





Intervention oriented observational studies

Terry Dwyer



Increasing focus on obtaining high quality evidence to underpin public health interventions.

There is some controversy about whether observational studies (in humans) can provide this



Particularly in the non-communicable disease (NCD) area

The older term ‘chronic disease’ may be preferable

or even better

‘diseases of long latency’

Cochrane collaboration gradings

Concato NEJM 2000

I Evidence obtained from at least one properly randomized, controlled trial.

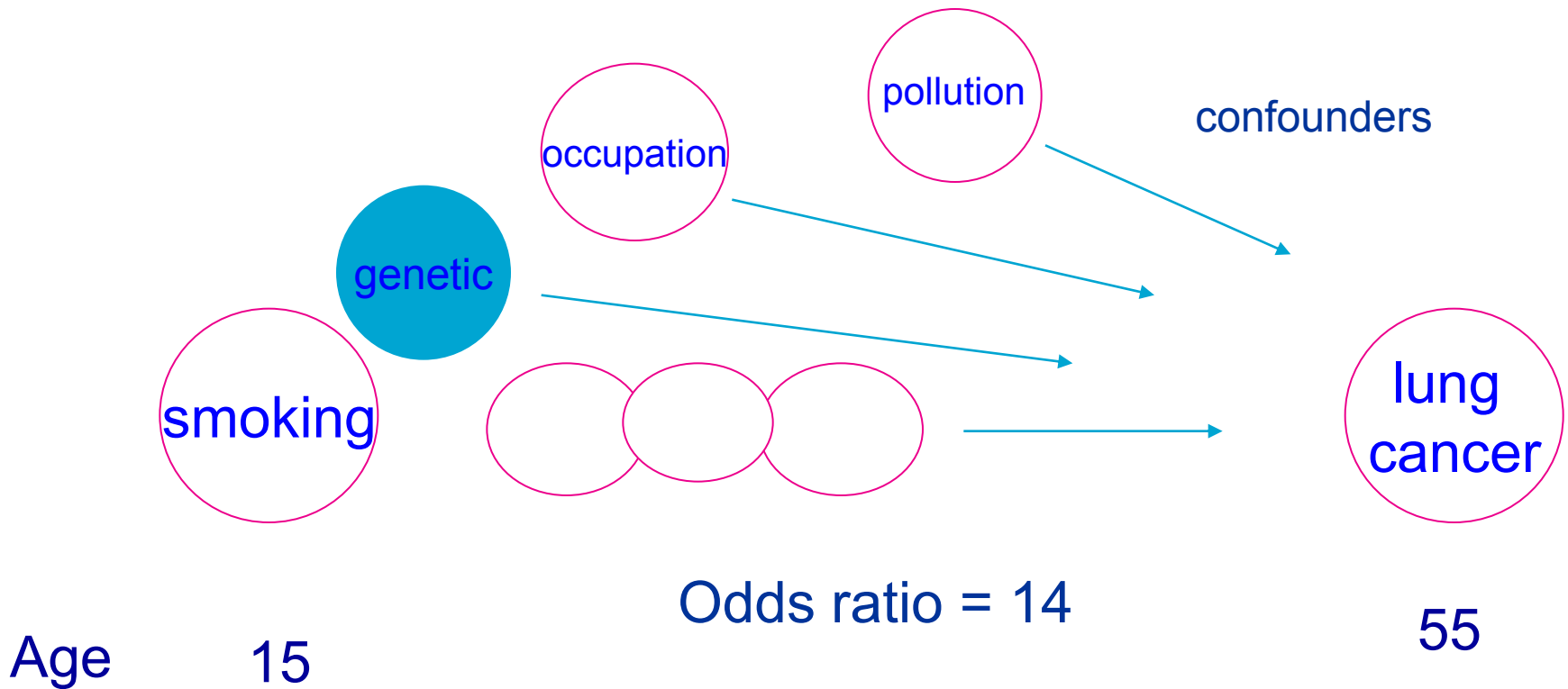
II-1 Evidence obtained from well-designed controlled trials without randomization.

II-2 Evidence obtained from well-designed cohort or case–control analytic studies.

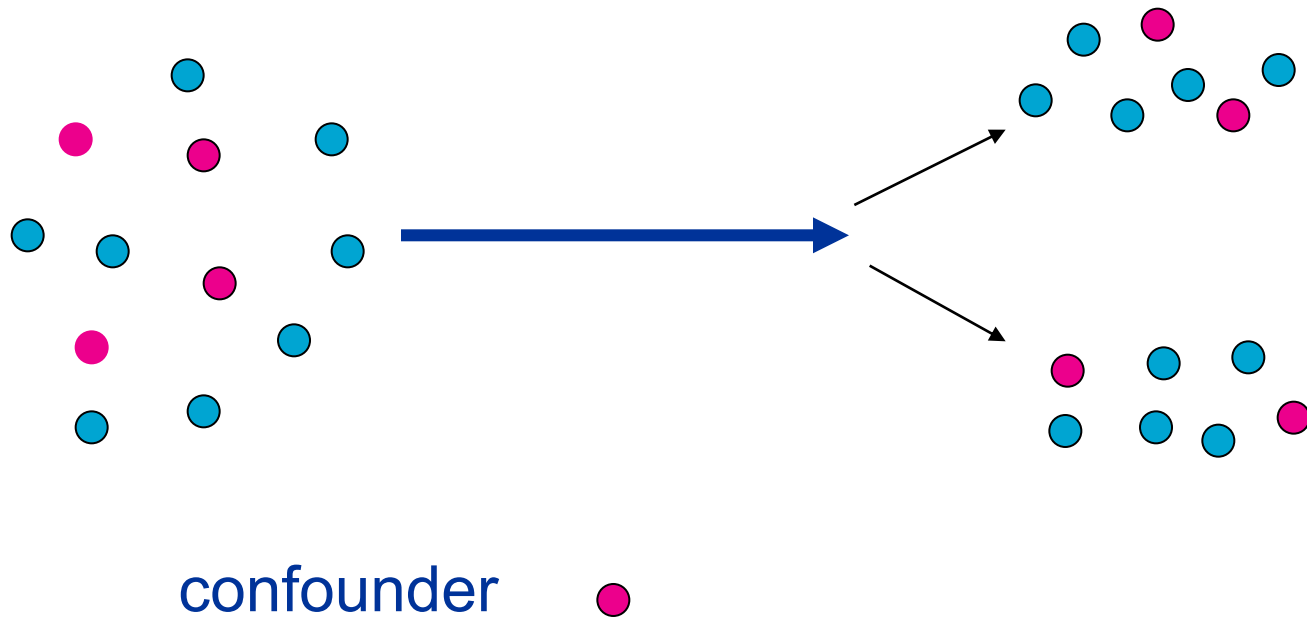
II-3 Evidence obtained from multiple time series with or without the intervention.

