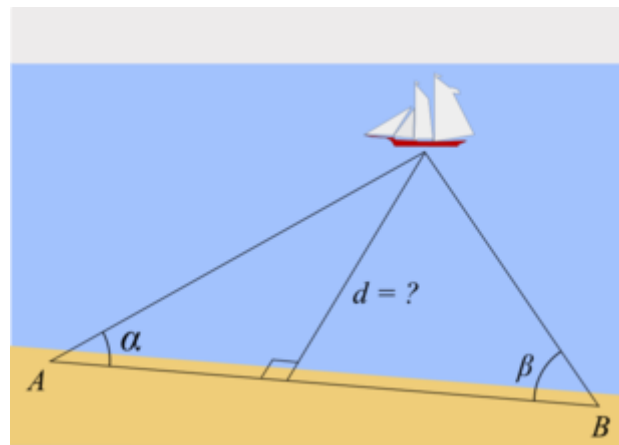


Triangulation in aetiological epidemiology



Irene Petersen,
Professor of Epidemiology and Health Informatics
Primary Care & Population Health

Today

- Introduction
- Triangulation

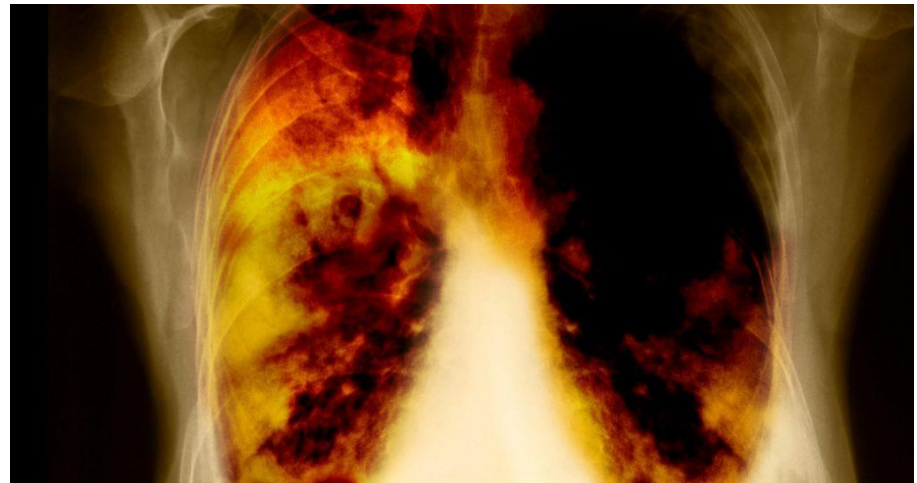
- Some examples
 - Low Systolic Blood Pressure and CHD
 - Smoking and cancer
 - Drugs in pregnancy and birth defects

- Implication for future research

Does low blood pressure prevent Coronary Heart Disease (CHD)?



Does smoking cause cancer?



Does treatment with drug x in pregnancy cause birth defects?



How do we answer these
questions?

Randomised Controlled Trials

- Well-conducted RCTs provide the best causal evidence
 - Evaluation of efficacy of treatments
- RCT not always feasible or ethical
 - Drug safety studies often need large sample size
 - Difficult to recruit patients
 - Un ethical, if there are concern about harm



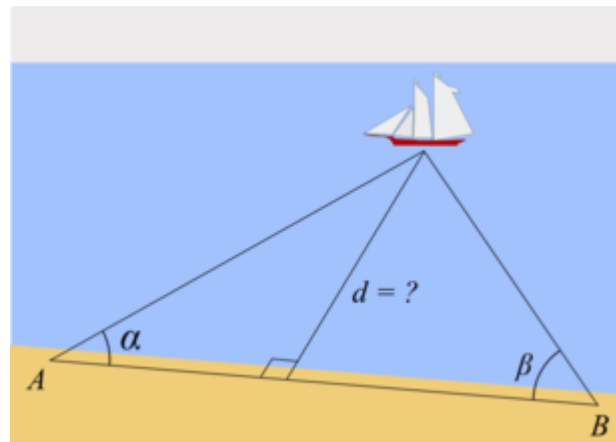
We still want to draw causal
inference

How do we draw causal inference (from non-randomised studies)

