Post-“Modern Epidemiology”: when methods meet matter

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American Journal of Epidemiology

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Commentary

Epidemiology: Back to the Future

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Initially submitted February 10, 2019; accepted for publication February 15, 2019.

In 2018, the Society for Epidemiologic Research and its partner journal, the *American Journal of Epidemiology*, assembled a working group to develop a set of papers devoted to the "future of epidemiology." These 14 papers covered a wide range of topic areas and perspectives, from thoughts on our profession, teaching, and methods to critical areas of substantive research. The authors of those papers considered current challenges and future opportunities for research and education. In light of past commentaries, 4 papers also include reflections on the discipline at present and in the future.

future; population health; public health

Abbreviation: *AJE*, *American Journal of Epidemiology*.

In 2018, the Society for Epidemiologic Research and the its partner journal, the *American Journal of Epidemiology* (*AJE*), assembled a working group to develop a set of *AJE* papers

PAST PERSPECTIVES (THE 90S)

As a framework for the papers in this issue, we will briefly

American Journal of Epidemiology

DOI: 10.1093/aje/kwy280

Commentary

A Future for Observational Epidemiology: Clarity, Credibility, Transparency

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Initially submitted November 12, 2018; accepted for publication December 18, 2018.

Observational studies are ambiguous, difficult, and necessary for epidemiology. Presently, there are concerns that the evidence produced by most observational studies in epidemiology is not credible and contributes to research waste. I argue that observational epidemiology could be improved by focusing greater attention on 1) defining questions that make clear whether the inferential goal is descriptive or causal; 2) greater utilization of quantitative bias analysis and alternative research designs that aim to decrease the strength of assumptions needed to estimate causal effects; and 3) promoting, experimenting with, and perhaps institutionalizing both reproducible research standards and replication studies to evaluate the fragility of study findings in epidemiology. Greater clarity, credibility, and transparency in observational epidemiology will help to provide reliable evidence that can serve as a basis for making decisions about clinical or population-health interventions.

causal inference; observational studies; quantitative bias analysis; quasi-experiments; reproducible research; research reporting; transparency

American Journal of Epidemiology

DOI: 10.1093/aje/kwz030

Commentary

The Future of Observational Epidemiology: Improving Data and Design to Align With Population Health

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Initially submitted September 22, 2018; accepted for publication January 30, 2019.

Improvements in data resources and computational power provide important opportunities to ensure the continued relevance and growth of observational epidemiology. To achieve that promise, rigorous statistical analyses are important but not sufficient. We must prioritize articulating relevant research questions and developing strong study designs. Relevance depends on designing observational research so it delivers actionable clinical or population health evidence. Expanding data sources, including administrative records and data from emerging technologies such as sensors, can potentially be leveraged to improve study design, statistical power, measurement, and availability of evidence on diverse populations. With these advantages, particularly evidence on the heterogeneity of treatment effects, observational research can better guide design of randomized trials. Evidence on the heterogeneity of treatment effects is also essential to extend the evidence from randomized trials beyond the narrow

American Journal of Epidemiology

DOI: 10.1093/aje/kwy222

Commentary

Epidemiology at the Heart of Population Health Science

Sandro Galea* and Katherine M. Keyes

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Initially submitted August 20, 2018; accepted for publication September 10, 2018.

Epidemiology has long been concerned with understanding the causes of health and disease states so that we can improve the health of populations. Despite broad agreement on this definition of the field, we continue to debate certain core goals of epidemiology: whether epidemiology is a pragmatic science or not, which methods constitute epidemiologic methods, and what our gold-standard thinking should be to understand causation. We suggest that recognizing epidemiology as the quantitative heart of population health science can push these tensions aside and allow us to focus our science on the health of populations and on the processes that shape that health. Seeing epidemiology as the core quantitative health science has implications for the questions we ask, how we organize ourselves as a field, and how we train the next generation of epidemiologists.

future; history; methods; philosophy

American Journal of Epidemiology

DOI: 10.1093/aje/kwz064

Commentary

Post–*Modern Epidemiology*: When Methods Meet Matter

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Initially submitted January 28, 2019; accepted for publication February 26, 2019.

In the last third of the 20th century, etiological epidemiology within academia in high-income countries shifted its primary concern from attempting to tackle the apparent epidemic of noncommunicable diseases to an increasing focus on developing statistical and causal inference methodologies. This move was mutually constitutive with the failure of applied epidemiology to make major progress, with many of the advances in understanding the causes of noncommunicable diseases coming from outside the discipline while ironically revealing the infectious origins of

Davey Smith G. ‘Post-Modern’ Epidemiology. Am J Epidemiol 2019, in press.

Description, prediction and cause (1957)

Jerry Morris: *"Uses of epidemiology"* (1957)

Historical study

Community diagnosis

Workings of the health service

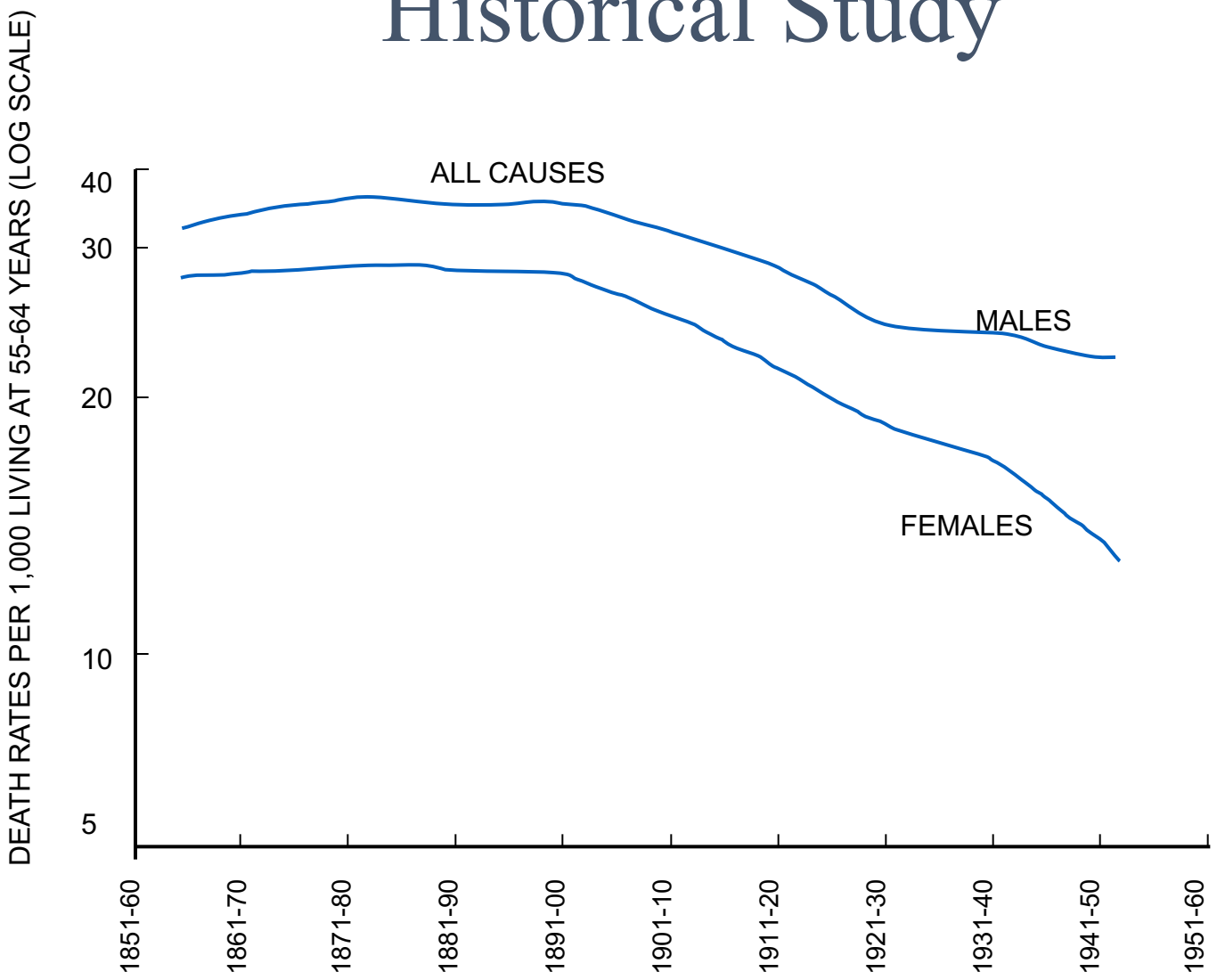
The individual's risk of disease

Completing the clinical picture

Identifying syndromes

Search for causes

Historical Study



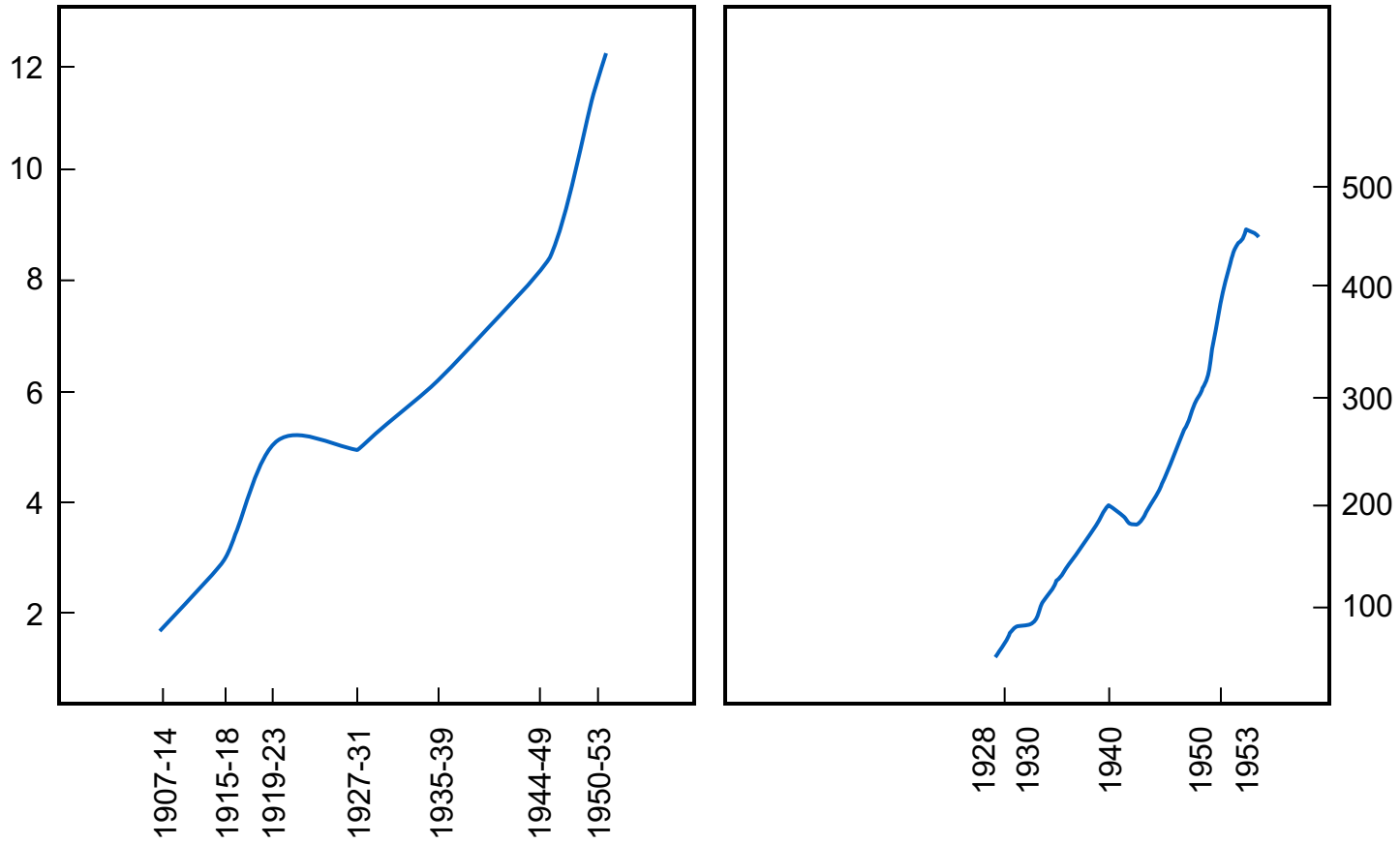
JM Morris, *Uses of Epidemiology*, 1st Ed. 1957

Recent Coronary Thrombosis and/or Acute Myocardial Infarction

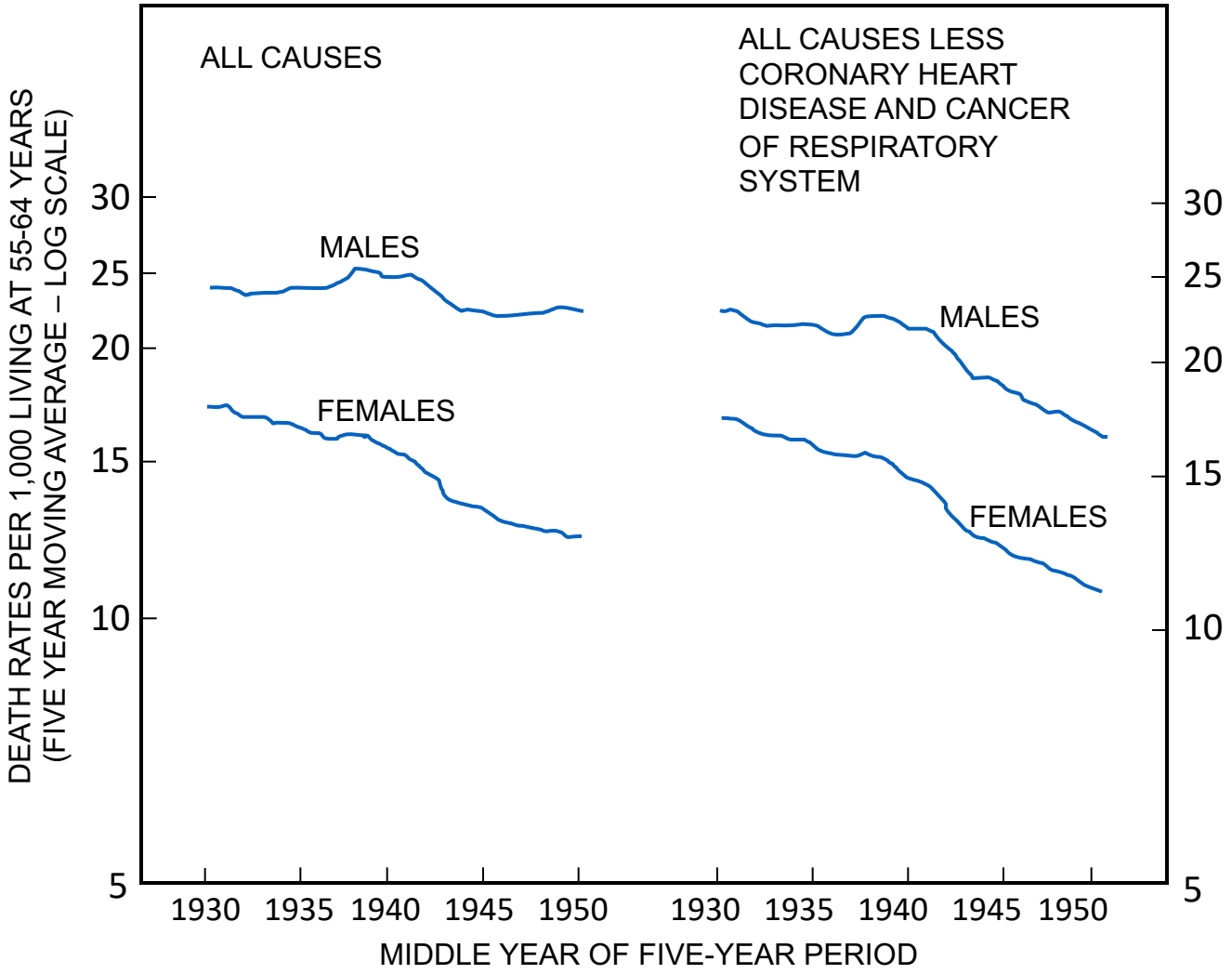
London Hospital – Males 35-69 years
Average No. of Necropsies

Coronary Heart Disease

England and Wales – Males 55-64 years
Death rates per 100,000

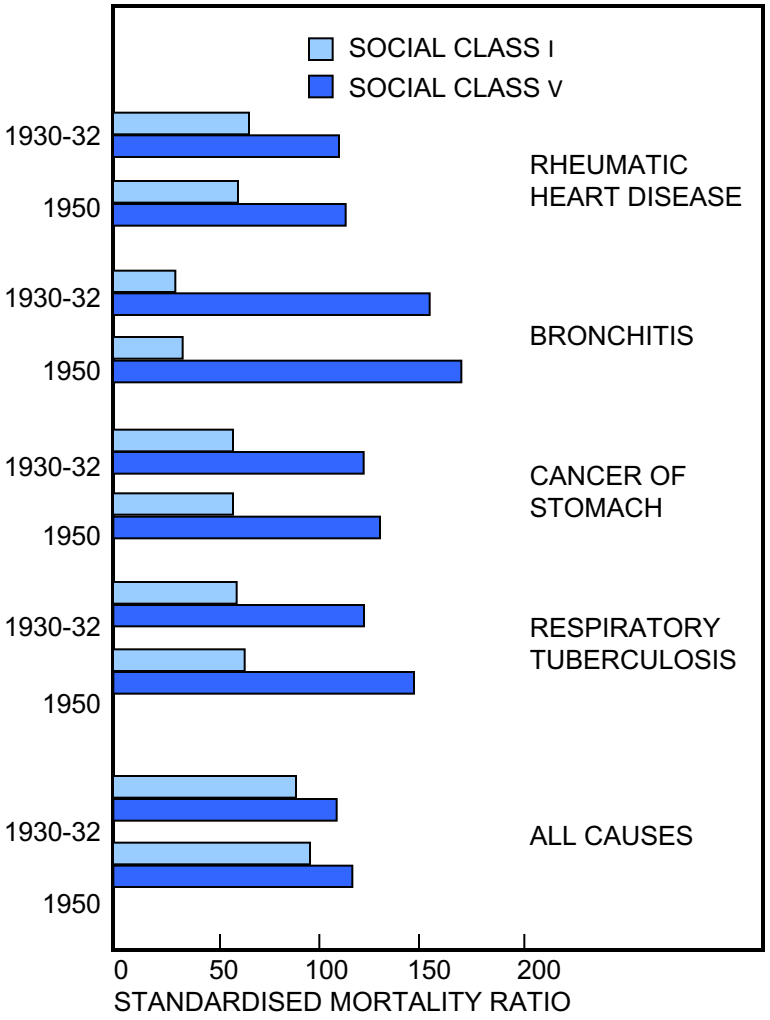


JM Morris, *Uses of Epidemiology*, 1st Ed. 1957



JM Morris, *Uses of Epidemiology*, 1st Ed. 1957

Community Diagnosis



Differences in mortality between Social Class I and Social Class V, 1930-32 and in 1950.
England and Wales. Males. Ages 20-64 incl.