III Opinions of respected authorities,

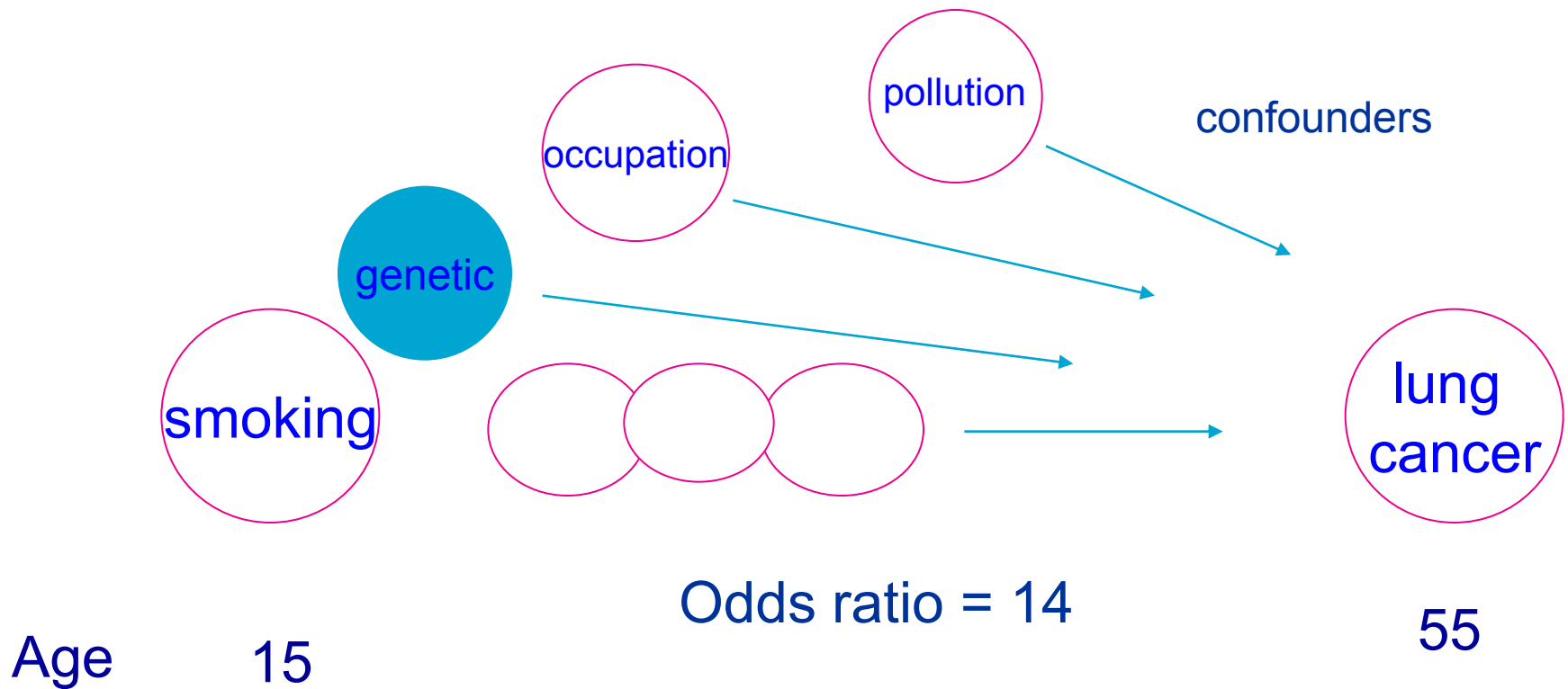
This is perhaps not surprising!



Randomised trials

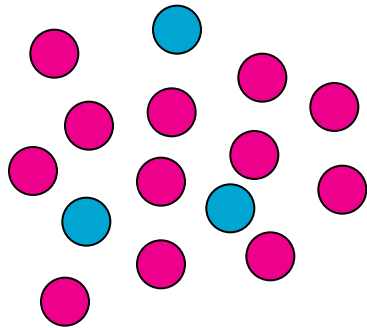


Why not use randomised trials?



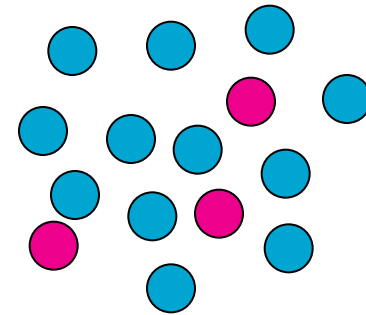
Case-control studies

Compare a group of patients or 'cases' with 'controls' free of disease



cases

exposed



controls

Prospective Cohort studies



Healthy subjects
some exposed some not

cases ●



Is it worthwhile using these options?



I will attempt to demonstrate to you that it is not only worthwhile, but it is evidence from this type of study

that has been central to the most important public health interventions in the non-communicable disease field in the last half century

though, the evidence was not readily embraced when it first appeared

BRITISH MEDICAL JOURNAL

LONDON SATURDAY SEPTEMBER 30 1950

SMOKING AND CARCINOMA OF THE LUNG

PRELIMINARY REPORT

BY

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AND

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In England and Wales the phenomenal increase in the number of deaths attributed to cancer of the lung provides one of the most striking changes in the pattern of mortality recorded by the Registrar-General. For example, in the quarter of a century between 1922 and 1947 the annual number of deaths recorded increased from 612 to 9,287, or roughly fifteenfold. This remarkable increase is, of course, out of all proportion to the increase of population—both in total and, particularly, in its older age groups. Stocks (1947), using standardized death rates to allow for these population changes, shows the following trend: rate per 100,000 in 1901–20, males 1.1, females 0.7; rate per 100,000 in 1936–9, males 10.6, females 2.5. The rise seems to have been particularly rapid since the end of the first world war; between 1921–30 and 1940–4 the death rate of men at ages 45 and over increased sixfold and of women of the same ages approximately threefold. This increase is still continuing. It has occurred, too, in Switzerland, Denmark, the U.S.A., Canada, and Australia, and has been reported from Turkey and Japan.

Many writers have studied these changes, considering whether they denote a real increase in the incidence of the disease or are due merely to improved standards of diagnosis. Some believe that the latter factor can be regarded as wholly, or at least mainly, responsible—for example, Willis (1948), Clemmesen and Busk (1947), and Steiner (1944). On the other hand, Kennaway and Kennaway (1947) and Stocks (1947) have given good reasons for believing that the rise is at least partly real. The latter, for instance, has pointed out that "the increase of certified respiratory cancer mortality during the past 20 years has been as rapid in country districts as in the cities with the best diagnostic facilities, a fact which does not support the view that such increase merely reflects improved diagnosis of cases previously certified as bronchitis or other respira-

whole explanation, although no one would deny that it may well have been contributory. As a corollary, it is right and proper to seek for other causes.

Possible Causes of the Increase

Two main causes have from time to time been put forward: (1) a general atmospheric pollution from the exhaust fumes of cars, from the surface dust of tarred roads, and from gas-works, industrial plants, and coal fires; and (2) the smoking of tobacco. Some characteristics of the former have certainly become more prevalent in the last 50 years, and there is also no doubt that the smoking of cigarettes has greatly increased. Such associated changes in time can, however, be no more than suggestive, and until recently there has been singularly little more direct evidence. That evidence, based upon clinical experience and records, relates mainly to the use of tobacco. For instance, in Germany, Müller (1939) found that only 3 out of 86 male patients with cancer of the lung were non-smokers, while 56 were heavy smokers, and, in contrast, among 86 "healthy men of the same age groups" there were 14 non-smokers and only 31 heavy smokers. Similarly, in America, Schrek and his co-workers (1950) reported that 14.6% of 82 male patients with cancer of the lung were non-smokers, against 23.9% of 522 male patients admitted with cancer of sites other than the upper respiratory and digestive tracts. In this country, Thelwall Jones (1949—personal communication) found 8 non-smokers in 82 patients with proved carcinoma of the lung, compared with 11 in a corresponding group of patients with diseases other than cancer; this difference is slight, but it is more striking that there were 28 heavy smokers in the cancer group, against 14 in the comparative group.

