Introduction to Cochrane systematic reviews and relevance to guidelines

Karsten Juhl Jørgensen

Deputy Director, MD, DrMedSci

Nordic Cochrane Centre

Purposes

- *Evidence based treatment*:

Treatments should be based on the best available evidence.

- *Overview of the literature*.

What do we know? What don't we know? Systematic literature search.

- *Independent assessment.*

Use of standardised, empirically founded criteria for risk of bias and confidence.

Why are independent, standardised assessments important?

Euro NCAP 20 years of crash testing - Honda Jazz vs Rover 100 Comparison.mp4

Do we have similar independent tests of medical interventions?

News

New Director General of the Danish Medicines Agency

11 January 2016

Contact

Head of Press

Danish Ministry of Health

Thomas Bille Winkel

”I am very satisfied that we have appointed Thomas Senderovitz as Director General of the Danish Medicines Agency. He has strong professional skills, and with his drive and extensive experience he will create a new medicines agency that will be able to support the Danish pharmaceutical and medical device industries in the best possible way, while at the same time monitoring companies closely,” says Minister for Health Sophie Løhde.

His career includes more than 15 years working intensively with medicinal products and he has held several senior positions in international biopharmaceutical companies (Ferring Pharmaceuticals, UCB Pharma, Grünenthal GmbH). Most recently, Thomas Senderovitz was a member of the management team of the global CRO (Contract Research Organisation) PAREXEL engaging in clinical research for pharmaceutical and biotechnological companies.

Economic importance

- Export from ”Lifescience” sector: **90 billion DKR (~15 billion USD).**
- Directly employed: **36.000 persons.**

Rasmussen LI. Politiken 8. februar 2017.

What about the EMA?

BMJ

BMJ 2011;342:d2686 doi: 10.1136/bmj.d2686

ANALYSIS

Opening up data at the European Medicines Agency

Widespread selective reporting of research results means we don't know the true benefits and harms of prescribed drugs. **Peter Gøtzsche** and **Anders Jørgensen** describe their efforts to get access to unpublished trial reports from the European Medicines Agency

Peter C Gøtzsche *professor*, Anders W Jørgensen *PhD student*

Nordic Cochrane Centre, Rigshospitalet and University of Copenhagen, Dept 3343, Blegdamsvej 9, DK-2100 Copenhagen Ø, Denmark

Cochrane Database of Systematic Reviews

Industry sponsorship and research outcome

New search | Review | Methodology

Andreas Lundh, Joel Lexchin, Barbara Mintzes, Jeppe B Schroll, Lisa Bero

First published: 16 February 2017

Editorial Group: Cochrane Methodology Review Group

DOI: 10.1002/14651858.MR000033.pub3 View/save citation

Cited by (CrossRef): 0 articles Check for updates

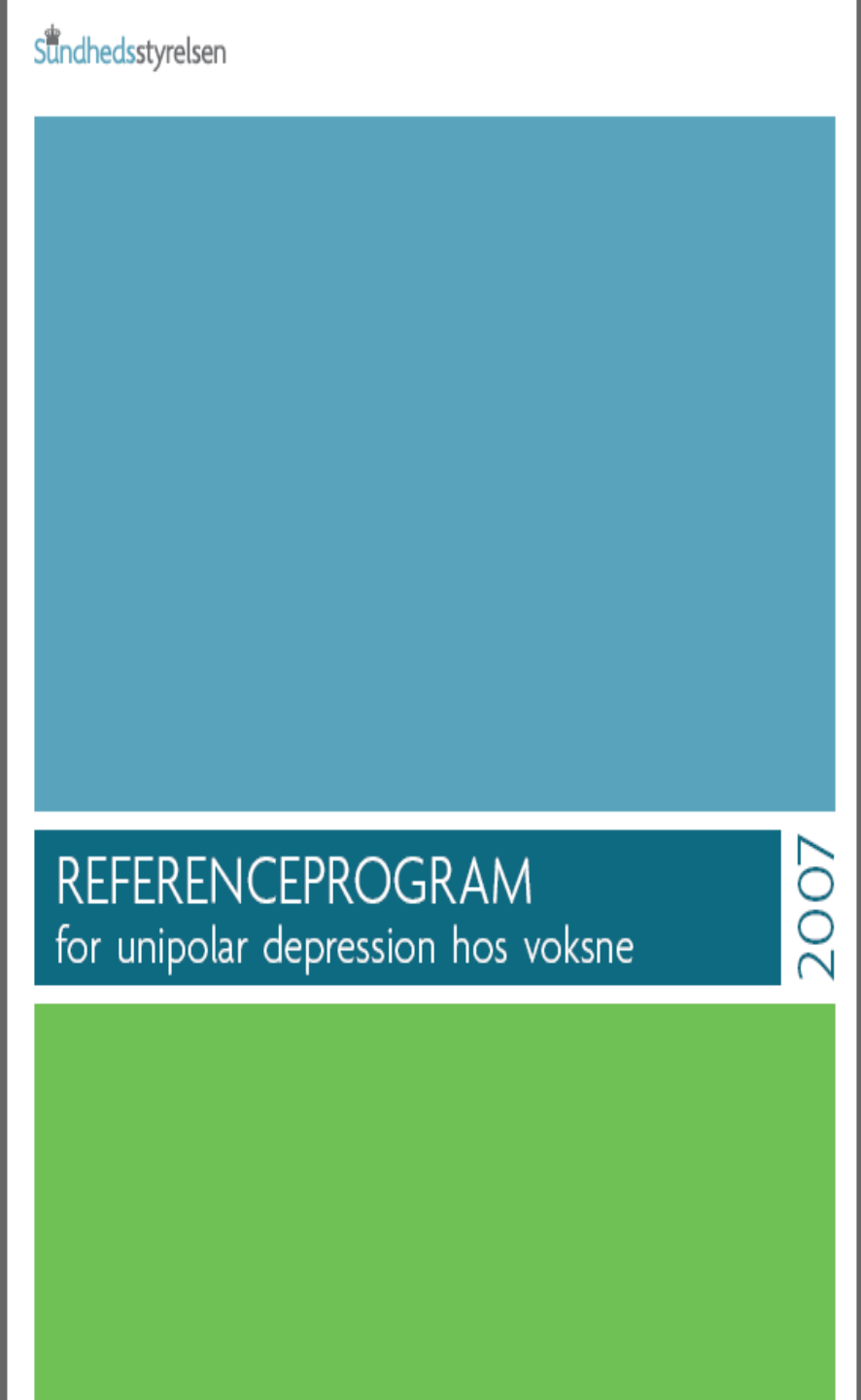
Am score 344

Abstract

National Clinical Guidelines

- 80 million Danish Crowns
- 3 years to develop 47 guidelines
- Systematic literature search
- Cochrane's Risk of Bias Tool
- GRADE

Reference programmes: An example.



”There is conflicting information in the literature regarding the effect of systematic screening for depression to ensure that more are treated. A recent Cochrane-review only showed minimal impact of systematic screening on diagnoses, use of treatment and treatment effects for depression. However, there is general agreement that screening for depression in high risk groups can improve outcomes, e.g. in patients with apoplexia or heart disease.”

Systematic screening was not recommended, but:

”High risk groups:

It is recommended to routinely track down depression in the forllowing groups (IIa):

Previous depression, Familiar disposition for depression, Heart disease, Apoplexia, Cronisc pain conditions, Diabetes, CroniC obstructive lungdisease (COPD), Cancer, Parkinsons disease, Epilepsy, Other psychiatric disease (due to comorbidity with depression). Routine screening for depression is also recommended for women who are pregnant or have just given birth, in refugees and for immigrants.”

What does the most reliable evidence tell us?

”There is substantial evidence that routinely administered case finding/screening questionnaires for depression have minimal impact on the detection, management or outcome of depression by clinicians. Practice guidelines and recommendations to adopt this strategy, in isolation, in order to improve the quality of healthcare should be resisted.”

Gilbody et al. Cochrane Database of Syst Rev: 2005 issue 3.

SUNDHEDSSTYRELSEN

NATIONAL KLINISK RETNINGSLINJE FOR NON-FARMAKOLOGISK BEHANDLING AF UNIPOLAR DEPRESSION

2016

ADHD påvirker ofte patienterne hele dagen[1-3]

DKSTR00468 – august 2015

Hvornår på dagen er dine patienter udfordrede?

- Svært ved at komme ud af sengen?
- Kommer ofte til at skælde sine børn ud på vej ud af døren?
- Distraheres nemt på jobbet?
- Svært ved at fastholde venskaber?
- Glemmer sine eftermiddagsaftaler?
- Svært ved at slappe af med sin partner efter arbejde?
- Vil gerne dyrke sport, men kan oftest ikke overskue det?
- Svært ved at falde i søvn om aftenen?

Referencer:
1. Davidson MA. J Atten Disord 2008; 11 : 628-641. 2. Brod Metal. Qual Life Res 2012; 21 : 795-799. 3. Barkley RA. J Clin Psychiatry 2002; 63 (Suppl 12): 10- 15. 4. Adler et al. Journal of Clinical Psychopharmacology, 2009; 29(1): 44–50. 5. Wehmeier et al. Child Adolesc. Mental Health, 2009; 3: 1-10. 6. Strattera produktresume 16.maj 2014

Se produktinformation på side 1764

Lilly

strattera® atomoxetin HCl

Sundhedsstyrelsen

NATIONAL KLINISK RETNINGSLINJE FOR UDREDNING OG BEHANDLING AF ADHD HOS VOKSNE

– MED FORSTYRRELSE AF AKTIVITET OG OPMÆRKSOMHED SAMT OPMÆRKSOMHEDSFORSTYRRELSE UDEN HYPERAKTIVITET

2015

7.5 Gennemgang af evidens

Der var en lille effekt af atomoxetin på funktionsniveau, ADHD-kernesymptomer og livskvalitet, men kvaliteten af evidensen var lav til meget lav. Der var ikke overbevisende effekt på angstsymptomer, baseret på evidens af moderat kvalitet. Interventionsgruppen havde signifikant højere puls, mens der ikke var signifikant forskel i blodtryk mellem de to grupper. Patienterne i interventionsgruppen havde tillige andre skadevirkninger, fx søvnløshed. Der var tilsyneladende ingen forskel mellem de to grupper i brugen af alkohol og marihuana. Effekten af interventionen på kriminalitet blev ikke belyst.
Opfølgningstiden i de inkluderede studier er for kort til at vurdere langtidseffekter og skadevirkninger som hjertekarsygdomme.

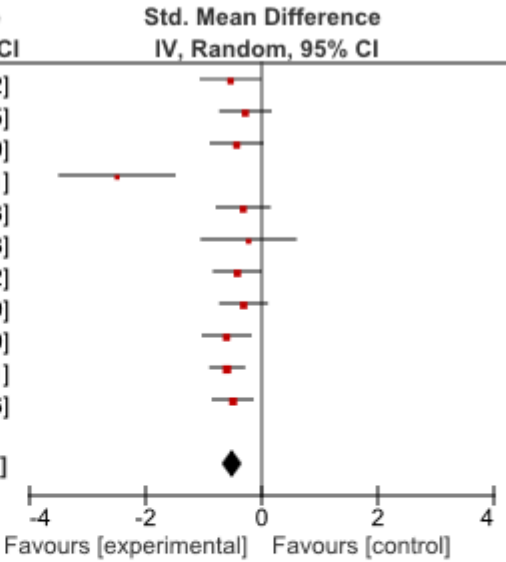
Mange af studierne inkluderede kun patienter, hvor det forud var vurderet, at de responderede positivt på behandlingen. De gavnlige virkninger kan derfor være overvurderet og de skadelige virkninger undervurderet i metaanalyserne. En mellemliggende behandlingsfri periode, inden selve studierne startede, kan gøre resultaterne yderligere vanskelige at tolke.

https://sundhedsstyrelsen.dk/da/udgivelser/2015/nkr-adhd-hos-voksne

Methylphenidate for ADHD in adults

Study or Subgroup	Std. Mean Difference	SE	Weight	Std. Mean Difference IV, Random, 95% CI
Bouffard 2003	-0.5362	0.2631	7.9%	-0.54 [-1.05, -0.02]
Casas 2013	-0.2816	0.2192	9.6%	-0.28 [-0.71, 0.15]
Casas 2013	-0.4309	0.2206	9.6%	-0.43 [-0.86, 0.00]
Ginsberg 2012 A	-2.4917	0.5024	3.0%	-2.49 [-3.48, -1.51]
Jain 2007	-0.3177	0.228	9.2%	-0.32 [-0.76, 0.13]
Konstenius 2010	-0.2253	0.4098	4.2%	-0.23 [-1.03, 0.58]
Medori 2008	-0.4185	0.2045	10.3%	-0.42 [-0.82, -0.02]
Medori 2008	-0.3112	0.2043	10.3%	-0.31 [-0.71, 0.09]
Medori 2008	-0.6063	0.2069	10.2%	-0.61 [-1.01, -0.20]
Rösler 2009	-0.5982	0.1453	13.5%	-0.60 [-0.88, -0.31]
Weisler 2012	-0.4928	0.1711	12.0%	-0.49 [-0.83, -0.16]
Total (95% CI)			**100.0%**	**-0.50 [-0.69, -0.32]**

Heterogeneity: Tau² = 0.05; Chi² = 19.63, df = 10 (P = 0.03); I² = 49%
Test for overall effect: Z = 5.28 (P < 0.00001)



Risk of bias legend
(**A**) Random sequence generation (selection bias)
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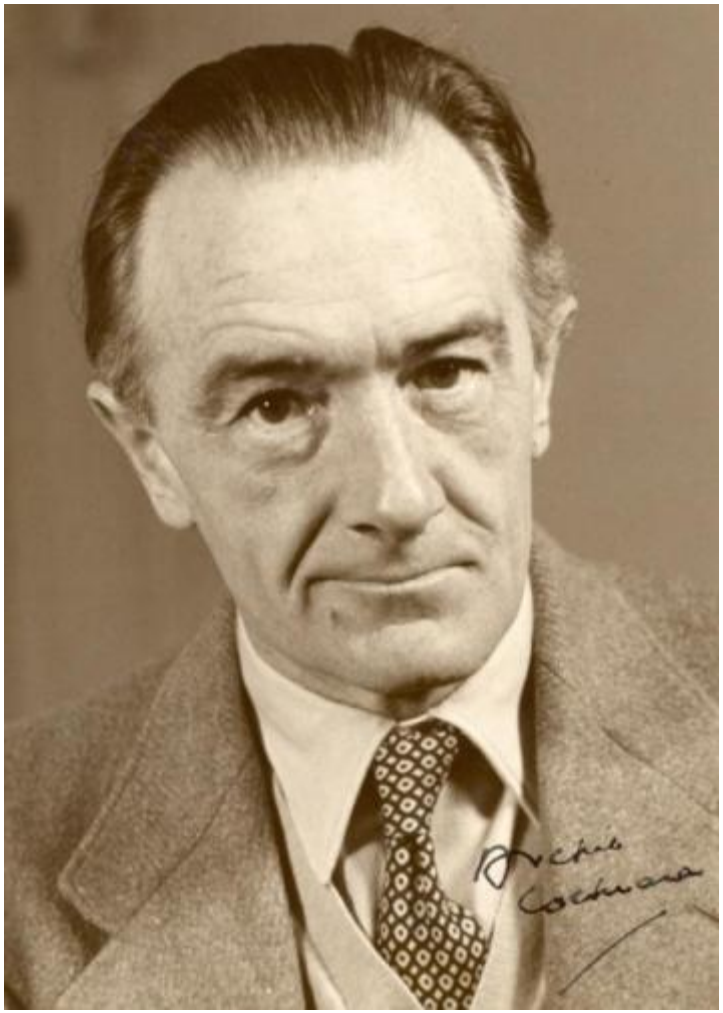
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

ADHD symptoms


Search
Immediate-release
onlinelibrary.wiley.com/doi/10.1002/14651858.CD005041.pub3/full
Cochrane Library
Trusted evidence.
Informed decisions.
Better health.
Cochrane.org
Log in / Register
Search title, abstract, keyword
Browse
Advanced Search
Cochrane Reviews
Trials
More Resources
About
Help
Go to old article view
Cochrane Database of Systematic Reviews
PDF
Info
Withdrawn from publication
Version History
Text size
Share
Comment
Reason for withdrawal from publication
What's new
History
Sources of support
Immediate-release methylphenidate for attention deficit hyperactivity disorder (ADHD) in adults
Withdrawn
Review
Intervention
Reason for withdrawal from publication
This review has been withdrawn from The Cochrane Library as of Issue 5, 2016. The authors have been unable to provide a satisfactory response to a number of criticisms received on the review. In addition, they contravene Cochrane's Commerical Sponsorship Policy.
DA
08:26
06-06-2016

Thank you!

Archie Cochrane's challenge



"It is surely a great criticism of our profession that we have not organised a critical summary, by specialty or subspecialty, adapted periodically, of all relevant randomised controlled trials."

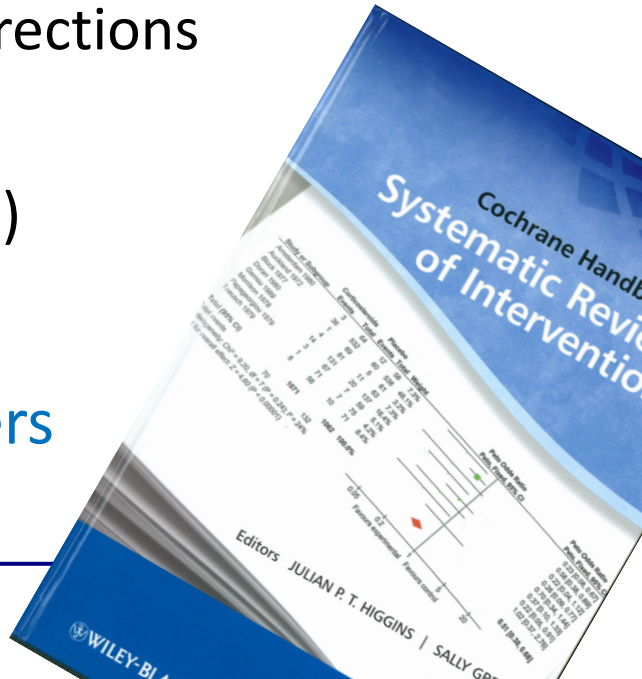
Cochrane 1979

Photograph: Cardiff University Library, Cochrane Archive, University Hospital Llandough

The Cochrane Handbook for Systematic Reviews of Interventions

- essential guidance for entire review process
- available
  - online www.cochrane.org/training/cochrane-handbook
    - also lists what's new and future corrections
  - via Help menu in RevMan
  - textbook for purchase (Wiley Blackwell)

Look out for pointers to relevant chapters



An international organisation

Declaration of interest

- sponsorship of a review by a commercial source is prohibited
- other sponsors must not delay or prevent publication, or interfere with the independence of authors
- all potential conflicts of interest should be declared
  - financial (all sources of funding & in-kind support)
  - personal (e.g. authorship of a potentially included study)

See Code of Conduct, Box 2.6.a in the Handbook

Structure and purpose

- International non-profit collaboration, main functions are systematic review production and methodology research.

- Published in The Cochrane Library – online database. National license in Denmark, by subscription in Russia.

Hierarchy of evidence

Ia Systematic reviews of RCT's

- Ib Randomised trials
- IIa Controlled, non-randomised study
- IIb Cohort study
- III Case-control study
- IV Descriptive studies
- Non-systematic reviews (overview papers)
- Consensus reports (Reference programmes)
- Editorials

OPEN ACCESS Freely available online PLoS MEDICINE

Conflicts of Interest at Medical Journals: The Influence of Industry-Supported Randomised Trials on Journal Impact Factors and Revenue – Cohort Study

Andreas Lundh[1,2¤]*, Marija Barbateskovic[1], Asbjørn Hróbjartsson[1], Peter C. Gøtzsche[1,2]

1 The Nordic Cochrane Centre, Rigshospitalet, Copenhagen, Denmark, **2** Institute of Medicine and Surgery, Faculty of Health Sciences, University of Copenhagen, Copenhagen, Denmark

Abstract

Background: Transparency in reporting of conflict of interest is an increasingly important aspect of publication in medical journals. Publication of large industry-supported trials may generate many citations and journal income through reprint sales and thereby be a source of conflicts of interest for journals. We investigated industry-supported trials' influence on journal impact factors and revenue.

Methods and Findings: We sampled six major medical journals (*Annals of Internal Medicine*, *Archives of Internal Medicine*, *BMJ*, *JAMA*, The *Lancet*, and *New England Journal of Medicine* [*NEJM*]). For each journal, we identified randomised trials published in 1996–1997 and 2005–2006 using PubMed, and categorized the type of financial support. Using Web of Science, we investigated citations of industry-supported trials and the influence on journal impact factors over a ten-year period. We contacted journal editors and retrieved tax information on income from industry sources. The proportion of trials with sole industry support varied between journals, from 7% in *BMJ* to 32% in *NEJM* in 2005–2006. Industry-supported trials were more frequently cited than trials with other types of support, and omitting them from the impact factor calculation decreased journal impact factors. The decrease varied considerably between journals, with 1% for *BMJ* to 15% for *NEJM* in 2007. For the two journals disclosing data, income from the sales of reprints contributed to 3% and 41% of the total income for *BMJ* and The *Lancet* in 2005–2006.

Conclusions: Publication of industry-supported trials was associated with an increase in journal impact factors. Sales of reprints may provide a substantial income. We suggest that journals disclose financial information in the same way that they require them from their authors, so that readers can assess the potential effect of different types of papers on journals' revenue and impact.

"The Agency's Executive Director Prof Rasi is indeed mentioned on a number of patents, even beyond those referred to in footnote 15 of your complaint letter, but only as inventor, not as owner of the patents. Prof Rasi does not own any patent together with Sigma-Tau. He is named as inventor on 2 patent families for which Sigma-Tau is named as applicant or patentee. He is not even the beneficiary of those patent families. Hence there was and there is no obligation for him to declare these patents in his DoI as EMA staff member in accordance with EMA's proceedings on the handling of DoIs."

"We would also like to clarify that Prof Rasi has never worked with or for Sigma-Tau and that no former Sigma-Tau employee joined EMA since 2011 with the exception of Mr S. Marino, who was indeed the former General Counsel at Sigma-Tau […]."

Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gordon C S Smith, Jill P Pell

Conclusions: As with many interventions intended to prevent ill health, the effectiveness of parachutes has not been subjected to rigorous evaluation by using randomised controlled trials. Advocates of evidence based medicine have criticised the adoption of interventions evaluated by using only observational data. We think that everyone might benefit if the most radical protagonists of evidence based medicine organised and participated in a double blind, randomised, placebo controlled, crossover trial of the parachute.

What can we learn?

- No evidence for effect is not the same as evidence of no effect.
- Evidence from other sources than RCT's are valuable
- Very few medical interventions have as convincing an effect as parachutes.
- The parachute analogy is often misused.

Reporting guidelines

For a randomised controlled trial, the appropriate completed CONSORT checklist showing on which page of your manuscript each checklist item appears, the CONSORT-style structured abstract, and the CONSORT flowchart (CONSORT has several extension statements, eg for cluster RCTs). To find research reporting guidelines and statements such as CONSORT you may find it easiest to go to the website of the EQUATOR network, where they are all available in one place. Because we aim to improve *BMJ* papers' reporting and increase reviewers' understanding we ask our research authors to follow such reporting guidelines and to complete the appropriate reporting checklist before submission (or before external peer review if not done sooner). We do not, however, use reporting guidelines as critical appraisal tools to evaluate study quality or filter out articles.

QUOROM checklist and flowchart for a systematic review

- MOOSE checklist and flowchart for a meta-analysis of observational studies
- STARD checklist and flowchart for a study of diagnostic accuracy
- STROBE checklist for an observational study

Systematic review

Systematic assessmen of the literature based on a pre-specified protocol.

Meta-analysis

Statistial method to quantitatively summarise effect estimates from several independent studies into a single effect estimate.

Systematic reviews

Metods section that describe:

- Where, when and how the studies were identified.

Systematic reviews

Metods section that descibe:

- Where, when and how the studies were identified.
- Criteria for in- and exclusion.

Systematic reviews

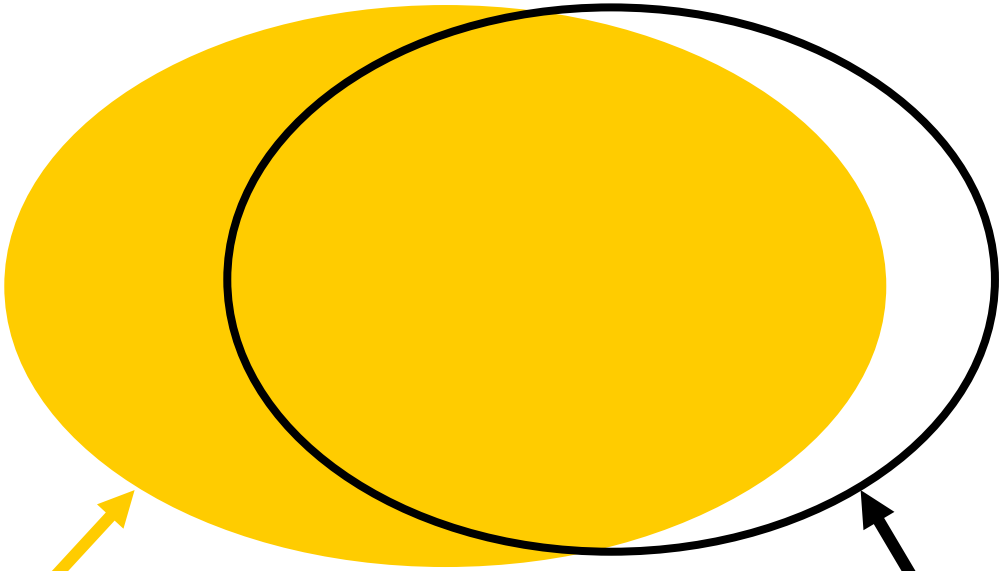
Metods section that descibe:

- Where, when and how the studies were identified.
- Criteria for in- and exclusion.
- How the methodological quality was assessed

Metodological quality

- Blinded allocation.
- Double blinding.
- Intention-to-treat analyses.

Important difference!



Systematic reviews

Meta-analyses

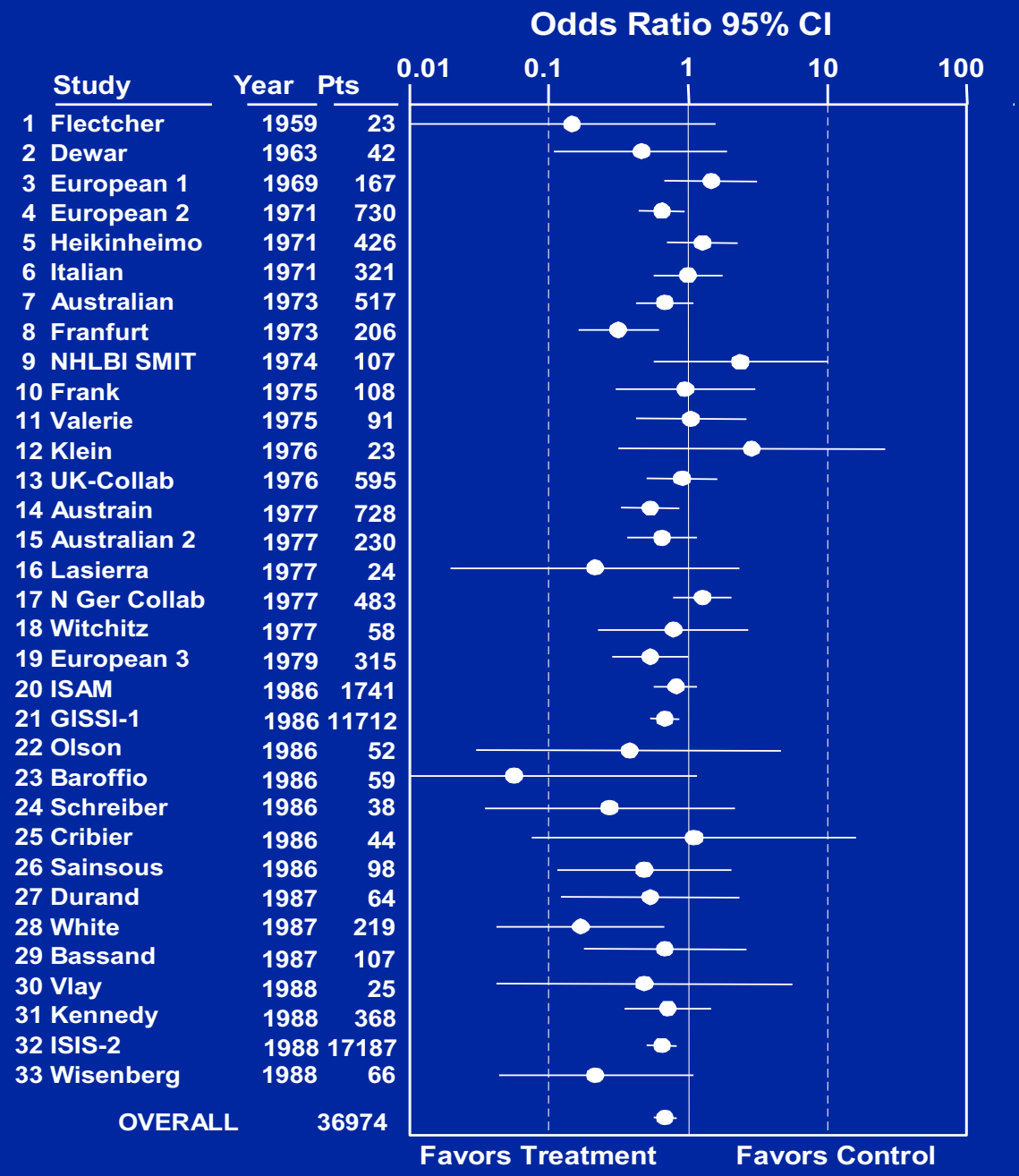
Use of meta-analyses

- Increases statistical power.
- Allows new calculations of effect, e.g. **N**umbers **N**eeded to **T**reat (NNT).
- Uncovers patterns.

Use of systematic reviews

- National clinical guidelines and health technology assessments (HTA).
- Local procedural guidelines.
- Prior to start of randomisered trials.
- Overview of the litterature for the clinician.

Intravenous Streptokinase Therapy for Acute Myocardial Infarction



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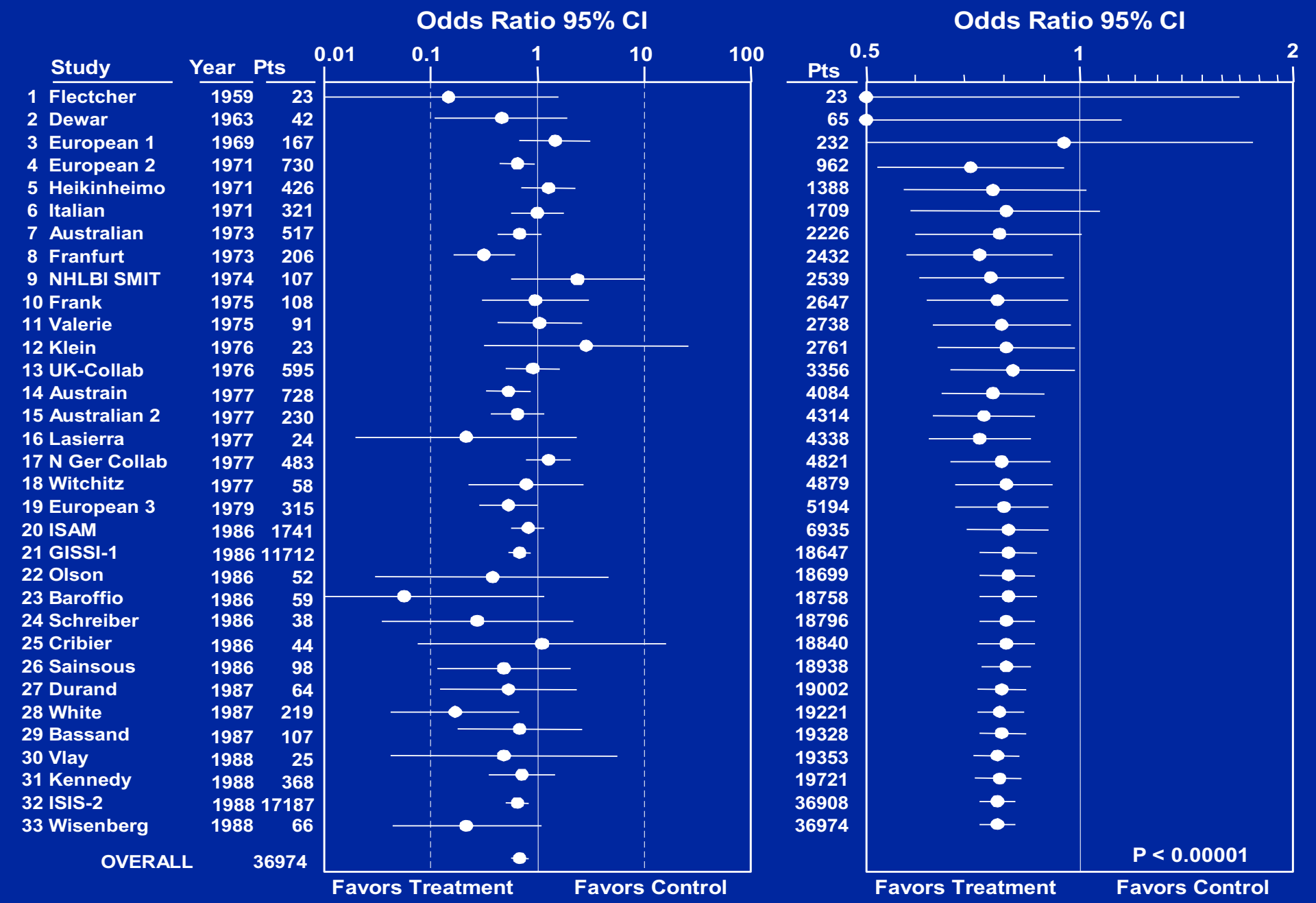
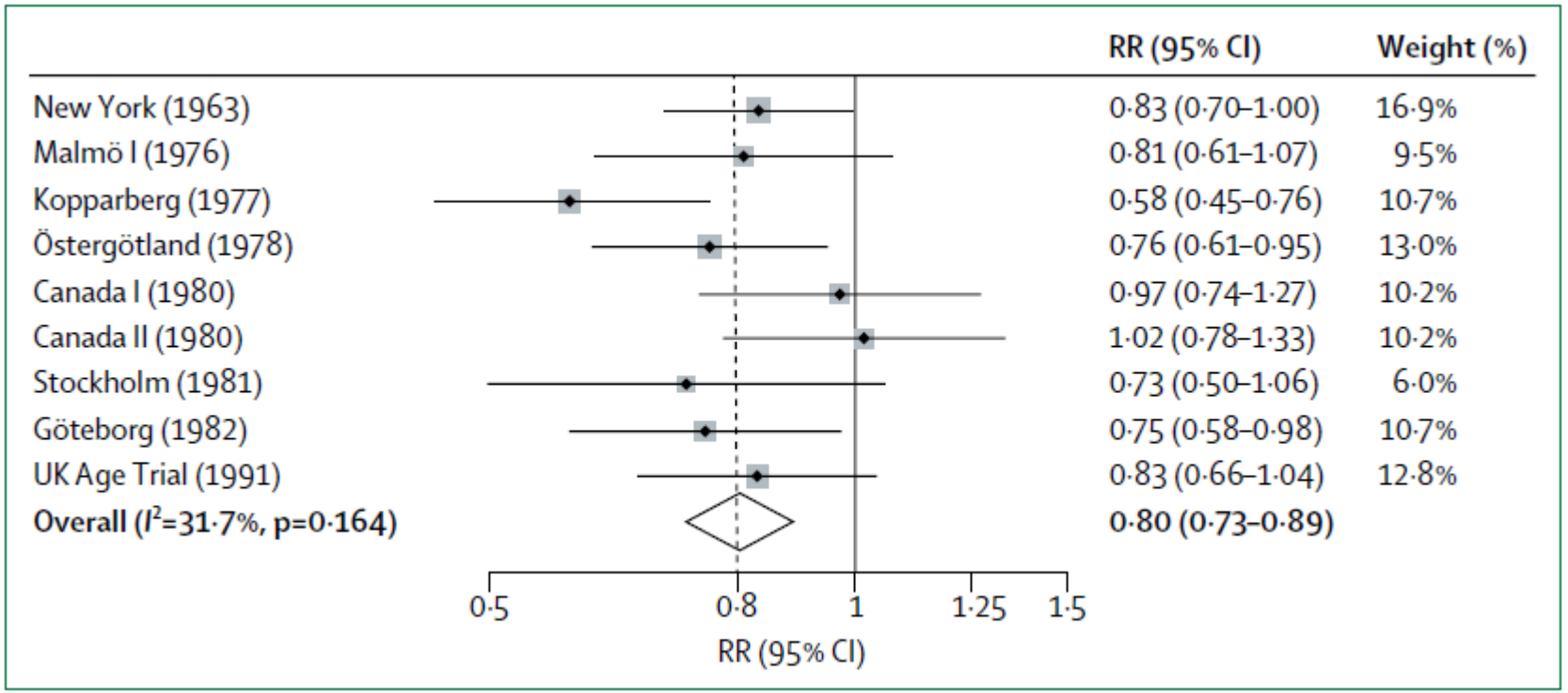
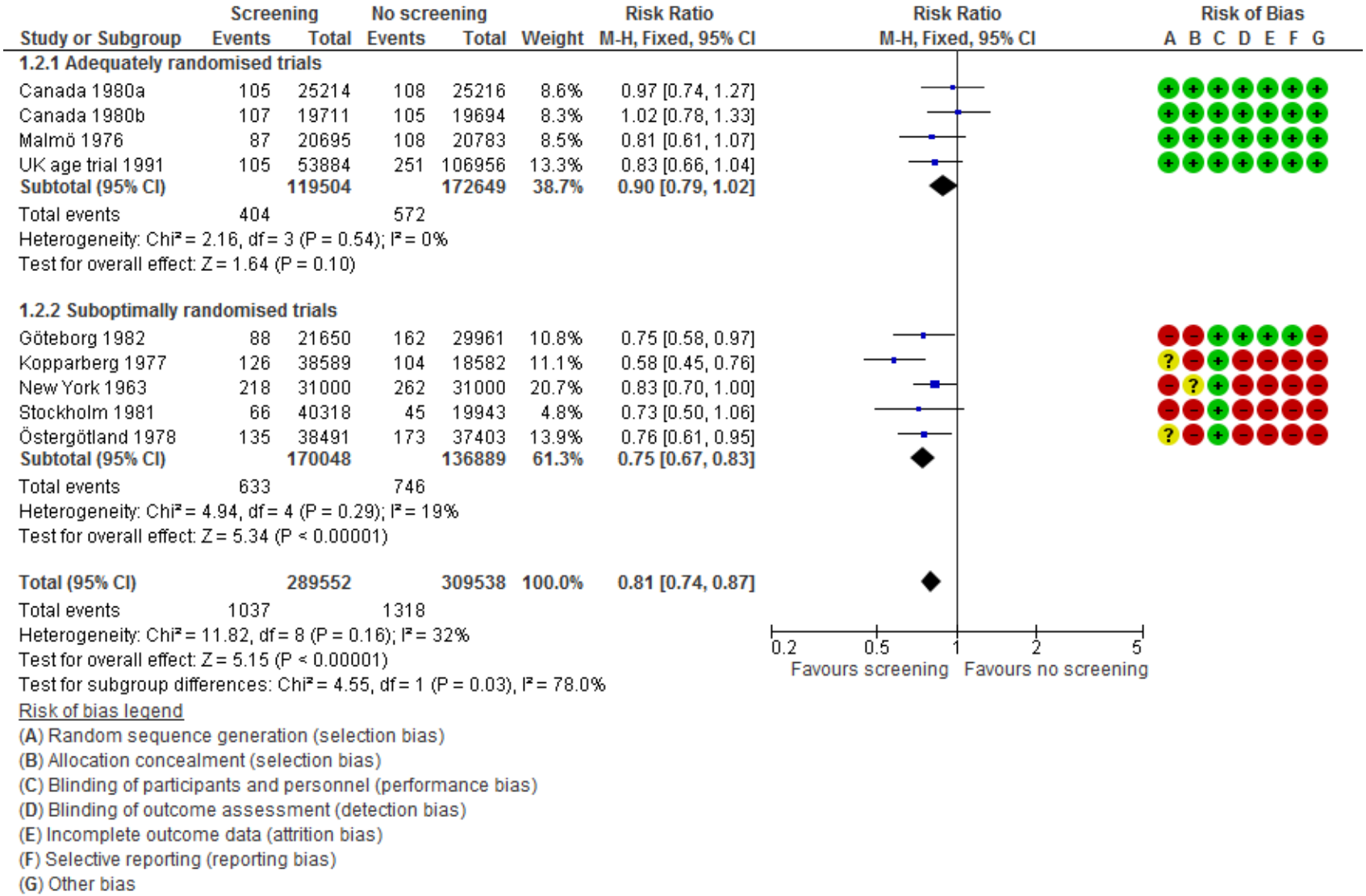


Pitfalls

- Compatible effect estimates between studies – differences should be explainable through statistical variation.
- Publication bias may skew results.
- Doubtful metodological quality of studies can provide misleading effect estimates.



