

# Observational studies to improve clinical outcomes

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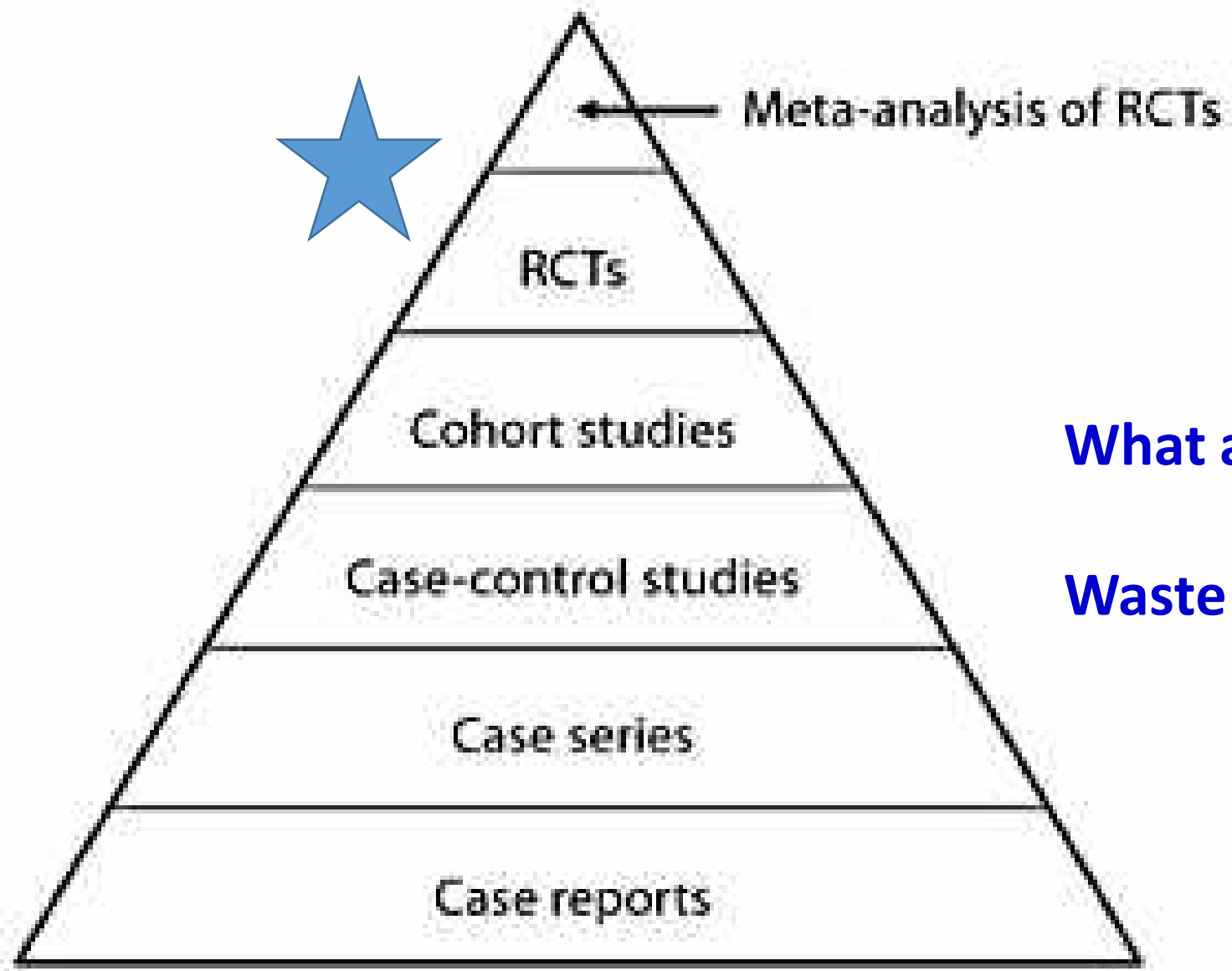
## Definition

- All Non-RCTs are observational studies

## Main types

- Cohort studies
- Case-control studies
- Cross-sectional studies
- Clinical audits
- Systematic reviews of observational studies

# RCTs are the gold standard

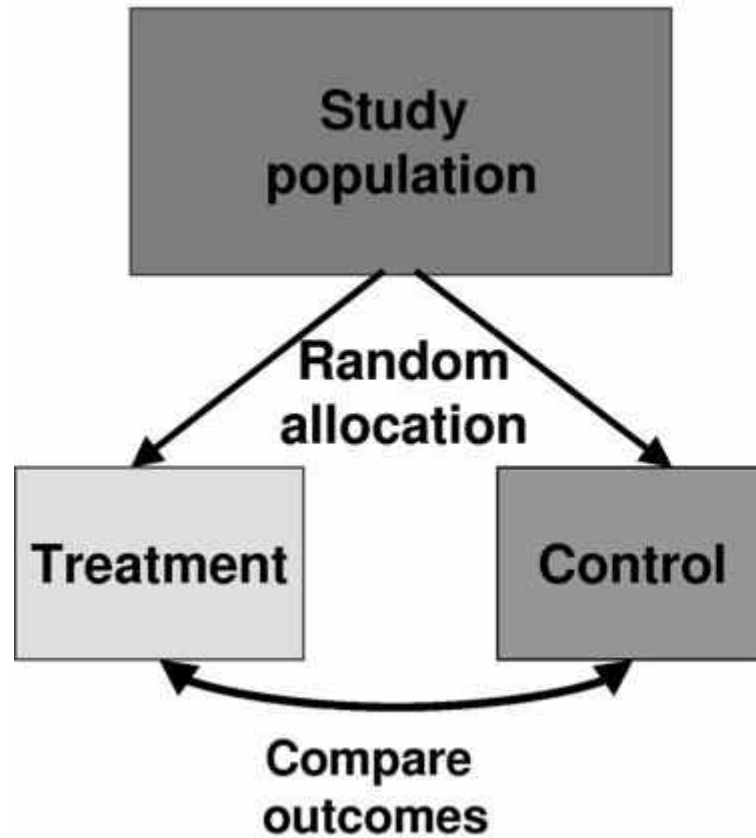


**What about the rest?**

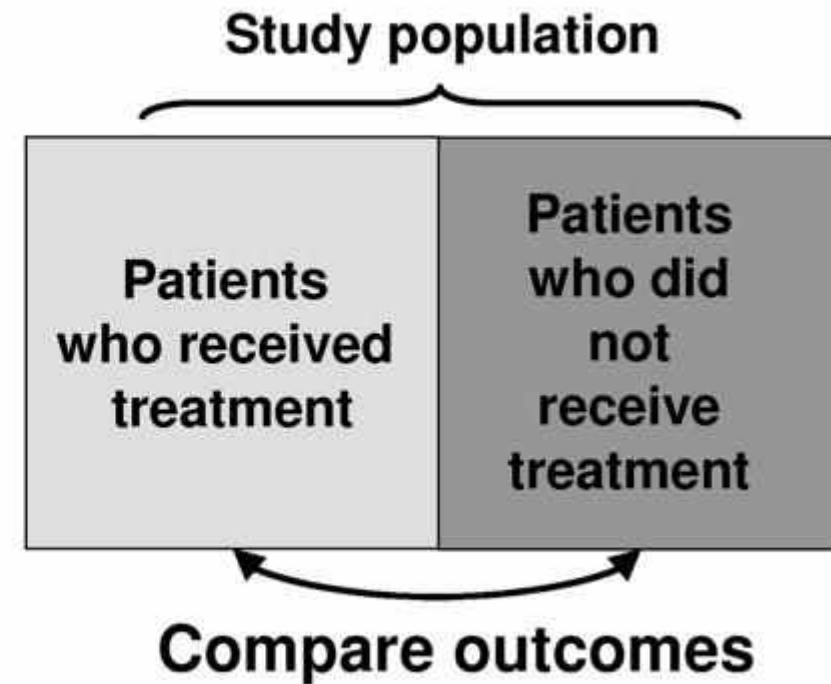
**Waste of time??**

## Basic RCT design

*Controlled experiment*



## Basic observational study design



# **Observational studies that have improved our health**

Case control study

# BRITISH MEDICAL JOURNAL

LONDON SATURDAY SEPTEMBER 30 1950

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## 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*

**"heavy smokers are  
50 times as likely as  
non-smokers to get  
lung cancer"**

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 1,287, or roughly fifteenfold. This remarkable increase is,

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



## Risk Assessment Tool for Estimating Your 10-year Risk of Having a Heart Attack

Age:

years

Gender:

Female  Male

Total Cholesterol:

mg/dL

HDL Cholesterol:

mg/dL

Smoker:

No  Yes

Systolic Blood Pressure:

mm/Hg

Are you currently on any medication to treat high blood pressure.

