如何成為卓越的醫師科學家
Adventures in Environmental and Occupational Health Sciences

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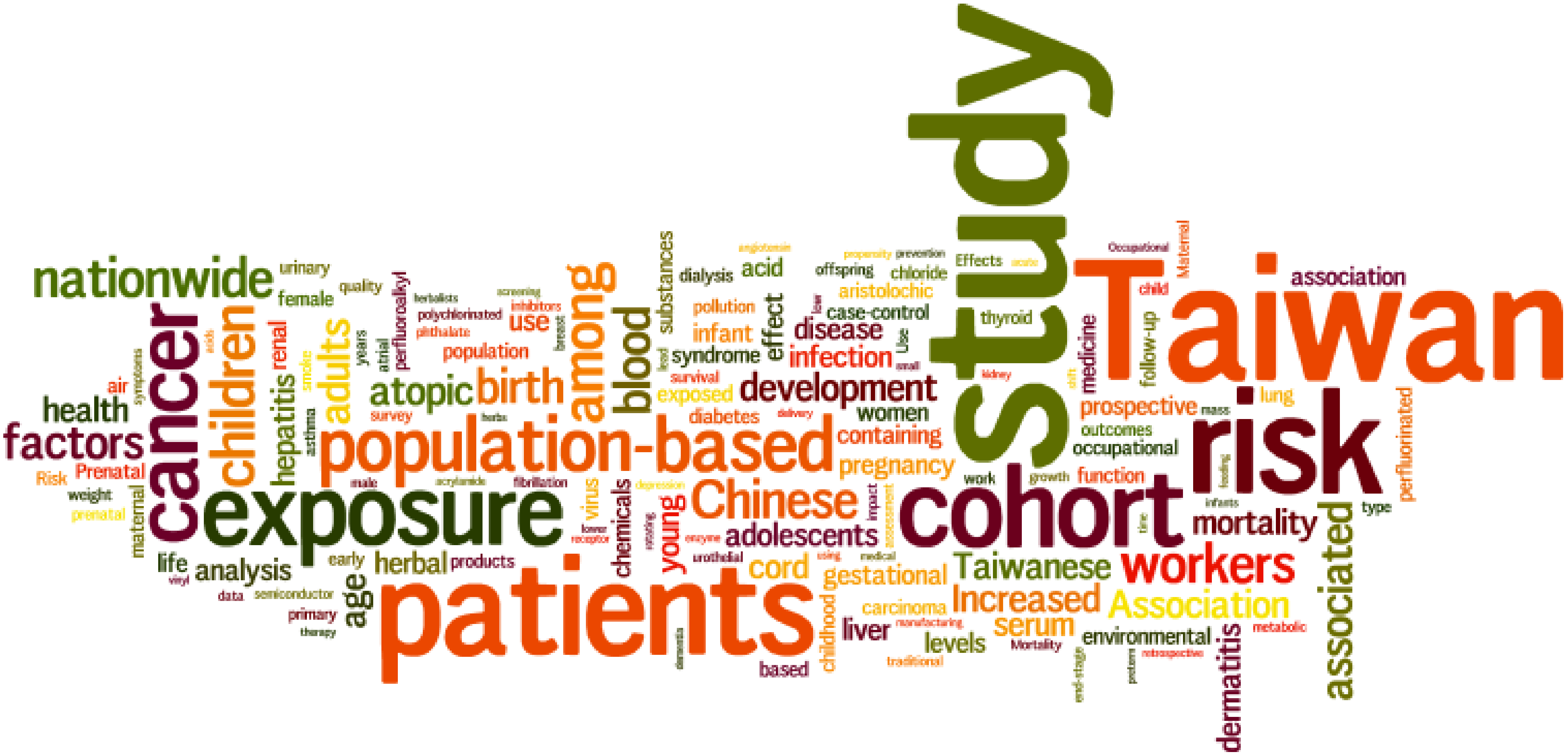
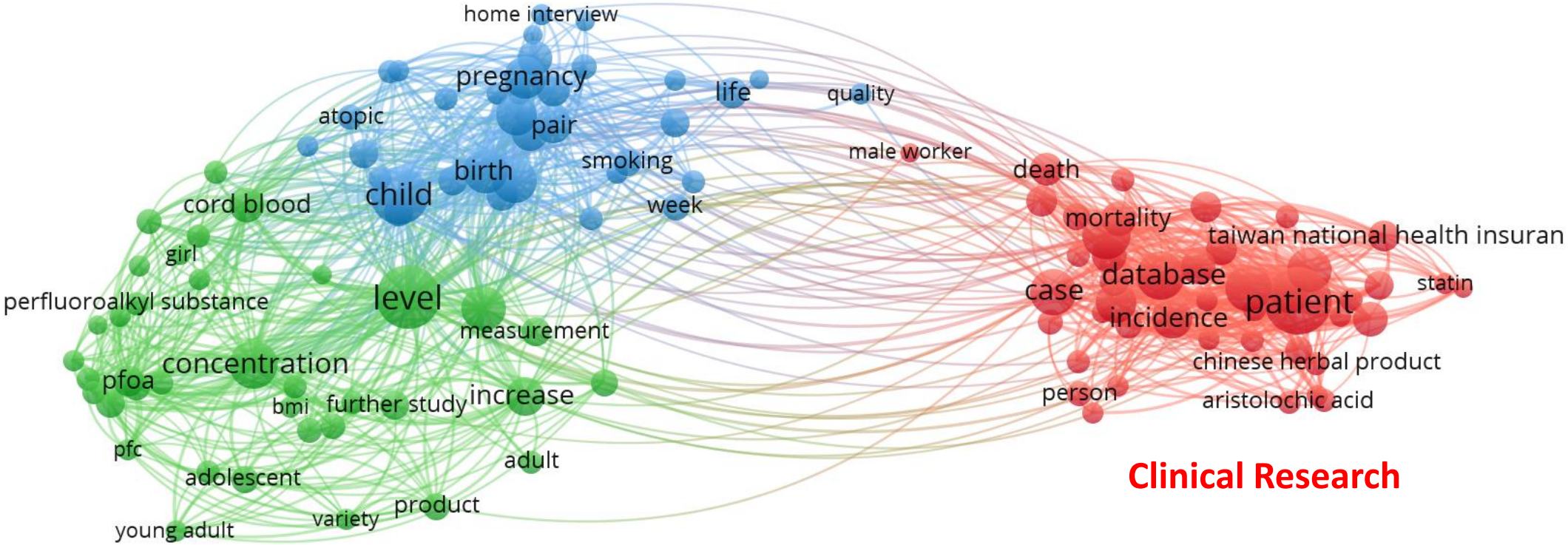
National Taiwan University College of Public Health
National Taiwan University Hospital
September 10, 2020


Association
Research
Health
Safety
Complementary
Pediatric
Clinical
Cancer
Formosan
Epidemiology
International
Medicine
Perspectives
Taiwan
Toxicology
Pharmacoepidemiology
Neonatology
Metabolism
Experimental
PLoS
Archives
Medical
Pediatrics
Environmental
Allergy
Taipei
Science
Drug
American
Cardiology
Pediatric
Paediatrics
Care
BMC
Hazardous
Public
Journal
Occupational
ONE
Diabetes
Environment
Immunology
Gastroenterology
Pollution
Medicine-Oxford
Nursing
Alternative
Chinese
European
Respiratory



study
Taiwan
risk
cohort
patients
exposure
population-based
cancer
children
nationwide
factors
health
among
blood
birth
atopic
adults
hepatitis
renal
Chinese
adolescents
development
infection
disease
syndrome
workers
Association
associated
mortality
Taiwanese
Increased
serum
gestational
pregnancy
containing
prospective
occupational
outcomes
function
dermatitis
environmental
levels
liver
cord
herbal
products
analysis
life
age
young
chemicals
virus
exposed
diabetes
women
infant
pollution
aristolochic
case-control
thyroid
medicine
follow-up
association
lung
perfluorinated
carcinoma
childhood
based
Prenatal
Risk
weight
prenatal
maternal
air
female
urinary
quality
dialysis
acid
offspring
chloride
Effects
use
population
substances
effect
primary
data
semiconductor
survey
early
work
growth
type
metabolic
traditional
Mortality

Maternal, Reproductive, and Child Health

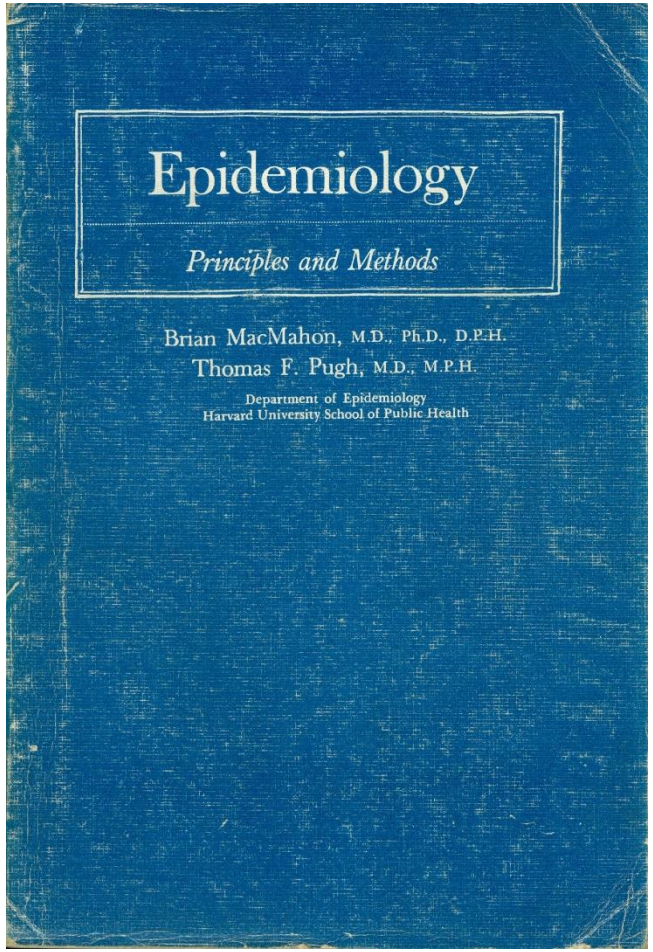


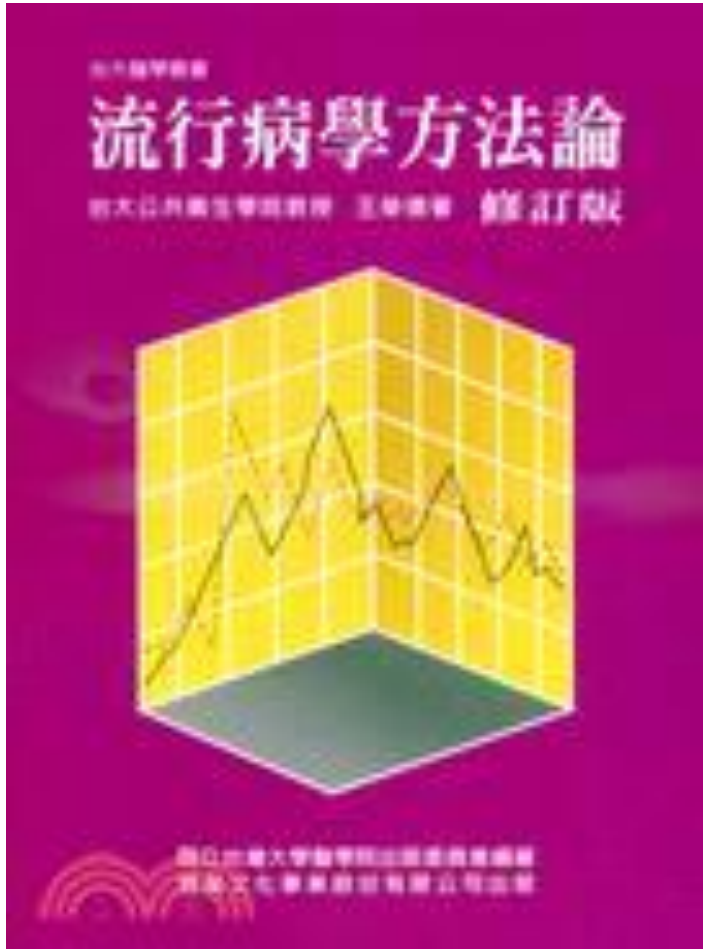
Clinical Research

Occupational and Environmental Medicine

VOSviewer

Epidemiology

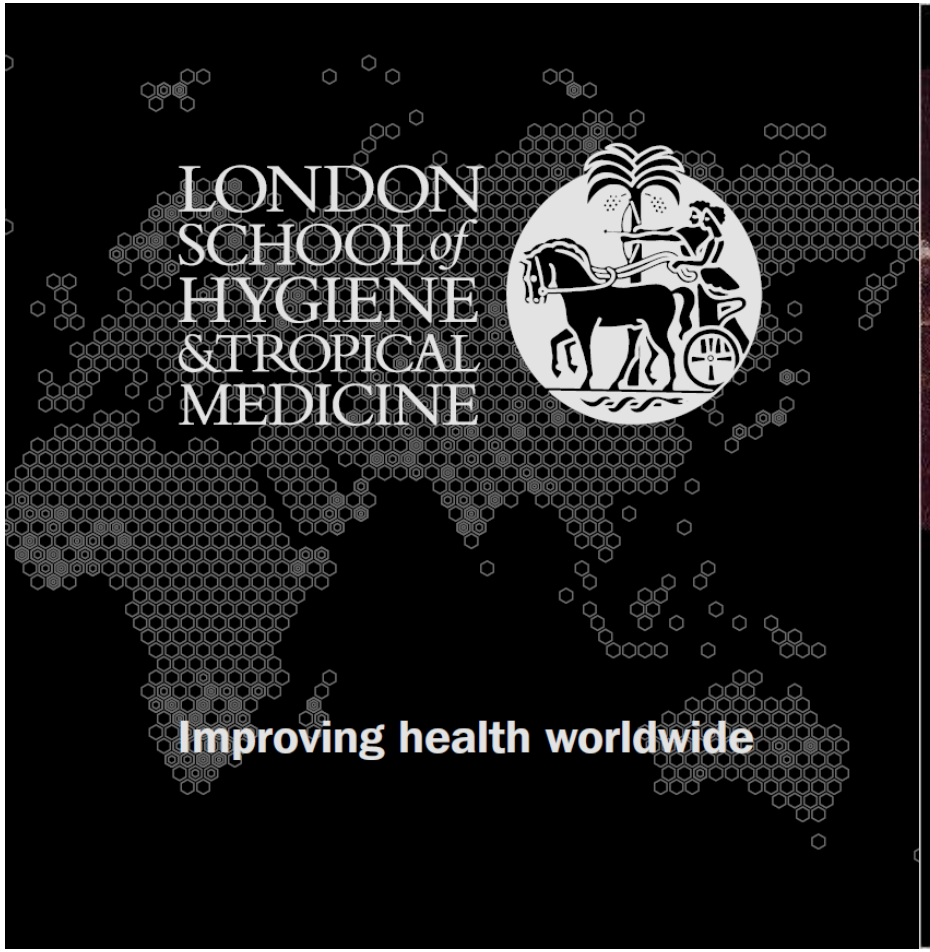


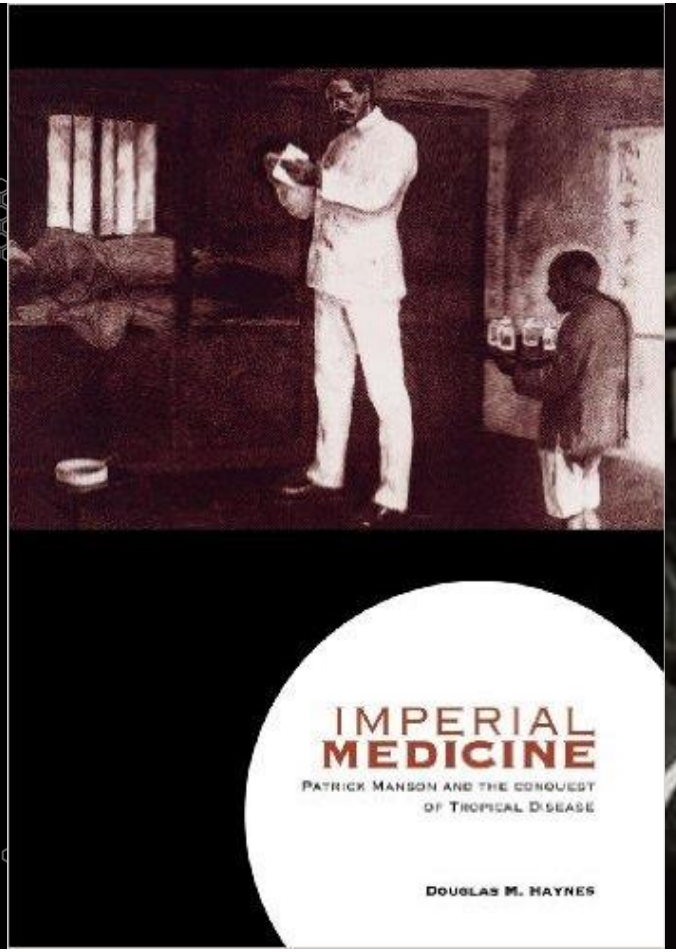


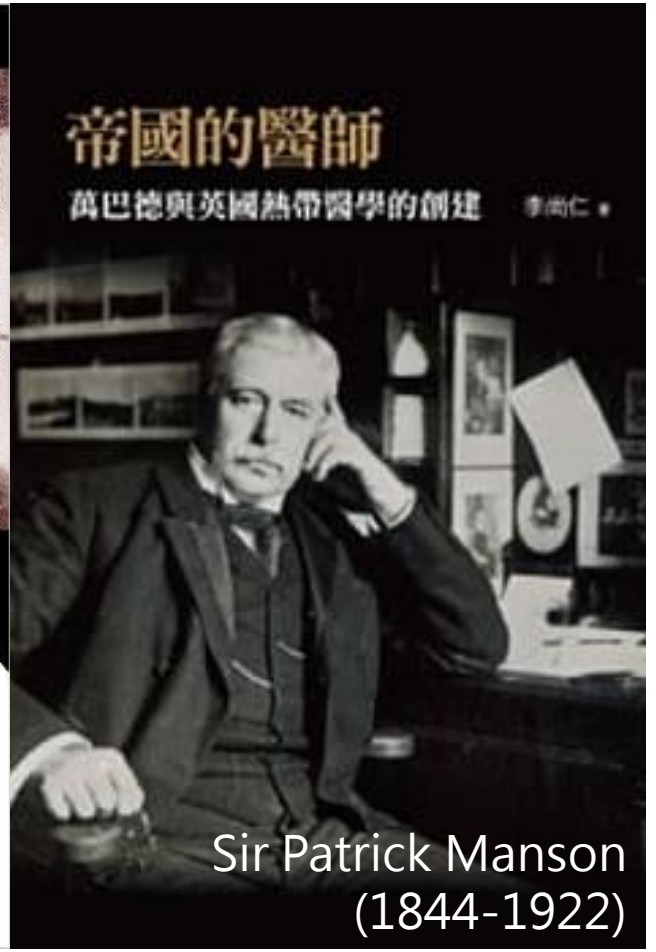
Epidemiology

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

120 YEARS of HEALTH INNOVATION 1899~2019







Sir Patrick Manson (1844-1922)

Manson started a long career in tropical medicine at Takao, Formosa (Kaohsiung, Taiwan) in the mid-19th Century.

A GOSSIP ABOUT FORMOSA.

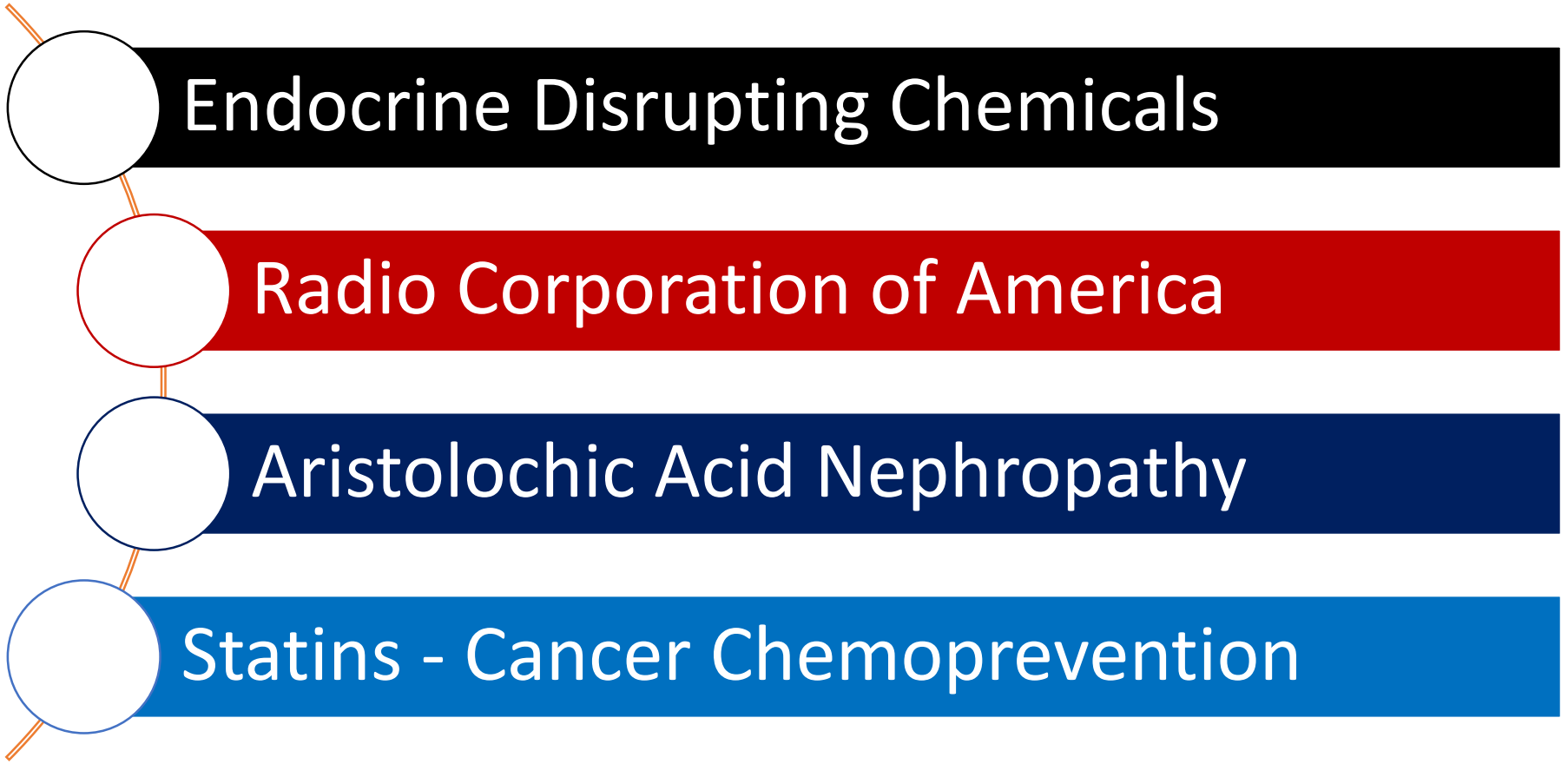
BY A FORMER RESIDENT.

"How long were you in Formosa?" we are often asked. "Five years," we reply. "Good heavens, how could you exist so long in such an outlandish hole. You could have no society there, no amusements, a blazing sun and murderous savages." We are pitied, and when we express our liking for the place, our truthfulness or our sanity is doubted. Yet we do like the place; in our memory it is a pleasant corner, and over the time we passed there we often sigh "The days that are no more."

