111年度衛生福利部衛生福利資料科學中心

統計軟體與研究實務課程

干擾因子與傾向分數

使用統計軟體R及SAS為例

講師：劉品崧　統計分析師

花蓮慈濟醫院

課程大綱

- 課程前導
- 因果推論
  - 因果關係、因果推論、試驗模式、仿真試驗、推論目標、干擾因子
- 傾向分數
  - 核心理念、應用模式、差異評估、研究範例
- 實作流程
  - 研究目的、定義模型、評估分佈、應用模式、消除干擾、執行分析
- 軟體實作

2022課程推廣重點：研究實務

- 讓大家瞭解研究設計到統計分析的實務流程
  - 定義問題、研究設計、理解資料、流程管理、統計分析
  - 同時開授SAS軟體以及R軟體的場次
  - 你可以拿老師的code去改
  - 但你一定先理解我原本在做什麼
- 研究設計類型
  1. 橫斷研究： 4/8(五)慈大、4/11(一)成大、4/23(六)北醫
  2. 追蹤研究：8/15(一)高醫、8/16(二)成大、8/17(三)國衛院、8/18(四)台科大
  3. 干擾因子：10/28(五)臺科大、11/3(四)成大、11/4(五)高醫

過去課程精華收錄

- 2020年：基礎課程
  - R軟體基本應用，使用`data.table`套件進行資料處理

109年度R基礎課程-劉品崧老師

https://github.com/PSLiu/NHIRD-R-2020

- 2021年：進階課程
  - 統計繪圖、存活分析、CCI指標、群組資料、預測模型

https://github.com/PSLiu/NHIRD-R-2021

課前學員自我準備

- 下載課前寄發材料(Google Drive連結)
  - 解壓縮所有材料，不建議放在One Drive 或 路徑當中含有中文之地方
- 路徑請修改為自己放置資料的地方
- R場次的學員，先不要開啟script，先修改RStudio設定
  - 請將RStudio的指令稿設定為UTF-8儲存
    - Tools → Global options → Code → Saving → Default text encoding → UTF-8
  - 自行下載課程當中所需的套件，瞭解將會使用的函數
    - 本課程將不會花太多時間講解細部指令語法

課程參與注意事項

- 有問題隨時可以舉手/開麥克風發問，問問題很重要！
- 課程所使用模擬檔數據不得作為研究發表用途
  - 因為模擬數據本來就是假的 XD
- 本課程的操作是基於講師的個人邏輯，不代表所有研究皆可適用
  - 研究方法、生物統計、統合分析有學理基礎架構
  - 依據資料、產業、醫療科別不同，需要對應的domain knowledge
  - 本次課程無法容納之處請大家一定要先看書+看paper瞭解之後再用

課程材料版權聲明

- 本次課程的所有內容依據台灣創用CC條款進行授權
  - 講義
  - 程式碼
  - 但不包含衛生福利部統計處提供之模擬資料檔，僅提供報名學員使用
- 授權類別 
  - 姓名標示─非商業性─禁止改作
  - 本授權條款允許使用者重製、散布、傳輸著作，但不得為商業目的之使用，亦不得修改該著作。使用時必須按照著作人指定的方式表彰其姓名。

因果推論

- 因果關係、因果推論
- 試驗模式、仿真試驗
- 推論目標、干擾因子

Hill's Criteria for Inferring Causality

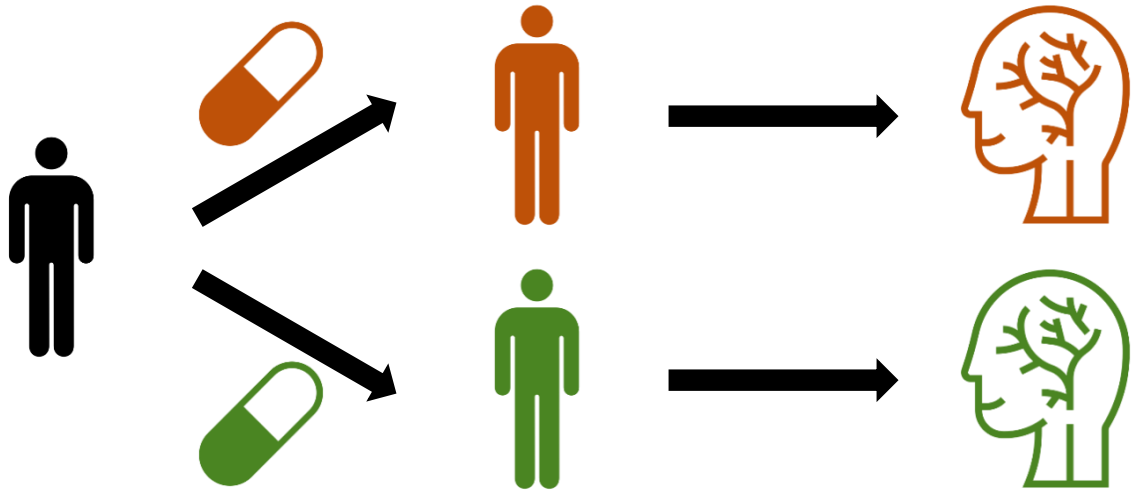
1. Strength
2. Consistency
3. Specificity
4. Temporality
5. Biological gradient
6. Plausibility
7. Coherence
8. Experiment
9. Analogy

- 這些只是原則概念
- 到底怎麼實際驗證？

Hill (1965) doi: 10.1177/003591576505800503

Miguel A Hernán & James M Robins的因果推論概念

- 將介入（事實）與非介入（反事實）的結果進行比較



- 現實上無法搭時光機回來重新觀察反事實
- 但是學理 / 數學上發展出在一定假設上的可行方式

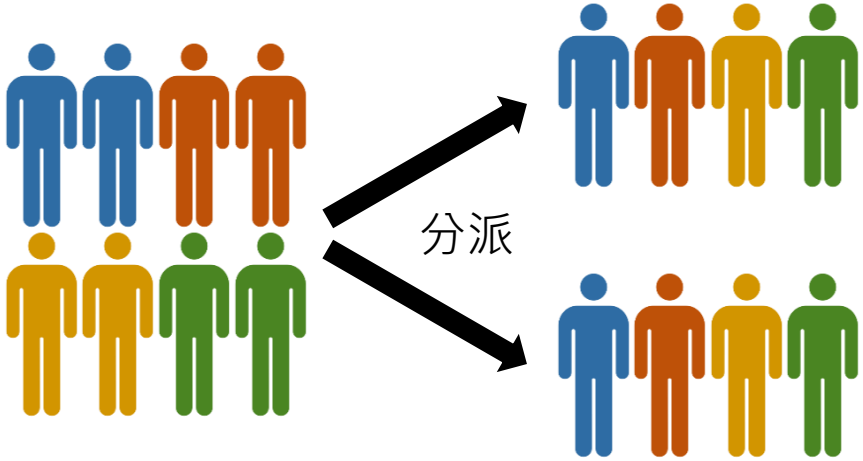
Hernán (2020) https://www.hsph.harvard.edu/miguel-hernan/causal-inference-book/