- A single study or approach is rarely enough to provide causal inference
- Need triangulation i.e. to integrate evidence from several approaches

Triangulation

- An old method that calculates a distance that is difficult (or impossible) to measure
- Using the known mathematical properties of triangles



Triangulation in epidemiological research



International Journal of Epidemiology, 2016, 1866–1886

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Original article



Approaches to causal inference

Triangulation in aetiological epidemiology

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Triangulation in epidemiological research

*“The practice of **strengthening causal inferences** by **integrating results** from several **different approaches**, where each approach has different (and assumed to be largely unrelated) key sources of potential bias.”*

Lawlor DA, Tilling K, Davey Smith G. Triangulation in aetiological epidemiology. *Int J Epidemiol*. 2016 Dec 1;45(6):1866–86.

Triangulation - Compare the results of different approaches

Approaches with different study designs

- RCT
- Cohort study
- Case-control study

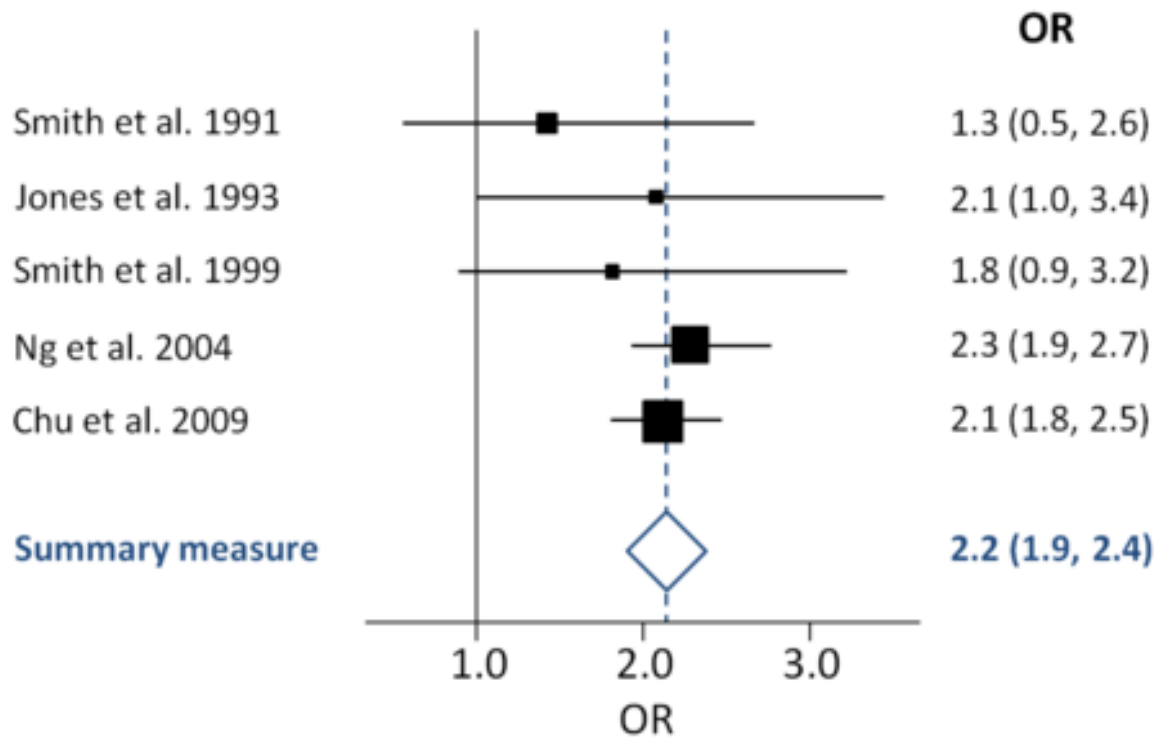
Approaches within same study design

- Negative control studies
- Cross-context comparisons
- Mendelian Randomization (MR)

