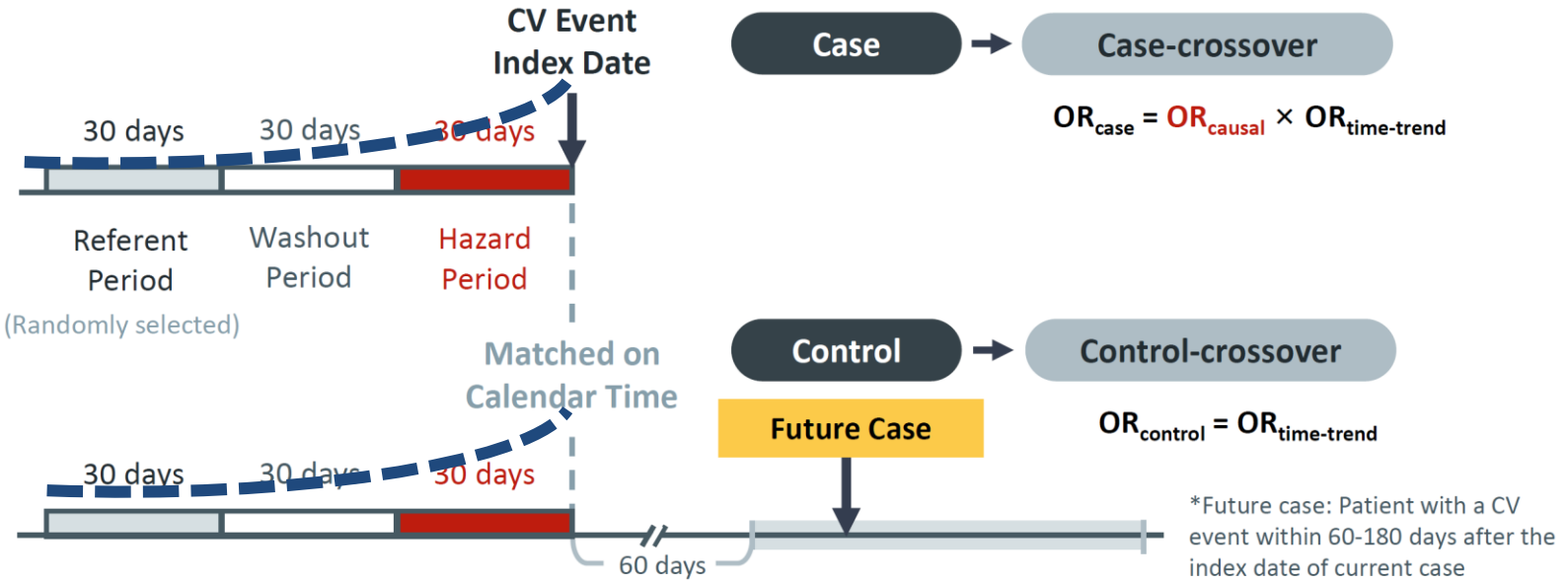
Corrected association = $OR_{case} / OR_{control} = OR_{causal}$

30

問題二: 個體趨勢

Case-Case-Time-Control

Control of Individual Exposure Trend Bias & Protopathic Bias



Corrected association = OR_{case} / $OR_{control}$ = OR_{causal}

CCTC 變成主分析

同時校正了群體與個體趨勢

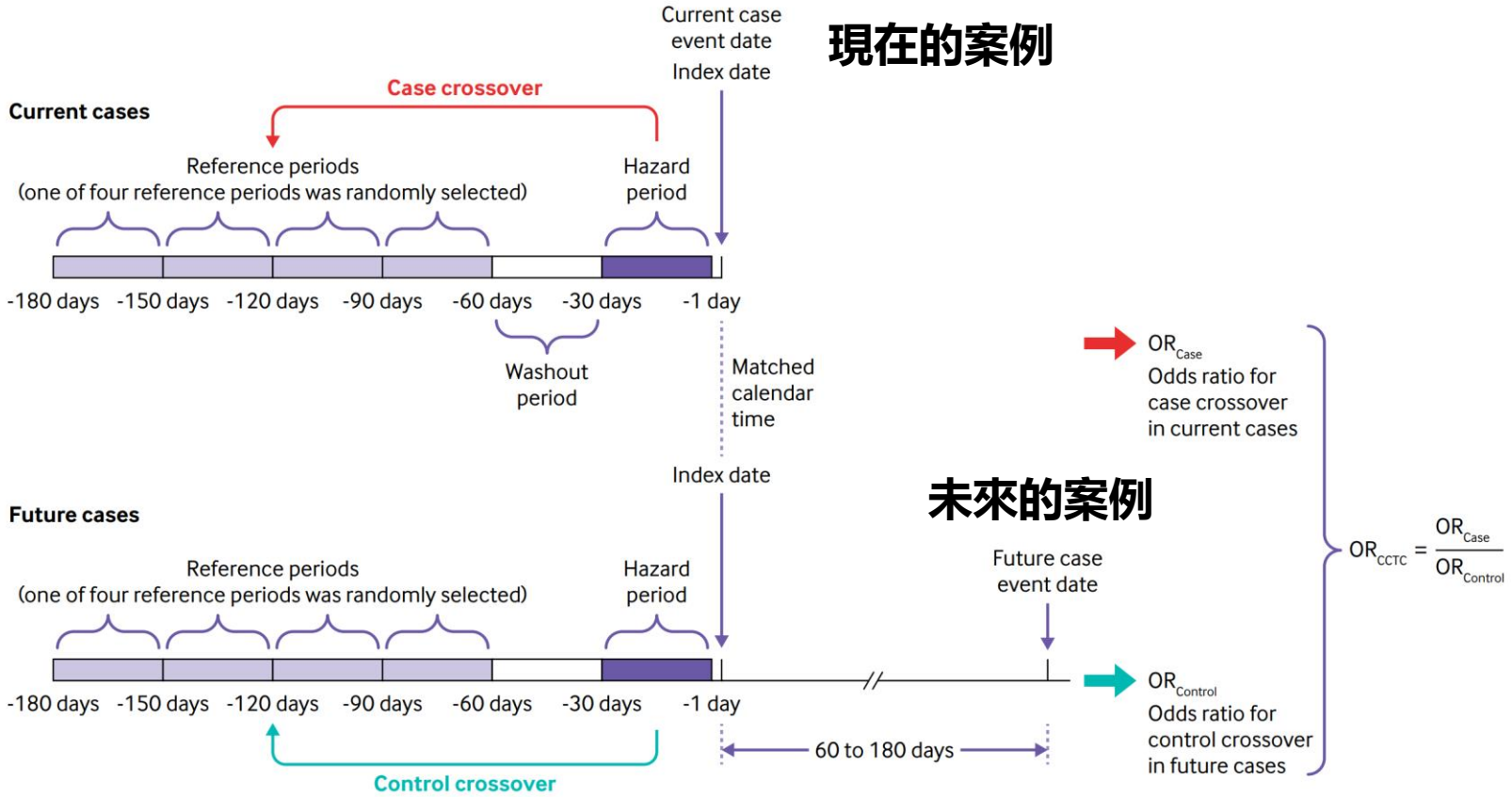


Fig 1 | Case-case-time-control (CCTC) design and details of time windows. The case-case-time-control analysis incorporated two self-controlled analyses—a case crossover analysis and a control crossover analysis consisting of future cases to address confounding by indication and potential protopathic bias, respectively

Introduction

The onset of anticholinergic effects can be rapid after taking a drug, which increases the likelihood of acute cardiovascular events. Research is needed examining the risk of acute cardiovascular events in the light of recently increased anticholinergic burden. Therefore, this study aimed to evaluate the association between recently raised anticholinergic burden and the risk of acute cardiovascular events. Additionally, patients receiving anticholinergic drugs might have several morbidities, leading to possible confounding by indications compared with those not receiving anticholinergic drugs.