No  Yes

**Risk Score\***

Less than 1%

Means less than 1 of 100



# Framingham heart study

## Massachusetts, USA

- 1948: Project to identify risk factors for heart disease
- Established after the death of President Roosevelt, from cerebral haemorrhage with a BP of 300/190 mmHg
- **Observational study: Prospective Cohort**
- *Mahmood et al. The Framingham Heart study, Historical perspective, Lancet, 2014*

- 5,200 Healthy Men and Women between 30-62 Years
- Their children and grand children: currently 3<sup>rd</sup> generation
- Current sample size: approximately 15000
- *Mahmood et al. The Framingham Heart study, Historical perspective, Lancet, 2014*

## Because of Framingham study

- We know that High BP increases the risk of heart disease
- Cigarette smoking increases the risk of heart disease
- LDL cholesterol increases the risk
- HDL Cholesterol decreases the risk

- Want a more recent example?

# International Agency for Research on Cancer

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**PRESS RELEASE  
N° 240**

**26 October 2015**

**IARC Monographs evaluate consumption of red meat and processed meat**

# A Working Group of 22 experts from 10 countries convened by IARC

- Based on a review of >800 research papers
  - Processed meat: carcinogenic to humans (Group 1)
    - Colorectal cancer
  - Red meat as probably carcinogenic to humans (Group 2A)
    - Colorectal cancer
    - Pancreatic cancer
    - Prostate cancer
  - *“The most influential evidence came from **large prospective cohort studies**”.*

# International Agency for Research on Cancer

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PRESS RELEASE  
N° 240

26 October 2015

IARC Monographs evaluate consumption of red meat and processed meat

**Association: Yes**

**Cause and effect: Not sure**

**Awareness: Yes**

**Controversy: Some people have labelled it **Bacon-gate!!!****

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News

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## Carcinogenicity of consumption of red and processed meat





## Safe to Sleep<sup>®</sup>

### Public Education Campaign

Led by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development in collaboration with other organizations



Home   About SIDS/Safe Infant Sleep   **Campaign Materials**   Explore the C

Home [Printer-F](#)

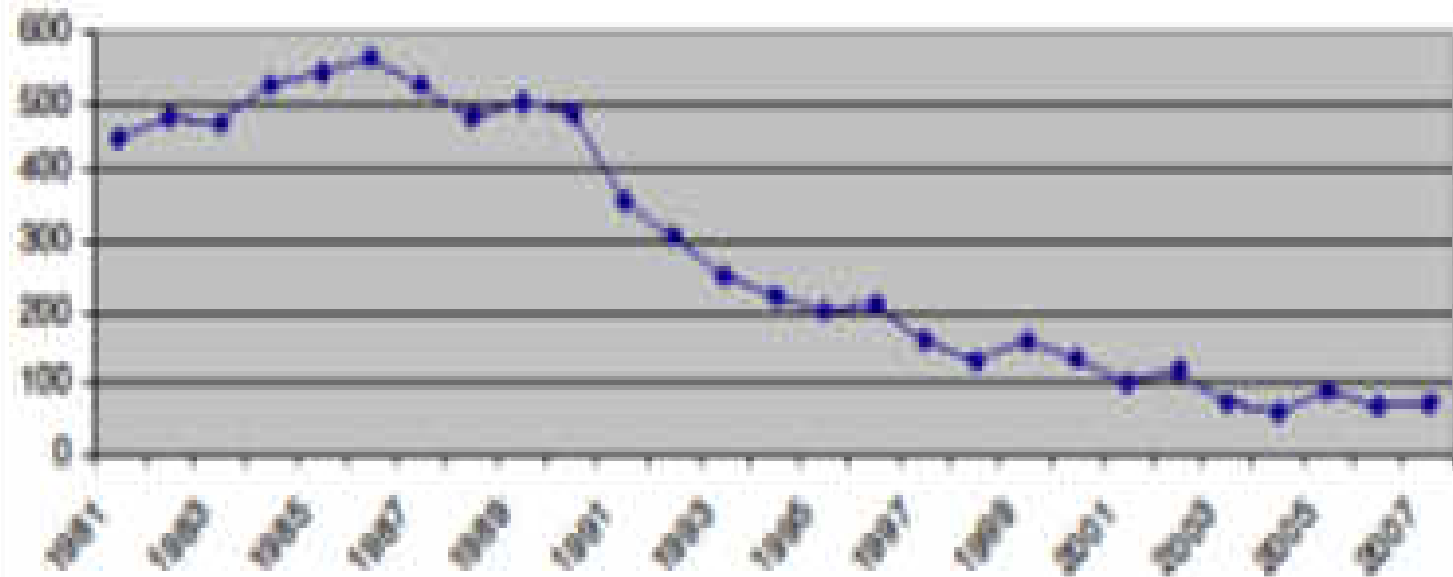
# Safe to Sleep<sup>®</sup> turns 20

## Prone position increases the risk of SIDS

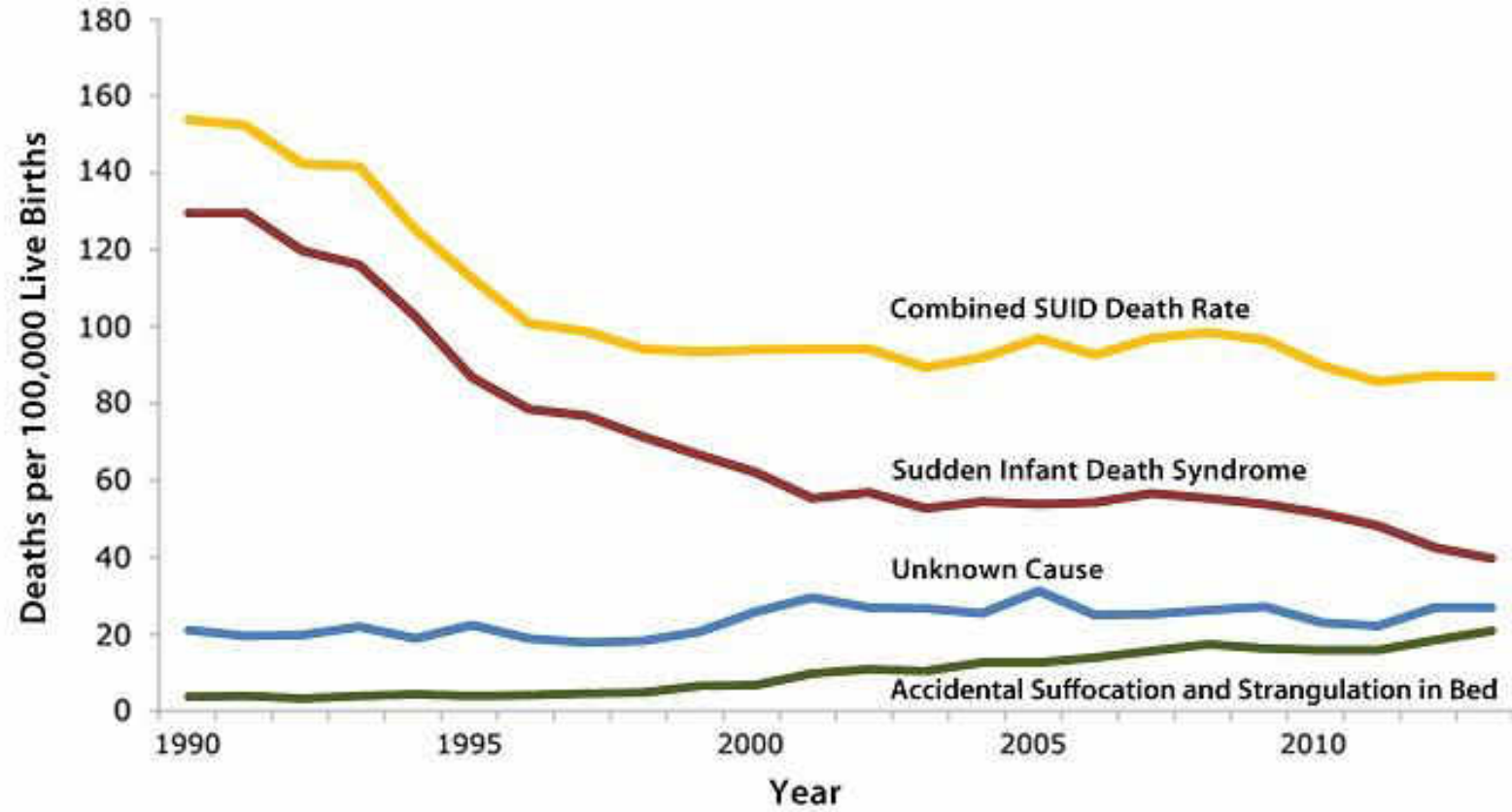
- Fleming PJ. *interaction between bedding and sleeping position in SIDS: a population based **case-control study***. Br Med J. 1990. **Bristol, UK**
- Mitchell EA. *Results from the first year of the **New Zealand cot death study***. N Z Med J. 1991. **Case-Control study**
- Dwyer T . *Prospective **cohort study** of prone sleeping position and SIDS*. Lancet. 1991 **Tasmania, Australia**
- Dwyer T et al. *Prone sleeping position and SIDS: evidence from **case-control and cohort studies** in Tasmania*. JPCH, 1991