Triangulation versus standard approaches

- **Triangulation**
 - Assumptions
 - Unrelated sources of bias between different approaches
 - Qualitative comparison
 - Expect different results
- **Standard approach e.g. systematic reviews**
 - Assumptions
 - Studies are unbiased
 - All studies estimating same causal effect
 - Quantitative estimate of effect

Systematic reviews integrate results from similar approaches



Criteria for triangulation

1. Two different approaches (as a minimum)
 - with differing and unrelated potential biases
2. Same underlying causal question
3. Duration and timing of exposure is taken into account
4. Key sources of bias are explicitly acknowledged
5. The expected direction of bias are made explicit
6. Choose approaches with potential biases in opposite directions

Let's try to apply triangulation

What is the causal cumulative effect of lower systolic blood pressure (SBP) on CHD risk?

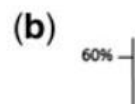
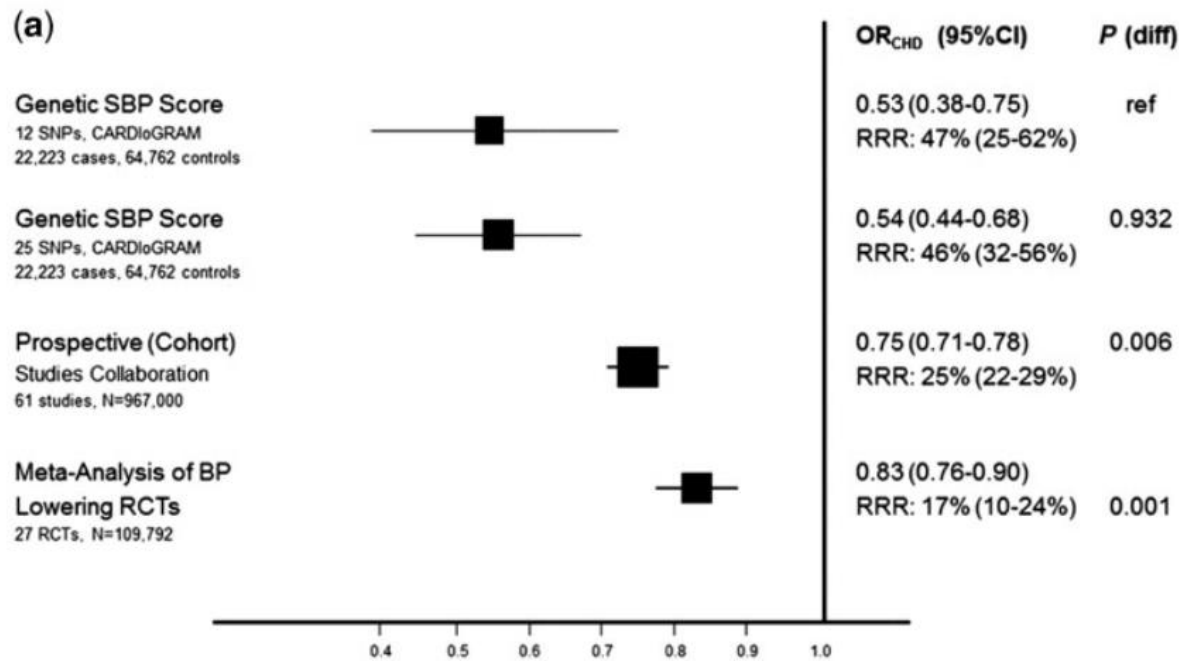


Ference et al. Clinical effect of naturally random allocation to lower systolic blood pressure beginning before the development of hypertension. Hypertension 2014

Lawlor DA, Tilling K, Davey Smith G. Triangulation in aetiological epidemiology. *Int J Epidemiol.* 2016 Dec 1;45(6):1866–86.

