



# Drug Safety in Pregnancy

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Henrik Toft Sørensen

Aarhus University Hospital

Department of Clinical Epidemiology

Boston University

Department of Epidemiology



# Pharmacoepidemiology and Drug-induced Birth Defects

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- ◆ Birth defects are part of the human condition observed throughout history
- ◆ Major birth defects affect approximately 3-4% of live-born infants
- ◆ Just over 50 years ago, it was believed that the placenta protected the foetus from noxious agents
- ◆ That belief was shattered by the recognition in 1941 that maternal rubella infection produced a distinctive pattern of birth defects
- ◆ In 1961 the thalidomide disaster demonstrated that drugs could be teratogenic



# Why Epidemiological Studies?

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- ◆ For most known human teratogens (including thalidomide) results of animal tests vary so much as to seriously limit their predictive value
- ◆ Structure or activity of the drug are generally not predictive of teratogenesis
- ◆ Thalidomide and glutethimide are structurally closely related, but there is no evidence that the latter is teratogenic
- ◆ Pregnant women are excluded from premarketing studies and clinical trials because of fear of teratogenicity



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- ◆ Epidemiologic issues involved in the study of birth defects are similar to those of other adverse outcomes, but the following considerations are especially important for birth defects:
    - ◆ Sample size
    - ◆ Definition of exposure and outcome
    - ◆ Confounding
    - ◆ Biologic plausibilities



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Birth defects cannot be considered as a single homogenous outcome.

Physical birth defects include a wide range of malformations that vary in many ways including:

- ◆ Gestational timing
- ◆ Embryological tissue of origin
- ◆ Mechanism of development



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## *Examples:*

- ◆ Chromosomal abnormalities generally preclude conception
- ◆ Neural tube defects occur in the earliest week of gestation
- ◆ Cleft palate occurs toward the end of the first trimester
- ◆ Microcephaly can occur relatively late in pregnancy



## Teratogens do not uniformly increase the rates of all birth defects but rather increase rates of selected defects

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### *Examples:*

- Thalidomide - limb defects
- Isotretinoin - ear, central nervous system and cardiac defects
- Valproic acid - neural tube defects
- Warfarin - cartilage defects
- ACE-inhibitors\* - renal defects