JM Morris, *Uses of Epidemiology*, 1st Ed. 1957


8
WEMBLEY
SLT 59

Sudden Deaths of Conductors & Drivers, Aged 35-64, in Relation to Uniform, Trouser-Waist Measurement, 1949-58*

London Busmen – Rates per 1,000 per annum

Trouser Waist

Age Group (yrs)	**Grade**	32 or less	34-37	38 or more	Total
35-64	Drivers	1.1	0.8	2.0	1.2
	Conductors	0.5	0.5	0.7	0.7

- The figures for drivers refer to 1953-58 only

JA Heady, JN Morris, A Kagan & PAB Raffle, Brit J. Soc. Med, 1961

The Lancet · Saturday 10 September 1966

INCIDENCE AND PREDICTION OF ISCHÆMIC HEART-DISEASE IN LONDON BUSMEN

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MEDICAL RESEARCH COUNCIL'S SOCIAL MEDICINE RESEARCH UNIT, THE LONDON HOSPITAL, LONDON E.1

P. A. B. RAFFLE
M.D. Lond., D.P.H., D.I.H.
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BETWEEN 1956 and 1960 A. K. examined a sample of 687 drivers and male conductors working on London Transport's central buses. The examination included many factors known, or suspected, to be related to the incidence of ischæmic heart-disease, and about 5 years later D. C. P. re-examined the men. 93% have now been seen (or have died) and useful medical information is available on most of the remainder. During this follow-up we found that ischæmic heart-disease had Minnesota code 1_{1-2}, Blackburn et al. [1960]); they had no other evidence of ischæmic heart-disease. Changes were agreed by three observers.

At the initial examination, 20 men were found to have ischæmic heart-disease of categories II/IV; they have not been considered further in this incidence study. We are dealing therefore with a sample of 667 busmen—who when first examined had no evidence of infarction or angina nor a pathological Q wave—47 of whom developed ischæmic heart-disease during 5 years of observation

Results

INCIDENCE OF ISCHÆMIC HEART-DISEASE

Age

6 of the 128 men who were in their forties when first examined newly developed the disease (an incidence-rate

TABLE I—INCIDENCE OF ISCHÆMIC HEART-DISEASE IN SAMPLE OF LONDON BUSMEN DURING 5 YEARS, BY AGE AT INITIAL EXAMINATION

Age (yr.)	No. of new cases in 5 years	No. of men examined	Incidence-rate per 100 men in 5 years	No. of man-years of observation	Incidence-rate per 100 man-years of observation
30–39	1	32	(3·1)	175	(0·6)
40–49	6	128	4·7	689	0·9
50–59	24	300	8·0	1461	1·6
60–64	13	170	7·6	917	1·4
65–69	3	37	(8·1)	207	(1·4)

The Lancet · Saturday 10 September 1966

INCIDENCE AND PREDICTION OF ISCHÆMIC HEART-DISEASE IN LONDON BUSMEN

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Discriminant Analysis

We adopted the method of linear discriminant function analysis (Fisher 1936, Cornfield 1962). Multivariate analysis of a large set of data is more practicable now that there is direct access to electronic computers and some library programmes are available.

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Old men heading into the twilight have often complained that epidemiology is embracing irrelevance through its focus on complex approaches ….

Edmond A Murphy
1925 - 2009

"multivariate analysis (which in certain quarters is being substituted for scientific perception), can spread its soporific effect" and that (with respect to some analyses) "I am driven to believe that however excellent the prediction, the formula, from an aetiological and ontological standpoint, provides no insights whatsoever"

Murphy EA. Epidemiological strategies and genetic factors. *Int J Epidemiol* 1978; 7:7-14.

RA Stallones
1923 –1986

Recent work in epidemiology demonstrates a “continuing concern for methods, and especially the dissection of risk assessment, that would do credit to a Talmudic scholar and that threatens at times to bury all that is good and beautiful in epidemiology under an avalanche of mathematical trivia and neologisms”

Stallones RA. To advance epidemiology. *Annu Rev Public Health* 1980; 1:69–82.

Abraham Lilienfeld
1920 - 1984

"Perhaps the most dangerous aspect of the state of our discipline today is that there is an unhealthy emphasis on HOW one conducts an epidemiologic study and not WHY and WHAT one does in such a study. Simply put, we are training *technocrats".*

Lilienfeld A. Epidemiology and the Public Health Movement: A Historical Perspective. Journal of Public Health Policy 1982;3:140-149

American Journal of Epidemiology

Vol. 185, No. 11
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Advance Access publication:
May 23, 2017

Invited Commentary

Invited Commentary: When Case-Control Studies Came of Age

Kenneth J. Rothman*

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Initially submitted February 8, 2017; accepted for publication March 20, 2017.

In his 1976 paper "Estimability and Estimation in Case-Referent Studies" (*Am J Epidemiol*. 1976;103(2):226–235), Miettinen weaved together a patchwork of new ideas into a coherent view of case-control studies. His article spurred theoretical development in epidemiologic methods and became a platform for teaching about some key concepts in epidemiologic study design.

case-control study; epidemiologic methods; estimation; rate ratio; risk ratio

By 1976, when "Estimability and Estimation in Case-Referent Studies" was published, case-control studies had

demiologic thinking as to the fundamen-

parative information over the strata to attain an overall comparison free of con-

were the comparison series for the cases, they should be just

non-exposed equals the ratio of the odds of

sought through the use of multivariate models and analytic technics, but this

American Journal of Epidemiology
Vol. 99, No. 6
Printed in U.S.A. 8:1978

SYNERGY AND ANTAGONISM IN CAUSE-EFFECT RELATIONSHIPS[1]

KENNETH J. ROTHMAN[2]

In describing cause and effect relationships, difficulties may arise when two agents both act as causes of a particular outcome. The complications result from the possibility that either of the agents modifies the extent to which the other produces the effect. Such an interaction implies that the two causal chains have at least one part in common; thus the evaluation of the combined effect of two causes is pertinent to the study of the causal mechanisms involved.

Measuring the effect

The assessment of interaction depends on the ability to measure the effect in a meaningful way. Arbitrary transformations of the scale of observation can falsely suggest or mask the presence of interaction. Epidemiologists have tended to adopt statistical techniques used in model building and prediction, for which the sole criteria of utility are ease and accuracy of description or forecasting. These tech- causal research. The key issue, therefore, is to determine the appropriate scale of measurement to use in quantitating the effect. Such a scale would be a "natural scale" in the sense that it would be the one that most directly measures effect.

Let us consider a simple situation in which a cause can produce an all-or-none effect. If the cause is not a sufficient cause (and virtually all causes in medical science are not sufficient), it produces the effect only if some other set of circumstances is met. The presence of the necessary complementary circumstances cannot be a consequence of the cause, as this would make the cause sufficient. Thus, other factors *unrelated* to the cause determine in each situation whether the effect will occur. The unrelated nature of the determinants of the effect seems to suggest a random or probabilistic component in bringing the complement of the cause together with the cause in question. The cause will bring about the effect only in those circumstances when the

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Kenneth J Rothman

"Biologic interaction" … would "provide clues to the behaviour of the causal mechanisms involved"

Rothman KJ. Synergy and Antagonism in Cause -Effect Relationships. Am J Epidemiol 1974;99(6):385-388.

George Davey Smith

MODERN EPIDEMIOLOGY

KENNETH J. ROTHMAN

LITTLE, BROWN AND COMPANY

Diana Petitti

… had found “less and less evidence of scientific creativity and more and more striking deficits in the understanding of biology”.

Petitti D. The implications of alternative reviews about causal inference. In: Rothman KJ (ed). *Causal Inference*. Massachusetts: Chestnut Hill; 1988

Diana Petitti

… had found “less and less evidence of scientific creativity and more and more striking deficits in the understanding of biology”.

… and the epidemiological literature becoming “an archive of the results of information derived from mechanical applications of multivariate analysis”

Petitti D. The implications of alternative reviews about causal inference. In: Rothman KJ (ed). *Causal Inference*. Massachusetts: Chestnut Hill; 1988

Jerry Morris
1910 - 2009

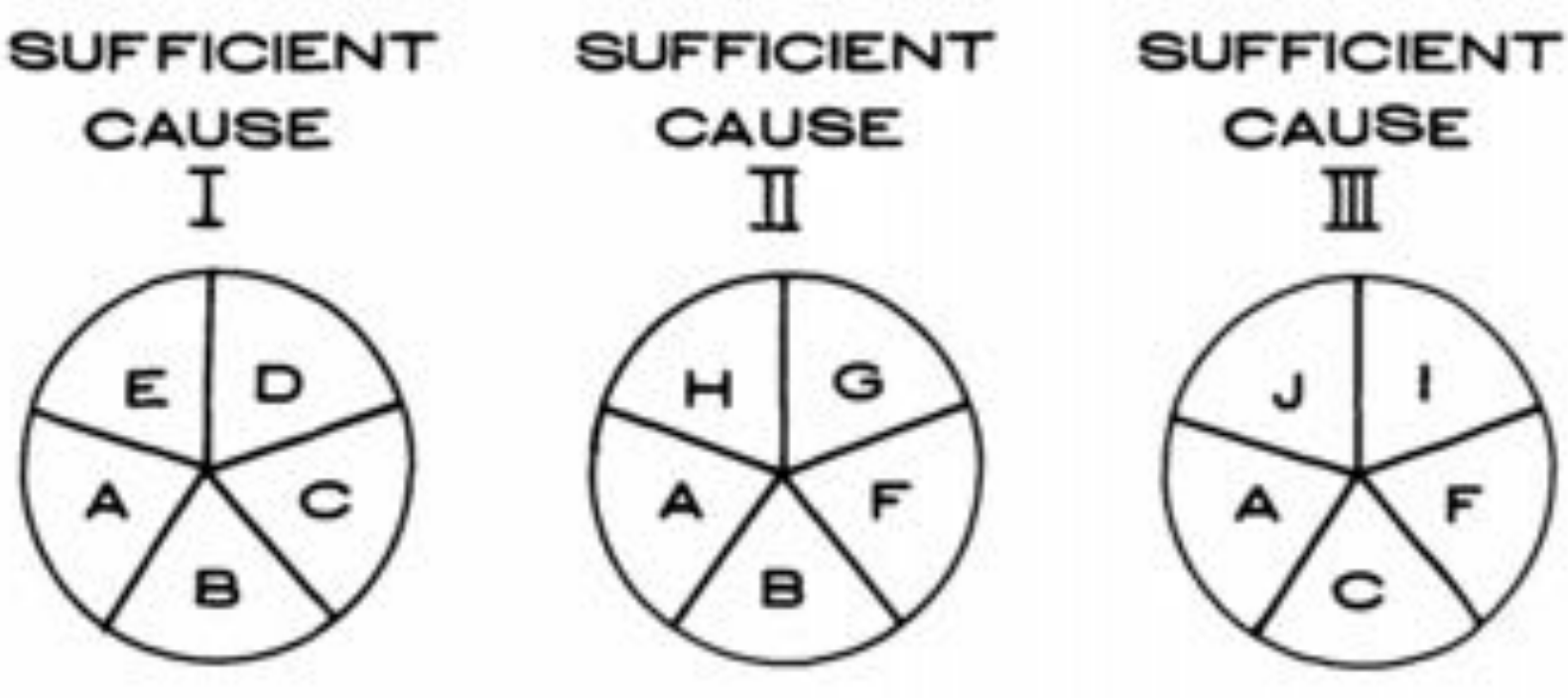
"SIR – I share Elwood's high regard for Rothman's *Modern Epidemiology*, and am at present treating myself to a refresher course on it (much reassured in the process by the author's confidence in my statistical capability). However, as a guide to modern epidemiology the book has serious limitations.

Morris JN. Letter to the Editor: Modern Epidemiology?. *J Epidemiol Community Health* 1988;42:100

Jerry Morris
1910 - 2009

“The student coming to it afresh could not gather that epidemiology is the basic science of public health. Thus in close on 150 years of epidemiological research (Dr Rothman doesn't have much space for history) it continues plausible that the main determinants of the health of populations and sizable subgroups in them are their economic-social-cultural conditions. The data on this are mostly cross-sectional and inevitably derived from studies of populations and groups as the unit, rather than from aggregation of individuals with their various attributes.” (p. 100)

Morris JN. Letter to the Editor: Modern Epidemiology? J Epidemiol Community Health 1988;42(1):100.



Rothman KJ. Causes. Am J Epidemiol 1976;104(6):587-592.

"In our ignorance of these hidden causal components, the best we can do in assessing risk is to assign the average value to everyone exposed to a given pattern of known causal risk indicators. As knowledge expands the risk estimates assigned to people will approach one of the extreme values, zero or unity".(p. 12)

Rothman KJ. *Modern Epidemiology*. Boston: Little Brown & Co; 1986.

COMMENT

A call to police the whole data-analysis pipeline, not just P values

Does Nicholas Stern's global vision admit ground truth?

