Understanding determinants of phenotypic variation: a “gloomy prospect“?

George Davey Smith

Centre for Causal Analyses in Translational Epidemiology (CAiTE)

University of Bristol

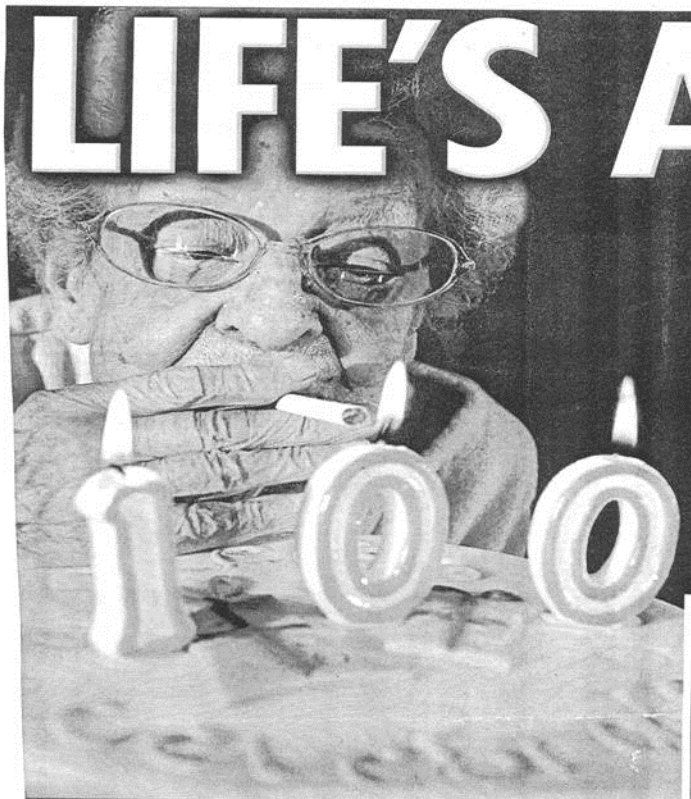
Why do epidemiologists get up in the morning?

Why do epidemiologists get up in the morning?

- to identify modifiable causes of disease that can be utilized to leverage improved population health

  (top of Jerry Morris' list of seven "Uses of epidemiology" – "in search of causes")

LIFE'S A DRAG



Winnie, 100 smokes for 93 YEARS and she ain't quitting now

Wartime memories . . Winnie had her first cigarette in 1914

By GARETH DORRIAN

DEFIANT smoker Winnie Langley celebrates reaching 100 yesterday — by lighting her 170,000th cigarette from a candle on her birthday cake.

She started having a puff an incredible 93 years ago aged seven — just after the First World War broke out in June 1914. She has got through five a day ever since.

Winnie has no plans to quit — even after the nationwide ban forcing smokers outside — and reckons tobacco has never made her ill.

She gets her 100th birthday telegram from the Queen after outliving a husband, Robert, and son, Donald, who died two years ago aged 72.

Nerves

The former launderette worker said she started smoking weeks after the assassination of Archduke Franz Ferdinand in Sarajevo sparked the First World War.

Winnie, of Croydon, Surrey, said smoking helped "steady the nerves" during two World Wars.

And the reason why Winnie has never suffered because of the habit? She said: "I never inhaled."

STINK'S ON THE HOUSE

A PUB is squirting round cigarette-scented spray — after drinkers moaned the smoking ban had ruined the atmosphere.

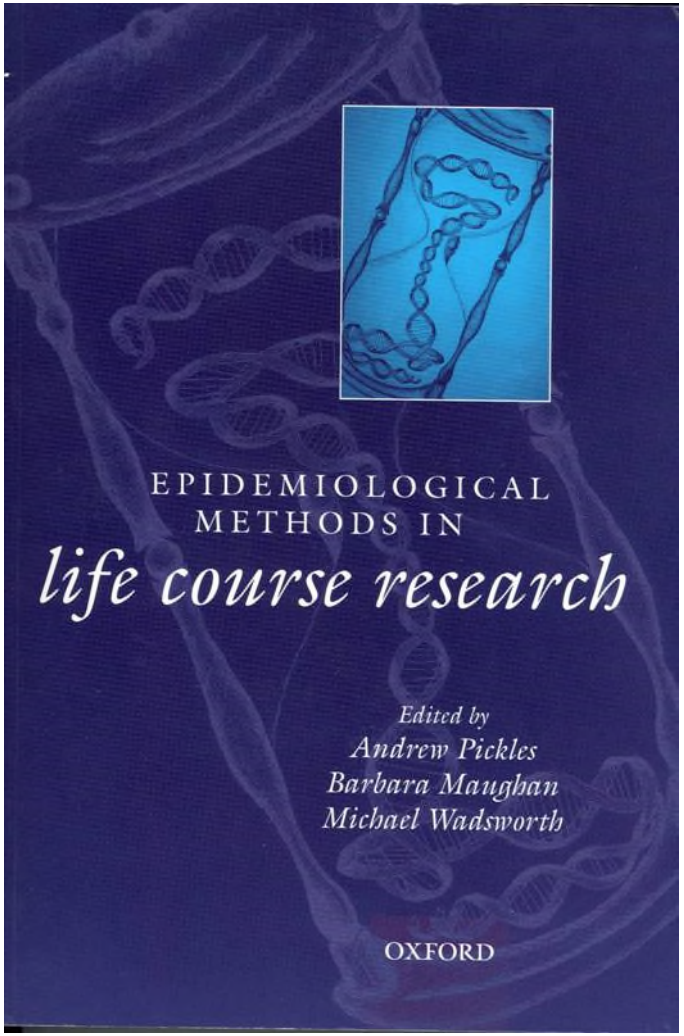
Landlady Sarah Thornton, 34, *below*, found the special effects product called Fag Ash on the internet.

She said at the Craven Arms in Birmingham: "Punters love it. Some sit there with unlit ciggies in their mouths.

"Without smoke it stinks of sweaty bodies."

Heaven scent . . Sarah with spray

Chapter 2. Measurement and design for life course studies of individual differences and development , *Jane Costello and Adrian Angold*



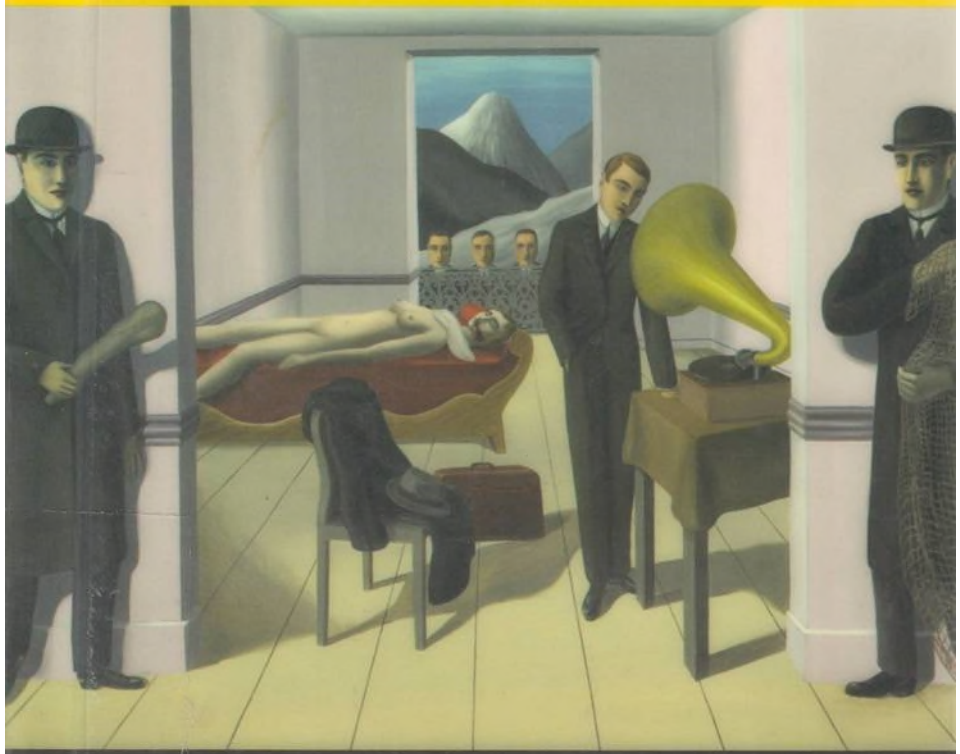
Studying changes within individuals: the causes of offending

