WCE
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Teaching epidemiology: global perspectives

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EPIDEMIOLOGY The study of the occurrence and distribution of health-related events, states, and processes in specified populations, including the study of the DETERMINANTS influencing such processes, and the application of this knowledge to control relevant health problems.

Study includes surveillance, observation, screening, hypothesis testing, analytic research, experiments, and prediction. *Distribution* refers to analysis by time, place (or space), and population (i.e., classes or subgroups of persons affected in an organization, population, or society, or at regional and global scales). *Determinants* are the geophysical, biological, behavioral, social, cultural, economic, and political factors that influence health. *Health-related events, states, and processes* include outbreaks, diseases, disorders, causes of death, behaviors, environmental and socioeconomic processes, effects of preventive programs, and use of health and social services. *Specified populations* are those with common contexts and identifiable characteristics. *Application to control*... makes explicit the aim of epidemiology—to promote, protect, and restore health, and to advance scientific knowledge.

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EPIDEMIOLOGY The study of the occurrence and distribution of health-related events, states, and processes in specified populations, including the study of the DETERMINANTS influencing such processes, and the application of this knowledge to control relevant health problems.

The primary "knowledge object" of epidemiology as a scientific discipline are causes of health-related events, states, and processes in groups and populations. In the past 90 years, the definition has broadened from concern with communicable disease epidemics to **include all phenomena related to health in populations**.

Therefore, epidemiology is much more than a branch of medicine treating of epidemics.

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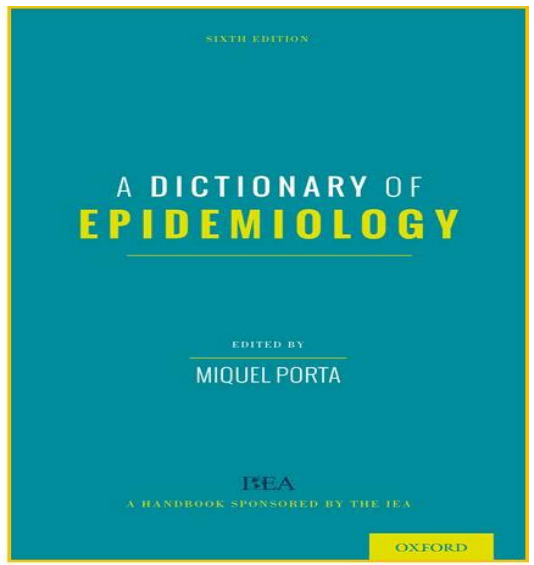
RISK FACTOR (Syn: determinant) A factor that is causally related with a change in the RISK of a relevant health process, outcome or condition. The causal nature of the relationship is established on the basis of scientific evidence (including, naturally, evidence from EPIDEMIOLOGICAL RESEARCH) and CAUSAL INFERENCE. The causal relationship is inherently probabilistic, as it happens in many other spheres of nature and human life.[101] Examples of types of risk factors are offered throughout this book; they may be a socioeconomic characteristic, personal behavior or lifestyle, environmental exposure, inherited characteristic or another TRAIT. Risk factors for human health often have individual and social components; even when individual and social risk factors can be separated, they often interact.

To prevent MEDICALIZATION of life and IATROGENESIS, the RELEVANCE and SIGNIFICANCE of the factor-outcome risk relationship must be cautiously assessed; so must uncertainties and ambiguities in risk-related concepts, as well as different legitimate meanings of risk across and within cultures.[1,2,3,5,6,9,13,29,33,38,42,56,58,91,106-108,113,158,215,248,270,279,292,303,304,332-336,350, 361,426,539,600,603,712-718]



Sick individuals and sick populations

Geoffrey Rose

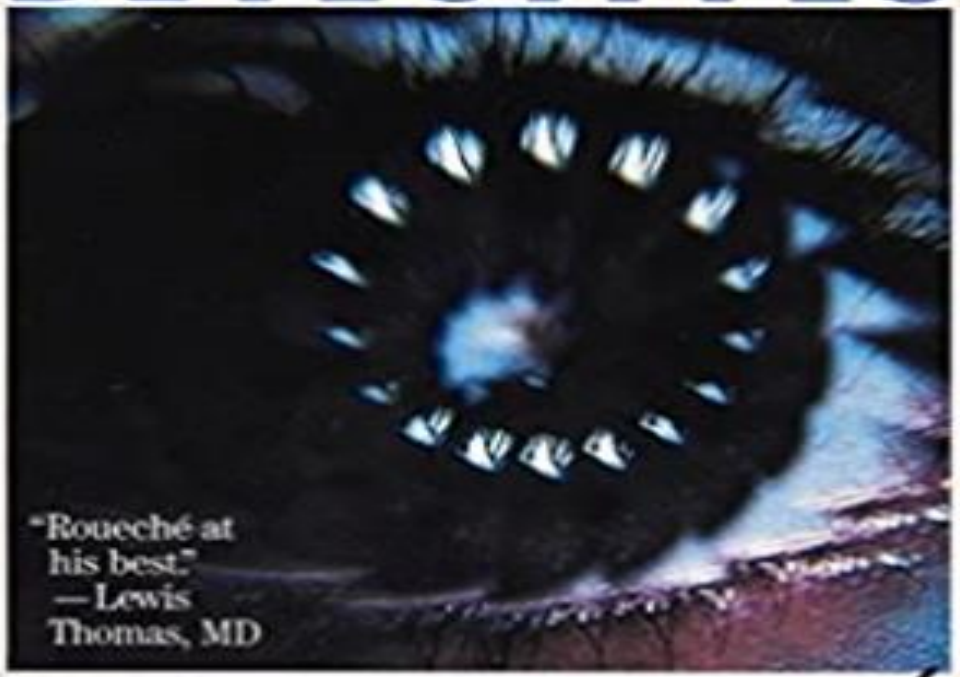
Rose G (Department of Epidemiology, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK). Sick individuals and sick populations. *International Journal of Epidemiology* 1985;**14**:32–38.

Aetiology confronts two distinct issues: the determinants of individual cases, and the determinants of incidence rate. If exposure to a necessary agent is homogeneous within a population, then case/control and cohort methods will fail to detect it: they will only identify markers of susceptibility. The corresponding strategies in control are the 'high-risk' approach, which seeks to protect susceptible individuals, and the population approach, which seeks to control the causes of incidence. The two approaches are not usually in competition, but the prior concern should always be to discover and control the causes of incidence.

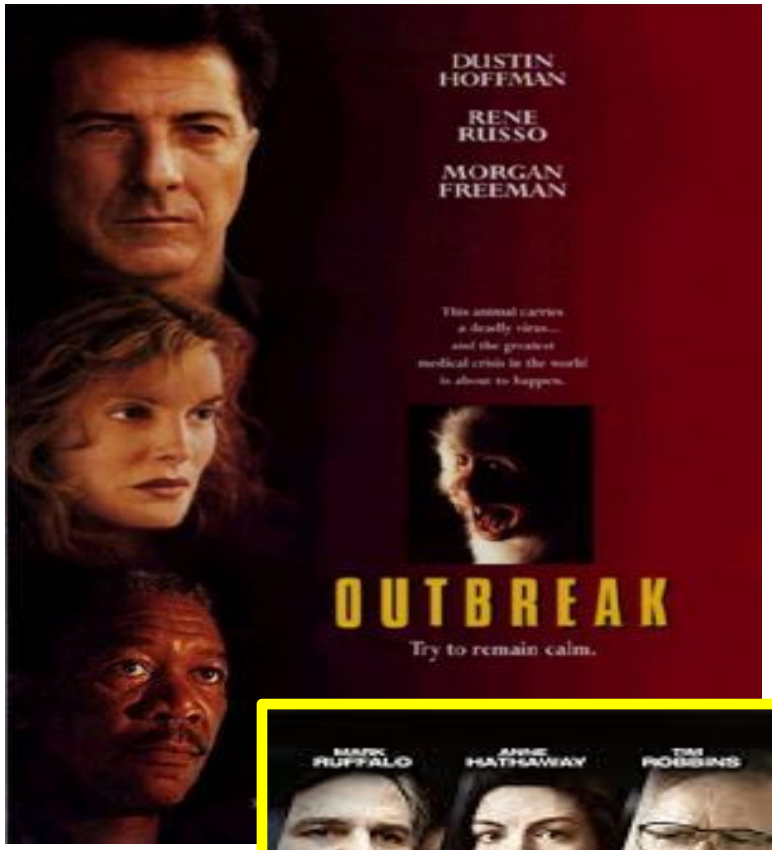
Based on a lecture to the Xth Scientific Meeting of the International Epidemiological Association, 27 August 1984, Vancouver, Canada.