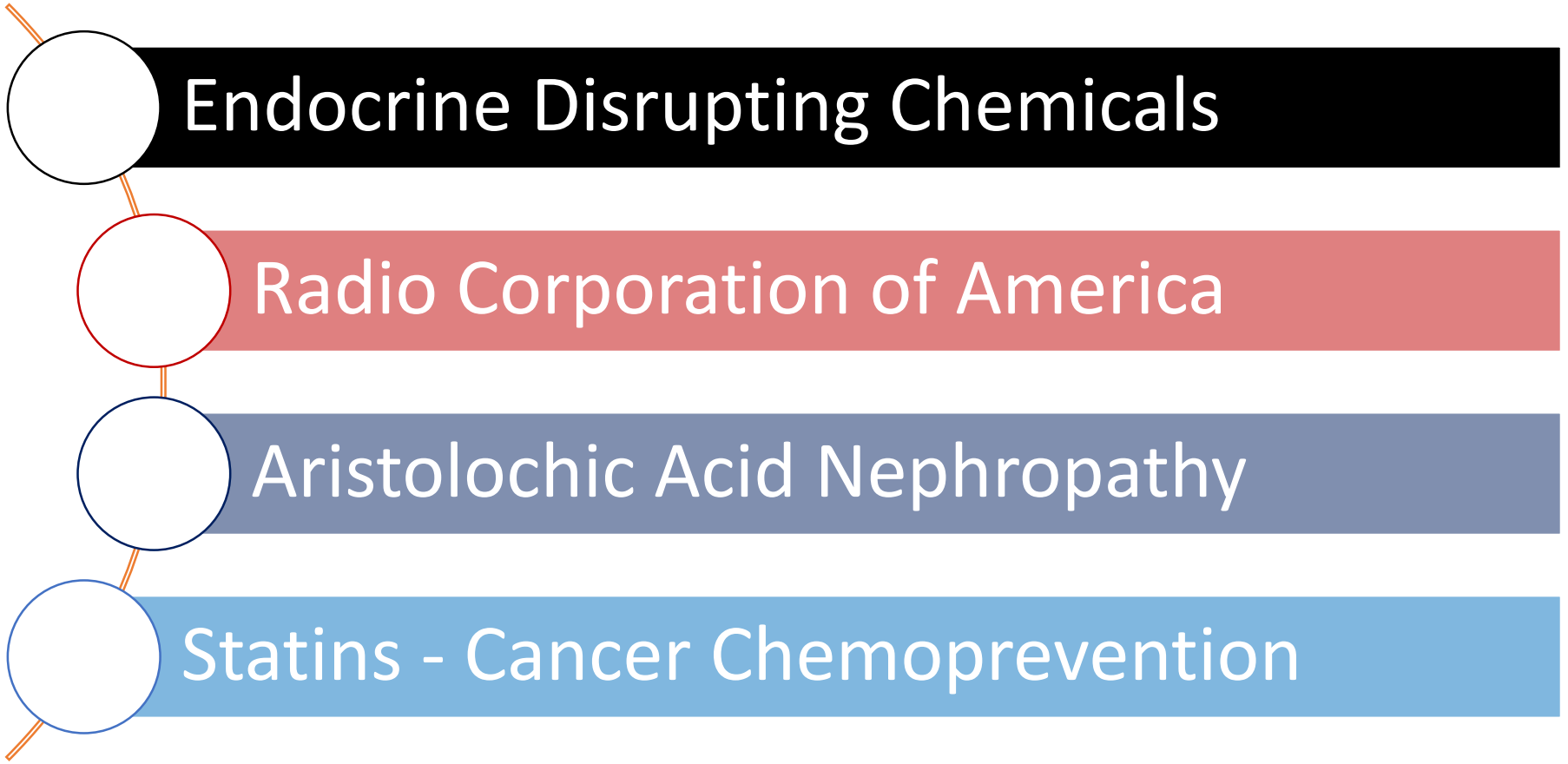
The steamer-travelled tourist, who only

Wikipedia; China Review 1873

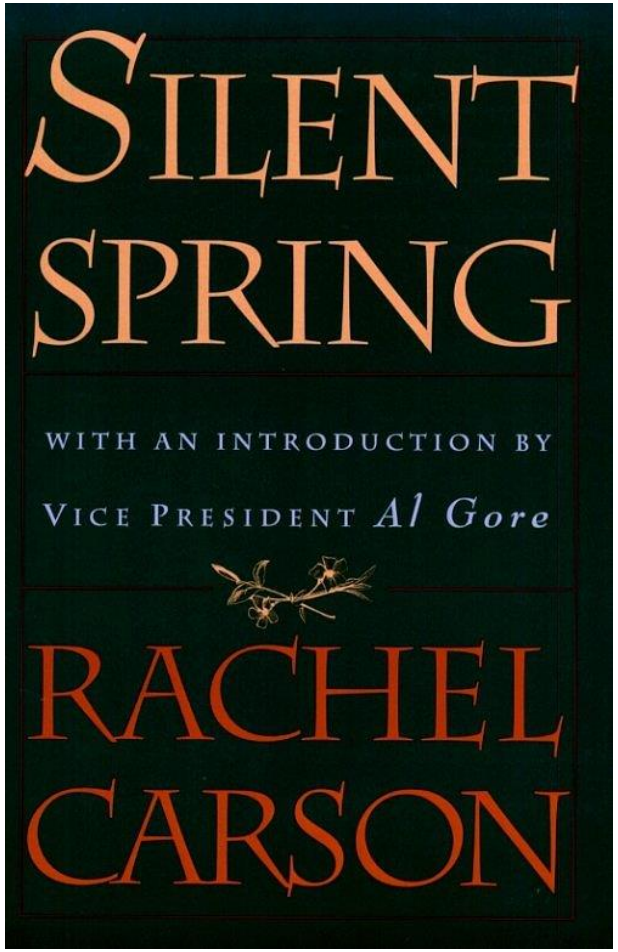
Adventures in Environmental and Occupational Health Sciences

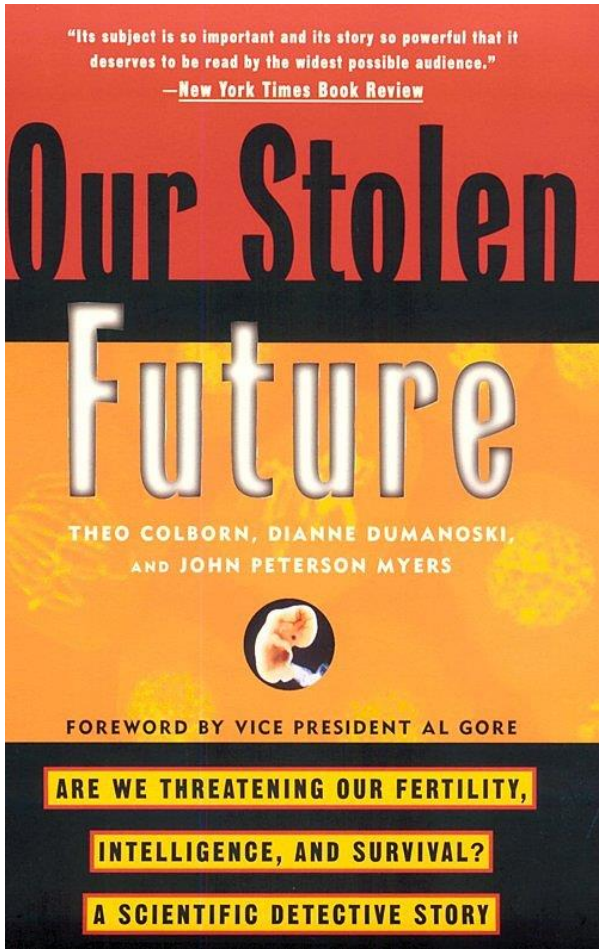


Adventures in Environmental and Occupational Health Sciences



Silent Spring to Silent Sperm?

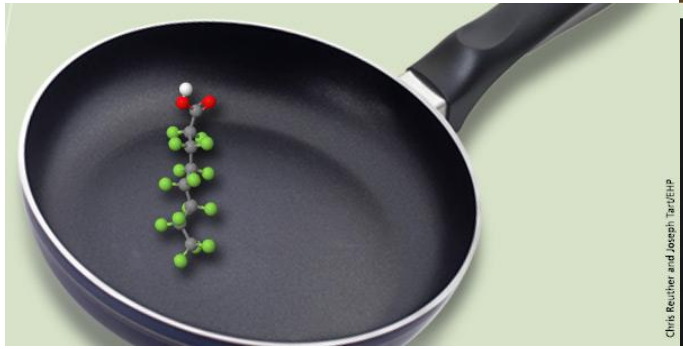




Endocrine Disrupting Chemicals

- Pesticides (insecticides such as o,p'-DDT, endosulfan, dieldrin, methoxychlor, kepone, dicofol, toxaphene, chlordane; herbicides such as alachlor, atrazine and nitrofen; fungicides such as benomyl, mancozeb and tributyl tin; nematocides such as aldicarb and dibromochloropropane)
- Industrial chemicals (polychlorinated biphenyls (PCBs), dioxin and benzo(a)pyrene)
- Brominated flame retardants (polybrominated diphenyl ethers, PBDEs)
- **Perfluoroalkyl substances (PFASs)**
- Products associated with plastics (bisphenol A, phthalates)
- Ordinary household products (breakdowns products of detergents and associated surfactants, including nonylphenol and octylphenol);
- Pharmaceuticals (drug estrogens - birth control pills, diethylstilbestrol (DES), cimetidine)
- Heavy metals (lead, mercury, arsenic, and cadmium)

Perfluoroalkyl Substances: What is the Evidence Telling Us?



Laboratory mice exposed prenatally to PFOS and PFOA develop more slowly and suffer a higher rate of neonatal mortality than nonexposed mice (left). Once PFOA-exposed mice reach adulthood, however, they are more likely to become obese (above).

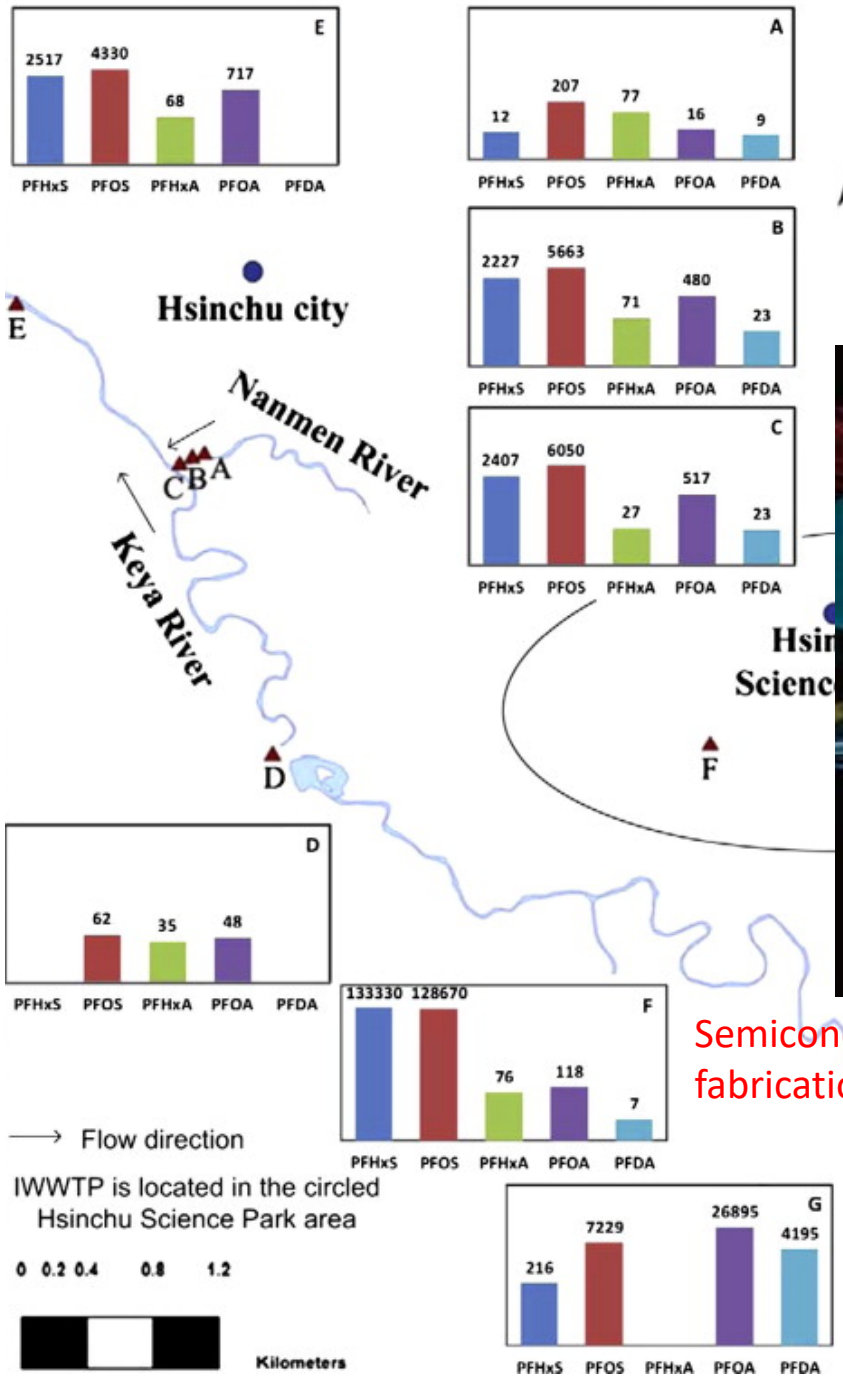
Environ Health Perspect 2007

What are PFASs?

- Fully fluorinated hydrophobic linear carbon chain attacked to various hydrophilic heads
- Chemical and thermal stability, ideal surfactants (water and oil resistant)
- Over 200 industrial and consumer applications since 1950s



Chemosphere 2010; 80:1167-74



Semiconductor fabrication plant

Optoelectronics plant

Studies in Children's Environmental Health

Birth Cohort

Prospective Pregnancy Cohort in Taipei (PPCT), 1984-87

Birth Cohorts

Taiwan Birth Cohort Study (TBCS), 2005

Taiwan Birth Panel Study (TBPS1), 2004-05

Taiwan Birth Panel Study (TBPS2), 2011-12

Network Studies

Young Taiwanese Cardiovascular Cohort Study (YTCC), 2006-08

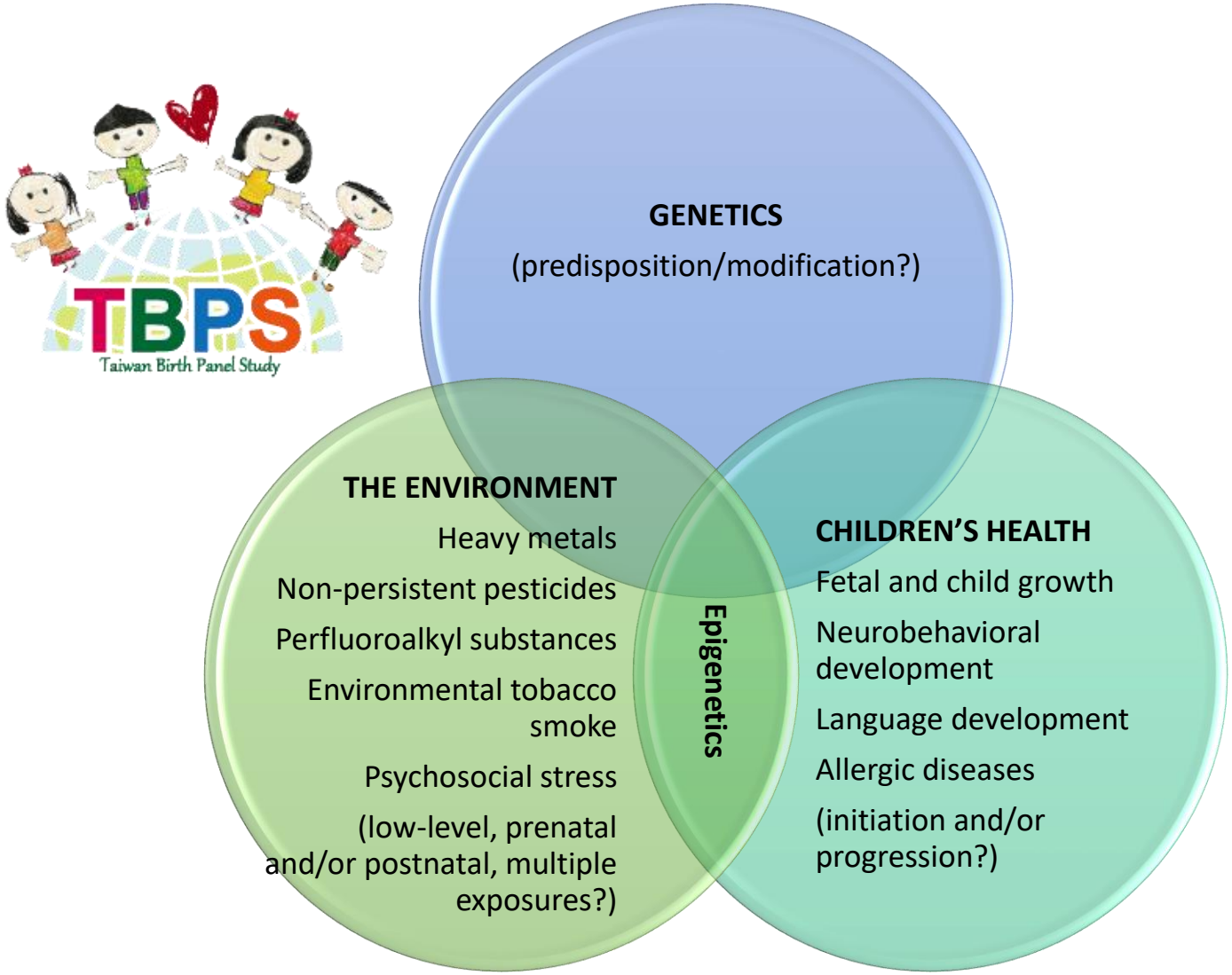
Genetic and Biomarkers Study for Childhood Asthma (GBCA), 2009-10

Birth Cohort Consortium of Asia (BiCCA), 2012-

General Population

Biomonitoring and Epidemiology Pilot Study in Taiwan, 2019-20

Taiwan Birth Panel Study



Taiwan Birth Panel Study

- Study design
  - 486 children born during 2004-2005
- Main questionnaire
  - Mothers, infants, families, and environmental exposures
  - Face-to-face interview
- Biological specimen
  - Maternal blood and urine
  - Umbilical cord blood and placenta
- Outcomes
  - Birth outcomes from hospital medical records
  - Growth and development, allergic diseases

Taiwan Birth Panel Study

Birth

Questionnaire,
Hospital medical record,
Neonatal neurobehavioral examination

Maternal blood & urine, cord blood & placenta

4 months

Questionnaire,
Fetal growth & development,
Temperament

6 months

Questionnaire,
Fetal growth & development,
Allergic diseases,
Neurobehavioral development,
HOME learning environment

1 years

Questionnaire,
Child growth & development,
Temperament

2 years

Questionnaire,
Child growth & development,
Temperament,
Child behavior checklist,
Allergic diseases,
Neurobehavioral development,
HOME learning environment,
Pediatric Daily Occupation Inventory,
International Classification of Functioning, Disability and Health,
Parenting stress index

Blood, urine, saliva & hair

3 years

Questionnaire,
Child growth & development,
Child behavior checklist,
Allergic diseases,
Parenting stress index

5 years

Questionnaire,
Child growth & development,
Child behavior checklist,
Allergic diseases,
Electromagnetic wave questionnaire,
Motor development,
Attention deficit/ hyperactivity disorder,
Parenting stress index,
Child motivation;
SNAP-IV,
Movement ABC

Urine

7 years

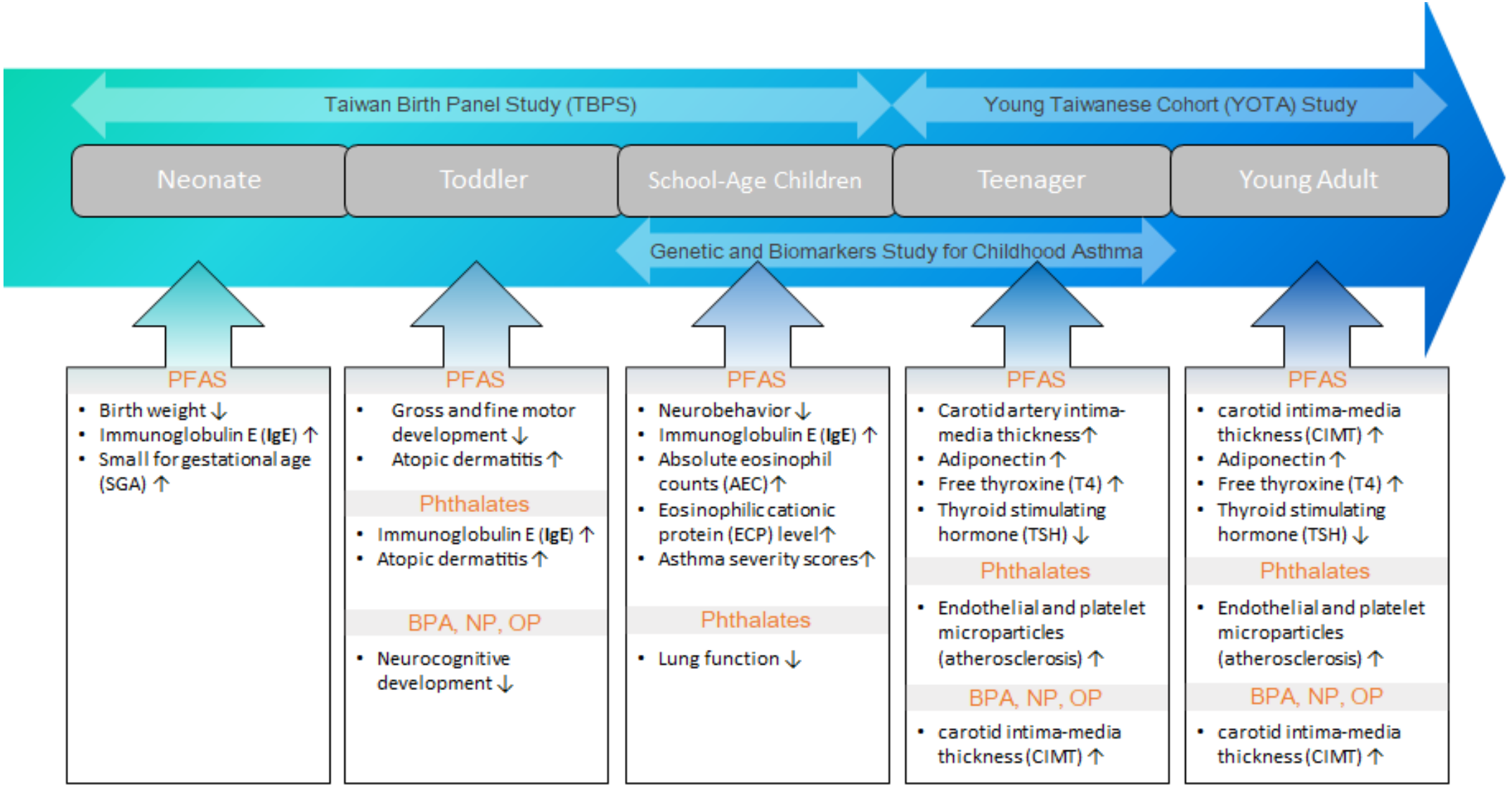
Questionnaire,
Child behavior checklist,
Phthalates questionnaire,
SDQ,
SNAP-IV,
WISC-IV,
SPM+,
AGD

Urine

9-10 years

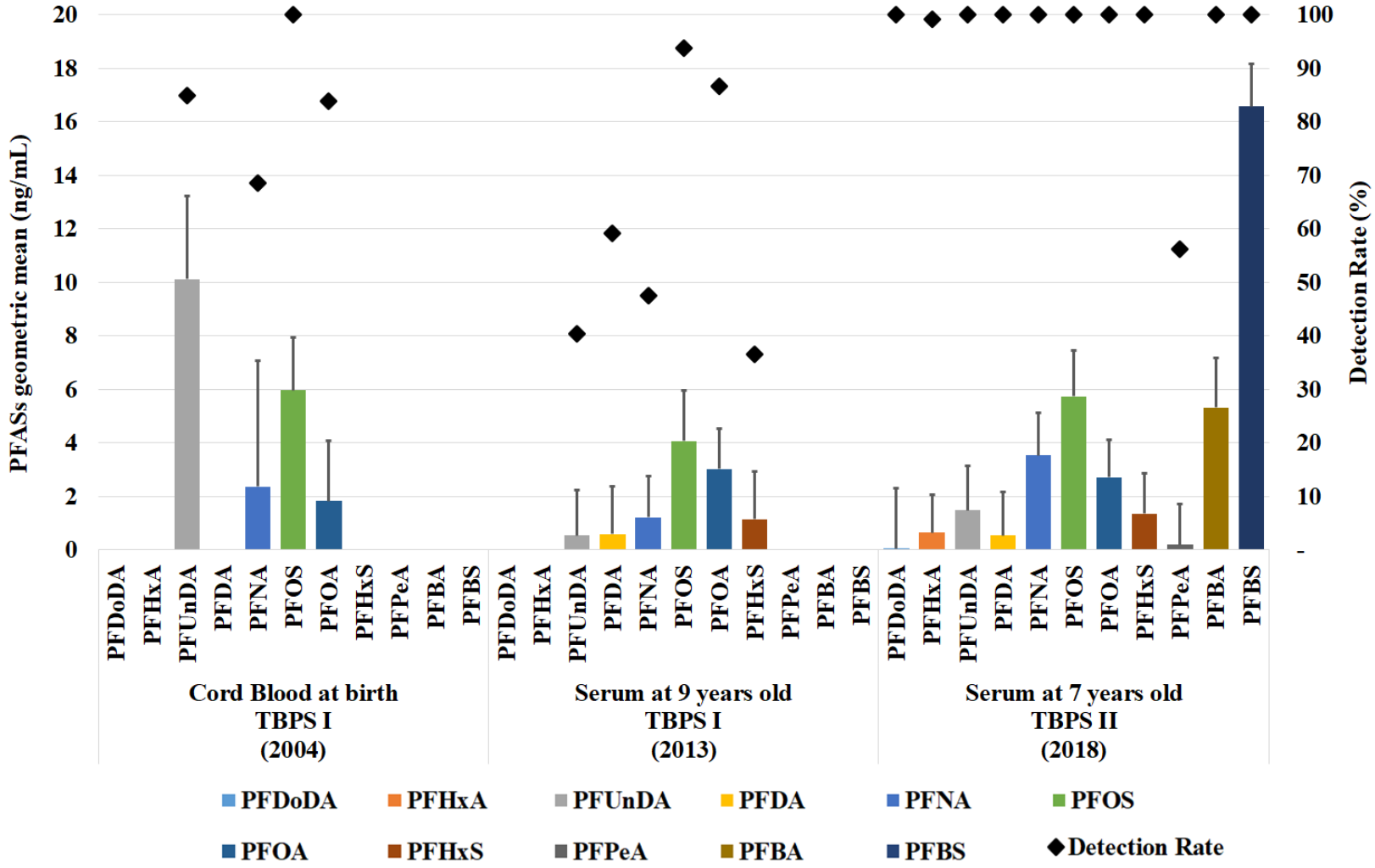
Questionnaire,
Child growth & development,
Child behavior checklist,
Allergic diseases,
Neurobehavioral development,
Lung function,
Bone age,
Physical activity;
Dietary,
Disease history

Blood &urine



www.rhlab.org

Serum Perfluoroalkyl Substances in Children



Melamine and Nephrolithiasis in Children in Taiwan, 2009

Melamine and Nephrolithiasis in Children in Taiwan

TO THE EDITOR: The adverse renal effects of melamine-tainted formula have raised international concern. To address public concerns about melamine, the department of health in Taiwan initiated services to screen exposed children.