"The concept of cause inevitably involves the concept of change within individual units … This is not true of randomized experiments on variations between individuals, however, because – with large samples - the randomization ensures that the average individual in one condition is equivalent to the average person in another .."

DP Farrington in M Rutter (editor) Studies in Psychosocial Risk, 1988

A Cultural History of CAUSALITY

Stephen Kern



SCIENCE, MURDER NOVELS, AND SYSTEMS OF THOUGHT

Causality in murder novels (and systems of thought)

Ancestry – animal, genetic and “imprinting”

Childhood – “blank slate”, Freud

Sexuality – compulsion, hormones, impotence

Emotion – jealousy, revenge, greed

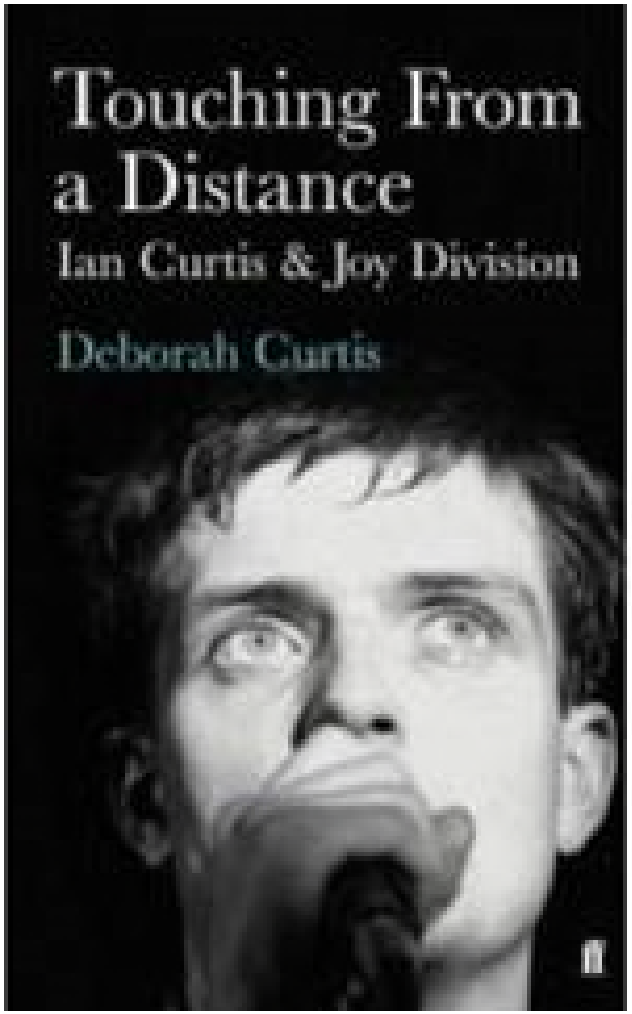
Mind – mental illness, sociopathy

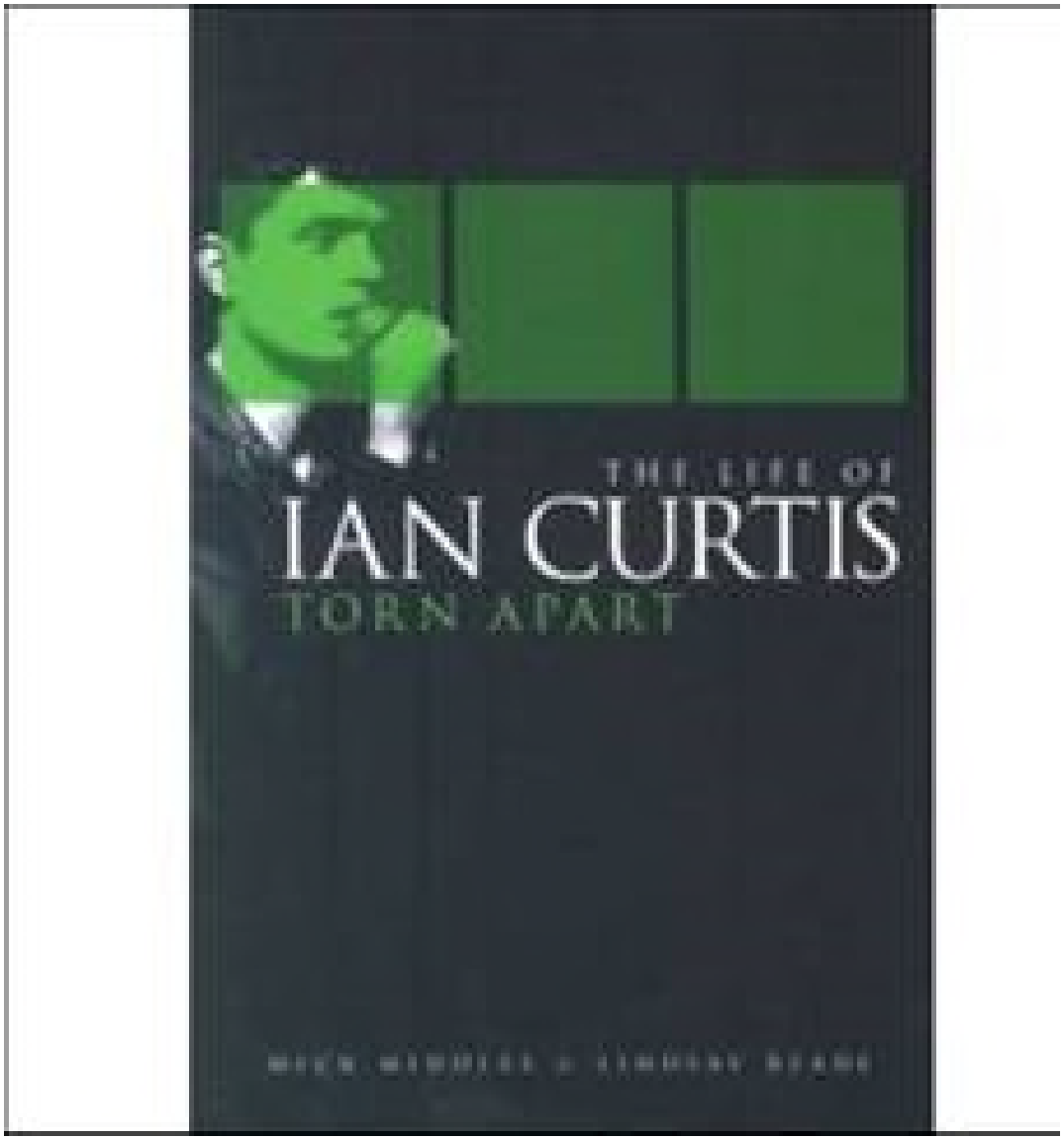
Ideas – nihilism, beyond good and evil

Society – epidemiologists know all about that!