The Classic Collection of Award–Winning Medical Investigative Reporting

THE MEDICAL DETECTIVES



BERTON ROUECHÉ


DUSTIN HOFFMAN
RENE RUSSO
MORGAN FREEMAN
OUTBREAK
Try to remain calm.


BLU-RAY
STEVEN SODERBERGH
CLIVE OWEN
THE KNICK
THE COMPLETE FIRST SEASON - L'INTÉGRALE DE LA PREMIÈRE SAISON
MODERN MEDICINE HAD TO START SOMEWHERE
CINEMAX
HBO

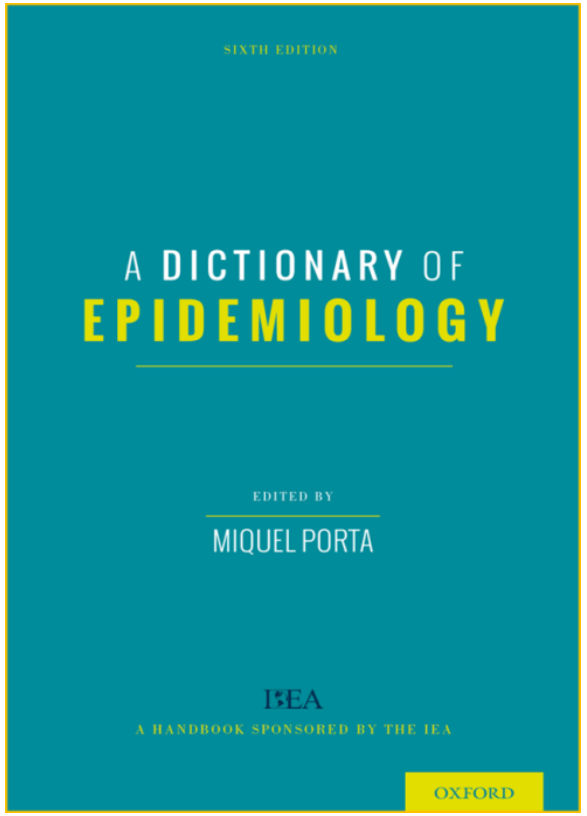

MARION COTILLARD
MATT DAMON
LAURENCE FISHBURNE
JUDE LAW
GWYNETH PALTROW
KATE WINSLET
NOTHING SPREADS LIKE FEAR
CONTAGION
SEPTEMBER 9
IN THEATERS AND IMAX


MARK RUFFALO
ANNE HATHAWAY
TIM ROBBINS
BILL PULLMAN
A TODD HAYNES FILM
DARK WATERS
12
ONE OF THE DEADLIEST COVER-UPS IN AMERICAN HISTORY
12


CHERNOBYL
HBO

RELEVANCE

1. The importance for existing ideas or practices. The degree to which a study, program, policy, or organization should theoretically change or can actually influence knowledge, beliefs, ideas, attitudes, decisions, actions, policies, structures, procedures, techniques, or processes of all sorts (social, cultural, political, organizational, individual, medical, biological, etc.).
2. In epidemiology, a relevant study or program may be one that makes a practical or a theoretical contribution to the identification, characterization, understanding, or solution of a public health, environmental, social, clinical, biological, or technological problem. EPIDEMIOLOGICAL RESEARCH usually aims at having social, environmental, or public health relevance; epidemiological studies often also have clinical, biological, methodological, or technological relevance.
3. In clinical and epidemiological research, *relevance* is commonly used as a synonym of importance and of SIGNIFICANCE. Statistical significance must be distinguished from clinical and public health significance. A statistically significant effect may be found in a study with a large number of participants and yet lack clinical or public health significance (because the magnitude of the effect is small, for instance). Hence, statistical significance should never be assumed to equal *significance*, and *significance* encompasses more than statistical significance. Clinical studies usually aim at being clinically significant, important, or relevant for the care of patients. Sometimes, epidemiological and clinical studies are also mechanistically relevant; e.g., they produce knowledge on mechanisms of disease.[1-3,5-9,25,26,28,91,101,202,222] See also MECHANISTIC EPIDEMIOLOGY; MINIMALLY IMPORTANT DIFFERENCE; SIGNIFICANCE, CLINICAL.



EPIDEMIOLOGICAL RESEARCH Scientific research among human populations and defined groups of individuals into the frequency of occurrence, distribution and causes of phenomena of public health, clinical, social, or biological RELEVANCE, with valid selection of subjects and measurements, and formal CAUSAL INFERENCES on the DETERMINANTS of such phenomena.[1-3,5-9,24-26,39-42,58,85,128,202,270,279] See also CREATIVITY; INTEGRATIVE RESEARCH.

RESEARCH A class of activities designed to develop or contribute to knowledge. In applied science, the goal is generalizable knowledge, where the latter consists of theories, principles, relationships, products, or the accumulation of information on which these are based that can be corroborated by acceptable scientific methods of observation, inference, or experiment. When humans are the subjects of EPIDEMIOLOGICAL RESEARCH, ethical review is mandatory; however, there is a blurry boundary between research, which must undergo review, and common clinical or public health practice (e.g., SURVEILLANCE and epidemic control), to which the same rules may not apply, but that still must comply with ethical requirements.[1,3,5-9,26,202,270] See also INTEGRATIVE RESEARCH.

Source: Porta M, ed. A dictionary of epidemiology. 6th. edition (2014).

EPIDEMIOLOGICAL RESEARCH Scientific research among human populations and defined groups of individuals into the frequency of occurrence, distribution and causes of phenomena of public health, clinical, social, or biological RELEVANCE, with valid selection of subjects and measurements, and formal CAUSAL INFERENCES on the DETERMINANTS of such phenomena.[1-3,5-9,24-26,39-42,58,85,128,202,270,279] See also CREATIVITY; INTEGRATIVE RESEARCH.

INTEGRATIVE RESEARCH Research that integrates knowledge, data, methods, techniques, reasoning, and other scientific and cultural referents from multiple disciplines, approaches, and levels of analysis to generate knowledge that no discipline alone could achieve. For instance, research that integrates cultural, economic, and other "macro-level" or contextual factors with individual factors, as in MUTILEVEL ANALYSIS; analyses of the relationships among gene structure, expression, and function; research on the relationships among molecular pathways, PATHOPHYSIOLOGY, and clinical phenotypes, as in clinical pharmacology and clinical genetics; research that integrates interactions among environmental, genetic, and epigenetic processes.[1,13,26,33,80,146,202,323,339,411,548,799] Epidemiology is an inherently integrative discipline, and so are many of its subspecialities, and approaches, like CLINICAL and MOLECULAR EPIDEMIOLOGY, SOCIAL EPIDEMIOLOGY or ENVIRONMENTAL EPIDEMIOLOGY; DEVELOPMENTAL AND LIFE COURSE EPIDEMIOLOGY, for instance, attempts to integrate biological and social risk processes.[23,25] See also CLINICAL STUDY; HEALTH IMPACT ASSESSMENT; TRANSDISCIPLINARITY; REDUCTIONISM.

INTEGRATION

1. The action or process of integrating. To integrate: to make a new whole; to combine parts into a new system and get them to interact so that the system expresses functions unavailable to the parts. The organizing of elements to form a coherent whole or system. Integration of knowledge from different scientific disciplines yields knowledge that no discipline alone may achieve.
2. In HEALTH PROMOTION and disease PREVENTION, strategies that target several risk factors, use multiple STRATEGIES at various levels of influence, and require INTERSECTORAL ACTION.[121] Integration entails multiplicity (more than one RISK FACTOR, level, sector, agent), and synergy resulting from multiplicity.[17]

Integration is no less crucial to science than to the functioning of postmodern societies. Examples: quality public transportation favors integration of disabled individuals and disadvantaged groups into society; integration of racial and ethnic minorities into the educational system; integration of preventive services into clinical care.[25,33,426,548] Synonyms, analogies, and METAPHORS are here useful as well: *integration* involves and refers to interaction, dialogue, complicity, performance, symbiosis, sharing, pooling, porousness, amalgamation, merging, coalescing, fusing, welding, blending, weaving.