- Mendelian Randomisation (MR) studies
- Meta-analysis of prospective cohort studies
- Meta-analysis of IV ratio estimates from RCTs of antihypertensive treatment

Exposure to 10 mmHg lower systolic blood pressure (SBP) on risk of coronary heart disease (CHD)



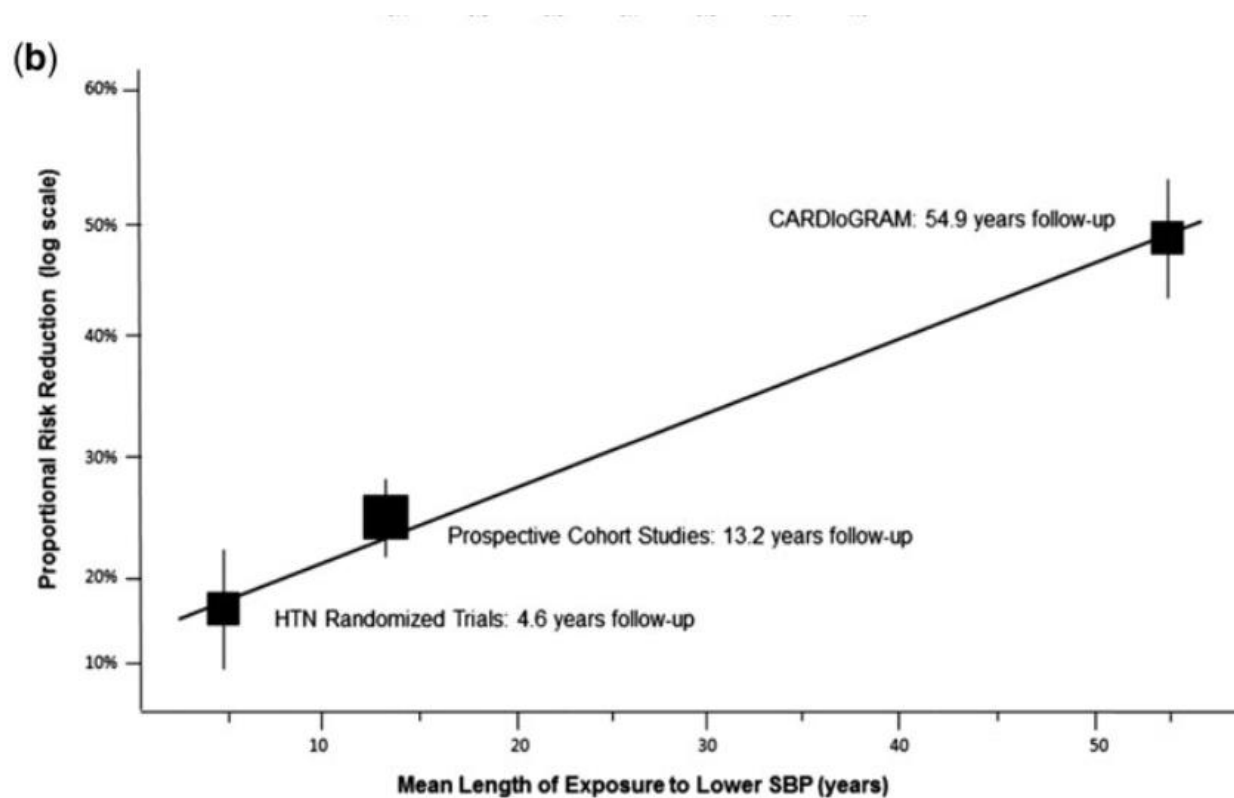
Results of all approaches point in same direction 😊

Effect size differs – why?