### Australia. AIDS 1981-2007

Over the last ten years an average of 100 deaths per annum  
Source: Australian Bureau of Statistics



# SIDS in USA



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# THE LANCET

Volume 271, Issue 7030, 24 May 1958, Pages 1094–1097

Originally published as Volume 1, Issue 7030

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ORIGINAL ARTICLES

## INFLUENCE OF LIGHT ON THE HYPERBILIRUBINÆMIA OF INFANTS

[R.J. Cremer](#), M.B. Lond., D.C.H. (PÆDIATRIC REGISTRAR), [P.W. Perryman](#), M.Sc. Lond. (BIOCHEMIST), [D.H. Richards](#), F.I.M.L.T. (CHIEF TECHNICIAN, BIOCHEMISTRY DEPARTMENT)

GENERAL HOSPITAL, ROCHFORD, ESSEX, United Kingdom

- The sister of the unit had **observed**
  - Fading away of yellow pigmentation in the skin of jaundiced babies
    - When they had been a short time in the sun
- Their team conducted an **observational study**
- Exposed jaundiced babies and measured serial bilirubin

Case number	Bilirubin before sunlight treatment (mg/dl)	Duration of exposure Hours	Bilirubin after sunlight therapy
1	25	2	21
2	24	3	18
3	16	2	12
4	21	2	14
5	20	2	14
...			
13	19	4	15

Jaundice quickly disappeared from the exposed areas of skin but persisted in areas which remained in the shade.

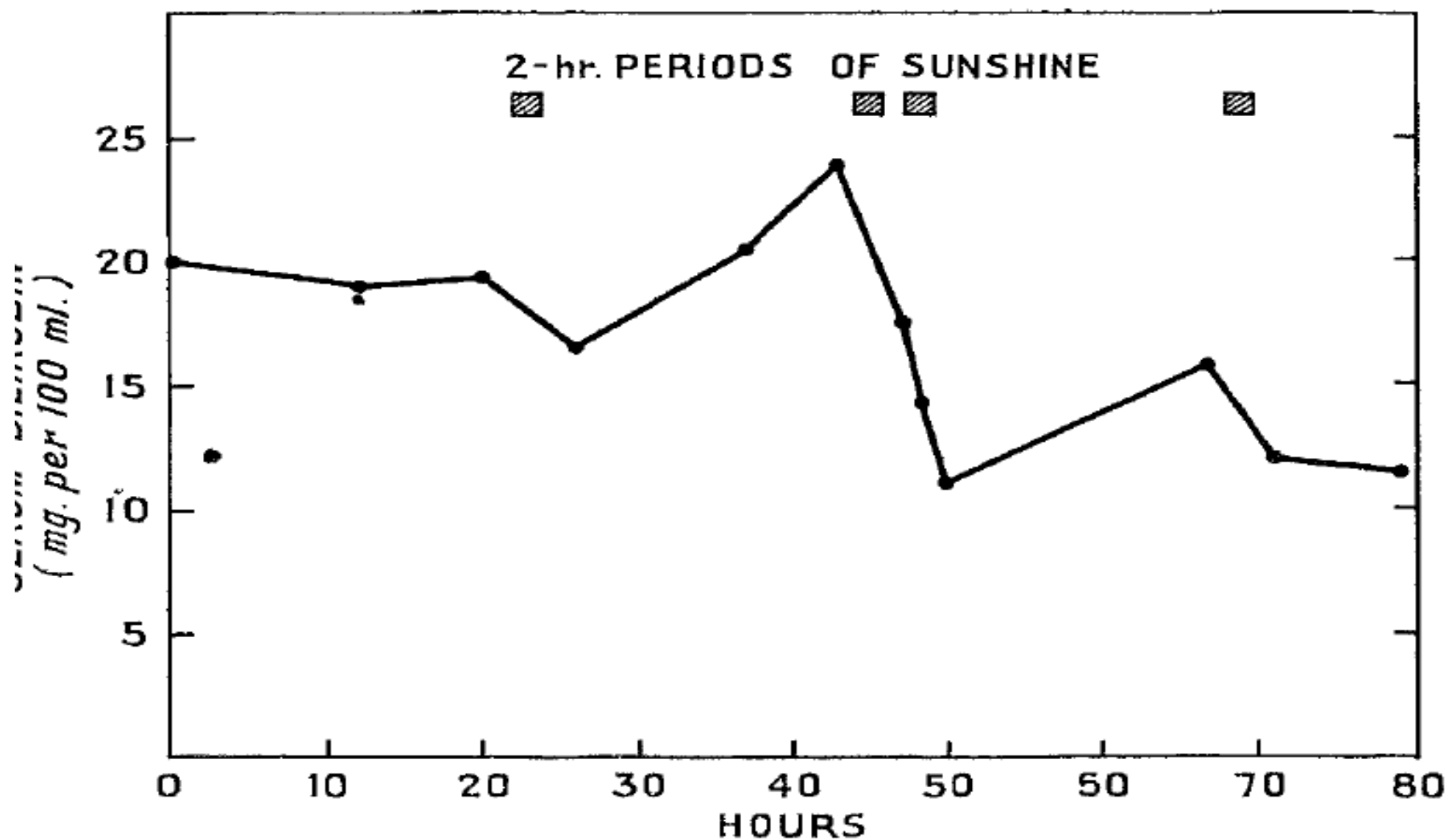
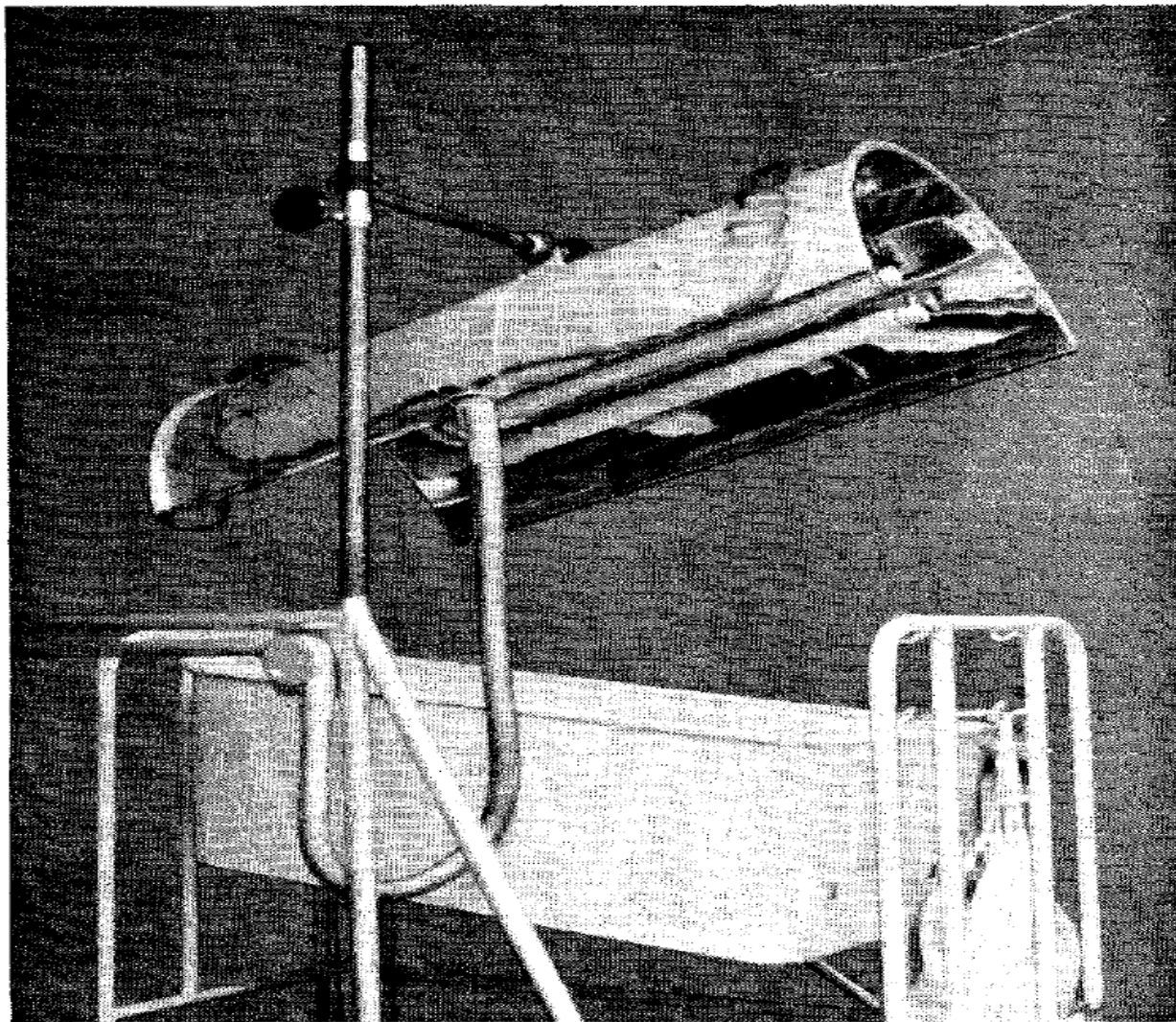