Source: Porta M, ed. A dictionary of epidemiology. 6th. edition (2014).

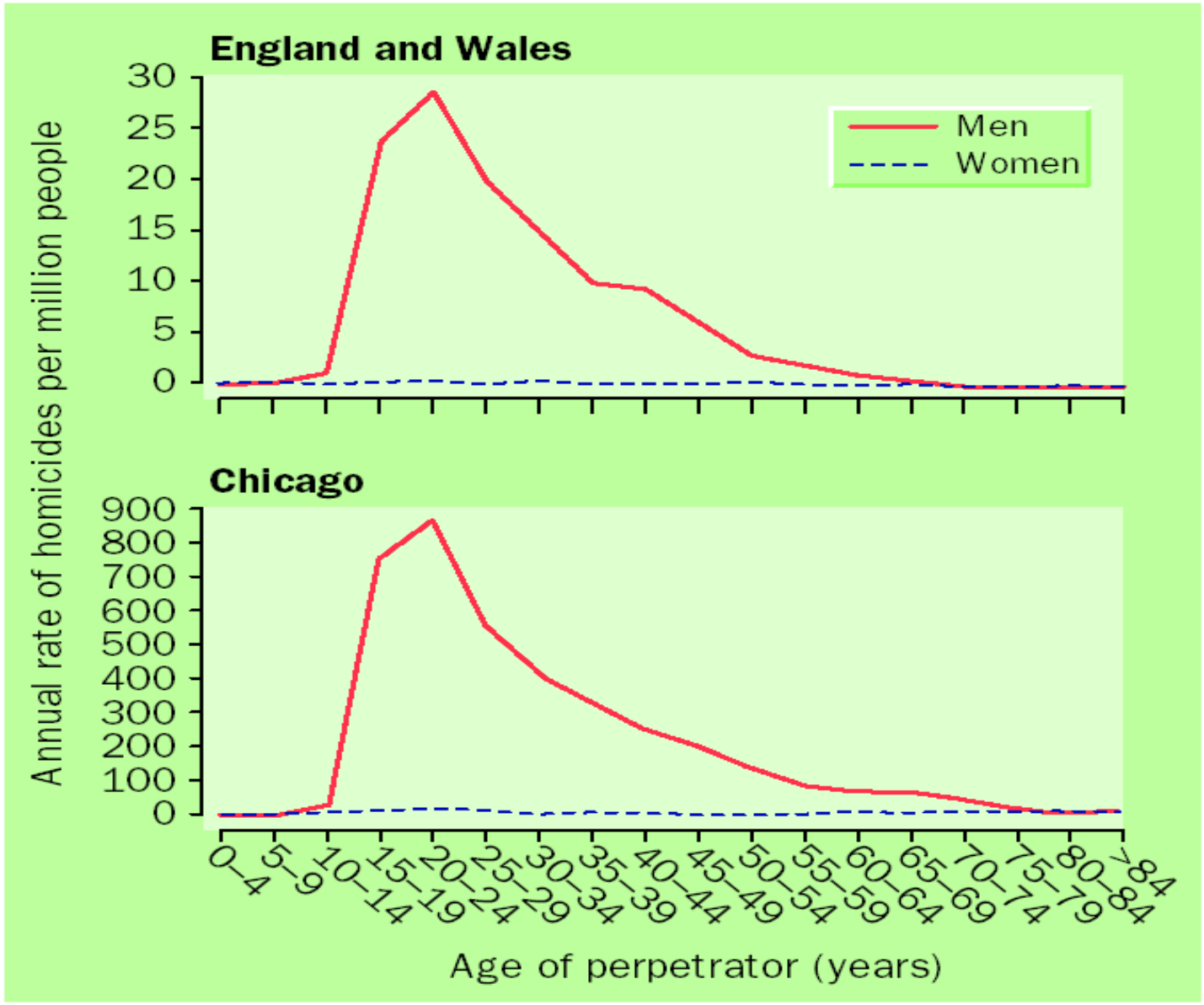


Figure 1: **Rates of homicide in Chicago and England and Wales by age and sex of perpetrator**

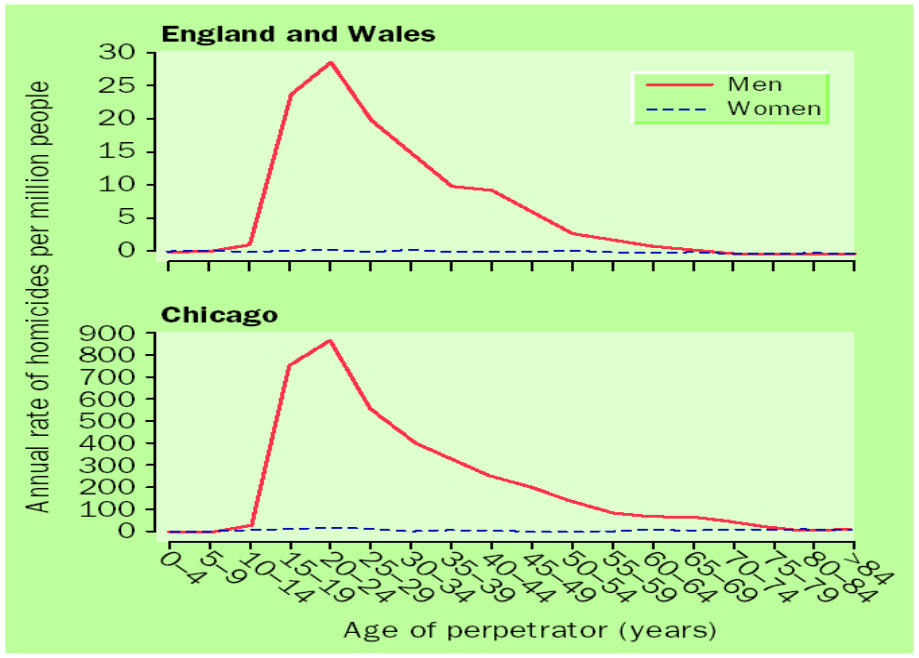


Figure 1: **Rates of homicide in Chicago and England and Wales by age and sex of perpetrator**

violence and gender:
it is often good to **integrate**
all dimensions of the question:
structural, mediating, individual...
political, cultural...

Sex vs gender.

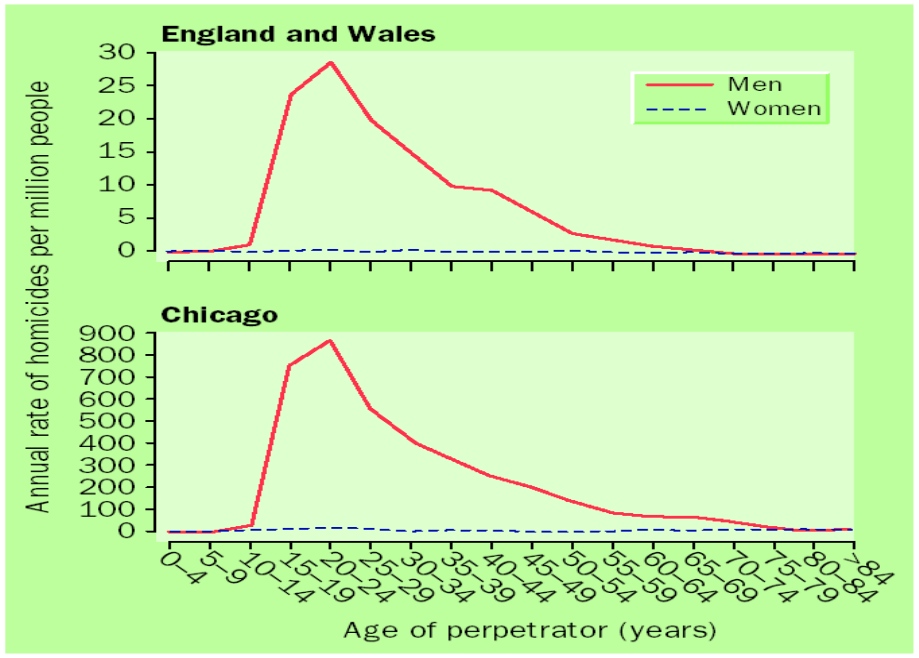
Age, birth cohort, historical period.