Metaphor pile-up obscures the meaning of junk DNA

Grind, politics and dirty tricks in life of polio-vaccine pioneer

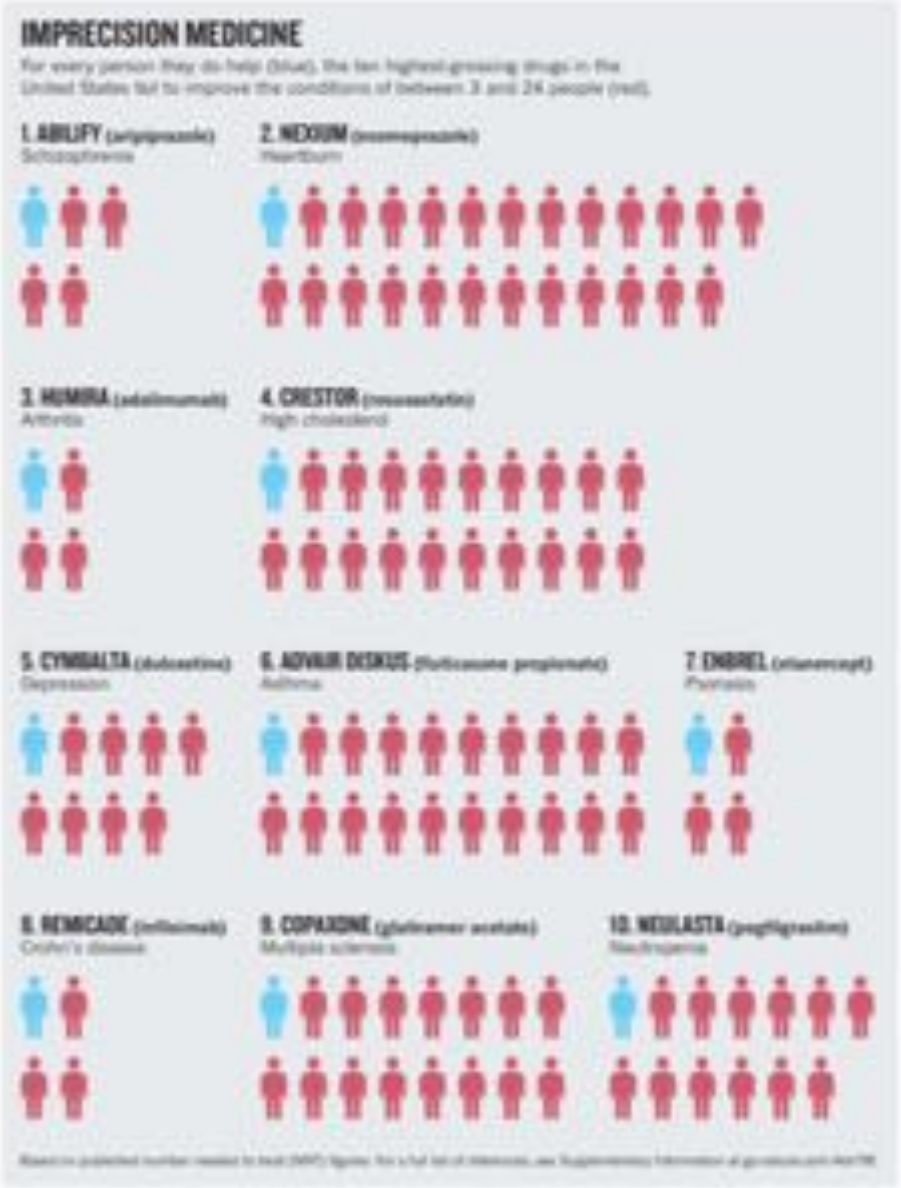
Time for one-person trials

Precision medicine requires a different type of clinical trial that focuses on individual, not average, responses to therapy, says **Nicholas J. Schork**.

Every day, millions of people are taking medications that will not help them. The top ten highest-grossing drugs in the United States help between 1 in 25

US$215-million national Precision Medicine Initiative. This includes, among other things, the establishment of a national database of the genetic and other data of one million people

may prescribe one drug for hypertension and monitor its effect on a person's blood pressure before trying a different one. But few clinicians or researchers have formalized this



Schork NJ. Time for one – person trials. Nature 2015;520:609-611

Social Science & Medicine 210 (2018) 2–21

Contents lists available at ScienceDirect

Social Science & Medicine

journal homepage: www.elsevier.com/locate/socscimed

Understanding and misunderstanding randomized controlled trials

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[b] National Bureau of Economic Research, USA
[c] University of Southern California, USA
[d] Durham University, England
[e] UC San Diego, USA

ARTICLE INFO

Keywords:
RCTs
Balance
Bias
Precision
External validity
Transportation of results
Health
Economic development

ABSTRACT

Randomized Controlled Trials (RCTs) are increasingly popular in the social sciences, not only in medicine. We argue that the lay public, and sometimes researchers, put too much trust in RCTs over other methods of investigation. Contrary to frequent claims in the applied literature, randomization does not equalize everything other than the treatment in the treatment and control groups, it does not automatically deliver a precise estimate of the average treatment effect (ATE), and it does not relieve us of the need to think about (observed or unobserved) covariates. Finding out whether an estimate was generated by chance is more difficult than commonly believed. At best, an RCT yields an unbiased estimate, but this property is of limited practical value. Even then, estimates apply only to the sample selected for the trial, often no more than a convenience sample, and justification is required to extend the results to other groups, including any population to which the trial sample belongs, or to any individual, including an individual in the trial. Demanding 'external validity' is unhelpful because it expects too much of an RCT while undervaluing its potential contribution. RCTs do indeed require minimal assumptions and can operate with little prior knowledge. This is an advantage when persuading distrustful audiences, but it is a disadvantage for cumulative scientific progress, where prior knowledge should be built upon, not discarded. RCTs can play a role in building scientific knowledge and useful predictions but they can only do so as part of a cumulative program, combining with other methods, including conceptual and theoretical development, to discover not 'what works', but 'why things work'.

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journal homepage: www.elsevier.com/locate/socscimed

Challenging the hegemony of randomized controlled trials: A commentary on Deaton and Cartwright

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I appreciate the opportunity to comment on the article by Angus Deaton and Nancy Cartwright (D&C) (Deaton and Cartwright, 2018), which touches on the foundations of causal inference.

My comments are a mixture of a welcome and a puzzle; I welcome D&C's stand on the status of randomized trials, and I am puzzled by how they choose to articulate the alternatives.

D&C's main theme is as follows: "We argue that any special status for RCTs is unwarranted. Which method is most likely to yield a good causal inference depends on what we are trying to discover as well as on what is already known."

As a veteran skeptic of the supremacy of the RCT, I welcome D&C's challenge wholeheartedly. Indeed, *The Book of Why* (Pearl and Mackenzie, 2018, http://bayes.cs.ucla.edu/WHY/) quotes me as saying: "If our conception of causal effects had anything to do with randomized experiments, the latter would have been invented 500 years before Fisher." In this, as well as in my other writings I go so far as claiming that the RCT earns its legitimacy by mimicking the *do*-op-

My only qualm with D&C's proposal is that, in their passion to advocate the integration strategy, they have failed to notice that, in the past decade, a formal theory of integration strategies has emerged from the brewery of causal inference and is currently ready and available for empirical researchers to use. I am referring of course to the theory of Data Fusion, which formalizes the integration scheme in the language of causal diagrams, and provides theoretical guarantees of feasibility and performance (see Bareinboim and Pearl (2016)).

Let us examine closely D&C's main motto: "Which method is most likely to yield a good causal inference depends on what we are trying to discover as well as on what is already known." Clearly, to cast this advice in practical settings, we must devise notation, vocabulary, and logic to represent "what we are trying to discover" as well as "what is already known" so that we can infer the former from the latter. To accomplish this nontrivial task we need tools, theorems and algorithms to assure us that what we conclude from our integrated study indeed follows from those precious pieces of knowledge that are "already

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The "average" treatment effect: A construct ripe for retirement. A commentary on Deaton and Cartwright

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[b] Harvard Center for Population & Development Studies, Cambridge, MA, USA
[c] Department of Sociology, Yale University, New Haven, CT, USA
[d] Department of Medicine, Yale University, New Haven, CT, USA
[e] Yale Institute for Network Science, Yale University, New Haven, CT, USA

"Don't cross a river if it is (on average) four feet deep".
-Nassim Nicholas Taleb, 2016 p.160

1. Introduction

When summarizing or analyzing a population, regardless of whether it consists of hundreds or millions of individuals, it is the norm in most social, medical, and health research to characterize it in terms of a single number: the *average*. The reliance on average is pervasive in descriptive, explanatory, or causal analyses. There is nothing inherently wrong with an "on average" view of the world. But whether such a view is actually meaningful, for populations or individuals, is another matter. The average can obscure as much as it illuminates. It is a lean summary of a distribution with no recognition of the rich variation between and

Instead of expecting ATE from an RCT to work for any individual or population, Deaton and Cartwright argue that we can do better with "*judicious use of theory, reasoning by analogy, process tracing, identification of mechanisms, sub-group analysis, or recognizing various symptoms that a causal pathway is possible*" (Deaton and Cartwright, 2018). Their hypothetical example of an RCT based on a classroom innovation in two schools, St Joseph's and St Mary's, is most intuitive in this regard. Deaton and Cartwright argue that even if the innovation turns out to be successful on average, actual experiences in the school with comparable composition may be more informative when other schools decide to adopt and scale up the same innovation (Deaton and Cartwright, 2018).

Following a brief introduction to the problems of averages, we elaborate on why variation or heterogeneity matters from a substantive perspective and develop a generalized modeling framework to assessing

“ Statins are effective in lowering cholesterol for as few as 1 in 50 individuals”

Subramanian SV et al. The “average” treatment effect: A construct ripe for retirement. A commentary on Deaton and Cartwright. Social Science and Medicine 2018;210:77-82.

Ann. Hum. Genet., Lond. (1965), **29**, 51
Printed in Great Britain

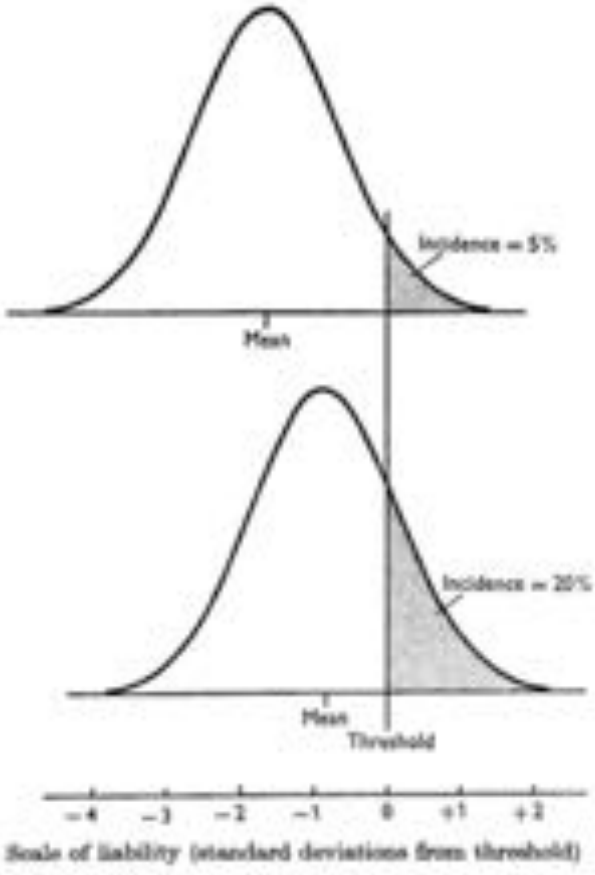
The inheritance of liability to certain diseases, estimated from the incidence among relatives

BY D. S. FALCONER*
Institute of Animal Genetics, West Mains Road, Edinburgh

INTRODUCTION

It is now commonly recognized that many diseases that are not inherited in a simple manner have, nevertheless, some hereditary basis. The evidence that heredity plays some part comes from the observation that the incidence of the disease is higher among the relatives of affected individuals than it is in the general population. An increased incidence among relatives does not, however, go far toward providing an answer to the important question of how strong the hereditary factor is, because the difference of incidence has no simple genetic interpretation. The relative importance of heredity and environment in such a case is clearly a problem of quantitative genetics. The usual methods of quantitative genetics, however, are not immediately applicable because these are based on correlations between relatives in respect of some 'graded' character measurable on a continuous scale. Data in the form of incidences refer, in contrast, to an 'all-or-none' classification; individuals either have the disease or they do not. Though the

Falconer DS. The inheritance of liability to certain diseases, estimated from the incidence among relatives. Annals of Human Genetics 1965;29:51.



Illustrations of two populations or groups with different mean liabilities. The liability is normally distributed, with the same variance in the two groups. The groups are compared by reference to a fixed threshold. The stippled portions are the affected individuals with the incidences shown

Falconer DS. The inheritance of liability to certain diseases, estimated from the incidence among relatives. Annals of Human Genetics 1965;29:51.

FAMILIAL PREDISPOSITION IN MAN

J. H. EDWARDS M.R.C.P.

Department of Social Medicine
University of Birmingham

Almost all disorders in man are familial in that they are more likely to afflict someone with an affected relative than someone with an equivalent set of unaffected relatives. Further, all disorders are genetic in the sense that we could anticipate drastically changing their incidence by selective breeding within the same environment.

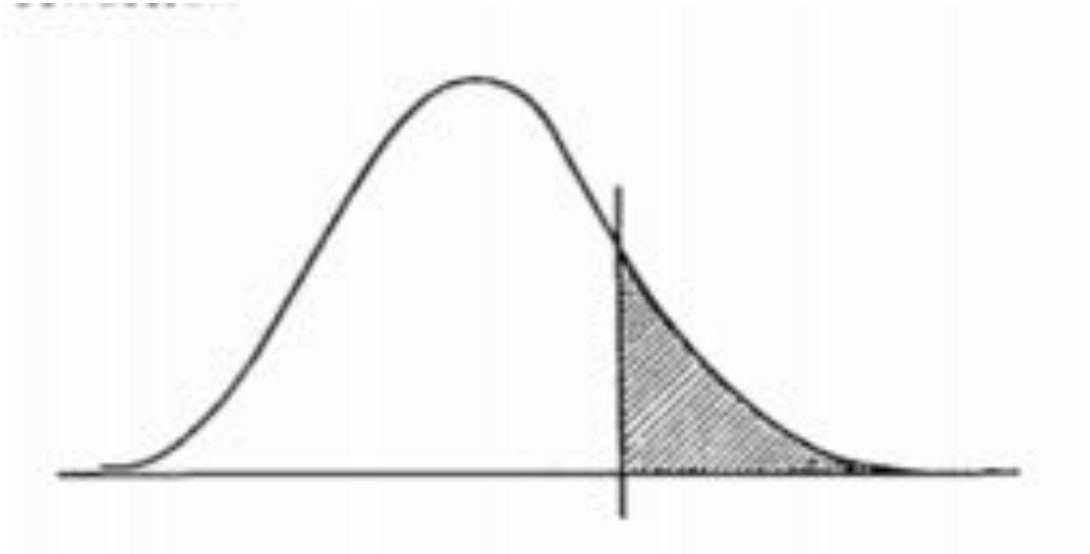
Some disorders show a more intense familial concentration than others, and in some the pattern of inheritance implies a very simple one-to-one relationship between what is observed, the phenotype, and what can be inferred, the set of hereditary utilize another model, or to manage without a model and assimilate the data raw.

1. Mechanisms of Disease Not Determined by Single Factors

The fundamental difficulty of devising genetic models for conditions not explicable in simple genetic terms lies in the nature of the phenotypic discontinuity, a feature elegantly explained by the half-chance of an autosomal gene's being passed to any child in the single-factor case. The simplest explanation for disorders not adequately explained by single-factor inheritance is to introduce the escape clause of penetrance, so that a factor, or a pair of factors, is necessary but not sufficient. In its simplest form affliction is apparently chosen by lot. Since it is difficult to contemplate an indifference of the allelic partner, of the total contribution of other genes, or of the environment, this model merges imperceptibly, as the penetrance declines, into the many-factor model to be considered below. Various methods of distinguishing these hypotheses have been described, but most assume the arbitrary allocation of a constant penetrance unaffected by the genetic background and lack realism.

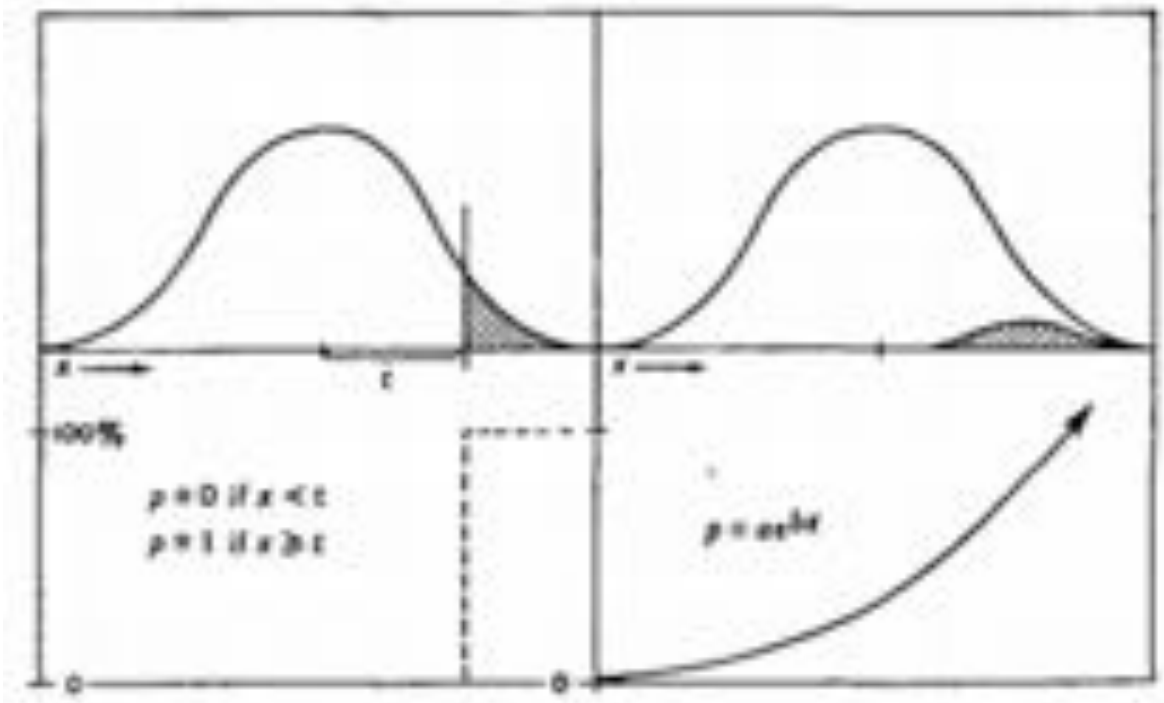
An alternative and historically older explanation, once again in vogue, assumes very numerous determinants, both inherited and acquired, whose individually weak and largely independent actions lead to a distribution which is correlated in families, so that we may infer the intensity of familial concentration by measuring some variable, such as height or blood pressure, or coding some attribute, such as tallness or hypertension, or identifying some consequence related to a predisposition within and between families.