Discussion of potential biases

- Cohort studies
 - Residual confounding in multiple regression analysis
 - Exaggerate positive effect
- RCT studies
 - Effect of both systolic and diastolic blood pressure
 - Exaggerate positive effect
- Mendelian Randomisation
 - Violation of the exclusion restriction criteria (IV only affects the outcome 'Y' (CHD) through its effect on the risk factor 'X')
 - Sensitivity analyses suggest no bias in this case

Effect size may differ due to difference in length of exposure

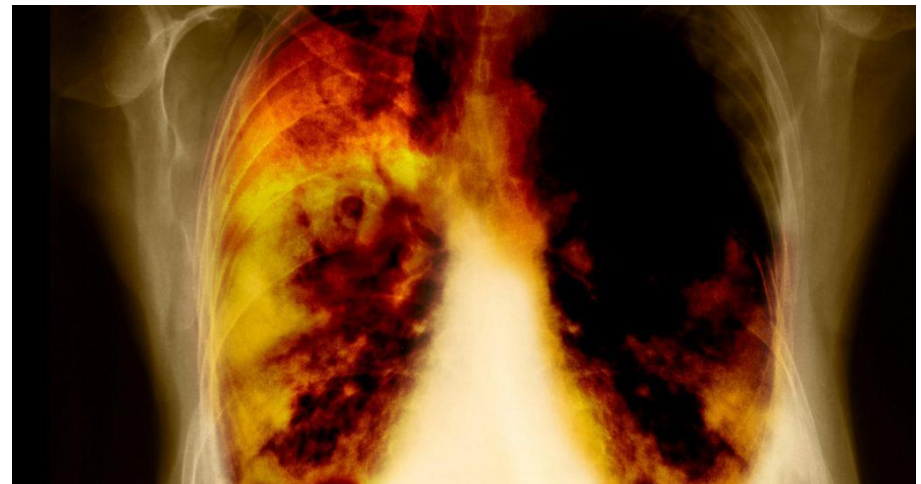


Triangulation suggests

- Lower systolic blood pressure (SBP) reduces Coronary Heart Disease (CHD) risk
- The greater duration of exposure to lower SBP, the greater the CHD risk reduction

A few other examples

Does smoking cause cancer?



Smoking

- For a long time smoking was advertised as healthy...



Smoking and carcinoma of the lung

- Case-control study + ecological study

BRITISH MEDICAL JOURNAL

LONDON SATURDAY SEPTEMBER 30 1950

SMOKING AND CARCINOMA OF THE LUNG

PRELIMINARY REPORT

BY

RICHARD DOLL, M.D., M.R.C.P.