Fig. 5—Sunshine treatment of an icteric infant with jaundice of prematurity (case 6).





**Fig. 6—Artificial-light apparatus for cradle illumination of infants.**

35 years after introduction of phototherapy, there were two RCTs

- *Bryla DA, **RCT** of phototherapy for neonatal hyperbilirubinemia. Pediatrics 1985*
- *Martinez et al. Hyperbilirubinemia in the breast-fed newborn: a **controlled trial**. Pediatrics, 1993*

# The first RCT of sunlight for jaundice



*Slusher et al, Pediatrics, 2014*

**Safe and efficacious**



Hospital setting

*Slusher et al, Pediatrics, 2014*

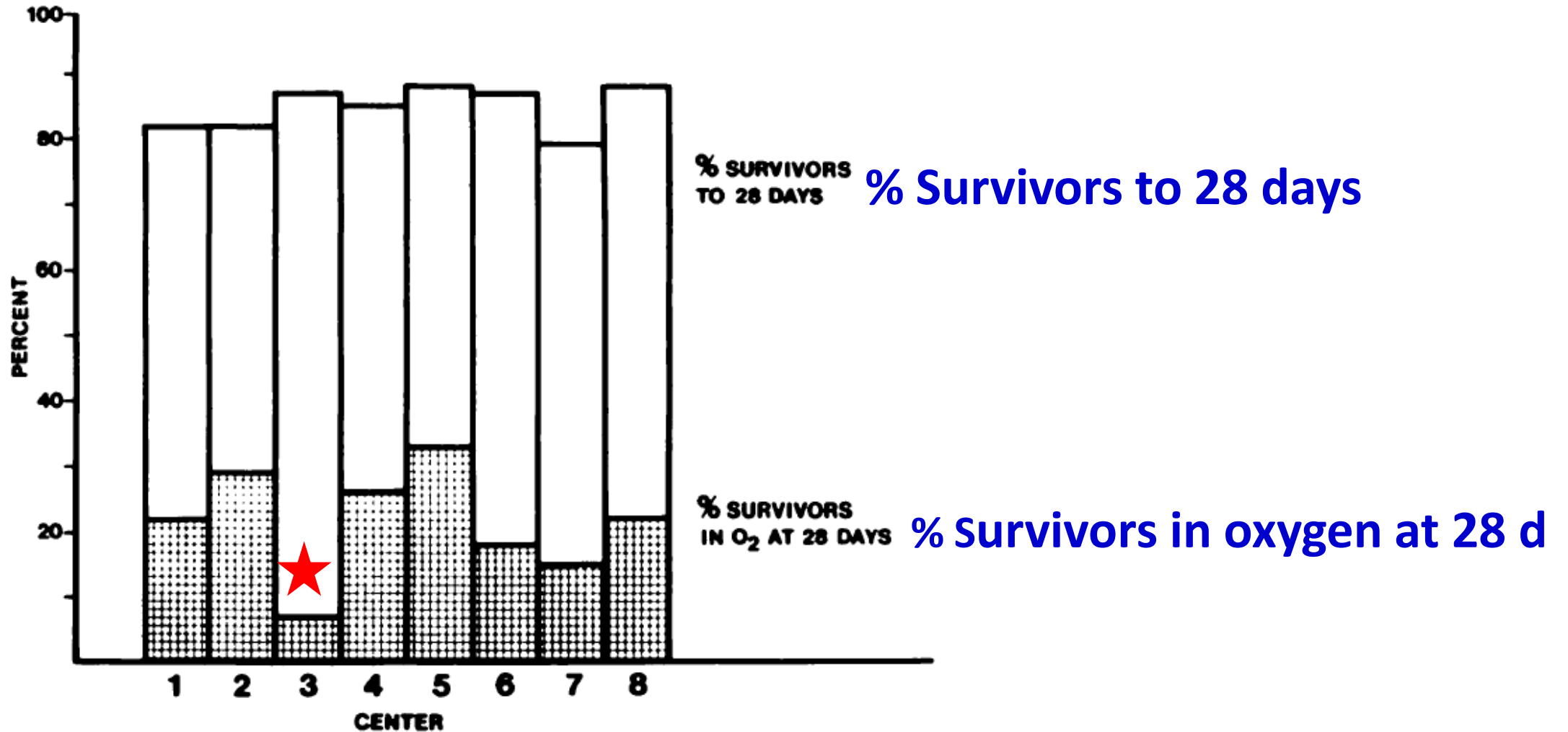
# **Is Chronic Lung Disease in Low Birth Weight Infants Preventable? A Survey of Eight Centers**

PEDIATRICS®

1987

**Mary Ellen Avery, MD, William H. Tooley, MD, Jacob B. Keller, MPH, Suzanne S. Hurd, PhD, M. Heather Bryan, MD, Robert B. Cotton, MD, Michael F. Epstein, MD, Pamela M. Fitzhardinge, MD, Cheryl B. Hansen, RN, Thomas N. Hansen, MD, W. Alan Hodson, MD, L. Stanley James, MD, Joseph A. Kitterman, MD, Heber C. Nielsen, MD, Theresa A. Poirier, RN, William E. Truog, MD, and Jen-Tien Wung, MD**

*From Brigham and Women's Hospital, Boston; University of California, San Francisco; National Heart, Lung, and Blood Institute, Bethesda; Mt Sinai Hospital, Toronto; Vanderbilt University, Nashville, TN; Baylor University, Houston; University of Washington, Seattle; Columbia Presbyterian Medical Center, New York; and Southwestern Medical School, Dallas*



**Figure.** Shaded areas are percentages of infants in oxygen at 28 days of age; open areas are survivors without added oxygen at 28 days. Note that center 3 has lowest percentage of infants who were dependent on oxygen and among the highest percentage of survivors.