改變主分析

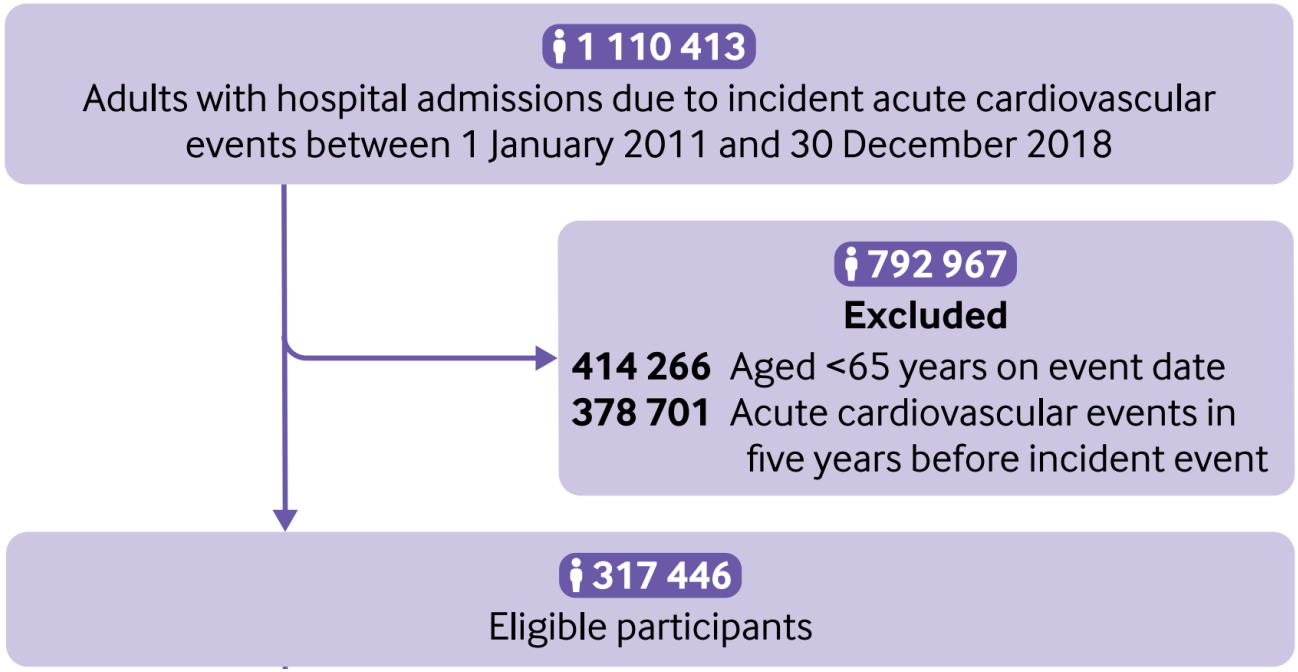


Fig 3 | Flowchart of study population and selection of eligible patients

Table 1 | Baseline characteristics of eligible patients and current cases

Characteristics	Eligible patients (n=317 446)	Current cases (n=248 579)
Age (years), mean (SD)	78.4 (0.01)	78.3 (0.02)
Male	169 485 (53.4)	133 158 (53.6)
Comorbidities		
Hypertension	197 349 (62.2)	155 411 (62.5)
Heart failure	33 910 (11.3)	26 627 (10.7)
Diabetes mellitus	102 673 (32.3)	81 330 (32.7)
Dyslipidaemia	76 099 (24.0)	60 442 (24.3)
Chronic kidney disease	63 408 (20.0)	49 676 (20.0)
Chronic liver disease	21 356 (6.7)	16 997 (6.8)
Asthma	22 249 (7.0)	17 661 (7.1)
Chronic obstructive pulmonary disease	51 496 (16.2)	40 677 (16.4)
Gastrointestinal ulcer or GERD	58 103 (18.3)	45 864 (18.5)
Dementia	35 252 (11.1)	27 290 (11.0)
Parkinson's disease	12 097 (3.8)	9459 (3.8)
Epilepsy	2748 (0.9)	2103 (0.9)
Mental illness*	34 009 (10.7)	26 868 (10.8)
Schizophrenia	1433 (0.5)	1145 (0.5)
Osteoporosis	23 028 (7.3)	18 129 (7.3)
Alcohol or drug abuse	420 (0.1)	352 (0.1)
Use of drugs with anticholinergic activity		
Antihistamines	218 816 (68.9)	171 518 (69.0)
Gastrointestinal antispasmodics	129 764 (40.9)	102 000 (41.0)
Diuretics	107 398 (33.8)	84 003 (33.8)
Bronchodilators	86 946 (27.4)	68 181 (27.4)
Antiemetics or antivertigo agents	65 409 (20.6)	51 136 (20.6)
Antipsychotics	56 576 (17.8)	44 122 (17.8)
Antidepressants	35 718 (11.3)	27 874 (11.2)
Antiepileptics	29 021 (9.1)	22 600 (9.1)
Muscle relaxants	26 740 (8.4)	20 916 (8.4)
Genitourinary antispasmodics	26 381 (8.3)	20 614 (8.3)
Antiparkinson agents	17 377 (5.5)	13 550 (5.5)
Antiarrhythmic drugs	277 (0.1)	219 (0.1)

Values are numbers (%), unless indicated otherwise. Eligible patients were identified as those with a diagnosis of major cardiovascular event and current cases as eligible patients matched with future cases.
GERD=gastroesophageal reflux disease; SD=standard deviation.
*Mental illness included depression, bipolar disorder, and anxiety.

有匹配到future case的病人

Table 2 | Results of case-case-time-control analysis

Total anticholinergic burden score	Total	Higher burden in hazard period*	Higher burden in reference period	Odds ratio (95% CI)
1-2 v 0 points				
Case crossover	26 110	17 603	8507	1.86 (1.83 to 1.90)
Control crossover	24 683	14 247	10 436	1.35 (1.33 to 1.38)
Case-case-time-control†	—	—	—	1.38 (1.34 to 1.42)
≥3 v 0 points				
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)
Case-case-time-control†	—	—	—	2.03 (1.98 to 2.09)
≥3 v 1-2 points				
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)
Case-case-time-control†	—	—	—	1.48 (1.44 to 1.52)

Data are numbers of participants unless indicated otherwise. The case-case-time-control analysis incorporated two self-controlled analyses—a case crossover analysis and a control crossover analysis consisting of future cases to address confounding by indication and potential protopathic bias, respectively.
CI=confidence interval.
*Number of patients with higher burden in the hazard period for each corresponding anticholinergic burden category; for 1-2 *v* 0 group, patients with total burden of 1-2 points and 0 points in the reference period were counted; for ≥3 *v* 1-2 group, patients with total burden of ≥3 points and 1-2 points in the reference period were counted; and so on.
†The odds ratios of case-case-time-control analysis were obtained by dividing odds ratio of case crossover by odds ratio of control crossover.

假設不同情境之下
這些證據都還是一致的?