Member of the Statistical Research Unit of the Medical Research Council

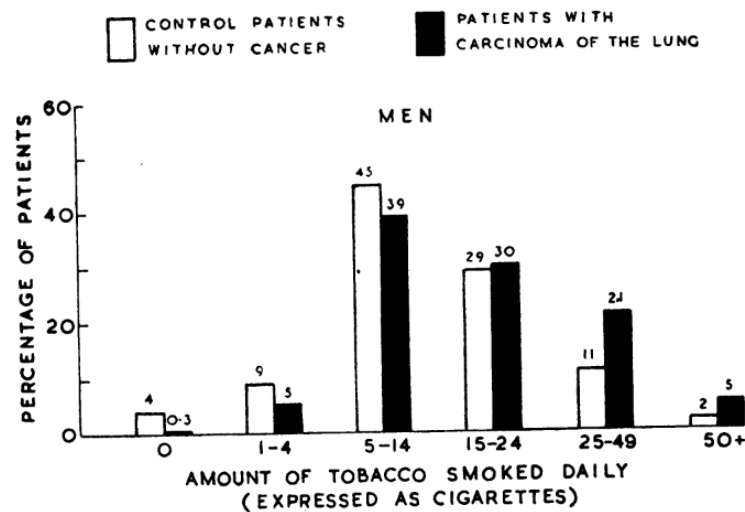
AND

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

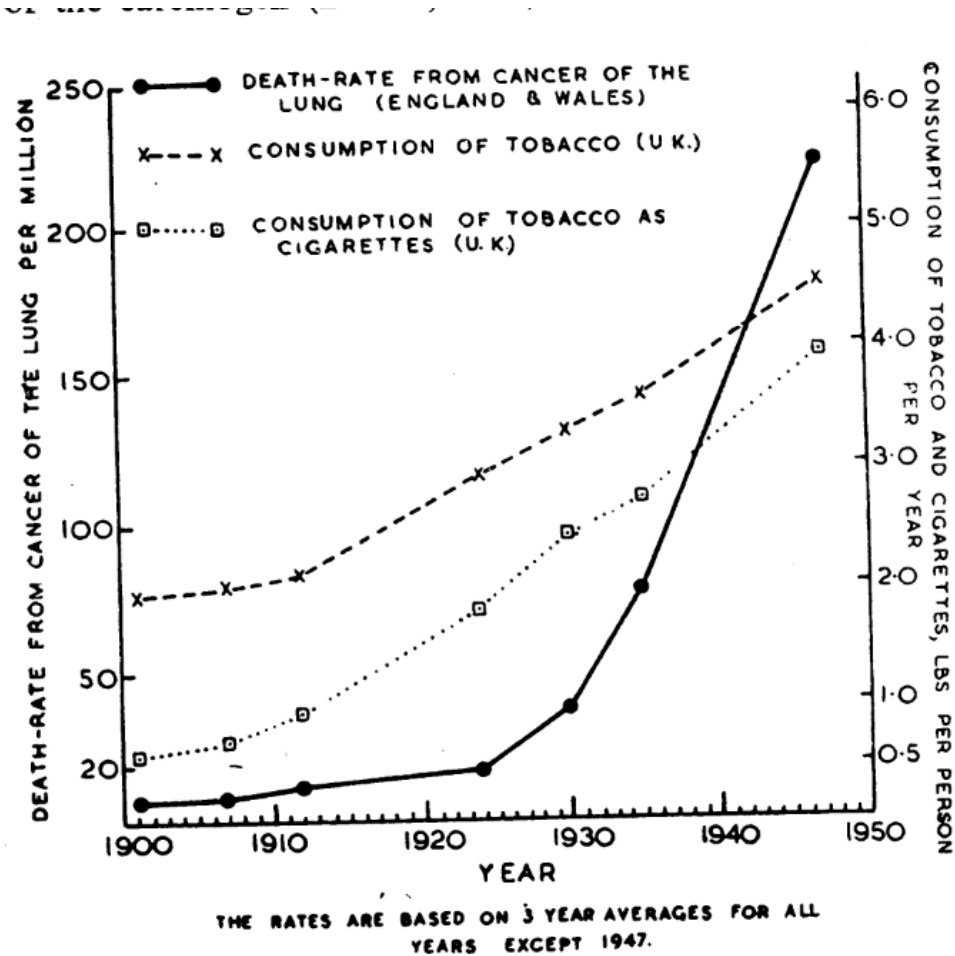
Professor of Medical Statistics, London School of Hygiene and Tropical Medicine; Honorary Director of the Statistical Research Unit of the Medical Research Council

Used different approaches

- Case-control studies
 - Compared smoking habits in people with and without lung cancer
 - Compared quantity of smoking



Ecological studies



Cohort study

BRITISH MEDICAL JOURNAL

LONDON SATURDAY JUNE 26 1954

THE MORTALITY OF DOCTORS IN RELATION TO THEIR SMOKING HABITS

A PRELIMINARY REPORT

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British Doctors study

- Cohort study
- 40,701 British doctors
- Smoking habits

- Increase risk of lung cancer + other outcomes
- Smoking decreases life span up to 10 years
- Demonstrated that timing and duration of smoking may be important

Smoking and Cancer in a triangulation framework

Different approaches – different biases

- Case-control studies
 - Recall bias
 - Residual confounding
- Cohort studies
 - Residual confounding, but not recall bias
- Ecological studies

Alternative approaches

- Negative exposures/outcomes
- Cross context studies - ecological studies in different countries

Study approaches for triangulation

- RCT
- Multivariable regressions methods
- Different control groups
- Cross context comparisons
- Natural experiments
- Within sibling design
- Instrumental Variables
 - Mendelian Randomisation
- Exposure negative control
- Outcome negative control
- Ecological studies
- Self-controlled studies

Over to you

Does treatment with drug x in pregnancy cause birth defects?



