

Jean Ribstein

Hypertension artérielle et risque

- Introduction
la maladie et ses causes
risque et facteurs de risque
- Hypertension artérielle
étiologie,
épidémiologie,
physiopathologie



Olim Cous nunc Monspeliensis Hippocrates

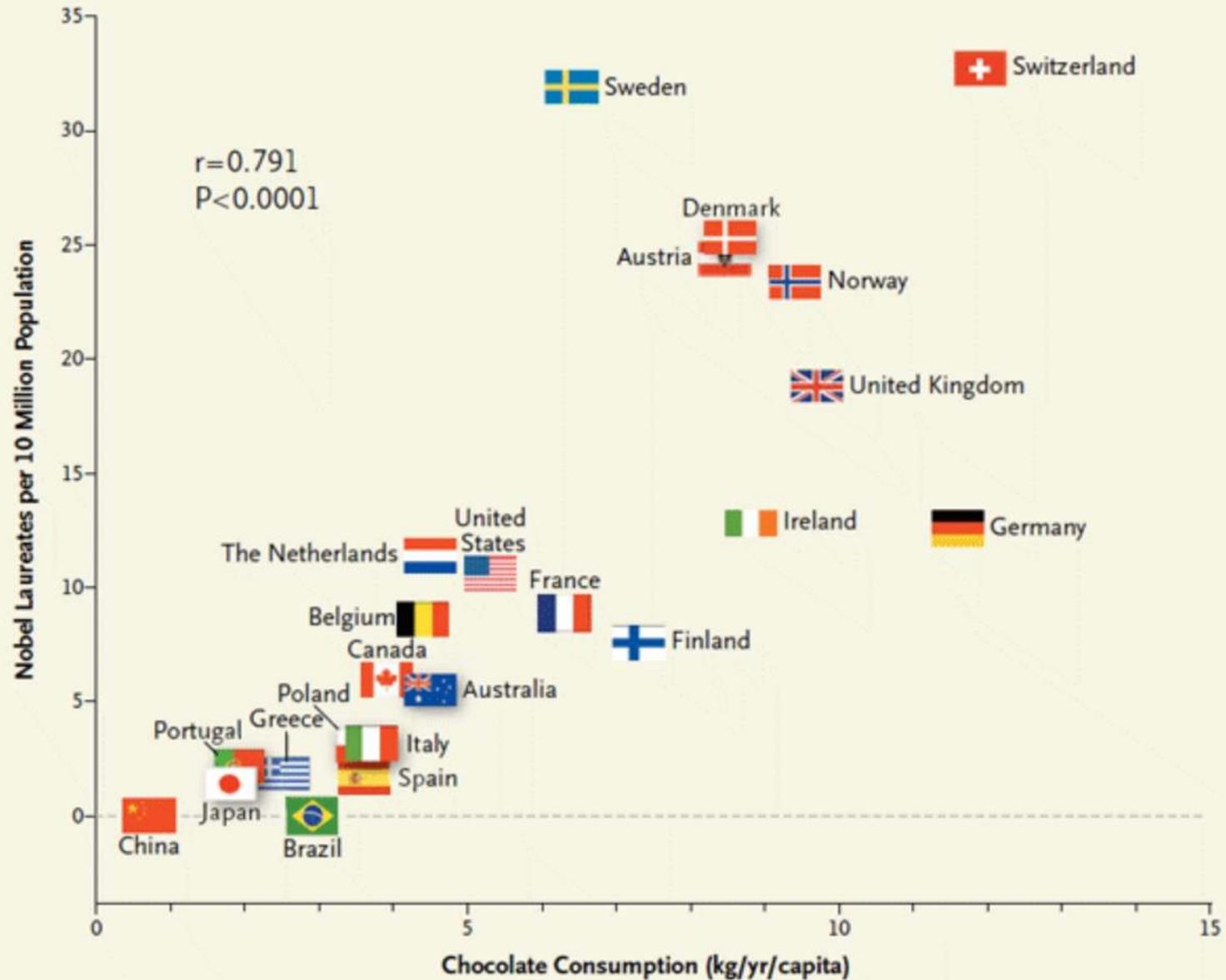
Today's Random Medical News

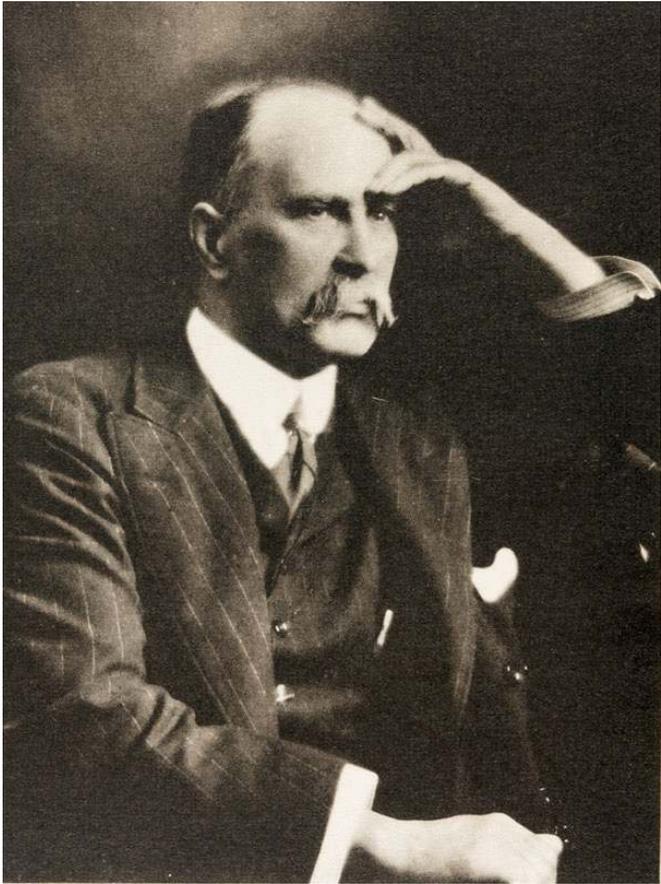
from the New England
Journal of
Panic-Inducing
Gobbledygook

W. B. G. H. A. N.



Une corrélation entre consommation de chocolat et prix Nobel !?





William Osler (1849-1919)

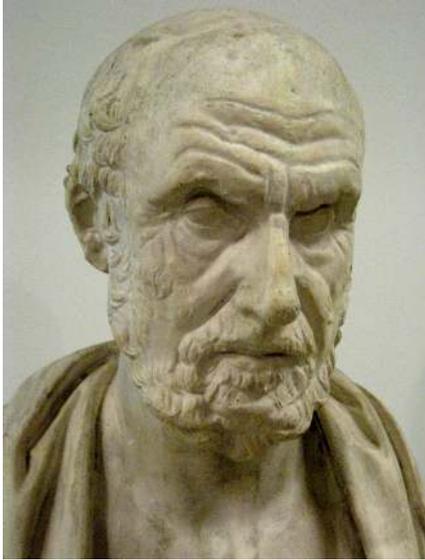
*“ La médecine est une science de l’incertitude
et un art de la probabilité ”*

Expliquer et comprendre la maladie. Faire des prédictions ?

Le concept de risque et la recherche de preuves

Hippocrate

c. 460-370 BC



'La vie (bios) est courte, l'art (teckne) est long, l'occasion (kairos) fugitive, l'expérience (peira) trompeuse, le jugement (crisis) difficile'

(Aphorismes I.1)

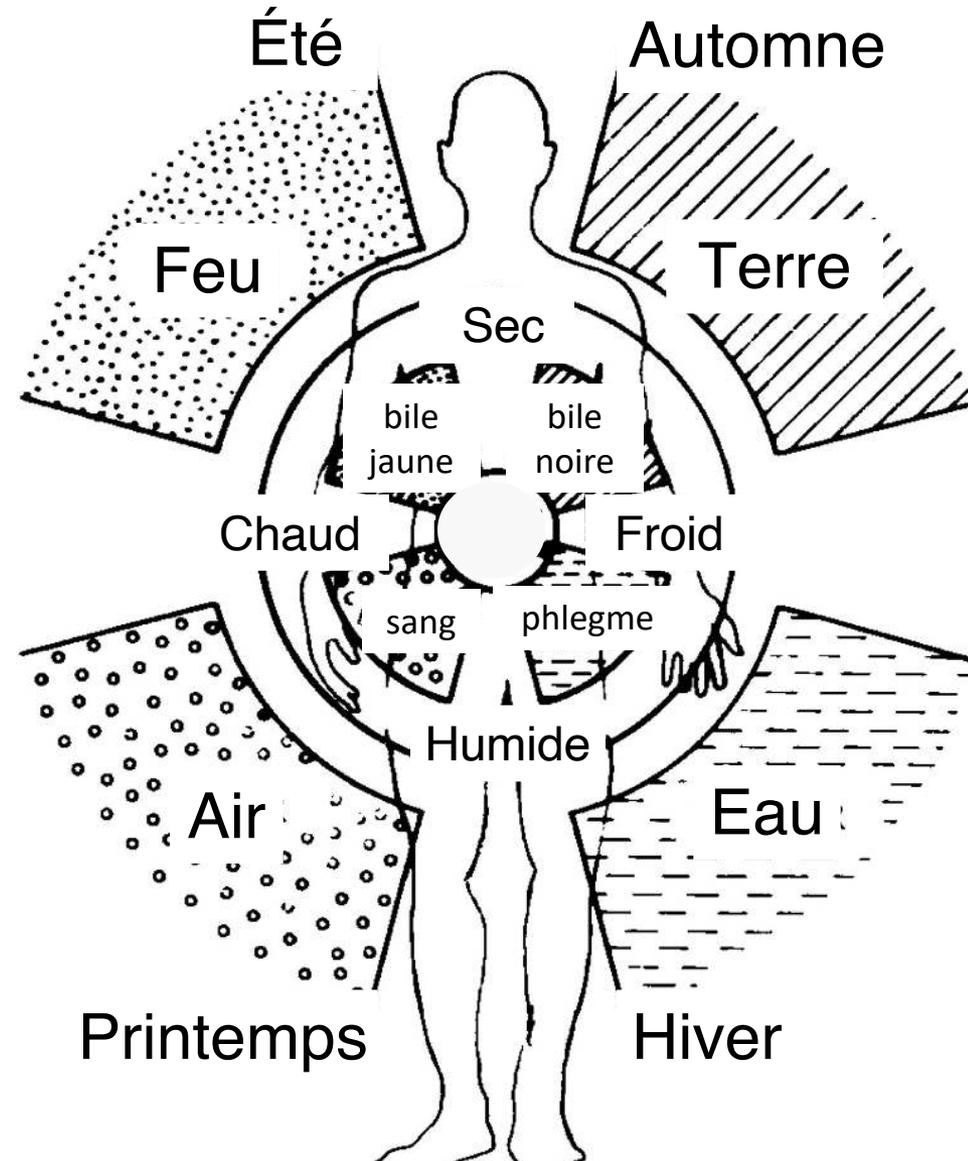
'Pour moi, je ne ferai point de telles divinations, mais j'écris les signes par lesquels on doit conjecturer, parmi les malades, quels guériront et quels mourront, quels guériront et quels mourront en peu ou en beaucoup de temps'

(Prorrhétique II)

De l'élaboration du pronostic au diagnostic des causes ...

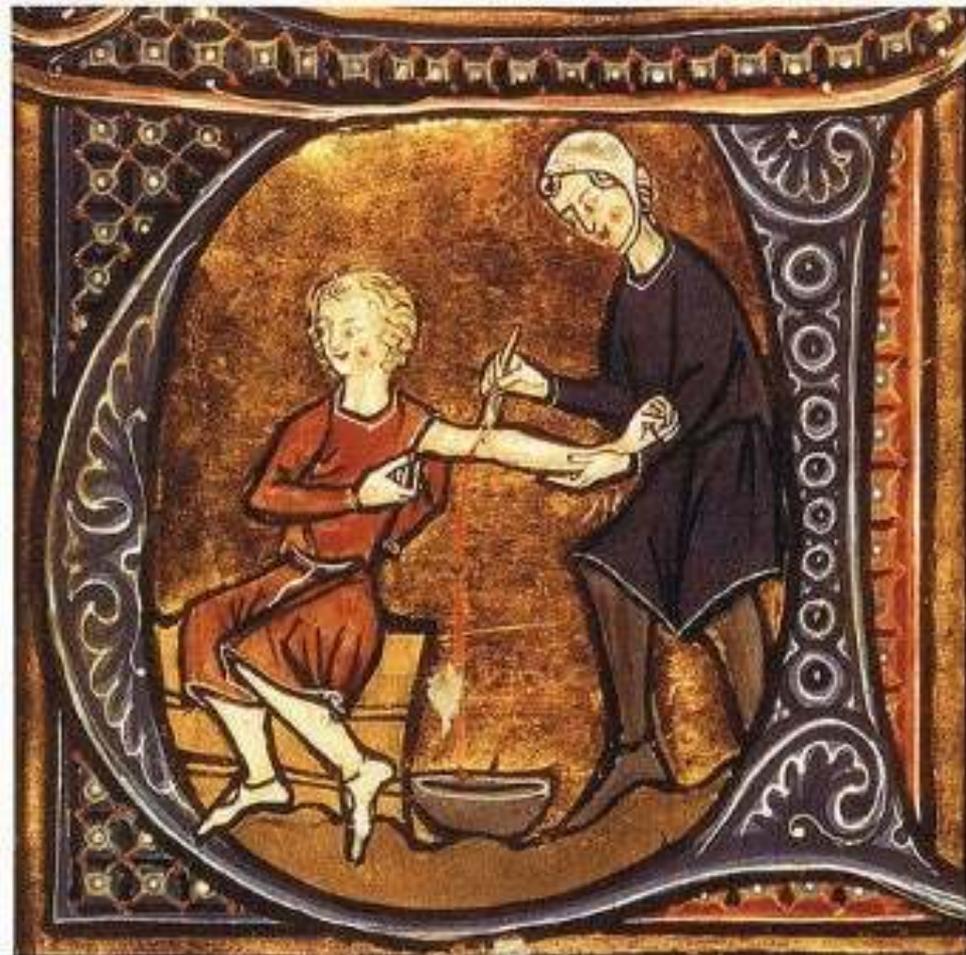
*'Cherchons les causes
de ce qui leur arrive'*

*De fait, si l'on connaissait
la cause de la maladie, on
serait en mesure
d'administrer au corps ce
qui est utile, en partant
des contraires pour
s'opposer à la maladie
(Des Vents, I. 4)*



... et à partir de là
s'allier à la *vis medicatrix naturae*
en remédiant au déséquilibre des *humeurs*

(Une "base théorique" de la saignée)

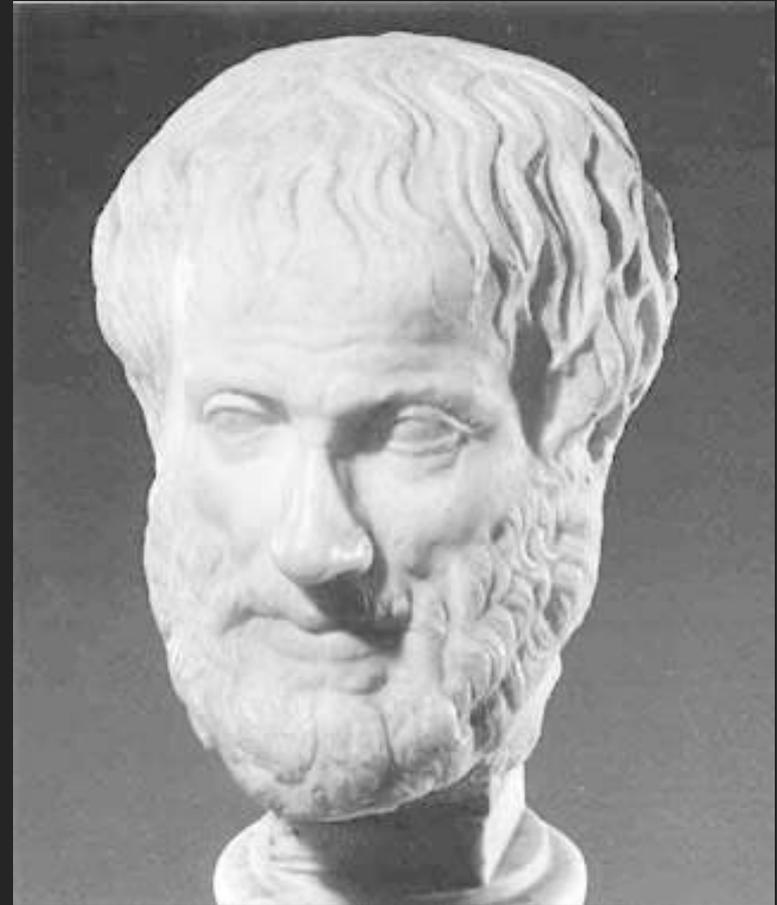


Le principe de causalité

'Tout événement a une cause'

Pour Aristote (384-322 BC),
l'objet 'statue' renvoie à un
ensemble de 'causes'

matérielle (le marbre),
efficiente (l'action du ciseau),
formelle (l'idée qui transforme),
finale (l'intention du sculpteur)

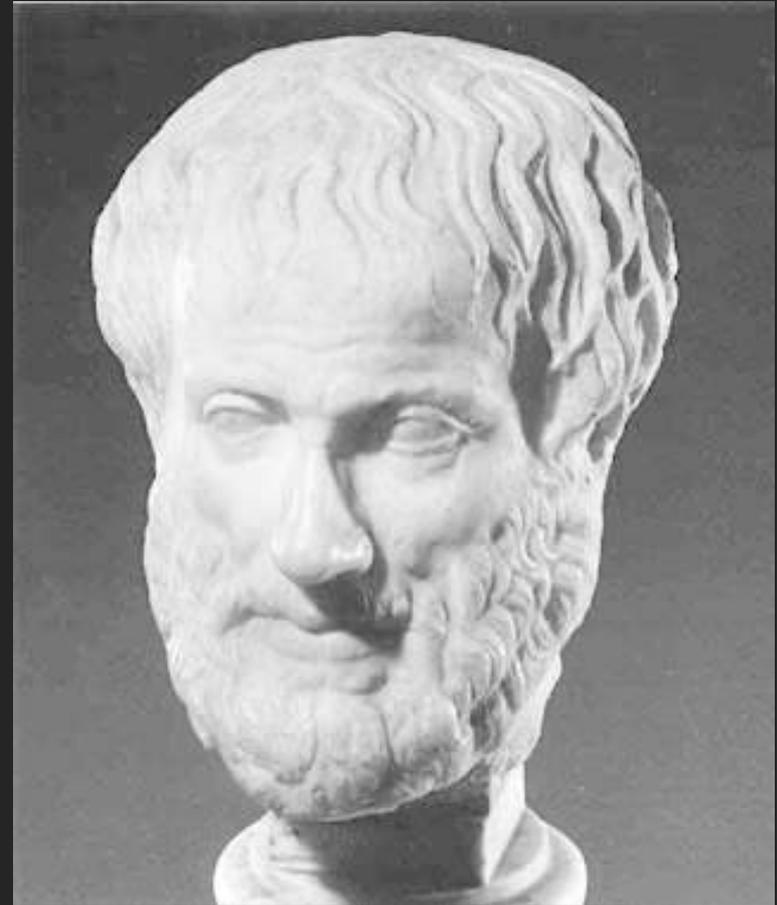


Le vrai et le probable

La sophistique donne une
apparence de réalité,

La dialectique permet une
approche du probable,

L'étude philosophique /
scientifique
porte sur la vérité





Νεμεσις

Τυχη



Fortune

sort

alea

chance

az zahr



Le mot *risque* (XVI°) désigne ce qui s'est appelé *péril* (X°), *aventure* (XI°), *hasard* (XII°)
Son origine est incertaine (risco, rixa, rizk)



Natural and Political
OBSERVATIONS
Mentioned in a following INDEX,
and made upon the
Bills of Mortality.

BY
Capt. **JOHN GRAUNT**,
Fellow of the Royal Society.

With reference to the *Government, Religion, Trade, Growth, Air, Diseases,* and the
several Charges of the said CITY.

— *Non, sine ut miratur Turba, laboro,
Contentus pauci Lett'oribus.* —

The Fifth Edition, much Enlarged.

LONDON,

Printed by *John Moxley*, Printer to the
Royal Society, at the Sign of the Bell in St. Paul's
Church-yard. MDCLXXXVI,



CAPTAIN JOHN GRAUNT

(1620-1674)

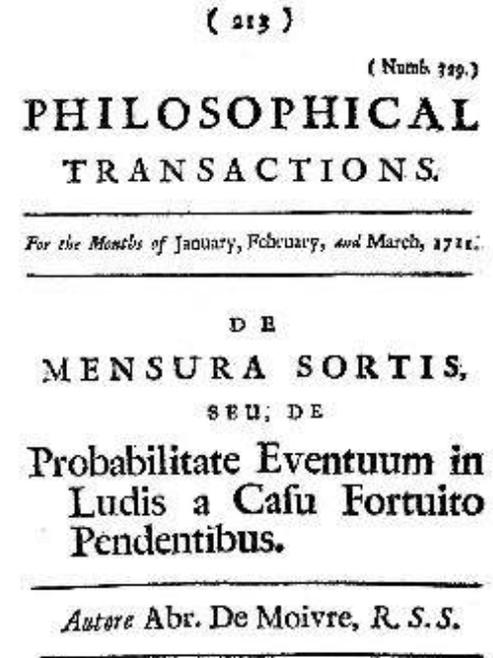
La naissance des statistiques - 1662

Le calcul du risque lié au jeu - 1560-1663

Girolamo Cardano
(1501 – 1576)

Liber de ludo aleae
1560, 1663





Le risque est l'espérance
mathématique d'une
fonction de probabilité
d'événements

Daniel Bernoulli (1700-1782)

Specimen theoriae novae de mensura sortis, 1738



Pierre-Simon Laplace

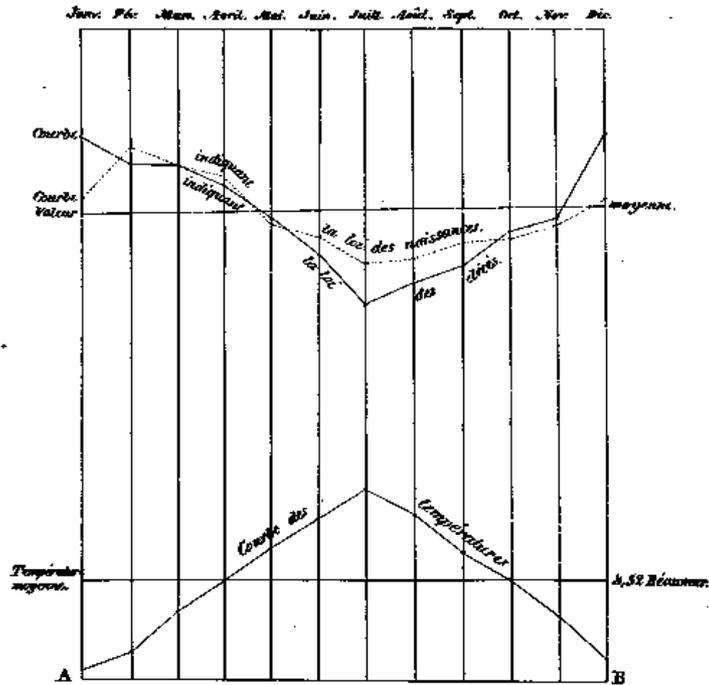
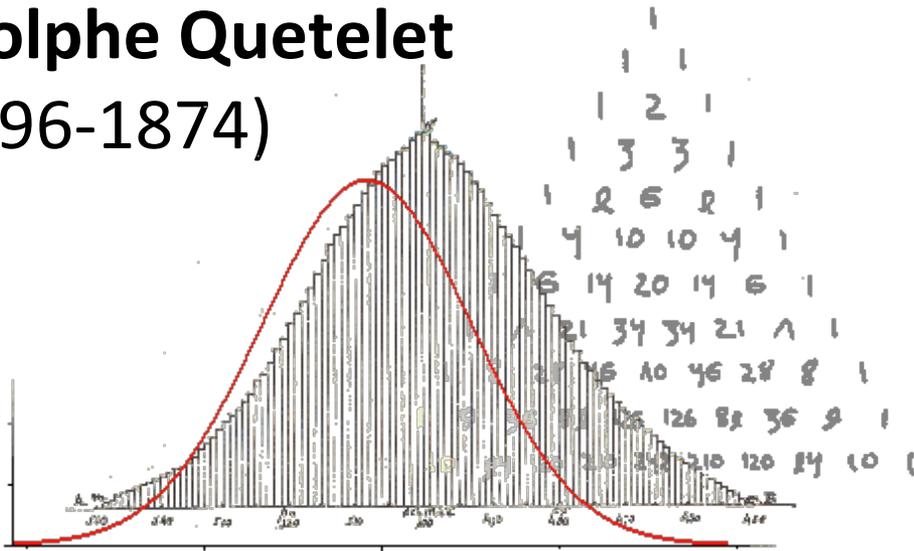
(1749 - 1827)

*Nous devons
envisager l'état
présent de l'univers
comme l'effet de son
état antérieur, et
comme la cause
de celui qui va suivre*

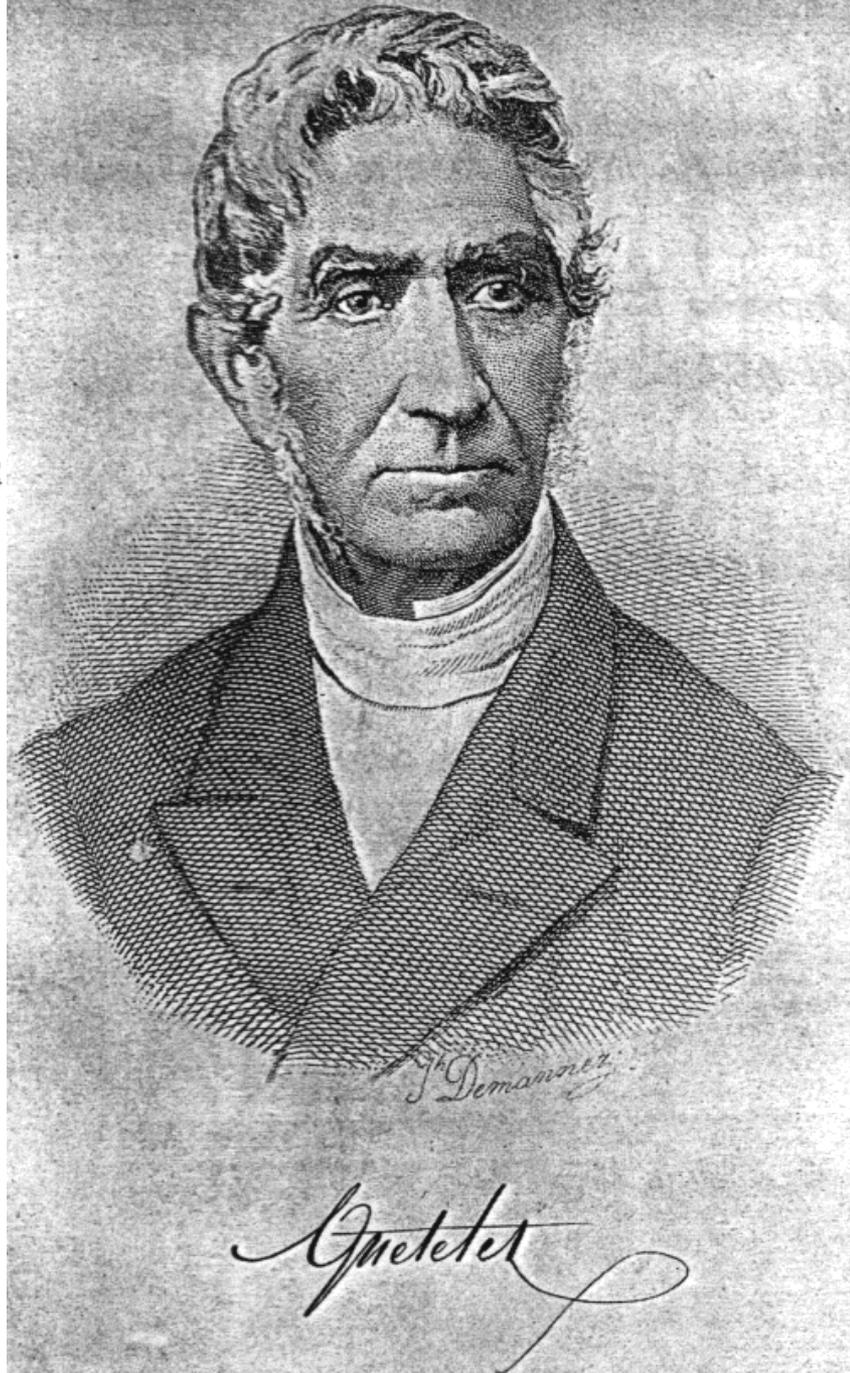
*La théorie des probabilités
n'est au fond que du sens
commun réduit au calcul ; elle nous
rend capables d'apprécier avec
exactitude ce qu'un esprit fin ressent
avec une sorte d'instinct dont il est
souvent incapable de rendre compte*

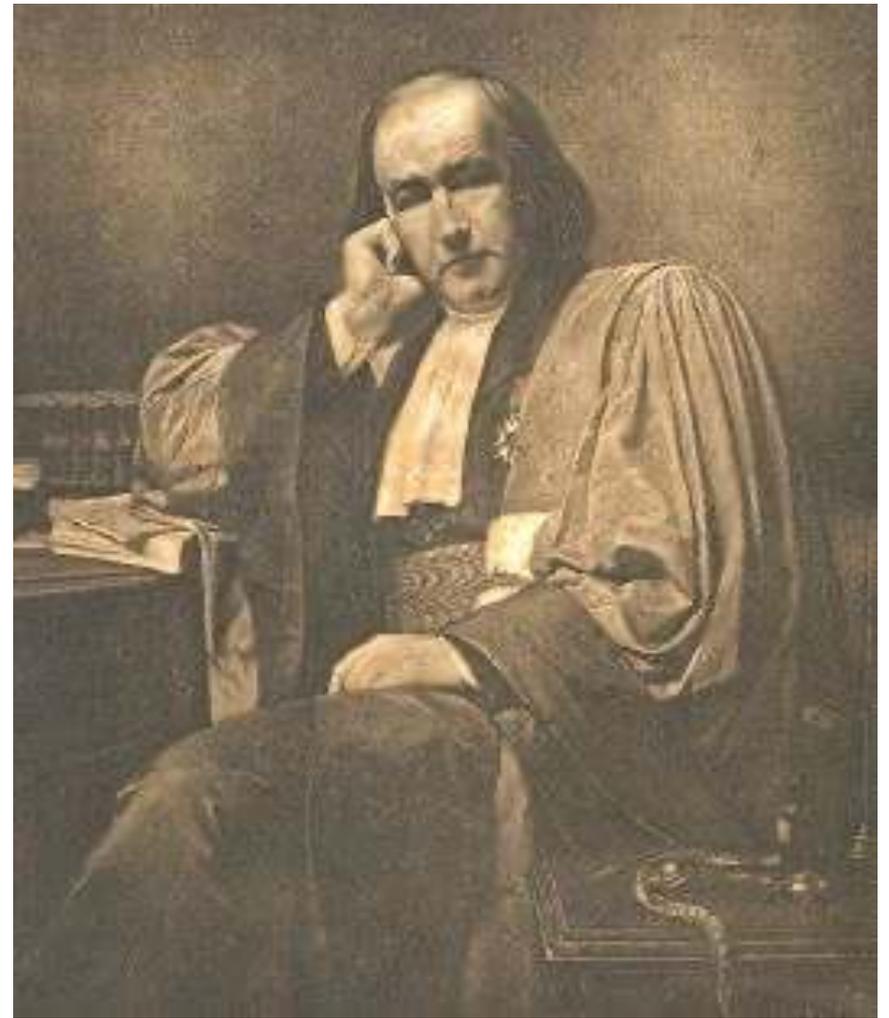
Adolphe Quetelet

(1796-1874)



Lois des naissances et des décès à Bruxelles, pendant le cours d'une année, et après 45 ans d'observation, comparées à la loi de variation des températures. (Les longueurs des perpendiculaires, élevées de la base A B, représentent les valeurs des naissances, des décès et des températures.)





Pierre Louis (1787-1872), promoteur de la 'méthode numérique' : *la statistique est la base fondamentale et unique de toutes les sciences médicales.*

Claude Bernard (1813-1878), tenant de la 'médecine expérimentale' : *l'usage des moyennes et l'emploi de la statistique, en médecine et en physiologie, conduisent pour ainsi dire nécessairement à l'erreur.*

Au total, le **risque**,

- défini comme la **probabilité** qu'un événement se réalise,
- plutôt perçu comme un danger ou une menace, quelle que soit la possibilité de le mesurer

se distingue du **hasard**, qui est de l'ordre de

- l'inexplicable (il paraît sans cause ni raison),
- le contingent (il aurait pu ne pas se produire),
- le fortuit (il reste imprévisible, imprédictible)

La **prédiction** reste

- impossible (si le phénomène est indéterminé)
- imprécise (en matière de connaissance - insuffisante)
- **incertaine** (en matière de croyance à lui accorder)

Comment agir dans un contexte d'incertitude ?

« distinguer entre traitement médical légitime et magie requiert soit que des procédures valides soient basées sur une compréhension scientifique, soit qu'une preuve empirique indique que le traitement proposé soit efficace »



Moïse Maïmonide 1135-1204



616.39

A
T R E A T I S E
ON THE
S C U R V Y.

L 57j

IN THREE PARTS.



CONTAINING

An Inquiry into the Nature, Causes,
and Cure, of that Disease.

Together with

A Critical and Chronological View of what
has been published on the Subject.

By *JAMES LIND*, M. D.

Fellow of the Royal College of Physicians in *Edinburgh*.

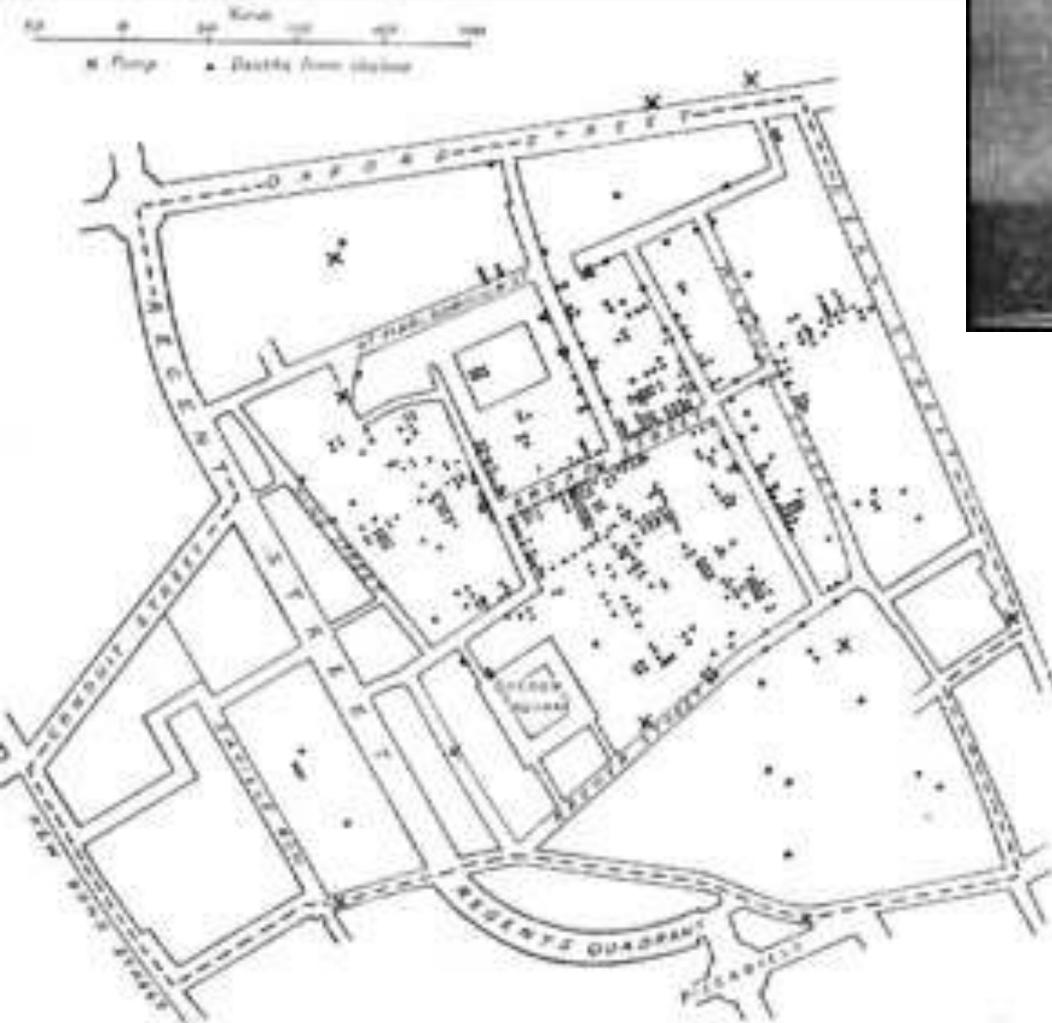
The SECOND EDITION corrected, with Additions
and Improvements.

L O N D O N:

Printed for A. MILLAR in the *Strand*,

MDCCLVII:

John Snow - 1854



À la recherche des causes des maladies épidémiques



Robert Koch
1843-1910



Jakob Henle
1809-1885

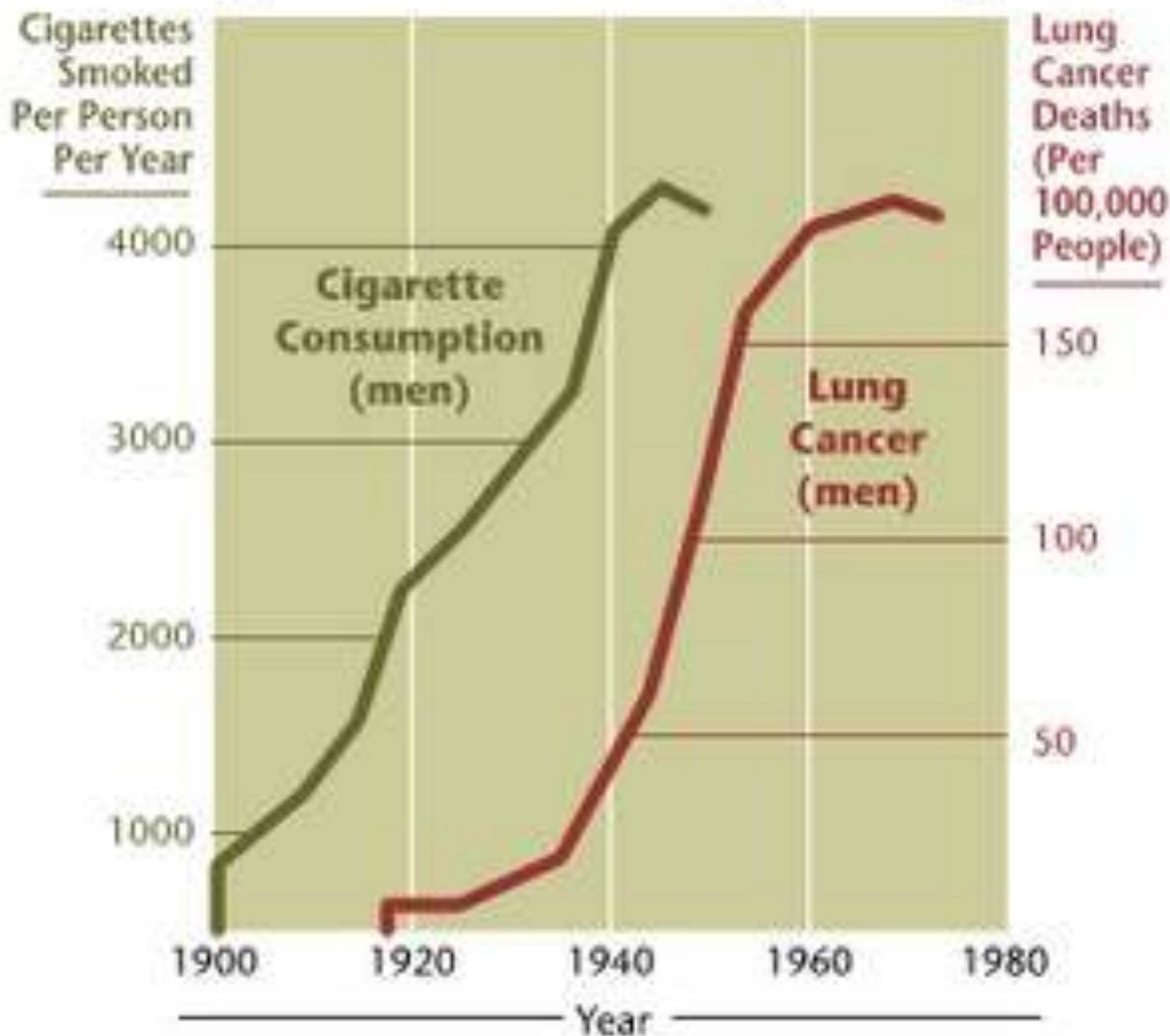
Postulats sur la causalité (en matière infectieuse)

- présent // maladie - absent // santé
- isolable chez l'animal, cultivable en culture
- responsable de la maladie originale par inoculation à l'animal sain, et à nouveau isolable en culture

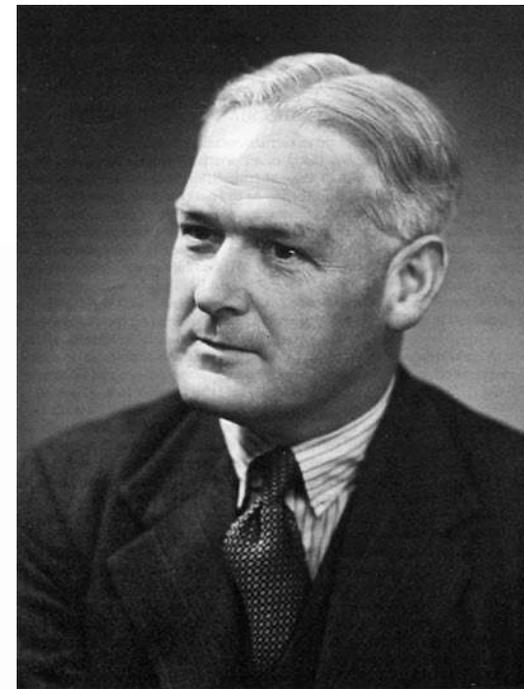
Avant d'expliquer les 'épidémies' du XX^e siècle

La recherche des 'signes des maladies obscures'

20-Year Lag Time Between Smoking and Lung Cancer



Les critères (points de vue sur les causes) de *Austin Bradford Hill*

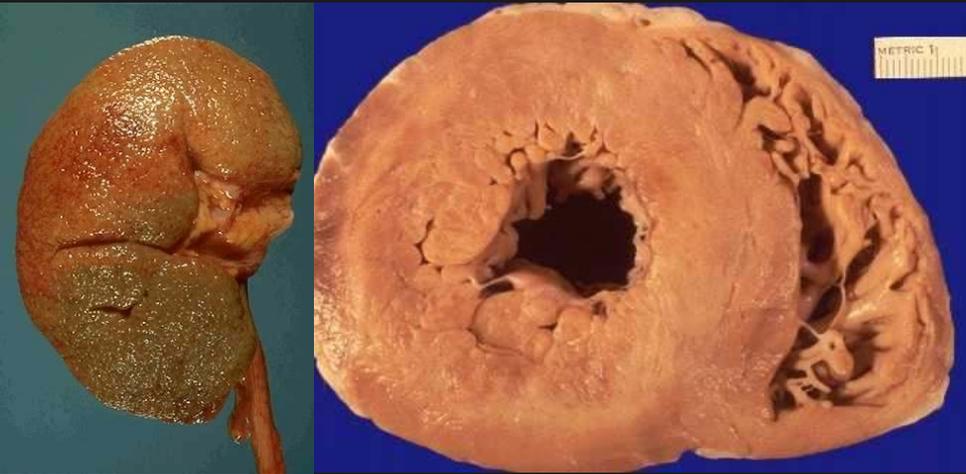


- (1) l'association est-elle forte ?
- (2) l'observation est-elle reproductible ?
- (3) le facteur présumé est-il spécifique ?
- (4) la temporalité est-elle respectée ?
- (5) y a-t-il un gradient exposition / effet ?
- (6) y a-t-il un mécanisme biologique plausible ?
(et/ou n'y a-t-il aucune explication alternative ?)
- (7) l'observation est-elle cohérente avec ce que l'on sait
par ailleurs de la maladie
- (8) la relation concorde-t-elle avec un test expérimental
(ou un essai clinique de traitement) ?