Economy, school, education, moral, laws, culture, policies...
lobbies (arms control)...

Individual, family, neighborhood, society, the State...

☑ No: look at ony one dimension of the problem.

☑ **YES: integrate** all dimensions, weighing.



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structural, mediating, individual...
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Main differences between England & Wales and Chicago?

→ Socio-economic inequalities?

→ Regulation of acces to arms?

Political questions, public health questions:
most influential on the health, life and death / mortality
of individuals and societies.

PUBLIC HEALTH Like most sculptures, symphonies, and other works of art, certain important things in life have several dimensions. The definition of public health has four dimensions. Public health is:

1. The health of a whole society. It can be measured and assessed through quantitative and qualitative indicators and analytic processes.
2. The specific policies, services, programs and other essential efforts agreed (ideally, and often, democratically), organized, structured, financed, monitored, and evaluated by society to collectively protect, promote, and restore the people's health and its determinants.
3. The institutions, public and private organizations—including private and public companies—, and other citizens organizations, that plan, develop, fund, and implement such efforts, and which are thus an integral part of local, national, regional, and global public health systems.
4. The scientific disciplines and professions, knowledge, methods, art, and craft essential to positively influence HEALTH DETERMINANTS, and thus prevent disease and disability, prolong life, and promote HEALTH through the organized and collective efforts of society.

A dictionary of epidemiology. 6th. edition (2014).

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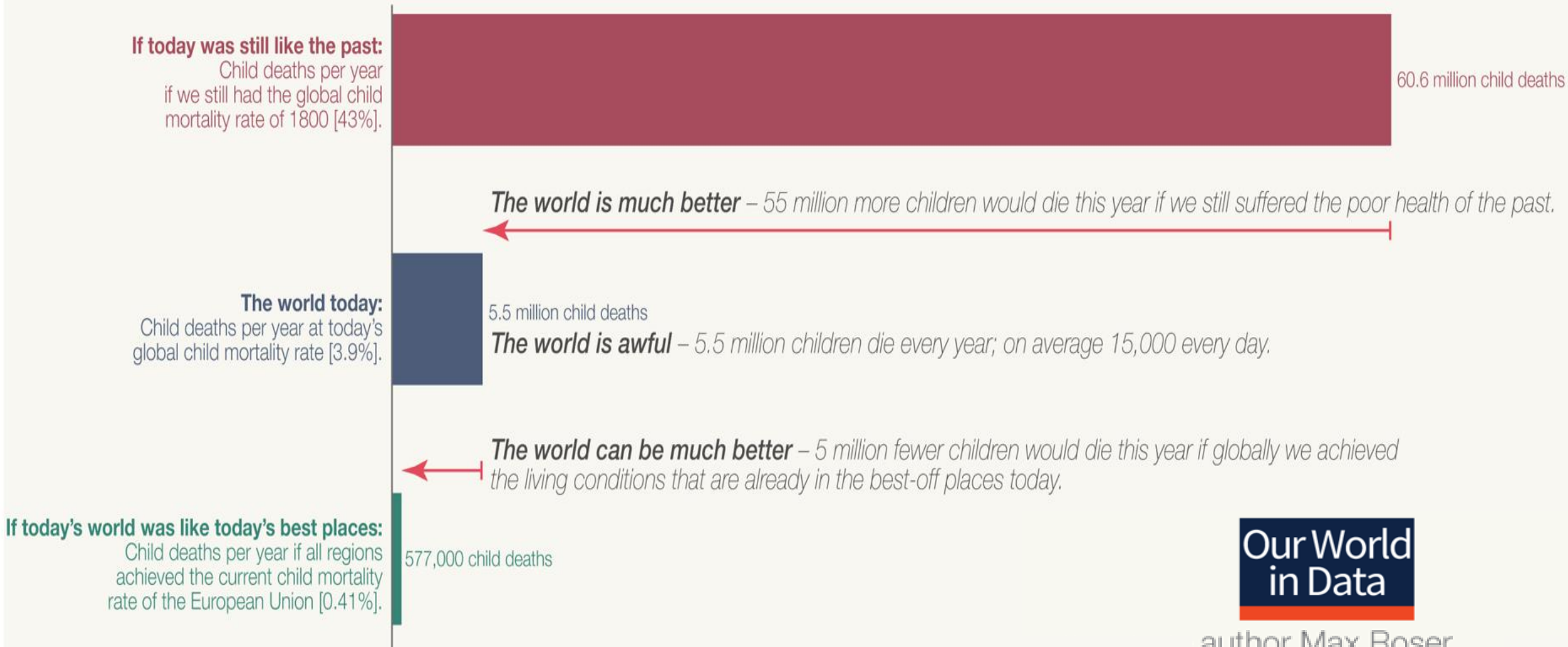
actions of public health + and −
during the pandemic made it clear massively.

Public health takes care daily of what we breathe, drink, and eat, how we work, move, and live together. Economic, environmental, social, educational, occupational, medical, and other policies intertwined with public health change with changing social values and networks, policies and technologies; yet, the goals—diverse as they are in democratic societies—remain the same: to reduce the amount of health-related suffering, disease, disability, and premature death in the population. Public health is a SYSTEM of professions and scientific disciplines, social organizations and institutions, values, and actions.

epidemiology & public health are
already existing realities,
partly (in)visible.
and a diverse set of proposals
(political, cultural, ethical, civic).

The world is much better; The world is awful; The world can be much better



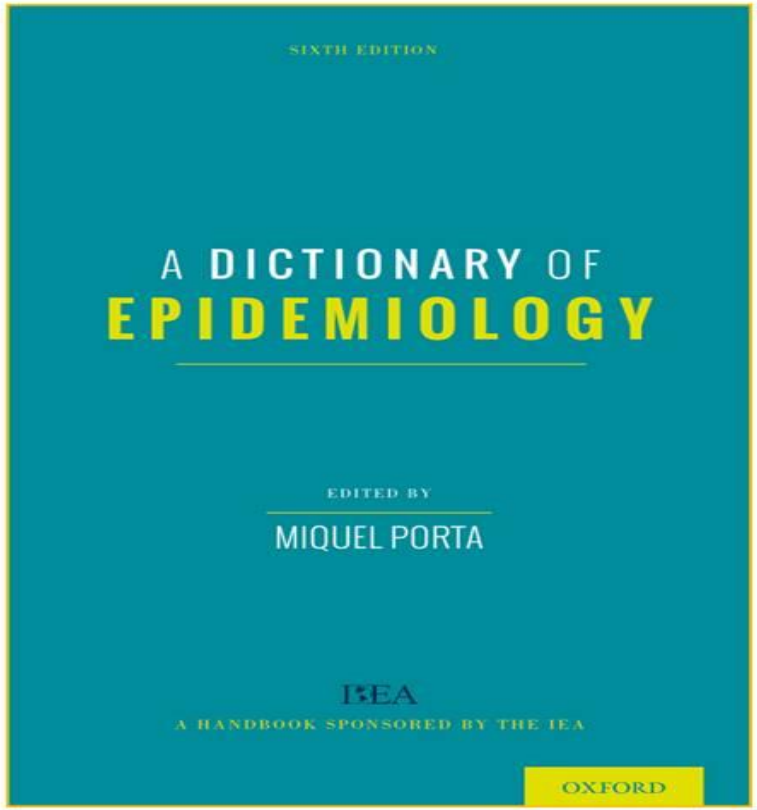
Our World in Data

author Max Roser.

A profound methodological renewal
—or perhaps "revolution"— is ongoing.

It is partly or completely changing basic concepts such as, *risk, rate, attributable fraction, bias, selection bias, confounding, interaction, cumulative and density sampling, generalizability, open population, test hypothesis, null hypothesis, causal null, causal inference, Berkson's bias, Simpson's paradox, representativeness, missing data, standardization, or overadjustment*.

It is also reflected in terms as *collider, M-bias, causal diagram, backdoor (biasing path), instrumental variable, negative controls, inverse probability weighting, identifiability, transportability, positivity, ignorability, collapsibility, exchangeable, g-estimation, marginal structural models, risk set, immortal time bias, Mendelian randomization, counterfactual outcome, potential outcome, sample space*.