”The Panel’s primary conclusions about breast cancer mortality are based on data reported in the Cochrane review…”



Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk with intervention				
Total mortality Deaths Follow-up: 4-22 years	**75 per 1000**	**74 per 1000** (71 to 77)	**RR 0.99** (0.95 to 1.03)	155,899 (9 studies)	⊕⊕⊕⊕ **high**	
Cardiovascular mortality Deaths from cardiovascular causes Follow-up: 4-22 years	**37 per 1000**	**38 per 1000** (34 to 43)	**RR 1.03** (0.91 to 1.17)	152,435 (8 studies)	⊕⊕⊕○ **moderate**	There was substantial heterogeneity which may reflect the different outcome definitions used in the trials
Cancer mortality Cancer deaths Follow-up: 4-22 years	**21 per 1000**	**21 per 1000** (19 to 24)	**RR 1.01** (0.92 to 1.12)	139,290 (8 studies)	⊕⊕⊕⊕ **high**	

*The **assumed risk** is the median control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

NEWSPAPER OF THE YEAR

THE TIMES

The woman behind that M&S campaign Times2

NHS checks on over-40s condemned as 'useless'

Call for £300 million scheme to be scrapped

Name, set and match to Miss Sugarpova

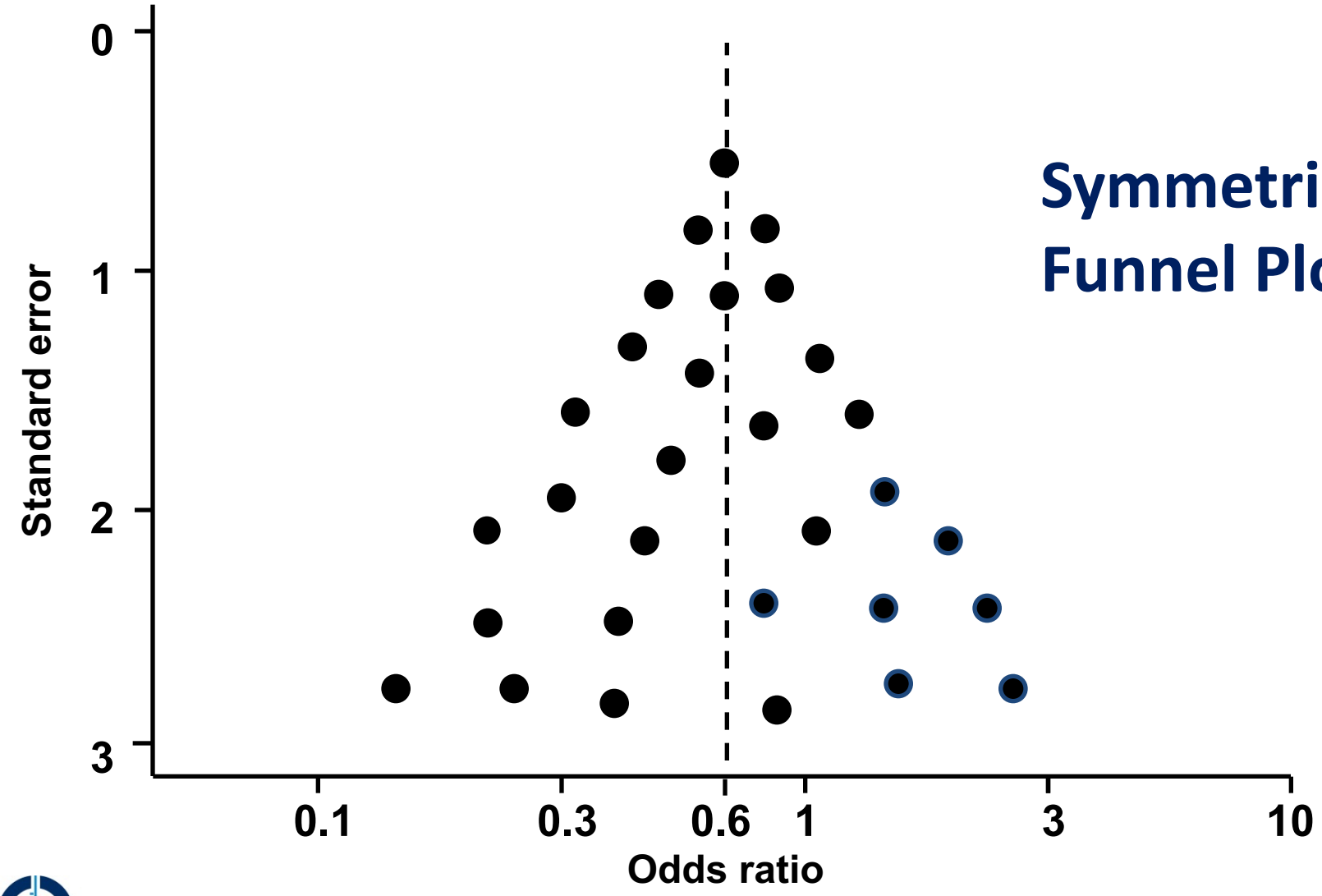
IN THE NEWS

Mubarak to be freed | Anti-fracking arrests | Crimefighter resigns | Schools in gay row | Emerging markets hit | Blues go sky high

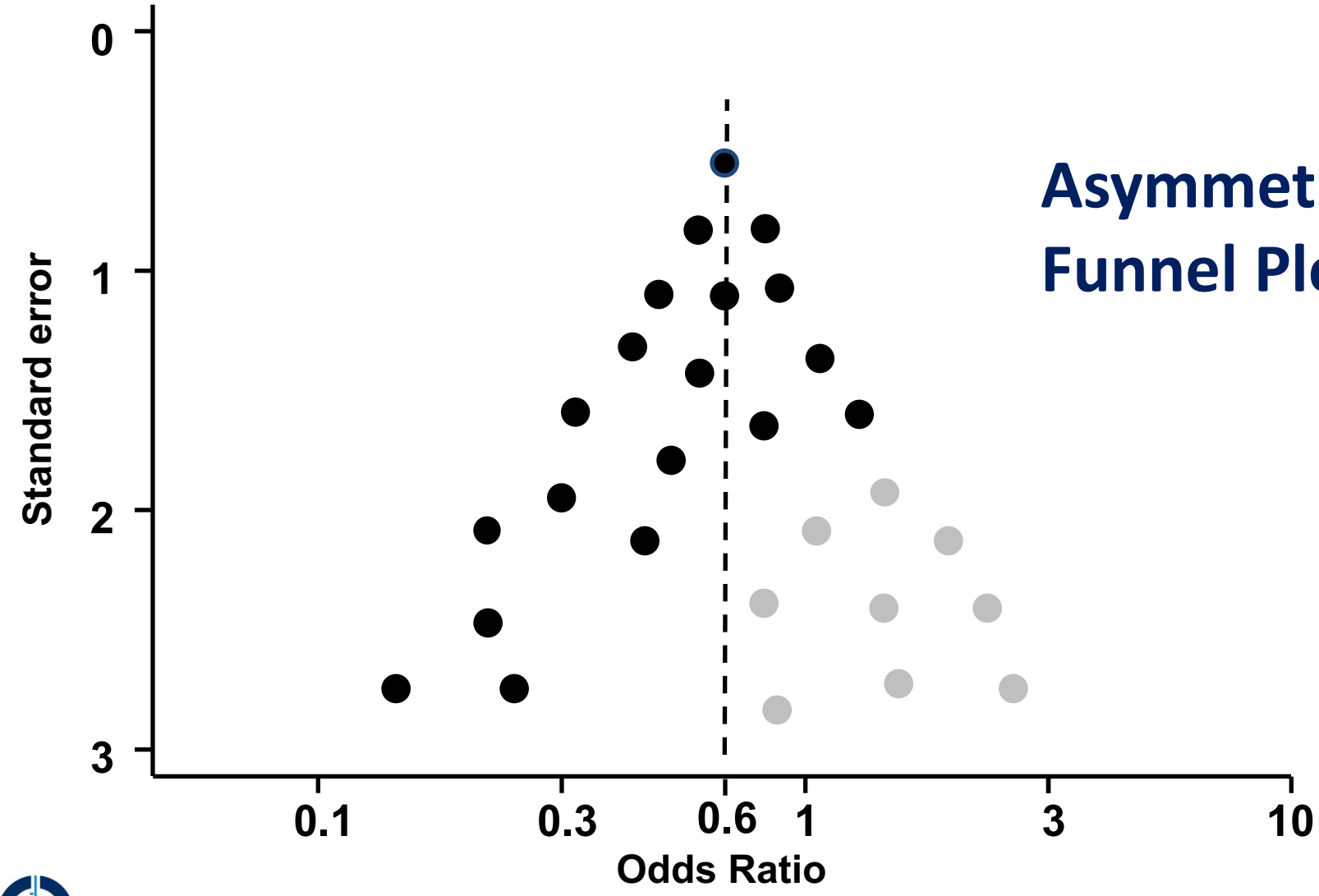
20 Aug 2013

Health check check

Interview and Letter
by Krogsbøll et al.



Symmetrical Funnel Plot



Asymmetrical Funnel Plot

Conclusions

- Systematic reviews are always relevant to provide and overview of benefits and harms of an intervention.

- Meta-analyses require that certain prerequisites are fulfilled and should be intepreted with caution.

Additional databases

- RCT's (CENTRAL): 600,472
- Other reviews (DARE): 11,447 (only abstracts)
- Methods studies: 12,200
- HTA: 7,596

Intercessory prayer for the alleviation of ill health (Review)

Roberts L, Ahmed I, Hall S, Davison A

THE COCHRANE COLLABORATION®

Journal of Negative Results in BioMedicine

Commentary

Divine intervention? A Cochrane review on intercessory prayer gone beyond science and reason

Karsten Juhl Jørgensen, Asbjørn Hróbjartsson and Peter C Gøtzsche*

Address: The Nordic Cochrane Centre, Rigshospitalet, Dept. 3343, Blegdamsvej 9, DK-2100 Copenhagen, Denmark

Email: Karsten Juhl Jørgensen - kj@cochrane.dk; Asbjørn Hróbjartsson - ah@cochrane.dk; Peter C Gøtzsche* - pcg@cochrane.dk

* Corresponding author

Published: 10 June 2009

Journal of Negative Results in BioMedicine 2009, 8:7 doi:10.1186/1477-5751-8-7

Received: 15 December 2008
Accepted: 10 June 2009

This article is available from: http://www.jnrbm.com/content/8/1/7

Abstract

We discuss in this commentary a recent Cochrane review of 10 randomised trials aimed at testing

ADHD påvirker ofte patienterne hele dagen[1-3]

DKSTR00468 – august 2015

Hvornår på dagen er dine patienter udfordrede?

- Svært ved at komme ud af sengen?
- Kommer ofte til at skælde sine børn ud på vej ud af døren?
- Distraheres nemt på jobbet?
- Svært ved at fastholde venskaber?
- Glemmer sine eftermiddagsaftaler?
- Svært ved at slappe af med sin partner efter arbejde?
- Vil gerne dyrke sport, men kan oftest ikke overskue det?
- Svært ved at falde i søvn om aftenen?

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Se produktinformation på side 1764

Lilly

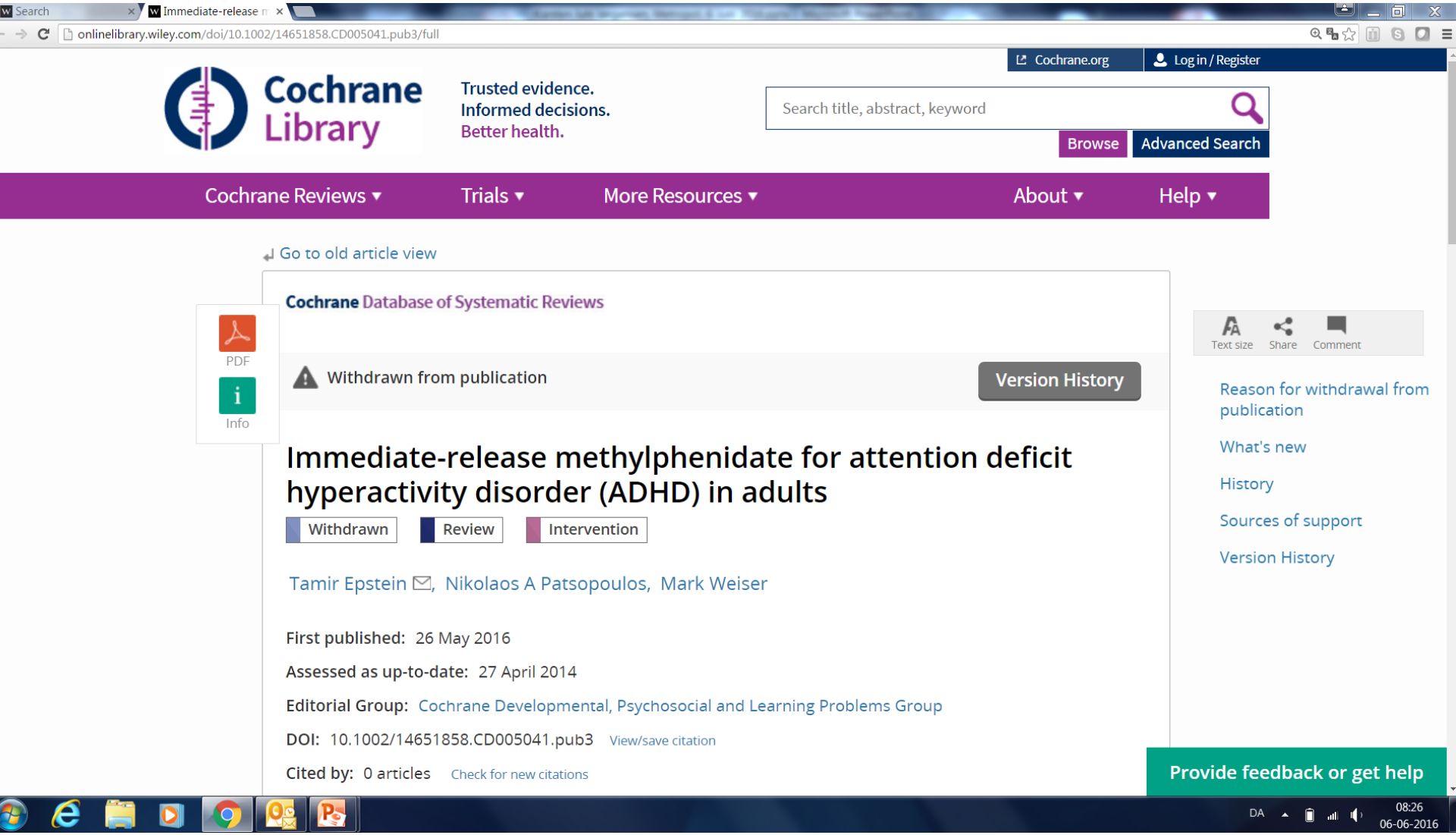
strattera® atomoxetin HCl

7.5 Gennemgang af evidens

Der var en lille effekt af atomoxetin på funktionsniveau, ADHD-kernesymptomer og livskvalitet, men kvaliteten af evidensen var lav til meget lav. Der var ikke overbevisende effekt på angstsymptomer, baseret på evidens af moderat kvalitet. Interventionsgruppen havde signifikant højere puls, mens der ikke var signifikant forskel i blodtryk mellem de to grupper. Patienterne i interventionsgruppen havde tillige andre skadevirkninger, fx søvnløshed. Der var tilsyneladende ingen forskel mellem de to grupper i brugen af alkohol og marihuana. Effekten af interventionen på kriminalitet blev ikke belyst.
Opfølgningstiden i de inkluderede studier er for kort til at vurdere langtidseffekter og skadevirkninger som hjertekarsygdomme.

Mange af studierne inkluderede kun patienter, hvor det forud var vurderet, at de responderede positivt på behandlingen. De gavnlige virkninger kan derfor være overvurderet og de skadelige virkninger undervurderet i metaanalyserne. En mellemliggende behandlingsfri periode, inden selve studierne startede, kan gøre resultaterne yderligere vanskelige at tolke.

https://sundhedsstyrelsen.dk/da/udgivelser/2015/nkr-adhd-hos-voksne


Search
Immediate-release
onlinelibrary.wiley.com/doi/10.1002/14651858.CD005041.pub3/full
Cochrane.org
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Trusted evidence.
Informed decisions.
Better health.
Search title, abstract, keyword
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Trials
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Help
Go to old article view
Cochrane Database of Systematic Reviews
PDF
Info
Withdrawn from publication
Version History
Text size
Share
Comment
Reason for withdrawal from publication
What's new
History
Sources of support
Version History
Immediate-release methylphenidate for attention deficit hyperactivity disorder (ADHD) in adults
Withdrawn
Review
Intervention
Tamir Epstein, Nikolaos A Patsopoulos, Mark Weiser
First published: 26 May 2016
Assessed as up-to-date: 27 April 2014
Editorial Group: Cochrane Developmental, Psychosocial and Learning Problems Group
DOI: 10.1002/14651858.CD005041.pub3 View/save citation
Cited by: 0 articles Check for new citations
Provide feedback or get help
DA
08:26
06-06-2016

Reason for withdrawal from publication
This review has been withdrawn from *The Cochrane Library* as of Issue 5, 2016. The authors have been unable to provide a satisfactory response to a number of criticisms received on the review. In addition, they contravene Cochrane's Commerical Sponsorship Policy.

Screening for abdominalt aortaaneurisme

Evidensgrundlag: 4 RCT'er, 137,214 mænd over 65 år, > 10 års opfølgning, gennemført i 1980erne og 1990erne.

GODT	SKIDT
RRR: 50%	

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Ingen opfølgende invasive US	

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GODT	SKIDT
RRR: 50%	ARR: 0,46% (-77% i dag)
Harmløs undersøgelse	
Afgrænset målgruppe	
Kun én undersøgelse	
Ingen opfølgende invasive US	

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RRR: 50%	ARR: 0,46% (-77% i dag)
Harmløs undersøgelse	ODX: 176 / 10,000 (1:4)
Afgrænset målgruppe	
Kun én undersøgelse	
Ingen opfølgende invasive US	

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Harmløs undersøgelse	ODX: 176 / 10,000 (1:4)
Afgrænset målgruppe	Overbeh.: 37 / 10,000
Kun én undersøgelse	
Ingen opfølgende invasive US	

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Harmløs undersøgelse	ODX: 176 / 10,000 (1:4)
Afgrænset målgruppe	Overbeh.: 37 / 10,000
Kun én undersøgelse	Unødige dødsfald: 2 / 10,000
Ingen opfølgende invasive US	

Screening for abdominalt aortaaneurisme

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RRR: 50%	ARR: 0,46% (-77% i dag)
Harmløs undersøgelse	ODX: 176 / 10,000
Afgrænset målgruppe	Overbeh.: 37 / 10,000
Kun én undersøgelse	Unødige dødsfald: 2 / 10,000
Ingen opfølgende invasive US	Øvrige kompl: 12/10,000

Johansson, Jørgensen, Brodersen. *Lancet* 2015; doi:10.1016/S0140-6736(15)00472-9

thebmj

BMJ 2016;353:i2230 doi: 10.1136/bmj.i2230 (Published 9 May 2016)

ANALYSIS

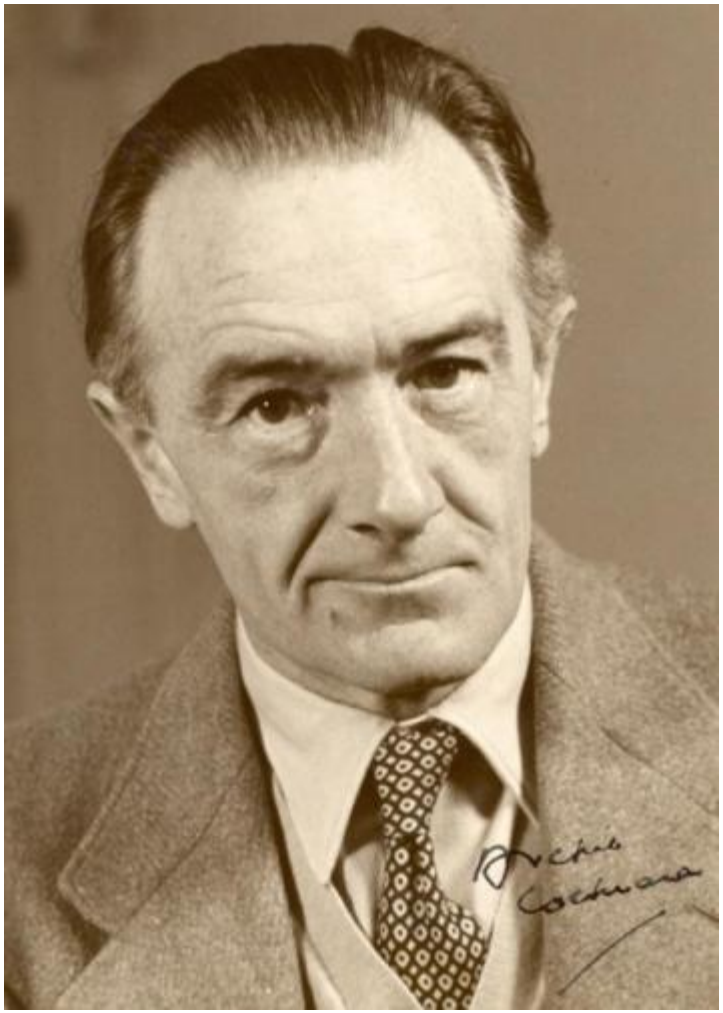
"Informed choice" in a time of too much medicine—no panacea for ethical difficulties

Providing information to enable informed choices about healthcare sounds immediately appealing to most of us. But **Minna Johansson and colleagues** argue that preventive medicine and expanding disease definitions have changed the ethical premises of informed choice and our good intentions may inadvertently advance overmedicalisation

Minna Johansson *PhD student*[1 2], Karsten Juhl Jørgensen *senior researcher*[3], Linn Getz *professor*[4], Ray Moynihan *senior research fellow*[5]

[1]Department of Public Health and Community Medicine, Institute of Medicine, University of Gothenburg, Gothenburg, Sweden; [2]Research Unit and Section for General Practice, FoUU-centrum Fyrbodal, Vänersborg, Sweden; [3]Nordic Cochrane Centre, Rigshospitalet, Copenhagen, Denmark; [4]General Practice Research Unit, Norwegian University of Science and Technology, Trondheim, Norway; [5]Centre for Research in Evidence Based Practice, Bond University, Australia

Archie Cochrane's challenge



"It is surely a great criticism of our profession that we have not organised a critical summary, by specialty or subspecialty, adapted periodically, of all relevant randomised controlled trials."

Cochrane 1979

Photograph: Cardiff University Library, Cochrane Archive, University Hospital Llandough

Struktur og formål

- Internationalt non-profit samarbejde, der bl.a. udarbejder systematiske oversigtsartikler.

- Udgives i Cochrane Library – database på Internettet. Fri adgang i Danmark.

Evidenshierakiet

Ia Systematisk review af RCT'er

- Ib Randomiseret studie
- IIa Kontrolleret, non-randomiseret studie
- IIb Kohorte studie
- III Case-control studie
- IV Deskriptive studier
- Non-systematiske reviews (oversigtsartikler)
- Konsensus rapport (Reference program)
- Lederartikler

OPEN ACCESS Freely available online PLoS MEDICINE

Conflicts of Interest at Medical Journals: The Influence of Industry-Supported Randomised Trials on Journal Impact Factors and Revenue – Cohort Study

Andreas Lundh[1,2¤]*, Marija Barbateskovic[1], Asbjørn Hróbjartsson[1], Peter C. Gøtzsche[1,2]

1 The Nordic Cochrane Centre, Rigshospitalet, Copenhagen, Denmark, **2** Institute of Medicine and Surgery, Faculty of Health Sciences, University of Copenhagen, Copenhagen, Denmark

Abstract

Background: Transparency in reporting of conflict of interest is an increasingly important aspect of publication in medical journals. Publication of large industry-supported trials may generate many citations and journal income through reprint sales and thereby be a source of conflicts of interest for journals. We investigated industry-supported trials' influence on journal impact factors and revenue.

Methods and Findings: We sampled six major medical journals (*Annals of Internal Medicine*, *Archives of Internal Medicine*, *BMJ*, *JAMA*, The *Lancet*, and *New England Journal of Medicine* [*NEJM*]). For each journal, we identified randomised trials published in 1996–1997 and 2005–2006 using PubMed, and categorized the type of financial support. Using Web of Science, we investigated citations of industry-supported trials and the influence on journal impact factors over a ten-year period. We contacted journal editors and retrieved tax information on income from industry sources. The proportion of trials with sole industry support varied between journals, from 7% in *BMJ* to 32% in *NEJM* in 2005–2006. Industry-supported trials were more frequently cited than trials with other types of support, and omitting them from the impact factor calculation decreased journal impact factors. The decrease varied considerably between journals, with 1% for *BMJ* to 15% for *NEJM* in 2007. For the two journals disclosing data, income from the sales of reprints contributed to 3% and 41% of the total income for *BMJ* and The *Lancet* in 2005–2006.

Conclusions: Publication of industry-supported trials was associated with an increase in journal impact factors. Sales of reprints may provide a substantial income. We suggest that journals disclose financial information in the same way that they require them from their authors, so that readers can assess the potential effect of different types of papers on journals' revenue and impact.

BMJ

BMJ 2011;342:d2686 doi: 10.1136/bmj.d2686

ANALYSIS

Opening up data at the European Medicines Agency

Widespread selective reporting of research results means we don't know the true benefits and harms of prescribed drugs. **Peter Gøtzsche** and **Anders Jørgensen** describe their efforts to get access to unpublished trial reports from the European Medicines Agency

Peter C Gøtzsche *professor*, Anders W Jørgensen *PhD student*

Nordic Cochrane Centre, Rigshospitalet and University of Copenhagen, Dept 3343, Blegdamsvej 9, DK-2100 Copenhagen Ø, Denmark

Hvad vil vi opnå?

- Evidensbaseret behandling; dvs. at behandlingsprincipper skal baseres på den bedste, tilgængelige viden.
- Oversigt over litteraturen. Hvad ved vi? Hvad ved vi ikke?
- Uhildet bedømmelse af litteraturen ud fra standardiserede, empirisk funderede retningslinier.

Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gordon C S Smith, Jill P Pell

Conclusions: As with many interventions intended to prevent ill health, the effectiveness of parachutes has not been subjected to rigorous evaluation by using randomised controlled trials. Advocates of evidence based medicine have criticised the adoption of interventions evaluated by using only observational data. We think that everyone might benefit if the most radical protagonists of evidence based medicine organised and participated in a double blind, randomised, placebo controlled, crossover trial of the parachute.

Hvad kan vi lære?

- Ingen evidens for effekt er ikke det samme som evidens for ingen effekt.
- Evidens fra andre kilder end RCT'er kan bruges
- Meget få medicinske interventioner har så overbevisende effekt som faldskærme.
- Falskærms-analogien misbruges ofte.

Retningslinier for rapportering

For a randomised controlled trial, the appropriate completed CONSORT checklist showing on which page of your manuscript each checklist item appears, the CONSORT-style structured abstract, and the CONSORT flowchart (CONSORT has several extension statements, eg for cluster RCTs). To find research reporting guidelines and statements such as CONSORT you may find it easiest to go to the website of the EQUATOR network, where they are all available in one place. Because we aim to improve *BMJ* papers' reporting and increase reviewers' understanding we ask our research authors to follow such reporting guidelines and to complete the appropriate reporting checklist before submission (or before external peer review if not done sooner). We do not, however, use reporting guidelines as critical appraisal tools to evaluate study quality or filter out articles.

QUOROM checklist and flowchart for a systematic review

- MOOSE checklist and flowchart for a meta-analysis of observational studies
- STARD checklist and flowchart for a study of diagnostic accuracy
- STROBE checklist for an observational study

Systematisk review

Systematisk litteraturgennemgang, der følger en præspecificeret protokol

Meta-analyse

Statistisk metode til kvantitativ opsummering.

Kombinerer resultater fra flere uafhængige studier til ét overordnet effektestimat.

Systematiske reviews

Metodeafsnit, der angiver:

- Hvor, hvornår og hvordan man har fundet studier, der indgår.

Systematiske reviews

Metodeafsnit, der angiver:

- Hvor, hvornår og hvordan man har fundet studier, der indgår.
- Kriterier for in- og eksklusion.

Systematiske reviews

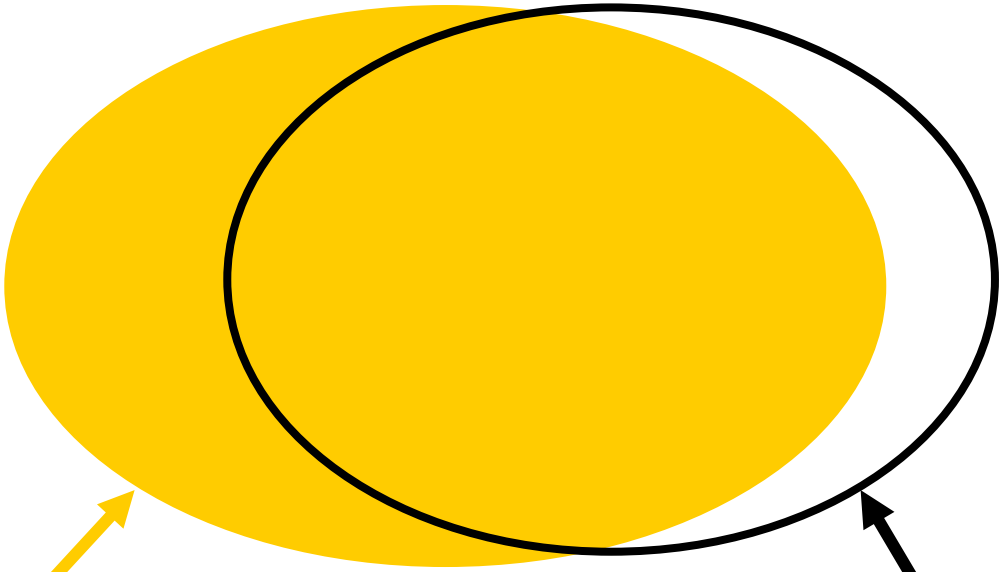
Metodeafsnit, der angiver:

- Hvor, hvornår og hvordan man har fundet studier, der indgår.
- Kriterier for in- og eksklusion.
- Hvordan studiernes metodologiske kvalitet er vurderet.

Metodologisk kvalitet

- Maskering af allokering.
- Dobbeltblinding.
- Intention-to-treat analyse.

Vigtig forskel!