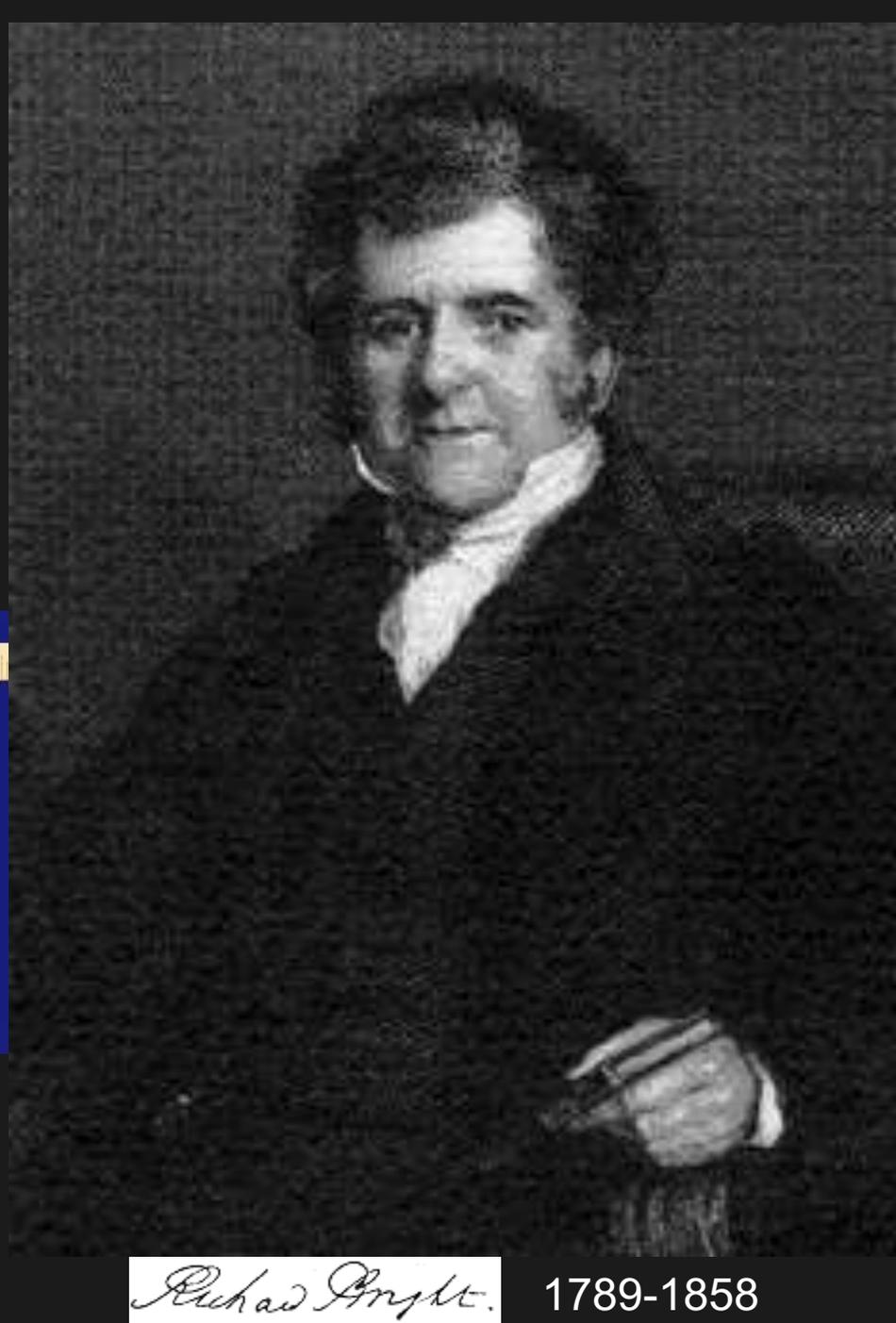
The Environment and Disease : Association or Causation ? 1965
Observation and experiment, 1953

En ce qui concerne l'hypertension artérielle

À l'origine, une hypothèse mécanistique



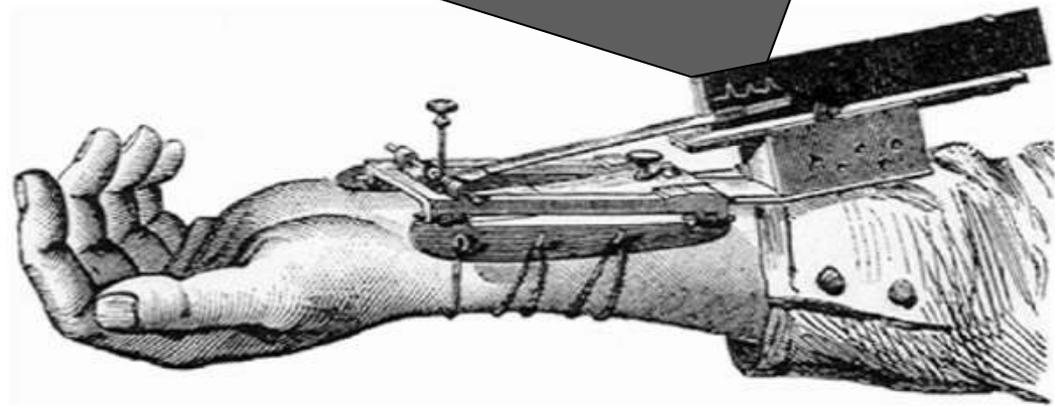
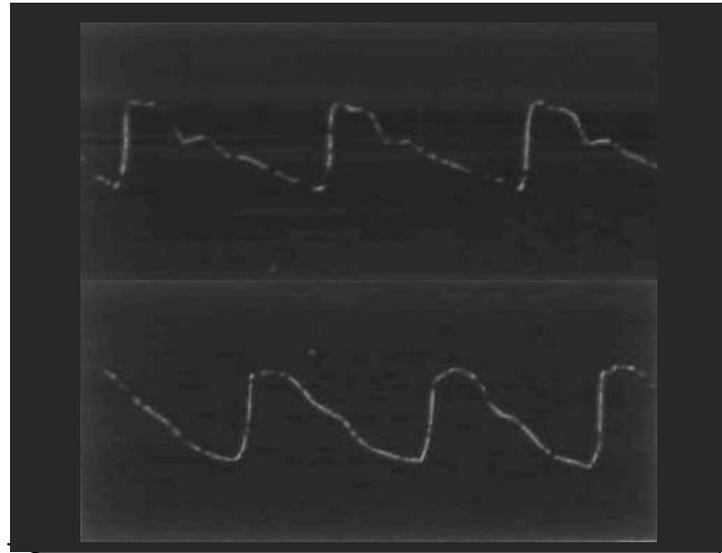
Guy's Hospital Reports, London,
1836 ;1:338-400



Richard Bright.

1789-1858

... antérieure aux mesures



Sphygmographe de Marey (1860)

Frederick Akbar Horatio Mahomed (1849-1884)

1905 1896



Nikolai Korotkoff (1874-1920)

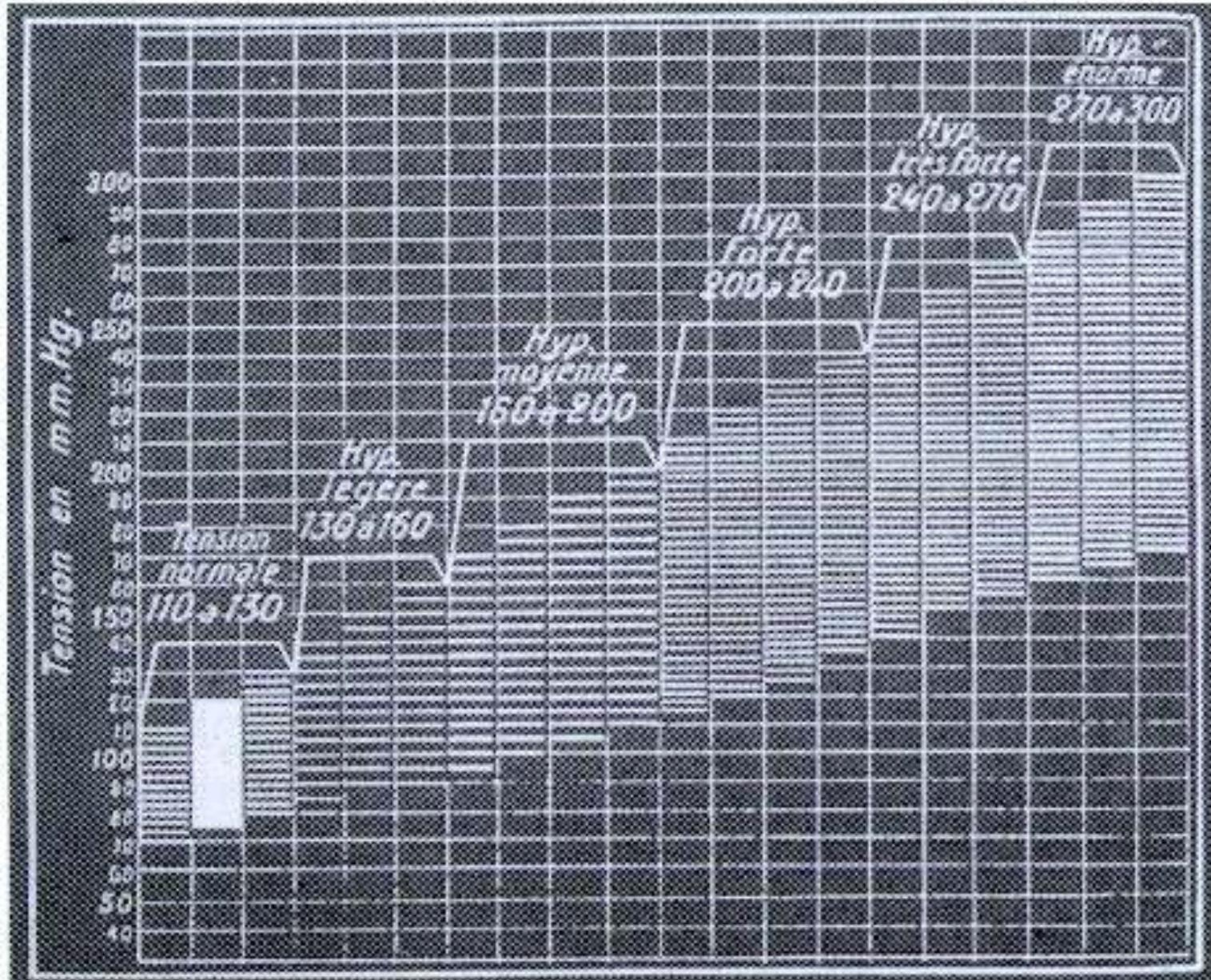


Scipione Riva-Rocci (1863-1937)

Et ce sera la première 'maladie quantitative'



Louis Gallavardin. La tension artérielle en clinique. Sa mesure, sa valeur sémiologique (1910. Masson 1920)



L'*invention* de l'hypertension artérielle dans le cadre des préoccupations de l'assurance-vie

De fait, les médecins du XIX^{ème} siècle cherchaient à 'découvrir les grands signes des maladies obscures'

- Anonyme. *Traité complet de l'examen médical dans les assurances sur la vie*. Warnier libraire éd., Paris 1887
- Moritz. *De l'examen du coeur en matière d'assurance vie*. 1^{er} congrès des médecins d'assurance vie. Bruxelles, 1899

Fischer JW. *The diagnostic value of the sphygmo-manometer in examinations for life insurance.* JAMA 1914;63:1752-4

Espérance de vie (ans)

0 10 20 30 40



homme âge 35: 41,5 ans



homme âge 45: 32 ans

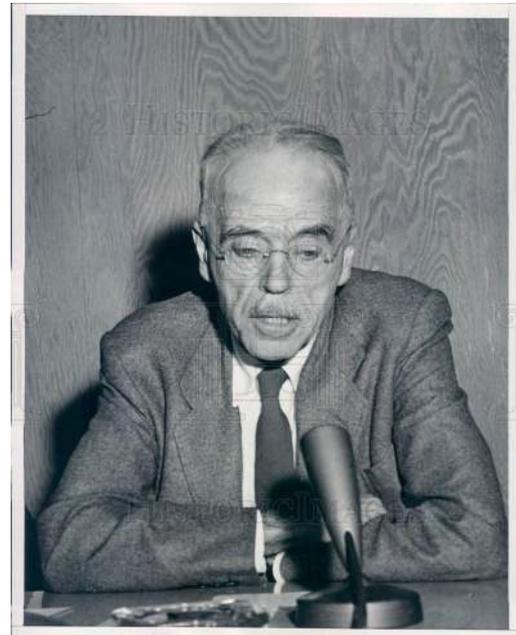


homme âge 55: 23,5 ans

mmHg

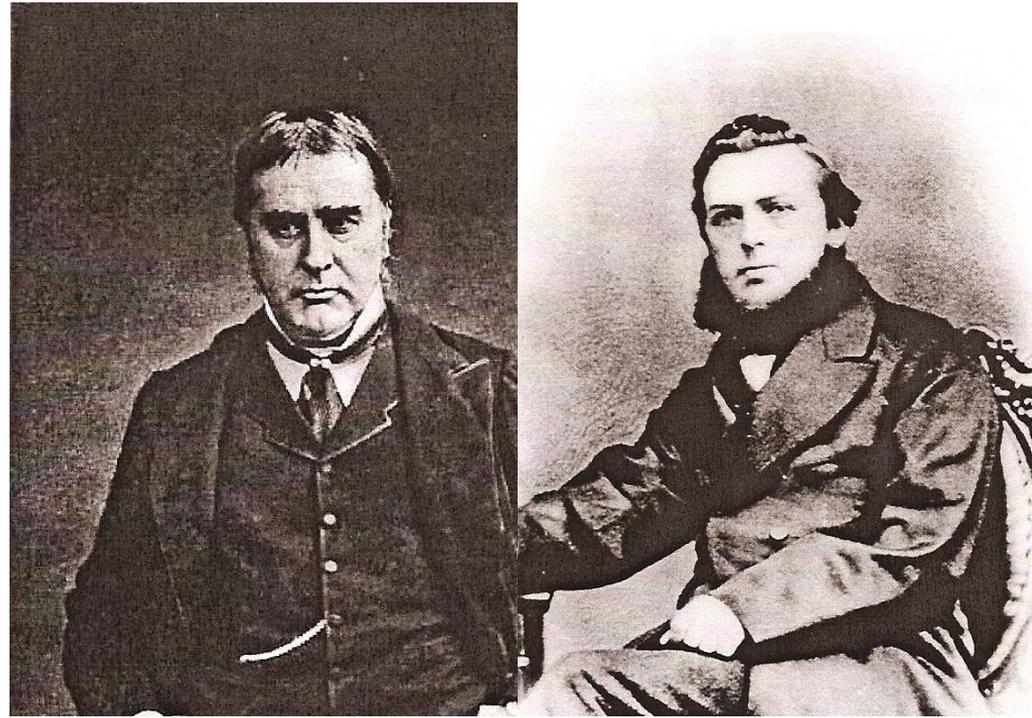
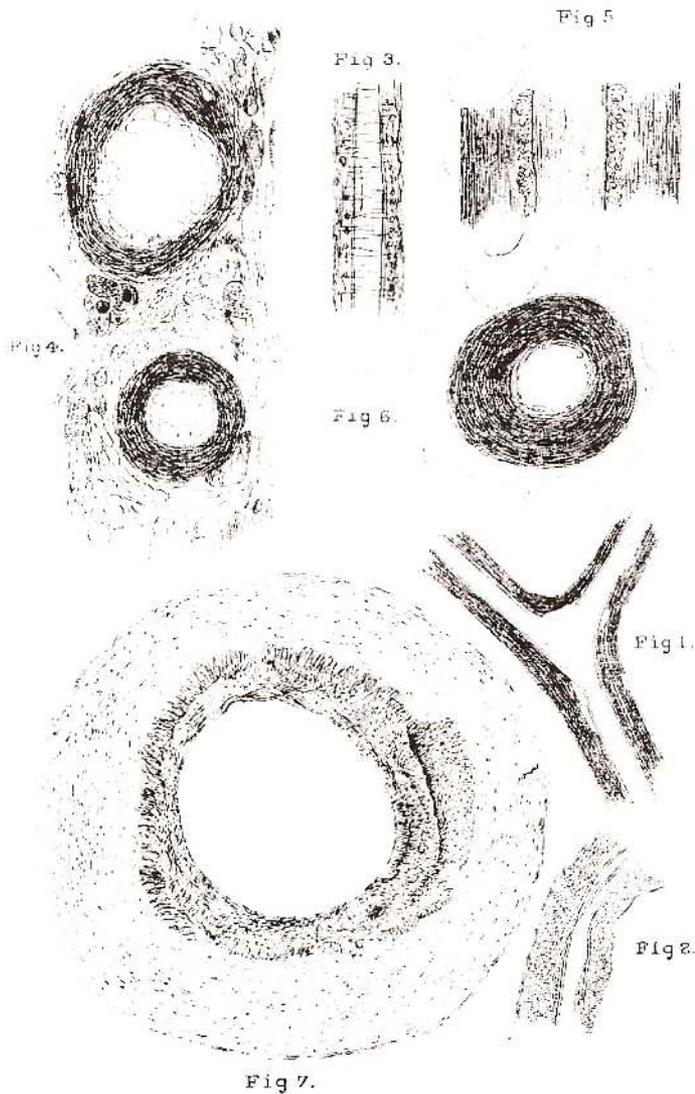
Metropolitan Life Insurance Company, 1961
in Lew EA. *Am J Med* 1973;55:281-94

La signification de
l'hypertension artérielle
pour la pratique médicale
va rester longtemps
controversée ...



"the treatment of the hypertension itself is a difficult and almost hopeless task in the present state of our knowledge and in fact, for ought we know the hypertension may be an important compensatory process which should not be tampered with even were it certain that we could control it"

*Paul Dudley White. Heart Disease.
MacMillan Med, New York, 1931*



William W Gull & Henry G Sutton
On the pathology of the morbid state commonly called chronic Bright's disease with contracted kidney ("arterio-capillary fibrosis"). Medico-Chirurgical Transactions, London, 1872, 55: 273-326

... comme aussi l'interprétation anatomo-clinique de la maladie hypertensive



INTRODUCTION

The association of cardiac enlargement and renal contraction has been recognized since Bright's classical case reports in 1836. Shortly thereafter Johnson added diffuse disease of the smallest arteries to the pathological anatomy of Bright's disease and in 1873 proposed the theory that renal disease was primary with subsequent diffuse thickening of the walls of the smallest arteries leading to increased peripheral resistance, elevated blood pressure and cardiac hypertrophy.

Subsequent observations added complexity rather than simplification to the problem. Gull and Sutton reported widespread small vessel disease called by them "arterio-capillary fibrosis," and observed that "these changes are, or may be, independent of renal disease, and that the renal change in chronic Bright's disease with contracted kidneys, when present, is but a part of a general morbid condition." They concluded that the diffuse vascular disease was a primary pathological change responsible for increased resistance to blood flow. Confirming this general hypothesis were the early clinical observations on blood pressure by Mahomed to the effect that high blood pressure precedes the clinical signs of renal damage.

The Kidney in Essential Hypertension

Victim or Culprit

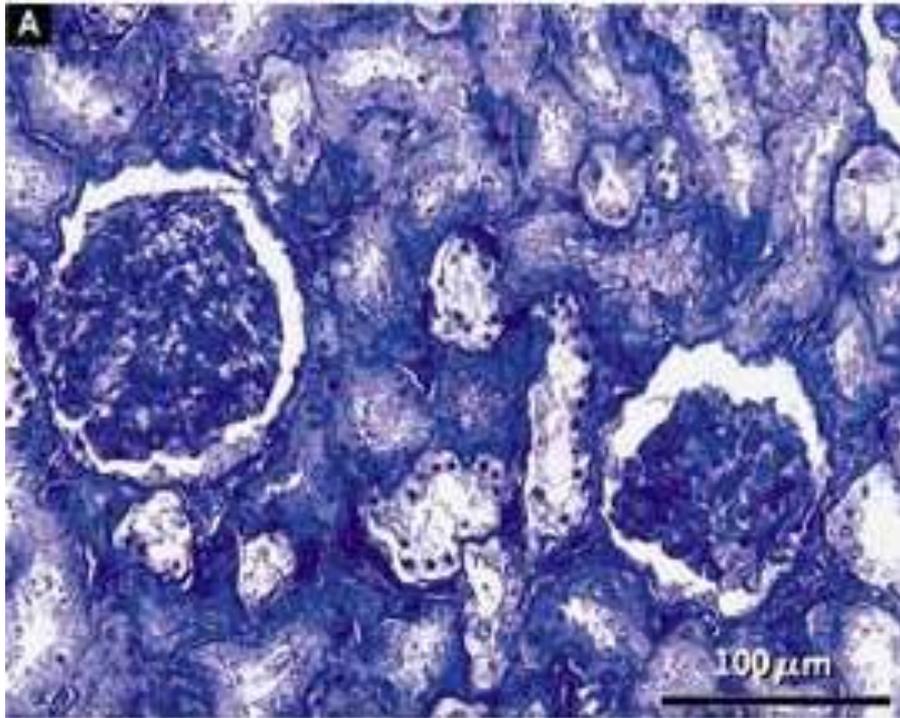
By HERBERT CHASIS, M.D., AND DAVID S. BALDWIN, M.D.

It is apparent from this review that the structural and functional abnormalities thus far demonstrated have not established the pathogenetic role of the kidney in essential hypertension. Aside from its inability to characterize the dynamics of the renal circulation, the anatomic approach does not permit one to choose between the primary or secondary nature of the vascular changes. On the other hand, the renal hemodynamic and functional alterations (relative renal ischemia, increased filtration fraction, decreased maximal tubular excretory capacity, reduced sodium excretion relative to filtration, decreased formation of free water, and impaired elaboration of an osmotically concentrated urine) are demonstrable early in essential hypertension and favor a primary renal mechanism. Continued exploration of the kidneys' hemodynamics and functions early in essential hypertension has resulted in the disclosure of an increasing number of abnormalities. We believe that further study may well establish its role as culprit.

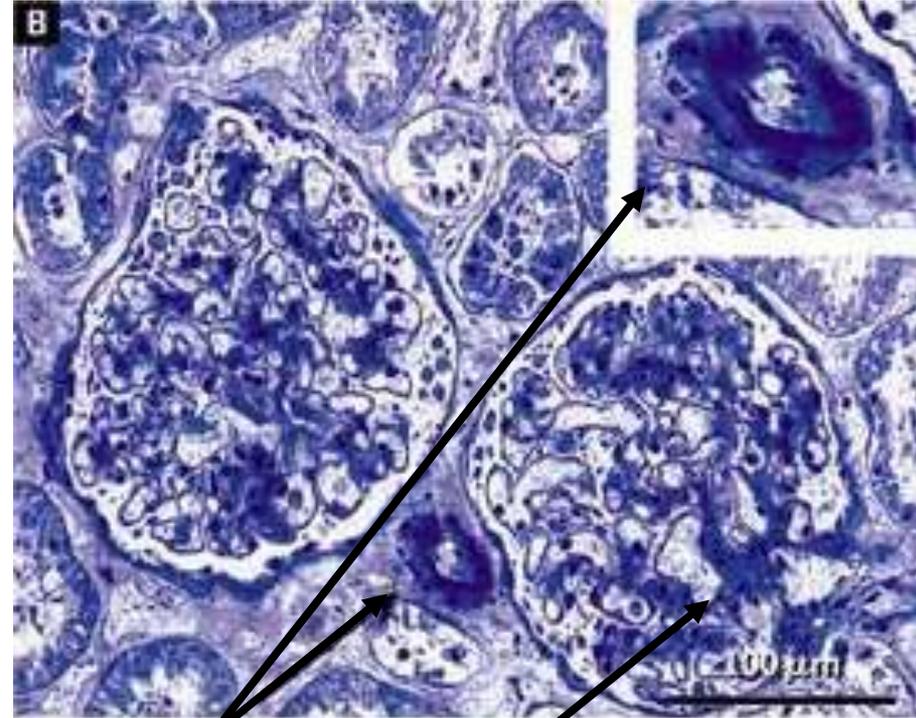
Nephron Number in Patients with Primary Hypertension

Gunhild Keller, M.D., Gisela Zimmer, M.D., Gerhard Mall, M.D.,
Eberhard Ritz, M.D., and Kerstin Amann, M.D.

normotensive control

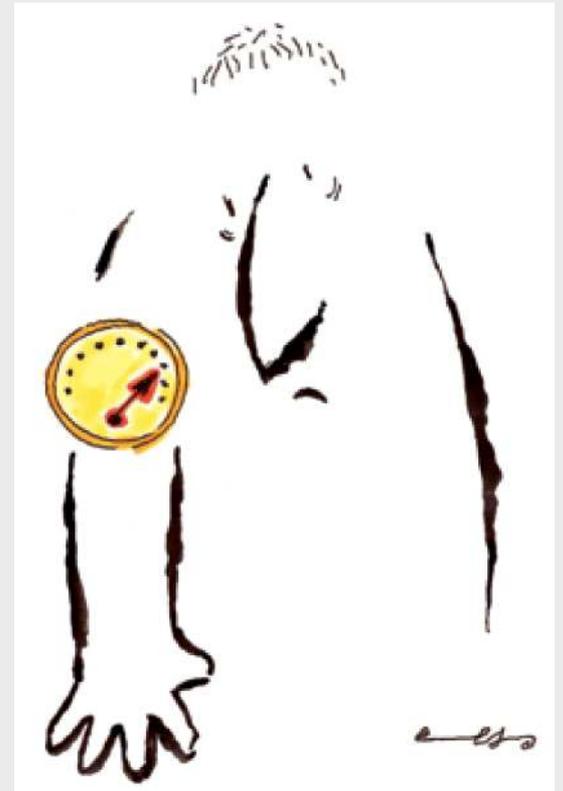


hypertensive patient



arteriolar
hyalinosis

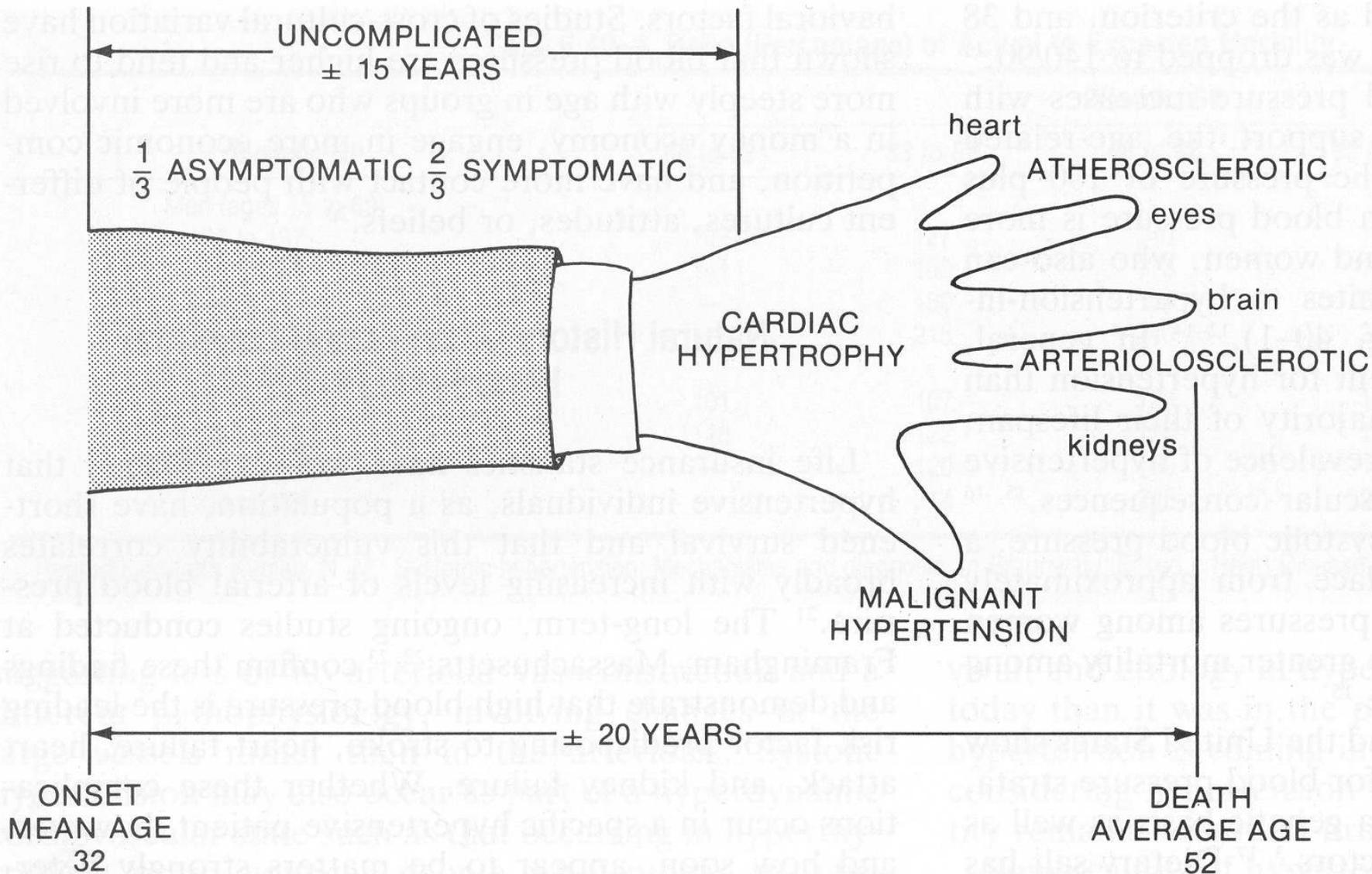
glomerular
enlargement



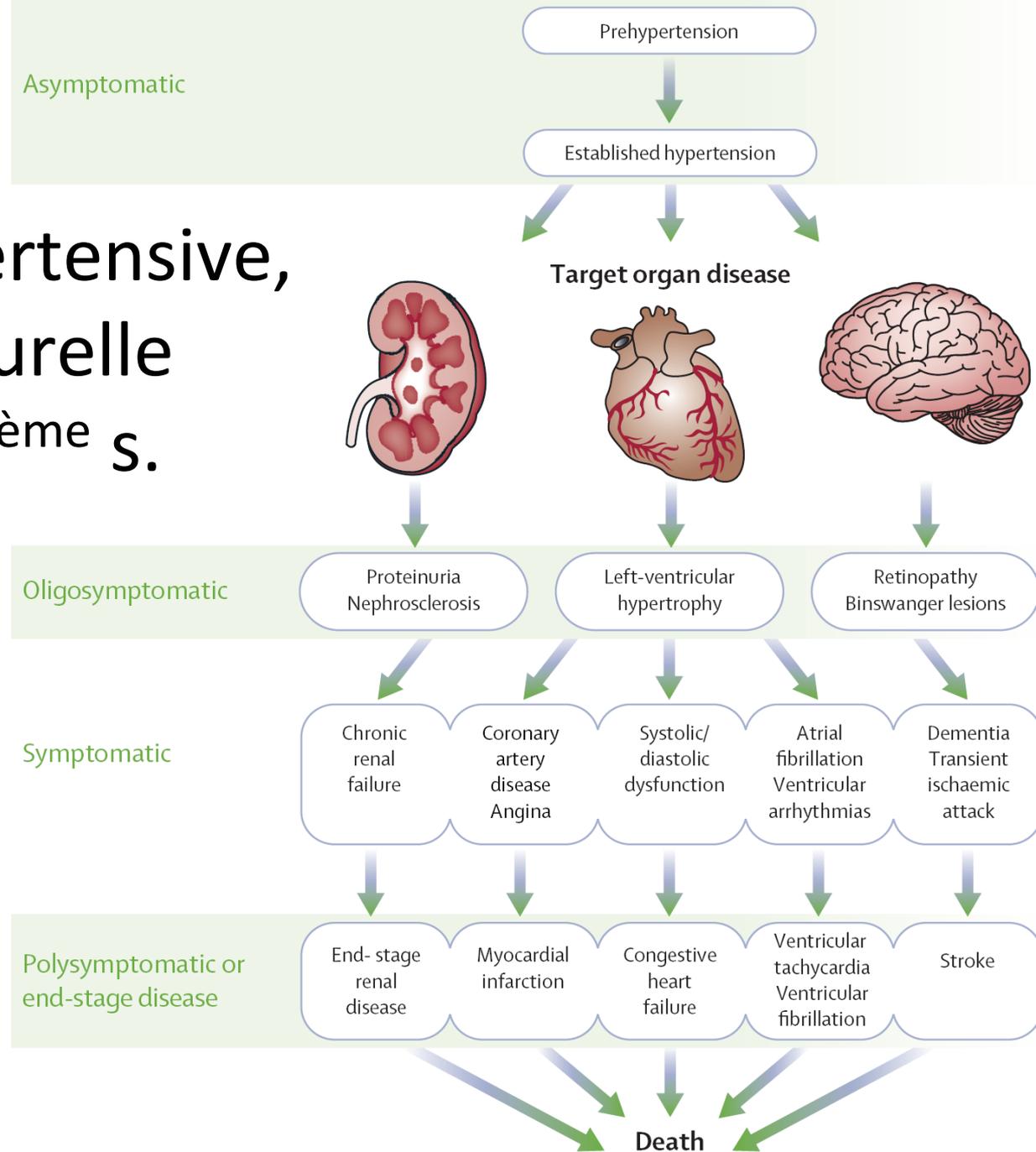
Du côté de la maladie, une entité à construire

L'hypertension artérielle, une maladie "essentielle" ?

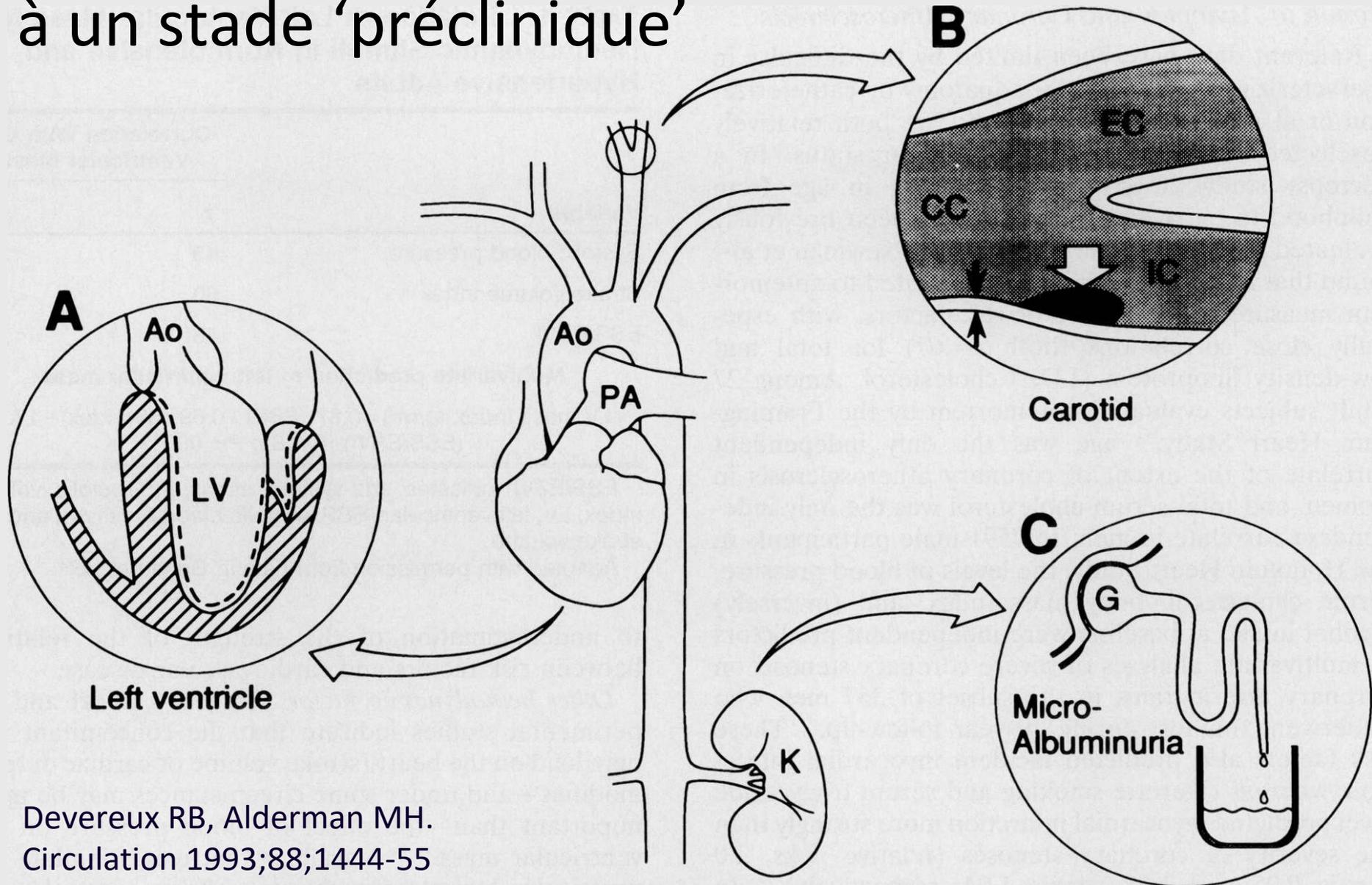
L'hypertension artérielle 'essentielle' : son 'histoire naturelle' au milieu du XX° s.



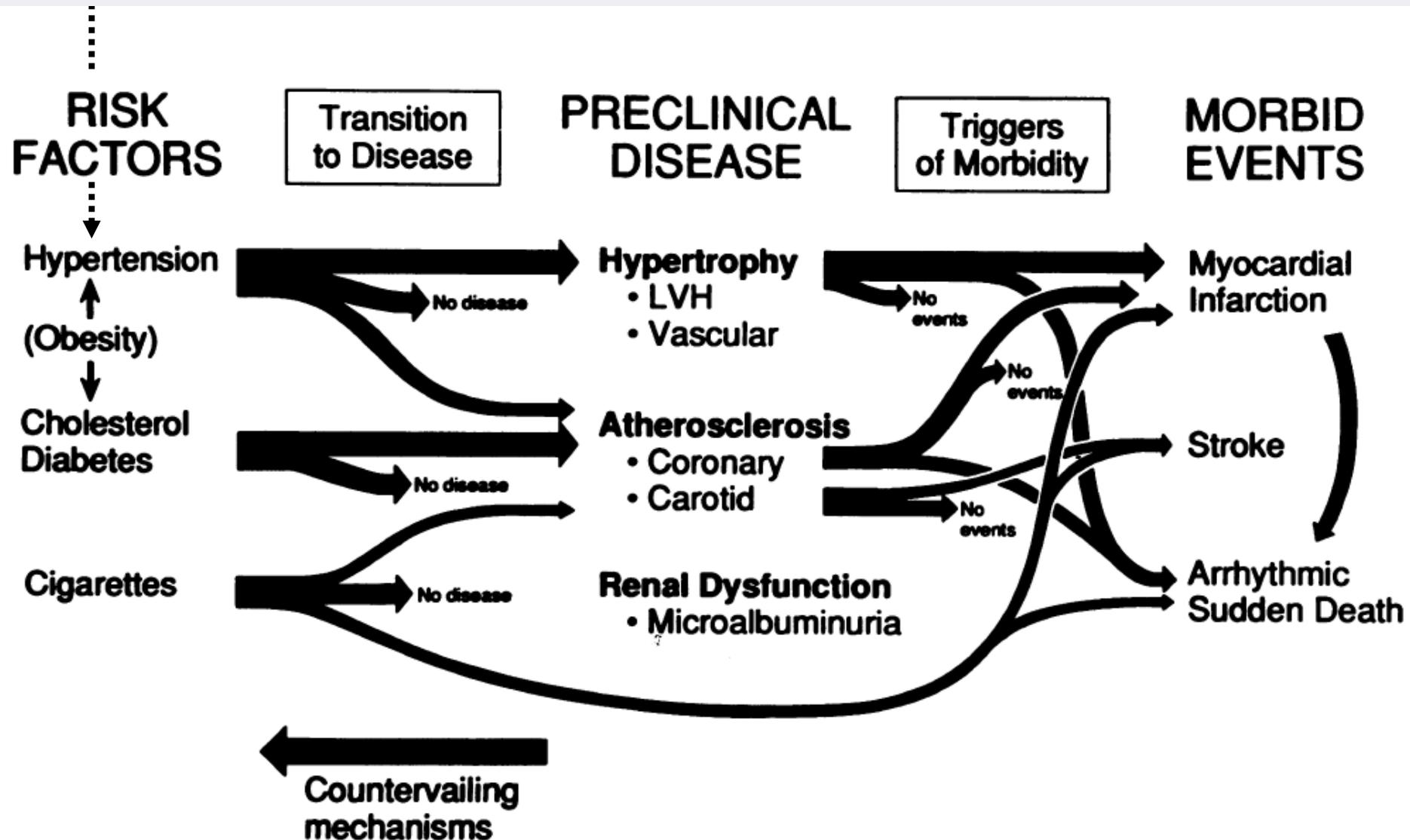
La maladie hypertensive, son histoire naturelle au début du XXI^{ème} s.



Une maladie éventuellement détectable à un stade 'préclinique'



... ou une *entité* cardiovasculaire / cardiométabolique
'causée' par des 'facteurs de risque'



Des facteurs de risque ou des mécanismes, plutôt que des causes

**Constitution (*généétique*),
environnement,
hygiène de vie**

Le sel, première cible de traitement



Le côté de Guermantes (III, 208) 1920

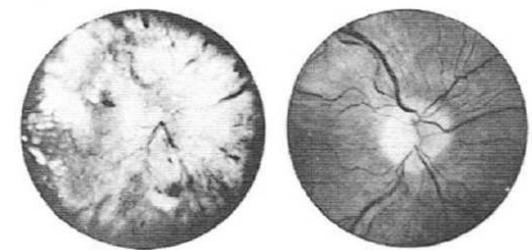
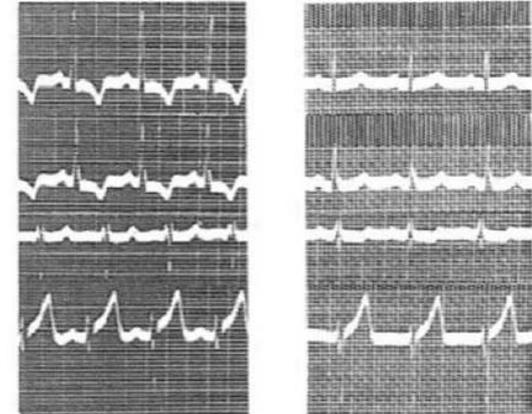
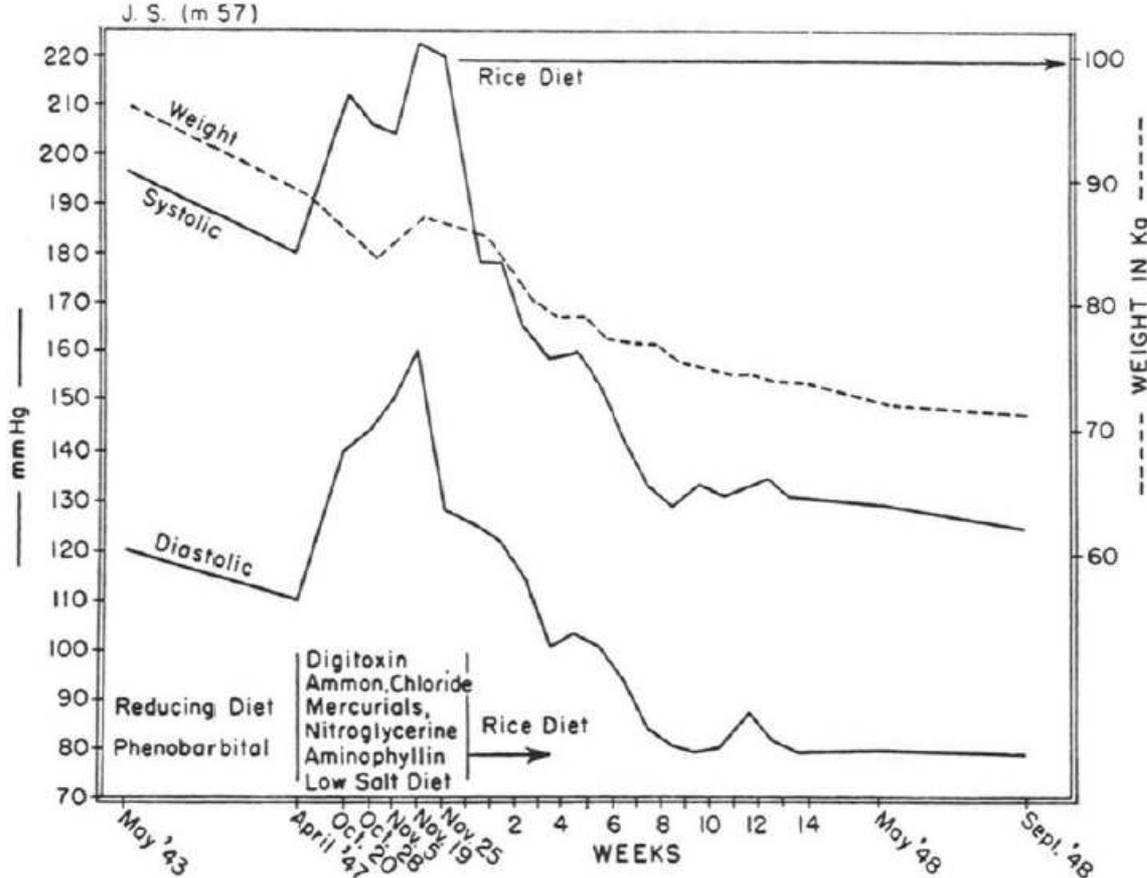
• *‘Cottard essaya, pour calmer l’agitation de sa malade, le régime lacté. Mais **les perpétuelles soupes au lait ne firent pas d’effet parce que ma grand’mère y mettait beaucoup de sel** (Widal n’ayant pas encore fait ses découvertes), **dont on ignorait l’inconvénient en ce temps-là**. Car la médecine étant un compendium des erreurs successives et contradictoires des médecins, en appelant à soi les meilleurs d’entre eux on a grande chance d’implorer une vérité qui sera reconnue fausse quelques années plus tard.’*

Walter Kempner 1903-1997

Treatment of kidney disease and hypertensive vascular disease with the rice diet. N C Med J 1944 ... 1945

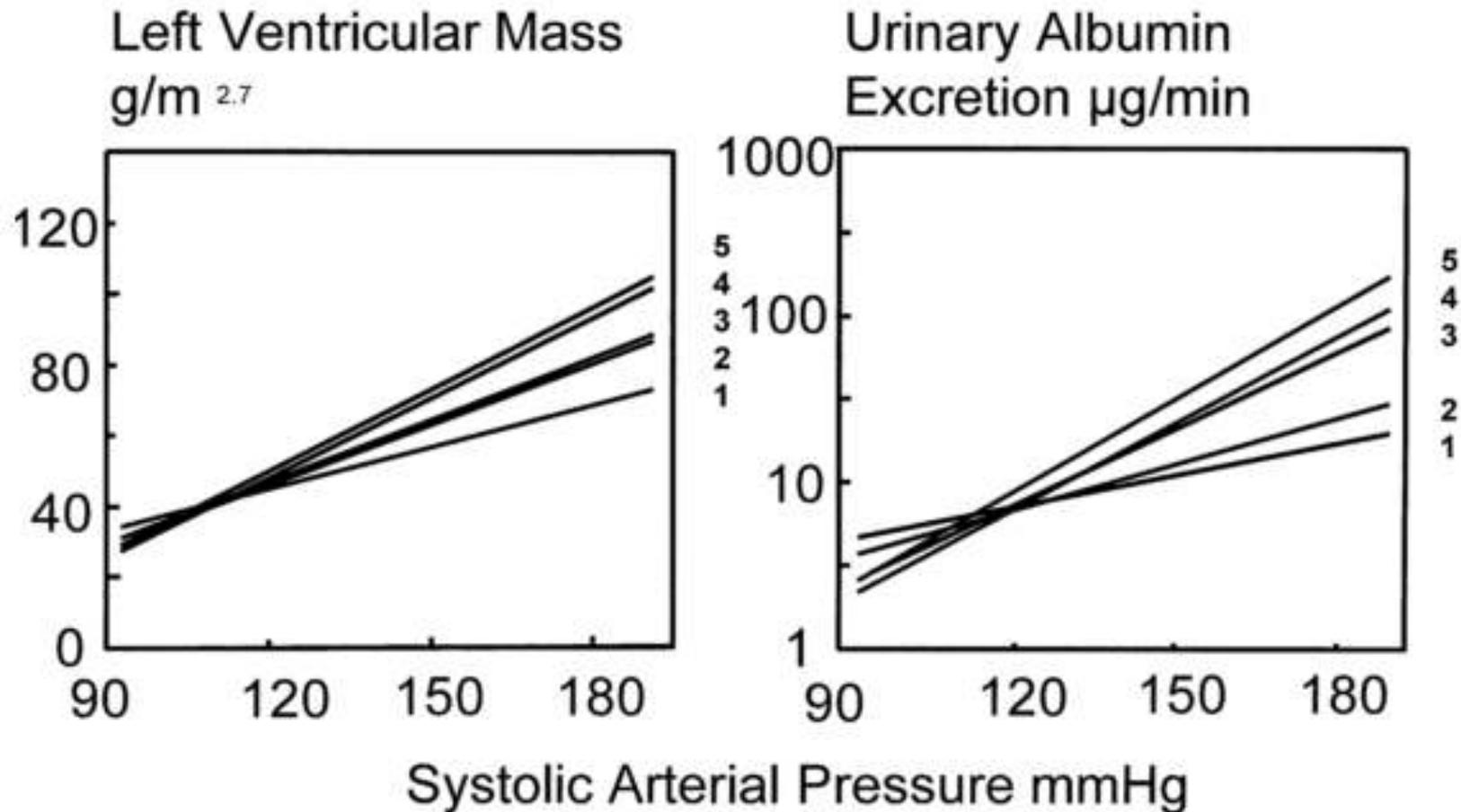
Treatment of heart and kidney disease and of hypertensive and arteriosclerotic vascular disease with the rice diet.