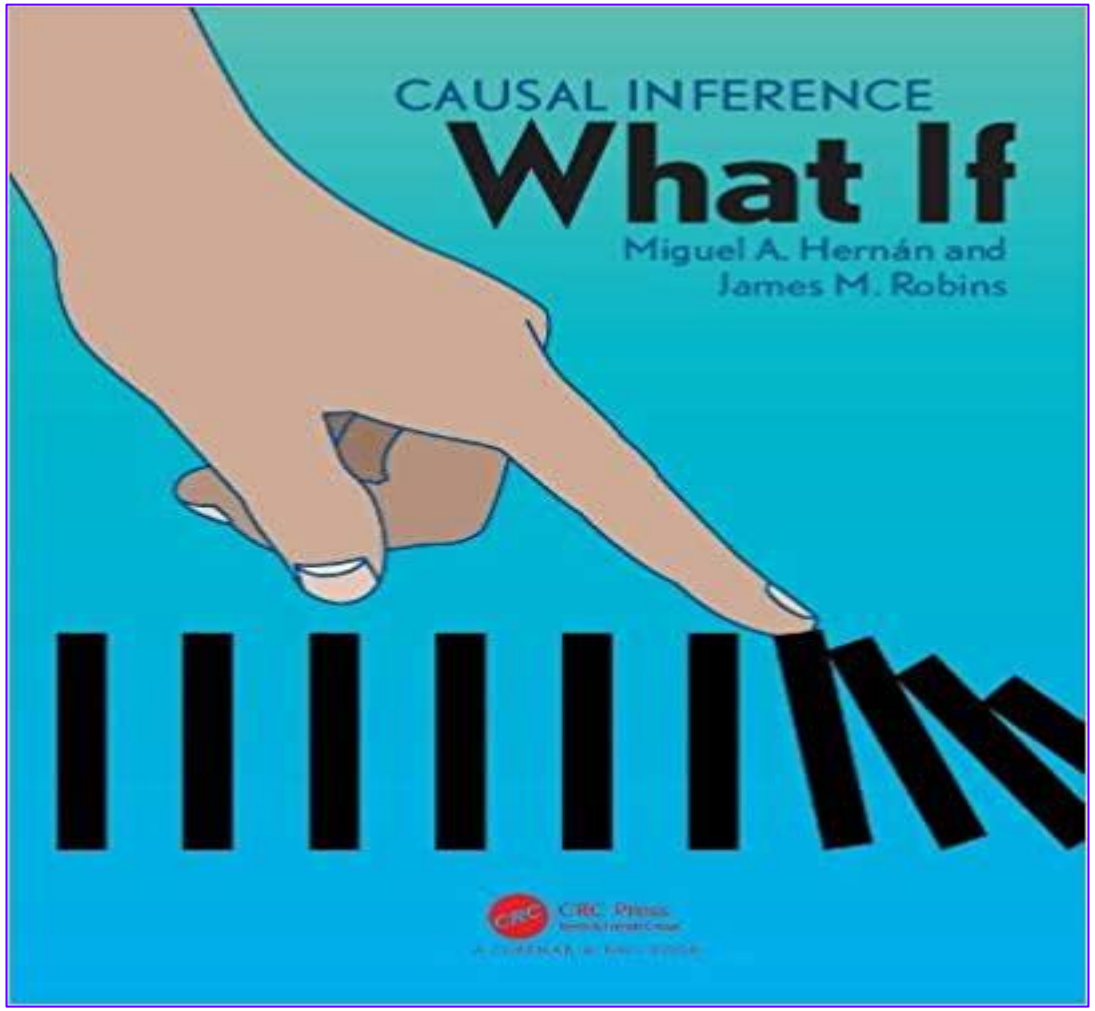


Eur J Epidemiol (2015)

The current deconstruction of paradoxes: one sign of the ongoing methodological "revolution"

Miquel Porta[1,2,3] · **Paolo Vineis**[4,5] · **Francisco Bolúmar**[3,6,7]

Abstract The current deconstruction of paradoxes is one among several signs that a profound renewal of methods for clinical and epidemiological research is taking place; perhaps for some basic life sciences as well. The new methodological approaches have already deconstructed and explained long puzzling apparent paradoxes, including the (non-existent) benefits of obesity in diabetics, or of smoking in low birth weight. Achievements of the new methods also comprise the elucidation of the *causal structure* of long-disputed and highly complex questions, as Berkson's bias and Simpson's paradox, and clarifying reasons for deep controversies, as those on estrogens and endometrial cancer, or on adverse effects of hormone replacement therapy. These are signs that the new methods can go deeper and beyond the methods in current use. A major example of a highly relevant idea is: when we condition on a common effect of a pair of variables, then a spurious association between such pair is likely. The implications of these ideas are potentially vast. A substantial number of apparent paradoxes may simply be the result of *collider biases*, a source of selection bias that is common not just in epidemiologic research, but in many types of research in the health, life, and social sciences. The new approaches develop a new framework of concepts and methods, as collider, instrumental variables, d-separation, backdoor path and, notably, Directed Acyclic Graphs (DAGs). The current theoretical and methodological renewal—or, perhaps, "revolution"—may be changing deeply how clinical and epidemiological research is conceived and performed, how we assess the validity and relevance of findings, and how causal inferences are made. Clinical and basic researchers, among others, should get acquainted with DAGs and related concepts.



https://www.hsph.harvard.edu/miguel-hernan/causal-inference-book/

https://pubmed.ncbi.nlm.nih.gov/26164615/

http://blog.oup.com/2014/10/deconstruction-paradoxes-sociology-epidemiology/

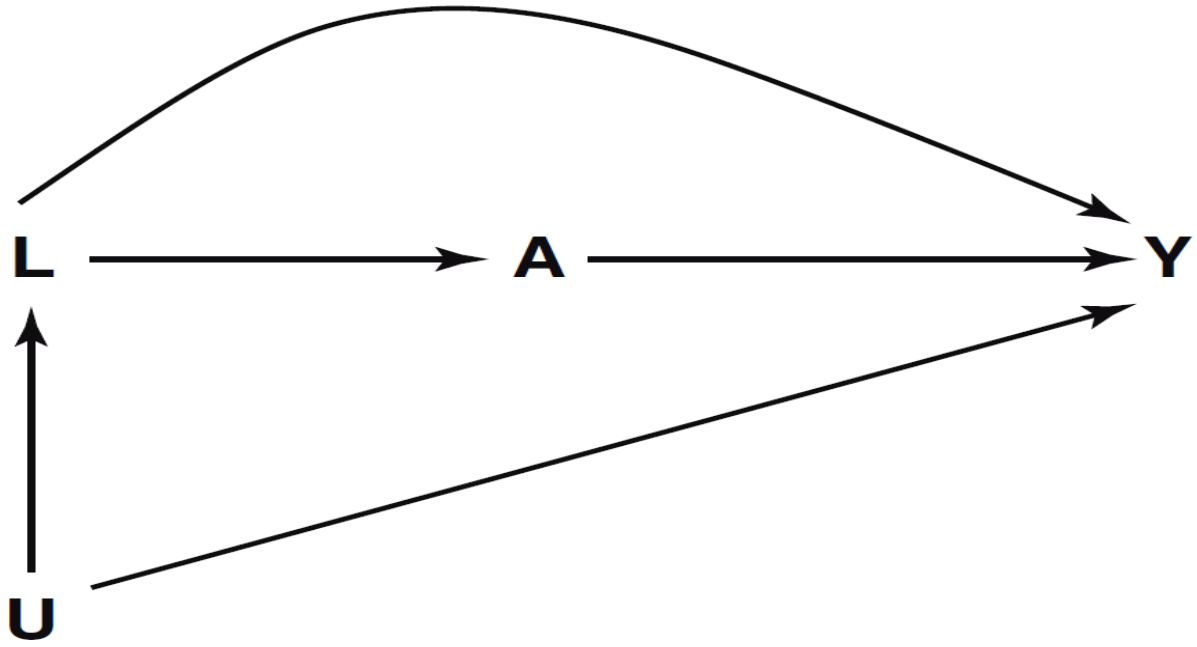
https://www.oxfordreference.com/page/medicineandhealth/medicine-and-health#Featured-author

