

# Pros and cons with registry-based research

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My focus this time is on clinical studies more than on etiologic research



# Health data registers

- Cancer Register
- Medical Birth Register including congenital malformation surveillance
- Hospital Patient Register
- Prescribed Drug Register
  
- Cause of Death Register

# Examples of Quality registers in Sweden

- Hip replacement surgery
- Knee replacement surgery
- Hip fracture
- Cataract surgery
- Bladder cancer
- Rectal cancer
- Stroke
- Cardiac intensive care
- Heart surgery
- Diabetes
- Rheumatoid arthritis
- Hernia surgery
- Coronary angiography and angioplasty
- Ear, nose and throat
- In total, about 100 registries

## Pros with registry-based research

- There are many registries available
- Data are already there, no delay in collecting data
- Unselected ("real world") populations
- Large populations
- Long-term effects
- New hypotheses can be tested retrospectively with prospectively collected data

# Cons with registry-based research

- ...

## Cons with registry-based research

- Registration is time-consuming for health care personell if not integrated into medical records, avoid double registration
- Legislation and interpretation of laws
- Bad conducted observational (registry-based) studies

# Study design:

- Randomised controlled trials
- Observational studies
  - Longitudinal cohort studies
  - Longitudinal case-control studies

Ongoing debate: Can we trust observational studies?

## Advocates of RCTs state:

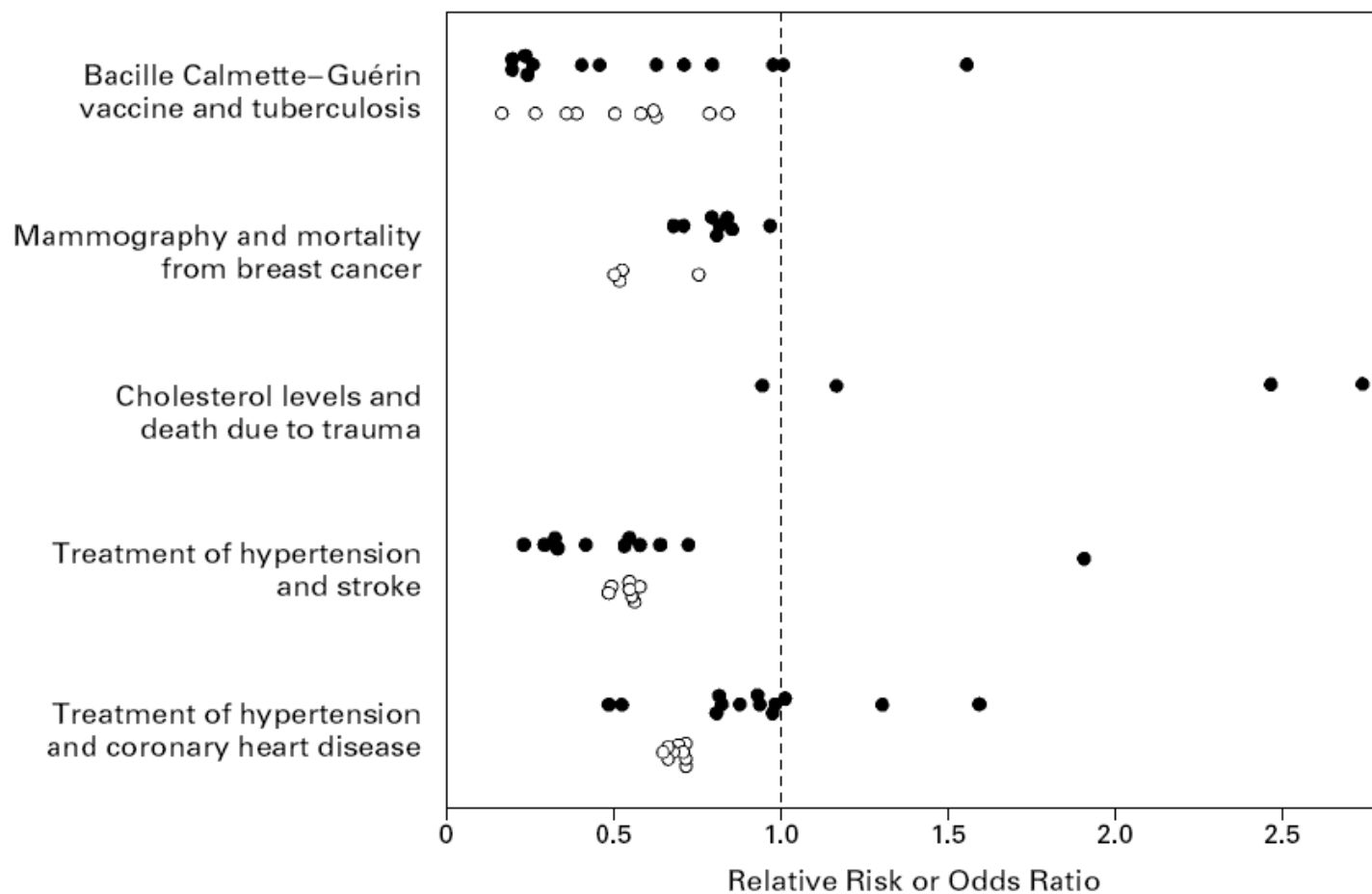
Observational studies often overestimate the effects of an intervention

others disagree...