\* Angiotensin converting enzyme



# Walker & Stampfer

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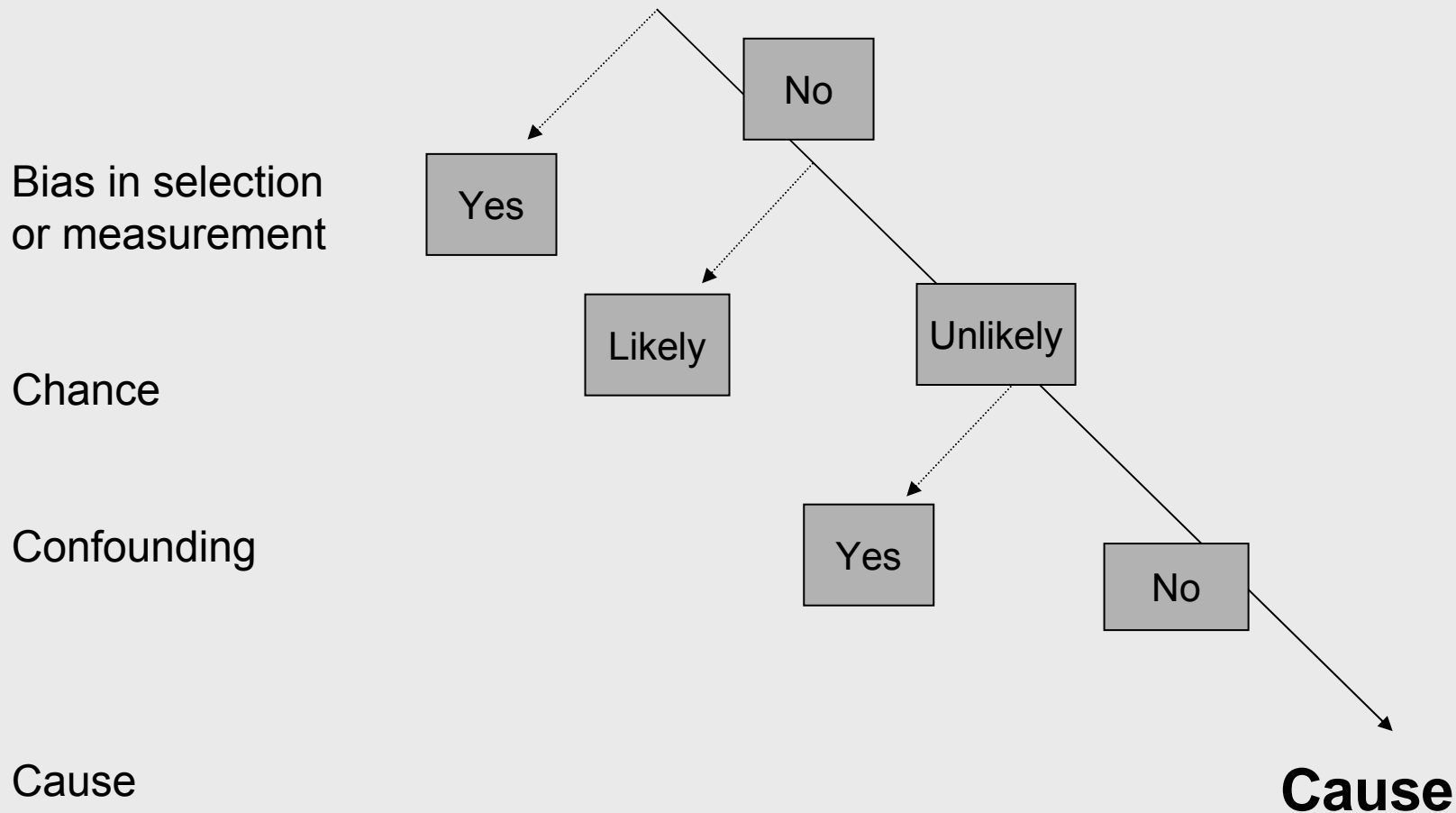
*...”Most of what we learn, and will continue to learn, about adverse drug effects are from observational studies”*

Lancet 1996;348:489



# Explanation

# Finding





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The fear that pharmacoepidemiologic studies must consider specific rather than overall rates of birth defects has a dramatic effect on sample size requirements.

To detect a doubling risk of a relatively common specific birth defect ( $1/1000$  ~ oral clefts) one would require a sample size of 23,000 exposed pregnancies.