	Total anticholinergic burden score		
	1-2 v 0 points	≥3 v 0 points	≥3 v 1-2 points
Main analysis*	1.38 (1.34 to 1.42)	2.03 (1.98 to 2.09)	1.48 (1.44 to 1.52)
Subgroup analysis			
Myocardial infarction	1.34 (1.24 to 1.45)	2.20 (2.05 to 2.37)	1.64 (1.52 to 1.77)
Ischaemic stroke	1.42 (1.35 to 1.50)	2.05 (1.96 to 2.15)	1.44 (1.37 to 1.52)
Haemorrhage stroke	1.26 (1.16 to 1.37)	1.62 (1.50 to 1.74)	1.28 (1.18 to 1.40)
Arrhythmias	1.41 (1.33 to 1.49)	2.17 (2.06 to 2.28)	1.54 (1.46 to 1.63)
Conduction disorder	1.29 (1.08 to 1.53)	1.82 (1.56 to 2.13)	1.42 (1.19 to 1.68)
Syncope	1.19 (1.00 to 1.42)	1.84 (1.58 to 2.15)	1.55 (1.31 to 1.83)
Cardiovascular death	1.43 (1.32 to 1.55)	2.43 (2.25 to 2.63)	1.70 (1.58 to 1.83)
Sensitivity analysis			
Cut-off point for anticholinergic burden 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)	—
Length of hazard and 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)
Length of 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)
Length of interval between event dates of future cases and 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 drug 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 drug 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)
Other scales for measuring burden			
ADS	1.40 (1.36 to 1.44)	2.20 (2.15 to 2.26)	1.57 (1.53 to 1.61)
GABS	1.42 (1.38 to 1.46)	2.25 (2.19 to 2.31)	1.59 (1.54 to 1.63)
m-ACB	1.36 (1.32 to 1.40)	2.07 (2.02 to 2.13)	1.52 (1.48 to 1.56)
KABS	1.41 (1.37 to 1.45)	2.08 (2.03 to 2.13)	1.48 (1.43 to 1.52)
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 cardiovascular drugs§	1.48 (1.40 to 1.55)	1.99 (1.91 to 2.06)	1.35 (1.28 to 1.42)
Crude case crossover analysis (n=317 446)	1.83 (1.80 to 1.86)	2.93 (2.89 to 2.98)	1.60 (1.57 to 1.63)
Case-time-control analysis (n=263 165)	1.59 (1.55 to 1.64)	2.46 (2.39 to 2.52)	1.54 (1.50 to 1.59)
Restriction analysis by 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)

Values are odds ratios (95% confidence intervals).
ADS=Anticholinergic Drug Scale; GABS=German Anticholinergic Burden Scale; KABS=Korean Anticholinergic Activity Scale; m-ACB=Modified Anticholinergic Cognitive Burden Scale.
*Median time interval between event dates of current and future cases in main analysis 62 days; mean time interval 68.4 days.
†Corresponding fields are 1-4 *v* 0, ≥5 *v* 0, and ≥5 *v* 1-4; 1-9 *v* 0, ≥10 *v* 0; the comparisons of ≥5 *v* 1-4 and ≥10 *v* 1-9 were omitted because no additional information was required.
‡Median time interval between event dates of current and future cases in sensitivity analysis 122 days; mean time interval 129.0 days.
§Patient number after exclusion: current cases=114 838, future cases=116 223.

Meaning of the study: possible explanations and implications

Our findings were supported by biological plausibility from existing evidence. Drugs with anticholinergic ac… …ic eff… …em plays an important role in the regulation of cardiac automaticity and contractility, and the inhibition of parasympathetic control over the cardiovascular system could increase haemodynamic lability.[46 47] This el… o… h… ir… death. Furthermore, cardiac ischaemic events can cause cardiac dysrhythmias.[15 48] Other mechanisms, such as automatic imbalance and inflammatory responses …

that the onset of anticholinergic effects can be rapid after using certain drugs.[47 53] Biological plausibility supports that recently raised anticholinergic burden could be associated with adverse events.

藥物機轉上解釋得通

有過去的文獻指出類似的結果

藥物的效果可能很快

臨床意義

Protopathic bias might arise from the increased use of drugs to manage early symptoms of cardiovascular events before diagnosis. Determining whether the anticholinergic burden caused the events or if the events led to increased drug use is challenging. To minimise possible protopathic bias, we conducted con… …l… …est… …e source of protopathic bias. The trends were then further adjusted for in the case-case-time-control analysis (supplementary information 2).[16 28 54 55] We also obtained a lower risk estimate when we manipulated the lag time to investigate the drugs in the sensitivity analyses. These findings highlighted the need to consider protopathic bias when interpreting the results from observational studies on this topic.

研究需要注意因果關係

研究意義

WHAT IS ALREADY KNOWN ON THIS TOPIC

Previous studies have reported an association between anticholinergic burden and increased cardiovascular risk, but have not considered the potential issue of protopathic bias

Research has investigated the relation between anticholinergic burden and long term cardiovascular events, but variations in anticholinergic burden over time require investigation

Studies examining the effect of a recently raised anticholinergic burden on the risk of cardiovascular events are lacking

WHAT THIS STUDY ADDS

A recently raised anticholinergic burden was associated with an increased risk of acute cardiovascular events, even after addressing the issue of protopathic bias

A dose-response relation was found between anticholinergic burden and risk of acute cardiovascular events

The findings highlight the need to consider protopathic bias when interpreting the results from observational studies

Clinical Epidemiology

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REVIEW

Taiwan's National Health Insurance Research Database: past and future

This article was published in the following Dove Press journal:
Clinical Epidemiology

the National Health Insurance Database is **not** perfect

Edward Chia-Cheng Lai[1,7]

established a Health and Welfare Data Center (HWDC), a data repository site that centralizes

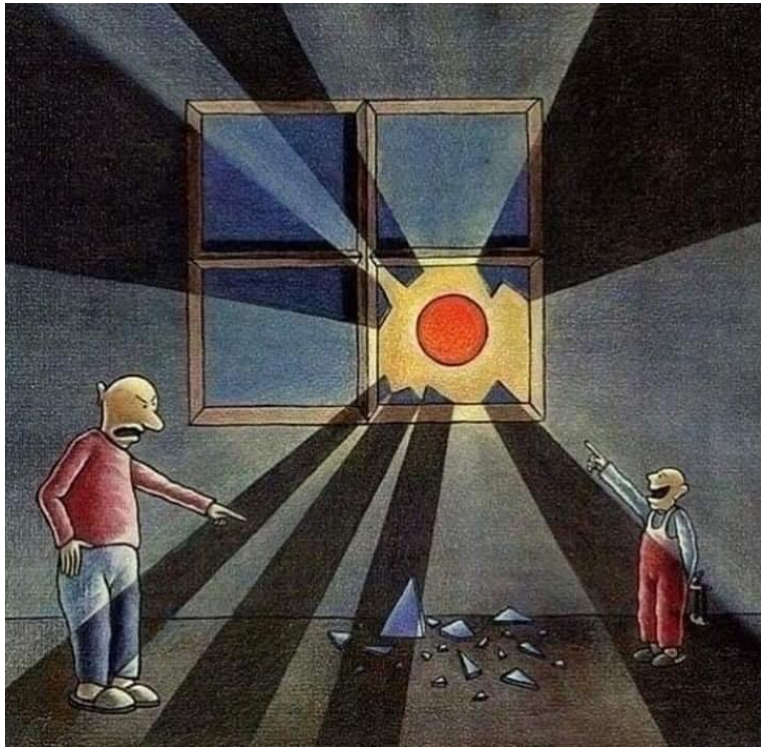
Internal validity threats

External validity threats

researchers will have greater opportunity to distill knowledge from the NHIRD linked to