將事實與反事實比較因果的三大基礎條件

- Exchangeability 可交換性
  - 不論被分派 / 分類至哪一組，都不影響樣本自身發生事件的機率
  - 分派組別與樣本自身發生事件的機率互相獨立
- Positivity 正向機率性
  - 每一個樣本都有機會(>0)可以接受到任一一種治療
  - 樣本之間差異不會太大，具有背景可比較性、治療可適用性
- Consistency 一致性
  - 樣本實際進行處理的結果 = 樣本假設進行處理的結果
  - 介入反應與預期效用相等

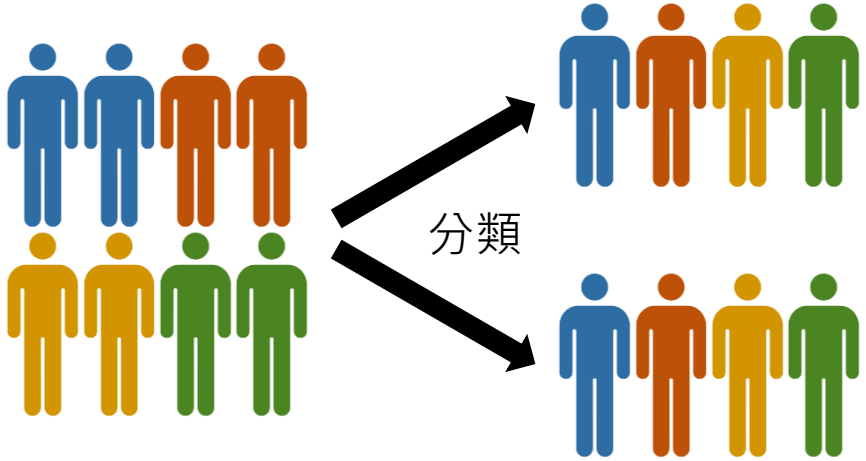
要如何透過試驗來找出可以推論因果的證據？

- 隨機分派試驗(RCT)



  - 優點：隨機分派、統計簡單
  - 缺點：時間較久、失去追蹤
  - 注意：隨機程序、介入盲性

- 真實世界資料(RWD)



  - 優點：較快完成、追蹤完整
  - 缺點：資料複雜、統計困難
  - 注意：正確分類、干擾因子

RCT: randomized controlled trial; RWD: real-world data

要如何將讓觀察性研究像RCT執行？執行因果推論？

- 從設計層面消除選樣問題 → Target trial emulation
  - 先參考/設定/假想一個RCT，用觀察性資料仿照執行，避免設計/選樣偏差
- 從統計層面消除干擾因子 → Model、Propensity score
  - 迴歸模型校正、傾向分數配對、傾向分數加權

ORIGINAL ARTICLE

Observational Studies Analyzed Like Randomized Experiments

An Application to Postmenopausal Hormone Therapy and Coronary Heart Disease

Miguel A. Hernán,[a,b] *Alvaro Alonso,*[c] *Roger Logan,*[a] *Francine Grodstein,*[a,d] *Karin B. Michels,*[a,d,e] *Walter C. Willett,*[a,d,f] *JoAnn E. Manson,*[a,d,g] *and James M. Robins*[a,h]

Hernán (2008) doi: 10.1097/EDE.0b013e3181875e61
Hernán (2011) doi: 10.1097/EDE.0b013e3182114039
Hernán (2016) doi: 10.1093/aje/kwv254
Hernán (2020) https://www.hsph.harvard.edu/miguel-hernan/causal-inference-book/

設定問題以及推論目標

- ATE：Average treatment effect
  - 平均處理效果
  - 非瓣膜疾病問題AF病人使用dabigatran與warfarin對預防中風的效果

    =（發生中風 | 全部AF都使用dabigatran）－（發生中風 | 全部AF都使用warfarin）
- ATT：Average treatment effect among the treated population
  - 治療組平均處理效果
  - 懷孕女性服用抗精神藥物導致胎兒畸形的影響

    =（胎兒畸形 | 女性有需要且有用藥）－（胎兒畸形 | 女性有需要但無用藥）⬅ 真正具有意義的對照組

    ⬆ 透過統計處理產生

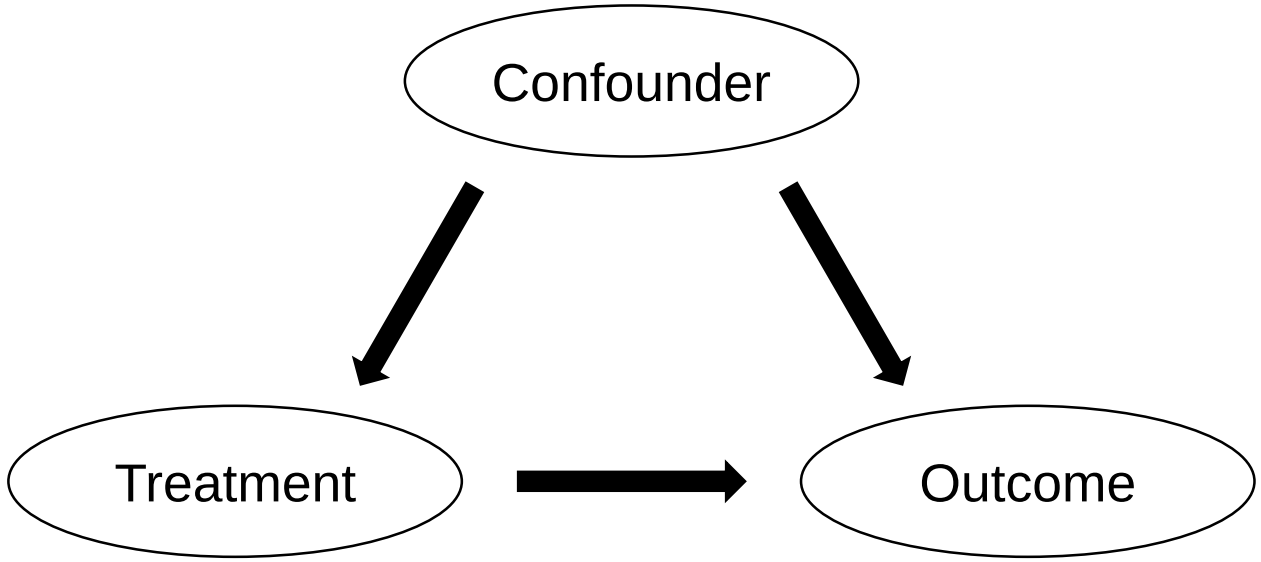
    （胎兒畸形 | 女性沒有抗精神藥物）⬅ 實際上可以找的對照組

AF, atrial fibrillation
心房顫動

 Desai (2019) doi: 10.1136/bmj.l5657

真實世界常見的干擾因子類型

- Indication：血糖控制狀況對應藥物處方
- Severity of illness：到達急診的GCS分數與死亡預後
- Contraindication：腎功能不佳無法使用NOAC