**Centre 3, Columbia had the lowest incidence of CLD  
And highest use of CPAP**

ORIGINAL ARTICLE

2008

## Nasal CPAP or Intubation at Birth for Very Preterm Infants

Colin J. Morley, M.D., Peter G. Davis, M.D., Lex W. Doyle, M.D.,  
Luc P. Brion, M.D., Jean-Michel Hascoet, M.D., and John B. Carlin, Ph.D.,  
for the COIN Trial Investigators\*

The NEW ENGLAND JOURNAL of MEDICINE

2010

ORIGINAL ARTICLE

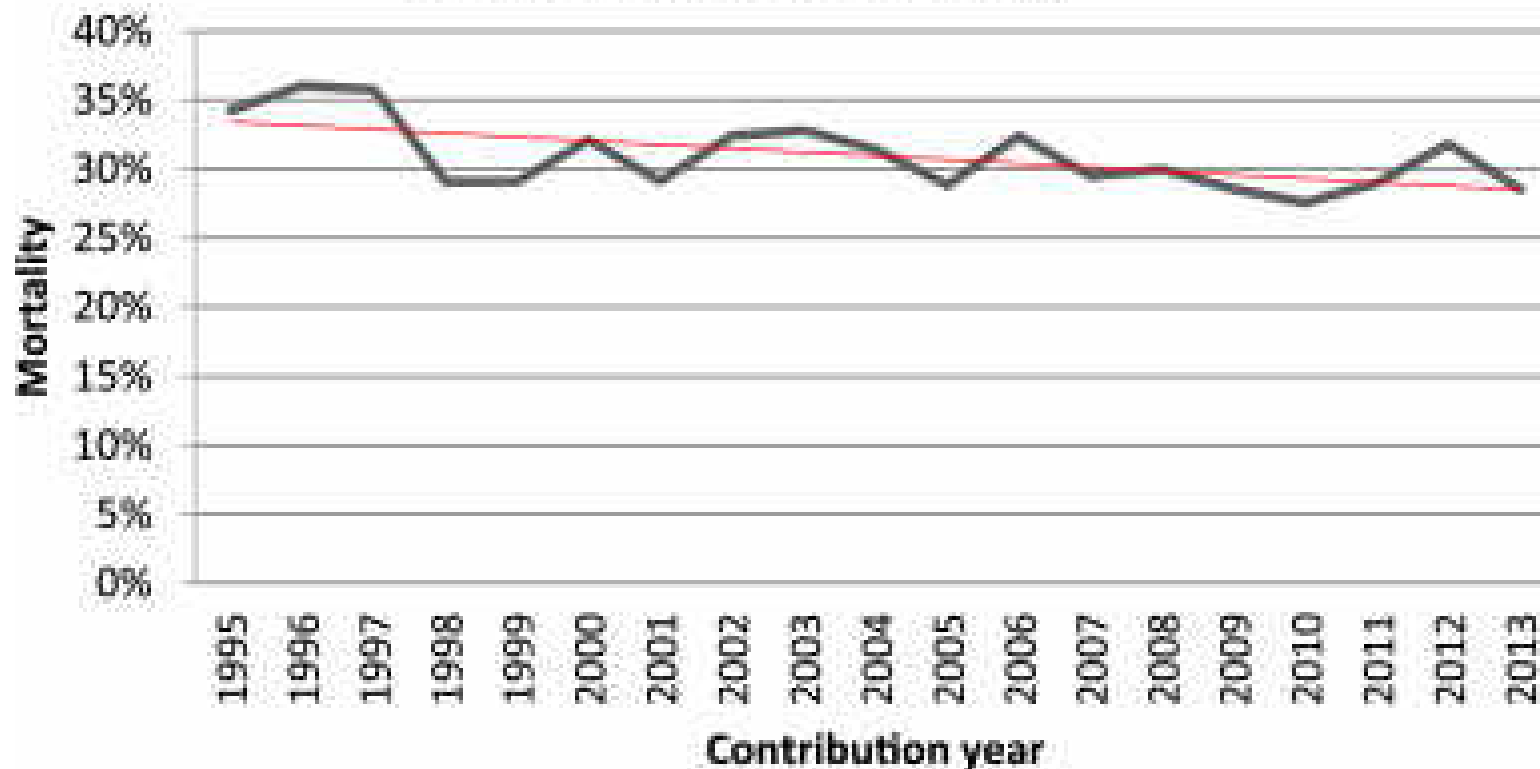
## Early CPAP versus Surfactant in Extremely Preterm Infants

SUPPORT Study Group of the Eunice Kennedy Shriver NICHD  
Neonatal Research Network\*

**Majority of the NICUs use CPAP  
even in tiny babies now**

# Congenital diaphragmatic hernia registry, 66 centres from all over the world

## CDHSG Overall Mortality



8279 patients in the  
database



## Because of the CDH registry, we know that

Caesarean section	Probably unnecessary
ECMO	Probably useful
Surfactant	Probably not necessary
Prematurity	High mortality
Overall mortality	30%

Note the word “**Probably**” because the results are from observational data

# Observational studies

- Can enable change in practice
- Can generate hypothesis for RCTs
- Provide benchmarking
- Can create controversy!!

- **Do the results of observational studies correlate with RCTs?**

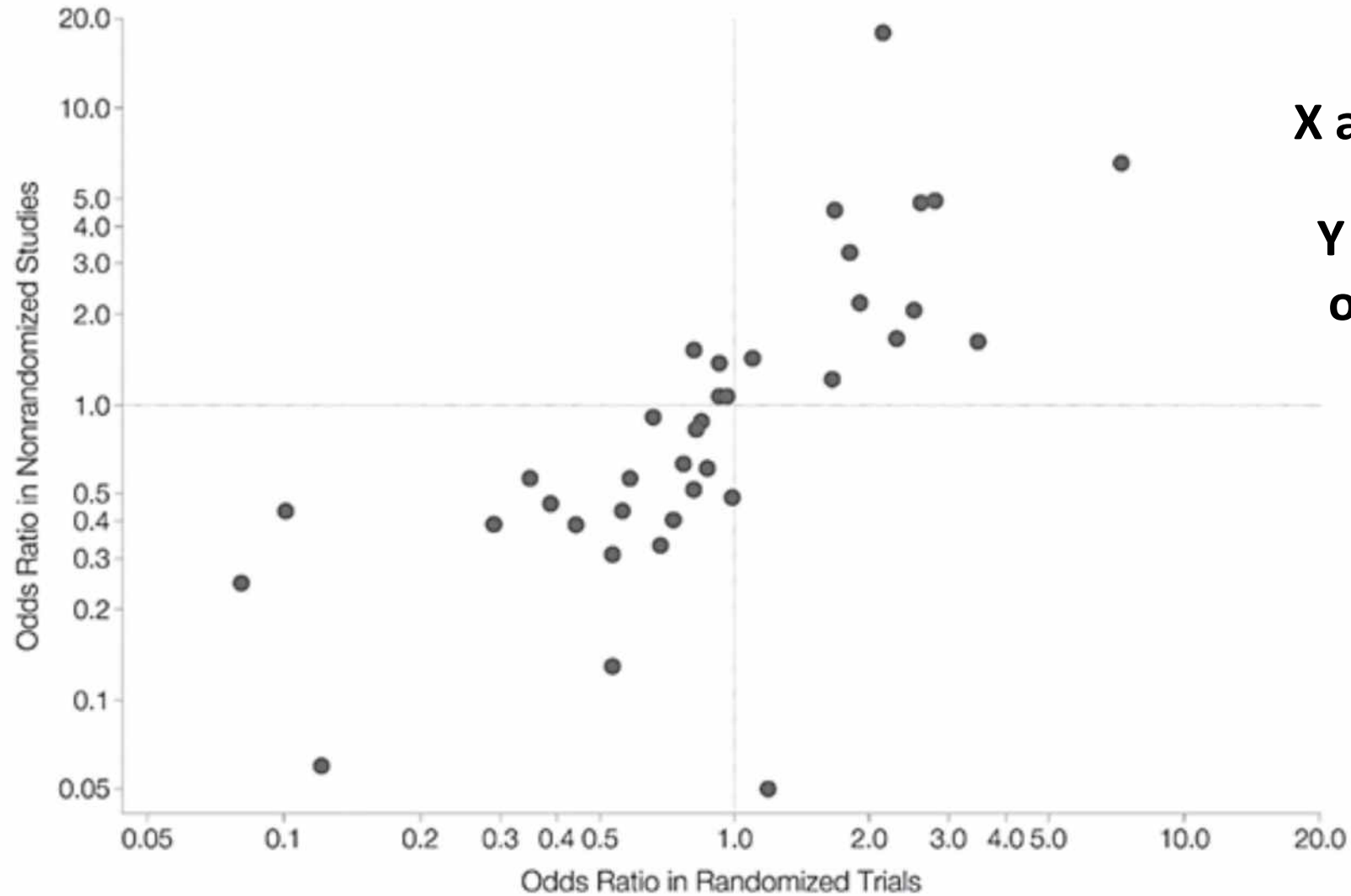
# Concordance between Observational studies and RCTs