Ann Intern Med 1949;31:821-56

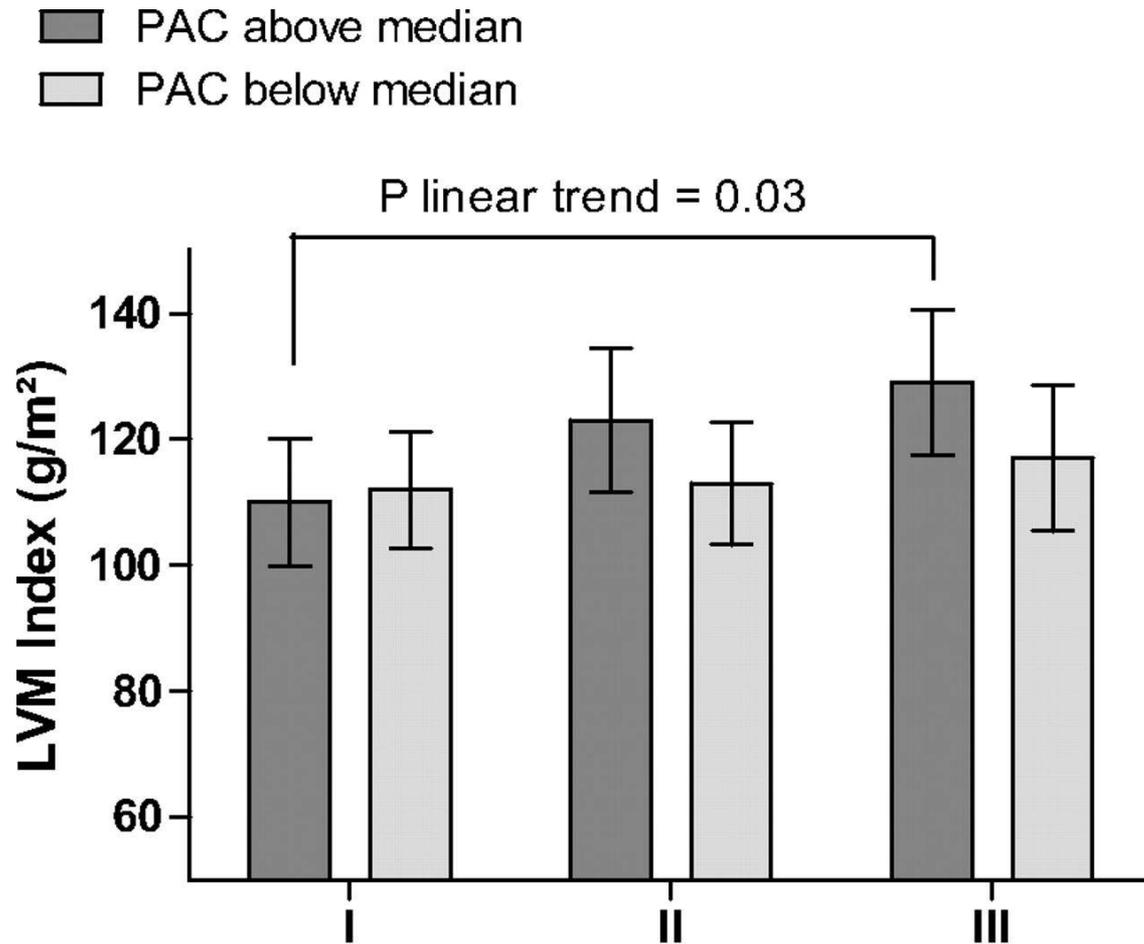


Relation between BP and TOD in EH patients according to quintiles of urinary sodium excretion

Montpellier cohort



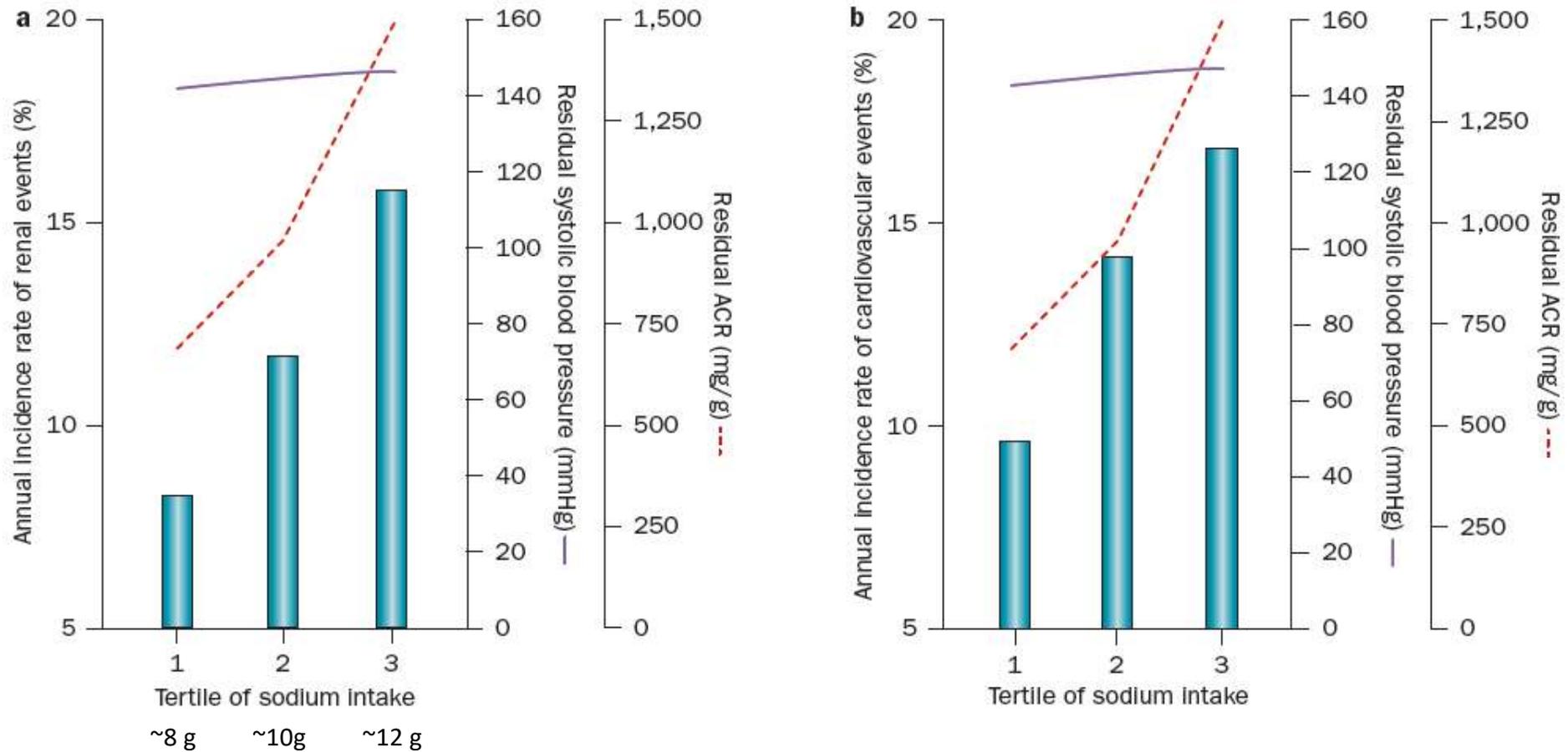
Follow-up LVMI in EH subjects according to aldosterone levels and sodium excretion



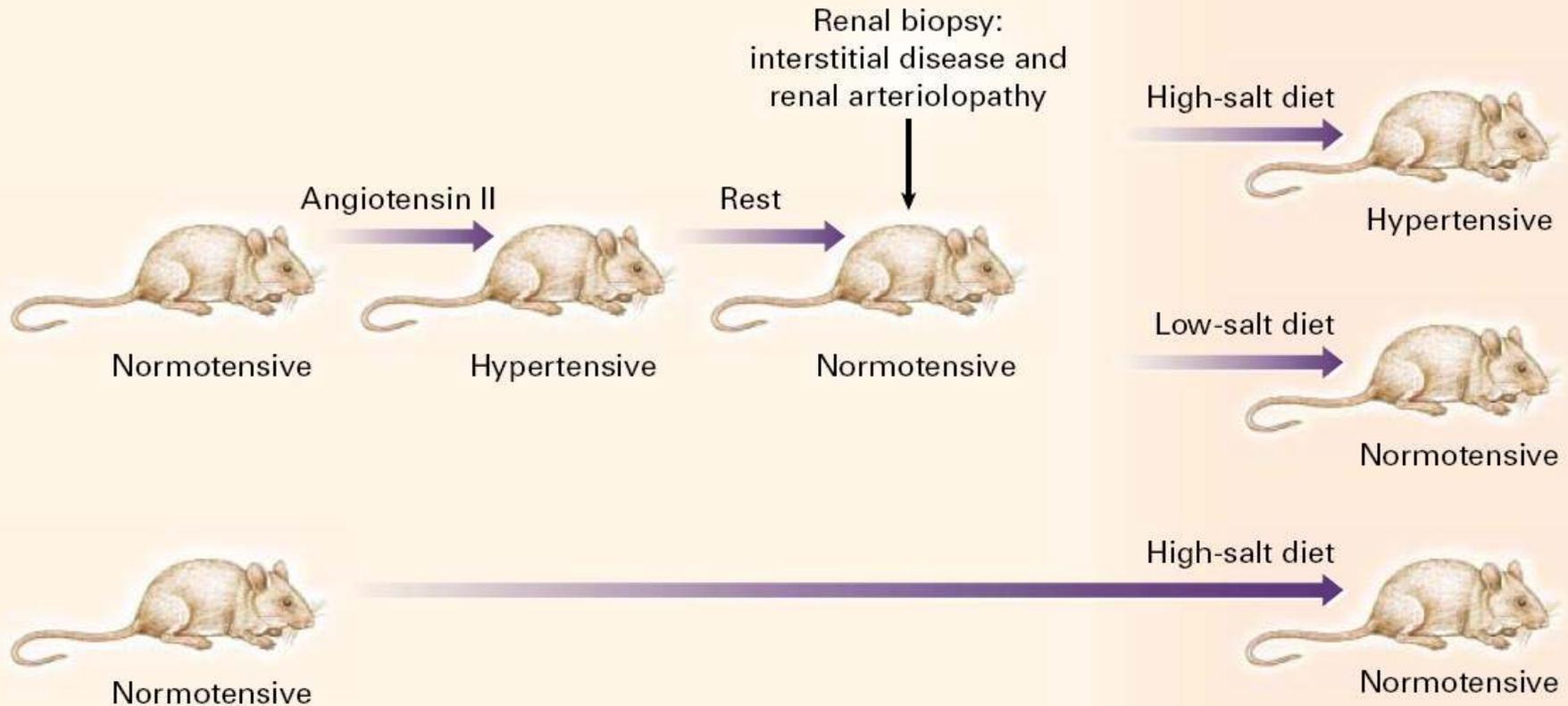
Sex-specific tertiles of 24-hour UNaV (mean and 95% CI)

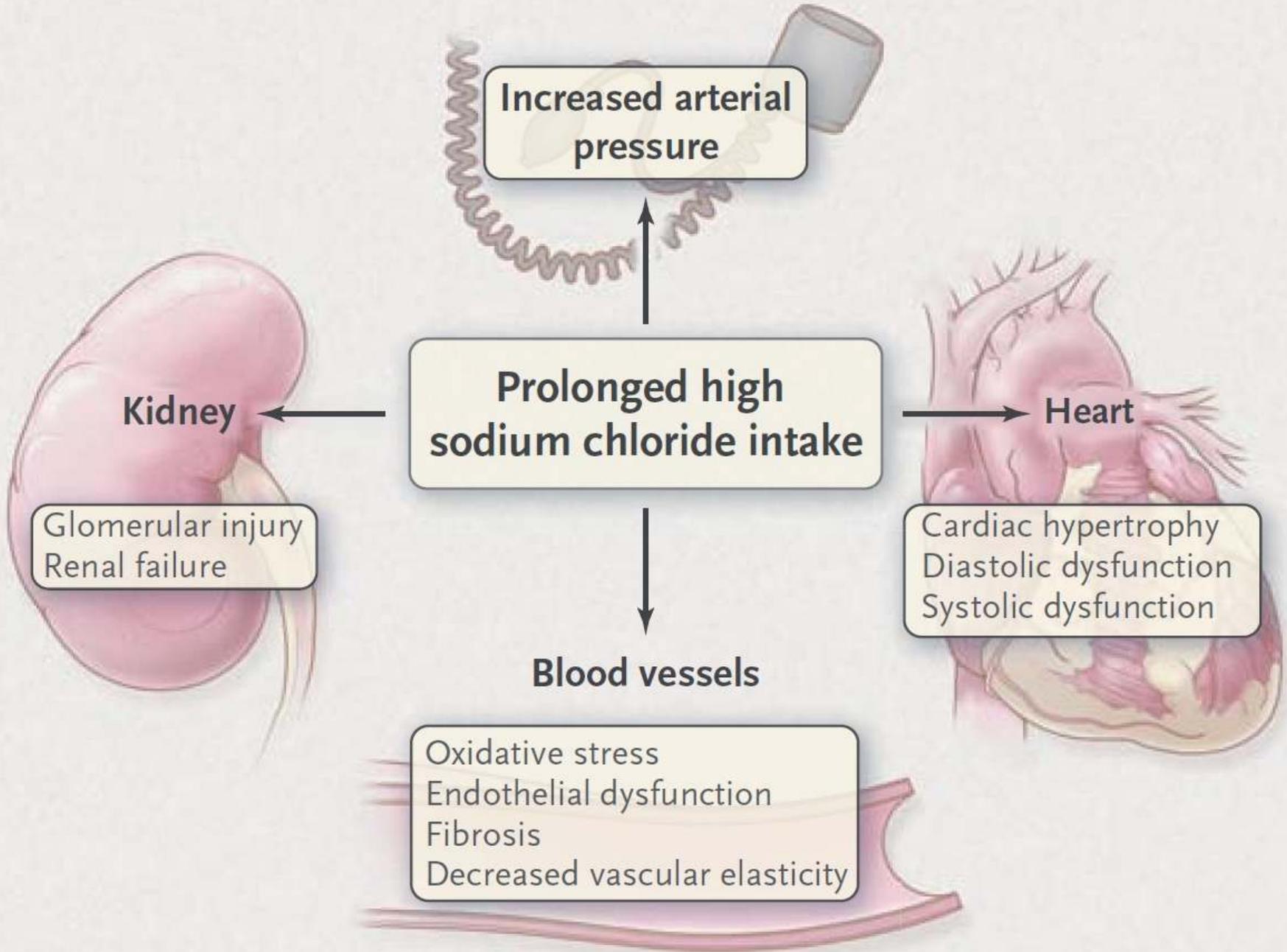
Sodium status & adverse event rates during RAS blockade

RENAAL & IDNT trials

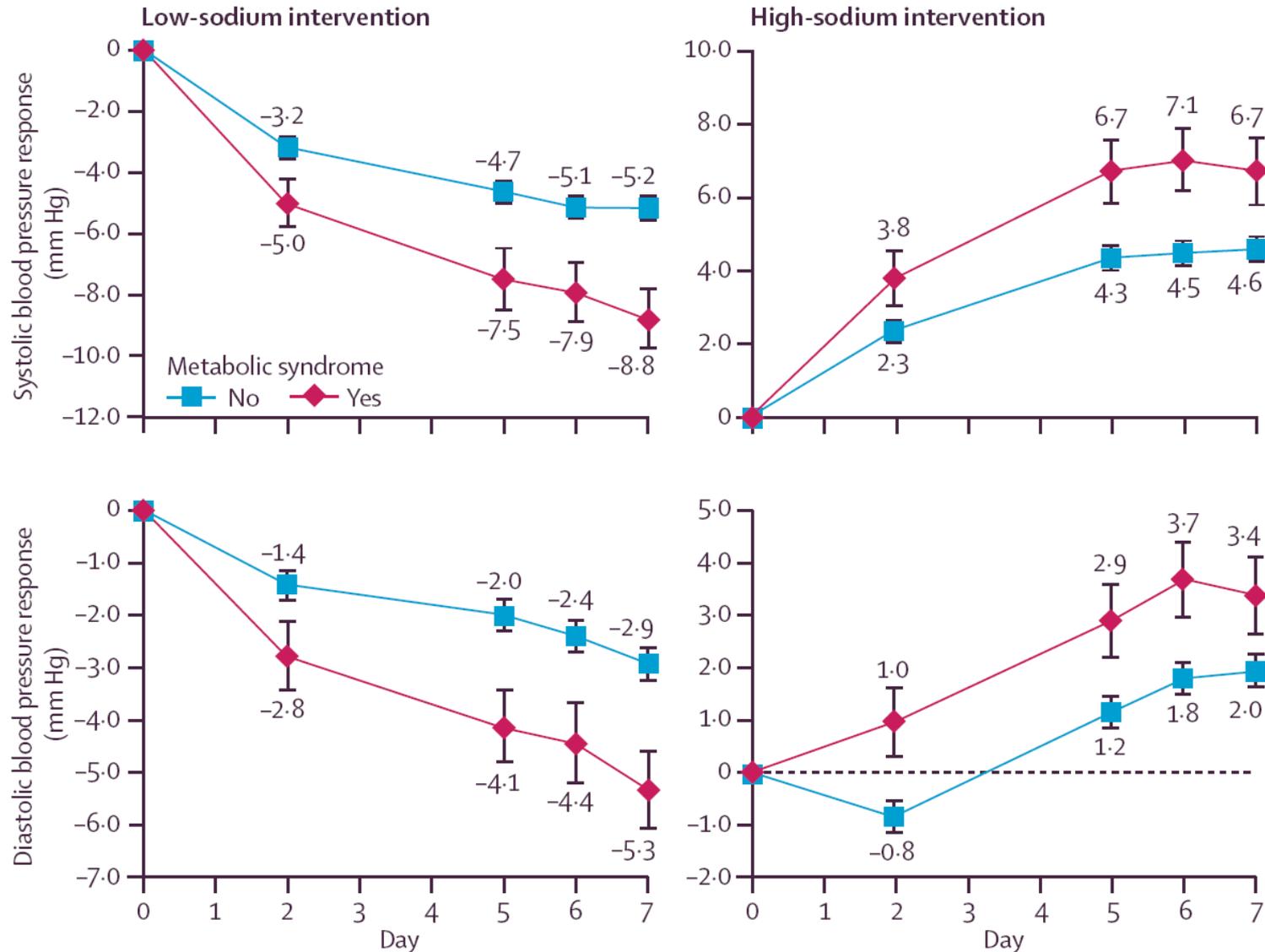


Development of salt-sensitive hypertension in rats after exposure to angiotensin II



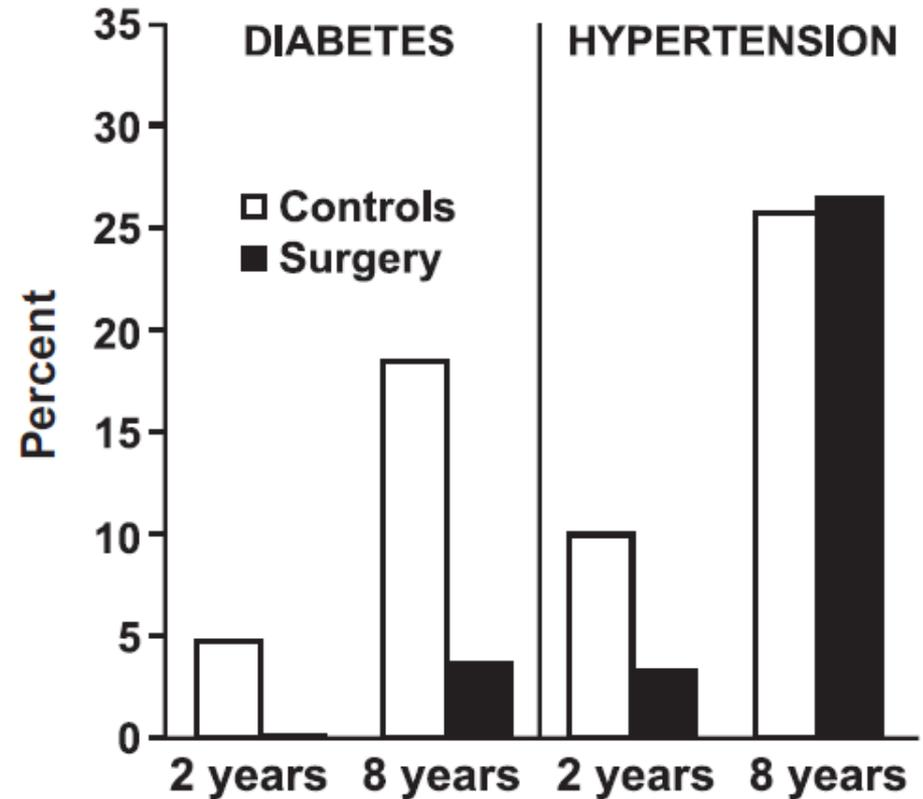
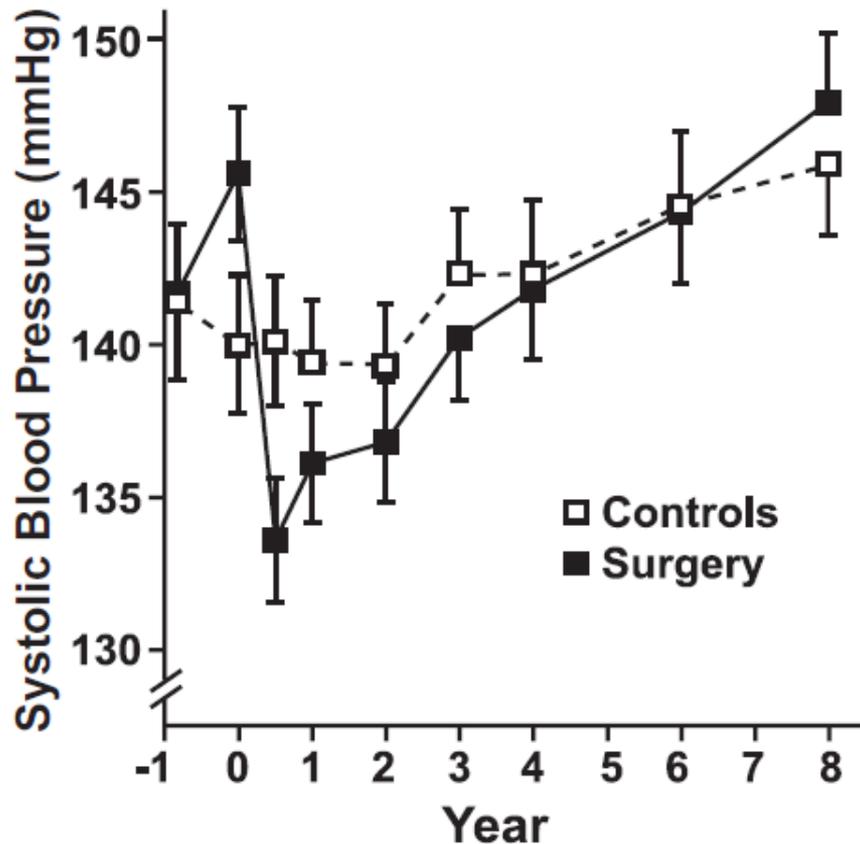


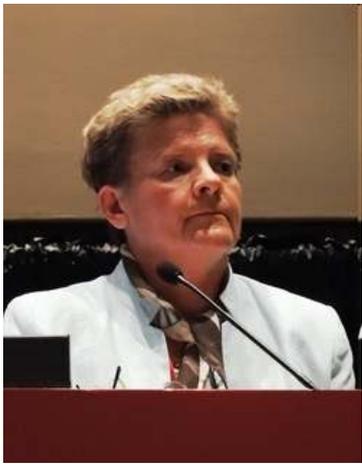
Gensalt : age- and sex-adjusted BP responses to low- and high-sodium intake



Réduction pondérale (par chirurgie bariatrique) et baisse tensionnelle (non pérenne)

the Swedish Obesity Study

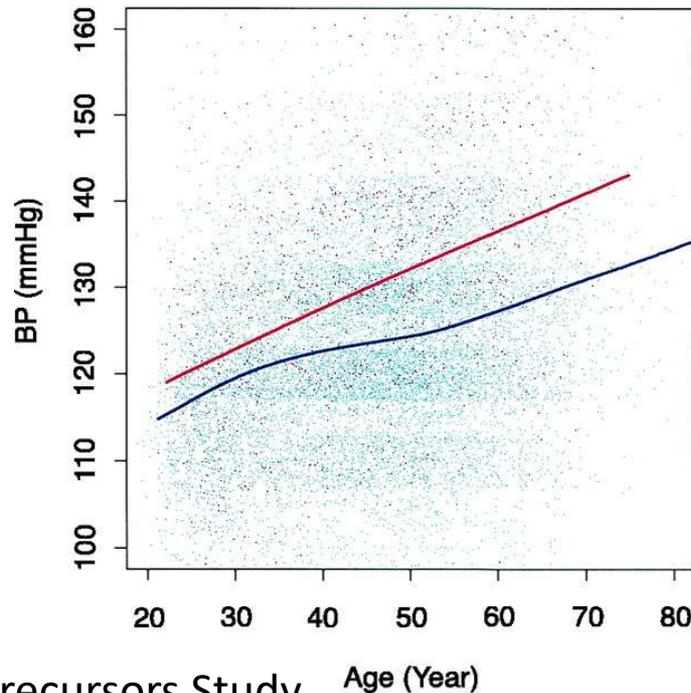




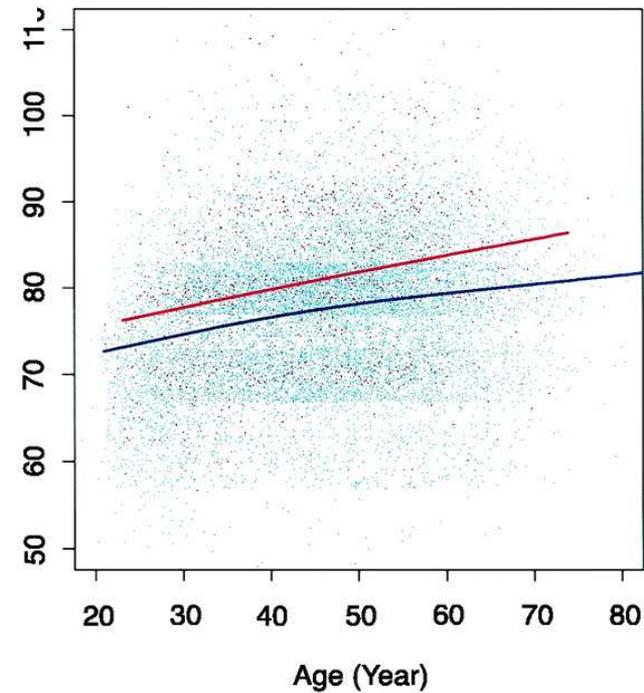
Hannele Yki-Järvinen :
“Diabetes is a cardiovascular disease
which you diagnose by measuring blood glucose.”

Mean BP by age among individuals who
remained nondiabetic / developed type 2 diabetes

Systolic



Diastolic



Impact of health behaviours on BP

Intervention	Systolic BP (mmHg)	Diastolic BP (mmHg)
Diet and weight control	-6.0	-4.8
Reduced salt/sodium intake	- 5.4	- 2.8
Reduced alcohol intake (heavy drinkers)	-3.4	-3.4
DASH diet	-11.4	-5.5
Physical activity	-3.1	-1.8
Relaxation therapies	-3.7	-3.5
Multiple interventions	-5.5	-4.5

THE SURGICAL PROBLEM OF HYPERTENSION

LOYAL DAVIS, M.D., AND M. HERBERT BARKER, M.D.

CHICAGO, ILL.

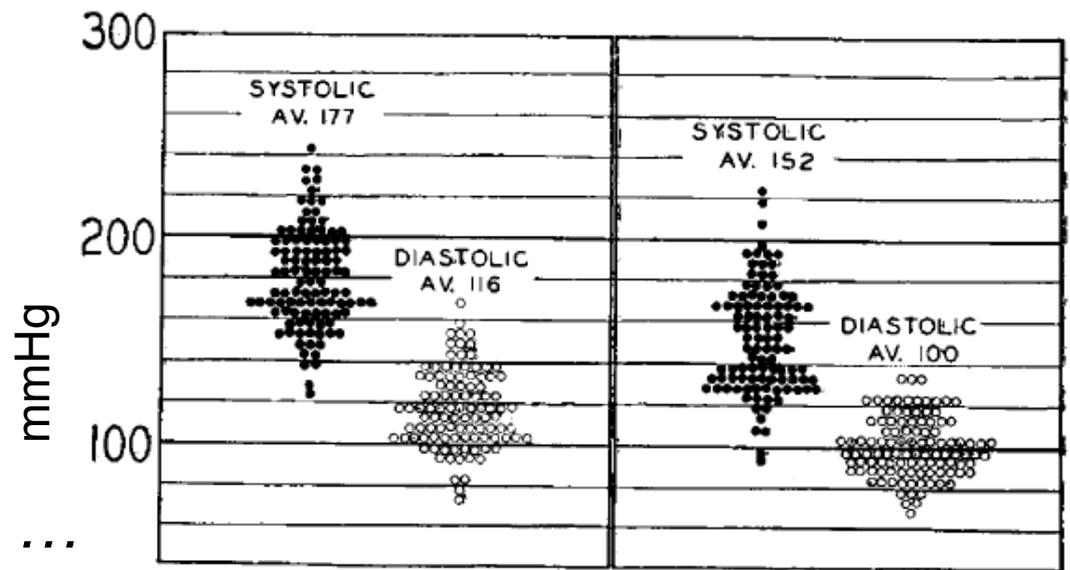
FROM THE DIVISIONS OF SURGERY AND MEDICINE, NORTHWESTERN UNIVERSITY MEDICAL SCHOOL, CHICAGO, ILL.

BASED upon the assumption that removal of the sympathetic supply in cases of Raynaud's disease results in a permanent dilatation of the blood vessels of an extremity, Rowntree and Adson¹ applied the same surgical principle to the treatment of patients with essential hypertension.

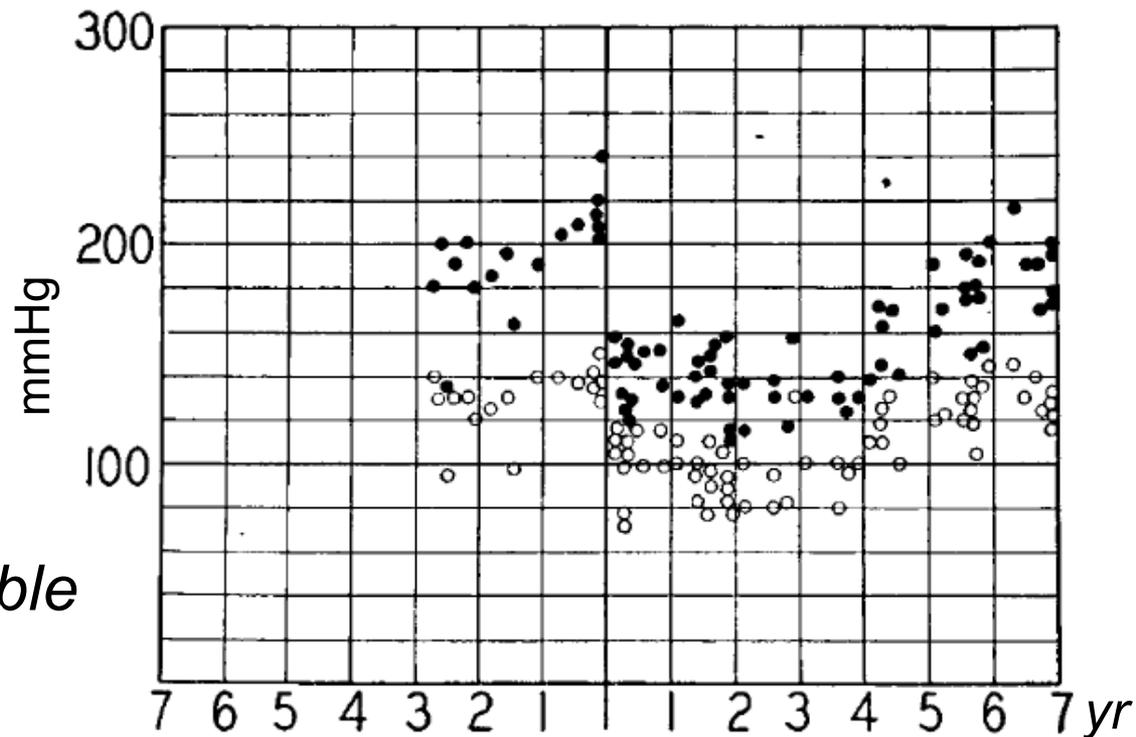
Lack of complete knowledge of anatomic and physiologic facts concerning the sympathetic nervous system makes it difficult to evaluate the results of surgical intervention. In several instances in the past, the indiscriminate clinical employment of operations upon the sympathetic nervous system has eventually proven to have been a mistake, and has retarded the acceptance of other procedures logical in their conception and successful in their application.

Largement utilisée
chez l'hypertendu,
la sympathectomie

a eu un effet consistant ...



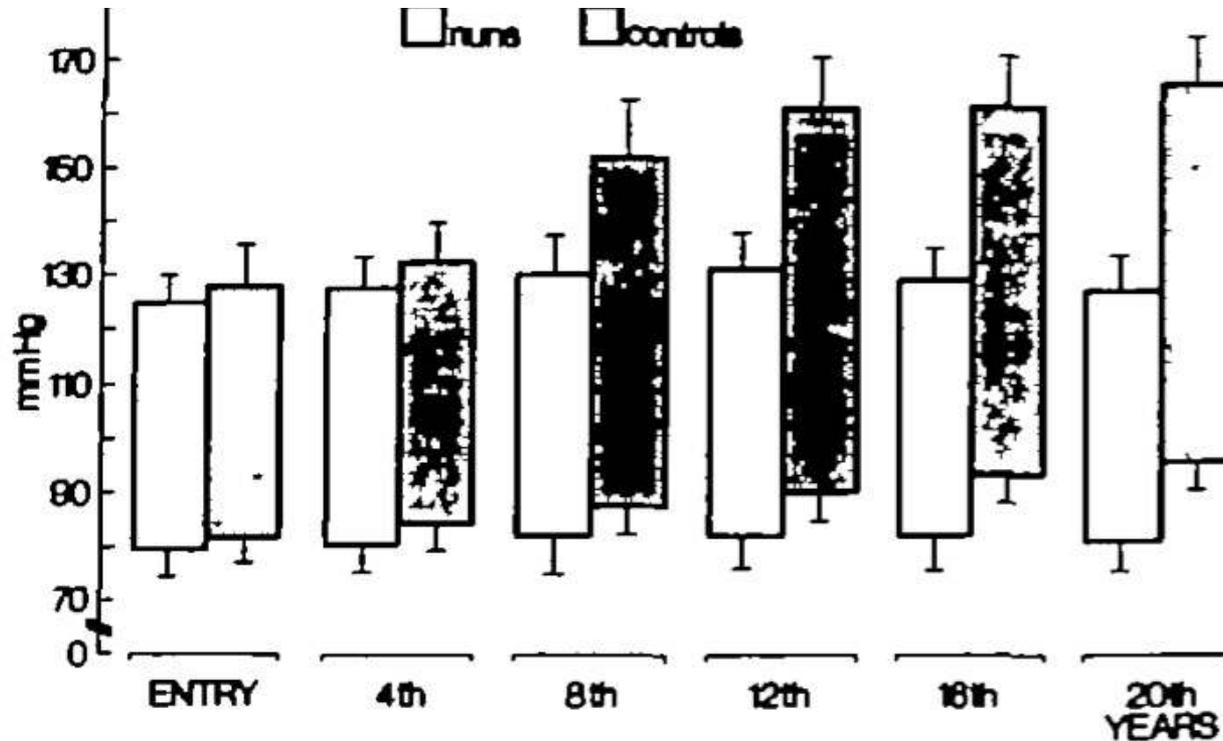
... mais pas toujours durable



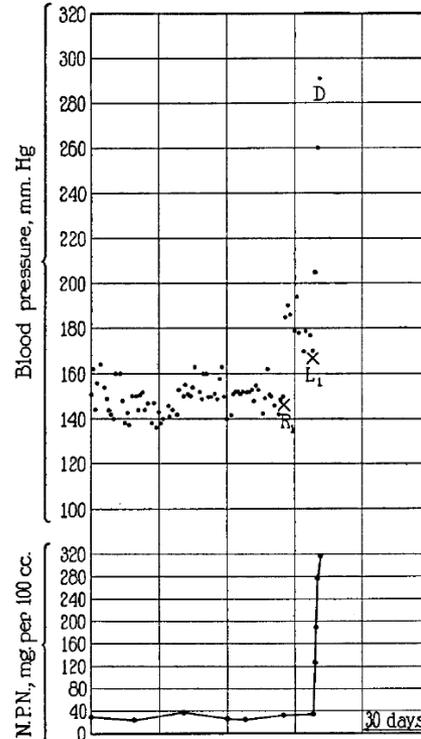
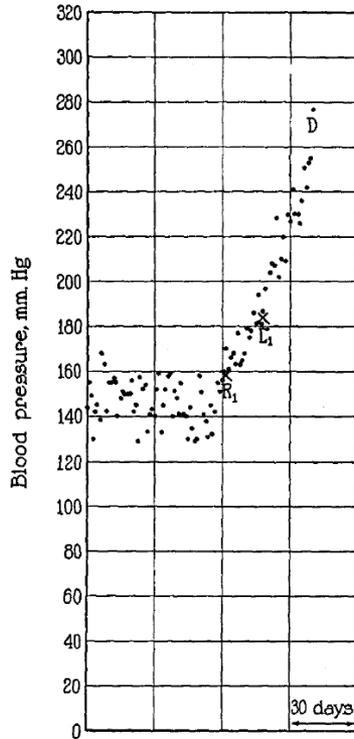
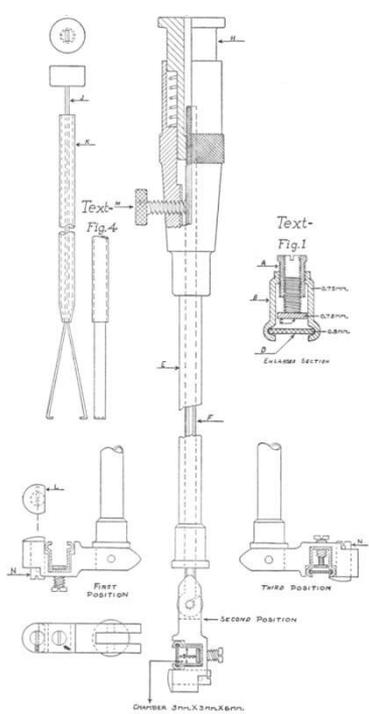
Age and Blood Pressure Changes

A 20-Year Follow-up Study in Nuns in a Secluded Order

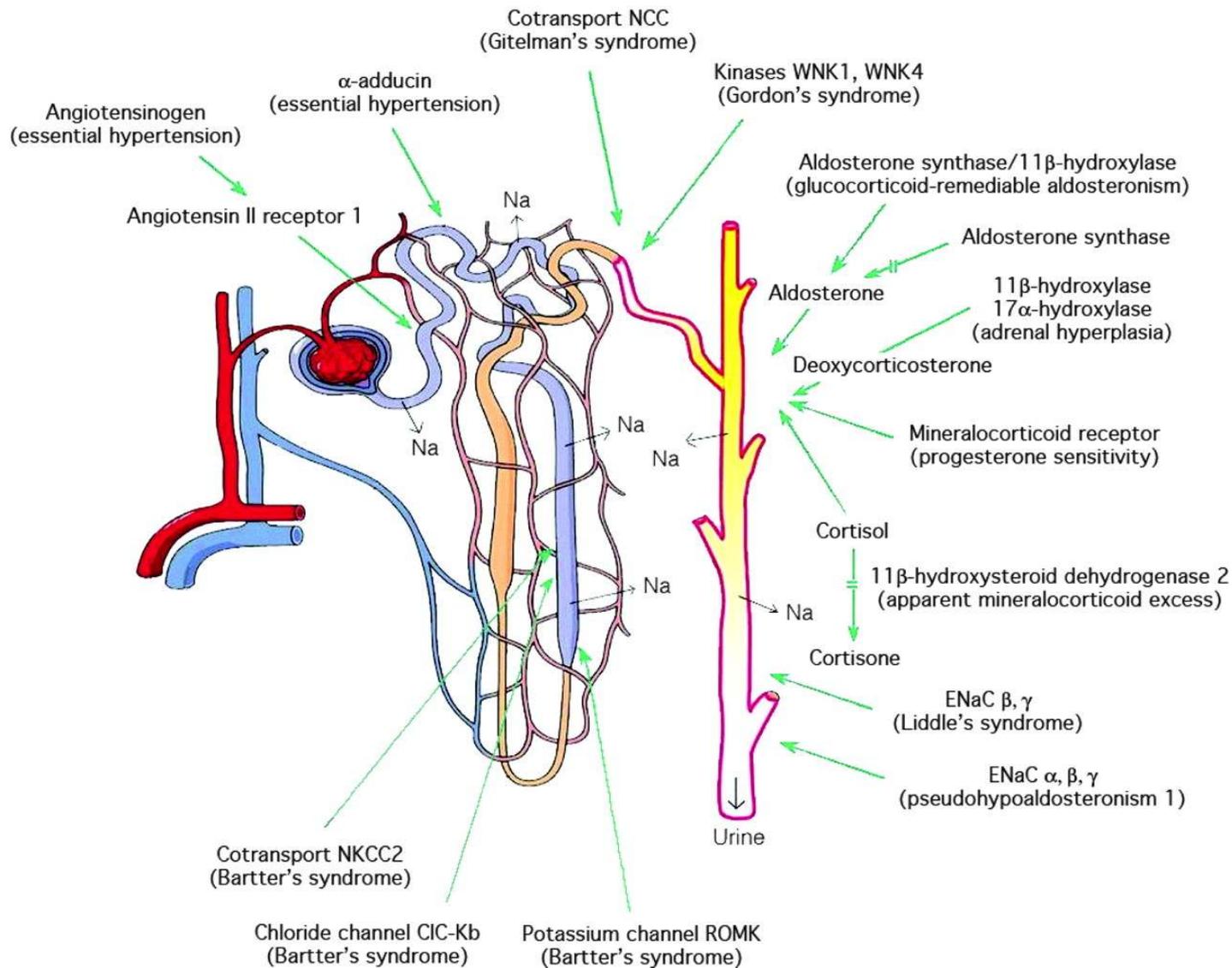
MARIO TIMIO, PAOLO VERDECCHIA, SANDRO VENANZI,
SIMONETTA GENTILI, MAURIZIO RONCONI, BIANCA FRANCUCCI,
MAURO MONTANARI, AND ETTORE BICHISAO



Mean values (\pm SD) of systolic and diastolic blood pressure obtained every 4 years to the end of the study.