傾向分數

- 核心理念
- 應用模式
- 差異評估
- 研究範例

傾向分數 (propensity score, PS)

- 在給訂條件下預測事件發生（接受治療）的機率
  - 預測目標：以高血壓(htn) 預測被使用NOAC(noac = 1)的機率
  - 建立模型： $ln(\frac{P(NOAC=1)}{P(NOAC=0)}) = 0.6602 + (-0.3853 * \text{HTN})$

	pin	noac	htn	noac_ps
1	2	1	1	0.5682927
2	3	1	1	0.5682927
3	4	0	0	0.6593002
4	6	0	1	0.5682927

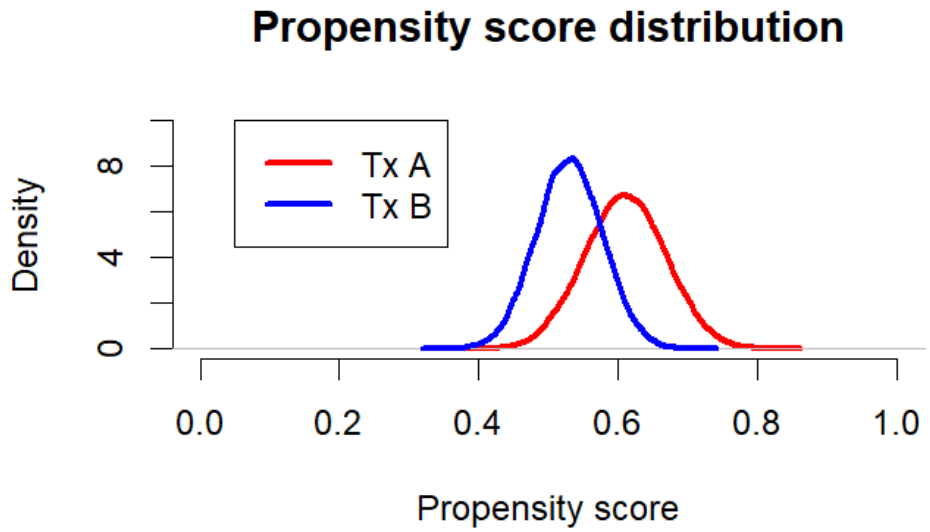
$$\hat{p} = \frac{1}{1 + e^{(-(\alpha + \beta_1 X_1))}}$$

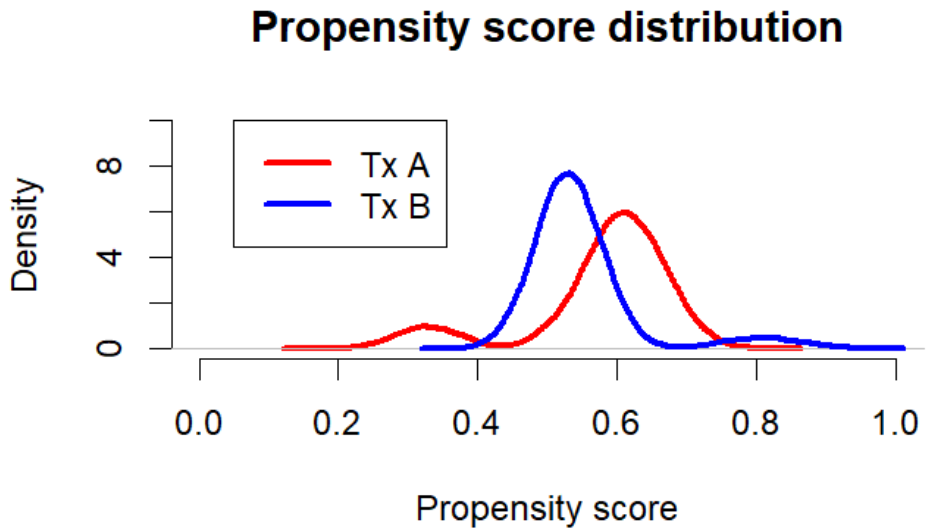
傾向分數

Rubin (1983) doi: 10.1093/biomet/70.1.41
Austin (2011) doi: 10.1080/00273171.2011.568786

如何解讀傾向分數的分布以及異常狀況

- 一般狀況
  - 兩種處方的傾向集中狀況
  - 可以被模型捕捉且預測
- 異常狀況 (尾巴)
  - Off-label use、最後的一搏
  - 禁忌症、拒絕接受治療
  - 不適當處方、模型錯誤
  - Unmeasured confounder





應用模式

- 讓治療分組與觀察到的干擾因子之間獨立 → 形成隨機分派的效果
- PS配對 (propensity score matching, PSM)
  - 找PS相近的樣本進行配對
- PS加權 (Inverse probability of treatment weighting, IPTW)
  - 用PS的倒數加權
- PS分層 (fine stratification)
  - 利用PS分層後在各層內重新平衡
- PS調整 (propensity score adjustment)
  - 將干擾因子降低維度，成為一個傾向分數用來校正

Austin (2011) doi: 10.1080/00273171.2011.568786
Austin (2015) doi: 10.1002/sim.6607
Austin (2017) doi: 10.1177/0962280215584401
Cepeda (2003) doi: 10.1093/aje/kwg115.
Desai (2019) doi: 10.1136/bmj.l5657

Why IPTW works?

noac	htn	sub_n	tot_n	noac_ps	noac_ep	iptw	sub_wn	tot_wn
1	1	233	591	0.5683	0.6201	1.0912	254	591
1	0	358	591	0.6593	0.6201	0.9406	337	591
0	1	177	362	0.5683	0.6201	0.8799	156	362
0	0	185	362	0.6593	0.6201	1.1149	206	362

- noac：治療組別，1 = NOACs，0 = warfarin
- htn：高血壓病史，1 = 有，0 = 無。NOAC組是39% (233 / 591)，warfarin組是48% (177 / 362)
- sub_n：依據 treatment 和 covariates 歸納出的子群人數；tot_n：treatment組內總人數
- noac_ps：根據已知條件計算會被處以NOAC治療的預測機率 = 傾向分數(propensity score)
- noac_ep：整體樣本中的NOAC治療盛行率(exposure prevalence)是62.01% (591 / (591+362))
- iptw：for NOAC = noac_ep * (1 / noac_ps)；for warfarin = (1 - noac_ep) * (1 / (1 - noac_ps))
- sub_wn：加權後的子群人數；tot_wn：加權後treatment組內總人數
- 加權後的高血壓病史，NOAC組是42% (254 / 591)，warfarin組是43% (156 / 362)

