中國醫藥大學附設醫院
真實世界數據結合臨床試驗產生的真實世界證據之應用
《**GCP** 課程》

隨機雙盲臨床試驗與真實世界數據之間的說服力比較(二)

美兆健檢資料庫腎病相關研究

1）論文解說:**腎病、運動、肝病、高血壓、心跳、菸害**

2）從新冠肺炎比較隨機雙盲臨床試驗與**真實世界數據**之間的說服力

温啓邦

國家衛生研究院

中國醫藥大學


國家衛生研究院
National Health Research Institutes

國衛院風水好

- 綠意盎然白鷺多
- 心曠神怡伏龍臥
- 運動強身新桃源
- 好山好水好寂寞

DryLab 今年目標200
個人貢獻11+4

心跳的死亡風險比美高血壓，甚至還更大

- 1）肝功能SGOT偏高，減壽十年以上，比SGPT偏高重要太多。 (10.24),
- 2）蛋白尿的出現是洗腎的預兆 (25.34)(Lancet 糖尿病),
- 3）900萬人大資料，將腎病資料融入心血管的風險預測內 (新Lancet),
- 4) PAI 與死亡率(6.76),
- 5）**發炎指數與自殺的關係**(4.17),
- 6) 中風與吸菸之悖論(似非而是、看似矛盾)(7.19),

糞便潛血的檢查，比美大腸鏡，甚至還更好

- 台灣的菸害防制何去何從
- 7）按照世衛組織建議作法，急起直追，但是五十年後仍不能達標。(6.22)
- 8）台灣施行低菸價被煙商耍了。(6.22)
- 9）今日空污是新吸菸嗎?**(6.22)**
- 10）青少年吸電子煙是否刺激轉吸傳統菸?**(6.22)**
- 11)中國醫護人員新冠肺炎死亡率，隨時間遞減

寫論文

就是在講故事

- 故事要新鮮
  - Something new
- 真實重要故事 繞樑三日
  - Something important
- 科學上站得住腳
- --Scientifically valid
- 要聽得懂的感人故事
  - Moving story flows well
  - 英文通順

- Reviewer's criteria
- Novelty
- Importance
- Validity
- Easy to understand

共22種

15年來

從30膨脹至60

所有雜誌都膨脹

今天的 4 是

15年前的 2

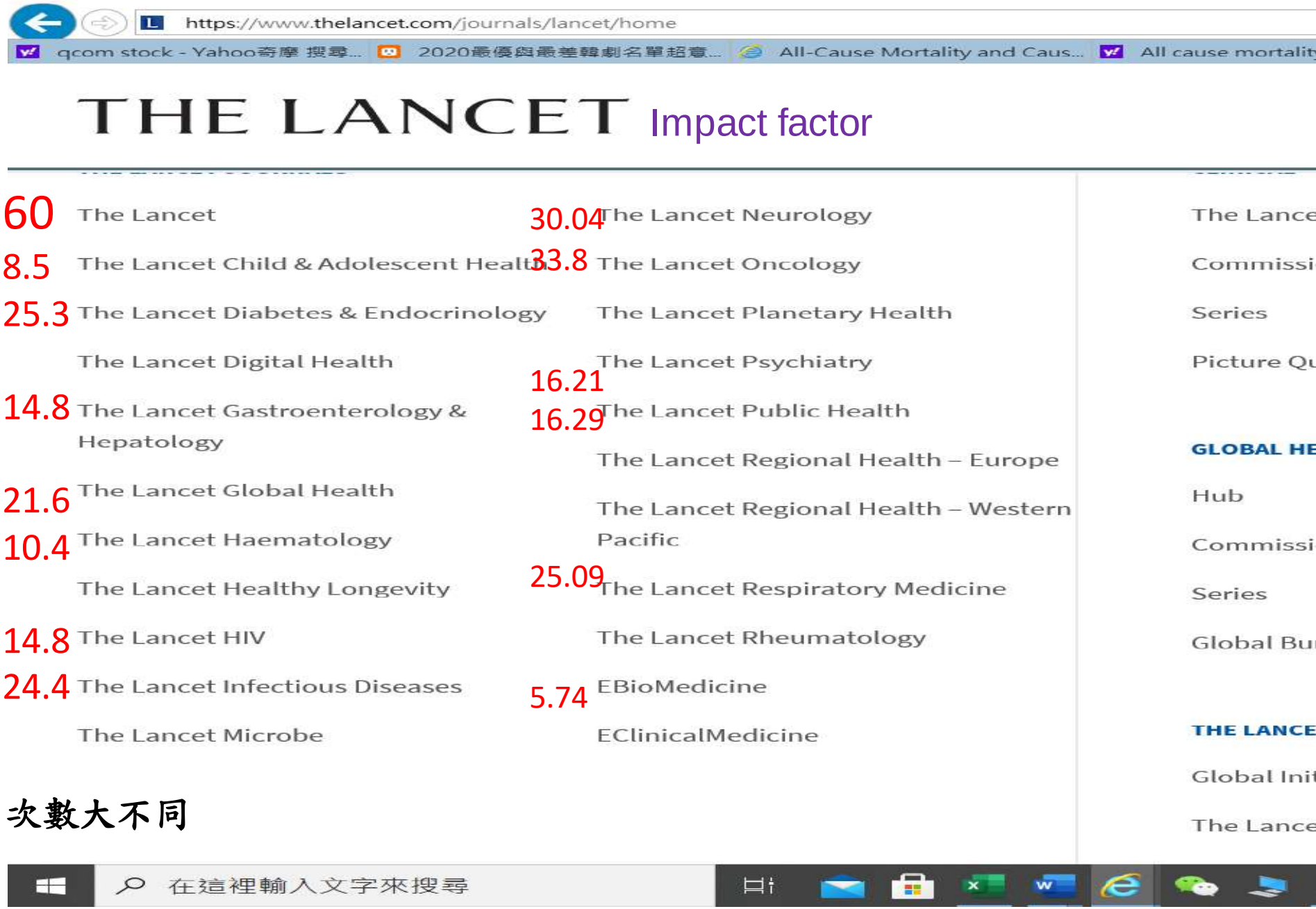
今天的 2 是

15年前的 1 or 0

看 Impact factor

不如看被引用次數

同樣Impact factor被引用次數大不同



慢性腎臟病

1) 在台灣Chronic Kidney Disease

2）CKD機制、擴大得心血管疾病機率

1) 柳葉刀Lancet被引用次數

863

All-cause mortality attributable to chronic kidney disease: a prospective cohort study based on 462 293 adults in Taiwan

Chi Pang Wen, Ting [illegible]an David Cheng, Min Kuang Tsai, Yen Chen Chang, Hui Ting Chan, Shan Pou Tsai, Po Huang Chiang, Chih Cheng Hsu, Pei Kun Sung, Yi Hua Hsu, Sung Feng Wen

Summary

Background Both end-stage renal disease and chronic kidney disease are increasing worldwide; however, the full effect of chronic kidney disease is unknown because mortality risks for all five stages are unavailable. We assessed prevalence and mortality risks for all stages of chronic kidney disease and quantified its attributable mortality in Taiwan.

Methods The cohort consisted of 462 293 individuals aged older than 20 years who participated in a standard medical screening programme since 1994. As of Dec 31, 2006, we identified 14 436 deaths. Chronic kidney disease was determined by glomerular filtration rate and urinary protein. We estimated national prevalence in Taiwan from the cohort by adjusting age and educational levels. Hazard ratios (HRs) were calculated with Cox proportionate hazards model. We calculated mortality attributable to chronic kidney disease for national population and for low socioeconomic status.

Findings The national prevalence of chronic kidney disease was 11·93% (95% CI 11·66–12·28), but only 3·54% (3·37–3·68) of participants in the cohort were aware of their disorder. Prevalence was substantially higher in the group with low socioeconomic status than in the high status group (19·87% [19·84–19·91] *vs* 7·33% [7·31–7·35]). 56 977 (12%) of cohort participants had chronic kidney disease; those with disease had 83% higher mortality for all cause (HR 1·83 [1·73–1·93]) and 100% higher for cardiovascular diseases (2·00 [1·78–2·25]), in a cohort that was observed for 13 years with median follow-up of 7·5 years (IQR 4·0–10·1). 10·3% (95% CI 9·57–11·03) of deaths in the entire population were attributable to chronic kidney disease, but 17·5% (16·27–18·67) of deaths in the low socioeconomic status population. 2350 (39%) deaths occurred before 65 years of age in those with chronic kidney disease. Regular users of Chinese herbal medicines had a 20% (odds ratio 1·20 [1·16–1·24]) increased risk of developing chronic kidney disease.

Interpretation The high prevalence of chronic kidney disease and its associated all-cause mortality, especially in people with low socioeconomic status, make reduction of this disorder a public-health priority. Promotion of its recognition through the general public knowing their glomerular filtration rate and testing their urine is crucial to reduce premature deaths from all causes and to attenuate this global epidemic.

Lancet 2008; 371: 2173–82

See Comment page 2147

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Correspondence to: Chi-Pang Wen, Center for Health Policy Research and Development, National Health Research Institutes, 35 Keyan Road, Zhunan, Miaoli County 350, Taiwan cwengood@nhri.org.tw

2) 柳葉刀Lancet被引用次數

1226

Global Kidney Disease 5

Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention

Ron T Gansevoort, Ricardo Correa-Rotter, Brenda R Hemmelgarn, Tazeen H Jafar, Hiddo J Lambers Heerspink, Johannes F Mann, Kunihiro Matsushita, Chi Pang Wen

Since the first description of the association between chronic kidney disease and heart disease, many epidemiological studies have confirmed and extended this finding. As chronic kidney disease progresses, kidney-specific risk factors for cardiovascular events and disease come into play. As a result, the risk for cardiovascular disease is notably increased in individuals with chronic kidney disease. When adjusted for traditional cardiovascular risk factors, impaired kidney function and raised concentrations of albumin in urine increase the risk of cardiovascular disease by two to four times. Yet, cardiovascular disease is frequently underdiagnosed and undertreated in patients with chronic kidney disease. This group of patients should, therefore, be acknowledged as having high cardiovascular risk that needs particular medical attention at an individual level. This view should be incorporated in the development of guidelines and when defining research priorities. Here, we discuss the epidemiology and pathophysiological mechanisms of cardiovascular risk in patients with chronic kidney disease, and discuss methods of prevention.

Lancet 2013; 382: 339–52

Published Online May 31, 2013 http://dx.doi.org/10.1016/S0140-6736(13)60595-4

This online publication has been corrected. The corrected version first appeared at thelancet.com on July 26, 2013

This is the fifth in a Series of six papers about global kidney disease

- 知名醫學期刊「**刺胳針**（Lancet）」六月底刊出**國家衛生研究院**研究員**溫啟邦**的研究指出，台灣每八個成年人，就有一個罹患慢性腎病，高血壓、糖尿病、吸菸或肥胖者，特別容易罹患，但是，百分之九十五的人不知道腎臟病正在侵襲健康，建議及早監測尿蛋白及血中的肌肝酸，試算腎絲球過濾率，延緩或阻止慢性腎病惡化到洗腎。

- **溫啟邦**是以**美兆健康管理機構**提供四十六萬名成人健檢資料進行分析，推估全台灣慢性腎臟性疾病的人數約有二百萬人，**每十個台灣人就有一人死於慢性腎病**，它還是老人病及窮人病，六十五歲以上老人幾乎每三人就有一人是這種病人，低社經地位的弱勢族群則每五人就有人罹患，比高社經地位者多二點五倍，二、三十歲的世代，也有百分之五的比例出現蛋白尿。

- **溫啟邦**指出，糖尿病、高血壓、吸菸或肥胖者是有慢性腎病的高危險群，經常使用中藥者，罹患慢性腎病的風險也增多百分之二十，長期服用止痛藥者，也增加慢性腎病的風險。

- 他說，慢性腎病對國人死亡率的貢獻度達到百分之十，只是死亡證明書上往往不會寫慢性腎病，大約四成的慢性腎病患者是在六十五歲以前死亡，**死因是心血管疾病**，而慢性腎病會顯著增加心血管疾病的危險。

- 至於尿中出現蛋白質，溫啟邦表示，是慢性腎病的警訊，慢性腎病的病程分為五個階段，在前兩個的蛋白尿階段，病患好好控制血壓、血糖等慢性病，可望停止惡化，一旦惡化到第五期就要洗腎，然而一般人 包括 醫師對本疾病不甚了解，大部份的患者都是要到快洗腎時才知道自己罹病。

- 資料顯示，台灣目前洗腎人口約九萬人，洗腎人口之多，領先全球，比日本及美國還高，也是歐洲國家的二到四倍，洗腎費用的健保支出近新台幣六百五十億元，超過治療癌症的總健保費用。

- 「**刺胳針**」日前發出新聞稿，強調慢性腎臟病正在全球默默流行中，國際媒體如**華盛頓郵報**以「世界各地都在增加中的慢性腎臟性疾病」為題，認為亞洲人也不例外；**路透社**引述**溫啟邦**的研究成果，以「慢性腎臟性疾病為常見的提早死亡死因」為題，希望所有人都能重視及預防。

- **溫啟邦**說，預防慢性腎病從運動、戒菸、減肥的生活習慣做起，並且減少及控制高血壓及高血糖；至於成年人應在何時開始驗尿、驗尿來早期監測腎功能，他將進一步研究做出政策建議。

CKD 慢性腎臟病

defined by KDOQI and endorsed by KDIGO (2002)

Stage	Description	腎絲球過濾率 GFR	
1	Kidney damage (蛋白尿)	≧ 90	
2	Kidney damage (蛋白尿)	60-89	
3	Moderate ↓ in GFR	30-59	
4	Severe in ↓ GFR	15-29	
5	ESRD (Kidney failure)	≦15	

KDOQI: Kidney Disease Outcome Initiative
KDIGO: Kidney Disease Improving Global Outcomes

慢性腎臟病 (CKD) 在台灣 202萬人

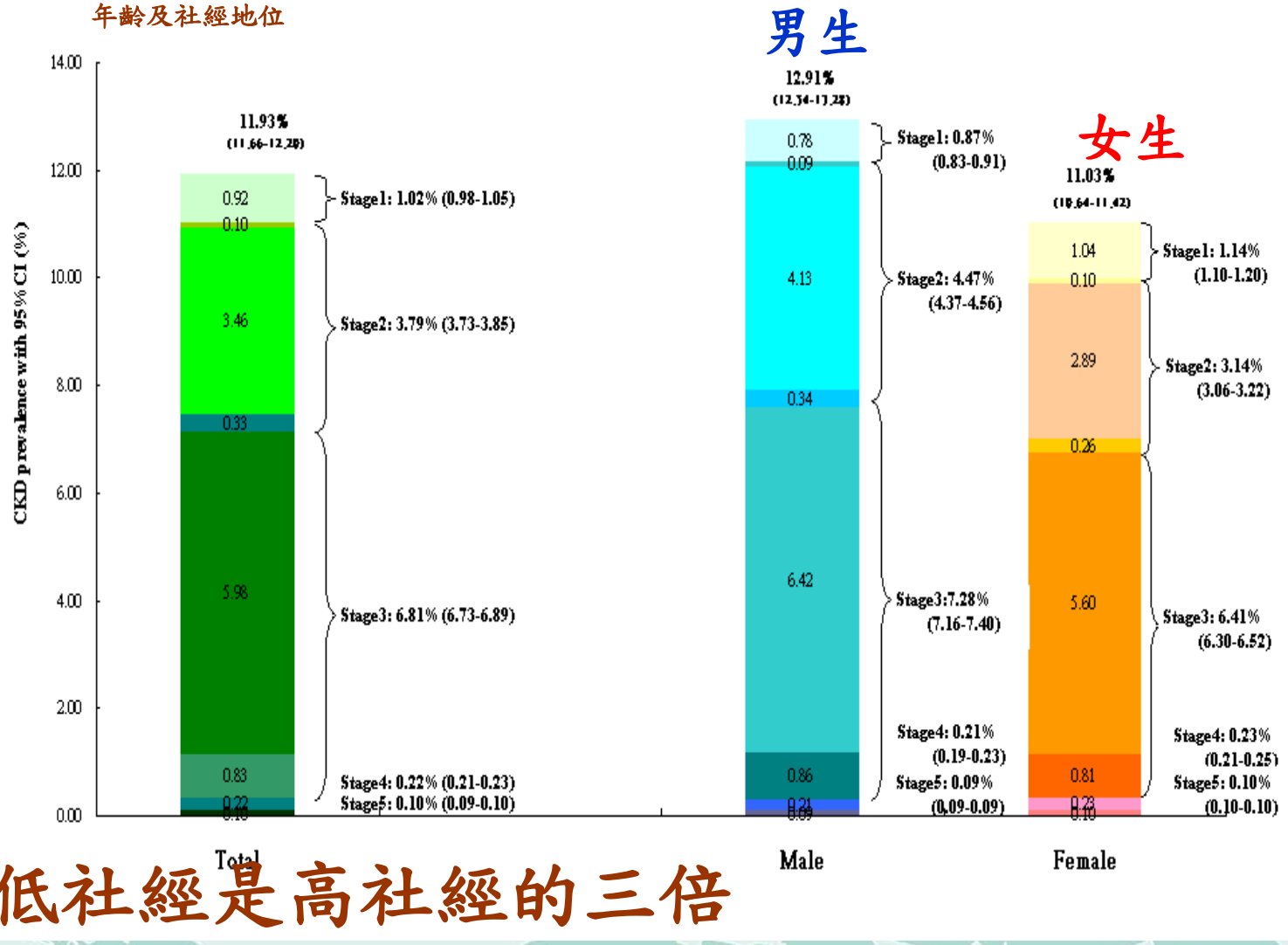
分期	定義	人口	每年死亡人數
慢性腎臟病	有蛋白尿 或GFR < 60	202萬人 (11.9%)	14,000人
第一期	GFR ≧90　有蛋白尿	17萬人(1.0%)	1,500人
第二期	GFR 60~89　有蛋白尿	65萬人(3.8%)	4,000人
第三期	GFR 30-59	115萬人(6.8%)	6,400人
第四期	GFR 15-29	37,000人(0.2%)	1,300人
第五期	GFR ＜15	17,000人(0.1%)	1,100人

認知:“您曾患腎炎/腎病嗎?”

GFR:腎絲球過濾率＝186 ×肌酸酐 $^{-1.154}$ × 年齡 $^{-0.203}$ × 0.742 (女性)(ml/min/1.73 m^2)

台灣盛行率

年齡及社經地位



低社經是高社經的三倍

Fig2. National prevalence of CKD among adults in Taiwan.

教育程度低的男生慢性腎臟病最多

Early recognition and prevention of chronic kidney disease (早期發現及預防慢性腎臟病)

Matthew T James, Lancet April 10. 2010

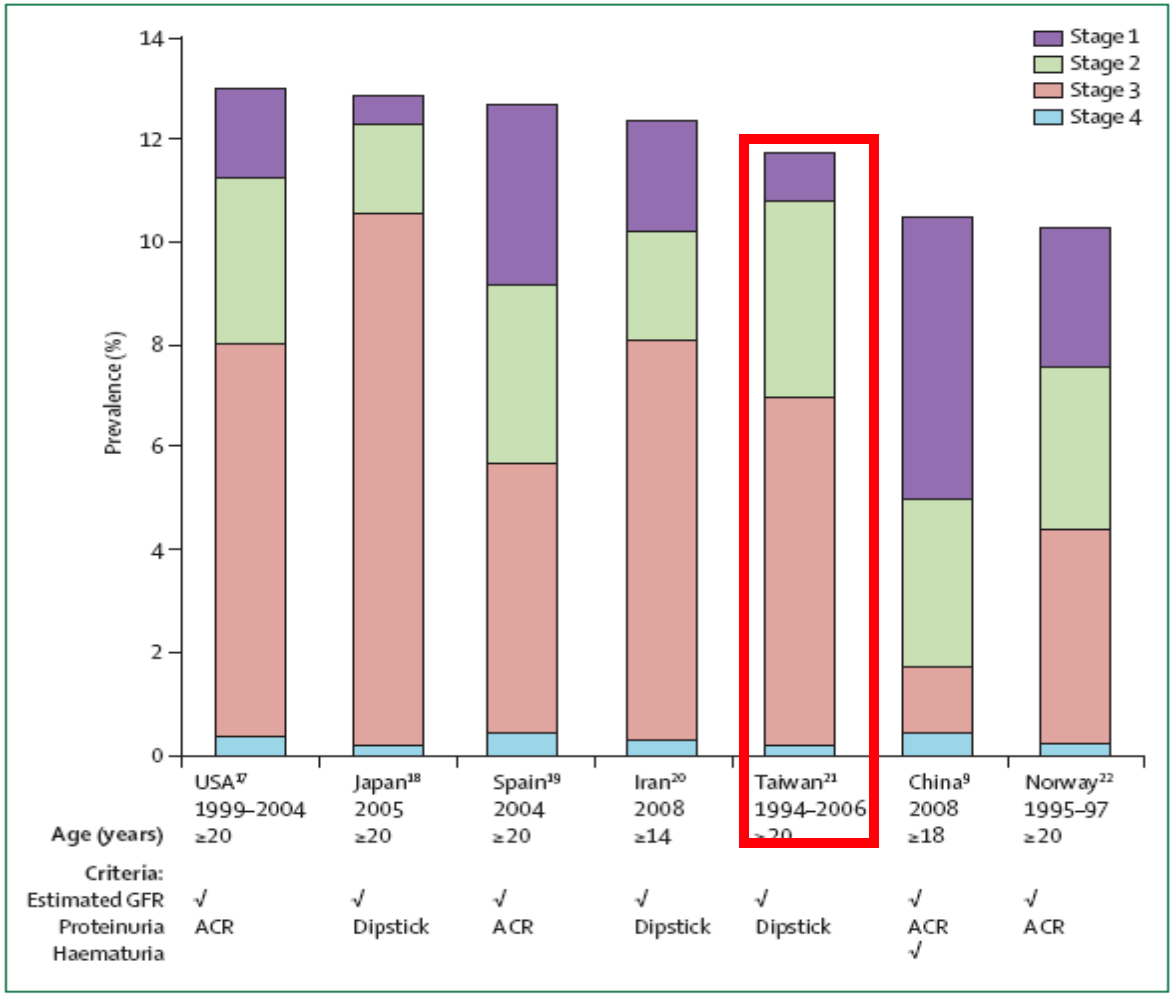


Figure 1: **Population-based estimates of prevalence of chronic kidney disease**
ACR=albumin-to-creatinine ratio. GFR=glomerular filtration rate.

台灣paper超過1500次的不多


每天運動15分鐘 可多活3年

首見大型研究 顛覆過往建議 不限年齡、性別 懶人動一動 健康不是夢

15分鐘懶人運動法

日看6小時電視 少活5年

聯合報

美國心臟學會轉載

Journal of the American College of Cardiology

柳葉刀Lancet被引用次數

1673


Minimum amount of physical activity for reduced mortality and extended life expectancy: a prospective cohort study

Chi Pang Wen*, Jackson Pui Man Wai*, Min Kuang Tsai, Yi Chen Yang, Ting Yuan David Cheng, Meng-Chih Lee, Hui Ting Chan, Chwen Keng Tsao, Shan Pou Tsai, Xifeng Wu

Summary

Background The health benefits of leisure-time physical activity are well known, but whether less exercise than the recommended 150 min a week can have life expectancy benefits is unclear. We assessed the health benefits of a range of volumes of physical activity in a Taiwanese population.

Methods In this prospective cohort study, 416 175 individuals (199 265 men and 216 910 women) participated in a standard medical screening programme in Taiwan between 1996 and 2008, with an average follow-up of 8·05 years (SD 4·21). On the basis of the amount of weekly exercise indicated in a self-administered questionnaire, participants were placed into one of five categories of exercise volumes: inactive, or low, medium, high, or very high activity. We calculated hazard ratios (HR) for mortality risks for every group compared with the inactive group, and calculated life expectancy for every group.

Findings Compared with individuals in the inactive group, those in the low-volume activity group, who exercised for an average of 92 min per week (95% CI 71–112) or 15 min a day (SD 1·8), had a 14% reduced risk of all-cause mortality (0·86, 0·81–0·91), and had a 3 year longer life expectancy. Every additional 15 min of daily exercise beyond the minimum amount of 15 min a day further reduced all-cause mortality by 4% (95% CI 2·5–7·0) and all-cancer mortality by 1% (0·3–4·5). These benefits were applicable to all age groups and both sexes, and to those with cardiovascular disease risks. Individuals who were inactive had a 17% (HR 1·17, 95% CI 1·10–1·24) increased risk of mortality compared with individuals in the low-volume group.

Interpretation 15 min a day or 90 min a week of moderate-intensity exercise might be of benefit, even for individuals at risk of cardiovascular disease.

Funding Taiwan Department of Health Clinical Trial and Research Center of Excellence and National Health Research Institutes.

Introduction

Much evidence suggests that 150 min or more a week of leisure-time physical activity (LTPA) can have substantial health benefits for an individual.[1,2] Guidelines such as the 2008 physical activity guidelines for Americans[3] and WHO's 2010 Global Recommendations on Physical Activity for Health[4,5] have drawn attention to the health benefits of this amount of weekly exercise. Because barriers exist to meet this 30 min a day, 5 day a week recommendation (eg, time constraints or an individual's uncertainty about the amount of exercise needed to benefit health), LTPA is an underused public health intervention. East Asians tend to be less physically active than individuals in western countries, and also tend to exercise at lower intensity.[4,5] A third of the American adult population met this recommendation,[3] whereas less than a fifth of the adult population did in East Asian countries such as China, Japan, or Taiwan.[4,5] Whether levels of physical activity below the recommended 150 min a week are adequate to generate health benefits is unclear.

Identification of a minimum amount of exercise—or minimum dose[6]—sufficient to reduce mortality is desirable because a small amount of exercise can be easier to achieve. Furthermore, patients might be more easily motivated to exercise if their doctor recommends an easily manageable amount, especially if health messages are simple. Because east Asians visit their doctors frequently,[4] plenty of opportunities for health communication and prescription of exercise exist.[7] However, such opportunities to prescribe exercise are sometimes missed because most doctors are expected to treat only diseases, having little time to modify a behaviour that is not directly related to the disease if not requested by a patient. If health-enhancing physical activity were to be prescribed, it should be related to the disease in question, and the recommended amount should be kept to a minimum to increase the chances of adherence.

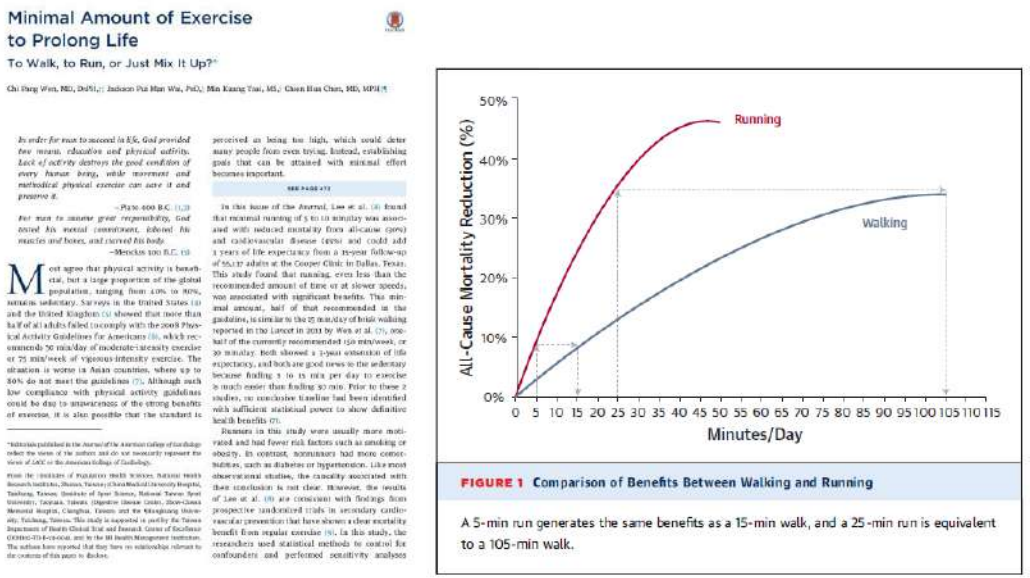
The objective of this study is to assess the health benefits of different volumes of physical activity in a large cohort in Taiwan, and to investigate whether less than 150 min a week of exercise is sufficient to reduce mortality or extend life expectancy.

Methods

Data collection

In this historically prospective cohort study, the cohort consisted of 416 175 healthy individuals aged 20 years or older (199 265 men and 216 910 women) who participated

- 以走路健走好，還是以慢慢跑步好？何者可延長壽命？


Minimal Amount of Exercise to Prolong Life

To Walk, to Run, or Just Mix It Up?*

Chi Pang Wen, MD, DrPH,†; Jackson Pui Man Wai, PhD,†; Min Kuang Tsai, MS,†; Chien Hua Chen, MD, MPH,¶

In order for man to succeed in life, God provided two means, education and physical activity. Lack of activity destroys the good condition of every human being, while movement and methodical physical exercise can save it and preserve it.

—Plato 400 B.C. [1,2]

But man to assume great responsibility, God created his mental commitment, likened his muscles and bones, and revived his body.

—Menekius 100 B.C. [3]

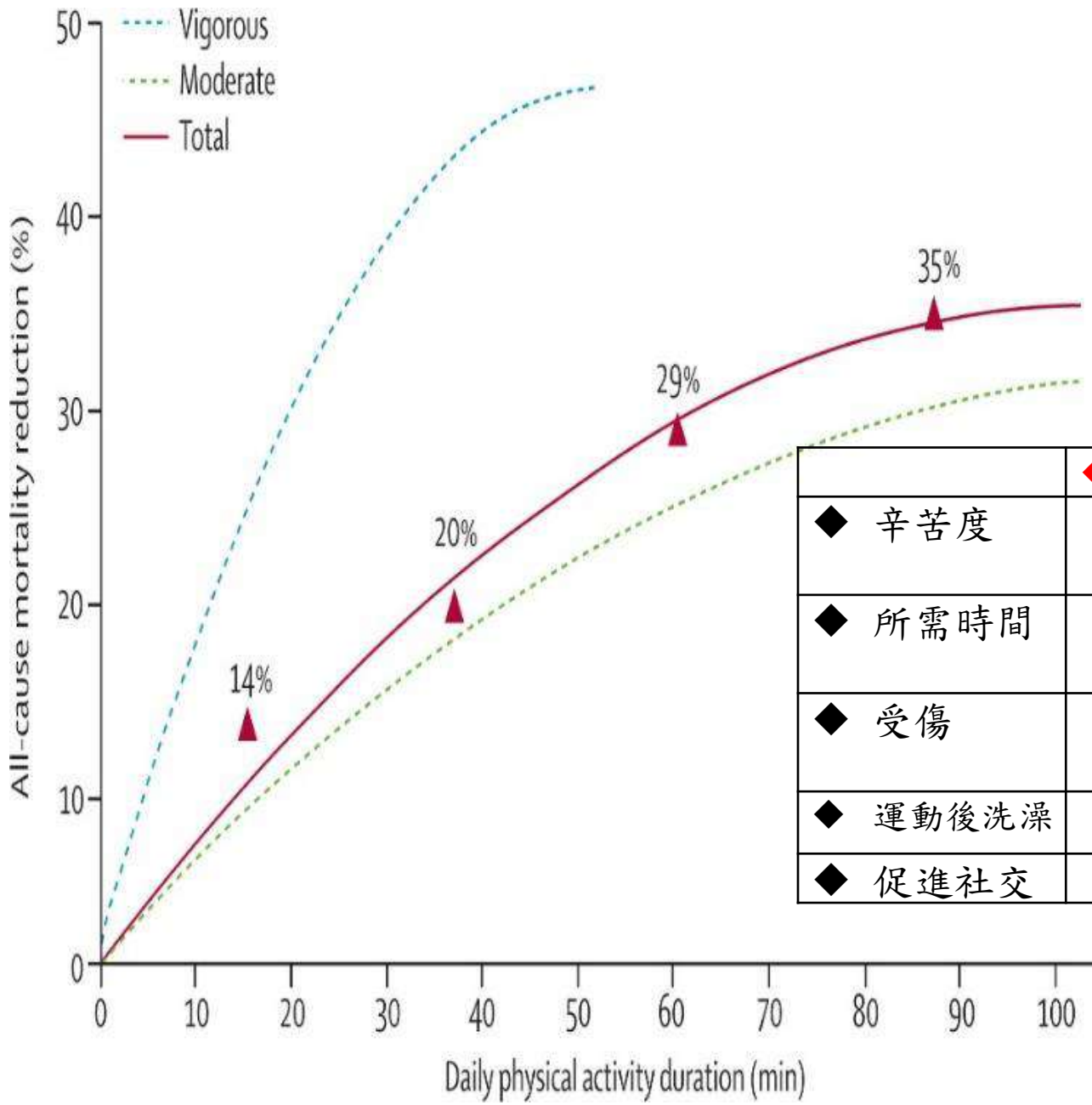
Most agree that physical activity is beneficial, but a large proportion of the global population, ranging from 40% to 80%, remains sedentary. Surveys in the United States [3] and the United Kingdom [4] showed that more than half of all adults failed to comply with the 2008 Physical Activity Guidelines for Americans [5], which recommends 30 min/day of moderate-intensity exercise or 75 min/week of vigorous-intensity exercise. The situation is worse in Asian countries, where up to 86% do not meet the guidelines [7]. Although such low compliance with physical activity guidelines could be due to unawareness of the strong benefits of exercise, it is also possible that the standard is perceived as being too high, which could deter many people from even trying. Instead, establishing goals that can be attained with minimal effort becomes important.