EXPERIMENTAL STUDY A study in which the investigator intentionally alters one or more factors and controls the other study conditions in order to analyze the effects of so doing. A study in which conditions are under the direct control of the investigator.[7,101]

INTENTION-TO-TREAT ANALYSIS (ITT) A fundamental way to analyze a RANDOMIZED CONTROLLED TRIAL in which all subjects allocated to each arm of the trial are analyzed "as intended" upon randomization, whether or not they actually received the exposure allocated or completed treatment.[1,2,24,272,443-445,641,800] Failure to follow this approach defeats the main purpose and advantage of RANDOM ALLOCATION and can cause serious CONFOUNDING BIAS. This approach is virtually always required as part of the primary analysis of studies aiming to influence clinical or public-health decisions and policy formulation. It may be complemented by an explanatory analysis, in which subjects are analyzed according to the exposure they actually experienced (with adjustment for possible confounders, i.e., with an analytic approach similar to an observational cohort study), or in which some participants (e.g., subjects who complied poorly with the protocol) are excluded from analyses.[1,6,9,26,58,101,270,272,641,800] An intention-to-treat analysis does not determine whether and how to impute missing data on the outcome measure. Because of its pragmatic nature, ITT can underestimate treatment efficacy or have a low explanatory capacity

OBSERVATIONAL STUDY (Syn: nonexperimental study) A study that does not involve any intervention (experimental or otherwise) on the part of the investigator.[1-3,6,9,25,26,39-42,197,239,269,270,272,795] A study with RANDOM ALLOCATION of treatments or other exposures is inherently experimental or nonobservational. Observations are not just a haphazard collection of facts; in their own way, observational studies must apply the same rigor as experiments, and vice versa.[201,276] Many important preclinical, clinical, and epidemiological studies (and studies in other branches of science) are completely observational or have strong observational components.[101] Dismissive attitudes toward observational research have a weak scientific basis. In the health, life, and social sciences—and in other sciences as well—there has long been a fruitful dialectic tension between observation and experiment; facts and reasons; actions, explanations, mechanisms.[1,3,6,9,26,38-42,64,83,101,201-203,639-641,798,800] Often, observational and experimental studies on the apparently same issue actually answer *different questions*; for example, a randomized clinical trial will compare women allocated to hormone replacement therapy (HRT) and women allocated to another therapy or a placebo, and perform an INTENTION-TO-TREAT ANALYSIS, whereas an observational study will compare rather different women (than those included in a RCT) who were actually exposed to HRT and women exposed to other therapies or none; characteristics of subjects, context, exposures, timing, confounders, and interactions are just six of the many reasons that usually make different designs answer different questions. Also, different designs have different strengths and weaknesses to help make decisions and CAUSAL INFERENCES. Some observational studies may be analyzed as experiments; and some experiments, as observational studies.[2,641,800] See also CASE REPORTS; CLINICAL STUDY.

CAUSAL DIAGRAM (Syn: causal graph, path diagram) A graphical display of causal relations among variables, in which each variable is assigned a fixed location on the graph (called a *node*), and in which each direct causal effect of one variable on another is represented by an arrow with its tail at the cause and its head at the effect.[100] Direct noncausal associations are usually represented by lines without arrowheads. Graphs with only directed arrows (in which all direct associations are causal) are called *directed graphs*. Graphs in which no variable can affect itself (no feedback loop) are called *acyclic*. Methods have been developed to determine from causal diagrams which sets of variables are sufficient to control CONFOUNDING and for when control of variables leads to BIAS.



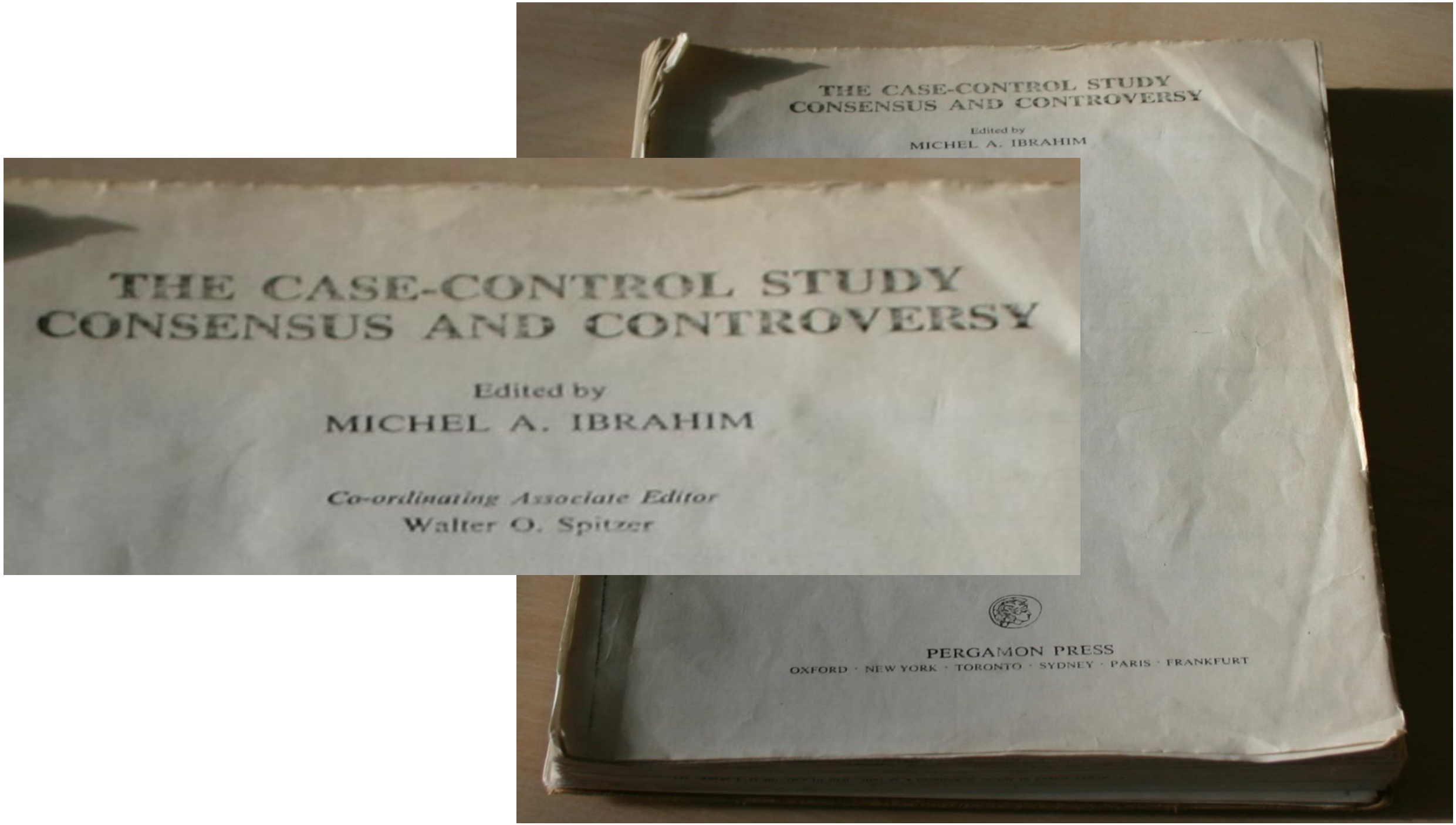
Causal diagram representing outcome Y, exposure A, their unmeasured common cause U, and risk factor L. Graph theory can be used to show that data on L are sufficient to eliminate the confounding, caused by the presence of U, for the effect of A on Y.

COLLIDER A variable directly affected by two or more other variables ("parents" of the variable) in the CAUSAL DIAGRAM;[1,2,34,100,101,209,242,243] e.g., a variable that is the common effect of an exposure and an outcome. In the following "inverted fork" $X \rightarrow C \leftarrow Y$ the arrow represents a direct effect of the tail variable on the head variable; C is then a collider on the X-C-Y pathway in the graph. Conditioning on a collider (i.e., controlling for the collider through stratification, restriction, or adjustment) will tend to induce a noncausal association (often referred to as *collider bias*) between the parent variables (i.e., the shared direct causes) of the collider.