使用SMD評估不同治療組別之間是否背景特質相近

- Standardized mean difference (SMD), Cohen's d < 0.1
- For dichotomous variable

$$d = \frac{(\hat{p}_{\text{treatment}} - \hat{p}_{\text{control}})}{\sqrt{\frac{\hat{p}_{\text{treatment}}(1-\hat{p}_{\text{treatment}}) + \hat{p}_{\text{control}}(1-\hat{p}_{\text{control}})}{2}}}$$

- For numerical variable

$$d = \frac{(\bar{x}_{\text{treatment}} - \bar{x}_{\text{control}})}{\sqrt{\frac{s^2_{\text{treatment}} + s^2_{\text{control}}}{2}}}$$

p: prevalence or mean of the dichotomous variable
x: sample mean of the covariate
s^2:sample variance of the covariate

Austin (2009) doi: 10.1002/sim.3697
Cohen (1988) doi: 10.4324/9780203771587
Gandhi (2013) doi: 10.1001/jama.2013.282426

NOAC and dementia using PSM

Journal of the American Heart Association

ORIGINAL RESEARCH

Lower Risk of Dementia in Patients With Atrial Fibrillation Taking Non-Vitamin K Antagonist Oral Anticoagulants: A Nationwide Population-Based Cohort Study

Jin-Yi Hsu, MD; Peter Pin-Sung Liu, MS; An-Bang Liu, MD, PhD; Shu-Man Lin, MD; Huei-Kai Huang, MD; Ching-Hui Loh, MD, PhD

Table 2. Risk of Dementia in Patients With Atrial Fibrillation Receiving Different Anticoagulants After Propensity Score Matching

	Non-Vitamin K Antagonist Oral Anticoagulants (n=6034)	Warfarin (n=6034)
Event number	304	360
Person-years	19 701	18 580
Incidence rate*	15.40	19.40
Univariable model		
HR†	0.82	1.00
95% CI	0.73–0.92	Reference
P value	0.0004	

Statistical Analysis

We used propensity score matching to balance baseline characteristics, including age, sex, income level, index year, time interval between AF diagnosis and anticoagulant use, CHA_2DS_2-VASc score, HAS-BLED score, Charlson Comorbidity Index, comorbidities, and medication use. The propensity scores, which calculate the probability of a patient with AF using NOACs or warfarin, were estimated for NOACs versus warfarin comparison using a logistic regression model. Within the propensity score matching, we used nearest-neighbor matching algorithms without replacements and adopted a caliper width equal to 0.2 of the SD of the logit of the propensity score. Difference of baseline characteristics were assessed by standardized difference, and values with significant differences were defined as standardized difference values of >0.1. Considering that mortality is an important competing risk among elderly patients, the cumulative incidence

Hsu (2021) doi: 10.1161/JAHA.120.016437

NOAC and fracture using PSM

ESC European Society of Cardiology

European Heart Journal (2020) **41**, 1100–1108
doi:10.1093/eurheartj/ehz952

CLINICAL RESEARCH
Atrial fibrillation

Fracture risks among patients with atrial fibrillation receiving different oral anticoagulants: a real-world nationwide cohort study

Huei-Kai Huang [1,2,3], Peter Pin-Sung Liu [4], Jin-Yi Hsu [2,4], Shu-Man Lin [2,5], Carol Chiung-Hui Peng [6], Jen-Hung Wang [3], and Ching-Hui Loh [2,4]*

Huang (2020) doi: 10.1093/eurheartj/ehz952

AFDAS & recurrent stroke using IPTW

frontiers | Frontiers in Cardiovascular Medicine

Oral anticoagulant decreases stroke recurrence in patients with atrial fibrillation detected after stroke

Jin-Yi Hsu[1,2], Peter Pin-Sung Liu[1,3], Luciano A. Sposato[4,5,6,7], Huei-Kai Huang[2,8,9], An-Bang Liu[2,10], Edward Chia-Cheng Lai[11], Swu-Jane Lin[12], Cheng-Yang Hsieh[11,13]* and Ching-Hui Loh[1,2,8]*

Hsu (2022) doi: 10.3389/fcvm.2022.929304

NOAC & DM complications using IPTW

Annals of Internal Medicine

ORIGINAL RESEARCH

Diabetes-Related Complications and Mortality in Patients With Atrial Fibrillation Receiving Different Oral Anticoagulants

A Nationwide Analysis

Huei-Kai Huang, MD; Peter Pin-Sung Liu, MS; Shu-Man Lin, MD; Jin-Yi Hsu, MD; Jih-I Yeh, MD, PhD; Edward Chia-Cheng Lai, PhD; Carol Chiung-Hui Peng, MD; Kashif M. Munir, MD; Ching-Hui Loh, MD, DrPH; and Yu-Kang Tu, DDS, MSc, PhD

Study Population and Exposure

We pursued a target trial design to emulate a randomized controlled trial with observational data (Supplement Table 1, available at Annals.org) (17–19). We initially retrieved data on adult patients aged 20 years or older, with diagnoses of both AF and DM, who received oral anticoagulants between 2012 and 2017.

. . .

This as-started design (analog of intention to treat) emulated a target trial to strengthen causal inference from observational data (17).

Propensity Score Methods

We used 2 propensity score methods, namely stabilized inverse probability of treatment weighting (IPTW) and propensity score matching, to reduce the systematic differences in baseline characteristics between NOAC and warfarin groups (24–26). The analyses with stabilized IPTW estimated the average treatment effect in the whole population (27); those with propensity score matching estimated the average treatment effect among the treated population (24). The details of and reasons why we used propensity score methods are described in Supplement Notes 4 and 5 (available at Annals.org).