In this issue of the Journal, Lee et al. [8] found that minimal running of 5 to 10 min/day was associated with reduced mortality from all-cause (30%) and cardiovascular disease (45%) and could add 3 years of life expectancy from a 19-year follow-up of 55,137 adults at the Cooper Clinic in Dallas, Texas. This study found that running, even less than the recommended amount of time or at slower speeds, was associated with significant benefits. This seminal concept, half of that recommended in the guidelines, is similar to the 15 min/day of brisk walking reported in the Lancet in 2011 by Wen et al. [7], one-half of the currently recommended 150 min/week, or 30 min/day. Both showed a 3-year extension of life expectancy, and both are good news to the sedentary because finding 5 to 15 min per day to exercise is much easier than finding 30 min. Prior to these 2 studies, no conclusive baseline had been identified with sufficient statistical power to show definitive health benefits [9].

Runners in this study were usually more motivated and had fewer risk factors such as smoking or obesity. By contrast, nonrunners had more comorbidities, such as diabetes or hypertension. Like most observational studies, the causality associated with their conclusion is not clear. Moreover, the results of Lee et al. [8] are consistent with findings from prospective randomized trials in secondary cardiovascular prevention that have shown a clear mortality benefit from regular exercise [10]. In this study, the researchers used statistical methods to control for confounders and performed sensitivity analyses

FIGURE 1 Comparison of Benefits Between Walking and Running

A 5-min run generates the same benefits as a 15-min walk, and a 25-min run is equivalent to a 105-min walk.



同樣運動量，

激烈運動比

中強度運動好很多，

兩倍以上。

鼓勵激烈運動。

	◆ 健走	◆ 跑步
◆ 辛苦度	輕鬆愉快	易喘、易累
◆ 所需時間	較長(如15分)	較短(如5分)
◆ 受傷	不易	膝蓋腰部較易受傷
◆ 運動後洗澡	不需要	需要
◆ 促進社交	可適用	不適用

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每天運動15分鐘 可多活3年

首見大型研究 顛覆過往建議 不限年齡、性別 懶人動一動 健康不是夢

【記者陳俐君／台北報導】每天快走或慢跑十五分鐘，就可多活三年。國家衛生研究院與國立台灣體育大學針對台灣民眾的大型研究，顛覆了國際間提倡每次運動卅分鐘、每周運動一百五十分鐘，以及國內的「運動三三三」建議。懶人量力動一動，延壽健康不是夢。

這篇昨天登在英國「刺胳針」（The Lancet）期刊網路版的論文，是由國衛院客座研究員暨中國醫藥大學名譽講座教授溫啓邦研究團隊，與體大教授衛沛文共同研究。分析一九九六年至二〇〇八年間，共四十一萬六千一百七十五人的健檢報告，每個個案平均追蹤八年。

研究團隊針對受訪者填寫的「健康問卷」，把個案分成不運動、低運動量、中運動量、高運動量與非常高運動量等五類，將各類組與「不運動組」進行危險比較，並算出平均餘命。

溫啓邦表示，比起不運動的人，每天運動十五分鐘者，平均壽命可多三年，癌症死亡風險少一成，心血管疾病死亡風險少兩成，總死亡率也降低了一成四。

另外，養成每天運動十五分鐘習慣者，運動量每增加十五分鐘，就可再減少百分之四至六的死亡率；相對地，不運動者的總死亡率高了一成七，但若願意改變生活習慣，開始每天運動十五分鐘，就能減少六分之一死亡率。

溫啓邦指出，每天運動十五分鐘的優點，不限年齡、性別，統統適用；對患有心血管疾病、代謝症候群等慢性疾病患者，或是吸菸、肥胖者，一樣有很好效果。他並提到，有每天運動卅分鐘習慣的吸菸者，總死亡率相當於不吸菸卻不運動者，因此除了戒菸，還要每天運動。

溫啓邦提到，國外已有不少研究證實，少於卅分鐘運動，有益健康，但首度進行大規模定量分析是第一次。他表示，國內廿五至四十四歲的青壯年最不愛運動，愛運動的馬總統，應號召全民培養運動習慣，每天十五分鐘，就能提升健康。 相關新聞見A5

日看6小時電視 少活5年

【編譯戴定國／報導】「英國運動醫學雜誌」刊出的澳洲研究指出，平均每天看電視六小時的人，因久坐不動影響健康，壽命可能縮短五年左右。

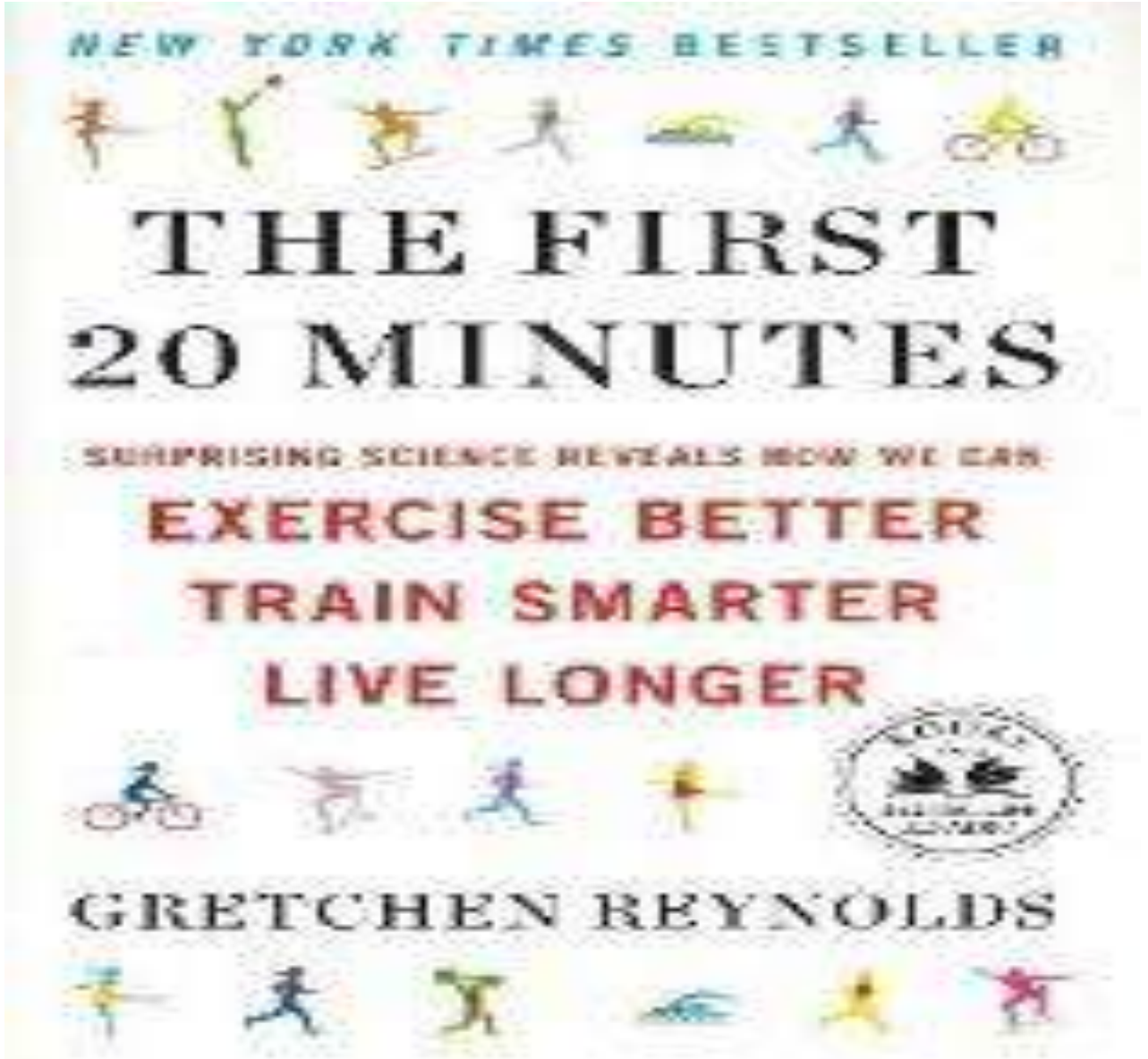
澳洲昆士蘭大學研究人員說，無論在發達國家或開發中國家，經常看電視可能已像抽菸和肥胖那樣，成爲一種公衛健康問題。經常看電視的人通常久坐不動，這種生活方式與多種高死亡風險相關，尤其是心臟病和中風。

研究人員在澳洲分析了一萬一千名廿五歲以上成人生活方式，發現每看電視一小時，會減壽廿二分鐘。把各種死因考慮在內，一個人平均每天看電視六小時，將減壽約五年。

曾有研究顯示，吸菸者的壽命比非吸菸者平均短約四年，換算起來每抽一根菸約減壽十一分鐘。換句話說，看電視一小時，對壽命的危害相當於抽兩根菸。

神奇的第一個十五分鐘

運動一刻值千金



DryLab 今年目標200
個人貢獻11+4

心跳的死亡風險比美高血壓，甚至還更大

- 1）肝功能SGOT偏高，減壽十年以上，比SGPT偏高重要太多。 (10.24),
- 2）蛋白尿的出現是洗腎的預兆 (25.34)(Lancet 糖尿病),
- 3）900萬人大資料，將腎病資料融入心血管的風險預測內 (新Lancet),
- 4) PAI 與死亡率(6.76),
- 5）**發炎指數與自殺的關係**(4.17),
- 6) 中風與吸菸之悖論(似非而是、看似矛盾)(7.19),

糞便潛血的檢查，比美大腸鏡，甚至還更好

- 台灣的菸害防制何去何從
- 7）按照世衛組織建議作法，急起直追，但是五十年後仍不能達標。(6.22)
- 8）台灣施行低菸價被煙商耍了。(6.22)
- 9）今日空污是新吸菸嗎?**(6.22)**
- 10）青少年吸電子煙是否刺激轉吸傳統菸?**(6.22)**
- 11)中國醫護人員新冠肺炎死亡率，隨時間遞減

肝功能
GOT與GPT
哪一個重要

AST(SGOT) vs. ALT(SGPT)重要

- 臨床醫師包括腸胃科都說

以肝病而言，

ALT(SGPT)比**AST(SGOT)重要，**

因為ALT(SGPT)是肝臟製造的

肝功能
GOT與GPT
哪一個重要

Am J of Gastroenterology

Impact Factor American Journal of Gastroenterology is 10.241,

AST(SGOT) 比 ALT(SGPT)重要

≧40 壽命短10年

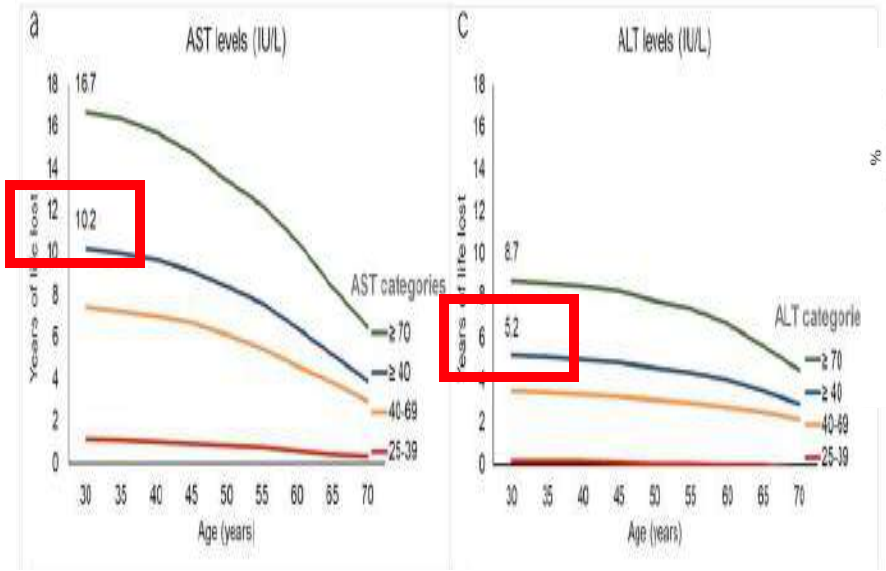
Those with elevated AST (≥40 IU/L) had life expectancy cut short by 10.2 years, doubled the number of years lost with elevated ALT. For all-cause and for liver-related mortality, AST was an important predictor, better than ALT.

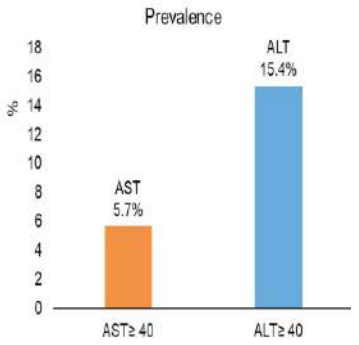
人數>40 I.U.

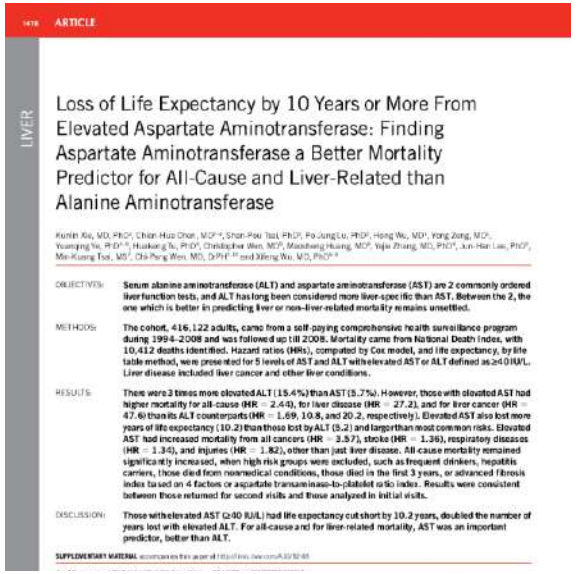
AST:5.7%

ALT: 15.4%

10.2 vs. 5.2







LIVER

ARTICLE

Loss of Life Expectancy by 10 Years or More From Elevated Aspartate Aminotransferase: Finding Aspartate Aminotransferase a Better Mortality Predictor for All-Cause and Liver-Related than Alanine Aminotransferase

Kunlin Xie, MD, PhD[1], Chien-Hua Chen, MD[2,3], Shan-Pou Tsai, PhD[4], Fa-Jung Lu, PhD[5], Hong Wu, MD[1], Yong Zang, MD[1], Yuanqing Ye, PhD[1,6], Huakang Tu, PhD[1], Christopher Wen, MD[4], Maosheng Huang, MD[4], Yaja Zhang, MD, PhD[4], Jun-Han Lee, PhD[4], Mei-Kuang Tsai, MS[7], Chi-Pang Wen, MD, DrPH[7,8] and Xifeng Wu, MD, PhD[1,9]

OBJECTIVES: Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are 2 commonly ordered liver function tests, and ALT has long been considered more liver-specific than AST. Between the 2, the one which is better in predicting liver or non-liver-related mortality remains unsettled.

METHODS: The cohort, 416,122 adults, came from a self-paying comprehensive health surveillance program during 1994-2008 and was followed up till 2008. Mortality came from National Death Index, with 10,412 deaths identified. Hazard ratios (HRs), computed by Cox model, and life expectancy, by life table method, were presented for 5 levels of AST and ALT with elevated AST or ALT defined as ≥40 IU/L. Liver disease included liver cancer and other liver conditions.

RESULTS: There were 2 times more elevated ALT (15.4%) than AST (5.7%). However, those with elevated AST had higher mortality for all-cause (HR = 2.44), for liver disease (HR = 27.2), and for liver cancer (HR = 47.6) than its ALT counterparts (HR = 1.69, 10.8, and 20.2, respectively). Elevated AST also lost more years of life expectancy (10.2) than those lost by ALT (5.2) and larger than most common risks. Elevated AST had increased mortality from all cancers (HR = 1.57), stroke (HR = 1.36), respiratory diseases (HR = 1.34), and injuries (HR = 1.82), other than just liver disease. All-cause mortality remained significantly increased, when high risk groups were excluded, such as frequent drinkers, hepatitis carriers, those died from nonmedical conditions, those died in the first 3 years, or advanced fibrosis index based on 4 factors or aspartate transaminase-to-platelet ratio index. Results were consistent between those returned for second visits and those analyzed in initial visits.

DISCUSSION: Those with elevated AST (≥40 IU/L) had life expectancy cut short by 10.2 years, doubled the number of years lost with elevated ALT. For all-cause and for liver-related mortality, AST was an important predictor, better than ALT.

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/B148

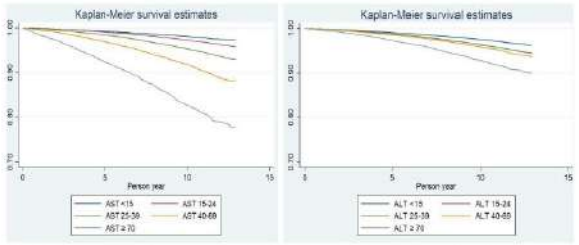


Figure 2. Kaplan-Meier survival curves for all-cause mortality by AST (left) and ALT (right) levels. ALT, alanine aminotransferase; AST, aspartate aminotransferase.

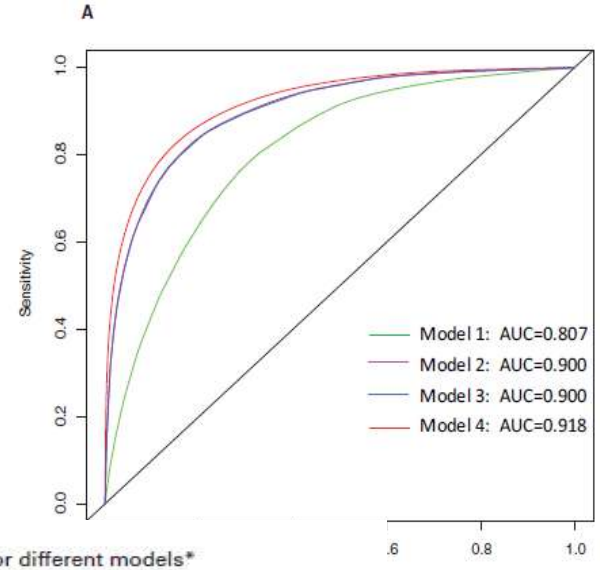


Table 3. The goodness of fit for different models*

10-year risk prediction	C-index (95% CI) Subcohort without HCV test	Subcohort with HCV test
Model 1—Health history		
Full dataset	0.810 (0.799 to 0.822)	0.798 (0.772 to 0.815)
Training set	0.813 (0.802 to 0.829)	0.783 (0.764 to 0.801)
Validation set	0.809 (0.798 to 0.820)	0.817 (0.797 to 0.836)
Model 2—Transaminase only		
Full dataset	0.903 (0.887 to 0.912)	0.914 (0.901 to 0.937)
Training set	0.904 (0.896 to 0.921)	0.915 (0.903 to 0.935)
Validation set	0.902 (0.892 to 0.916)	0.917 (0.903 to 0.938)
Model 3—Transaminase and health history		
Full dataset	0.904 (0.892 to 0.922)	0.915 (0.903 to 0.936)
Training set	0.905 (0.894 to 0.926)	0.916 (0.905 to 0.939)
Validation set	0.903 (0.889 to 0.917)	0.915 (0.904 to 0.936)
Model 4—Transaminase, health history, AFP, and HBV		
Full dataset	0.923 (0.910 to 0.939)	0.936 (0.913 to 0.958)
Training set	0.925 (0.913 to 0.942)	0.936 (0.911 to 0.960)
Validation set	0.922 (0.911 to 0.941)	0.941 (0.916 to 0.964)
Model 5—Transaminase, health history, AFP, HBV, and HCV		
Full dataset	—	0.941 (0.918 to 0.967)
Training set	—	0.942 (0.920 to 0.970)
Validation set	—	0.945 (0.928 to 0.975)

* The full dataset was split into half as the training and validation sets. C-index (measures model discriminatory accuracy) of each model was calculated to evaluate model goodness of fit in the full datasets, the training set, and the validation set . C-index = concordance index; CI = confidence

幾年前，已在JNCI發表AST、ALT可預測肝癌

AST 比 ALT 重要

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ARTICLE

Hepatocellular Carcinoma Risk Prediction Model for the General Population: The Predictive Power of Transaminases

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Background Risk prediction models for hepatocellular carcinoma are available for individuals with chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections who are at high risk but not for the general population with average or unknown risk. We developed five simple risk prediction models based on clinically available data from the general population.

Methods A prospective cohort of 428 584 subjects from a private health screening firm in Taiwan was divided into two subgroups—one with known HCV test results (n = 130 533 subjects) and the other without (n = 298 051 subjects). A total of 1668 incident hepatocellular carcinomas occurred during an average follow-up of 8.5 years. Model inputs included age, sex, health history–related variables; HBV or HCV infection–related variables; serum levels of alanine transaminase (ALT), aspartate transaminase (AST), and alfa-fetoprotein (AFP), as well as other variables of routine blood panels for liver function. Cox proportional hazards regression method was used to identify risk predictors of hepatocellular carcinoma. Receiver operating characteristic curves were used to assess discriminatory accuracy of the models. Models were internally validated. All statistical tests were two-sided.

Results Age, sex, health history, HBV and HCV status, and serum ALT, AST, AFP levels were statistically significant independent predictors of hepatocellular carcinoma risk (all $P < .05$). Use of serum transaminases only in a model showed a higher discrimination compared with HBV or HCV only (for transaminases, area under the curve [AUC] = 0.912, 95% confidence interval [CI] = 0.909 to 0.915; for HBV, AUC = 0.840, 95% CI = 0.833 to 0.848; and for HCV, AUC = 0.841, 95% CI = 0.834 to 0.847). Adding HBV and HCV data to the transaminase-only model improved the discrimination (AUC = 0.933, 95% CI = 0.929 to 0.949). Internal validation showed high discriminatory accuracy and calibration of these models.

Conclusion Models with transaminase data were best able to predict hepatocellular carcinoma risk even among subjects with unknown or HBV- or HCV-negative infection status.

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Table 1. Characteristics of subjects in the subcohort without HCV test and risk factors identified for hepatocellular carcinoma

Characteristics	Total subjects, %	Incidence, No. (%)	Model 1 Health history HR (95% CI)	Model 2 Transaminase HR (95% CI)	Model 3 Transaminase and health history HR (95% CI)	Model 4 Transaminase, health history, AFP, and HBV HR (95% CI)
Sex						
Female	52.2	390 (0.25)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
Male	47.8	862 (0.60)	1.79(1.54 to 2.07)	1.93 (1.71 to 2.19)	1.54 (1.33 to 1.79)	1.38 (1.19 to 1.61)
Age at baseline, y						
20–29	55.5	116 (0.07)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
40–59	31.8	479 (0.52)	6.66 (5.43 to 8.17)	5.34 (4.35 to 6.56)	5.24 (4.26 to 6.43)	5.28 (4.28 to 6.51)
≥60	12.7	595 (1.63)	19.06 (15.60 to 23.40)	13.71 (11.20 to 16.8)	13.46 (10.90 to 16.50)	14.85 (12.00 to 18.40)
Smoking, pack-year						
0	71.5	664 (0.31)	1.00 (referent)	—	1.00 (referent)	1.00 (referent)
1–9.9	13.9	196 (0.47)	1.35 (1.13 to1.61)	—	1.36 (1.14 to 1.63)	1.19 (0.99 to 1.42)
≥10	14.6	392 (0.90)	1.32 (1.13 to1.55)	—	1.39 (1.19 to 1.62)	1.38 (1.18 to 1.62)
Drinking†						
None or occasional	84.2	872 (0.35)	1.00 (referent)	—	1.00 (referent)	1.00 (referent)
Regular	15.8	380 (0.81)	1.56 (1.36 to 1.79)	—	1.2 (1.05 to 1.39)	1.26 (1.09 to 1.45)
Physical activity, MET-hour‡						
<3.75	52.6	634 (0.40)	1.00 (referent)	—	1.00 (referent)	1.00 (referent)
3.75–7.49	22.5	232 (0.35)	0.82 (0.70 to 0.95)	—	0.90 (0.77 to 1.06)	0.96 (0.82 to 1.12)
≥7.5	24.9	376 (0.51)	0.74 (0.65 to 0.84)	—	0.87 (0.77 to 1.00)	0.87 (0.76 to 0.99)
Diabetes						
No	96.9	1111 (0.38)	1.00 (referent)	—	1.00 (referent)	1.00 (referent)
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	33 (1.11 to 1.60)	1.34 (1.11 to 1.62)
AST, IU/L						
<25	77.0	213 (0.09)	—	1.00 (referent)	00 (referent)	1.00 (referent)
25–39	17.8	365 (0.69)	—	3.93 (3.21 to 4.83)	.00 (3.25 to 4.91)	3.31 (2.69 to 4.08)
40–59	3.3	260 (2.66)	—	14.58 (11.50 to 18.40)	1.43 (11.4 to 18.3)	8.51 (6.68 to 10.8)
≥60	1.9	413 (7.43)	—	39.58 (31.60 to 49.60)	3.34 (30.6 to 48.1)	10.92 (8.55 to 13.9)
ALT, IU/L						
<25	67.2	238 (0.12)	—	1.00 (referent)	00 (referent)	1.00 (referent)
≥25	32.8	1013 (1.04)	—	1.93 (1.71 to 2.19)	.47 (1.21 to 1.79)	1.29 (1.05 to 1.57)
AFP, ng/mL						
<2.5	51.8	183 (0.12)	—	—	—	1.00 (referent)
2.5–4.9	40.6	416 (0.35)	—	—	—	1.56 (1.30 to 1.87)
5.0–9.9	6.7	296 (1.49)	—	—	—	4.29 (3.52 to 5.22)
≥10.0	0.9	345 (13.24)	—	—	—	15.20 (12.30 to 18.90)
HBV						
Negative	84.3	615 (0.25)	—	—	—	1.00 (referent)
Positive	15.7	637 (1.38)	—	—	—	3.40 (3.00 to 3.84)

Table 2. Adjusted mortality risks of serum AST (IU/L), with 15–24 as reference, by all-cause and selected cause-specific deaths

Cause of death	Total deaths	<15			15–24		25–39			40–69			≥70			≥40			P trend
		Deaths	HR	95% CI	Deaths	HR	Deaths	HR	95% CI	Deaths	HR	95% CI	Deaths	HR	95% CI	Deaths	HR	95% CI	
All-cause mortality	10,412	484	1.39	(1.27, 1.53)	5,148	1.00	2,934	1.12	(1.07, 1.17)	1,088	1.96	(1.84, 2.10)	758	3.79	(3.51, 4.10)	1,846	2.44	(2.31, 2.58)	***
Liver disease, including liver cancer	1,365	4	0.36	(0.13, 0.97)	154	1.00	353	4.75	(3.92, 5.74)	414	26.72	(22.14, 32.25)	430	73.15	(60.55, 88.38)	844	39.18	(36.85, 46.72)	***
Non-liver disease	9,057	480	1.43	(1.30, 1.57)	4,994	1.00	2,581	1.01	(0.96, 1.06)	674	1.24	(1.15, 1.35)	328	1.70	(1.52, 1.91)	1,002	1.36	(1.27, 1.46)	***
Cancer	4,240	170	1.27	(1.09, 1.49)	1,974	1.00	1,146	1.18	(1.10, 1.27)	550	2.81	(2.55, 3.09)	400	5.75	(5.15, 6.41)	950	3.57	(3.30, 3.87)	***
Liver cancer	912	2	0.32	(0.08, 1.29)	91	1.00	233	5.26	(4.11, 6.71)	297	33.13	(26.09, 42.06)	289	88.10	(69.23, 112.13)	586	47.57	(37.95, 59.62)	***
Non-liver cancer	3,328	168	1.33	(1.13, 1.56)	1,883	1.00	913	0.99	(0.91, 1.07)	253	1.36	(1.19, 1.55)	111	1.71	(1.41, 2.07)	364	1.45	(1.29, 1.62)	***
Lung cancer	890	48	1.50	(1.11, 2.02)	532	1.00	223	0.82	(0.70, 0.96)	60	1.14	(0.87, 1.48)	27	1.45	(0.98, 2.14)	87	1.21	(0.96, 1.52)	0.74
Colon cancer	435	24	1.43	(0.93, 2.18)	254	1.00	106	0.84	(0.67, 1.06)	37	1.43	(1.01, 2.02)	14	1.58	(0.92, 2.72)	51	1.46	(1.08, 1.99)	0.18
Stomach cancer	273	14	1.29	(0.74, 2.24)	176	1.00	69	0.77	(0.58, 1.02)	11	0.63	(0.34, 1.16)	3	0.50	(0.16, 1.57)	14	0.60	(0.35, 1.04)	*
Breast cancer (women)	169	15	1.06	(0.61, 1.85)	101	1.00	43	1.52	(1.05, 2.20)	8	1.23	(0.59, 2.55)	2	0.84	(0.21, 3.42)	10	1.10	(0.56, 2.16)	0.18

Supplemental table 2. Adjusted mortality risks of ALT (IU/L), with 15-24 as reference, by all-cause and selected causes specific deaths for total cohort, male and female

Cause of death	<15			15-24		25-39			40-69			≥ 70			≥ 4			P trend
	Deaths	HR	95% CI	Deaths	HR	Deaths	HR	95% CI	Deaths	HR	95% CI	Deaths	HR	95% CI	Death	HR	95% CI	
All-cause mortality	2,160	1.19	(1.13 ,1.26)	3,823	1.00	2,200	1.04	(0.98 ,1.09)	1,261	1.36	(1.27 ,1.45)	968	2.39	(2.22 ,2.57)	2,22	1.69	(1.60 ,1.78)	***
Liver disease	50	0.59	(0.43 ,0.81)	163	1.00	298	3.48	(2.87 ,4.23)	379	10.18	(8.44 ,12.28)	465	28.44	(23.70 ,34.14)	84	16.13	(13.57 ,19.18)	***
Non-liver disease	2,110	1.24	(1.17 ,1.31)	3,660	1.00	1,902	0.93	(0.88 ,0.98)	882	0.98	(0.91 ,1.05)	503	1.28	(1.16 ,1.41)	1,38	1.07	(1.00 ,1.14)	**
Cancer	809	1.13	(1.04 ,1.23)	1,462	1.00	893	1.14	(1.05 ,1.24)	556	1.68	(1.52 ,1.85)	520	3.62	(3.26 ,4.01)	1,07	2.28	(2.10 ,2.48)	***
Liver cancer	25	0.53	(0.34 ,0.83)	95	1.00	210	4.29	(3.36 ,5.49)	245	11.83	(9.29 ,15.08)	337	37.06	(29.35 ,46.81)	58	20.21	16.16 ,25.28)	***
Non-liver cancer	784	1.18	(1.08 ,1.29)	1,367	1.00	683	0.93	(0.84 ,1.02)	311	0.99	(0.87 ,1.12)	183	1.35	(1.16 ,1.58)	49	1.09	(0.98 ,1.22)	*

1) AST **每增一單位，壽命減少2個月**
始自25單位
2) **運動**可防止減壽

Table 2. Adjusted mortality risks of serum AST (IU/L), with 15–24 as reference, by all-cause and selected cause-specific deaths

Cause of death	Total deaths	<15 Deaths	<15 HR	<15 95% CI	15–24 Deaths	15–24 HR	25–39 Deaths	25–39 HR	25–39 95% CI	40–69 Deaths	40–69 HR	40–69 95% CI	≥70 Deaths	≥70 HR	≥70 95% CI	≥40 Deaths	≥40 HR	≥40 95% CI	Ptrend
All-cause mortality	10,412	484	1.39	(1.27, 1.53)	5,148	1.00	2,934	1.12	(1.07, 1.17)	1,088	1.95	(1.84, 2.10)	758	3.79	(3.51, 4.10)	1,846	2.44	(2.31, 2.58)	***
Liver disease, including liver cancer	1,355	4	0.36	(0.13, 0.97)	154	1.00	353	4.75	(3.92, 5.74)	414	26.72	(22.14, 32.25)	430	73.15	(60.65, 88.36)	844	39.18	(32.85, 46.72)	***
Non-liver disease	9,057	480	1.43	(1.30, 1.57)	4,994	1.00	2,581	1.01	(0.96, 1.06)	674	1.24	(1.16, 1.35)	328	1.70	(1.52, 1.91)	1,002	1.36	(1.27, 1.45)	***
Cancer	4,240	170	1.27	(1.06, 1.49)	1,974	1.00	1,145	1.18	(1.10, 1.27)	550	2.81	(2.56, 3.09)	420	5.76	(5.15, 6.41)	970	3.57	(3.30, 3.87)	***
Liver cancer	912	2	0.32	(0.08, 1.29)	91	1.00	233	5.26	(4.11, 6.71)	297	33.13	(26.09, 42.06)	280	88.10	(69.33, 112.12)	586	47.57	(37.95, 59.62)	***
Non-liver cancer	3,328	168	1.33	(1.13, 1.56)	1,883	1.00	913	0.99	(0.91, 1.07)	253	1.36	(1.19, 1.55)	111	1.71	(1.41, 2.07)	364	1.45	(1.29, 1.62)	***
Lung cancer	890	48	1.50	(1.11, 2.02)	532	1.00	223	0.82	(0.70, 0.96)	60	1.14	(0.87, 1.48)	27	1.45	(0.98, 2.14)	87	1.21	(0.96, 1.52)	0.74
Colon cancer	435	24	1.43	(0.93, 2.18)	254	1.00	106	0.84	(0.67, 1.06)	37	1.43	(1.01, 2.02)	14	1.58	(0.92, 2.72)	51	1.46	(1.08, 1.99)	0.18
Stomach cancer	273	14	1.29	(0.74, 2.24)	176	1.00	69	0.77	(0.58, 1.02)	11	0.63	(0.34, 1.15)	3	0.50	(0.16, 1.57)	14	0.60	(0.35, 1.04)	*
Breast cancer (women)	169	15	1.06	(0.61, 1.85)	101	1.00	43	1.52	(1.05, 2.20)	8	1.23	(0.59, 2.55)	2	0.84	(0.21, 3.42)	10	1.10	(0.56, 2.16)	0.18
Diabetes	628	64	2.18	(1.72, 2.77)	344	1.00	134	0.60	(0.48, 0.76)	51	0.68	(0.48, 0.97)	35	3.90	(3.02, 5.02)	86	1.04	(0.81, 1.34)	0.25
Cardiovascular disease	2,001	83	1.30	(1.04, 1.62)	1,097	1.00	622	1.04	(0.94, 1.15)	143	1.10	(0.92, 1.31)	56	1.25	(0.95, 1.64)	199	1.13	(0.97, 1.32)	0.07
Ischemic heart	568	23	1.14	(0.76, 1.75)	328	1.00	164	0.91	(0.75, 1.10)	30	0.75	(0.52, 1.10)	13	0.94	(0.54, 1.64)	43	0.81	(0.58, 1.11)	0.17
Stroke	830	32	1.25	(0.87, 1.79)	442	1.00	259	1.07	(0.92, 1.25)	71	1.38	(1.07, 1.77)	26	1.41	(0.94, 2.11)	97	1.36	(1.08, 1.70)	**
Respiratory system	601	23	1.42	(0.93, 2.18)	313	1.00	207	1.14	(0.96, 1.36)	36	1.10	(0.78, 1.56)	22	1.93	(1.26, 2.99)	58	1.34	(1.01, 1.77)	*
Genitourinary system	331	31	2.75	(1.86, 4.06)	167	1.00	97	1.07	(0.83, 1.37)	28	1.38	(0.92, 2.07)	8	1.12	(0.55, 2.29)	36	1.30	(0.90, 1.87)	0.21
Acute/chronic liver disease	443	2	0.40	(0.10, 1.66)	63	1.00	120	4.02	(2.96, 5.47)	117	17.66	(12.93, 24.12)	141	51.97	(38.17, 70.76)	258	27.24	(20.49, 36.21)	***
Injury	644	28	1.08	(0.70, 1.52)	345	1.00	183	1.10	(0.92, 1.32)	57	1.58	(1.19, 2.10)	31	2.40	(1.65, 3.49)	88	1.82	(1.43, 2.32)	***
Suicide	286	19	0.97	(0.60, 1.58)	157	1.00	79	1.25	(0.95, 1.65)	14	1.08	(0.59, 1.79)	7	1.45	(0.68, 3.11)	21	1.19	(0.75, 1.90)	0.23

Adjusted for 11 variables: age, sex, education, body mass index, smoking status, drinking status, physical activity, hypertension, diabetes, fibrosis index 4, and aspartate transaminase-to-platelet ratio index.
AST, aspartate aminotransferase; CI, confidence index.
*$P<0.05$. **$P<0.01$; ***$P<0.001$.