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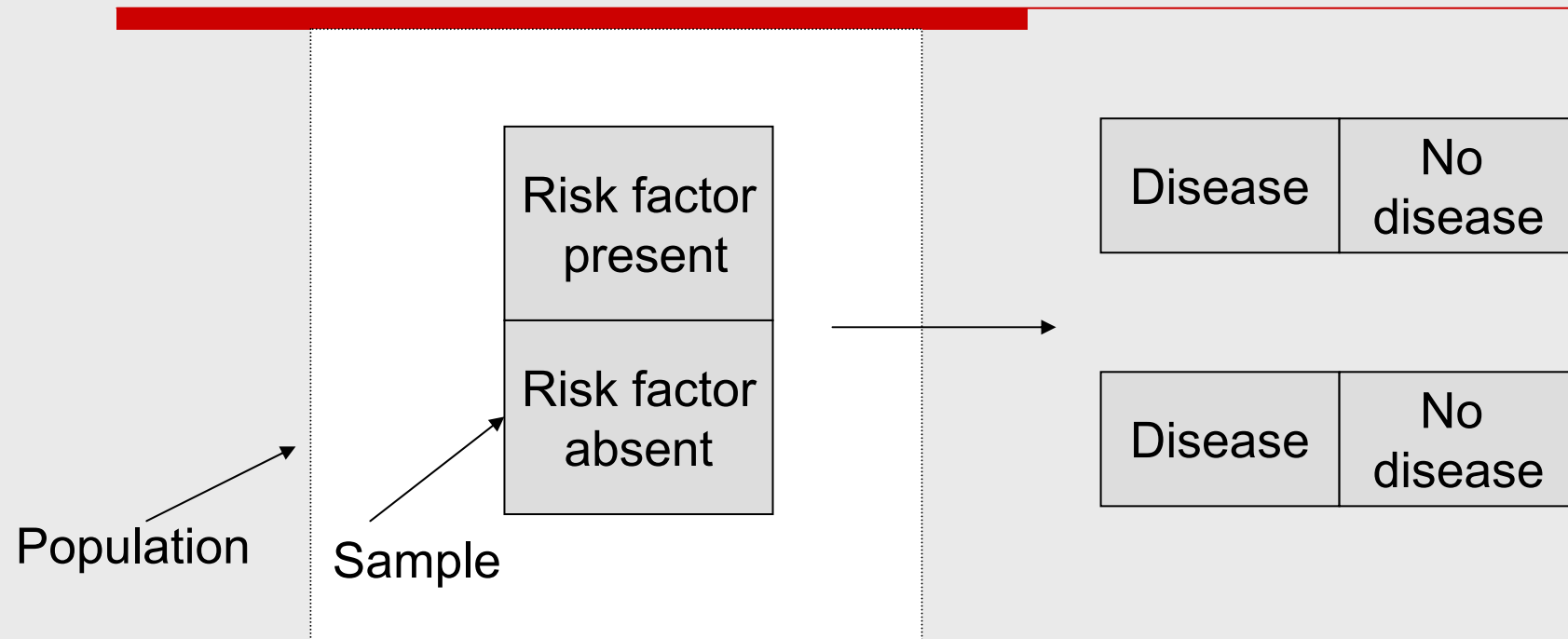
The rarity of birth defects in general, and specific defects in particular, argues for the use of large cohorts or case-control design in pharmaco-epidemiologic studies of birth defects.