(Language – Po-Mo guff)

Stephen Kern “A cultural history of causality” 2004


Touching From
a Distance
Ian Curtis & Joy Division
Deborah Curtis


THE LIFE OF
IAN CURTIS
TORN APART

bollywoodfilmsmovies.rediffiland.com/

<<previous | next>>

Thursday 24 January, 2008

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Major shocker from Hollywood...Heath Ledger is dead

Just read a few minutes ago that **Heath Ledger** the actor who played a macho gay cowboy in **Brokeback Mountain** was found dead at his **New Yor** apartment. He was apparently waiting for a masseuse and when his house keeper showed the masseur in they found him dead. He was sprawle head on the bed with a bottle of sleeping pills found close by.

He has recently separated from his wife who starred with him in the same movie and had a 2 year old daughter but apparently had no reason to commit suicide. was happy and would be always found around the neighbourhood along with his daughter. He has also recently refused quite a few **movies** but that was not unu as he was very choosy about the roles he did.

Check out the article in MSN.

Category: Movies | Permalink

Causation and scientific medicine

A great surgeon performs operations for stone by a single method; later he makes a statistical summary of deaths and recoveries, and he concludes from these statistics that the mortality law for this operation is two out of five. Well, I say that this ratio means literally nothing scientifically and gives us no certainty in performing the next operation; for we do not know whether the next case will be among the recoveries or the deaths.

Claude Bernard, *An Introduction to the Study of Experimental Medicine*, 1865

In the patient who succumbed, the cause of death was evidently something which was not found in the patient who recovered; this something we must determine, and then we can act on the phenomena or recognize and foresee them accurately …the law of large numbers never teaches us anything about any particular case. What a physician needs to know is whether his patient will recover, and only the search for scientific determinism may lead to this knowledge.

Claude Bernard, *An Introduction to the Study of Experimental Medicine*, 1865

Causation and scientific sociology (and epidemiology?)

"In a given state of society, a certain number of persons must put an end to their own life. This is the general law; and the special question as to who shall commit the crime depends of course upon special laws; which, however, in their action, must obey the large social law to which they are all subordinate. And the power of the larger law is so irresistible , that neither love of life nor the fear of another world can avail anything towards even checking its operation".

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Henry Thomas Buckle, 1857

“The word “cause” is so inextricably bound up with misleading associations as to make its complete extrusion from the philosophical vocabulary desirable…..The reason why physics has ceased to look for causes is that, in fact, there are no such things. The law of causality, I believe, like much that passes muster among philosophers, is a relic of a bygone age, surviving, like the monarchy, only because it is erroneously supposed to do no harm.”

Bertrand Russell, 1913

“Galton turning over two different problems in his mind reached the conception of correlation: *A* is not the sole cause of *B*, but it contributes to the production of *B*; there may be other, many or few, causes at work, some of which we do not know and may never know…. It was really possible to go on increasing the number of contributory causes until they might involve all the factors of the universe…. Henceforward the philosophical view of the universe was to be that of a correlated system of variates, approaching but by no means reaching perfect correlation, i.e. absolute causality.”

Karl Pearson, 1914

“an *exhaustive* causal investigation of any concrete phenomenon in its full reality is not only practically impossible - it is simply nonsense…. The more “general”, i.e the more abstract the laws, the less they can contribute to the causal imputation of *individual* phenomena.”

Max Weber, 1904

Why are children in the same family so different from one another?

Why are children in the same family so different from one another?

Why are children in the same family so different from one another?

- Genetics apart, siblings no more similar than two randomly selected individuals from the population they are from
- They share many of the things that lifecourse epidemiologists have been interested in!

Plomin and Daniels, Behavioral and Brain Sciences, 1987

What accounts for differences in health and other outcomes?

Partition of variance in twin studies (and other family based studies including adoption studies) into genetic contribution, shared environmental contribution (i.e. shared between people brought up in the same home environment) and non-shared environmental contribution.

What accounts for differences in health and other outcomes?

Partition of variance in twin studies (and other family based studies including adoption studies) into genetic contribution, shared environmental contribution (i.e. shared between people brought up in the same home environment) and non-shared environmental contribution.

Such studies generally generate zero or near zero estimates of the influence of shared environment

Categories of “environmental” factors that cause children in same family to differ

- Measurement error (non-shared environment is from subtraction)

- “Non-systematic non-shared environment” – stochastic processes during development and beyond

Plomin and Daniels, Behavioral and Brain Sciences, 1987

Categories of “environmental” factors that cause children in same family to differ

- Systematic non-shared environment

- birth order, gender differences
- sibling interaction
- parental treatment
- extrafamilial networks: peer groups, teachers, television

Plomin and Daniels, Behavioral and Brain Sciences, 1987

The gloomy prospect

"What is happening environmentally to make children in the same family so different from one another? One gloomy prospect is that the salient environment might be unsystematic, idiosyncratic, or serendipitous events, such as accidents, illnesses, and other traumas, as biographies often attest"

Plomin and Daniels, Behavioral and Brain Sciences, 1987

The voyage of the *Beagle* has been by far the most important event in my life, and has determined my whole career; yet it depended on so small a circumstance as my uncle offering to drive me thirty miles to Shrewsbury, which few uncles would have done, and on such a trifle as the shape of my nose

The gloomy prospect

"It is possible that nonshared environmental influences could be unsystematic in the sense of stochastic events that, when compounded over time, make children in the same family different in unpredictable ways. Such capricious events, however, are likely to prove a dead end for research. More interesting heuristically are possible systematic sources of differences within families"

Plomin and Daniels, Behavioral and Brain Sciences, 1987

The gloomy prospect

"When we said 'such capricious events are likely to prove a dead end for research' we did not mean to minimize the possible importance of such events as sources of non-shared environment. Our point was that it makes sense to start the search by looking for systematic sources of variance"

Plomin and Daniels, Behavioral and Brain Sciences, 1987

searching for your
keys under the
street light

ychological Bulletin
00, Vol. 126, No. 1, 78–108

0033-2909/00/$5.00 DOI: 10.1037//0033-2909.126.1.

Nonshared Environment: A Theoretical, Methodological, and Quantitative Review

Eric Turkheimer and Mary Waldron
University of Virginia

When genetic similarity is controlled, siblings often appear no more alike than individuals selected at random from the population. Since R. Plomin and D. Daniels' seminal 1987 review, it has become widely accepted that the source of this dissimilarity is a variance component called nonshared environment. The authors review the conceptual foundations of nonshared environment, with emphasis on distinctions between components of environmental variance and causal properties of environmental events and between the effective and objective aspects of the environment. A statistical model of shared and nonshared environmental variables is developed. A quantitative review shows that measured nonshared environmental variables do not account for a substantial portion of the nonshared variability posited by biometric studies of behavior. Other explanations of the preponderance of nonshared environmental variability are suggested.