# Point estimates for RCT (filled circles) and observational studies (unfilled circles)



Källa: Concato et. al. NEJM 2000;342:1887-92.



## **Conclusions (Concato et al NEJM 2000;342:1887-92)**

- Viewed individually, the observational studies had less variability in point estimate than RCT on the same topic
- The results of well-designed observational studies do not systematically overestimate the magnitude of the effects of treatment as compared with those in RCT

## **Conclusions from Benson & Hartz, NEJM 2000;342:1878-86.**

- In most cases, the estimates of the treatment effects from observational studies and RCT were similar
- We found little evidence that estimates of treatment effects in observational studies reported after 1984 are either consistently larger than or qualitatively different from those obtained in RCTs.



# Meta-analysis of adverse effects derived from RCT and observational studies

- "The pooled ratio of odds ratios of RCTs compared to observational studies was estimated to be 1.03 (95% CI 0.93-1.15)"
- "There was less discrepancy with larger studies"
- "No consistent difference between risk estimates"
- Conclusion: "Systematic reviews of adverse effects should not be restricted to specific study types"

Su Golder et al. Meta-analyses of adverse effects data derived from randomised controlled trials as compared to observational studies; Methodological overview. PLoS Med 2011;8:1-13.



**But, observational studies have misled us  
sometimes  
Why?**



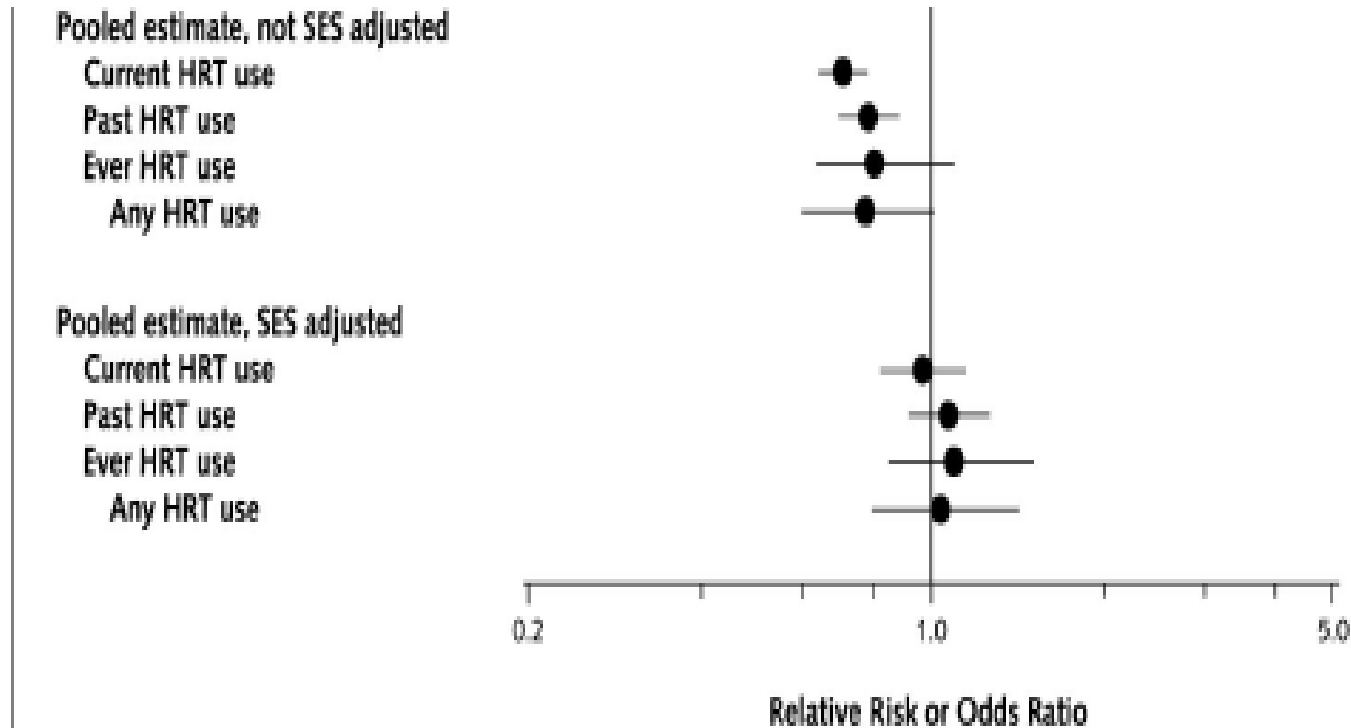
# Can you trust observational studies? Why do they sometimes come to the wrong conclusions?