... Although it has been suggested (Fahr) that renal ischemia, by itself, may play an important part in the development of the hypertension which is associated with more or less diffuse vascular disease in man, the validity of this contention has not, up to the present time, been investigated experimentally in animals by a study designed to test the effect on blood pressure of renal ischemia alone. In the investigation here reported, **the working hypothesis adopted was that ischemia limited to the kidney may be the initial condition in the pathogenesis of the hypertension that is associated with nephrosclerosis** [Goldblatt HG, et al. *J Exp Med* 1934;59:347-79]

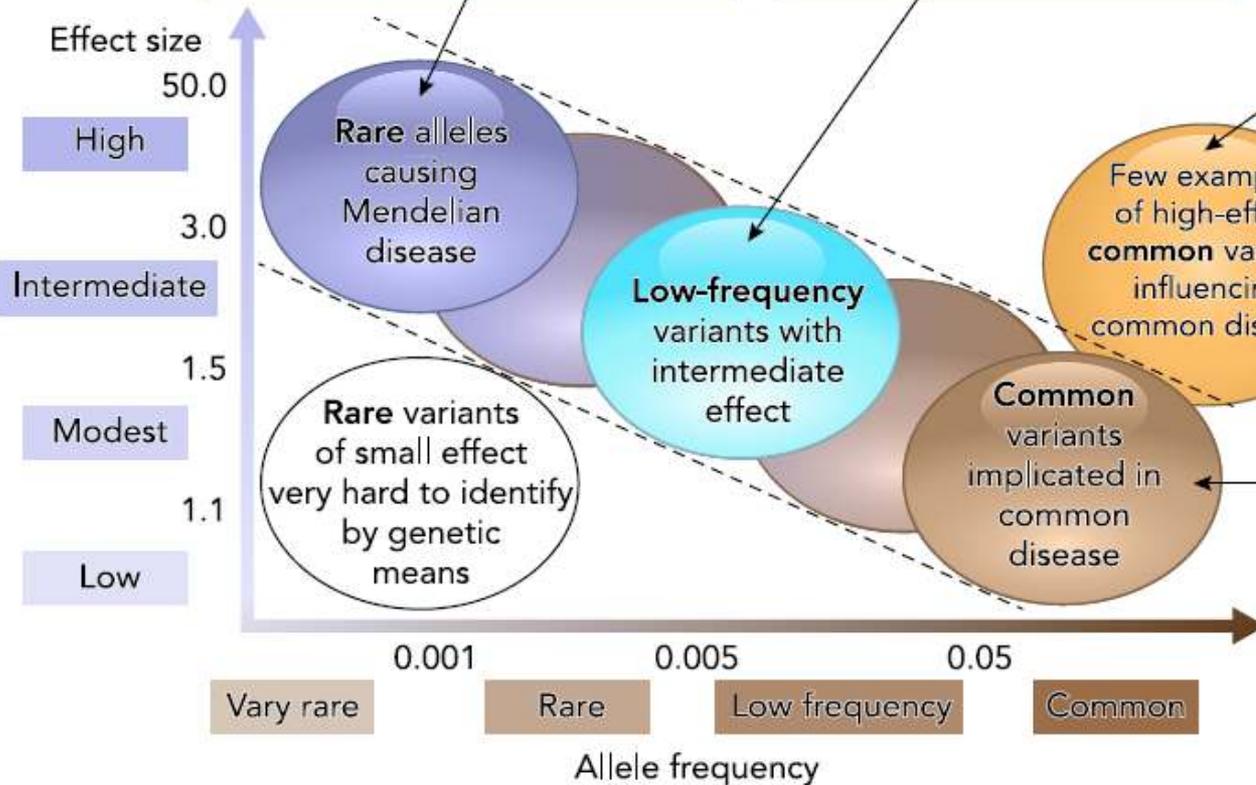


Les rares formes mendéliennes d'anomalies tensionnelles sont quasiment toutes liées à la balance sodée

Box A
 Rare alleles causing Mendelian forms of hypertension (salt-retaining)
Adrenal gland
CYP11B2, CYP11B1
CYP17, KCNJ5, CACNA1D
ASDN
HSD11B2, NR3C2, WNK1, WNK4, CUL3, KLHL3, SCNN1A, SCNN1B, SCCNN1C

Box B
 Low-frequency variants preventing hypertension (salt-losing)
ASDN
SLC12A3
SLC12A1
KCNJ1

Box D
 Common variant with high effect in favoring hypertension (salt-retaining)
ASDN
UMOD
 Heart (atrium)
CORIN

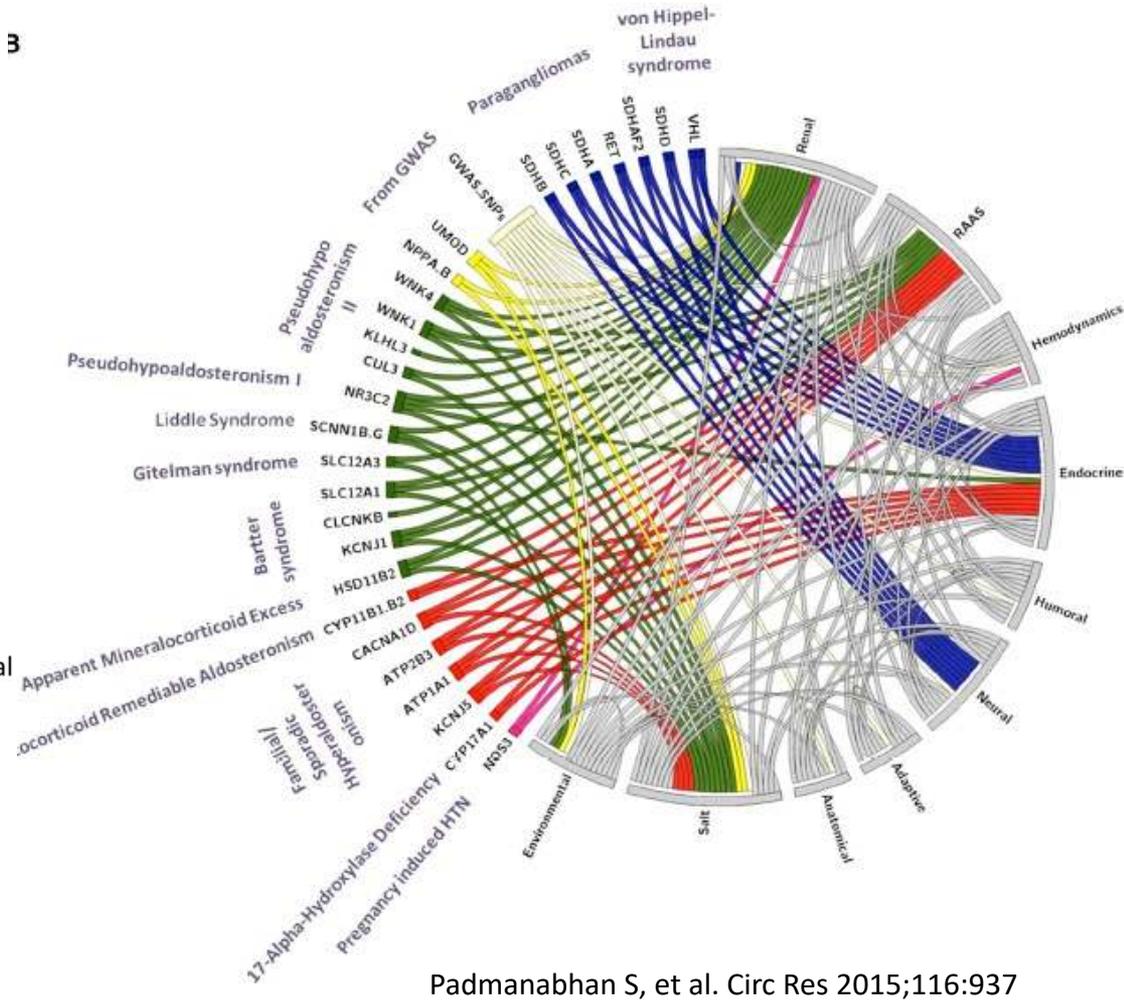
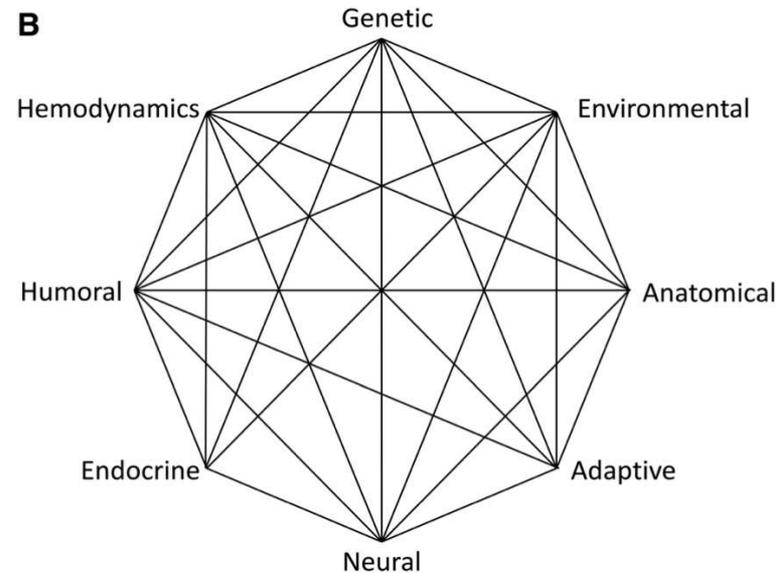
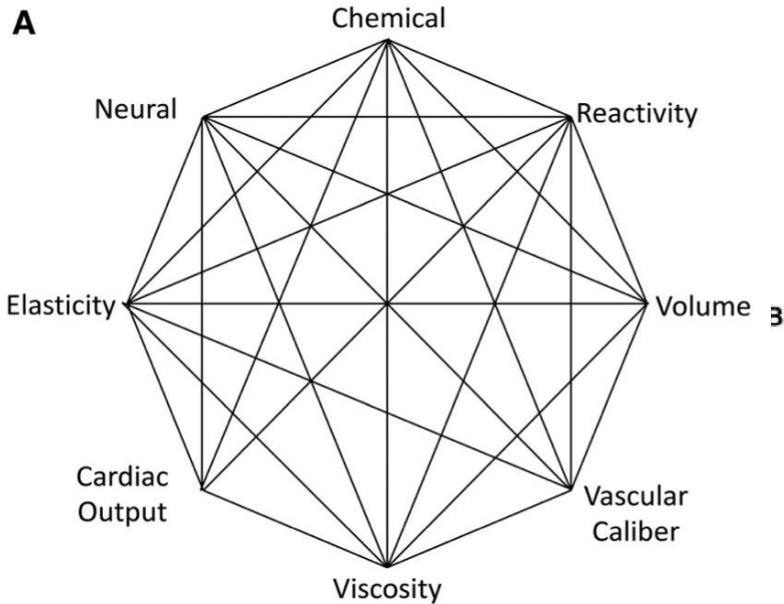


Box C
 Common variant with small effect implicated in hypertension by GWAS
Adrenal
CYP 17
CYP3A
Liver
AGT

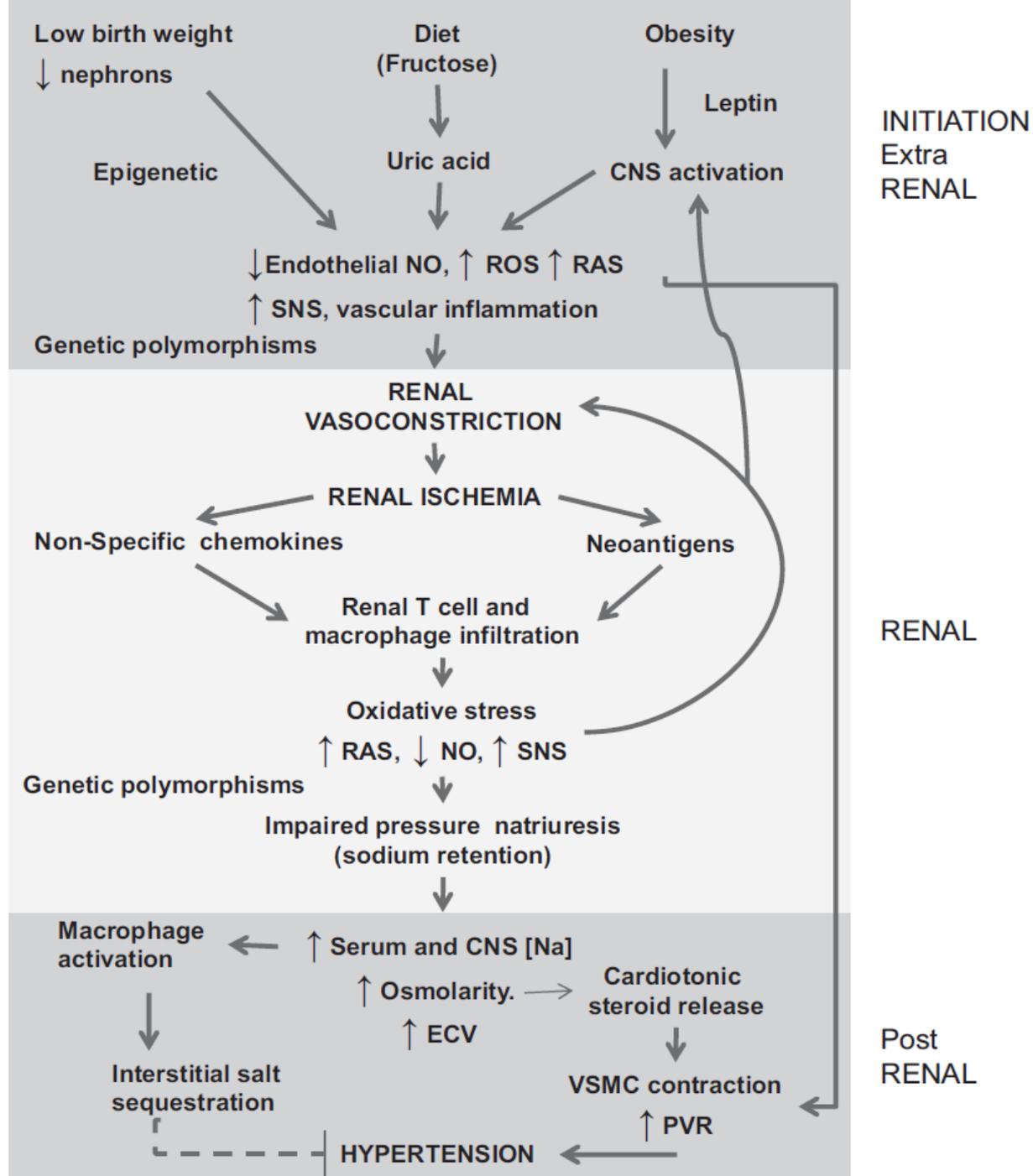
Genetics of hypertension: spectrum of allele frequency and effect size - Rossier 2017

La mosaïque des mécanismes impliqués dans l'hypertension artérielle

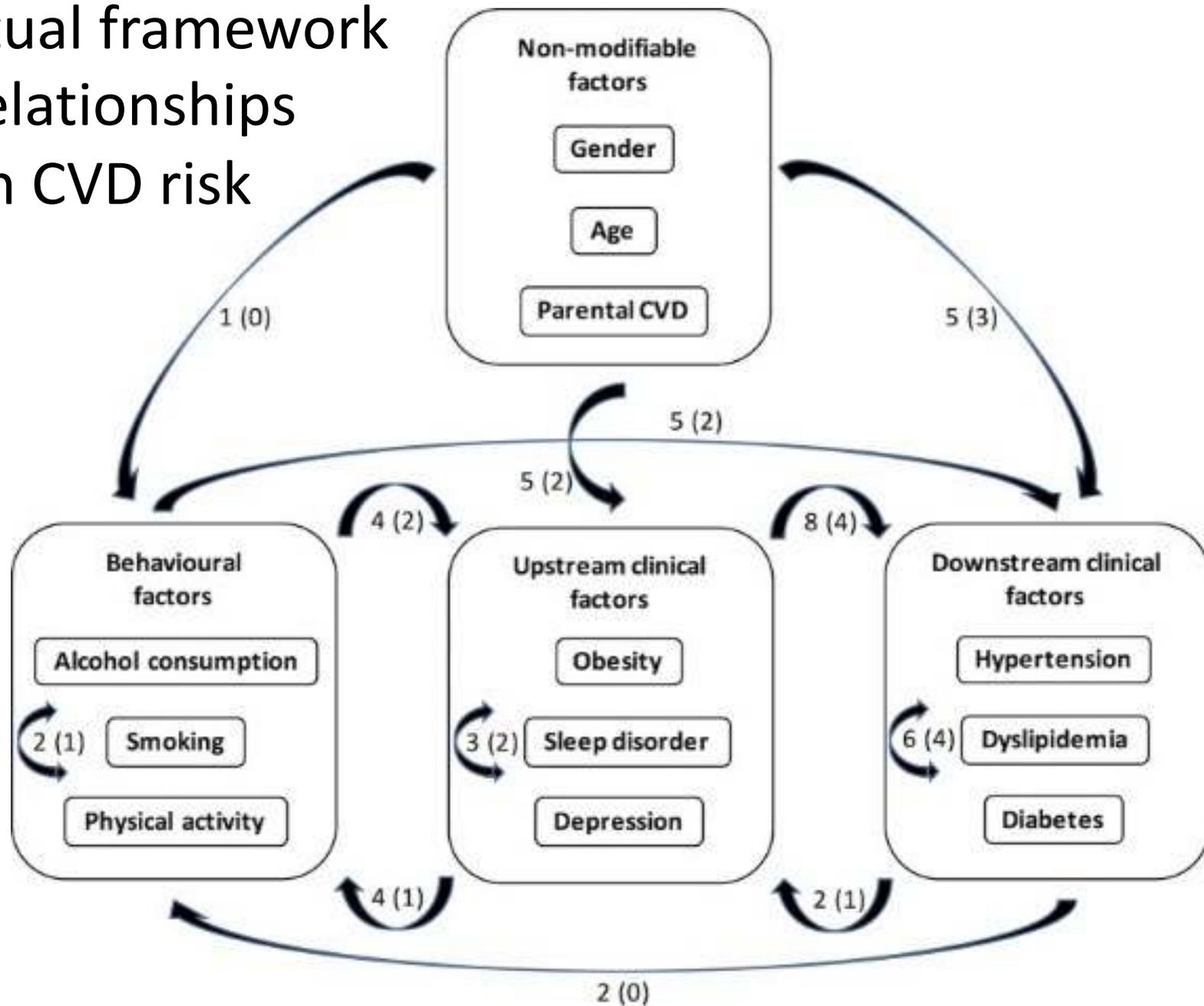
D'Irvine Page (1960) à une version 'actualisée' un demi-siècle plus tard



Une hypothèse sur les mécanismes de développement de l'hypertension artérielle 'essentielle'



Conceptual framework of the relationships between CVD risk factors



Maladie ou facteur de risque ? Définir l'hypertension artérielle

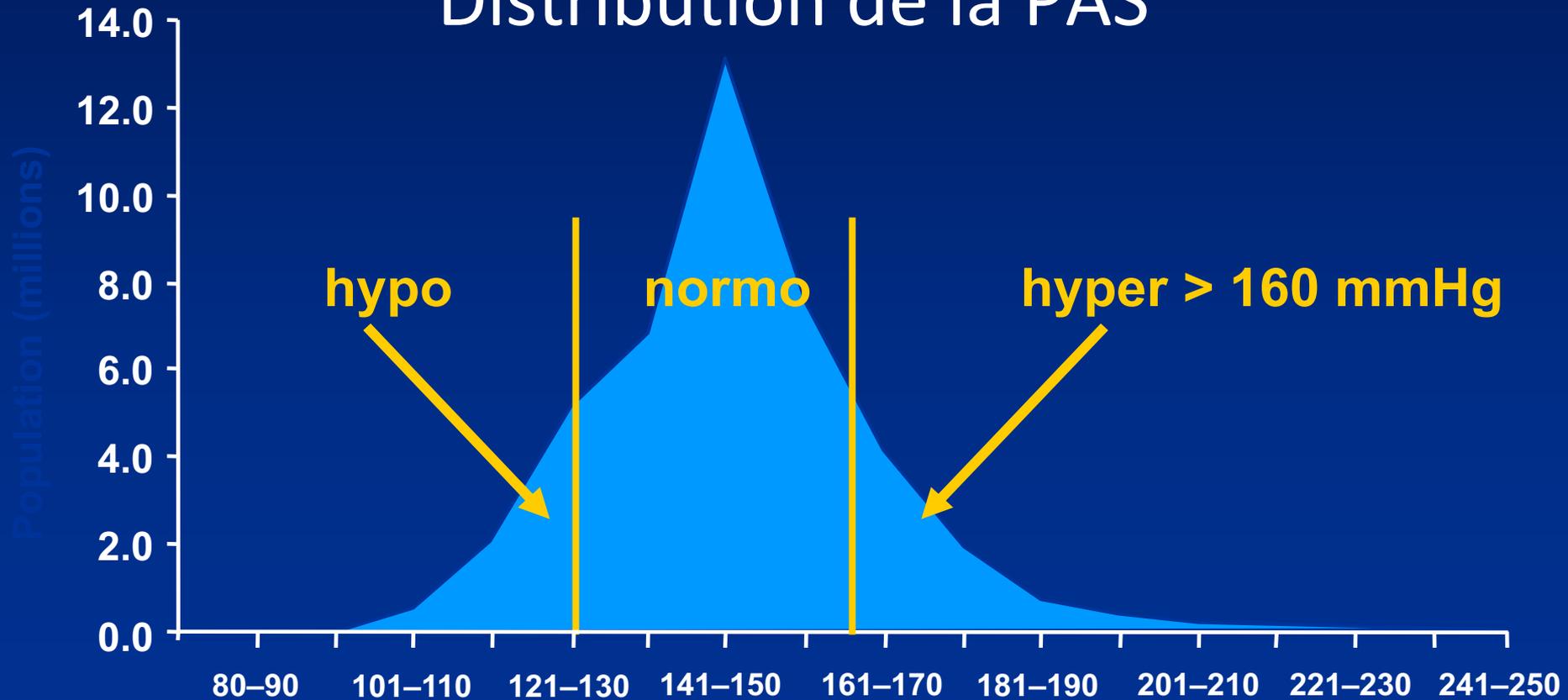
L'hypertension artérielle à l'échelle de la population

Les valeurs 'anormales' peuvent être définies par une approche

- ... statistique (distribution dans la population générale)
- ... descriptive (suivi de cohorte) ou
- ... pragmatique (démonstration d'un bénéfice thérapeutique)

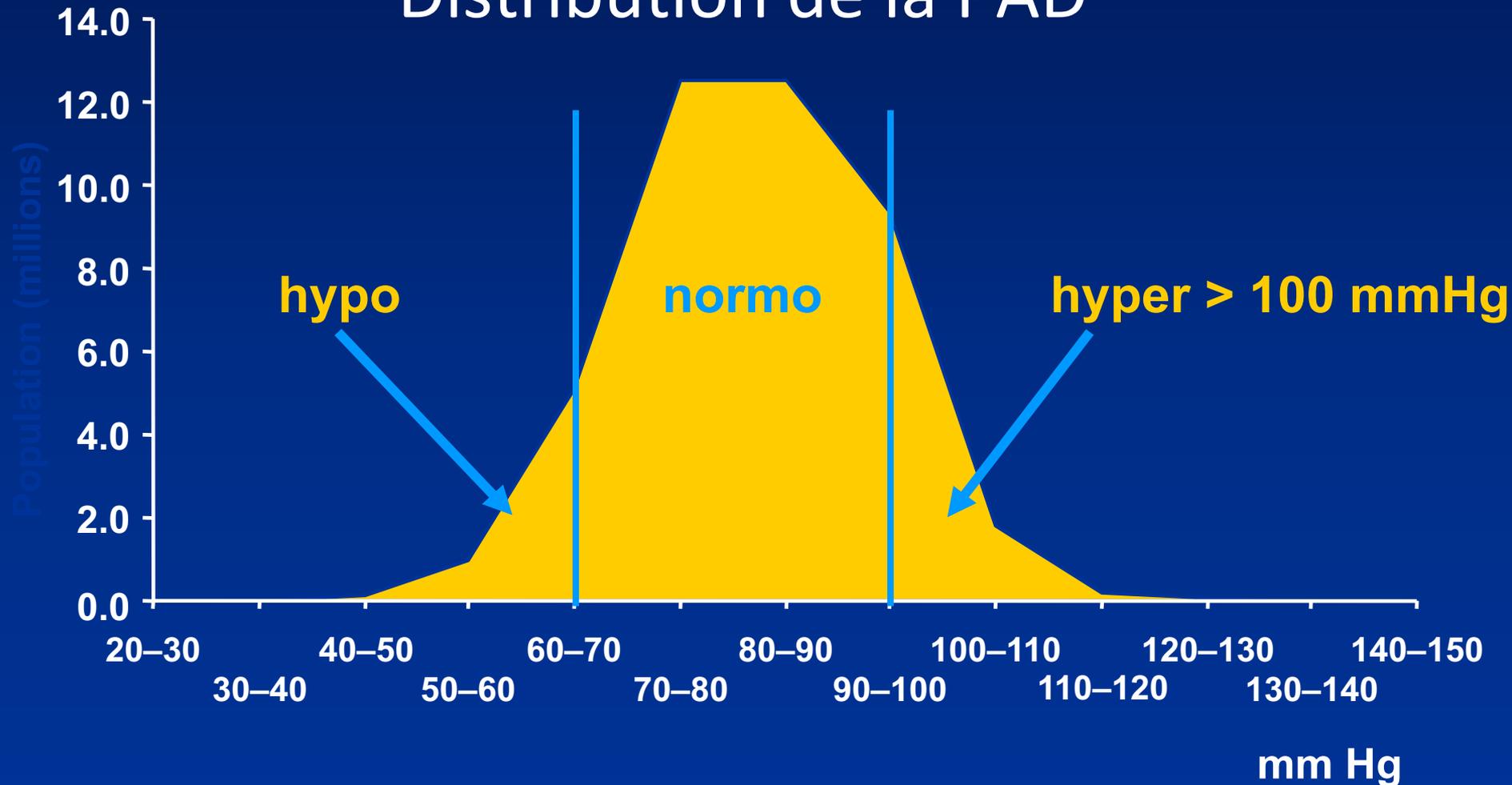
Comment définir l'hypertension ?

Distribution de la PAS



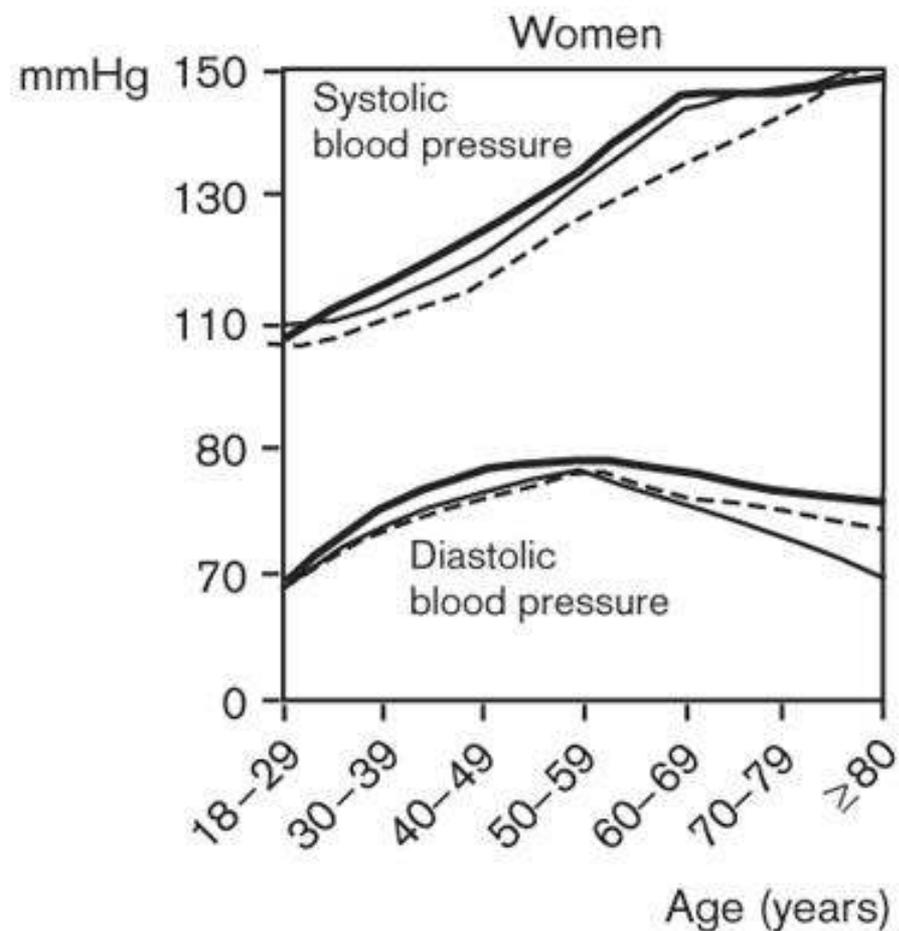
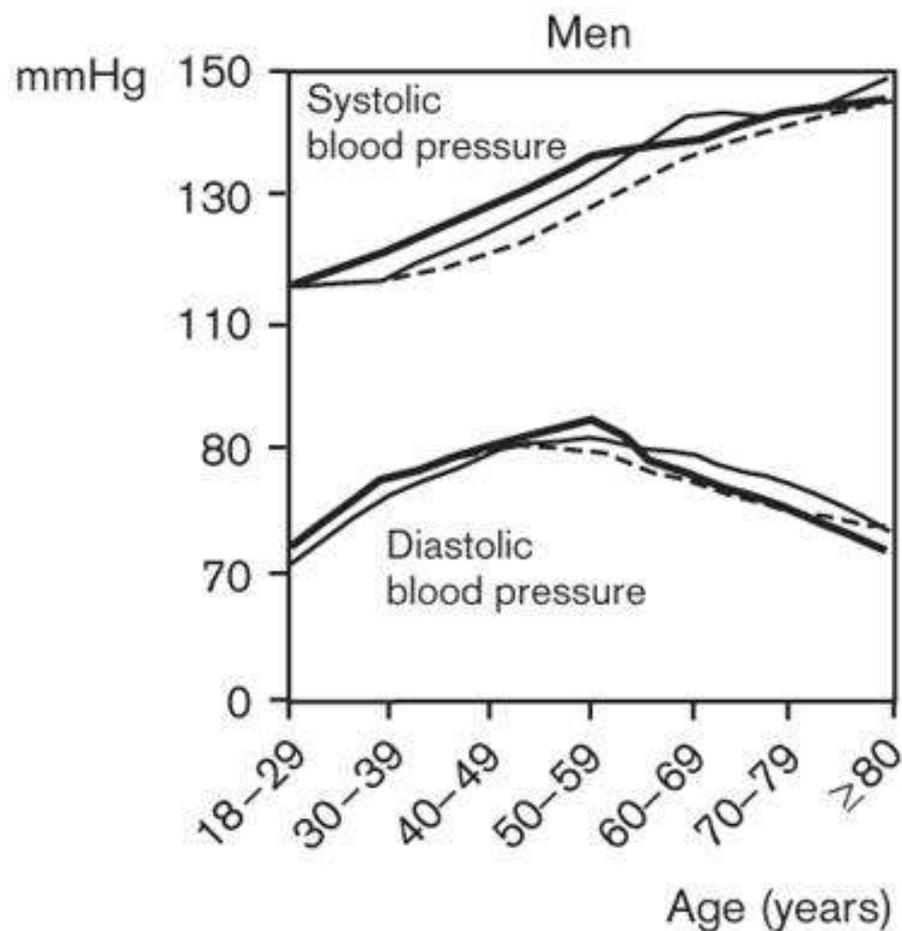
data : the National Health and Nutrition Examination Survey NHANES 1988-94 (USA)

Distribution de la PAD



data : the NHANES, National Health and Nutrition Examination Survey 1988-94 (USA)

PA systolique et diastolique moyenne (par age, ethnicite, et sexe) (d'après Burt et coll. NHANES)



- Non-Hispanic black
- - - Non-Hispanic white
- Mexican American

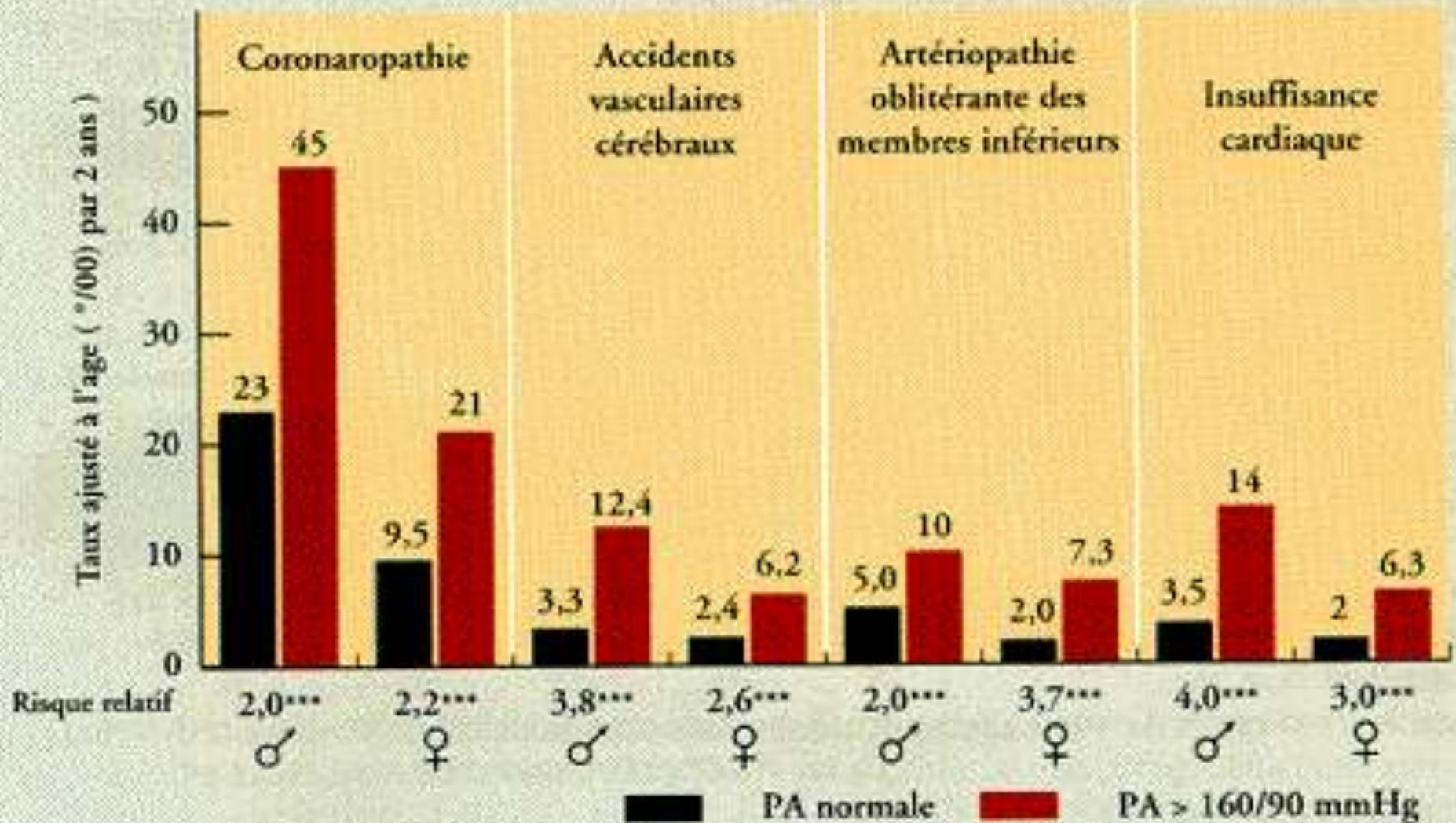
Framingham Heart Study



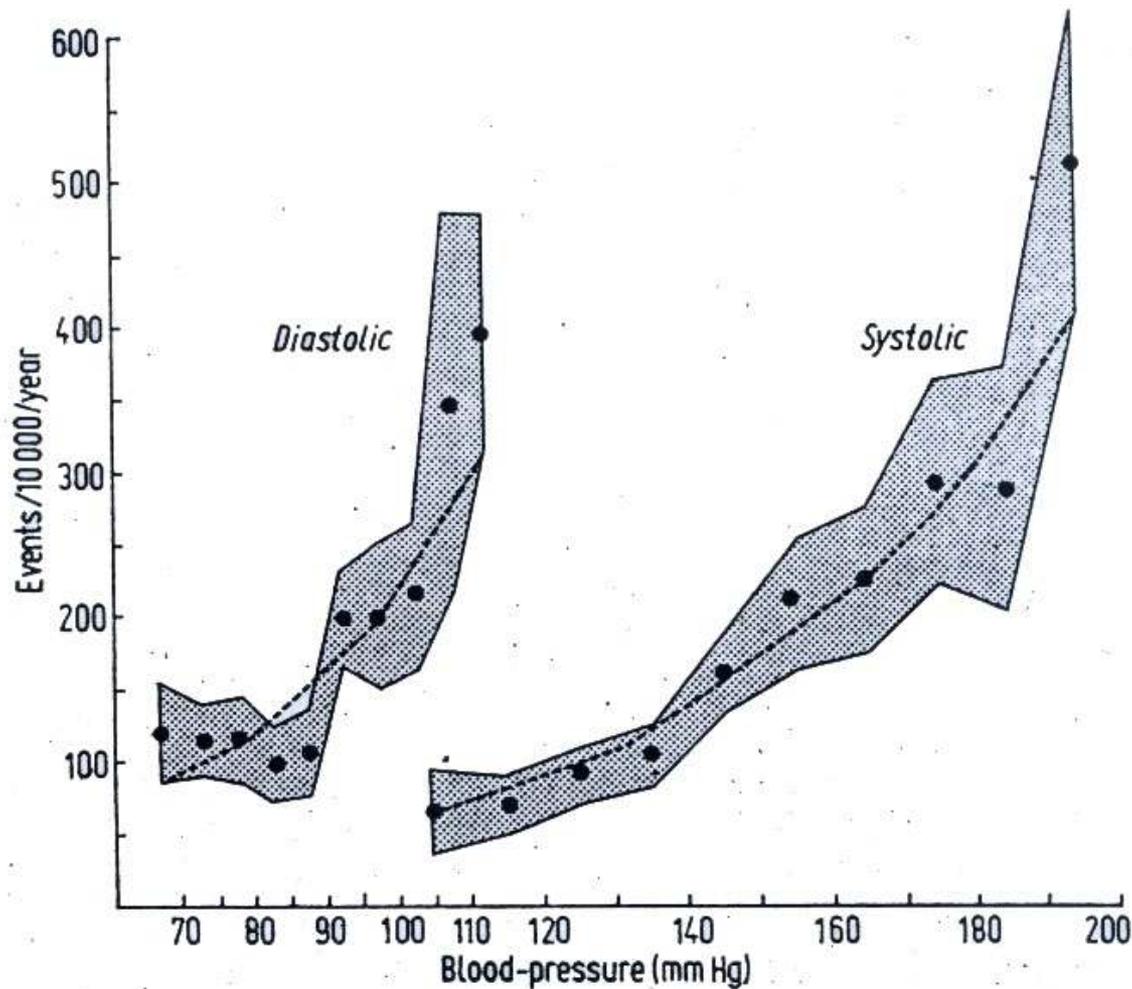
Massachusetts



L'enquête de Framingham montre que l'élévation tensionnelle comporte un risque



Risque de survenue d'évènements cardio-vasculaires dans l'étude de Framingham en fonction du niveau de pression artérielle (sujets âgés de 35 à 64 ans - suivi 36 ans)

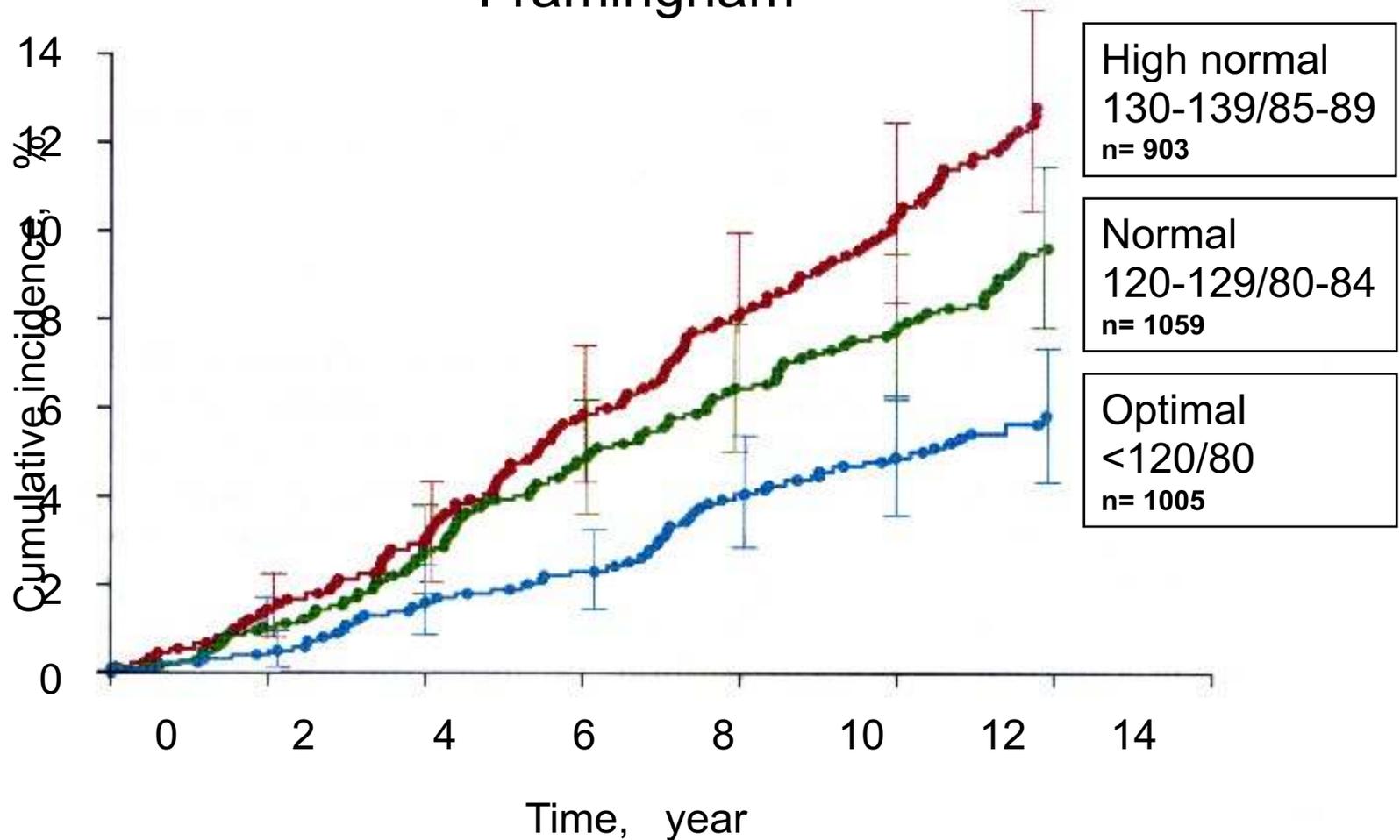


Risque absolu :
 probabilité de
 survenue d'un
 événement pendant
 un intervalle de
 temps défini, pour
 un individu aux
 caractères définis

FHS -Tension artérielle et atteinte coronaire

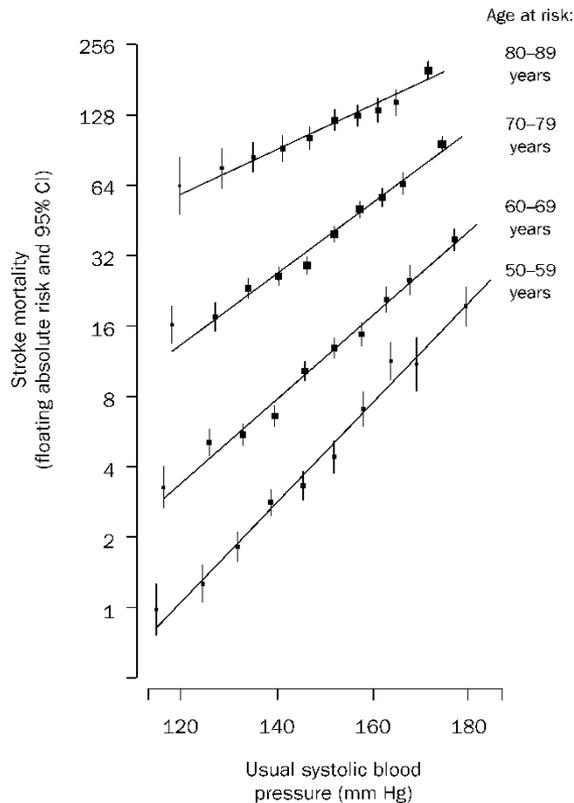
Incidence annuelle sur 18 ans

Cumulative incidence of cardiovascular events in men without hypertension. Framingham

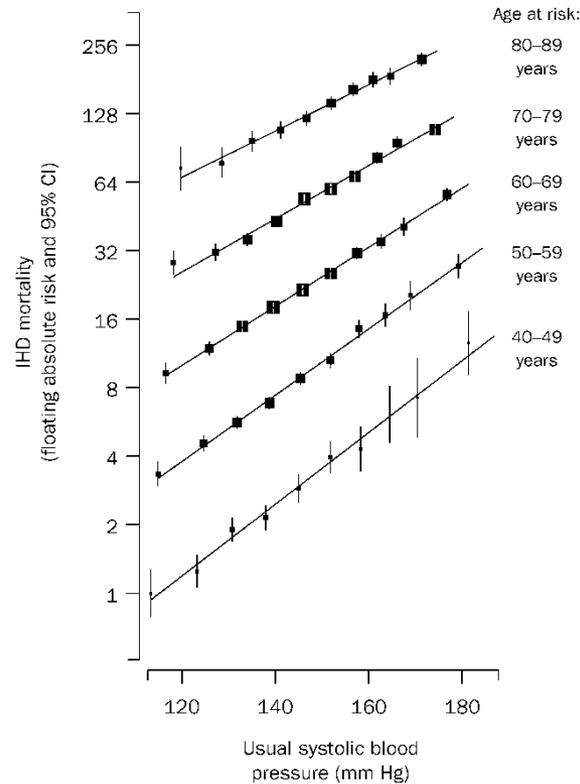


Mortalité vasculaire & pression artérielle (risque relatif)

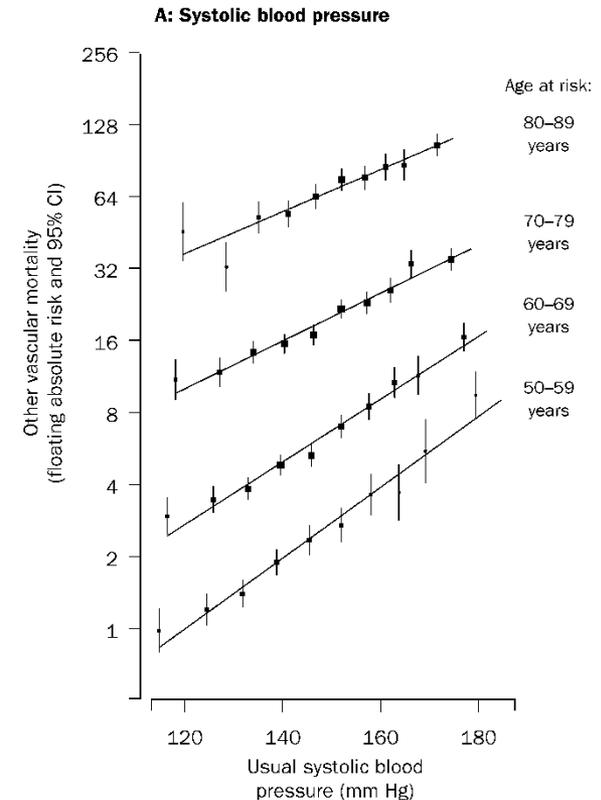
cérébrale



coronarienne



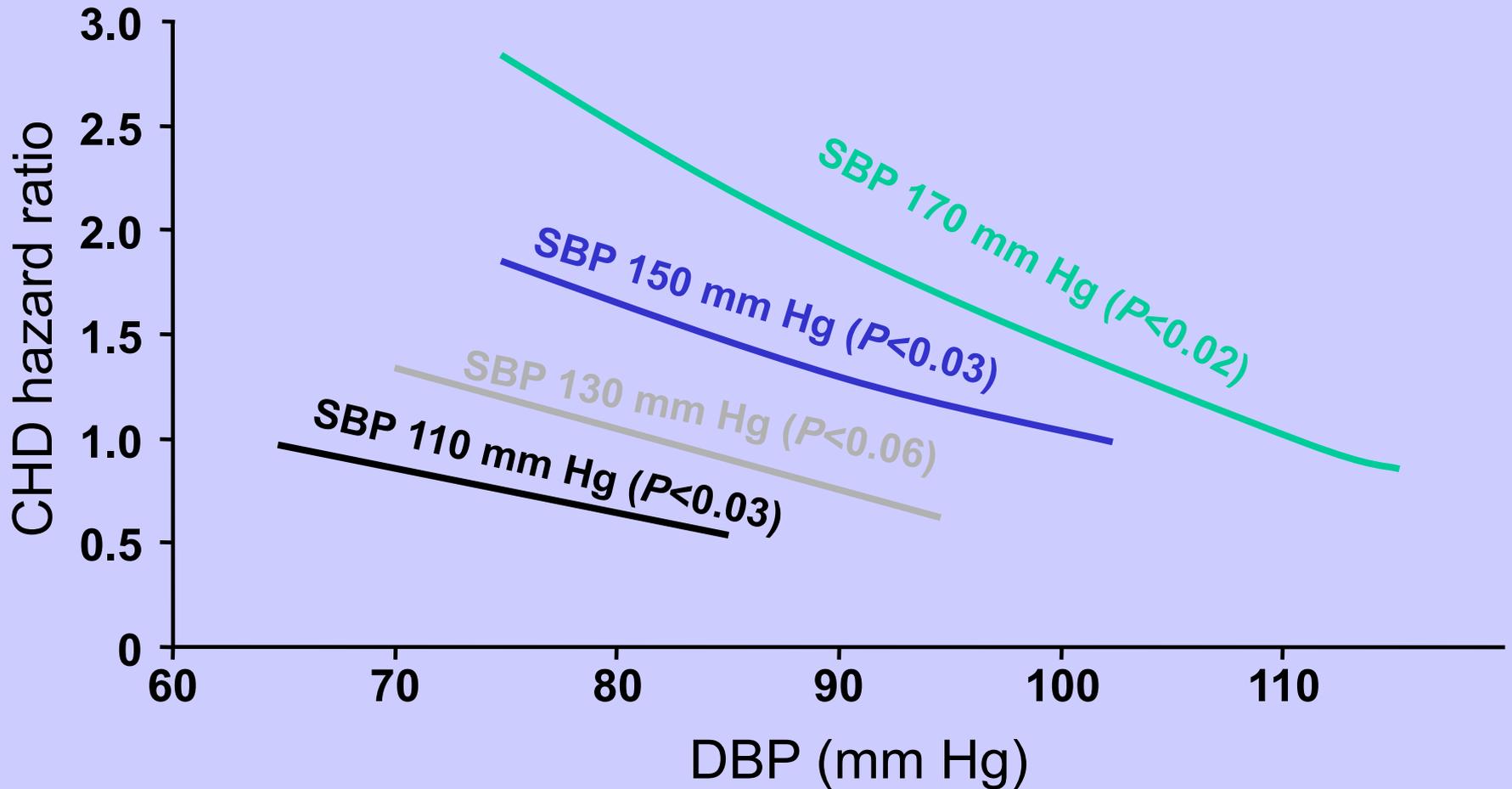
autre



L'élévation de la pression artérielle au-delà de 115/75 mmHg est associée à une augmentation significative et progressive du risque de mortalité vasculaire