From September 24 through October 23, 2008, we screened 1129 children in Taiwan who had possible exposure to contaminated formula, investigating the clinical symptoms and risk factors for nephrolithiasis. Clinical presentation and urinary calcium and creatinine levels were evaluated, and urinalysis and renal ultrasonography were performed. We categorized our patients into three groups, according to exposure history.[1,2] The high-

Table 1. Baseline Characteristics of the Study Children, According to Melamine Exposure.*

Variable	High Exposure (>2.5 ppm) (N=44)	Low Exposure (0.05–2.5 ppm) (N=607)	Control (<0.05 ppm) (N=478)	P Value
Age — yr	4.32±2.60	3.97±2.72	4.26±3.60	0.28
Male sex — no.	22	324	292	0.03
Urinalysis findings — no.				
Occult blood (>2+)	1	26	22	0.77
Hematuria (red-cell count, >5/HPF)	0	13	14	0.40
Pyuria (white-cell count, >5/HPF)	0	25	11	0.11
Proteinuria (>2+)	0	3	3	0.85
Hypercalciuria (calcium:creatinine, >0.2)	0	7	5	0.77
Nephrolithiasis on renal ultrasonography — no.	9	2	1	<0.001
Clinical symptoms and history — no.				
Abdominal pain	0	10	3	0.23
Flank pain	0	0	2	0.26
Dysuria	2	16	7	0.24
Increased urinary frequency	2	9	7	0.28
History of UTI	1	8	3	0.40
Family history of nephrolithiasis	0	7	6	0.76
History of residence in the mainland of China	37	41	105	<0.001

* Plus–minus values are means ±SD. HPF denotes high-power field, and UTI urinary tract infection.

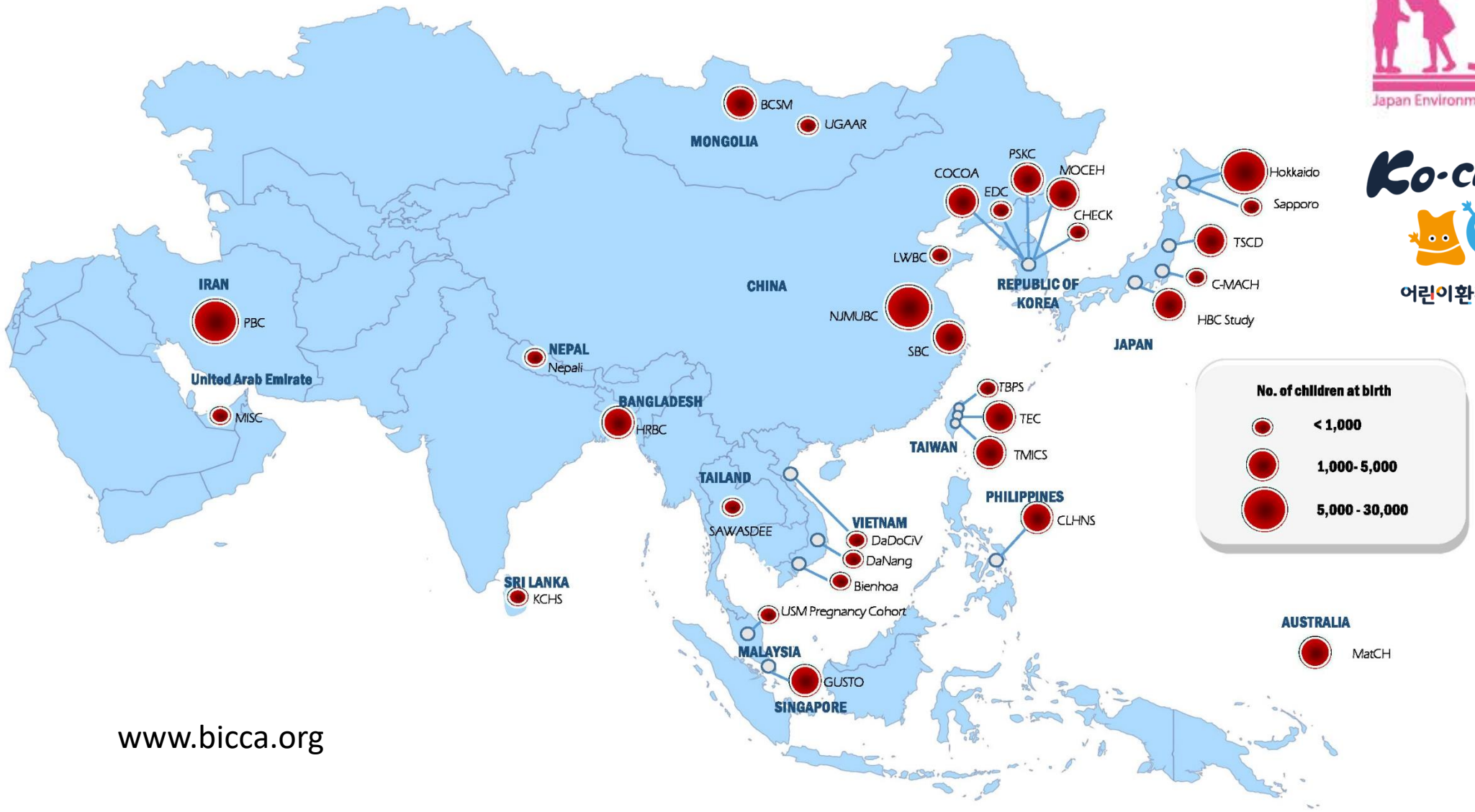
BiCCA
Birth Cohort Consortium of Asia

EDCs

BiCCA
Birth Cohort Consortium of Asia

JECS
Japan Environment and Children's Study

Ko-CHENS!
어린이환경보건출생코호트



www.bicca.org

National Taiwan University Hospital

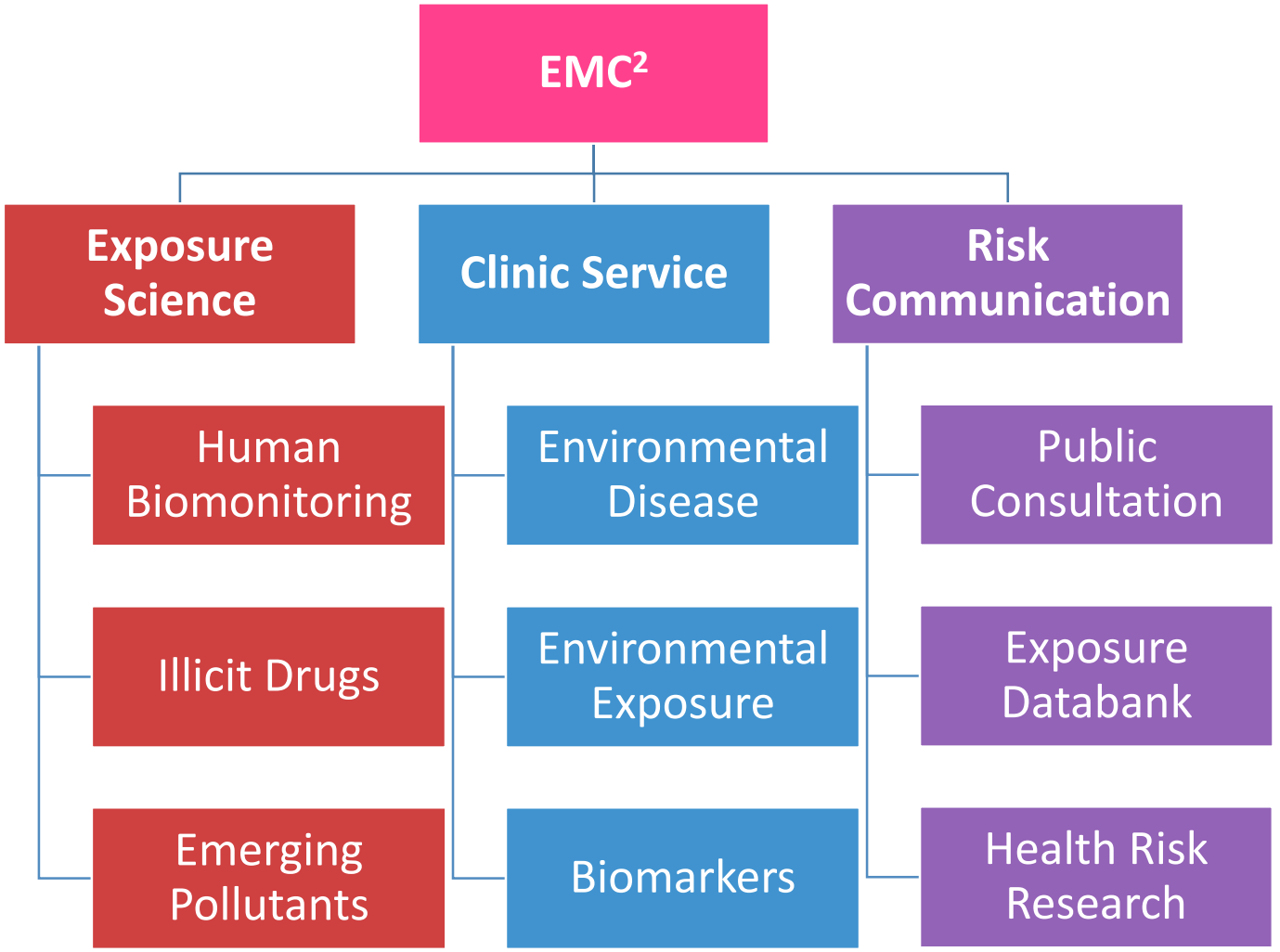
NTU College of Medicine

Department of Environmental and Occupational Medicine, NTUH

- Center for Occupational Disease and Injury Service*
- Center for Occupational Disease and Injury Management and Service*
- Workers' Health Center*
- Environmental Medicine Coordination Center

*Funded by Occupational Safety and Health Administration, Ministry of Labor

Environmental Medicine Collaboration Center (EMC²), 2014



Outpatient Clinical Service

減少塑化劑暴露教你知

塑化劑是用來使原本堅硬的聚合物變得柔軟，增加其可塑性與彈性的添加物總稱，例如鄰苯二甲酸酯類可增強塑膠的彈性，進而應用於容器或包裝產品的製造。這類物質可能經由吸入、食入、皮膚接觸吸收、或經由靜脈內管路（點滴注射)進入人體，影響免疫發炎反應、內分泌系統、生殖功能或成人慢性病等。

生活習慣的改變，例如：減少塑膠製品(尤其是回收代碼 3、6 號)的使用，清潔室內地板落塵並多洗手，避免香味強烈的化妝保養品，可有效降低暴露塑化劑的風險。孕婦或嬰幼兒的產品尤其要慎選產品的成分。而體內的塑化劑及代謝物大多會於數天內，經由尿液或糞便排出體外。

若您的檢驗結果顯示塑化劑的體內濃度偏高，請遵照醫師指示，避免接觸可能的暴露來源 (請參見表格)，並定期回診追蹤。

表：接觸鄰苯二甲酸酯類的來源

鄰苯二甲酸酯類化合物	量測的代謝物	暴露的可能來源
鄰苯二甲酸二(2-乙基己基)酯	Mono- ethylhexyl phthalate (MEHP) Mono-2-ethyl-5-oxohexyl phthalate (MEOHP) Mono-2-ethyl-5-hydroxylhexyl phthalate (MEHHP)	★ 含聚氯乙烯 (PVC)材質的醫療管路、血袋、醫療設備等 ★ 食物汙染、食物包裝袋、塑膠材質包裝紙 ★ 室內空氣、牆面塗料、桌布、乙烯材料地磚、傢俱坐墊、浴簾、塑膠水管 ★ 雨衣、尿布、布偶、塑膠玩具、鞋 ★ 交通工具坐墊、汽車頂篷、底片膠卷、電線及電纜包覆
鄰苯二甲酸二乙酯	Mono-ethyl phthalate (MEP)	★ 化妝品、指甲油、防臭劑、香水、古龍水、化妝水、鬚後乳霜、草本植物產品 ★ 藥物 ★ 殺蟲劑
鄰苯二甲酸丁酯苯甲酯	Mono-benzyl phthalate (MBzP)	★ 塑膠地板、傢俱坐墊、乙烯材料地磚、方塊地毯 ★ 黏著劑、密封劑 ★ 食物包裝袋 ★ 人造皮革
鄰苯二甲酸二丁酯	Mono-isobutyl phthalate (MiBP) Mono-n-butyl phthalate (MnBP) Mono-3-carboxy-propyl-phthalate (MCPP)	★ 指甲油、化妝品、鬚後乳霜、香水、草本植物產品、睫毛膏、某些染料的溶劑 ★ 藥物 ★ 螢光棒 ★ 醋酸纖維製膠板(可做眼鏡框)
鄰苯二甲酸二甲酯	Mono-methyl phthalate (MMP)	★ 洗髮精、鬚後乳霜、頭髮定型產品 ★ 室內空氣 ★ 殺蟲劑 ★ 黏著劑
鄰苯二甲酸二異壬酯	Mono-isooctyl phthalate (MiNP)	★ 食品包裝材料和容器 ★ 髮膠、指甲油 ★ 幼童玩具 ★ 黏著劑、
鄰苯二甲酸二正辛酯	Mono-n-octyl phthalate (MOP)	★ 醫用的導管和血液儲存袋 ★ 食品包裝材料和容器 ★ 化妝品添加劑 ★ 幼童玩具
鄰苯二甲酸二環己酯	Mono-cyclohexyl phthalate (MCHP)	★ 紙飾面、膠粘劑製造、絲網印刷油墨、防潮塗料, 紙張防水助劑

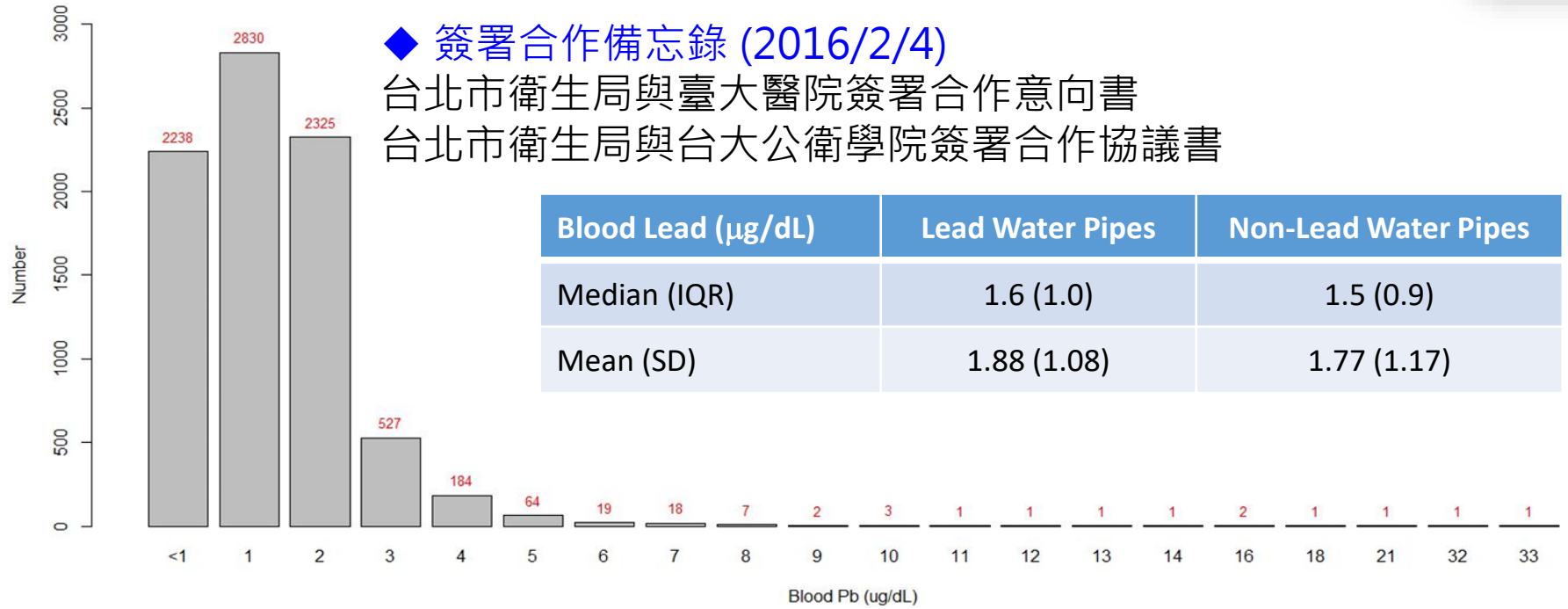
Lead Water Pipes Removal, 2015

◆ 簽署合作備忘錄 (2016/2/4)

台北市衛生局與臺大醫院簽署合作意向書

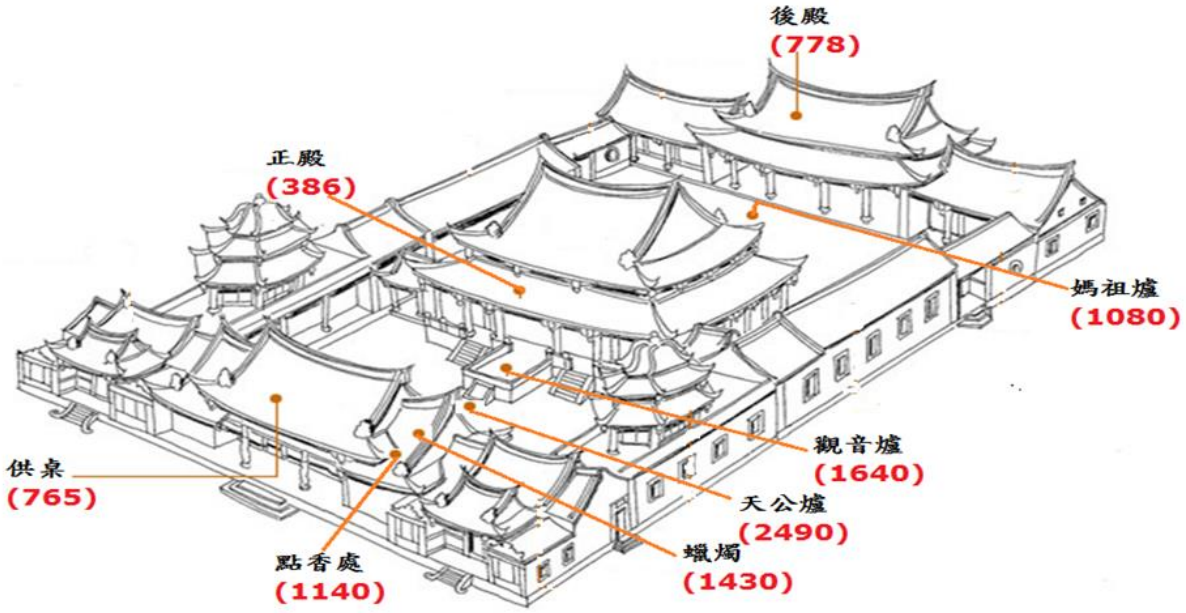
台北市衛生局與台大公衛學院簽署合作協議書

Blood Lead (μg/dL)	Lead Water Pipes	Non-Lead Water Pipes
Median (IQR)	1.6 (1.0)	1.5 (0.9)
Mean (SD)	1.88 (1.08)	1.77 (1.17)

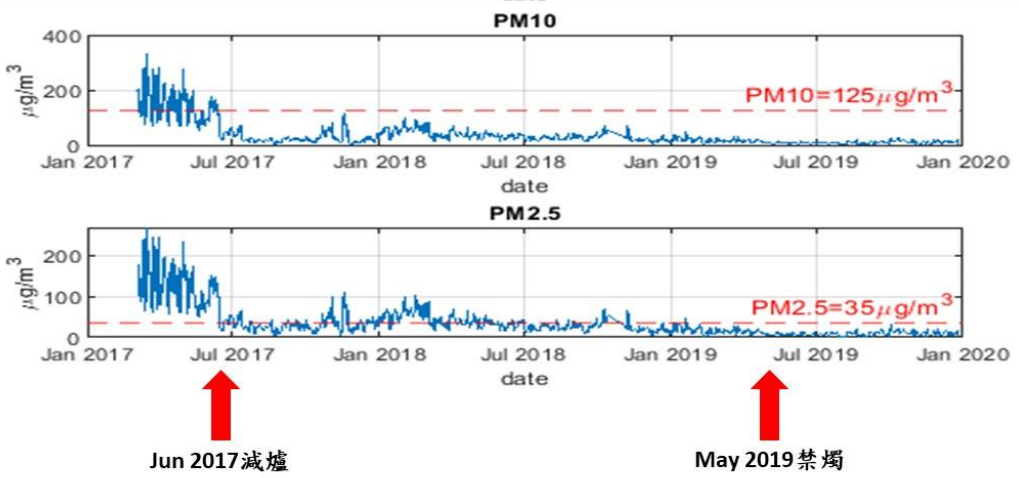


Incense Burning Reduction, 2017-19

- PM2.5細懸浮微粒
- PAHs多環芳香烴
- VOCs揮發性有機氣體
- Metals重金屬



280年古蹟艋舺龍山寺減爐禁燭



康健出版

環境醫學專家陳保中教你：

減塑｜防空污｜安全住

打造不受污染的健康世代

毒懂你的生活

陳保中——著
邱宜君——採訪撰文

塑化劑　雙酚A　PM2.5　甲醛　全氟碳化物

人們日常生活中身不由己地透過食入、吸入、接觸，暴露在種種的環境毒物當中，侵蝕健康而不自知。

因為「毒」總是知道如何進入我們的生活，
所以環境醫學專家陳保中教你「讀」懂生活中的「毒」，並提醒：
「關心正確的資訊，不求能做到百分之百，但做得到的，就要去做；做不到的也不用勉強，放在心裡，繼續努力！」