COLLIDER BIAS See COLLIDER.

DAG (DIRECTED ACYCLIC GRAPH) See CAUSAL DIAGRAM.

PATH DIAGRAM The original term for what has commonly come to be called a CAUSAL DIAGRAM.


THE CASE-CONTROL STUDY
CONSENSUS AND CONTROVERSY
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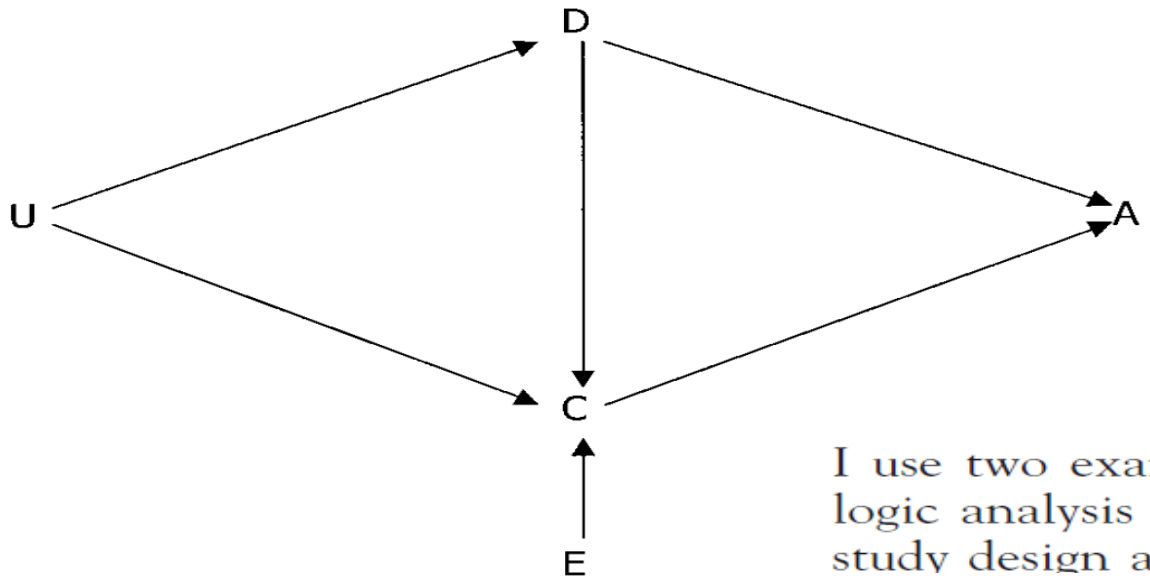
Data, Design, and Background Knowledge in Etiologic Inference

James M. Robins



DAG 9

I use two examples to demonstrate that an appropriate etiologic analysis of an epidemiologic study depends as much on study design and background subject-matter knowledge as on the data. The demonstration is facilitated by the use of causal graphs. (Epidemiology 2001;11:313–320)

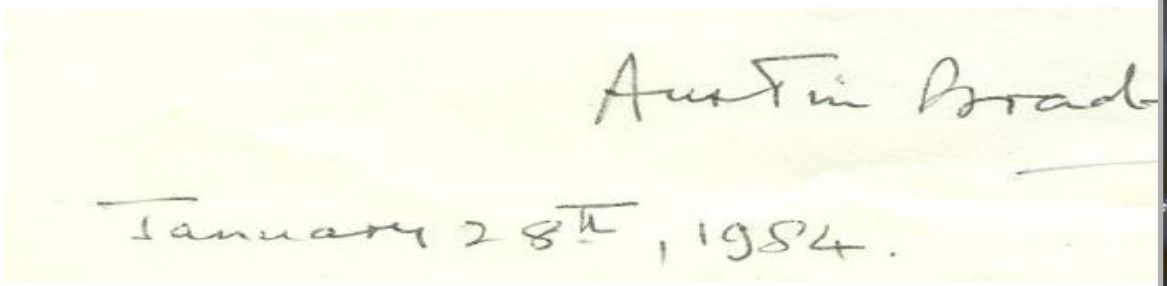
FIGURE 3. DAG for Thought Experiment 2. D = endometrial cancer; A = ascertained endometrial cancer; C = vaginal bleeding; E = exogenous estrogens; U = an unmeasured common cause of D and C.

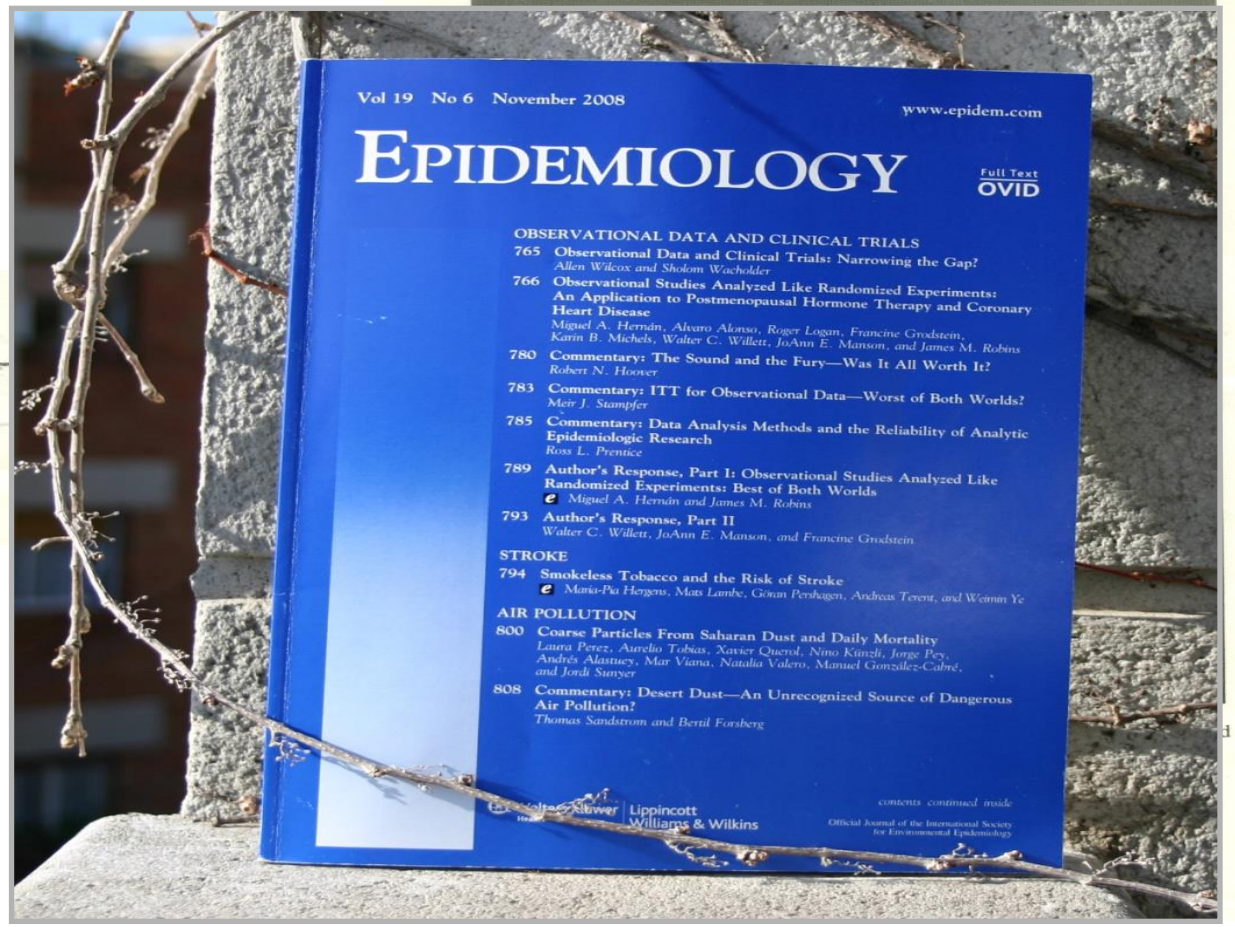
- Many such controversies (among highly intelligent scientists) have been deconstructed and overcome by the new methods (Hernán, Robins, Greenland, VanderWeele...).

Observational Studies Analysed Like Randomised Experiments

The ongoing methodological revolution?