Clearly none of these small-scale inquiries can be accepted as conclusive, but they all point in the same direc-

Evidence from case-control studies led to a reduction in the commonest cause of male cancer in the 20th Century

Doll and Hill 1950

lung cancer

controls

smokers	647 (99.7%)	622 (95.8%)
non-smokers	2	27


OR = 14 p<.001

Doll noted:

‘It had been recognised long before 1950 that smoking could cause disease but it was not until 1950 that a large amount of data was obtained in a sufficiently representative, responsible way to lead more than a handful of people to believe that smoking might actually be responsible for causing a material amount of disease’

‘The evidence is purely
circumstantial, it is obtained
from statistical evaluation of
clinical material’

Lancet editorial 1951



‘ the Medical Research Council
has advised me that the
relationship between smoking
and lung cancer is not
necessarily causal.’

British Minister for Health 1953

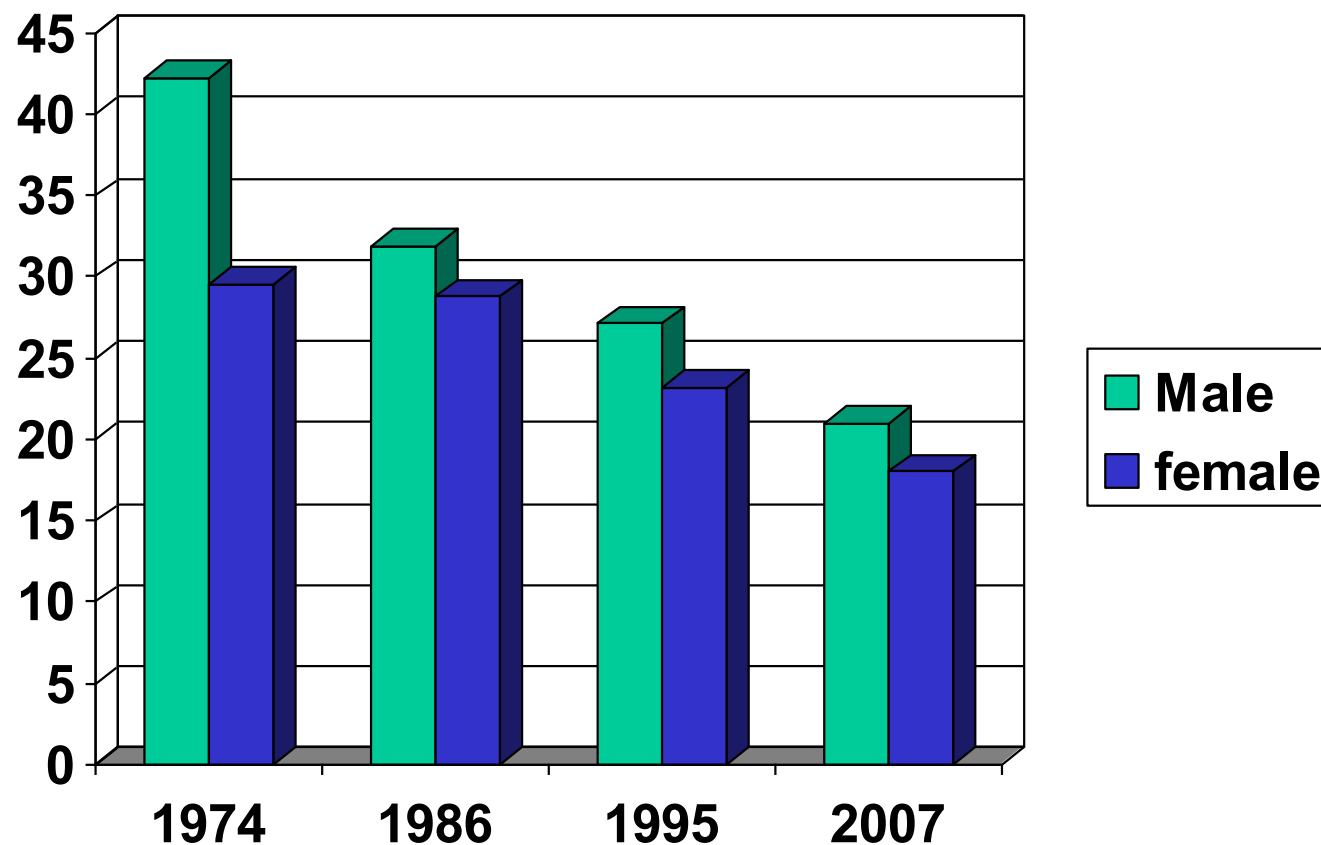
'We accept an interest in people's health as a basic responsibility paramount to every other consideration in our business.....

but do not believe that tobacco products are injurious to health'

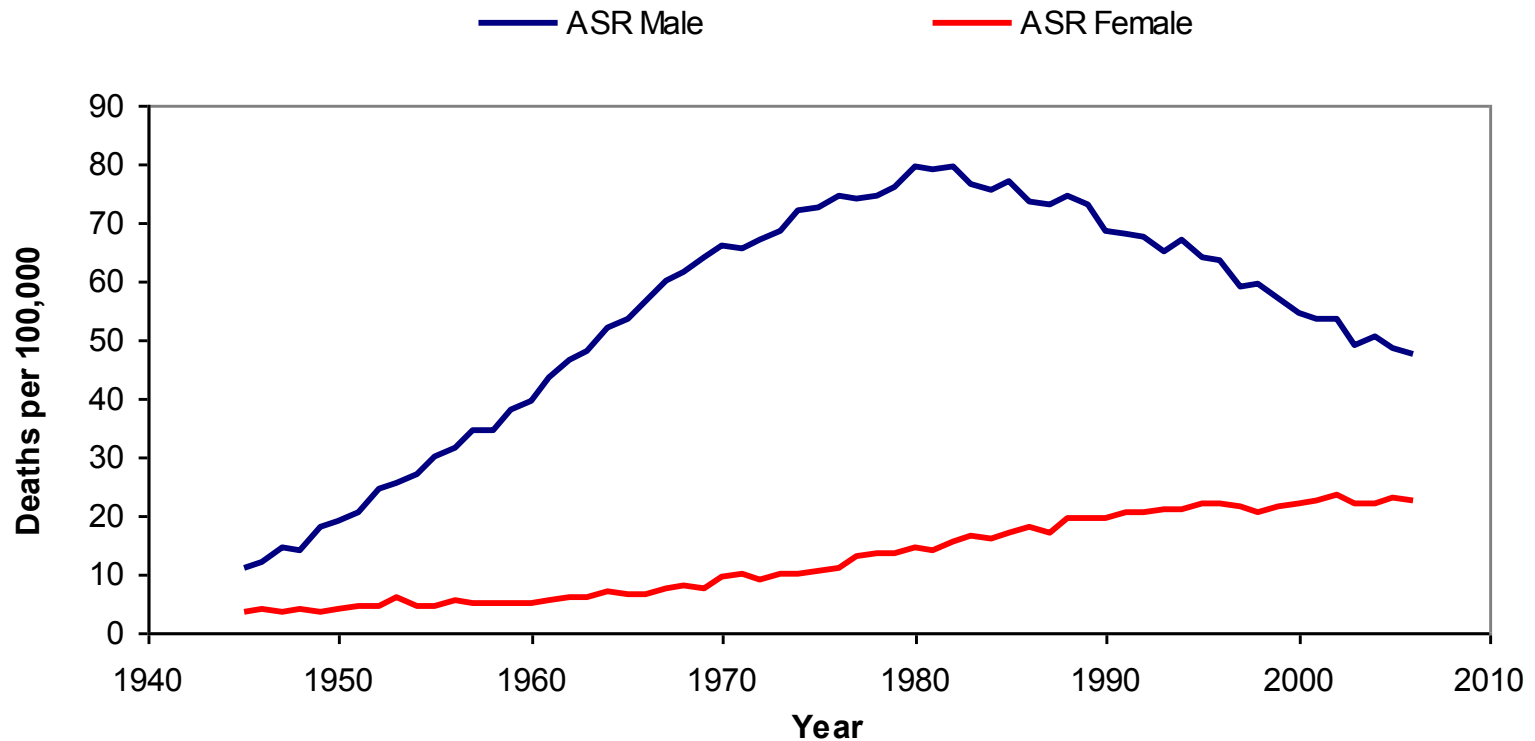
American Tobacco Industry statement 1954