Huang (2022) doi: 10.7326/M21-3498

NOAC & DM complications using IPTW

Supplement Table 1. Specification and emulation of a target trial evaluating the effect of NOAC versus warfarin on hazards of diabetes complications using real-world data from Taiwan's NHIRD

Component	Target trial	Emulated trial using real-world data
Aim	To estimate the relative effect of NOAC versus warfarin on hazards of diabetes complications and mortality in AF patients with DM	Same
Eligibility	Adult patients aged ≥20 years previously diagnosed with AF and DM without severe valvular heart disease or end stage renal disease No prior use of oral anticoagulants.	Same, but with the exclusion of patients with a previous diagnosis of rheumatic heart disease, congenital heart disease, or who had received valve replacement surgery, because severe valvular heart disease is hard to define using diagnostic codes in NHIRD directly

Huang (2022) doi: 10.7326/M21-3498

NOAC & DM complications using IPTW

Statistical Code

1. Statistical software information

Our study used SAS for executing data management and the following analytic methods/procedures: propensity score calculation, stabilized inverse probability of treatment weighting (IPTW), propensity score matching, cause-specific Cox proportional hazard model, Fine-Gray competing risk regression model, and estimation of cumulative incidences and difference in cumulative incidences. The software R was applied to estimate the sub-distribution hazard ratio which clustered within an individual hospital using the crrSC package. All figures were graphed
information is described below:

- SAS Version: 9.4; Statistical r
- STATA Version: 15
- R Version: 4.1.1; additional pa

id	noac	age	sex	cci	yg	hosp_id	ps	prev_noac	iptw	macrovas_ft	macrovas_crr
A1	1	84	1	2	1213	H55	0.8714	0.6747	0.7743	2.26	0
A2	1	77	2	5	1415	H75	0.5881	0.6747	1.1473	3.72	2
…	…	…	…	…		…	…	…	…	…	…
B1	0	69	1	4	1213	H37	0.5363	0.6747	0.7015	1.51	1
B2	0	50	2	3	1617	H19	0.4456	0.6747	0.5868	4.33	0
…	…	…	…	…		…	…	…	…	…	…

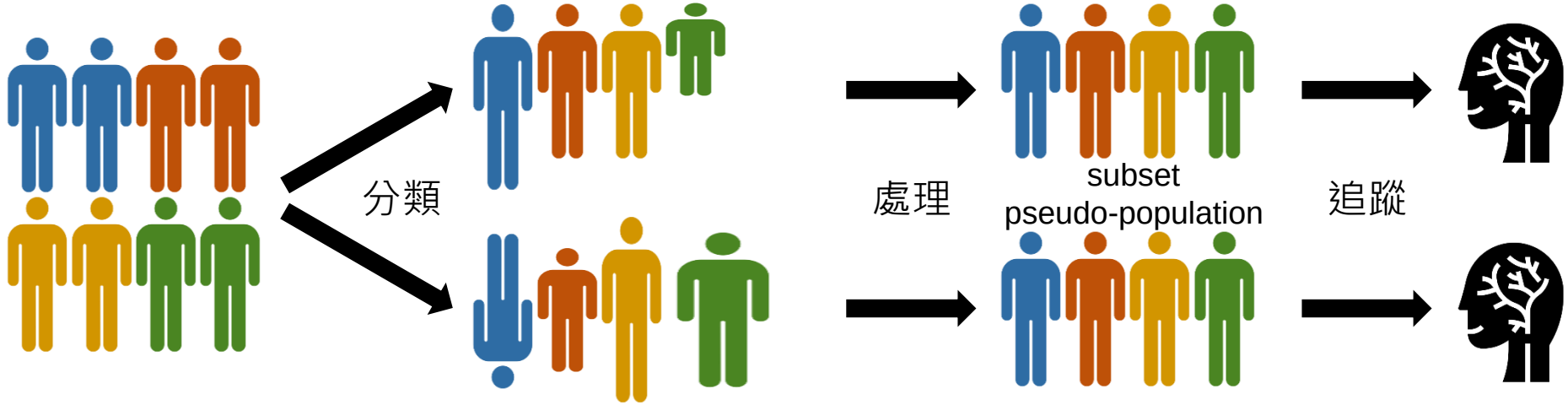
Huang (2022) doi: 10.7326/M21-3498

實作流程

- 研究目的、定義模型
- 評估分佈、應用模式
- 消除干擾、執行分析

比較AF病人使用NOAC與warfarin對於預防中風效果

- 2014年有心房震顫(AF)診斷且使用口服抗凝血劑(OACs)病人
  - 排除過去中風病史、具有心臟瓣膜問題、CKD/ESRD不適合研究對象
- 以他們首次使用的OACS進行分類 (1) NOAC (2) warfarin



- 追蹤未來(~2015.12.31)發生缺血性中風的事件

AF, atrial fibrillation; OACs, oral anticoagulant;
CKD, chronic kidney disease
ESRD, End-Stage Renal Disease

模擬資料編碼說明(1)

- 病人基本資料

	id	male	age	noac	index_date
1	S029357	1	88	0	2014-09-24
2	S057861	1	55	0	2014-12-02
3	S062883	0	53	1	2014-04-14
4	S084891	0	66	0	2014-10-09
5	S007435	1	60	0	2014-07-29
6	S047168	0	73	1	2014-06-09
7	S021947	0	66	0	2014-08-31
8	S096428	0	65	0	2014-06-15
9	S005566	1	69	0	2014-03-14
10	S086586	0	78	0	2014-12-04

變項名稱	中文意義	編碼說明
id	身分證號	虛擬編號
male	男性	1 = 男性 ; 0 = 女性
age	年齡	單位：歲
noac	治療分組	1 = NOAC ; 0 = warfarin
index_date	指標日期	開始使用OACS的西元日期 格式：YYYY-MM-DD
stroke_ot	中風事件	1 = 是 ; 0 = 否
stroke_date	中風日期	觀察期間發生中風的西元日期 若無發生事件則為2015/12/31 格式：YYYY-MM-DD
stroke_ft	追蹤時間	中風日期 − 指標日期 單位：年
dm	病史：糖尿病	1 = 是 ; 0 = 否
htn	病史：高血壓	1 = 是 ; 0 = 否
hyperlipidemia	病史：高血脂	1 = 是 ; 0 = 否
malignancy	病史：惡性腫瘤	1 = 是 ; 0 = 否

模擬資料編碼說明(2)

- 觀察期間中風發生

	id	stroke_ot	stroke_date	stroke_ft
1	S029357	0	2015-12-31	1.26849315
2	S057861	0	2015-12-31	1.07945205
3	S062883	0	2015-12-28	1.70684932
4	S084891	0	2015-12-31	1.22739726
5	S007435	1	2015-03-16	0.63013699
6	S047168	0	2015-12-28	1.55342466
7	S021947	1	2014-11-15	0.20821918
8	S096428	0	2015-12-29	1.53972603
9	S005566	1	2014-03-29	0.04109589
10	S086586	0	2015-12-31	1.07397260