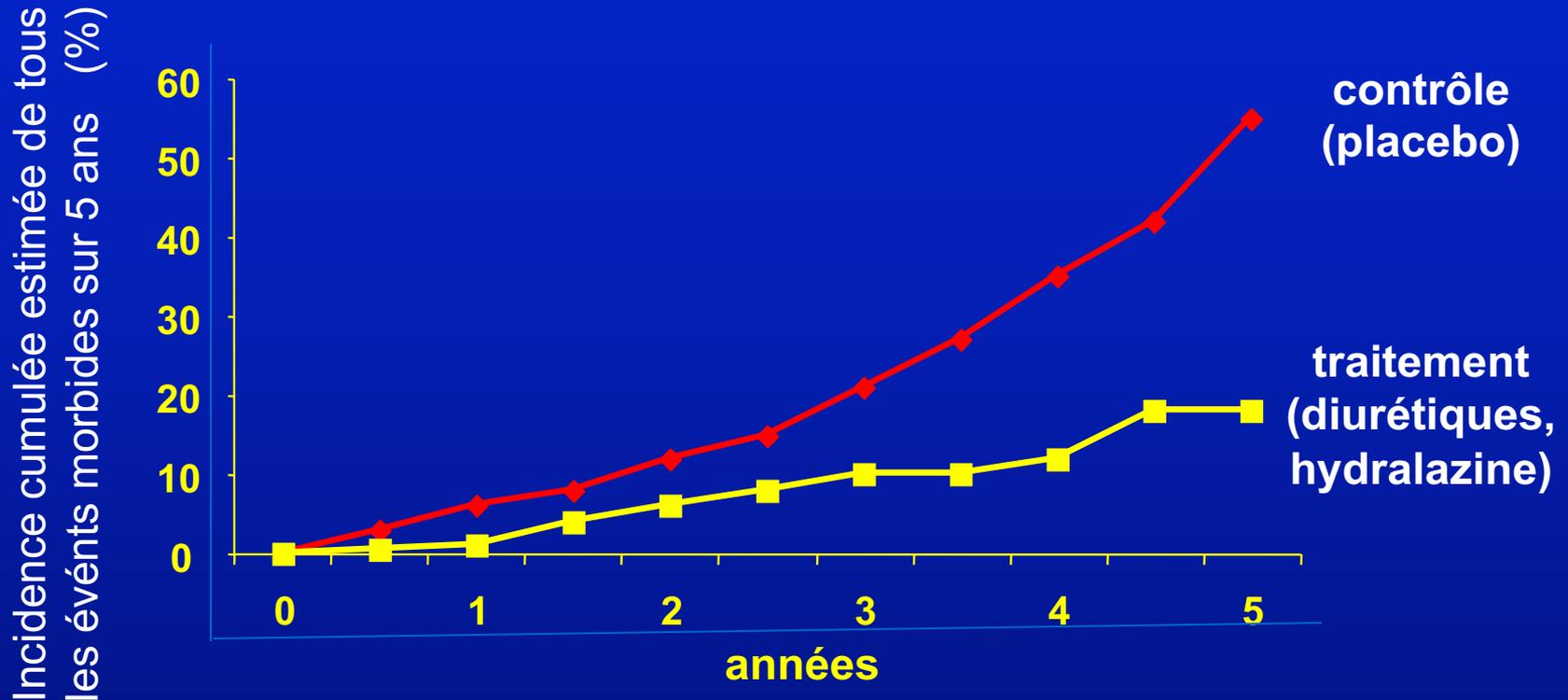
[le risque double entre 120/80 et 140/90]

Relations entre PAS / PAD et risque coronarien



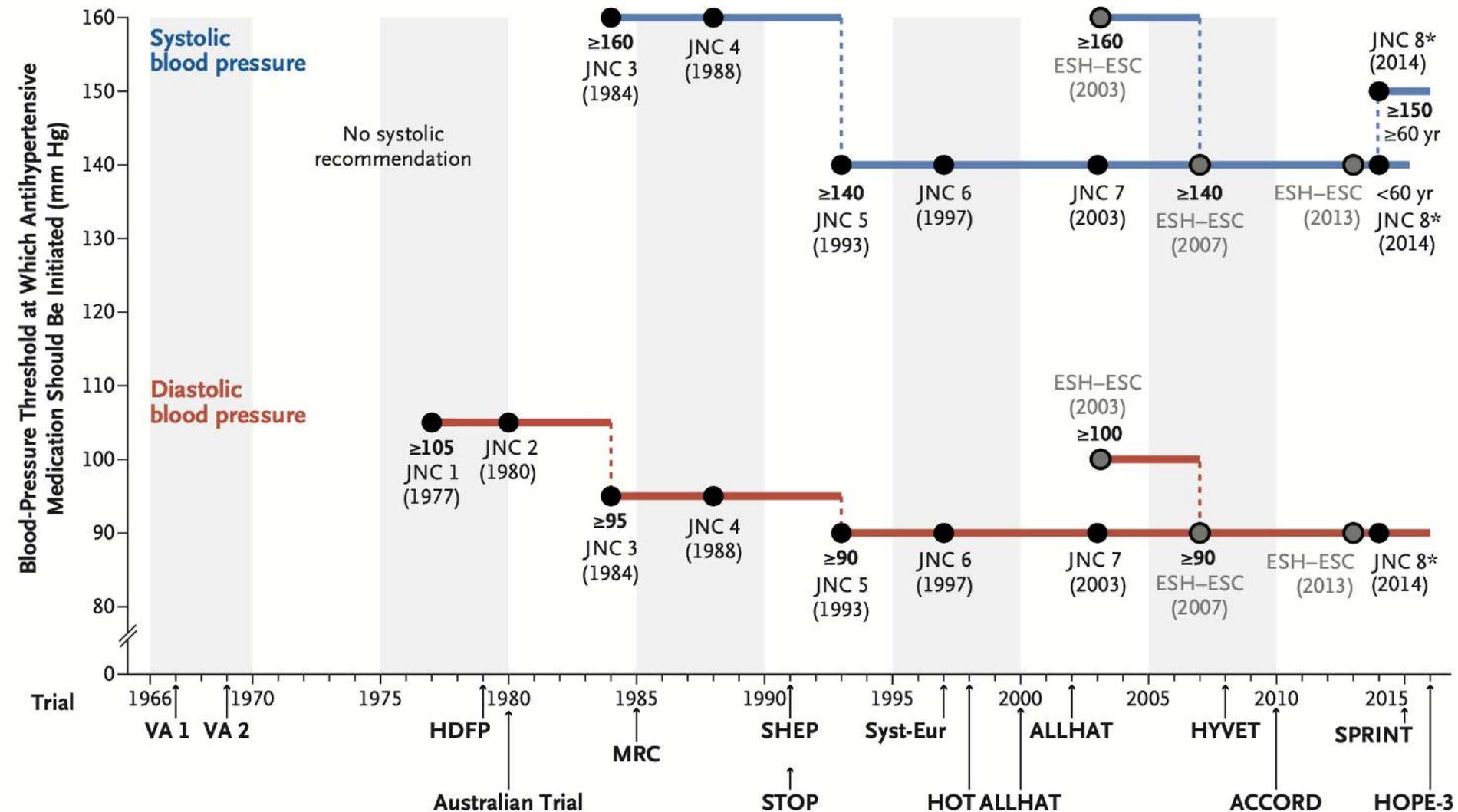
Framingham Heart Study. Franklin et al. Circulation 1999;100:354

Un essai contrôlé démontrera que le traitement antihypertenseur diminue la morbi-mortalité



Veterans Administration Cooperative Study Group on antihypertensive agents
JAMA 1970;213:1143-52

Jusqu'où baisser la tension artérielle ?

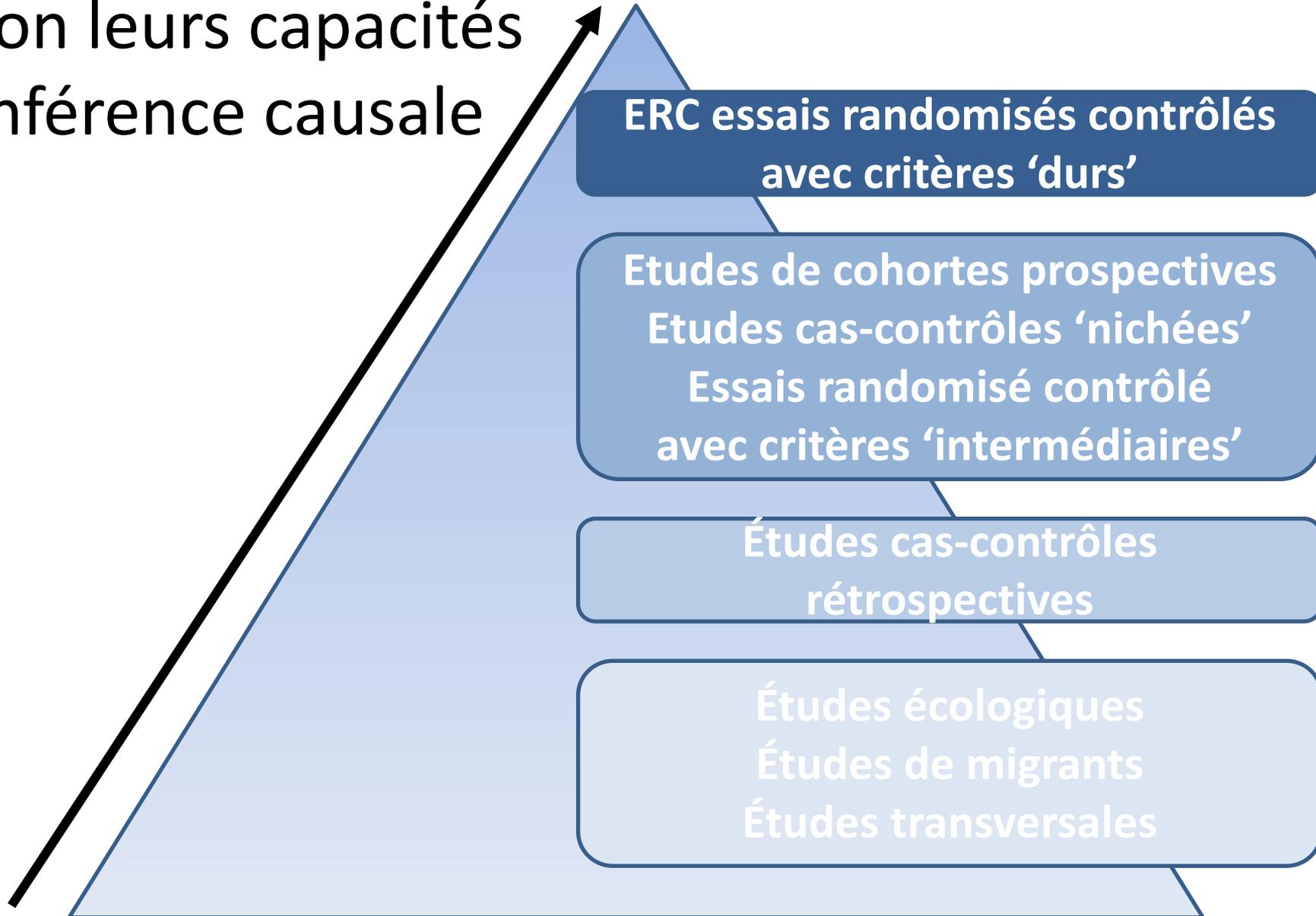


Lessons in uncertainty and humility. Clinical trials involving hypertension.
 Pfeffer MA, McMurray JJV. N Engl J Med 2016; 375:1756-66

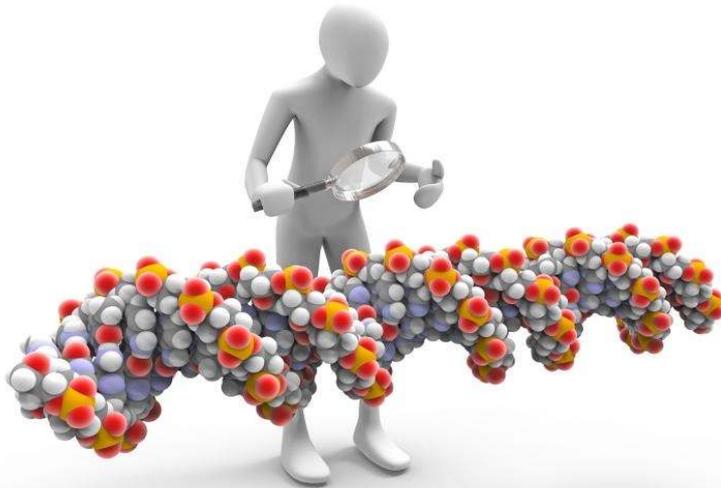
L'hypertension artérielle existe-t-elle ?

- La pression artérielle est une variable biologique distribuée selon une loi quasi normale
- Le diagnostic d'hypertension est basé sur un seuil arbitraire
- L'atteinte cardiovasculaire et rénale attribuée à l'hypertension artérielle est liée de façon continue et linéaire au niveau tensionnel
- La moitié de cette atteinte survient pour des niveaux tensionnels inférieur au seuil 'commun' définissant l'hypertension

Hiérarchie des types d'études selon leurs capacités d'inférence causale



New Blood Pressure–Associated Loci Identified in Meta-Analyses of 475 000 Individuals



Aldi T. Kraja, DSc, PhD; James P. Cook, PhD; Helen R. Warren, PhD; Praveen Surendran, PhD; Chunyu Liu, PhD; Evangelos Evangelou, PhD; Alisa K. Manning, PhD; Niels Grarup, MD, PhD; Fotios Drenos, PhD; Xueling Sim, PhD; Albert Vernon Smith, PhD; Najaf Amin, DSc, PhD; Alexandra I.F. Blakemore, PhD; Jette Bork-Jensen, PhD; Ivan Brandslund, MD; Aliki-Eleni Farmaki, PhD; Cristiano Fava, MD, PhD; Teresa Ferreira, PhD; Karl-Heinz Herzig, MD, PhD; Ayush Giri, PhD; Franco Giulianini, PhD; Megan L. Grove, MSc; Xiuqing Guo, PhD; Sarah E. Harris, PhD; Christian T. Have, PhD; Aki S. Havulinna, DSc; He Zhang, PhD; Marit E. Jørgensen, MD, PhD; AnneMari Käräjämäki, MD; Charles Kooperberg, PhD; Allan Linneberg, MD, PhD; Louis Little; Yongmei Liu, MD, PhD; Lori L. Bonnycastle, PhD; Yingchang Lu, MD, PhD; Reedik Mägi, PhD; Anubha Mahajan, PhD; Giovanni Malerba, PhD; Riccardo E. Marioni, PhD; Hao Mei, PhD; Cristina Menni, PhD; Alanna C. Morrison, PhD; Sandosh Padmanabhan, MD, PhD; Walter Palmas, MD; Alaitz Poveda, PhD; Rainer Rauramaa, MD, PhD; Nigel William Rayner, PhD; Muhammad Riaz, PhD; Ken Rice, PhD; Melissa A. Richard, PhD; Jennifer A. Smith, PhD; Lorraine Southam, MSc; Alena Stančáková, MD, PhD; Kathleen E. Stirrups, PhD; Vinicius Tragante, PhD; Tiinamaija Tuomi, MD, PhD; Ioanna Tzoulaki, PhD; Tibor V. Varga, PhD; Stefan Weiss, PhD; Andrianos M. Yiorkas, MSc; Robin Young, PhD; Weihua Zhang, PhD; Michael R. Barnes, PhD; Claudia P. Cabrera, PhD; He Gao, PhD; Michael Boehnke, PhD; Eric Boerwinkle, PhD; John C. Chambers, MD, PhD; John M. Connell, MD; Cramer K. Christensen, MD, DMSc; Rudolf A. de Boer, MD, PhD; Ian J. Deary, PhD; George Dedoussis, PhD; Panos Deloukas, PhD; Anna F. Dominiczak, MD, FRCP; Marcus Dörr, MD; Roby Joehanes, PhD; Todd L. Edwards, PhD; Tõnu Esko, PhD; Myriam Fornage, PhD; Nora Franceschini, MD; Paul W. Franks, PhD; Giovanni Gambaro, MD, PhD; Leif Groop, MD, PhD; Göran Hallmans, MD, PhD; Torben Hansen, MD, PhD; Caroline Hayward, PhD; Oksa Heikki, MD, PhD; Erik Ingelsson, MD, PhD; Jaakko Tuomilehto, MD, PhD; Marjo-Riitta Jarvelin, MD, PhD; Sharon L.R. Kardina, PhD; Fredrik Karpe, MD, PhD; Jaspal S. Kooner, MD; Timo A. Lakka, MD, PhD; Claudia Langenberg, MD, PhD; Lars Lind, MD, PhD; Ruth J.F. Loos, PhD; Markku Laakso, MD, PhD; Mark I. McCarthy, MD; Olle Melander, MD, PhD; Karen L. Mohlke, PhD; Andrew P. Morris, PhD; Colin N.A. Palmer, PhD; Oluf Pedersen, MD, DMSc; Ozren Polasek, MD, MPH, PhD; Neil R. Poulter, FMedSci; Michael A. Province, PhD; Bruce M. Psaty, MD, PhD; Paul M. Ridker, MD; Jerome I. Rotter, MD; Igor Rudan, PhD; Veikko Salomaa, MD, PhD; Nilesh J. Samani, MD; Peter J. Sever, MD; Tea Skaaby, MD, PhD; Jeanette M. Stafford, MSc; John M. Starr, PhD; Pim van der Harst, MD, PhD; Peter van der Meer, MD, PhD; The Understanding Society Scientific Group, Cornelia M. van Duijn, PhD; Anne-Claire Vergnaud, PhD; Vilmundur Gudnason, MD, PhD; Nicholas J. Wareham, MD, PhD; James G. Wilson, MD; Cristen J. Willer, PhD; Daniel R. Witte, PhD; Eleftheria Zeggini, PhD; Danish Saleheen, PhD; Adam S. Butterworth, PhD; John Danesh, PhD; Folkert W. Asselbergs, MD, PhD; Louise V. Wain, PhD; Georg B. Ehret, MD; Daniel I. Chasman, PhD; Mark J. Caulfield, MD; Paul Elliott, PhD; Cecilia M. Lindgren, PhD; Daniel Levy, MD; Christopher Newton-Cheh, MD*; Patricia B. Munroe, PhD*; Joanna M.M. Howson, PhD*; on behalf of the CHARGE EXOME BP, CHD Exome+, Exome BP, GoT2D:T2DGenes Consortia, The UK Biobank Cardio-Metabolic Traits Consortium Blood Pressure Working Group†

Received April 4, 2017; accepted August 17, 2017.

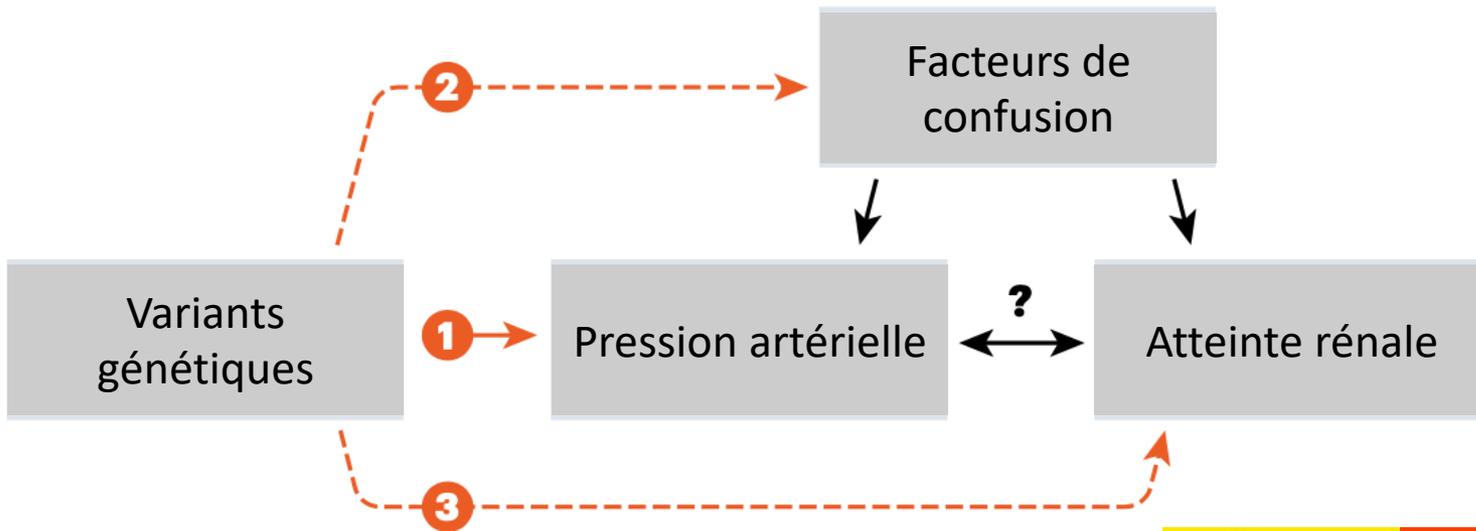
†A list of all study participants is given in the Data Supplement.

*Drs Newton-Cheh, Munroe, and Howson coauthors jointly supervised this project.

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Circ Cardiovasc Genet is available at <http://circgenetics.ahajournals.org>

DOI: 10.1161/CIRCGENETICS.117.001778



Staplin N, et al. Hypertension 2022;79:2671-81

Yu Z, et al. Kidney Int 2020;98:708-16

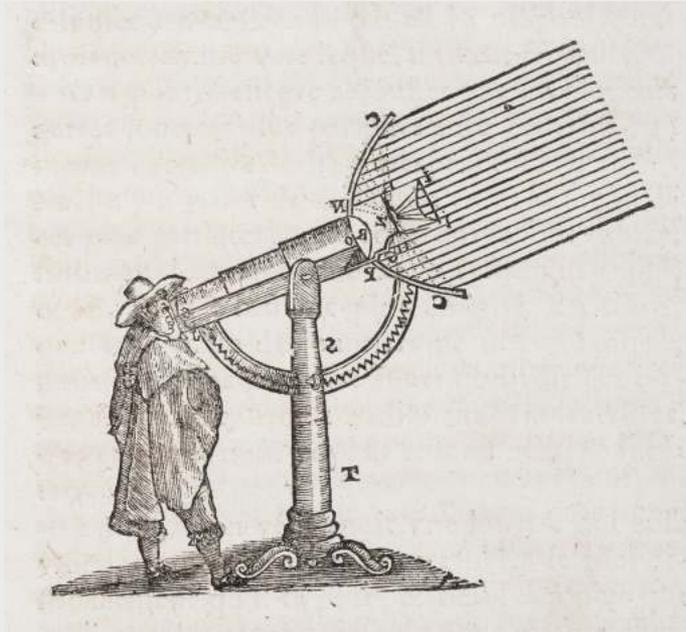
Haas ME, et al. Am J Hum Genet. 2018;103:461-73

Randomisation mendelienne

Trois présupposés

1. pertinence
2. indépendance
3. exclusion restriction

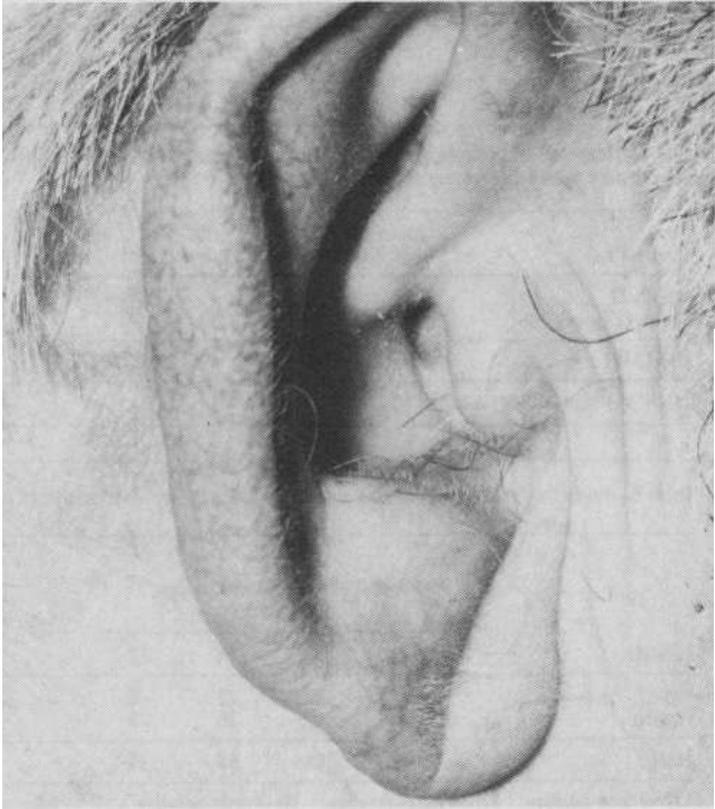




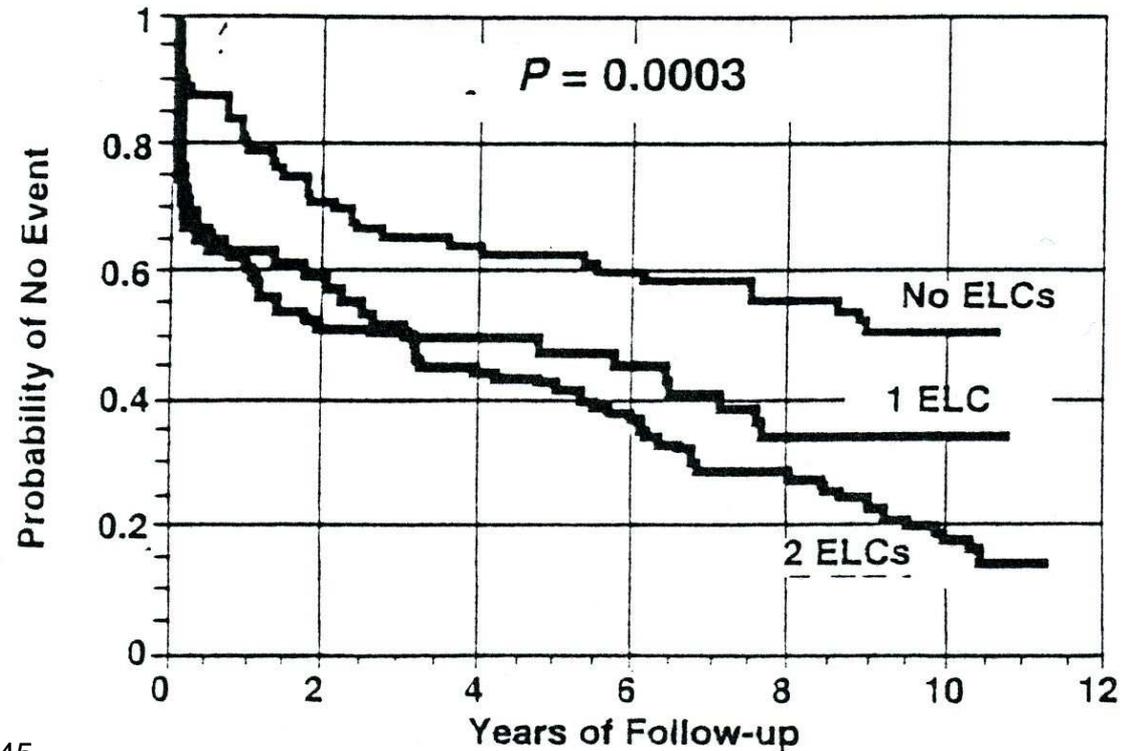
Estimer la probabilité de survenue d'événements

Les scores de risque

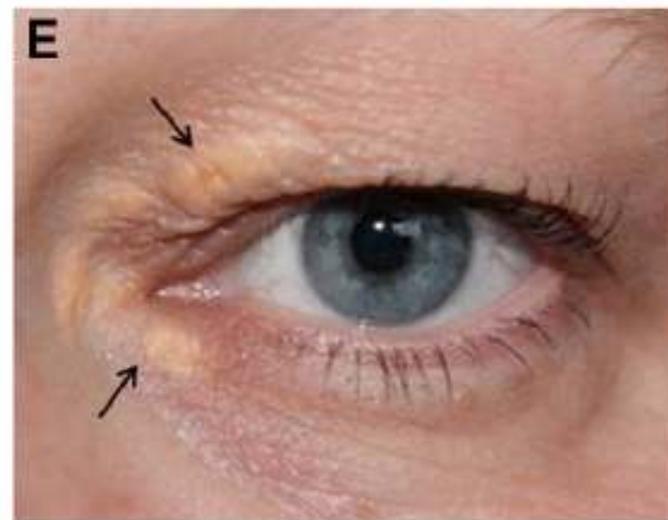
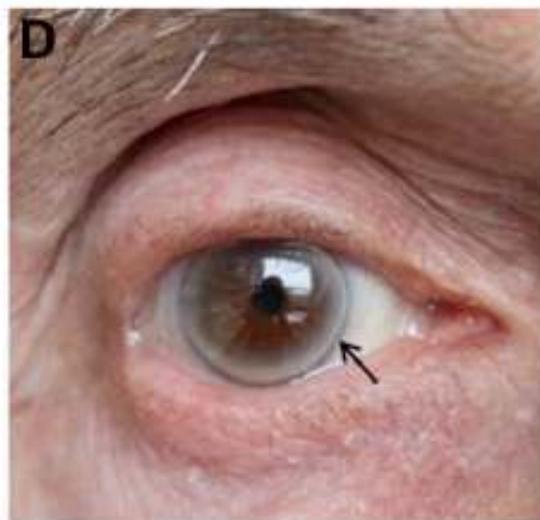
Des signes cliniques ?



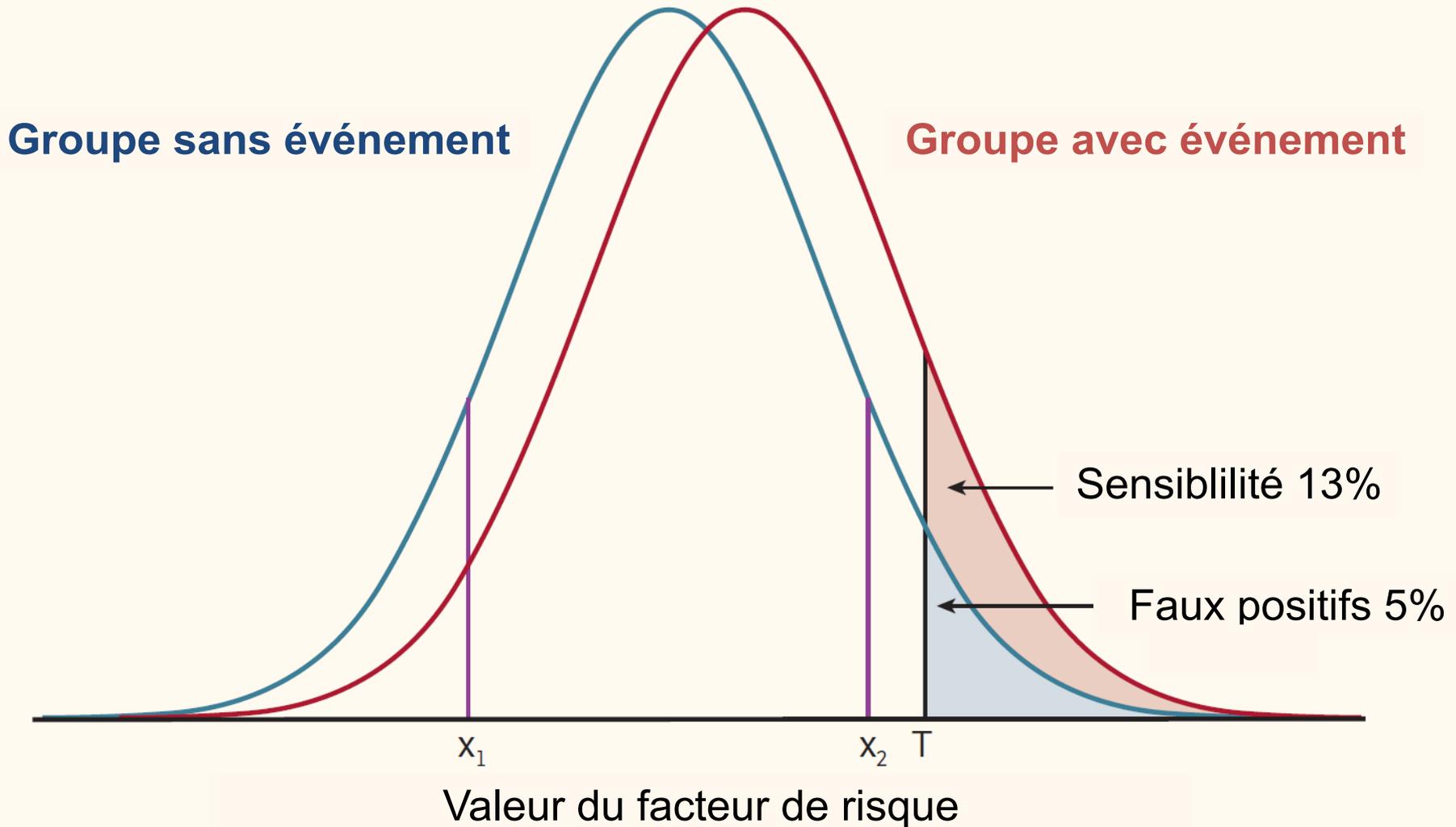
The ear-crease sign in coronary artery disease



Visible age-related signs and risk of ischemic heart disease in the general population:

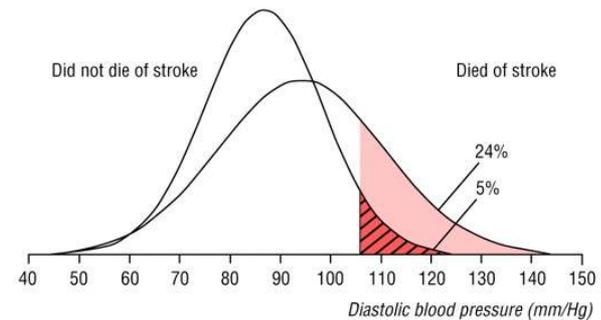
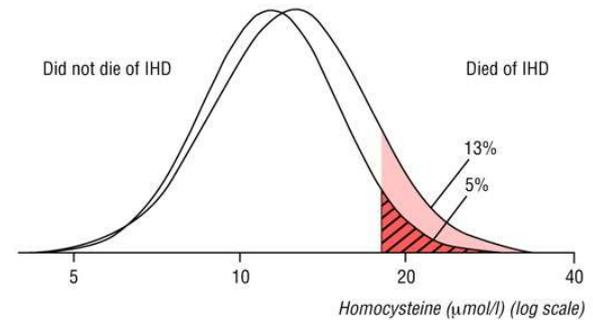
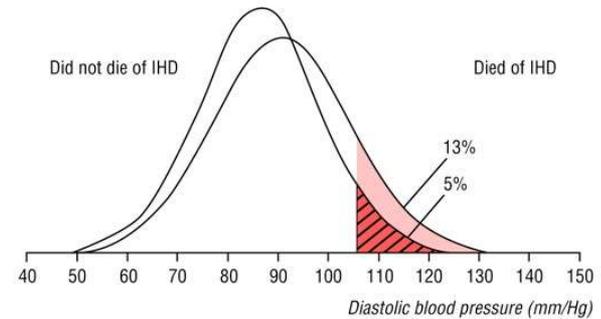
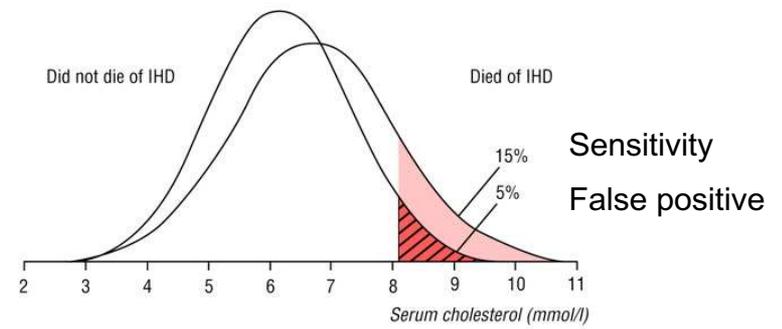


Fonctions de densités de probabilité d'un facteur de risque parmi des sujets chez qui surviendra (ou non) l'événement

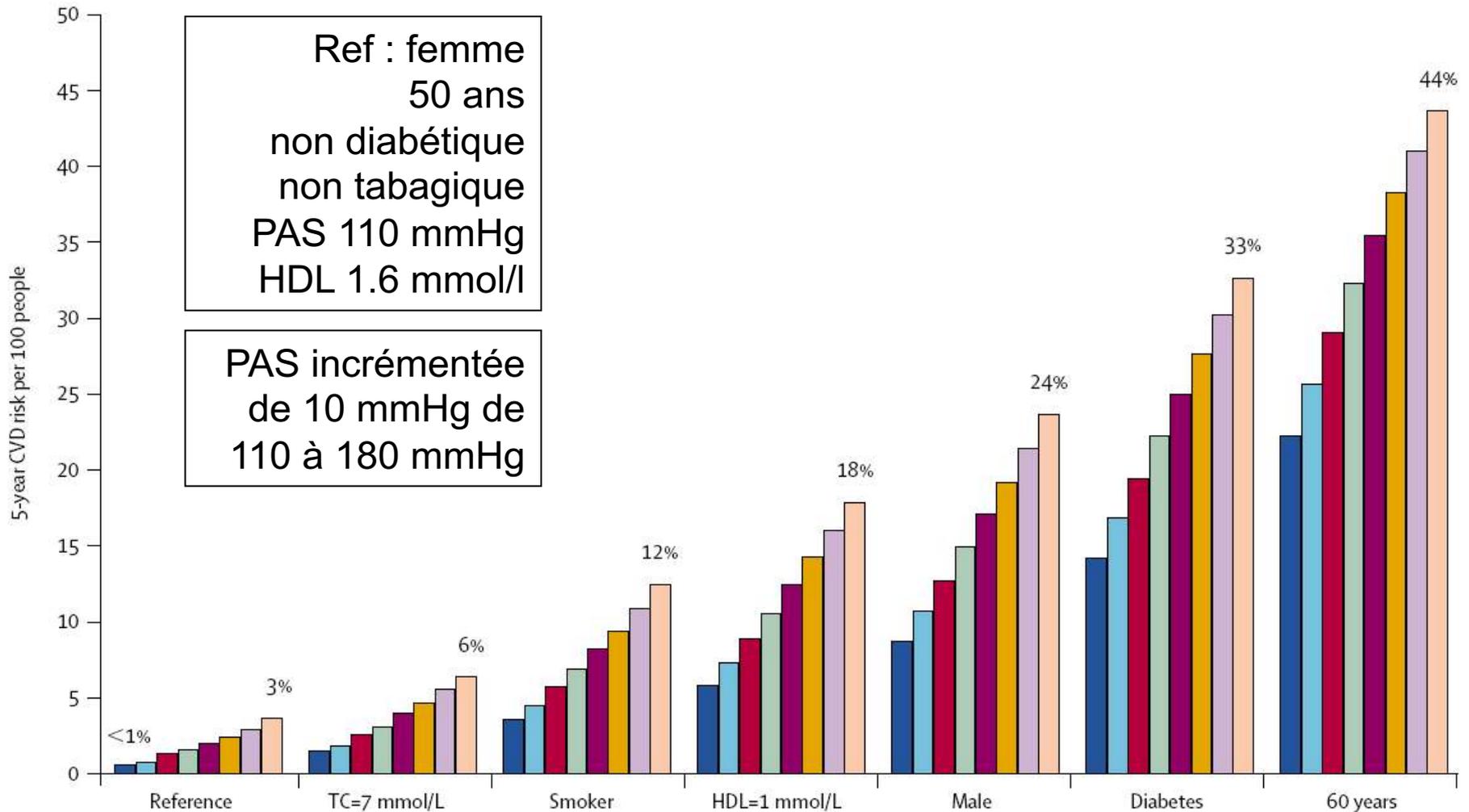


Relative distributions of risk factors in men who subsequently died (or not) of IHD or stroke

Gaussian distribution fitted to data from a cohort of 22 000 men followed prospectively for 10 years (the BUPA study)



Risque cardiovasculaire absolu à 5 ans par PAS à niveaux spécifiés des autres facteurs de risque



Population d'étude & événements

L'échantillonnage doit être identifié et suffisant

- population générale : Framingham, ASSIGN, SCORE (Systematic COronary Risk Evaluation)
- employés (mâles) de l'industrie : PROCAM (Prospective Cardiovascular Münster)
- clientèle de médecine générale : QRISK

Le critère final doit être standardisé et pertinent

- (coronarien ou global)

Méthodes de modélisation

La dérivation de la fonction d'estimation la plus utilisée est un modèle de risque proportionnel,

- paramétrique (Weibull) ou
- semiparamétrique (Cox)
- de préférence à une régression logistique

Une validation externe est nécessaire

- généralement supérieure chez le femme et moindre chez le sujet âgé

Evaluation d'un score

Méthodologie de constitution

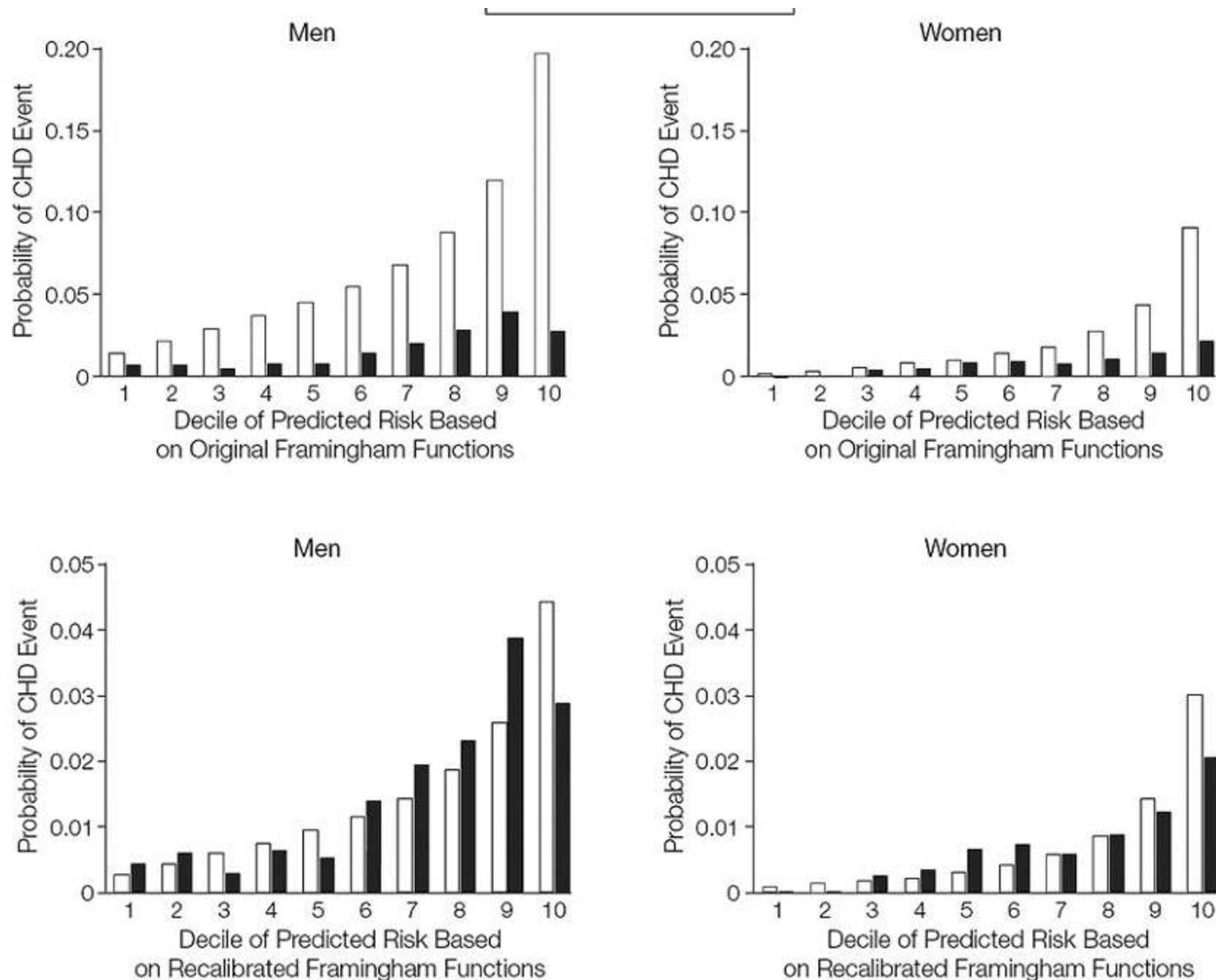
Performance de la fonction (validité int / ext)

- discrimination (sensibilité, spécificité, valeurs prédictives/AUROC, Harrell's C statistic)
- calibration (Hosmer-Lemeshow goodness of fit)
- classification

Inclusion des facteurs appropriés

'Usabilité' et 'utilité ('efficacité mesurable')

Improved Calibration of Framingham Function in Chinese Cohort After Recalibration



Quels éléments inclure ?

- Age * et Sexe : non modifiables (sic)
- Tabagisme
- Cholestérolémie
- Pression artérielle (quel marqueur ?)
- HDL-C (ou autre marqueur lipidique), HbA1c, hsCRP, ...
- atteinte d'un 'organe-cible' (de l'hypertension), CAC (ou autre marqueur d'athérosclérose), ...