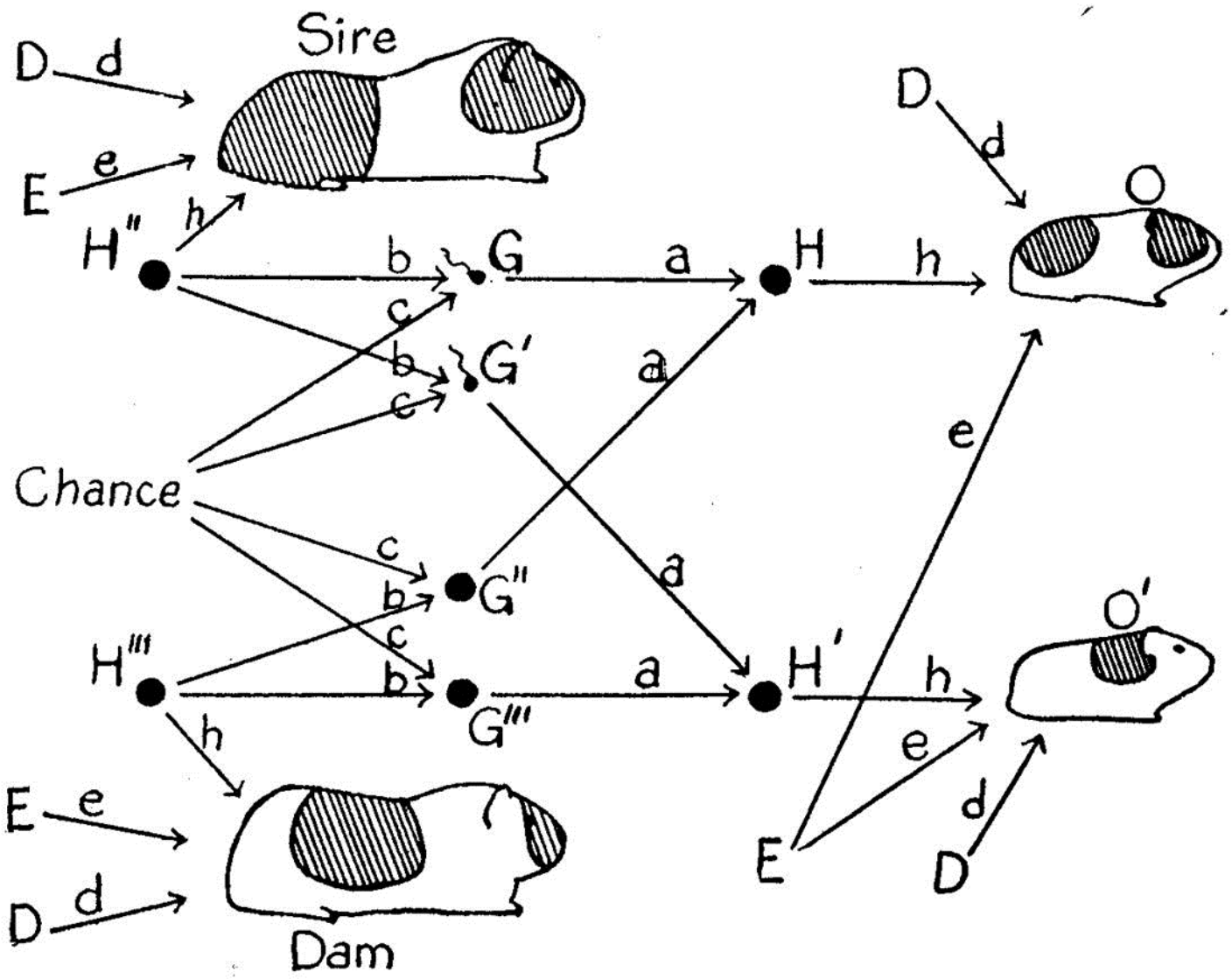
Why Are Children in the Same Family So Different?

In what may have been the most influential article ever written
the field of developmental behavior genetics, Plomin and

gate the origins of nonshared environmental variance. The follo
ing is typical:

Research on nonshared environment can be categorized into (a) an

Random phenotypic variance? Piebald pattern in guinea pigs



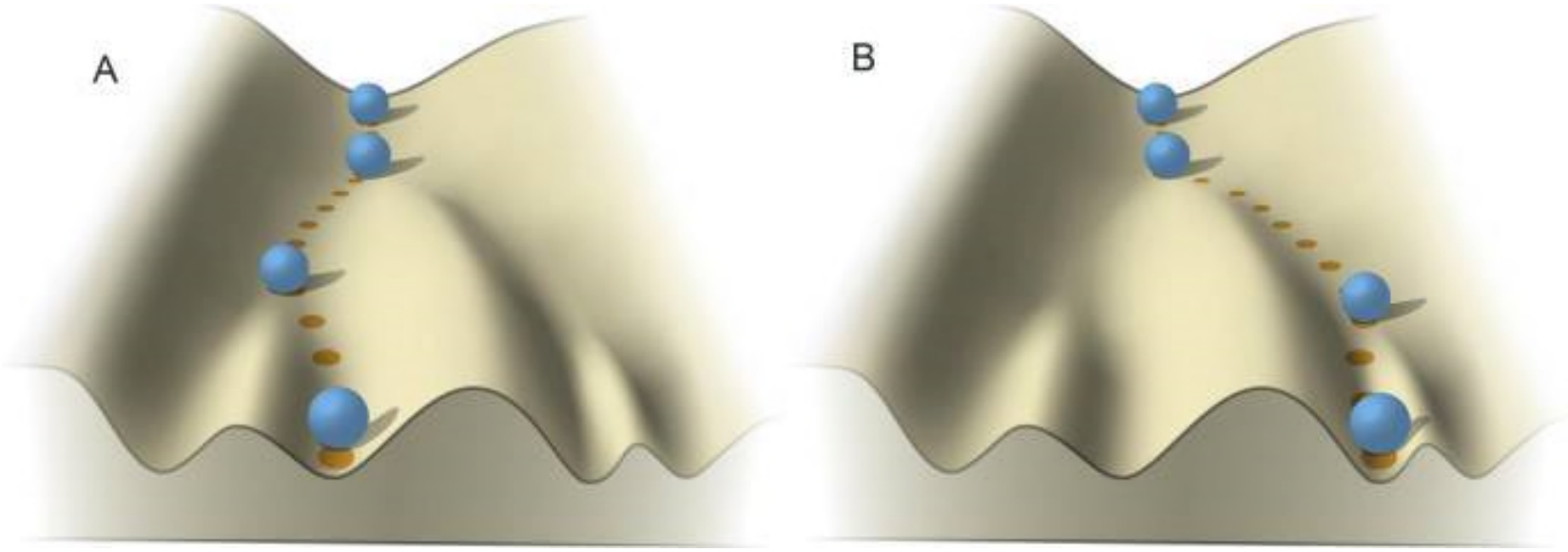
Sewall Wright 1921

58% of the variance intangible ..

“differences .. must be due to irregularities in development due to the intangible sort of causes to which the word chance is applied”

Sewall Wright 1921


If they ask you anything you don't know, just
just say it's due to epigenetics.



Waddington’s epigenetic landscape

Laboratory Animals (1990) **24**, 71–77

A third component causing random variability beside environment and genotype. A reason for the limited success of a 30 year long effort to standardize laboratory animals?

KLAUS GÄRTNER

Medizinische Hochschule Hannover, Abt. Versuchstierkunde Konstanty-Gutschow-Str. 8, D-3000 Hannover, Federal Republic of Germany

Summary

This paper is a review of experiments, performed in our laboratory during the past 20 years, designed to analyse the significance of different components of random variability in quantitative traits in laboratory rats and mice. Reduction of genetic variability by using inbred strains and than the consequence of heterogeneous environmental influences. In a group of inbred rats, the males with the highest chance of parenting the next generation were gathered in the central classes of the distribution of the body weight.

Keywords: Components of variance of body

ELSEVIER

Could Nonshared Environmental Variance Have Evolved to Assure Diversification Through Randomness?