- Hormone replacement therapy and risk of CHD
- Antioxidants and CHD
- Beta carotene and lungcancer

# What factors have the strongest impact on health?

- Living conditions
- Education
- Occupation
- Economy
- Social position
- Lifestyles
  
- i.e. socio-economic conditions

# Risk for CHD after hormone replacement therapy (HRT) before and after control for socioeconomic factors



Källa: Humphrey LL et al Ann Intern Med 2002;137:273-84



# Who take vitamins?

- "Intake of vitamins A, C and E and fruits and vegetables was significantly more in better educated" (Singhal et al, 1998)
- "..women who were socio-economically deprived were much less likely to take folic acid.." (Relton et al, 2005)
- "unhealthy dietary patterns in the USA especially among low-income households.." (Bhargava A, 2004)
- "...people from poorer socioeconomic positions at any time had lower vitamin concentrations" (Lawlor DA et al, 2004)

## Drugs on equal terms?

Drugs	Low education level	Moderate education level	High education level
Beta-blockers	M 1.2 F 1.3	M 1.2 F 1.3	M 1.0 F 1.0
Anti-psykotics	M 2.0 F 1.9	M 1.4 F 1.4	M 1.0 F 1.0
Oestrogenes	F 0.64	F 0.87	F 1.0
Erectile dysfunction.	M 0.64	M 0.87	M 1.0
Angiotensin receptor blockers (ARB)	M 0.88 F 1.01	M 1.00 F 1.12	M 1.0 F 1.0
Antibacterials	M 0.94 F 0.85	M 0.98 F 0.95	M 1.0 F 1.0



## What is the percentage of observational treatment studies controlling for socio-economic factors?

- Less than 30 % of all observational treatment studies in 2006 controlled for socio-economic factors in the Lancet, NEJM, BMJ and JAMA.

Source: Rosén, Axelsson, Lindblom. Lancet 2009;373:2026.



# Conclusions

- Well-conducted RCTs are often more valid than observational studies in estimating effects of treatments
- Most RCTs have not focused on adverse side effects of treatments, are not designed to answer those questions and have too short time of follow-up.
- Well-conducted observational studies with good control for confounders and selection biases must be upgraded as an appropriate study design for studies of adverse effects of interventions
- In most cases observational studies and RCTs show similar results
- Control for socio-economic factors are of utmost importance in observational studies, especially for non-acute interventions which are demanded by well-educated patients



# Examples where observational studies have had substantial impact on the grading of evidence in SBU reports?

- Vaccination for measles, mumps and rubella and the risk of autism
- Choice of antipsychotic drugs for patients with schizophrenia

# Vaccination for measles, mumps and rubella and the risk of autism

- Cohort study of all children born in Denmark 1991 – 1998, 537 303 children
- 440 655 children were vaccinated and 96 648 were not vaccinated
- Record linkage of several registries
- Confounding control for many baseline characteristics of the children including socio-economic factors
- Results: The RR for autism among vaccinated children compared to unvaccinated was 0.92 (0.68 – 1.24)

## Recommended antipsychotic drugs

- According to recommendation ("Kloka Listan") in Stockholm clozapine is suggested as a third-line alternative in treatment for schizophrenia
- This is primarily based on risks for weight gain and agranulocytosis
- What about mortality and suicide?

# Risk of suicide and suicide attempts with clozapine compared to other antipsychotic drugs among patients with schizophrenia

- RCT: Clozapine vs olanzapine (2 years of follow-up), hazard ratio = 0.76 (0.58 – 0.97) for suicidality
- FIN 11: Finnish registry-based cohort study: Antipsychotic drugs (11 years of follow-up)
- Swedish registry-based study (SBU): Antipsychotic drugs ( ~4 years of follow-up)



# FIN11, 66 881 individuals with schizophrenia, cohort study, 11 years of follow-up

Drugs	Suicide	HR
Clozapine	27	0.34 (0.20 – 0.57)
Haloperidol	7	0.61 (0.27 – 1.37)
...		
Olanzapine	57	0.94 (0.61 – 1.45)
Perphenazine (ref)	33	1.0

Source: Tiihonen J et al. Lancet 2009;374:620-627



# Swedish registry-based study, 25 325 individuals with schizophrenia, case-control, ~4 years of follow-up

Läkemedel	Självordsförsök	OR
Clozapine	42	0.44 (0.28 – 0.70)
Olanzapine	87	0.61 (0.41 – 0.91)
...		
Perphenazine	48	1.03 (0.66 – 1.61)
Haloperidol (ref)	36	1.0

Source: Ringbäck et al and SBU rapport nr 213 2012 Schozofreni



## Benefit versus risk: Suicide attempts vs agranulocytosis

- Among all treated for schizophrenia between 2006-2009 in Sweden
  - 1 death in agranulocytosis
  - 23 treated for agranulocytosis
  - 222 suicides
  - 831 suicide attempts
- Comparison clozapine and first generation of antipsychotic drugs (an estimation using etiologic fraction)
  - Using clozapine instead of first generation of drugs could have prevented 95 suicide attempts (OR=2.14).

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