WHAT IS KNOWN

- ALT and AST are indicators of liver dysfunction. We previously showed that transaminases were the strongest predictors in the integrative risk prediction model for hepatocellular carcinoma development. The associated all-cause mortality and life-shortening effects of transaminases from liver and non-liver causes have not been well studied.

WHAT IS NEW HERE

- There is a J-shape relationship between aminotransferase and all-cause mortality.
- Participants with AST ≥ 40 IU/L showed a loss of life expectancy of 10.2 years, with <15–24 IU/L as reference. There is a linear relationship with reversed longevity, with a 2-month shortening for every unit above 25 IU/L. For AST, the causes of excess mortality included liver diseases, cancers, and stroke. In comparison, elevated ALT was contributed mainly from liver, with loss of life expectancy less than half of that from elevated AST.
- Physical activity attenuated the loss of life years due to elevated serum transaminases.

DryLab 今年目標200
個人貢獻11+4

心跳的死亡風險比美高血壓，甚至還更大

- 1）肝功能SGOT偏高，減壽十年以上，比SGPT偏高重要太多。 (10.24),
- 2）蛋白尿的出現是洗腎的預兆 (25.34)(Lancet 糖尿病),
- 3）900萬人大資料，將腎病資料融入心血管的風險預測內 (新Lancet),
- 4) PAI 與死亡率(6.76),
- 5）發炎指數與自殺的關係(4.17),
- 6) 中風與吸菸之悖論(似非而是、看似矛盾)(7.19),

糞便潛血的檢查，比美大腸鏡，甚至還更好

- 台灣的菸害防制何去何從
- 7）按照世衛組織建議作法，急起直追，但是五十年後仍不能達標。(6.22)
- 8）台灣施行低菸價被煙商耍了。(6.22)
- 9）今日空污是新吸菸嗎?(6.22)
- 10）青少年吸電子煙是否刺激轉吸傳統菸?(6.22)
- 11)中國醫護人員新冠肺炎死亡率，隨時間遞減

Change in albuminuria and subsequent risk of end-stage kidney disease: an individual participant-level consortium meta-analysis of observational studies

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Summary

Background Change in albuminuria as a surrogate endpoint for progression of chronic kidney disease is strongly supported by biological plausibility, but empirical evidence to support its validity in epidemiological studies is lacking. We aimed to assess the consistency of the association between change in albuminuria and risk of end-stage kidney disease in a large individual participant-level meta-analysis of observational studies.

Methods In this meta-analysis, we collected individual-level data from eligible cohorts in the Chronic Kidney Disease Prognosis Consortium (CKD-PC) with data on serum creatinine and change in albuminuria and more than 50 events on outcomes of interest. Cohort data were eligible if participants were aged 18 years or older, they had a repeated measure of albuminuria during an elapsed period of 8 months to 4 years, subsequent end-stage kidney disease or mortality follow-up data, and the cohort was active during this consortium phase. We extracted participant-level data and quantified percentage change in albuminuria, measured as change in urine albumin-to-creatinine ratio (ACR) or urine protein-to-creatinine ratio (PCR), during baseline periods of 1, 2, and 3 years. Our primary outcome of interest was development of end-stage kidney disease after a baseline period of 2 years. We defined an end-stage kidney disease event as initiation of kidney replacement therapy. We quantified associations of percentage change in albuminuria with subsequent end-stage kidney disease using Cox regression in each cohort, followed by random-effects meta-analysis. We further adjusted for regression dilution to account for imprecision in the estimation of albuminuria at the participant level. We did multiple subgroup analyses, and also repeated our analyses using participant-level data from 14 clinical trials, including nine clinical trials not in CKD-PC.

Findings Between July, 2015, and June, 2018, we transferred and analysed data from 28 cohorts in the CKD-PC, which included 693 816 individuals (557 583 [80%] with diabetes). Data for 675 904 individuals and 7461 end-stage kidney disease events were available for our primary outcome analysis. Change in ACR was consistently associated with subsequent risk of end-stage kidney disease. The adjusted hazard ratio (HR) for end-stage kidney disease after a 30% decrease in ACR during a baseline period of 2 years was 0·83 (95% CI 0·74–0·94), decreasing to 0·78 (0·66–0·92) after further adjustment for regression dilution. Adjusted HRs were fairly consistent across cohorts and subgroups (ie, estimated glomerular filtration rate, diabetes, and sex), but the association was somewhat stronger among participants with higher baseline ACR than among those with lower baseline ACR ($p_{interaction}<0·0001$). In individuals with baseline ACR of 300 mg/g or higher, a 30% decrease in ACR over 2 years was estimated to confer a more than 1% absolute reduction in 10-year risk of end-stage kidney disease, even at early stages of chronic kidney disease. Results were generally similar when we used change in PCR and when study populations from clinical trials were assessed.

Interpretation Change in albuminuria was consistently associated with subsequent risk of end-stage kidney disease across a range of cohorts, lending support to the use of change in albuminuria as a surrogate endpoint for end-stage kidney disease in clinical trials of progression of chronic kidney disease in the setting of increased albuminuria.

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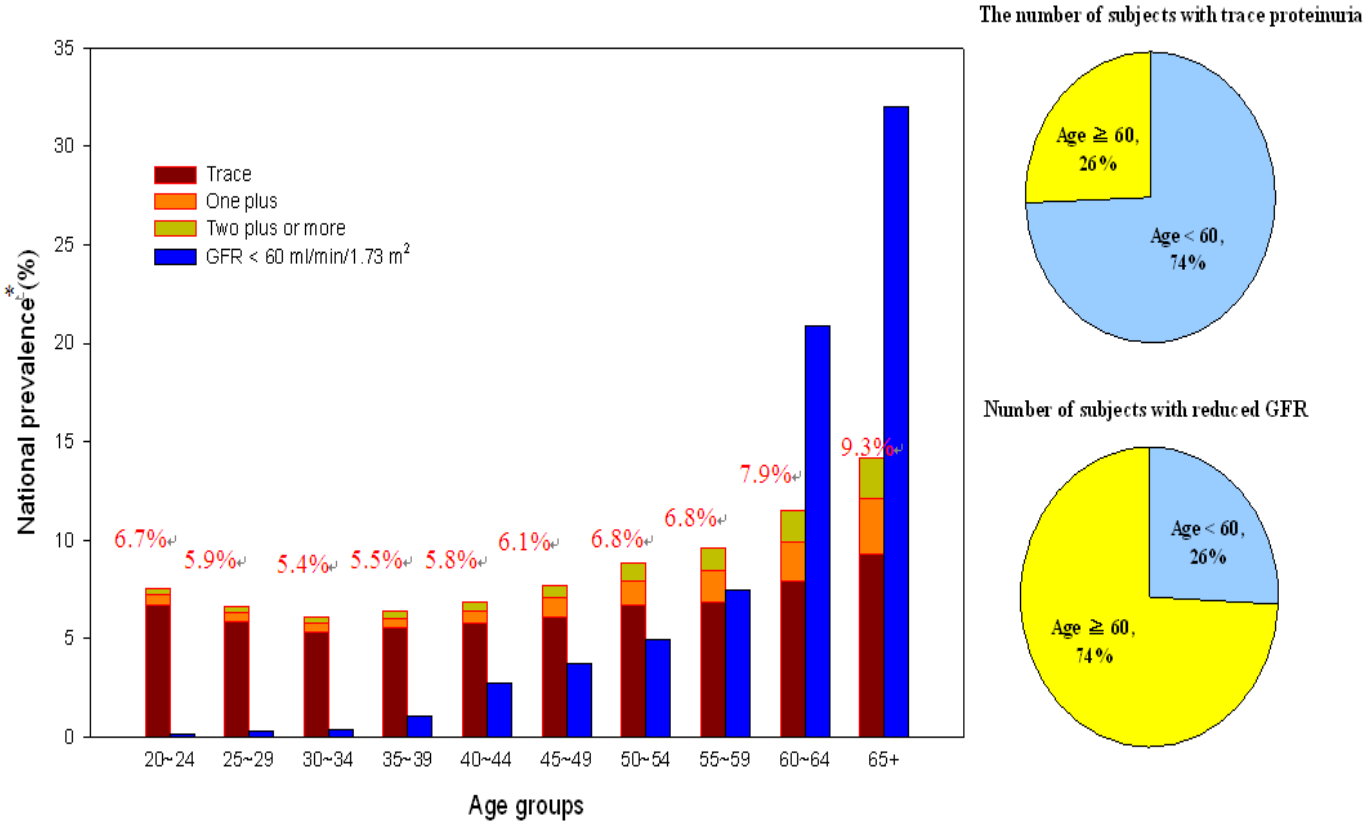
蛋白尿的出现是洗肾的预兆

- 28 cohort

- 共693,816人
- 洗肾7461人

GFR異常隨年齡增加而增加

蛋白尿不然



年輕人蛋白尿不少，

大部分不知

- 少量蛋白尿，在臨床上根本不引起注意

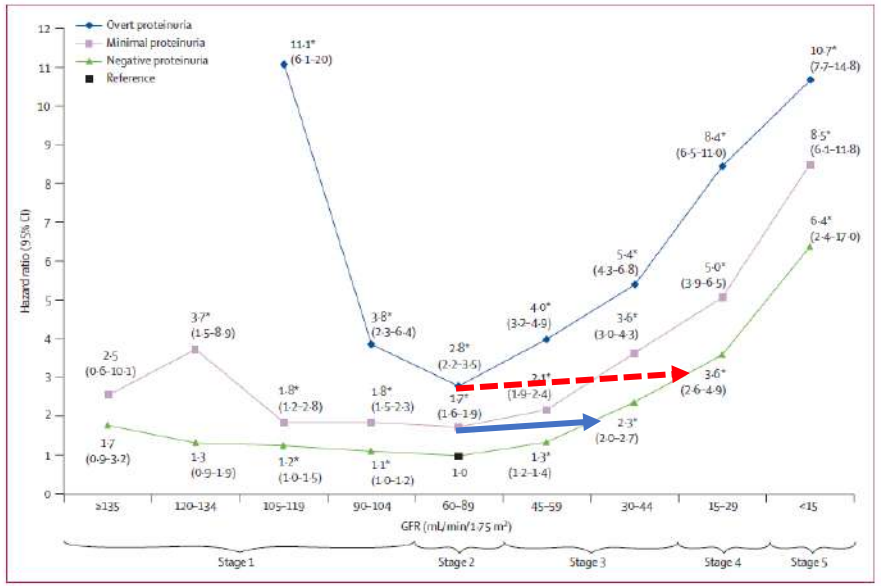


Figure 4: **Hazard ratios for all-cause mortality by stages of chronic kidney disease in cohort participants**
For the hazard ratios, comparison was made with participants with negative urine protein and glomerular filtration rate (GFR) between 60 and 89 mL/min/1·73 m² as reference group, by adjustment for age, sex, smoking, systolic blood pressure, triglyceride, glucose, body-mass index, and cholesterol in a multivariate Cox model

- 蛋白尿穩定增加CKD的死亡率
- Macro 相當於 Stage 4 CKD
  - 2+ or more
- Micro 相當於 Stage 3b CKD
  - Trace + 1+

Trace 蠅量蛋白尿

洗腎風險增4-50倍

減壽七歲

試紙驗尿蛋白
Dipstick

			Male			Female	
92%	Negative (-)	92.1%	1.00 (reference)	1.00 (reference)	92.9%	1.00 (reference)	1.00 (reference)
8%	Trace (±) or Positive (≥1+)	7.9%	2.11 (2.02-2.20)*	2.01 (1.90-2.13)*	7.1%	2.44 (2.31-2.58)*	2.18 (2.02-2.35)*
6%	Trace (±)	5.9%	1.72 (1.62-1.82)*	1.69 (1.57-1.81)*	5.3%	1.80 (1.67-1.95)*	1.73 (1.57-1.91)*
1%	Positive (1+)	1.3%	2.23 (2.05-2.42)*	2.33 (2.07-2.63)*	1.1%	2.72 (2.47-2.99)*	2.34 (2.02-2.71)*
1%	Positive (≥2+)	0.8%	3.74 (3.44-4.07)*	3.89 (3.47-4.36)*	0.7%	4.61 (4.18-5.08)*	4.91 (4.26-5.65)*

Dipstick

試紙驗尿蛋白

在家醫科很重要

腎科醫師看不起

Dipstick試紙

- 1) 馬上有結果
- 2) 九成結果是陰性
- 3) 費用低廉可篩檢健康大眾

ACR定量

Albumin Creatinine Ratio

- 1)等實驗室的報告
- 2) 九成結果是陰性，ACR 白做了
- 3) 費用高，不能篩檢健康大眾

腎科醫師看不起

dipstick試紙驗尿蛋白

但預測死亡卻很類似

ACR

試紙驗尿蛋白

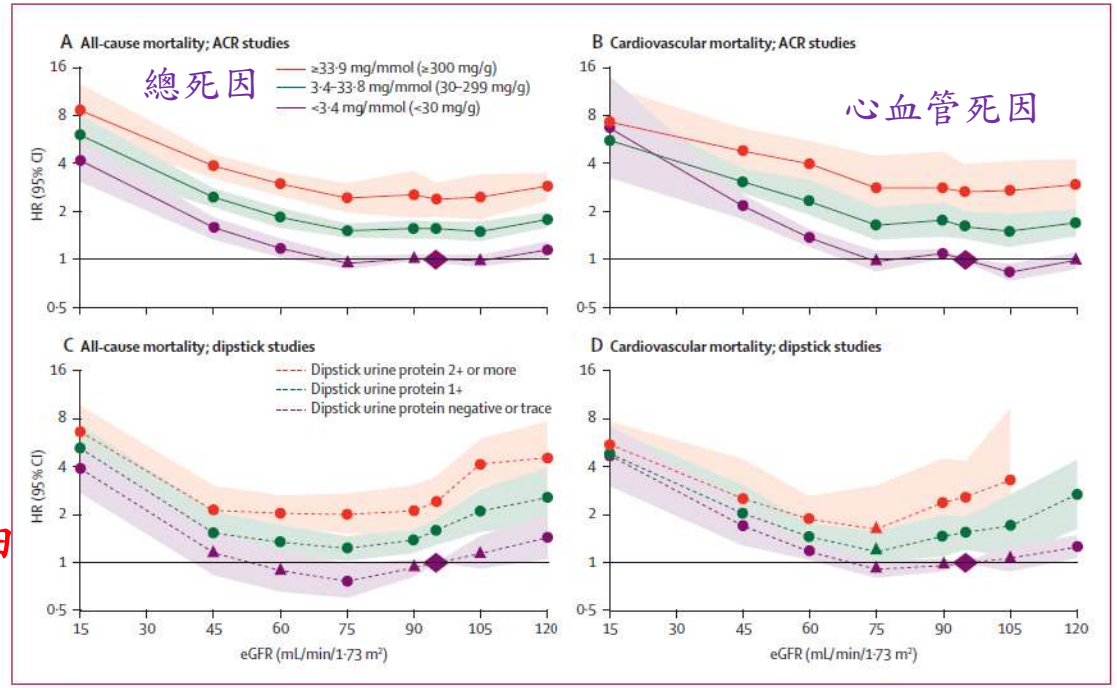


Figure 3: **Hazard ratios and 95% CIs for all-cause and cardiovascular mortality according to spline estimated glomerular filtration rate (eGFR) and categorical albuminuria**

Shaded areas represent 95% CIs. Models included spline eGFR, categorical albuminuria, and their interaction terms as well as adjustment for age, sex, ethnic origin, history of cardiovascular disease, systolic blood pressure, diabetes, smoking, and total cholesterol. The reference (diamond) was eGFR 95 mL/min/1·73 m² plus ACR less than 3·4 mg/mmol (30 mg/g) or dipstick test result negative or trace. Circles represent statistically significant and triangles represent not significant. The estimated HR and 95% CI at eGFR 120 mL/min/1·73 m² with dipstick 2+ or more for cardiovascular mortality were omitted, since only two studies contributed to reliable estimation. To convert ACR in mg/g to mg/mmol multiply by 0·113.

蛋白尿的洗腎風險

Trace

洗腎風險

比沒蛋白尿

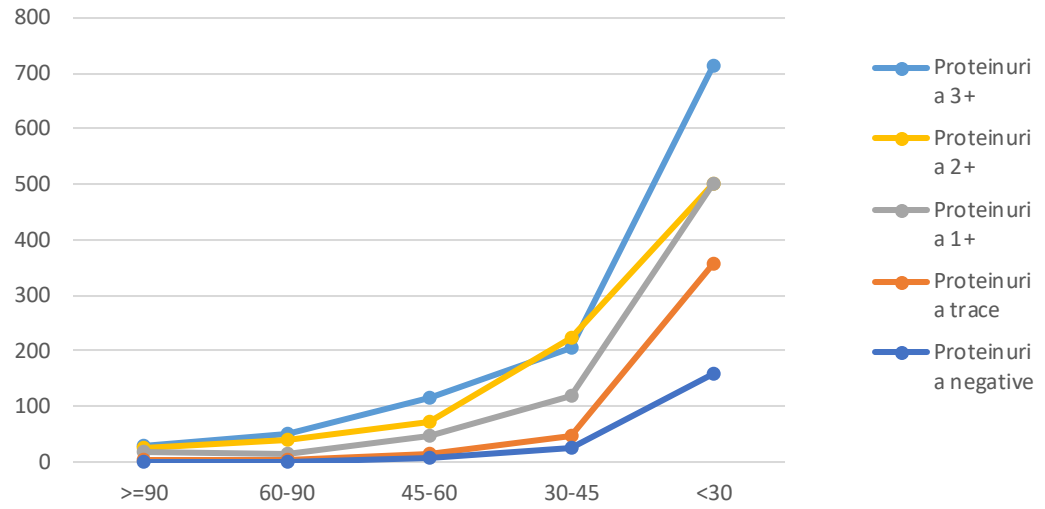
GFR

60-90 4 倍

45-60 17 倍

30-45 27 倍

<30 50 倍



	GFR											
	>=90			60-90			45-60			30-45			<30		
	HR	(95% CI)		HR	(95% CI)		HR	(95% CI)		HR	(95% CI)		HR	(95% CI)	
Proteinuria negative	1.00			1.34	(1.12,1.61)		5.48	(4.34,6.91)		23.40	(17.62,31.07)		151.42	(107.94,212.43)	
Proteinuria minimal	5.60	(4.36,7.19)		5.93	(4.81,7.31)		20.25	(15.89,25.80)		73.14	(56.98,93.89)		400.88	(316.58,507.64)	
Proteinuria overt	25.72	(17.48,37.86)		40.65	(31.74,52.05)		87.91	(67.55,114.42)		203.78	(158.41,262.15)		576.11	(457.56,725.37)	
Proteinuria negative	1.00			1.35	(1.13,1.62)		5.58	(4.43,7.05)		24.10	(18.15,32.02)		156.90	(111.81,220.16)	
Proteinuria trace	4.06	(3.02,5.44)		4.21	(3.32,5.35)		13.88	(10.36,18.59)		47.29	(33.80,66.17)		356.01	(267.66,473.54)	
	83			215			104			77			119		
Proteinuria 1+	17.77	(12.33,25.60)		15.89	(12.09,20.88)		45.20	(33.76,60.51)		119.68	(90.04,159.09)		500.60	(378.70,661.72)	
Proteinuria 2+	26.51	(17.08,41.14)		38.42	(28.72,51.38)		72.48	(50.95,103.11)		223.29	(165.30,301.62)		498.98	(372.84,667.80)	
Proteinuria 3+	27.11	(13.32,55.19)		49.69	(35.70,69.18)		113.29	(82.79,155.02)		206.07	(150.42,282.29)		714.65	(551.84,925.50)	

Appendix table 1. Hazard ratios (HR) for selected causes of death by proteinuria status for the entire cohort (n=464,709)

		Proteinuria status										
		Negative		Trace			1+			2+ or more		
Number of subjects		428,157		27,044			5,879			3,629		
Age-adjusted mortality rate per 100,000 person year		382		828			1,927			3,458		
Cause of death	ICD-9	Deaths	HR§	Deaths	HR§	95% CI	Deaths	HR§	95% CI	Deaths	HR§	95% CI
All causes	001-998	12,912	1	1,799	1.70*	(1.58,1.81)	1,015	2.31*	(2.07,2.58)	991	3.62*	(3.25,4.04)
All cancer	140-208	5,270	1	602	1.52*	(1.35,1.70)	268	1.97*	(1.61,2.41)	175	1.76*	(1.36,2.28)
Esophagus cancer食道癌	150	112	1	24	2.87*	(1.58,5.22)	5	2.92	(0.88,9.70)	2	0.98	(0.13,7.22)
Stomach cancer 胃癌	151	337	1	39	1.83*	(1.21,2.77)	16	1.21	(0.44,3.30)	13	1.88	(0.69,5.16)
Colorectal cancer 大腸癌	153-154	527	1	63	1.59*	(1.12,2.25)	25	1.64	(0.86,3.14)	13	1.01	(0.37,2.76)
Liver cancer 肝癌	155	1100	1	151	1.85*	(1.38,2.21)	65	3.21*	(2.18,4.55)	54	3.69*	(2.29,5.35)
Lung cancer 肺癌	162	1155	1	120	1.39*	(1.09,1.78)	47	1.46	(0.91,2.36)	26	1.21	(0.64,2.28)
Bladder cancer 膀胱癌	188	72	1	16	3.02*	(1.39,6.57)	10	6.71*	(2.45,18.39)	6	3.81	(0.86,16.90)
Kidney cancer 腎臟癌	189	82	1	12	2.74*	(1.37,5.49)	16	8.78*	(3.82,20.21)	7	4.01	(0.94,17.10)
Non-Hodgkin's lymphoma	200,202,203	197	1	26	1.36	(0.74,2.49)	10	0.98	(0.24,4.03)	4	1.56	(0.38,6.46)
Diabetes mellitus	250	619	1	165	1.97*	(1.53,2.53)	132	3.09*	(2.22,4.30)	212	9.14*	(7.06,11.84)
Cardiovascular disease	390-459	2,469	1	403	1.63*	(1.41,1.90)	251	2.17*	(1.72,2.74)	237	2.91*	(2.29,3.70)
Ischemic heart disease	410-414	658	1	112	1.48*	(1.11,1.98)	59	1.99*	(1.28,3.10)	72	3.53*	(2.35,5.29)
Cerebrovascular disease (Stroke)	430-438	1082	1	177	1.71*	(1.36,2.14)	118	2.19*	(1.53,3.13)	98	2.12*	(1.40,3.22)
Chronic obstructive pulmonary disease (COPD)	491-496	373	1	41	1.69*	(1.09,2.63)	29	2.10	(0.97,4.57)	14	2.37	(0.95,5.90)
Liver cirrhosis	571	468	1	94	2.92*	(2.36,4.29)	35	2.94*	(1.44,5.01)	28	2.38*	(0.95,4.97)
Kidney diseases	580-589	163	1	69	5.97*	(3.90,9.16)	86	19.16*	(11.97,30.66)	144	59.54*	(39.80,89.07)

Micro 相當於 GFR Stage 3b
Macro 相當於 GFR Stage 4

GFR

Normal
3a
3b
4

	ACR		Microalbuminuria	Macroalbuminuria
	<1·1 mg/mmol (<10 mg/g)	1·1–3·3 mg/mmol (10–29 mg/g)	3·4–33·8 mg/mmol (30–299 mg/g)	≥33·9 mg/mmol (≥300 mg/g)
All-cause mortality				
≥105 mL/min/1·73 m²	1·14 (1·02–1·27)	1·52 (1·28–1·81)	2·32 (2·00–2·70)	5·26 (2·80–9·85)
90–104 mL/min/1·73 m²	Reference	1·48 (1·29–1·69)	1·61 (1·39–1·87)	3·65 (2·13–6·27)
75–89 mL/min/1·73 m²	1·00 (0·91–1·09)	1·40 (1·26–1·55)	1·78 (1·58–2·01)	2·50 (1·89–3·31)
60–74 mL/min/1·73 m²	1·02 (0·92–1·15)	1·49 (1·34–1·66)	1·95 (1·67–2·27)	3·09 (2·56–3·72)
45–59 mL/min/1·73 m²	1·28 (1·05–1·57)	1·95 (1·73–2·20)	2·51 (2·16–2·90)	4·10 (3·39–4·95)
30–44 mL/min/1·73 m²	1·97 (1·59–2·43)	2·65 (2·19–3·22)	3·66 (2·91–4·60)	5·08 (4·20–6·15)
15–29 mL/min/1·73 m²	5·39 (3·30–8·80)	3·66 (2·43–5·50)	4·85 (3·26–7·21)	6·96 (5·28–9·19)
Cardiovascular mortality				
≥105 mL/min/1·73 m²	0·93 (0·74–1·16)	1·33 (1·04–1·72)	2·46 (1·88–3·23)	2·69 (1·36–5·32)
90–104 mL/min/1·73 m²	Reference	1·63 (1·20–2·19)	1·82 (1·36–2·45)	4·77 (3·16–7·22)
75–89 mL/min/1·73 m²	1·03 (0·85–1·24)	1·48 (1·23–1·78)	1·73 (1·29–2·32)	4·01 (2·62–6·14)
60–74 mL/min/1·73 m²	1·09 (0·92–1·29)	1·58 (1·31–1·91)	2·18 (1·58–3·02)	4·23 (2·95–6·06)
45–59 mL/min/1·73 m²	1·52 (1·18–1·97)	2·38 (1·91–2·96)	3·13 (2·32–4·22)	4·97 (3·70–6·66)
30–44 mL/min/1·73 m²	2·40 (1·80–3·21)	3·07 (1·73–5·44)	4·12 (2·84–5·98)	6·10 (4·08–9·10)
15–29 mL/min/1·73 m²	13·51 (4·89–37·35)	7·99 (1·95–32·81)	5·60 (3·66–8·57)	9·49 (4·97–18·10)

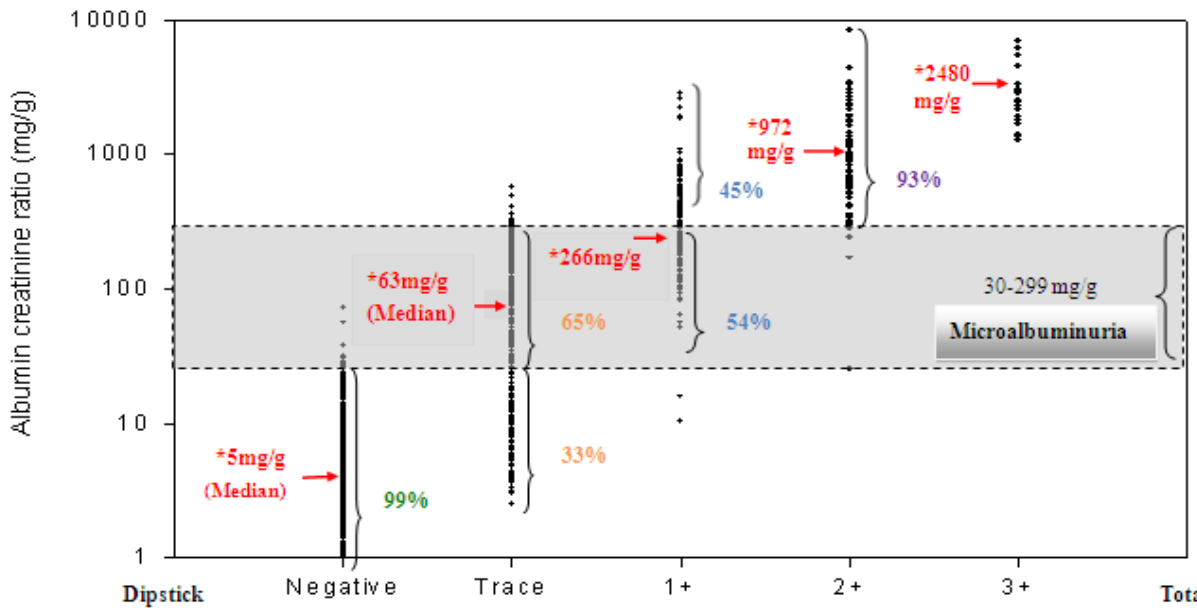
eGFR=estimated glomerular filtration rate. ACR=urine albumin-to-creatinine ratio. Hazard ratios and 95% CIs adjusted for age, ethnic origin, sex, history of cardiovascular disease, systolic blood pressure, diabetes, smoking, and total cholesterol concentration.