變項名稱	中文意義	編碼說明
id	身分證號	虛擬編號
male	男性	1 = 男性；0 = 女性
age	年齡	單位：歲
noac	治療分組	1 = NOAC；0 = warfarin
index_date	指標日期	開始使用OACS的西元日期 格式：YYYY-MM-DD
stroke_ot	中風事件	1 = 是；0 = 否
stroke_date	中風日期	觀察期間發生中風的西元日期 若無發生事件則為2015/12/31 格式：YYYY-MM-DD
stroke_ft	追蹤時間	中風日期 − 指標日期 單位：年
dm	病史：糖尿病	1 = 是；0 = 否
htn	病史：高血壓	1 = 是；0 = 否
hyperlipidemia	病史：高血脂	1 = 是；0 = 否
malignancy	病史：惡性腫瘤	1 = 是；0 = 否

模擬資料編碼說明(3)

- 研究樣本過去病史

	id	dm	htn	hyperlipidemia	malignancy
1	S029357	0	1	0	0
2	S057861	0	1	0	0
3	S062883	0	0	0	0
4	S084891	0	0	0	0
5	S007435	1	1	0	0
6	S047168	1	1	1	0
7	S021947	0	1	0	0
8	S096428	0	0	0	0
9	S005566	0	0	0	0
10	S086586	0	1	0	0

變項名稱	中文意義	編碼說明
id	身分證號	虛擬編號
male	男性	1 = 男性 ; 0 = 女性
age	年齡	單位：歲
noac	治療分組	1 = NOAC ; 0 = warfarin
index_date	指標日期	開始使用OACS的西元日期 格式：YYYY-MM-DD
stroke_ot	中風事件	1 = 是 ; 0 = 否
stroke_date	中風日期	觀察期間發生中風的西元日期 若無發生事件則為2015/12/31 格式：YYYY-MM-DD
stroke_ft	追蹤時間	中風日期 − 指標日期 單位：年
dm	病史：糖尿病	1 = 是 ; 0 = 否
htn	病史：高血壓	1 = 是 ; 0 = 否
hyperlipidemia	病史：高血脂	1 = 是 ; 0 = 否
malignancy	病史：惡性腫瘤	1 = 是 ; 0 = 否

背景特質比較

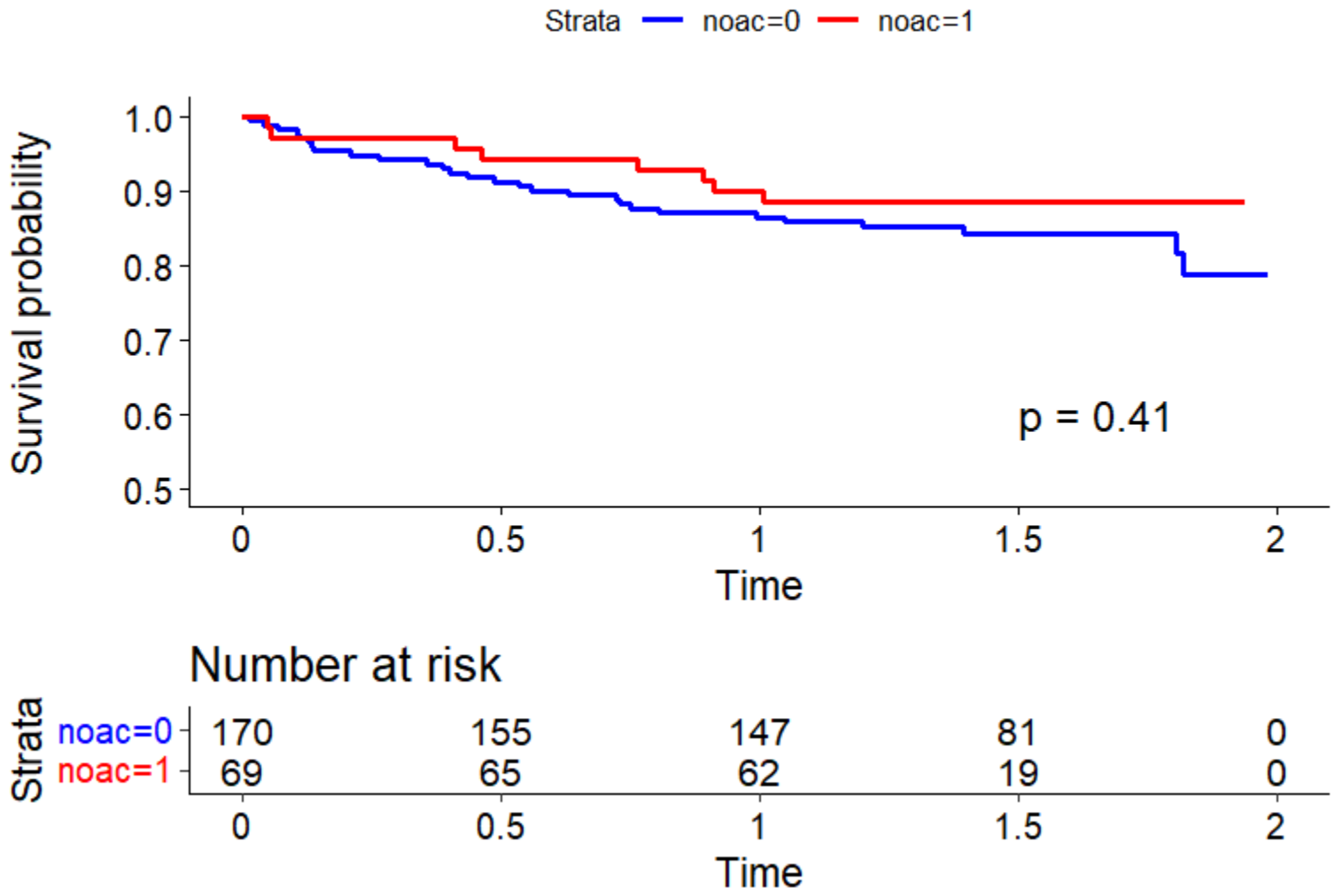
Table 1. Baseline characteristics of patients

Variable	Warfarin N = 170		NOAC N = 69		SMD
	N	(%)	N	(%)	
Male	93	54.7	47	68.1	0.278
Age*	71.2	13.4	74.0	11.5	0.226
HTN	100	58.8	40	58	0.017
DM	39	22.9	19	27.5	0.106
Hyperlipidemia	35	20.6	19	27.5	0.163
Malignancy	12	7.1	4	5.8	0.051

* Expressed as mean and SD.

Abbreviations: n, number; SD, standard deviation; HTN, Hypertension; DM, diabetes mellitus.