Edward M. Miller
Professor of Economics and Finance, University of New Orleans

One of the more striking findings of modern human behavior genetics is the relatively small role for shared environmental experience and the large role for what is called non-

STOCHASTICITY IN GENE EXPRESSION: FROM THEORIES TO PHENOTYPES

Mads Kærn[*], *Timothy C. Elston*[‡], *William J. Blake*[§] *and James J. Collins*[§]

Abstract | Genetically identical cells exposed to the same environmental conditions can show significant variation in molecular content and marked differences in phenotypic characteristics. This variability is linked to stochasticity in gene expression, which is generally viewed as having detrimental effects on cellular function with potential implications for disease. However, stochasticity in gene expression can also be advantageous. It can provide the flexibility needed by cells to adapt to fluctuating environments or respond to sudden stresses, and a mechanism by which population heterogeneity can be established during cellular differentiation and development.

ISOGENIC
Genetically identical. Individual cells within an isogenic population are typically the progeny of a single ancestor.

[*]*Department of Cellular and Molecular Medicine and Ottawa Institute of Systems Biology, University of Ottawa, 451 Smyth Road, Ottawa, Ontario K1H8M5, Canada.*
[‡]*Department of Pharmacology, University of North Carolina, Chapel Hill, North Carolina 27599, USA.*
[§]*Department of Biomedical Engineering and Center for BioDynamics, Boston University, 44 Cummington Street, Boston, Massachusetts 02215, USA.*
Correspondence to M.K.

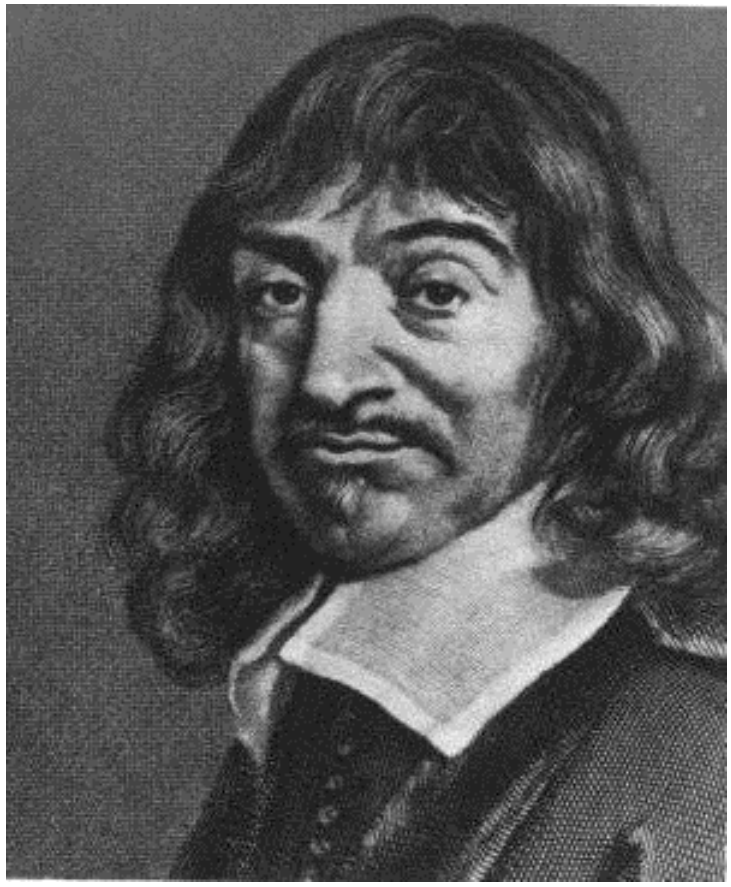
Stochasticity in gene expression arises from fluctuations in transcription and translation, despite constant environmental conditions. This phenomenon has attracted interest for many years because of its implications for cellular regulation and non-genetic individuality[1–7]. Recent advances in techniques for single-cell analysis have provided an impetus for novel experimental and theoretical investigations that, in turn, have led to fundamental new insights in this field. As a result, a coherent picture of stochasticity in prokaryotic and eukaryotic gene expression is beginning to emerge.

Here, we discuss the theoretical mechanisms that are thought to cause fluctuations in the expression levels of single genes and the experiments that have been used to validate these ideas. We also describe experimental studies of stochastic effects in gene-regulatory networks. Special emphasis is given to stochastic mechanisms that can lead to the emergence of phenotypically distinct subgroups within ISOGENIC cell populations. We conclude by discussing the possibility that stochasticity in gene expression is an evolvable trait, and the growing evidence for a role of stochasticity in development and disease.

The control of transcription is mediated by factors that bind at upstream promoter elements or influence the binding of other molecules to *cis*-regulatory elements within or near the promoter. Because such binding events are the result of random encounters between molecules, some of which are present in small numbers, the biochemical processes that regulate transcription initiation are inherently stochastic. In addition, the multi-step processes that lead to the synthesis and degradation of mRNA and protein molecules are subject to similar molecular-level noise. The model in FIG. 1 is simple in comparison with the true complexity of gene expression[8]. However, it has provided a good theoretical framework for understanding the effects of stochasticity on prokaryotic and eukaryotic gene expression[9–48], and underlies the theoretical investigations used to design and interpret many of the experiments discussed in this review.

The origins and consequences of molecular-level noise on the expression of a single gene can be demonstrated by comparing the intracellular protein concentrations obtained from stochastic and deterministic simulations of the model in FIG. 1. Deterministic simu-

Oh goodie! Philosophy!



Oh goodie! Philosophy!

So what about epidemiology?

© International Epidemiological Association 1985 Printed in Great Britain

International Journal of Epidemiology 2001;30:427–432

REITERATION

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.

The Determinants of Individual Cases

In teaching epidemiology to medical students, I have often encouraged them to consider a question which I first heard enunciated by Roy Acheson: 'Why did *this* patient get *this* disease at *this* time?'. It is an excellent starting-point, because students and doctors feel a natural concern for the problems of the individual. Indeed, the central ethos of medicine is seen as an acceptance of responsibility for sick individuals.

It is an integral part of good doctoring to ask not only, 'What is the diagnosis, and what is the treatment?' but also, 'Why did this happen, and could it have been prevented?'. Such thinking

To confine attention in this way to within-population comparisons has caused much confusion (particularly in the clinical world) in the definition of normality. Laboratory 'ranges of normal' are based on what is common within the local population. Individuals with 'normal blood pressure' are those who do not stand out from their local contemporaries; and so on. What is common is all right, we presume.

Applied to aetiology, the individual-centred approach leads to the use of relative risk as the basic representation of aetiological force: that is, 'the risk in exposed individuals relative to risk in non-exposed individuals'. Indeed, the concept of relative risk

In teaching epidemiology to medical students, I have often encouraged them to consider a question which I first heard enunciated by Roy Acheson: 'Why did *this* patient get *this* disease at *this* time?'. It is an excellent starting-point, because students and doctors feel a natural concern for the problems of the individual. Indeed, the central ethos of medicine is seen as an acceptance of responsibility for sick individuals.