Systematiske reviews

Meta-analyser

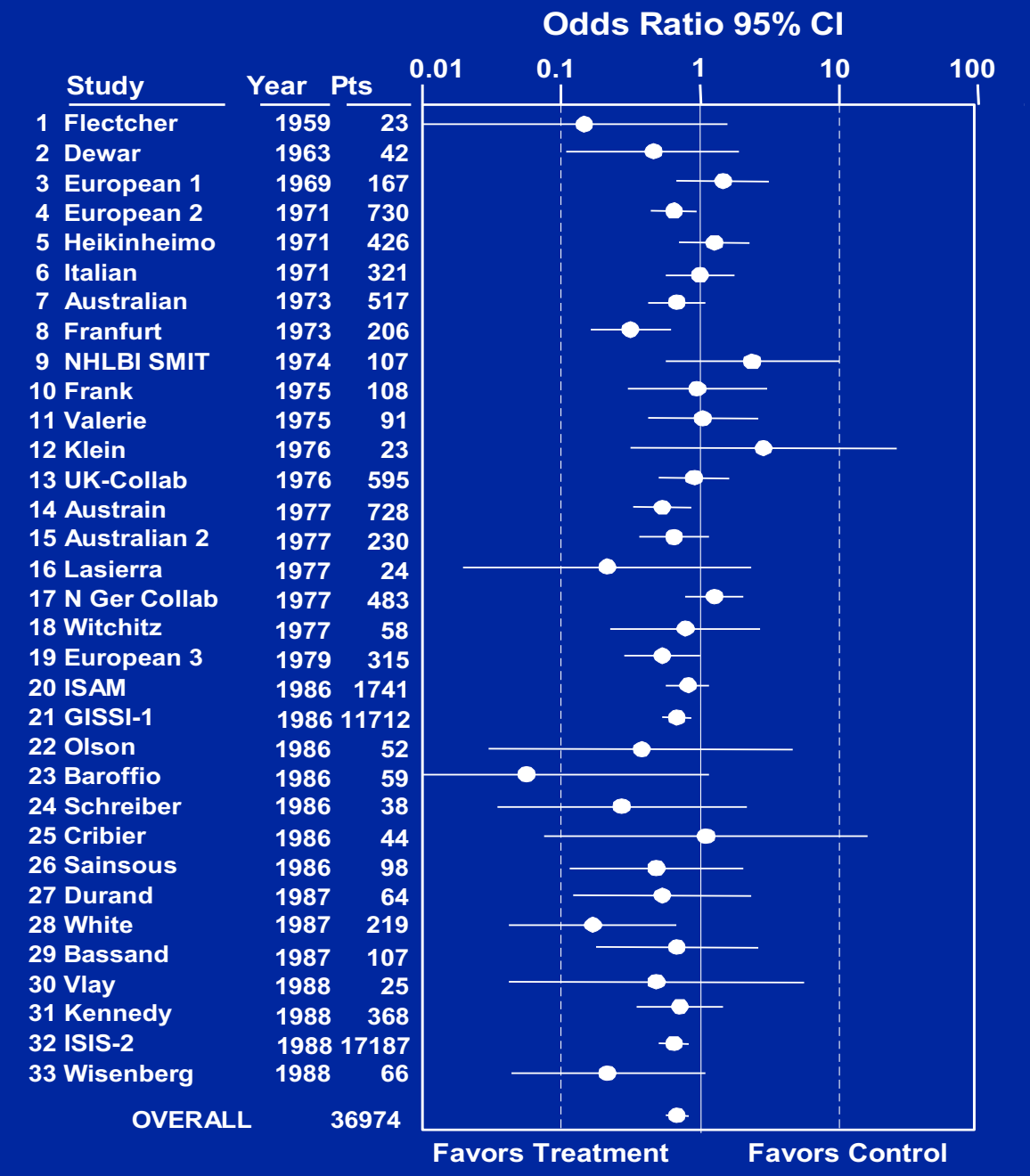
Anvendelse af meta-analyser

- Øge statistisk styrke.
- Et tal for effekten af en behandling f. eks. **N**umbers **N**eeded to **T**reat (NNT).
- Afdække mønstre.

Anvendelse af systematiske oversigtsartikler

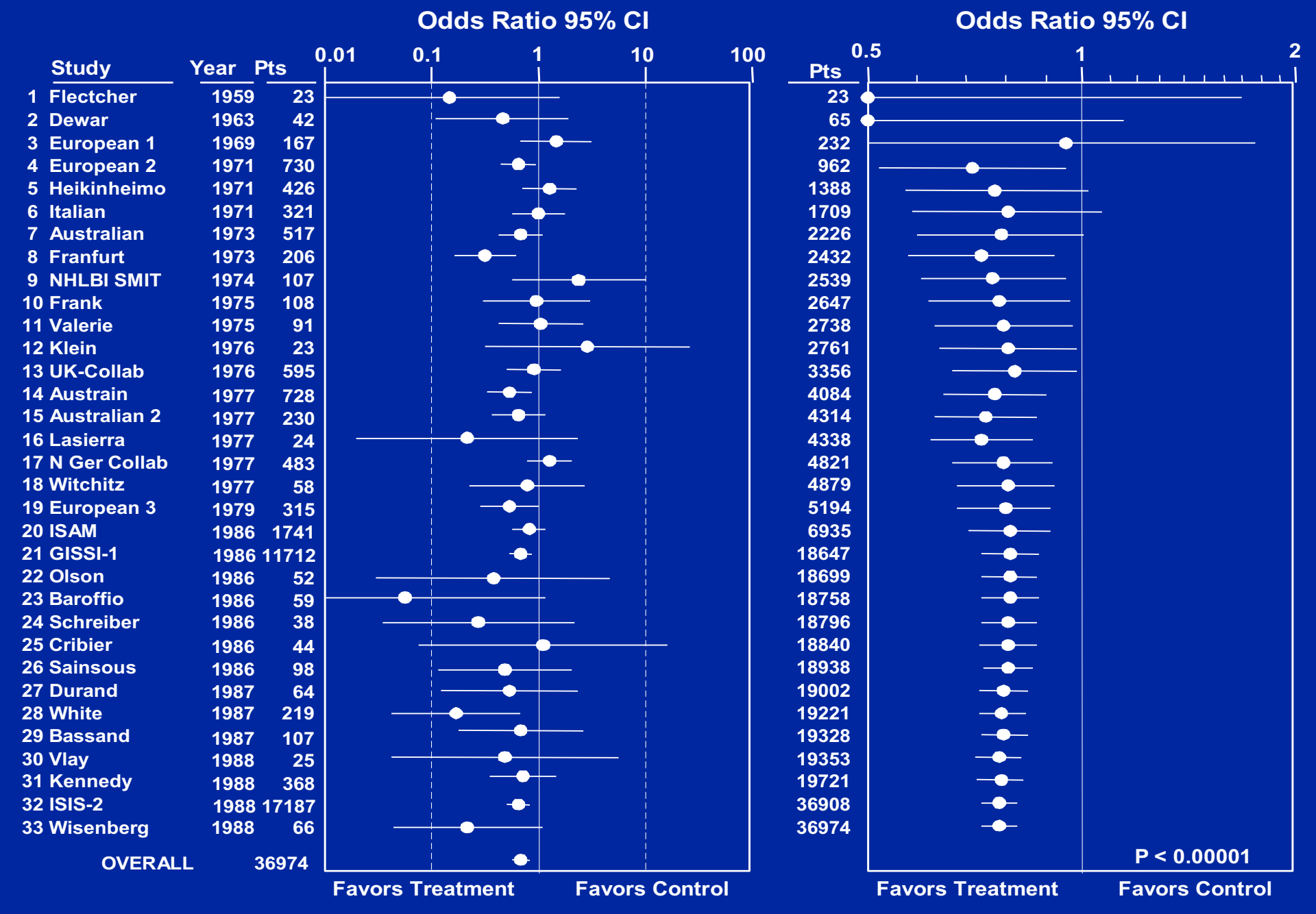
- Ved udarbejdelse af nationale guidelines og vurdering af sundhedsinterventioner (HTA).
- Ved udarbejdelse af lokale instrukser.
- Forud for iværksættelse af randomiserede kliniske forsøg.
- Overblik over litteraturen om en given intervention for klinikeren.

Intravenous Streptokinase Therapy for Acute Myocardial Infarction



	Study	Year	Pts
1	Flectcher	1959	23
2	Dewar	1963	42
3	European 1	1969	167
4	European 2	1971	730
5	Heikinheimo	1971	426
6	Italian	1971	321
7	Australian	1973	517
8	Franfurt	1973	206
9	NHLBI SMIT	1974	107
10	Frank	1975	108
11	Valerie	1975	91
12	Klein	1976	23
13	UK-Collab	1976	595
14	Austrain	1977	728
15	Australian 2	1977	230
16	Lasierra	1977	24
17	N Ger Collab	1977	483
18	Witchitz	1977	58
19	European 3	1979	315
20	ISAM	1986	1741
21	GISSI-1	1986	11712
22	Olson	1986	52
23	Baroffio	1986	59
24	Schreiber	1986	38
25	Cribier	1986	44
26	Sainsous	1986	98
27	Durand	1987	64
28	White	1987	219
29	Bassand	1987	107
30	Vlay	1988	25
31	Kennedy	1988	368
32	ISIS-2	1988	17187
33	Wisenberg	1988	66
	OVERALL		36974

Intravenous Streptokinase Therapy for Acute Myocardial Infarction



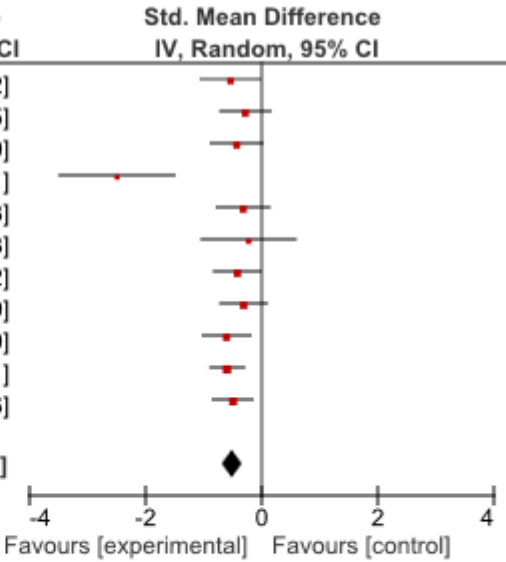
Faldgruber

- Ensartet effekt mellem de enkelte studier - forskelle kan forklares med statistisk variation.
- Publikationsbias kan skævvride resultatet.
- Tvivlsom metodologisk kvalitet af studier kan give et vildledende resultat.

Methylphenidate ved ADHD hos voksne

Study or Subgroup	Std. Mean Difference	SE	Weight	Std. Mean Difference IV, Random, 95% CI
Bouffard 2003	-0.5362	0.2631	7.9%	-0.54 [-1.05, -0.02]
Casas 2013	-0.2816	0.2192	9.6%	-0.28 [-0.71, 0.15]
Casas 2013	-0.4309	0.2206	9.6%	-0.43 [-0.86, 0.00]
Ginsberg 2012 A	-2.4917	0.5024	3.0%	-2.49 [-3.48, -1.51]
Jain 2007	-0.3177	0.228	9.2%	-0.32 [-0.76, 0.13]
Konstenius 2010	-0.2253	0.4098	4.2%	-0.23 [-1.03, 0.58]
Medori 2008	-0.4185	0.2045	10.3%	-0.42 [-0.82, -0.02]
Medori 2008	-0.3112	0.2043	10.3%	-0.31 [-0.71, 0.09]
Medori 2008	-0.6063	0.2069	10.2%	-0.61 [-1.01, -0.20]
Rösler 2009	-0.5982	0.1453	13.5%	-0.60 [-0.88, -0.31]
Weisler 2012	-0.4928	0.1711	12.0%	-0.49 [-0.83, -0.16]
Total (95% CI)			**100.0%**	**-0.50 [-0.69, -0.32]**

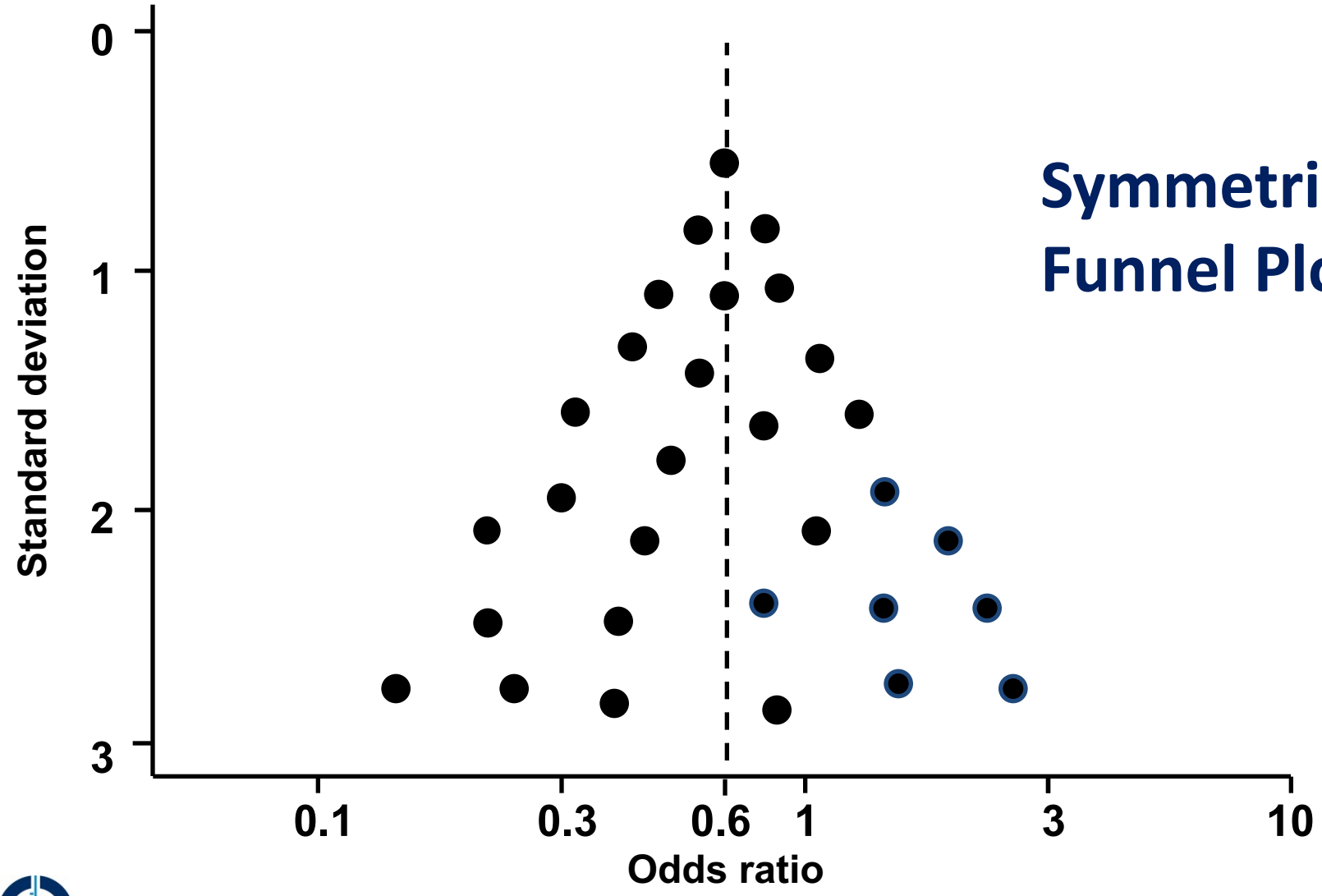
Heterogeneity: Tau² = 0.05; Chi² = 19.63, df = 10 (P = 0.03); I² = 49%
Test for overall effect: Z = 5.28 (P < 0.00001)

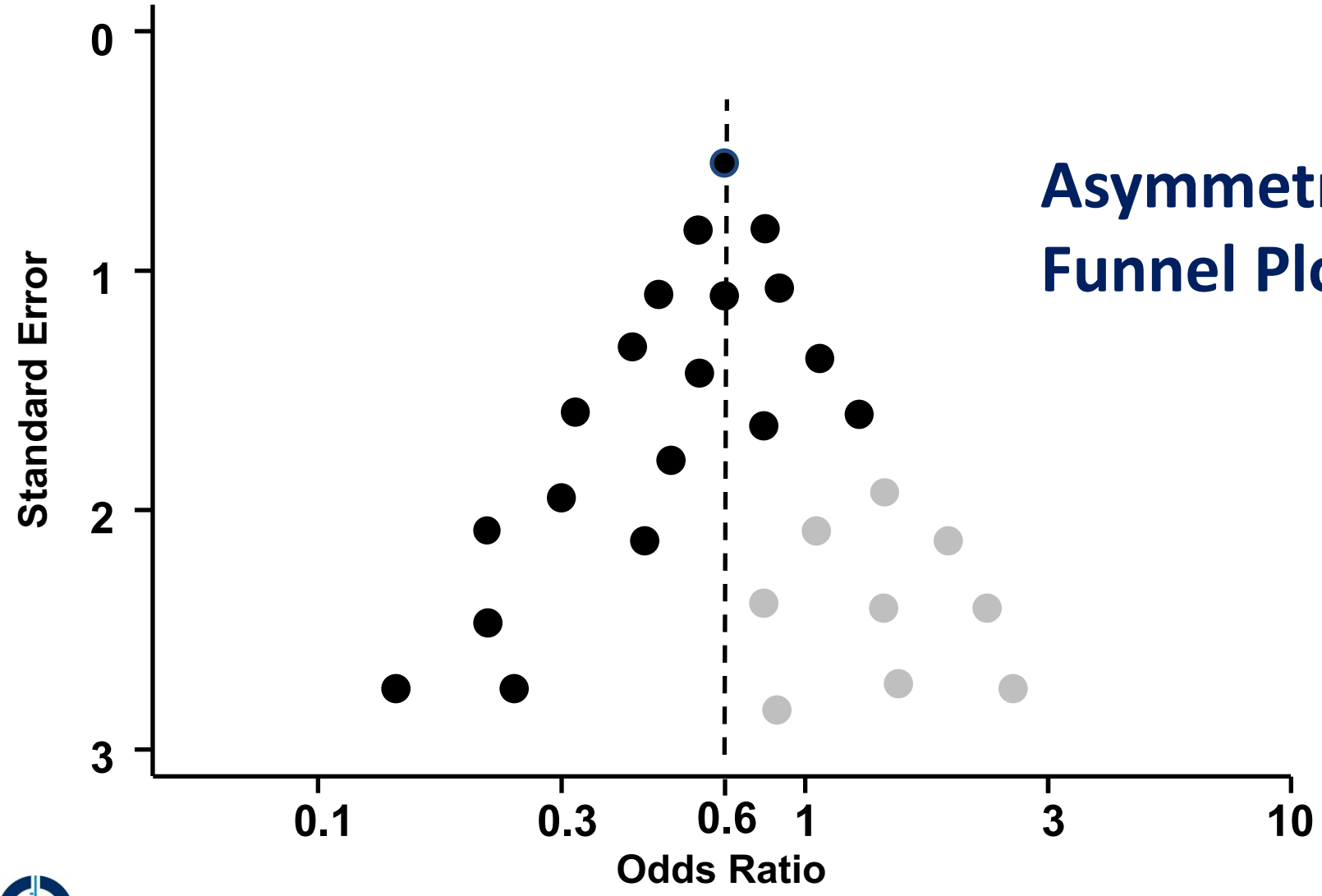


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

ADHD symptomer (Connor's Adult ADHD Rating Scale)

Symmetrisk Funnel Plot





Asymmetrisk Funnel Plot

Konklusioner

- Systematiske reviews vil altid være relevante, når man skal danne sig et overblik over effekten og bivirkningerne af en behandling.

- Meta-analyser kræver, at visse forudsætninger er opfyldt, og skal fortolkes med omhu.

Øvrige databaser

- RCT'er (CENTRAL): 600,472
- Andre reviews (DARE): 11,447 (kun abstracts)
- Metode studier: 12,200
- HTA: 7,596

Referenceprogrammer: Et eksempel.

”Der er i litteraturen modstridende oplysninger om effekten af systematisk screening for depression i forhold til at sikre, at flere kommer i behandling. Et nyere Cochrane-review viste således kun minimal indflydelse af systematisk screening på graden af diagnostik, behandling og udfald ved depression. Der er derimod generel enighed om, at screening for depression i risikogrupper kan bedre udfaldet, fx hos patienter med apopleksi eller hjertesygdom.”

Systematisk screening anbefales ikke, men:

Risikogrupper:

Der anbefales rutinemæssig opsporing af depression hos følgende risikogrupper (IIa):

Tidligere depression, Familiær disposition for depression, Hjertesygdom, Apopleksi, Kroniske smertetilstande, Diabetes, Kronisk obstruktiv lungesygdom (KOL), Cancer, Parkinsons sygdom,

Epilepsi, Andre psykiske sygdomme (pga. comorbiditet med depression). Desuden anbefales rutinemæssig screening for depression hos kvinder, der er gravide, eller lige har født, og hos flygtninge og indvandrere.

Hvad siger den bedste, tilgængelige evidens?

”There is substantial evidence that routinely administered case finding/screening questionnaires for depression have minimal impact on the detection, management or outcome of depression by clinicians. Practice guidelines and recommendations to adopt this strategy, in isolation, in order to improve the quality of healthcare should be resisted.”

Gilbody et al. Cochrane Database of Syst Rev: 2005 issue 3.

AGREE II

- Instrument til vurdering af kliniske vejledninger og referenceprogrammer.
- ’Baseret på teoretiske antagelser og ikke empirisk evidens’
- En god rettesnor, men pas på ’kogebogs-effekten’!

Intercessory prayer for the alleviation of ill health (Review)

Roberts L, Ahmed I, Hall S, Davison A

THE COCHRANE COLLABORATION®

Journal of Negative Results in BioMedicine

Commentary

Divine intervention? A Cochrane review on intercessory prayer gone beyond science and reason

Karsten Juhl Jørgensen, Asbjørn Hróbjartsson and Peter C Gøtzsche*

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Email: Karsten Juhl Jørgensen - kj@cochrane.dk; Asbjørn Hróbjartsson - ah@cochrane.dk; Peter C Gøtzsche* - pcg@cochrane.dk

* Corresponding author

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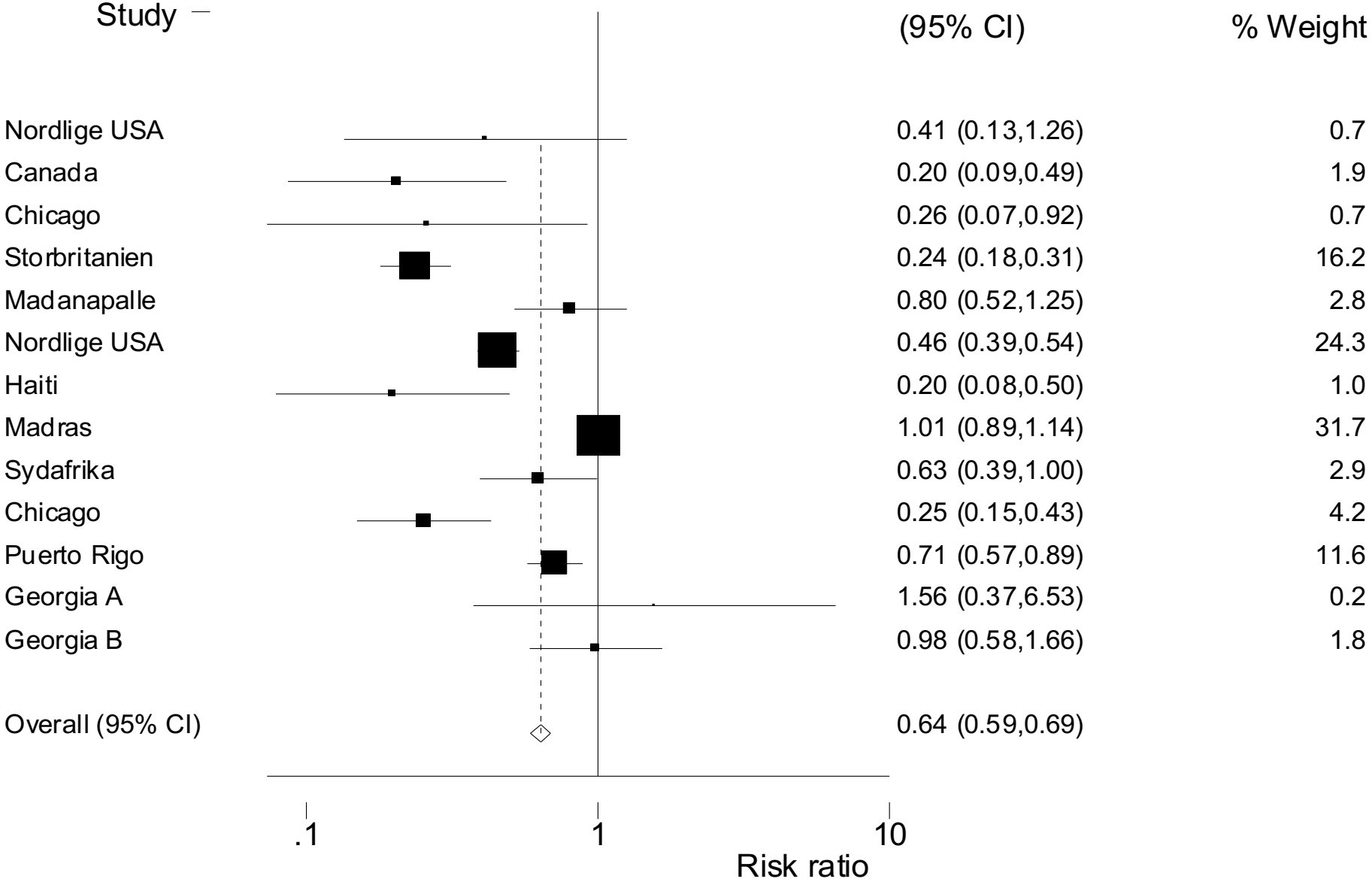
This article is available from: http://www.jnrbm.com/content/8/1/7

Abstract

We discuss in this commentary a recent Cochrane review of 10 randomised trials aimed at testing


Study
Risk ratio
(95% CI)
% Weight
Nordlige USA
0.41 (0.13,1.26)
0.7
Canada
0.20 (0.09,0.49)
1.9
Chicago
0.26 (0.07,0.92)
0.7
Storbritanien
0.24 (0.18,0.31)
16.2
Madanapalle
0.80 (0.52,1.25)
2.8
Nordlige USA
0.46 (0.39,0.54)
24.3
Haiti
0.20 (0.08,0.50)
1.0
Madras
1.01 (0.89,1.14)
31.7
Sydafrika
0.63 (0.39,1.00)
2.9
Chicago
0.25 (0.15,0.43)
4.2
Puerto Rigo
0.71 (0.57,0.89)
11.6
Georgia A
1.56 (0.37,6.53)
0.2
Georgia B
0.98 (0.58,1.66)
1.8
Overall (95% CI)
0.64 (0.59,0.69)
.1
1
10
Risk ratio

Special Communication

Breast Cancer Screening for Women at Average Risk
2015 Guideline Update From the American Cancer Society

Kevin C. Oeffinger, MD; Elizabeth T. H. Fontham, MPH, DrPH; Ruth Etzioni, PhD; Abbe Herzig, PhD; James S. Michaelson, PhD; Ya-Chen Tina Shih, PhD; Louise C. Walter, MD; Timothy R. Church, PhD; Christopher R. Flowers, MD, MS; Samuel J. LaMonte, MD; Andrew M. D. Wolf, MD; Carol DeSantis, MPH; Joannie Lortet-Tieulent, MSc; Kimberly Andrews; Deana Manassaram-Baptiste, PhD; Debbie Saslow, PhD; Robert A. Smith, PhD; Otis W. Brawley, MD; Richard Wender, MD

IMPORTANCE Breast cancer is a leading cause of premature mortality among US women. Early detection has been shown to be associated with reduced breast cancer morbidity and mortality.

OBJECTIVE To update the American Cancer Society (ACS) 2003 breast cancer screening guideline for women at average risk for breast cancer.

PROCESS The ACS commissioned a systematic evidence review of the breast cancer screening literature to inform the update and a supplemental analysis of mammography registry data to address questions related to the screening interval. Formulation of recommendations was based on the quality of the evidence and judgment (incorporating values and preferences) about the balance of benefits and harms.

EVIDENCE SYNTHESIS Screening mammography in women aged 40 to 69 years is associated with a reduction in breast cancer deaths across a range of study designs, and inferential evidence supports breast cancer screening for women 70 years and older who are in good health. Estimates of the cumulative lifetime risk of false-positive examination results are greater if screening begins at younger ages because of the greater number of mammograms, as well as the higher recall rate in younger women. The quality of the evidence for overdiagnosis is not sufficient to estimate a lifetime risk with confidence. Analysis examining the screening interval demonstrates more favorable tumor characteristics when premenopausal women are screened annually vs biennially. Evidence does not support routine clinical breast examination as a screening method for women at average risk.

RECOMMENDATIONS The ACS recommends that women with an average risk of breast cancer should undergo regular screening mammography starting at age 45 years (strong recommendation). Women aged 45 to 54 years should be screened annually (qualified recommendation). Women 55 years and older should transition to biennial screening or have the opportunity to continue screening annually (qualified recommendation). Women should have the opportunity to begin annual screening between the ages of 40 and 44 years (qualified recommendation). Women should continue screening mammography as long as their overall health is good and they have a life expectancy of 10 years or longer (qualified recommendation). The ACS does not recommend clinical breast examination for breast cancer screening among average-risk women at any age (qualified recommendation).

CONCLUSIONS AND RELEVANCE These updated ACS guidelines provide evidence-based recommendations for breast cancer screening for women at average risk of breast cancer. These recommendations should be considered by physicians and women in discussions about breast cancer screening.

Editorial page 1569

Author Video Interview, Author Audio Interview, Animated Summary Video, and JAMA Report Video at jama.com

Related articles pages 1615 and 1635 and JAMA Patient Page page 1658

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CME Quiz at jamanetworkcme.com and CME Questions page 1640

Related article at jamaoncology.com
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JAMA. 2015;314(15):1599-1614. doi:10.1001/jama.2015.12783

ACS recommendations 2015

- Continued screening for women with >10 year life expectancy.
- Women >55 years should transition from annual to beinnial screening. But with the option to continue annual screening.

Pooled estimates for relative breast cancer mortality reductions after approximately 13 years of follow-up were similar for 2 meta-analyses of RCTs using random-effects models (UK Independent Panel,[31] relative risk [RR], 0.80; 95% CI, 0.73-0.89; and Canadian Task Force,[32] RR, 0.82; 95% CI, 0.74-0.94) and for the Cochrane analysis,[30] which used a fixed-effects model (RR, 0.81; 95% CI, 0.74-0.87).

BREAST CANCER

Updated screening guidelines — much ado about small improvements

Karsten Juhl Jørgensen and Peter C. Gøtzsche

The recently updated breast cancer screening guidelines from the American Cancer Society are less aggressive than previous versions and clearer about overdiagnosis. However, a lack of attention was placed on the differences in effect estimates between trials at high and low risk of bias, and the authors failed to quantify the most serious harm.

Refers to Oeffinger, K. C. *et al.* Breast cancer screening for women at average risk. 2015 guideline update from the American Cancer Society. JAMA 314, 1599–1614 (2015).

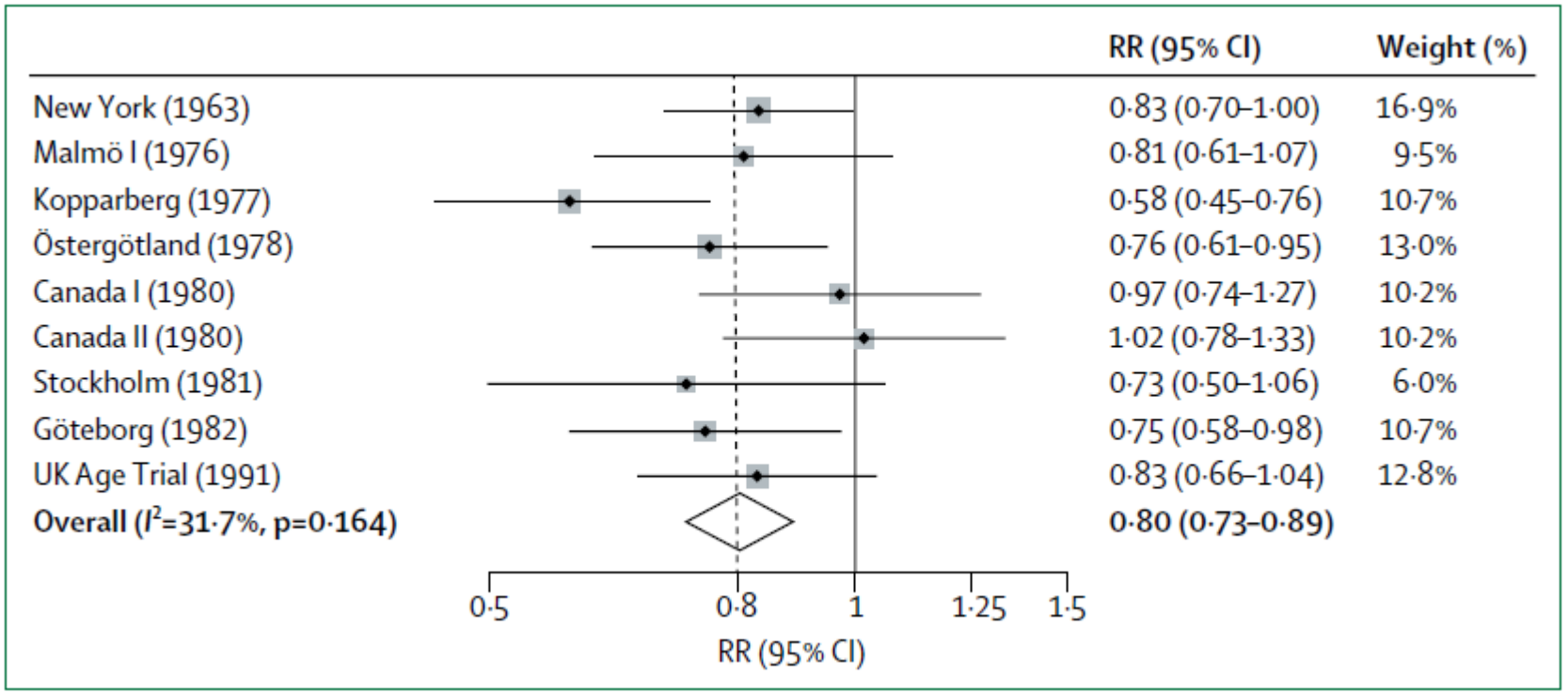
Updated guidelines on breast-cancer screening from the American Cancer Society (ACS) were published late in 2015 (REF. 1), replacing those published in 2003 (REF. 2). The most-marked change is that regular clinical breast examination is now no longer recommended for women of any age group, reflecting that the face value of cancer screening is no longer taken for granted: evidence that the benefits outweigh the harms is required. Furthermore, the previous guidelines advised that women aged ≥20 years should be informed about breast self-examination (BSE), but noted that it was "acceptable for women to choose not to do BSE" (REF. 2). The updated recommendations do not include statements on BSE "due to lack of evidence", but the ACS claim that this represents "no change" (REF. 1).

In addition, the target age range for screening mammography has been slightly reduced: the ACS now recommend that women begin undergoing annual screening from the age of 45 years, up from 40 years — although, women aged 40–44 years should continue to be offered the "opportunity to begin screening" (REF. 1). Moreover, instead of continuing screening mammography for "as long as a woman is in reasonably good health" (REF. 2), the new guidelines indicate that the women should have a 10-year life expectancy[1]. Both of these recommendations are 'fuzzy', as they depend on clinical judgment, which might introduce disparities in the use of screening. Women aged 55 years and older receive the even more ambiguous advice to transition from annual to biennial screening, but with the opportunity to continue annual screening[1].

The ACS recommendations were decided through votes. For screening mammography, the vote was informed by a systematic review of the available randomized trials and observational studies that was commissioned by the ACS, and was published concurrently with the updated recommendations[3]. Of note, well-defined methods for guideline development that have emerged over the past decade were used in the process of updating the guidelines. Specifically, the relevant populations, interventions, comparisons, outcomes, timings, and settings (PICOTS) were specified for each question, and the authors claimed to have used the Grading of Recommendation, Assessment, Development, and Evaluation (GRADE) methodology[4] to establish the level of confidence in the intervention effects[1]. At the heart of these tools is the intent to standardize and make transparent the quality assessment of the evidence, to ensure that benefits and harms are given equal attention, and to safeguard that the most reliable evidence forms the basis for recommendations[4,5].

Offering regular mammography screening to women aged 45–55 years is the only recommendation defined as being 'strong' in the updated guidelines[1]. Annual, rather than biennial, screening for this age group is deemed a "qualified recommendation" (REF. 1). 'Qualified' is an accepted term in the GRADE approach[5], but this denotation is not justified in this context because the recommendation is based on observational data that contradict evidence from randomized trials: no connection between the screening interval and the effect estimate was seen in the available randomized trials[6]; the appropriate GRADE term for the recommendation of annual screening is, therefore, 'weak', rather than 'qualified' — if justified at all.