Table 2: Pooled estimates of adjusted hazard ratios (95% CI) for all-cause and cardiovascular mortality according to categories of eGFR (listed in the left column) and ACR

Table 1 Classification of proteinuria

Diagnostic test	Normal albuminuria	Microalbuminuria	Albuminuria	Proteinuria
24 hour urine albumin collection	<30 mg/24 hours	30–300 mg/24 hours	>300 mg/24 hours	>300 mg/24 hours
Spot urine dipstick	<30 mg/dL	N/A	>30 mg/dL	>30 mg/dL
Spot urine albumin to creatinine ratio	<17 mg/g (men) <25 mg/g (women) <2.5 mg/mmol (men) <3.5 mg/mmol (women) <30 ug/mg	17–250 mg/g (men) 25–355 mg/g (women) <35 mg/mmol 30–300 ug/mg	>250 mg/g (men) >355 mg/g (women) >35 mg/mmol >300 ug/mg	N/A
Spot urine protein to creatinine ratio	<200 mg/g <45 mg/mmol	N/A	N/A	>200 mg/g >45 mg/mmol

Figure2. Distribution of ACR by different urinary dipstick results in their relationships to microalbuminuria based on selected samples (N=1311).



	Negative	Trace	1+	2+	3+	Total
Tested samples	773	300	142	72	24	1311
Representing proportions of entire cohort	92.1%	5.8%	1.3%	0.5%	0.3%	100%
(actual number of subjects in the cohort)	(428,157)	(27,044)	(5,879)	(2,194)	(1,435)	(464,709)

Screening for Proteinuria in US Adults

A Cost-effectiveness Analysis

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Neil R. Powe, MD, MPH, MBA

Context Chronic kidney disease is a growing public health problem. Screening for early identification could improve health but could also lead to unnecessary harms and excess costs.

Objective To assess the value of periodic, population-based dipstick screening for early detection of urine protein in adults with neither hypertension nor diabetes and in adults with hypertension.

Design, Setting, and Population Cost-effectiveness analysis using a Markov decision analytic model to compare a strategy of annual screening with no screening (usual care) for proteinuria at age 50 years followed by treatment with an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin II-receptor blocker (ARB).

Main Outcome Measure Cost per quality-adjusted life-year (QALY).

Results For persons with neither hypertension nor diabetes, the cost-effectiveness ratio for screening vs no screening (usual care) was unfavorable ($282 818 per QALY; incremental cost of $616 and a gain of 0.0022 QALYs per person). However, screening such persons beginning at age 60 years yielded a more favorable ratio ($53 372 per QALY). For persons with hypertension, the ratio was highly favorable ($18 621 per QALY; incremental cost of $476 and a gain of 0.03 QALYs per person). Cost-effectiveness was mediated by both chronic kidney disease progression and death prevention benefits of ACE inhibitor and ARB therapy. Influential parameters that might make screening for the general population more cost-effective include a greater incidence of proteinuria, age at screening ($53 372 per QALY for persons beginning screening at age 60 years), or lower frequency of screening (every 10 years: $80 700 per QALY at age 50 years; $6195 per QALY at age 60 years; and $5486 per QALY at age 70 years).

Conclusions Early detection of urine protein to slow progression of chronic kidney disease and decrease mortality is not cost-effective unless selectively directed toward high-risk groups (older persons and persons with hypertension) or conducted at an infrequent interval of 10 years.

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CHRONIC KIDNEY DISEASE IS A growing public health problem. More than 10 million US adults have some kidney damage (serum creatinine levels ≥1.5 mg/dL [132.6 µmol/L]), and the number of persons with end-stage renal disease (ESRD) exceeds 300 000. Persons with ESRD, who have a poor quality of life and accrue high health care costs, are projected to exceed 600 000 in 2010.[1-4] Early identification and treatment of patients who are more likely to progress to ESRD to decrease mortality, morbidity, and costs associated with chronic kidney disease has been debated. Controversy exists because many patients do not progress to ESRD, however, the majority of those who do progress go undetected until it is too late to intervene.[5]

Growing evidence indicates that the presence of relatively low levels of urine protein can be an early marker of increased risk of progressive kidney disease, poor cardiovascular outcomes, and death.[6,7] Prescription of angiotensin-converting enzyme (ACE) inhibitor or angiotensin II-receptor blocker (ARB) therapy in persons with proteinuria and chronic kidney disease has been demonstrated to decrease both the progression of kidney disease toward ESRD as well the incidence of cardiovascular events and death.[6,8-12]

Dipstick urinalysis has imperfect accuracy in the diagnosis of persistent proteinuria, but it is an inexpensive test that can be performed in most medical settings.[13] For persons with diabetes, routine screening for urine protein has been shown to be cost-effective.[12,14-16] In contrast, although there is accruing evidence that the use of ACE inhibitor therapy decreases the incidence of death and slows clinical progression of disease for persons with chronic, nondiabetic proteinuric nephropathies, there is little evidence addressing the cost-effectiveness of routine screening.[9,10,17] It is not clear whether screening of the entire US adult population by physicians is warranted. If screening followed by the implementation of ACE inhibitor or ARB therapy were beneficial in slowing progression toward ESRD, patients could benefit from lengthened survival and im-

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AJKD

Editorial

Urine Dipstick to Detect Trace Proteinuria: An Underused Tool for an Underappreciated Risk Marker

Related Article, p. 19

In the medical evaluations of healthy individuals, urinalysis receives relatively little attention compared with blood work. However, one finding from the urinalysis, proteinuria, carries a risk far higher than many abnormalities identified from blood studies.[1-4] Even small quantities of albumin in the urine (an albumin-creatinine ratio [ACR] of 30-300 mg/g, often termed "microalbuminuria") is not only a sign of kidney damage,[5] but is also associated with an increased risk for cardiovascular diseases,[1] certain cancers,[6,7] and increased all-cause mortality.[1-3]

Although the classification of chronic kidney disease (CKD) in the 2002 publication of the National Kidney Foundation's KDOQI (Kidney Disease Outcome Quality Initiative) guidelines[5] established sustained albuminuria as a marker of kidney damage sufficient for the diagnosis of CKD, it is not clear who should be screened for proteinuria and what method of screening should be used. In a healthy population, nearly 9 out of 10 people have ACR < 30 mg/g.[1] Quantifying albuminuria by ACR is slow, cumbersome, and expensive. In contrast, dipstick screening for proteinuria is a simple, instantaneous laboratory test that can be easily performed in most medical offices. A major challenge for the prevention of CKD complications is limited awareness of CKD (more than 90% of CKD patients are unaware of their condition[3,8,9]), therefore a simpler screening test for kidney damage is an attractive way to improve detection and awareness. However, the dipstick test for proteinuria may be viewed as inadequate by many nephrologists, who prefer having ACR results. This reluctance to rely on urine dipstick testing for proteinuria is understandable given that few studies have evaluated urine dipstick testing in comparison with the gold standard of ACR.[10-12]

In this issue of the *American Journal of Kidney Diseases*, White et al[13] studied the relationship between urine dipstick and urine ACR by analyzing urine collected in 1999 and 2000 from 10,944 randomly selected Australian healthy adults from AusDiab (Australian Diabetes, Obesity and Lifestyle Study), which was designed to examine diabetes, heart disease, and kidney diseases. They report that a dipstick reading of 1+ or more was seen in nearly all of those with larger quantities of albumin in the urine (ACR above 300 mg/g, termed "macroalbuminuria"). However, the investigators did not find the 1+ cutoff in dipstick urinalysis sufficiently sensitive to detect urine ACR of 30-300 mg/g. Although the sensitivity of screening by dipstick urinalysis can be improved by decreasing the threshold for a positive test to a trace proteinuria reading, the authors caution that this increases the false-positive rate for detecting an ACR of 30-300 mg/g to nearly 73%. Although this point is important, the lack of outcome data for various dipstick results may have obscured the value of findings in the range of proteinuria equivalent to an ACR less than 30 mg/g.

Previous studies have shown that trace proteinuria by urine dipstick is a powerful predictor of mortality risk.[1] In a pooled meta-analysis of 1.1 million individuals with normal glomerular filtration rate (GFR), those with trace proteinuria had a hazard ratio of 1.78 for cardiovascular mortality and 1.44 for all-cause mortality.[1] The risks associated with trace proteinuria at a normal level of GFR were more similar to those for ACR of 10-29 mg/g than ACR of 30-300 mg/g. Figure 1 shows the relationship between all-cause mortality risk and proteinuria in a cohort of approximately 500,000 Taiwanese individuals.[3] This analysis, which was adjusted for 12 risk factors, fit a curvilinear line through hazard ratios associated with negative, trace, 1+, 2+, and 3+ dipstick results. The magnitude of the increased risk due to trace proteinuria (1.70) is approximately equivalent to the risk from smoking (1.55).[14] It is intriguing that detecting trace proteinuria in the office and obtaining history about smoking yield similar information about health risk. When trace and 1+ were considered together as mild proteinuria in a study investigating mortality risk in a Canadian cohort of nearly 1 million individuals, the all-cause mortality risk was 2.1,[15] a result similar to the large Taiwanese study.[3]

Three mechanisms may explain why the risks of trace proteinuria were so high in these studies. First, the median ACR corresponding to trace proteinuria was 65 mg/g in healthy adults in the Taiwanese data[3] and 48 mg/g in 2,321 community-based, healthy participants in Takahata, Japan.[13] Given the hazard ratios of 1.40 and 1.78 for ACRs of 10-29 and 30-299 mg/g,[1] respectively, the relative mortality risk of trace proteinuria of 1.44 (or 1.70 in Taiwan study; Fig 1)

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	Median		
Negative	5mg/g		
Trace:	63mg/g	20-150 mg/g	micro
1+:	266mg/g	150-400 mg/g	
2+:	972mg/g	400-1500 mg/g	
3+:	2480mg/g	>1500 mg/g	macro

試紙驗尿蛋白與ACR的關係

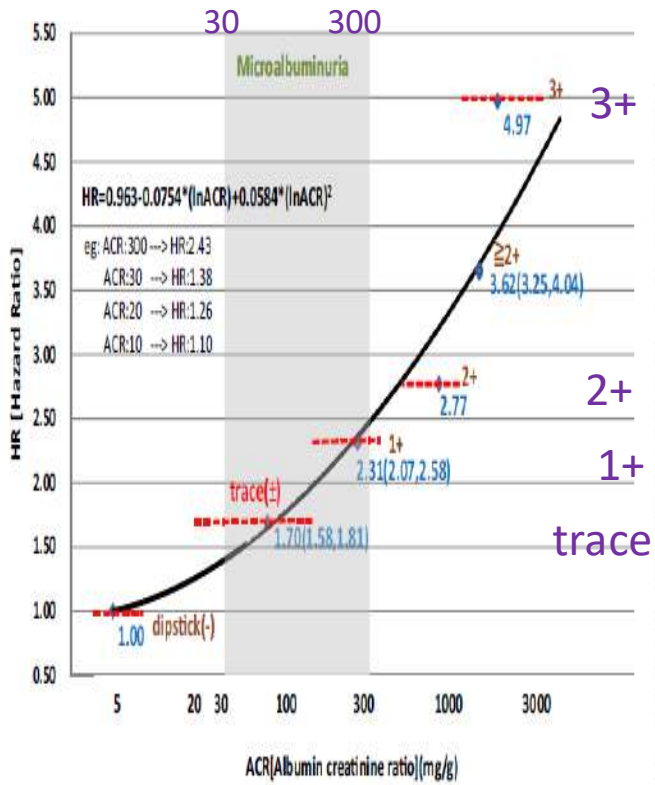


Figure 1. The dose-response relationship between albumin-creatinine ratio (ACR) and hazard ratio (HR) observed by fitting a curvilinear line through the 5 levels of all-cause mortality risk identified by dipstick testing in a Taiwanese cohort. The hazard ratios, adjusted for 12 risk factors, came from a cohort of 464,709 adults recruited since 1994, with ACR values additionally analyzed on a subset with dipstick results classified as negative (n = 773), trace proteinuria (n = 300), 1+ (n = 142), 2+ (n = 72), and 3+ (n = 24) in 2007. The age, sex, and educational distributions of individuals in each dipstick category in this subset have been tested and found to be grossly similar to those in the overall cohort. Dashed lines indicate 25th-75th percentiles of ACR. Source: Wen et al.[3]

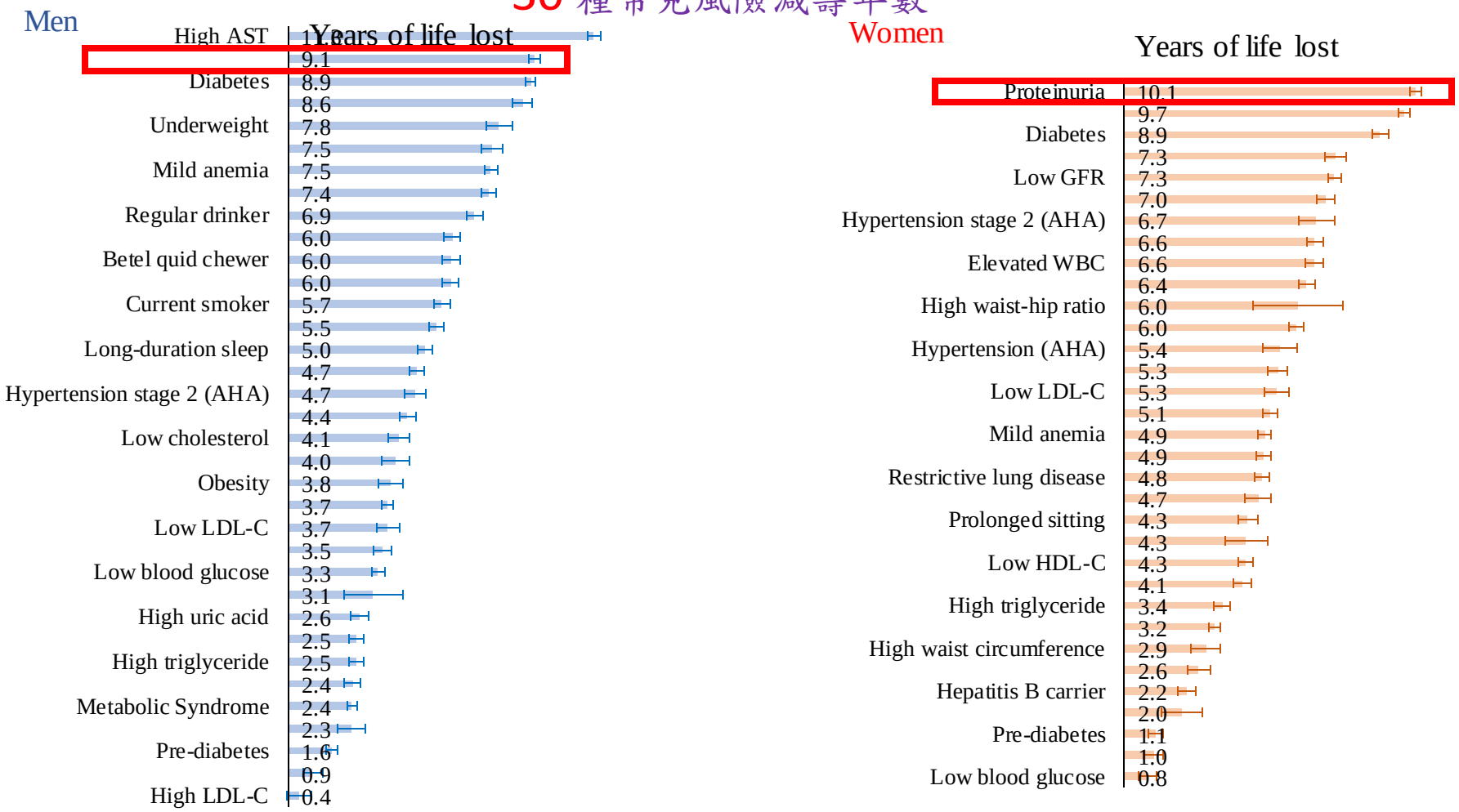
3+

2+

1+

trace

30 種常見風險減壽年數



從減壽年數
死亡率
GFR下降與蛋白尿
誰較嚴重?

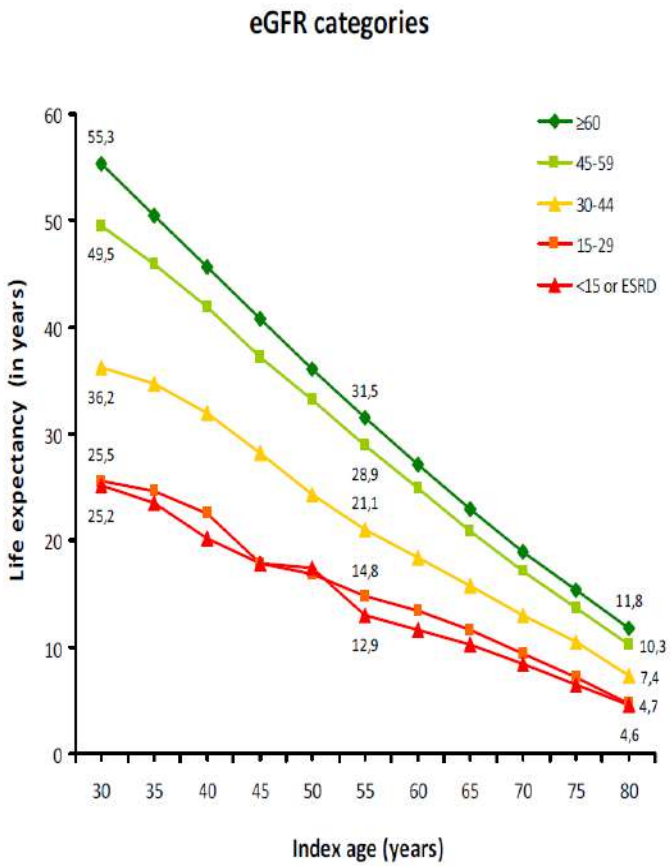
- 台灣
- CKD減壽年數

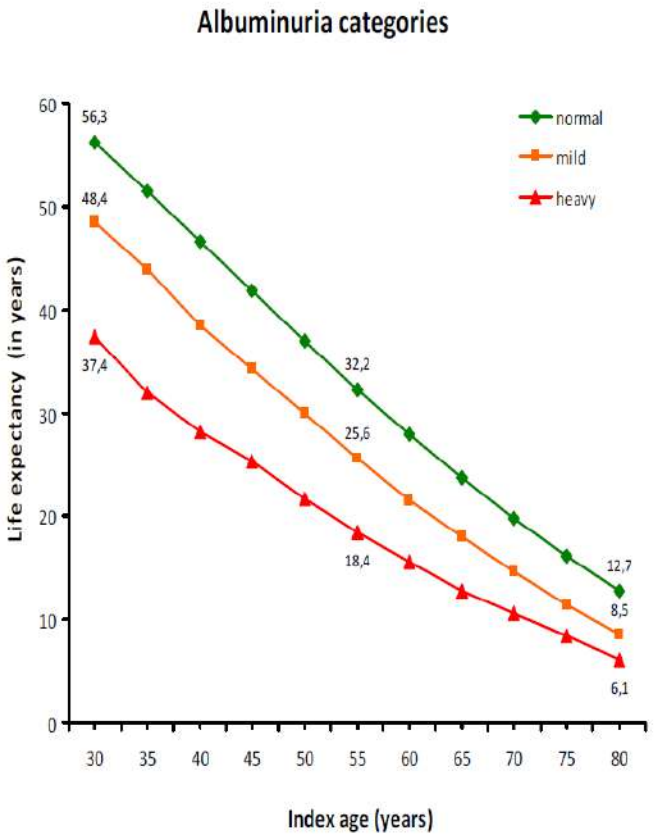
- GFR<60 5.5歲
- HR=1.39-1.84
- 蛋白尿 9.6歲
- (trace - 3+)
- HR=2.01-2.18

- 加拿大

	Normal	Mild (30-300)	Heavy (>300)
GFR >60		8.6	14.3
3a GFR 45-59	3.0	12.3	16.2
3b GFR 30-44	16.6	18.2	18.2
4 GFR 15-29	26.8		

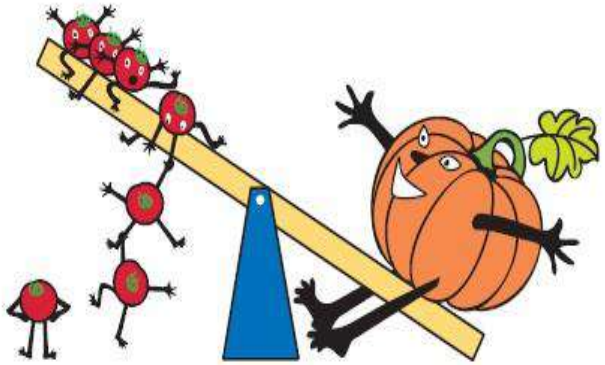
蛋白尿有無，壽命差19歲





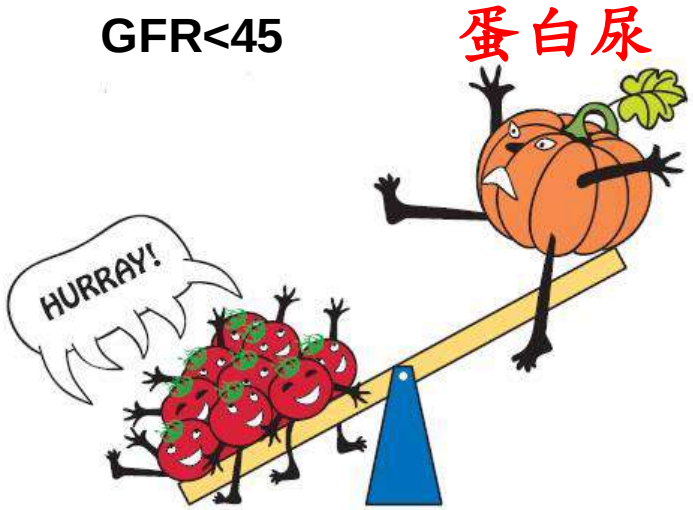
GFR<60

蛋白尿



GFR<45

蛋白尿

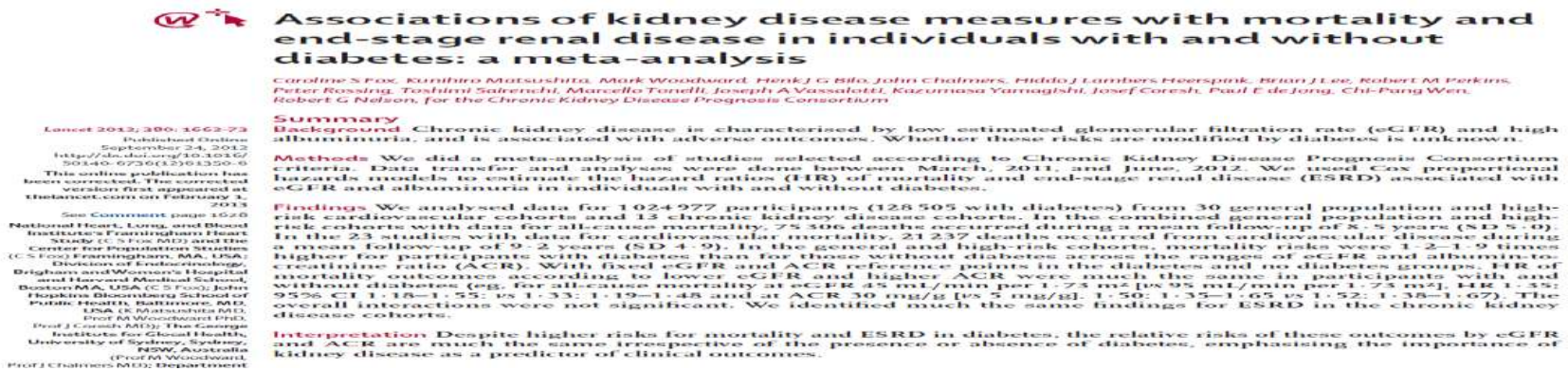


論文 第二篇

蛋白尿的改善
可代表洗腎風險減少

慢性腎臟病 (CKD) 在台灣 **202萬人(11.9%)**

分期	定義	人口	認知	每年死亡人數
慢性腎臟病	有蛋白尿 或GFR < 60	202萬人 (11.9%)	3.5%	14,000人
第一期	GFR ≧90 有蛋白尿	17萬人(1.0%)	2.7%	1,500人
第二期	GFR 60~89 有蛋白尿	65萬人(3.8%)	2.7%	4,000人
第三期	GFR 30-59	115萬人(6.8%)	4.1%	6,400人
3a	GFR 45-59	101萬人(6.0%)	4.7%	4,600人
3b	GFR 30-44	14萬人(0.8%)	3.8%	1,800人
第四期	GFR 15-29	37,000人(0.2%)	23.7%	1,300人
				1,100人



Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis

Caroline S Fox, Kunihiro Matsushita, Mark Woodward, Henk J G Bilo, John Chalmers, Hiddo J Lambers Heerspink, Brian J Lee, Robert M Perkins, Peter Rossing, Toshimi Sairenchi, Marcello Tonelli, Joseph A Vassalotti, Kazumasa Yamagishi, Josef Coresh, Paul E de Jong, Chi-Pang Wen, Robert G Nelson, for the Chronic Kidney Disease Prognosis Consortium

Summary

Background Chronic kidney disease is characterised by low estimated glomerular filtration rate (eGFR) and high albuminuria, and is associated with adverse outcomes. Whether these risks are modified by diabetes is unknown.

Methods We did a meta-analysis of studies selected according to Chronic Kidney Disease Prognosis Consortium criteria. Data transfer and analyses were done between March, 2011, and June, 2012. We used Cox proportional hazards models to estimate the hazard ratios (HR) of mortality and end-stage renal disease (ESRD) associated with eGFR and albuminuria in individuals with and without diabetes.

Findings We analysed data for 1 024 977 participants (128 505 with diabetes) from 30 general population and high-risk cardiovascular cohorts and 13 chronic kidney disease cohorts. In the combined general population and high-risk cohorts with data for all-cause mortality, 75 346 deaths occurred during a mean follow-up of 8·5 years (SD 3·9). In the 23 studies with data for cardiovascular mortality, 21 237 deaths occurred from cardiovascular disease during a mean follow-up of 9·2 years (SD 4·9). In the general and high-risk cohorts, mortality risks were 1·2–1·9 times higher for participants with diabetes than for those without diabetes across the ranges of eGFR and albumin-to-creatinine ratio (ACR). With fixed eGFR and ACR reference points in the diabetes and no diabetes groups, HR of mortality outcomes according to lower eGFR and higher ACR were much the same in participants with and without diabetes (eg, for all-cause mortality at eGFR 45 ml/min per 1·73 m² [vs 95 ml/min per 1·73 m²], HR 1·35; 95% CI 1·18–1·55; vs 1·33; 1·19–1·48 and at ACR 30 mg/g [vs 5 mg/g], 1·50; 1·35–1·65 vs 1·52; 1·38–1·67). The overall interactions were not significant. We identified much the same findings for ESRD in the chronic kidney disease cohorts.

Interpretation Despite higher risks for mortality and ESRD in diabetes, the relative risks of these outcomes by eGFR and ACR are much the same irrespective of the presence or absence of diabetes, emphasising the importance of kidney disease as a predictor of clinical outcomes.

- ***The Lancet Diabetes & Endocrinology***
  2019;7(2), 115-127.

重複檢測蛋白尿的重要

- 改善蛋白尿30% (2 years)；
  - 不論30 mg/g
  - 300 mg/g
  - 600 mg/g
- 洗腎減少20% (0.83-0.79)

	Individuals with diabetes					Individuals without diabetes				
	ACR <10, PCR <15, or dipstick negative	ACR 10–29, PCR 15–49, or dipstick trace	ACR 30–299, PCR 50–499, or dipstick 1+	ACR ≥300, PCR ≥500, or dipstick ≥2+	Overall	ACR <10, PCR <15, or dipstick negative	ACR 10–29, PCR 15–49, or dipstick trace	ACR 30–299, PCR 50–499, or dipstick 1+	ACR ≥300, PCR ≥500, or dipstick ≥2+	Overall
All-cause mortality										
eGFR ≥105	1·27*; 1·07–1·51	1·58*; 1·29–1·94	2·43*; 1·90–3·11	4·38*; 2·97–6·46	1·21*; 1·06–1·39	1·27*; 1·14–1·41	1·62*; 1·35–1·96	2·39*; 1·93–2·82	5·40*; 3·33–8·76	1·20*; 1·12–1·30
eGFR 90–104	Reference	1·41*; 1·24–1·59	1·73*; 1·45–2·05	2·95*; 2·22–3·91	Reference	Reference	1·47*; 1·32–1·64	1·82*; 1·64–2·03	3·23*; 2·39–4·37	Reference
eGFR 75–89	0·94; 0·87–1·01	1·33*; 1·16–1·54	1·59*; 1·35–1·87	1·42*; 1·89–3·11	0·95; 0·90–1·01	0·94; 0·89–1·00	1·30*; 1·18–1·44	1·60*; 1·40–1·84	2·57*; 1·98–3·34	0·94*; 0·90–0·98
eGFR 60–74	0·99; 0·92–1·07	1·32*†; 1·16–1·49	1·86*; 1·60–2·16	2·98*; 2·36–3·76	1·04; 0·97–1·12	1·01; 0·95–1·09	1·38*†; 1·20–1·59	1·86*; 1·64–2·12	2·41*; 1·88–3·10	1·01; 0·95–1·07
eGFR 45–59	1·15*; 1·01–1·30	1·82*; 1·60–2·07	1·97*; 1·66–2·35	3·23*; 2·53–4·15	1·18*†; 1·07–1·30	1·22*; 1·09–1·35	1·70*; 1·49–1·93	2·10*; 1·75–2·53	3·15*; 2·44–4·06	1·19*†; 1·10–1·29
eGFR 30–44	1·81*; 1·35–2·44	2·25*; 1·87–2·70	3·13*; 2·57–3·80	4·61*; 3·64–5·84	1·65*; 1·48–1·83	1·71*; 1·44–2·02	2·54*; 2·26–2·86	1·89*; 1·31–3·61	4·00*; 2·92–5·48	1·53*; 1·36–1·73
eGFR 15–29	2·69*; 1·78–4·06	3·30*; 2·43–4·46	4·96*; 3·19–7·72	6·80*; 4·76–9·70	2·28*; 1·91–2·72	3·16*; 2·25–4·45	4·01*; 2·86–5·62	3·90*; 2·93–5·20	6·69*; 4·94–9·08	2·27*; 1·86–2·77
eGFR <15	12·0*; 3·02–47·6	5·88*; 2·43–14·2	9·55*; 4·53–20·1	14·5*; 8·84–23·8	4·46*; 3·26–6·10	6·55*; 3·53–12·1	8·56*; 5·73–12·8	6·91*; 4·67–10·2	12·0*; 8·84–16·4	4·06*; 3·33–4·95
Overall	Reference	1·35*; 1·27–1·44	1·72*; 1·61–1·86	2·67*; 2·31–3·08	-	Reference	1·31*; 1·23–1·41	1·67*; 1·54–1·82	2·38*; 2·07–2·75	-
Cardiovascular mortality										

DryLab 今年目標200
個人貢獻11+4

心跳的死亡風險比美高血壓，

甚至還更大

- 1）肝功能SGOT偏高，減壽十年以上，比SGPT偏高重要太多。 (10.24),
- 2）蛋白尿的出現是洗腎的預兆 (25.34)(Lancet 糖尿病),
- 3）900萬人大資料，將腎病資料融入心血管的風險預測內 (新Lancet),
- 4) PAI 與死亡率(6.76),
- **5）發炎指數與自殺的關係**(4.17),
- 6) 中風與吸菸之悖論(似非而是、看似矛盾)(7.19),

糞便潛血的檢查，比美大腸鏡，

甚至還更好

- 台灣的菸害防制何去何從
- 7）按照世衛組織建議作法，急起直追，但是五十年後仍不能達標。(6.22)
- 8）台灣施行低菸價被煙商耍了。(6.22)
- 9）今日空污是新吸菸嗎?**(6.22)**
- 10）青少年吸電子煙是否刺激轉吸傳統菸?**(6.22)**
- 11)中國醫護人員新冠肺炎死亡率，隨時間遞減

900萬人大資料，將腎病資料融入心血管的風險預測內

EClinicalMedicine 27 (2020) 100552

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journal homepage: https://www.journals.elsevier.com/eclinicalmedicine

Research Paper

Incorporating kidney disease measures into cardiovascular risk prediction: Development and validation in 9 million adults from 72 datasets

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Chronic kidney disease
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risk prediction
meta-analysis

ABSTRACT

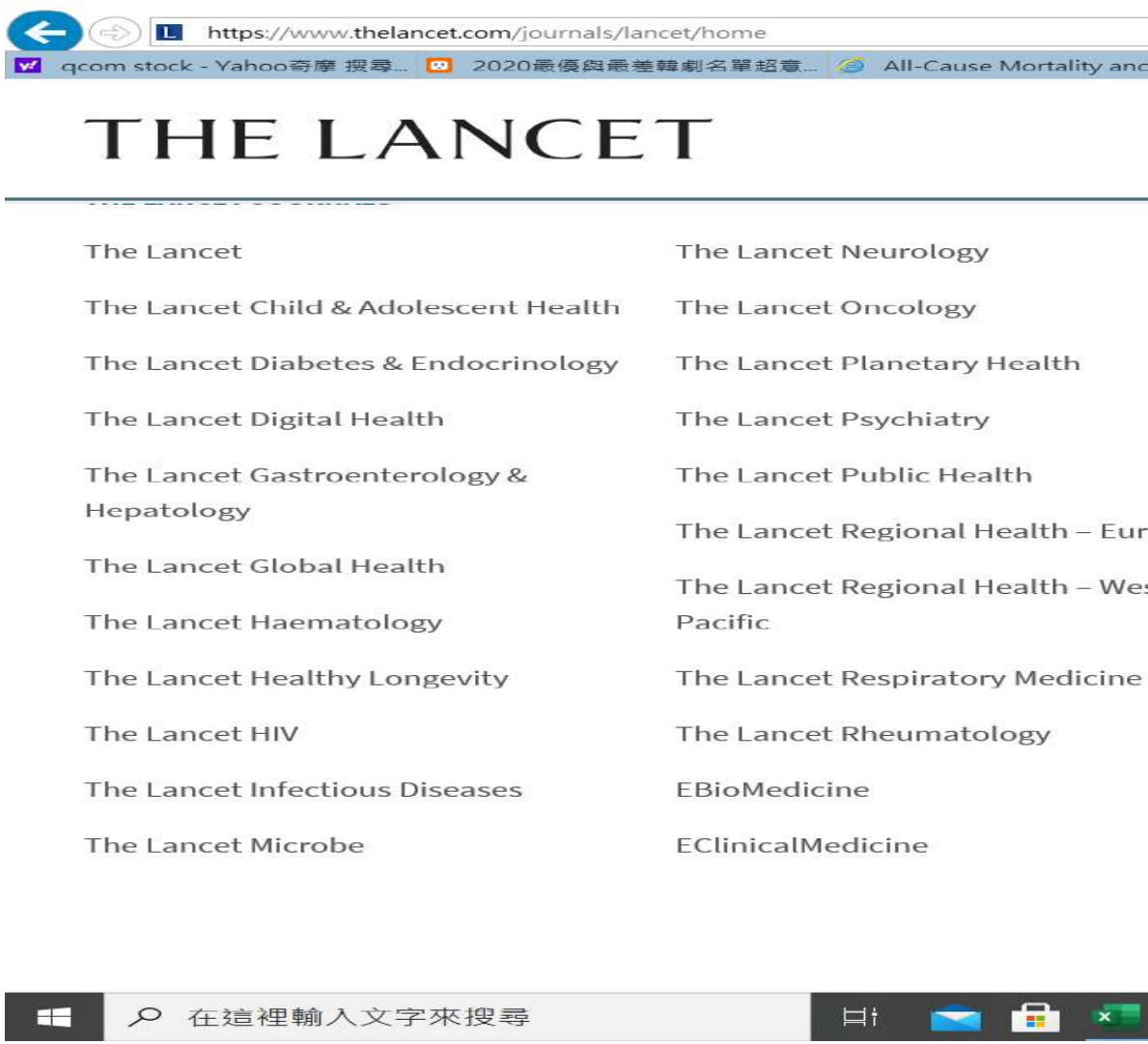
Background: Chronic kidney disease (CKD) measures (estimated glomerular filtration rate [eGFR] and albuminuria) are frequently assessed in clinical practice and improve the prediction of incident cardiovascular disease (CVD), yet most major clinical guidelines do not have a standardized approach for incorporating these measures into CVD risk prediction. "CKD Patch" is a validated method to calibrate and improve the predicted risk from established equations according to CKD measures.