Randomised Experiments Analysed Like Observational Studies





IMIM hospitaldelmar

UAB Universitat Autònoma de Barcelona

THE CLINICAL TRIAL

A. BRADFORD HILL Ph.D. D.Sc.

Professor of Medical Statistics
London School of Hygiene and Tropical Medicine

Honorary Director, Statistical Research Unit
Medical Research Council

British Medical Bulletin
1951; 7(4): 278-282.

The New England
Journal of Medicine

Volume 247 JULY 24, 1952 Number 4

THE CLINICAL TRIAL*

A. BRADFORD HILL, C.B.E., D.Sc., PH.D.†

LONDON, ENGLAND

The New England
Journal of Medicine

Volume 248 JUNE 11, 1953 Number 24

OBSERVATION AND EXPERIMENT*

A. BRADFORD HILL, C.B.E., D.Sc., Ph.D.†

LONDON, ENGLAND

SIR AUSTIN BRADFORD HILL

[Photograph taken by Bassano Studios/Elliott and Fry. Reproduced by kind permission of the Editor, *Journal of the Royal Statistical Society, Series A.*]

Austin Bradford Hill

January 28th, 1954.

To Dr Miquel Porta with best wishes from

Austin Bradford Hill

my luck with the Navy. So I went for a character interview and a medical examination. The only test of hearing I recall was the "forced whisper." An attendant turned down the flap of my deaf ear, the medical officer gave a four figure number in a forced whisper. I repeated it. Now for the crunch. Fortunately (for me) their coordination had not been perfected. The medical officer made his whisper a fraction of a second before the flap of my good ear was closed. Giving a slight pause I repeated the number. There I was, undeniably fit for flying duties.

J. chron. Dis. 1967, Vol. 20, pp. 637–648. Pergamon Press Ltd. Printed in Great Britain

EXPLANATORY AND PRAGMATIC ATTITUDES IN THERAPEUTICAL TRIALS

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INFLUENCE OF ADHERENCE TO TREATMENT AND RESPONSE OF CHOLESTEROL ON MORTALITY IN THE CORONARY DRUG PROJECT

THE CORONARY DRUG PROJECT RESEARCH GROUP

Abstract The Coronary Drug Project was carried out to evaluate the efficacy and safety of several lipid-influencing drugs in the long-term treatment of coronary heart disease. The five-year mortality in 1103 men treated with clofibrate was 20.0 per cent, as compared with 20.9 per cent in 2789 men given placebo ($P = 0.55$). Good adherers to clofibrate, i.e., patients who took 80 per cent or more of the protocol prescription during the five-year follow-up period, had a substantially lower five-year mortality than did poor adherers to clofibrate (15.0 vs. 24.6 per cent; $P = 0.00011$). However, similar findings were noted in the placebo group, i.e., 15.1 per cent mortality for good adherers and 28.3 per cent for poor adherers ($P = 4.7 \times 10^{-16}$). These findings and various other analyses of mortality in the clofibrate and placebo groups of the project show the serious difficulty, if not impossibility, of evaluating treatment efficacy in subgroups determined by patient responses (e.g., adherence or cholesterol change) to the treatment protocol after randomization. (N Engl J Med. 1980; 303:1038-41.)

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good adherers and 28.3 per cent for poor adherers
($P = 4.7 \times 10^{-16}$).

5-year Mortality (%)	Clofibrate (n=1.065)	Placebo (n=2.695)
TOTAL	18,2	19,4
C <80%	24,6	28,2
C ≥80%	15,0	15,1

5-year Mortality (%) Figures adjusted for 40 baseline characteristics	Clofibrate	Placebo
TOTAL	18,0	19,5
C <80%	22,5	25,8
C ≥80%	15,7	16,4

(«Poor adherers» had slightly more risk factors at baseline)

* Adjusting for baseline characteristics «explains little».
* It is difficult to identify predictors of response, of adherence.
* **It is NOT CORRECT to evaluate treatment efficacy in subgroups determined** by patient responses to the treatment protocol (e.g., adherence or cholesterol change) **AFTER randomisation.**
* Only comparisons between groups defined BEFORE randomisation are VALID.
* Hay que asegurarse de que los pacientes que van a ser aleatorizados aceptarán cualquiera de los posibles tratamientos.

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Murray and Hernán *Trials* (2018)

Improved adherence adjustment in the Coronary Drug Project

Background: The survival difference between adherers and non-adherers to placebo in the Coronary Drug Project has been used to support the thesis that adherence adjustment in randomized trials is not generally possible and, therefore, that only intention-to-treat analyses should be trusted. We previously demonstrated that adherence adjustment can be validly conducted in the Coronary Drug Project using a simplistic approach. Here, we re-analyze the data using an approach that takes full advantage of recent methodological developments.

Methods: We used inverse-probability weighted hazards models to estimate the 5-year survival and mortality risk when individuals in the placebo arm of the Coronary Drug Project adhere to at least 80% of the drug continuously or never during the 5-year follow-up period.

Results: Adjustment for post-randomization covariates resulted in 5-year mortality risk difference estimates ranging from −0.7 (95% confidence intervals (CI), −12.2, 10.7) to 4.5 (95% CI, −6.3, 15.3) percentage points.

Conclusions: Our analysis confirms that appropriate adjustment for post-randomization predictors of adherence largely removes the association between adherence to placebo and mortality originally described in this trial.

The C-Word: Scientific Euphemisms Do Not Improve Causal Inference From Observational Data

Am J Public Health. 2018

Miguel A. Hernán

causation. The analysis of the observational study is necessarily associational, even though the goal of the observational study is causal.

Interestingly, the same is true of randomized trials. All we can estimate from randomized trials data are associations; we just feel more confident giving a causal interpretation to the association between treatment assignment and outcome because of the expected lack of confounding that physical randomization entails.

However, the association measures from randomized trials cannot be given a free pass. Although randomization eliminates systematic confounding, even a perfect randomized trial only provides probabilistic bounds on "random confounding"—as reflected in the confidence interval of the association measure—and many randomized trials are far from perfect.

Confounding by the indication (CFI)
occurs when a set of clinical signs, symptoms
or an *indication* for treatment whatsoever
assessed by a health professional [or by the patient herself],
is associated both with the prescription of a *drug*
and with a higher probability of a particular *outcome*.

Thus, CFI **stems from an initial lack of similarity**
in the prognostic expectations of treated and nontreated subjects.

No statistical or methodological recipe will be of help
unless we have an in-depth knowledge
(*expert knowledge* or *subject-matter knowledge*)
of the **reasons why the drug was prescribed.**

it is always necessary to integrate
subject-matter knowledge
and methodological knowledge

there cannot be
methodological decisions
in a vacuum
of expert knowledge

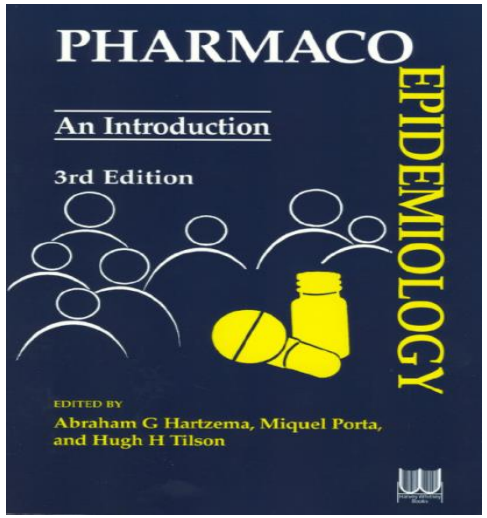
the design, conduct, analysis, and interpretation of studies must be based on the following[90]:

1. a *causal model hypothesis*, which includes knowledge of the basic and clinical pharmacology of the drug and of the molecular biology, pathophysiology, and clinical course of the disease; and
2. a *healthcare pathway hypothesis*, which in turn includes knowledge of patient behavior, referral patterns, actual diagnostic and therapeutic strategies, as well as other aspects of the functioning of the health system relevant to the assessment of potential selection and information biases.

most important: integrate
subject-matter knowledge
and methodological knowledge

1 **The Contribution of Epidemiology to the Study of Drug Uses and Effects**

Miquel Porta
Abraham G Hartzema
Hugh H Tilson



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