本書內容

民以食為天：
如何減塑、挑選安心食物，遠離環境荷爾蒙，為家人頂住一片天！

家是避風港：
買房或許很難，但打造保護全家的無毒小窩有妙方！

呼吸如作戰：
空污危機不限戶外，室內、車內也馬虎不得，擬定策略趨吉避凶保安康！

本書特色

- ✔ 融合研究、教學與生活，透過實際發生的故事，教大眾認識毒、學會預防生活中的毒，從生殖以至慢性病，全面展開。
- ✔ 用「安心勾勾表 checklist」自我檢測，每天為健康儲蓄。

ISBN 978-986-95993-4-4
書號 BHHU0010P　定價360元
www.cwbook.com.tw
康健出版 天下雜誌群

專家推薦——

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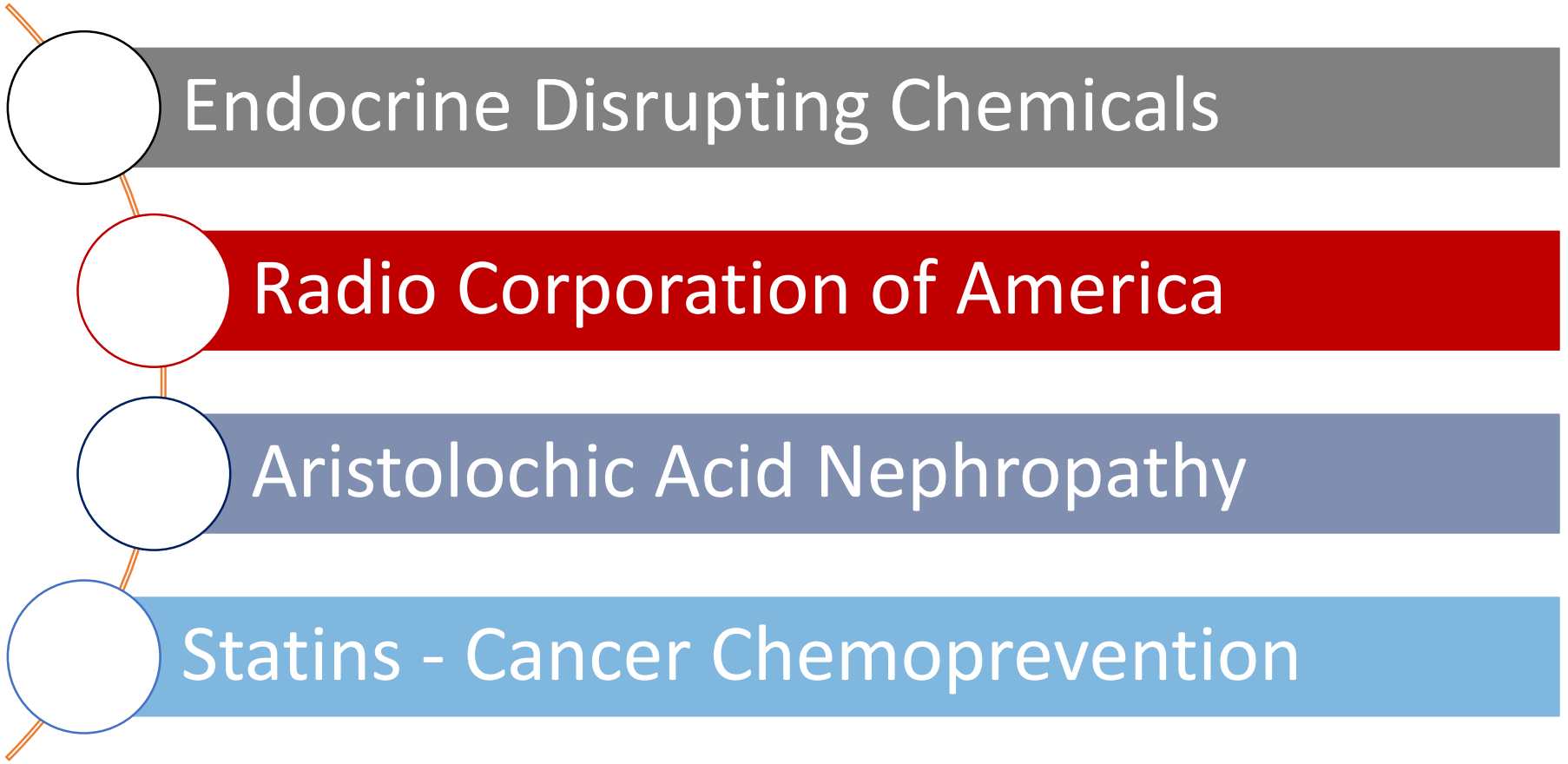
空汙世代的肺部養護全書
PM2.5、霧霾威脅下，
口罩族的求生指南
三采健康館
129
空汙世代的肺部養護全書
台大職業醫學與工業衛生研究所所長 陳保中
台大醫院胸腔外科主任 陳晉興
suncolor
為何肺癌連續多年成為最要命的新國病？
不抽菸、愛運動，竟然得肺癌？
身處空汙世代，你最需要的一本書！
目前，肺癌是死亡率最高的癌症，
過去研究指出，抽菸是肺癌最大致病因子，
但在台灣，肺癌患者抽菸比率不到五成！
難道空汙、PM2.5 是元凶？
愈來愈多研究指出，
空汙不只造成肺部疾病，對於心血管更是重創，
且嚴重損害孩童肺部健康，更對大腦造成永久性傷害。
聯合國兒童基金會直接指出，
空汙將是本世紀威脅孩童健康的致命殺手！
肺癌權威 X 環境醫學專家攜手
讓每一口呼吸，都化為健康！
LDCT，發現初期肺癌最佳工具！
比戶外更致命的室內空汙！
看懂規格，口罩安心戴
打造健康宅 3 祕訣
空汙環境下，健康運動 2 大關鍵
創造清新空氣 5 關鍵
鍛練肺功能的特別呼吸法
空氣清淨機正確擺放位置
不可忽視
比病從口入更難預防的
呼吸致病
造成每年
800萬人
提早死亡威脅
專業推薦
中央研究院院士 陳建仁
臺北市立聯合醫院和平婦幼院區
小兒科專任主治醫師 陳佩琪
主婦聯盟環保基金會董事長
賴曉芬
（依姓氏筆畫排列）
揮別空汙從這裡著手！
辦公室
居家
運動
飲食
通勤
新書講座
2/15（五）
10:30~11:30
台北國際書展
台北世界貿易中心展覽一館
藍沙龍
活動詳情▶
定價NT$360
三采書碼 108010101129
suncolor
三采文化集團
SUN COLOR GROUP
suncolor 三采文化

Adventures in Environmental and Occupational Health Sciences



奇蹟背後
永不妥協

紀錄觀點【奇蹟背後】

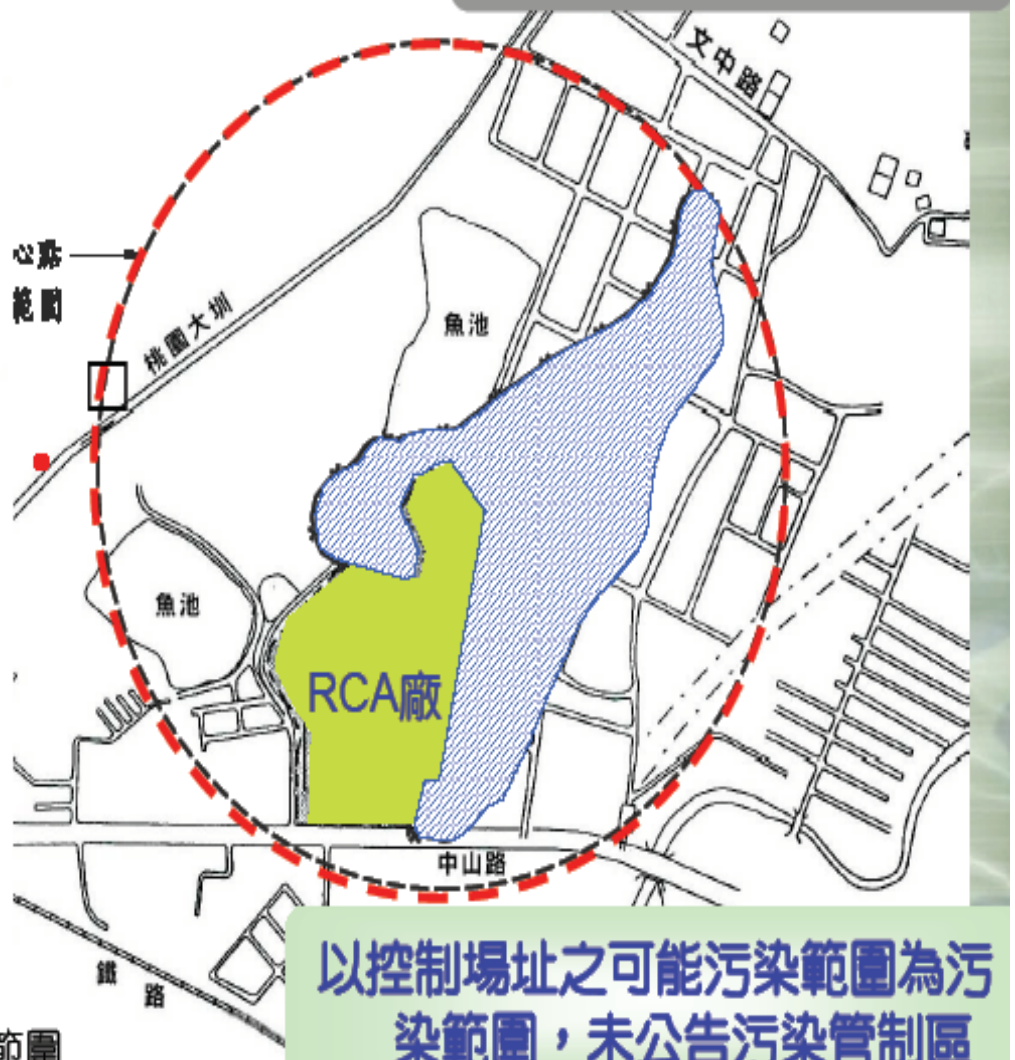
臺灣美國無線電公司(RCA)污染事件

- 臺灣美國無線電公司(RCA)污染事件，又稱RCA事件、RCA污染事件或者RCA污染案，是一件發生於台灣桃園縣桃園市的土壤及地下水污染公害事件。
- RCA在1970年於桃園縣桃園市中山路、文中路與富裕街之間設置桃園廠為總廠，生產電子產品、電器產品、電視機之電腦選擇器。
- 1994年6月3日當時的立法委員、前行政院環境保護署署長趙少康召開記者會，舉發RCA長期挖井傾倒有機溶劑等有毒廢料，導致廠區之土壤及地下水遭受嚴重污染。
- 2007年由法律扶助基金會、台北律師公會、民間司法改革基金會、及台灣人權促進會等多位律師共同籌組了義務律師團，除以RCA為被告外，並將奇異公司及湯普笙公司列為被告，透過法律訴訟爭取賠償。2009年11月11日，台北地方法院首次傳喚受害人出庭作證，RCA案正式進入訴訟程序。
- 2015年4月17日，臺北地方法院一審宣判自救會勝訴，RCA、湯姆笙公司須賠償新臺幣5億6445萬元。
- 2017年10月27日，台灣高等法院經兩年審理，宣判RCA等四家公司須連帶賠償486人，賠償金額增加到新台幣7億1840萬元。
- 2018年8月16日，最高法院判RCA、奇異等4家業者須連帶賠償其中262位員工或家屬共5億餘元確定，另246求償案發回更審，全案部分確定。
- 2019年12月27日，臺北地方法院一審作出**第二波**求償判決，RCA、奇異等4家業者再次敗訴，合計應賠償1,120人23億餘元。
- 資料來源：Wikipedia

RCA(地下水整治場址)

1. 81年關廠，廠內污染最高為管制標準（四氯乙烯0.05 mg/l）的30倍，廠區外最高為標準5倍
2. 93年5月提出地下水調查評估計畫(94.04已核定)
3. RCA公司目前已將地下水污染整治計畫送桃園縣政府審查

以場址北端為中心
半徑500公尺為污染範圍

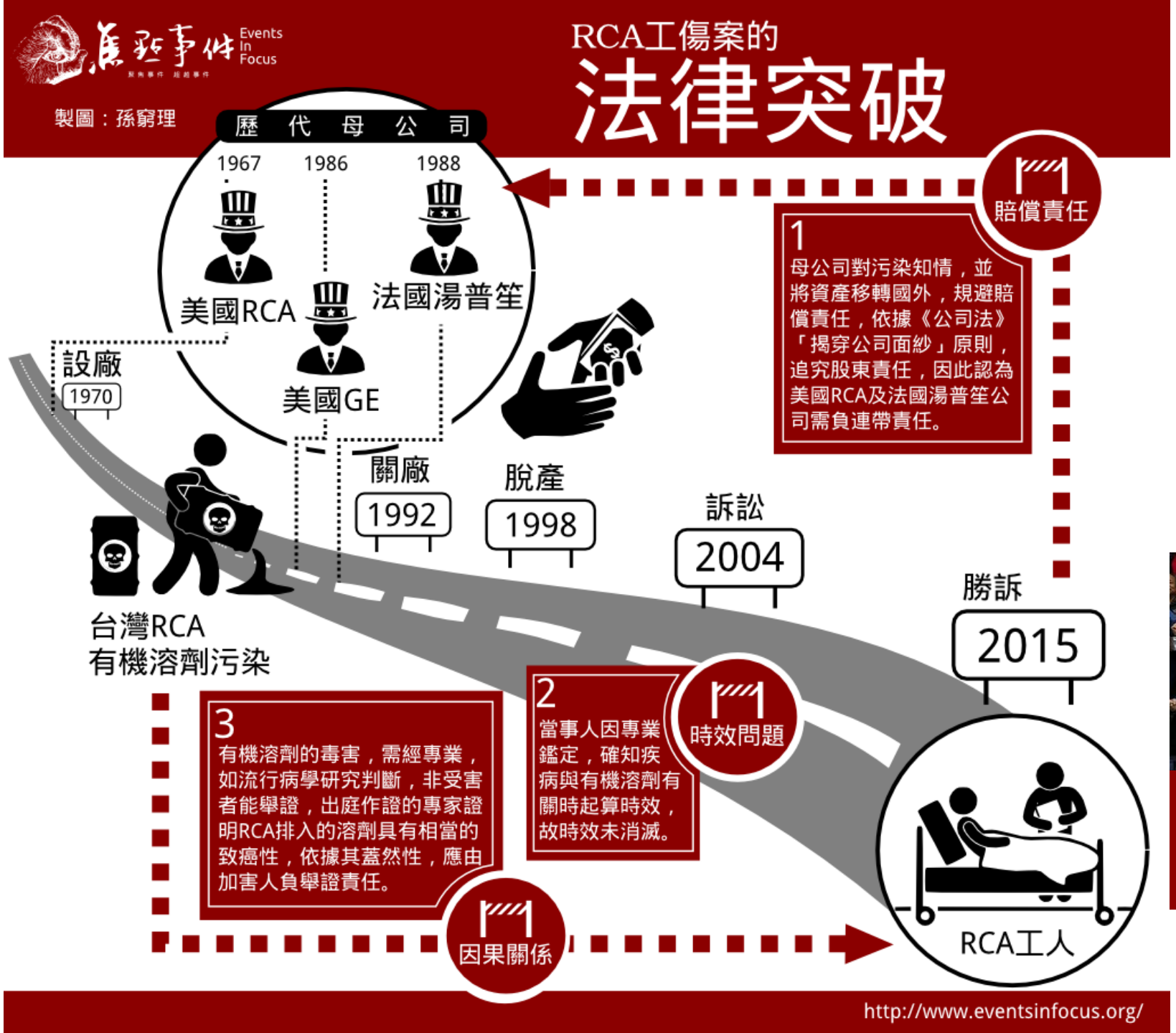


以控制場址之可能污染範圍為污染範圍，未公告污染管制區

：廠區範圍　：推估地下水 污染範圍

RCA桃園廠附近民井地下水

- 1994年工研院就RCA桃園廠附近民井地下水分析結果，共含有十二種含氯有機溶劑，其濃度超過飲用水水質標準數千倍
- 四氯乙烯：4,800 ppb，比飲用水標準5 ppb，超過將近一千倍
- 三氯乙烯：930 ppb，比飲用水標準5 ppb，超過將近二百倍
- 二氯乙烯：1,417.5 ppb，比飲用水標準7 ppb，超過二百多倍



第二波勝訴2019

4 未罹病但健康權受損

5 總額裁判

BMC Public Health

BioMed Central

Research article

Open Access

Increased standardized incidence ratio of breast cancer in female electronics workers

Tzu-I Sung[1], Pau-Chung Chen[1,2], Lukas Jyuhn-Hsiarn Lee[3], Yi-Ping Lin[2,4], Gong-Yih Hsieh[1] and Jung-Der Wang*[1,2,5]

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Available online at www.sciencedirect.com

ScienceDirect

Reproductive Toxicology 25 (2008) 115–119

Reproductive Toxicology

Developmental Basis of Health and Disease

www.elsevier.com/locate/reprotox

Increased risk of cancer in the offspring of female electronics workers

Tzu-I. Sung[a], Jung-Der Wang[a,b,c], Pau-Chung Chen[a,c,*]

Birth Defects Research (Part A) 85:119–124 (2009)

Increased Risks of Infant Mortality and of Deaths Due to Congenital Malformation in the Offspring of Male Electronics Workers

Tzu-I Sung,[1] Jung-Der Wang,[1,2,3] and Pau-Chung Chen[1,2*]

國立台灣大學公共衛生學院

職業醫學與工業衛生研究所碩士論文

指導教授：陳保中 博士

潛在暴露於含氯碳氫化合物污染地下水與居民下一代早產之研究

The Study of Preterm Delivery among the Offspring of Residents Potentially Exposed to Groundwater Contaminated with Chlorinated Hydrocarbons

研究生：任鈺鈴 撰

中華民國九十年六月

鑑定證人

- 2013/7/4主詰問
- 2013/7/11主詰問
- 2013/8/1反詰問
- 2013/8/8反詰問
- 2013/12/13反詰問
- 2014/1/3反詰問
- 2014/1/10反詰問、覆主詰問、覆反詰問
- 總共出庭7天14次，筆錄記載高達50小時

居民(環保署)

- 死因勝算比(MOR)
  男性總癌症及肝癌
- 健康風險評估
  增加**肝癌**的風險
- 生殖危害
  子代有較高的**早產**風險
- 動物實驗
  污染混合物會增加**雄鼠肝腫瘤**及**雌鼠乳腺瘤、卵巢囊腫及子宮內膜增生**

員工(勞委會)

- 癌症比例死因比(PCMR)
  女性乳癌較其他電子廠與紡織廠高
- 癌症標準化死亡比(SMR)
  未達統計上顯著水準
- 癌症標準化發生比(SIR)
  未達統計上顯著水準
- 乳癌病例對照研究
  未達統計上顯著水準

員工(衛生署)

- 癌症標準化發生比(SIR)
  女性乳癌顯著較高
- 女性生殖危害
  子代有較高的**癌症**風險，特別是**白血病**
- 男性生殖危害
  子代有較高的**嬰兒死亡**風險，特別是**先天性心臟病**

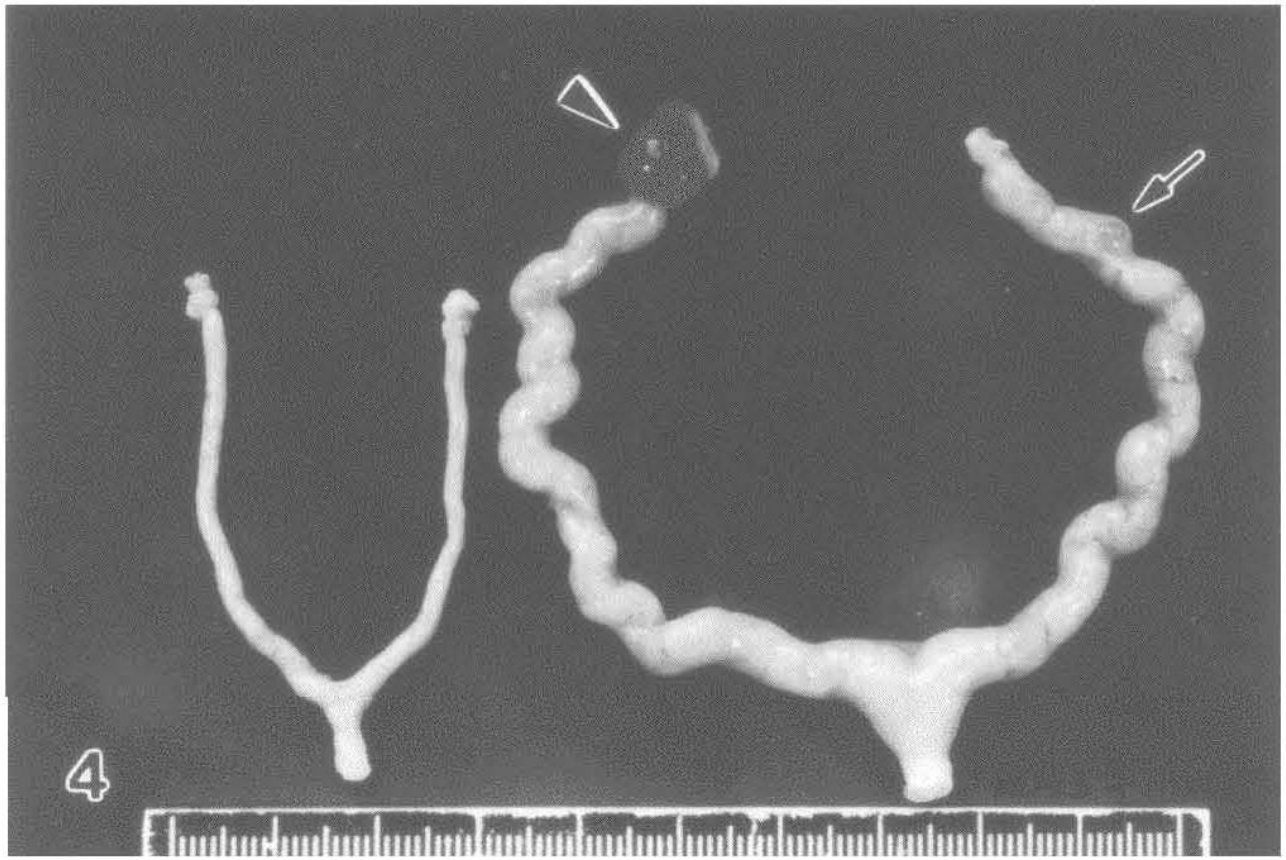


FIGURE 4. Bilateral diffuse endometrial hyperplasia together with luminal dilatation (right) are present more frequently in female ICR mice treated with CA mixture. Notice the cystic endometrium (arrow) and the ovarian cyst (arrowhead). A normal uterus is shown on the left for comparison.

Hill's Criteria for Causation

- Strength
- Consistency
- Specificity
- Temporality
- Biological gradient
- Plausibility
- Coherence
- Experiment
- Analogy

7 *Section of Occupational Medicine* 295

Meeting January 14 1965

The Environment and Disease: Association or Causation?

President's Address

by Sir Austin Bradford Hill CBE DSC FRCP(hon) FRS
(*Professor Emeritus of Medical Statistics, University of London*)

Amongst the objects of this newly-founded Section of Occupational Medicine are firstly 'to provide a means, not readily afforded elsewhere, whereby physicians and surgeons with a special knowledge of the relationship between sickness and injury and conditions of work may discuss their problems, not only with each other, but also with colleagues in other fields, by holding joint meetings with other Sections of the Society'; and, secondly, 'to make available information about the physical, chemical and psychological hazards of occupation, and in particular about those that are rare or not easily recognized'.