- Experiments in dogs supportive
- No randomised trial data in humans

Percentage of Australians smoking



Trends in death rates for Lung cancer (ICD10 C33, C34), Australia, 1945–2006



Epidemiological Approaches to Heart Disease: The Framingham Study*

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THE use of the word "epidemiology" and the concept of what epidemiology as a discipline may encompass has varied widely since the days of Peter Panum and John Snow. There are today many differing definitions of the word, but nearly all workers in the field will agree on one element of the definition: The word "epidemiology" by etymology refers to the study of something "which is thrust upon the people." There are still some who insist that epidemiology deals only with epidemics of infectious diseases, but current usage suggests that most workers would now agree that epidemiology deals with "the fundamental questions as to where a given disease is found, when it thrives, where and when it is not found . . . in other words it is the ecology of disease"¹ without regard to whether the disease is believed to be infectious.

Frost gave an analytical definition when he wrote that epidemiology "includes the orderly arrangement of facts into chains of inference which extend more or less beyond the bounds of direct observation."² His definition might be called the essence of the "epidemiological method" except for the fact that it has been used by the physician since the time of Hippocrates to arrive at his clinical

diagnosis. Thus, today, the epidemiological approach is used to explore certain relationships in health and disease which, with present technological methods, cannot be observed directly. In addition to the many studies of the infectious diseases, there have been epidemiological studies in the fields of nutritional imbalance, metabolic disorders, occupational hazards, accidents, cancer, and rheumatic fever—to mention only a few.

In the field of cardiovascular diseases, studies using the epidemiological method have led to findings of considerable practical importance for prevention and treatment. Mention may be made, for example, of the studies of nutritional diseases, such as beriberi, pellagra, and scurvy, and of the infectious diseases such as syphilis, hemolytic streptococcal infections, and streptococcus viridans bacteremia. Rubella and other virus diseases have been implicated as etiological factors in congenital malformations of the heart, but further epidemiological study is still required to establish these relationships beyond the possibility of reasonable doubt.³ Even in rheumatic fever, where fundamental etiology is still obscure, epidemiological studies have helped to demonstrate the relationship of streptococcal infection to subsequent rheumatic activity, and this has led to

Evidence from a cohort study underpinned the successful interventions to reduce mortality for the commonest cause of death in the developed world

Table 10—Serum Total Cholesterol in Relation to Incidence of ASHD in Four-Year Follow-Up, Males 45–62

	Population at Risk	New Disease	Rate/1,000
All persons	898	52	58
Cholesterol measured at Examinations I or II:			
260 mg per cent and over	172	21	122
225–259 mg per cent	265	12	45
Less than 225 mg per cent	445	18	40
Unknown	16	1	*
Cholesterol measured at Examination I: †			
260 mg per cent and over	131	16	122
225–259 mg per cent	188	8	42
Less than 225 mg per cent	334	13	39
Unknown	228	14	61

* Rate not computed for base less than 50.

† Included above.

laboratories participating in the Cooperative Lipoprotein Study.

Cholesterol determinations were not made during the early stages of the program, and as a consequence 228 of the 898 men in the age group under study did not have a value recorded at the time of the first examination. All but 16 of the 228 did, however, have a cholesterol value recorded at their second examination, and that value has been used for classifying those men. As a result, seven of 51 new events occurred in men prior to the recording of a cholesterol value; one man died before the second anniversary of his initial examination and is not represented in the series. In Table 10 the data are presented in two ways: first, based on the first cholesterol value recorded for each man, whether it was measured at Examination I or Examination II; and the second, showing results using only data

in persons with elevated cholesterol levels ($X^2 = 16.2$, $n = 2$, $p < 0.001$), but no apparent gradient below a level of 260 mg per cent. The division at 260 mg per cent is an arbitrary one and well above the mean level of 225.5 mg per cent found for the entire group of Framingham men in this age range.

The Interaction of High Blood Pressure, Obesity, and Hypercholesteremia with Respect to Risk of ASHD

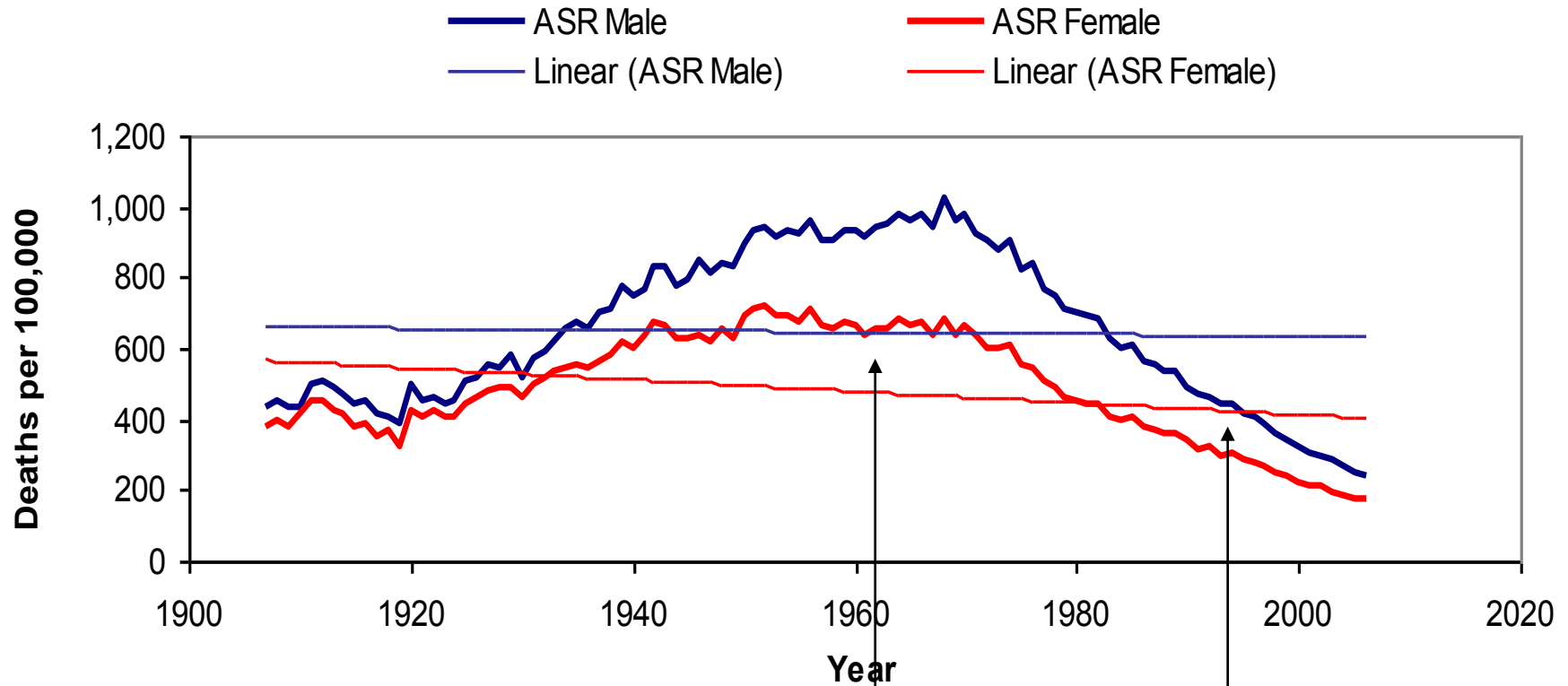
The data in the preceding section indicated that hypertension, obesity, and hypercholesteremia were each associated with increased risk of ASHD in a group of men 45–62. In this section it will be shown that these attributes appear to make independent but varying contributions to risk, and the joint elevation of two or three is associated with a greatly increased risk.