- Forty-five diverse topics were identified
  - For which both RCTs (n = 240) and non-RCTs (n = 168) had been performed
- Very good correlation between the odds ratios of RCTs and non-RCTs
- $r = 0.75; P < .001$

• *Ioannidis, JAMA, 2001*

***Stanford University***

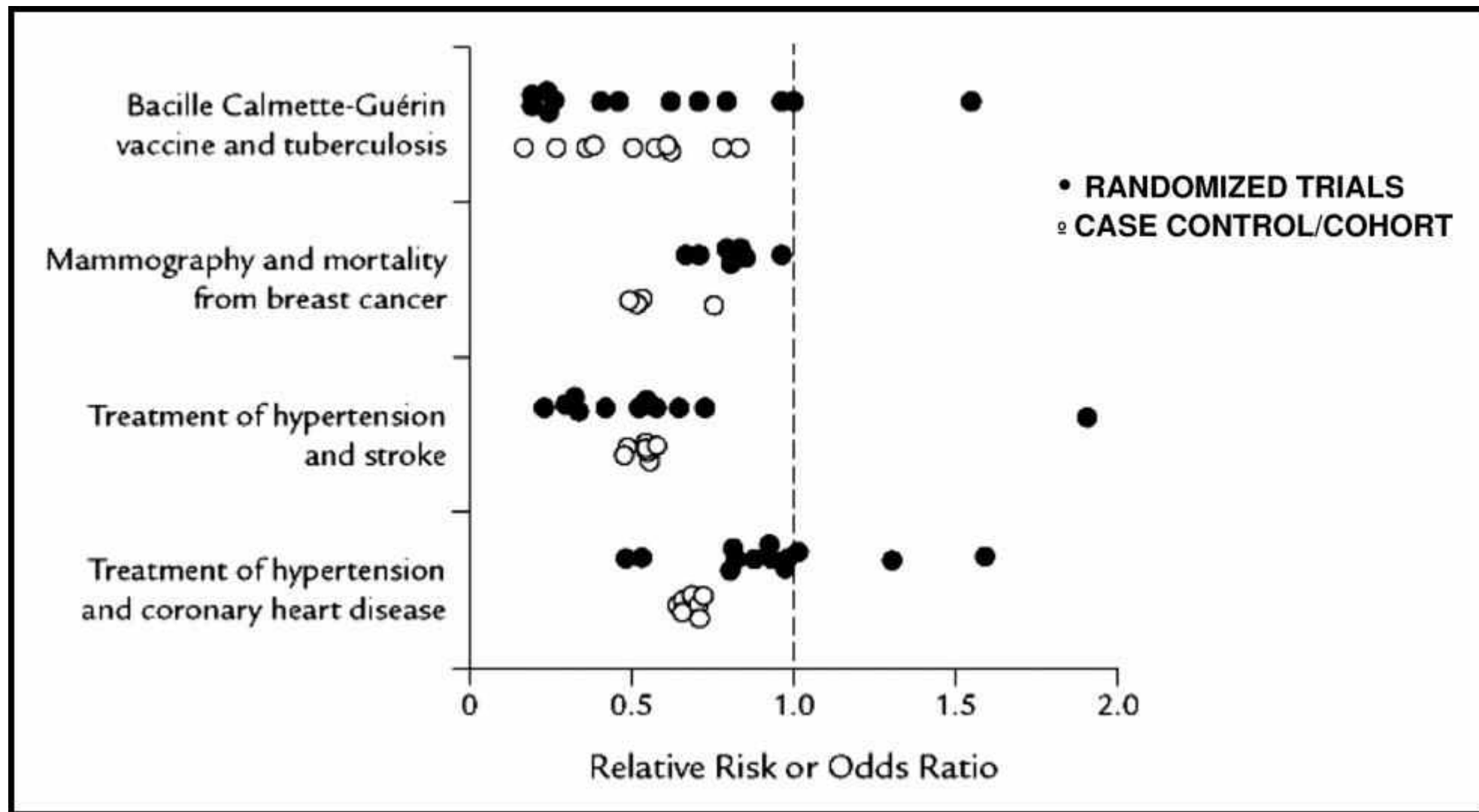
- *Ioannidis, JAMA, 2001*



**X axis: Odds ratios in RCTs**

**Y Axis: Odds ratios in observational studies**

# Concordance between Observational studies and RCTs



- Before we get too excited about observational studies

# Vitamin D and risk of future hypertension: meta-analysis of 283,537 participants

## Meta analysis of observational studies

For each 10 ng/mL increment in baseline Vitamin D levels, the risk of hypertension decreased by 12%

*Kunutsor et al, Eur J Epidemiology, 2013*

**What did the RCTs find?**



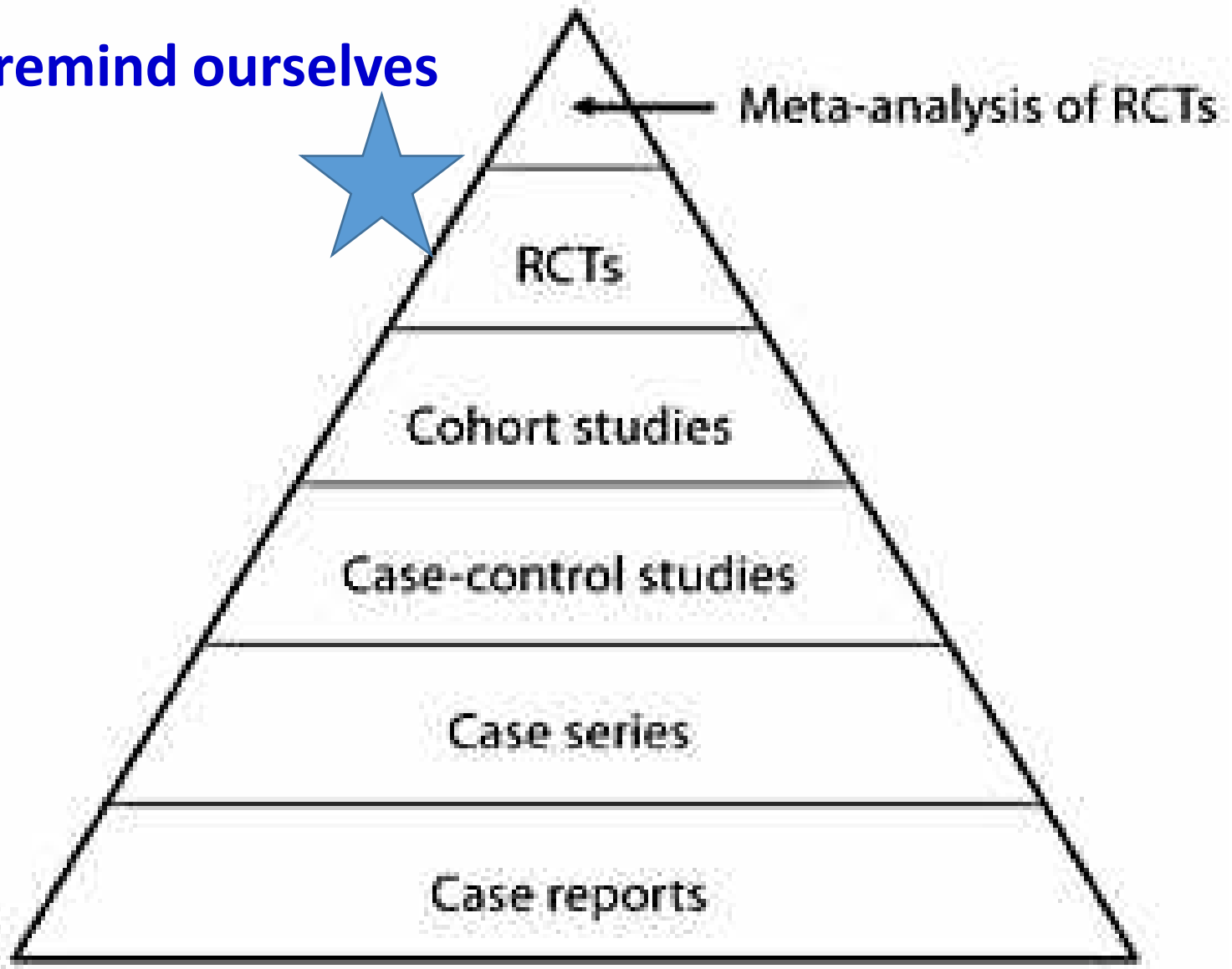
## Meta analysis of RCTs

- 46 RCTs
- 4500 participants
- **No benefit of vitamin D supplementation**
  
- SBP: Mean difference: 0 (95% CI: -0.8, 0.8) mm Hg
- DBP: Mean difference: -0.1 [95% CI, -0.6 to 0.5] mm Hg

*Beveridge, JAMA Intern Med. 2015 May*

# RCTs are the gold standard

Just to remind ourselves



It is also important to know that

- ***“A well designed observational study is preferable to a poorly designed RCT”***

- *Britton A, Health Technology assessment, 1998*

- **Observational studies are used quite extensively in surgical field**
- **Reason: Surgical RCTs are challenging/difficult**

BMJ. 2002 Jun 15;324(7351):1448-51.