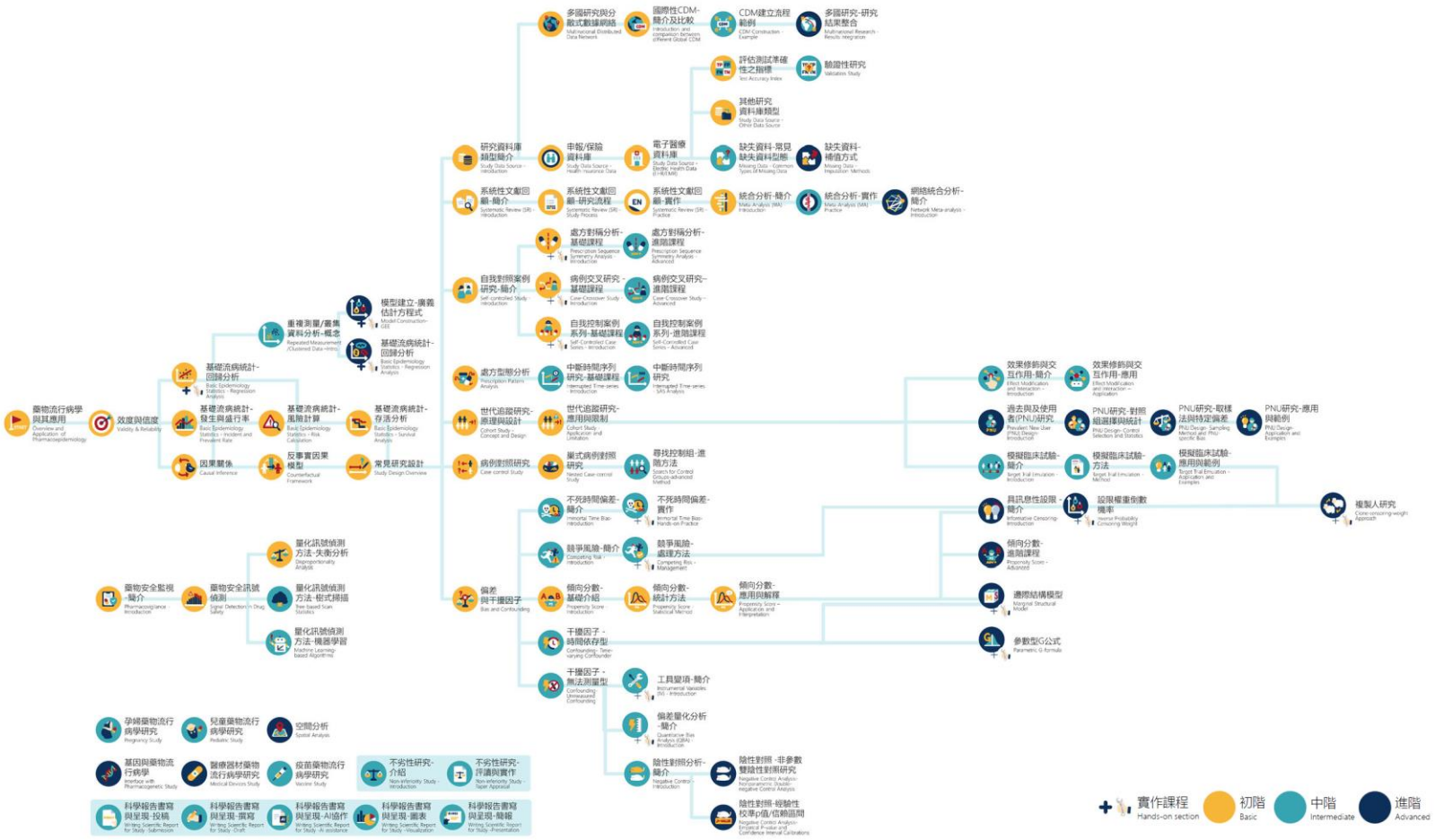
No underlying biological information

Internal Medicine, Ditmanson Medical Foundation Chiayi Christian Hospital, Chiayi City, Taiwan; [5]Department of Information Management a... Healthcare Information Ma... National Chung Cheng Uni... County, Taiwan; [6]Departme... Systems, Outcomes & Polic... Pharmacy, University of Illi... Chicago, IL, USA; [7]Departm... Pharmacy, National Cheng K... Hospital, Tainan, Taiwan



缺口就是光的入口

群體健康數據中心
Population Health Data Center (PHD center)



感謝

賴嘉鎮

Edward Lai, PhD

Professor, FISPE

Edward_Lai@mail.ncku.edu.tw

+886-2353535 ext 6209

National Cheng Kung University, Tainan, Taiwan

Clinical Epidemiology

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ORIGINAL RESEARCH

Cross-Regional Data Initiative for the Assessment and Development of Treatment for Neurological and Mental Disorders

Daniel Hsiang-Te Tsai[1,2], J Simon Bell[3], Shahab Abtahi[4], Brenda N Baak[5], Marloes T Bazelier[4], Ruth Brauer[6], Adrienne YL Chan[6–9], Esther W Chan[9–12], Haoqian Chen[13], Celine SL Chui[9,14,15], Sharon Cook[16], Stephen Crystal[16], Poonam Gandhi[13], Sirpa Hartikainen[17], Frederick K Ho[18], Shao-Ti Hsu[1], Jenni Ilomäki[3], Ju Hwan Kim[19], Olaf H Klungel[4], Marjaana Koponen[17], Wallis CY Lau[6,8,9], Kui Kai Lau[20,21], Terry YS Lum[22], Hao Luo[22], Kenneth KC Man[6,8,9], Jill P Pell[18], Soko Setoguchi[13,23], Shih-Chieh Shao[1,24], Chin-Yao Shen[1], Ju-Young Shin[19,25,26], Patrick C Souverein[4], Anna-Maija Tolppanen[17], Li Wei[6,9], Ian CK Wong[6,8,9,27], Edward Chia-Cheng Lai[1]

[1]School of Pharmacy, Institute of Clinical Pharmacy and Pharmaceutical Sciences, College of Medicine, National Cheng Kung University, Tainan, Taiwan; [2]Centre for Neonatal and Paediatric Infection, St George's University of London, London, UK; [3]Centre for Medicine Use and Safety, Faculty of Pharmacy and Pharmaceutical Sciences, Monash University, Melbourne, Australia; [4]Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, the Netherlands; [5]PHARMO Institute for Drug Outcomes Research, Utrecht, the Netherlands; [6]Research Department of Practice and Policy, UCL School of Pharmacy, London, UK; [7]Groningen Research Institute of Pharmacy, Unit of Pharmacotherapy, -Epidemiology and -Economics, University of Groningen, Groningen, the Netherlands; [8]Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, University of Hong Kong, Hong Kong, Special Administrative Region, People's Republic of China; [9]Laboratory of Data Discovery for Health (D^{2}4H), Hong Kong Science Park, Hong Kong, Special Administrative Region, People's Republic of China; [10]Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, University of Hong Kong, Hong Kong, Special Administrative Region, People's Republic of China; [11]Department of Pharmacy, the University of Hong Kong-Shenzhen Hospital, Shenzhen, People's Republic of China; [12]The University of Hong Kong Shenzhen Institute of Research and Innovation, Shenzhen, People's Republic of China; [13]Center for Pharmacoepidemiology and Treatment Science (PETS), Institute for Health, Rutgers University, New Brunswick, NJ, USA; [14]School of Nursing, Li Ka Shing Faculty of Medicine, University of Hong Kong, Hong Kong, Special Administrative Region, People's Republic of China; [15]School of Public Health, Li Ka Shing Faculty of Medicine, University of Hong Kong, Hong Kong, Special Administrative Region, People's Republic of China; [16]Center for Health Services Research, Rutgers University, New Brunswick, NJ, USA; [17]Kuopio Research Centre of Geriatric Care and School of Pharmacy, University of Eastern Finland, Kuopio, Finland; [18]School of Health and Wellbeing, University of Glasgow, Glasgow, UK; [19]School of Pharmacy, Sungkyunkwan University, Suwon, South Korea; [20]Division of Neurology, Department of Medicine, School of Clinical Medicine, Li Ka Shing Faculty of Medicine, University of Hong Kong, Hong Kong, Special Administrative Region, People's Republic of China; [21]State Key Laboratory of Brain and Cognitive Sciences, University of Hong Kong, Hong Kong, Special Administrative Region, People's Republic of China; [22]Department of Social Work and Social Administration, University of Hong Kong, Hong Kong, Special Administrative Region, People's Republic of China; [23]Department of Medicine, Rutgers Robert Wood Johnson Medical School and Pharmacoepidemiology and Treatments Science, Institute for Health, Rutgers University, New Brunswick, NJ, USA; [24]Department of Pharmacy, Keelung Chang Gung Memorial Hospital, Keelung, Taiwan; [25]Samsung Advanced Institute for Health Sciences & Technology, Sungkyunkwan University, Seoul, South Korea; [26]Department of Biohealth Regulatory Science, Sungkyunkwan University, Seoul, South Korea; [27]Aston Pharmacy School, Aston University, Birmingham, UK

Correspondence: Edward Chia-Cheng Lai, School of Pharmacy and Institute of Clinical Pharmacy and Pharmaceutical Sciences, College of Medicine, National Cheng Kung University, Tainan, Taiwan, Email edward_lai@mail.ncku.edu.tw

Purpose: To describe and categorize detailed components of databases in the Neurological and Mental Health Global Epidemiology Network (NeuroGEN).