In a marked change from the previous recommendations, overdiagnosis of breast cancer is now recognized by the ACS as "the greatest possible harm" from mammographic screening, and was correctly prespecified as a 'critical', rather than 'important', outcome[1] — critical outcomes are those deemed absolutely necessary to consider when making

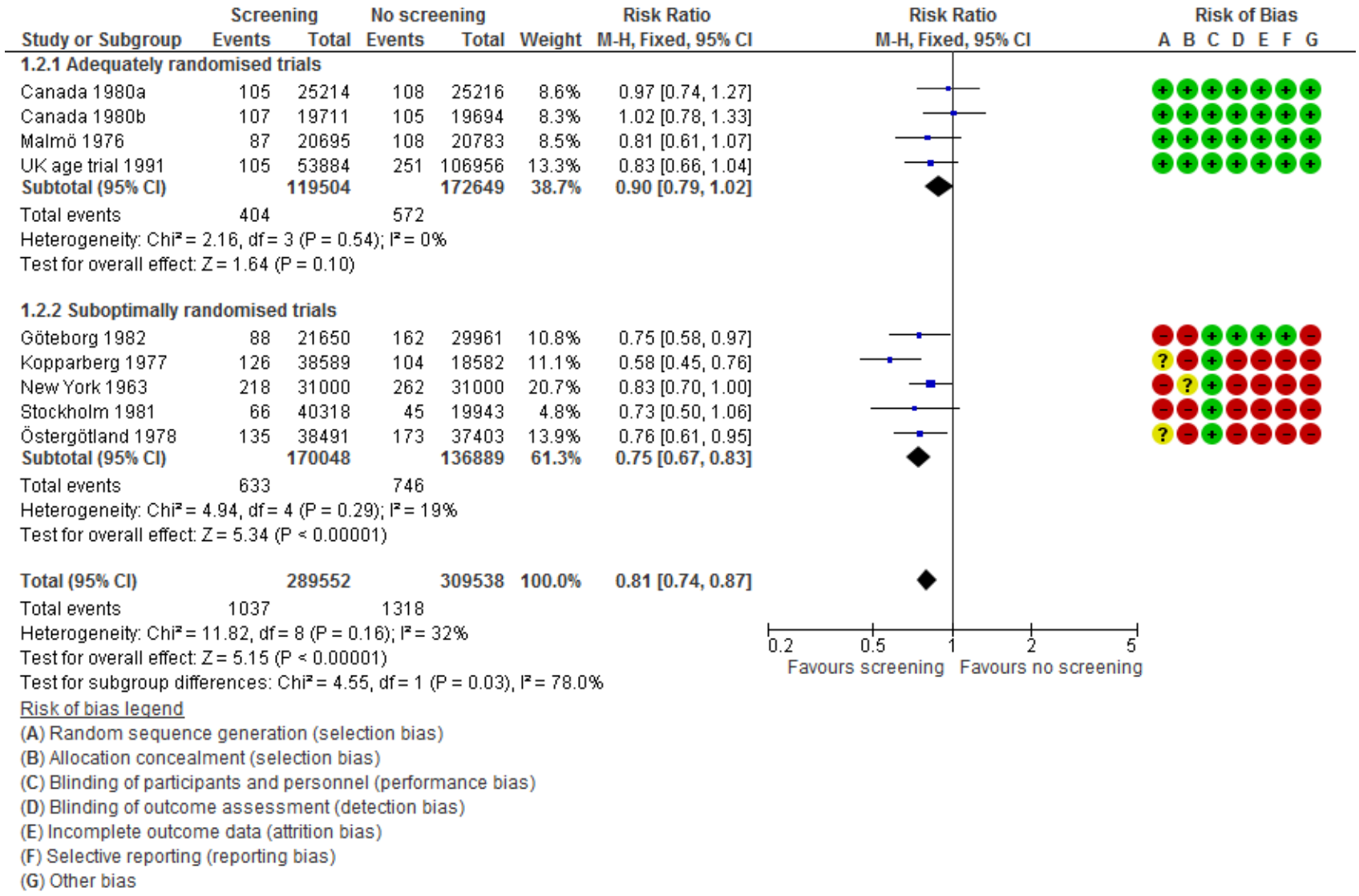


”The Panel’s primary conclusions about breast cancer mortality are based on data reported in the Cochrane review…”

What is heterogeneity?

Variation or differences

- three broad types:
  - clinical
  - methodological
  - statistical



Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

GRADE

”When (…) a sensitivity analysis suggests differences in estimates between studies with higher and lower risk of bias, we suggest, in accordance with the standard GRADE approach, using the estimates from the lower risk of bias studies, with no need to rate down confidence for risk of bias”

Iorio A et al. BMJ 2015;350:h870

A	B
100% participation	~80% participation
4-5 rounds	2-4 rounds
2 view	1 view
2 readers	1 reader
Screening every 12 month	Screening every 24-33 month

Gøtzsche PC, Nielsen M. Cochrane Database syst. Rev. 2011, Issue 1. Art. No.: CD001877.
Baines CJ. AJR Am J Roentgenol 2013;200:W96-7.

A	B
100% participation	~70% participation
4-5 rounds	2-4 rounds
2 view	1 view
2 readers	1 reader
Screening every 12 month	Screening every 24-33 month
A finds smaller average size tumors than B	

Gøtzsche PC, Nielsen M. Cochrane Database syst. Rev. 2011, Issue 1. Art. No.: CD001877.
Baines CJ. AJR Am J Roentgenol 2013;200:W96-7.

A	B
100% participation	~70% participation
4-5 rounds	2-4 rounds
2 view	1 view
2 readers	1 reader
Screening every 12 month	Screening every 24-33 month
A finds smaller average size tumors than B	
Individual randomisation	Cluster-randomisation (45)
Presents demographic data	Do not present demographic data
Consistent, transparent reporting	Inconsistent, unclear reporting
Blinded, external cause of death evaluation	No blinded cause of death evaluation

Gøtzsche PC, Nielsen M. Cochrane Database syst. Rev. 2011, Issue 1. Art. No.: CD001877.
Baines CJ. AJR Am J Roentgenol 2013;200:W96-7.

A	B
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Individual randomisation	Cluster-randomisation (45)
Presents demographic data	Do not present demographic data
Consistent, transparent reporting	Inconsistent, unclear reporting
Blinded, external cause of death evaluation	No blinded cause of death evaluation
3% reduction (-26% to +27%)* 2% increase(-22% to + 33%)*	42% reduction (-55% to -3%)* 24% reduction (-39% til -5%)*

* Thirteen years follow-up

Gøtzsche PC, Nielsen M. Cochrane Database syst. Rev. 2011, Issue 1. Art. No.: CD001877.
Baines CJ. AJR Am J Roentgenol 2013;200:W96-7.

Published in final edited form as:
Ann Intern Med. 2014 July 15; 161(2): 104–112. doi:10.7326/M13-2867.

Personalizing Age of Cancer Screening Cessation Based on Comorbidity: Model estimates of harms and benefits

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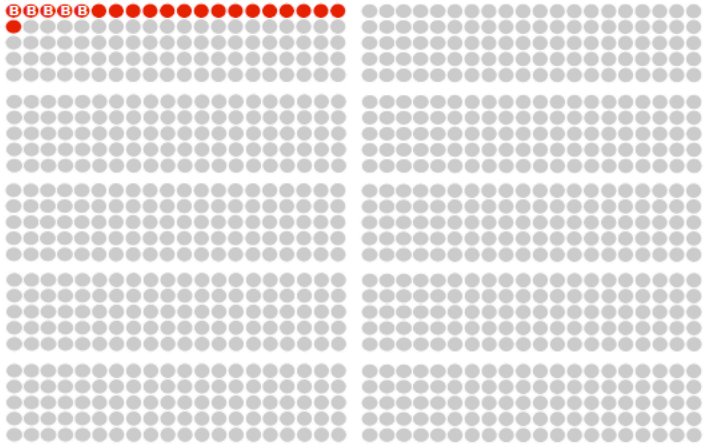
Breast Cancer Early Detection

HARDING CENTER FOR RISK LITERACY

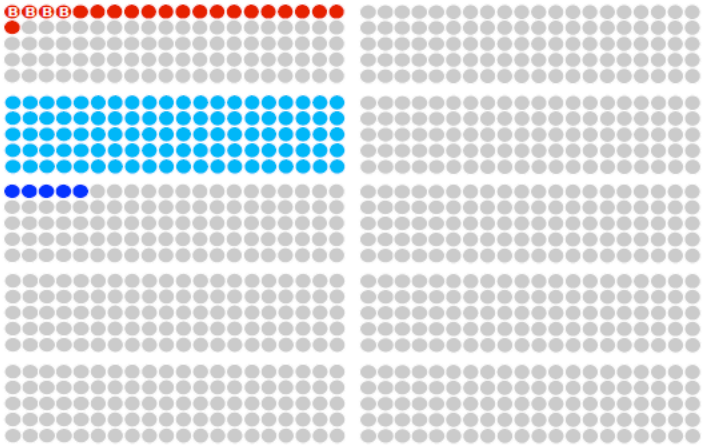
by mammography screening

Numbers for women aged 50 years or older who participated in screening for 10 years or more

1000 women without screening:

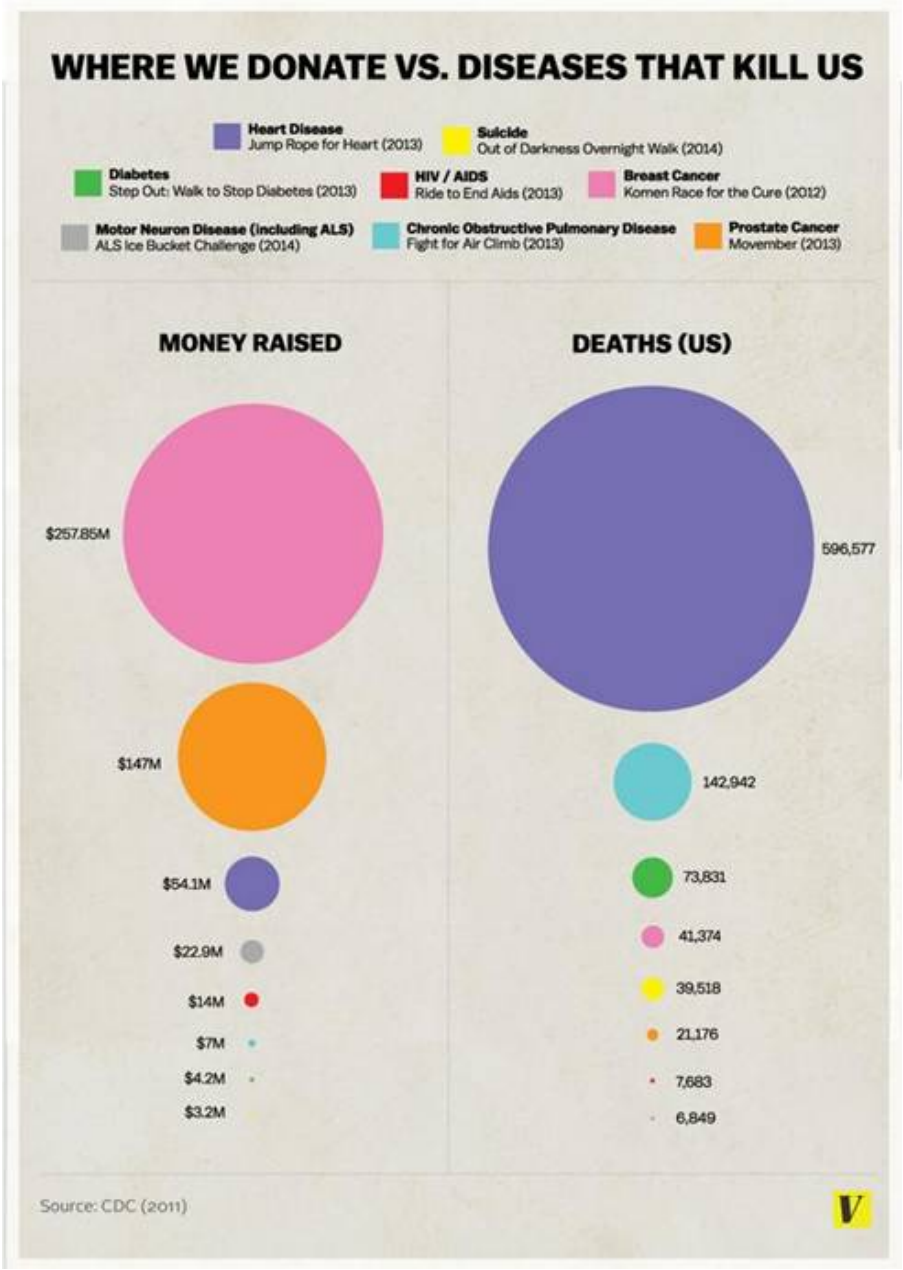


1000 women with screening:



Women who died from breast cancer:	5	4
Women who died from all types of cancer:	21	21
Women who learned after a biopsy that their diagnosis was a false-positive:	–	100
Women who were diagnosed and treated for breast cancer unnecessarily:	–	5
Remaining women:	979	874

Source:
Gøtzsche, PC, Jørgensen, KJ (2013). *Cochrane Database of Systematic Reviews* (6): CD001877
Numbers in the facts box are rounded. Where no data for women above 50 years of age are available, numbers refer to women above 40 years of age.
www.harding-center.mpg.de


WHERE WE DONATE VS. DISEASES THAT KILL US
Heart Disease
Jump Rope for Heart (2013)
Suicide
Out of Darkness Overnight Walk (2014)
Diabetes
Step Out: Walk to Stop Diabetes (2013)
HIV / AIDS
Ride to End Aids (2013)
Breast Cancer
Komen Race for the Cure (2012)
Motor Neuron Disease (including ALS)
ALS Ice Bucket Challenge (2014)
Chronic Obstructive Pulmonary Disease
Fight for Air Climb (2013)
Prostate Cancer
Movember (2013)
MONEY RAISED
$257.85M
$147M
$54.1M
$22.9M
$14M
$7M
$4.2M
$3.2M
DEATHS (US)
596,577
142,942
73,831
41,374
39,518
21,176
7,683
6,849
Source: CDC (2011)

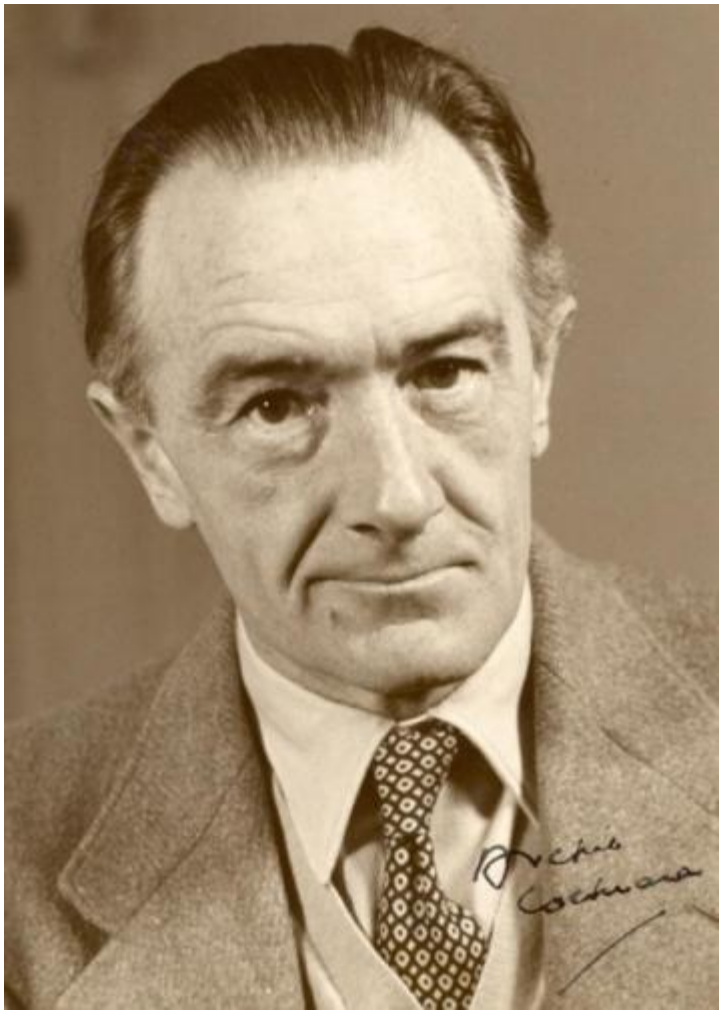

If you haven't had a mammogram, you need more than your breasts examined.
A mammogram is a safe, low-dose X-ray that can detect breast cancer before there's a lump. In other words, it could save your life and your breast.
If you're a woman over 35, be sure to schedule a mammogram. Unless you're still not convinced of its importance.
In which case, you may need more than your breasts examined.
Find the time.
Have a mammogram.
AMERICAN CANCER SOCIETY®
Give yourself the chance of a lifetime.

“…one can simplify a message so much that one is lying. Too much of that has happened in breast cancer over the past 30 years...“

- Otis Brawley, MD, Chief Medical Officer, ACS

http://www.medpagetoday.com/OBGYN/BreastCancer/54228

Archie Cochrane's challenge



"It is surely a great criticism of our profession that we have not organised a critical summary, by specialty or subspecialty, adapted periodically, of all relevant randomised controlled trials."

Cochrane 1979

Photograph: Cardiff University Library, Cochrane Archive, University Hospital Llandough

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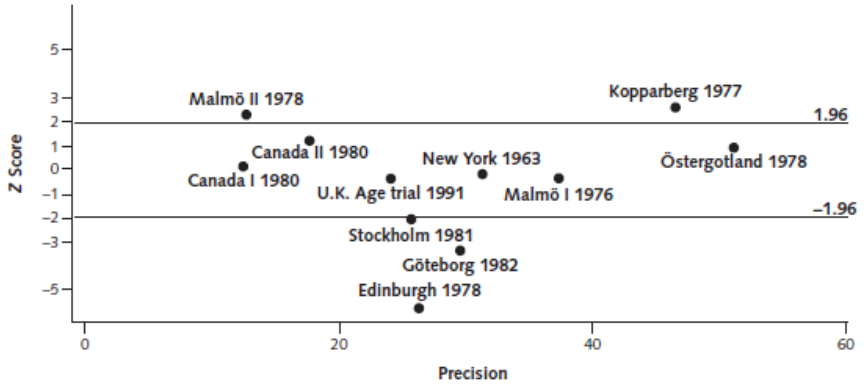
Drafting of the article: P. Jüni.
Critical revision of the article for important intellectual content: P. Jüni, M. Zwahlen.
Final approval of the article: P. Jüni, M. Zwahlen.
Statistical expertise: P. Jüni, M. Zwahlen.
Administrative, technical, or logistic support: P. Jüni.
Collection and assembly of data: P. Jüni, M. Zwahlen.

Appendix Figure. **Modified Galbraith plot of the estimated effects of mammography screening on deaths from causes other than breast cancer against the statistical precision of 11 screening trials.**



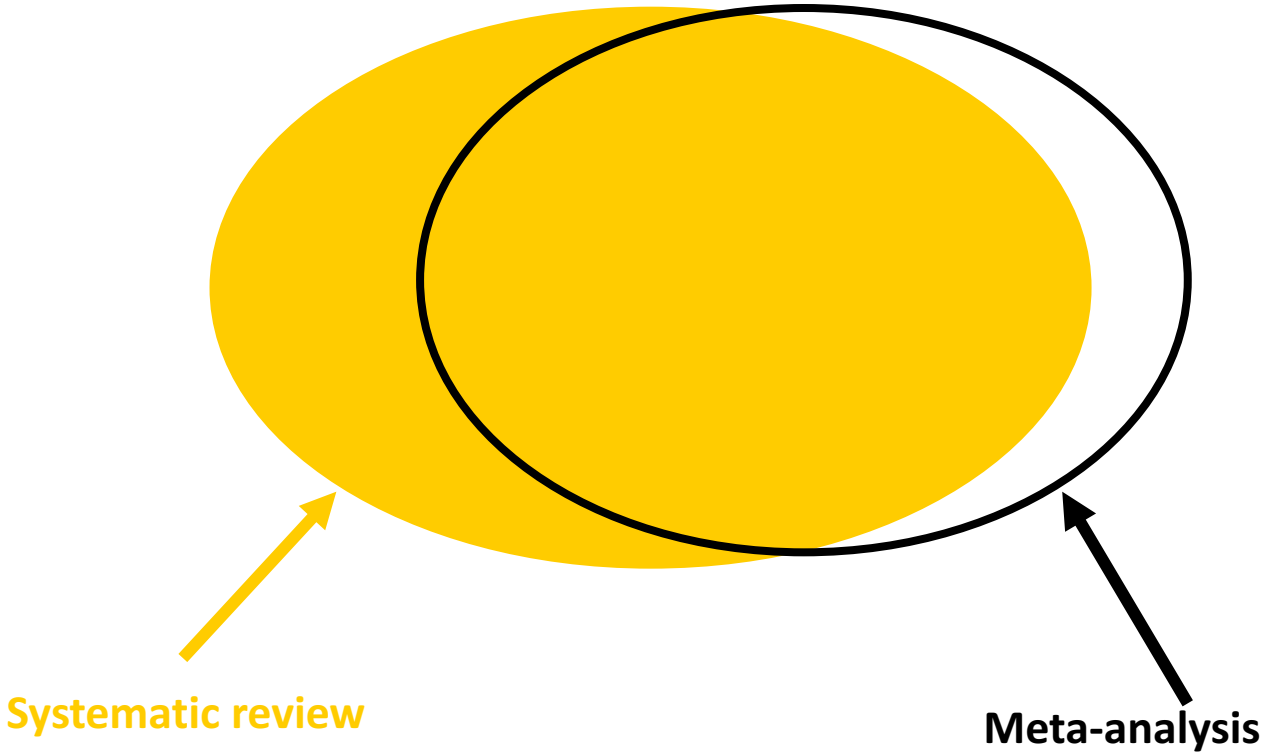
The Z score was calculated as ln(RR)/[SE of the ln(RR)]; statistical precision was calculated as 1/[SE of the ln(RR)]. The fixed Z score boundaries at -1.96 and 1.96, represented by the solid lines, divide the plot into areas of significant differences between the screening and control groups ($Z < -1.96$ and $Z > 1.96$, respectively) and nonsignificant differences ($-1.96 < Z < 1.96$). Three trials (Edinburgh 1978, Göteborg 1982, Stockholm 1981) are below the bounds and are associated with a significant benefit of mammography screening on deaths from other causes, whereas 2 others (Malmö II 1978 and Kopparberg 1977) are above the bounds and are associated with a significant harm from mammography screening. If the true RR equals 1, then 1 trial will be outside the boundaries with a probability of 43.1%, 2 trials with 10.2%, and 3 trials with 1.5%. The probability that 5 trials lie outside the boundaries, as is the case, is 0.01%. Data are from reference 5. RR = relative risk.

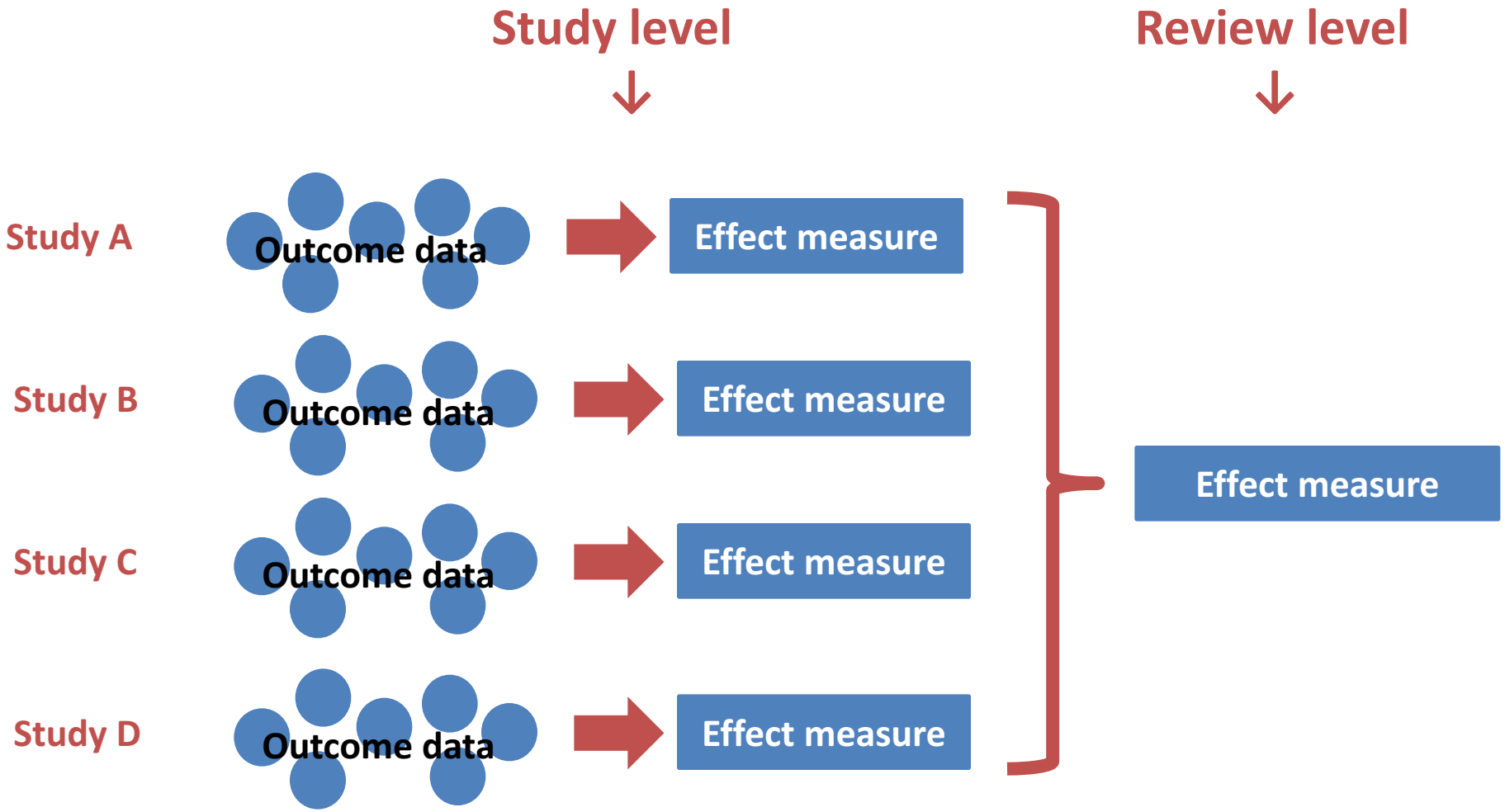
Methodological diversity

- design
  - e.g. randomised vs non-randomised, crossover vs parallel, individual vs cluster randomised
- conduct
  - e.g. risk of bias (allocation concealment, blinding, etc.), approach to analysis


Cochrane

Systematic review and meta-analysis





Source: Jo McKenzie & Miranda Cumpston

Why perform a meta-analysis?

- quantify treatment effects and their uncertainty
- increase power
- increase precision
- explore differences between studies
- settle controversies from conflicting studies
- generate new hypotheses

Source: Julian Higgins

When can you do a meta-analysis?

- more than one study has measured an effect
- the studies are sufficiently similar to produce a meaningful and useful result
- the outcome has been measured in similar ways
- data are available in a format we can use

When not to do a meta-analysis

- **mixing apples with oranges**
  - each included study must address same question
    - consider comparison and outcomes
    - requires your subjective judgement
  - combining a broad mix of studies answers broad questions
  - answer may be meaningless and genuine effects may be obscured if studies are too diverse

Source: Julian Higgins

Hierarchy of evidence

Ia Systematic review of RCT's

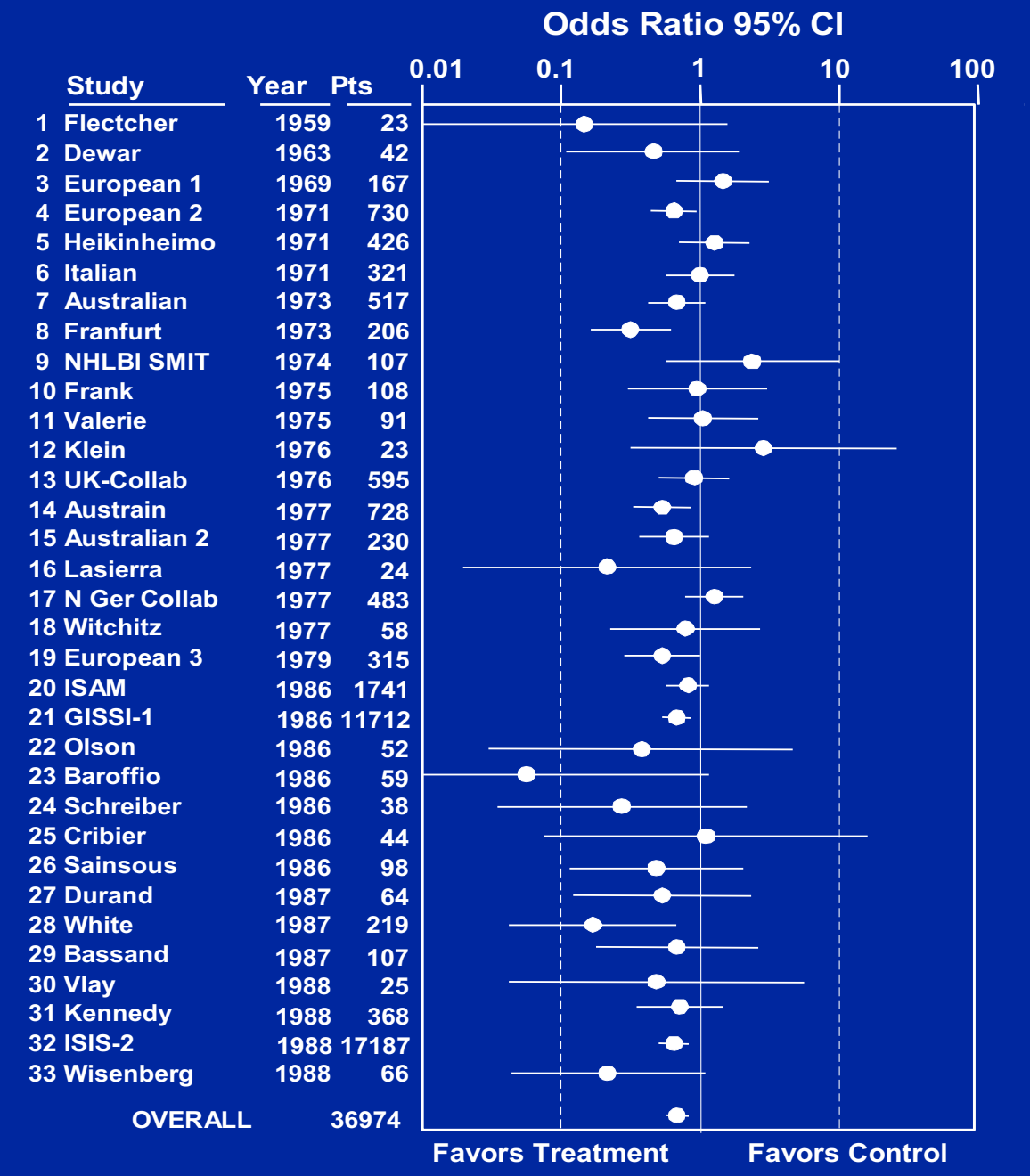
- Ib Randomised trials
- IIa Controlled, non-randomisered studies
- IIb Cohorte studies
- III Case-control studies
- IV Descriptive studies
- Non-systematic reviews (overview papers)
- Consensus reports (Clinical guidelines)
- Editorials

Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gordon C S Smith, Jill P Pell

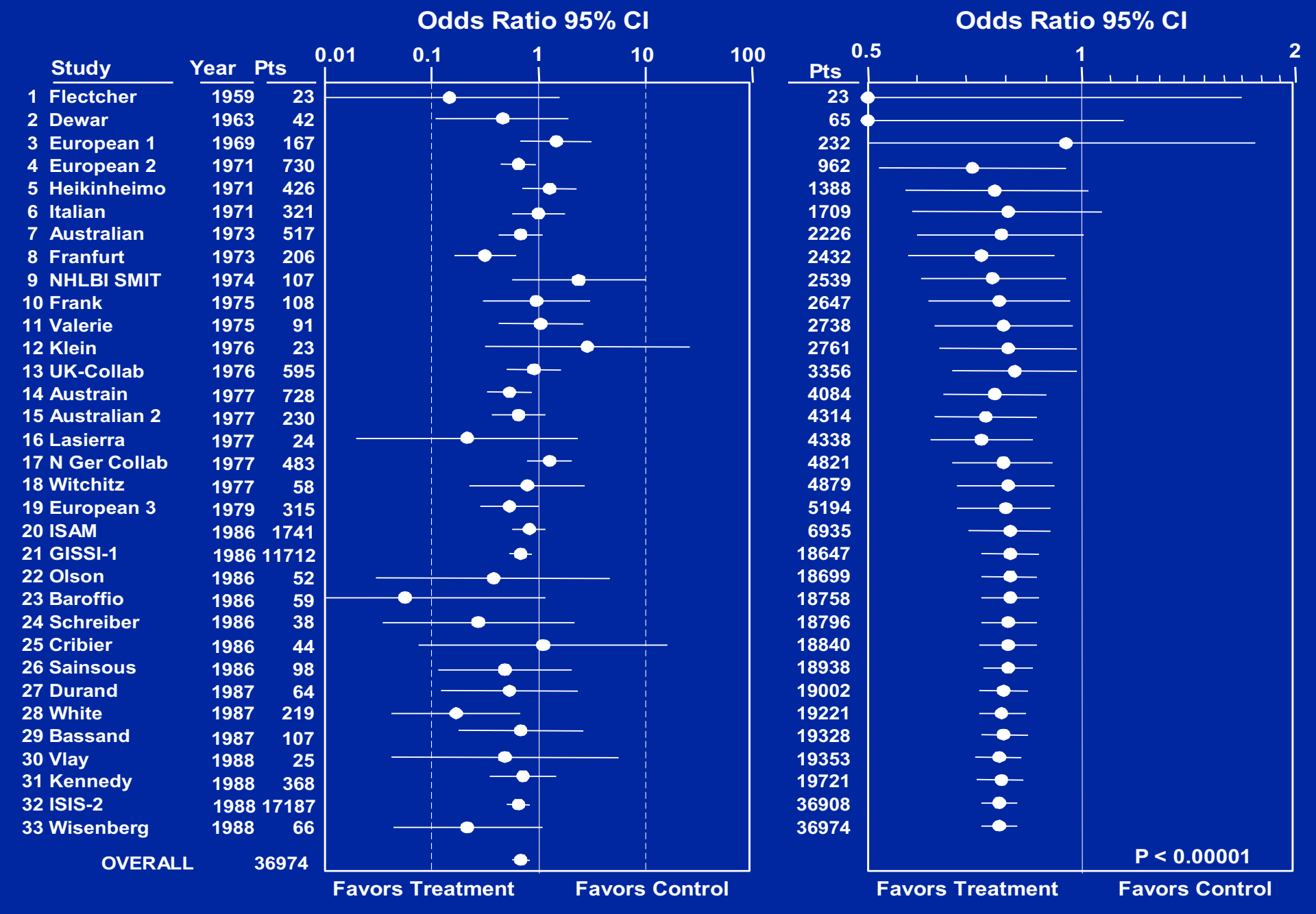
Conclusions: As with many interventions intended to prevent ill health, the effectiveness of parachutes has not been subjected to rigorous evaluation by using randomised controlled trials. Advocates of evidence based medicine have criticised the adoption of interventions evaluated by using only observational data. We think that everyone might benefit if the most radical protagonists of evidence based medicine organised and participated in a double blind, randomised, placebo controlled, crossover trial of the parachute.