* de fait plutôt un substitut de la durée d'exposition à tous les facteurs de risque

Évaluation pré-clinique de la maladie cardiovasculaire

Quantification fonctionnelle, mécanique, structurelle par techniques d'imagerie non invasive

- artery intima-media thickness (IMT = EIM),
- pulse-wave velocity and analysis (PWV = VOP),
- brachial artery flow-mediated dilatation (FMD),
- left ventricular geometry (LVM = MVG),
- coronary artery calcification (CAC).

Stratégie vis-à-vis d'une population asymptomatique à risque

Score de risque

Faible <6%

Intermédiaire : zone grise

Haut $\geq 20\%$

Histoire familiale

Test athérosclérose

Diabète sucré ...

optionnel

Reclassification

Risque faible

Risque intermédiaire

Risque élevé

Reclassification With CIMT Added to Framingham Risk Score

Without events

		Framingham Risk With CIMT		
		<5%	5%-20%	>20%
Framingham Risk	<5%	20271 →	867	-
	5-20%	1115	← 17280 →	362
	>20%		315	← 1611

Total without events, No. (%)

39162 (93.6)	No change
1229 (2.9%)	Up classification
1430 (3.4%)	Down classification

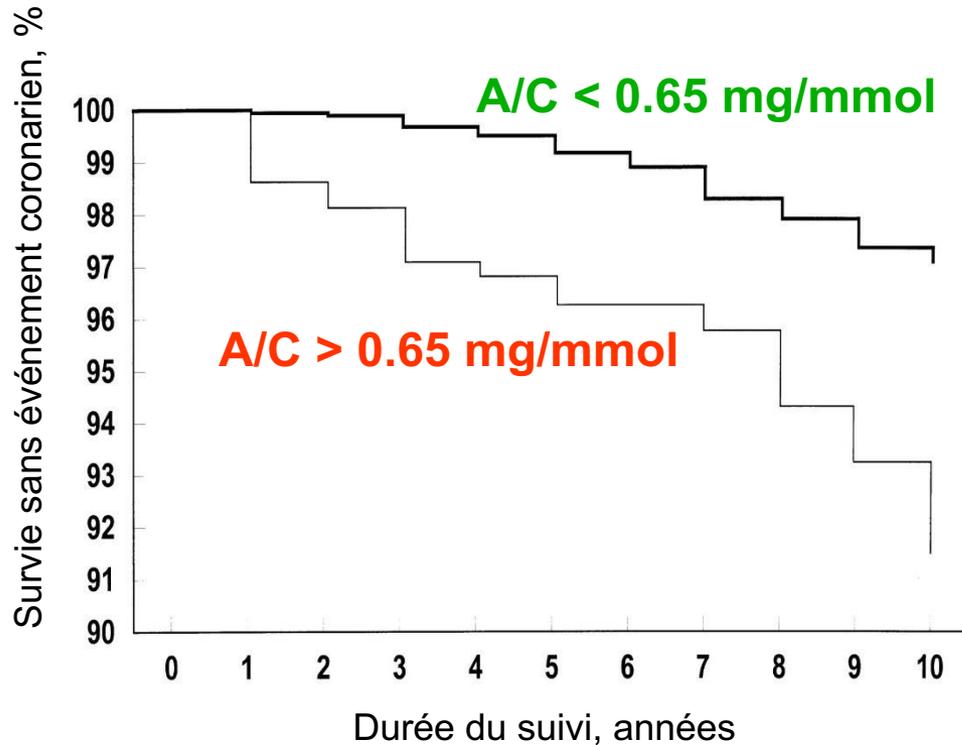
With events

		Framingham Risk With CIMT		
		<5%	5%-20%	>20%
Framingham Risk	<5%	537 →	67	-
	5-20%	69	← 2410 →	102
	>20%		85	← 737

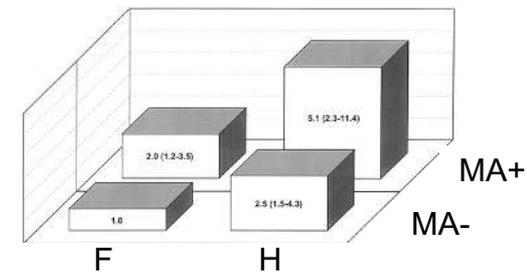
Total with events, No. (%)

3684 (91.9%)	No change
169 (4.2%)	Up classification
154 (3.8%)	Down classification

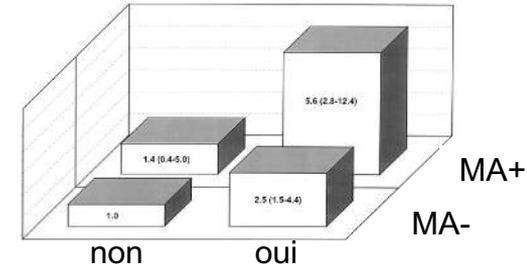
La microalbuminurie est un prédicteur du risque cardiovasculaire dans la population générale



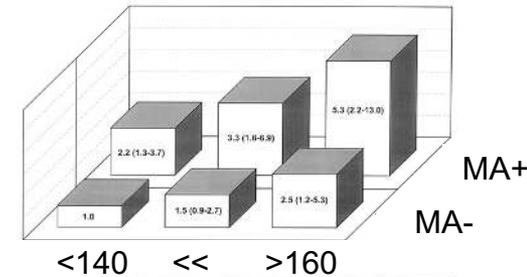
genre



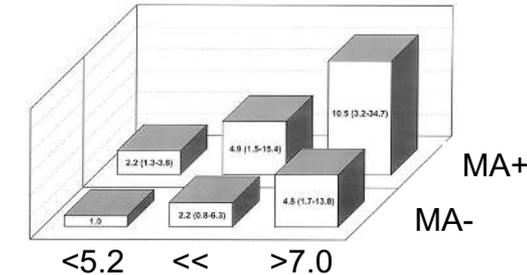
tabac



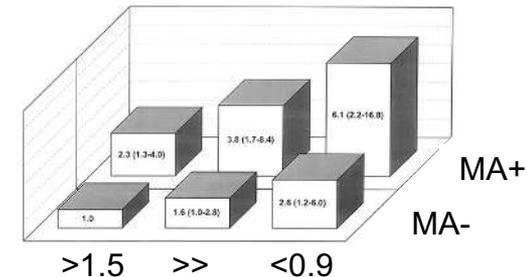
PAS



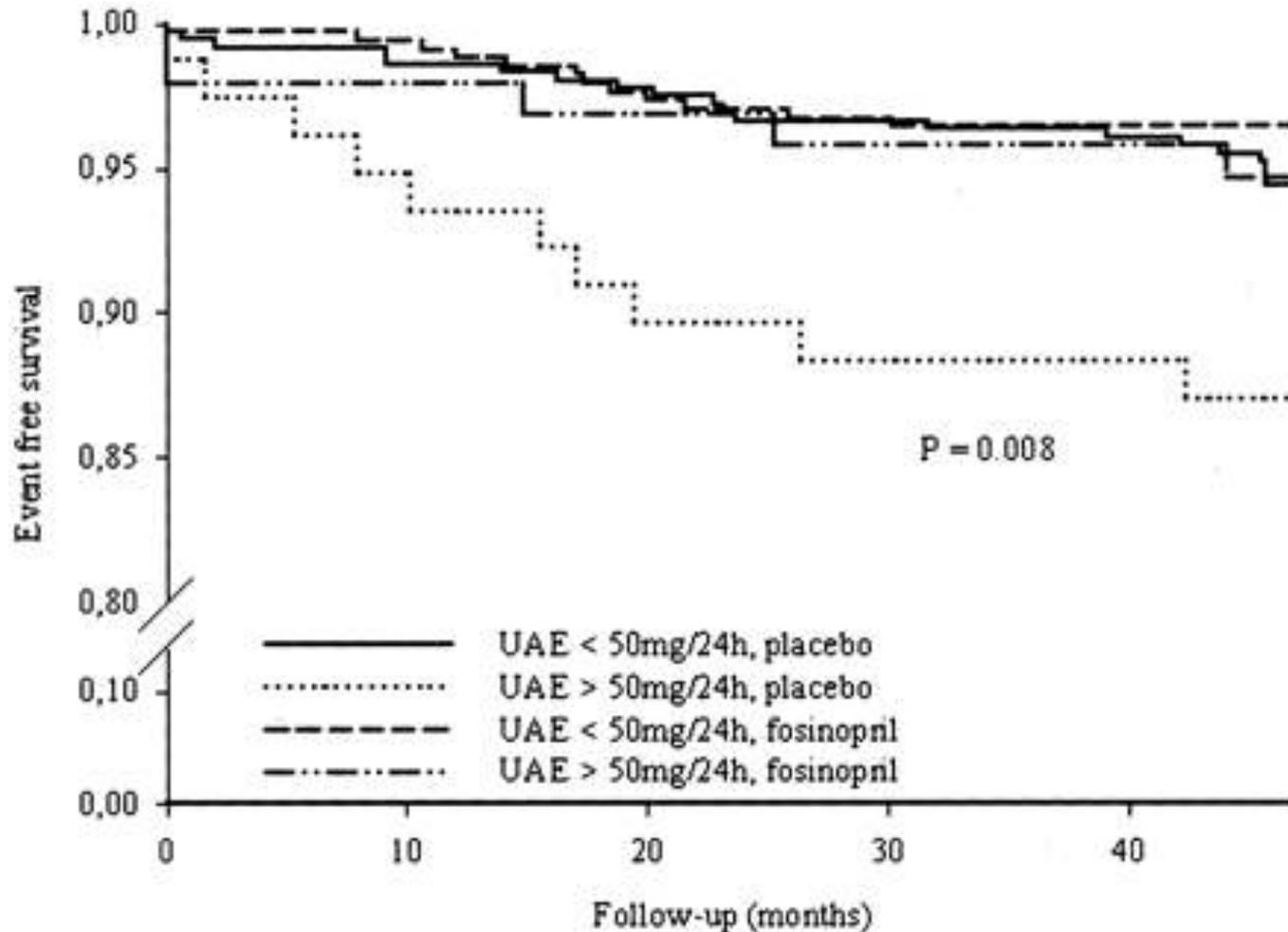
tot-chol



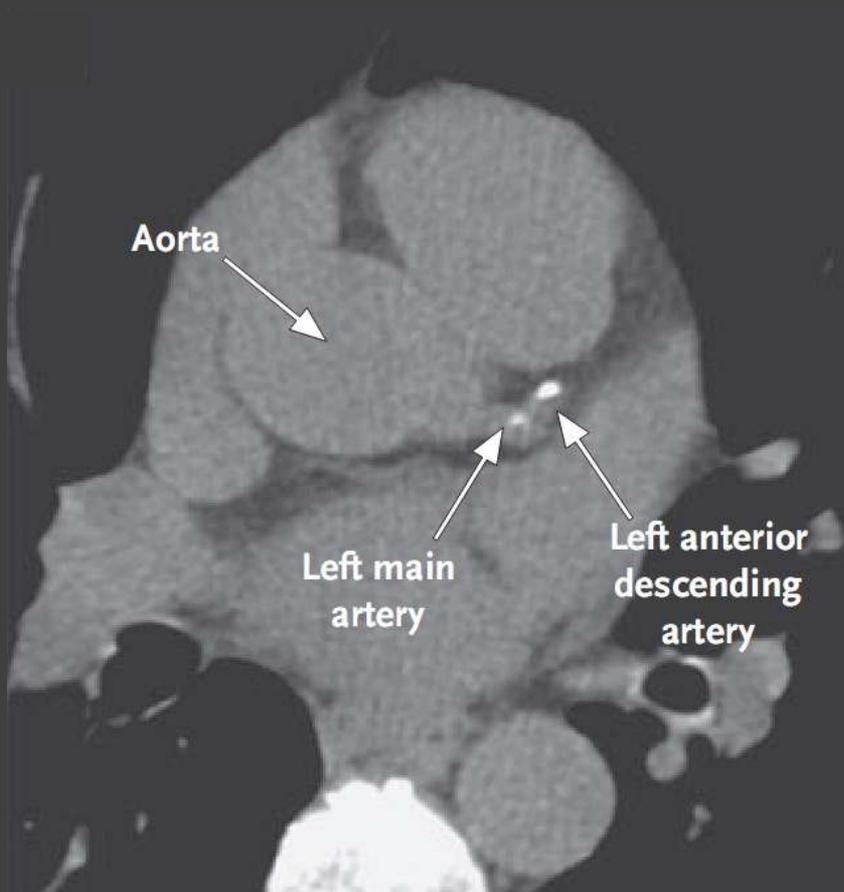
HDL-chol



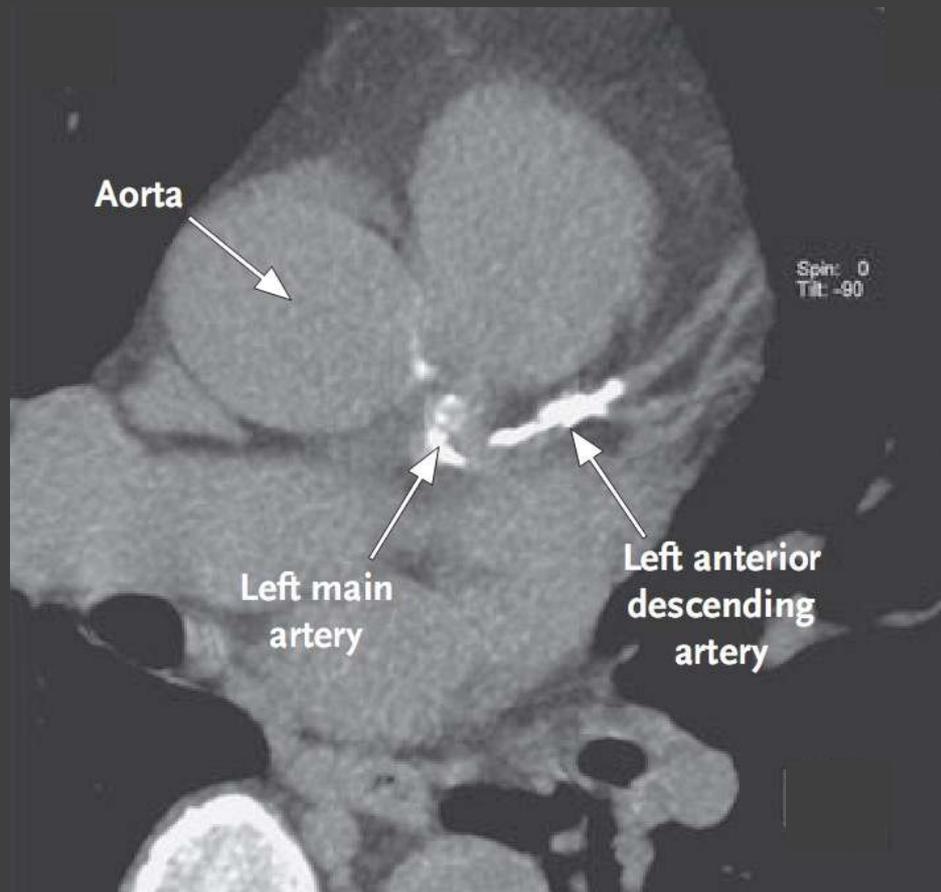
Seuil d'albuminurie et impact du traitement



CT Scans : calcifications of the Left Coronary Artery in asymptomatic men



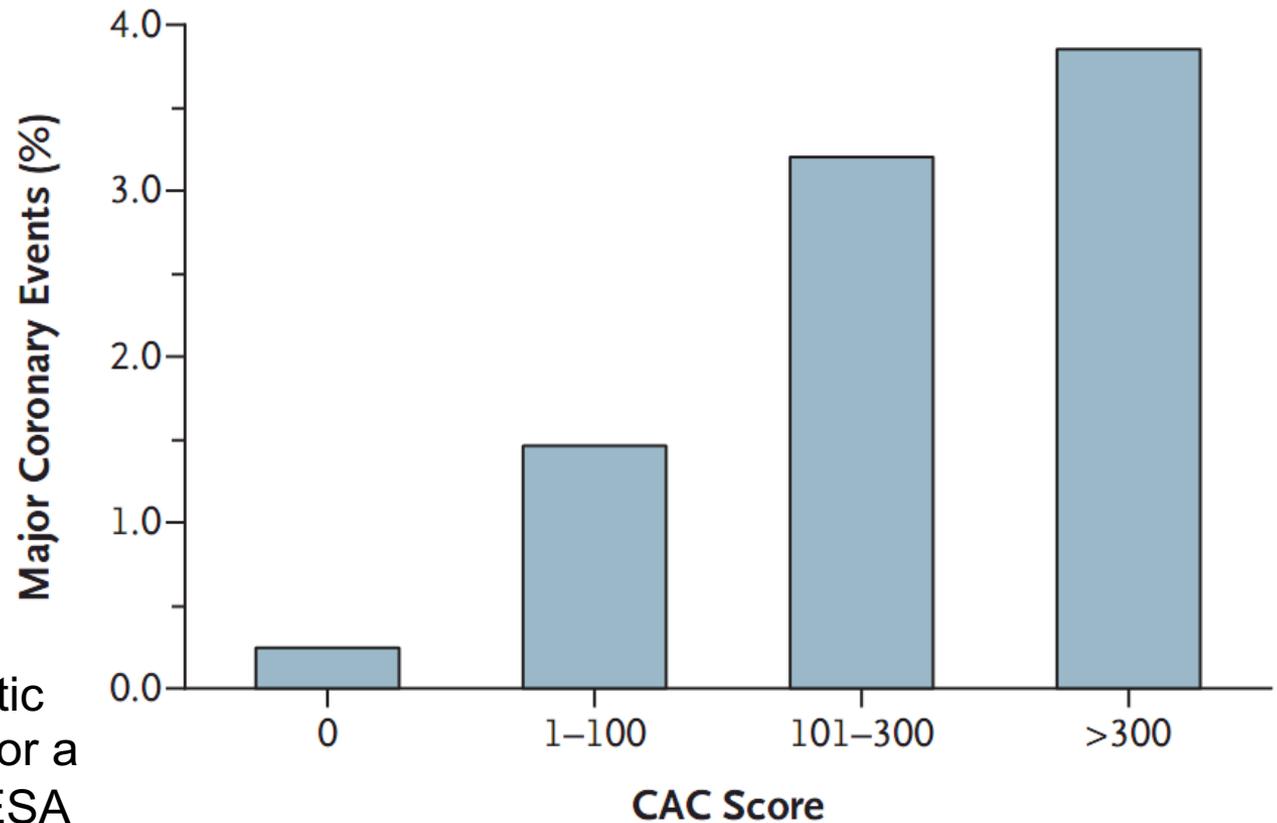
age 51, CACs 80 : 85° percentile



age 81, CACs 1054 : 70° percentile

Risk of major coronary events with increasing Coronary-Artery Calcium score

6722 initially asymptomatic healthy adults, followed for a median of 3.8 years - MESA

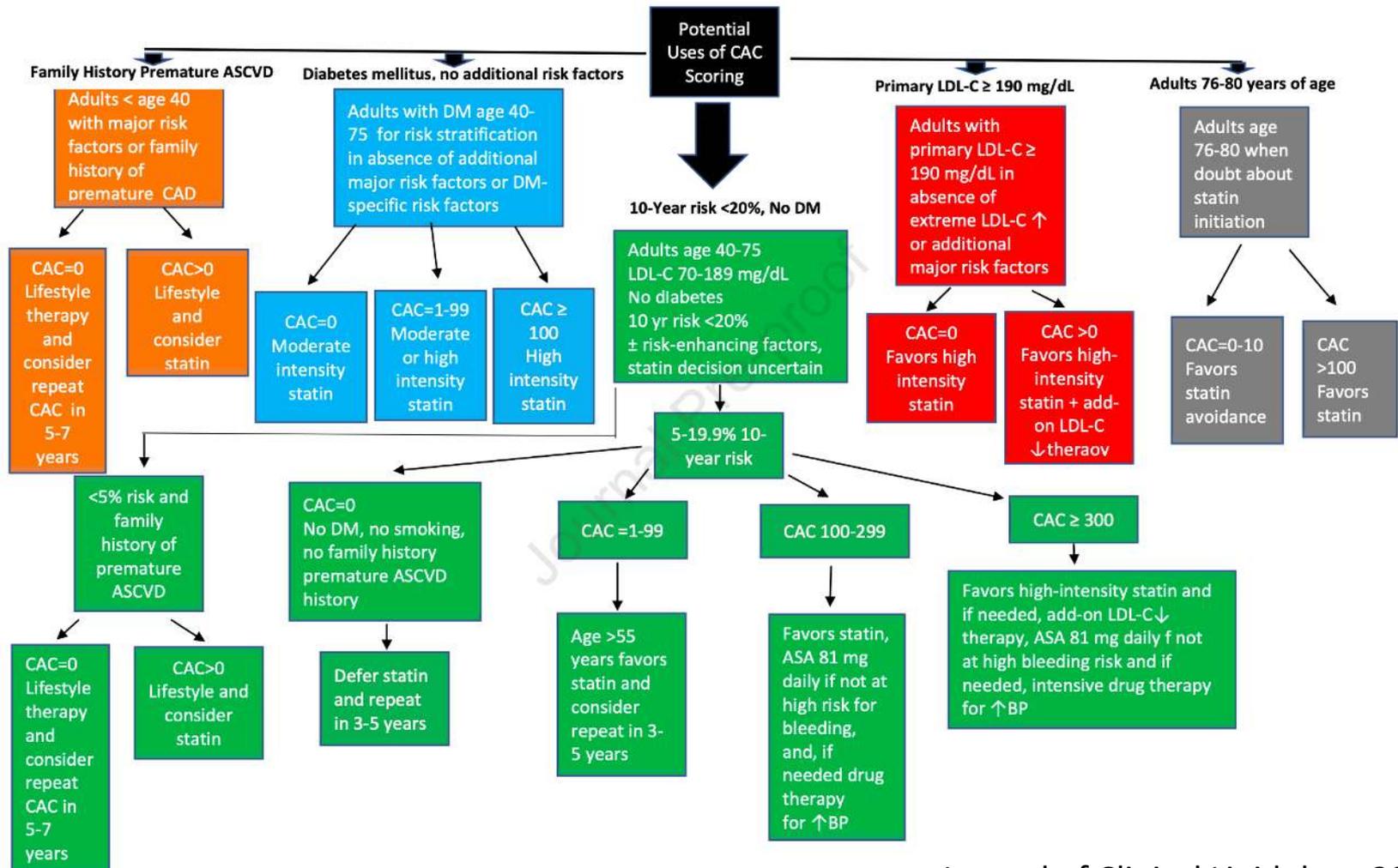


No. of Events	8	25	24	32
No. at Risk	3409	1728	752	833
Hazard Ratio	1.00	3.89	7.08	6.84
(95% CI)		(1.72–8.79)	(3.05–16.47)	(2.93–15.99)

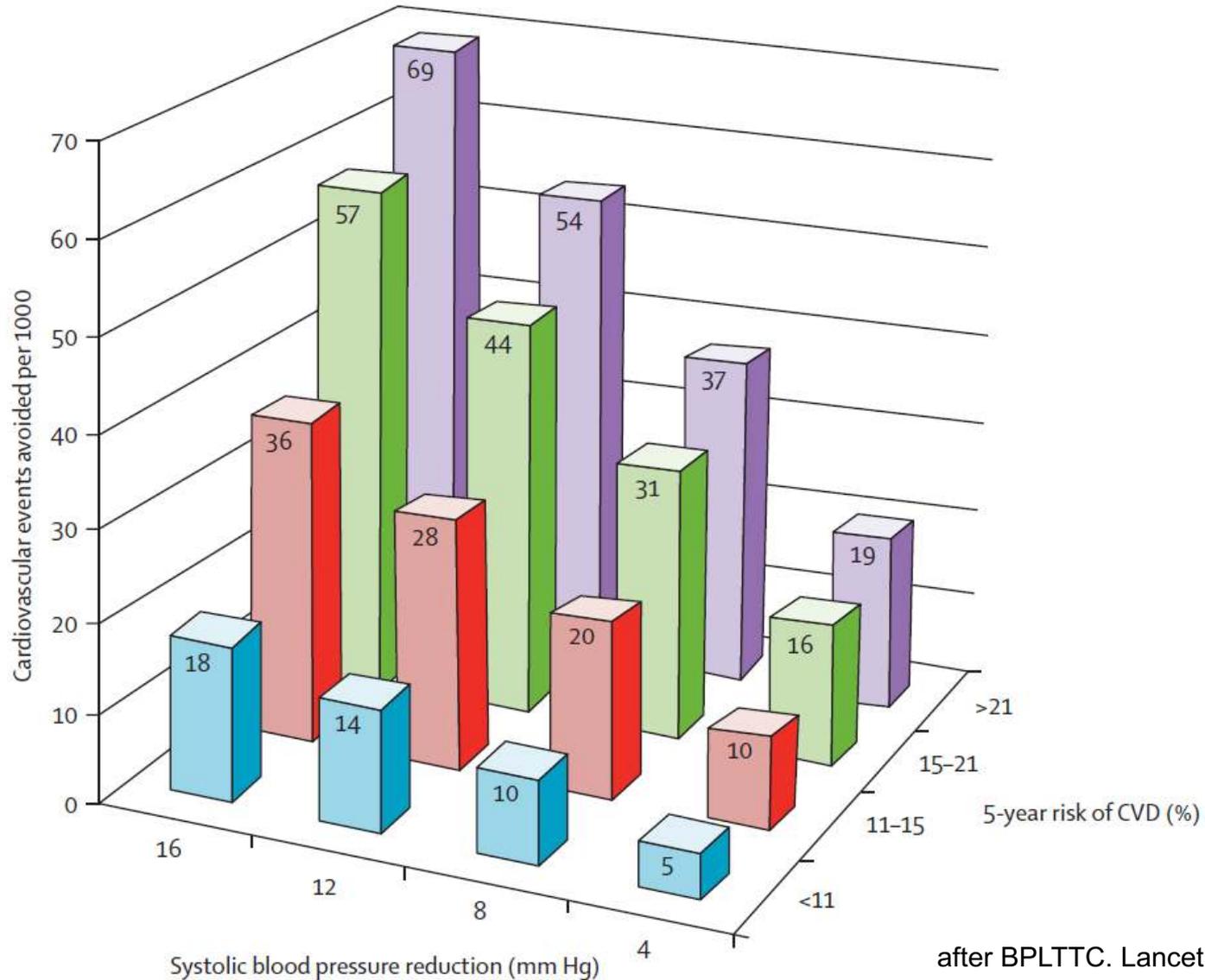
Study ^{a†}	Patient Type	No. of Patients in Full Study	Mean Age, y	Follow-Up Duration, y	Events in Persons With CAC=0 Scores, n	Events Per Year in CAC=0 Patients, Mean	Total No. of Persons With CAC=0	Annual Event Rate in CAC=0 Patients, Per 100 People
Georgiou et al ⁴	Emergency room patients with chest pain	192	53	4.2	0	0	76	0
Schenker et al ⁶	Referred for cardiac evaluation	606	61	1.4	11	7.7	213	3.6
Rozanski et al ⁸	Mixed sample of self-referred and MD-referred	1,153	58.4	2.7	3	1.1	252	0.47
Greenland et al ⁹	Asymptomatic with at least 1 risk factor	1,312	66	7.0	14	2.0	316	0.63
Keelan et al ¹⁰	Coronary angiography patients	288	56	6.9	0	0	48	0
Arad et al ¹¹	Asymptomatic	1,173	53	3.6	2	0.55	496	0.11
Raggi et al ¹²	Asymptomatic	632	52	2.7	1	0.37	292	0.13
Wong et al ¹³	Asymptomatic	926	54	3.3	0	0	392	0
Arad et al ¹⁴	Asymptomatic	4,613	59	4.3	8	1.8	1504	0.12
Kondos et al ¹⁵	Self-referred—mostly asymptomatic	5,635	51	3.1	5	1.6	1816	0.09
Anand et al ¹⁶	Asymptomatic type 2 diabetic patients	510	53	3.0	1	0.33	274	0.12
Taylor et al ¹⁷	Asymptomatic	2000	43	3.0	2	0.67	1791	0.04
Church et al ¹⁸	Preventive evaluation patients	10,746	54	3.5	7	2.0	5472	0.04
Becker et al ¹⁹	Asymptomatic	1,726	58	3.3	0	0	367*	0

*12 patients with CAC=0 had coronary revascularization. Number includes only the patients with CAC=0 who had no interventions at all.

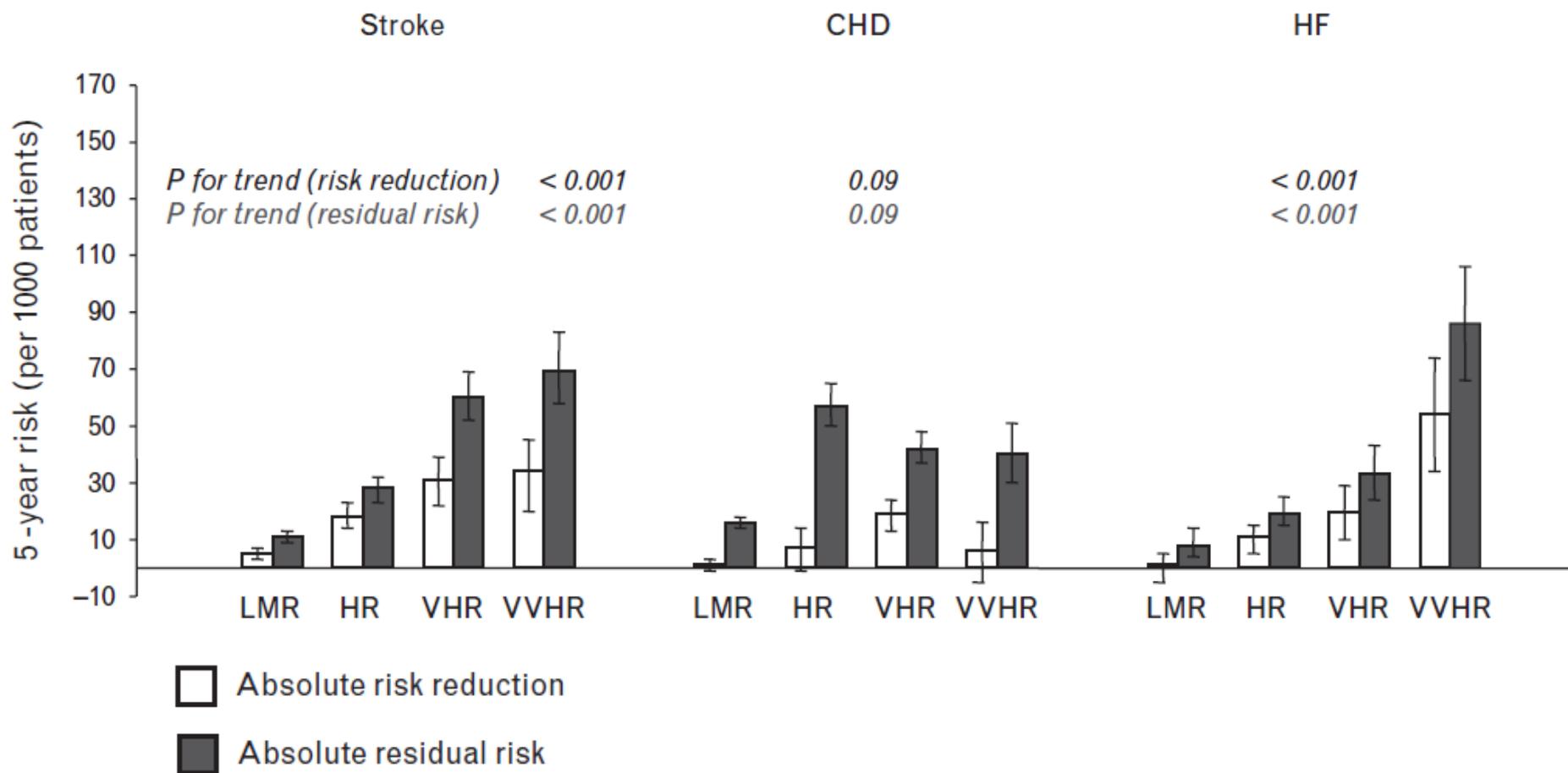
	Risk Communication	In Whom to Use
Absolute CAC Score	Best predictor of absolute cardiovascular risk	All patients
CAC Score Percentile	Predicts relative risk vs. age, sex, and race/ethnicity-matched peers Predicts lifetime risk trajectory	Young patients (i.e. age <50) Older patients (i.e. age >70)



Avoidable events by baseline risk and extent of blood pressure lowering

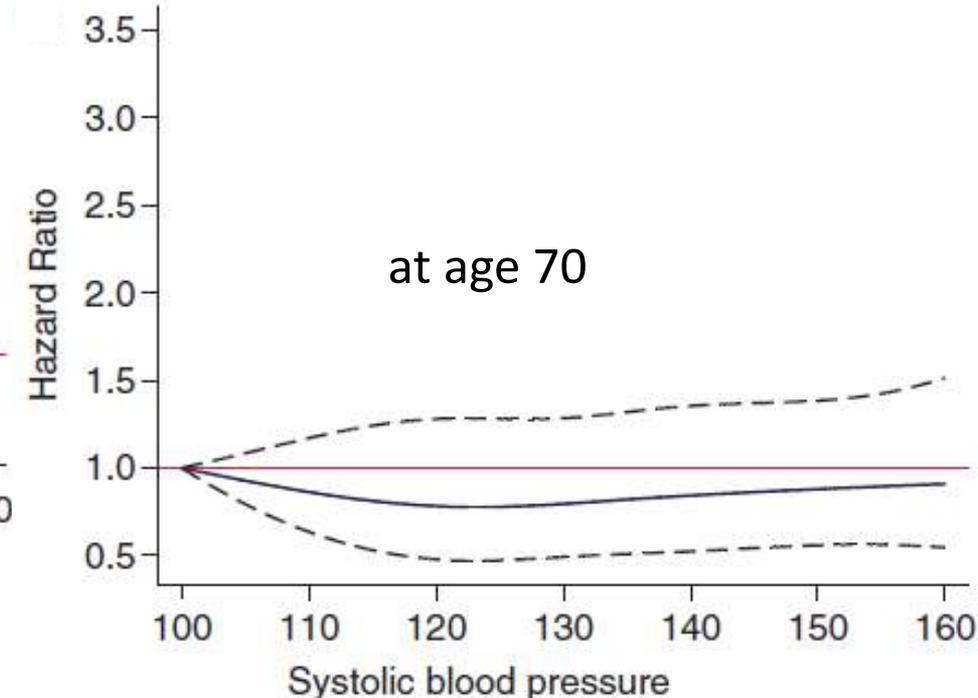
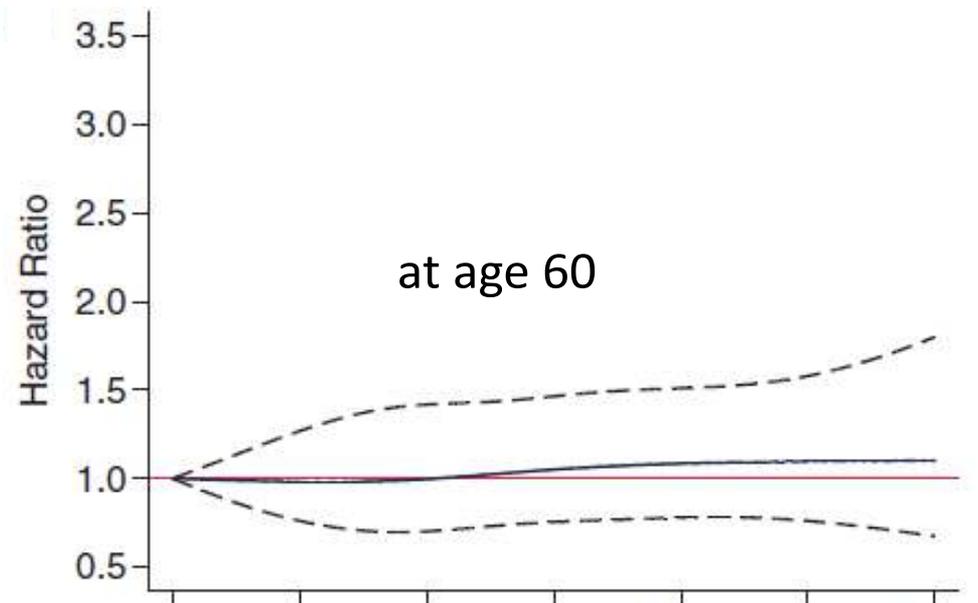
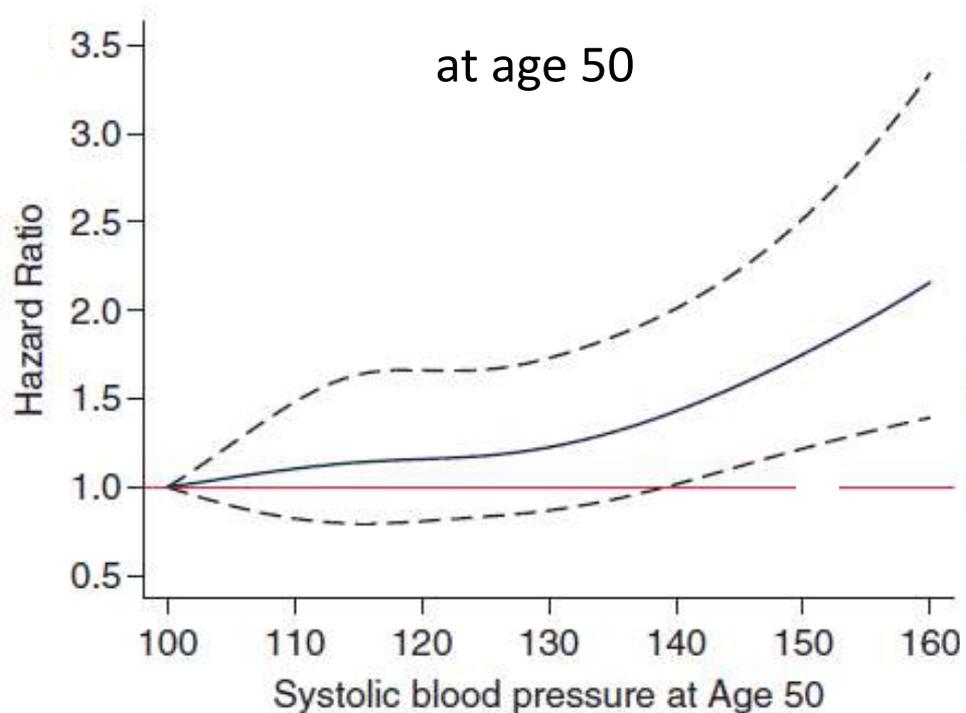


Absolute RR by BP-lowering treatment (standardized to 10/5mmHg SBP/DBP) & residual risk in trials stratified by increased level of CV risk in the control group



Quid d'autres cibles ?

Association entre PAS et
démence ultérieure

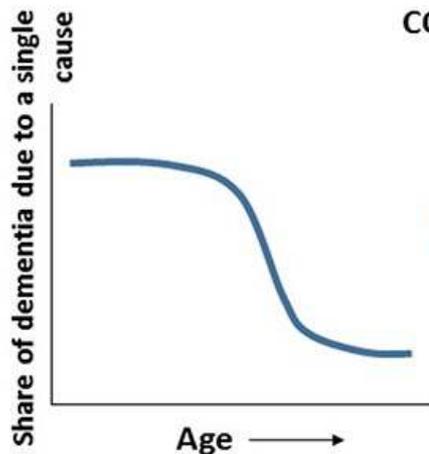
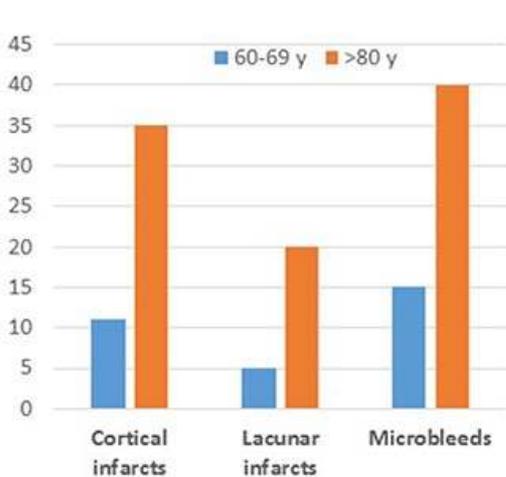


Cohorte Whitehall II, n=8639 (1/3 F)

Abell JG, et al. Eur Heart J 2018;39:3119

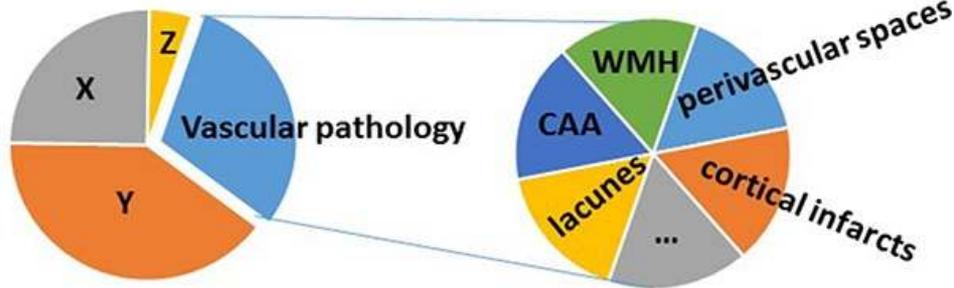
The epidemiology of vascular dementia: nosology in a time of epimomics

Frank J. Wolters and M. Arfan Ikram, Erasmus Medical Centre Rotterdam



The increasing prevalence of various pathologies with age ensures that in most patients, dementia is due to various contributing pathologies.

COGNITIVE IMPAIRMENT WITH A VASCULAR CONTRIBUTION



Like any other pathology, vascular disease is rarely as a cause on its own, calling for appropriate attribution of for example 'a cortical infarct along with factor X and Y' in the origin of dementia in an individual patient.