Methods: An online 132-item questionnaire was sent to key researchers and data custodians of NeuroGEN in North America, Europe, Asia and Oceania. From the responses, we assessed data characteristics including population coverage, data follow-up, clinical information, validity of diagnoses, medication use and data latency. We also evaluated the possibility of conversion into a common data model (CDM) to implement a federated network approach. Moreover, we used radar charts to visualize the data capacity assessments, based on different perspectives.

Results: The results indicated that the 15 databases covered approximately 320 million individuals, included in 7 nationwide claims databases from Australia, Finland, South Korea, Taiwan and the US, 6 population-based electronic health record databases from Hong Kong, Scotland, Taiwan, the Netherlands and the UK, and 2 biomedical databases from Taiwan and the UK.

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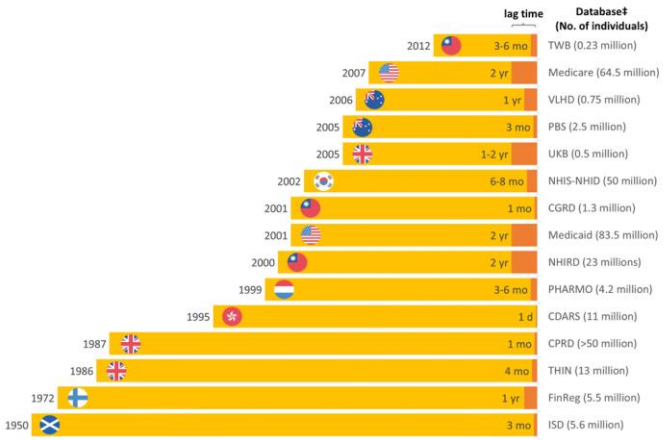

Figure 1 NeuroGEN databases.
‡**Abbreviations**: PBS, Pharmaceutical Benefits Scheme 10% sample dataset; VLHD, Victorian Linked Health Data; FinReg, Finnish national healthcare registers; CDARS, Clinical Data Analysis and Reporting System; NHIS-NHID, National Health Insurance Service-National Health Insurance Database; ISD, Public Health Scotland; CGRD, Chang Gung Research Database; NHIRD, Taiwan's National Health Insurance Research Database; TWB, Taiwan Biobank; PHARMO, PHARMO Data Network; CPRD, Clinical Practice Research Datalink; THIN, The Health Improvement Network; UKB, United Kingdom Biobank; Medicaid, Medicaid & CHIP Research data; Medicare, 20% sample of Medicare.

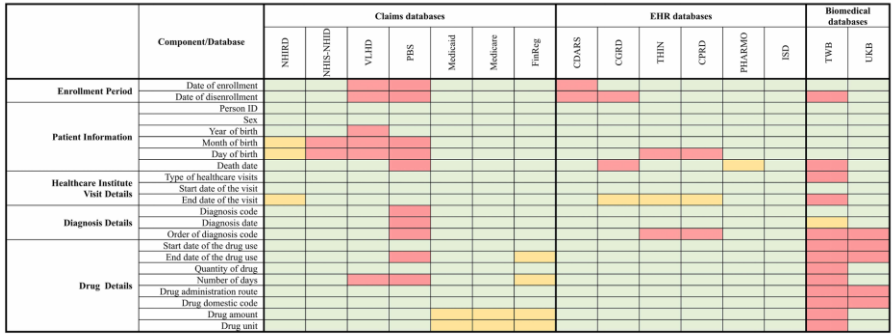

Figure 3 Assessment for common data model conversion.
Notes: Green indicates that the data were available from the database and could be converted into CDM without additional data. Yellow indicates that the data could be captured by additional data or use of a proxy. Red indicates that the data were not available in the database, and it therefore could not be converted to CDM.

nature medicine

Article

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Maternal diabetes and risk of attention-deficit/hyperactivity disorder in offspring in a multinational cohort of 3.6 million mother–child pairs

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Check for updates

A list of authors and their affiliations appears at the end of the paper

Previous studies report an association between maternal diabetes mellitus (MDM) and attention-deficit/hyperactivity disorder (ADHD), often overlooking unmeasured confounders such as shared genetics and environmental factors. We therefore conducted a multinational cohort study with linked mother–child pairs data in Hong Kong, New Zealand, Taiwan, Finland, Iceland, Norway and Sweden to evaluate associations between different MDM (any MDM, gestational diabetes mellitus (GDM) and pregestational diabetes mellitus (PGDM)) and ADHD using Cox proportional hazards regression. We included over 3.6 million mother–child pairs between 2001 and 2014 with follow-up until 2020. Children who were born to mothers with any type of diabetes during pregnancy had a higher risk of ADHD than unexposed children (pooled hazard ratio (HR) = 1.16, 95% confidence interval (CI) = 1.08-1.24). Higher risks of ADHD were also observed for both GDM (pooled HR = 1.10, 95% CI = 1.04-1.17) and PGDM (pooled HR = 1.39, 95% CI = 1.25-1.55). However, siblings with discordant exposure to GDM in pregnancy had similar risks of ADHD (pooled HR = 1.05, 95% CI = 0.94-1.17), suggesting potential confounding by unmeasured, shared familial factors. Our findings indicate that there is a small-to-moderate association between MDM and ADHD, whereas the association between GDM and ADHD is unlikely to be causal. This finding contrast with previous studies, which reported substantially higher risk estimates, and underscores the need to reevaluate the precise roles of hyperglycemia and genetic factors in the relationship between MDM and ADHD.

Globally, 16% of pregnant women experience hyperglycemia[1,2]. The prevalence of maternal diabetes mellitus (MDM) has increased worldwide, which is associated with the growing epidemic of obesity, advancing maternal age and improved diagnostic approaches for MDM[3,4]. There are calls for greater attention to the risks associated with diabetes in pregnancy given the increasing trend of gestational diabetes and preexisting type 2 diabetes[5]. Animal studies have demonstrated the adverse effects of hyperglycemia during pregnancy on inflammatory responses, intrauterine oxidative stress and imbalance in epigenetic mechanisms, which may contribute to poor neurodevelopment in the offspring[6,7].

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by hyperactivity, impulsivity and inattentiveness[8]. Currently, ADHD is estimated to affect 2% to 7% of children worldwide[9,10], making it one of the most common disorders among school-aged children. ADHD not only adversely impacts the

e-mail: carolyn.cesta@ki.se; edward_lai@mail.ncku.edu.tw; h.zoega@unsw.edu.au; kenneth.man@ucl.ac.uk; wongick@hku.hk

Impact factor = 82

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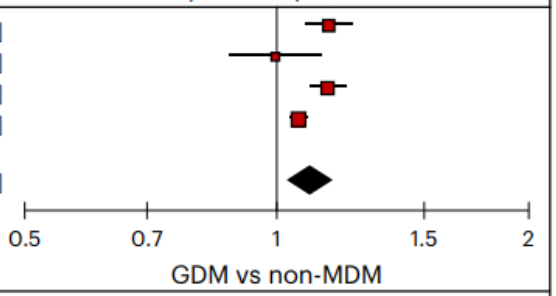
傳統 世代研究設計

Study or subgroup	log[HR]	s.e.	GDM Total	Non-MDM Total	Weight	HR IV, random, 95% CI
Hong Kong	0.1432	0.0320	28,662	351,942	24.9%	1.15 [1.08, 1.23]
New Zealand	−0.0040	0.0632	11,335	498,817	13.6%	1.00 [0.88, 1.13]
NorPRESS	0.1398	0.0247	85,911	1,801,081	28.2%	1.15 [1.10, 1.21]
Taiwan	0.0598	0.0114	104,890	681,832	33.3%	1.06 [1.04, 1.09]
Total (95% CI)			230,798	3,333,672	100.0%	1.10 [1.04, 1.17]