Intravenous Streptokinase Therapy for Acute Myocardial Infarction



	Study	Year	Pts
1	Flectcher	1959	23
2	Dewar	1963	42
3	European 1	1969	167
4	European 2	1971	730
5	Heikinheimo	1971	426
6	Italian	1971	321
7	Australian	1973	517
8	Franfurt	1973	206
9	NHLBI SMIT	1974	107
10	Frank	1975	108
11	Valerie	1975	91
12	Klein	1976	23
13	UK-Collab	1976	595
14	Austrain	1977	728
15	Australian 2	1977	230
16	Lasierra	1977	24
17	N Ger Collab	1977	483
18	Witchitz	1977	58
19	European 3	1979	315
20	ISAM	1986	1741
21	GISSI-1	1986	11712
22	Olson	1986	52
23	Baroffio	1986	59
24	Schreiber	1986	38
25	Cribier	1986	44
26	Sainsous	1986	98
27	Durand	1987	64
28	White	1987	219
29	Bassand	1987	107
30	Vlay	1988	25
31	Kennedy	1988	368
32	ISIS-2	1988	17187
33	Wisenberg	1988	66
	OVERALL		36974

Intravenous Streptokinase Therapy for Acute Myocardial Infarction

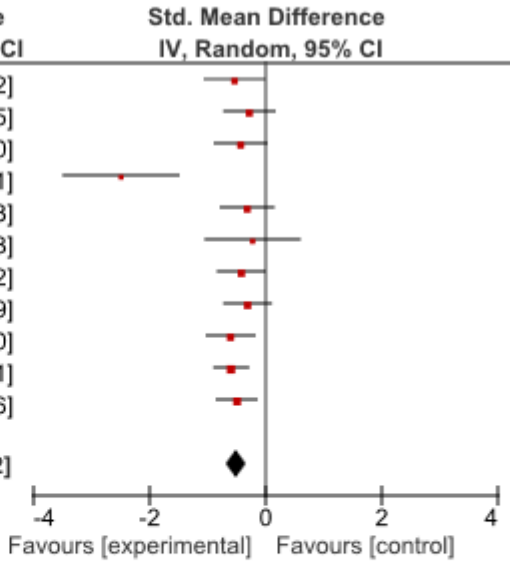


Methylphenidate for ADHD in adults

Study or Subgroup	Std. Mean Difference	SE	Weight	Std. Mean Difference IV, Random, 95% CI
Bouffard 2003	-0.5362	0.2631	7.9%	-0.54 [-1.05, -0.02]
Casas 2013	-0.2816	0.2192	9.6%	-0.28 [-0.71, 0.15]
Casas 2013	-0.4309	0.2206	9.6%	-0.43 [-0.86, 0.00]
Ginsberg 2012 A	-2.4917	0.5024	3.0%	-2.49 [-3.48, -1.51]
Jain 2007	-0.3177	0.228	9.2%	-0.32 [-0.76, 0.13]
Konstenius 2010	-0.2253	0.4098	4.2%	-0.23 [-1.03, 0.58]
Medori 2008	-0.4185	0.2045	10.3%	-0.42 [-0.82, -0.02]
Medori 2008	-0.3112	0.2043	10.3%	-0.31 [-0.71, 0.09]
Medori 2008	-0.6063	0.2069	10.2%	-0.61 [-1.01, -0.20]
Rösler 2009	-0.5982	0.1453	13.5%	-0.60 [-0.88, -0.31]
Weisler 2012	-0.4928	0.1711	12.0%	-0.49 [-0.83, -0.16]
Total (95% CI)			**100.0%**	**-0.50 [-0.69, -0.32]**

Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 19.63$, df = 10 (P = 0.03); $I^2 = 49\%$

Test for overall effect: Z = 5.28 (P < 0.00001)



Risk of bias legend

(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

ADHD symptoms

ADHD påvirker ofte patienterne hele dagen[1-3]

DKSTR00468 – august 2015

Hvornår på dagen er dine patienter udfordrede?

- Svært ved at komme ud af sengen?
- Kommer ofte til at skælde sine børn ud på vej ud af døren?
- Distraheres nemt på jobbet?
- Svært ved at fastholde venskaber?
- Glemmer sine eftermiddagsaftaler?
- Svært ved at slappe af med sin partner efter arbejde?
- Vil gerne dyrke sport, men kan oftest ikke overskue det?
- Svært ved at falde i søvn om aftenen?

Referencer:
1. Davidson MA. J Atten Disord 2008; 11 : 628-641. 2. Brod Metal. Qual Life Res 2012; 21 : 795-799. 3. Barkley RA. J Clin Psychiatry 2002; 63 (Suppl 12): 10- 15. 4. Adler et al. Journal of Clinical Psychopharmacology, 2009; 29(1): 44–50. 5. Wehmeier et al. Child Adolesc. Mental Health, 2009; 3: 1-10. 6. Strattera produktresume 16.maj 2014

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Lilly

strattera® atomoxetin HCl

Steps in a meta-analysis

- *identify comparisons to be made*
- *identify outcomes to be reported and statistics to be used*
- collect data from each relevant study
- combine the results to obtain the summary of effect
- explore differences between the studies
- interpret the results

Selecting comparisons

Hypothetical review: Caffeine for daytime drowsiness

caffeinated coffee vs decaffeinated coffee

- break your topic down into pair-wise comparisons
- each review may have one or many
- use your judgement to decide what to group together, and what should be a separate comparison

Selecting effect measures

Hypothetical review: Caffeine for daytime drowsiness

caffeinated coffee vs decaffeinated coffee

- asleep at end of trial (RR)
- irritability (MD/SMD)
- headaches (RR)

- for each comparison, select outcomes
- for each outcome, select an effect measure
  - may depend on the available data from included studies

Calculating the summary result

- collect a summary statistic from each contributing study
- how do we bring them together?
  - simple average?
    - weights all studies equally – some studies closer to the truth
  - **weighted average**

Weighting studies

- more weight to the studies which give more information
  - more participants, more events, narrower confidence interval
  - calculated using the effect estimate and its variance

$$\text{weight} = \frac{1}{\text{variance of estimate}} = \frac{1}{SE^2}$$

- inverse-variance method:

$$\text{pooled estimate} = \frac{\text{sum of}(\text{estimate} \times \text{weight})}{\text{sum of weights}}$$

For example

Headache	Caffeine	Decaf	Weight
Amore-Coffea 2000	2/31	10/34	
Deliciozza 2004	10/40	9/40	
Mama-Kaffa 1999	12/53	9/61	
Morrocona 1998	3/15	1/17	
Norscafe 1998	19/68	9/64	
Oohlahlazza 1998	4/35	2/37	
Piazza-Allerta 2003	8/35	6/37	

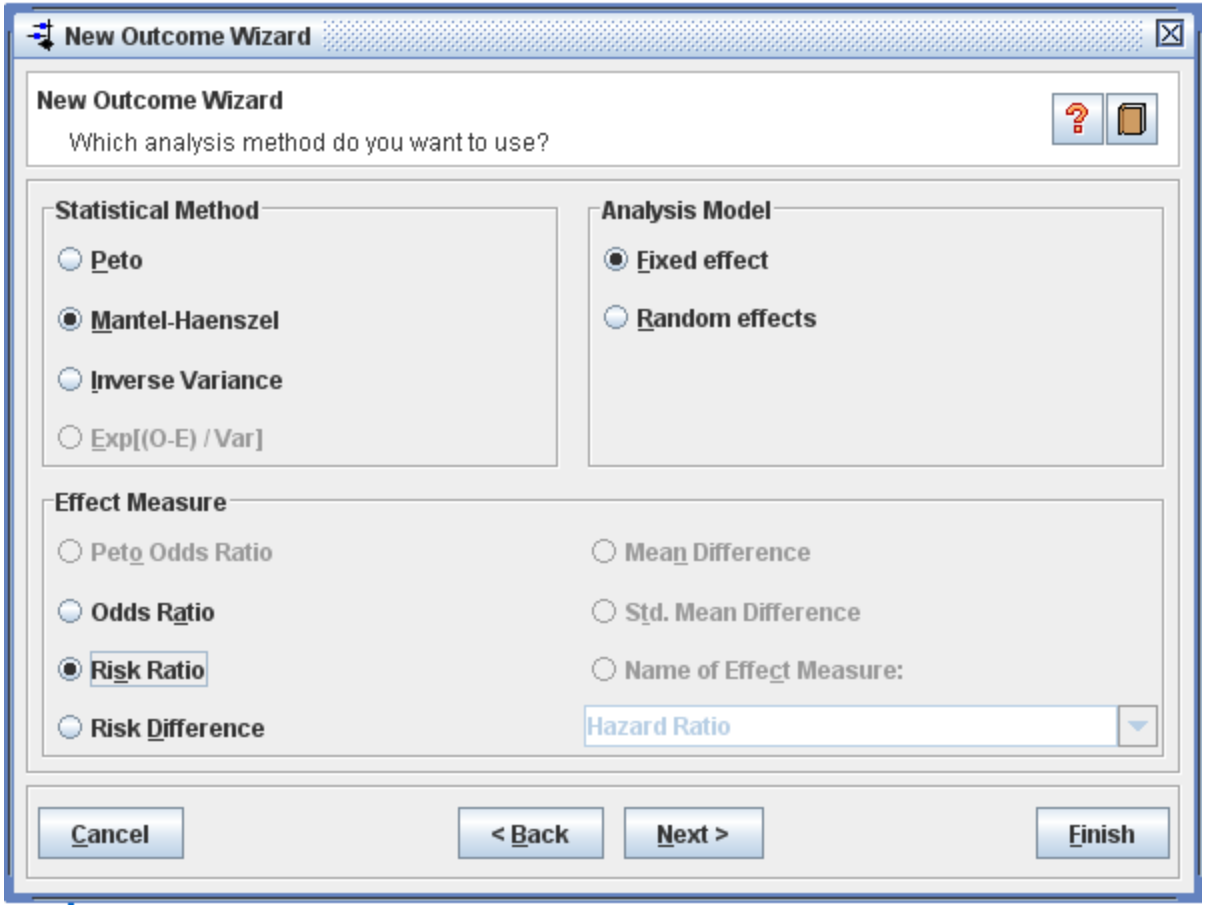
For example

Headache	Caffeine	Decaf	Weight
Amore-Coffea 2000	2/31	10/34	6.6%
Deliciozza 2004	10/40	9/40	21.9%
Mama-Kaffa 1999	12/53	9/61	22.2%
Morrocona 1998	3/15	1/17	2.9%
Norscafe 1998	19/68	9/64	**26.4%**
Oohlahlazza 1998	4/35	2/37	5.1%
Piazza-Allerta 2003	8/35	6/37	14.9%

Meta-analysis options

- for dichotomous or continuous data
  - inverse-variance
    - straightforward, general method
- for dichotomous data only
  - Mantel-Haenszel (default)
    - good with few events – common in Cochrane reviews
    - weighting system depends on effect measure
  - Peto
    - for odds ratios only
    - good with few events and small effect sizes (OR close to 1)

Meta-analysis options



Interpreting confidence intervals

- always present estimate with a confidence interval
- **precision**
  - point estimate is the best guess of the effect
  - CI expresses uncertainty – range of values we can be reasonably sure includes the true effect
- **significance**
  - if the CI includes the null value
    - rarely means evidence of no effect
    - effect cannot be confirmed or refuted by the available evidence
  - consider what level of change is clinically important

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Take home message

- there are several advantages to performing a meta-analysis but it is not always possible (or appropriate)
- plan your analysis carefully, including comparisons, outcomes and meta-analysis methods
- forest plots display the results of meta-analyses graphically
- interpret your results with caution

Exploring heterogeneity

Clinical diversity

- participants
  - e.g. condition, age, gender, location, study eligibility criteria
- interventions
  - intensity/dose, duration, delivery, additional components, experience of practitioners, control (placebo, none, standard care)
- outcomes
  - follow-up duration, ways of measuring, definition of an event, cut-off points

Statistical heterogeneity

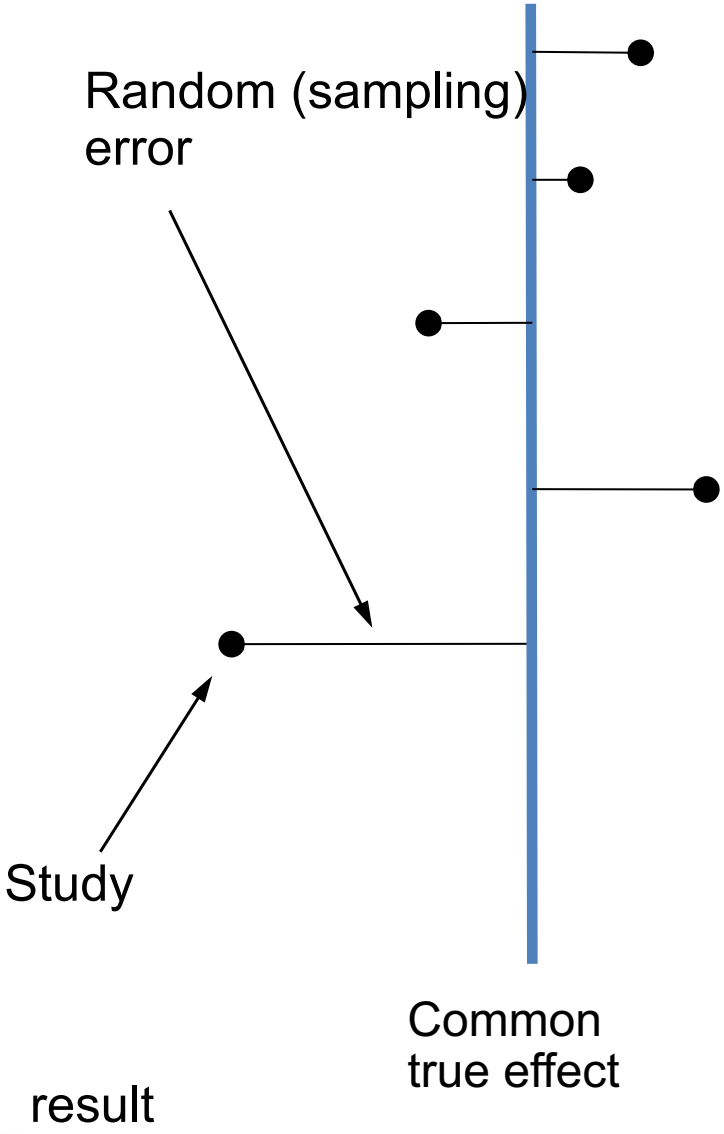
- there will always be some random (sampling) variation between the results of different studies

- heterogeneity is variation between the **effects being evaluated** in the different studies
  - caused by clinical and methodological diversity
  - alternative to homogeneity (identical true effects underlying every study)
  - study results will be **more** different from each other than if random variation is the only reason for the differences between the estimated intervention effects

Fixed-effect vs random-effects

- two models for meta-analysis available in RevMan
- make different assumptions about heterogeneity
- pre-specify your planned approach in your protocol

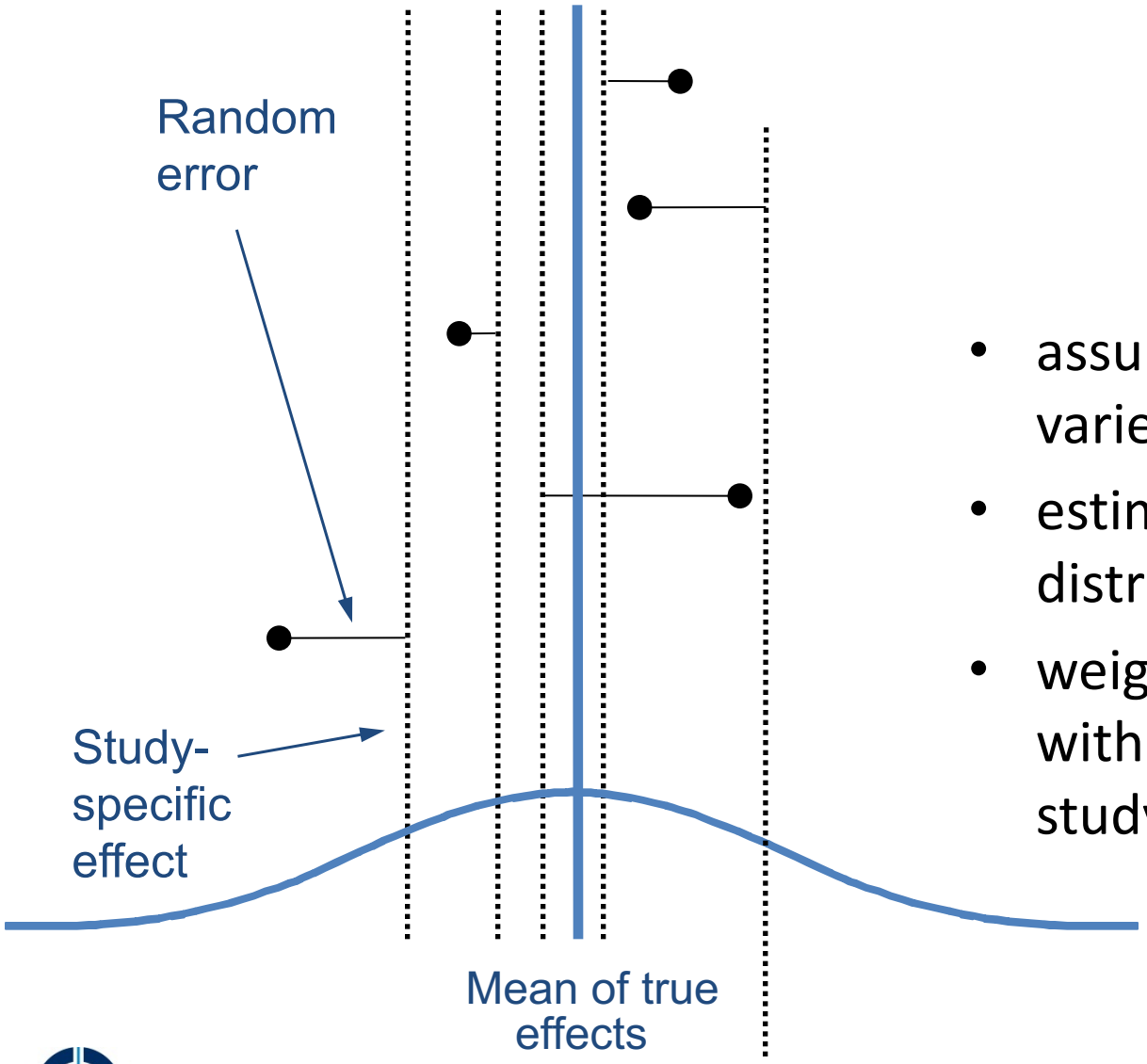
Fixed-effect model



- assumes all studies are measuring the same treatment effect
- estimates that one effect
- if not for random (sampling) error, all results would be identical

Source: Julian Higgins

Random-effects model



- assumes the treatment effect varies between studies
- estimates the **mean** of the distribution of effects
- weighted for both within-study and between-study variation (tau^2, τ^2)

Source: Julian Higgins

What's the difference?

- random-effects meta-analyses are:
  - **almost identical** to fixed-effect when there is no heterogeneity
  - **similar** to fixed-effect but with **wider confidence intervals** when there is heterogeneity of the sort assumed by random effects model
  - **different** from fixed-effect meta-analyses when results are related to study size
    - Random effects model gives relatively more weight to smaller studies

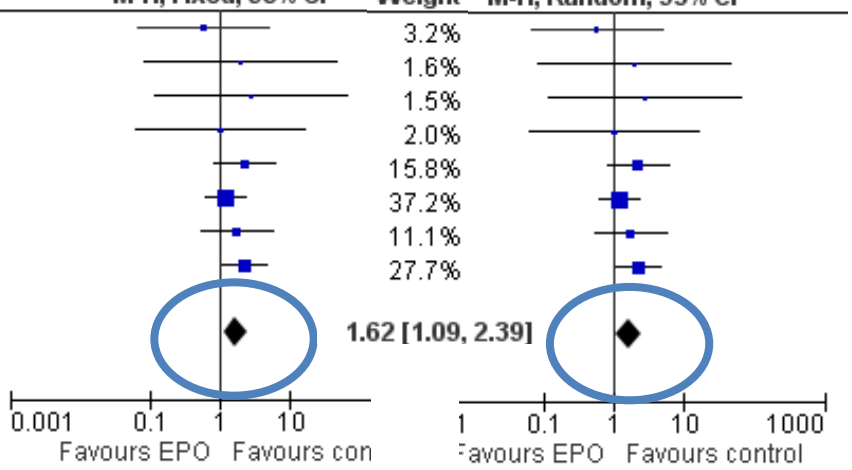
$$\text{weight} = \frac{1}{\text{variance within} + \text{variance between}} = \frac{1}{SE^2 + tau^2}$$

No heterogeneity

Study or Subgroup	Treatment Events	Treatment Total	Control Events	Control Total	Fixed Weight	Risk Ratio M-H, Fixed, 95% CI	Random Weight	Risk Ratio M-H, Random, 95% CI
Bierer 2006	1	7	2	8	5.1%	0.57 [0.06, 5.03]	3.2%	
Fauchère 2008	1	24	0	15	1.7%	1.92 [0.08, 44.29]	1.6%	
Haiden 2005	1	21	0	19	1.4%	2.73 [0.12, 63.19]	1.5%	
Maier 1994	1	120	1	121	2.7%	1.01 [0.06, 15.94]	2.0%	
Maier 2002	12	67	5	62	14.3%	2.22 [0.83, 5.94]	15.8%	
Ohls 2001A	17	87	14	85	39.0%	1.19 [0.62, 2.25]	37.2%	
Ohls 2001B	7	59	4	59	11.0%	1.75 [0.54, 5.66]	11.1%	
Romagnoli 2000	20	115	9	115	24.8%	2.22 [1.06, 4.67]	27.7%	
Total (95% CI)		**500**		**484**	**100.0%**	**1.65 [1.12, 2.43]**		**1.62 [1.09, 2.39]**
Total events	60		35					

Heterogeneity: Tau² = 0.00; Chi² = 3.14, df = 7 (P = 0.87); I² = 0%

Test for overall effect: Z = 2.41 (P = 0.02)



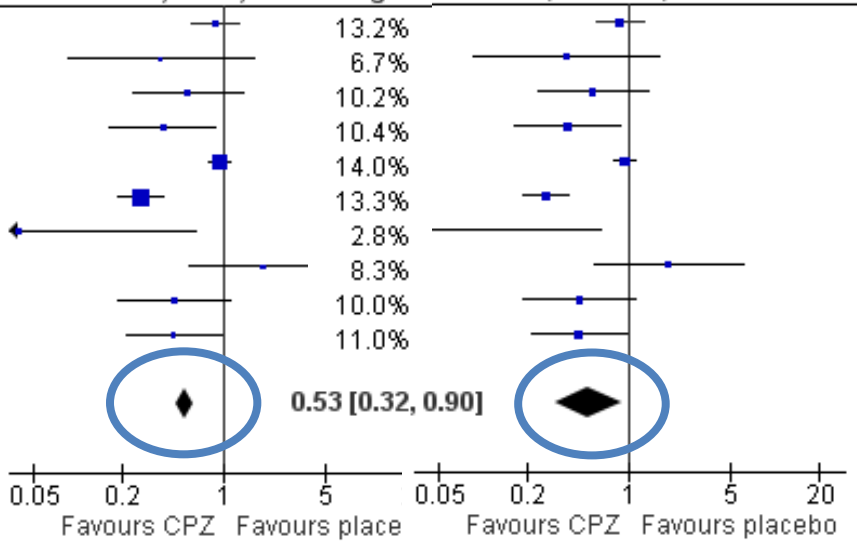
Adapted from Ohlsson A, Aher SM. Early erythropoietin for preventing red blood cell transfusion in preterm and/or low birth weight infants. *Cochrane Database of Systematic Reviews* 2006, Issue 3.

Substantial heterogeneity

Study or Subgroup	Chlorpromazine Events	Total	Placebo Events	Total	Fixed Weight	Risk Ratio M-H, Fixed, 95% CI	Random Weight
Chouinard 1990	14	21	16	21	6.5%	0.88 [0.60, 1.29]	13.2%
Clark 1970a	2	15	5	14	2.1%	0.37 [0.09, 1.62]	6.7%
Clark 1970b	10	53	6	18	3.7%	0.57 [0.24, 1.34]	10.2%
Fleming 1959	5	21	13	21	5.3%	0.38 [0.17, 0.89]	10.4%
Hall 1955	65	87	70	88	28.4%	0.94 [0.80, 1.10]	14.0%
Prien 1968	37	416	70	212	37.8%	0.27 [0.19, 0.39]	13.3%
Schiele 1961	0	20	12	20	5.1%	0.04 [0.00, 0.63]	2.8%
Serafetinides 1972	6	14	3	13	1.3%	1.86 [0.58, 5.94]	8.3%
Smith 1961	4	13	10	15	3.8%	0.46 [0.19, 1.12]	10.0%
Somerville 1960	5	15	22	30	6.0%	0.45 [0.22, 0.96]	11.0%
Total (95% CI)		**675**		**452**	**100.0%**	**0.55 [0.47, 0.63]**	**0.53 [0.32, 0.90]**
Total events	148		227				

Heterogeneity: Tau² = 0.50; Chi² = 72.76, df = 9 (P < 0.00001); I² = 88%

Test for overall effect: Z = 2.37 (P = 0.02)



Adapted from Adams CE, Awad G, Rathbone J, Thornley B. Chlorpromazine versus placebo for schizophrenia. *Cochrane Database of Systematic Reviews* 2007, Issue 2.

Small study effects

Study or Subgroup	Magnesium Events	Magnesium Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Abraham 1987	1	48	1	46	0.0%	0.96 [0.06, 15.77]
Bhargava 1995	3	40	3	38	0.1%	0.95 [0.18, 5.00]
Ceremuzynski 1989	1	25	3	23	0.1%	0.28 [0.03, 2.88]
Feldstedt 1991	10	150	8	148	0.3%	1.25 [0.48, 3.26]
Gyamlani 2000	2	50	10	50	0.4%	0.17 [0.03, 0.81]
ISIS-4 1995	2216	29008	2103	29038	71.6%	1.06 [1.00, 1.13]
MAGIC 2000	475	3113	472	3100	14.8%	1.00 [0.87, 1.15]
Morton 1984	1	40	2	36	0.1%	0.44 [0.04, 5.02]
Nakashima 2004	1	89	3	91	0.1%	0.33 [0.03, 3.27]
Raghu 1999	6	169	18	181	0.6%	0.33 [0.13, 0.86]
Rasmussen 1986	4	56	14	74	0.4%	0.33 [0.10, 1.06]
Santoro 2000	0	75	1	75	0.1%	0.33 [0.01, 8.20]
Shechter 1990	1	50	9	53	0.3%	0.10 [0.01, 0.82]
Shechter 1991	2	21	4	25	0.1%	0.55 [0.09, 3.37]
Shechter 1995	4	96	17	98	0.6%	0.21 [0.07, 0.64]
Singh 1990	6	81	11	81	0.4%	0.51 [0.18, 1.45]
Smith 1986	2	92	7	93	0.3%	0.27 [0.06, 1.35]
Thogersen 1995	4	130	8	122	0.3%	0.45 [0.13, 1.54]
Urek 1996	1	31	0	30	0.0%	3.00 [0.12, 76.58]
Woods 1992	90	1150	118	1150	4.0%	0.74 [0.56, 0.99]
Wu 1992	5	125	12	102	0.5%	0.31 [0.11, 0.92]
Zhu 2002	101	1691	134	1488	4.9%	0.64 [0.49, 0.84]
Total (95% CI)		**36330**		**36142**	**100.0%**	**0.99 [0.94, 1.04]**
Total events	2936		2958			

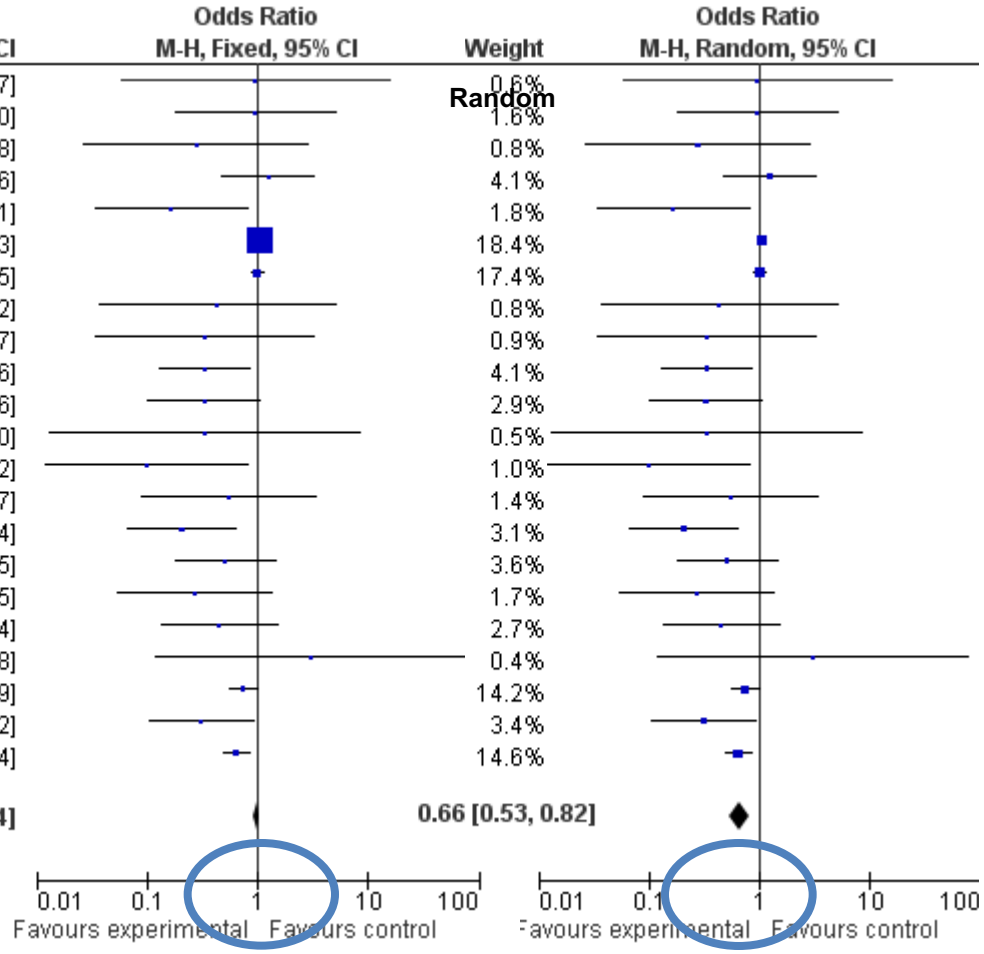
Heterogeneity: Chi² = 57.78, df = 21 (P < 0.0001); I² = 64%

Test for overall effect: Z = 0.48 (P = 0.63)

Total events 2936 2958

Heterogeneity: Tau² = 0.07; Chi² = 57.78, df = 21 (P < 0.0001); I² = 64%

Test for overall effect: Z = 3.69 (P = 0.0002)



Which to choose?

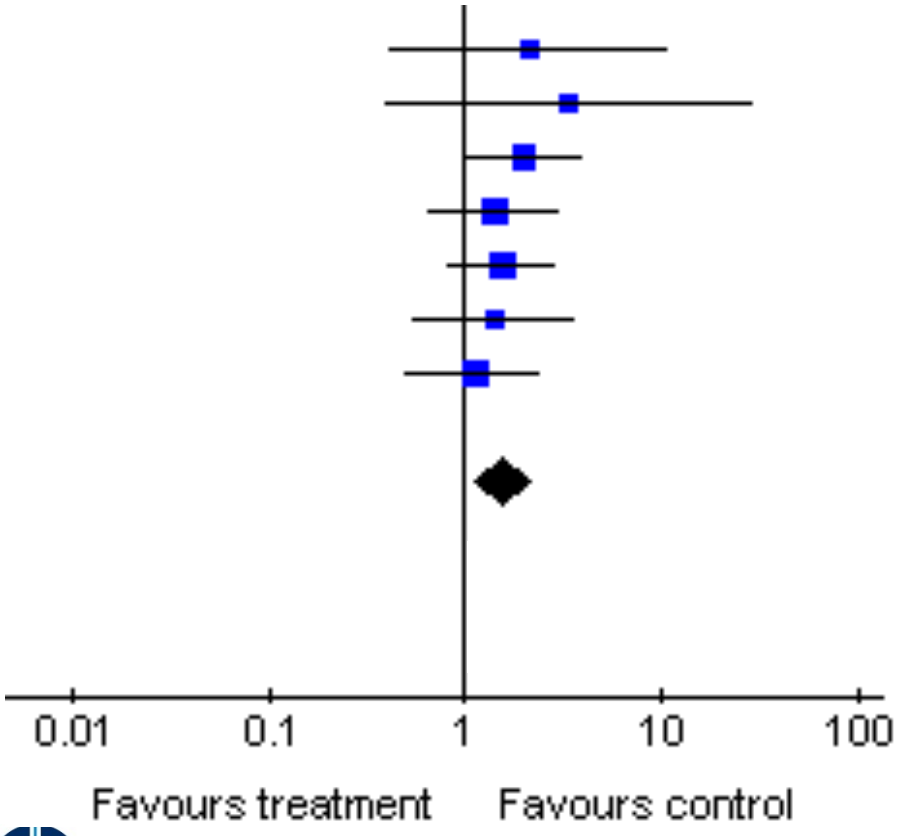
- plan your approach at the protocol stage
- do you expect your results to be very diverse?
- consider the underlying assumptions of the model
  - fixed-effect
    - may be unrealistic – ignores heterogeneity
  - random-effects
    - allows for heterogeneity
    - estimate of distribution of studies may not be accurate if biases are present, few studies or few events

Identifying heterogeneity

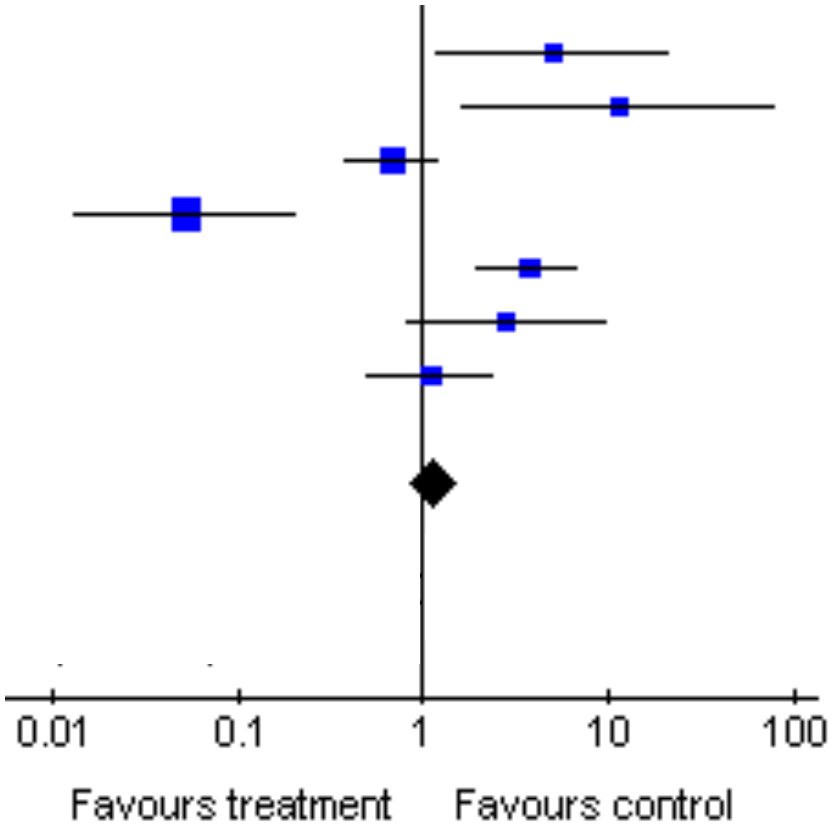
- visual inspection of the forest plots
- chi-squared (χ^2) test (Q test)
- I^2 statistic to quantify heterogeneity

Visual inspection

Forest plot A



Forest plot B



The I^2 statistic

- I^2 statistic describes the percentage of variability due to heterogeneity rather than chance (0% to 100%)
  - low values indicate no, or little, heterogeneity
  - high values indicate a lot of heterogeneity
- calculated automatically by RevMan
- be cautious in interpreting; CI's may be wide

What to do about heterogeneity

- check that the data are correct
- consider in your interpretation
  - especially if the direction of effect varies
- if heterogeneity is very high
  - interpret fixed-effect results with caution
    - consider sensitivity analysis – would random-effects have made an important difference?
  - may choose not to meta-analyse
    - average result may be meaningless in practice
    - consider clinical & methodological comparability of studies
  - avoid
    - changing your effect measure or analysis model
    - excluding outlying studies
- **explore** heterogeneity

Exploring your results

- what factors appear to modify the effect?
  - clinical diversity (population, interventions, outcomes)
  - methodological diversity (study design, risk of bias)
- plan your strategy in your protocol
  - identify a limited number of important factors to investigate
  - have a scientific rationale for each factor chosen
  - declare any post-hoc investigations

Two methods available

- subgroup analysis
  - Group studies by pre-specified factors
  - look for differences in results and heterogeneity
- meta-regression
  - examine interaction with categorical and continuous variables
  - not available in RevMan

Nordic Cochrane Centre

Interpreting subgroup analyses

- look at results and heterogeneity within subgroups
- are the subgroups genuinely different?
  - if only 2 subgroups – do the confidence intervals overlap?
  - statistical tests for subgroup difference
- can be more confident about:
  - pre-specified analyses
  - within-study analyses
  - effect is clinically plausible and supported by indirect evidence
  - effect is clinically important and will alter recommendations

Sensitivity analysis

- not the same as subgroup analysis
- testing the impact of decisions made during the review
  - inclusion of studies in the review
  - definition of low risk of bias
  - choice of effect measure
  - assumptions about missing data
  - cut-off points for dichotomised ordinal scales
  - correlation coefficients
- repeat analysis using an alternative method or assumption
  - don’t present multiple forest plots – just report the results
  - if difference is minimal, can be more confident of conclusions
  - if difference is large, interpret results with caution

Intercessory prayer for the alleviation of ill health (Review)

Roberts L, Ahmed I, Hall S, Davison A

THE COCHRANE COLLABORATION®

”Monitoring the effectiveness of screening.