## **Randomised trials in surgery: problems and possible solutions.**

McCulloch P<sup>1</sup>, Taylor I, Sasako M, Lovett B, Griffin D.

Surgery. 2009 Jun;145(6):598-602. doi: 10.1016/j.surg.2009.03.008. Epub 2009 Apr 28.

## **Challenges in performing surgical randomized controlled trials in Japan.**

Sasako M<sup>1</sup>, Kurokawa Y.

Orthop Clin North Am. 2010 Apr;41(2):145-55. doi: 10.1016/j.ocl.2009.11.001.

## **Challenges of randomized controlled surgical trials.**

Campbell AJ<sup>1</sup>, Bagley A, Van Heest A, James MA.

J Minim Invasive Gynecol. 2015 May-Jun;22(4):573-82. doi: 10.1016/j.jmig.2015.02.012. Epub 2015 Feb 23.

## **Studying surgical innovations: challenges of the randomized controlled trial.**

Unger CA<sup>1</sup>, Barber MD<sup>2</sup>.

# If surgical RCTs are challenging and rare

- Options
  - Strive Hard to promote RCTs
  - At the same time, conduct good quality observational studies
  - I will give some of our observational studies that have improved outcomes for our babies



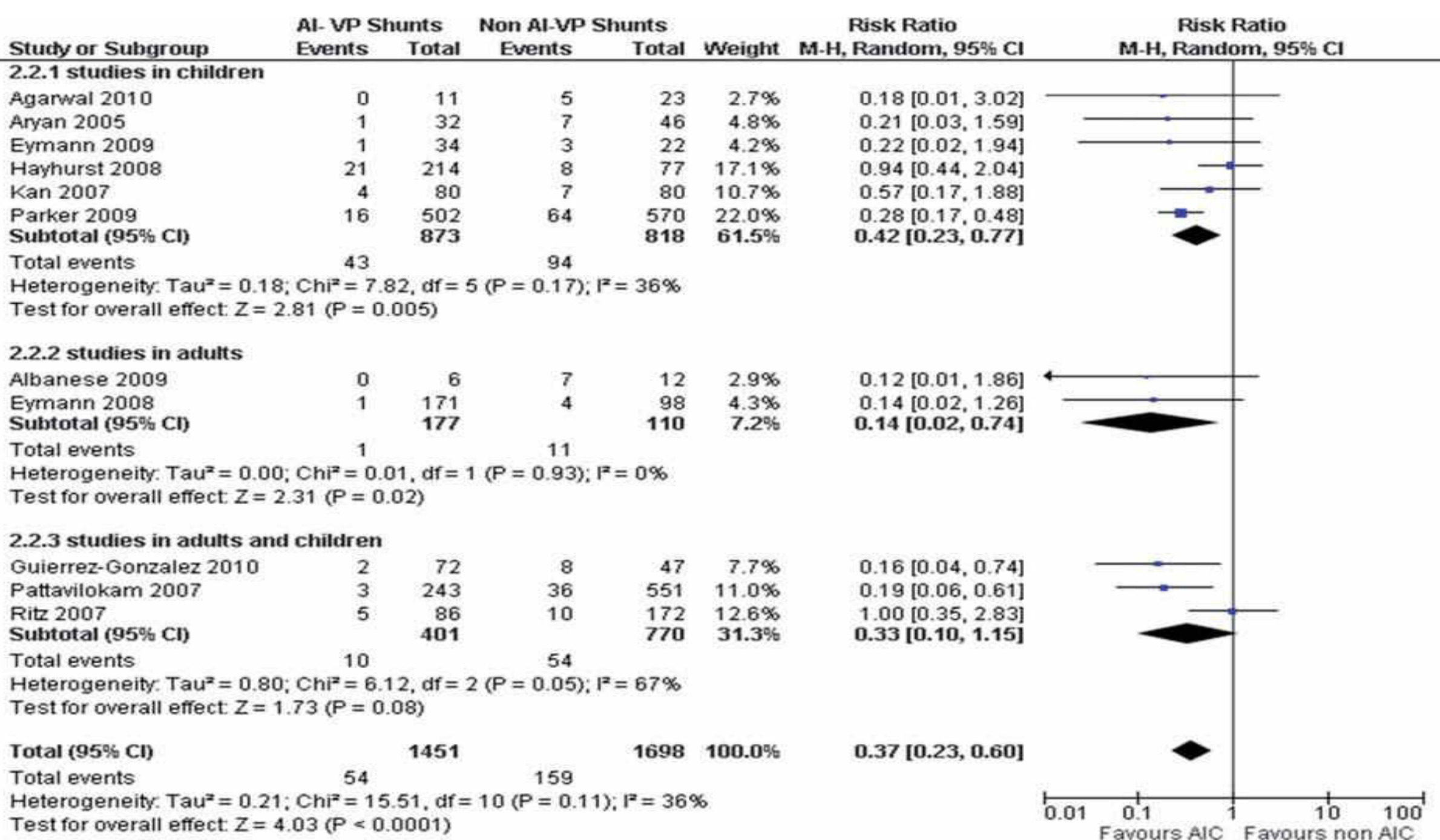
## We had very high incidence of VP shunt infections

Year	2002-2006
CSF Shunt infections	6/23 (26%)

**We were desperate**

# Antibiotic impregnated VP shunts: Meta analysis of observational studies

- 12 studies (paediatric, adult and neonate)
- Only one was RCT
- *Thomas, Lee , Patole & Rao, British Journal of Neurosurgery, 2011*



## Antibiotic impregnated catheters have reduced the incidence of CSF shunt infections in our unit


Year	2002-2006	2007-2015	P value
CSF Shunt infections	6/23 (26%)	1/26 (4%)	We don't mind!!

## Ward reduction of gastroschisis: retrospective study



## Ward reduction of gastroschisis: retrospective study

	Ward reduction N=11	Silo or reduction under GA N=27	Odds Ratio	P Values
Iatrogenic Necrosis of bowel	27%	4%	10.7	0.08
TPN>60 D	18%	4%	4.1	0.33
Unplanned return to theatre	27%	7%	3.9	0.22

- We stopped doing ward reductions
- We use silo reduction 
- Since the past five years (n=50),
  - No case of iatrogenic gut necrosis
  - No case of unplanned return to theatre



# Surgical management of perforated NEC

- We had noticed that
  - Preterm infants undergoing primary peritoneal drainage for NEC Perforation had high morbidity
- Hence, we did an observational study
- (Retrospective cohort)