The many-factor model, where the factors are so numerous,



Pearson's univariate model, in which a proportion of a population differing a defined amount from the mean is affected by some condition

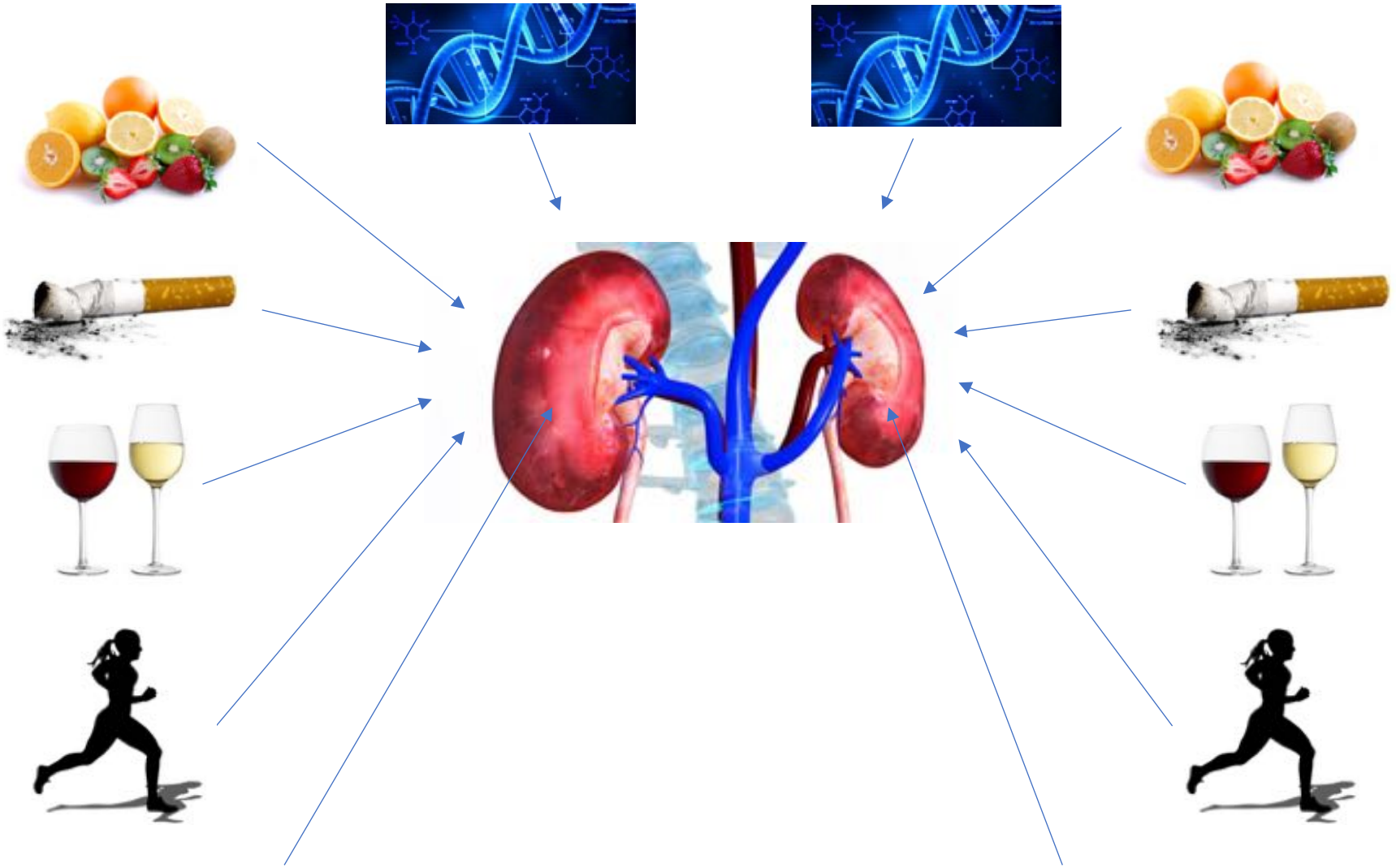
Edwards JH. Familial predisposition in man. Br Med Bull 1969:58-64



Abrupt and gradual models relating many state genotype to two-state phenotype

Edwards JH. Familial predisposition in man. Br Med Bull 1969:58-64

The major contribution of stochastic events and bounds to personalised medicine: cancers of bilateral organs



Joung et al, Cancer Res Treat 2018

Variation of growth of genetically identical marbelled crayfish in an aquarium

How well would epidemiologists be able to predict outcome?

Vogt et al. J Exp Biol 2008;211:510-23

"The chance events that contribute to disease aetiology can be analysed at many levels, from the social to the molecular. Consider Winnie; why has she managed to smoke for 93 years without developing lung cancer? Perhaps her genotype is particularly resilient in this regard? Or perhaps many years ago the postman called at one particular minute rather than another, and when she opened the door a blast of wind caused Winnie to cough, and through this dislodge a metaplastic cell from her alveoli? Individual biographies would involve a multitude of such events, and even the most enthusiastic lifecourse epidemiologist could not hope to capture them. Perhaps chance is an under-appreciated contributor to the epidemiology of disease".[44]

Davey Smith, Epidemiology, epigenetics and the gloomy prospect. IJE 2011

Thought experiment ...

- Everyone in Bristol has to smoke 20 cigarettes a day from adolescence on
- No-one in Bath smokes at all
- Follow up for 50 years ... Where has more lung cancer?
- Within Bristol – how does smoking relate to lung cancer risk?
- Within Bristol – what causes one individual rather than another to get lung cancer?
- Between Bristol and Bath what causes the huge difference in rate of lung cancer?
- At a population level an exposure may be responsible for nearly all cases, but account for little of the difference in risk between individuals …..
- Between individuals chance may be a major factor in who gets disease

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NATIONAL UNION OF MINEWORKERS (SOUTH WALES AREA)

DEFEND SOUTH WALES MINERS

The funds of the NUM in South Wales are being plundered. But the miners will not be intimidated or starved back to work.

We will stand firm in our fight to retain our pits, our jobs and our communities.

WE CAN ONLY DO IT WITH YOUR HELP

NO SURRENDER


LESBIANS & GAYS
SUPPORT THE MINERS

HEALTH EDUCATION RESEARCH
Theory & Practice

Vol.4 no.3 1989
Pages 329–340

Inheriting heart trouble: the relevance of common-sense ideas to preventive measures

Charlie Davison, Stephen Frankel and George Davey Smith

Abstract

This paper is concerned with the cultural norms and common-sense ideas about inherited health and inherited heart trouble that were encountered and been absorbed by the knowledge of heart trouble which was already in the population at large. Such ideas about health and illness in general, and heart trouble in particular, form part of the wide-ranging cultural heritage bestowed on all members of our

Davison C et al. Inheriting heart trouble: the relevance of common-sense ideas to preventive measures. Health Education Research 1989;4:329-40.

Soc. Sci. Med. Vol. 34, No. 6, pp. 675–685, 1992

0277-9536/92 $5.00 + 0.00

THE LIMITS OF LIFESTYLE: RE-ASSESSING 'FATALISM' IN THE POPULAR CULTURE OF ILLNESS PREVENTION

CHARLIE DAVISON,[1]* STEPHEN FRANKEL[1] and GEORGE DAVEY SMITH[2]

[1]Health Care Evaluation Unit, University of Bristol, Bristol, U.K.
[2]Department of Public Health Medicine, U.C.L., London, U.K.

Abstract—This paper is concerned with the development of preventive medicine in the field of Coronary Heart Disease. It is based on an in-depth, ethnographic investigation into the popular culture of prophylactic behaviour carried out in South Wales (U.K.) during 1988 and 1989. The focus of the data and analysis presented here is the operation of cultural norms and practices related to the understanding and explanation of the cause and distribution of illness and death from heart ailments. The paper illustrates how the everyday cultural practice of 'lay epidemiology' is involved in accounting for illness misfortune and in assessing the potential benefits of prophylactic behaviour change. A central issue dealt with here is the relationship of lifestyle to environment in the popular understanding of chronic disease. Lay notions of luck, fate, destiny, randomness and chaos in the distribution of heart disease are explored. In conclusion, some implications for health education in this field are put forward.

Key words—beliefs, fatalism, prevention, coronary heart disease

COMMENT · 27 NOVEMBER 2018

Statistical pitfalls of personalized medicine

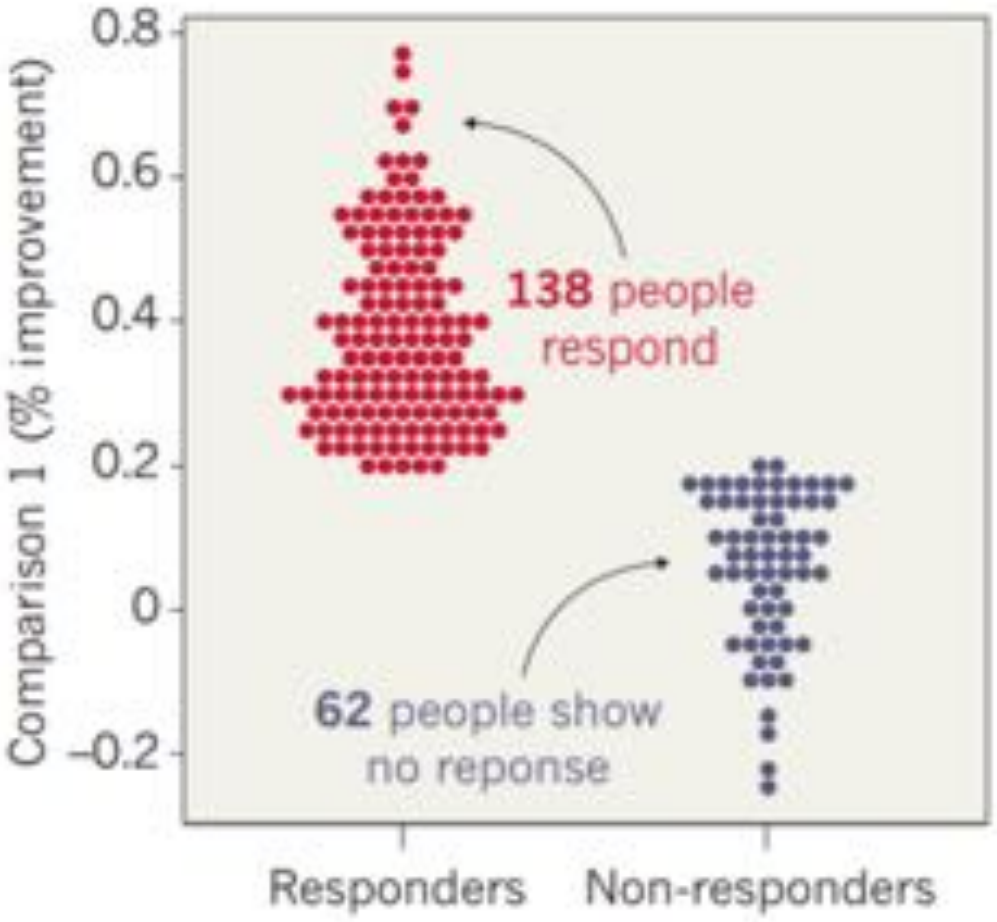
Misleading terminology and arbitrary divisions stymie drug trials and can give false hope about the potential of tailoring drugs to individuals, warns Stephen Senn.

Stephen Senn

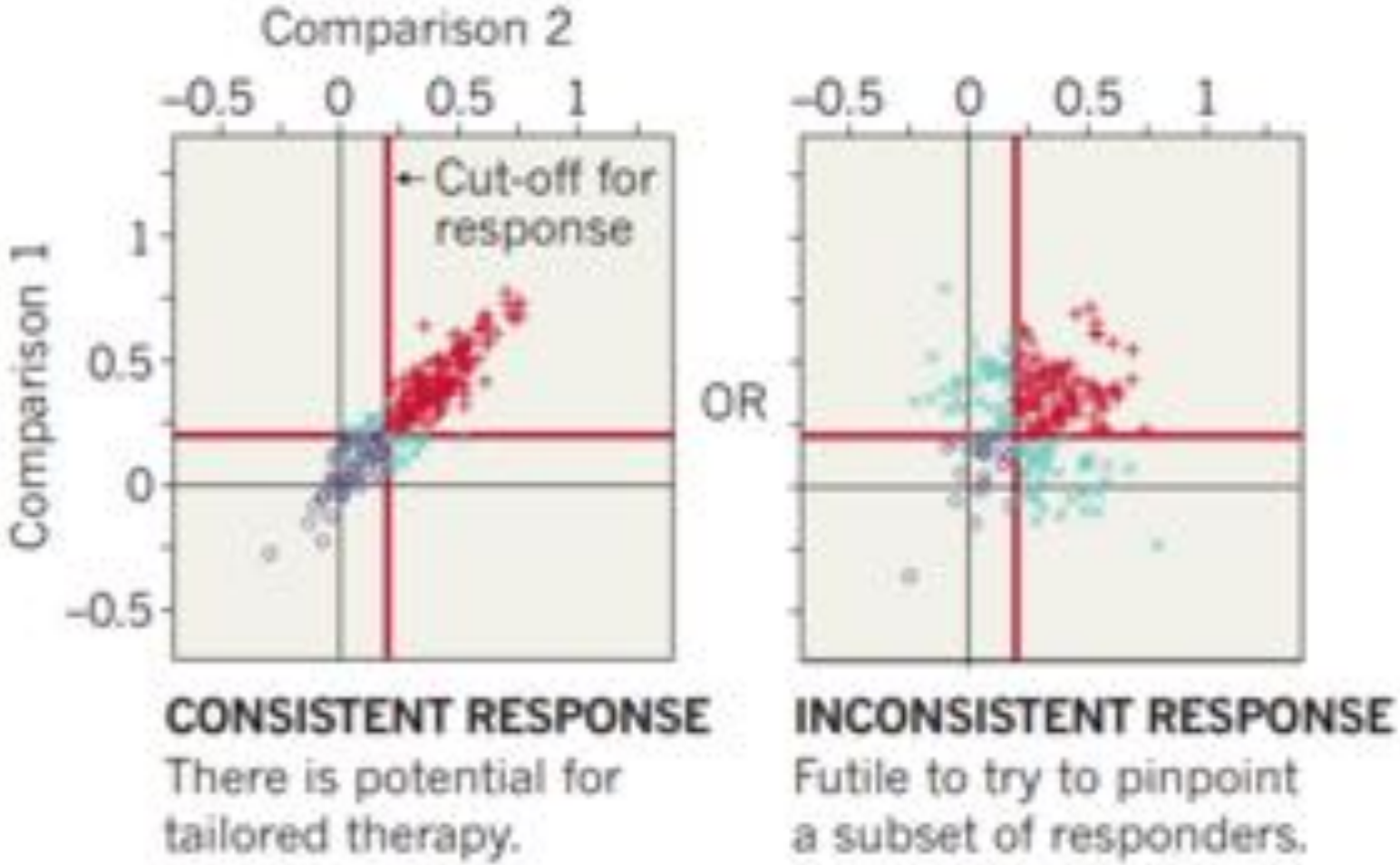
Illustration by David Parkins

Personalized medicine aims to match individuals with the therapy that is best suited to them and their condition. Advocates proclaim the

PDF version



Senn S. Statistical pitfalls of personalized medicine. Nature 2018;563:619-621



Senn S. Statistical pitfalls of personalized medicine. Nature 2018;563:619-621

JAMA Psychiatry | Original Investigation

Evaluation of Differences in Individual Treatment Response in Schizophrenia Spectrum Disorders
A Meta-analysis

Stephanie Winkelbeiner, PhD; Stefan Leucht, MD; John M. Kane, MD; Philipp Homan, MD, PhD

Supplemental content

IMPORTANCE An assumption among clinicians and researchers is that patients with schizophrenia vary considerably in their response to antipsychotic drugs in randomized clinical trials (RCTs).

OBJECTIVE To evaluate the overall variation in individual treatment response from random variation by comparing the variability between treatment and control groups.