Methods: Utilizing data from 4,143,535 adults from 35 datasets, we developed several "CKD Patches" incorporating eGFR and albuminuria, to enhance prediction of risk of atherosclerotic CVD (ASCVD) by the Pooled Cohort Equation (PCE) and CVD mortality by Systematic COronary Risk Evaluation (SCORE). The risk enhancement by CKD Patch was determined by the deviation between individual CKD measures and the values expected from their traditional CVD risk factors and the hazard ratios for eGFR and albuminuria. We then validated this approach among 4,932,824 adults from 37 independent datasets, comparing the original PCE and SCORE equations (recalibrated in each dataset) to those with addition of CKD Patch.

Findings: We confirmed the prediction improvement with the CKD Patch for CVD mortality beyond SCORE and ASCVD beyond PCE in validation datasets (Δc-statistic 0.027 [95% CI 0.018–0.036] and 0.010 [0.007–0.013] and categorical net reclassification improvement 0.080 [0.032–0.127] and 0.056 [0.044–0.067], respectively). The median (IQI) of the ratio of predicted risk for CVD mortality with CKD Patch vs. the original prediction with SCORE was 2.64 (1.89–3.40) in very high-risk CKD (e.g., eGFR 30–44 ml/min/1.73m^2 with albuminuria ≥30 mg/g), 1.86 (1.48–2.44) in high-risk CKD (e.g., eGFR 45–59 ml/min/1.73m^2 with albuminuria 30–299 mg/g), and 1.37 (1.14–1.69) in moderate risk CKD (e.g., eGFR 60–89 ml/min/1.73m^2 with albuminuria 30–299 mg/g), indicating considerable risk underestimation in CKD with SCORE. The corresponding estimates for ASCVD with PCE were 1.55 (1.37–1.81), 1.24 (1.10–1.54), and 1.21 (0.98–1.46).

Interpretation: The "CKD Patch" can be used to quantitatively enhance ASCVD and CVD mortality risk prediction equations recommended in major US and European guidelines according to CKD measures, when available.

Funding: US National Kidney Foundation and the NIDDK.



全民運動的
建議量

1995 以前

- 20-60 min/day 激烈運動

1995 以後

- 30 min/day 中強度運動
  - X5 day
- 150 min/week 中強度運動
- Or
- 25min/day 激烈運動
  - X3 day
- 75 min/week 激烈運動

- 問卷很難量化運動
  - 強度
  - 時間
  - 次數
- Moderate intensity 中強度
- Vigorous 激烈
- 少量
- 輕量
- 中量
- 重量

PAI Health

Personalized Activity Intelligence

手錶或手環

有量心跳的

- Garmin
- Fitbit
- Apple health
- Zepp
- Polar
- 小米

CLINICAL RESEARCH STUDY

THE AMERICAN JOURNAL of MEDICINE®

Personalized Activity Intelligence (PAI) for Prevention of Cardiovascular Disease and Promotion of Physical Activity

Bjarne M. Nes, PhD,[a] Christian R. Gutvik, PhD,[b] Carl J. Lavie, MD,[c] Javaid Nauman, PhD,[a,1] Ulrik Wisløff, PhD[a,d,1]

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ABSTRACT

PURPOSE: To derive and validate a single metric of activity tracking that associates with lower risk of cardiovascular disease mortality.

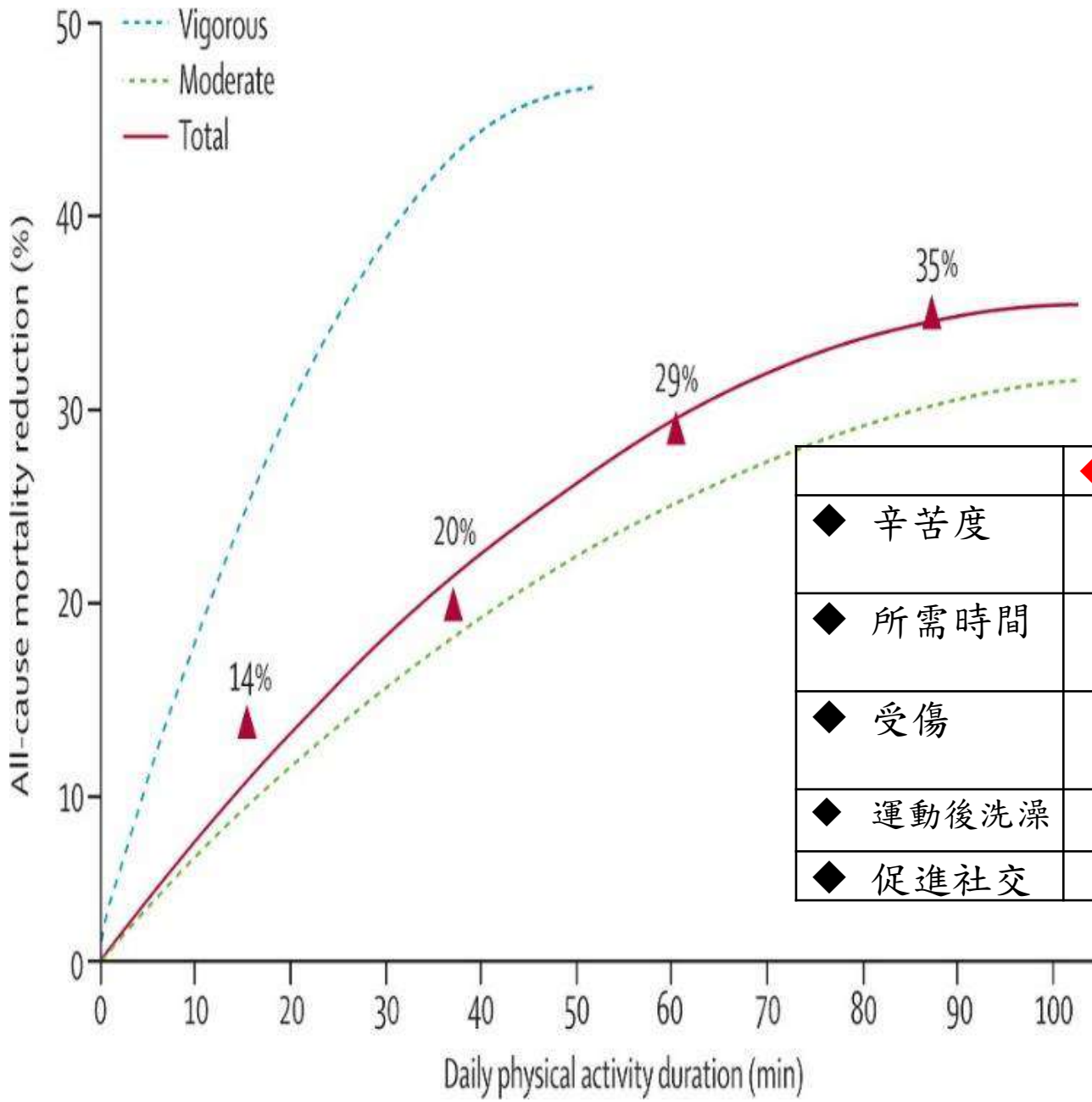
METHODS: We derived an algorithm, Personalized Activity Intelligence (PAI), using the HUNT Fitness Study (n = 4631), and validated it in the general HUNT population (n = 39,298) aged 20-74 years. The PAI was divided into three sex-specific groups (≤50, 51-99, and ≥100), and the inactive group (0 PAI) was used as the referent. Hazard ratios for all-cause and cardiovascular disease mortality were estimated using Cox proportional hazard regressions.

RESULTS: After >1 million person-years of observations during a mean follow-up time of 26.2 (SD 5.9) years, there were 10,062 deaths, including 3867 deaths (2207 men and 1660 women) from cardiovascular disease. Men and women with a PAI level ≥100 had 17% (95% confidence interval [CI], 7%-27%) and 23% (95% CI, 4%-38%) reduced risk of cardiovascular disease mortality, respectively, compared with the inactive groups. Obtaining ≥100 PAI was associated with significantly lower risk for cardiovascular disease mortality in all prespecified age groups, and in participants with known cardiovascular disease risk factors (all *P*-trends <.01). Participants who did not obtain ≥100 PAI had increased risk of dying regardless of meeting the physical activity recommendations.

CONCLUSION: PAI may have a huge potential to motivate people to become and stay physically active, as it is an easily understandable and scientifically proven metric that could inform potential users of how much physical activity is needed to reduce the risk of premature cardiovascular disease death.

 • The American Journal of Medicine (2017) 130, 328-336

KEYWORDS: Activity tracking; Cardiovascular disease mortality; Physical activity; Prevention



同樣運動量，
激烈運動比
中強度運動好很多，
兩倍以上。

鼓勵激烈運動。

	◆ 健走	◆ 跑步
◆ 辛苦度	輕鬆愉快	易喘、易累
◆ 所需時間	較長(如15分)	較短(如5分)
◆ 受傷	不易	膝蓋腰部較易受傷
◆ 運動後洗澡	不需要	需要
◆ 促進社交	可適用	不適用

PAI
你今天運動夠嗎?
超越步數、時間的算法

以心跳加速得分

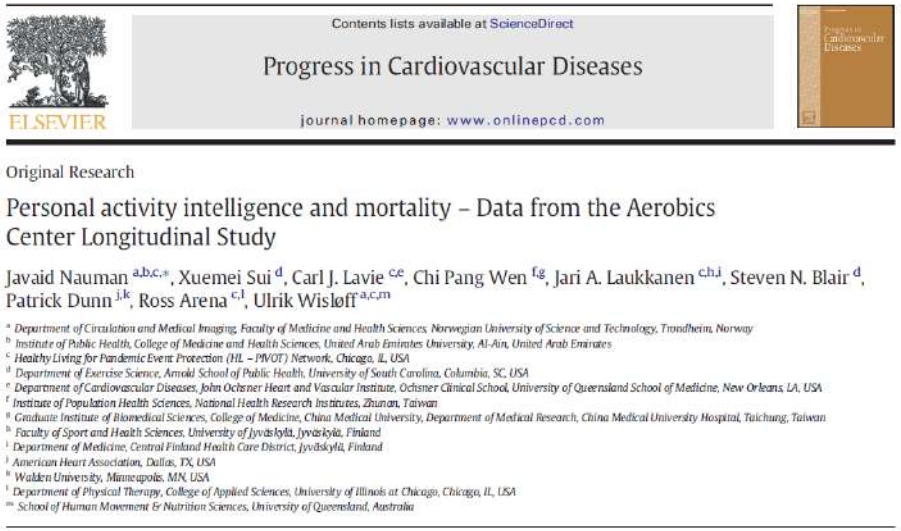
賺PAI

- 運動以時間、強度可分為
- 輕度、中度、重度
- 靜止時心跳: 60-70
- 輕度運動時心跳: <96
- 中度運動時心跳: 96-128 **1-7** PAI/20min
- 重度運動時心跳: 128-160 **1-3** PAI/min

- 運動目標: 100 PAI/week
- 死亡減少 20%-30% 多活5年

PAI 與死亡率

Impact Factor: 6.763



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Original Research

Personal activity intelligence and mortality – Data from the Aerobics Center Longitudinal Study

Javaid Nauman [a,b,c,*], Xuemei Sui [d], Carl J. Lavie [c,e], Chi Pang Wen [f,g], Jari A. Laukkanen [c,h,i], Steven N. Blair [d], Patrick Dunn [j,k], Ross Arena [c,l], Ulrik Wisløff [a,c,m]

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[l] Department of Physical Therapy, College of Applied Sciences, University of Illinois at Chicago, Chicago, IL, USA
[m] School of Human Movement & Nutrition Sciences, University of Queensland, Australia

挪威Nord Trondelag 居民十萬，2006-2008 邀請所有居民參與

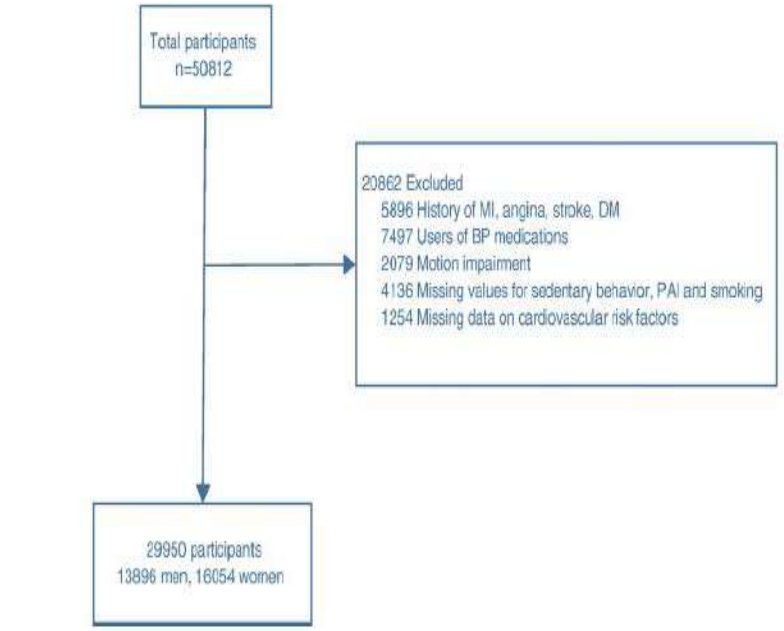
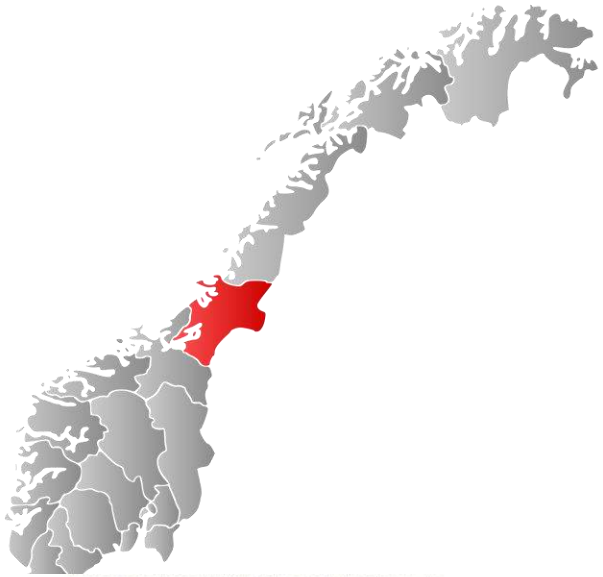


Fig 1 – Flow of participants in the study cohort. *Abbreviations:* MI, myocardial infarction; DM, diabetes mellitus; BP, blood pressure, PAI, personal activity intelligence.



PROGRESS IN CARDIOVASCULAR DISEASES 60 (2017) 89–95

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ELSEVIER

Personal Activity Intelligence (PAI), Sedentary Behavior and Cardiovascular Risk Factor Clustering – the HUNT Study

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Exercise intensity
Cardiovascular disease
Cardiovascular disease risk factors
Sedentary behavior

ABSTRACT

Prolonged sedentary behavior (SB) positively associates with clustering of risk factors for cardiovascular disease (CVD). The recently developed metric for physical activity (PA) tracking called Personal Activity Intelligence (PAI) takes into account age, sex, resting and maximum heart rate, and a score of ≥100 weekly PAI has been shown to reduce the risk of premature CVD death in healthy as well as individuals with known CVD risk factors, regardless of whether or not the current PA recommendations were met. The aim of the present study was to examine if PAI modifies the associations between SB and CVD risk factor (CV-RF) clustering in a large apparently healthy general population cohort (n = 29,950, aged ≥20 years). Logistic regression revealed that in those with ≥100 weekly PAI, the likelihood of CV-RF clustering prevalence associated with prolonged SB was attenuated across age groups. Monitoring weekly PAI-level could be useful to ensure that people perform enough PA to combat SB's deleterious association with CV-RF.

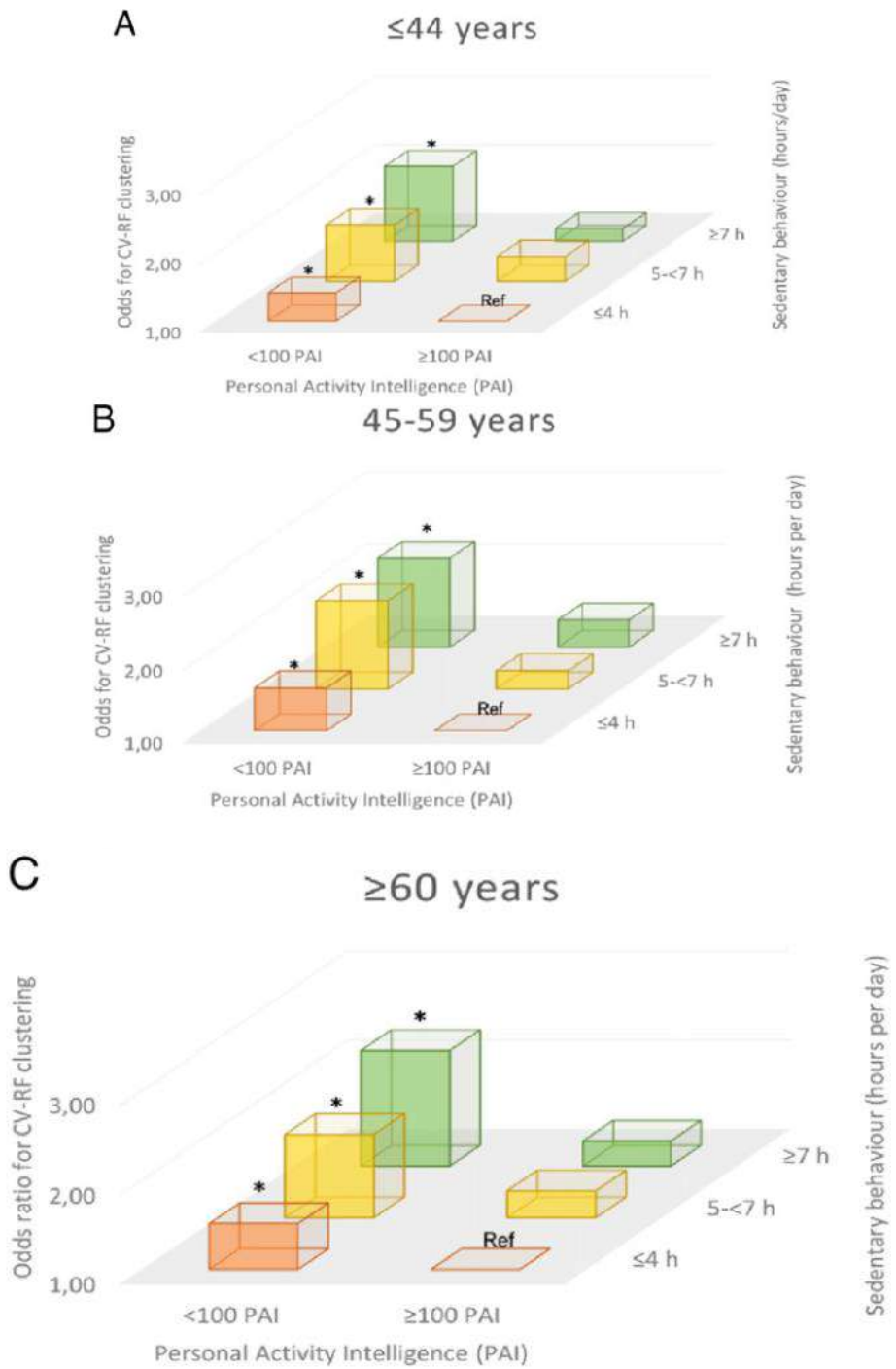
Table 1 – Descriptive characteristics of participants according to Physical Activity Intelligence.

	Personal Activity Intelligence (PAI) [a]			
	0 (n = 6190)	≤50 (n = 7083)	51–99 (n = 3469)	≥100 (n = 13,208)
Women, no. (%)	2418 (39.1)	4183 (59.1)	2140 (61.7)	7313 (55.4)
Age (years)	45.9 (13.5)	51.4 (14.7)	47.4 (14.0)	45.7 (13.6)
Weight (kg)	82.0 (16.0) [c]	77.3 (14.5) [d]	77.8 (15.2) [d]	77.7 (14.0) [d]
Waist circumference (cm)	94.5 (12.3) [c]	92.1 (11.5) [c]	91.4 (11.9) [c]	89.7 (11.0) [c]
Systolic blood pressure (mmHg)	128.0 (16.3) [e]	128.7 (17.8) [e]	126.8 (17.2) [c]	125.6 (15.9) [c]
Diastolic blood pressure (mmHg)	73.5 (11.1) [e]	73.2 (11.1) [e]	72.1 (10.8) [c]	71.5 (10.6) [c]
Total cholesterol (mmol/L)	5.5 (1.1) [f]	5.6 (1.1) [c]	5.5 (1.1) [f]	5.4 (1.1) [c]
HDL cholesterol (mmol/L)	1.3 (0.3) [c]	1.4 (0.4) [g]	1.4 (0.3) [g]	1.4 (0.4) [c]
Glucose (mmol/L)	5.4 (1.3) [e]	5.4 (1.2) [e]	5.3 (1.0) [c]	5.3 (0.9) [c]
Triglycerides (mmol/L)	1.7 (1.1) [c]	1.6 (1.0) [c]	1.5 (0.9) [c]	1.4 (0.9) [c]
BMI (kg/m^2)	27.2 (5.0) [c]	26.6 (4.1) [g]	26.6 (4.2) [g]	26.1 (3.8) [c]
Obesity status, (BMI ≥ 30), no.(%) [h]	1455 (23.5)	1267 (17.9)	644 (18.6)	1875 (14.2)
Smoking, no. (%) [h]				
Never	2328 (37.6)	3062 (43.2)	1616 (46.6)	6691 (50.7)
Former	1542 (24.9)	2095 (29.5)	972 (28.0)	4025 (30.5)
Current	1782 (28.8)	1418 (20.0)	592 (17.1)	1381 (10.5)
Occasional	538 (8.7)	507 (7.2)	289 (8.3)	1111 (8.4)
Sedentary behavior, no. (%) [b,h]				
≤4	2418 (39.1)	2729 (38.5)	1357 (39.1)	4912 (37.2)
5 to <7	1823 (29.5)	2213 (31.2)	1029 (29.7)	3786 (28.7)
≥7	1949 (31.5)	2141 (30.2)	1083 (31.2)	4510 (34.1)

Numbers are mean (SD) unless otherwise stated.
BMI, body mass index.
[a] Sample-specific quartiles of personal activity intelligence (PAI).
[b] In hours per day.
[c] Significantly different from all other PAI categories.
[d] Significantly different from 0 PAI category.
[e] Significantly different from 51–99 PAI and ≥100 PAI category.
[f] Significantly different from ≤50 PAI and ≥100 PAI category.
[g] Significantly different for 0 PAI and ≥100 PAI category.
[h] Significant difference between groups (Chi-square test).

PAI

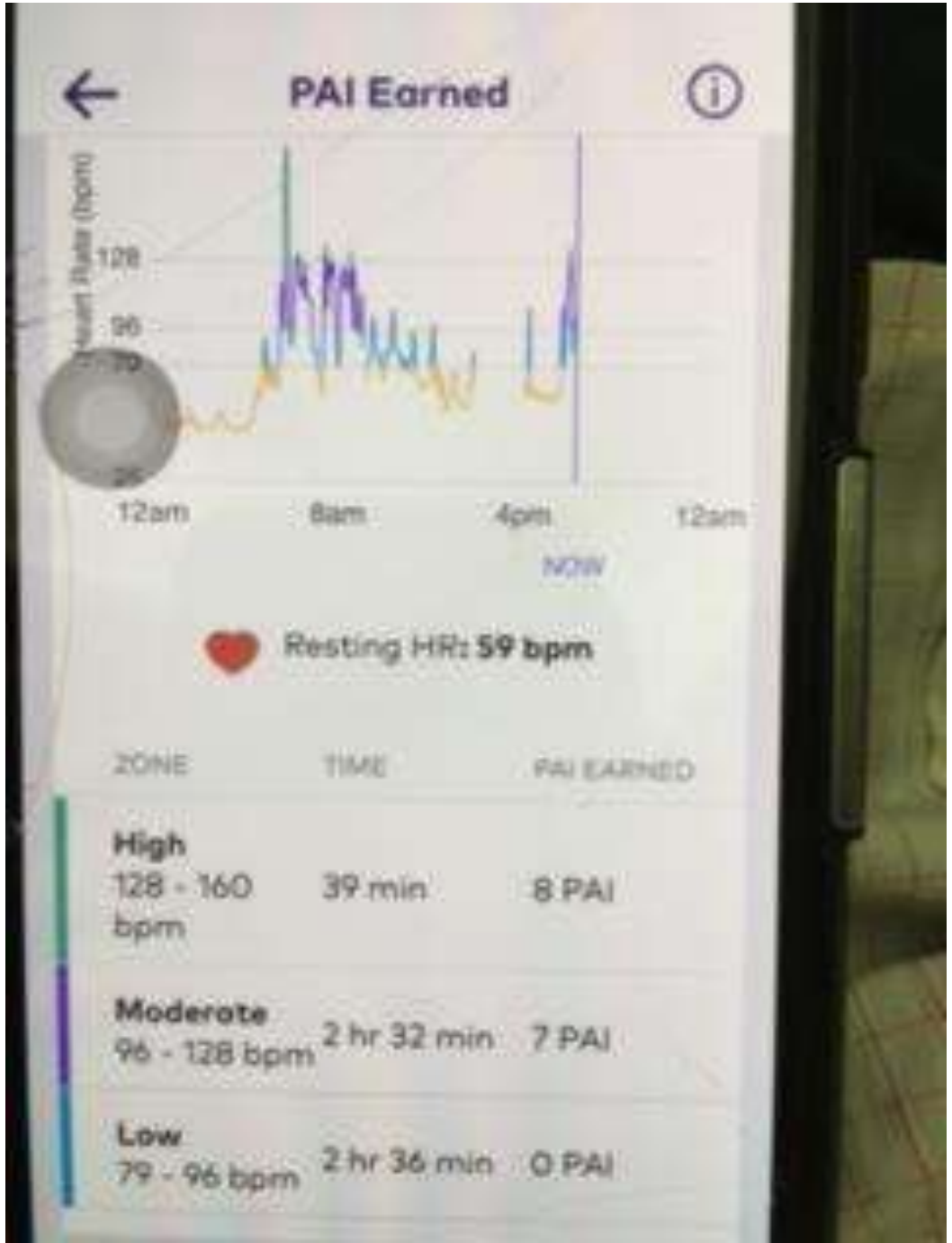
- 0 20.7%
- ≦50 23.6%
- 50-99 11.6%
- ≧100 44.1%



- 運動
  - 強度
  - 時間
  - 次數

Moderate intensity 中強度

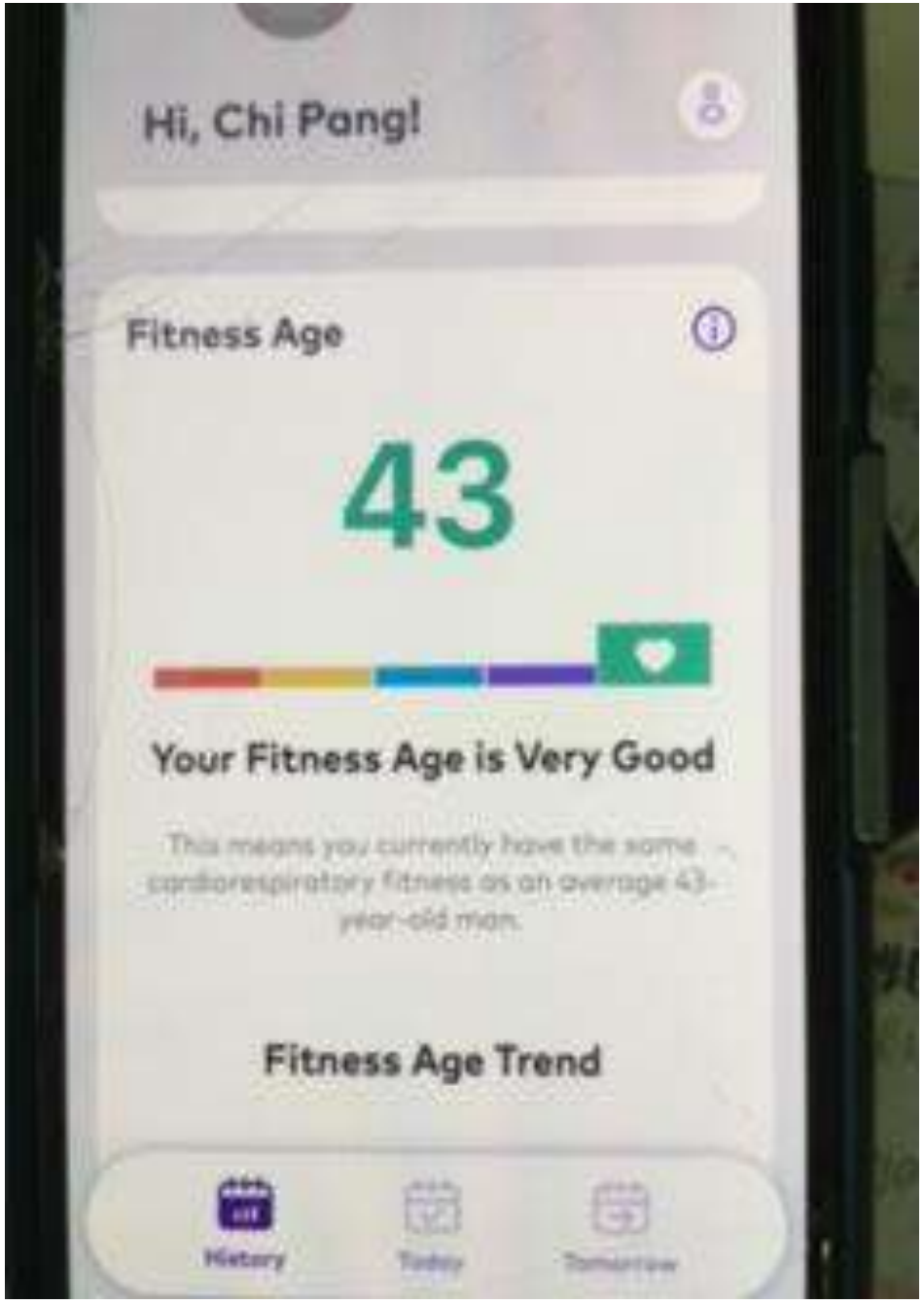
Vigorous 激烈



- 靜止時心跳: 60/min
- >128/min
  - 1 PAI in 5 minutes
  - 39 min 拿到 8 PAI
- 96-128/min
  - 1 PAI in 22 minutes
  - 2 hour 32 min. 拿到 7 PAI
- <96/min
  - 2 hour 36 min No PAI


Hi, Chi Pang!
PAI History
Week
Month
Year
Tue, Nov 17 — Mon, Nov 23
Average PAI: 287 PAI
Total 287 285 283 288 290 291 290
300
250
200
150
100
50
0
History
Today

體適能年齡


Hi, Chi Pang!
Fitness Age
43
Your Fitness Age is Very Good
Fitness Age Trend
History
Today

60萬人
心跳分佈

	40-59	60-69	70-79	80-89	90-99	>100	80-99	
Male	12.5%	33.9%	33.0%	15.1%	4.3%	1.4%	58,634	(19.4)
Female	6.8%	29.1%	38.0%	19.0%	5.4%	1.8%	81,069	(24.3)

1/8

67%

22%

雖然今日治高血壓藥有數十種，醫師垂手可得減緩心跳的藥卻一種也沒有，醫師束手無策，我們不要忘掉眼前最便宜，最無副作用，又能治百病的萬靈藥--運動。

	無運動	有運動	相差
男生 71.3	71.8	67.5	4.3/min
女生 73.7	73.8	70.0	3.8 /min

一小時；240 下
24小時；5,760
一年； 200萬
20年: 4000萬
40年: 8000萬下

高血壓
是全球死亡負擔的單一最大貢獻者。

- Lancet Seminar

- Raised blood pressure is the biggest single contributor to the global burden of disease and to global mortality.
- The numbers of people affected and the prevalence of high blood pressure worldwide are expected to increase over the next decade
- 死亡人數正逐漸增加中
- Three-drug combinations can control hypertension in about 90% of patients but only if resources allow identification of patients and drug delivery is affordable. Furthermore, assessment of optimal drug therapy for each ethnic group is needed.
- 三藥合併使用可控制90%的高血壓

- 高血壓是全球疾病負擔與全球死亡的單一最大貢獻者。

Hypertension

Neil R Poulter, Dorairaj Prabhakaran, Mark Caulfield

Raised blood pressure is the biggest single contributor to the global burden of disease and to global mortality. The numbers of people affected and the prevalence of high blood pressure worldwide are expected to increase over the next decade. Preventive strategies are therefore urgently needed, especially in less developed countries, and management of hypertension must be optimised. Genetic advances in some rare causes of hypertension have been made lately, but the aggregate effect on blood pressure of all the genetic loci identified to date is small. Hence, intervention on key environmental determinants and effective implementation of trial-based therapies are needed. Three-drug combinations can control hypertension in about 90% of patients but only if resources allow identification of patients and drug delivery is affordable. Furthermore, assessment of optimal drug therapy for each ethnic group is needed.