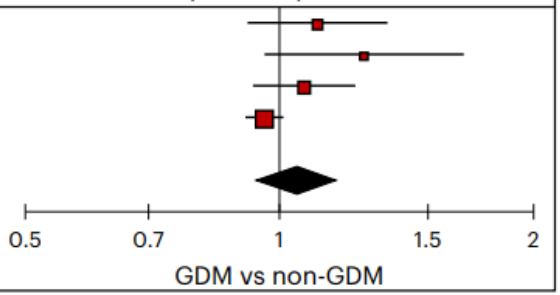
Heterogeneity: $Tau^2 = 0.00$; $\chi^2 = 14.58$, df = 3 ($P = 0.002$); $I^2 = 79\%$
Test for overall effect: Z = 3.18 ($P = 0.001$)



改良後 **手足對照**研究: **控制了家族, 環境, 基因等因子**

Study or subgroup	log[HR]	s.e.	GDM Total	Non-MDM Total	Weight	HR IV, random, 95% CI
Hong Kong	0.1044	0.0959	8,004	8,624	19.4%	1.11 [0.92, 1.34]
New Zealand	0.2311	0.1387	3,772	4,418	11.8%	1.26 [0.96, 1.65]
NorPreSS	0.0677	0.0713	28,437	32,632	26.3%	1.07 [0.93, 1.23]
Taiwan	0.0408	0.0266	32,578	29,408	42.4%	0.96 [0.91, 1.01]
Total (95% CI)			72,791	75,082	100.0%	1.05 [0.94, 1.17]

Heterogeneity: $Tau^2 = 0.01$; $\chi^2 = 6.96$, df = 3 ($P = 0.07$); $I^2 = 57\%$
Test for overall effect: Z = 0.87 ($P = 0.38$)



Conclusion

無法測量的干擾因子

In this large multinational cohort study, including over 3.6 million mother–child pairs and leveraging a common data model and analytic approach, we found that MDM overall, GDM and PGDM were associated with a small-to-moderate risk of ADHD in offspring. After controlling for shared familial genetic and social factors in the sibling-matched analyses, risks of ADHD did not differ between siblings with discordant exposure to GDM in pregnancy. Due to the discrepancy around the within- and between-family analyses, we speculate that the relationship between GDM exposure and ADHD may be confounded by familial factors.

Conclusion

The incidence of falls and fractures was especially high in the pretreatment period, suggesting that factors other than drugs, such as underlying diseases, should be taken into consideration when evaluating the association between the risk and the use of cholinesterase inhibitors and other drugs. The treatment periods were also associated with a higher risk of falls and fractures compared with the non-treatment period although the magnitude was much lower than during the pretreatment period. Strategies for prevention and close monitoring of the risk of falls are still necessary until there is evidence that patients have regained a more stable physical and mental state.

適應症干擾

BMJ 2021;374:n1925

Conclusions

Our study found an association between recently raised anticholinergic burden and an increased risk of acute cardiovascular events, even after addressing the issue of protopathic bias. We also showed a dose-response relation between anticholinergic burden and the risk of acute cardiovascular events, indicating probable causation. The findings were robust throughout a series of analyses that controlled for protopathic bias and confounders unless otherwise indicated by the presence of residual confounding. Many commonly used drugs have anticholinergic effects as a secondary or primary mechanism of action, healthcare providers should increase their awareness of these effects and consider reducing unnecessary drug use.

倒果為因

BMJ 2023;382:e076045

看似一個代數問題　其實是一個幾何問題

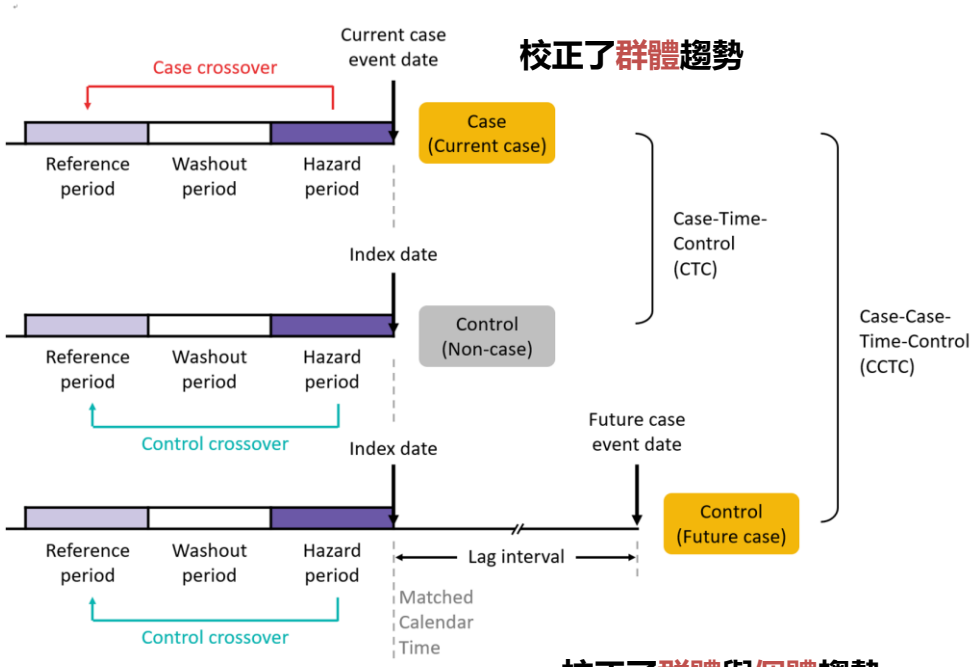
＜＜嫌疑犯X的獻身＞＞

如果CCTC同時校正了群體與個體趨勢
如果CTC校正了群體趨勢

Strengths and weaknesses of this study

This study evaluates the association between recent anticholinergic burden and risk of acute cardiovascular events. We considered variation in total anticholinergic burden in different periods befo[illegible]gs for anti[illegible]drugs wer[illegible]time-con[illegible]ding by indication owing to the self-controlled design. Our study revealed a substantial difference in the results obtained through case-case-time-control analysis compared with case-time-control analysis, highlighting the issues of protopathic bias encountered in previous studies.[12-14 16 28] However, the case-case-time-control analysis and the sensitivity analysis with different lag times addressed these concerns and revealed the robustness of the association. These findings suggest a strong association between recently raised anticholinergic burden and an increased risk of acute cardiovascular events.

比較 CCTC and CTC
就知道哪一個是影響主因



Establishment of Research Models for *International* Multi-database Pharmacoepidemiologic Studies (106-2320-B-006 -025 - **MY2**; 2016-2018)

External validity

Multi-country study
(racial and ethnic difference)

More comprehensive analysis to prompt identification of medical products' effects

Single country, single database clinical study

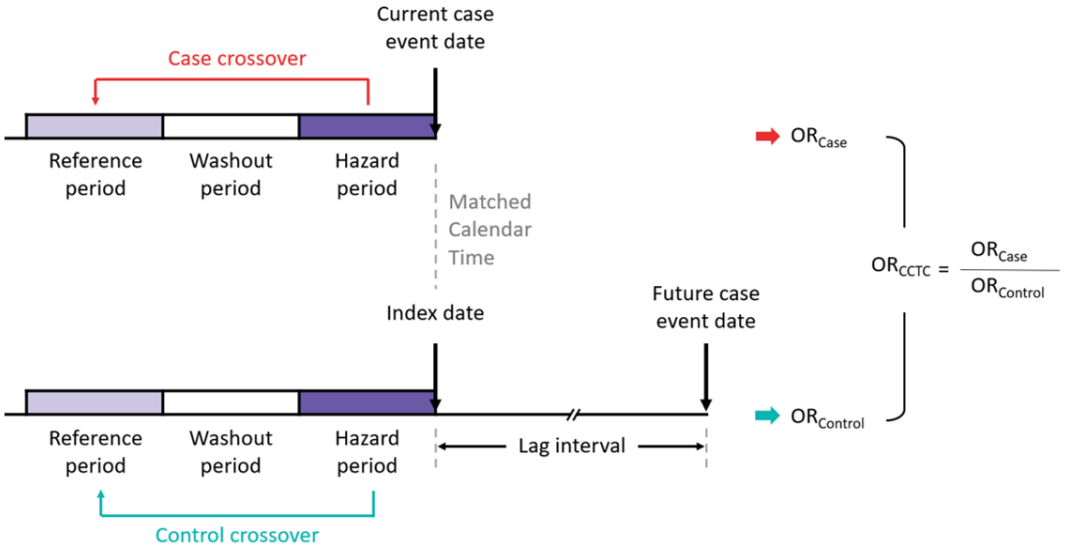
Multiple database study
(claims data + EHR + registry)