DATA SOURCES Cochrane Schizophrenia, MEDLINE/PubMed, Embase, PsycINFO, Cochrane CENTRAL, BIOSIS Previews, ClinicalTrials.gov, and World Health Organization International Clinical Trials Registry Platform from January 1, 1955, to December 31, 2016.

STUDY SELECTION Double-blind, placebo-controlled, RCTs of adults with a diagnosis of schizophrenia spectrum disorders and prescription for licensed antipsychotic drugs.

DATA EXTRACTION AND SYNTHESIS Means and SDs of the Positive and Negative Syndrome Scale pretreatment and posttreatment outcome difference scores were extracted. Data quality and validity were ensured by following the PRISMA guidelines.

MAIN OUTCOMES AND MEASURES The outcome measure was the overall variability ratio of treatment to control in a meta-analysis across RCTs. Individual variability ratios were weighted by the inverse-variance method and entered into a random-effects model. A personal element of response was hypothesized to be reflected by a substantial overall increase in variability in the treatment group compared with the control group.

Attribution of the apparent improvement in the status of epidemiology (1986)

… “stems in large part from the emergence of a clearer understanding of the epidemiologic concepts that have become the basis of modern epidemiology”.

Rothman KJ. *Modern Epidemiology*. Boston: Little Brown & Co; 1986.

"Epidemiology has established a toehold as a scientific discipline. Whereas epidemiologic results were once greeted mainly with scepticism, they are now generally accorded some degree of respect. At mid-century, epidemiologist had trouble persuading the scientific community of a relation between smoking and lung cancer. By 1984, the situation had changed so much that a weak epidemiologic association observed between beta-carotene and cancer occurrence was the stimulus for a biochemical hypothesis on anti-oxidants, which was published in Science. The paper begins with the observation that

[E]pidemiological studies indicate that the incidence of cancer may be slightly lower among individuals with an above-average intake of beta-carotene and other carotenoids [Burton and Ingold, 1984].

The respectability evinced by this integration of epidemiology into the fold of the biologic sciences stems in large part from the emergence of a clearer understanding of the epidemiologic concepts that have become the basis of modern epidemiology." (p. 5)

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Rothman KJ, Greenland S. *Modern Epidemiology* (second edition). Philadelphia, PA: Lippincott-Raven; 1998

Bradford Hill "Criteria"

"wrong" … "useless and misleading" … "saddled with reservations".

Rothman KJ. *Modern Epidemiology*. Boston: Little Brown & Co; 1986.

Peter Spirtes

"the 'epidemiological criteria for causality' were an intellectual disgrace and the level of argument .. was sometimes more worthy of literary critics than scientists",

Spirtes P, Glymour C, Scheines R. *Causation, Prediction, and Search*. New York: Springer-Verlag; 1993.

Bradford Hill's criteria for causality

1) Temporal Relationship
2) Strength
3) Dose response Relationship
4) Consistency
5) Plausibility
6) Coherence
7) Analogous explanations
8) Specificity
9) Experiment

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Sterne J. An Introduction to causal inference. Presented at the 2018 Society for Research Synthesis Methodology meeting. Bristol, UK, July 17–19, 2018

Mid-1980s non-communicable disease epidemiology questions

Was HDL-cholesterol (HDL-C) protective against coronary disease?

Did higher triglyceride level increase CHD risk?

Why was stomach cancer incidence declining?

What was the major aetiological factor in cervical cancer?

Could alcohol protect against CHD?

Was inflammation important in cardiovascular disease?

Did antioxidants reduce the risk of cancer and cardiovascular disease?

What caused peptic ulcer?

SPECIAL ARTICLE

EPIDEMIOLOGY AS A GUIDE TO CLINICAL DECISIONS

The Association between Triglyceride and Coronary Heart Disease

STEPHEN B. HULLEY, M.D., M.P.H., RAY H. ROSENMAN, M.D., RICHARD D. BAWOL, PH.D., AND RICHARD J. BRAND, PH.D.

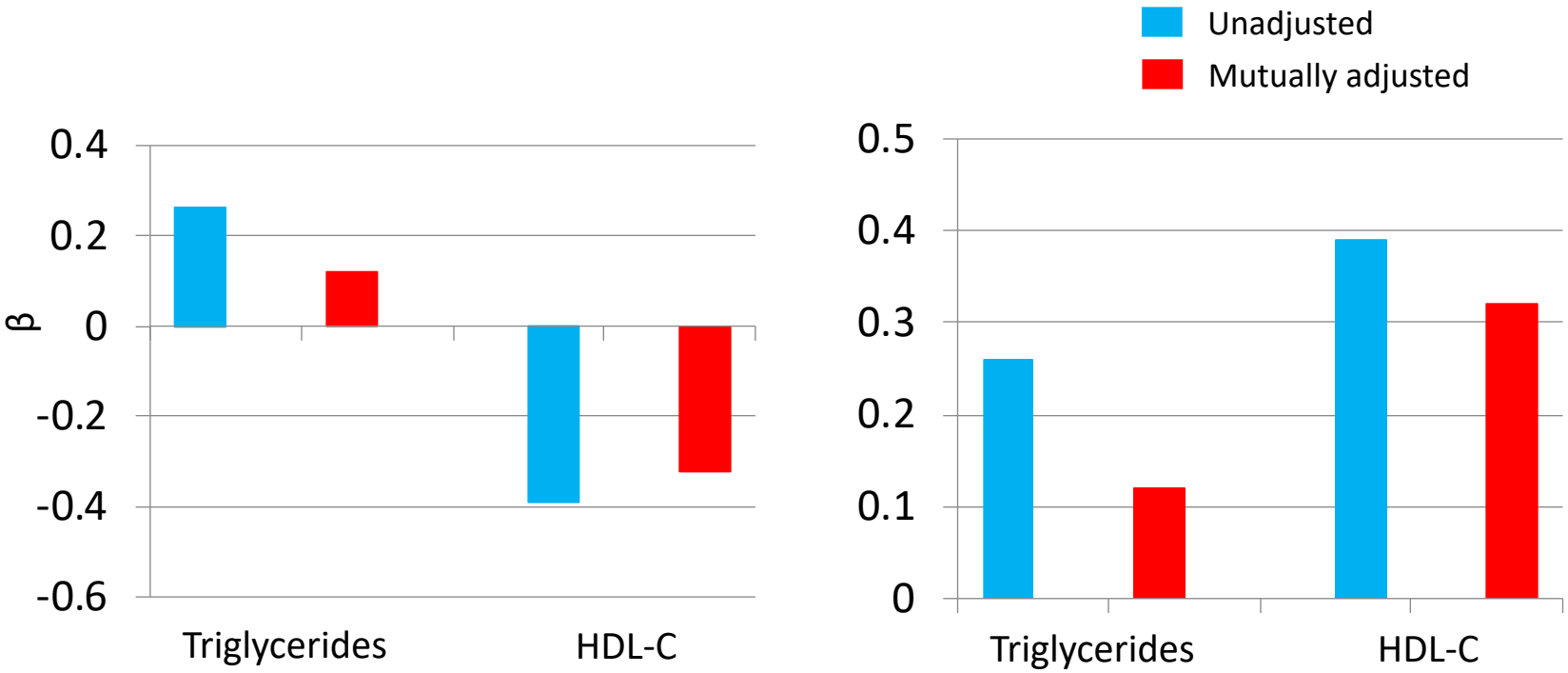
Abstract The hypothesis that triglyceride is a cause of coronary heart disease, although unconfirmed and never universally accepted, has nonetheless strongly influenced the practice of preventive medicine. We have examined the epidemiologic association between triglyceride and coronary heart disease to evaluate the validity of inferring that there is a causal relation between the two. Neither the evidence from published studies nor an analysis of data from the Western Collaborative Group Study provides strong support for the causal hypothesis. Information from other scientific disciplines is also meager, contrasting with the coherence of diverse evidence supporting the hypothesis that cholesterol is a cause of coronary heart disease.

These arguments fall short of disproving the belief that lowering triglyceride will prevent coronary heart disease, especially since triglyceride and cholesterol are inextricably associated through mutual lipoprotein carriers. But we propose that the ethics of preventive medicine place the burden of proof on the proponents of intervention. We therefore recommend that widespread screening and treatment of healthy persons for hypertriglyceridemia be abandoned until more persuasive evidence becomes available. (N Engl J Med. 1980; 302:1383-9.)

IN 1959, Albrink and Man found high serum levels of triglyceride in men with a history of myocardi-

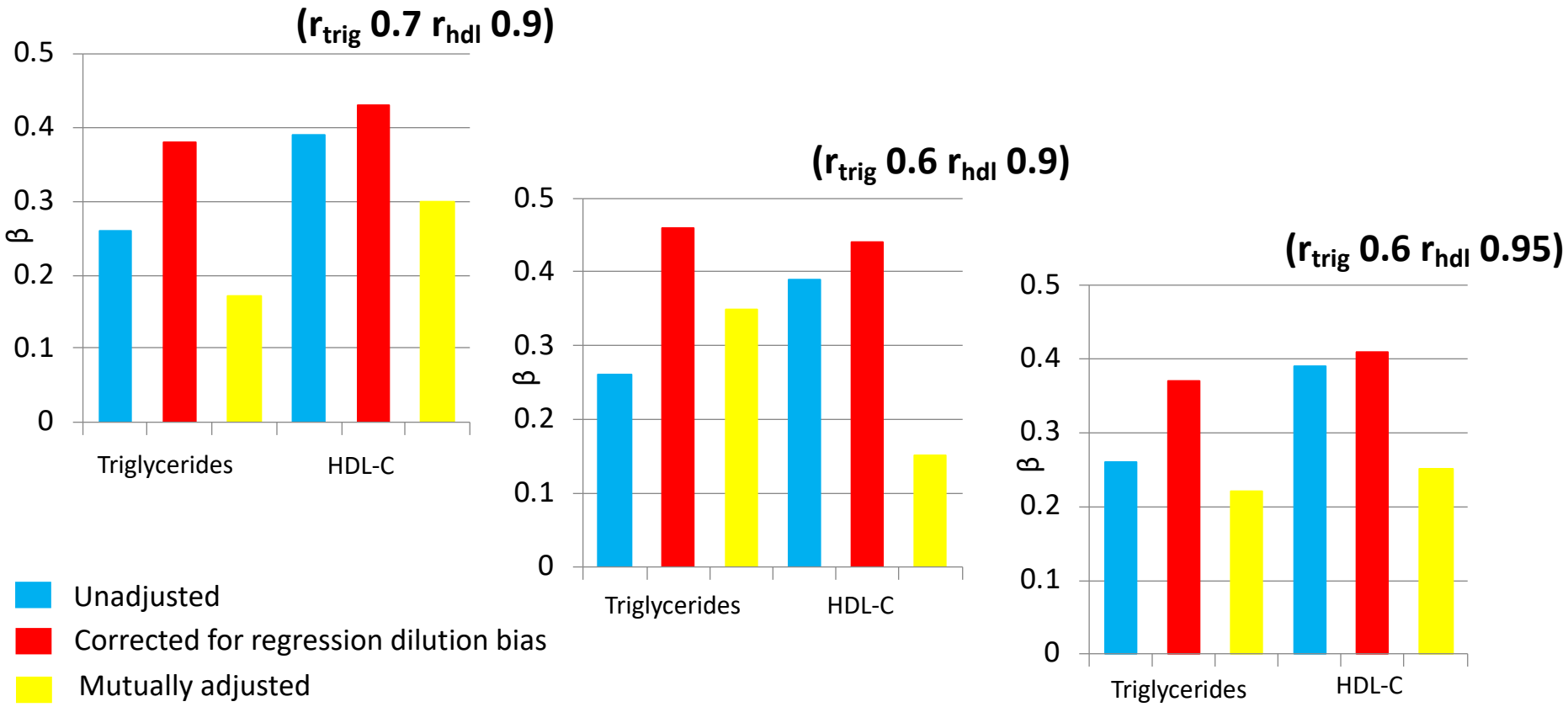
prescribing diet and drugs for otherwise healthy persons with hypertriglyceridemia[34,35] has given way to a

Triglycerides and HDL cholesterol – which has the stronger association with coronary heart disease?



Phillips A, Davey Smith G. How independent are "independent" effects? Relative risk estimation when correlated exposures are measured imprecisely. J Clin Epidemiol 1991;44:1223-31.

Triglycerides and HDL cholesterol with measurement error. Which now has the stronger association with coronary heart disease?



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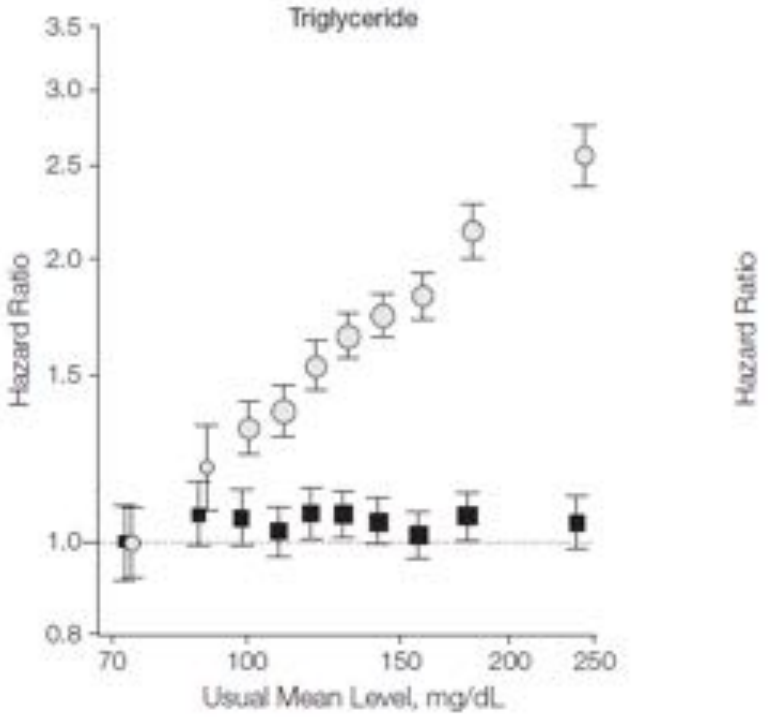
Risk of coronary heart disease according to triglyceride level, with and without adjustment



The Emerging Risk Factors Collaboration. Major lipids, apolipoprotiens and risk vascular disease. JAMA 2009; 302: 1993-2000