At this first meeting of the Section and before, with however laudable intentions, we set about instructing our colleagues in other fields, it will be proper to consider a problem fundamental to our own. How in the first place do we detect these relationships between sickness, injury and conditions of work? How do we determine what are physical, chemical and psychological hazards of occupation, and in particular those that are rare and not easily recognized?

There are, of course, instances in which we can reasonably answer these questions from the general body of medical knowledge. A particular, and perhaps extreme, physical environment cannot fail to be harmful; a particular chemical is known to be toxic to man and therefore suspect on the factory floor. Sometimes, alternatively, we may be able to consider what *might* a particular environment do to man, and then see whether such consequences are indeed to be found. But more often than not we have no such guidance, no such means of proceeding; more often than not we are dependent upon our observation and enumeration of defined events for which we then seek antecedents. In other words we see that the event B is associated with the environmental feature A, that, to take a specific example, some form of respiratory illness is associated with a dust in the environment. In what circumstances can we pass from this observed *association* to a verdict of *causation*? Upon what basis should we proceed to do so?

I have no wish, nor the skill, to embark upon a philosophical discussion of the meaning of 'causation'. The 'cause' of illness may be immediate and direct, it may be remote and indirect underlying the observed association. But with the aims of occupational, and almost synonymously preventive, medicine in mind the decisive question is whether the frequency of the undesirable event B will be influenced by a change in the environmental feature A. *How* such a change exerts that influence may call for a great deal of research. However, before deducing 'causation' and taking action we shall not invariably have to sit around awaiting the results of that research. The whole chain may have to be unravelled or a few links may suffice. It will depend upon circumstances.

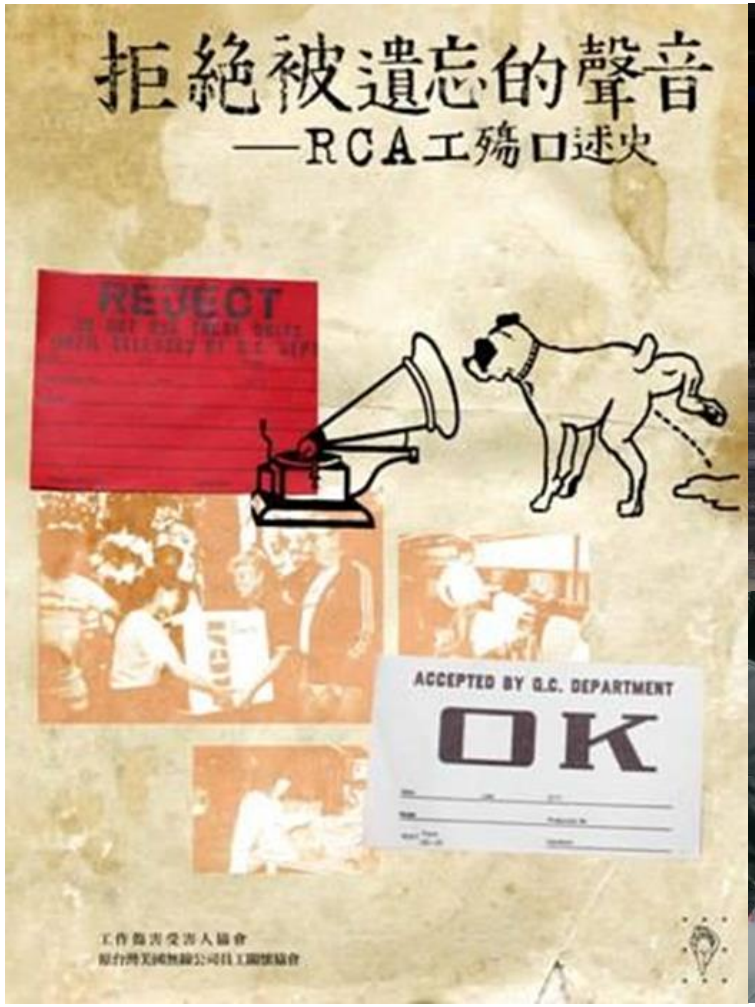
Disregarding then any such problem in semantics we have this situation. Our observations reveal an association between two variables, perfectly clear-cut and beyond what we would care to attribute to the play of chance. What aspects of that association should we especially consider before deciding that the most likely interpretation of it is causation?

(1) *Strength*. First upon my list I would put the strength of the association. To take a very old example, by comparing the occupations of patients with scrotal cancer with the occupations of patients presenting with other diseases, Percival Pott could reach a correct conclusion because of the *enormous* increase of scrotal cancer in the chimney sweeps. 'Even as late as the second decade of the twentieth century', writes Richard Doll (1964), 'the mortality of chimney sweeps from scrotal cancer was some 200 times that of workers who were not specially exposed to tar or mineral oils and in the eighteenth century the relative difference is likely to have been much greater.'

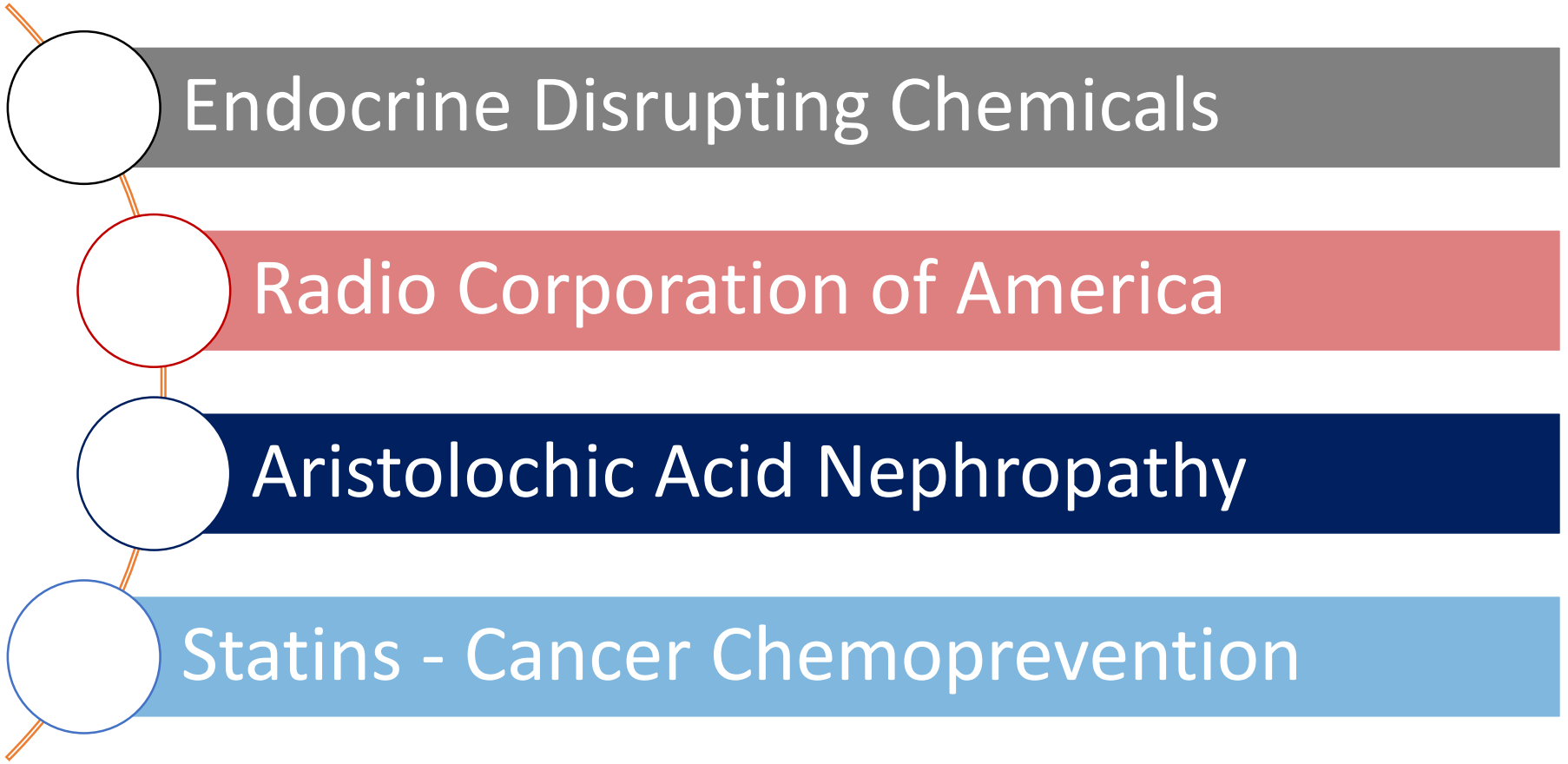
To take a more modern and more general example upon which I have now reflected for over fifteen years, prospective inquiries into smoking have shown that the death rate from cancer of the lung in cigarette smokers is nine to ten times the rate in non-smokers and the rate in heavy cigarette smokers is twenty to thirty times

Sir Austin Bradford Hill (1897–1991) in 1965

期許



Adventures in Environmental and Occupational Health Sciences



Slimming Regimen, Belgium, 1990-92

Adulteration

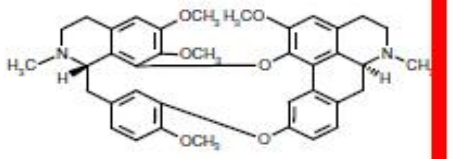
Substitution

Han Fangji

Stephaniae tetrandrae radix

Stephania tetrandra S.MOORE

Menispermaceae



Tetrandrin

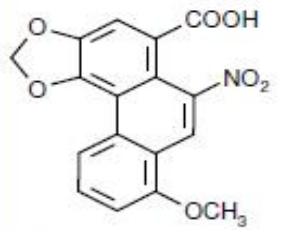
- More than 100 kidney intoxications in Belgium („Aristolochia nephropathia“)
- More than 40 women now depend on dialysis
- Several cases of kidney cancer

Guang Fangji

Aristolochiae fangchi radix

Aristolochia fangchi WU

Aristolochiaceae

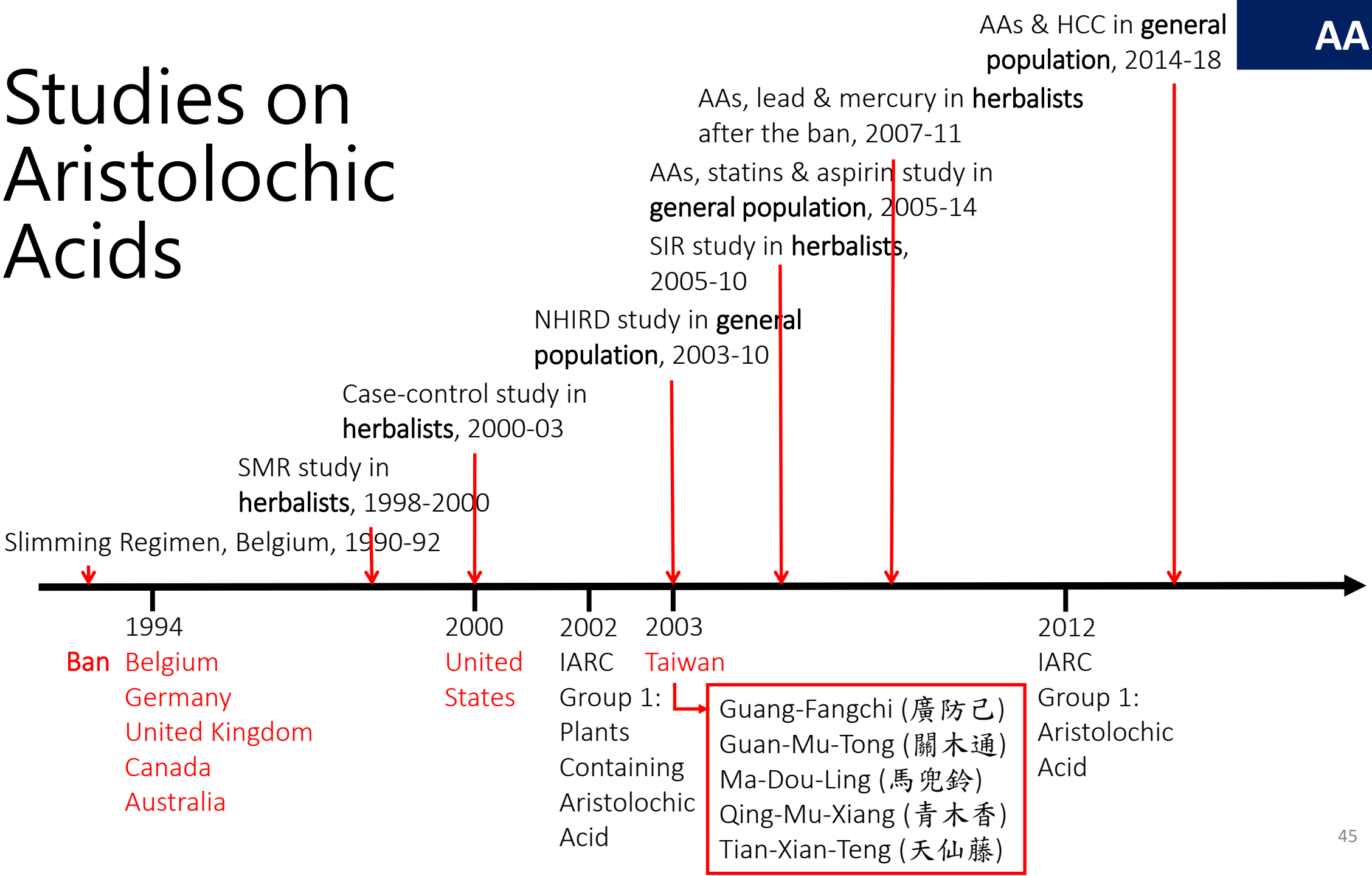


Aristolochic acid A

Violon, *J. Pharm. Belg.* 52, 7-27(1997); Reginster *et al.*, *Nephrology, Dialysis, Transplantation* 12, 81-86 (1997); Vanherweghem, *J. Altern. Complement. Med.* 4, 9-13 (1998); Pokhrel u. Ergil, *Clin. Acupunct. Orient. Med.* 1, 161-166 (2000); Nortier et al., *N. Engl J. Med.* 342, 1686 (2000)

Aristolochic Acid Nephropathy

Studies on Aristolochic Acids

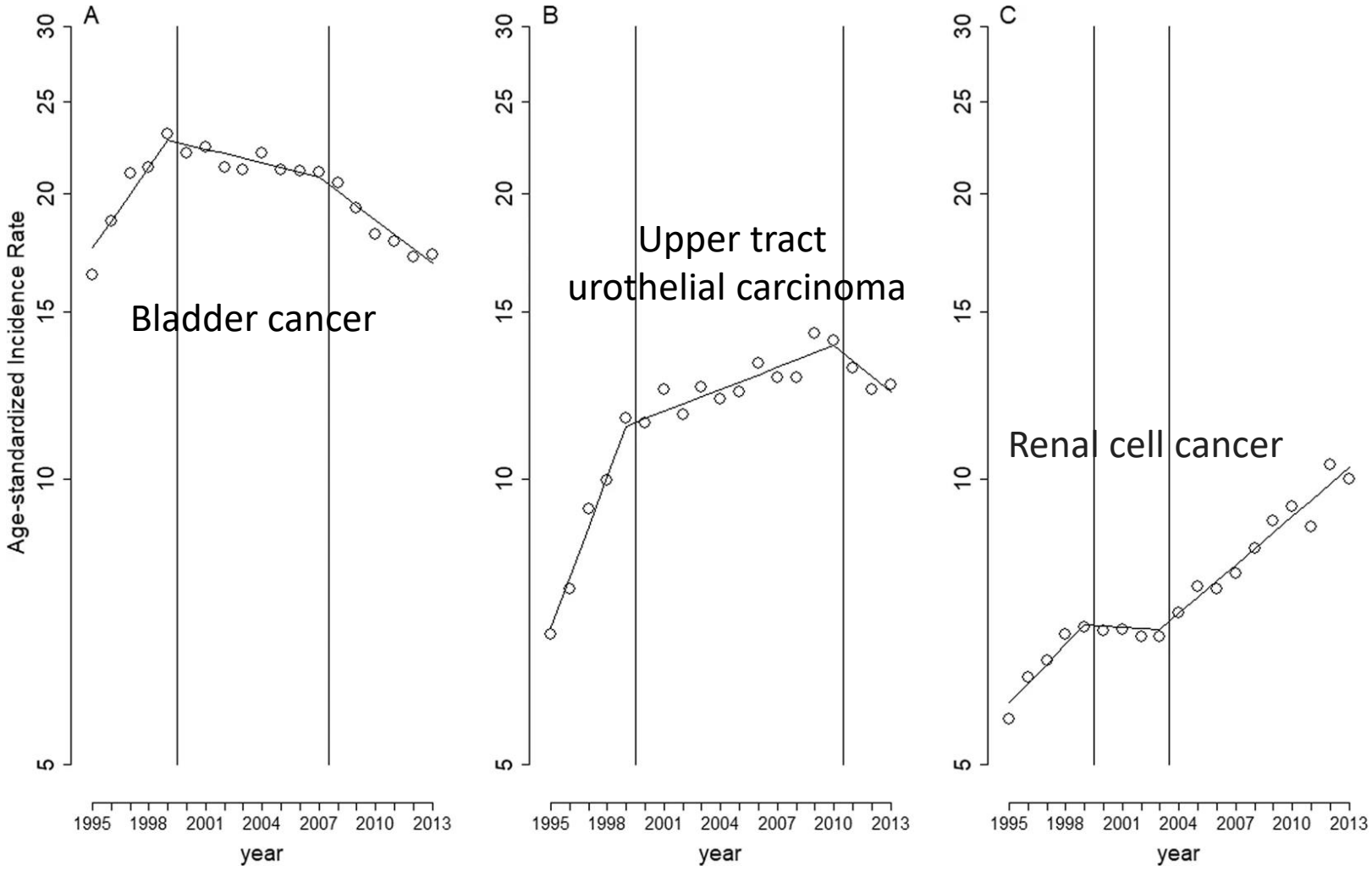


Aristolactam (AL)-DNA adducts and TP53 mutations in urothelial carcinoma of the upper urinary tract (UUC) cases from Taiwan

Cases	All	Males	Females
Cases with AL-DNA adducts	**89/148 (60%)**	**45/82 (55%)**	**44/66 (67%)**
Cases with TP53 mutations	84/151 (56%)	34/82 (41%)	50/69 (72%)
Cases with TP53 A→T transversions	47/151 (31%)	17/82 (21%)	30/69 (43%)
Cases with AL-DNA adducts and TP53 A→T transversions	38/148 (26%)	14/82 (17%)	24/66 (36%)
AL-DNA adduct-positive cases with TP53 A→T transversions	38/89 (43%)	14/45 (31%)	24/44 (55%)
TP53 A→T transversion cases with AL-DNA adducts	**38/45 (84%)**	**14/17 (82%)**	**24/28 (86%)**

PNAS 2012;109:8241-6

Reduction in the Incidence of Urological Cancers after the Ban on Chinese Herbal Products Containing Aristolochic Acid



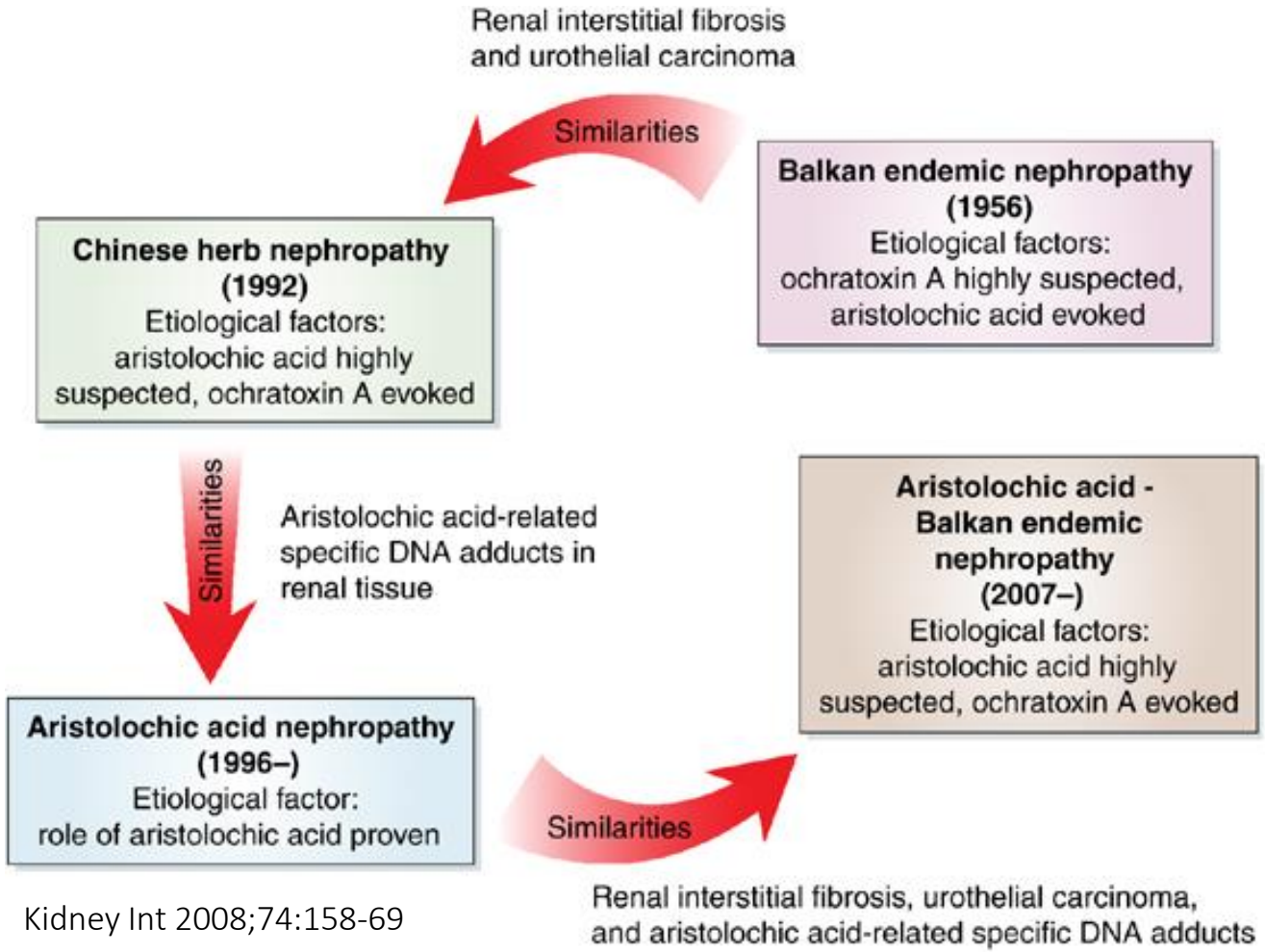
Scientific Reports 2019

Sequence of Establishing Causality

- **Clinical observation**
- **Many case reports**
- **Epidemiological studies**
  - Cohorts of consumption of single material in Belgium
  - Occupational exposure in Chinese herbalists of Taiwan
  - Consumptions of mixtures of multiple Chinese herbs in general population of Taiwan
  - High incidence of end-stage renal disease in Taiwan
  - Environmental contamination among farming material and epidemic among residents consuming contaminated bread in Balkan countries
- **Biological plausibility from human and animal studies**
  - TP53 gene mutation and AL-DNA adducts
  - Molecular mechanisms of renal damage or tumor formation
- **Preventive actions after causal inference**
  - Total ban of aristolochic acid associated herbs
  - Early recognition and/or diagnosis of AA-associated nephropathy and cancer
  - Establishment of pharmacovigilance system for herbs