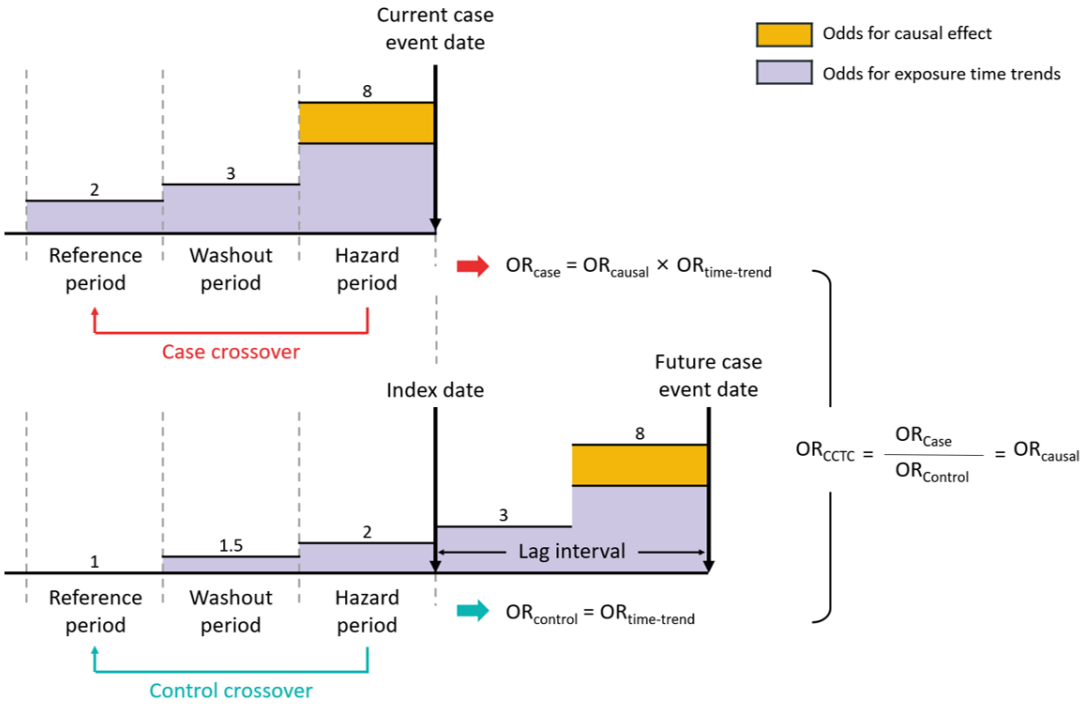
Internal validity

Translational research
(basic + clinical study)

Developing Data Protective Analytical Approaches for combination of Medical *Big Data* with *Small Validation* (107-2320-B-006 -070 –**MY3**; 2018-2021)

underlying biological information


Current case event date
Case crossover
Reference period
Washout period
Hazard period
Matched Calendar Time
Index date
Future case event date
Lag interval
Control crossover
OR_{Case}
$OR_{Control}$
$OR_{CCTC} = \frac{OR_{Case}}{OR_{Control}}$


Current case event date
Odds for causal effect
Odds for exposure time trends
8
3
2
Reference period
Washout period
Hazard period
$OR_{case} = OR_{causal} \times OR_{time\text{-}trend}$
Case crossover
Index date
Future case event date
8
3
2
1.5
1
Lag interval
$OR_{control} = OR_{time\text{-}trend}$
Control crossover
$OR_{CCTC} = \frac{OR_{Case}}{OR_{Control}} = OR_{causal}$

Example 1

白內障手術 與 眼睛中風

Cataract Surgery and Incidence of Retinal Vascular Occlusion: Population-Based Cohort Study Using a Target Trial Emulation Framework

LI-AN WANG, AVERY SHUEI-HE YANG, YU-CHEN SU, SHENG-MIN HSU, YI-HSUN HUANG, CHAW-NING LEE, SHIH-CHIEH SHAO, SWU-JANE LIN, JIA-HORUNG HUNG, AND EDWARD CHIA-CHENG LAI

• BACKGROUND: Previous studies suggested an association between cataract surgery and retinal vascular occlusion. However, the association may be attributable to detection bias because postoperative monitoring may be more frequent for those who receive cataract surgery than for those who do not.
• DESIGN: Population-based cohort study using target trial emulation framework.
• METHODS: We included patients with cataract aged 50 years and older receiving cataract surgery or nonsurgical interventions identified from the Taiwan National Health Insurance Research Database between 2003 and 2018, matched by propensity score. The primary outcome was retinal vascular occlusion. Cox proportional hazards models were used to compare surgery and control groups. Additional analyses were restricted to patients who had undergone fundoscopic examination within 6 months prior to cataract surgery to address the issue of detection bias.
• RESULTS: We included 577,129 cataract surgery and control pairs. We found the hazard ratio (HR) for retinal vascular occlusion after cataract surgery was 1.23 (95% confidence interval (CI): 1.17-1.29), compared with the control group. Secondary outcome analyses yielded similar results for retinal artery occlusion (HR: 1.13, 95% CI: 1.02-1.26) and retinal vein occlusion (HR: 1.26, 95% CI: 1.20-1.33). However, no risk of retinal vascular occlusion was observed among patients who had received fundoscopic examinations (HR: 1.06, 95% CI: 0.98-1.15) at baseline.
• CONCLUSIONS: Our study underscored the importance of conducting complete baseline fundoscopic examinations before cataract surgery to clarify whether postoperative conditions are due to patients' underlying diseases or unintended complications of cataract surgery. (Am J Ophthalmol 2024;268: 143–154. © 2024 Elsevier Inc. All rights are reserved, including those for text and data mining, AI training, and similar technologies.)

AJO.com Supplemental Material available at AJO.com.
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From the Department of Ophthalmology (L.W., Y.S., S.H., Y.H., J.H.), National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan; Population Health Data Center (A.Y., C.L., S.S., J.H., E.L.), National Cheng Kung University, Tainan, Taiwan; School of Pharmacy (A.Y., C.L., S.S., E.L.), Institute of Clinical Pharmacy and Pharmaceutical Sciences, College of Medicine, National Cheng Kung University, Tainan, Taiwan; Department of Dermatology (C.L.), National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan; Department of Pharmacy (S.S.), Keelung Chang Gung Memorial Hospital, Keelung, Taiwan; Department of Pharmacy Systems (S.L.), Outcomes and Policy College of Pharmacy, University of Illinois, Chicago, Illinois, USA; Institute of Clinical Medicine (J.H.), College of Medicine, National Cheng Kung University, Tainan, Taiwan.
Inquiries to Edward Chia-Cheng Lai, School of Pharmacy, Institute of Clinical Pharmacy and Pharmaceutical Sciences, College of Medicine, National Cheng Kung University, Tainan, Taiwan; Jia-Horung Hung, Department of Ophthalmology, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan.; e-mail: hungjh@mail.ncku.edu.tw, Edward_lai@mail.ncku.edu.tw