觀察期間中風事件之KM curves比較



觀察期間中風事件之發生率比較與治療效果

Table 2. Risk of ischemic stroke

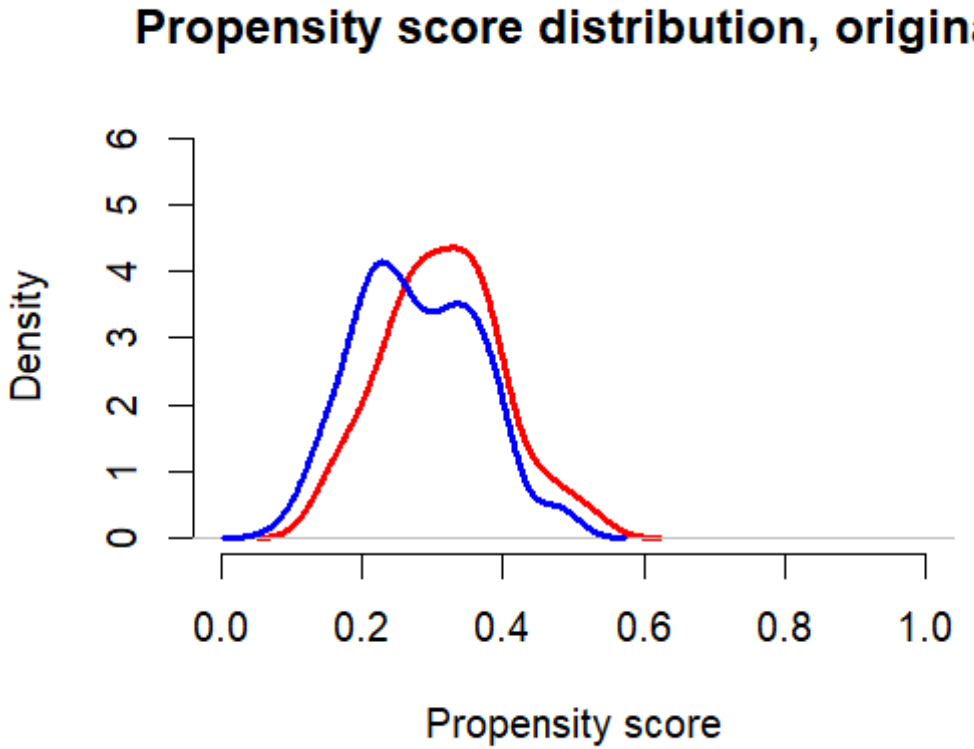
	N	Events	FU	IR	aHR (95% CI)	p value
NOAC	69	8	89	8.99	0.67 (0.30-1.49)	0.331
Warfarin	170	28	231	12.13	1.00 (reference)	

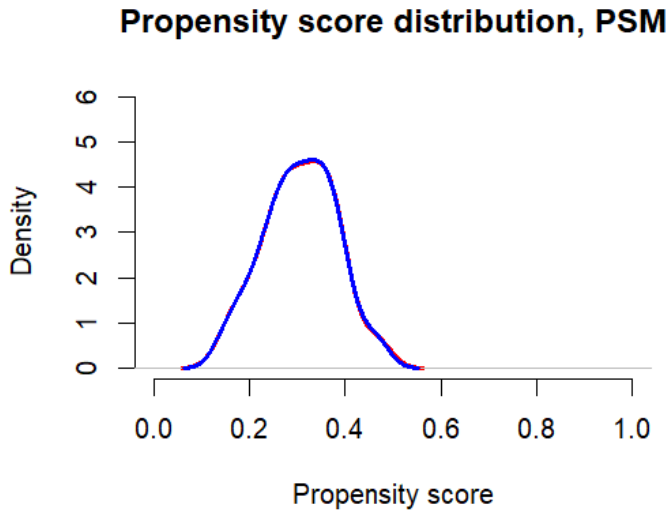
Abbreviations: n, number; FU, follow-up time (days); IR, incidence rate; aHR, adjusted hazard ratio; CI, confidence intervals.

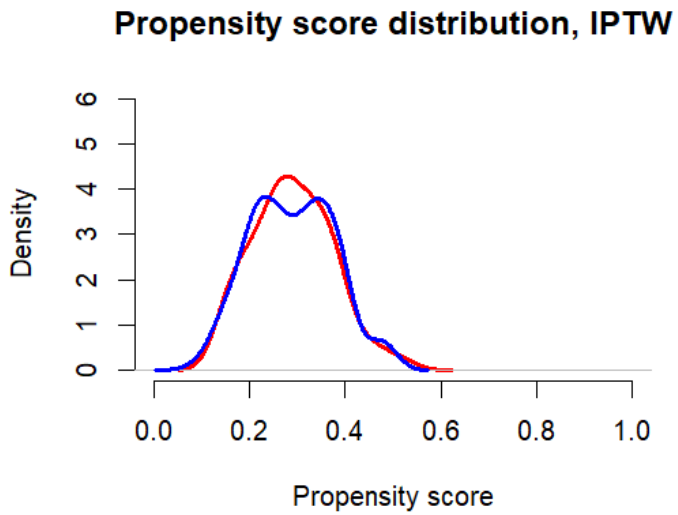
兩組研究樣本之傾向分數計算、評估與應用

outcome = noac (是接受治療/觀察分組的變數喔!!!)

predictors = male, age, dm, htn, hyperlipidemia, malignancy







背景特質比較 (IPTW) 所有baseline的SMD < 0.1

Table 3. Baseline characteristics of patients (IPTW pseudo-population)

Variable	Warfarin N = 170		NOAC N = 69		SMD
	N	(%)	N	(%)	
Male	100	58.6	41	59.7	0.023
Age*	72.0	13.1	72.0	13.0	0.003
HTN	99	58.3	39	56.9	0.028
DM	41	23.9	16	23.3	0.014
Hyperlipidemia	39	22.7	16	22.8	0.004
Malignancy	11	6.5	4	5.3	0.052

* Expressed as mean and SD.

Abbreviations: n, number; SD, standard deviation; HTN, Hypertension; DM, diabetes mellitus.

觀察期間中風事件之發生率比較與治療效果 (IPTW)

Table 4. Risk of ischemic stroke (IPTW pseudo-population)

	N	Events	FU	IR	aHR (95% CI)	p value
NOAC	69	8	89	8.96	0.72 (0.31-1.63)	0.424
Warfarin	170	28	232	12.24	1.00 (reference)	

Abbreviations: n, number; FU, follow-up time (days); IR, incidence rate; aHR, adjusted hazard ratio; CI, confidence intervals.