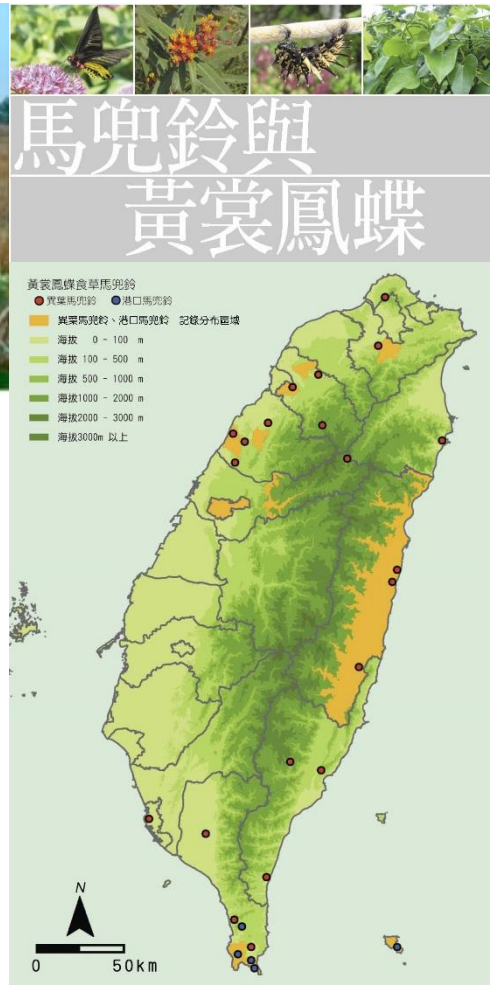
BioMed Res Int 2014;2014:569325

Aristolochic Acid Nephropathy A Worldwide Problem



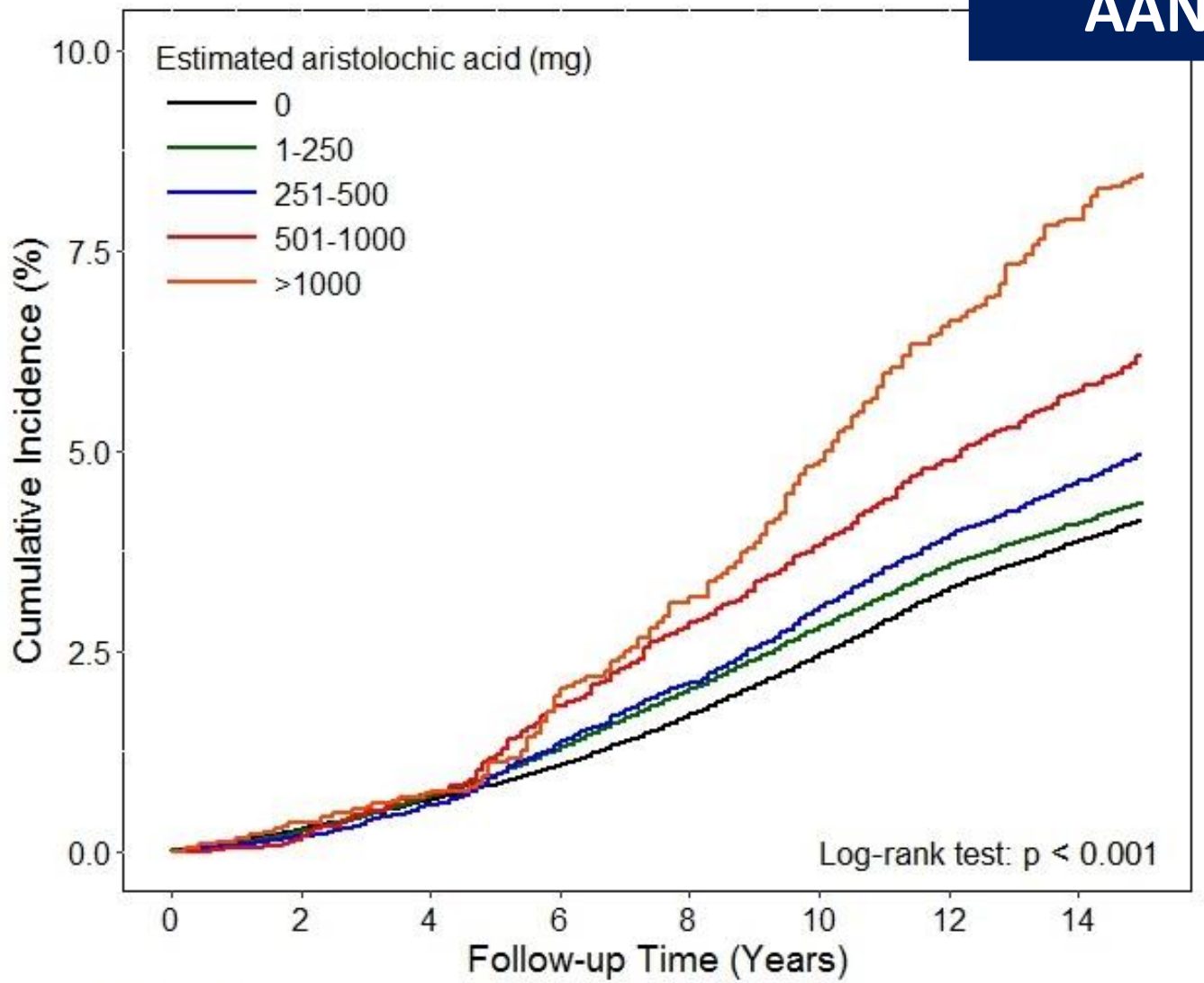
Kidney Int 2008;74:158-69

In the Balkan regions, the exposure to AA found in flour obtained from wheat contaminated with seeds of *Aristolochia clematitis* could be responsible for the so-called Balkan-endemic nephropathy.



Herbal medicine containing aristolochic acid and the risk of hepatocellular carcinoma in patients with hepatitis B virus infection

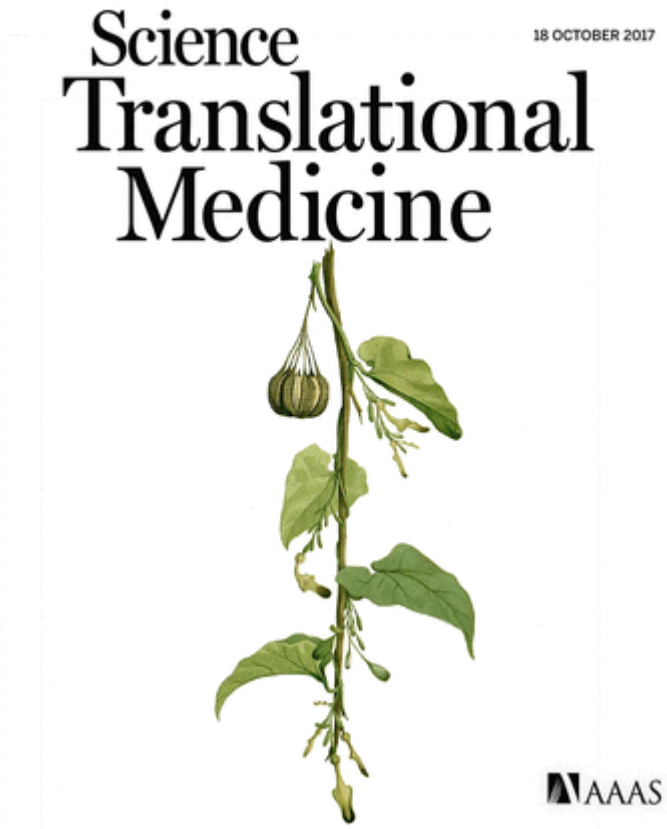
IJC 2018; 143(7): 1578-87
Cancer Epidemiol Biomarkers Prev 201; 28(11): 1876-83



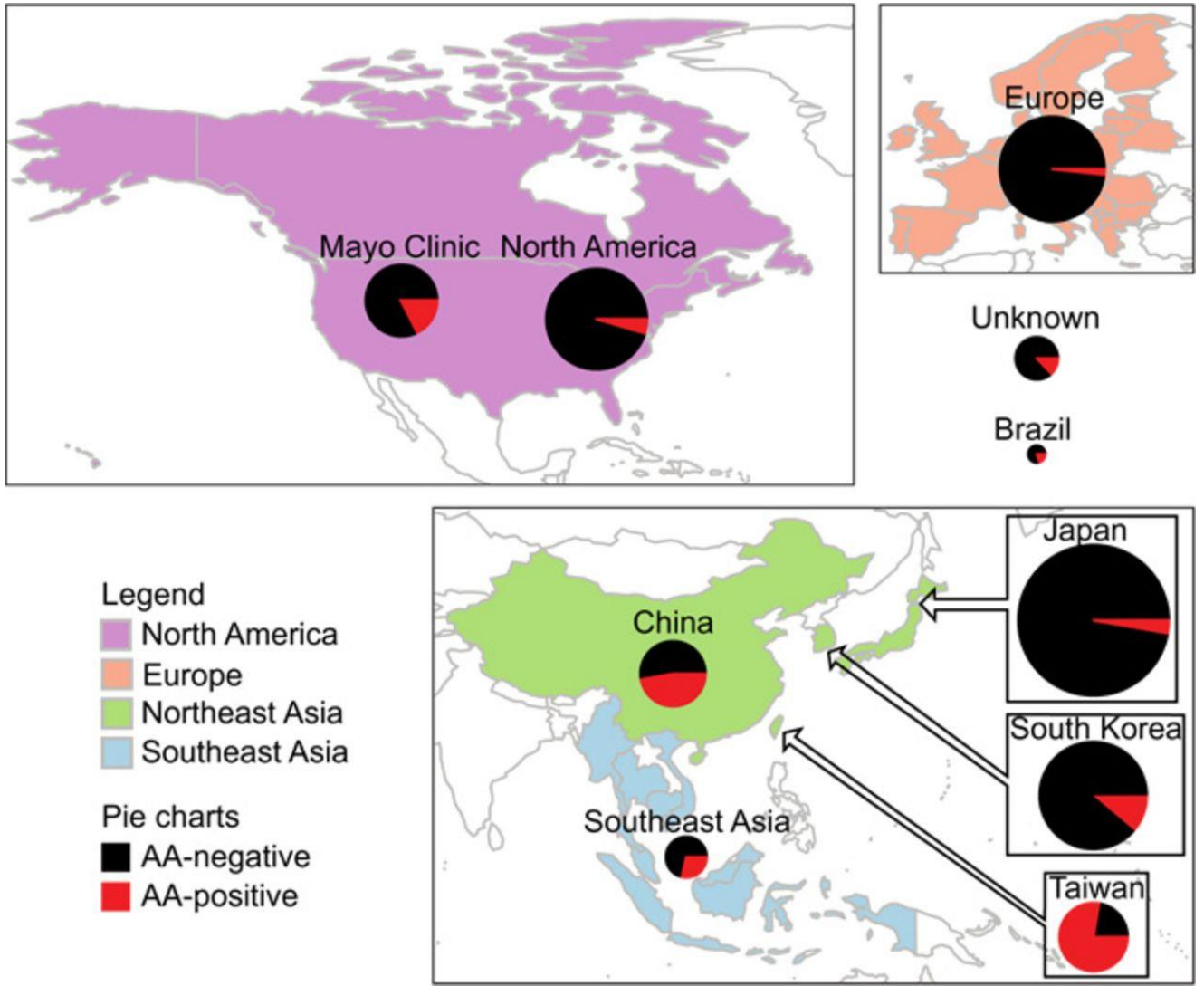
Number at risk

0	325527	324292	322443	320050	316619	312029	306726	302064
1-250	449261	447727	444613	440152	434406	427908	421041	415304
251-500	18378	18327	18220	18004	17758	17481	17194	16928
501-1000	6940	6924	6876	6777	6666	6548	6418	6276
>1000	2536	2525	2513	2465	2420	2347	2290	2238

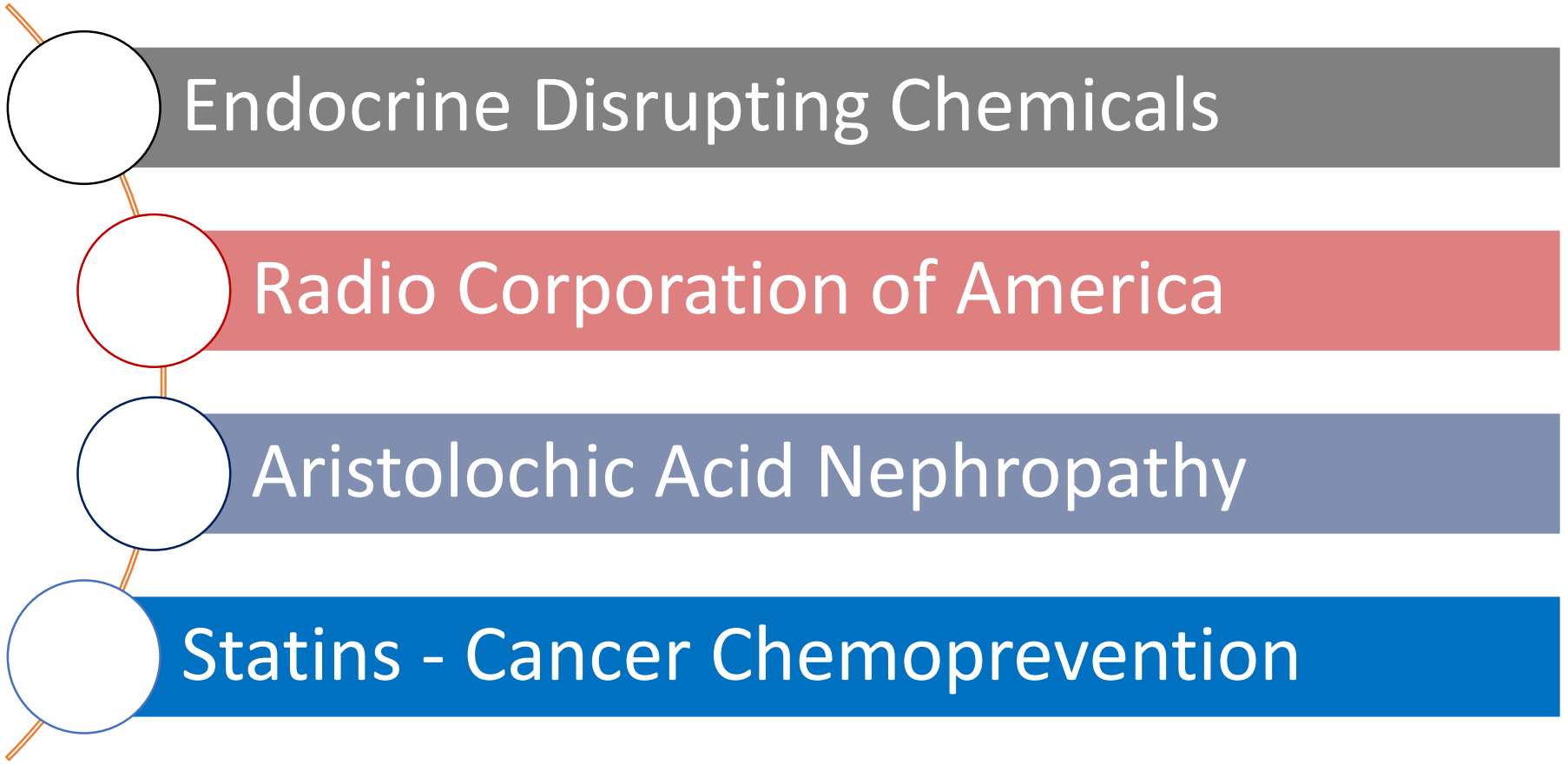
Global distribution of mutagenesis associated with aristolochic acid and derivatives in HCCs



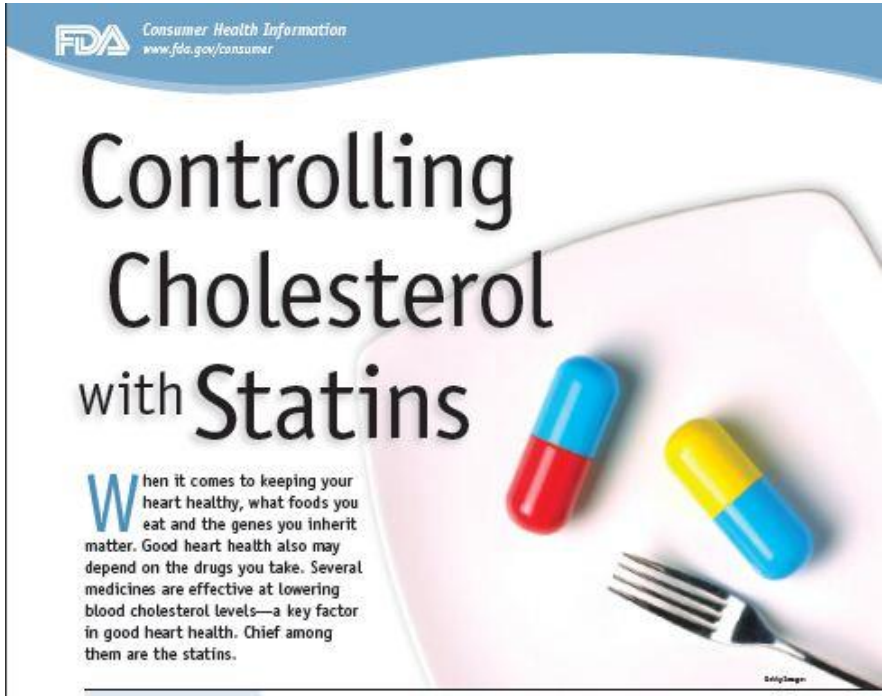
Sci Transl Med 2017; 9: eaan6446



Adventures in Environmental and Occupational Health Sciences

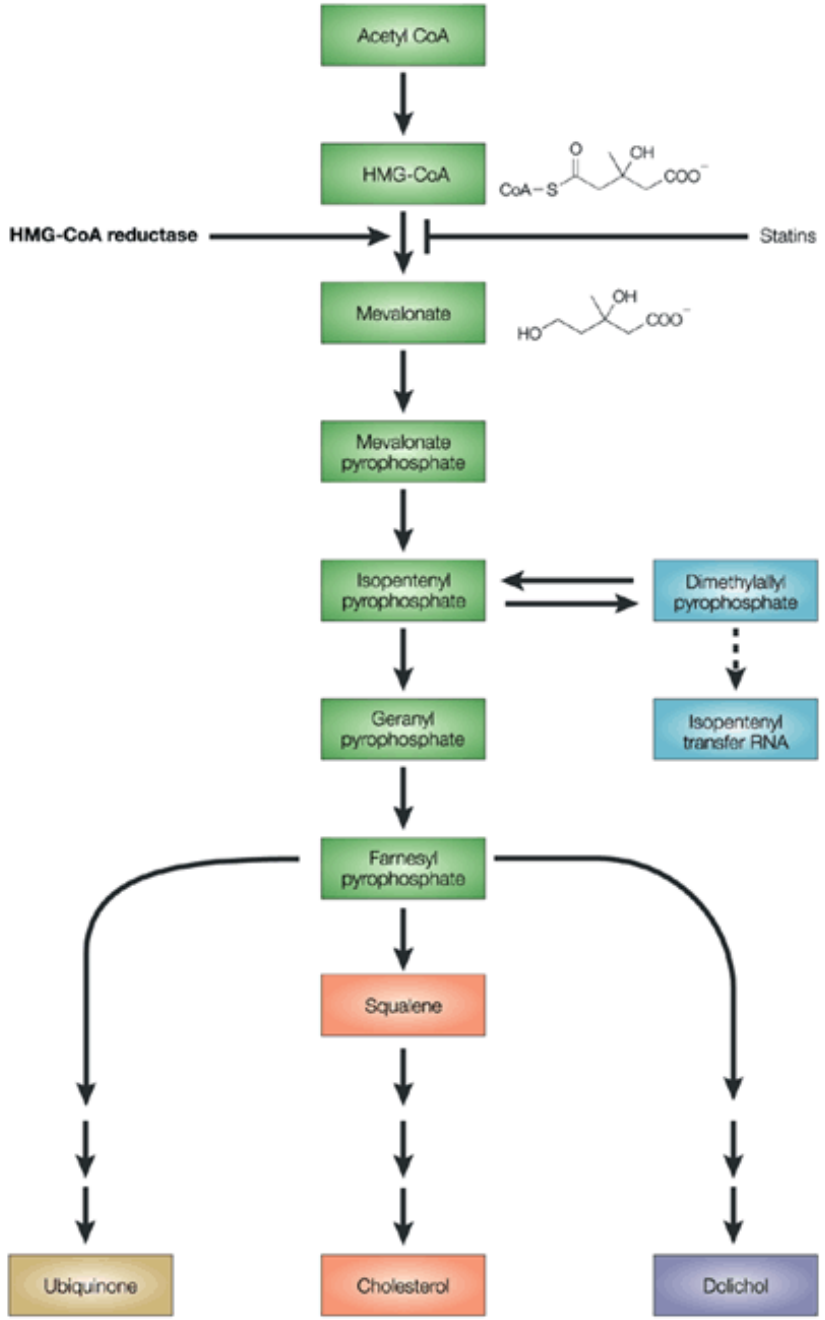


Statins



The HMG-CoA reductase pathway, which is blocked by statins via inhibiting the rate limiting enzyme HMG-CoA reductase.

http://www.cdc.gov; Nature Reviews Drug Discovery 2003; 2: 517-526



VOLUME 30 · NUMBER 6 · FEBRUARY 20 2012

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Statins and the Risk of Hepatocellular Carcinoma in Patients With Hepatitis B Virus Infection

Yu-Tse Tsan, Chang-Hsing Lee, Jung-Der Wang, and Pau-Chung Chen

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Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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ABSTRACT

Purpose
Statins have potential protective effects against cancers, but no studies have focused on patients with chronic hepatitis B virus (HBV) infection. The purpose of this study was to investigate the association between the use of statins in HBV-infected patients and the risk of hepatocellular carcinoma (HCC).

Patients and Methods
We conducted a population-based cohort study from the Taiwan National Health Insurance Research Database. A total of 33,413 HBV-infected patients were included as the study cohort. Each patient was individually tracked from 1997 to 2008 to identify incident cases of HCC since 1999. Subsequent use of statin, other lipid-lowering agents, aspirin, and angiotensin-converting enzyme inhibitors was identified. Cox proportional hazards regression was used to calculate the hazard ratios (HRs) and 95% CIs for the association between the use of statins and the occurrence of HCC in the HBV-infected cohort.

Results
There were 1,021 HCCs in the HBV cohort during the follow-up period of 328,946 person-years; the overall incidence rate was 310.4 HCCs per 100,000 person-years. There was a dose-response relationship between statin use and the risk of HCC in the HBV cohort. The adjusted HRs were 0.66 (95% CI, 0.44 to 0.99), 0.41 (95% CI, 0.27 to 0.61), and 0.34 (95% CI, 0.18 to 0.67) for statin use of 28 to 90, 91 to 365, and more than 365 cumulative defined daily doses (cDDDs), respectively, relative to no statin use (< 28 cDDDs).

Conclusion
Statin use may reduce the risk for HCC in HBV-infected patients in a dose-dependent manner. Further mechanistic research is needed.

J Clin Oncol 30:623-630. © 2012 by American Society of Clinical Oncology

VOLUME 30 · NUMBER 20 · JULY 10 2012

JOURNAL OF CLINICAL ONCOLOGY

CORRESPONDENCE

Statins and Risk Reduction in Hepatocellular Carcinoma: Fact or Fiction?

TO THE EDITOR: In the February 20, 2012 issue of *Journal of Clinical Oncology*, Tsan et al[1] published an article entitled "Statins and the Risk of Hepatocellular Carcinoma in Patients With Hepatitis B Virus Infection." In this population-based cohort study that used the Taiwan National Health Insurance Research Database, the authors reported that statin use may reduce the risk of hepatocellular carcinoma (HCC) in patients with hepatitis B virus (HBV) infection. Tsan et al[1] followed 33,413 patients with HBV infection from 1997 to 2008, of which 8.3% used statins and noted 1,021 incident HCC cases in this HBV cohort. The incidence rate (per 100,000 person-years) of HCC in patients on statins was 210.9, compared with an incidence rate of 319.5 in nonusers ($P < .001$). The crude and adjusted hazard ratios (95% CIs) for HCC in statin users compared with nonusers was 0.66 (0.51 to 0.86) and 0.47 (0.36 to 0.61), respectively. The authors appropriately adjusted for potential confounders (age, sex, cirrhosis, diabetes, and medica-

The antineoplastic effect of metformin is believed to be mediated by the activation of adenosine monophosphate-activated protein kinase and the consequent inhibition of the mammalian target of rapamycin pathway.[8] In addition, metformin may inhibit cell growth by inhibiting cyclin D1 expression and retinoblastoma protein phosphorylation.[9] Thiazolidinediones have been postulated to induce cell-growth arrest and prevent cancer-cell invasion through the inhibition of the ubiquitin-proteasome system and/or the extracellular signal-regulated kinase pathway. In addition, thiazolidinediones also induce apoptosis by increasing proapoptotic p53 and phosphatase and tensin homolog and reducing antiapoptotic Bcl-2 and survivin levels.[10]

In our opinion, although Tsan et al[1] adjusted for multiple potential confounding medications, an important omission was antidiabetic therapy, especially metformin and thiazolidinediones. Overall, 26.4% of patients in the cohort were diabetic, and that statistic rose to 61.9% in the group with statin use. Many of these patients would have been on antidiabetic therapy of various types, and adjustment for diabetes alone did not take into account the potential effects of these drugs on HCC risk. Hence, although statins may lower risk of HCC in this population, part of the risk reduction may actually have been attributable to the effect of

Do Statins Reduce Patients' Risk of Hepatocellular Carcinoma?