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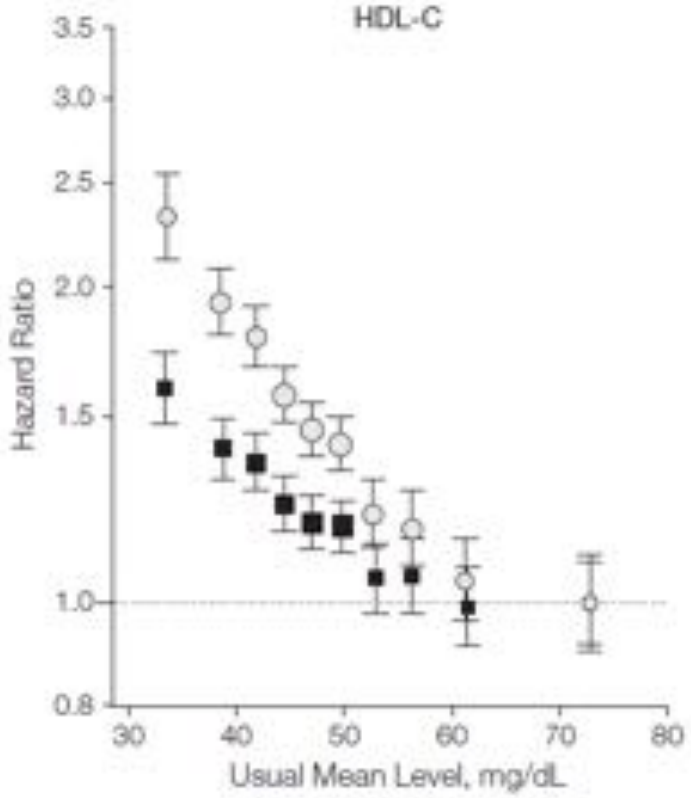
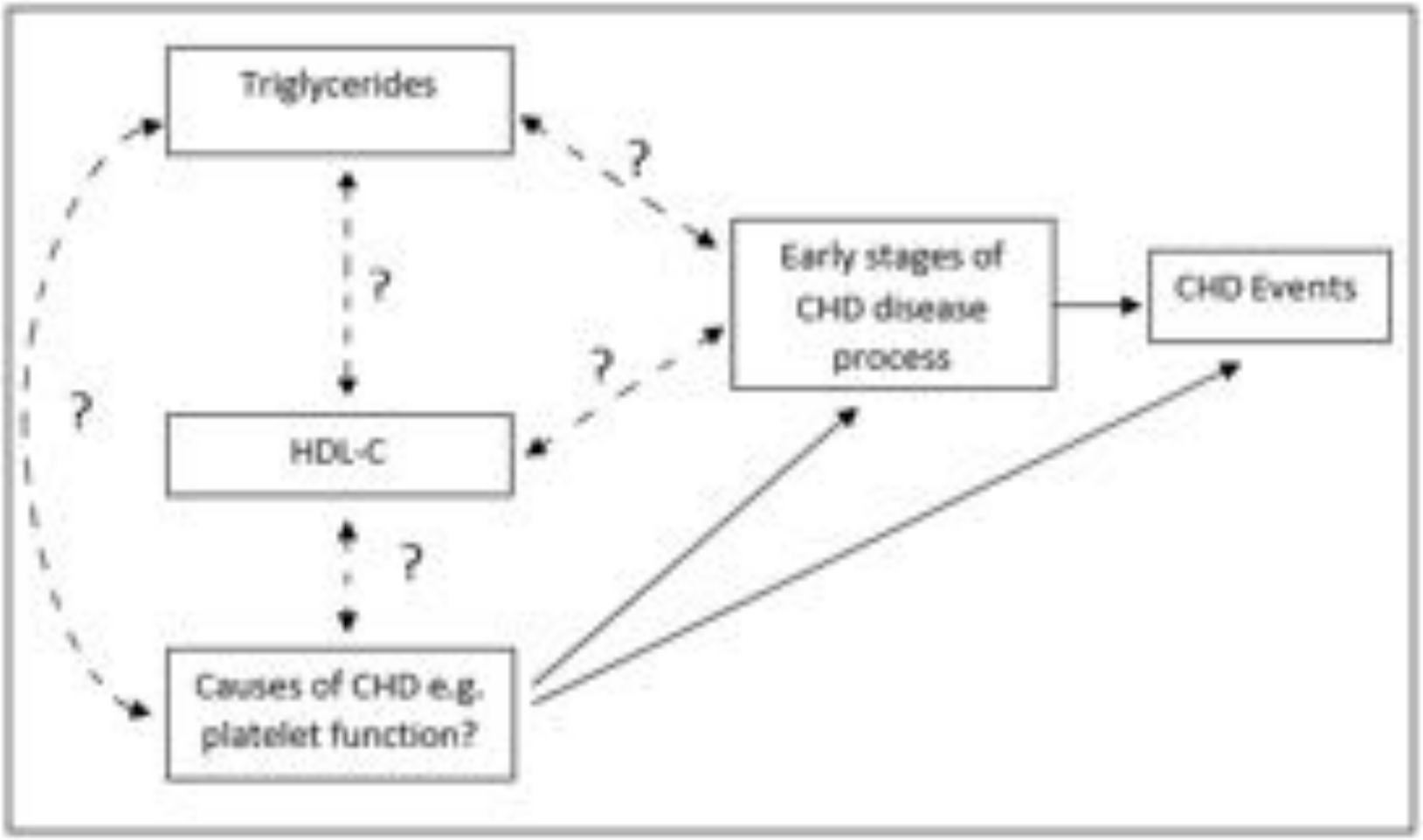


The Emerging Risk Factors Collaboration. Major lipids, apolipoprotiens and risk vascular disease. JAMA 2009; 302: 1993-2000

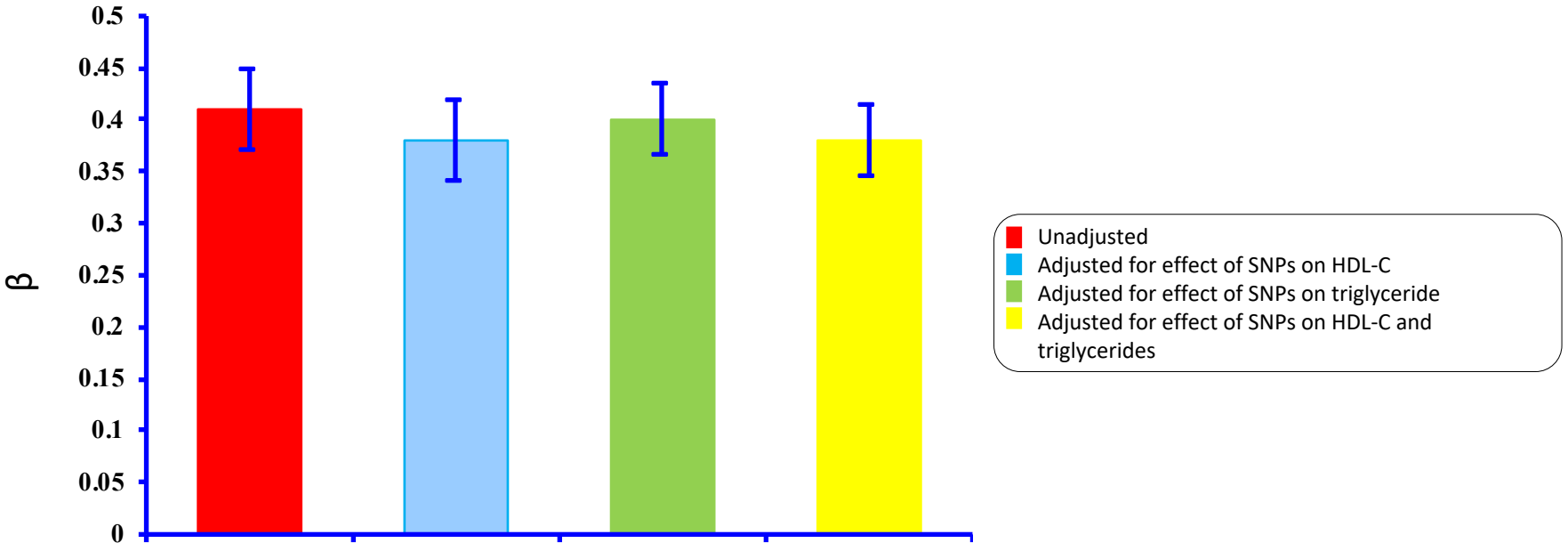
“The current findings suggest that therapy directed at HDL-C as well as non-HDL-C may generate substantial additional benefit”

The Emerging Risk Factors Collaboration. Major lipids, apolipoprotiens and risk vascular disease. JAMA 2009; 302: 1993-2000



Davey Smith G, Phillips AN. Correlation without a cause: an epidemiological odyssey. Int J Epidemiol. 2019, in press

Association of strength of a SNP's effect on LDL-C with its strength of effect on CHD risk, with adjustment



Do R et al. Common variants associated with plasma triglycerides and risk for coronary artery disease. Nature Genetics 2013;45:1345–1352

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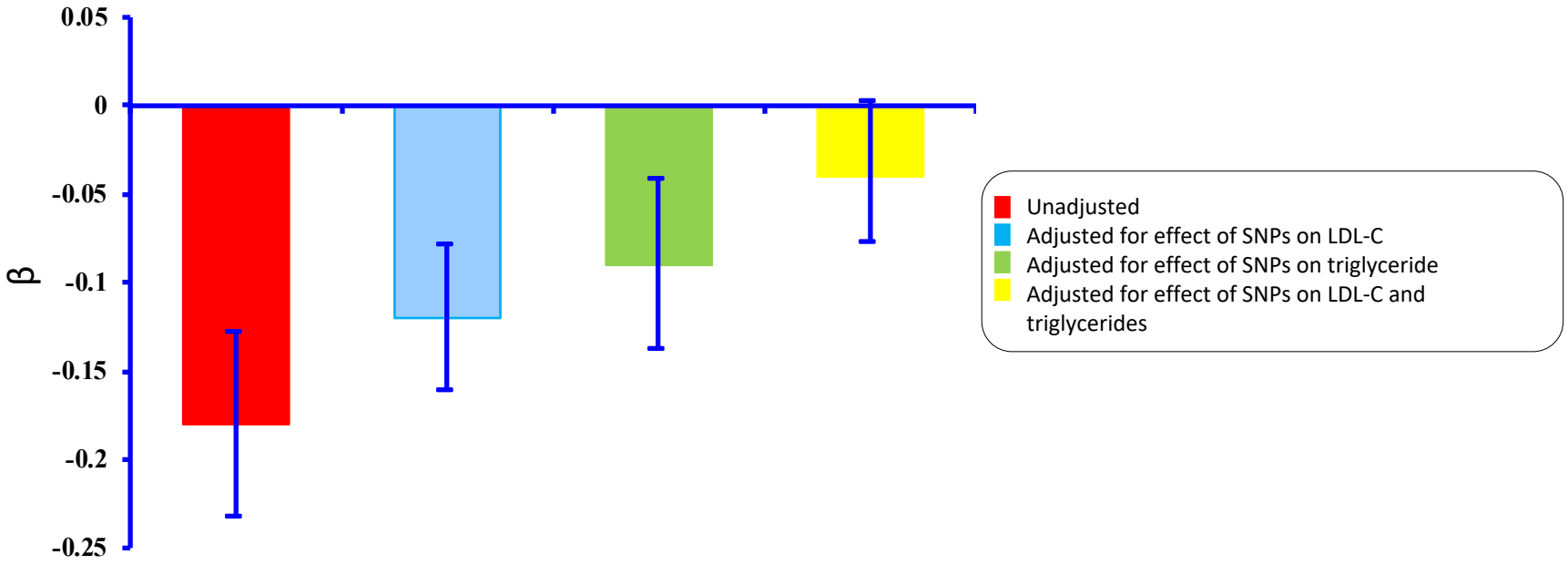

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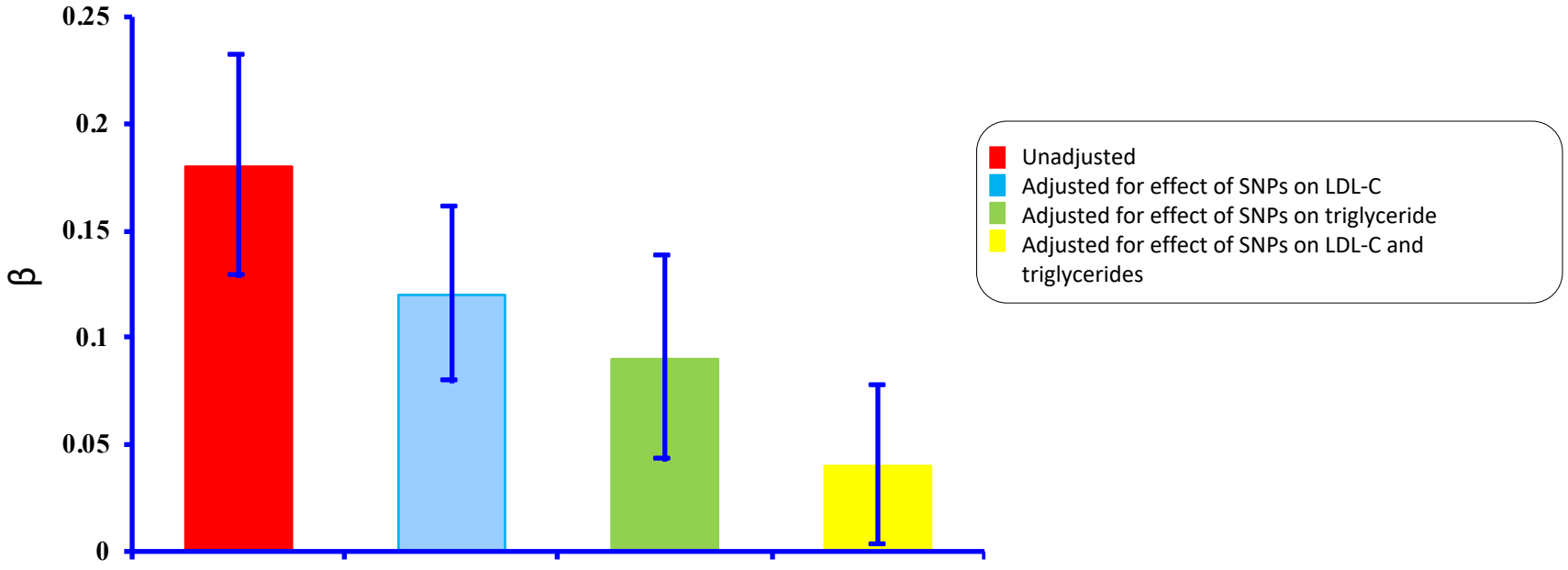

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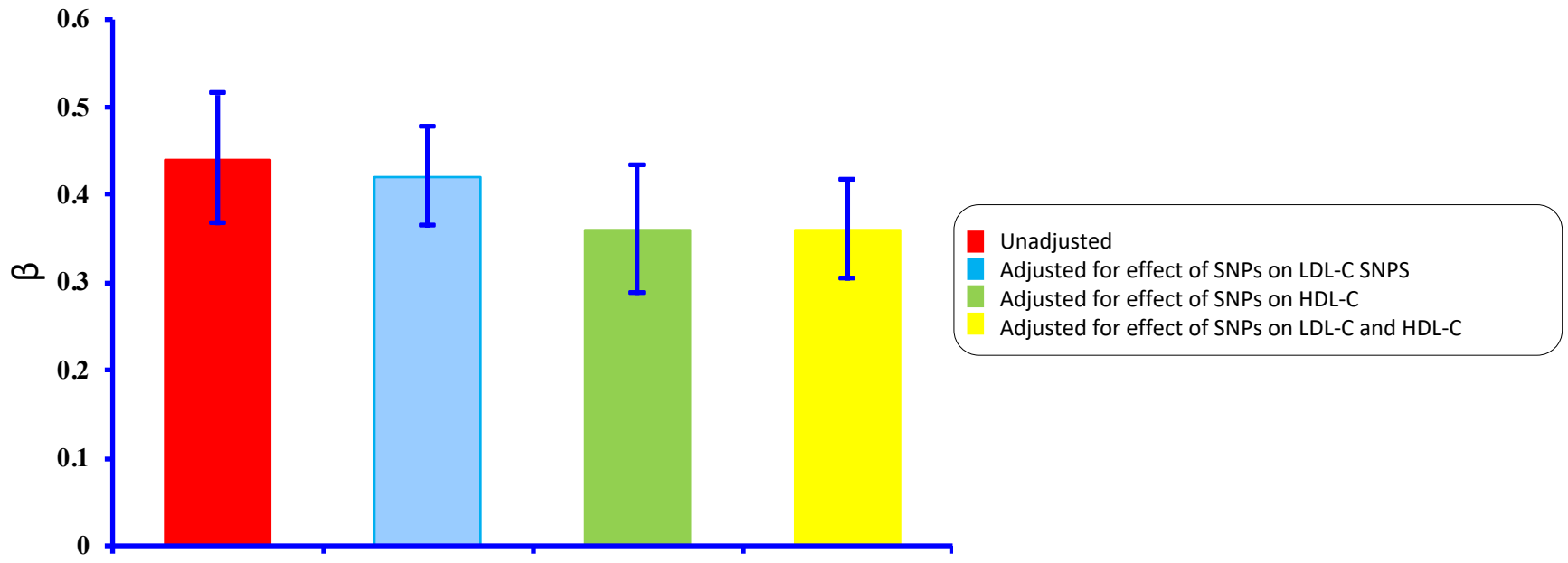
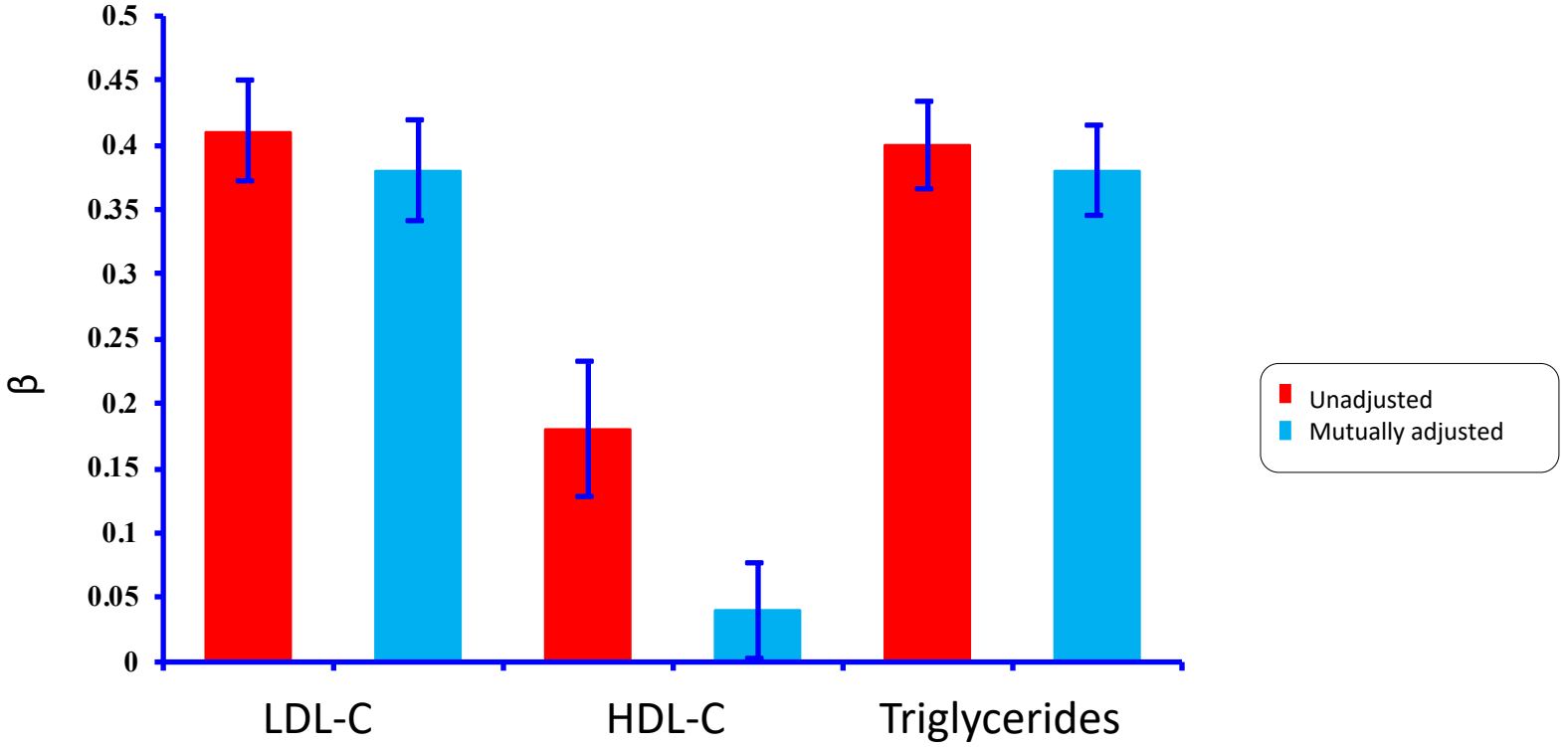