軟體實作

- 關鍵指令講解
- 軟體實際操作

R：兩組基本特性比較

```
dt_1_baseline_all <- c("male", "htn",..., "age")
dt_1_baseline_cat <- c("male", "htn", ...)

dt_1_baseline <- CreateTableOne(
  data = dt_1, # 分析所使用的dataset
  vars = dt_1_baseline_all, # 定義要分析變項的名稱向量
  factorVars = dt_1_baseline_cat, # 定義哪一些是類別變數
  strata = "noac", # 樣本分群比較的變項名稱
  test = FALSE) # 不進行統計假設檢定(t-test / χ2 test)

print(dt_1_baseline, smd = TRUE) # 列印報表並使用SMD作為差異評估
```

R：KM curves & Log-rank test

```
dt_2_km_model <- survfit(Surv(stroke_ft, stroke_ot) ~ noac, data = dt_2)
                                  # time-to-event架構    # 主要分組      # 資料集
dt_2_km <- ggsurvplot(
  fit = dt_2_km_model, data = dt_2,
  palette = c("blue", "red"), # 線條顏色
  censor = F, # 不要出現censor的標記
  risk.table = T, risk.table.height = 0.3 # 顯示number at risk且佔畫面30%
  ylim = c(0.5, 1), break.y.by = 0.1, # y軸的範圍是0.5 ~ 1，每0.1一個間隔
  xlim = c(0, 2), break.x.by = 0.5, # x軸的範圍是0 ~ 2，每0.5一個間隔
  pval = TRUE, pval.coord = c(1.5, 0.6)) # 顯示p值在坐標軸x = 1.5, y = 0.6
```

R：Cox model

```
coxph(Surv(stroke_ft, stroke_ot) ~ noac, data = dt_1)
        # time-to-event架構   # 主要分組

coxph(Surv(stroke_ft, stroke_ot) ~ noac + male + age + ..., data = dt_1)
        # time-to-event架構   # 主要分組 + covariates

coxph(Surv(stroke_ft, stroke_ot) ~ noac + strata(subclass), data = dt_3)
        # time-to-event架構   # 主要分組     # 成對變數名稱

coxph(Surv(stroke_ft, stroke_ot) ~ noac, data = dt_3, weights = iptw)
        # time-to-event架構   # 主要分組                # 權重變數名稱
```

R：傾向分數計算

```
dt_1_model_ps <-
  glm(noac ~ male + age + ..., data = dt_1, family = binomial())
 # 目標結果 ~ 預測因子                                    # 二項式分布

dt_1$noac_ps <- predict(dt_1_model_ps, data = dt_1, type = "response")
# 預測機率              # 預測用模型     # 放入的資料來源 # 回傳機率而非logit值
```

R：傾向分數配對

```
dt_2 <-
  matchit(noac ~ male + age + ..., # 目標結果 = 預測因子
  data = dt_1,
  caliper = 0.2, # 容許PS相匹配的距離
  ratio = 1) # 1:1配對
dt_2 <- match.data(dt_2) # 取出已經配對好的那些樣本
# 會新生成一個變數 subclass 代表每一個成對的編號
# 預設參數 std.caliper = TRUE，代表caliper的單位是logit of PS的標準差
# 預設參數 method = "nearest"，代表最近/貪婪(greedy)演算法
# 預設參數 m.order = "largest"，代表從treated group裡面PS最大的樣本開始進行配對
#                    亦有"smallest"或是"random"搭配set.seed()可以使用
```

R：Survey design [R only]

```
svydesign(ids = ~ 1, data = dt_3, weights = ~ iptw)
                                          # 加權變數名稱


dt_3_baseline <- svyCreateTableOne(
  vars = dt_3_baseline_all,
  factorVars = dt_3_baseline_cat,
  strata = "noac", data = dt_3_weighted, test = FALSE)



print(dt_3_baseline, smd = TRUE)
```

SAS：兩組基本特性比較

```
proc tabulate data = temp.dt_1; # 分析所使用的dataset
  class noac;
  class male htn ... / descending; # 定義類別變數，descending讓1在上0在下
  var age; # 定義連續變數

  table (age), noac * (mean std);
  table (male htn ...), noac * (n pctn);
run;

# SMD請使用Excel附件表格來計算
```

SAS：KM curves & Log-rank test

```
proc lifetest
    data = temp.dt_1 # 資料集
    method = km
    plots = survival(
      nocensor # 不要出現censor的標記
      atrisk = 0 to 2 by 0.5 # 顯示number at risk
      outside) # 將risk table顯示在外側
    notable; # 不要顯示所有time point的人數及事件
  time stroke_ft *stroke_ot(0); # time-to-event架構
  strata noac / test = logrank; # 主要分組並對分組進行log-rank test
run;
```

SAS：Cox model

```
proc phreg data = temp.dt_1;
  model stroke_ft * stroke_ot(0) = noac / rl; # rl = 信賴區間
run;    # time-to-event          = 主要分組

  model stroke_ft * stroke_ot(0) = noac male age ... / rl; # 信賴區間
run;    # time-to-event          = 主要分組 covariates

  model stroke_ft * stroke_ot(0) = noac / rl; # rl = 信賴區間
  strata _MatchID; #成對變數名稱
run;

  model stroke_ft * stroke_ot(0) = noac / rl; # rl = 信賴區間
  weight iptw; # 權重變數
run;
```

SAS：傾向分數計算

```
proc logistic data = temp.dt_1;
  class noac(ref = '0'); # 指定結果變數要用哪一個level當參考組
  model noac = male age dm ...; # 目標結果 = 預測因子
  output out = temp.dt_1 # 將帶有預測機率值的資料儲存
  predicted = noac_ps; # 給預測機率值新的名稱
run;
```

SAS：傾向分數配對

```
proc psmatch data = temp.dt_2 region = treated;
  class noac;
  psmodel noac(Treated = '1') = male age dm ...; # 目標結果 = 預測因子
  match
    method = greedy(k = 1) # 1:1配對貪婪(greedy)演算法配對
    caliper = 0.2; # 容許PS相匹配的距離
  output
    out(obs = match) = temp.dt_2 # 取出已經配對好的那些樣本儲存為dataset
    matchid = _MatchID; # 成對樣本的標記變項
run;
# 預設參數 order = descending，代表從treated group裡面PS最大的樣本開始進行配對
#                  亦有ascending或是random搭配seed可以使用
# 預設參數 distance = lps，caliper的單位是logit of PS
```

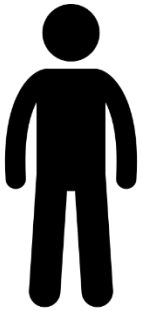
Final remark

- 因果推論
  - 設計謹慎、消除干擾
- 傾向分數
  - 模型完整、目標正確
- 研究實作
  - 核心理念、工作心流、技術實踐

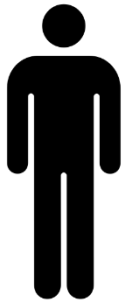
- 劉品崧
  - 研究設計
  - 統計分析
  - 策略諮詢

- **Email**：psliu520@gmail.com
- **PubMed**：Peter Pin-Sung Liu

使用圖片版權來源宣告



Created by Gan Khoon Lay
from the Noun Project



Created by Studio Het Mes
from the Noun Project

Created by Jamison Wieser
from the Noun Project

Created by Eucalyp

Created by Eucalyp