This can be done approximately by examining trends in age-specific breast cancer mortality available from routine statistics.”

The Forrest Report, 1986

Breast screening in Denmark

- 17 year with differential access to screening
- 100,000 women aged 50 to 69 years in areas offering screening.
- 400,000 women aged 50 to 69 years in areas not offering screening.

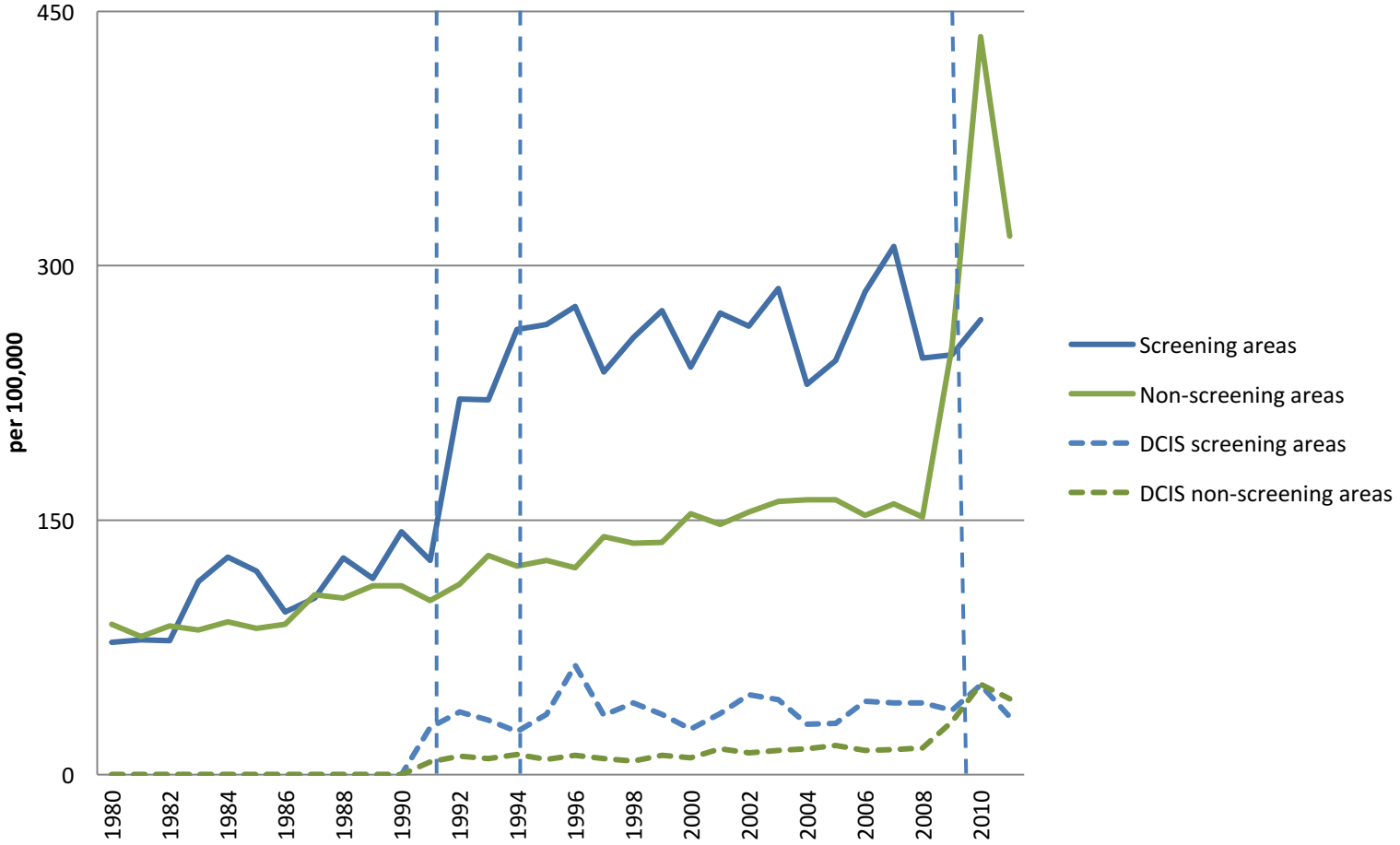
The data:

- All Danish women aged 35 to 84 years.
- Data from two independent sources; the national Danish cancer registry and a clinical database (Danish Breast Cancer Group)
- Data from 1980 to 2010
- Tumors <20mm considered non-advanced
- Tumors 20mm and above considered advanced

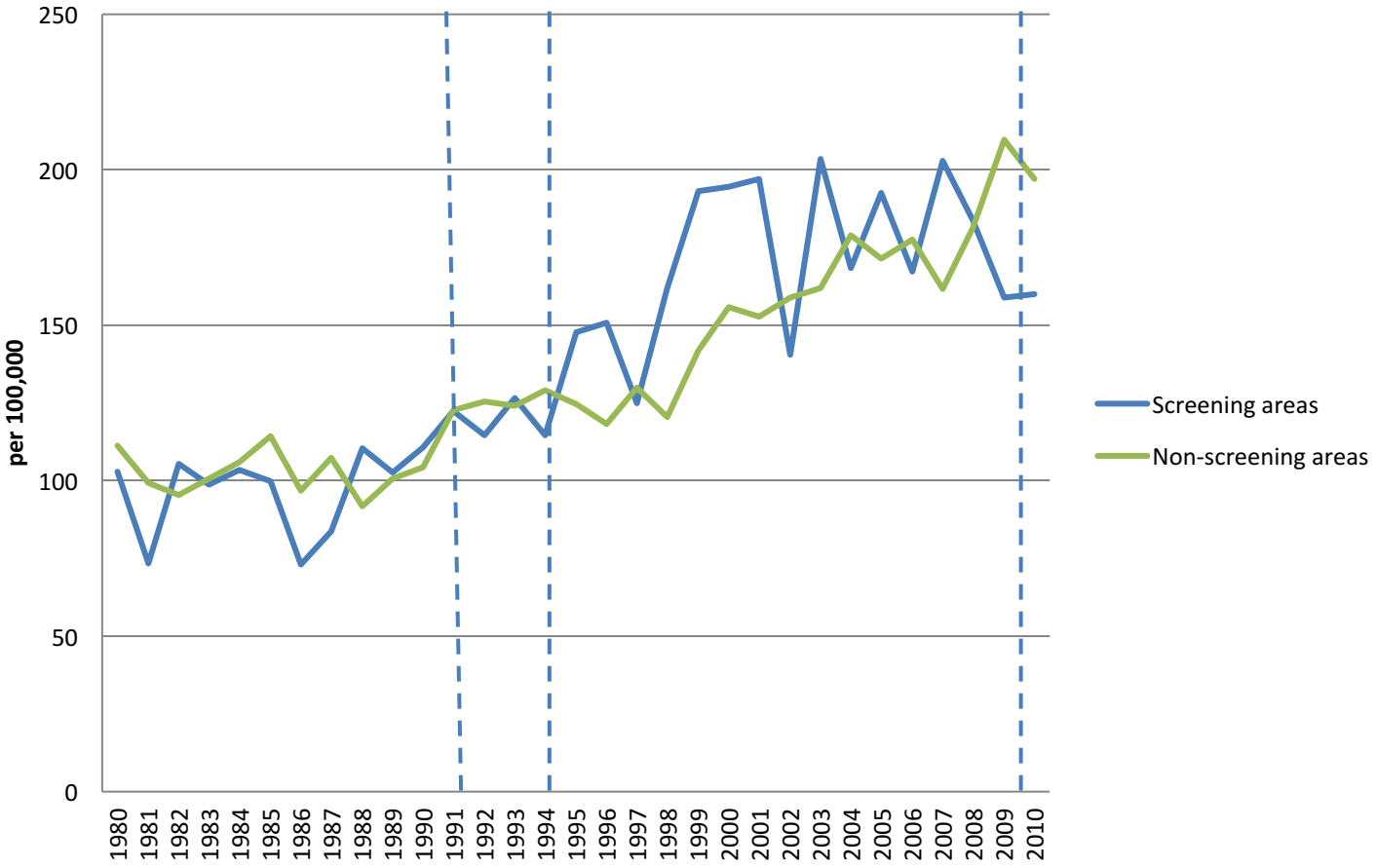
Analyses:

- **Impact on stage:** Poisson regression analyses, taking pre-screening trends and non-screened age groups into account
- **Overdiagnosis (Method 1):** compared incidence in the screening period of advanced and non-advanced cancers in the age group 50 to 84 years.
- **Overdiagnosis (Method 2):** analysed trends in incidence in the pre– and screening period for the age-groups 35-49, 50-69, and 70-84 years.

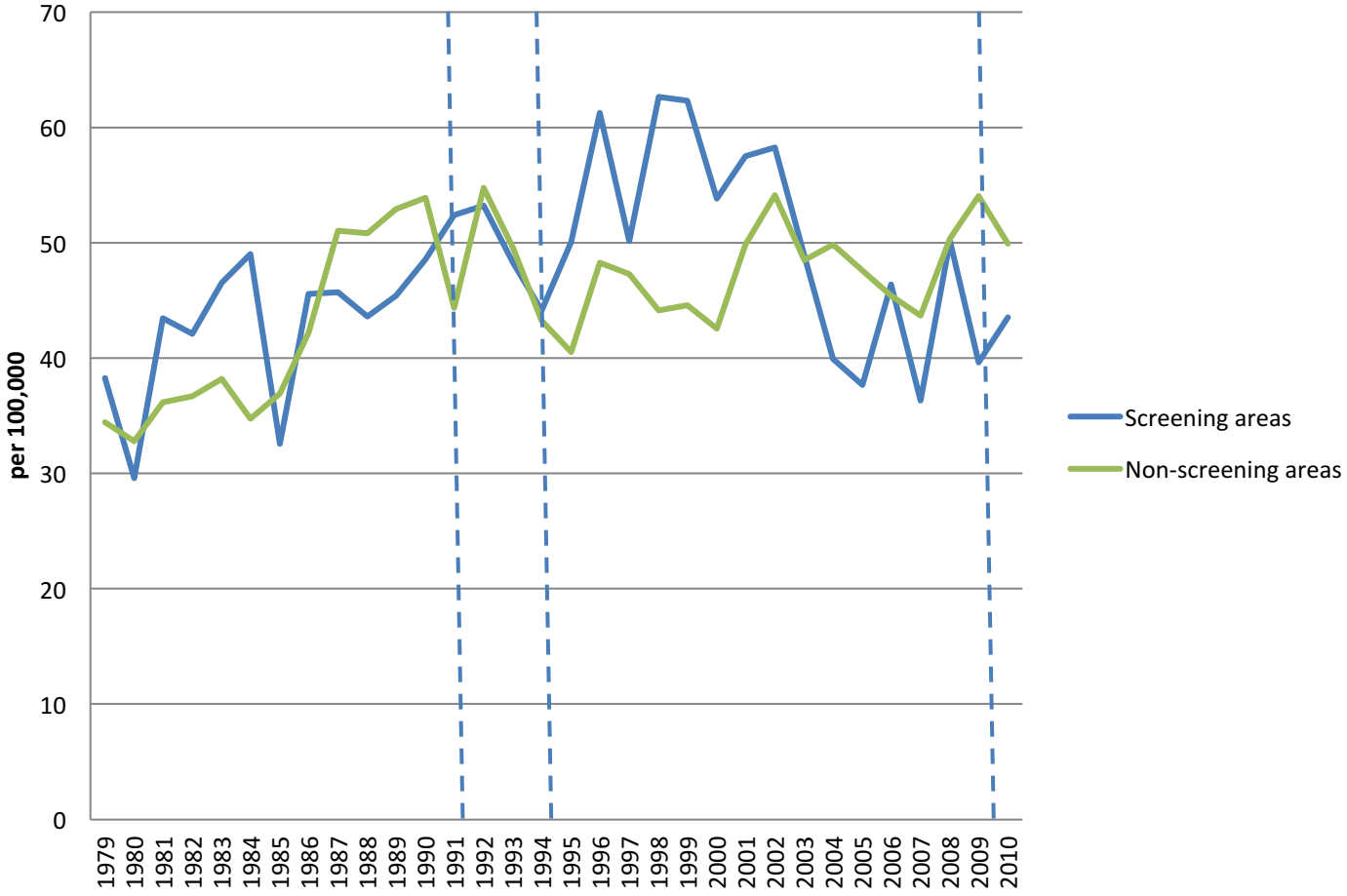
Non-advanced cancers in women aged 50 to 69 years. The dotted lines indicate screening start in Copenhagen (1991), Funen (1993-4), and the rest of Denmark (2008-9).



Non-advanced cancers in women aged 70 to 85 years. The dotted lines indicate screening start in Copenhagen (1991), Funen (1993-4), and the rest of Denmark (2008-9).



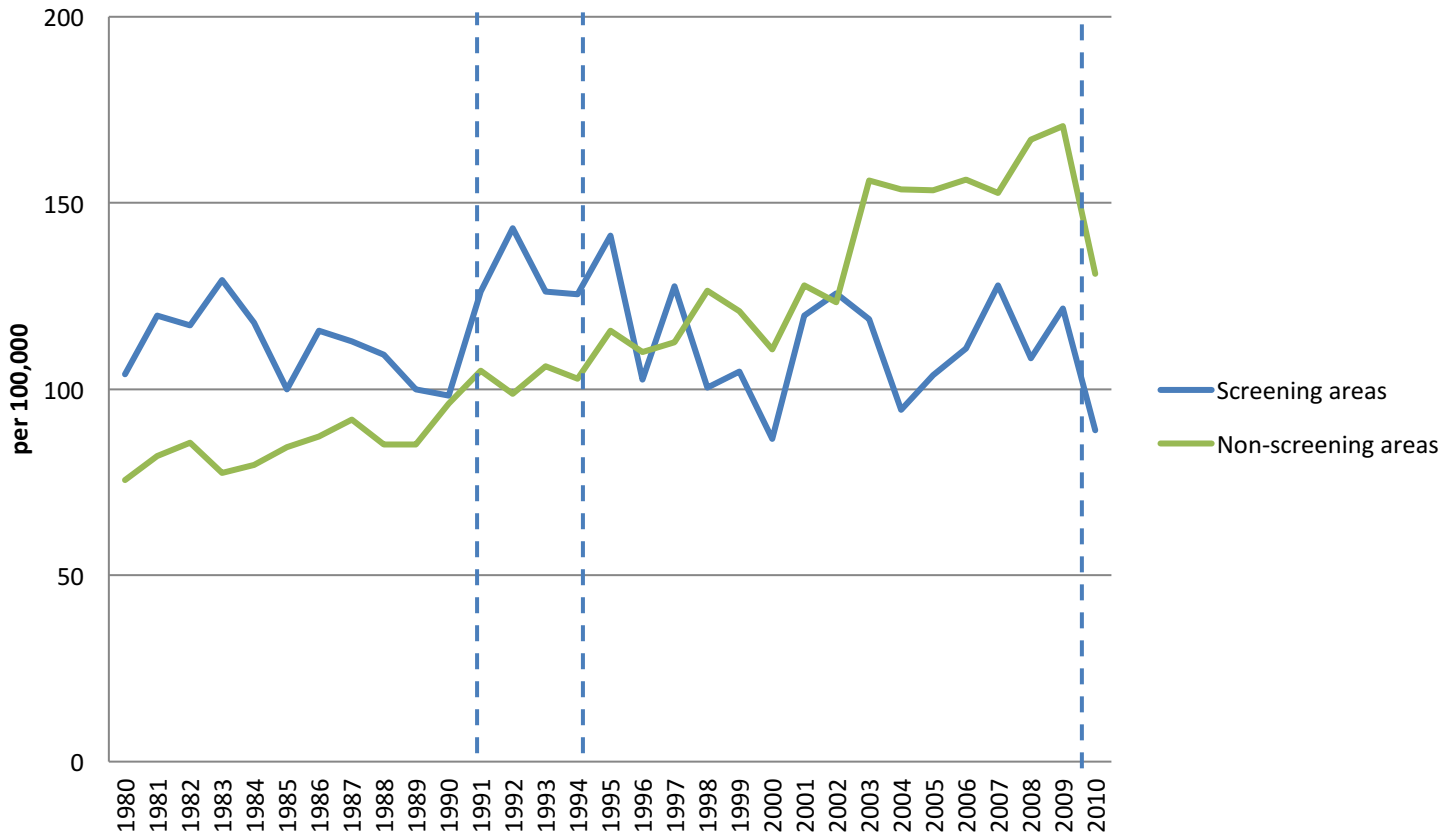
Non-advanced cancers in women aged 35 to 49 years. The dotted lines indicate screening start in Copenhagen (1991), Funen (1993-4), and the rest of Denmark (2008-9).



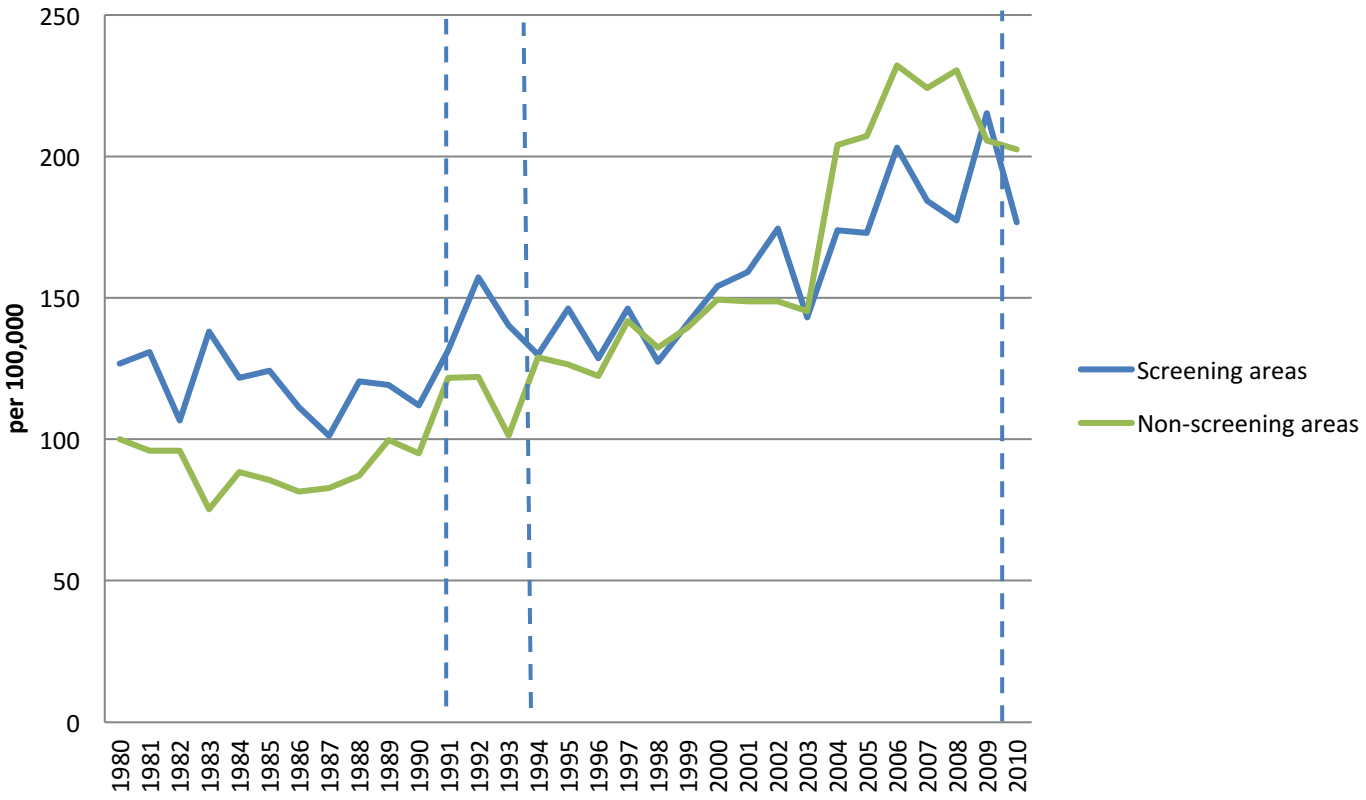
Impact of screening on non-advanced breast cancer incidence.

- Clearly visible and sustained increase in the screened age group; hazard ratio 1.50 (95% CI 1.45 to 1.55) compared to before screening.
- No visible reduction in previously screened women above the screening age.
- Comparable incidence and trends between regions in women below the screening age.

Advanced cancers in women aged 50 to 69 years. The dotted lines indicate screening start in Copenhagen (1991), Funen (1993-4), and the rest of Denmark (2008-9).



Advanced cancers in women aged 70 to 85 years. The dotted lines indicate screening start in Copenhagen (1991), Funen (1993-4), and the rest of Denmark (2008-9).



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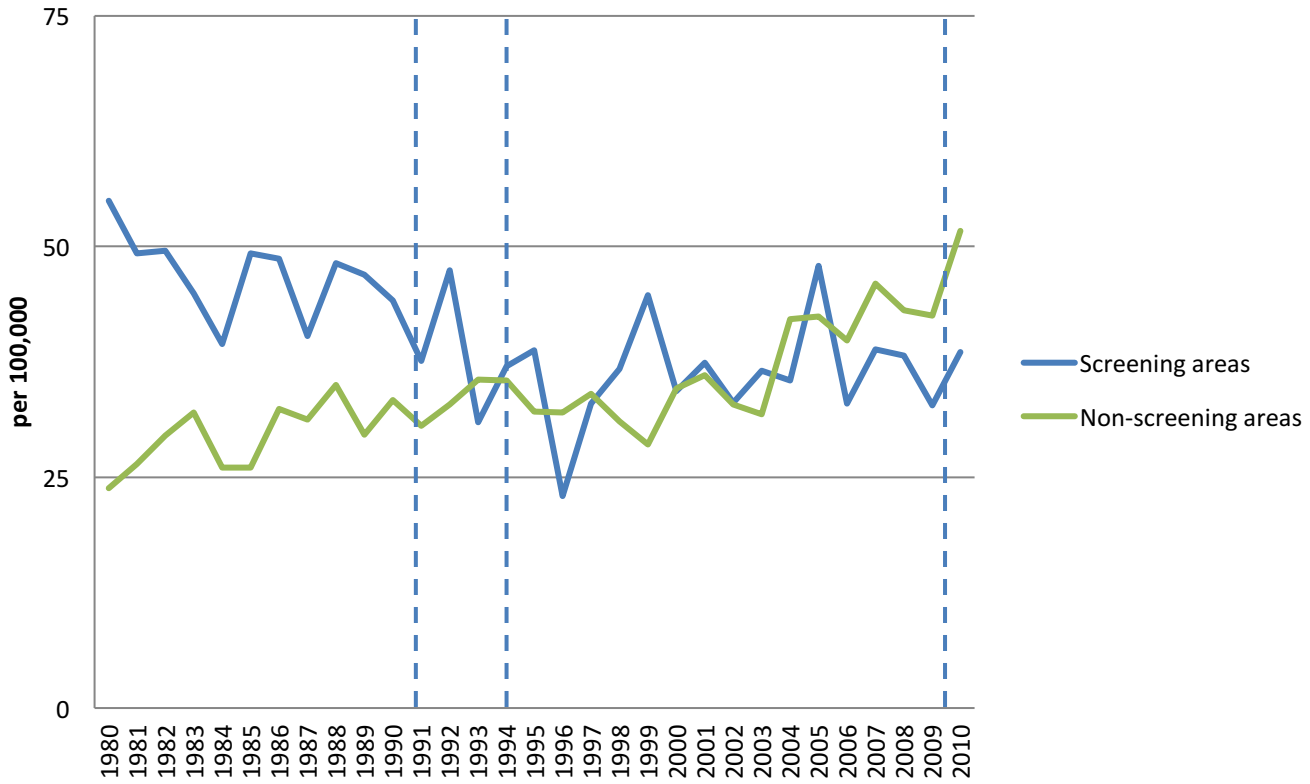


Impact of screening on advanced breast cancer incidence.

- Regional differences unrelated to screening complicate interpretation.
- Most change between regions occured prior to screening.
- No clear difference between screened and non-screened areas when comparing screened and non-screened age groups.

Estimates of overdiagnosis

Method 1: Incidence difference for the age group 50 to 69, subtracting any reduction in women aged 70 to 84 years: **24.4%** including DCIS, **14.7%** for invasive cancers only.

Method 2: Taking trends in the pre-screening period and in women below the screening age into account, screening increased the risk of a breast cancer diagnisis by **45%** in the invited age group, including DCIS.

Conclusions

- Clear increase in non-advanced breast cancers with screening.
- No clear effect of screening on advanced breast cancers.
- Incidence of advanced breast cancers influenced by factors other than screening.
- Observational studies that do not consider the pre-screening period and non-screened age groups may provide misleading results

Age 50-69 years. Annual percentage change (APC) and relative change (HR) with 95% confidence intervals (95% CI) in incidence of breast cancer comparing pre-screening and screening periods in the screening and non-screening areas from 1980 to 2010 (2007 for the non-screening areas).

*data censored in 2007

	Area	1980-91		After 1991		Relative change	
		APC	95% CI	APC	95% CI	HR	95% CI
Advanced	Screening	-0.5	-1.9 to 0.9	-1.1	-1.8 to -0.3	1.01	0.95 to1.08
	Non-screening	1.7	0.8 to 2.6	3.0	2.6 to 3.3	1.55	1.49 to 1.60
Non-advanced	Screening	4.4	3.0 to 6.0	0.6	0.1 to 1.0	2.40	2.27 to 2.54
	Non-screening*	3.1	2.2 to 3.9	1.8	1.4 to 2.2	1.50	1.45 to 1.55

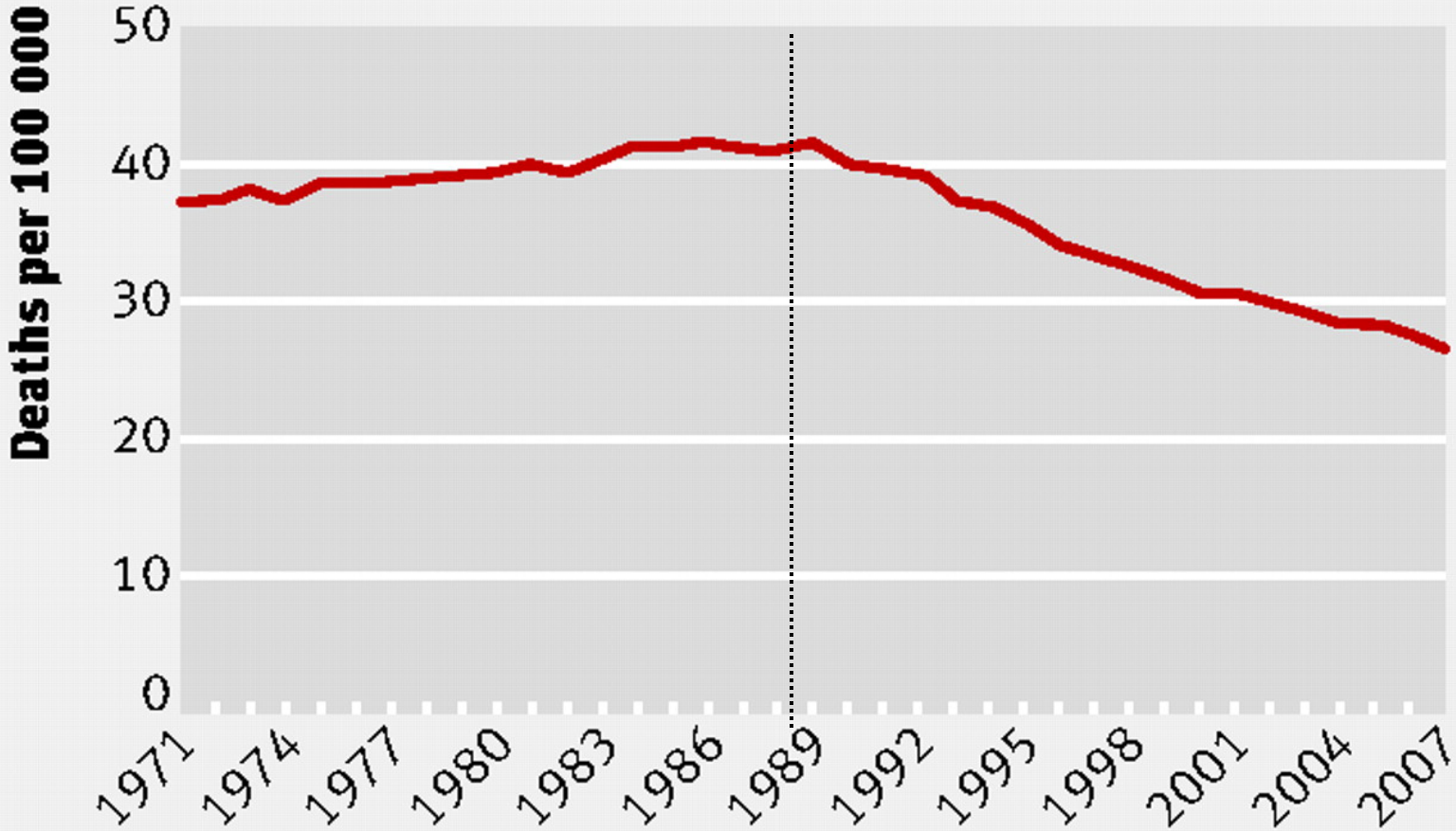
Age 35-49 years. Annual percentage change (APC) and relative change (HR) with 95% confidence intervals (95% CI) in incidence of advanced and non-advanced breast cancer comparing pre-screening and screening periods in the screening and non-screening areas from 1980 to 2010.

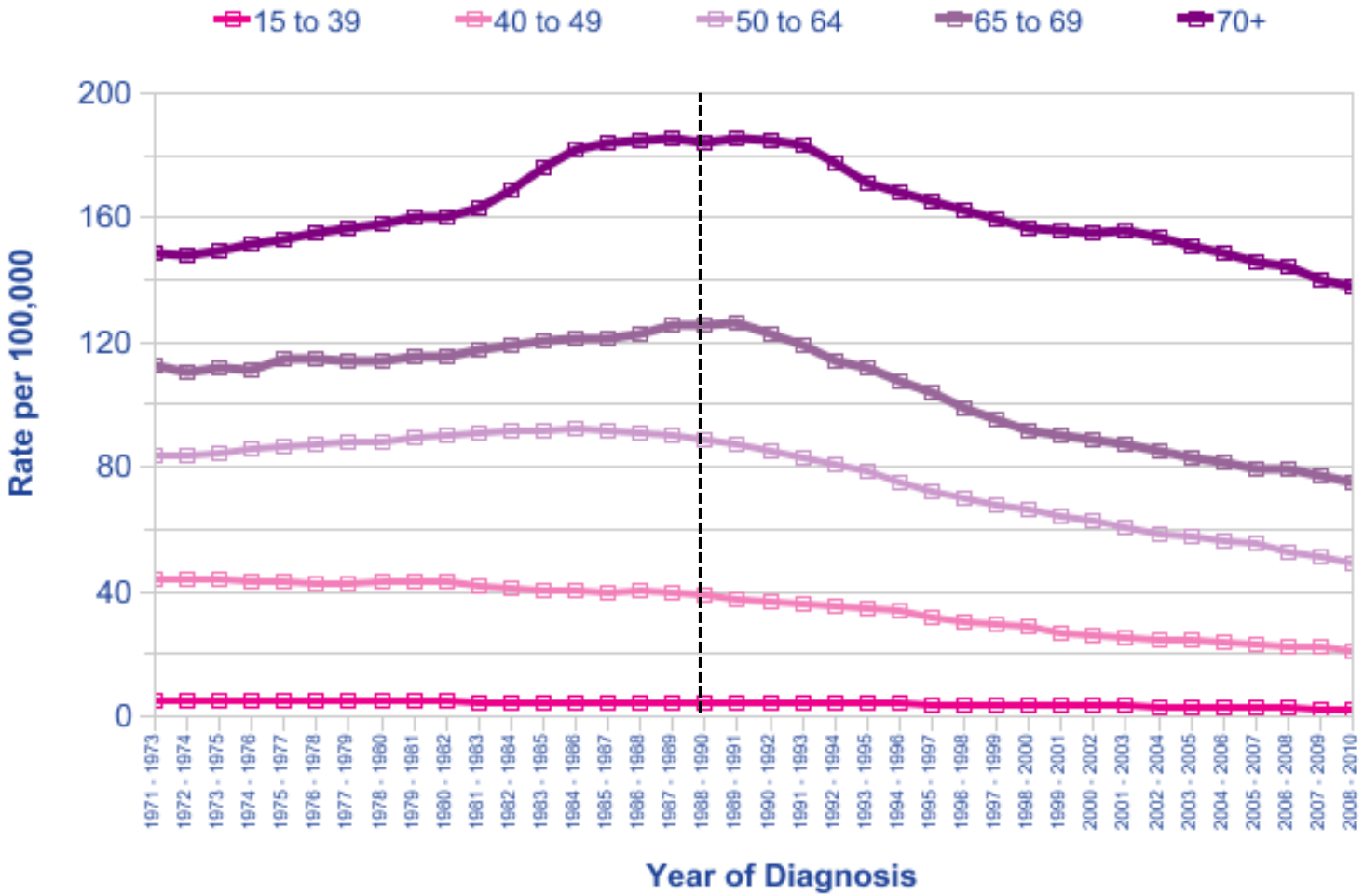
	Area	1980-91		After 1991		Relative change	
		APC	95% CI	APC	95% CI	HR	95% CI
Advanced	Screening	-1.8	-3.9 to 0.4	0.2	-0.9 to 1.3	0.80	0.73 to 0.88
	Non-screening	2.0	0.8 to 3.4	2.3	1.7 to 2.8	1.25	1.18 to 1.31
Non-advanced	Screening	2.5	0.3 to 4.8	-1.5	-2.4 to -0.6	1.13	1.03 to 1.24
	Non-screening	4.3	3.3 to 5.5	0.3	-0.2 to 0.8	1.12	1.07 to 1.17

Age 70-84 years. Annual percentage change (APC) and relative change (HR) with 95% confidence intervals (95% CI) in incidence of breast cancer comparing pre-screening and screening periods in the screening and non-screening areas from 1980 to 2010.