Do R et al. Common variants associated with plasma triglycerides and risk for coronary artery disease. Nature Genetics 2013;45:1345–1352

Association of strength of a SNP's effect on a lipid fraction with its strength of effect on CHD risk, with before and after mutual adjustment



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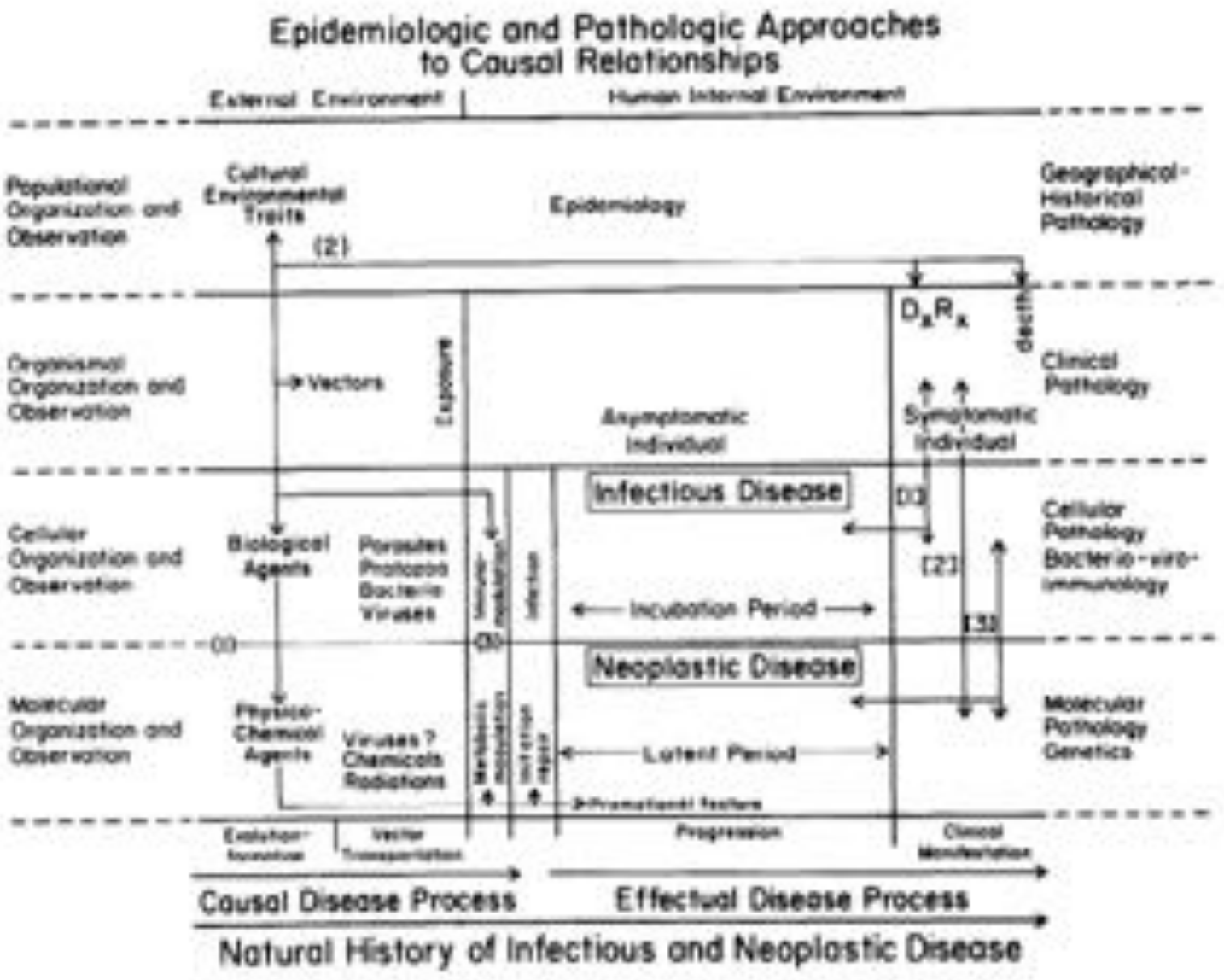


Lower GM Jr. Systematic epidemiologic theory: conceptual foundations and axiomatic elements. Med Hypotheses. 1983;11(2):195-215.

tissue-dependent regulatory mechanisms

across the human phenome

Tom G Richardson[1*], Gibran Hemani[1], Tom R Gaunt[1], Caroline L Relton[1], George Davey Smith[1]

[1] MRC Integrative Epidemiology Unit (IEU), Population Health Sciences, Bristol Medical School, University of Bristol, Oakfield House, Oakfield Grove, Bristol, BS8 2BN, United Kingdom

Richardson T et al. A transcriptome-wide Mendelian randomization study to uncover tissue-dependent regulatory mechanisms across the human phenome. bioRxiv 2019

Triangulation and the Bradford Hill Criteria

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

Hill AB. The Environment and Disease: Association or Causation? Proc R Soc Med. 1965;58: 295–300.

Smoking and low birth weight

- Time trends and between populations
- Observational studies
- Cross-contextual comparisons
- Negative control studies
- Within-sibship studies
- Children of twins
- Mendelian randomization (MR)
- Non-genetic instrumental variables
- Randomized controlled trials (RCTs)

Krieger N, Davey Smith G. The tale wagged by the DAG: broadening the scope of causal inference and explanation for epidemiology. Int J Epidemiol 2016; 45: 1787-1808.

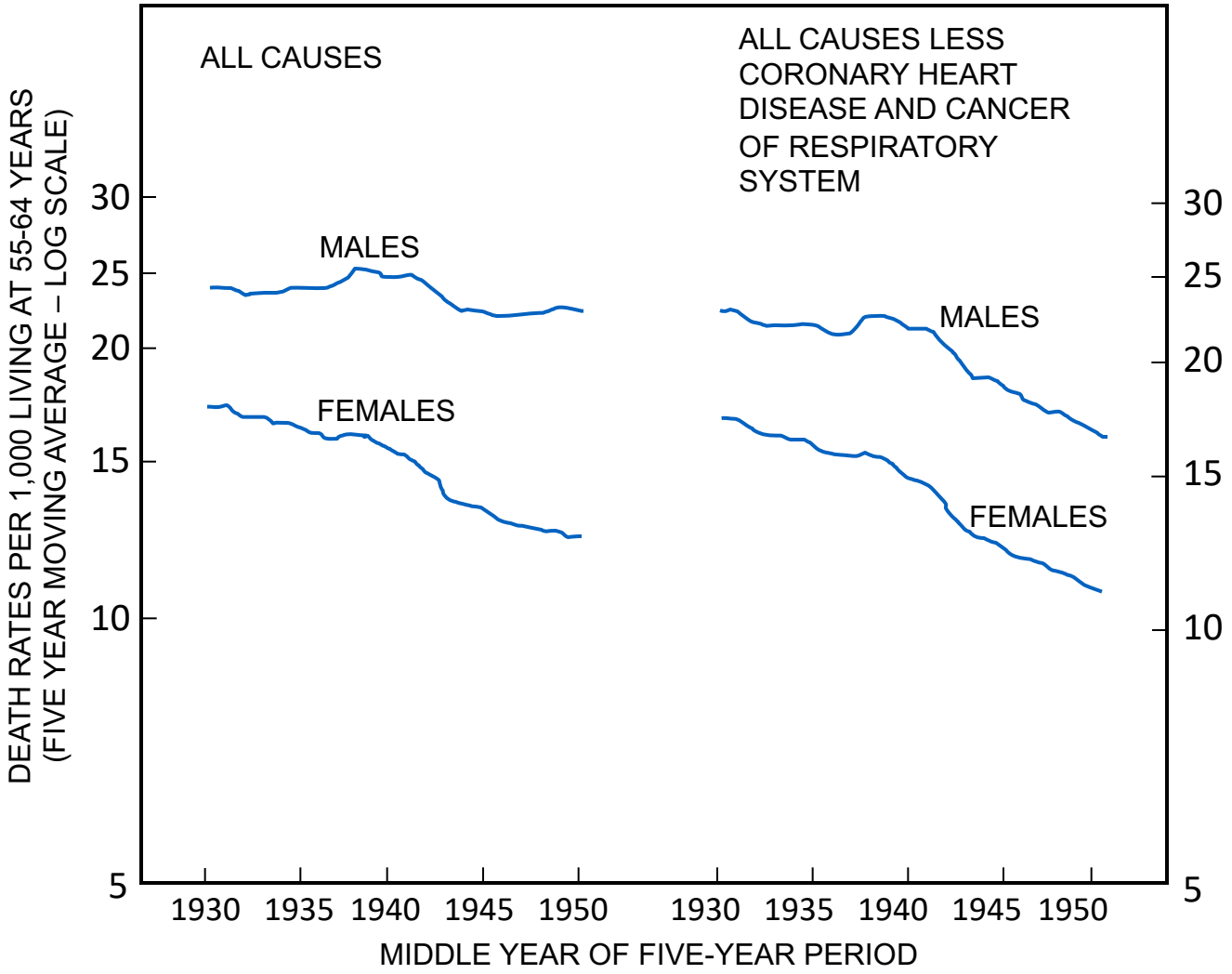
TABLE V.—*Standardized Death Rates Per Year Per 1,000 Men Aged 35 Years or More, in Relation to the Most Recent Amount Smoked**

Cause of Death	No. of Deaths	Death Rate Among:					
		All Men	Non-smokers	All Smokers	Men Smoking a Daily Average of		
					1–14 g.	15–24 g.	25 g. or More
Lung cancer	84†	0·82	0·07	0·90	0·47	0·86	1·66
Other cancer	230	2·02	2·04	2·02	2·01	1·56	2·43
Other respiratory diseases	126	1·10	0·81	1·13	1·00	1·11	1·41
Coronary thrombosis	508	4·78	4·22	4·87	4·64	4·60	5·09
Other causes	739	6·79	6·11	6·89	6·82	6·38	7·19
All causes	1,714	15·48	13·25	13·78	14·92	14·49	18·84

* That is, at November 1, 1951, for those smoking at that time and at the date of giving up for those who had given up at November 1, 1951.

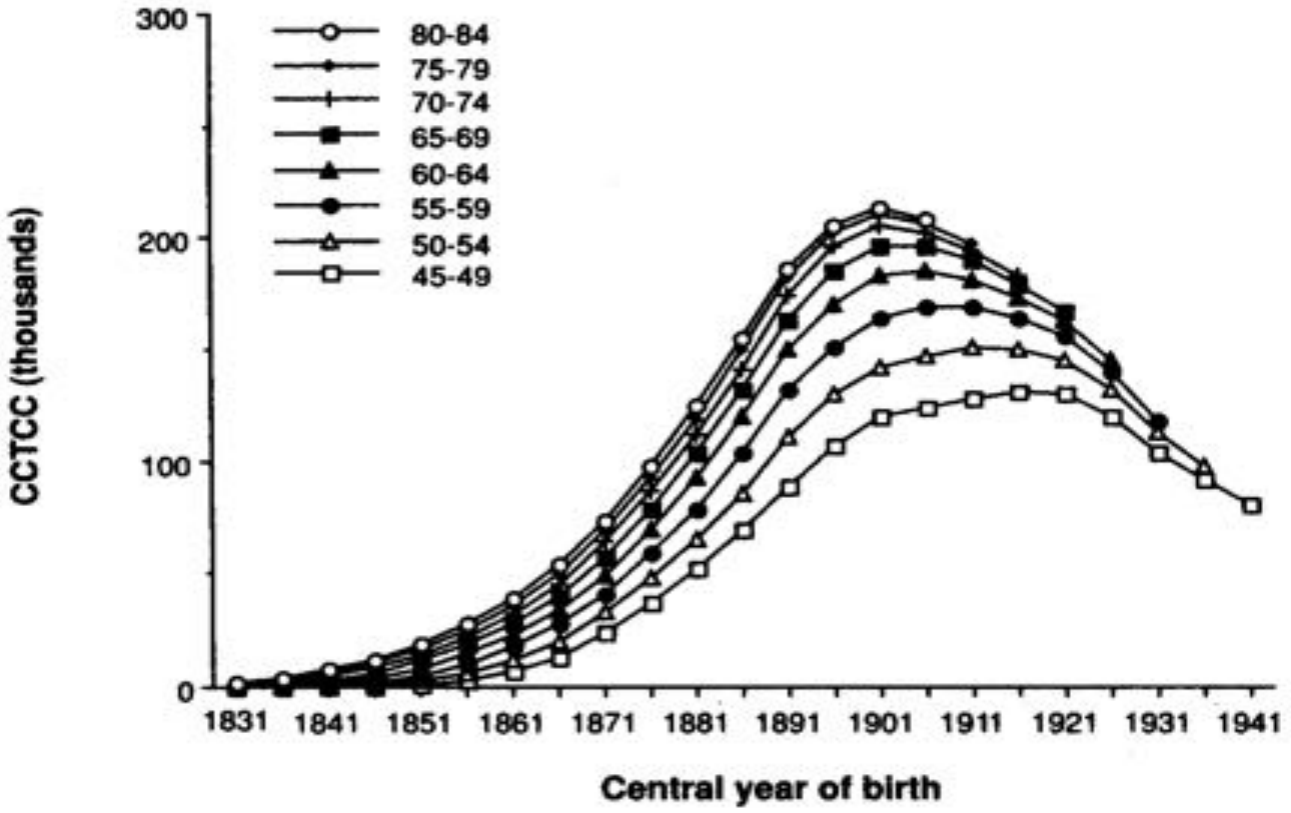
† The three cases in which lung cancer was recorded as a coincidentary but not a direct cause of death are included under both lung cancer and the cause to which death was assigned by the Registrar-General.