How would you design such study?

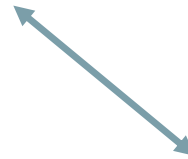
- Which approaches would you use?
- What biases might you expect from each approach?
- Timing?
- Strength of treatment?

Comparative study of women with different anticonvulsant exposures

Valproate



Lamotrigine or carbamazepine



Petersen et al. Risk and Benefits of psychotropic medication in pregnancy, NIHR library 2016

No treatment before or in pregnancy

Comparative study of women with different anticonvulsant exposures

Valproate

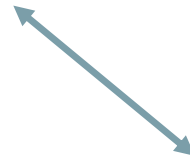


Triple risk of major congenital malformations

RR (adj): 3.15 (1.98, 5.00)

Triple risk of neurodevelopmental and behavioural problems

RR (adj): 2.83 (2.11, 3.81)



No treatment before or in pregnancy

Potential biases

- Residual confounding
- In particular confounding by indication

Comparative study of women with different anticonvulsant exposures

Valproate



Lamotrigine or carbamazepine

Double risk of major congenital malformations

RR (adj): 1.85 (1.02, 3.36)

Double risk of neurodevelopmental and behavioural problems

RR (adj): 2.10 (1.43, 3.08)

Confounding by indication

- Which factors may be associated with valproate prescribing?



- Are these factors also associated with the outcome?
- Are these factors captured in the dataset?

Confounding by indication

- What are the indications for valproate?
 - Epilepsy
 - Absence seizures, partial seizures and generalized seizures
 - Bipolar disorder
 - Prevent migraine headaches
- Is there link between the indications and the outcomes?

Epilepsy and autism spectrum disorder (ASD)

- Swedish Population registry study
 - 85 000 patients with epilepsy
- Strong association between epilepsy and ASD
 - Individuals with epilepsy (HR **10.49** (9.55-11.53))
 - Siblings of epilepsy patients (HR **1.62** (1.43-1.83))
 - Offspring of epilepsy patients (HR **1.64** (1.46 – 1.84))
 - Offspring of mothers with epilepsy (HR **1.91** (1.63 – 2.23))

Bipolar disorder and autism spectrum disorder (ASD)



Review

Genetic overlap between autism, schizophrenia and bipolar disorder

Liam S Carroll and Michael J Owen

Address: MRC Centre for Neuropsychiatric Genetics and Genomics, Department of Psychological Medicine and Neurology, Cardiff University, Henry Wellcome Building, Heath Park, Cardiff CF14 4XN, UK.

Correspondence: Michael J Owen. Email: OwenMJ@cf.ac.uk

Abstract

There is strong evidence that genetic factors make substantial contributions to the etiology of autism, schizophrenia and bipolar disorders, with heritability estimates being at least 50% for each. These illnesses have complex inheritance, with multiple genetic and environmental factors influencing disease risk; however, in psychiatry, complex genetics is further compounded by pheno-

The majority of psychiatric disorders, like other common conditions, are genetically complex. In psychiatry, genetic complexity has been compounded by phenotypic complexity. Psychiatric diagnosis cannot be made on the basis of biological investigation or validated against a common pathogenesis. Psychiatric 'disorders' such as autism, schizophrenia and bipolar disorder are therefore effectively

- Some research suggest a genetic link between bipolar disorder and ASD
- Perhaps less clear cut