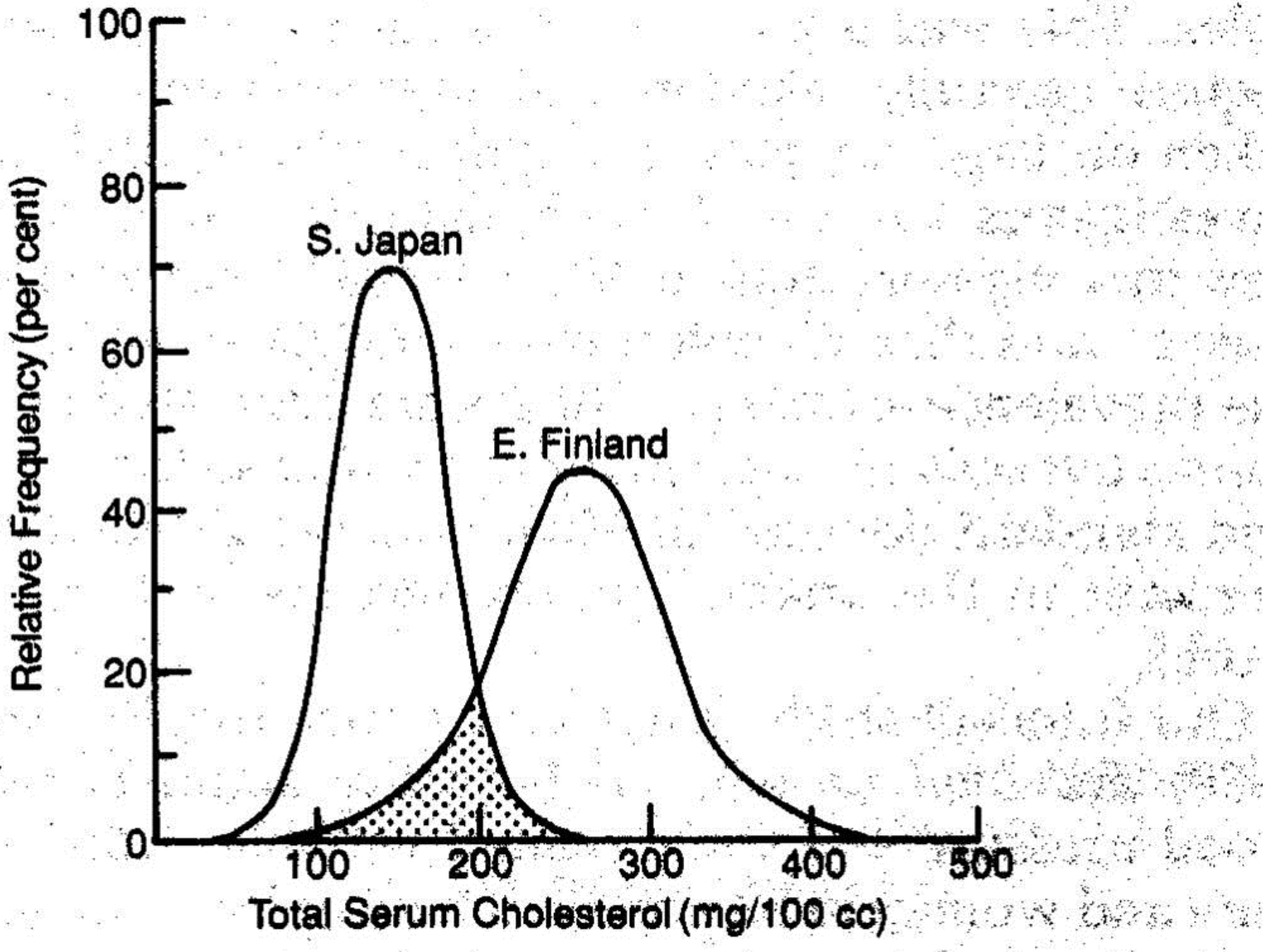
Rose G. Sick Individuals and Sick Populations, 1985.

‘It has long been a commonplace observation in the discipline of social anthropology that cultural systems of explanation or accountability [for the occurrence of a misfortune] need to address two distinct issues. In the first place the general kind of misfortune: how and why does it happen? In the second place, the site and time of particular misfortune require explanation: how and why did it happen to this person at this time? ... In our own society, where the development of science has shaped so many other cultural institutions, it is sometimes overlooked that this pair of explanations is still required. This is so because it is a central pillar of the Western scientific tradition that the two explanatory systems are unified.’

Davison C, Davey Smith G, Frankel S. Lay epidemiology and the prevention paradox: the implications of coronary candidacy for health education. Sociology of Health and Illness 1991; 13: 1-19

Sick individuals and sick populations

- **causes of cases vs causes of incidence**


100
80
60
40
20
0
Relative Frequency (per cent)
S. Japan
E. Finland
100
200
300
400
500
Total Serum Cholesterol (mg/100 cc)

Risk factors for unemployment

- Low level of education
- > 50 years old
- Short stature
- Minority ethnic group
- Unkempt appearance
- Lack of deference at interview

Risk factors for unemployment

- The same factors would explain a high percentage of the intra-individual variance in risk of being unemployed at a time when the prevailing unemployment rate is 1% or 14%
- Clearly individual level studies give the "right answer to the wrong question" (Schwartz S, Carpenter KM. "The right answer to the wrong question". Am J Public Health 1999;89:1175-80)

Davey Smith G et al. "How policy informs the evidence". BMJ 2001;322:184-5

Unemployment roared to two million, chased towards three million, and Norman Tebbitt famously said the unemployed should get on their bikes and look for work. Unemployment was the result of the unemployed not trying hard enough. In which case what a peculiar economic century we had.

Mark Steel “Reasons to be cheerful”, 2001

The population must have gone through a period of laziness at the end of the 19th century, then felt a sudden spurt of energy and got jobs. Until the 1930s, when they got lazy again. Then they perked up around 1938, which was handy as it was just in time for the war. This was fine until 1980, when everyone changed their mind and decided to stay in bed all day, which makes sense as this coincides with the invention of the duvet.

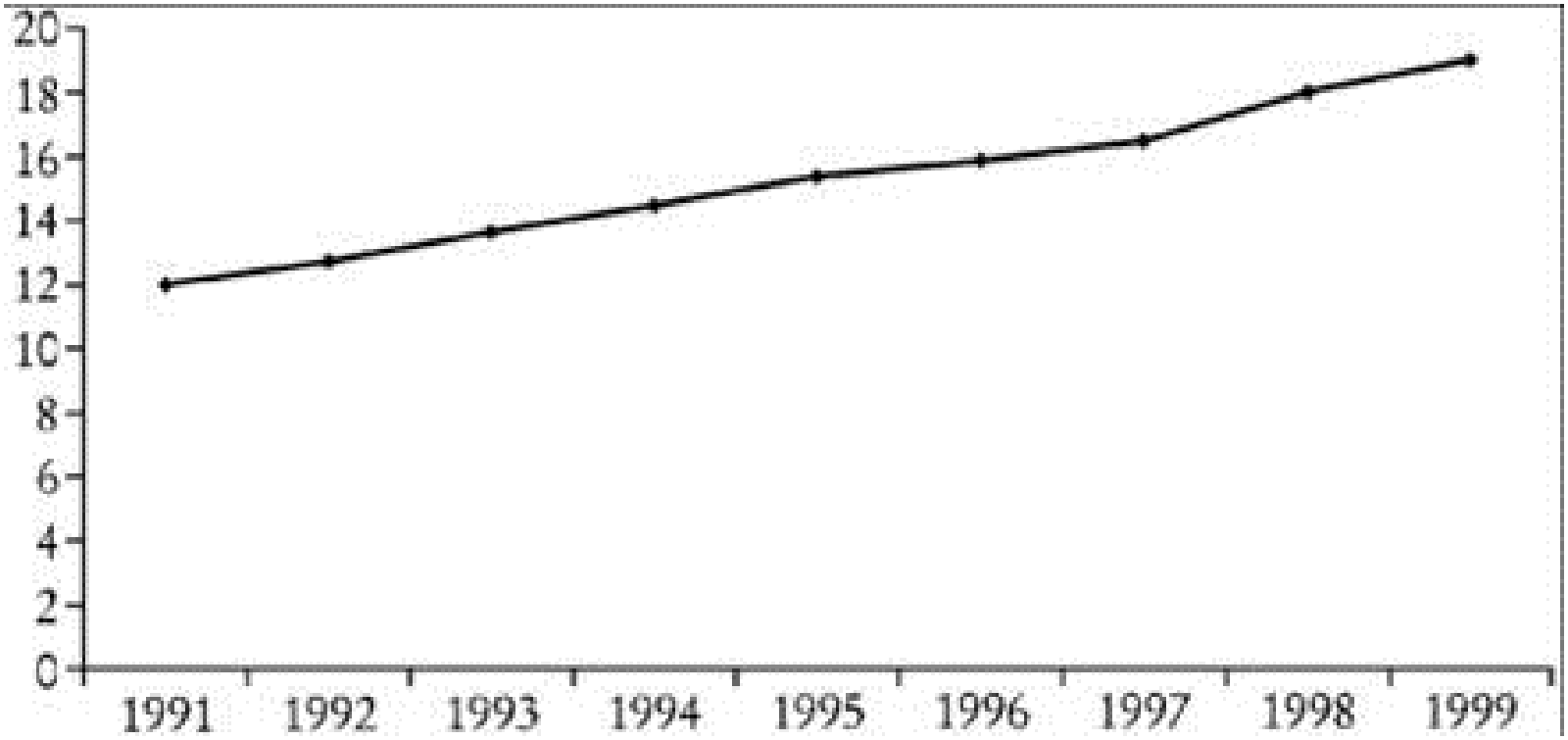
Mark Steel “Reasons to be cheerful”, 2001