Tsan Y-T, Lee C-H, Wang J-D, Chen P-C. Statins and the risk of hepatocellular carcinoma in patients with hepatitis B virus infection. *J Clin Oncol*. 2012;30:623-630.

Statins, a class of drugs used to lower cholesterol, are known to help prevent against cardiovascular disease and stroke.[1] Interestingly, statins have also been explored as anticancer agents, with several lines of preclinical evidence pointing to potential anticancer activity. For example, statins have antiproliferative, proapoptotic, prodifferentiation, anti-invasive, and radiosensitizing properties.[2,3] One of the potential mechanisms explaining the antitumor effect of statins involves suppression of the mevalonate pathway, resulting in depletion of isoprenoids; these downstream products have a role in cell cycle progression, cell signaling, and membrane integrity.[4,5]

a unit recommended by the World Health Organization, which is the assumed average maintenance dose per day of a drug consumed for its main indication. In this study, the number of DDDs was calculated as the total amount of the drug divided by the amount of drug in a DDD. This number was then used to estimate the sum of dispensed statins, which resulted in the cumulative DDD (cDDD); this latter value is an indicator of the exposed duration. Statin nonusers were defined as those with fewer than 28 cDDDs.

In this population-based cohort study, a total of 33,413 patients (58.2% male) were identified from the Taiwan National Health Insurance Research Database

Gastroenterology and Hepatology 2012;8:320-1

Perspective

Do statins reduce the risk of hepatocellular carcinoma in patients with chronic hepatitis B?

James Fung[1,2], Ching-Lung Lai[1,2], Man-Fung Yuen[1,2], Irene Oi-Lin Ng[2,3]

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Scan to your mobile device or view this article at: http://www.thehbsn.org/article/view/1278

In subjects with chronic hepatitis B (CHB), the lifetime risk of developing hepatocellular carcinoma (HCC) is estimated to be 25-37 times compared to non-infected subjects. The process of hepatocarcinogenesis is complex and involves well-documented host, viral, and environmental risk factors. The most important risks include host factors such as older

the effect was attenuated in a sub-analysis of patient without known liver diseases (OR 0.63). In another population-based case-control study from Taiwan, Chiu *et al.* examined 1,166 liver cancer cases with an equal number of controls matched for age and sex (3). The adjusted OR was 0.62 (95% CI, 0.42-0.91) for the group which had been prescribed statin

Hepatobiliary Surgery and Nutrition 2013;2:1-3

VOLUME 31 · NUMBER 12 · APRIL 20 2013

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Statins and the Risk of Hepatocellular Carcinoma in Patients With Hepatitis C Virus Infection

Yu-Tse Tsan, Chang-Hsing Lee, Wen-Chao Ho, Meng-Hung Lin, Jung-Der Wang, and Pau-Chung Chen

See accompanying editorial on page 1499

Yu-Tse Tsan, Chang-Hsing Lee, and Pau-Chung Chen, National Taiwan University; Pau-Chung Chen, National Taiwan University Hospital, Taipei; Yu-Tse Tsan, Taichung Veterans General Hospital and Chung Shan Medical University; Wen-Chao Ho and Meng-Hung Lin, China Medical University, Taichung; Chang-Hsing Lee, Ton Yen General Hospital, Hsinchu; and Jung-Der Wang, National Cheng Kung University, Tainan, Taiwan.

Published online ahead of print at www.jco.org on March 18, 2013.

Written on behalf of the Health Data Analysis in Taiwan Research Group.

The interpretation and conclusions of this report do not represent those of the Bureau of National Health Insurance, Department of Health, or National Health Research Institutes of Taiwan.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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ABSTRACT

Purpose
Statins may have protective effects against cancer, but no studies have focused on their effects in patients with chronic hepatitis C virus (HCV) infection. The purpose of this study was to investigate the association between use of statins and risk of hepatocellular carcinoma (HCC) in HCV-infected patients.

Patients and Methods
Ours was a population-based cohort study of 260,864 HCV-infected patients enrolled in the Taiwan National Health Insurance Research Database since January 1, 1999, and observed through December 31, 2010. Cox proportional hazards regression with time-dependent covariates for drug exposures was employed to evaluate the association between statin use and HCC risk.

Results
There were 27,883 cases of HCC in the HCV cohort during a follow-up period of 2,792,016.6 person-years. Among the 35,023 patients using statins (defined as ≥ 28 cumulative defined daily doses [cDDDs]), 1,378 had HCC. Among the 225,841 patients not using statins (< 28 cDDDs), 26,505 were diagnosed with HCC. A dose-response relationship between statin use and HCC risk was observed. The adjusted hazard ratios were 0.66 (95% CI, 0.59 to 0.74), 0.47 (95% CI, 0.40 to 0.56), and 0.33 (95% CI, 0.25 to 0.42) for patients with 28 to 89, 90 to 180, and > 180 cDDDs per year, respectively, relative to nonusers. The reduction in risk also demonstrated a progressive duration-response relationship in patients with ≥ 28 cDDDs per year when compared with nonusers.

Conclusion
Among patients with HCV infection, statin use was associated with reduced risk of HCC. Further research is needed to elucidate the mechanism responsible for this effect.

J Clin Oncol 31:1514-1521. © 2013 by American Society of Clinical Oncology

VOLUME 31 · NUMBER 12 · APRIL 20 2013

JOURNAL OF CLINICAL ONCOLOGY

EDITORIAL

An Ounce of Prevention Is Better Than a Pound of Cure: A Patient-Centered Approach to Hepatocellular Carcinoma

Abby B. Siegel, *Columbia University Medical Center, New York, NY*

See accompanying article on page 1514

Hepatocellular carcinoma (HCC) is one of the leading causes of cancer deaths worldwide. Though it is less commonly seen in the United States, age-adjusted incidence rates have tripled here over the last three decades, and overall survival remains poor for those with advanced disease.[1] Host factors, including viral hepatitis, metabolic syndrome, alcohol use, and genetic disorders, contribute to HCC pathogenesis, both singly and in combination. HCC is notable for having particularly varied etiologies in different populations. Hepatitis B vaccination programs have begun to show dramatic decreases in HCC incidence, but for those with other underlying risk factors, primary prevention efforts have been disappointing.

In the article that accompanies this editorial, Tsan et al[2] provide compelling evidence for an association between statin use and a significantly lower risk of HCC development in patients with hepatitis C infection (HCV). The authors examine a population-based cohort of 260,864 patients infected with HCV from Taiwan between January 1, HCC in the observational studies, but no benefit attributable to statins in the randomized trials.[9] Such differences between observational studies and randomized trials are not unusual, and may reflect length of follow-up and patient selection factors such as risk and country of origin.

Additionally, observational studies are susceptible to bias. The study by Tsan et al[2] has several limitations related to its design. First, because the differences between the groups are seen after just 28 to 89 cumulative daily doses of statin therapy (hazard ratio [HR] 0.66), one might suspect that other nonbiologic factors are playing a role. Second, confounding by indication can be seen if those with more advanced liver disease are less likely to be given a statin because of concerns for hepatotoxicity (or less concern about high lipids) in patients with advanced cirrhosis. The authors stratify by cirrhosis status and still show that the protective effects persisted in both groups. However, it is possible that cirrhosis, especially compensated

VOLUME 31 · NUMBER 32 · NOVEMBER 10 2013

JOURNAL OF CLINICAL ONCOLOGY

CORRESPONDENCE

Statins and Reduced Risk of Hepatocellular Carcinoma in Patients With Hepatitis C Virus Infection: Further Evidence Is Warranted

Georgios Nikolopoulos
National Development and Research Institutes, New York, NY

Nikolaos M. Sitaras
University of Athens, Athens, Greece

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Statins May Protect Against Hepatocellular Carcinoma Development in Patients Infected With Hepatitis C Virus, but What Are the Mechanisms?

ical rationale exists that may provide the basis for a potential protective action of statins. HCV directly affects the host lipid metabolism, thereby favoring its own replication, morphogenesis, and secretion.[6] Thus, inhibitors of lipid synthesis, such as statins, decrease viral replication[7,8] and egress[9] in vitro and, to a varying extent, in patients.[10] Recently, we have shown that the genotype 3 of HCV downregulates the phosphatase and tensin homolog deleted on chromosome 10 (PTEN), thereby inducing steatosis,[11] on

Common Flaws in Pharmacoepidemiologic Study Design and Analysis

and acceptable adjuvant strategy for preventing HCC in HCV-infected patients."[2(p1520)]

When designing observational studies, careful attention must be given to the temporality of study inclusion criteria and to measurement of exposures, covariates, and outcomes. The cohort study conducted by

HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases

HEPATOLOGY *ELSEWHERE*

Statins for Prevention of Hepatocellular Cancer: One Step Closer?

Tsan YT, Lee CH, Ho WC, Lin MH, Wang JD, Chen PC. Statins and the risk of hepatocellular carcinoma in patients with hepatitis C virus infection. J Clin Oncol 2013;31:1514-1521 (Reproduced with permission.)

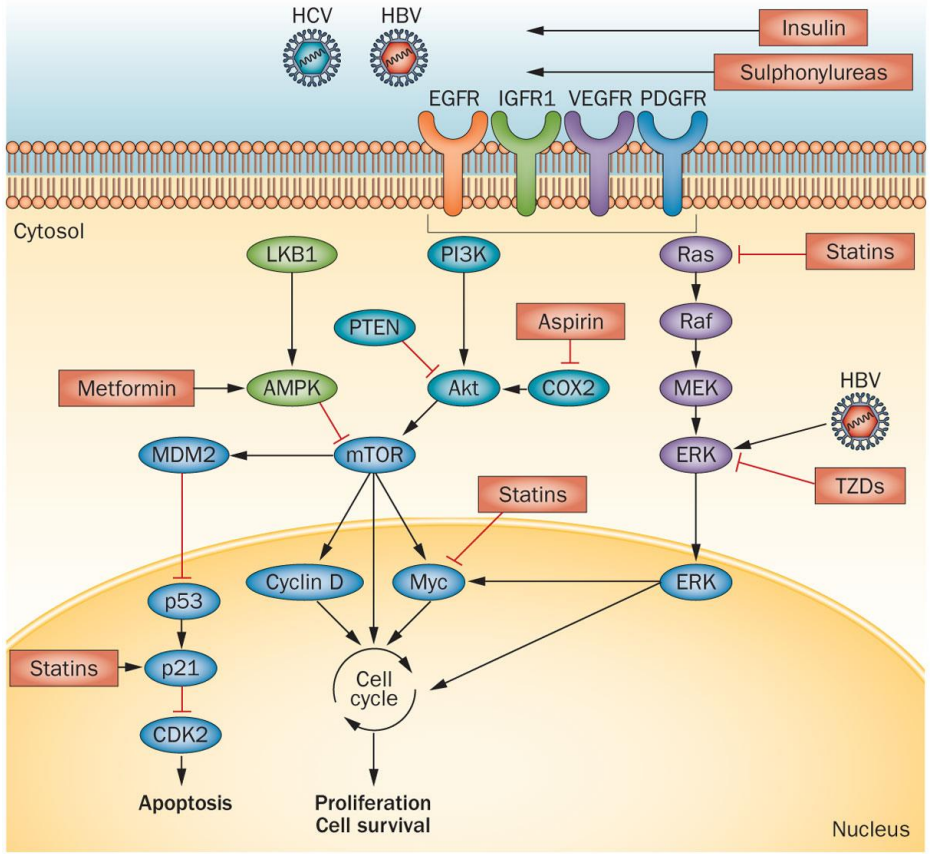
Abstract

Purpose: Statins may have protective effects against cancer, but no studies have focused on their effects in patients with chronic hepatitis C virus (HCV) infection. The purpose of this study was to investigate the association between use of statins and risk of hepatocellular carcinoma (HCC) in HCV-infected patients. Patients and Methods: Ours was a population-based cohort study of 260,864 HCV-infected patients enrolled in the Taiwan National Health Insurance Research Database since January 1, 1999, and observed through December 31, 2010. Cox proportional hazards regression with time-dependent covariates for drug exposures was employed to evaluate the association between statin use and HCC risk. Results: There were 27,883 cases of HCC in the HCV cohort during a follow-up period of

medication in the United States.[3] Preclinical as well as epidemiologic studies have shown that besides cholesterol reduction, statins may be protective against inflammation-driven cancers.[4-6] Statins have antiproliferative, proapoptotic, antiangiogenic, immunomodulatory, and antiinfective effects.[7] By competitive inhibition of 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase, statins inhibit products of the mevalonate pathway, preventing posttranslational modification of Ras/Rho proteins. Myc activation is a critical step in hepatocarcinogenesis, and its inactivation using atorvastatins has been shown to induce sustained regression of HCC.[8] Besides their direct effect on hepatocarcinogenesis, statins have also been shown to have antiinfective effects against HCV.[9] There is a growing body of evidence suggesting a protective association between statin use and risk of incident HCC.[10,11]

In their population-based cohort study, Tsan et al.[12] used the comprehensive Taiwanese National Health Insurance Database to study the association between statin use and risk of HCV-associated HCC. They followed

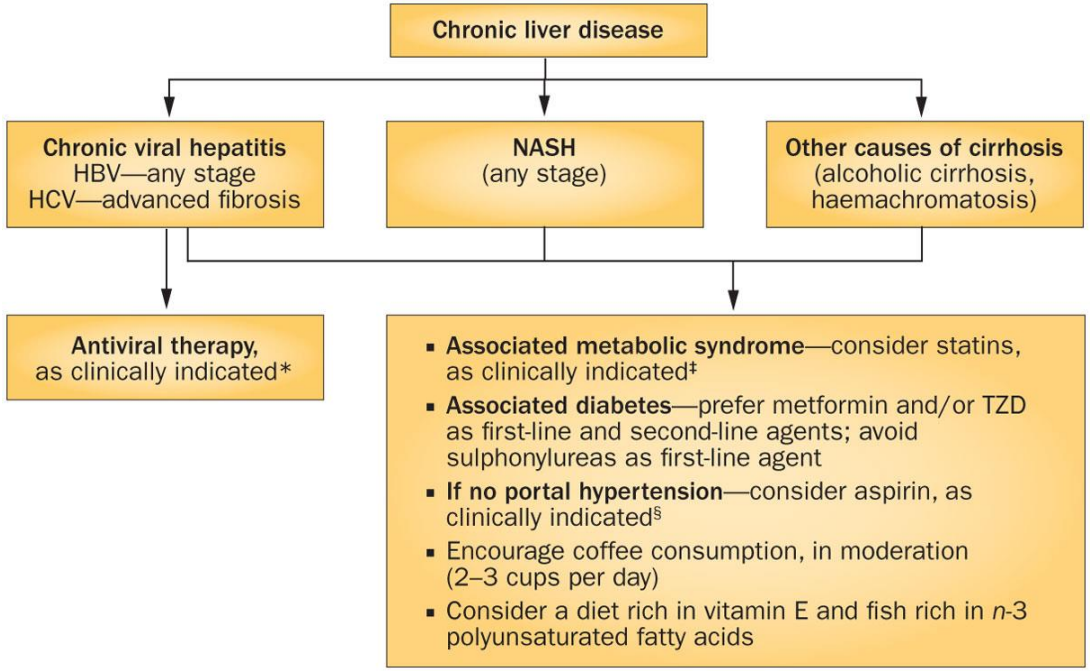
Pathogenesis of HCC And Targets for Chemopreventive Agents



Singh, S. *et al.* (2013) Chemopreventive strategies in hepatocellular carcinoma *Nat. Rev. Gastroenterol. Hepatol.* doi:10.1038/nrgastro.2013.143

nature REVIEWS GASTROENTEROLOGY & HEPATOLOGY

Proposed algorithm for chemoprevention in patients at risk of hepatocellular carcinoma



Singh, S. *et al.* (2013) Chemopreventive strategies in hepatocellular carcinoma *Nat. Rev. Gastroenterol. Hepatol.* doi:10.1038/nrgastro.2013.143

nature REVIEWS GASTROENTEROLOGY & HEPATOLOGY

Statins

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Statin Use After Diagnosis of Hepa Associated With Decreased Mortal

Aaron P. Thrift,*,‡ Yamini Natarajan,§,‖ Yan Liu,

*Section of Epidemiology and Population Sciences, Departmer
§Section of Gastroenterology and Hepatology, Department of M
for Innovations in Quality, Effectiveness and Safety, Michael E

BACKGROUND & AIMS: Statin use is associated with a l However, it is unclear whether po death in patients with HCC.

METHODS: We performed a retrospective anal Administration Central Cancer Re statin prescriptions that were fill dependent Cox regression models risk of death. We used a time-varyi (following up patients from 3 mont sensitivity analysis was conducted and start of follow-up evaluation.

RESULTS: Statin use after diagnosis was rec diagnosis statin use was associated 0.85; 95% CI, 0.77–0.93) and all-ca of these inverse associations were and the inverse associations rema months after HCC diagnosis). We statin use, or by presentation- or with prediagnosis statin use.

CONCLUSIONS: In a retrospective analysis of data after a diagnosis of HCC was assoc

Keywords: VA; Liver Cancer; Prognosis; Medication Use.

Hepatocellular carcinoma (HCC) is a rapidly increasing, highly fatal cancer.[1,2] For patients who present with early stage HCC, treatment modalities including transplant, resection, and local ablation have been shown to improve overall survival.[3] However, despite the existence of guidelines for screening and detection of incident HCC among high-risk patients, the majority of HCC patients, especially those with alcohol-related or nonalcoholic fatty liver disease–related HCC,[4] still present with advanced-stage disease that is not amenable to curative treatment. Curative treatment modalities are only available to HCC patients with good functional status, and patients with decompensated cirrhosis often are not candidates.[3] For patients with advanced disease, the only available treatment until recently was sorafenib, but this drug may have low efficacy in advanced liver disease as well as increased risk for adverse effects.[5] There is a need for additional treatment

ORIGINAL RESEARCH

Lipophilic Statins and Risk for Hepa Patients With Chronic Viral Hepatiti Swedish Population

Tracey G. Simon, MD, MPH; Ann-Sofi Duberg, MD, PhD; Soo Aler Long H. Nguyen, MD, MPH; Hamed Khalili, MD, MPH; Raymond

Background: Whether statin type influences hepatocellular carcinoma (HCC) incidence or mortality in chronic hepatitis B or C virus infection is unknown.

Objective: To assess the relationship between lipophilic or hydrophilic statin use and HCC incidence and mortality in a nationwide population with viral hepatitis.

Design: Prospective propensity score (PS)-matched cohort.

Setting: Swedish registers, 2005 to 2013.

Participants: A PS-matched cohort of 16 668 adults (8334 who initiated statin use [6554 lipophilic and 1780 hydrophilic] and 8334 nonusers) among 63 279 eligible adults.

Measurements: Time to incident HCC, ascertained from validated registers. Statin use was defined from filled prescriptions as 30 or more cumulative defined daily doses (cDDDs).

Results: Compared with matched nonusers, 10-year HCC risk was significantly lower among lipophilic statin users (8.1% vs. 3.3%; absolute risk difference [RD], −4.8 percentage points [95% CI, −6.2 to −3.3 percentage points]; adjusted subdistribution hazard ratio [aHR], 0.56 [CI, 0.41 to 0.79]) but not hydrophilic statin users (8.0% vs. 6.8%; RD, −1.2 percentage points [CI, −2.6 to 0.4 percentage points]; aHR, 0.95 [CI, 0.86 to 1.08]). The in-

Cancer Epidemiology

Approximately 500 000 cases of hepatocellular carcinoma (HCC) are diagnosed worldwide each year (1), related primarily to chronic infection with hepatitis B virus (HBV) or hepatitis C virus (HCV) (2). In the United States and Europe, the incidence of HCC has tripled since the 1970s, and mortality is increasing more rapidly for HCC than for any other type of cancer (1, 3). The disease carries a grim prognosis, with limited treatment options and median survival of less than 1 year (2, 3). Although HCC risk is reduced with HBV suppression or HCV eradication, it may persist in high-risk patients or in those with advanced fibrosis (2, 4). Consequently, there is an urgent need to identify effective primary prevention strategies to reduce HCC-related morbidity and mortality.

Accumulating data suggest that in chronic liver disease, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) may improve clinical outcomes

See also:

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Statin use and risk of liver cancer population-based studies

Kim Tu Tran [1], Úna C. McMenamin [1], Helen G. Coleman [1,2], C Amanda J. Lee [4] and Aaron P. Thrift [5,6]

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[2]Centre for Cancer Research and Cell Biology, Queen's University Belfast, Bel
[3]Academic Primary Care, Institute of Applied Health Sciences, University of A
[4]Medical Statistics Team, Institute of Applied Health Sciences, University of
[5]Section of Epidemiology and Population Sciences, Department of Medicine,
[6]Dan L Duncan Comprehensive Cancer Center, Baylor College of Medicine, H

Epidemiological studies of statin use and liver cancer risk have p between statin use and risk of primary liver cancer in two large i covariates and main indications of statins such as high cholester control study within the Scottish Primary Care Clinical Informatic with primary liver cancer and we used conditional logistic regres intervals (CIs) for associations with statin use. We also conducte self-reported statin use and cancer-registry recorded primary live hazard ratios (HRs) and 95% CIs. In the PCCIU case–control anal In the UK Biobank cohort, 182 out of 475,768 participants devel lower risk of liver cancer in the PCCIU (adjusted OR 0.61, 95% CI cancer in the UK Biobank, statin use was associated with lower r CI, 0.24–0.94) but not intrahepatic bile duct carcinoma (IBDC; ad a consistent inverse relationship between statin use and risk of

Introduction

Liver cancer (85–90% hepatocellular carcinoma [HCC]) is a rapidly increasing, highly fatal cancer.[1] In the United States, age-adjusted mortality rates for liver cancer increased by 43% between 2000 and 2016.[2] Increasing secular trends in incidence and mortality have been observed across many countries including the United Kingdom,[3] Poland, Brazil, Germany and Norway.[4] Major risk factors for liver cancer include hepatitis C virus (HCV) infection, hepatitis B virus (HBV) infection,

Key words: statins, liver cancer, hepatocellular carcinoma, intrahepatic bile duct carcinoma
Conflict of interest: All authors have no conflict of interest to declare.
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ORIGINAL

Statin Use is Protective Agair in Patients With Nonalcc

A Case-co

Margarita N. German, MD,† Megan K*
Richard J. Bruce, MD,†‡ a

Background and Goal: The incidence of nonalcoholic fatty liver disease (NAFLD) associated hepatocellular carcinoma (HCC) is rising. We aimed to characterize risk factors for NAFLD-HCC development.

Methods: We performed a retrospective case-control study of HCC cases from a cohort of NAFLD patients who underwent at least 2 computed tomography scans. NAFLD-HCC cases confirmed on contrast imaging and/or biopsy were included. Controls were NAFLD patients without HCC matched by sex and age. Clinical variables were assessed. Visceral adipose tissue and subcutaneous adipose tissue were measured by computed tomography at 2 time-points: before HCC diagnosis and at diagnosis.

Results: We identified 102 subjects [34 HCC cases, 68 controls, 65% (n = 66) males, mean age: 69 y] from 2002 to 2016. Cirrhosis was present in 91%. In multivariate analysis, statin use was protective against HCC [odds ratio (OR) = 0.20, 95% confidence interval (CI): 0.07-0.60, $P = 0.004$], while hypertension was a risk factor for HCC (OR = 5.80, 95% CI: 2.01-16.75, $P = 0.001$). In multivariate analysis, visceral adipose tissue in males was higher before HCC diagnosis and declined by HCC diagnosis in 86%, which was a significant difference compared with controls (OR = 2.78, 95% CI: 1.10-7.44, $P = 0.04$).

Conclusions: In a cohort of NAFLD-HCC patients, statin use was protective against HCC, while hypertension conferred an increased risk. Visceral adiposity at baseline was not a risk factor, but was higher in male patients before HCC development, declining in the majority by HCC diagnosis.