INTRODUCTION

CATARACT IS THE LOSS OF LENS TRANSPARENCY DUE to opacification of the lens,[1] leading to visual impairments estimated to affect over 83 million people worldwide.[2] Cataract surgery is the most commonly performed ophthalmic procedure for visual rehabilitation, with a global estimate exceeding 20 million surgeries performed annually.[3] Modern cataract surgery is considered to be safe, and more than 84 percent of patients experience vision improvement after undergoing the surgery.[4,5] However, postoperative complications can include corneal decompensation, cystoid macular oedema, retinal detachment, full-thickness macular hole and endophthalmitis.[6] Postoperative retinal vascular occlusion has also been reported.[7-15]

Retinal vascular occlusion is a vision-threatening retinal vascular disorder. It refers to a group of retinopathies characterized by blood flow blockage in retinal arteries or veins,[16] referred to as retinal artery occlusion (RAO) and retinal vein occlusion (RVO), respectively.[17-19] The incidence of RAO is approximately 1 to 10 in 100,000, and it presents with acute painless loss of monocular vision. It is considered a form of stroke, with a similar clinical ap-

Am J Ophthalmol 2024;268: 143–154

大數據分析 白內障手術 不會增加眼中風風險

2024/08/09 05:30

白內障是水晶體逐漸混濁，進而影響視力；圖為情境照，圖中人物與本文無關。（照片來源：shutterstock）

記者吳柏軒 / 台北報導

白內障為常見眼科疾病，全球約8300萬人因此視力喪失，但過去認為白內障手術恐增視網膜血管阻塞（俗稱眼中風）風險，成大團隊以大數據分析57萬多人資料，發現若術前完整眼底檢查，排除潛在或高風險眼中風病人，白內障術後發生眼中風的風險就與未接受手術的人相當。相關研究成果已刊登在頂尖眼科期刊《美國眼科學雜誌》。

成大團隊：術前完整眼底檢查 可降低風險

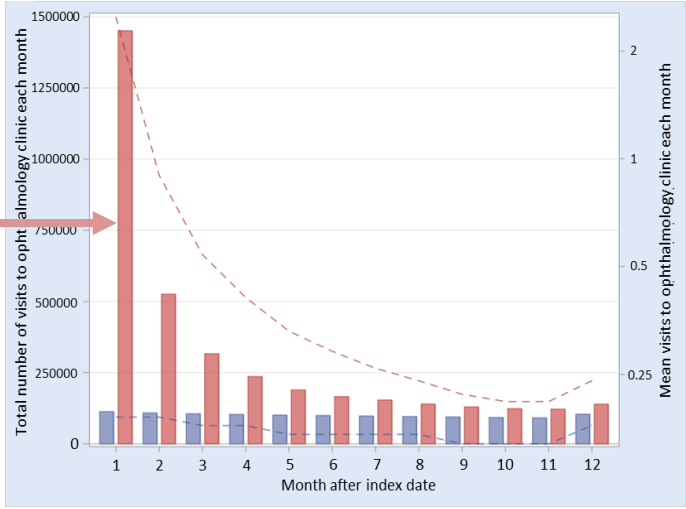
該研究由成大醫院眼科部醫師洪嘉鴻與成大群體健康數據中心主任賴嘉鎮共同合作。洪嘉鴻表示，白內障是水晶體逐漸混濁進而影響視力，全球約8300萬人導致因此視力喪失。依我國健保資料，台灣每年逾100萬人治療白內障，其中約12萬人接受白內障手術，該手術現今成功率達95%以上，但過去有研究指出白內障術後可能會增加眼中風發生風險，眼中風為視網膜動脈或靜脈發生阻塞，通常無明顯疼痛，延誤就診恐致視覺永久損失。

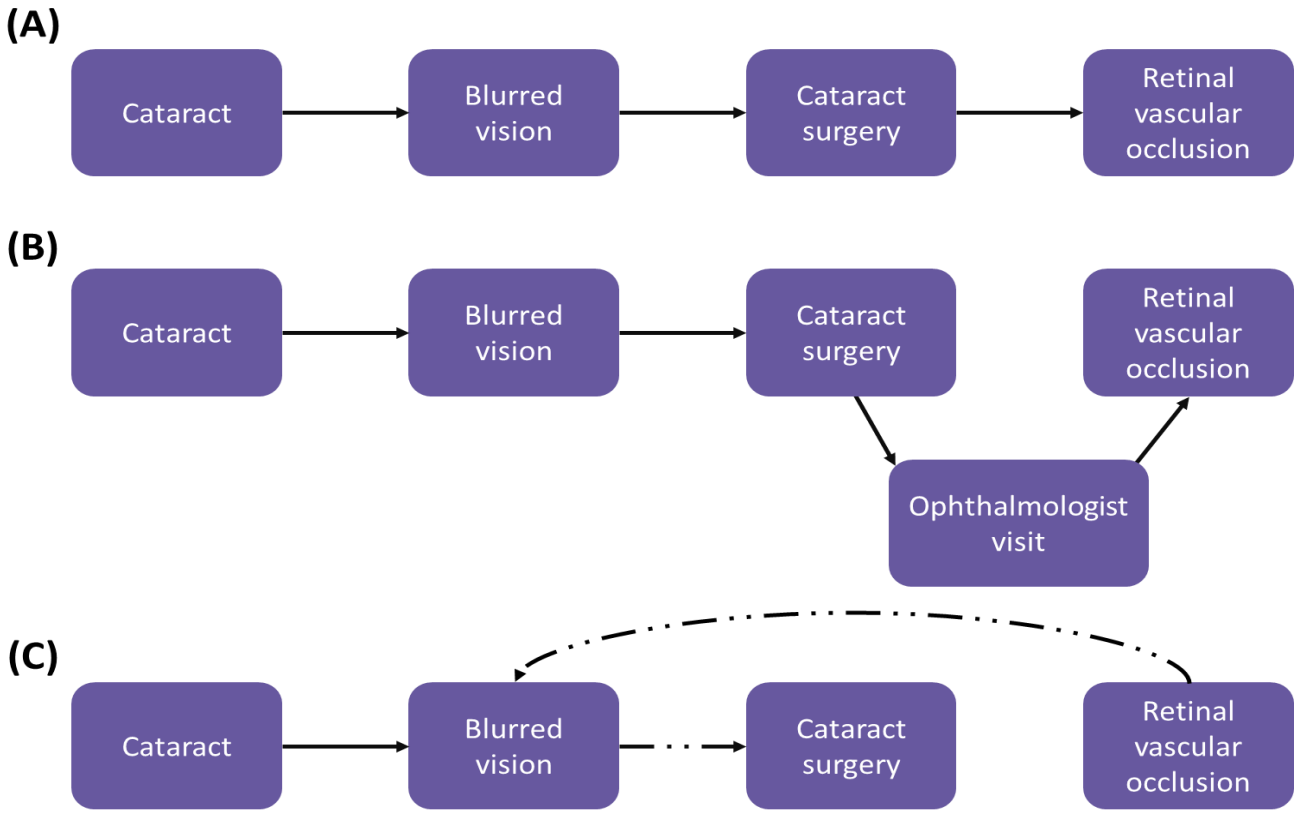
TABLE 2. Main Analysis and Secondary Outcome Analysis of This Study

	Original Cohort	
	Incidence Rate (per 100,000 Person-Year)	HR (95% CI)
Main analysis		
Surgery group	158.89	1.23 (1.17-1.29)
Control group	129.89	Reference
Secondary outcomes		
RAO		
Surgery group	35.00	1.13 (1.02-1.26)
Control group	29.20	Reference
RVO		
Surgery group	131.13	1.26 (1.20-1.33)
Control group	105.60	Reference

CI = confidence interval; HR = hazard ratio; RAO = retinal artery occlusion; RVO = retinal vein occlusion.
*We included 239,683 patients in the surgery group and 128,736 patients in the control group.

手術組的
回診次數較高





Conclusions

Cataract surgery was associated with **an increased risk** of retinal vascular occlusion; however, this association may be attributable to **detection bias**. The findings suggested **fundoscopic examination** before cataract surgery is important to confirm patients' underlying disease and to avoid unnecessary postoperative arguments about spurious associations.