LARGE-SCALE OMICS DATA TO FURTHER IMPROVE CLINICAL PHENOTYPING

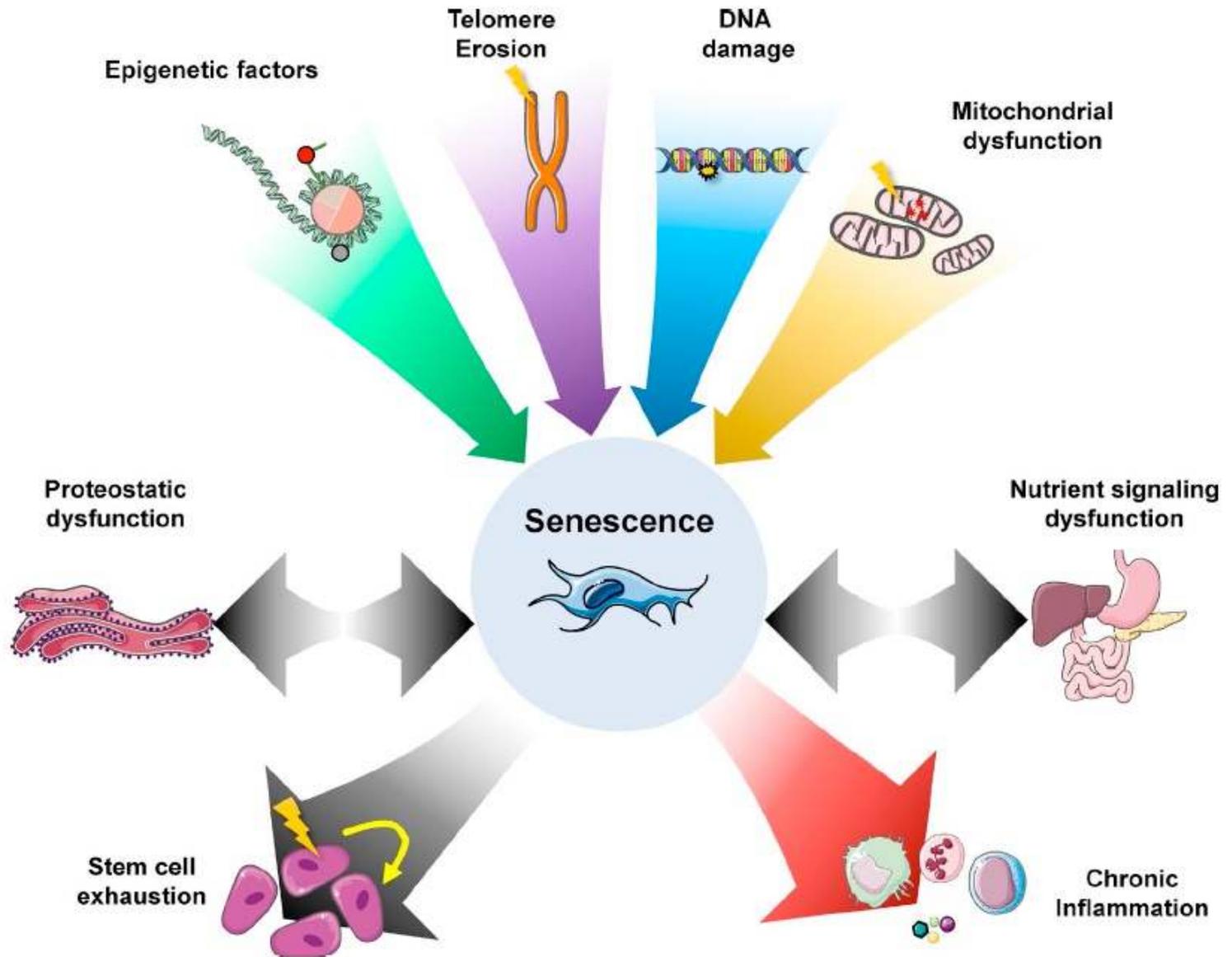


KEY TO PREVENTION

modifiable risk factors account for 25% of dementia

stroke increases dementia risk about 2-fold

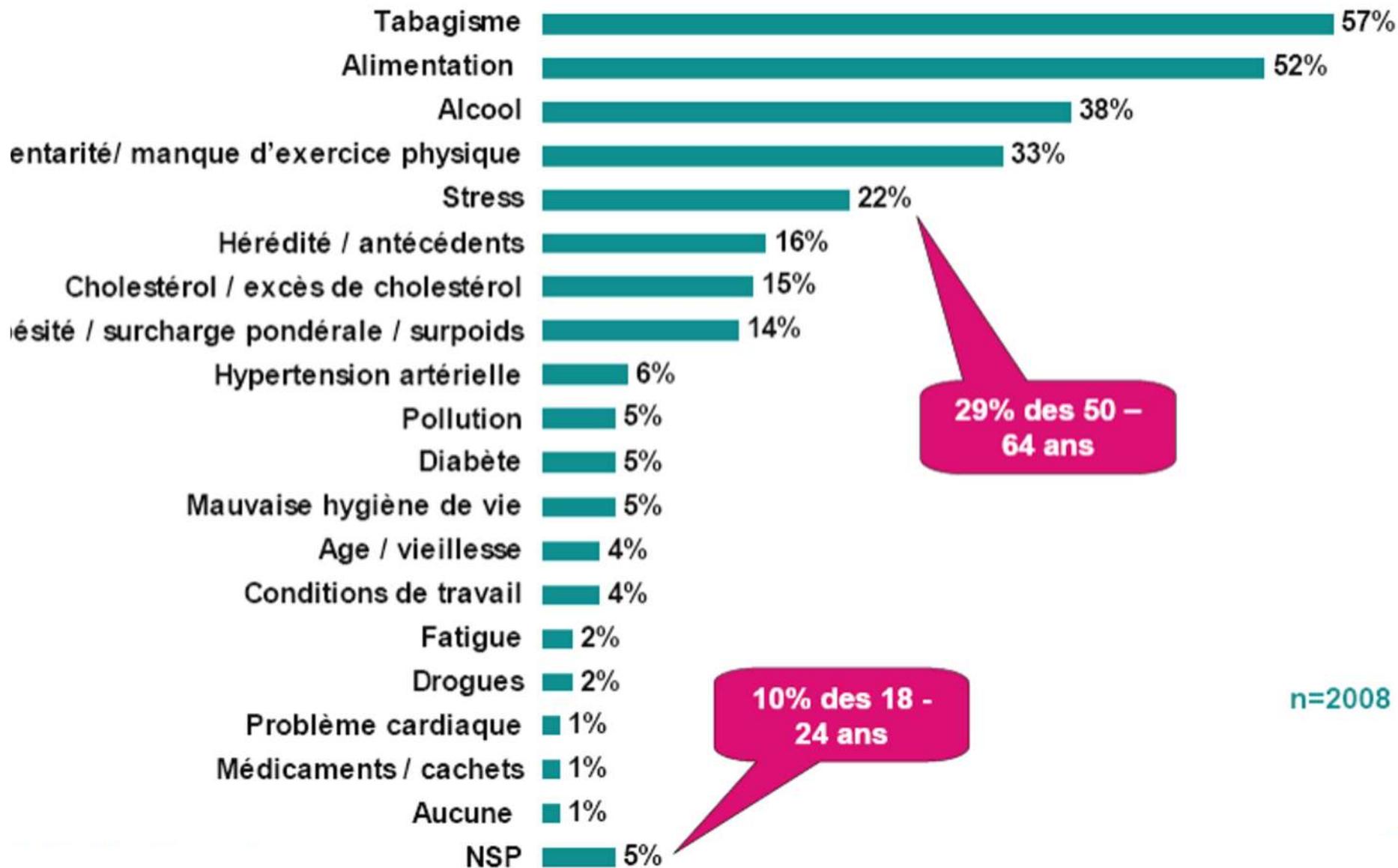
Vieillesse ou sénescence



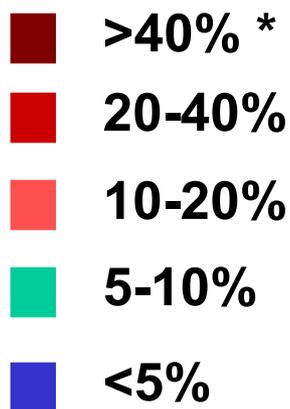
Une synthèse des données

Représentation et communication du risque

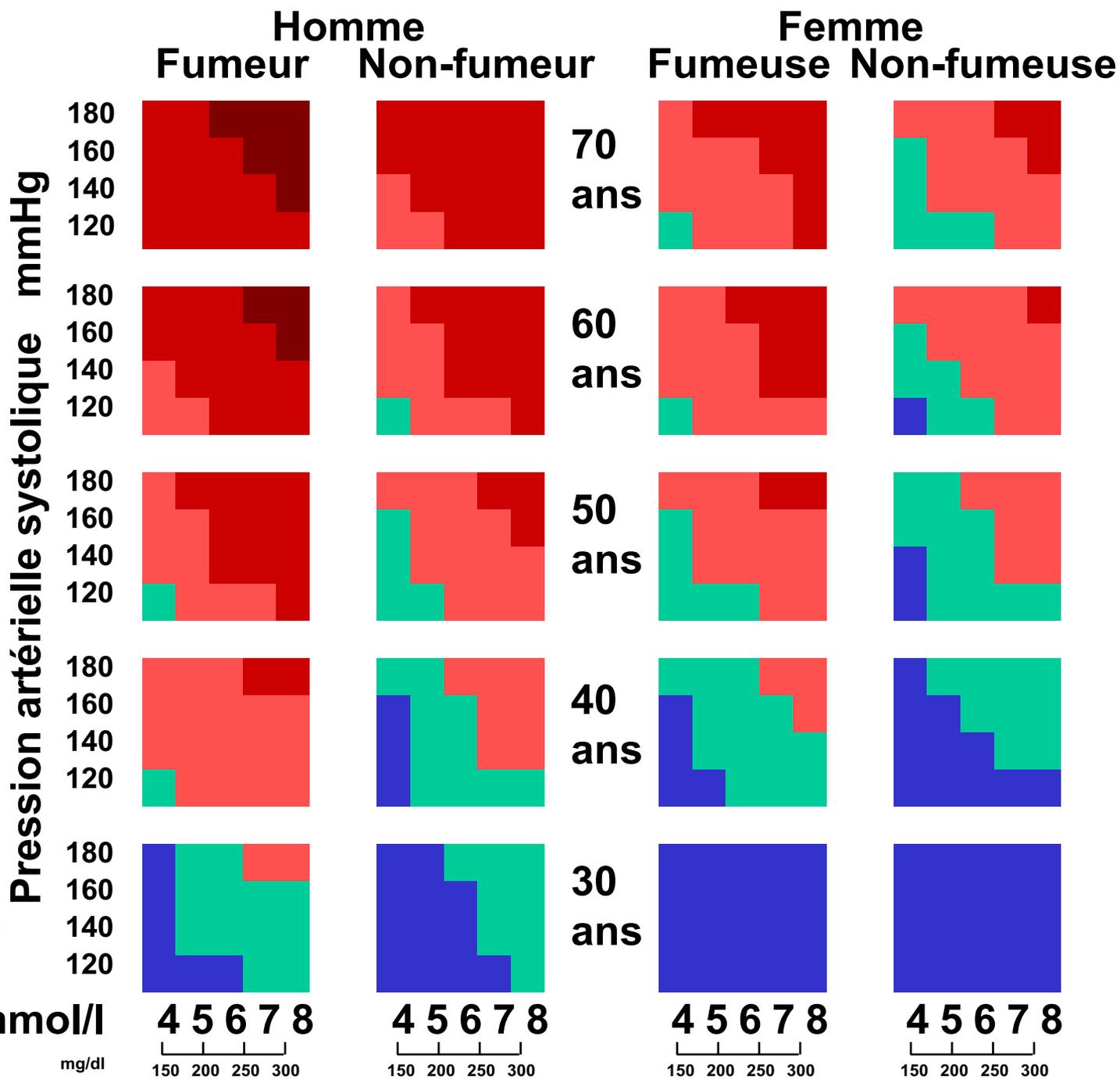
A votre avis, quelles sont les causes, les facteurs de risque des maladies cardiovasculaires ?



Risque coronaire absolu à 10 ans



* majoré si
 .diabète sucré (x2)
 .histoire familiale
 .anomalie lipidique
 (HDL<1et/ou TG>2mmol/l)



SCORE2 risk prediction algorithms

1. Model development

Sex-specific, competing risk-adjusted risk models derived in 45 prospective cohorts in 13 countries (~680,000 individuals, and ~30,000 CVD events)

Recalibration to four risk regions in Europe using age-, sex-, and region-specific risk factor values and CVD incidence rates (derived using data on ~10.8 million individuals)

2. Model validation

External validation in 25 prospective cohorts in 15 European countries (~1.1 million individuals, and ~43,000 CVD events)

C-indices ranged from 0.67 (95% confidence interval [CI] 0.65-0.68) to 0.81 (95% CI 0.76-0.86)

SCORE2 risk prediction algorithms key features



Sex-specific risk prediction models



Estimate 10-year risk of fatal and non-fatal CVD



Calibrated to the most contemporary and representative CVD rates



Available for four distinct European risk regions



Can be rapidly updated to reflect future CVD incidence and risk factor profiles



Individual example

Patient risk factors:

50 years old
Smoker
SBP: 140 mmHg
Cholesterol: 5.5 mmol/L
HDL-c: 1.3 mmol/L



10-year risk depending on risk region

Low risk

Moderate risk

High risk

Very high risk

Low risk

Moderate risk

High risk

Very high risk

4.2%

5.1%

6.9%

13.7%

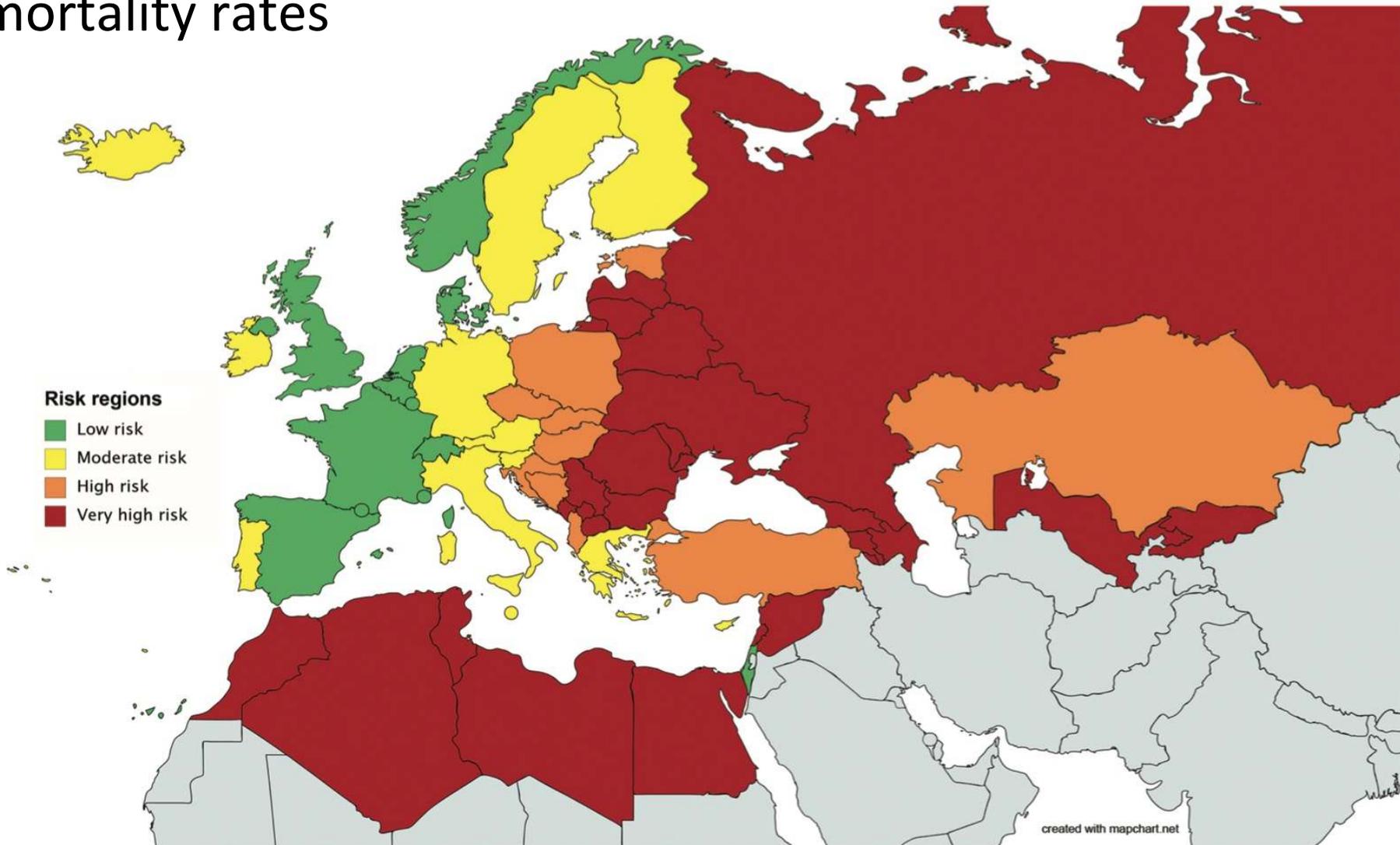
5.9%

7.5%

8.1%

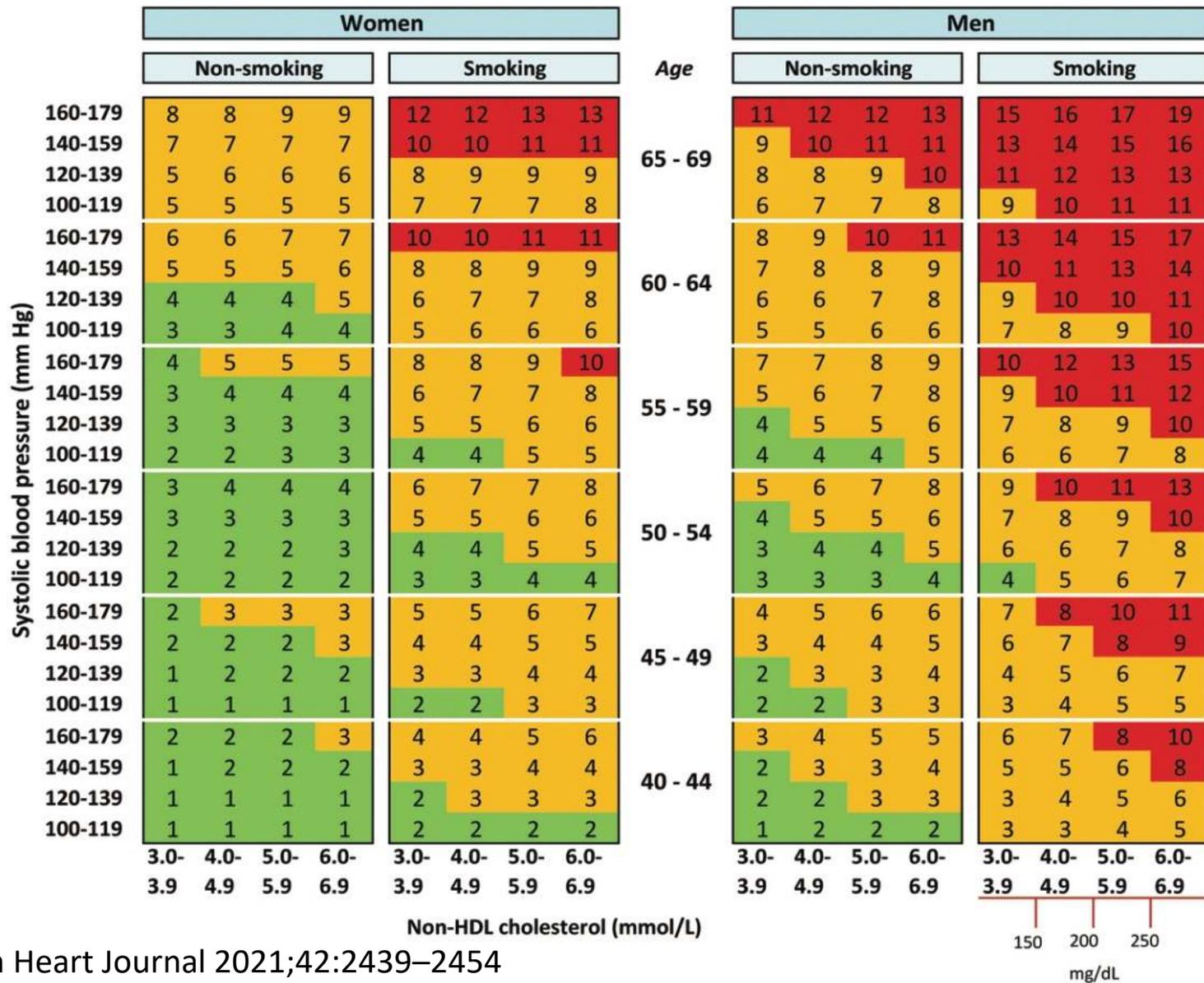
14.0%

Risk regions based on standardised cardiovascular disease mortality rates



SCORE2

10-year risk of (fatal and non-fatal)
CV events in populations at
low CVD risk



SCORE2-OP: estimating incident cardiovascular event risk in older persons in four geographical risk regions

1. Model derivation

Competing risk-adjusted, sex-specific coefficients were derived in ~28,500 participants from the prospective CONOR study



2. Model recalibration

The model was recalibrated to four geographical risk regions using contemporary region-specific CVD event rates and risk factor levels



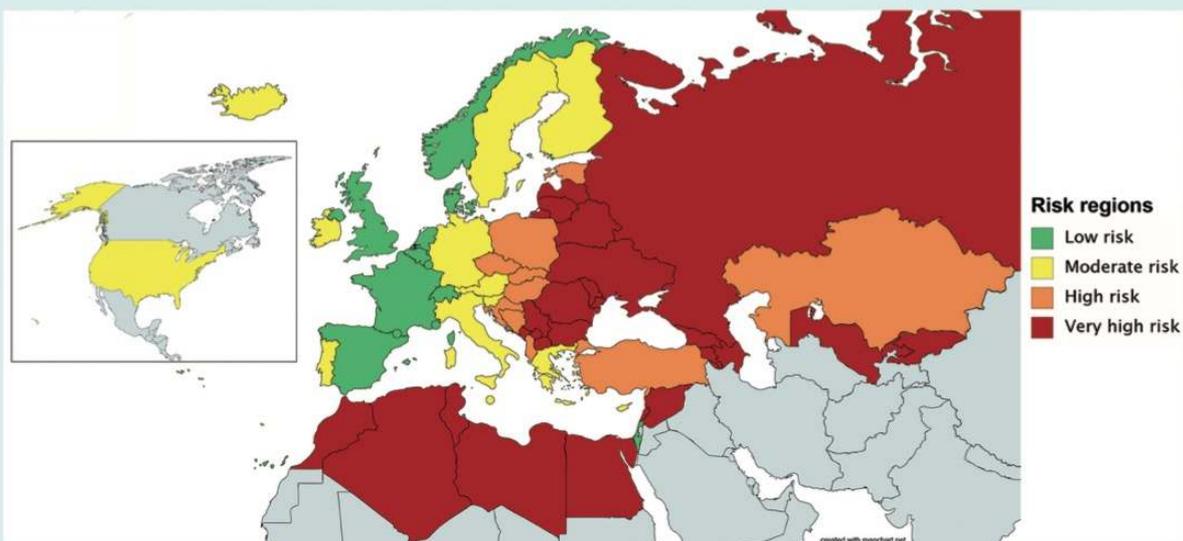
3. External validation

The model was externally validated in ~340,000 individuals from different risk regions



4. Individualized predictions

An individual's risk factor levels can be applied to the two-dimensional SCORE2-OP charts or to an online calculator to estimate their 5- and 10-year CVD event risk according to their risk region of origin



Individual example

Patient risk factors

75 years old
Smoker
No diabetes
SBP: 140 mmHg
Cholesterol: 4.5 mmol/L
HDL-c: 1.4 mmol/L

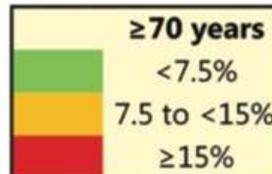


10-year risk depending on risk region:

Female patient				Male patient					
Risk region	Low risk	Moderate risk	High risk	Very high risk	Risk region	Low risk	Moderate risk	High risk	Very high risk
10-year risk	14%	18%	28%	44%	16%	21%	24%	37%	

SCORE2-OP

10-year risk of CV events in older persons in populations at low CVD risk



Women

Non-smoking Smoking

Systolic blood pressure (mm Hg)	Non-smoking				Smoking			
	3.0-3.9	4.0-4.9	5.0-5.9	6.0-6.9	3.0-3.9	4.0-4.9	5.0-5.9	6.0-6.9
160-179	28	29	30	31	31	32	33	34
140-159	26	27	28	29	29	30	31	32
120-139	24	25	26	27	27	28	29	30
100-119	23	24	25	26	25	26	27	28
160-179	20	21	22	23	25	26	28	29
140-159	18	19	20	21	23	24	25	26
120-139	16	17	18	19	20	21	22	23
100-119	15	15	16	17	18	19	20	21
160-179	15	15	16	17	21	22	23	24
140-159	13	13	14	15	18	19	20	21
120-139	11	11	12	13	15	16	17	18
100-119	9	10	10	11	13	14	15	15
160-179	10	11	12	12	17	18	19	20
140-159	9	9	10	10	14	15	16	16
120-139	7	7	8	8	11	12	13	14
100-119	6	6	6	7	9	10	10	11

Men

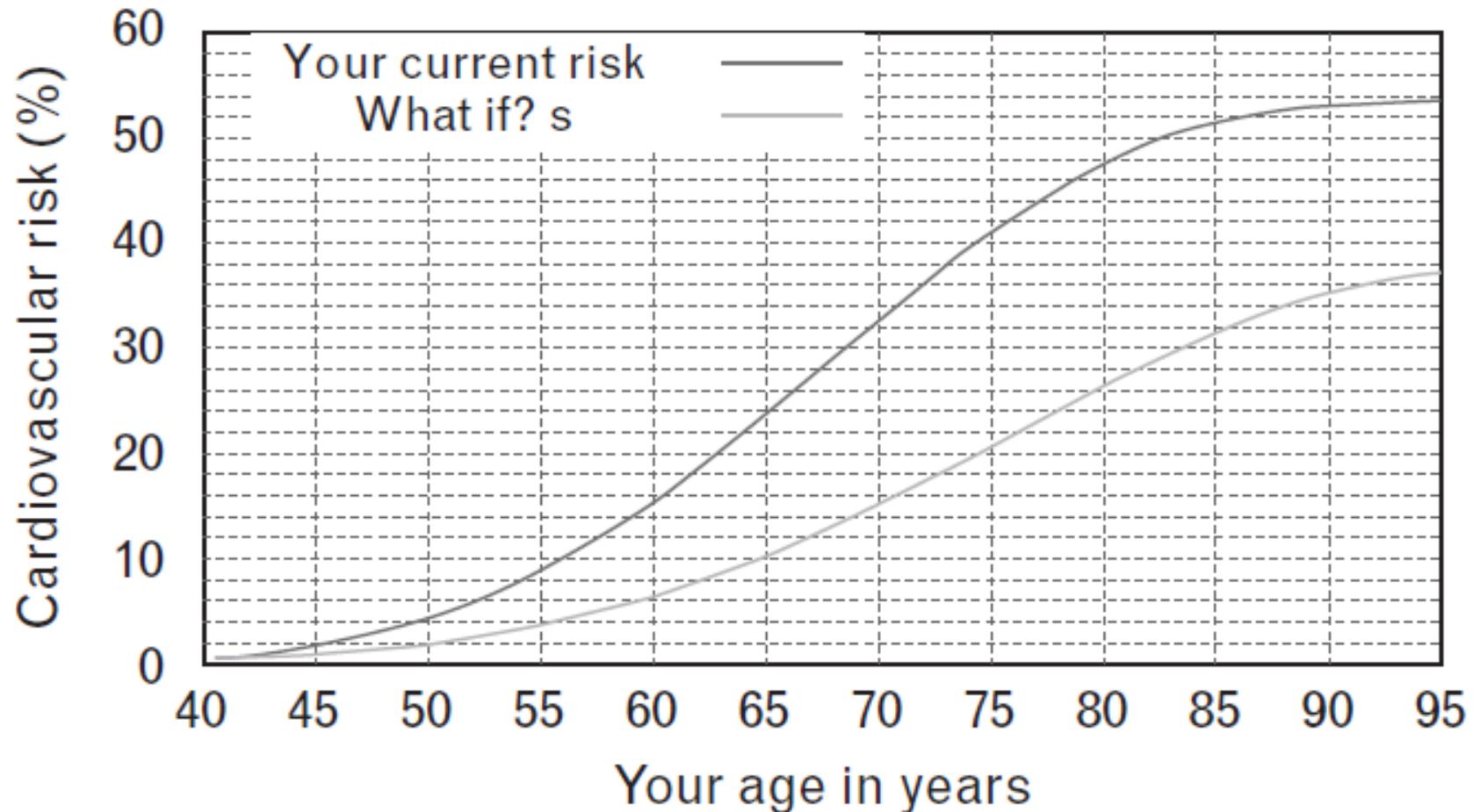
Non-smoking Smoking

Age	Non-smoking				Smoking			
	3.0-3.9	4.0-4.9	5.0-5.9	6.0-6.9	3.0-3.9	4.0-4.9	5.0-5.9	6.0-6.9
85 - 89	29	35	42	49	29	35	42	49
	28	33	40	47	27	33	40	47
	26	32	38	45	26	32	38	45
	25	30	36	43	25	30	36	43
80 - 84	23	27	32	37	26	31	36	41
	21	25	29	34	24	28	33	38
	19	22	26	31	22	25	30	34
	17	20	24	28	19	23	27	31
75 - 79	19	21	24	27	24	27	31	34
	16	18	21	23	21	23	26	30
	14	15	18	20	18	20	23	26
	12	13	15	17	15	17	19	22
70 - 74	15	16	18	19	22	24	26	28
	12	13	14	16	18	19	21	23
	10	11	12	13	14	16	17	19
	8	8	9	10	12	13	14	15

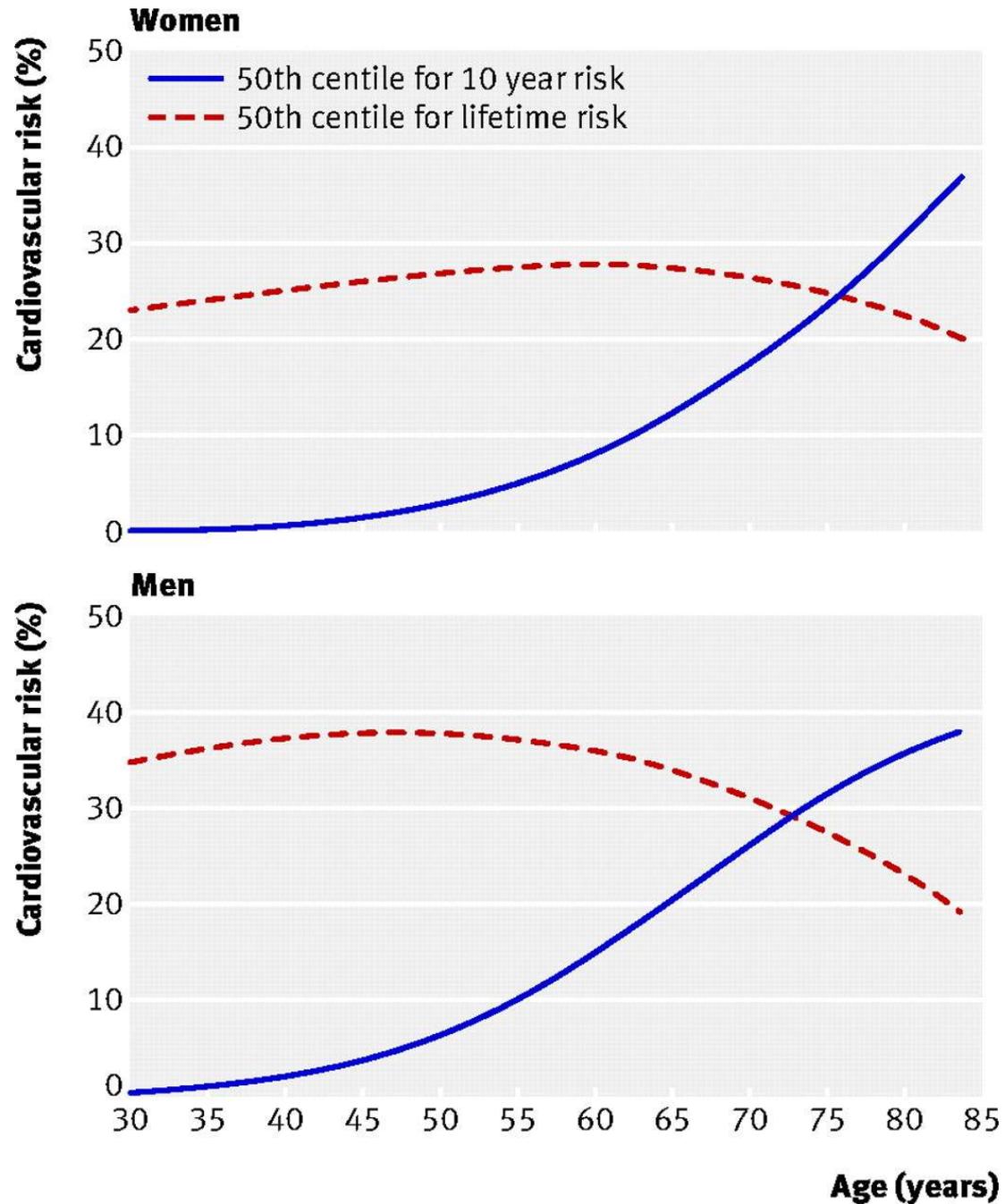
Non-HDL cholesterol (mmol/L)

150 200 250
mg/dL

QRISK model to estimate lifetime risk of cardiovascular disease



Comparaison de la distribution du risque cardiovasculaire vie entière versus 10 ans sur la base de QRISK2 (2010)



indicateurs du bénéfice attendu d'une intervention

Risque Absolu	RA
Risque Relatif	$RR = [RA/RA_{ref}]$
Réduction Relative du risque	$RRR = [1-RR]$
Réduction Absolue du risque	$RAR = [RA_{ref} - RA]$
Nombre de sujets à traiter	$NST = [1/RAR]$ ou $[1/ (RA_{ref} \times RRR)]$

Le langage de l'individu ou du groupe

*Homme 74 ans, 175/85 mmHg, sous antidiabétiques oraux
SHEP*

	Taux d'événements des pts		RR	RRR	RRA	NST
	contrôles	/ traités				
	%	%	%	%	%	5ans
Mort. totale	10.2	9.0	0.88	12	1.2	83
Mort. CV	4.7	3.8	0.81	19	0.9	111
Mort. ictus	0.59	0.42	0.71	29	0.17	588
Tous ictus	6.9	4.5	0.65	35	2.4	42
Tous events CV	17.5	12.2	0.70	30	5.3	19

La connaissance du risque ou le risque de connaître

Epidemiology

General Cardiovascular Risk Profile for Use in Primary Care The Framingham Heart Study

Ralph B. D'Agostino, Sr, PhD; Ramachandran S. Vasan, MD; Michael J. Pencina, PhD;
Philip A. Wolf, MD; Mark Cobain, PhD; Joseph M. Massaro, PhD; William B. Kannel, MD

Background—Separate multivariable risk algorithms are commonly used to assess risk of specific atherosclerotic cardiovascular disease (CVD) events, ie, coronary heart disease, cerebrovascular disease, peripheral vascular disease, and heart failure. The present report presents a single multivariable risk function that predicts risk of developing all CVD and of its constituents.

Methods and Results—We used Cox proportional-hazards regression to evaluate the risk of developing a first CVD event in 8491 Framingham study participants (mean age, 49 years; 4522 women) who attended a routine examination between 30 and 74 years of age and were free of CVD. Sex-specific multivariable risk functions (“general CVD” algorithms) were derived that incorporated age, total and high-density lipoprotein cholesterol, systolic blood pressure, treatment for hypertension, smoking, and diabetes status. We assessed the performance of the general CVD algorithms for predicting individual CVD events (coronary heart disease, stroke, peripheral artery disease, or heart failure). Over 12 years of follow-up, 1174 participants (456 women) developed a first CVD event. All traditional risk factors evaluated predicted CVD risk (multivariable-adjusted $P < 0.0001$). The general CVD algorithm demonstrated good discrimination (C statistic, 0.763 [men] and 0.793 [women]) and calibration. Simple adjustments to the general CVD risk algorithms allowed estimation of the risks of each CVD component. Two simple risk scores are presented, 1 based on all traditional risk factors and the other based on non-laboratory-based predictors.

Conclusions—A sex-specific multivariable risk factor algorithm can be conveniently used to assess general CVD risk and risk of individual CVD events (coronary, cerebrovascular, and peripheral arterial disease and heart failure). The estimated absolute CVD event rates can be used to quantify risk and to guide preventive care. (*Circulation*. 2008;117:743-753.)

Key Words: cardiovascular diseases ■ coronary disease ■ heart failure ■ risk factors ■ stroke



A man is as old
as his arteries

Thomas Sydenham 1624-1689

Langage 'médecin'

'% de risque à 10 ans'

Table 8. CVD Risk for Men

Points	Risk, %
≤ -3 or less	<1
-2	1.1
-1	1.4
0	1.6
1	1.9
2	2.3
3	2.8
4	3.3
5	3.9
6	4.7
7	5.6
8	6.7
9	7.9
10	9.4
11	11.2
12	13.2
13	15.6
14	18.4
15	21.6
16	25.3
17	29.4
18+	>30

Langage 'patient'

'âge vasculaire'

Table 10. Heart Age/Vascular Age for Men

Points	Heart Age, y
<0	<30
0	30
1	32
2	34
3	36
4	38
5	40
6	42
7	45
8	48
9	51
10	54
11	57
12	60
13	64
14	68
15	72
16	76
≥17	>80

L'âge des artères pour tous

Pour chaque question, trouvez le nombre de points correspondant à votre sexe et à votre situation. Le total des points vous permet de calculer votre âge vasculaire.

1. Quel âge avez-vous ?

	Femme	Homme
30 - 34	0	0
35 - 39	2	2
40 - 44	4	5
45 - 49	5	6
50 - 54	7	8
55 - 59	8	10
60 - 64	9	11
65 - 69	10	12
70 - 74	11	14
75 et +	12	15

2. Êtes-vous fumeur ?

	Femme	Homme
Non	0	0
Oui	3	4

3. Êtes-vous diabétique ?

	Femme	Homme
Non	0	0
Oui	4	3

4. Quelle est votre pression systolique ?

(La pression artérielle est définie par 2 chiffres : le premier, le plus haut, correspond à la pression systolique)

Si vous êtes **non traité** par des médicaments pour l'hypertension

	Femme	Homme
< 120	-3	-2
120 - 129	0	0
130 - 139	1	1
140 - 149	2	2
150 - 159	4	2
160 et +	5	3

Si vous êtes **traité** par des médicaments pour l'hypertension

	Femme	Homme
< 120	-1	0
120 - 129	2	2
130 - 139	3	3
140 - 149	5	4
150 - 159	6	4
160 et +	7	5

5. Quel est votre taux de cholestérol total en g/l ?

	Femme	Homme
< 1,60	0	0
1,60 - 1,99	1	1
2,00 - 2,39	3	2
2,40 - 2,79	4	3
2,80 et +	5	4

6. Quel est votre taux de HDL cholestérol en g/l ?

	Femme	Homme
0,6 et +	-2	-2
0,50 - 0,59	-1	-1
0,45 - 0,49	0	0
0,35 - 0,44	1	1
< 0,35	2	2

Votre total de points est :

Estimez l'âge de vos artères en reportant le total de vos points

Total des points	Femme	Homme
< 0	< 30 ans	< 30 ans
1	31 ans	32 ans
2	34 ans	34 ans
3	36 ans	36 ans
4	39 ans	38 ans
5	42 ans	40 ans
6	45 ans	42 ans
7	48 ans	45 ans
8	51 ans	48 ans
9	55 ans	51 ans
10	59 ans	54 ans
11	64 ans	57 ans
12	68 ans	60 ans
13	73 ans	64 ans
14	79 ans	68 ans
15 et +	> 80 ans	
15		72 ans
16		76 ans
17 et +		> 80 ans

Votre âge réel : ans

Votre âge vasculaire estimé : ans

La stratégie des actions de prévention

Gérer le risque

Top five causes of global DALYs

1990

1 Lower respiratory infections
2 Diarrhoea
3 Preterm birth complications
4 Ischaemic heart disease
5 Stroke

2010

1 Ischaemic heart disease
2 Lower respiratory infections
3 Stroke
4 Diarrhoea
5 HIV/AIDS

■ Communicable, maternal, neonatal, and nutritional disorders
■ Non-communicable diseases

Leading five risk factors for poor health

1990

1 Childhood underweight
2 Household air pollution from solid fuels
3 Tobacco smoking, excluding second-hand smoke
4 High blood pressure
5 Suboptimal breastfeeding

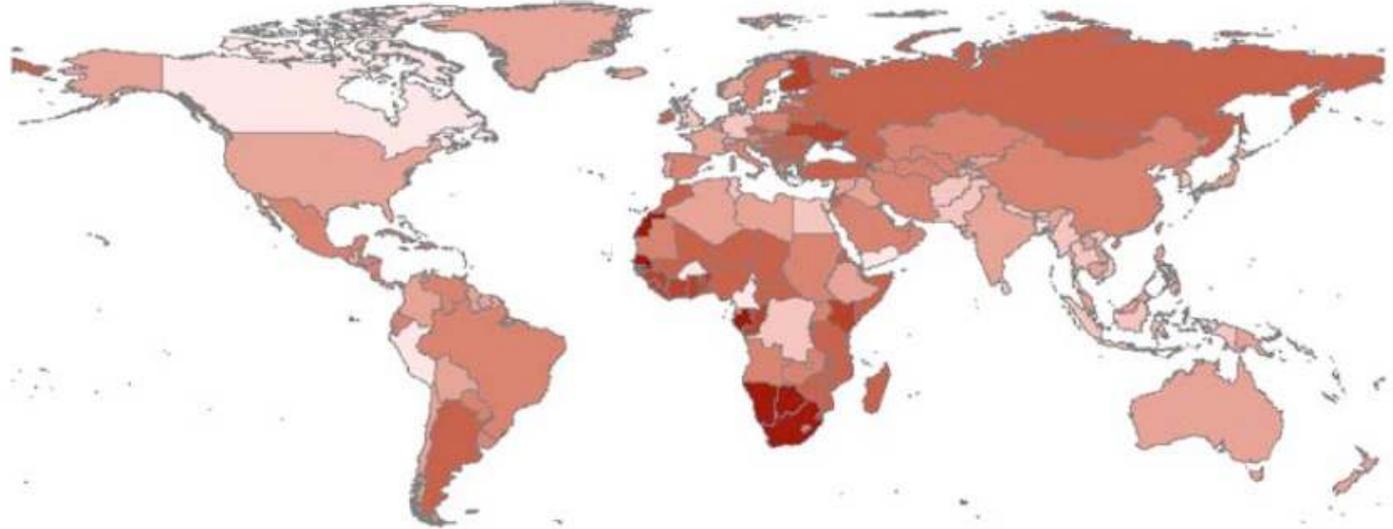
2010

1 High blood pressure
2 Tobacco smoking, excluding second-hand smoke
3 Alcohol use
4 Household air pollution from solid fuels
5 Diet low in fruits

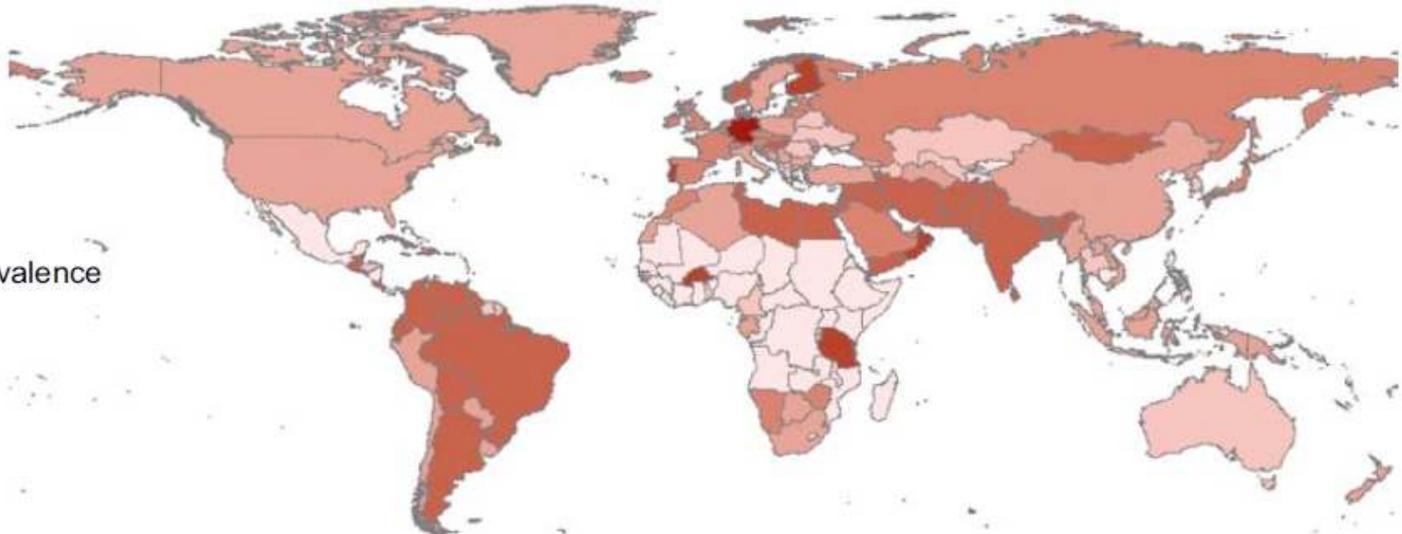
— Ascending order in rank
- - - Descending order in rank

Age- and sex-standardized prevalence of hypertension in adults 20 years and older

2010



2000

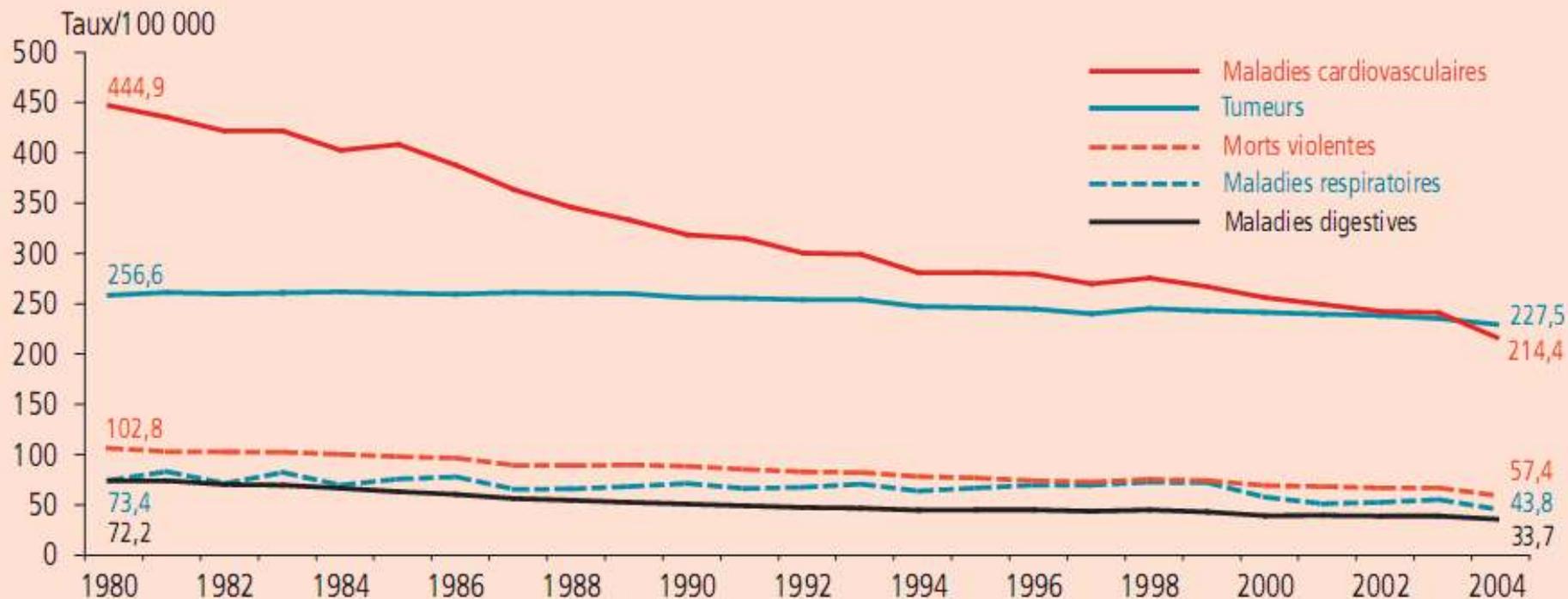


Hypertension Prevalence



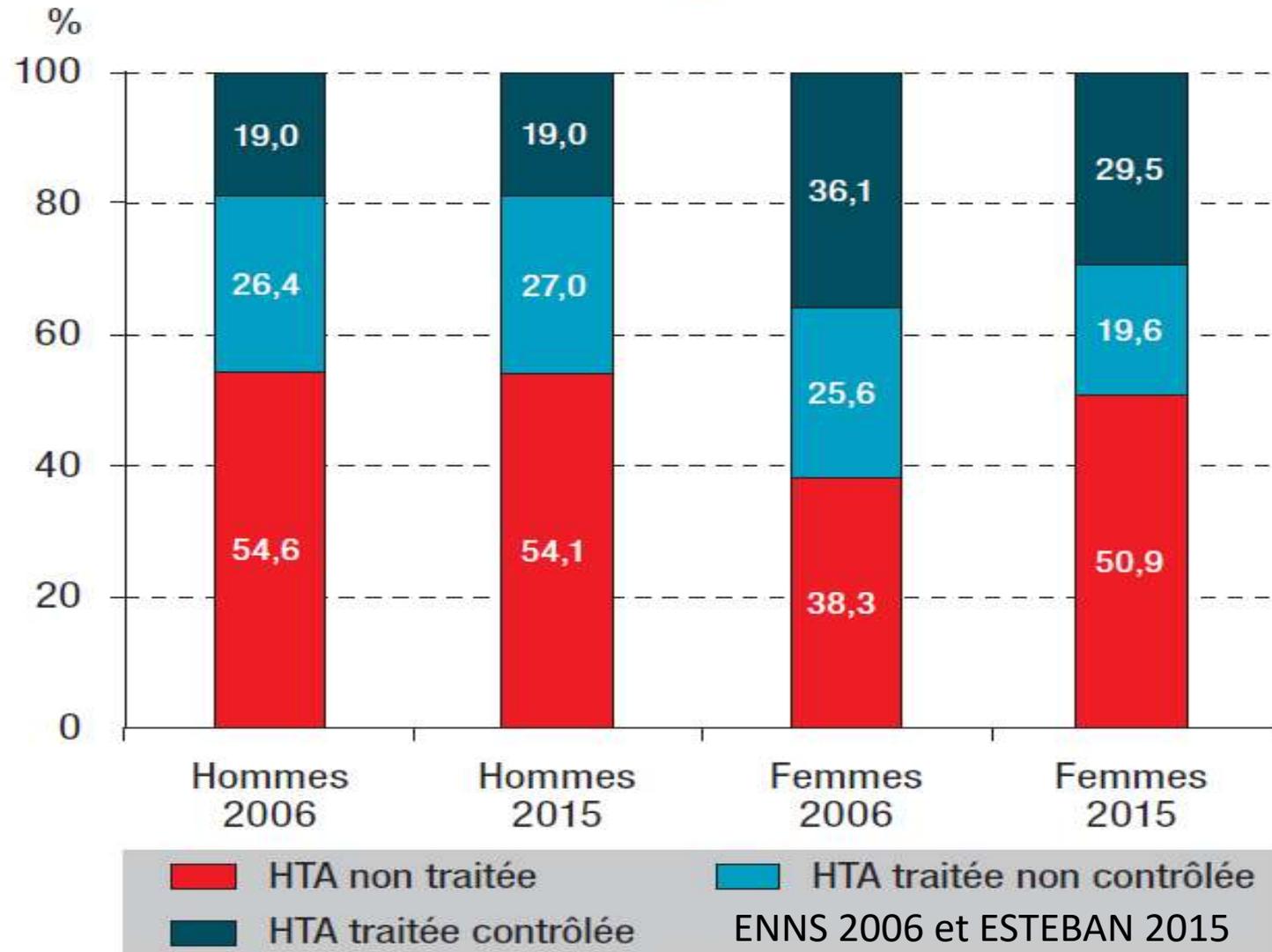
Evolution des taux de décès

1980-2004, France métropolitaine, deux sexes



* Taux de décès standardisés pour 100 000

Prévalence de l'hypertension en France - ESTEBAN

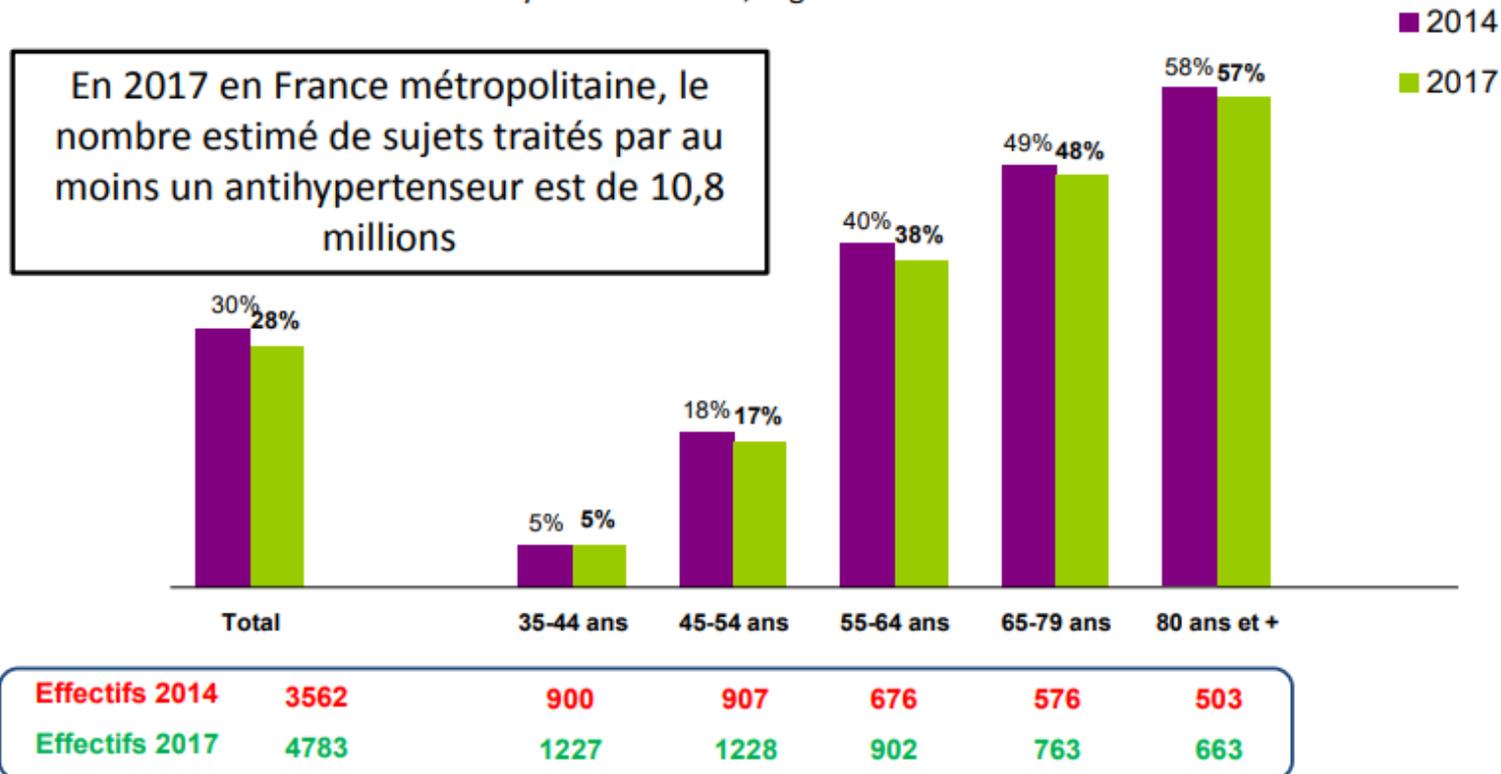


Prévalence de l'hypertension en France - FLASHS

FLASHS
2014
2017



Prise d'un médicament pour l'hypertension artérielle en 2014 et 2017
Analyse selon le sexe, l'âge dans les études FLASHS



Q1 : Actuellement, prenez-vous un médicament pour traiter l'hypertension artérielle ?