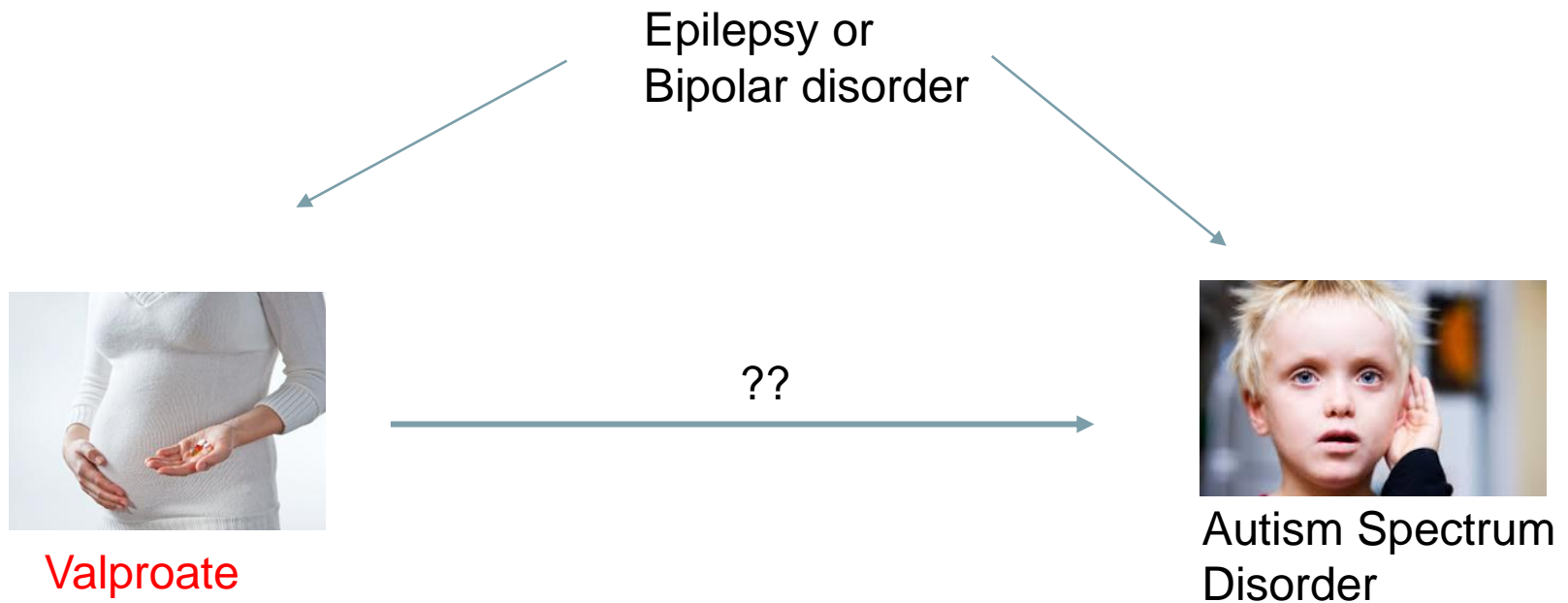


The article you requested is

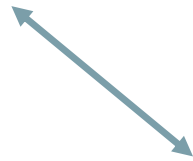
Examining the Comorbidity of Bipolar Disorder and Autism Spectrum Disorders: A Large Controlled Analysis of Phenotypic and Familial Correlates in a Referred Population of Youth With Bipolar I Disorder With and Without Autism Spectrum Disorders

Gagan Joshi, MD; Joseph Biederman, MD; Carter Petty, MA; Rachel L. Goldin, BA; Stephanie L. Furtak, BA; and Janet Wozniak, MD

Confounding by indication



- Suggest that the comparison between valproate and no treatment was biased



So what about this comparison?

Valproate



Lamotrigine or
carbamazepine

Double risk of major congenital malformations

RR (adj): 1.85 (1.02, 3.36)

Double risk of neurodevelopmental and behavioural problems

RR (adj): 2.10 (1.43, 3.08)

- Suggest that valproate may increase risk of
 - Major congenital malformation
 - Neurodevelopmental and behavioural problems
- Could still be subject to confounding by indication
 - Indications the same for lamotrigine and carbamazepine as for valproate?

Alternative approaches to evaluate drug safety in pregnancy

- Sibling design
 - Siblings with different exposures
- Negative controls
 - Paternal exposure
 - Before pregnancy exposure
 - Postnatal exposure



Implication for future research

- Triangulation has considerable potential to improve causal inference in aetiological epidemiology
- Still need for further development
 - Quantify range of effect estimates