	Area	1980-91		After 1991		Relative change	
		APC	95% CI	APC	95% CI	HR	95% CI
Advanced	Screening	-0.6	-2.2 to 1.1	2.1	1.3 to 3.0	1.31	1.22 to 1.41
	Non-screening	1.3	0.0 to 2.5	4.3	3.8 to 4.8	1.77	1.69 to 1.86
Non-advanced	Screening	1.7	-0.1 to 3.7	2.2	1.3 to 3.1	1.63	1.50 to 1.76
	Non-screening	0.5	-0.4 to 1.7	3.0	2.6 to 3.5	1.48	1.41 to 1.55

BREAST CANCER IN UK WOMEN




15 to 39
40 to 49
50 to 64
65 to 69
70+
Rate per 100,000
200
160
120
80
40
0
1971 - 1973
1972 - 1974
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1974 - 1976
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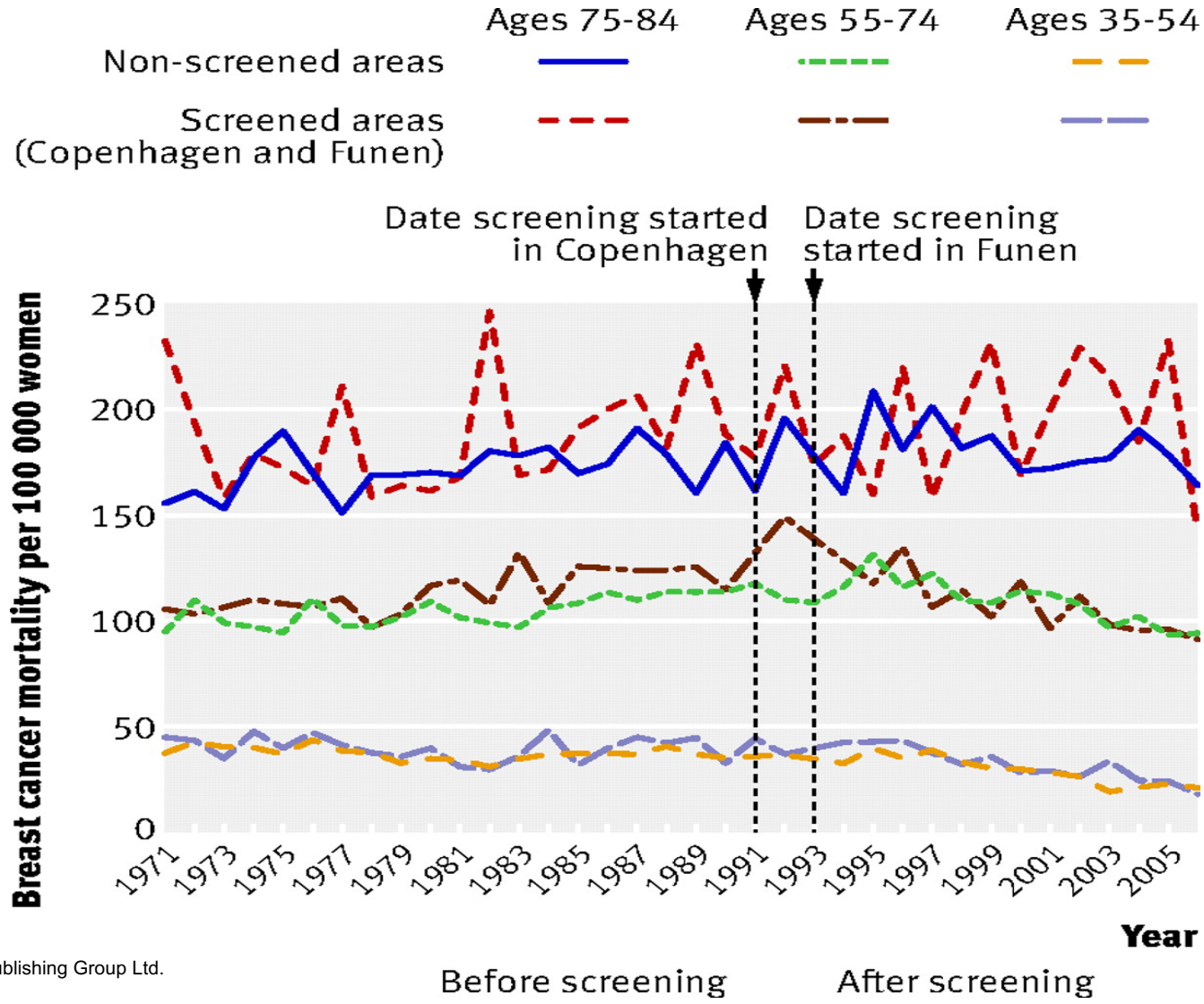
Year of Diagnosis

"Between the late 1980s and 2008-2010, breast cancer mortality rates fell by 50% in the 15-39 age group, by 47% in the 40-49 age group, 45% in the 50-64 age group, 40% in the 65-69 age group and by 26% in women aged over 70 years."[1]

1: http://www.cancerresearchuk.org/cancer-info/cancerstats/types/breast/mortality/uk-breast-cancer-mortality-statistics

Breast cancer mortality rates for screened and non-screened areas in Denmark



Jørgensen KJ, Zahl PH, Gøtzsche PC. BMJ 2010;340:c1241

Observational studies of screening effects should include data from the pre-screening era, and for non-screened age groups.

The Benefits and Harms of Breast Cancer Screening:

An Independent Review

Authors:
The Independent UK Panel on Breast Cancer Screening

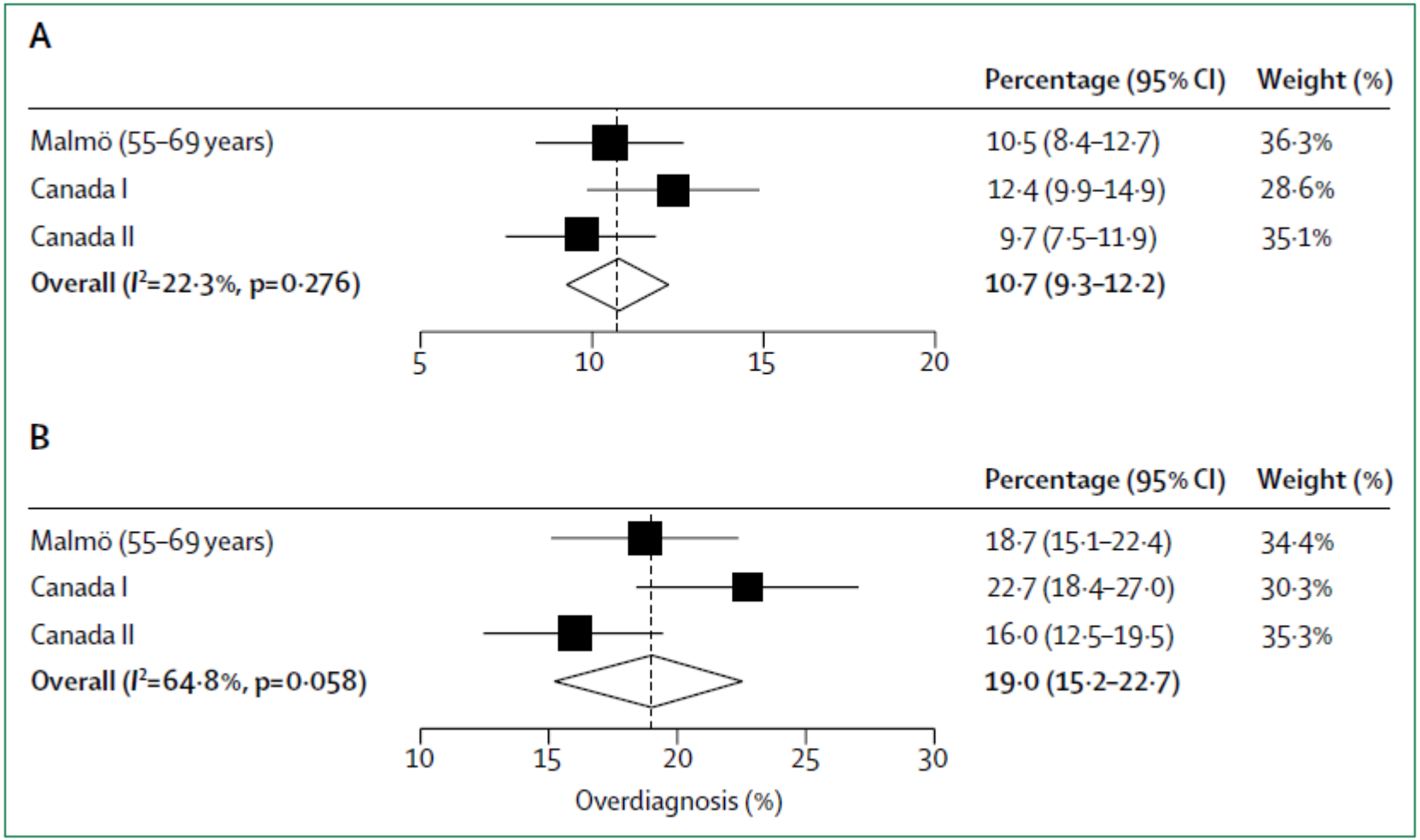
IBSR
Independent Breast Screening Review

A report jointly commissioned by
Cancer Research UK and the Department of Health (England).

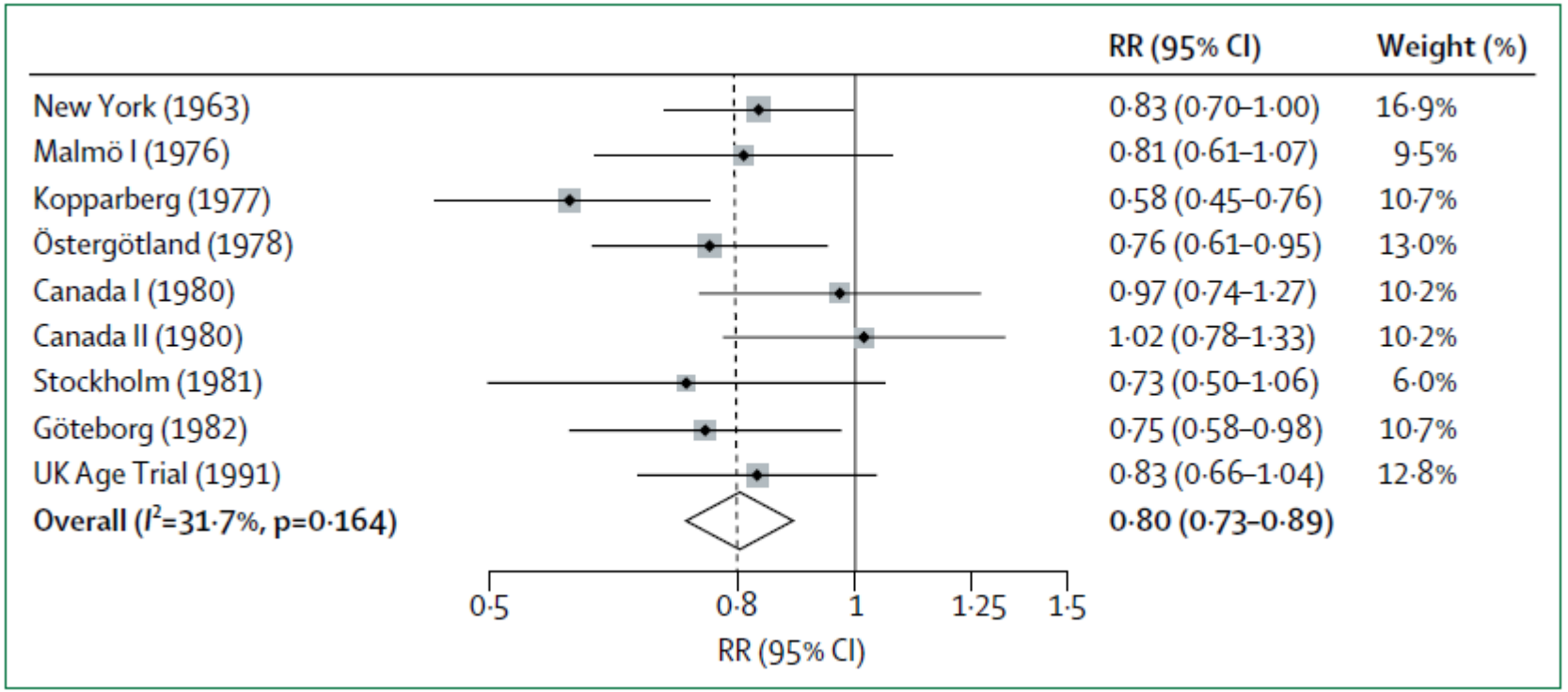
October 2012

Main results:

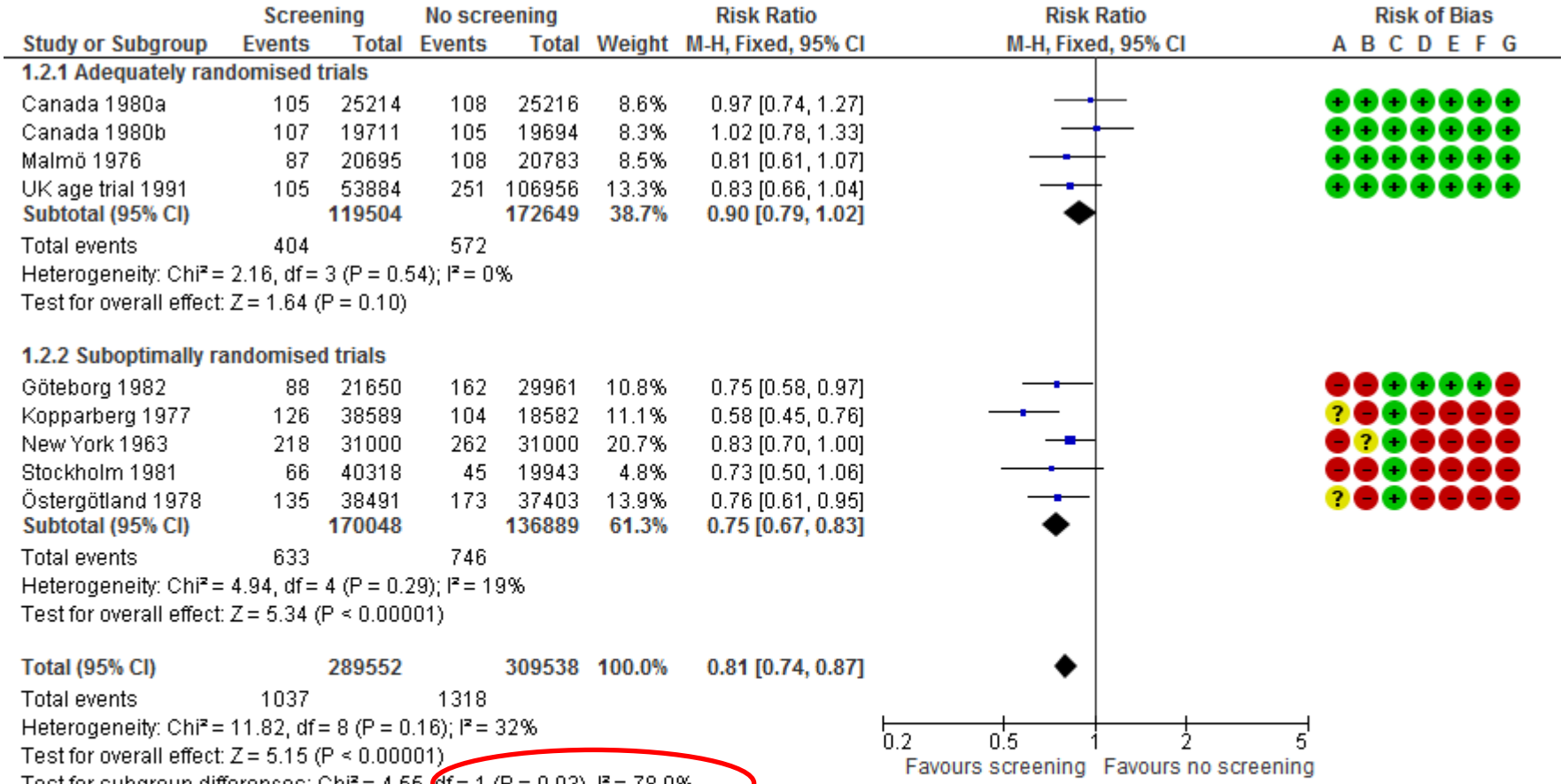
1 woman avoids a breast cancer death for every 3 overdiagnosed; 1 300 and 4 000 women per year, respectively, in the UK.



A: Excess cancers as a proportion of cancers diagnosed over long-term follow- up.
B: Excess cancers as a proportion of cancers diagnosed during the screening period.



”The Panel’s primary conclusions about breast cancer mortality are based on data reported in the Cochrane review…”



Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

GRADE

”When (…) a sensitivity analysis suggests differences in estimates between studies with higher and lower risk of bias, we suggest, in accordance with the standard GRADE approach, using the estimates from the lower risk of bias studies, with no need to rate down confidence for risk of bias”

Iorio A et al. BMJ 2015;350:h870

A	B
100% participation	~80% participation
4-5 rounds	2-4 rounds
2 view	1 view
2 readers	1 reader
Screening every 12 month	Screening every 24-33 month

Gøtzsche PC, Nielsen M. Cochrane Database syst. Rev. 2011, Issue 1. Art. No.: CD001877.
Baines CJ. AJR Am J Roentgenol 2013;200:W96-7.

A	B
100% participation	~70% participation
4-5 rounds	2-4 rounds
2 view	1 view
2 readers	1 reader
Screening every 12 month	Screening every 24-33 month
A finds smaller average size tumors than B	

Gøtzsche PC, Nielsen M. Cochrane Database syst. Rev. 2011, Issue 1. Art. No.: CD001877.
Baines CJ. AJR Am J Roentgenol 2013;200:W96-7.

A	B
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Screening every 12 month	Screening every 24-33 month
A finds smaller average size tumors than B	
Individual randomisation	Cluster-randomisation (45)
Presents demographic data	Do not present demographic data
Consistent, transparent reporting	Inconsistent, unclear reporting
Blinded, external cause of death evaluation	No blinded cause of death evaluation

Gøtzsche PC, Nielsen M. Cochrane Database syst. Rev. 2011, Issue 1. Art. No.: CD001877.
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Individual randomisation	Cluster-randomisation (45)
Presents demographic data	Do not present demographic data
Consistent, transparent reporting	Inconsistent, unclear reporting
Blinded, external cause of death evaluation	No blinded cause of death evaluation
3% reduction (-26% to +27%)* 2% increase(-22% to + 33%)*	42% reduction (-55% to -3%)* 24% reduction (-39% til -5%)*

* Thirteen years follow-up

Gøtzsche PC, Nielsen M. Cochrane Database syst. Rev. 2011, Issue 1. Art. No.: CD001877.
Baines CJ. AJR Am J Roentgenol 2013;200:W96-7.

"Between the late 1980s and 2008-2010, breast cancer mortality rates fell by 50% in the 15-39 age group, by 47% in the 40-49 age group, 45% in the 50-64 age group, 40% in the 65-69 age group and by 26% in women aged over 70 years."[1]

1: http://www.cancerresearchuk.org/cancer-info/cancerstats/types/breast/mortality/uk-breast-cancer-mortality-statistics

BMJ

BMJ 2011;343:d4411 doi: 10.1136/bmj.d4411

RESEARCH

Breast cancer mortality in neighbouring European countries with different levels of screening but similar access to treatment: trend analysis of WHO mortality database

Philippe Autier *research director*[1], Mathieu Boniol *senior statistician*[1], Anna Gavin *director*[2], Lars J Vatten *professor*[3]

[1]International Prevention Research Institute, 95 Cours Lafayette, 69006 Lyon, France; [2]Northern Ireland Cancer Registry, Belfast, Northern Ireland, UK; [3]Department of Public Health, Norwegian University of Science and Technology, Trondheim, Norway

Conclusions The contrast between the time differences in implementation of mammography screening and the similarity in reductions in mortality between the country pairs suggest that screening did not play a direct part in the reductions in breast cancer mortality.

Table 1 | Changes in breast cancer mortality between 1989 and 2006 in European countries ranked according to overall decline in mortality

Country	Mean mortality*		Mortality change for all ages (%)				Mortality change 1989-2006 by age group (%)						Quality of data on cause of death§
			For 1989-2006				Annual change			Overall change			
	1987-9	2004-6†	Annual	Overall	Year for start of decline‡	Annual change 1999-2006	<50	50-69	≥70	<50	50-69	≥70	
Iceland	33.1	23.5	−3.4	−44.5	1995	1.1	−8.1	−2.5	−3.1	−76.3	−35.0	−41.5	High
England and Wales	41.9	28.1	−2.5	−34.9	1989	−2.0	−3.2	−3.0	−1.5	−42.1	−40.1	−22.6	High
Luxembourg	36.3	22.9	−2.4	−34.1	1988	−2.8	−5.3	−2.5	−1.3	−60.0	−34.9	−19.9	Medium
Scotland	39.3	29.0	−2.1	−29.9	1990	−1.4	−2.9	−2.7	−0.7	−39.1	−37.2	−11.9	High
Northern Ireland	37.0	28.1	−2.0	−29.2	1991	−1.2	−3.8	−2.6	0.0	−48.2	−36.2	−0.7	High
Austria	31.8	24.5	−1.8	−26.8	1990	−1.6	−4.0	−1.7	−1.1	−50.3	−25.3	−16.9	Medium
Spain	23.7	18.9	−1.8	−26.8	1992	−2.2	−3.4	−2.1	−0.3	−44.7	−30.3	−4.6	Medium
Ireland	40.3	30.5	−1.8	−26.4	1991	−2.3	−3.2	−1.9	−1.0	−42.7	−27.2	−15.7	High
Netherlands	39.0	30.1	−1.7	−25.1	1993	−2.7	−1.7	−1.9	−1.4	−25.3	−27.8	−20.9	Medium
Norway	27.4	21.5	−1.6	−24.3	1995	−2.2	−2.5	−1.5	−1.4	−35.2	−22.6	−20.8	Medium
Italy	29.7	23.2	−1.5	−22.8	1991	−1.6	−2.7	−1.7	−0.7	−36.7	−24.9	−11.0	Medium
Switzerland¶	30.5	24.0	−1.5	−22.7	1985	−1.1	−2.2	−1.2	−1.7	−30.9	−18.5	−24.7	Medium
Germany	31.3	26.2	−1.4	−21.3	1999	−1.5	−3.5	−1.3	−0.5	−45.5	−20.2	−8.9	Medium
Denmark	40.5	32.0	−1.4	−20.8	1995	−2.6	−3.8	−1.7	0.1	−48.5	−25.7	1.3	Medium
Belgium	37.5	29.7	−1.3	−20.3	1986	−2.4	−2.7	−1.5	−0.4	−36.7	−22.0	−7.2	Medium
Portugal	23.9	NA	−1.1	−17.8	1992	−0.9	−2.7	−1.4	0.4	−36.9	−21.5	6.5	Low
Czech Republic	30.6	26.4	−1.1	−17.8	1994	−1.2	−3.7	−1.7	0.5	−47.2	−25.5	8.6	Medium
Slovenia	30.7	26.3	−1.0	−16.1	1993	−2.1	−4.1	−1.1	0.5	−51.3	−17.3	9.1	High
Sweden	25.6	22.0	−1.0	−16.0	1972	−0.6	−2.6	−1.0	−0.3	−35.7	−15.9	−4.3	Medium
Finland	24.5	21.4	−0.7	−11.7	1990	−1.5	−2.3	−0.7	0.0	−32.6	−10.8	0.1	High
Hungary	32.4	29.0	−0.7	−11.4	1994	−3.1	−2.4	−0.5	−0.1	−34.4	−8.3	−2.4	High
France	28.5	25.6	−0.7	−10.7	1994	−1.4	−0.9	−0.9	−0.1	−14.3	−14.9	−1.6	Medium
Poland	21.5	21.1	−0.4	−5.9	None	−0.1	−2.5	−0.3	0.8	−34.5	−4.3	14.6	Low
Slovakia	23.6	23.4	−0.1	−1.5	2000	−3.2	−2.1	−0.1	1.1	−30.7	−1.9	20.5	High

Evidence from Norway

- **Kalager et al.** (NEJM 2010):
  10% (CI: 0.78 to 1.04)
  average 6.6 years of follow-up
- **Olsen et al.** (Int J Cancer 2012):
  11% (CI: 0.77 to 1.12)
  ”up to 13 years of follow-up”

Annals of Oncology Advance Access published January 20, 2011

review

Annals of Oncology
doi:10.1093/annonc/mdq633

Advanced breast cancer incidence following population-based mammographic screening

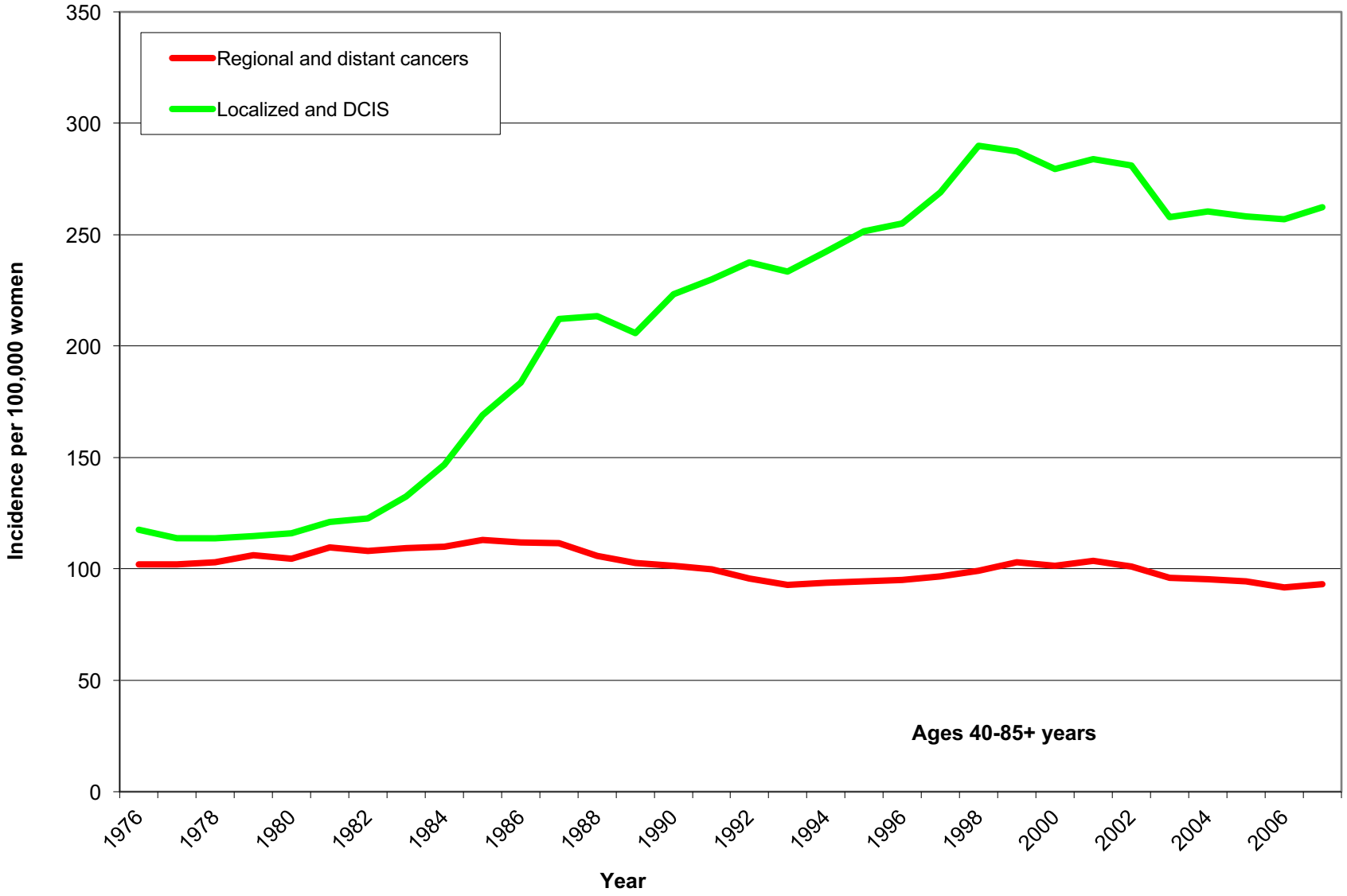
P. Autier[1]*, M. Boniol[1], R. Middleton[2], J.-F. Doré[3], C. Héry[3], T. Zheng[4] & A. Gavin[2]

[1]Department of Epidemiology and Biostatistics, International Prevention Research Institute (iPRI), Lyon, France; [2]Direction and Data Department, Northern Ireland Cancer Registry (NICR), Queens University Belfast, Belfast, UK; [3]Unit of Molecular Epidemiology, INSERM U 590, Lyon, France; [4]Department of Epidemiology and Public Health, Yale University School of Medicine, New Haven, USA

Received 22 September 2010; accepted 24 September 2010

Conclusions: In areas with widespread sustained mammographic screening, trends in advanced breast cancer incidence do not support a substantial role for screening in the decrease in mortality.

Stage-related breast cancer incidence in the USA.



Annals of Internal Medicine | ORIGINAL RESEARCH

Overdiagnosis of Invasive Breast Cancer Due to Mammography Screening: Results From the Norwegian Screening Program

Mette Kalager, MD; Hans-Olov Adami, MD, PhD; Michael Bretthauer, MD, PhD; and Rulla M. Tamimi, ScD

Background: Precise quantification of overdiagnosis of breast cancer (defined as the percentage of cases of cancer that would not have become clinically apparent in a woman's lifetime without screening) due to mammography screening has been hampered by lack of valid comparison groups that identify incidence trends attributable to screening versus those due to temporal trends in incidence.

Objective: To estimate the percentage of overdiagnosis of breast cancer attributable to mammography screening.

Design: Comparison of invasive breast cancer incidence with and without screening.

Setting: A nationwide mammography screening program in Norway (inviting women aged 50 to 69 years), gradually implemented from 1996 to 2005.

Participants: The Norwegian female population.

Measurements: Concomitant incidence of invasive breast cancer from 1996 to 2005 in counties where the screening program was implemented compared with that in counties where the program was not yet implemented. To adjust for changes in temporal trends in breast cancer incidence, incidence rates during the preceding decade were also examined. The percentage of overdiagnosis was calculated by accounting for the expected decrease in incidence following cessation of screening after age 69 years (approach 1) and by comparing incidence in the current screening group with incidence among women 2 and 5 years older in the historical screening groups, accounting for average lead time (approach 2).

Results: A total of 39 888 patients with invasive breast cancer were included, 7793 of whom were diagnosed after the screening program started. The estimated rate of overdiagnosis attributable to the program was 18% to 25% ($P < 0.001$) for approach 1 and 15% to 20% ($P < 0.001$) for approach 2. Thus, 15% to 25% of cases of cancer are overdiagnosed, translating to 6 to 10 women overdiagnosed for every 2500 women invited.

Limitation: The study was registry-based.

Conclusion: Mammography screening entails a substantial amount of overdiagnosis.

Primary Funding Source: Norwegian Research Council and Frontier Science.

Ann Intern Med. 2012;156:491-499. www.annals.org
For author affiliations, see end of text.

Marmot: breast screening should continue

But would the Panel also have recomended to implement breast screening if it did not already exist?

NEWSPAPER OF THE YEAR

THE TIMES

The woman behind that M&S campaign Times2

NHS checks on over-40s condemned as 'useless'

Call for £300 million scheme to be scrapped

Name, set and match to Miss Sugarpova

IN THE NEWS

Mubarak to be freed | Anti-fracking arrests | Crimefighter resigns | Schools in gay row | Emerging markets hit | Blues go sky high

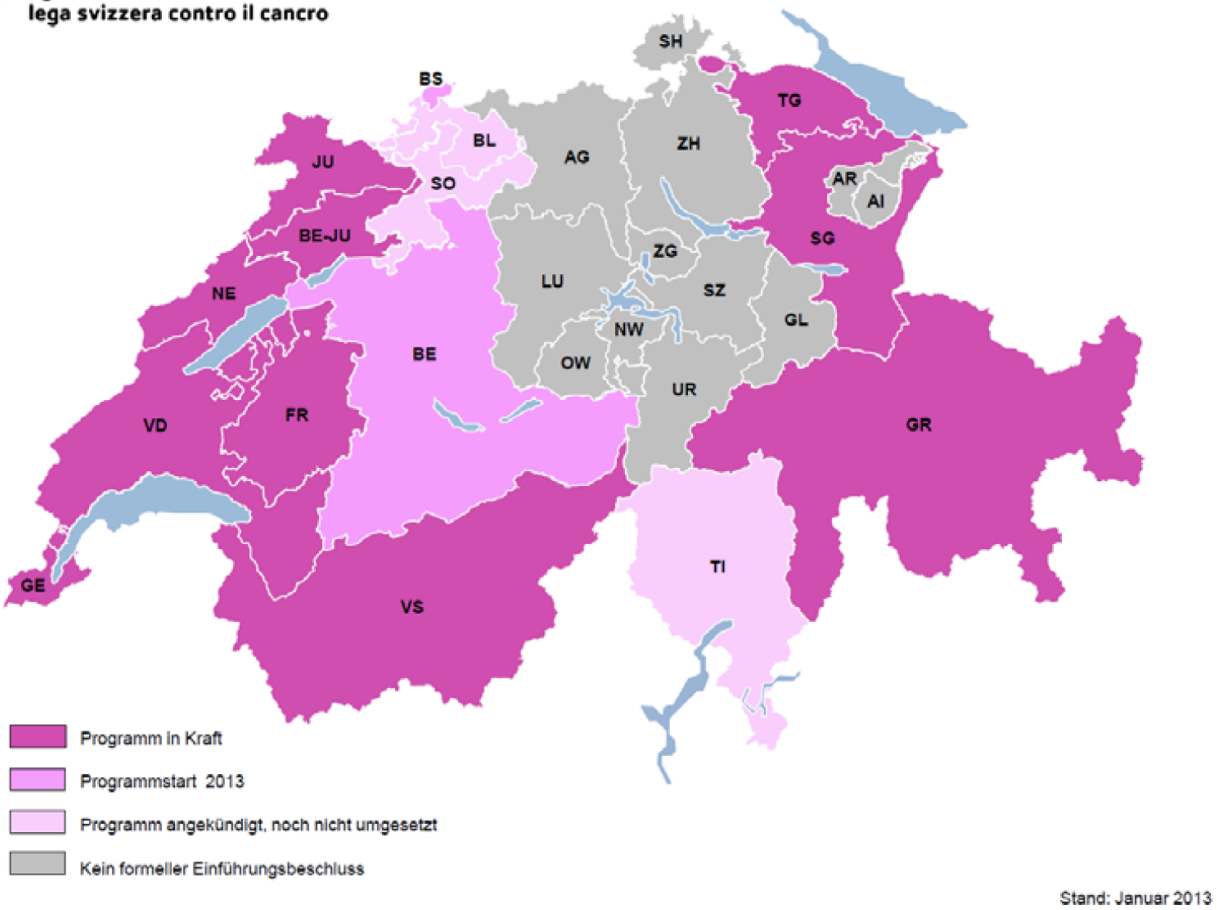
20 Aug 2013

Health check check

Interview and Letter
by Krogsbøll et al.

krebsliga schweiz
ligue suisse contre le cancer
lega svizzera contro il cancro

Mammografie-Screening-Programme in der Schweiz



Stand: Januar 2013

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

Abolishing Mammography Screening Programs? A View from the Swiss Medical Board

Nikola Biller-Andorno, M.D., Ph.D., and Peter Jüni, M.D.

In January 2013, the Swiss Medical Board, an independent health technology assessment initiative under the auspices of the Conference of Health Ministers of the Swiss Cantons, the Swiss Medical Association, and the Swiss Academy of Medical Sciences, was mandated to prepare a review of mammography screening. The two of us, a medical ethicist and a clinical epidemiologist, were members of the expert panel that

tail, however, we became increasingly concerned.

First, we noticed that the ongoing debate was based on a series of reanalyses of the same, predominantly outdated trials. The first trial started more than 50 years

Second, we were struck by how nonobvious it was that the benefits of mammography screening outweighed the harms. The relative risk reduction of approximately 20% in breast-cancer mortality associated with mammography that is currently described by most expert panels[2] came at the price of a considerable diagnostic cascade, with repeat mammography, subsequent

A few quotes

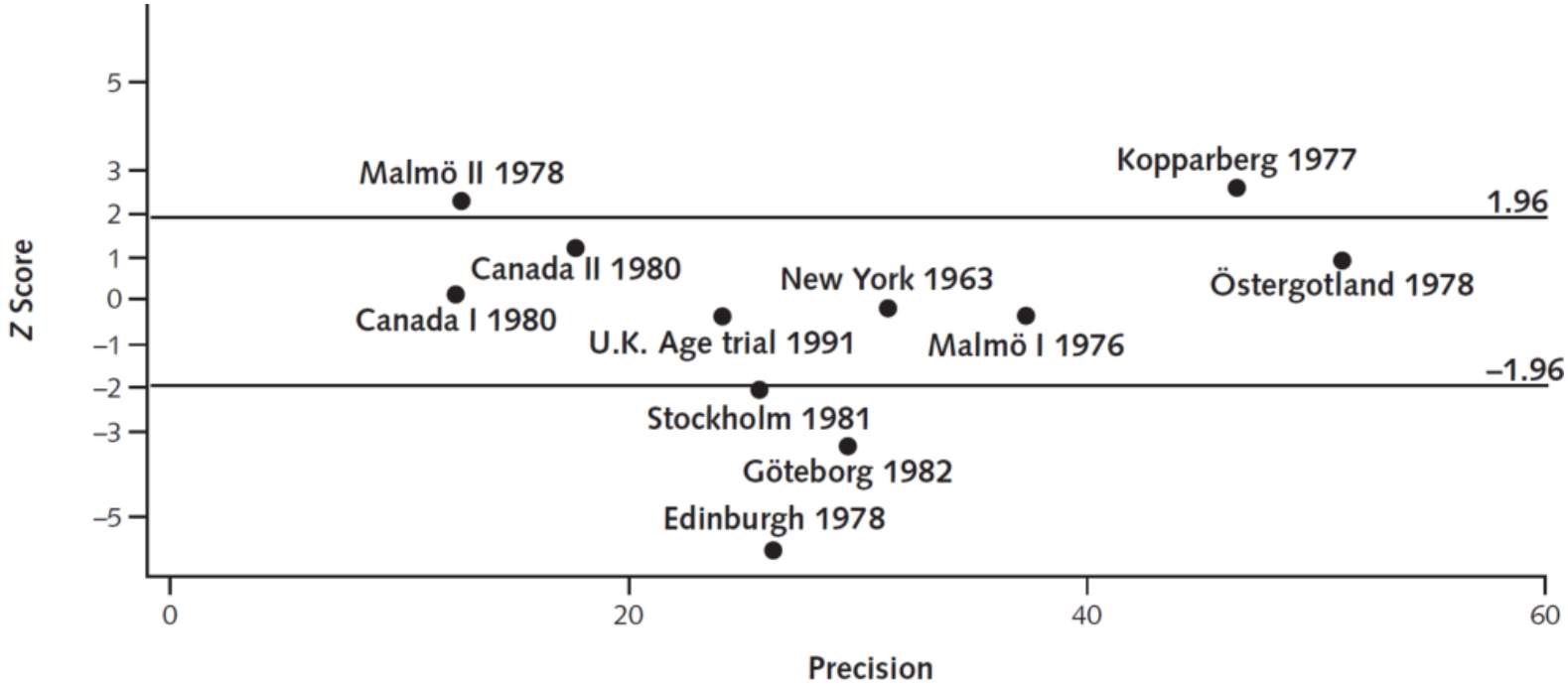
- *”When we reviewed the available evidence and contemplated its implications in detail (…) we became increasingly concerned.”*
- *”We would be in favour of mammography screening if [benefits were large]. Unfortunately, they are not, and we believe women need to be told so.”*
- *”From an ethical perspective, a public health program that does not clearly produce more benefits than harms is hard to justify.”*

Biller-Adorno and Jüni, New Engl J Med 2014.