Relative risk
for high
serum
cholesterol
and
coronary
heart
disease

RR = 3.05
p < .01

- Animal evidence supportive
- No convincing randomised trial evidence for cholesterol until late 1970's
- Controversy about causal connection

Trends in death rates for All circulatory diseases (ICD10 I00-I99), Australia, 1907–2006



↑ P:S
ratio

Statins



Murdoch Childrens
Research Institute

Healthier Kids. Healthier Future.

**But, have all the low hanging fruit
been picked?**



Annals of Epidemiology 2009

TRIUMPHS IN EPIDEMIOLOGY

in the 1980's and 1990's

Triumph	Study design	Authors
• Folic acid deficiency and neural tube defects	Case-control/Cohort	Godfrey Oakley
• Hepatitis B and Liver cancer	Cohort	R Palmer Beasley
• Lead and neurocognition	Cohort	Herbert Needleman
• HPV and Cervical cancer	Case-control	Laura Koutsky
• Infant sleeping position & SIDS	Cohort/Case-control	Terry Dwyer & Anne-Louise Ponsonby



A cohort study
starting at birth

Prospective cohort study of prone sleeping position and sudden infant death syndrome

TERENCE DWYER ANNE-LOUISE B. PONSONBY
NEVILLE M. NEWMAN LAURA E. GIBBONS

Studies of the link between prone sleeping position and sudden infant death syndrome have been criticised on grounds of recall bias and for not taking into account possible confounding effects. To avoid recall bias and to allow measurement of important biological factors a prospective cohort study of the cause of sudden infant death syndrome (SIDS) is being conducted. The infants included are those at high risk of the syndrome as assessed by a perinatal score. Of the 3110 members of the cohort born between January, 1988, and end of March, 1990, 23 infants later died of SIDS. Sleep position information was available for 15 of these. Matched analysis to control for the confounding effects of infant birthweight and maternal age indicated that prone sleeping position was associated with an increased risk of SIDS (OR 4.47 95% CI [1.30-15.43]). The findings are strengthened by the results of a concurrent retrospective case-control study of 42 SIDS cases in which the prone position was also associated with an increased risk of SIDS (unadjusted OR 3.45 [1.59-7.49]).

Lancet 1991; 337: 1244-47.

Introduction

Despite extensive research, sudden infant death syndrome (SIDS) remains a major determinant of infant mortality in developed countries. The apparent lack of progress in this disorder is due to the failure to find, in human studies, consistent strong associations that might be putative risk factors and that might readily be altered by public health measures. However, there is increasing evidence that the prone sleeping position is related to the risk of sudden infant death syndrome. The prone sleeping position has been found to be commoner among cases than controls in retrospective work, although this relation has not always been statistically significant, with odds ratios for prone sleeping position and SIDS varying from 1.7 to 12.5.¹⁻¹¹ In communities where infants rarely sleep prone, sudden infant death syndrome is uncommon.^{2,12}

Clearly such findings have important implications for prevention of SIDS. Already, in some locations these findings have stimulated a change in the way babies are positioned, with—in South Australia and the Netherlands, for example—a concomitant decline in SIDS incidence.^{13,14} Nevertheless, these observations and the inference that prone position might be an important causal factor in SIDS have not been received uncritically. Two important issues have been raised. The first issue is that of recall bias in the interview of bereaved parents;¹⁵⁻¹⁷ prospectively collected information is required to establish the validity of the data on risk factors such as prone position in sudden infant death.¹⁵ The second concern is that potentially important confounders, such as low birthweight and maternal education,¹⁸ have not been taken into account in much of the

Here we present data from a prospective study on the relation between SIDS and prone sleeping position. Several likely confounders are controlled for. In addition, the strength of association between SIDS and prone or non-prone position on the basis of prospectively collected data was compared with that found by retrospective data collected on the same infants.

Methods

Tasmania, the island state of Australia, has approximately 7000 livebirths per annum, and its rate of SIDS—3.5 per 1000 livebirths—is considerably higher than that in other Australian states.¹⁹ A prospective cohort study was started in January, 1988, to investigate the cause of SIDS in Tasmania. The six obstetric hospitals taking part cover approximately 93% of livebirths in the state. Infants born within these hospitals are assessed according to a local scoring system²⁰ to predict infants at high risk of SIDS. The composite score is based on maternal age, birthweight, season of birth, sex, duration of the second stage of labour, and infant feeding. Infants with a score over a cut-off point²⁰ are eligible for the study. The cut-off point identifies a group which represents approximately one fifth of livebirths in the state. Multiple births are also included in the study. Infants with severe neonatal disease or a major congenital anomaly and infants for adoption are excluded from the study.

Prospective cohort study

From January, 1988, until March, 1990, 3110 infants (20% of all livebirths) were eligible for the survey. 2977 (96%) of these eligible infants participated in the hospital interview and 2607 (84%) participated in both the hospital and home interviews.

Data are obtained by research assistants on three occasions. At the hospital interview conducted on day 4 of life, sociodemographic, obstetric, and perinatal data (including information on maternal nutrition and alcohol and smoking practice during pregnancy), birthweight, height, head circumference, and triceps and subscapular skinfold thicknesses are recorded. The second occasion is a home visit conducted during the fifth postnatal week, but for premature infants (≤ 36 weeks' gestation) this visit is done at 40 weeks post conceptional age. For babies kept in hospital because of complications the home visit is delayed until the infant has been at home for at least 2 weeks. At the home visit a comprehensive questionnaire is used to elicit information on usual sleep position, usual sleep pattern, body movement during sleep, infant illness and health service attendance, pattern and type of infant feeding, parental smoking practice, child's overnight clothing and bedding, home heating and housing, and other characteristics of the infant and of parental care. Anthropometric and temperature measurements are made on the infant and a developmental assessment is conducted. The physical features of the house are noted and humidity and 24 hour max-min infant bedroom temperature on day of home visit is recorded. The third occasion is a phone interview conducted when the infant is 10 weeks old to review infant progress, illness history, feeding, and immunisation.