# Cohort design

The Present

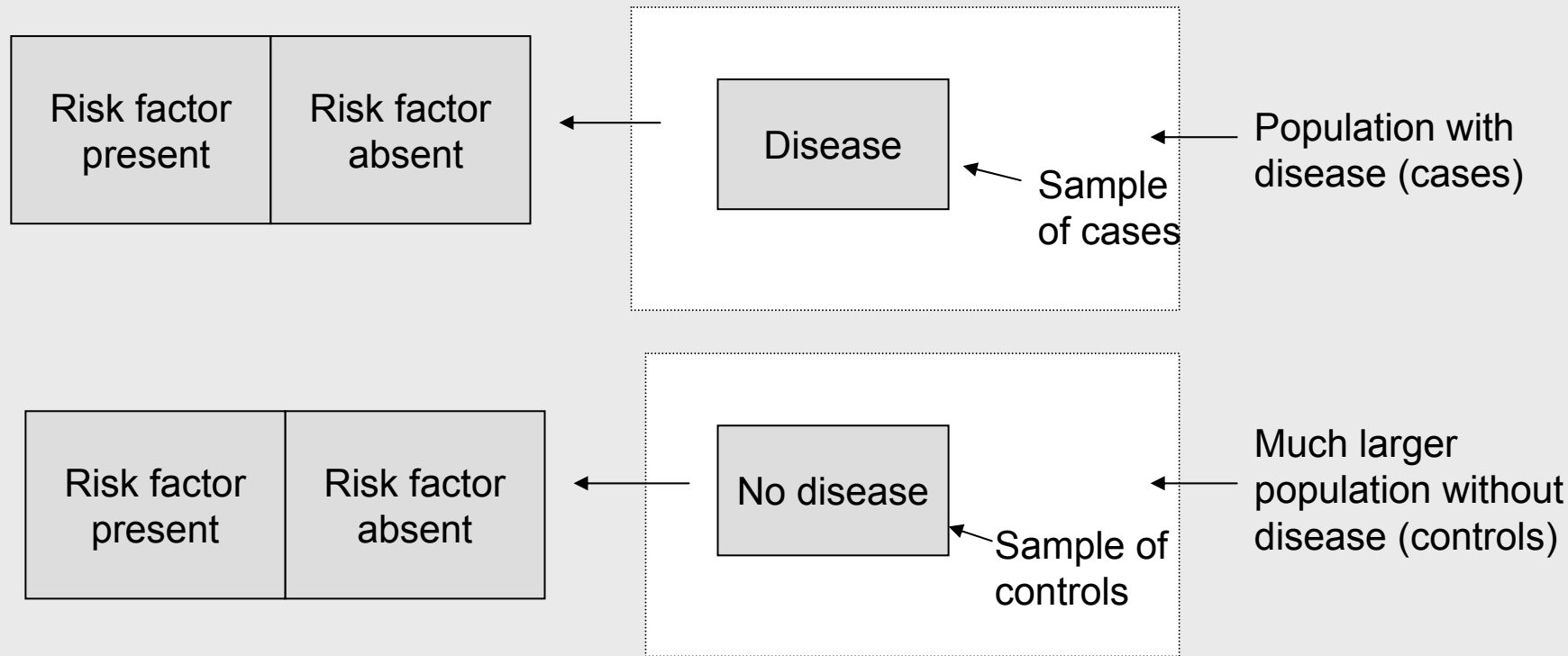
The Future



- Steps:**
1. Select a sample from the population
  2. Measure predictor variables (risk factor present or absent)
  3. Follow-up the cohort
  4. Measure outcome variables (disease present or absent)

## The Past or Present

## The Present



- Steps:**
1. Select a sample from a population of people with the disease (cases)
  2. Select a sample from a population at risk that is free of the disease (controls)
  3. Measure predictor variables



# Examples of Most Used Cohorts<sup>1</sup>:

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## **US Collaborative Perinatal Project (primary data collection)**

which enrolled over 50,000 women between 1959 and 1965, obtained detailed information on their pregnancies, and followed the children until age 7

(the overall size of the database is the major weakness)

## **Medicaid Program, US (prescription data)**

229,000 pregnancies

(the data quality and lack of records for the offspring are the major weaknesses)



# Examples of Most Used Cohorts<sup>2</sup>:

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## **Jutland County Cohort**

180,000 pregnant women

(the sample size is the major weakness)

## **The Danish National Birth Cohort**

approx. 100,000 pregnant women

## **Motherisk Program, The Toronto Teratogen Information Service, Canada**

## **The Swedish Birth Registry**

500,000 pregnancies



# Case-control Surveillance

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## 1. Hungary

The Hungarian Case-Control Surveillance of Congenital Abnormalities

23,000 cases and 38,000 controls

## 2. USA

The Case-control Surveillance, the Slone Epidemiology Unit

15,000 babies with birth defects

> 1000 cases of neural tube defects

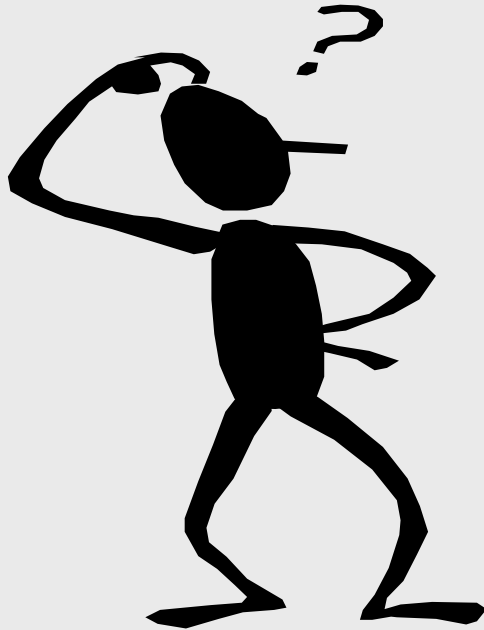
> 500 cases of cleft palate

> 80 cases of gastroschisis



# Problems with Case-control Studies

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Examples of problems in the Hungarian Case-Control Surveillance of Congenital Abnormalities

1. Most women treated with other drugs
2. Validation study has shown that recall bias is a problem: be careful with odds ratios less than 2
3. The response rate lower for controls than cases

## When an Entire Country Is a Cohort

Denmark has gathered more data on its citizens than any other country. Now scientists are pushing to make this vast array of statistics even more useful

For years, any woman who got an abortion had to accept more than the loss of her fetus: For some unknown reason, she also faced an elevated risk for breast cancer. At least that was what several small case-control studies had suggested before Mads Melbye, an epidemiologist at the Statens Serum Institute in Copenhagen, undertook the largest effort ever to explore the link. He and his colleagues obtained records on 400,000 women in Denmark's national Abortion Register, then checked how many of the same women were listed in the Danish Cancer Register. Their foray into the two databases led to a surprising result: As they reported in *The New England Journal of Medicine* in 1997, there appears to be no connection between abortion and breast cancer.