Epidemiology

Blood pressure is a normally distributed biological variable; values at the high end of the distribution are termed hypertension. The diagnosis of hypertension is based on an arbitrary cutoff point for a measure that has a continuous and graded relation across its whole range with the risk of various cardiovascular diseases.[1] Furthermore, 50% of the disease burden attributable to high blood pressure relates to values below this arbitrary cutoff point.[2] A pragmatic definition of hypertension, proposed by Geoffrey Rose decades ago, is the level of blood pressure for which investigation and management do more good than harm. In most national and international guidelines the threshold for the diagnosis of hypertension is a systolic blood pressure measured in a clinic or office of at least 140 mm Hg, a diastolic blood pressure of at least 90 mm Hg, or both.[3–5]

The latest data from the Global Burden of Disease project show that raised blood pressure (systolic >115 mm Hg) continues to be the biggest single contributor to the global burden of disease and to global mortality, leading to 9·4 million deaths each year.[6] The effect is largely mediated through coronary heart disease and stroke; the relative risks for both these events are similar for men and women.[7] However, the relative incidence ratios of coronary heart disease and stroke deaths vary extensively by geographical location, which presumably reflects the differential coexistence of other risk factors, particularly dyslipidaemia. Furthermore, extensive data from the UK suggest that the adverse effects of systolic and diastolic blood pressure on various cardiovascular endpoints are not concordant and that their relative importance is differentially affected by age.[8]

The numbers of people affected by hypertension are predicted to rise in all regions of the world from 2000 to 2025,[9] reflecting not only that the global population is growing and ageing—and blood pressure rises with age in almost all parts of the world—but also that more than 80% of the world is deemed to be developing. Hitherto the process of development has been associated with increased exposure to the main environmental determinants of high blood pressure, such as excess intakes of salt, calories, and alcohol.

Between 1980 and 2008, the global prevalence of hypertension fell marginally in men and women.[10] However, along with numbers affected, the prevalence is expected to rise between 2008 and 2015 in all regions of the world except possibly sub-Saharan Africa, in which changes in population distribution are likely to be limited.[9]

As a consequence of the predicted increase in global prevalence of about 10%, between 2000 and 2025 an estimated 560 million extra people will be affected by hypertension.[9] This prospect is daunting, given that in 2010 high blood pressure was already the biggest single contributor to worldwide deaths.[6]

In most low-income and middle-income countries, no robust epidemiological data are available for estimates of the prevalence of hypertension at present. However, the best available data suggest that the prevalence has increased in the past two decades to rates similar to those found in high-income countries (16·0–36·9% across 12 national surveys[11]), that rates are higher in urban than in rural environments, and that treatment and control rates are low though better in women than in men.[12,13] In their review from sub-Saharan Africa, Twagirumukiza and colleagues[14] predicted a 68% increase in numbers affected between 2008 and 2015; treatment and control rates were reported to be low, as of 2008. Similarly in India, but also based on suboptimal data, a highly significant

Search strategy and selection criteria

We searched Medline and PubMed from July 1, 2009, to June 30, 2014, using various combinations of the search terms "hypertension", "blood pressure", "epidemiology", "population", "recent advances", "guidelines", "Barker hypothesis", "intrauterine programming", "salt intake", "sodium intake", "reducing strategies", "genes", "blood-pressure monitoring", "developing countries", "low or low middle income countries", and "mHealth technology". We search the identified articles for additional studies of interest, some of which were over 5 years old. We filtered on quality and influence. The reference list was modified on the basis of comments from peer reviewers.

Appendix table 5. Comparison between heart rate and BP for all-cause and CVD mortality

	Prevalence		All-Cause (HR)*	CVD (HR)*	All-Cause (HR)**	CVD (HR)**
High normal RHR 90-99/min	4.80%	As a whole group	1.91 (1.80, 2.03)	2.69 (2.30, 3.14)	1.67 (1.59, 1.75)	1.58 (1.42, 1.75)
	1.70%	Subgroup with normal BP ≤120/80 mmHg	1.92 (1.72, 2.14)	2.14 (1.58, 2.88)		
BP≥ 140/90mmHg	16.10%	As a whole group	1.63 (1.56, 1.72)	2.93 (2.57, 3.35)	1.47 (1.42, 1.52)	2.55 (2.35, 2.77)
	3.90%	Subgroup with normal RHR at 60-69/min	1.43 (1.35, 1.52)	2.80 (2.42, 3.24)		
RHR 80-89/min	17.10%	As a whole group	1.47 (1.39, 1.54)	2.09 (1.81, 2.40)	1.28 (1.23, 1.32)	1.23 (1.14, 1.32)
	7.70%	Subgroup with normal BP ≤120/80 mmHg	1.26 (1.17, 1.35)	1.31 (1.07, 1.61)		
BP≥130/80 mmHg	35.20%	As a whole group	1.48 (1.41, 1.56)	2.52 (2.21, 2.87)	1.33 (1.29, 1.37)	2.12 (1.96, 2.29)
	9.30%	Subgroup with normal RHR at 60-69/min	1.29 (1.22, 1.36)	2.25 (1.96, 2.59)		
BP 140-159/ 90-99mmHg	11.20%	As a whole group	1.54 (1.45, 1.62)	2.59 (2.25, 3.00))	1.33 (1.28, 1.38)	2.15 (1.96, 2.35)
	2.90%	Subgroup with normal RHR at 60-69/min	1.31 (1.22, 1.40)	2.35 (2.01, 2.75)		
RHR 80-99/min	22.00%	As a whole group	1.58 (1.51, 1.67)	2.23 (1.94, 2.56)	1.37 (1.33, 1.41)	1.31 (1.22, 1.41)
	9.40%	Subgroup with normal BP ≤ 120/80 mmHg	1.38 (1.29, 1.48)	1.46 (1.21, 1.77)		

*: Reference group (identical reference): RHR at 60-69/min and BP < 120/80 mmHg

**: Reference group (different reference): For RHR is 60-69/min; for BP is < 120/80 mmHg

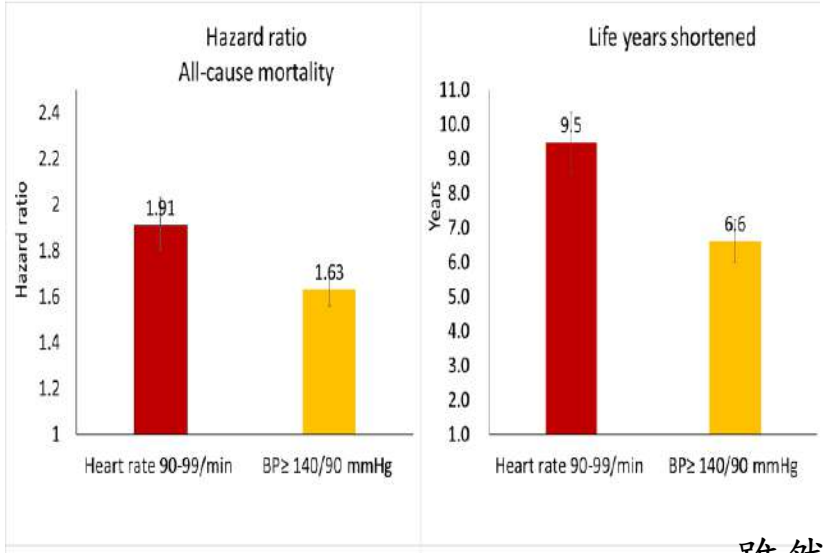
高血壓預測CVD

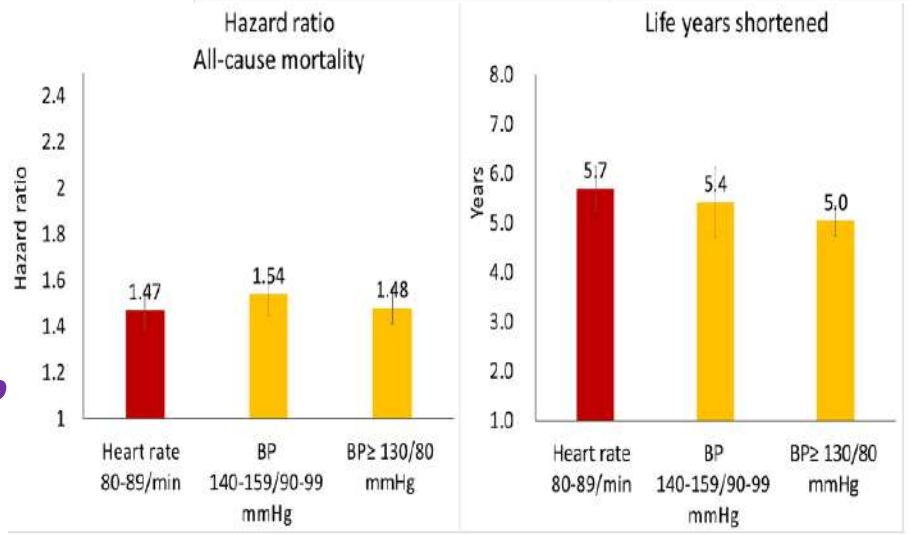
心跳預測CVD

以相同對照組比較，才知它會高估預測CVD

比較心跳與高血壓的殺傷力

- 心跳90-99/min，短壽9.5年，死亡率高過高血壓 BP≧140/90 mmHg
- 心跳80-89/min，死亡率與高血壓 BP≧130/80 mmHg **相同**
- 心跳70/min起，每增一拍，壽命短4個月，每增十拍，壽命短3.5年。
- 心跳80-99/min，死亡率與高血壓 BP≧130/80 mmHg **相同，但心跳人數較多(22% vs. 16%)**





雖然今日治高血壓藥有數十種，醫師垂手可得，減緩心跳的藥卻一種也沒有，醫師束手無策，我們不要忘掉眼前最便宜，最無副作用，又能治百病的萬靈藥--運動。

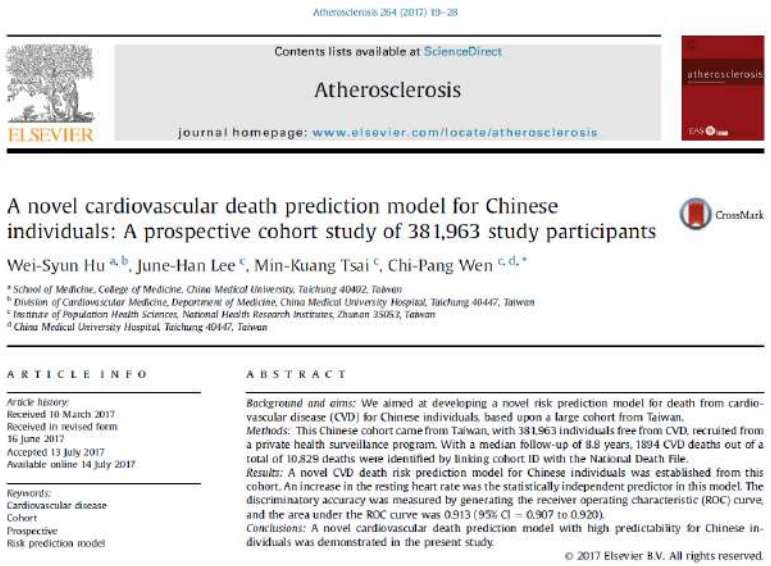
Conclusion: RHR at 90-99/min, shortened life by 9.5 years, had larger all-cause mortality risks than BP ≧140/90 mmHg. RHR at 80-89/min, an easily measured marker of increased mortality, had a similar life-threatening risk as total hypertension (BP ≧130/80 mmHg). Exercisers were associated with slower heart rate.

死因分析比較
90-99/min vs. >140/90 mmHg

Table 3. Comparison between heart rate and BP for cause-specific mortality, examining subgroups[1,2] with normal BP or normal heart rate

	Heart rate			Heart rate			BP			BP			BP		
	RHR (80-89/min) with normal BP[1] (N=48,954)			**RHR (90-99/min)** with normal BP[1] (N=10,521)			**BP ≥ 130/80 mmHg** with normal heart rate[2] (N=59,236)			**BP ≥ 140/90 mmHg** with normal heart rate[2] (N=25,087)			**BP 140-159/90-99 mmHg** with normal heart rate[2] (N=18,170)		
	N of deaths	HR	(95% CI)	N of deaths	HR	(95% CI)	N of deaths	HR	(95% CI)	N of deaths	HR	(95% CI)	N of deaths	HR	(95% CI)
All cause	2,093	1.26	(1.17 ,1.35)	654	1.92	(1.72 ,2.14)	7,652	1.29	(1.22 ,1.36)	5,076	1.43	(1.35 ,1.52)	2,992	1.31	(1.22 ,1.40)
Cardiovascular disease (CVD)	283	1.31	(1.07 ,1.61)	91	2.14	(1.58 ,2.88)	1,986	2.25	(1.96 ,2.59)	1,471	2.80	(2.42 ,3.24)	809	2.35	(2.01 ,2.75)
Stroke	91	1.29	(0.88 ,1.88)	30	2.19	(1.28 ,3.76)	730	2.80	(2.18 ,3.61)	542	3.62	(2.79 ,4.70)	305	3.23	(2.45 ,4.27)
Ischemic heart disease	72	1.39	(0.93 ,2.07)	22	2.44	(1.41 ,4.23)	509	2.26	(1.71 ,2.98)	367	2.64	(1.98 ,3.52)	199	2.15	(1.57 ,2.94)
Diabetes mellitus	118	1.92	(1.28 ,2.87)	46	4.38	(2.77 ,6.91)	413	2.05	(1.46 ,2.86)	293	2.15	(1.51 ,3.05)	162	1.93	(1.32 ,2.82)
Kidney diseases	53	1.79	(1.03 ,3.11)	20	3.19	(1.57 ,6.48)	251	1.90	(1.24 ,2.92)	183	2.13	(1.36 ,3.32)	87	1.65	(1.01 ,2.70)
Expanded CVD*	454	1.47	(1.24 ,1.74)	157	2.65	(2.11 ,3.33)	2,650	2.17	(1.91 ,2.45)	1,947	2.60	(2.28 ,2.95)	1,058	2.18	(1.90 ,2.51)
Cancer	908	1.22	(1.10 ,1.36)	236	1.44	(1.20 ,1.73)	2,521	1.07	(0.98 ,1.16)	1,519	1.11	(1.01 ,1.22)	967	1.08	(0.97 ,1.19)
Lung cancer	179	1.09	(0.86 ,1.38)	52	1.21	(0.79 ,1.85)	558	0.97	(0.81 ,1.16)	338	0.95	(0.78 ,1.16)	207	0.93	(0.75 ,1.16)
Liver cancer**	166	1.35	(0.66 ,2.77)	36	4.59	(1.87 ,11.30)	520	0.89	(0.52 ,1.52)	305	0.72	(0.38 ,1.37)	195	0.68	(0.33 ,1.40)
Liver disease (liver cancer or cirrhosis)**	226	1.39	(0.72 ,2.71)	61	4.46	(1.94 ,10.29)	713	1.01	(0.62 ,1.65)	424	0.83	(0.46 ,1.49)	267	0.80	(0.42 ,1.55)
Respiratory system	173	1.50	(1.15 ,1.96)	64	2.59	(1.77 ,3.79)	712	1.12	(0.92 ,1.36)	494	1.22	(0.99 ,1.50)	302	1.17	(0.93 ,1.47)
COPD	63	1.91	(1.20 ,3.02)	32	4.64	(2.60 ,8.28)	228	1.32	(0.92 ,1.88)	154	1.37	(0.94 ,2.00)	95	1.37	(0.91 ,2.08)
Suicide	92	1.13	(0.80 ,1.59)	20	1.77	(1.04 ,3.01)	91	0.89	(0.64 ,1.24)	46	1.00	(0.66 ,1.52)	33	1.00	(0.62 ,1.60)

心跳已發表
1）是預測CVD 重要指標
2）與自殺死亡有關



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A novel cardiovascular death prediction model for Chinese individuals: A prospective cohort study of 381,963 study participants

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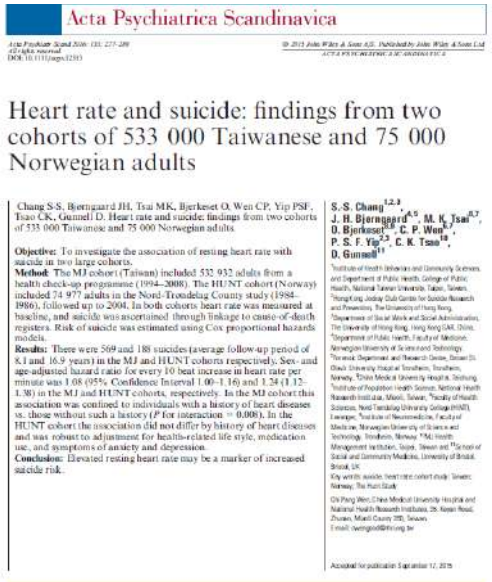
ABSTRACT

Background and aims: We aimed at developing a novel risk prediction model for death from cardiovascular disease (CVD) for Chinese individuals, based upon a large cohort from Taiwan.
Methods: This Chinese cohort came from Taiwan, with 381,963 individuals free from CVD, recruited from a private health surveillance program. With a median follow-up of 8.8 years, 1894 CVD deaths out of a total of 10,829 deaths were identified by linking cohort ID with the National Death File.
Results: A novel CVD death risk prediction model for Chinese individuals was established from this cohort. An increase in the resting heart rate was the statistically independent predictor in this model. The discriminatory accuracy was measured by generating the receiver operating characteristic (ROC) curve, and the area under the ROC curve was 0.913 (95% CI = 0.907 to 0.920).
Conclusions: A novel cardiovascular death prediction model with high predictability for Chinese individuals was demonstrated in the present study.



Acta Psychiatrica Scandinavica

Heart rate and suicide: findings from two cohorts of 533 000 Taiwanese and 75 000 Norwegian adults

Chang S-S, Bjerkeset O, Wen CP, Yip PSF, Tsao CK, Gunnell D. Heart rate and suicide: findings from two cohorts of 533 000 Taiwanese and 75 000 Norwegian adults.

Objective: To investigate the association of resting heart rate with suicide in two large cohorts.
Method: The MJ cohort (Taiwan) included 532 932 adults from a health check-up programme (1994–2008). The HUNT cohort (Norway) included 74 977 adults in the Nord-Trøndelag County study (1984–1986), followed up to 2004. In both cohorts heart rate was measured at baseline, and suicide was ascertained through linkage to cause-of-death registers. Risk of suicide was estimated using Cox proportional hazards models.
Results: There were 569 and 188 suicides (average follow-up period of 8.1 and 16.9 years) in the MJ and HUNT cohorts respectively. Sex- and age-adjusted hazard ratio for every 10 beat increase in heart rate per minute was 1.08 (95% Confidence Interval 1.00–1.16) and 1.24 (1.12–1.38) in the MJ and HUNT cohorts, respectively. In the MJ cohort this association was confined to individuals with a history of heart diseases vs. those without such a history (P for interaction = 0.008). In the HUNT cohort the association did not differ by history of heart diseases and was robust to adjustment for health-related life style, medication use, and symptoms of anxiety and depression.
Conclusion: Elevated resting heart rate may be a marker of increased suicide risk.

S. S. Chang, J. H. Bjerkeset, O. Bjerkeset, P. S. F. Yip, M. K. Tsai, C. P. Wen, C. K. Tsao, D. Gunnell

心跳 70-79 80-89 90-99 >100

減壽年數 3.2歲 5.7歲 9.5歲 14.1歲

血壓 130-139 140-159 >140

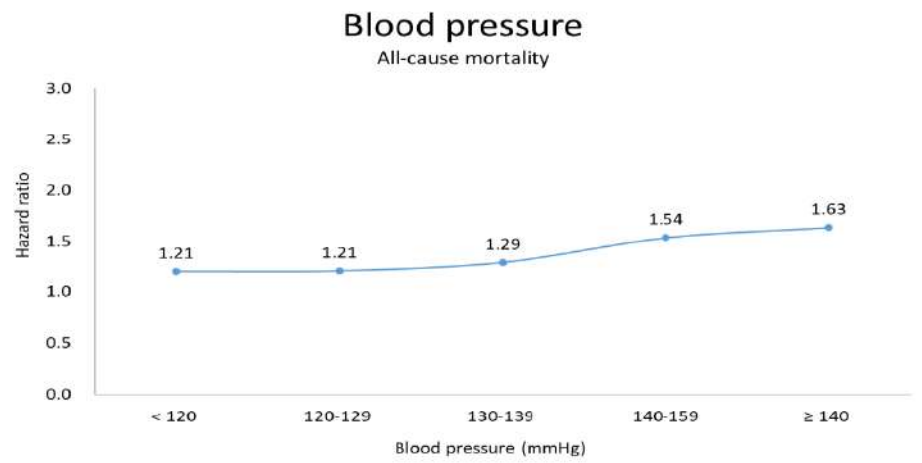
2.7歲 5.4歲 6.6歲

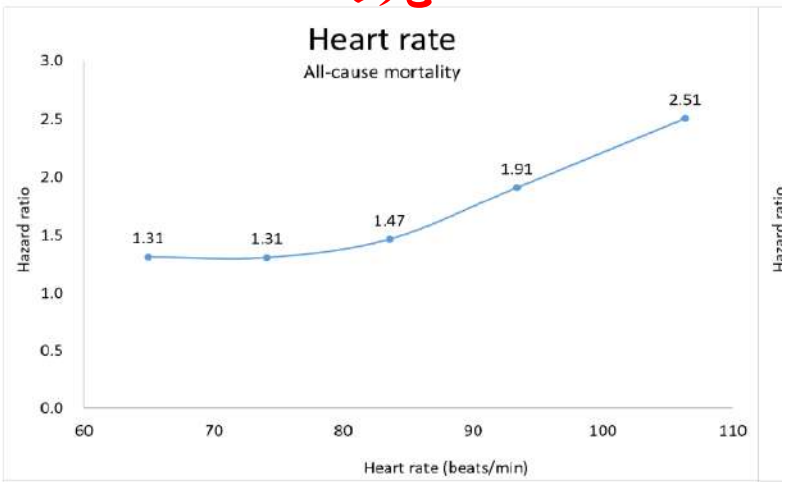
血壓

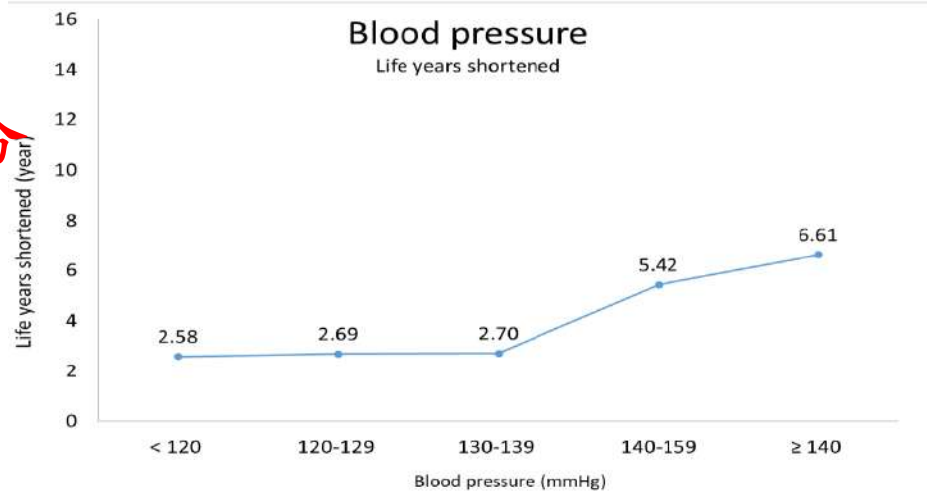
心跳

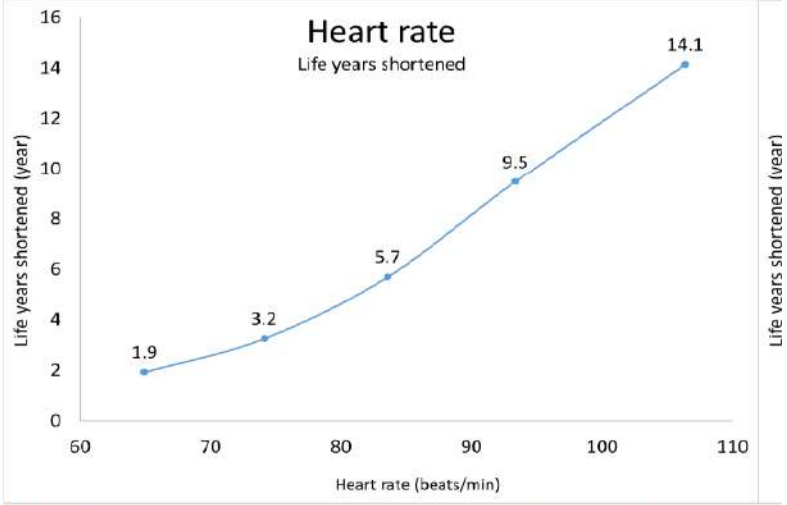
死亡率

平均餘命









How hard our heart works

Individual A：
Heart rate: **60** beats/min

Individual B：
Heart rate: **90** beats/min

Difference: 30 beats/Min

Extra 30 beats/min *60 = 1,800/hour

1,800/hour *24 = 43,200/day

43,200/day *365 = 15,768,000/year

15,768,000/year *20 =315,360,000/20year

一小時；1800 下
24小時；43, 200
一年； 1500萬
20年: 3億
40年: 6億下

(**In 20 years**, 多跳三億下
extra **315** million beats)

The slower the heart rate, the longer the life expectancy in mammals

Turtle	5-10	100 years
Whale	6-9	80 years
Elephant	30	80 years
Humans	70	80 years
Cat	120	10 years
Dog	100	15 years
Guinea pig	200	5 years
Hamster	300	3 years
Mouse	500	2 years

Giraffe

Heart rate: **40-60**

Life expectancy: **25**years

Pygmy Shrew ·
家鼩（錢鼠、臭鼩、香鼠）

Heart rate: **1000**

Life expectancy: **2-4** months

Mice

Heart rate: **500**

Life expectancy: **1-2** years

Hamster
倉鼠

Heart rate: **300-400**

Life expectancy: **2-3** years

Guinea pig
天竺鼠

Heart rate: **200-300**

Life expectancy: **5-6** years

Turtle

Heart rate: **5-10**

Life expectancy: **100** years

Whale鯨魚

Heart rate: **6-9**

Life expectancy: **80-100** years

Cat and dog

Heart rate: **120**

Life expectancy: **12** years

Human

Heart rate: **70**

Life expectancy: **80** years

Elephant

Heart rate: **30**

Life expectancy: **60-70** years

Humans: Marathon runner heart rate below 60

當高血壓的人心跳快時，
高血壓風險不一樣

- ≧140/90 mmHg　1.63
- +
- 90-99/min
- =　2.19
- Increased by　34%

- ≧130/80 mmHg　1.48
- +
- 90-99/min
- =　2.52
- Increased by　36%

When both co-existed

Hypertension	with high normal heart rate	Original BP risk	Risk for co-existed	BP risk for all cause amplified with heart rate considered	Original BP risk	Risk for co-existed	BP risk for CVD amplified with heart rate considered
BP≥140/90mmHg	with 90-99/min	1.63	2.19 (2.04 ,2.35)	34%	2.93	3.53 (2.98 ,4.19)	20%
BP≥130/80 mmHg	with 90-99/min	1.48	2.02 (1.89 ,2.15)	36%	2.52	3.06 (2.61 ,3.60)	22%

DryLab 今年目標200
個人貢獻11+4

心跳的死亡風險比美高血壓，甚至還更大

- 1）肝功能SGOT偏高，減壽十年以上，比SGPT偏高重要太多。 (10.24),
- 2）蛋白尿的出現是洗腎的預兆 (25.34)(Lancet 糖尿病),
- 3）900萬人大資料，將腎病資料融入心血管的風險預測內 (新Lancet),
- 4) PAI 與死亡率(6.76),
- 5）**發炎指數與自殺的關係**(4.17),
- 6) 中風與吸菸之悖論(似非而是、看似矛盾)(7.19),

糞便潛血的檢查，比美大腸鏡，甚至還更好

- 台灣的菸害防制何去何從
- 7）按照世衛組織建議作法，急起直追，但是五十年後仍不能達標。(6.22)
- 8）台灣施行低菸價被煙商耍了。(6.22)
- 9）今日空污是新吸菸嗎?**(6.22)**
- 10）青少年吸電子煙是否刺激轉吸傳統菸?**(6.22)**
- 11)中國醫護人員新冠肺炎死亡率，隨時間遞減

The **Lancet Diabetes** & **Endocrinology** has an **Impact Factor** of
25.340

Change in albuminuria and subsequent risk of end-stage kidney disease: an individual participant-level consortium meta-analysis of observational studies

Josef Coresh, Hiddo J L Heerspink, Yingying Sang, Kunihiro Matsushita, Johan Arnlöv, Brad C Astor, Carol Black, Rajat J Bhansali, Juan-Jesus Carrero, Harold I Feldman, Caroline S Fox, Lesley A Inker, Asieh Iohan, Sadayoshi Ito, Simerjot Jassal, Tsuneo Konta, Kasun Polkinghorne, Sofia Ramondetta, Marie D Sallo, Nikita Stempniewicz, Benedicte Stengel, Marcello Tonelli, Mitsuyasu Umesawa, Sushrut S Waikar, Chi-Pang Wen, Jack F M Wetzels, Mark Woodward, Morgan E Grams, Caitlin P Kennedy, Andrew S Levey, Ron T Gansevoort, for the Chronic Kidney Disease Prognosis Consortium and Chronic Kidney Disease Epidemiology Collaboration*

Summary

Background Change in albuminuria as a surrogate endpoint for progression of chronic kidney disease is strongly supported by biological plausibility, but empirical evidence to support its validity in epidemiological studies is lacking. We aimed to assess the consistency of the association between change in albuminuria and risk of end-stage kidney disease in a large individual participant-level meta-analysis of observational studies.