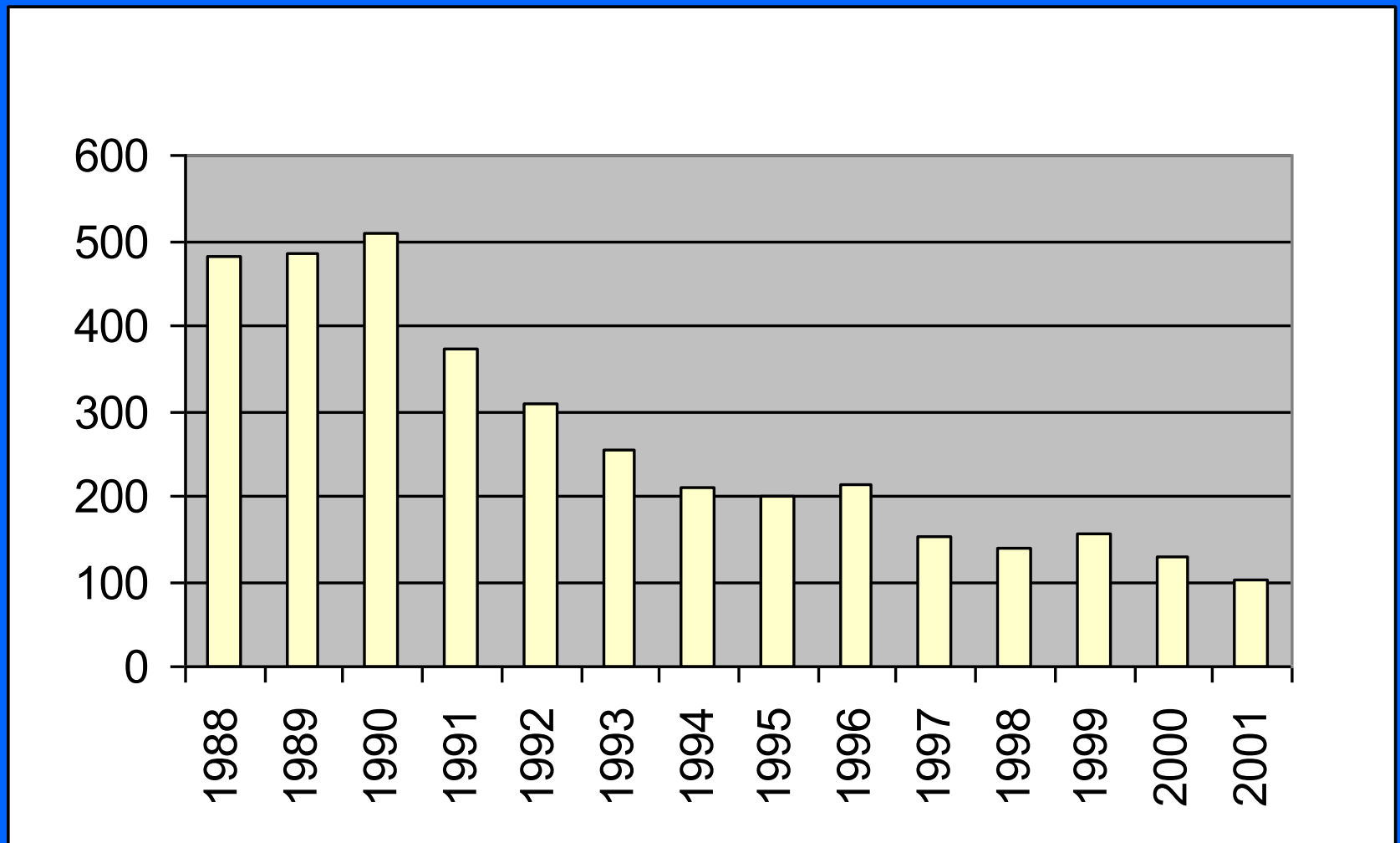
To collect information on sleeping position mothers are asked verbally "What position does your baby usually sleep in?". The prone position refers to the infant positions "on stomach, face to

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23/7/02

children's
ute
Their Future.

Australian SIDS deaths 1988-2001 (ABS)



‘ Discussion about potentially amenable risk factors such as the prone position ... may obscure the main goal of SIDS research ... understanding the final physiological pathways.’

NEJM 1993



**This is an impressive track
record**

Why has it been possible?