Their success underscores the value of a trove of data the Danish government has accumulated on its citizenry, which today totals about 5 million people. Other Scandinavian countries have created powerful database systems, but Denmark has earned a preeminent reputation for possessing the most complete and interwoven collection of statistics touching on almost every aspect of life. The Danish government has compiled nearly 200 databases, some begun in the 1930s, on everything from medical records to socioeconomic data on jobs and salaries. What makes the databases a boon for research tools is the fact that they can all be linked by a 10-

digit personal identification number, called the CPR, that follows each Dane from cradle to grave. According to Melbye, "our registers allow for instant, large cohort studies that are impossible in most countries."



**Beauty in numbers.** These Danish twins starred in a variety show at the turn of the 20th century; now it's their medical records, part of a database, that are in demand.

But Melbye and other scientists think they can extract even more from this data gold mine. They argue that not enough money is being spent on maintaining and expanding existing databases, and they say that red tape is hampering studies that require correlation of health and demographic data. The problem is that, while they have unfettered access to more than 80 medical databases maintained

by the Danish Board of Health and public hospitals, their use of 120 demographic databases overseen by the agency Statistics Denmark is tightly restricted. Statistics Denmark won't allow researchers to remove from its premises data coded by CPR, and the procedures for accessing information at all are unwieldy and expensive.

Statistics Denmark officials are reluctant to release data tied to CPRs, citing privacy concerns. "The public should have confidence that information identifying them as individuals does not reside outside of this institution," says the agency's Otto Andersen.

Last month, Danish research minister Birte Weiss formed a committee to break the impasse. Denmark's databases are "a resource which can be used more optimally," she told *Science*. "This should be a scientific flagship."