Methods In this meta-analysis, we collected individual-level data from eligible cohorts in the Chronic Kidney Disease Prognosis Consortium (CKD-PC) with data on serum creatinine and change in albuminuria and more than 50 events on outcomes of interest. Cohort data were eligible if participants were aged 18 years or older, they had a repeated measure of albuminuria during an elapsed period of 5 months to 4 years, subsequent end-stage kidney disease or mortality follow-up data, and the cohort was active during this consortium phase. We extracted participant-level data and quantified percentage change in albuminuria, measured as change in urine albumin-to-creatinine ratio (ACR) or urine protein-to-creatinine ratio (PCR), during baseline periods of 1, 2, and 3 years. Our primary outcome of interest was development of end-stage kidney disease after a baseline period of 2 years. We defined an end-stage kidney disease event as initiation of kidney replacement therapy. We quantified associations of percentage change in albuminuria with subsequent end-stage kidney disease using Cox regression in each cohort, followed by random-effects meta-analysis. We further adjusted for regression dilution to account for imprecision in the estimation of albuminuria at the participant level. We did multiple subgroup analyses, and also repeated our analyses using participant-level data from 14 clinical trials, including nine clinical trials not in CKD-PC.

Findings Between July, 2015, and June, 2018, we transferred and analysed data from 28 cohorts in the CKD-PC, which included 693 816 individuals (537 583 [80%] with diabetes). Data for 675 904 individuals and 7461 end-stage kidney disease events were available for our primary outcome analysis. Change in ACR was consistently associated with subsequent risk of end-stage kidney disease. The adjusted hazard ratio (HR) for end-stage kidney disease after a 30% decrease in ACR during a baseline period of 2 years was 0·83 (95% CI 0·74–0·94), decreasing to 0·78 (0·66–0·92) after further adjustment for regression dilution. Adjusted HRs were fairly consistent across cohorts and subgroups (ie, estimated glomerular filtration rate, diabetes, and sex), but the association was somewhat stronger among participants with higher baseline ACR than among those with lower baseline ACR ($p_{\text{heterogeneity}}$<0·0001). In individuals with baseline ACR of 300 mg/g or higher, a 30% decrease in ACR over 2 years was estimated to confer a more than 1% absolute reduction in 10-year risk of end-stage kidney disease, even at early stages of chronic kidney disease. Results were generally similar when we used change in PCR and when study populations from clinical trials were assessed.

Interpretation Change in albuminuria was consistently associated with subsequent risk of end-stage kidney disease across a range of cohorts, lending support to the use of change in albuminuria as a surrogate endpoint for end-stage kidney disease in clinical trials of progression of chronic kidney disease in the setting of increased albuminuria.

Funding US National Kidney Foundation and US National Institute of Diabetes and Digestive and Kidney Diseases.

Introduction

On March 15–16, 2018, a scientific workshop sponsored by the US National Kidney Foundation (NKF), in collaboration with the US Food and Drug Administration (FDA) and European Medicines Agency (EMA), investigated candidate surrogate endpoints for clinical trials of drugs designed to slow the progression of kidney disease, particularly among patients in the early stages of chronic kidney disease. For decades, change in albuminuria has been used in some clinical trials for the development of

蛋白尿的出現或改變
是洗腎風險的預兆

發炎指數與自殺的關係

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Evidence for an association between inflammatory markers and suicide: a cohort study based on 359,849 to 462,747 Taiwanese adults

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ABSTRACT

Background: Biological markers of suicide risk have the potential to inform prevention and treatment efforts. It has recently been hypothesised that inflammation may influence mood and in turn suicide risk. We investigated the association between indicators of systemic inflammation and suicide in a large cohort of Taiwanese adults.
Methods: White blood cell (WBC) count and levels of C-reactive protein (CRP) were measured in 462,747 and 359,849 adults in the Taiwan MJ cohort, respectively. The associations between WBC, CRP and suicide risk were investigated using Cox proportional hazards models adjusting for a range of potential confounding factors.
Results: During a mean 15.1 and 15.8 years of follow-up, 687 and 605 suicides were identified in participants who had information on WBC and CRP respectively. There was an association of suicide with WBC count (adjusted hazard ratio [aHR] = 1.13 per 1 standard deviation increase of log-transformed WBC, 95% confidence interval [CI] 1.09, 1.77). The association was driven by the highest quintile of WBC count (aHR = 1.39, 95% CI 1.09, 1.77; reference: the lowest quintile). No association between CRP and suicide was found.
Limitations: Our cohort was from a privately-run health check-up programme and had a lower suicide rate than that in the general population.
Conclusions: Individuals with the highest WBC counts may have increased risk of suicide. Peripheral markers of inflammation are potential biomarkers of suicide risk; however, this seems to vary by population and the marker investigated and could be influenced by a range of confounding factors.

- C-Reactive Protein

吸菸者早十一年中風

- The more you smoke,
- The earlier you stroke,
- And
- The longer sufferings you have to cope.

- 你吸菸吸得愈多，
- 會愈早中風，
- 你痛苦、長照的時間就愈長

- 吸菸中風機會加倍，早十一年中風
- 戒菸可扭轉風險。

Stroke

7.190

Smoking Paradox in Stroke Survivors?

Uncovering the Truth by Interpreting 2 Sets of Data

Hao-Kuang Wang, MD, PhD; Chih-Yuan Huang, MD, PhD; Yuan-Ting Sun, MD, PhD; Jie-Yuan Li, MD; Chih-Hung Chen, MD, PhD; Yu Sun, MD; Chung-Hsiang Liu, MD; Ching-Huang Lin, MD; Wei-Lun Chang, MD; Jiunn-Tay Lee, MD, PhD; Sheng-Feng Sung, MD; Po-Yen Yeh, MD; Ta-Chang Lai, MD; I-Ju Tsai, MD; Mei-Chen Lin, MD; Cheng-Li Lin, MD; Chi-Pang Wen, MD, PhD;* Chung Y. Hsu, MD, PhD;* for the Taiwan Stroke Registry Investigators†

Background and Purpose—The observation that smokers with stroke could have better outcome than nonsmokers led to the term "smoking paradox." The controversy of such a complex claim has not been fully settled, even though different case mix was noted. Analyses were conducted on 2 independent data sets to evaluate and determine whether such a paradox truly exists.

Methods—Taiwan Stroke Registry with 88 925 stroke cases, and MJ cohort with 541 047 adults participating in a medical screening program with 1630 stroke deaths developed during 15 years of follow-up (1994–2008). Primary outcome for stroke registry was functional independence at 3 months by modified Rankin Scale score ≤2, for individuals classified by National Institutes of Health Stroke Scale score at admission. For MJ cohort, mortality risk by smoking status or by stroke history was assessed by hazard ratio.

Results—A >11-year age difference in stroke incidence was found between smokers and nonsmokers, with a median age of 60.2 years for current smokers and 71.6 years for nonsmokers. For smokers, favorable outcome in mortality and in functional assessment in 3 months with modified Rankin Scale score ≤2 stratified by the National Institutes of Health Stroke Scale score was present but disappeared when age and sex were matched. Smokers without stroke history had a ≈2-fold increase in stroke deaths (2.05 for ischemic stroke and 1.53 for hemorrhagic stroke) but smokers with stroke history, 7.83-fold increase, overshadowing smoking risk. Quitting smoking at earlier age reversed or improved outcome.

Conclusions—"The more you smoke, the earlier you stroke, and the longer sufferings you have to cope." Smokers had 2-fold mortality from stroke but endured stroke disability 11 years longer. Quitting early reduced or reversed the harms. (***Stroke.*** **2020;51:1248-1256. DOI: 10.1161/STROKEAHA.119.027012.)**

Are e-cigarettes reviving the popularity of conventional smoking among Taiwanese male adolescents? A time-trend population-based analysis for 2004-2017

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ABSTRACT

Introduction In Taiwan, national tobacco use surveys show that e-cigarette use has increased since 2014 among youth, while, at the same time, conventional cigarette smoking has continuously decreased. The purpose of this study is to examine whether the increased popularity of e-cigarettes has undermined this favourable declining trend for cigarette smoking.

Methods We examined conventional cigarette and e-cigarette prevalence among male high school students (aged 16–18 years) and adults from 2004 to 2017, using data from cross-sectional nationally representative surveys. Applying interrupted time series analysis, we assessed whether there was a change in trend in 2014, when e-cigarette use started to gain popularity from long-term trends in prior years (2004–2013).

Results E-cigarette use prevalence increased from 2.5% in 2014 to 6.4% in 2017 among male high school students but was negligible among male adults, declining from 1.4% in 2015 to 0.8% in 2017. The annual relative decline in the cigarette smoking rate after e-cigarettes started to gain popularity was greater (−10%) than the long-term trend (−2%) among high school students. Among adults, the change in trend over time after e-cigarettes started to gain popularity was not significant (ie, not significantly different from 0).

Conclusions The increased popularity of e-cigarettes since 2014 is associated with a greater decline in youth smoking, compared with previous years. On the contrary, e-cigarette use has remained very low among Taiwanese male adults and no additional impact on the conventional smoking trend is found.

tax increase from its previous level of $NT21 8, and the implementation of a well-subsidised cessation service. In addition, according to the Taiwan Global Youth Tobacco Survey (TGYTS),[5] conducted by the Health Promotion Administration (HPA), an agency of the Ministry of Health and Welfare (MoHW), smoking prevalence among senior high school students continued a favourable decline, from 14.7% in 2011 to 8.3% in 2017,[3] reaching an historical low in every recent year.

While smoking prevalence declined, last 30-day use of e-cigarettes also declined from its low level of 0.9% in 2015[6] to 0.5% in 2017.[3] In contrast, the use of e-cigarettes among senior high school students increased from 2.1% in 2014 to 4.5% in 2017.[3] Chen and colleagues also found that around 2% of Taiwanese high school students were dual users (of both conventional cigarettes and e-cigarettes) in 2014–2016[7] and that e-cigarette users were more likely to attempt to quit smoking than students who exclusively smoked conventional cigarettes.[8]

Unlike many countries in Europe[9] and North America,[10] where e-cigarettes are legal, the MoHW has classified e-cigarette liquid (e-liquid) containing nicotine as a drug in Taiwan.[11] Since no legal licenses have been issued, such products are accordingly treated as illegal pharmaceutical products. However, vaping devices and e-liquids without nicotine can still be purchased in so-called vape shops while a wide range of flavoured e-liquids containing nicotine is readily available on the black market or over the internet. The main reason for these restrictive regulations is the concern that e-cigarette use

在台灣男性青少年吸電子煙是否刺激轉吸傳統菸?

6.221

- 台灣青少年吸電子煙雖有增加，傳統菸的吸菸率卻在減少。
- 可能有助於吸菸率的下降。

空污是新吸菸

WHO 幹事長DrTedros說的

譚德塞

世界衛生組織幹事長

空污不是新吸菸6.221

Special communication

OPEN ACCESS

Air pollution is not 'the new smoking': comparing the disease burden of air pollution and smoking across the globe, 1990–2017

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ABSTRACT

Air pollution has been labelled the 'new smoking', with news articles bearing titles such as 'If You Live in a Big City You Already Smoke Every Day' and 'The Air Is So Bad in These Cities, You May As Well Be Smoking'. Dr Tedros Adhanom Ghebreyesus, WHO Director-General, highlighted this attention-catching comparison, saying, 'The world has turned the corner on tobacco. Now it must do the same for the "new tobacco" – the toxic air that billions breathe every day' and 'Globally, with smoking on the decline, air pollution now causes more deaths annually than tobacco' at the First Global Conference on Air Pollution and Health in 2018. The suggestion that the world has turned the corner on tobacco control and the reference to air pollution as the 'new smoking' raise a number of concerns. We generate outputs from GBD Compare (the online data visualisation tool of the Global Burden of Diseases and Injuries (GBD) Study) to demonstrate historical disease burden trends in terms of disability-adjusted life years and age-standardised mortality attributable to air pollution and tobacco use from 1990 to 2017 across the globe. We find that the disease burden caused by ambient air pollution declined significantly faster than the burden caused by tobacco use. We conclude that the world is still far from turning the corner on the tobacco endemic. Further, the suggestion that air pollution is as bad as actual smoking is not only inaccurate but also potentially dangerous to public health.

Analogising other health risks as 'the new smoking' to highlight their danger is not new. This equivalence has been made for several other risk factors that received momentary media prominence, including prolonged sitting, obesity, high-protein diets and diets high in processed meats.[5] However, most of the 'new smoking' hypes have been short-lived,[6] and 'old smoking' continues to be the unresolved, second-largest cause of death worldwide.[7] Since this analogy is common, it is essential to consider how such a comparison could potentially affect global tobacco control and aspects of daily life such as outdoor physical activity.

There are a number of concerns raised by suggestions that the world has turned the corner on the tobacco endemic and that air pollution is the 'new smoking'.

FIRST, THE WORLD HAS NOT TURNED THE CORNER ON THE TOBACCO ENDEMIC

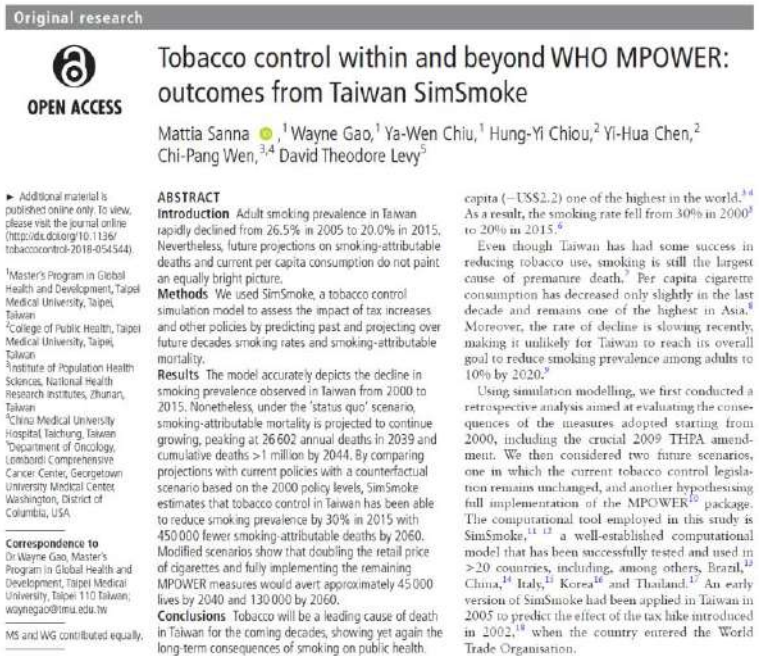
Smoking remains one of the top preventable causes of death and disability despite decades of tobacco control efforts and some promising successes. However, currently only two countries—Brazil and Turkey—have implemented all MPOWER measures at best-practice level as recommended by WHO.[8] Many countries with a high-disease burden from tobacco, such as China, Indonesia and even high-income countries like Germany, have seen limited progress in controlling the smoking and tobacco

- 兩者差別太大，危言聳聽
- 1）菸害死亡是全球第一位可預防，
- 2）菸害數目可驗證，有死亡診斷書
  - 空污死亡找不到死亡診斷書。發生在何地、年齡均不知。是數學模式推算，無法驗證。
- 3）減少吸菸者可減少死亡數，但減少空污看不到死亡數會減少，
- 4）空污的危害是菸的千分之一。

菸害將持續為台灣可預防死因之第一位，即使按照世衛組織建議大加菸價，

五十年內無法達到吸菸率<5%的境界

台灣政府持續採取低菸價政策(2011-2016)，結果菸商自抬菸價， 漲高價菸、不漲低價菸



Original research

OPEN ACCESS

Tobacco control within and beyond WHO MPOWER: outcomes from Taiwan SimSmoke

Mattia Sanna ,[1] Wayne Gao,[1] Ya-Wen Chiu,[1] Hung-Yi Chiou,[2] Yi-Hua Chen,[2] Chi-Pang Wen,[3,4] David Theodore Levy[5]

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MS and WG contributed equally.

ABSTRACT

Introduction Adult smoking prevalence in Taiwan rapidly declined from 26.5% in 2005 to 20.0% in 2015. Nevertheless, future projections on smoking-attributable deaths and current per capita consumption do not paint an equally bright picture.

Methods We used SimSmoke, a tobacco control simulation model to assess the impact of tax increases and other policies by predicting past and projecting over future decades smoking rates and smoking-attributable mortality.

Results The model accurately depicts the decline in smoking prevalence observed in Taiwan from 2000 to 2015. Nonetheless, under the 'status quo' scenario, smoking-attributable mortality is projected to continue growing, peaking at 26 602 annual deaths in 2039 and cumulative deaths >1 million by 2044. By comparing projections with current policies with a counterfactual scenario based on the 2000 policy levels, SimSmoke estimates that tobacco control in Taiwan has been able to reduce smoking prevalence by 30% in 2015 with 450 000 fewer smoking-attributable deaths by 2060. Modified scenarios show that doubling the retail price of cigarettes and fully implementing the remaining MPOWER measures would avert approximately 45 000 lives by 2040 and 130 000 by 2060.

Conclusions Tobacco will be a leading cause of death in Taiwan for the coming decades, showing yet again the long-term consequences of smoking on public health.

capita (~US$2.2) one of the highest in the world.[3 4] As a result, the smoking rate fell from 30% in 2000[3] to 20% in 2015.[6]

Even though Taiwan has had some success in reducing tobacco use, smoking is still the largest cause of premature death.[7] Per capita cigarette consumption has decreased only slightly in the last decade and remains one of the highest in Asia.[8] Moreover, the rate of decline is slowing recently, making it unlikely for Taiwan to reach its overall goal to reduce smoking prevalence among adults to 10% by 2020.[9]

Using simulation modelling, we first conducted a retrospective analysis aimed at evaluating the consequences of the measures adopted starting from 2000, including the crucial 2009 THPA amendment. We then considered two future scenarios, one in which the current tobacco control legislation remains unchanged, and another hypothesising full implementation of the MPOWER[10] package. The computational tool employed in this study is SimSmoke,[11 12] a well-established computational model that has been successfully tested and used in >20 countries, including, among others, Brazil,[13] China,[14] Italy,[15] Korea[16] and Thailand.[17] An early version of SimSmoke had been applied in Taiwan in 2005 to predict the effect of the tax hike introduced in 2002,[18] when the country entered the World Trade Organisation.

Exploiting a low tax system: non-tax-induced cigarette price increases in Taiwan 2011–2016

Wayne Gao,[1] Mattia Sanna,[1] J Robert Branston,[2] Hung-Yi Chiou,[3] Yi-Hua Chen,[3] Allison Wu,[1] Chi Pang Wen[4,5]

ABSTRACT

Introduction This study aims to analyse the non-tax-induced price increasing strategies adopted by tobacco industry in Taiwan, a high-income country with comprehensive tobacco control policies but low tobacco taxes and a declining cigarette market.

Methods Using governmental tax, price and inflation data, we analysed cigarette sales volume, affordability, affordability elasticity of demand, market share, pricing and net revenue of the top five tobacco companies in Taiwan from 2011 to 2016 when no tax increases occurred.

Results Total revenue after tax grew significantly for all the major transnational tobacco companies between 2011 and 2016 at the expense of the state-owned Taiwan Tobacco and Liquor Corporation. In terms of market share, Japan Tobacco (JT) was the leading company, despite experiencing a small decline, while British American Tobacco and Imperial Brands remained stable, and Philip Morris International increased from 4.7% to 7.0%. JT adopted the most effective pricing strategy by increasing the real price of its two most popular brands (Mevius and Mi-Ne) and, at the same time, doubling the sales of its cheaper and less popular brand Winston by leaving its nominal retail price unaltered.

Conclusions Low and unchanged tobacco taxes enable tobacco companies to use aggressive pricing and segmentation strategies to increase the real price of cigarettes without making them less affordable while simultaneously maintaining customers' loyalty. It is crucial to continue monitoring the industry's pricing strategies and to regularly increase taxes to promote public health and to prevent tobacco industry from profiting at the expense of government revenues.

Background

In the last two decades, Taiwan has made important progress in tobacco control, especially after 2009 when regulations were tightened in line with the guidelines provided by the Framework Convention on Tobacco Control (FCTC). Smoking has been forbidden in most work sites and public spaces, tobacco advertisement and promotion have been banned and pictorial health warnings have been introduced. Moreover, taxes were increased several times during the last two decades, with positive effects on tobacco consumption.[12–14] As a result of all these measures, during the 2009–2016 period, the smoking rate decreased from 20% to 15% among adults, and from 14.8% to 9.3% among senior high school students (16–18 years old).[15] Smoking is largely a male and age-related habit in Taiwan. In 2005, the age group with the highest smoking rate among men was the 40–44 years old group (57.4%),[16] while in 2015 it was the 50–54 one (47.4%).[17] During the same period, the smoking rate among men aged 25–29 years decreased from 47.9% to 22.4%. The daily consumption of adult smokers decreased from 19 cigarettes in 2008 to 17.3 cigarettes in 2016, while the cigarette consumption per capita above the age of 15 years old decreased by 5.9% from 1970 in 2009 to 1857 in 2016.[12] (Here and in the rest of the paper, the percentage change is calculated with the midpoint method).[18]

In Taiwan, manufactured cigarettes are by far the most common form of tobacco smoking, while the use of other products is extremely limited. In 2016, the entire market share of non-cigarette tobacco products, including everything from hand-rolling, chewing and pipe tobacco, to cigars and snuff, was

中國醫護人員新冠肺炎死亡率，隨時間遞減

RESEARCH ARTICLE

Geo-temporal distribution of 1,688 Chinese healthcare workers infected with COVID-19 in severe conditions—A secondary data analysis

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Abstract

Introduction

The COVID-19 outbreak is posing an unprecedented challenge to healthcare workers. This study analyzes the geo-temporal effects on disease severity for the 1,688 Chinese healthcare workers infected with COVID-19.

Methods

Using the descriptive results recently reported by the Chinese CDC, we compare the percentage of infected healthcare workers in severe conditions over time and across three areas in China, and the fatality rate of infected healthcare workers with all the infected individuals in China aged 22–59 years.

Results

Among the infected Chinese healthcare workers whose symptoms onset appeared during the same ten-day period, the percentage of those in severe conditions decreased significantly from 19.7% (Jan 11–20) to 14.4% (Jan 21–31) to 8.7% (Feb 1–11). Across the country, there was also a significant difference in the disease severity, with Wuhan being the most severe (17.3%), followed by Hubei Province (10.2%), and the rest of China (6.6%). The case fatality rate for the 1,688 infected Chinese healthcare workers was significantly lower than that for the 29,798 infected patients aged 20–59 years—0.3% (5/1,688) vs. 0.65% (193/29,798), respectively.

Conclusion

The disease severity among infected healthcare workers improved considerably over a short period of time in China. The more severe conditions in Wuhan compared to the rest of the country may be attributable to the draconian lockdown. The clinical outcomes of infected Chinese healthcare workers may represent a more accurate estimation of the severity of COVID-19 for those who have access to quality healthcare.

The **Lancet Diabetes & Endocrinology** has an **Impact Factor** of 25.340

Change in albuminuria and subsequent risk of end-stage kidney disease: an individual participant-level consortium meta-analysis of observational studies

Josef Coresh, Hiddo J L Heerspink, Yingying Sang, Kunihiro Matsushita, Johan Arnlov, Brad C Astor, Carol Blood, Nigel J Brunskill, Juan-Jesus Carrero, Harold I Feldman, Caroline S Fox, Lesley A Inker, Asif Iqbal, Sadayoshi Ito, Simerjit Jassal, Tsuneo Konta, Kasun Polkinghorne, Sofia Ref Romundstad, Marie D Sallo, Nikita Stempniewicz, Benedicte Stengel, Marcello Tonelli, Mitsuyoshi Umizumi, Sushrut S Waikar, Chi-Pang Wen, Jack F M Wetzels, Mark Woodward, Morgan E Grams, Caitlin P Kennedy, Andrew S Levey, Ron T Gansevoort, for the Chronic Kidney Disease Prognosis Consortium and Chronic Kidney Disease Epidemiology Collaboration*

Summary

Background Change in albuminuria as a surrogate endpoint for progression of chronic kidney disease is strongly supported by biological plausibility, but empirical evidence to support its validity in epidemiological studies is lacking. We aimed to assess the consistency of the association between change in albuminuria and risk of end-stage kidney disease in a large individual participant-level meta-analysis of observational studies.

Methods In this meta-analysis, we collected individual-level data from eligible cohorts in the Chronic Kidney Disease Prognosis Consortium (CKD-PC) with data on serum creatinine and change in albuminuria and more than 50 events on outcomes of interest. Cohort data were eligible if participants were aged 18 years or older, they had a repeated measure of albuminuria during an elapsed period of 3 months to 4 years, subsequent end-stage kidney disease or mortality follow-up data, and the cohort was active during this consortium phase. We extracted participant-level data and quantified percentage change in albuminuria, measured as change in urine albumin-to-creatinine ratio (ACR) or urine protein-to-creatinine ratio (PCR), during baseline periods of 1, 2, and 3 years. Our primary outcome of interest was development of end-stage kidney disease after a baseline period of 2 years. We defined an end-stage kidney disease event as initiation of kidney replacement therapy. We quantified associations of percentage change in albuminuria with subsequent end-stage kidney disease using Cox regression in each cohort, followed by random-effects meta-analysis. We further adjusted for regression dilution to account for imprecision in the estimation of albuminuria at the participant level. We did multiple subgroup analyses, and also repeated our analyses using participant-level data from 14 clinical trials, including nine clinical trials not in CKD-PC.

Findings Between July, 2015, and June, 2018, we transferred and analysed data from 28 cohorts in the CKD-PC, which included 693 816 individuals (537 583 [80%] with diabetes). Data for 675 904 individuals and 7461 end-stage kidney disease events were available for our primary outcome analysis. Change in ACR was consistently associated with subsequent risk of end-stage kidney disease. The adjusted hazard ratio (HR) for end-stage kidney disease after a 30% decrease in ACR during a baseline period of 2 years was 0·83 (95% CI 0·74–0·94), decreasing to 0·78 (0·66–0·92) after further adjustment for regression dilution. Adjusted HRs were fairly consistent across cohorts and subgroups (ie, estimated glomerular filtration rate, diabetes, and sex), but the association was somewhat stronger among participants with higher baseline ACR than among those with lower baseline ACR ($p_{heterogeneity}$<0·0001). In individuals with baseline ACR of 300 mg/g or higher, a 30% decrease in ACR over 2 years was estimated to confer a more than 15% absolute reduction in 10-year risk of end-stage kidney disease, even at early stages of chronic kidney disease. Results were generally similar when we used change in PCR and when study populations from clinical trials were assessed.

Interpretation Change in albuminuria was consistently associated with subsequent risk of end-stage kidney disease across a range of cohorts, lending support to the use of change in albuminuria as a surrogate endpoint for end-stage kidney disease in clinical trials of progression of chronic kidney disease in the setting of increased albuminuria.

Funding US National Kidney Foundation and US National Institute of Diabetes and Digestive and Kidney Diseases.

Introduction

On March 15–16, 2018, a scientific workshop sponsored by the US National Kidney Foundation (NKF), in collaboration with the US Food and Drug Administration (FDA) and European Medicines Agency (EMA), investigated candidate surrogate endpoints for clinical trials of drugs designed to slow the progression of kidney disease, particularly among patients in the early stages of chronic kidney disease. For decades, change in albuminuria has been used in some clinical trials for the development of

蛋白尿的出現或改變
是洗腎風險的預兆

發炎指數與自殺的關係

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Evidence for an association between inflammatory markers and suicide: a cohort study based on 359,849 to 462,747 Taiwanese adults

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ABSTRACT

Background: Biological markers of suicide risk have the potential to inform prevention and treatment efforts. It has recently been hypothesised that inflammation may influence mood and in turn suicide risk. We investigated the association between indicators of systemic inflammation and suicide in a large cohort of Taiwanese adults.

Methods: White blood cell (WBC) count and levels of C-reactive protein (CRP) were measured in 462,747 and 359,849 adults in the Taiwan MJ cohort, respectively. The associations between WBC, CRP and suicide risk were investigated using Cox proportional hazards models adjusting for a range of potential confounding factors.

Results: During a mean 15.1 and 15.8 years of follow-up, 687 and 605 suicides were identified in participants who had information on WBC and CRP respectively. There was an association of suicide with WBC count (adjusted hazard ratio [aHR] = 1.13 per 1 standard deviation increase of log-transformed WBC, 95% confidence interval [CI] 1.09, 1.77). The association was driven by the highest quintile of WBC count (aHR = 1.39, 95% CI 1.09, 1.77; reference: the lowest quintile). No association between CRP and suicide was found.

Limitations: Our cohort was from a privately-run health check-up programme and had a lower suicide rate than that in the general population.

Conclusions: Individuals with the highest WBC counts may have increased risk of suicide. Peripheral markers of inflammation are potential biomarkers of suicide risk; however, this seems to vary by population and the marker investigated and could be influenced by a range of confounding factors.

FDA approves for emergency use in early cases of COVID 19

Regeneron antibody cocktail

Inmazeb

- before patients are hospitalized or require oxygen therapy. The drug should be given as soon as possible after a positive viral test, according to the FDA.

Eli Lilly's

bamlanivimab

a monoclonal antibody

Genetic Vaccines

Vaccines that deliver one or more of the coronavirus's own genes into our cells to provoke an immune response.

PHASE 3

moderna NIH National Institutes of Health
Turning Discovery Into Health

Moderna develops vaccines based on messenger RNA (mRNA) to produce viral proteins in the body. They have yet to bring one to the market. In January, they began developing a vaccine for the coronavirus. The vaccine contains genetic instructions for building a coronavirus protein, known as spike. When injected into cells, the vaccine causes them to make spike proteins, which then get released into the body and provoke a response from the immune system.

The United States government bankrolled Moderna's efforts, providing

PHASE 2 PHASE 3 COMBINED PHASES

BIONTECH Pfizer FOSUN PHARMA

On Nov. 9, New York-based **Pfizer** and the German company **BioNTech** made history by presenting preliminary data indicating that their coronavirus vaccine was over 90 percent effective. It was the first time anyone had found such evidence. A week later, Moderna reported similar findings with a similar vaccine.

In May Pfizer and BioNTech launched a Phase 1/2 trial on two versions of a mRNA vaccine. They found that both versions caused volunteers to

PHASE 1 PHASE 2 COMBINED PHASES

Imperial College London MORNINGSIDE

Imperial College London researchers have developed a "self-amplifying" RNA vaccine, which boosts production of a viral protein to stimulate the immune system. They began Phase 1/2 trials on June 15 and have partnered with **Morningside Ventures** to manufacture and distribute the vaccine through a new company called VacEquity Global Health. The researchers expect to know if the vaccine is effective by the end of the year.

PHASE 1 PHASE 2 COMBINED PHASES

AnGes 大阪大学 OSAKA UNIVERSITY TaKaRa

On June 30, the Japanese biotechnology company **AnGes** announced they had started Phase 1 trials on a DNA-based vaccine, developed in partnership with **Osaka University** and **Takara Bio**. The company will present initial results of the trials in November and are planning for a Phase 3 trial by the end of the year.