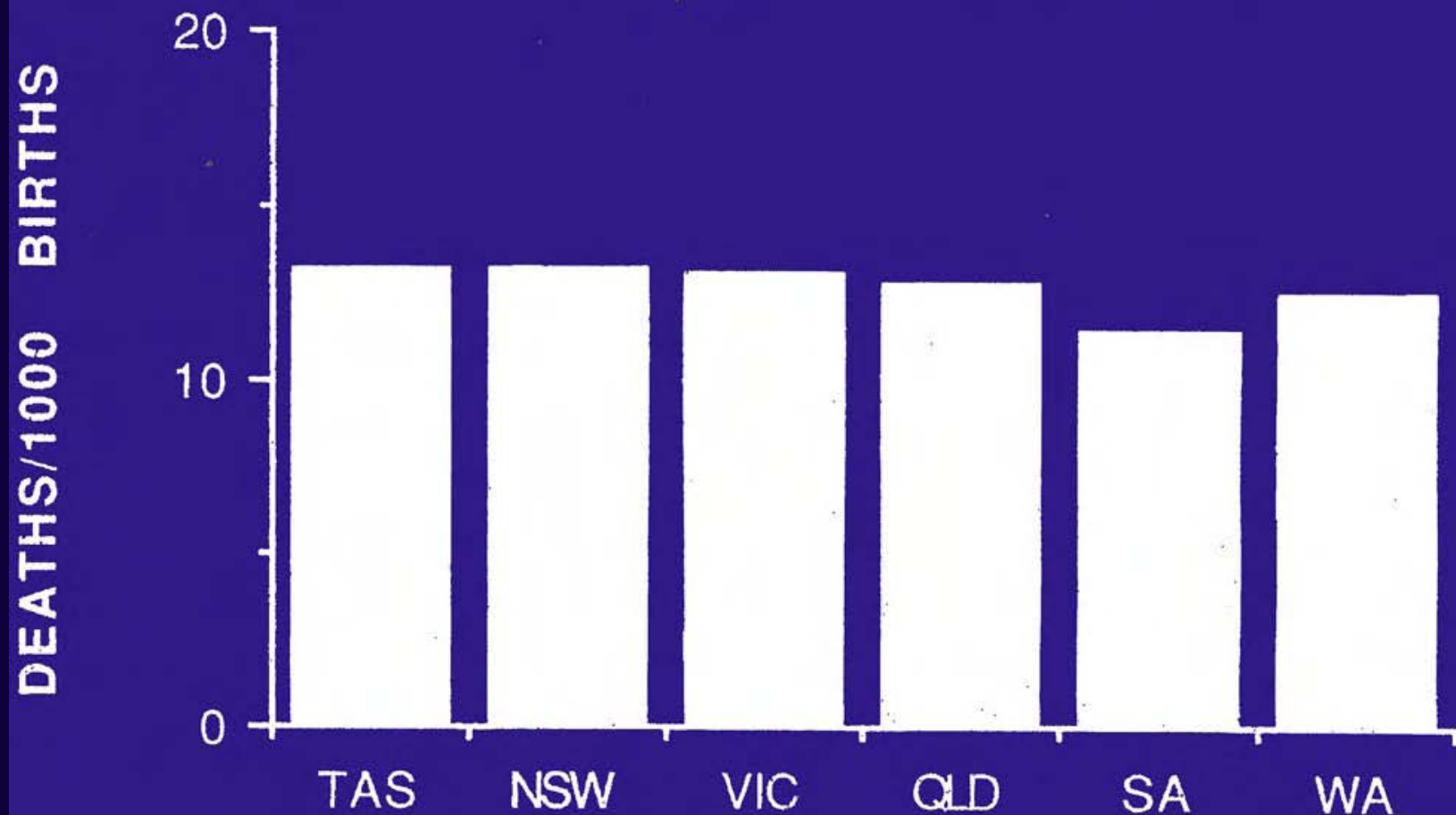


Because the opportunity is there

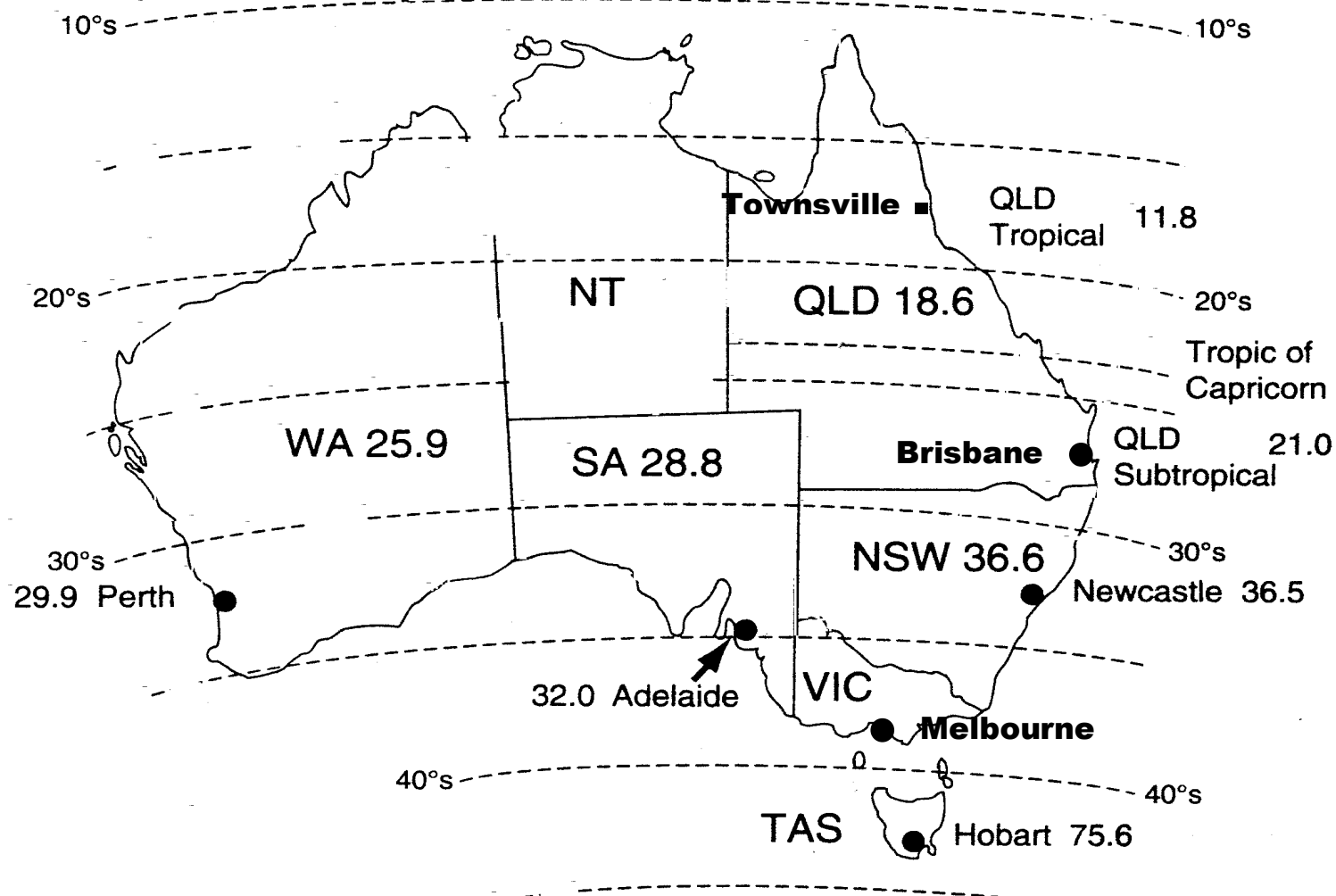
SIDS Mortality 1980 - 84



PERINATAL DEATH RATES BY STATE 1980-1984



Prevalence of multiple sclerosis in Australia



Age-standardised prevalence of multiple sclerosis per 100,000 population in Australia, 1981

**and because the approach is more
robust than the critics appreciate**

'The evidence is purely circumstantial,
it is obtained from statistical
evaluation of clinical material'

'It is just a correlation'

Lancet editorial 1951

good observational epidemiology involves a research paradigm not fully understood by the critics

- First, rigorous checks for confounding and other sources of bias

- Exhaustive attempts through other means to falsify or confirm the central hypothesis

Bradford Hill's Criteria for Causation(1965)

- **Strength**
- **Consistency**
- **Temporality**
- **Biological gradient**
- **Epidemiological coherence**
- **Biological coherence – incl. mechanism**



**Then the search for
novel opportunities**

Interaction between sleep position and infection in SIDS

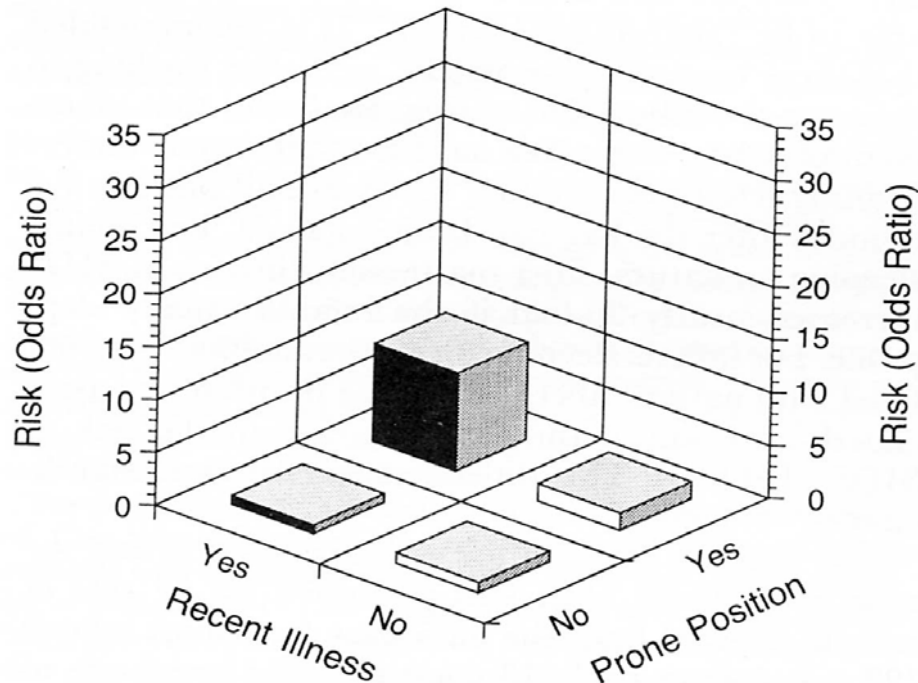


Figure 1. Risk Potentiation for SIDS: Recent Illness and Prone Position.

Ponsonby, NEJM
1993

If A is true then B should be true
and if they are both true, C
should also be true.