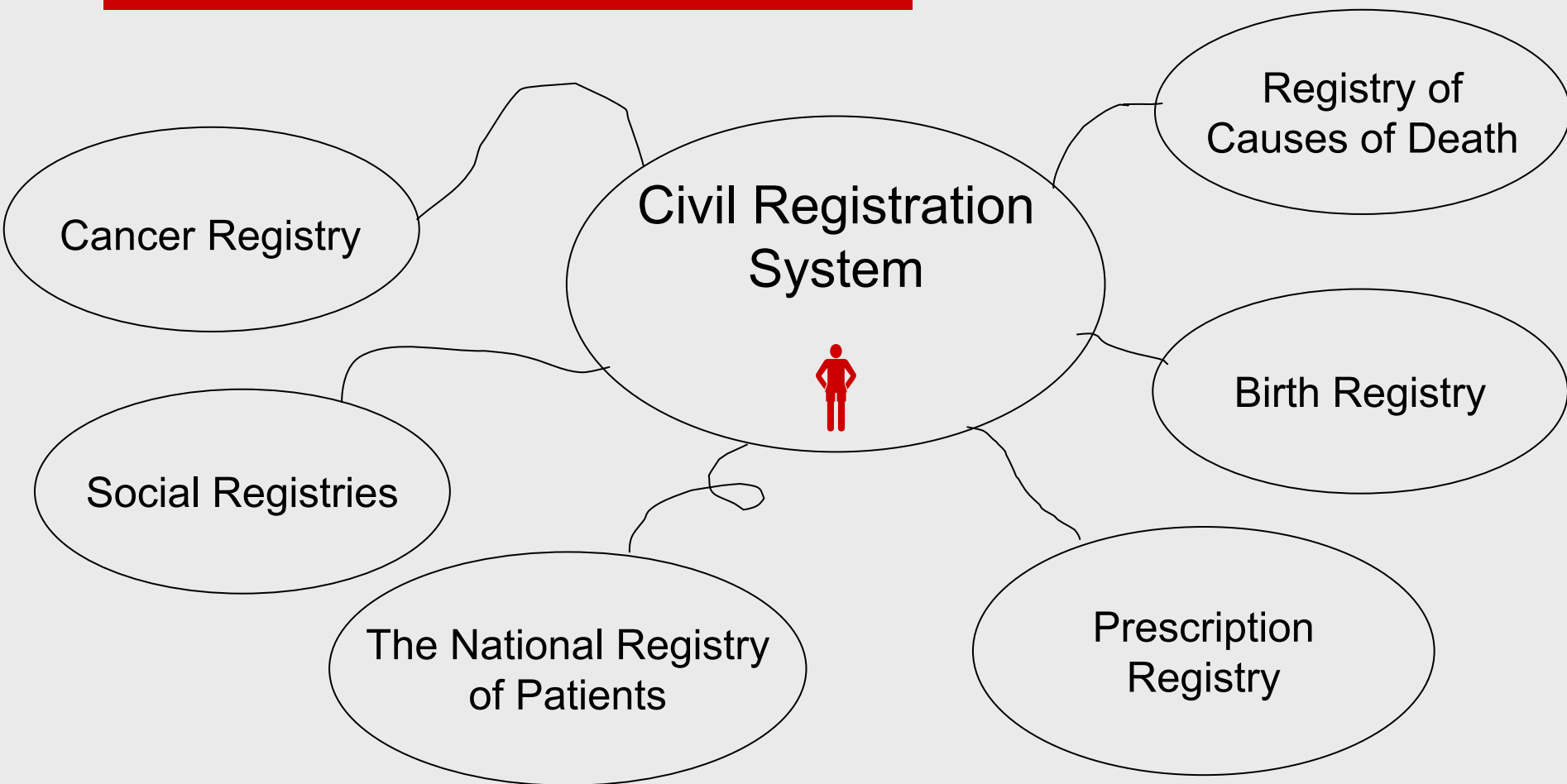
Working the health databases can yield powerful results. For years the U.S. National Institutes of Health has supported a study following z twins, hoping to tease out the relative contributions of genes and lifestyle to aging. Led by University of Southern Denmark gerontologist Kaare Christensen, the project has tapped the Danish Twin Register, which includes 110,000 pairs of twins born since 1870. After follow-

ing more than 2000 pairs of twins aged 70 or older, Christensen's group has so far tied to 0 genes about a quarter of the variation in human longevity. "The project is made possible by the unmatched age and completeness of the Danish twin Register," he says.

The health databases have proven invaluable for probing contradictions raised by smaller studies and following disease pro-



# Possibilities of Record Linkage





# Limitations of prescription databases and registries are often ignored and numerous

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## General

- The data collection methods are predetermined, and not controlled by research and sometimes impossible to validate. Misclassification exists in all data
- Poor data quality constitutes a permanent obstacle to registry-based research
- The relatively large number of data may lead to data dredging and misleading post hoc analysis



# Specific

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1. Examples of misclassification of exposure data
  - a. Non-compliance ~ bias towards null
  - b. Time period. Exposure determined after the day of reimbursement
  - c. Misclassification between mother and child
2. Lack of information on potential confounding factors: e.g. alcohol habits, smoking



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3. No information on the indications ~ “confounding by indication”, a serious problem. No information on co-morbidity or clinical status of the patients
  4. Misclassification of outcome data
    - random misclassification gives bias toward the null (under-estimation of the real effect)
  5. For rare events (e.g. congenital malformations), a prescription database will be too small as this type of research
  6. No data on prenatal diagnostic



# The Future

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Attention to:

- ◆ Statistical power - we need more and better data
- ◆ Data quality
- ◆ Secular trends in exposure (new drugs)
- ◆ Better integration of epidemiology, biostatistics, pharmacology and biology
- ◆ Integration of meta-analysis in order to solve some of the problems with statistical power
- ◆ Other end-points than birth defects – long-term follow-up of children



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# Thank you