Key Words: nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), visceral fat, hepatocellular carcinoma (HCC), statins

(*J Clin Gastroenterol* 2019;00:000–000)

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From the *Department of Medicine, Division of Gastroenterology and Hepatology; †William S. Middleton Veterans Affairs Medical Center; and ‡Department of Radiology, University of Wisconsin School of Medicine and Public Health, Madison, WI.
M.N.G., A.S., and M.K.L.: were involved in planning and conceptualization of the study, collecting and interpreting data and drafting the manuscript. A.S.: was involved in performing the statistical analysis for the study. P.J.P. and R.J.B.: were involved in the creation of the radiographic image analyzer and interpreting the radiographic images. All authors played a role in writing the manuscript and have approved the final draft submitted.
The authors declare that they have nothing to disclose.
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(e-mail: axs@medicine.wisc.edu).

DOI: 10.1097/MCG.0000000000001260

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Original

Statin Use and the Risk of Hepatocellular Carcinoma in Patients with Chronic Hepatitis B

Myung Ji Goh, Dong Hyun Sinn, Seonwoo Kim, Sook Young Woo, Hyun Cho, Wonseok Kang, Geum-Youn Gwak, Yong-Han Paik, Moon Seok Choi, Joon Hyeok Lee, Kwang Cheol Koh, Seung Woon Paik

First published: 25 September 2019 | https://doi.org/10.1002/hep.30973

PDF TOOLS SHARE

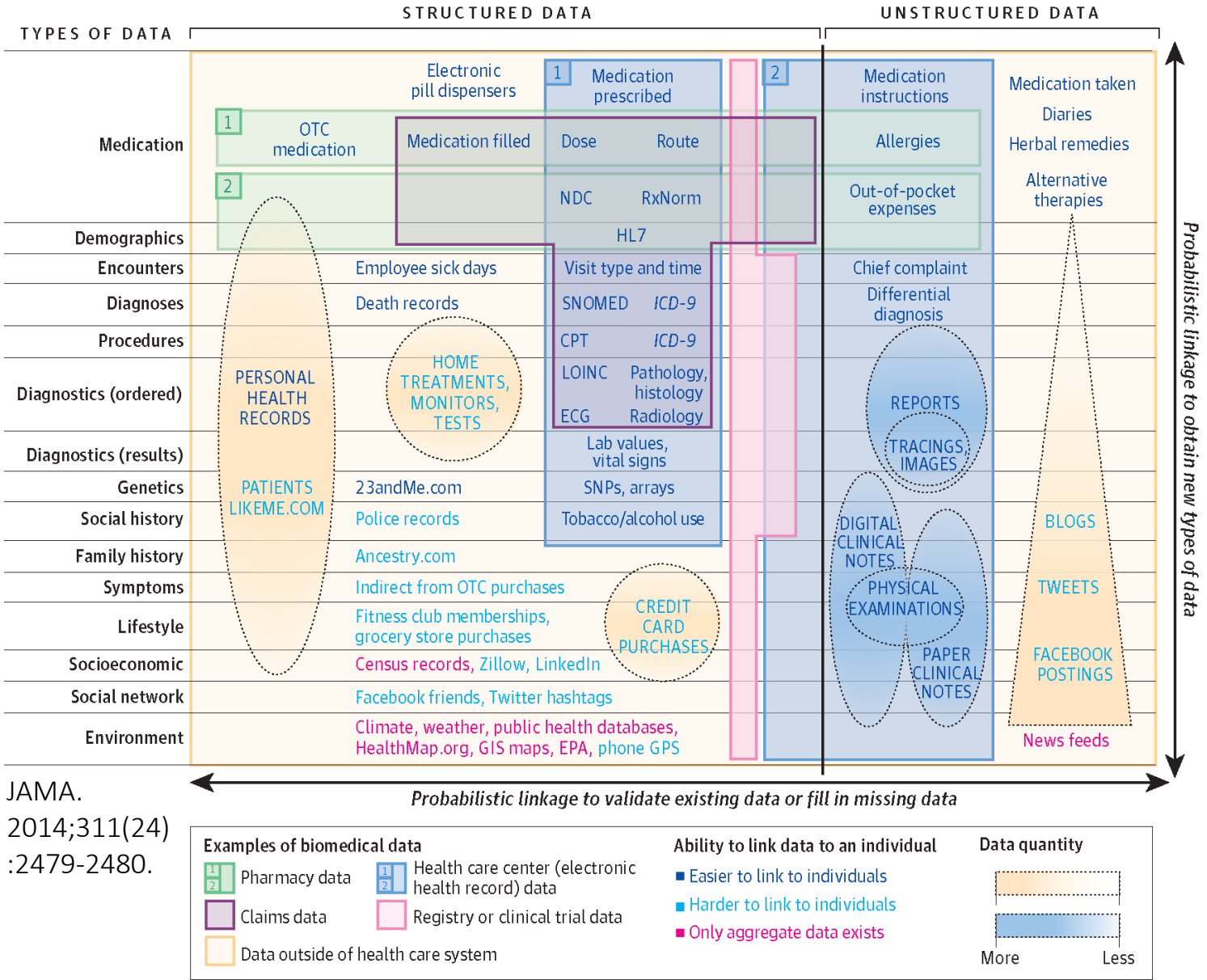
Abstract

Statins have pleiotropic effects which may include chemoprevention. Several observational studies have suggested that statins may prevent hepatocellular carcinoma (HCC) but they have not yet been fully studied in patients with chronic hepatitis B virus (HBV) infections. A hospital-based retrospective cohort of 7,713 chronic HBV-infected individuals between January 2008 and December 2012 were analyzed. The primary outcome was the development of HCC. Patients who used statins for at least 28 cumulative defined daily doses (cDDD) during the follow-up period were defined as statin users (n = 713). The association between the use of statin and the incidence of HCC was analyzed using the multivariable Cox regression model with time-dependent covariates. During a median follow-up of 7.2 years (min-max: 0.5-9.7), HCC newly developed in 702 patients (9.1%). Statin use was associated with a lower risk of HCC (adjusted hazard ratio (HR) = 0.36, 95% confidence interval (CI): 0.19-0.68, adjusted for age, sex, cirrhosis, diabetes, hypertension, serum alanine aminotransferase, cholesterol, HBV DNA level, antiviral treatment, and antiplatelet therapy). The observed benefit of the statin use was dose dependent (adjusted HR (95% CI), 0.63 (0.31-1.29); 0.51 (0.21-1.25); 0.32 (0.07,1.36); and 0.17 (0.06, 0.48) for patients with statin use of 28-365, 366-730, 731-1095, and more than 1095 cDDDs, respectively). In subgroup analysis, the association between statin use and reduced risk of HCC was observed in all pre-specified subgroups analyzed.

Conclusions

Statin use was associated with a reduced risk of HCC development in chronic HBV-infected patients, suggesting that statin may have chemopreventive role in this population. These findings warrant a prospective evaluation.

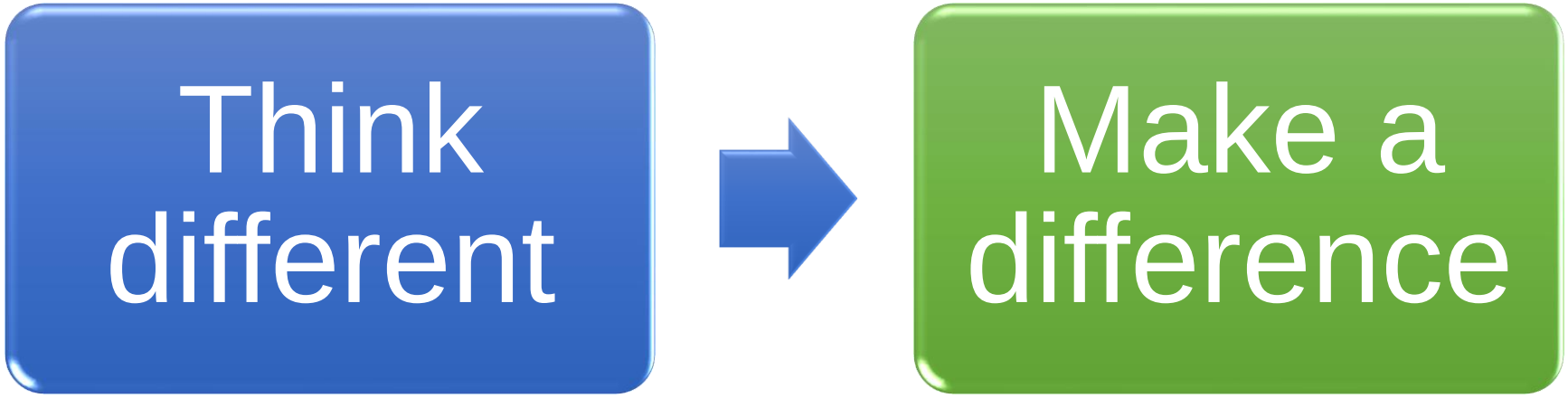
Finding the Missing Link for Big Biomedical Data



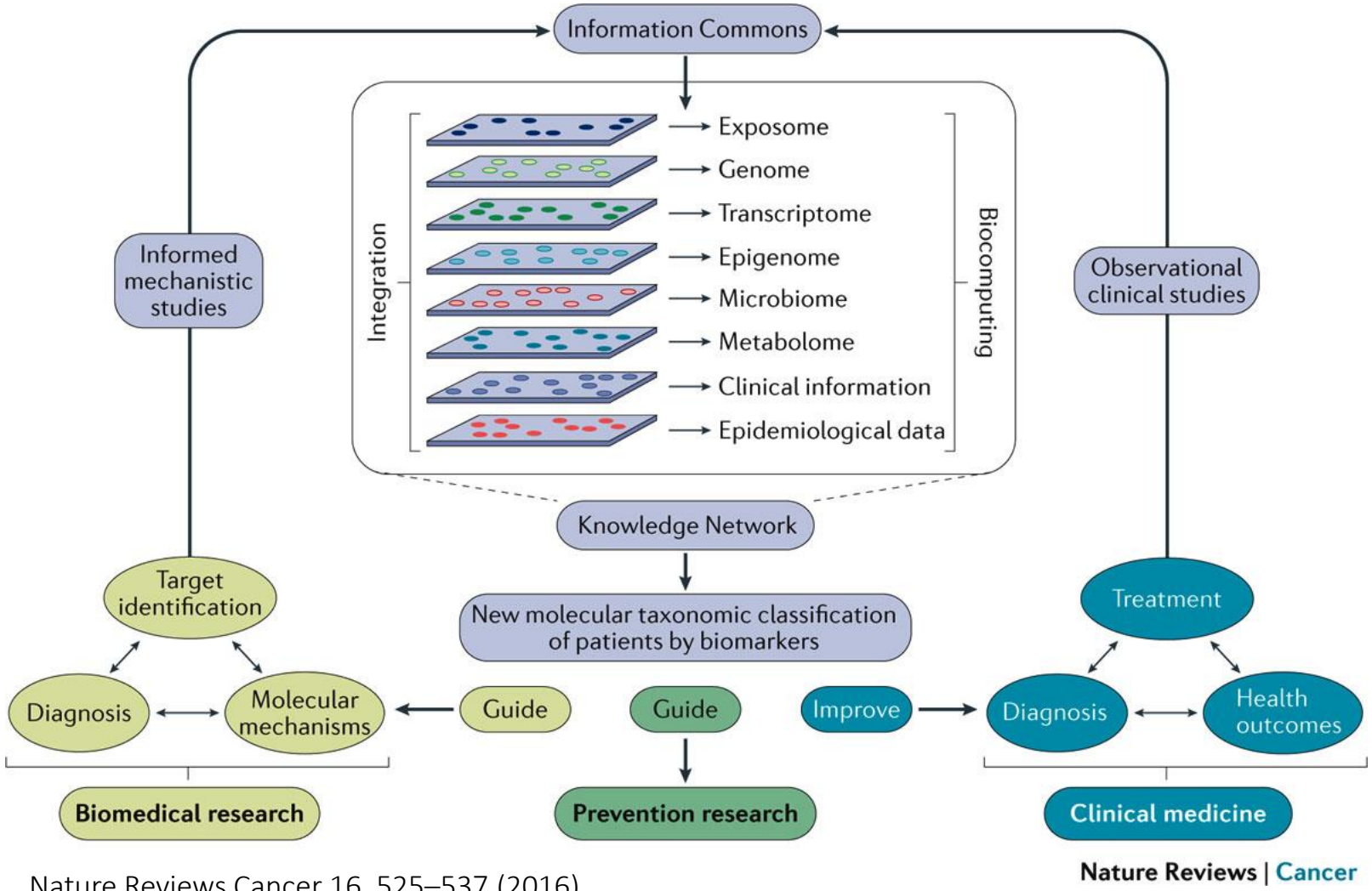
JAMA. 2014;311(24) :2479-2480.

結語

- Mastering the literature
- Being alert to new ideas and novelty
- Keeping the imagination roaming
- Considering practical and policy implications
- Having the courage to follow your heart and intuition



Precision Environmental Medicine



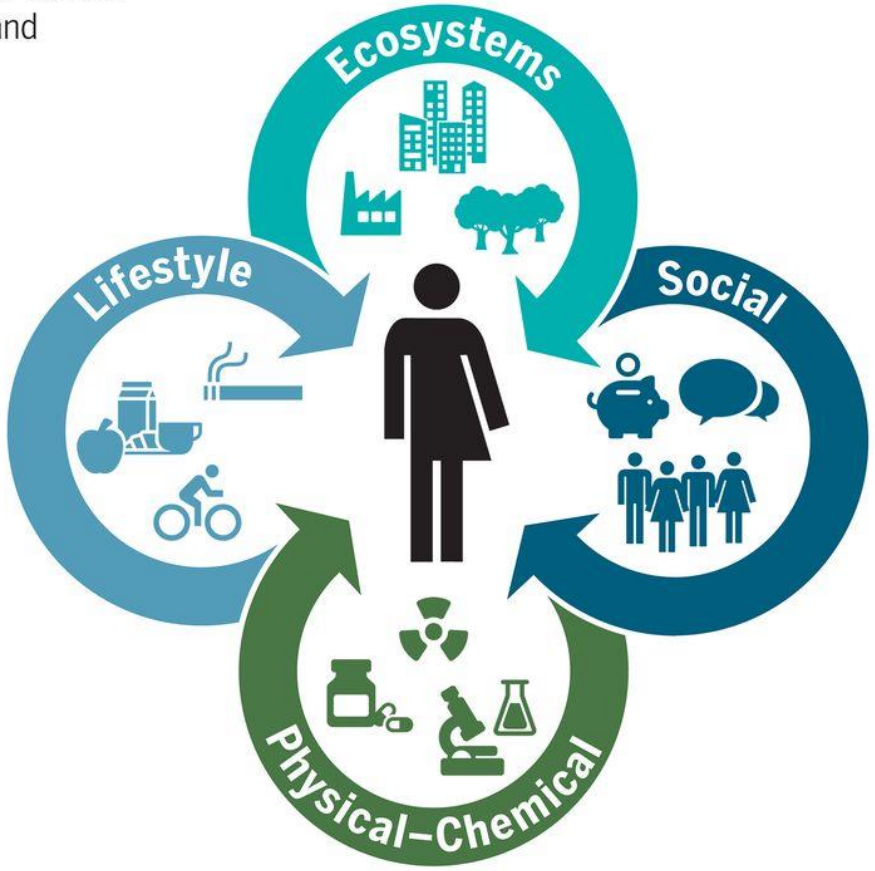
Nature Reviews Cancer 16, 525–537 (2016)

The Exposome Concept

Ecosystems
Food outlets, alcohol outlets
Built environment and urban land uses
Population density
Walkability
Green/blue space

Lifestyle
Physical activity
Sleep behavior
Diet
Drug use
Smoking
Alcohol use

Social
Household income
Inequality
Social capital
Social networks
Cultural norms
Cultural capital
Psychological and mental stress



Science 2020

Physical–Chemical
Temperature/humidity
Electromagnetic fields
Ambient light
Odor and noise
Point, line sources, e.g, factories, ports
Outdoor and indoor air pollution
Agricultural activities, livestock
Pollen/mold/fungus
Pesticides
Fragrance products
Flame retardants (PBDEs)
Persistent organic pollutants
Plastic and plasticizers
Food contaminants
Soil contaminants
Drinking water contamination
Groundwater contamination
Surface water contamination
Occupational exposures

The FOUR V's of Big Data

From traffic patterns and music downloads to web history and medical records, data is recorded, stored, and analyzed to enable the technology and services that the world relies on every day. But what exactly is big data, and how can these massive amounts of data be used?

As a leader in the sector, IBM data scientists break big data into four dimensions: **Volume, Velocity, Variety and Veracity**

Depending on the industry and organization, big data encompasses information from multiple internal and external sources such as transactions, social media, enterprise content, sensors and mobile devices. Companies can leverage data to adapt their products and services to better meet customer needs, optimize operations and infrastructure, and find new sources of revenue.

By 2015

4.4 MILLION IT JOBS

will be created globally to support big data, with 1.9 million in the United States

Volume

大

SCALE OF DATA

40 ZETTABYTES

[43 TRILLION GIGABYTES]

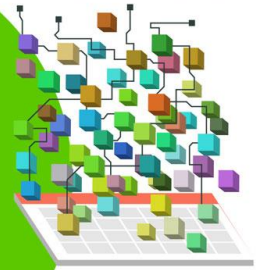
of data will be created by 2020, an increase of 300 times from 2005

It's estimated that

2.5 QUINTILLION BYTES

[2.3 TRILLION GIGABYTES]

of data are created each day



6 BILLION PEOPLE

have cell phones

WORLD POPULATION: 7 BILLION

Most companies in the U.S. have at least

100 TERABYTES

[100,000 GIGABYTES]

of data stored

Variety

雜

DIFFERENT FORMS OF DATA

As of 2011, the global size of data in healthcare was estimated to be

150 EXABYTES

[161 BILLION GIGABYTES]

30 BILLION PIECES OF CONTENT

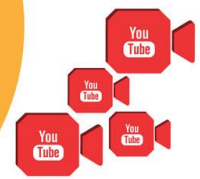
are shared on Facebook every month

By 2014, it's anticipated there will be

420 MILLION WEARABLE, WIRELESS HEALTH MONITORS

4 BILLION+ HOURS OF VIDEO

are watched on YouTube each month



400 MILLION TWEETS

are sent per day by about 200 million monthly active users

Velocity

快

ANALYSIS OF STREAMING DATA

The New York Stock Exchange captures

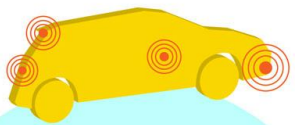
1 TB OF TRADE INFORMATION

during each trading session

Modern cars have close to

100 SENSORS

that monitor items such as fuel level and tire pressure



By 2016, it is projected there will be

18.9 BILLION NETWORK CONNECTIONS

– almost 2.5 connections per person on earth

Veracity

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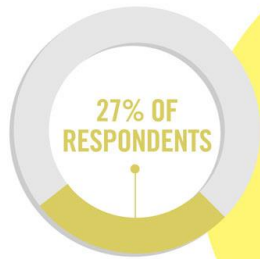
UNCERTAINTY OF DATA

1 IN 3 BUSINESS LEADERS

don't trust the information they use to make decisions



in one survey were unsure of how much of their data was inaccurate

Poor data quality costs the US economy around

$3.1 TRILLION A YEAR

Sources: McKinsey Global Institute, Twitter, Cisco, Gartner, EMC, SAS, IBM, MEPTEC, QAS

IBM

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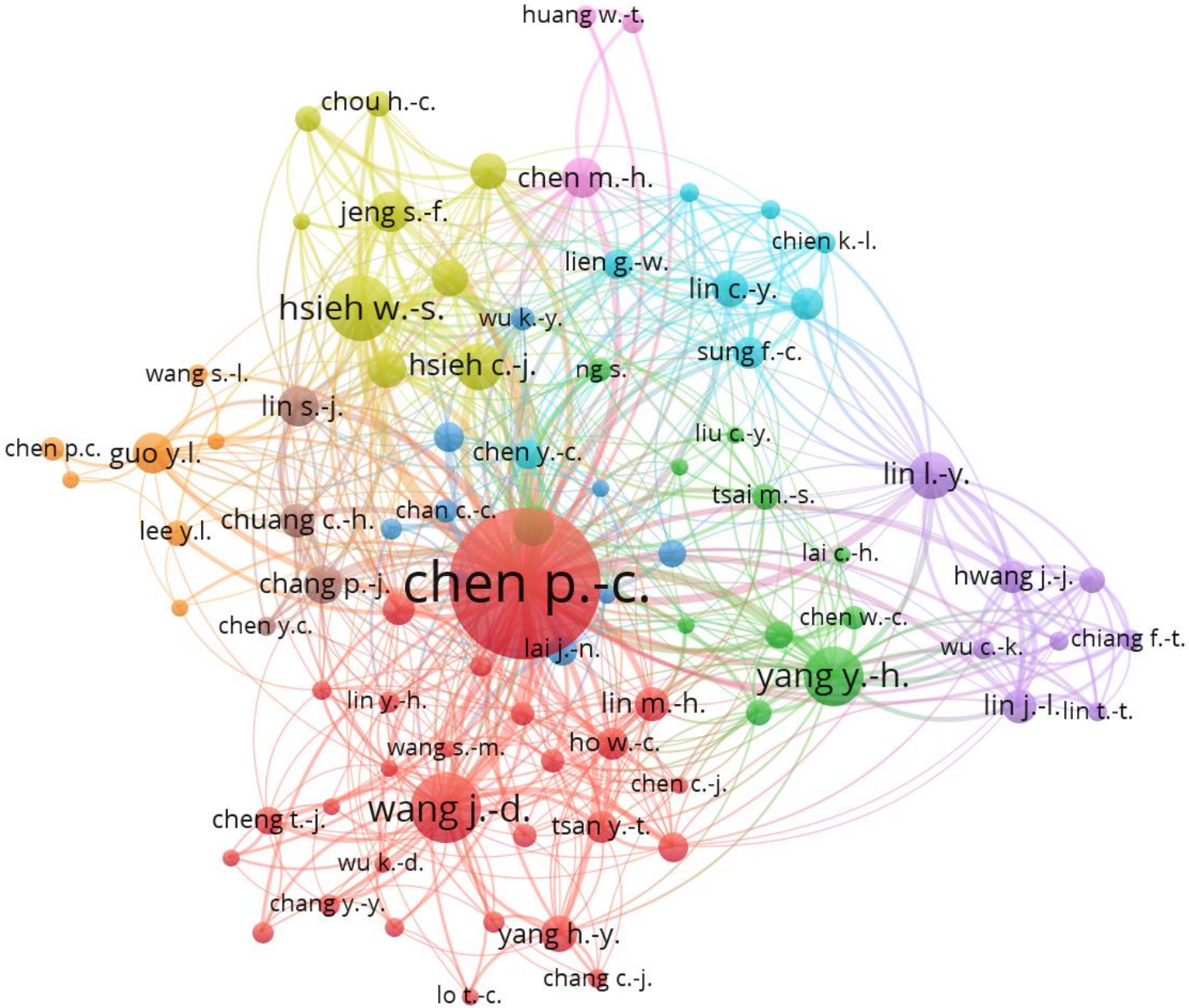
100 Ways of Using Data to Make Lives Better

http://www.farrinstitute.org/


huang w.-t.
chou h.-c.
chen m.-h.
jeng s.-f.
chien k.-l.
lien g.-w.
lin c.-y.
hsieh w.-s.
wu k.-y.
sung f.-c.
hsieh c.-j.
ng s.
wang s.-l.
lin s.-j.
liu c.-y.
chen p.c.
guo y.l.
chen y.-c.
lin l.-y.
tsai m.-s.
chuang c.-h.
chan c.-c.
lee y.l.
lai c.-h.
hwang j.-j.
chang p.-j.
chen p.-c.
chen w.-c.
chen y.c.
lai j.-n.
wu c.-k.
chiang f.-t.
yang y.-h.
lin y.-h.
lin m.-h.
lin j.-l.
lin t.-t.
wang s.-m.
ho w.-c.
chen c.-j.
cheng t.-j.
wang j.-d.
tsan y.-t.
wu k.-d.
chang y.-y.
yang h.-y.
chang c.-j.
lo t.-c.

VOSviewer

Either I will find a way, or I will make one.

Philip Sidney, Poet

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