Enquête FLASHS 2014- French League Against Hypertension Survey
Enquête FLASHS 2017- French League Against Hypertension Survey

www.comitehta.org

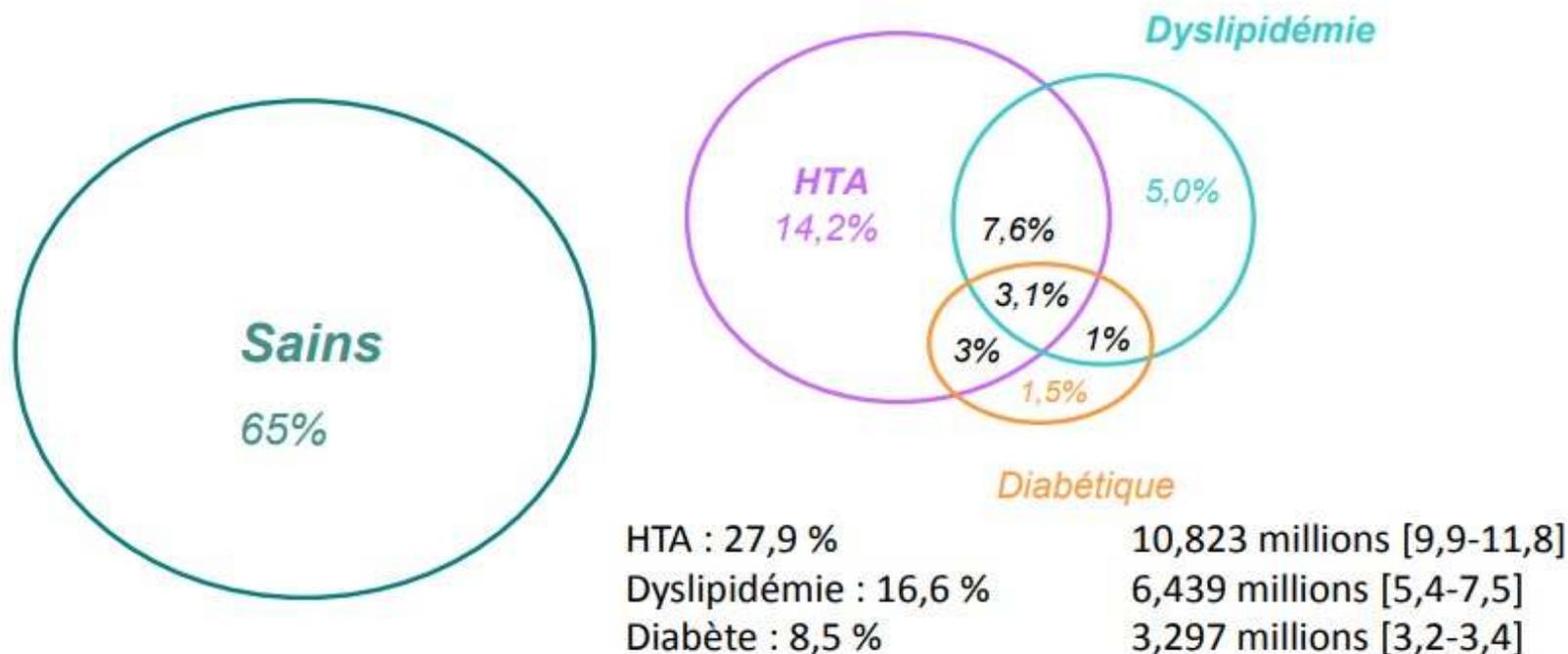
Prévalence de l'hypertension en France - FLASHS

FLASHS
2017



Traitement de l'HTA, du diabète, de la dyslipidémie chez les 35 ans et plus

En 2017 : 13,7 millions de sujets traités pour au moins un des 3 pathologies



Q1 : Actuellement, prenez-vous un médicament pour traiter l'hypertension artérielle?

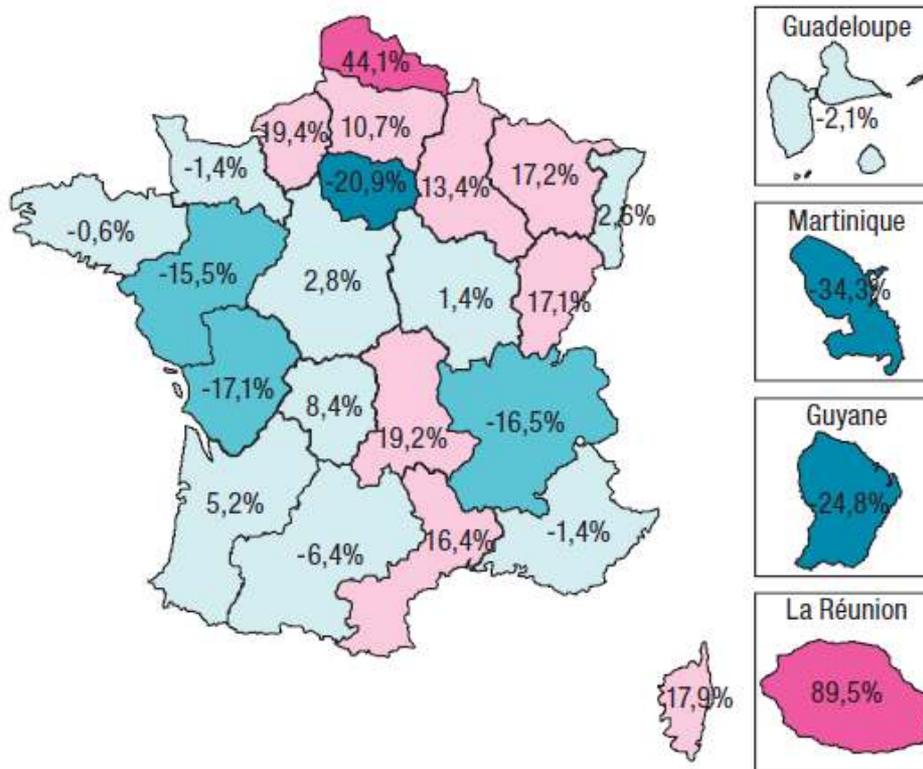
Q6 : Actuellement, prenez-vous un médicament pour traiter le cholestérol?

Q7 : Actuellement, prenez-vous un médicament pour traiter le diabète?

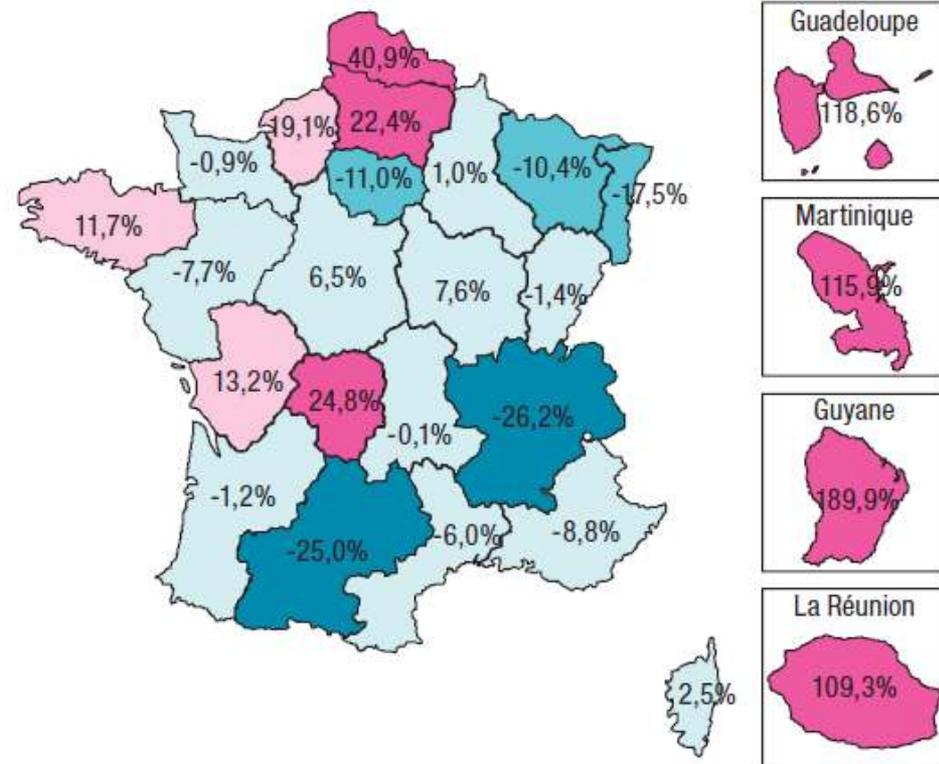
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Ensemble des individus âgés de 35 ans et plus (n=4783)

Disparités régionales de la mortalité cardiovasculaire prématurée France (2008-2010)



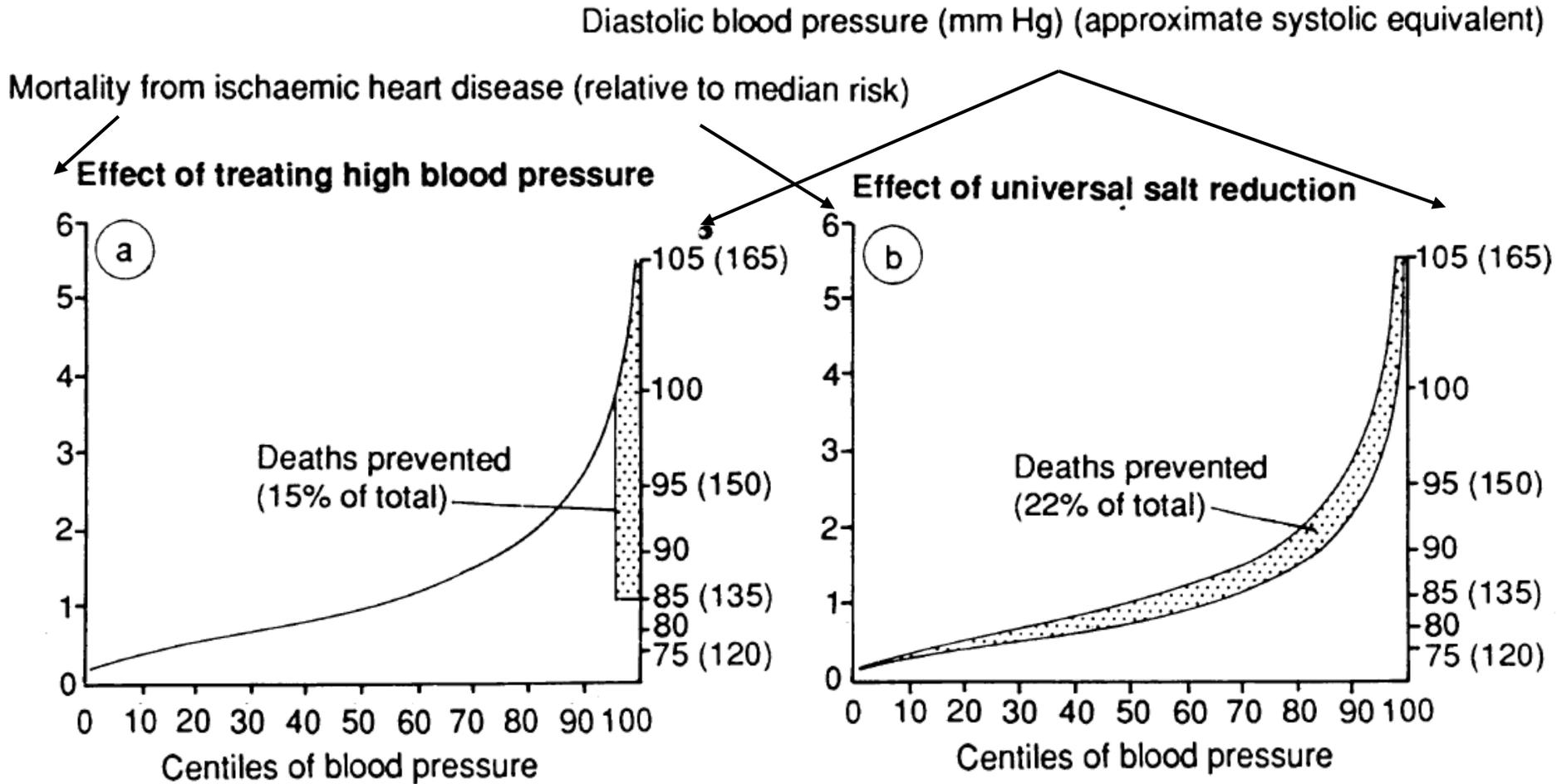
Cardiopathies ischémiques

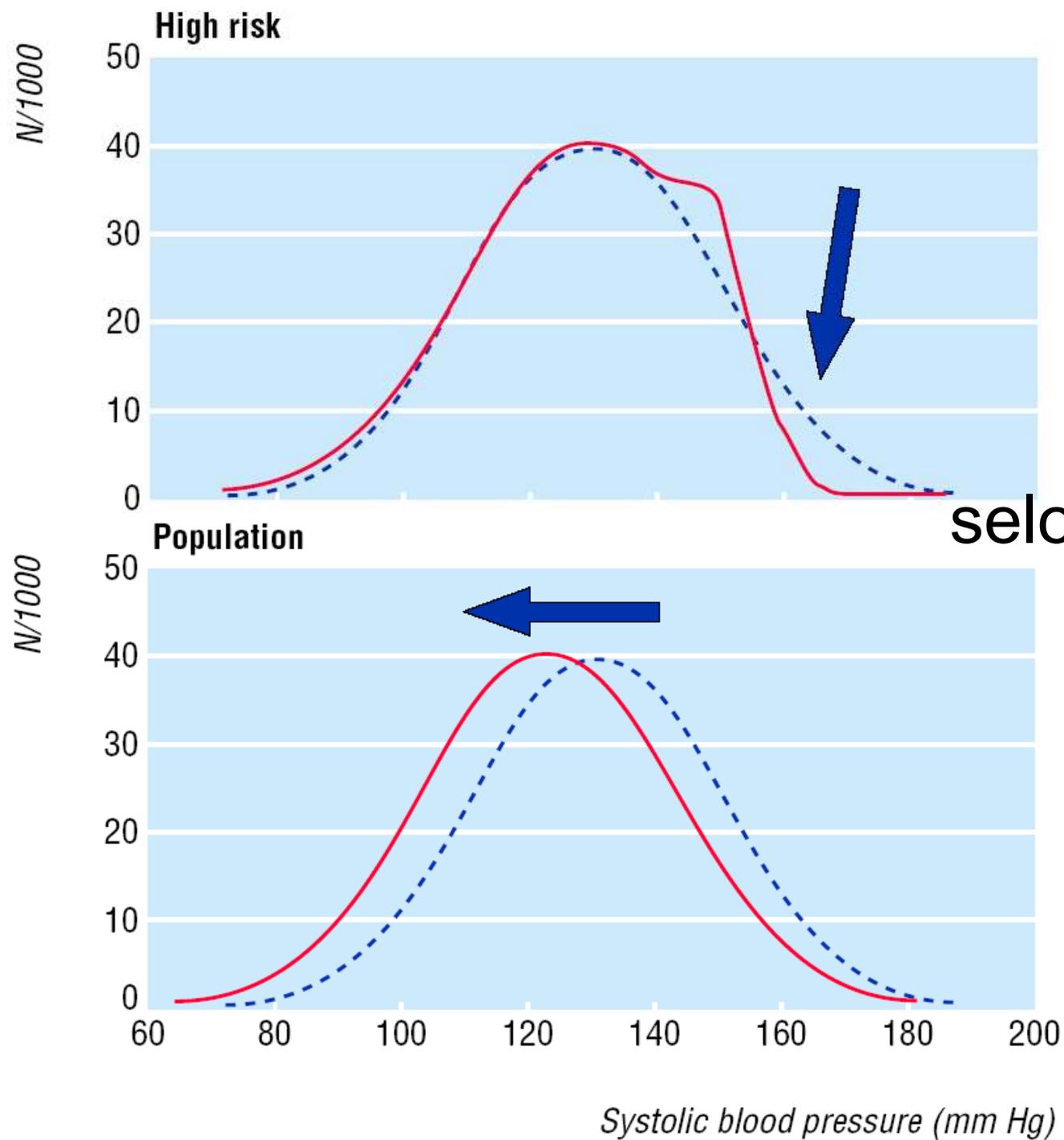


Accidents cérébro-vasculaires

Comparaison des approches thérapeutiques et préventives

(monothérapie antihypertensive vs réduction de l'apport sodé de 9 à 6 g/j)

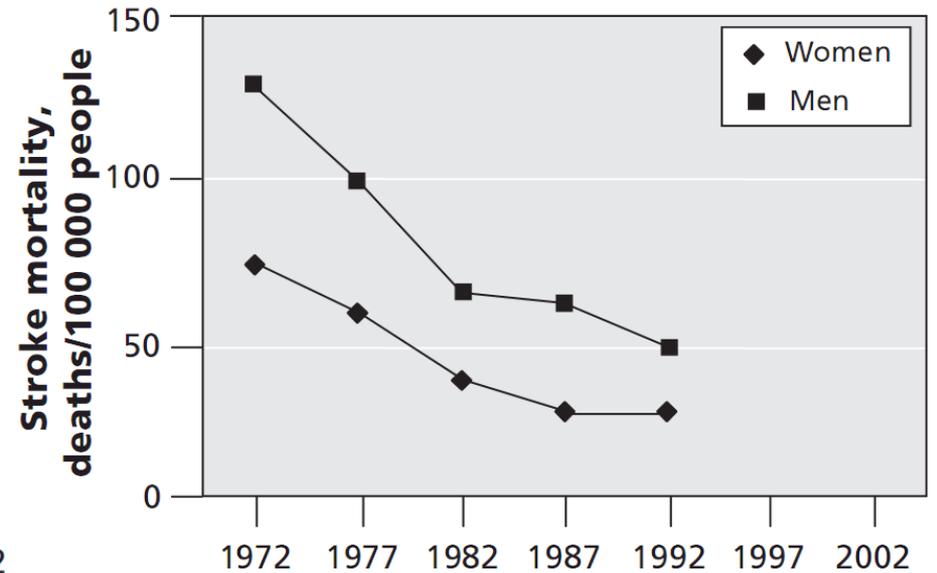
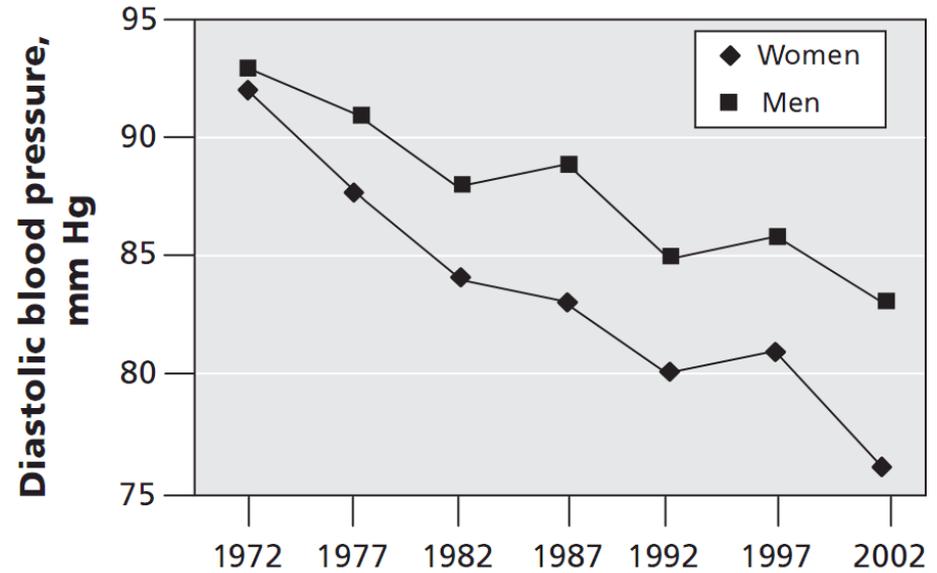
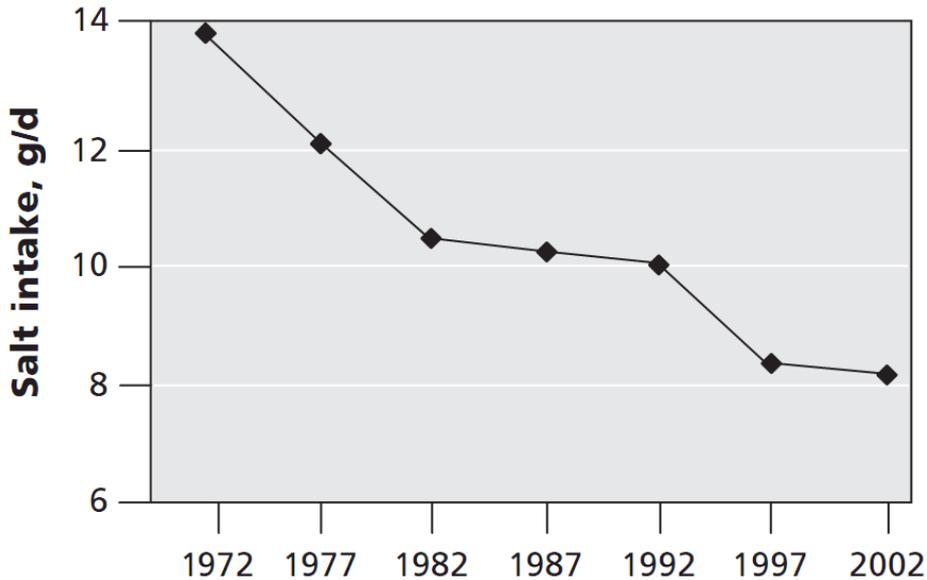




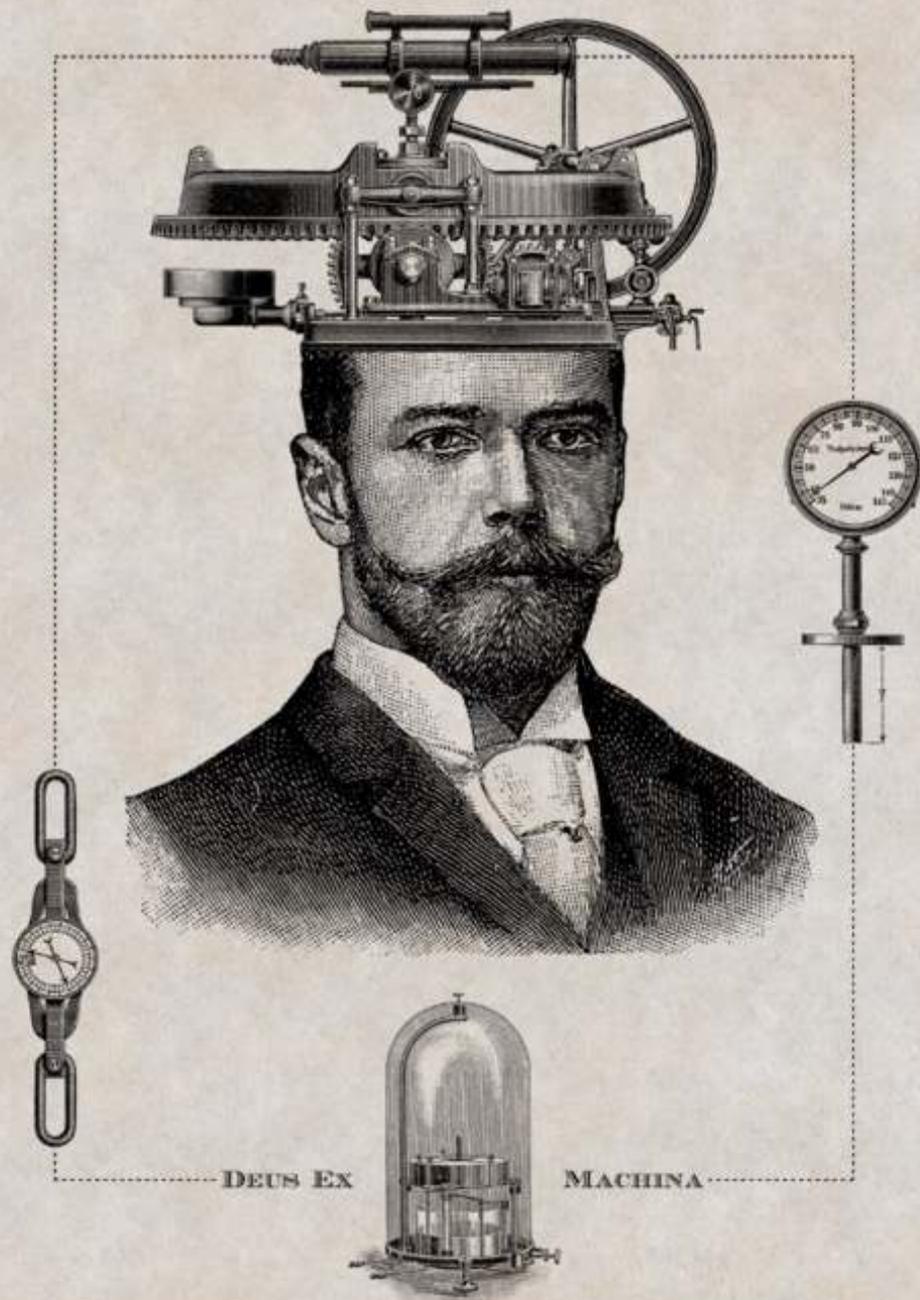
Impact sur une population idéale de deux stratégies de prévention : selon que l'on vise le segment à haut-risque ou l'ensemble

Campagne de réduction sodée : l'exemple finlandais

Pekka P, et al. Public Health Nutr 2002;5:245-51



Épilogue ?



L'ère des '-omiques'

exemple de l'analyse du microbiome intestinal humain

Composition

Biomarker profiling

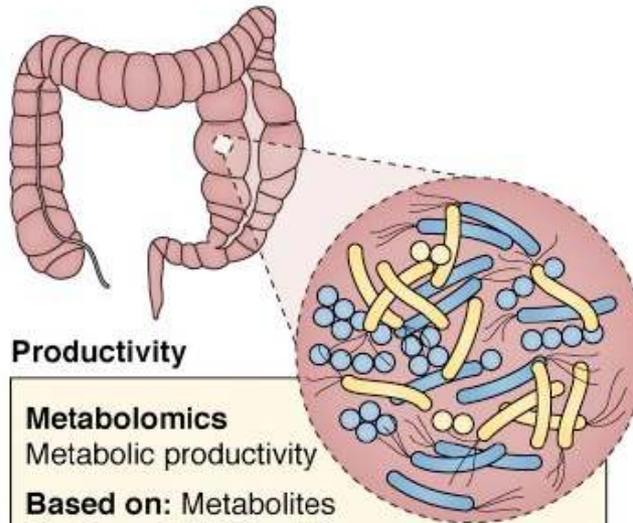
Microbiota composition

Based on: DNA

Platform: NGS

Pros: Cost-effective; semi-quantitative

Cons: Lacks functional information



Function

Metatranscriptomics

Microbial functional gene expression

Based on: RNA

Platform: NGS

Pros: Host and microbial gene transcripts

Cons: Samples require RNA preservation; host genes may predominate signal

Metagenomics

Microbiome functional gene capacity

Based on: DNA

Platform: NGS

Pros: Strain-level resolution

Cons: Expensive; computationally intensive

Productivity

Metabolomics

Metabolic productivity

Based on: Metabolites

Platform: LC/GC - MS

Pros: Semi-quantitative, targeted or untargeted

Cons: Origin of metabolite unclear

Metaproteomics

Protein expression

Based on: Proteins

Platform: LC/GC-MS

Pros: Semi-quantitative

Cons: Origin of proteins unclear

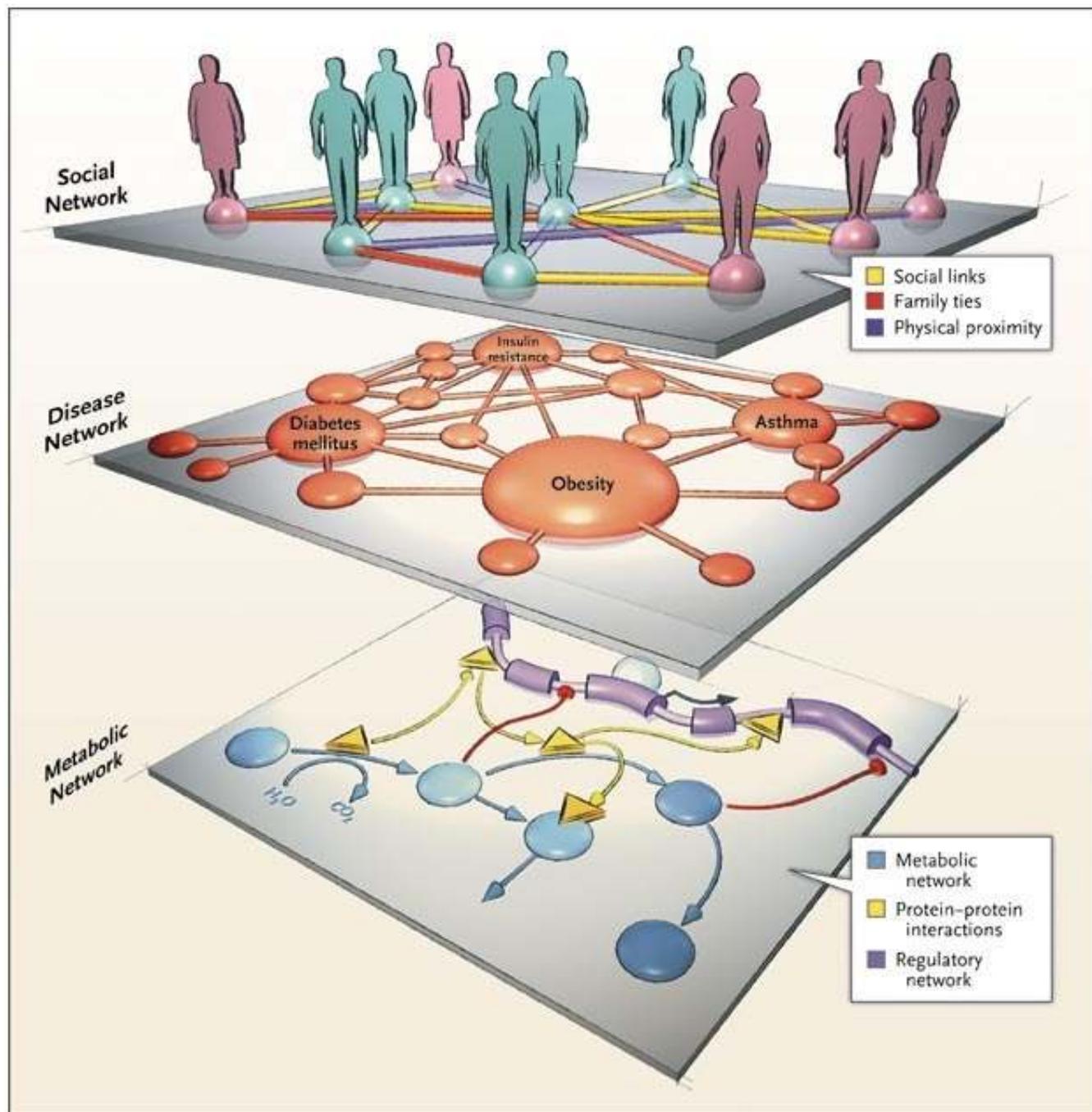
NGS, next-generation sequencing

LC/GC-MS, liquid/gas chromatography-mass spectrometry

L'ère des réseaux

Barabási, Albert-László.
Network medicine-
From obesity to the
“diseasome”.
N Engl J Med
2007;357;404-7

Christakis NA, Fowler JH.
The spread of obesity in
a large social network
over 32 years.
N Engl J Med
2007;357:370-9



A Spectrum from Philosophy to Math to Engineering

Philosophy



"How can we infer causal relations from observations?"

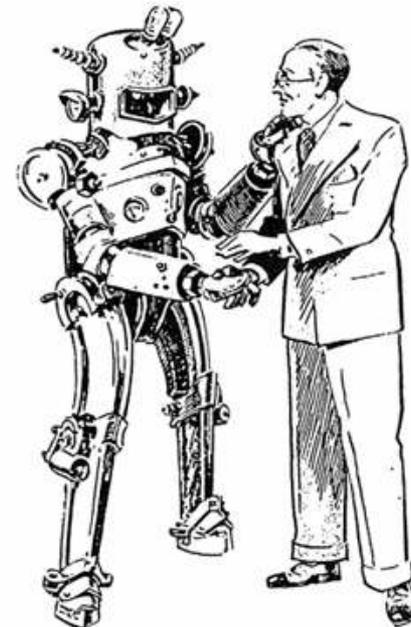
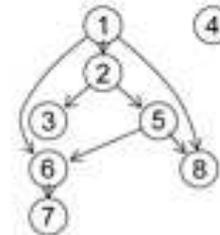
Math



$$p(X = x) = \prod_i p(X_i = x_i | PA_i = pa_i)$$

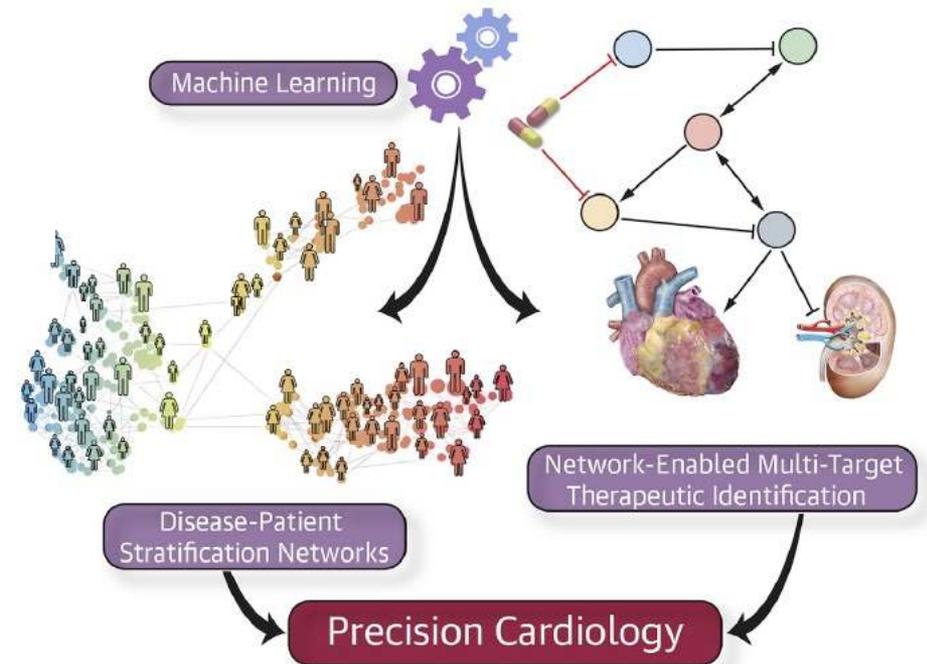
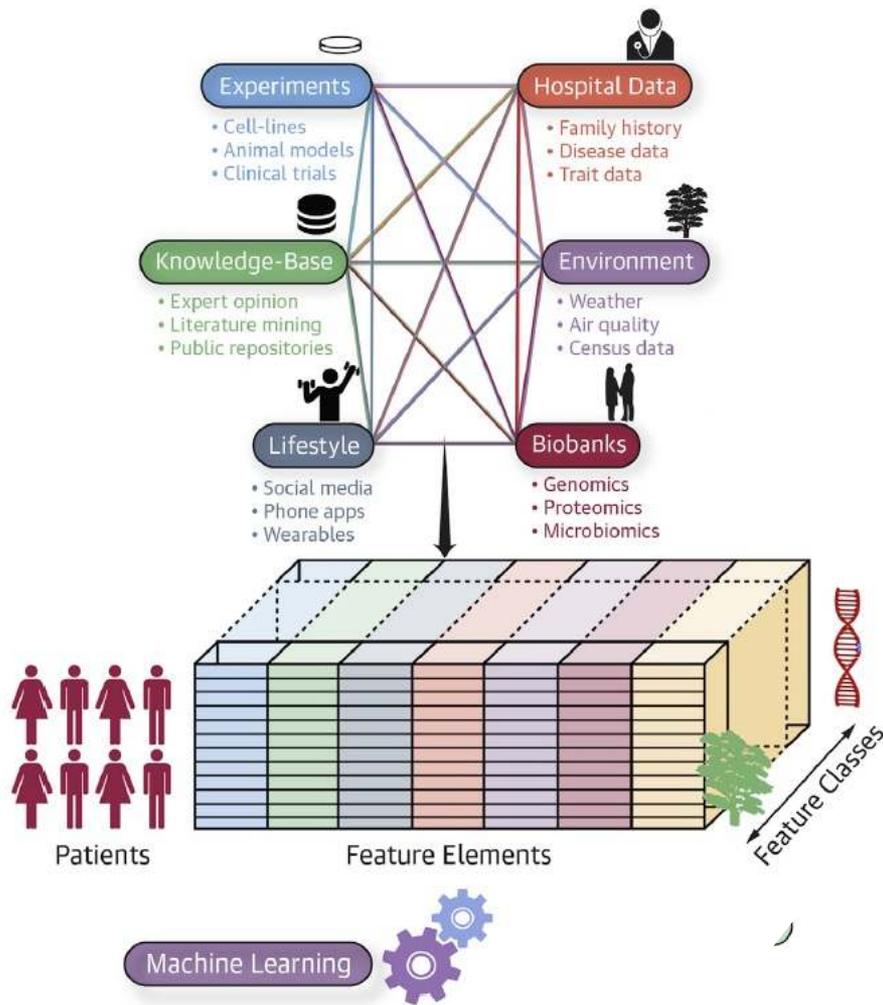
Engineering

```
R> require("gnalg")
R> data("gn2")
R> autoFitar <- list2l = auto(gn2$a), a = auto(gn2$b))
R> pc_fit <- skeleton(autoFitar, indepTest = gauss2test,
+ p = auto(gn2$b), Alpha = 0.01)
R> par2drow = c(1,2)
R> plot(gn2$d, main = "")
R> plot(pc_fit, main = "")
```

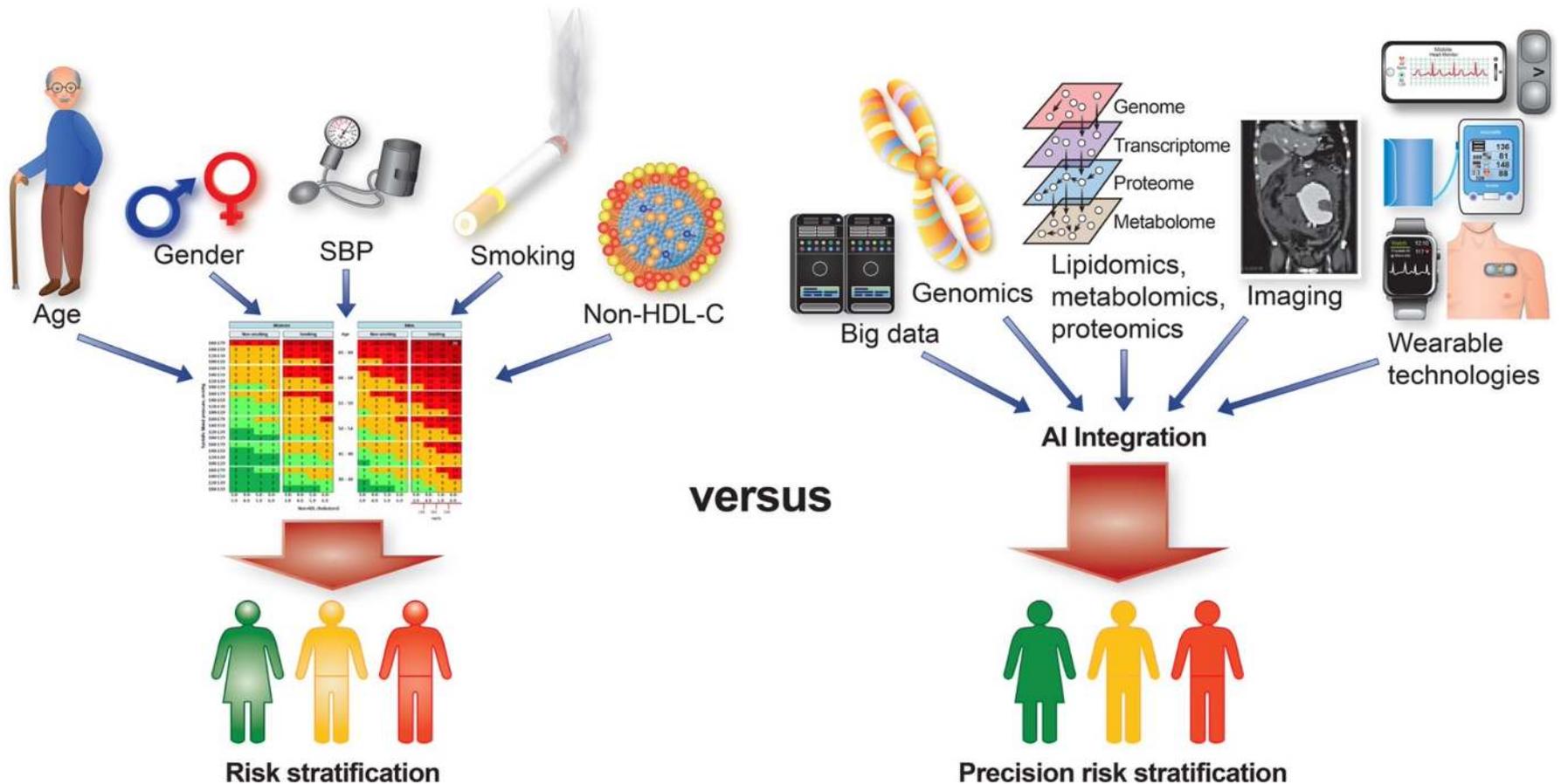


Aristote pose que le raisonnement inductif infère d'une série d'observations particulières une affirmation générale (de cause à effet). Sextus Empiricus, David Hume questionnent la validité de la connaissance ainsi basée. Judea Pearl pose que l'intelligence artificielle permet une approche déductive de l'inférence causale via la contrafactualité (Pearl J. *J Causal Infer* 2014;2:115-29)

Cardiologie de précision via l'apprentissage machine



The next frontier



Plutarque : l'opinion est l'ombre de la vérité



Pierre Soulages 1989