If A, B and C are true this takes it beyond
the improbable and circumstantial

The future

There will be many opportunities to identify preventable causes of ill health through properly conducted observational studies

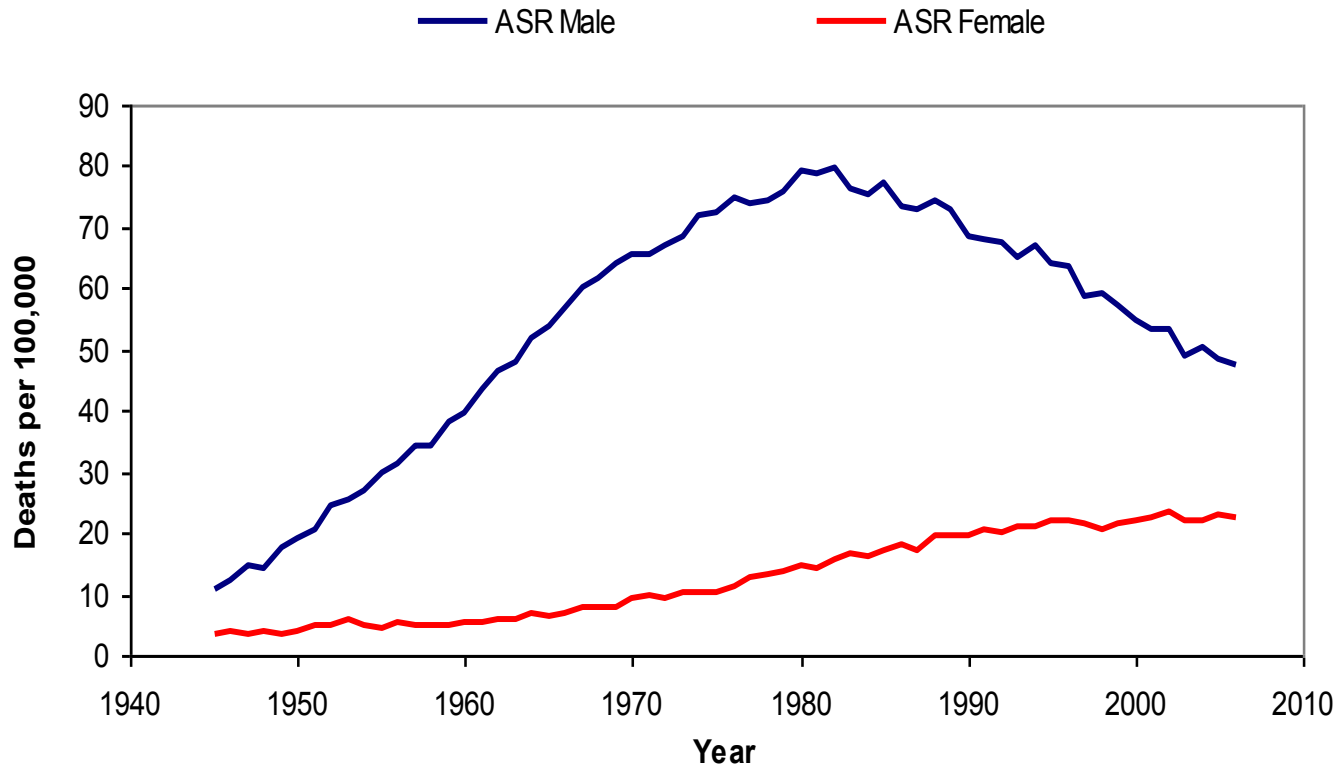
new conditions and new exposures including genes

where randomised trials can't provide the answer

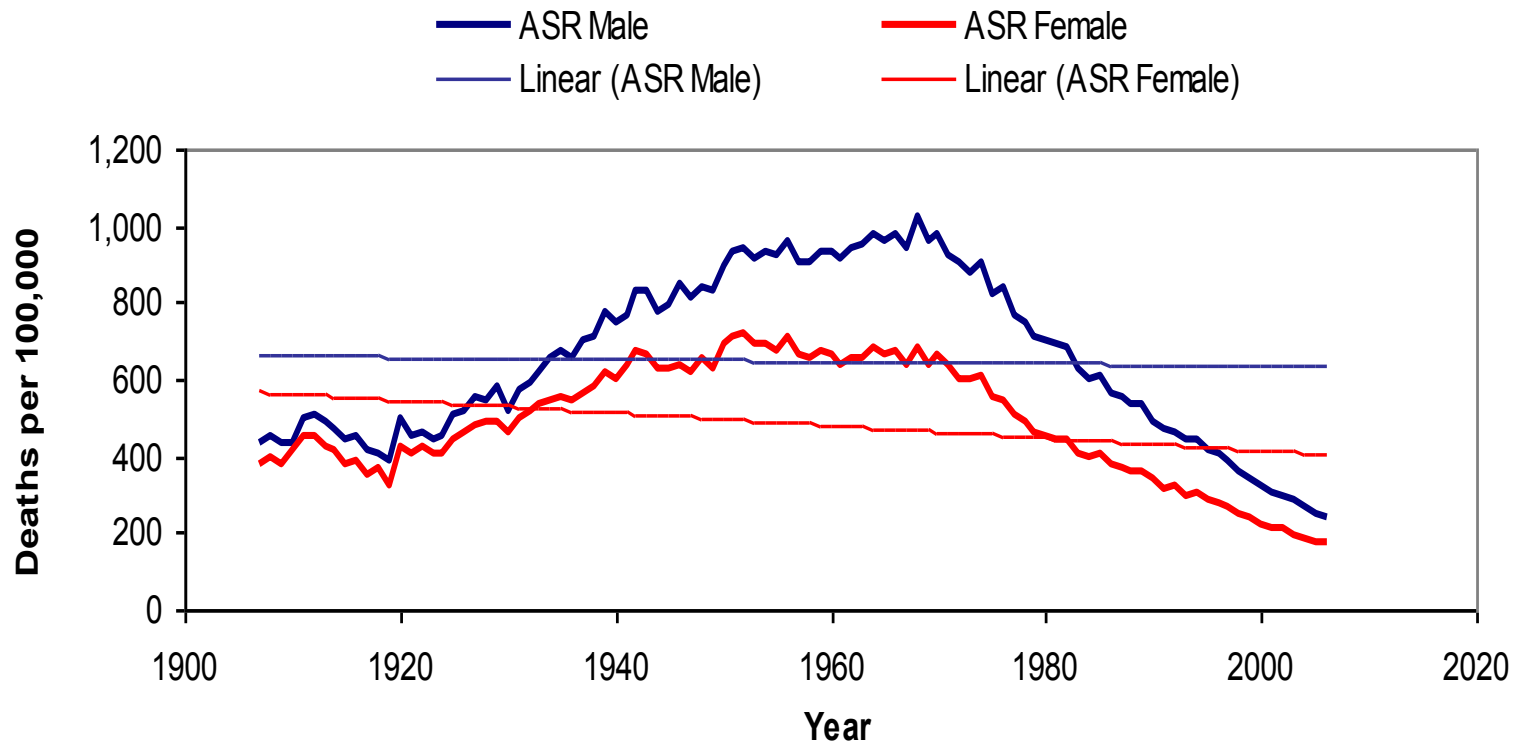


Should we formalise this
with a Bayesian statistical
approach?

Trends in death rates for Lung cancer (ICD10 C33, C34), Australia, 1945–2006



Trends in death rates for All circulatory diseases (ICD10 I00-I99), Australia, 1907–2006



- These comments sound as if they might come from laboratory based scientists or clinicians
- But caution comes from other directions too

Look for study specific opportunities to falsify the emerging hypothesis

Use optimal study design and analysis -

rule out chance/confounders/bias

The biostatistician's view

Beware of false positives.

A p value $< .05$ should not imbue too much confidence