Updated Sept. 30

PHASE 1 PHASE 2 COMBINED PHASES

ARCTURUS therapeutics DukeNUS Medical School

The California-based company **Arcturus Therapeutics** and **Duke-NUS Medical School** in Singapore have developed an mRNA vaccine. It has a "self-replicating" design that leads to a greater production of viral proteins. Tests on animals showed that it protected them against infection. In August, Arcturus launched a Phase 1/2 trial at Singapore General Hospital. On Nov. 9, the company announced that an interim analysis of the trial showed that the vaccine produced an immune response that's in the range of responses seen in people who recovered from Covid-19. Singapore

PHASE 2

INOVIO POWERING DNA MEDICINES

The American company **Inovio** has developed DNA-based vaccines which are delivered into the skin with electric pulses from a hand-held device. They have vaccines in clinical trials for a number of diseases, and in June they announced interim data from a Phase 1 trial on Covid-19. They found no serious adverse effects, and measured an immune response in 34 out of 36 volunteers. Inovio has yet to publish detailed results of these studies, however, and it is embroiled in several lawsuits with stockholders and a company partner. On Sept. 28, the F.D.A. put the vaccine on a partial hold due to questions about the delivery device. On Nov. 16, Inovio said that the F.D.A. had given them permission to move forward with their Phase 2 trial.

Updated Nov. 16

PHASE 1

Genexine

The Korean company **Genexine** started testing the safety of a DNA-based vaccine in June. They anticipate moving to Phase 2 trials in the fall.

Updated June 24

PHASE 1

ABOGEN WALVAX 沃森生物 WALVAX BIOTECHNOLOGY CO., LTD.

In June, Chinese researchers at the **Academy of Military Medical Sciences**, **Suzhou Abogen Biosciences** and **Walvax Biotechnology** announced they would start their country's first safety trials on a mRNA-

based vaccine, called ARCoV. Earlier studies on monkeys reportedly showed protective effects.

Updated June 26

PHASE 1

Chula Chulalongkorn University

Chula VRC
Chula Vaccine Research Center

Researchers at Thailand's **Chulalongkorn University** have been developing several potential vaccines for the coronavirus. The furthest along is an mRNA-based vaccine known as ChulaCov19. On Sept. 29, the **Chula Vaccine Research Center** registered a Phase 1 trial to test it in humans. In an interview with the Bangkok Post, the leader of the project said that up to 30 million doses might be produced for Thailand and six other Asian countries if the vaccine proved to be safe and effective.

Updated Sept. 30

PHASE 1

entos

The Canadian company **Entos Pharmaceuticals** has created a DNA vaccine for the coronavirus. Most other genetic vaccines carry the gene for the spike protein on the surface of the virus. Entos instead chose the gene for nucleocapsid, a protein that sits inside the virus's membrane. They are betting it can offer long-lasting immunity. In October, Entos launched a Phase 1 trial in Canada for their vaccine, called Covigenix VAX-001.

Updated Oct. 20

PHASE 1

symvivo

On Nov. 2, the Canadian company **Symvivo** announced they had administered a DNA vaccine to their first volunteer in a Phase 1 trial. The DNA is inserted into harmless bacteria, which volunteers swallow in a frozen liquid (the company is working on putting the bacteria into a pill). When the bacteria reach the intestines, the DNA slips into cells in the gut lining, which then make viral proteins.

Updated Nov. 3

PHASE 1

oncosec
IMMUNOTHERAPIES

New Jersey-based **OncoSec Immunotherapies** has developed experimental cancer treatments that deliver genes into tumors. There, the injected genes produce a natural signalling molecule called IL-12, which attracts the attention of immune cells that attack the cancer. In the spring, OncoSec began adapting their technology to make a vaccine for the coronavirus. The vaccine, called CORVax12, consists of a loop of DNA that encodes both the spike protein and IL-12. Causing the body to make extra IL-12 could potentially enhance the immune system's ability to make antibodies to the spike protein. On Nov. 13, the company registered a Phase 1 trial to test the safety of the CORVax12.

Updated Nov. 13

PRECLINICAL

SANOFI Translate BIO

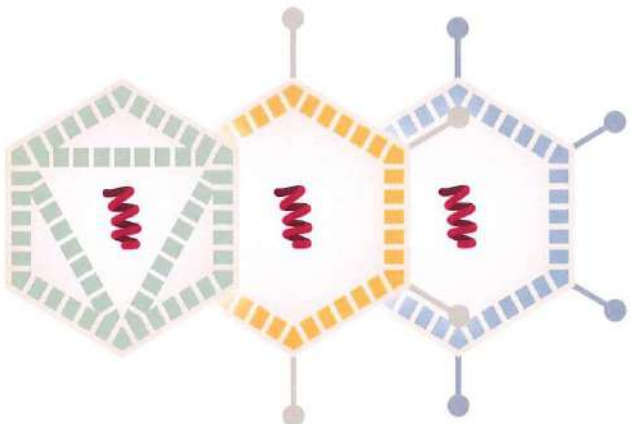
The French pharmaceutical company **Sanofi** is developing an mRNA vaccine in partnership with **Translate Bio.** They have found that it produces a strong antibody response in mice and monkeys and are planning on starting Phase 1 trials by December. It would become Sanofi's second Covid-19 vaccine candidate in clinical trials, along with their protein-based vaccine.

Updated Oct. 15

PRECLINICAL

Viral Vector Vaccines

Vaccines that contain viruses engineered to carry coronavirus genes. Some viral vector vaccines enter cells and cause them to make viral proteins. Other viral vectors slowly replicate, carrying coronavirus proteins on their surface.



PHASE 3 APPROVED FOR LIMITED USE IN CHINA

CanSinoBIO

The Chinese company **CanSino Biologics** developed a vaccine based on an adenovirus called Ad5, in partnership with the Institute of Biology at the country's **Academy of Military Medical Sciences**. In May, they published promising results from a Phase 1 safety trial, and in July they reported that their Phase 2 trials demonstrated the vaccine produced a strong immune response. In an unprecedented move, the Chinese military approved the vaccine on June 25 for a year as a "specially needed drug." CanSino would not say whether vaccination would be mandatory or optional for soldiers. Starting in August, CanSino began running Phase 3 trials in a number of countries, including Saudi Arabia, Pakistan and Russia.

Updated Sept. 24

PHASE 3 APPROVED FOR EARLY USE IN RUSSIA

МИНИСТЕРСТВО ЗДРАВООХРАНЕНИЯ РОССИЙСКОЙ ФЕДЕРАЦИИ

The **Gamaleya Research Institute**, part of Russia's Ministry of Health, launched clinical trials in June of a vaccine they called Gam-Covid-Vac. It is a combination of two adenoviruses, Ad5 and Ad26, both engineered with a coronavirus gene.

On Aug. 11, President Vladimir V. Putin announced that a Russian health care regulator had approved the vaccine, renamed Sputnik V, before Phase 3 trials had even begun. Vaccine experts decried the move as risky, and Russia later walked back the announcement, saying that the approval was a "conditional registration certificate," which would depend on positive results from Phase 3 trials. Those trials, initially planned for just 2,000 volunteers, were expanded to 40,000. In addition to Russia, volunteers were recruited in Belarus, the United Arab Emirates, and Venezuela. On Oct. 17, a Phase 2/3 trial was launched in India.

On Sept. 4, three weeks after Putin's announcement, Gamaleya researchers published the results of their Phase 1/2 trial. In a small study, they found that Sputnik yielded antibodies to the coronavirus and mild side effects. Meanwhile, Russia negotiated agreements to supply the vaccine to countries including Argentina, Brazil, Mexico and India.

On Nov. 11, the Russian Direct Investment Fund announced preliminary evidence from their Phase 3 trial indicating that the vaccine is effective. Based on 20 cases of Covid-19 among the trial participants, Russian

scientists estimated that the vaccine demonstrated 92 percent efficacy. Outside experts said that was possible, but they also said that data from more cases would be needed to see if that estimate held up. In their press release, the fund said that the results of the trial would be eventually published in a peer-reviewed scientific journal. The announcement came two days after Pfizer announced similar results on 94 volunteers in its own Phase 3 trial.

Updated Nov. 11

PHASE 3

Johnson & Johnson — Beth Israel Lahey Health, Beth Israel Deaconess Medical Center

A decade ago, researchers at **Beth Israel Deaconess Medical Center** in Boston developed a method for making vaccines out of a virus called Adenovirus 26, or Ad26 for short. **Johnson & Johnson** developed vaccines for Ebola and other diseases with Ad26 and have now made one for the coronavirus. In March they received $456 million from the United States government to support their move towards production. The vaccine has provided protection in experiments on monkeys. Johnson & Johnson began Phase 1/2 trials in July and launched a Phase 3 trial with up to 60,000 participants in September. Unlike other Phase 3 trials, Johnson & Johnson administered just a single dose instead of two.

In August, the federal government agreed to pay $1 billion for 100 million doses if the vaccine is approved. The European Union reached a similar deal on Oct. 8 for 200 million doses. The company is aiming for production of at least a billion doses in 2021.

On Oct. 12, Johnson & Johnson announced it put its trial on pause to investigate an adverse reaction in a volunteer. The trial resumed eleven days later. Despite the delay, the company expects to get results by the end of the year. On Nov. 16, Johnson & Johnson announced that they were launching a second Phase 3 trial to observe the effects of two doses of their vaccine, instead of just one.

Updated Nov. 16

PHASE 2 PHASE 3 COMBINED PHASES

AstraZeneca — University of Oxford

The British-Swedish company **AstraZeneca** and the **University of Oxford** developed a vaccine based on a chimpanzee adenovirus called ChAdOx1. In May, the United States awarded the project $1.2 billion in support for 300 million doses should the vaccine prove effective. A study on monkeys found that the vaccine protected the animals from the disease. In a Phase 1/2 trial, the vaccine developers did not detect any severe side effects. They found that the vaccine raised antibodies against the coronavirus as well as other immune defenses. The vaccine began Phase 2/3 trials in England and India (where it's known as Covishield). In addition, AstraZeneca launched Phase 3 trials in Brazil, South Africa, and the United States.

In August the European Union reached an agreement for AstraZeneca to deliver 400 million doses if the trials yield positive results. The company has said their total manufacturing capacity for the vaccine, if approved, stands at two billion doses. India's Serum Institute has already produced millions of doses to be used in trials.

On Sept. 6, AstraZeneca halted global trials of the vaccine to investigate one volunteer, who developed a form of inflammation called transverse myelitis. Within a week, the trials began in all countries except the United States. Meanwhile, a newspaper in Brazil reported on Oct. 21 that a volunteer in the trial there died of Covid-19. While AstraZeneca would not comment on the case, the trial was not paused, which led outside experts to conclude that the volunteer must have received a placebo. On Oct. 23, the F.D.A. authorized the restart of the trial. The C.E.O. of AstraZeneca said in a Nov. 5 interview with Bloomberg that the company expected results from their trial by the end of December.

Updated Nov. 6

PHASE 1

The Italian biotechnology company **ReiThera** has developed a Covid-19 vaccine, called GRAd-COV2, that is based on an adenovirus that infects gorillas. Working in collaboration with the **Lazzaro Spallanzani National Institute for Infectious Diseases** in Rome, they launched a Phase 1 trial at the end of July.

Updated Aug. 28

PHASE 1

While many vaccines are given as injections, some vaccines can be taken as a pill. Oral vaccines have been approved for diseases including polio, cholera, and typhoid fever. The small San Francisco company **Vaxart** specializes in developing oral vaccines. They have created and tested pills for influenza and other diseases. Earlier this year, Vaxart began work on an oral vaccine for Covid-19. It contains an adenovirus called Ad5 (the same viral vector in CanSinoBio's vaccine and in Russia's Sputnik V).

When Vaxart gave the pill to mice, they produced antibodies against the coronavirus. Mice don't suffer symptoms of Covid-19, however, so the researchers then switched to hamsters, which do. In an unpublished study, they found that the vaccine pill not only dramatically reduced the amount of coronavirus in sick hamsters, but also protected them from two important symptoms of the disease: weight loss and swollen lungs. In October, the company began giving the pill to volunteers in a Phase 1 clinical trial.

Although none of Vaxart's vaccines have yet been licensed, the company's stock price increased 3,600 percent in the first half of 2020. In June, The New York Times reported, a hedge fund that partly controlled the company sold off most of its shares, netting over $200 million in profits. In the wake of that reporting, the Department of Justice began investigating the company, while a number of shareholder lawsuits were brought against Vaxart, its executives and its board.

Updated Nov. 12

PHASE 1

The American company **Merck** acquired the Austrian firm **Themis Bioscience** in June and is working on a vaccine originally developed at **Institut Pasteur**. The vaccine uses a weakened measles virus that carries a gene for the coronavirus spike protein. Researchers launched a Phase 1 trial in August.

Updated Aug. 12

PHASE 1

In 2019, researchers at the **University of Hong Kong** and **Xiamen University** created a nasal-spray vaccine for the flu based on a genetically weakened form of the influenza virus. Earlier this year, they engineered the vaccine to produce part of the coronavirus spike protein as well. On Sept. 9, they received approval to start clinical trials in partnership with **Beijing Wantai Biological Pharmacy**.

Updated Sept. 9

PHASE 1

Three decades ago, the **German Center for Infection Research** developed a smallpox vaccine from a harmless virus called Modified Vaccinia Ankara, or MVA for short. In recent years, they adapted it to create a vaccine for MERS, a disease caused by another coronavirus. This spring, they made an MVA-based vaccine for SARS-CoV-2, the coronavirus that is causing the Covid-19 pandemic. It carries the gene for the spike protein, which is produced inside cells that it invades. On Sept. 29, the center and a consortium of German universities registered a Phase 1 trial. The vaccine is expected to be ready for approval by the end of 2021.

Updated Sept. 29

PHASE 1

In addition to its project with Themis, **Merck** is partnering with **IAVI** on a second viral vector vaccine. It is based on vesicular stomatitis viruses, the same approach Merck successfully used to produce the first approved vaccine for Ebola. They have designed their coronavirus vaccine as a pill, which could potentially make it easier to distribute than syringes for injections. Merck and IAVI received $38 million from the United States government to support their research, and on September 30 they registered a Phase 1 trial.

Updated Aug. 27

PHASE 1

The California-based company **ImmunityBio** launched a Phase 1 trial of a Covid-19 vaccine in October. The vaccine uses the Ad5 adenovirus, the same one used by CanSinBio and the Gamelaya Institute in Russia. ImmunityBio has engineered the Ad5 virus to carry genes for two genes from the coronavirus. In addition to the spike protein, it also carries the gene for a protein called nucleocapsid. The company hopes that this combination will provoke a strong immune response to the virus. The chairman and C.E.O. of ImmunityBio is billionaire Patrick Soon-Shiong, the owner of the Los Angeles Times.

Updated Oct. 27

PHASE 1

In the spring, the **Israel Institute for Biological Research** started work on a coronavirus vaccine based on vesicular stomatitis viruses. They engineered the viruses to carry the gene for the coronavirus spike protein. On Oct. 25, the Israeli government announced that the vaccine, called Brilife, would be going into Phase 1 trials. If the vaccine is successful in Phase 1 and Phase 2 trials, researchers hope to start Phase 3 trials in spring 2021.

Updated Oct. 26

PRECLINICAL

The Swiss company **Novartis** will manufacture a vaccine based on a gene therapy treatment developed by the Massachusetts Eye and Ear Hospital, Massachusetts General Hospital and the Gene Therapy Program at the University of Pennsylvania. A virus called an adeno-associated virus delivers coronavirus gene fragments into cells. Phase 1 trials are set to begin in late 2020.

Updated Aug. 24

Protein-Based Vaccines

Vaccines that contain coronavirus proteins but no genetic material. Some vaccines contain whole proteins, and some contain fragments of them. Some pack many of these molecules on nanoparticles.

PHASE 3

NOVAVAX
Creating Tomorrow's Vaccines Today

Maryland-based **Novavax** makes vaccines by sticking proteins onto microscopic particles. They've taken on a number of different diseases this way; their flu vaccine finished Phase 3 trials in March. The company launched trials for a Covid-19 vaccine in May, and the Coalition for Epidemic Preparedness Innovations has invested $384 million in the vaccine. In July the U.S. government awarded $1.6 billion to support the vaccine's clinical trials and manufacturing.

After getting promising results from preliminary studies in monkeys and humans, Novavax launched a Phase 2 trial in South Africa in August. The blinded, placebo-controlled trial on 2,900 people will measure not just the safety of the vaccine but its efficacy. The following month, Novavax launched a Phase 3 trial enrolling up to 15,000 volunteers in the United Kingdom. It could potentially deliver results by the start of 2021. A larger Phase 3 trial is in development to launch in the United States by the end of November.

In September Novavax reached an agreement with the Serum Institute of India, a major vaccine manufacturer, that they said would enable them to produce as many as 2 billion doses a year. If the trials succeed, Novavax expects to deliver 100 million doses for use in the United States by the first quarter of 2021. On Nov. 4 they announced another agreement to deliver 40 million doses to Australia.

Updated Nov. 6

PHASE 2 PHASE 3 COMBINED PHASES

medicago gsk

Canada-based **Medicago**, partly funded by the cigarette maker Philip Morris, uses a species of tobacco to make vaccines. They deliver virus genes into leaves, and the plant cells then create protein shells that mimic viruses. In July, Medicago launched Phase 1 trials on a plant-based Covid-19 vaccine in combination with adjuvants to boost the immune system's response to the viral proteins. In that study, they found that an adjuvant made by GSK produced promising levels of antibodies in volunteers. On Oct. 23, the company announced it had reached an agreement with the government of Canada to supply 76 million doses. A Phase 2/3 trial of the vaccine began on Nov. 12.

Updated Nov. 12

PHASE 2

ZF SW INSTITUTE OF MEDICAL BIOLOGY CHINESE ACADEMY OF MEDICAL SCIENCES

In July, the Chinese company **Anhui Zhifei Longcom** began Phase 2 trials for a vaccine that is a combination of viral proteins and an adjuvant that stimulates the immune system. The company is part of Chongqing Zhifei Biological Products and has partnered with the **Chinese Academy of Medical Sciences**. On Nov. 16, the Xinhua News Agency reported that Uzbekistan would host an upcoming Phase 3 trial of the vaccine.

Updated Nov. 16

PHASE 1 PHASE 2 COMBINED PHASES

IFV INSTITUTO FINLAY DE VACUNAS

On Aug. 18, the head of epidemiology at Cuba's public health ministry announced that the **Finlay Vaccine Institute** in Havana would start a clinical trial on a vaccine for Covid-19. The vaccine, called Soberana 1, contains a part of the spike protein, called RBD, along with two extra ingredients: proteins from a bacteria and aluminum hydroxide. These ingredients, known as adjuvants, boost the immune system's response to the coronavirus RBD.

Updated Oct. 28

PHASE 1 PHASE 2 COMBINED PHASES
APPROVED FOR EARLY USE IN RUSSIA

BEKTOP

On Aug. 26, the **Vector Institute**, a Russian biological research center, registered a Phase 1/2 trial for a coronavirus vaccine they call EpiVacCorona. The vaccine contains small portions of viral proteins, known as peptides. According to newspaper reports, the EpiVacCorona trials had already begun by then. On October 14, Vladimir Putin announced that Russia has granted regulatory approval to EpiVacCorona, making it the second vaccine to receive that designation after the Gamelaya

Institute's Sputnik V vaccine. Like the Sputnik vaccine, EpiVacCorona received approval before a Phase 3 trial to demonstrate that it was safe and effective. That trial is expected to start later this year.

Updated Oct. 14

PHASE 1 PHASE 2 COMBINED PHASES

SANOFI gsk

In addition to their mRNA vaccine, **Sanofi** developed a Covid-19 vaccine based on viral proteins. They produced the proteins with engineered viruses that grow inside insect cells. **GSK** supplemented these proteins with adjuvants that stimulate the immune system. The vaccine is based on the same design Sanofi used to create Flublok, an approved vaccine for influenza. The companies launched a Phase 1/2 clinical trial in September. They plan to start a Phase 3 trial in December and hope to know if the vaccine is safe and effective by the middle of 2021.

Starting before their clinical trials began, Sanofi negotiated several major deals to supply the vaccine, including a $2.1 billion agreement with the United States to provide 100 million doses. On Sept. 18 they closed another deal with the European Union for 300 million doses for an unspecified amount, and later reached an agreement with Canada for up to 72 million doses. In addition, Sanofi agreed to provide 200 million doses to COVAX, an international collaboration to deliver the vaccine equitably across the world. They have plans to make up to one billion doses in 2021.

Updated Oct. 28

PHASE 1 PHASE 2 COMBINED PHASES

spybiotech

SpyBiotech, a company spun off from the University of Oxford, announced in September that the first volunteers in an Australian Phase 1/2 trial were receiving their Covid-19 vaccine. The researchers created the vaccine from a mixture of proteins. Some of the proteins, from hepatitis B viruses, assemble themselves into hollow shells. The researchers decorated these shells with part of the coronavirus spike protein. The Serum Institute

of India, which licensed the technology from SpyBiotech, is running the trials.

Updated Sept. 24

PHASE 1 PHASE 2 COMBINED PHASES

Baylor College of Medicine

Texas Children's Hospital

Biological E. Limited Celebrating Life Every Day

DYNAVAX INNOVATING IMMUNOLOGY

After the SARS epidemic in 2002, **Baylor College of Medicine** researchers began developing a vaccine that could prevent a new outbreak. Despite promising early results, support for the research disappeared. Because the coronaviruses that cause SARS and Covid-19 are very similar, the researchers revived the project in partnership with the **Texas Children's Hospital**. The researchers have found that the Covid-19 vaccine produces antibodies in mice. The Indian company **Biological E** licensed it in August and launched a Phase 1/2 trial in November, combining the viral proteins with an adjuvant made by **Dynavax**. If trials confirm that the vaccine works, they hope to potentially make a billion doses a year.

Updated Nov. 16

PHASE 1

三叶草生物制药 Clover Biopharmaceuticals

gsk

DYNAVAX INNOVATING IMMUNOLOGY

Clover Biopharmaceuticals has developed a vaccine containing the spike protein from coronaviruses. To further stimulate the immune system, the vaccine is being given in conjunction with so-called adjuvants made by British drugmaker **GSK** and the American company **Dynavax**. Investments from CEPI will support the development of manufacturing that could lead to the production of hundreds of millions of doses a year.

Clover launched a Phase 1 trial in June. In September the company announced that it was expanding the trial and anticipated starting a Phase 2 trial by the end of 2020.

PHASE 1

THE UNIVERSITY OF QUEENSLAND AUSTRALIA

CSL

A vaccine from Australia's **University of Queensland** delivers viral proteins altered to draw a stronger immune response. Experiments on hamsters showed that the vaccine protected them from the coronavirus. The university launched Phase 1 trials in July, combining the proteins with an adjuvant made by **CSL**. If the results are positive, CSL will advance late stage clinical trials by the end of 2020. In September the vaccine makers reached an agreement with the Australian government to deliver 51 million doses if the trials deliver positive results. They expected their first supply of the vaccines to be ready in mid-2021.

Updated Sept. 8

PHASE 1

vaxine

The Australian company **Vaxine** developed a vaccine that combines viral proteins with an adjuvant that stimulates the immune system. A Phase 1 trial began over the summer, and Phase 2 trials are expected to commence by the end of the year.

Updated Sept. 29

PHASE 1

KBP Kentucky BioProcessing

A second tobacco-based vaccine is in development at **Kentucky**

BioProcessing, an American subsidiary of British American Tobacco, the maker of Lucky Strike and other cigarettes. Like Medicago, Kentucky BioProcessing engineers a species of tobacco called Nicotiana benthamiana to make viral proteins. The company previously used this technique to make a drug called Zmapp for Ebola. After preclinical testing in the spring, they registered a Phase 1 trial for their coronavirus vaccine in July. The trial is scheduled to start in November.

Updated Oct. 12

PHASE 1

Taiwan-based vaccine maker **Medigen** is making a vaccine made of a combination of spike proteins and an adjuvant from **Dynavax**. After a series of promising experiments on animals, they began injecting volunteers for a Phase 1 trial in early October.

Updated Oct. 13

PHASE 1

Taiwan-based vaccine manufacturer **Adimmune** got permission to launch a Phase 1 trial on Aug. 20. The vaccine contains the RBD section of the virus's spike protein.

Updated Aug. 20

PHASE 1

West China School of Medicine
West China Hospital of Sichuan University

In July, researchers at **West China Hospital of Sichuan University** published a study in Nature describing a vaccine made from the RBD region of the spike protein that could protect mice and monkeys from the coronavirus. On Aug. 24, they got approval to run a Phase 1 trial. To make the vaccine, researchers encode the RBD region in a gene, which they insert into a virus. They then infect insect cells with the virus, causing them to make the molecule in huge amounts.

Updated Aug. 27

PHASE 1

New York-based **COVAXX**, a subsidiary of United Biomedical, has created a vaccine containing parts of several viral proteins. On Sept. 11 they registered a Phase 1 trial in Taiwan. They have reached an agreement with authorities in Brazil to run their Phase 2/3 trial there.

Updated Sept. 15

PHASE 1

In the spring, researchers at the **University of Tübingen** in Germany created a vaccine made of eight parts of two viral proteins, along with an immune-stimulating adjuvant. In September they launched a Phase 1 trial.

Updated Sept. 15

PHASE 1

In October, Cuba's **Finlay Vaccine Institute** launched clinical trials on their second experimental vaccine for the coronavirus. Known as Sovereign 2, it contains the RBD part of the coronavirus spike protein. The RBD

fragment is fused to a standard tetanus vaccine, which makes it stable. It also uses aluminum hydroxide.

Updated Oct. 28

PHASE 1 ?

On July 18, **North Korea**'s State Commission of Science and Technology announced on their web site that they had started clinical trials on a vaccine based on part of the coronavirus spike protein. It's hard to independently determine how much truth there is in the claim from the isolated dictatorship. The commission claimed to have tested the vaccine on animals, but provided no data. What's more, it stated that effectiveness trials would have to be carried out in another country "since there is no case of Covid-19 in DPR Korea." That's a claim outside experts find highly doubtful.

Updated July 20

PRECLINICAL

University of Pittsburgh

A vaccine in development by the **University of Pittsburgh**, called PittCoVacc, is a skin patch tipped with 400 tiny needles made of sugar. When placed on the skin, the needles dissolve and deliver virus proteins into the body. Its creators are planning to start clinical trials in late 2020.

Updated Aug. 27

PRECLINICAL

Other protein-based vaccines in active preclinical development include vaccines from: Adaptive Phage Therapeutics; AdaptVac and Bavarian Nordic; Applied Biotechnology Institute; Artes Biotech; Axon Neuroscience; BiOMVis and University of Trento; City College of New York

Inactivated or Attenuated Coronavirus Vaccines

Vaccines created from weakened coronaviruses or coronaviruses that have been killed with chemicals.

Inactivated virus

PHASE 3 **APPROVED FOR LIMITED USE IN U.A.E.**

武汉生物制品研究所有限责任公司
WUHAN INSTITUTE OF BIOLOGICAL PRODUCTS CO.,LTD.

The **Wuhan Institute of Biological Products** developed an inactivated virus vaccine, which the state-owned Chinese company **Sinopharm** put into clinical tests. The Phase 1/2 trial showed that the vaccine produced antibodies in volunteers, some of whom experienced fevers and other side effects. They launched Phase 3 trials in the United Arab Emirates in July, and in Morocco and Peru the following month. Over the summer, the company later said, the government gave it approval to inject hundreds of thousands of people with its two experimental vaccines. On Sept. 14, the U.A.E. gave emergency approval for Sinopharm's vaccine to use on health care workers.

Updated Sept. 15

PHASE 3 **APPROVED FOR LIMITED USE IN U.A.E.**

Sinopharm also began testing a second inactivated virus vaccine, this one developed by the **Beijing Institute of Biological Products**. After running early clinical trials in China, they launched Phase 3 trials in the United Arab Emirates and Argentina. Over the summer, the company later said, the government gave it approval to inject hundreds of thousands of people with its two experimental vaccines. On Sept. 14, the U.A.E. gave emergency approval for Sinopharm's vaccine to use on health care workers before Sinopharm shared data indicating it was safe and effective. In October, the chairman of Sinopharm said the company was gearing up manufacturing for their two vaccines, with plans for producing a billion doses a year.

Updated Oct. 20

PHASE 3 APPROVED FOR LIMITED USE IN CHINA

sinovac

The private Chinese company **Sinovac Biotech** is testing an inactivated vaccine called CoronaVac. In June the company announced that Phase 1/2 trials on 743 volunteers found no severe adverse effects and produced an immune response. Sinovac then launched a Phase 3 trial in Brazil in July, followed by others in Indonesia and Turkey. On Sept. 16, they registered a Phase 1/2 trial of the vaccine for children. While Sinovac has yet to release late-stage trial data, on Oct. 19 officials in Brazil said that it was the safest of five vaccines they were testing in Phase 3 trials.

Reuters reported that the Chinese government gave the Sinovac vaccine an emergency approval for limited use in July. In October, authorities in the eastern Chinese city of Jiaxing announced they were giving CoronVac to people in relatively high-risk jobs, including medical workers, port inspectors and public service personnel.

Meanwhile, Sinovac has been preparing to manufacture the vaccine for global distribution, reaching an agreement to supply Indonesia with at least 40 million doses by March 2021. In September, Yin Weidong, the CEO of Sinovac, said the company planned on worldwide distribution of the vaccine in early 2021 — including the United States.

On Nov. 9, the Brazilian government announced they had paused the country's Sinovac trial the previous month because of an adverse event. The details of the pause were murky, raising suspicions that politics were involved. Two days after the announcement, the trial was allowed to resume.

Updated Nov. 12

PHASE 3

BHARAT BIOTECH icmr INDIAN COUNCIL OF MEDICAL RESEARCH

In collaboration with the **Indian Council of Medical Research** and the **National Institute of Virology**, the Indian company **Bharat Biotech** designed a vaccine called Covaxin based on an inactivated form of the coronavirus. Studies on monkeys and hamsters found that it provided protection against infection. When the company launched clinical trials in July, reports circulated that the vaccine would be ready by Aug. 15. But the C.E.O. of Bharat told reporters it would be available no sooner than early 2021. On Oct. 23, the company announced they were initiating a Phase 3 trial.

Updated Oct. 23

PHASE 2

INSTITUTE OF MEDICAL BIOLOGY
CHINESE ACADEMY OF MEDICAL SCIENCES

Researchers at the **Institute of Medical Biology at the Chinese Academy of Medical Sciences**, which has invented vaccines for polio and hepatitis A, started a Phase 2 trial of an inactivated virus vaccine in June.

Updated June 23

PHASE 1 PHASE 2 COMBINED PHASES

Russian Academy of Sciences

The **Chumakov Center** at the **Russian Academy of Sciences** has developed an inactivated coronavirus vaccine. On Oct. 14, the TASS news agency reported that clinical trials of the vaccine would begin in Kirov and St. Petersburg on Oct. 19. On its web site, the center stated that it would finish the first phase of trials the following month.

Updated Oct. 14

PHASE 1

RIBSP
Research Institute for Biological Safety Problems

The central Asian nation of Kazakhstan began research on a vaccine made from inactivated coronaviruses over the summer. On August 28, their **Research Institute for Biological Safety Problems** registered a Phase 1 trial on the vaccine, known as QazCovid.

Updated Aug. 28

PHASE 1

康泰生物
BIOKANGTAI

Shenzhen Kangtai Biological Products is a Chinese company that makes vaccines for diseases such as hepatitis B and measles. In August, AstraZeneca reached an agreement with them to supply China with their mRNA vaccine. In October Shenzen Kangtai launched a Phase 1 trial on 180 volunteers of its own vaccine, based on inactivated coronaviruses.

Updated Oct. 16

PHASE 1

ERCİYES ÜNİVERSİTESİ 1978

On Nov. 5, Turkey's **Erciyes University** announced they had begun injecting volunteers with an inactivated coronavirus vaccine. It is the first clinical trial of a coronavirus vaccine developed in Turkey.

Updated Nov. 16

PHASE 1

CODAGENIX INC.

New York-based **Codagenix** develops vaccines based on live attenuated viruses, but with a twist: they create the viruses from scratch. Researchers rewrite the genome of viruses, introducing hundreds of mutations. Then they manufacture RNA molecules encoding the rewritten genes. In special host cells, the molecules can give rise to full-blown viruses. But thanks to their numerous mutations, they are too weak to cause Covid-19 when they're delivered in a vaccine. After successful experiments in animals, a Phase 1 trial of their coronavirus vaccine was registered on Nov. 6.

Updated Nov. 10

PRECLINICAL

Other inactivated or attenuated coronavirus vaccines in active preclinical development include vaccines from: Valneva; Vivaldi Biosciences; Washington University; Western University.

Updated Nov. 7

Repurposed Vaccines

Vaccines already in use for other diseases that may also protect against Covid-19. Repurposed vaccines are not included in our vaccine count.

PHASE 3

murdoch children's research institute