Sick individuals and sick populations

- causes of cases vs causes of incidence
- **cannot identify effect of ubiquitous exposure**

What causes obesity?

- Twin studies show high heritability
- Population trends show that environmental factors are of overwhelming importance



Prevalence of obesity in US adults from 1991-1999

What causes obesity?

- Twin studies are perfectly matched on birth cohort – and thus on factors relating to secular trends
- Determinants of individual risk may be of very minor population health importance
- However determinants of individual risk may point to potentially modifiable risk processes that are of population health importance (through Mendelian randomization approaches wrt genetic variants)

"…so Dr. Frayling, carrying two copies of the gene gives you 3kg more body fat. Wow – that sounds complicated! Can you explain that in layman's terms?"
BBC Radio Cumbria

"Sir, Anyone over 70 years old will tell you that there were very few fat people during the war. Are the Oxford scientists telling us that the 'fat gene' did not exist 50 or 60 years ago?"
Letter to The Times

"Boffins revealed there is a gene which leads to lardyness — giving the 'big boned' the excuse they had been waiting for."
www.thesun.co.uk

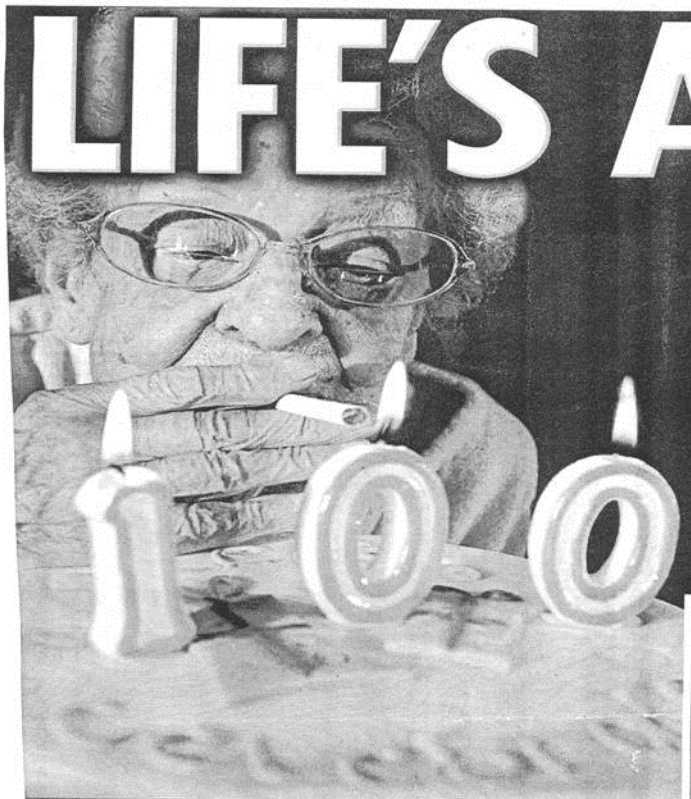
"Scientists say genetic engineering could mean obesity will become a thing of the past"
BBC Radio Plymouth

"…you don't see any fat jockeys or soldiers. How do the scientists explain that?"
Radio 5 Live

Sick individuals and sick populations

- causes of cases vs causes of incidence
- cannot identify effect of ubiquitous exposure
- **group vs individual level exposure and outcome data**

LIFE'S A DRAG



Winnie, 100 smokes for 93 YEARS and she ain't quitting now

Wartime memories . . Winnie had her first cigarette in 1914

By GARETH DORRIAN

DEFIANT smoker Winnie Langley celebrates reaching 100 yesterday — by lighting her 170,000th cigarette from a candle on her birthday cake.

She started having a puff an incredible 93 years ago aged seven — just after the First World War broke out in June 1914. She has got through five a day ever since.

Winnie has no plans to quit — even after the nationwide ban forcing smokers outside — and reckons tobacco has never made her ill.

She gets her 100th birthday telegram from the Queen after outliving a husband, Robert, and son, Donald, who died two years ago aged 72.

Nerves

The former launderette worker said she started smoking weeks after the assassination of Archduke Franz Ferdinand in Sarajevo sparked the First World War.

Winnie, of Croydon, Surrey, said smoking helped "steady the nerves" during two World Wars.

And the reason why Winnie has never suffered because of the habit? She said: "I never inhaled."

STINK'S ON THE HOUSE

A PUB is squirting round cigarette-scented spray — after drinkers moaned the smoking ban had ruined the atmosphere.

Landlady Sarah Thornton, 34, *below*, found the special effects product called Fag Ash on the internet.

She said at the Craven Arms in Birmingham: "Punters love it. Some sit there with unlit ciggies in their mouths.

"Without smoke it stinks of sweaty bodies."

Heaven scent . . Sarah with spray

Smoking and lung cancer

- lung cancer in cohort studies, pseudo-variance explained 5-10% at best
- lung cancer trends in US, 93% of variance (Whittmore 1989)
- geographical differences within US virtually all variance (Weinberg 1982)
- between-country differences ditto

Estimated R^2 measures in percent for death from coronary artery disease among British doctors calculated under Poisson and logistic regression

Model		Poisson Regression	Logistic Regression
(a)	Smoke	3.1	0.3
(b)	Age	90.9	9.0
(c)	Age + smoke	92.6	9.2
(d)	Age + age squared + smoke	98.7	9.7

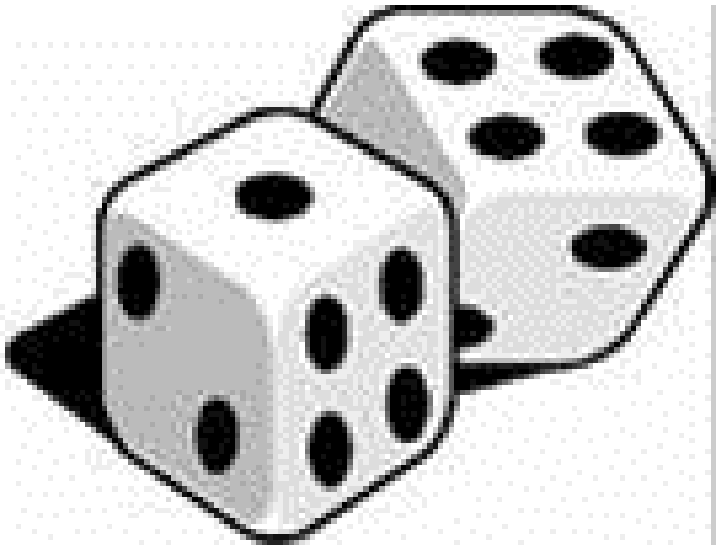
Source: Mittlböck M, Heinzl H. Journal of Clinical Epidemiology 2001;54:99-103.