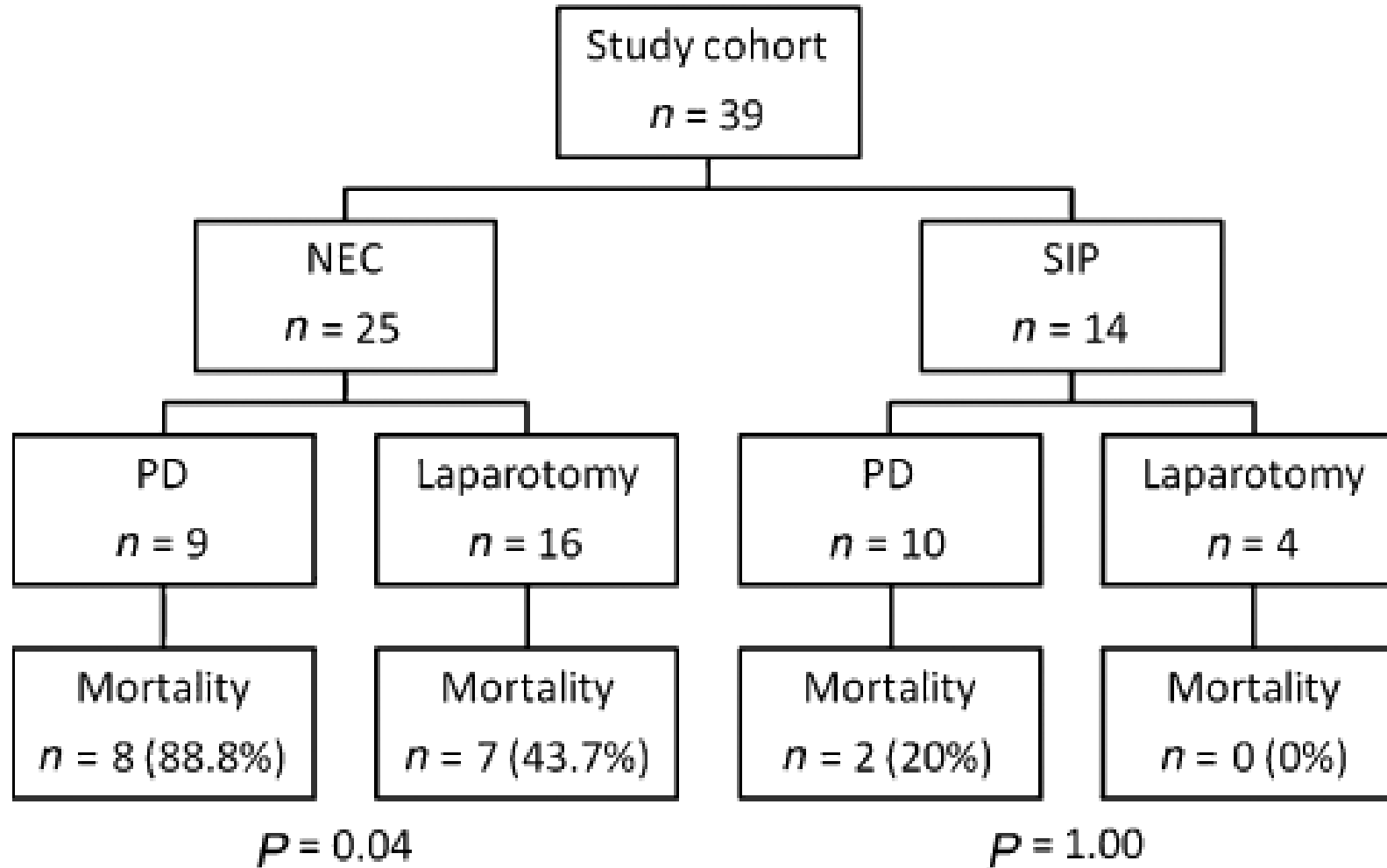
ORIGINAL ARTICLE

**Peritoneal drainage versus laparotomy for perforated  
necrotising enterocolitis or spontaneous intestinal perforation:  
A retrospective cohort study**

Abhijeet Rakshasbhuvankar,<sup>1,2,4</sup> Shripada Rao,<sup>2,4</sup> Corrado Minutillo,<sup>2</sup> Ian Gollow<sup>3</sup> and Satish Kolar<sup>3</sup>

	Primary peritoneal drainage N=19	Primary laparotomy N=20
Median gestational age (w)	24.7	25.2

# Results



# **Peritoneal drainage versus laparotomy as initial surgical treatment for perforated necrotizing enterocolitis or spontaneous intestinal perforation in preterm low birth weight infants (Review)**

**Rao SC, Basani L, Simmer K, Samnakay N, Deshpande G**

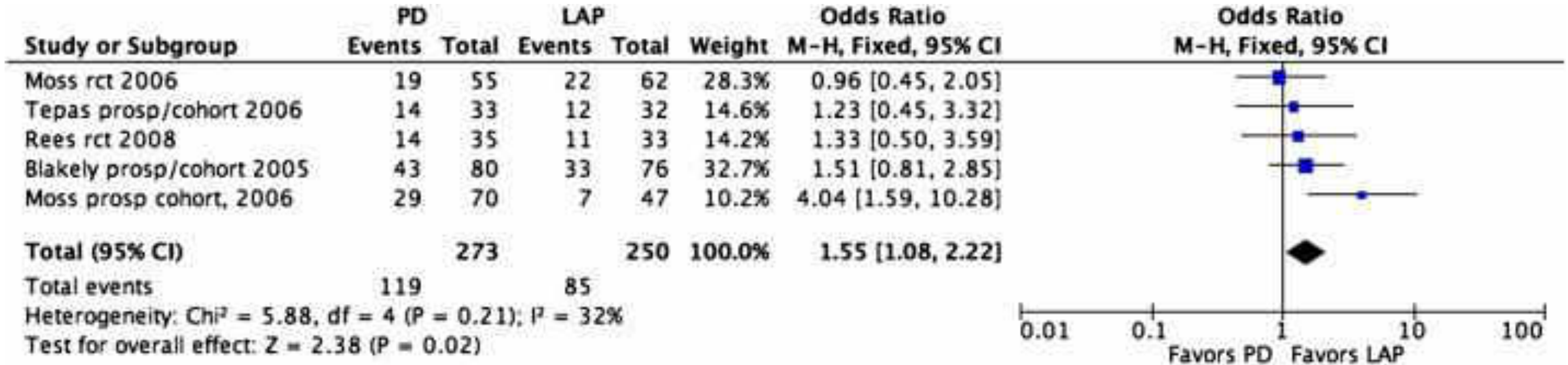


**Insufficient sample size;  
2 RCTS, 195 babies;  
No firm recommendations;  
RCTs are needed**

**THE COCHRANE  
COLLABORATION®**

***Rao, Basani, Simmer, Samnakay, Deshpande, 2012***

# Meta analysis of RCTs and observational studies



Peritoneal drainage was associated with increased odds of mortality

*Sola et al, J Surg Res. 2010*

- We rarely do primary peritoneal drainage as a definitive treatment
- Our outcomes have been better (an audit is underway)

## Current situation

- Nine of ten publications describe observational research

*Von Elm, BMJ, 2007*

- RCTs constitute less than 5% of all biomedical articles

*John Ioannidis, Lancet 2014*

- 9 of 10 research papers published are observational

*Stefania Boccia, Eur J Public Health. 2015*

## What it means?

- Whether we like it or not, observational studies are here to stay
- It is better to improve the quality of conduct and reporting



# Use STROBE guidelines for reporting observational studies

- The **St**rengthening the **R**eporting of **Ob**servational Studies in **E**pidemiology (STROBE) statement

*Epidemiology. 2007*

# Use MOOSE guidelines for reporting Meta analyses of observational studies

- **Meta-analysis Of Observational Studies in Epidemiology (MOOSE)**

*JAMA. 2000 Apr 19*

## Essential resources for writing and publishing health research



### Library for health research reporting

The Library contains a comprehensive searchable database of reporting guidelines and also links to other resources relevant to research reporting.



### Reporting guidelines for main study types

<a href="#">Randomised trials</a>	<a href="#">CONSORT</a>	<a href="#">Extensions</a>	<a href="#">Other</a>
<a href="#">Observational studies</a>	<a href="#">STROBE</a>	<a href="#">Extensions</a>	<a href="#">Other</a>
<a href="#">Systematic reviews</a>	<a href="#">PRISMA</a>	<a href="#">Extensions</a>	<a href="#">Other</a>
<a href="#">Case reports</a>	<a href="#">CARE</a>		<a href="#">Other</a>
<a href="#">Qualitative research</a>	<a href="#">SRQR</a>	<a href="#">COREQ</a>	<a href="#">Other</a>
<a href="#">Diagnostic / prognostic studies</a>	<a href="#">STARD</a>	<a href="#">TRIPOD</a>	<a href="#">Other</a>
<a href="#">Quality improvement studies</a>	<a href="#">SQUIRE</a>		<a href="#">Other</a>
<a href="#">Economic evaluations</a>	<a href="#">CHEERS</a>		<a href="#">Other</a>
<a href="#">Animal pre-clinical studies</a>	<a href="#">ARRIVE</a>		<a href="#">Other</a>
<a href="#">Study protocols</a>	<a href="#">SPIRIT</a>	<a href="#">PRISMA-P</a>	<a href="#">Other</a>



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# Conclusions

- Do not despair if you cannot do an RCT
  - Well designed observational studies can improve outcomes
  - Need to be conducted with the same rigour as RCTs
  - Know the strengths and limitations of observational studies
  - Should be considered as complimentary, not rival to RCTs
- *Ligthelm, R, Clinical therapeutics, 2007*

Thank you