Doll R et al. LUNG CANCER AND OTHER CAUSES OF DEATH IN RELATION TO SMOKING A SECOND REPORT ON THE MORTALITY OF BRITISH DOCTORS. BMJ 1956;10:1071-1081



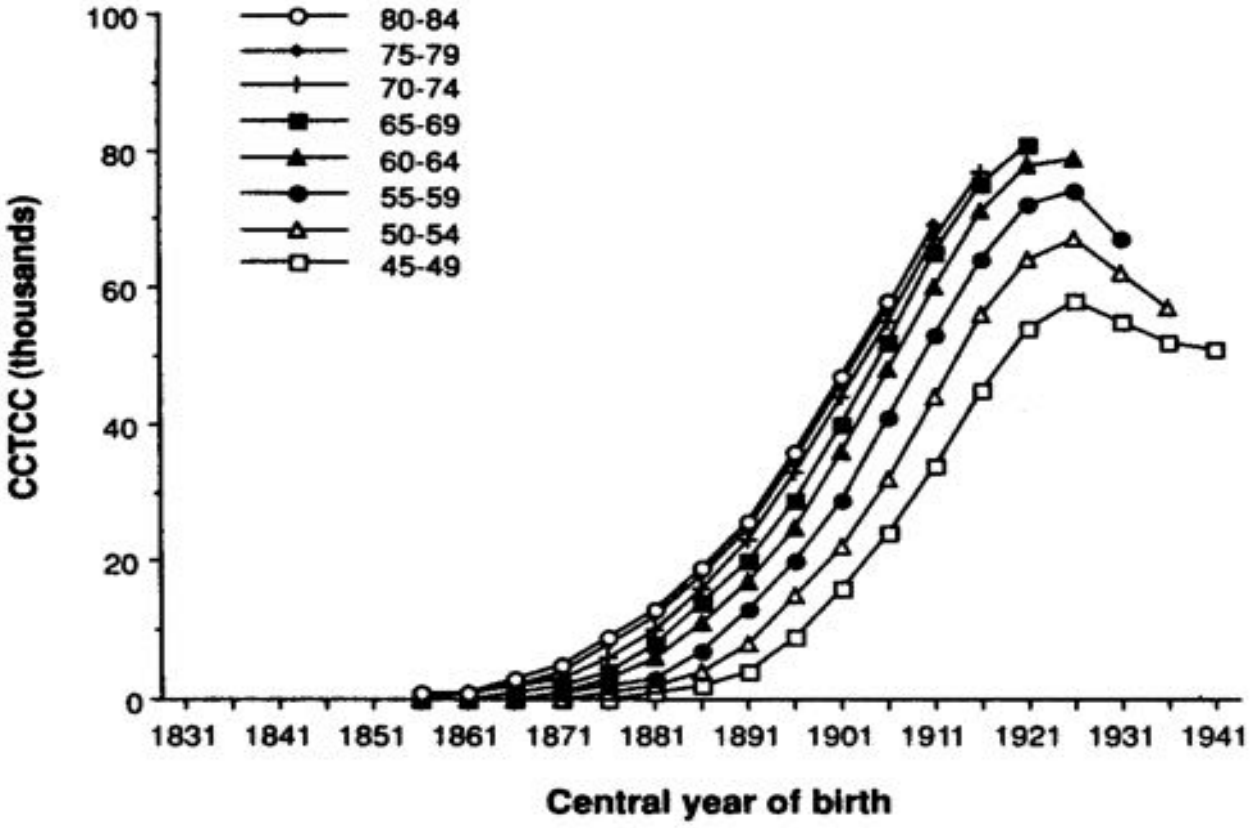
JM Morris, *Uses of Epidemiology*, 1st Ed. 1957

Age-specific cumulative lifetime cigarette consumption for males, England & Wales, by year of birth 1831-1941



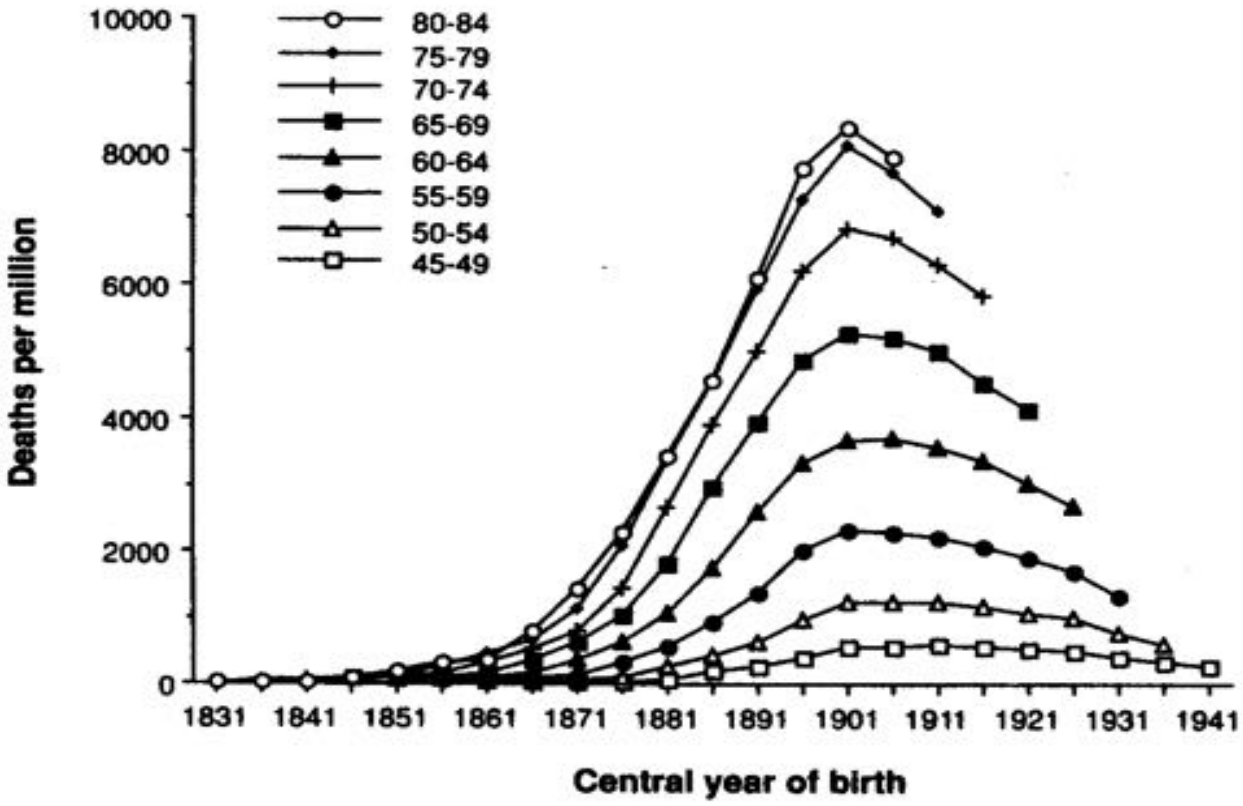
Lee *et al*

Age-specific cumulative lifetime cigarette consumption for females, England & Wales, by year of birth 1831-1941



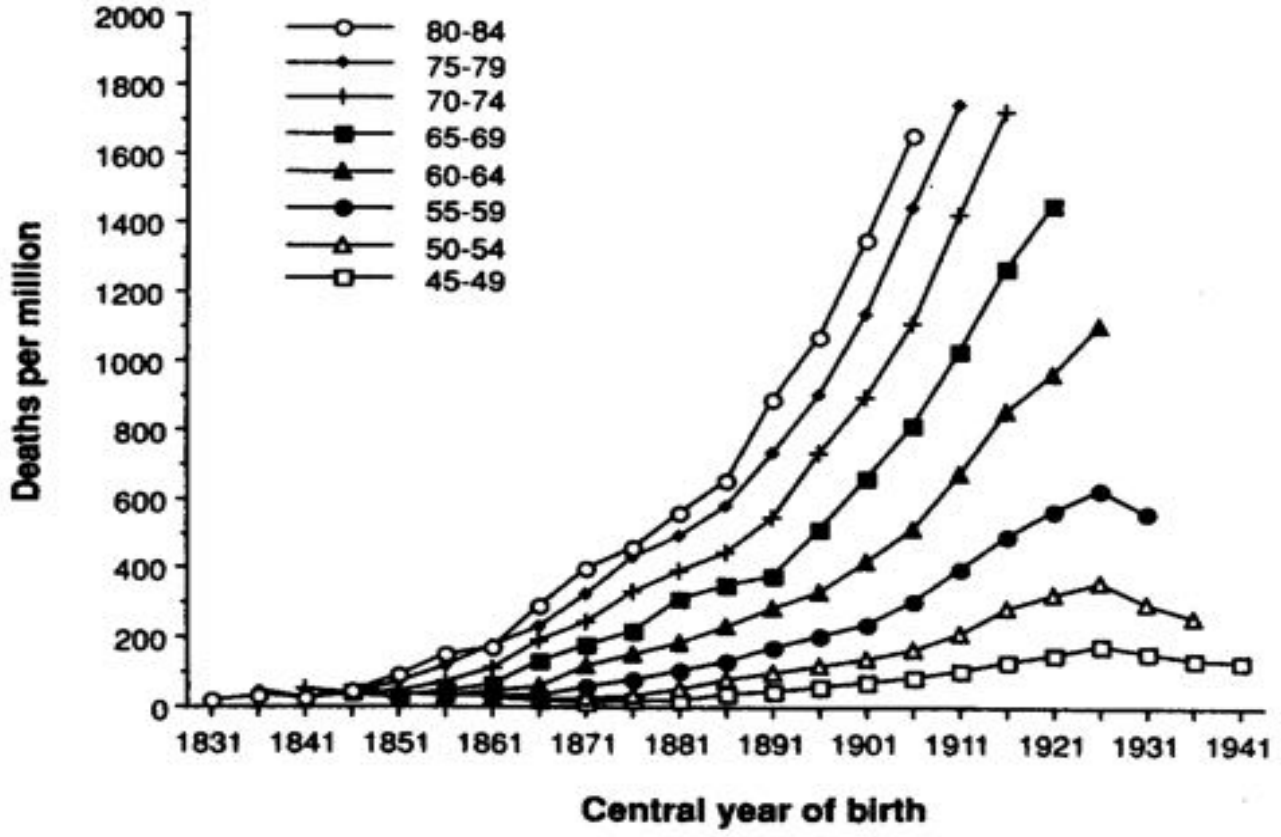
Lee *et al*

Age-specific lung cancer mortality rates for males,
England & Wales, by year of birth 1831-1941



Mortality data published by Office of Population Censuses and Surveys, London

Age-specific lung cancer mortality rates for females,
England & Wales, by year of birth 1831-1941



Mortality data published by Office of Population Censuses and Surveys, London

Table 3. Multivariable Adjusted Hazard Ratios Between Attendance at Religious Services and Cardiovascular Disease and Cancer Mortality in the Nurses' Health Study, 1996-2012[a]

Mortality	Attendance at Religious Services				*P* Value for Trend
	Never	Less Than Once per Week	Once per Week	More Than Once per Week	
All cardiovascular disease (n = 2721)					
Cases, No.	670	378	1116	557	
Age-adjusted HR (95% CI)	1 [Reference]	0.86 (0.74-0.99)	0.74 (0.66-0.82)	0.62 (0.54-0.71)	<.001
Multivariable HR (95% CI)	1 [Reference]	0.92 (0.79-1.06)	0.80 (0.70-0.91)	0.73 (0.62-0.85)	<.001
All cancer (n = 4479)					
Cases, No.	1255	692	1752	780	
Age-adjusted HR (95% CI)	1 [Reference]	0.78 (0.70-0.87)	0.71 (0.66-0.77)	0.59 (0.54-0.66)	<.001
Multivariable HR (95% CI)	1 [Reference]	0.91 (0.81-1.01)	0.86 (0.78-0.95)	0.79 (0.70-0.89)	<.001

Abbreviation: HR, hazard ratio.

[a] For the predictors the multivariable model adjusted for, see the Covariates subsection of the Methods section.

Li S et al, Association of religious service attendance with mortality among women. JAMA Internal Medicine 2016;176:777-785

Table 4: Percentage at least weekly church attendance 1973-2008*

	%								
	1973	1978	1981	1984	1985	1990	1991	1998	2008
All	92	91	83	-	88	81	65	57	40
RC	91	-	87	87	-	85	68	62	43

* %s for 1973-1990 are Eurobarometer statistics based on Figure 3.4 from Fahey, Hayes and Sinnott, 2005:42

Nic Ghiolla Phádraig, Máire. 2009. "Research Update: Religion in Ireland: No Longer an Exception?" Available at http://www.ark.ac.uk/publications/updates/update64.pdf.

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Approaches to causal inference

Triangulation in aetiological epidemiology

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Abstract

Triangulation is the practice of obtaining more reliable answers to research questio
through integrating results from several different approaches, where each approach h
different key sources of potential bias that are unrelated to each other. With respect
causal questions in aetiological epidemiology, if the results of different approaches
point to the same conclusion, this strengthens confidence in the finding. This is partic
larly the case when the key sources of bias of some of the approaches would predict th
findings would point in opposite directions if they were due to such biases. Where the
are inconsistencies, understanding the key sources of bias of each approach can help

COMMENT

Repeating experiments is not enough

Verifying results requires disparate lines of evidence — a technique called triangulation. **Marcus R. Munafò** and **George Davey Smith** explain.

Viewpoint

Should the mission of epidemiology include the eradication of poverty?

Kenneth J Rothman, Hans-Olov Adami, Dimitrios Trichopoulos

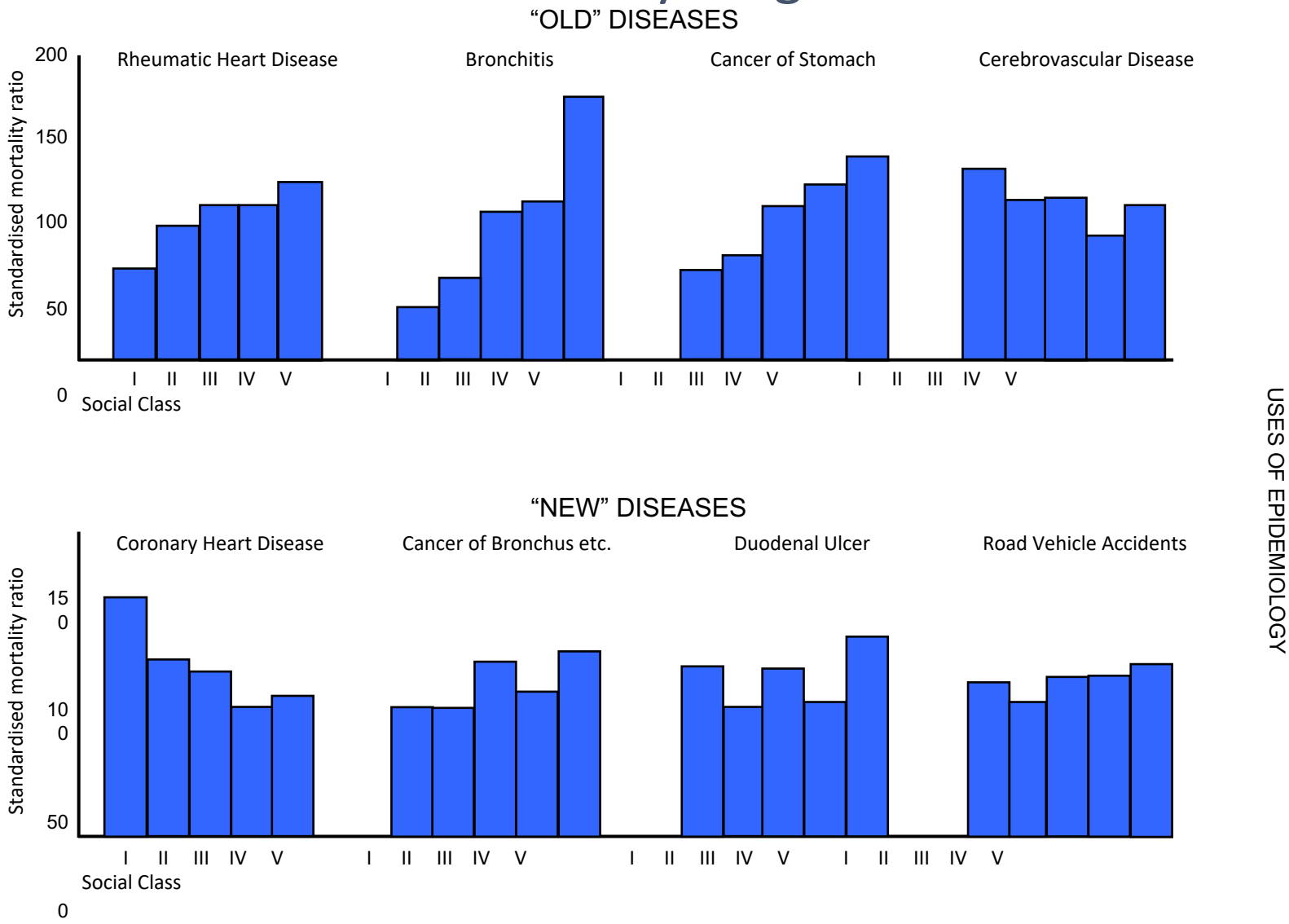
Physicists seem to have escaped the old criticism that their work is impractical. Perhaps the criticism was blunted by technological innovations that rest on physical theory. Nevertheless, even astrophysicists, whose work seldom induces engineering breakthroughs, can now pursue knowledge for its own sake without fear of being badgered about the practical relevance of their work. What

smallpox could not have been eradicated without a clever, global strategy to contain it, and malnutrition rooted in poverty cannot be prevented without societal interventions that ease the burden of poverty or that address malnutrition directly.

The distinction between individual and societal applications of epidemiological knowledge are at the core

Lancet 1998

Community Diagnosis



"Old" diseases and "new". Mortality among the different social classes in 1950. England and Wales. Males aged 20-64 incl.

JM Morris, *Uses of Epidemiology*, 1st Ed. 1957

Perhaps epidemiology is now poised to become modern?

Annual Jerry Morris Lecture

30th September 2019

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