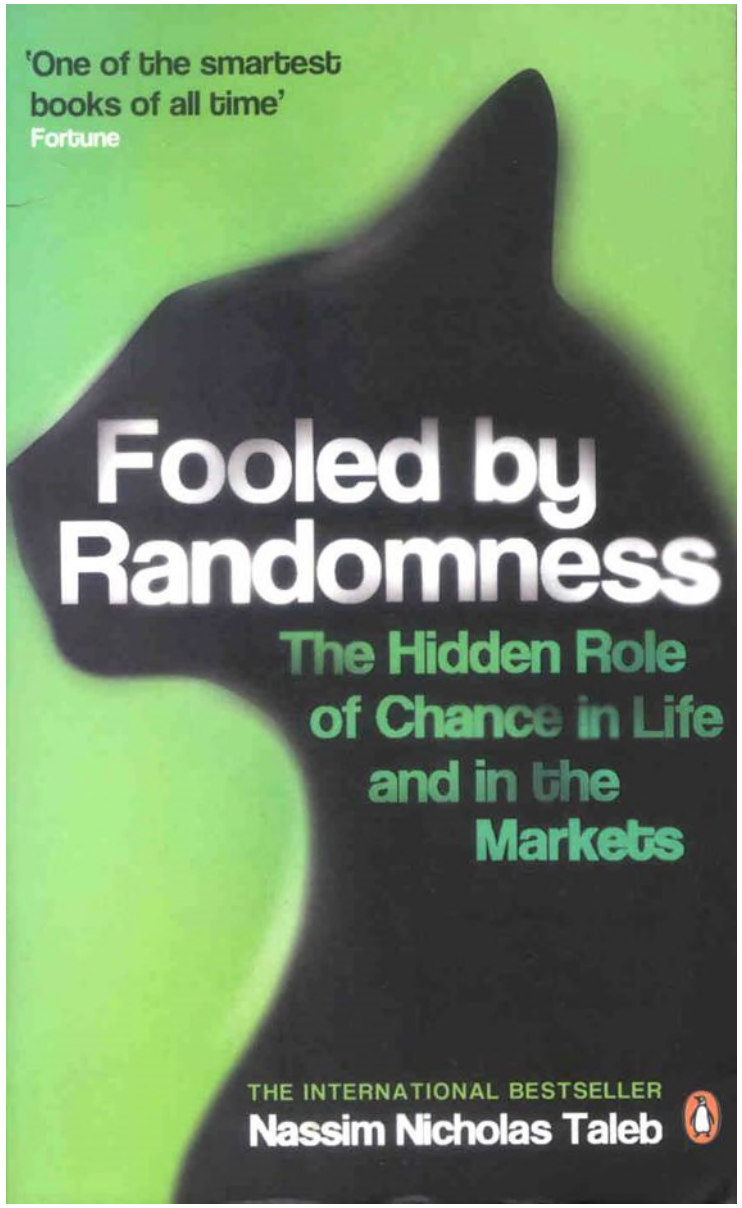
Sick individuals and sick populations

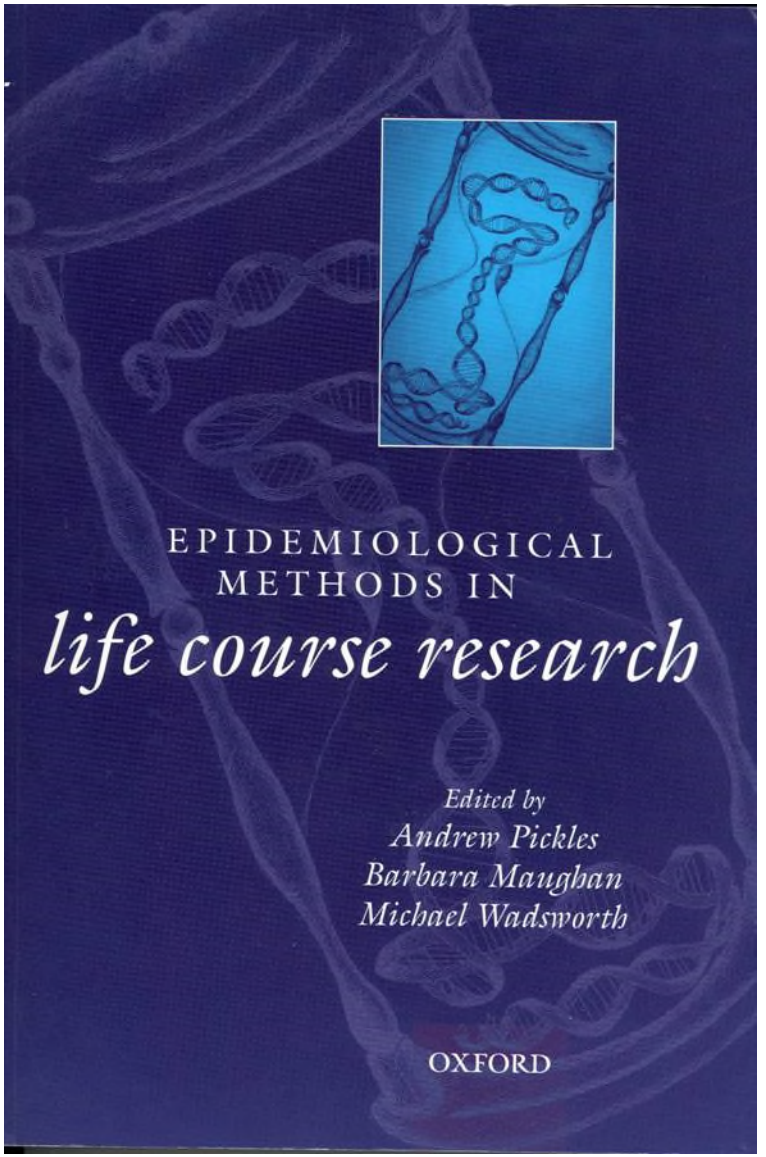
- causes of cases vs causes of incidence
- cannot identify effect of ubiquitous exposure
- group vs individual level exposure and outcome data
- **Inference is to group (at different levels) not to individual**

Sick individuals and sick populations

- causes of cases vs causes of incidence
- cannot identify effect of ubiquitous exposure
- group vs individual level exposure and outcome data
- Inference is to group (at different levels) not to individual
- **Attempting to improve individual level explanation may be unrewarding and diversionary**




'One of the smartest books of all time'
Fortune
Fooled by Randomness
The Hidden Role of Chance in Life and in the Markets
THE INTERNATIONAL BESTSELLER
Nassim Nicholas Taleb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Edited by
Andrew Pickles
Barbara Maughan
Michael Wadsworth
OXFORD