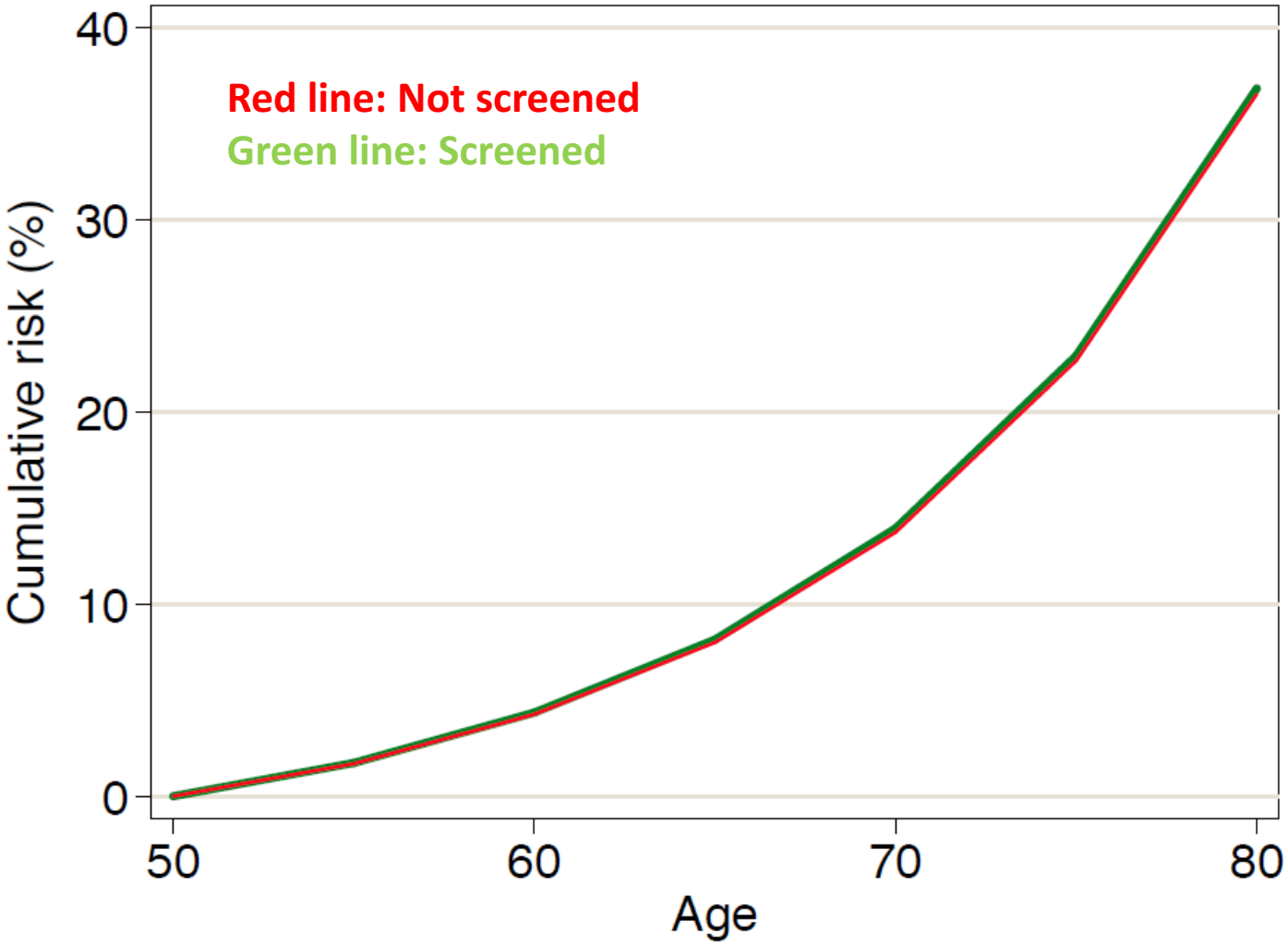
Annals of Internal Medicine
Established in 1927 by the American College of Physicians

From: It Is Time to Initiate Another Breast Cancer Screening Trial

Ann Intern Med. 2014; doi:10.7326/M14-0569



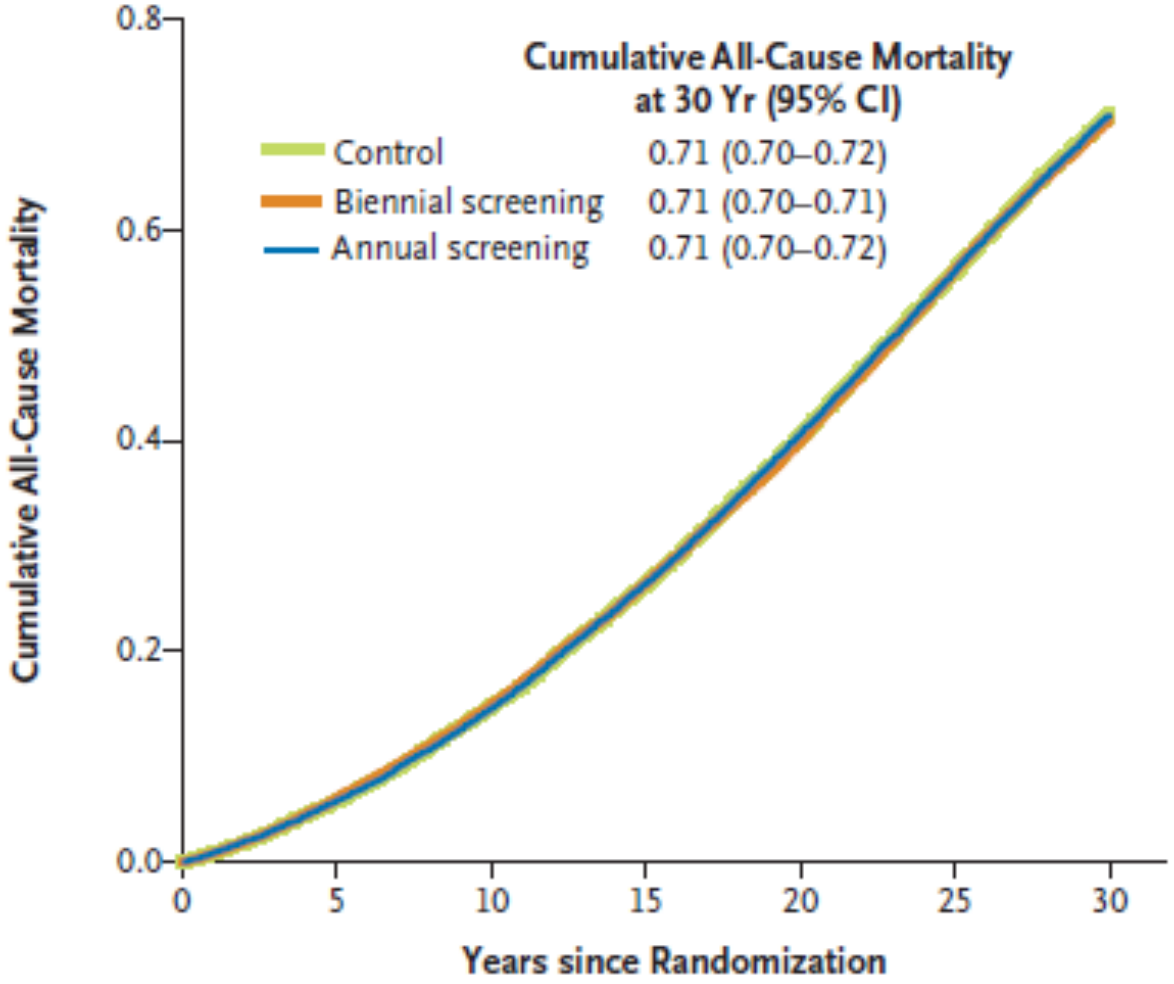
Total mortaliy (breast screening)



Nordic Cochrane Centre

Pharoah P, Professor of Cancer Epidemiology, Univ. of Cambridge.

Total mortality (FOBT)



Shaukat et al. N Engl J Med 2013; 369:1106-14.

Gavn – befolkningens vurdering

Hoffmann & Mar. JAMA Intern Med 2015;175:274-286.

thebmj

BMJ 2015;350:h2175 doi: 10.1136/bmj.h2175 (Published 5 May 2015)

OBSERVATIONS

THE ART OF RISK COMMUNICATION

Towards a paradigm shift in cancer screening: informed citizens instead of greater participation

Germany aims to stop nudging the public on screening

Gerd Gigerenzer *director, Harding Centre for Risk Literacy and Centre for Adaptive Behaviour and Cognition, Max Planck Institute for Human Development, Berlin, Germany*

Policy on screening people for cancer poses a dilemma: should we aim for higher participation rates or for better informed citizens? The dilemma is that both cannot be had. A focus on informing citizens risks lowering participation rates, because

Turning the tables in screening

But Germany's National Cancer Plan, which was initiated by the government in 2008 and coordinates screening and treatment, is now turning the tables. It was announced at a workshop in February 2015 that, on the basis of a 2013 law on improving the detection of cancer,[5] "the goal of informed participatory decision making is now ranked higher than the goal of a maximum participation rate in cancer screening."[6] To change policy so clearly and publicly is unprecedented and represents a potential paradigm shift in screening. Its implementation will require fundamental changes. In my view, these include the following.

Evidence based information

All screening pamphlets and websites aimed at the public need

Use of a decision aid including information on overdetection to support informed choice about breast cancer screening: a randomised controlled trial

Jolyn Hersch, Alexandra Barratt, Jesse Jansen, Les Irwig, Kevin McGeechan, Gemma Jacklyn, Hazel Thornton, Haryana Dhillon, Nehmat Houssami, Kirsten McCaffery

Summary

Background Mammography screening can reduce breast cancer mortality. However, most women are unaware that inconsequential disease can also be detected by screening, leading to overdiagnosis and overtreatment. We aimed to investigate whether including information about overdetection of breast cancer in a decision aid would help women aged around 50 years to make an informed choice about breast screening.

Methods We did a community-based, parallel-group, randomised controlled trial in New South Wales, Australia, using a random cohort of women aged 48–50 years. Recruitment to the study was done by telephone; women were eligible if they had not had mammography in the past 2 years and did not have a personal or strong family history of breast cancer. With a computer program, we randomly assigned 879 participants to either the intervention decision aid (comprising evidence-based explanatory and quantitative information on overdetection, breast cancer mortality reduction, and false positives) or a control decision aid (including information on breast cancer mortality reduction and false positives). Participants and interviewers were masked to group assignment. The primary outcome was informed choice (defined as adequate knowledge and consistency between attitudes and screening intentions), which we assessed by telephone interview about 3 weeks after random allocation. The primary outcome was analysed in all women who completed the relevant follow-up interview questions fully. This trial is registered with the Australian New Zealand Clinical Trials Registry, number ACTRN12613001035718.

Findings Between January, 2014, and July, 2014, 440 women were allocated to the intervention group and 439 were assigned to the control group. 21 women in the intervention group and 20 controls were lost to follow-up; a further ten women assigned to the intervention and 11 controls did not answer all questions on attitudes. Therefore, 409 women in the intervention group and 408 controls were analysed for the primary outcome. 99 (24%) of 409 women in the intervention group made an informed choice compared with 63 (15%) of 408 in the control group (difference 9%, 95% CI 3–14; p=0·0017). Compared with controls, more women in the intervention group met the threshold for adequate overall knowledge (122/419 [29%] *vs* 71/419 [17%]; difference 12%, 95% CI 6–18; p<0·0001), fewer women expressed positive attitudes towards screening (282/409 [69%] *vs* 340/408 [83%]; 14%, 9–20; p<0·0001), and fewer women intended to be screened (308/419 [74%] *vs* 363/419 [87%]; 13%, 8–19; p<0·0001). When conceptual knowledge alone was considered, 203 (50%) of 409 women in the intervention group made an informed choice compared with 79 (19%) of 408 in the control group (p<0·0001).

Interpretation Information on overdetection of breast cancer provided within a decision aid increased the number of women making an informed choice about breast screening. Becoming better informed might mean women are less likely to choose screening.

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February 18, 2015
http://dx.doi.org/10.1016/S0140-6736(15)60123-4

See Online/Comment
http://dx.doi.org/10.1016/S0140-6736(15)60258-6

Screening & Test Evaluation Program (STEP) (J Hersch MApplSc, J Jansen PhD, Prof L Irwig MBBCh, Prof N Houssami MBBS, Prof K McCaffery PhD), **Centre for Medical Psychology & Evidence-based Decision-making (CeMPED)** (J Hersch, J Jansen, Prof K McCaffery, Prof A Barratt MBBS, K McGeechan PhD, H Dhillon PhD), **School of Public Health** (G Jacklyn MPH), **and Central Clinical School** (H Dhillon), **The University of Sydney, Sydney, NSW 2006, Australia; and Department of Health Sciences, University of Leicester; Leicester, UK** (H Thornton Hon DSc)

Correspondence to:
Prof Kirsten McCaffery, School of Public Health, The University of Sydney, Sydney, NSW 2006, Australia
kirsten.mccaffery@sydney.edu.au

Annals of Internal Medicine | ORIGINAL RESEARCH

Aggregate Cost of Mammography Screening in the United States: Comparison of Current Practice and Advocated Guidelines

Cristina O'Donoghue, MD, MPH; Martin Eklund, PhD; Elissa M. Ozanne, PhD; and Laura J. Esserman, MD, MBA

Background: Controversy exists over how often and at what age mammography screening should be implemented. Given that evidence supports less frequent screening, the cost differences among advocated screening policies should be better understood.

Objective: To estimate the aggregate cost of mammography screening in the United States in 2010 and compare the costs of policy recommendations by professional organizations.

Design: A model was developed to estimate the cost of mammography screening in 2010 and 3 screening strategies: annual (ages 40 to 84 years), biennial (ages 50 to 69 years), and U.S. Preventive Services Task Force (USPSTF) guidelines (biennial for those aged 50 to 74 years and personalized based on risk for those younger than 50 years and based on comorbid conditions for those 75 years and older).

Setting: United States.

Patients: Women aged 40 to 85 years.

Intervention: Mammography annually, biennially, or following USPSTF guidelines.

Measurements: Cost of screening per year, using Medicare reimbursements.

Results: The estimated cost of mammography screening in the United States in 2010 was $7.8 billion, with approximately 70% of women screened. The simulated cost of screening 85% of women was $10.1 billion, $2.6 billion, and $3.5 billion for annual, biennial, and USPSTF guidelines, respectively. The largest drivers of cost (in order) were screening frequency, percentage of women screened, cost of mammography, percentage of women screened with digital mammography, and percentage of mammography recalls.

Limitation: Cost estimates and assumptions used in the model were conservative.

Conclusion: The cost of mammography varies by at least $8 billion per year on the basis of screening strategy. The USPSTF guidelines are based on the scientific evidence to date to maximize patient benefit and minimize harm but also result in far more effective use of resources.

Primary Funding Source: University of California and the Safeway Foundation.

Ann Intern Med. 2014;160:145-153. www.annals.org
For author affiliations, see end of text.

Breast screening controversy continues

”At what stage must we seriously consider whether this screening is a good use of £96m of the NHS budget?”

Fiona Godlee, Editor’s Choice, BMJ.

BMJ 2013;346:f477.

Informed choice in screening needs more than information

In *The Lancet*, Jolyn Hersch and colleagues report on a randomised controlled trial of two decision aids for women approaching the target age for starting breast screening (age 48–50 years): an intervention decision aid that included information about the most severe harm of breast cancer screening (overdiagnosis); and a control decision aid that did not have this information.[1] The aim of the trial was to see if including information on overdiagnosis would help women make an informed choice about breast screening. We could argue that to do a trial in which half of the participants are not given information about the harms of an intervention is ethically unacceptable. However, most breast screening programmes do not include information about overdiagnosis or other relevant harms of screening in their invitations,[2] which is why this study is so important. Of 409 women who received information about overdiagnosis in their decision aid, 99 (24%) were judged to have made an informed choice, the

Balanced comprehensive information is important from an ethical perspective; however, it might not have a substantial effect on the ability of women to make truly informed choices. In the study by Hersch and colleagues,[1] a woman was judged to have made an informed choice if she had sufficient knowledge and made a decision consistent with her personal preferences and values. We agree this definition of informed choice is useful in a research context, but it assumes that information speaking to people's intellect is easily integrated into understanding of risk. Yet research suggests that our understanding of risk relies mainly on emotions and that cognitive comprehension has little effect on decision making.[5,6] Furthermore, if emotionally charged messages have formed our perception of a particular risk, which is certainly the case for breast cancer, subsequent information is unlikely to change our understanding of that risk nor our attitudes or behaviour.[6] Therefore, emotional factors are likely

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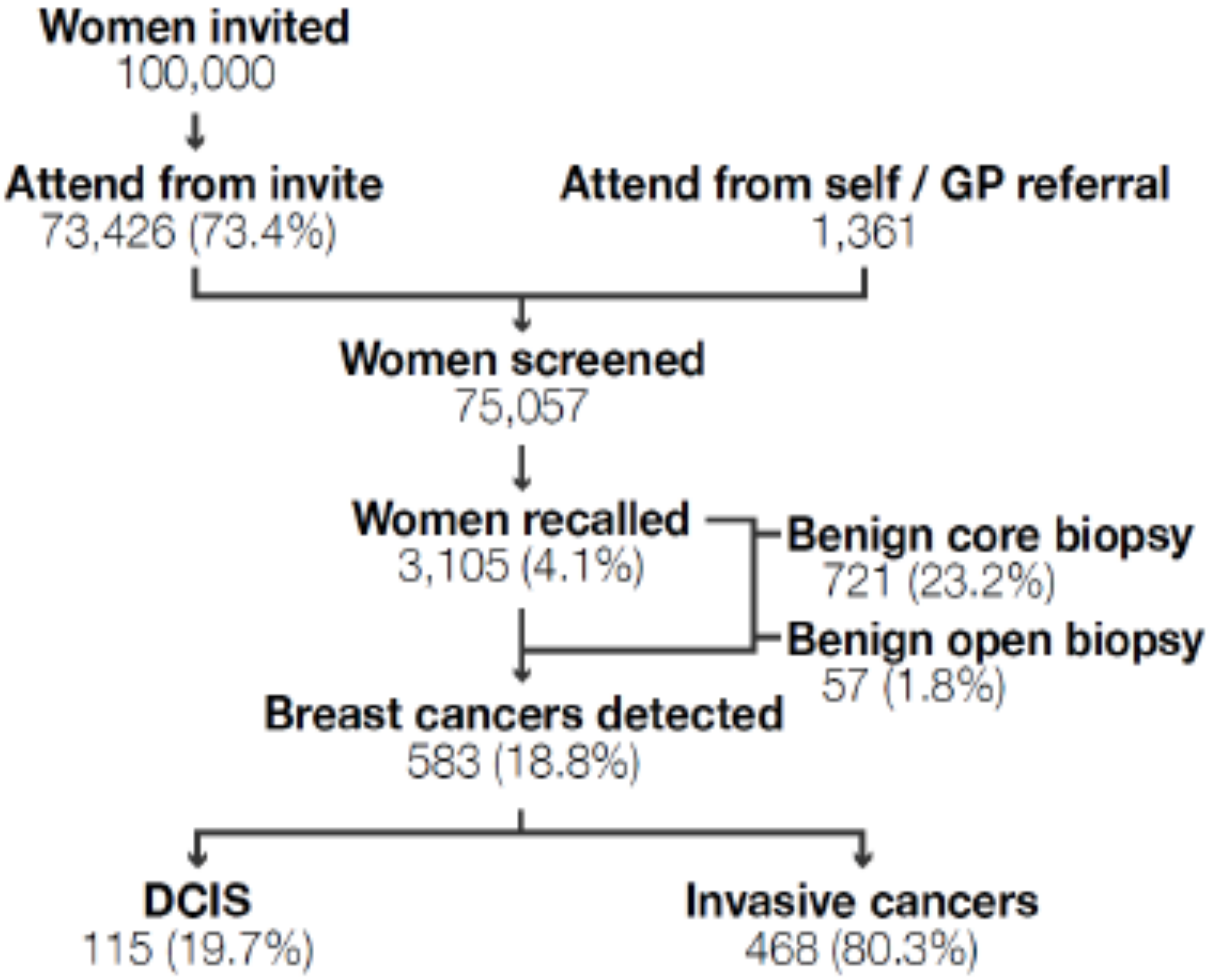
Published Online
February 18, 2015
http://dx.doi.org/10.1016/S0140-6736(15)60258-6

See Online/Articles
http://dx.doi.org/10.1016/S0140-6736(15)60123-4

Tumour size and breast screening

- Average tumour size in Denmark was reduced from 33 mm in 1978-9 to 24 mm in 1988-9.
- Average size reduction in the trials was 5 mm.

Rostgaard et al. *Acta Oncol* 2010;49:313-21


Women invited
100,000
Attend from invite
73,426 (73.4%)
Attend from self / GP referral
1,361
Women screened
75,057
Women recalled
3,105 (4.1%)
Benign core biopsy
721 (23.2%)
Benign open biopsy
57 (1.8%)
Breast cancers detected
583 (18.8%)
DCIS
115 (19.7%)
Invasive cancers
468 (80.3%)

2.7 million women invited in 2009[1].

- False positives: 65,094
- Benign core biopsies: 19,467
- Benign open biopsies: 1,539
- False negatives: ~33% of cases in a screened population were not detected
- Direct cost: £ 96 million

1: NHS Breast Screening Programme: Annual Review 2011.


More tests don't mean a healthier you: Review - Times Of India - Mozilla Firefox
articles.timesofindia.indiatimes.com/2012-10-17/mumbai/34524140_1_preventive-checks-preventive-tests-public-health
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MUMBAI: Annual health check-ups don't necessarily save lives, says a new Cochrane review of medical trials. Be it overall deaths or deaths specifically from killer diseases such as cancer and heart ailments, the review said the check-ups don't make much of a difference.
Annual checks have always been a grey zone, with its supporters and opponents alternately making a strong case (the former underline the value of a saved life for a family, while the latter scream poor public health economics). In India, the idea got a fillip in March 2012 when the Centre announced a tax rebate of up to Rs 5,000 for preventive tests. For the diagnostic segment that is growing at over 13% every year, the budgetary sop was the ultimate incentive.
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But the Cochrane review, which is respected for its independent and evidence-based studies, looked at 14 trials involving almost two lakh people to arrive at the conclusion. The trials divided participants into two groups: one in which participants were invited to general health checks and another in which they were not. The results were varied: people were more likely to be diagnosed with high blood pressure, high cholesterol or other abnormalities. What sealed
start
Indbakke - Mozilla Th...
More tests don't mea...
UfL - politisk reaktion....
100%
11:06

"Preventive health check-ups are an irrational battery of tests carried out on healthy people whose main indication is that they have money in their pockets. It is not scientific and can be completely avoided,“
Dr. Abhay Shukla, Centre for Enquiry in Health and Allied Themes (CEHAT), Pune.

*“*A hospital administrator said preventive cancer checks carried out in his hospital recently had revealed ovarian cancer in two of the 100 women who had signed up. "For them, it was a life-saving diagnosis," he said.”

http://articles.timesofindia.indiatimes.com/2012-10-17/mumbai/34524140_1_preventive-checks-preventive-tests-public-health

• ”..the UK breast screening programme confer significant benefit and should continue.”

• ”The Panel believes that overdiagnosis occurs”

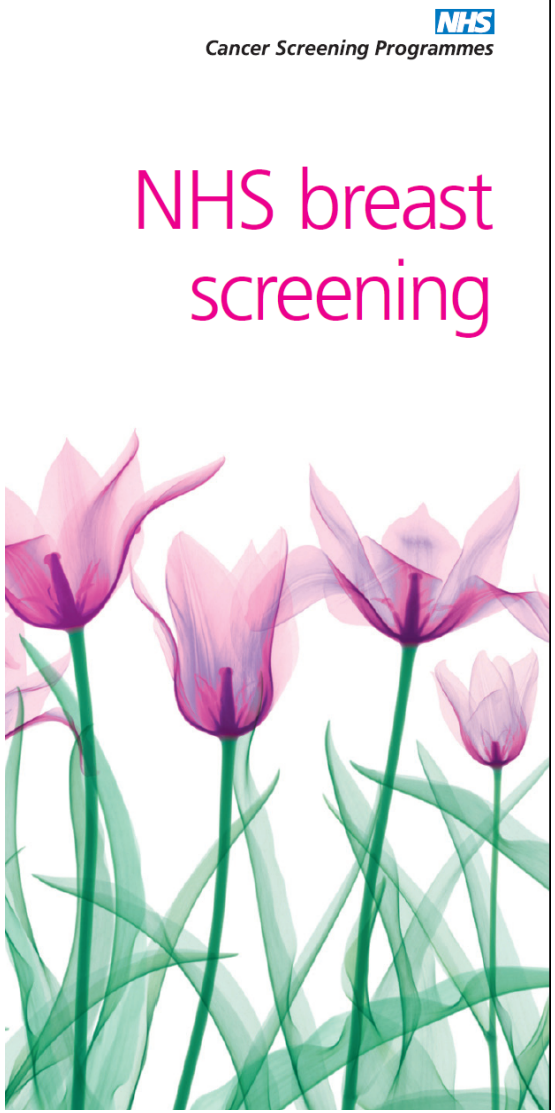
• ”Clear communication of these harms and benefits to women is essential and is the core of how a modern health system should function.”

• ”…the estimates provided are from studies with many limitations and [the] relevance to present-day screening programmes can be questioned, they have substantial uncertainty and should be regarded as only an approximate guide.”

• ”The Panel relied mainly on findings from randomised trials…”

• ”Randomised trials that elucidate the appropriate treatment of screen-detected ductal carcinoma of the breast are encouraged.”

• ”the overall cost-effectiveness of the UK breast cancer screening programme needs to be reassessed.”



"Designed to ensure that women are told what screening can and cannot achieve, the leaflet includes an explanation about false positive and false negative results […]".

"This means that women should be able to make a genuinely informed choice based on an understanding about why they are attending for screening".

NHS
Cancer Screening Programmes

NHS breast screening

Some statistics you might find helpful

- Breast cancer is the most common cancer in women. There are around 46,000 cases a year in the UK. Eight out of 10 breast cancers are found in women aged 50 and over.
- About 12,000 women die of breast cancer each year in the UK.
- For every 400 women screened regularly for 10 years, one less will die from breast cancer. This means that around 1,400 women are prevented from dying from breast cancer each year in England.

NHS
Cancer Screening Programmes

NHS breast screening

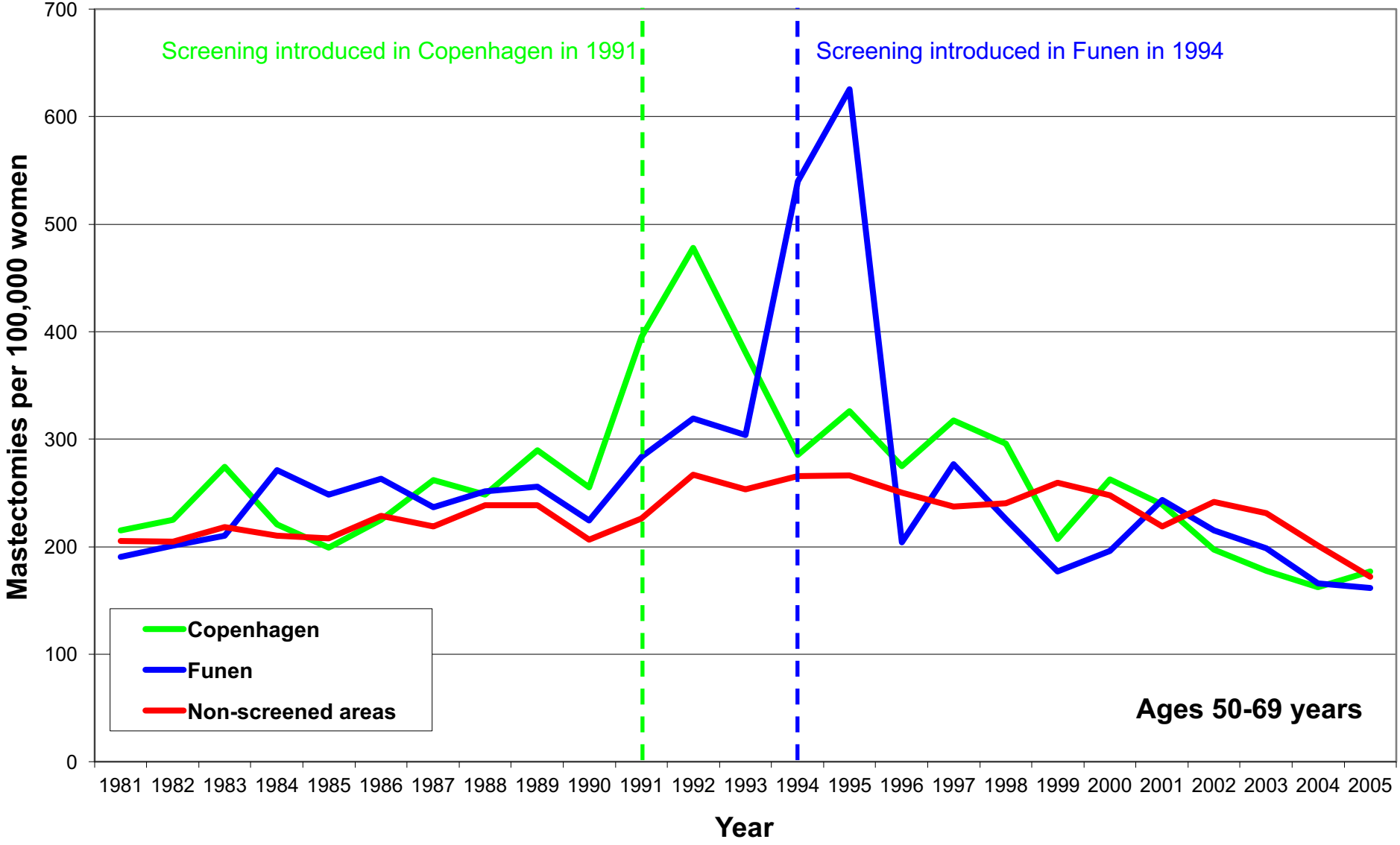
What are the benefits of breast screening?

- Regular screening prevents deaths from breast cancer.
- If a breast cancer is found early, you are less likely to have a mastectomy (your breast removed) or chemotherapy.

What are the downsides of being screened?

- Having a mammogram means your breasts are exposed to a small amount of radiation.
- Screening can find cancers which are treated but which may not otherwise have been found during your lifetime.

Mastectomy use in sreened and non-screened areas in Denmark



Jørgensen KJ et al. Radiology 2011; 260:621-7

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 23, 2010 VOL. 363 NO. 13

Effect of Screening Mammography on Breast-Cancer Mortality in Norway

Mette Kalager, M.D., Marvin Zelen, Ph.D., Frøydis Langmark, M.D., and Hans-Olov Adami, M.D., Ph.D.

RESULTS

We analyzed data from 40,075 women with breast cancer. The rate of death was reduced by 7.2 deaths per 100,000 person-years in the screening group as compared with the historical screening group (rate ratio, 0.72; 95% confidence interval [CI], 0.63 to 0.81) and by 4.8 deaths per 100,000 person-years in the nonscreening group as compared with the historical nonscreening group (rate ratio, 0.82; 95% CI, 0.71 to 0.93; P<0.001 for both comparisons), for a relative reduction in mortality of 10% in the screening group (P=0.13). Thus, the difference in the reduction in mortality between the current and historical groups that could be attributed to screening alone was 2.4 deaths per 100,000 person-years, or a third of the total reduction of 7.2 deaths.

CONCLUSIONS

The availability of screening mammography was associated with a reduction in the rate of death from breast cancer, but the screening itself accounted for only about a third of the total reduction. (Funded by the Cancer Registry of Norway and the Research Council of Norway.)

Screening for breast cancer with mammography (Review)

Gøtzsche PC, Jørgensen KJ

THE COCHRANE COLLABORATION®

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2013, Issue 6

http://www.thecochranelibrary.com

Why does vehement opposition to screening come from Denmark, which has one of Europe's highest breast cancer mortality rates?

Denmark still has one of the highest breast cancer mortality rates in Europe, similar to that of Serbia. On the other hand, Finland and Sweden have among the lowest breast cancer mortality rates in Europe, although all the Nordic countries use identical breast cancer treatment guidelines. The health care systems among these countries are similar in most other aspects as well, except that Finland and Sweden introduced nationwide screening more than two decades ago. The implementation of organized nationwide screening should dramatically decrease breast cancer mortality throughout Denmark, as has already happened in Sweden and Finland.

"The 10-year fatality of screen-detected tumours is 50% lower than that of symptomatic tumours"

Steven Duffy, Professor of Statistics, St. Barts & the London Medical and Dental Schools. NHS BSP Annual Review 2008.

Nyhedscenter

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Lavere overlevelse for danske kvinder med brystkræft

01. marts 2013

Kvinder i Danmark og Storbritannien har haft en lavere overlevelse efter brystkræft, end kvinder i Australien, Canada, Norge og Sverige i perioden 2000-2007. Det viser et nyt videnskabeligt studie, som offentliggøres i dag i British Journal of Cancer. Studiet er udført af International Cancer Benchmarking Partnership, som Sundhedsstyrelsen deltager i og har medfinancieret.

Tre-års overlevelsen for danske kvinder var 89 procent, hvilket var på niveau med Storbritannien, men lavere end i de andre fire lande, der lå på 91-94 procent. Studiet undersøgte, om forskellene mellem landene kunne forklares ved forskelle i sygdomsstadie på diagnosetidspunktet, og fandt at kun 30 procent af danske kvinder blev diagnosticeret i tidligt sygdomsstadie (stadium I), sammenlignet med 42-45 procent i de andre fem lande.

Ifølge forskerne kan en medvirkende forklaring på den lavere overlevelse blandt danske kvinder være, at kvinderne bliver diagnosticeret i senere stadier, formentlig på grund af at Danmark, som det eneste land i undersøgelsen, ikke havde udrullet et nationalt screeningsprogram for brystkræft før 2007.

Kvaliteten af behandlingen kan også forklare noget af forskellen mellem landene, men studiet peger på, at det først er fremmeste er tilfældet for Storbritannien, hvor den specifikke overlevelse for de enkelte sygdomsstadier generelt lå lavere end de øvrige seks lande.

Studiet er baseret på data fra 257.362 kvinder, der fik diagnosticeret brystkræft i årene 2000-2007, for danske kvinders vedkommende dog kun data for fire-års perioden 2004-2007.

Link

Link til artiklen i British Journal of Cancer

Fakta om screening for brystkræft

Screening for brystkræft med mammografi har siden 2009 været tilbudt til alle kvinder i Danmark i aldersgruppen 50-69 år. Mammografi er en standardiseret røntgenundersøgelse af brysterne, som tilbydes hvert andet år til kvinder uden symptomer. Mammografiscreening nedsætter ikke risikoen for brystkræft, men kan afsløre kræft i tidligere faser, det vil sige på et tidspunkt, hvor kvinden ikke har symptomer, og hvor risikoen for, at sygdommen har spredt sig, er mindre. Derved øges muligheden for helbredelse.

Kvaliteten af behandlingen følges blandt andet af en landsdækkende klinisk kvalitetsdatabase for brystkræft. Kræftbehandlingen i Danmark har fået et løft med indførelse af pakkeforløb, der har været med til at skabe hurtigere og veltilrettelagte forløb for en række patienter.

Information om brystkræftscreening på Sundhedsstyrelsens hjemmeside

Kontakt

Enhedschef
Søren Brostrøm
Sundhedsstyrelsen
Telefon: 72 22 78 67

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på nyheder og nyhedsbreve

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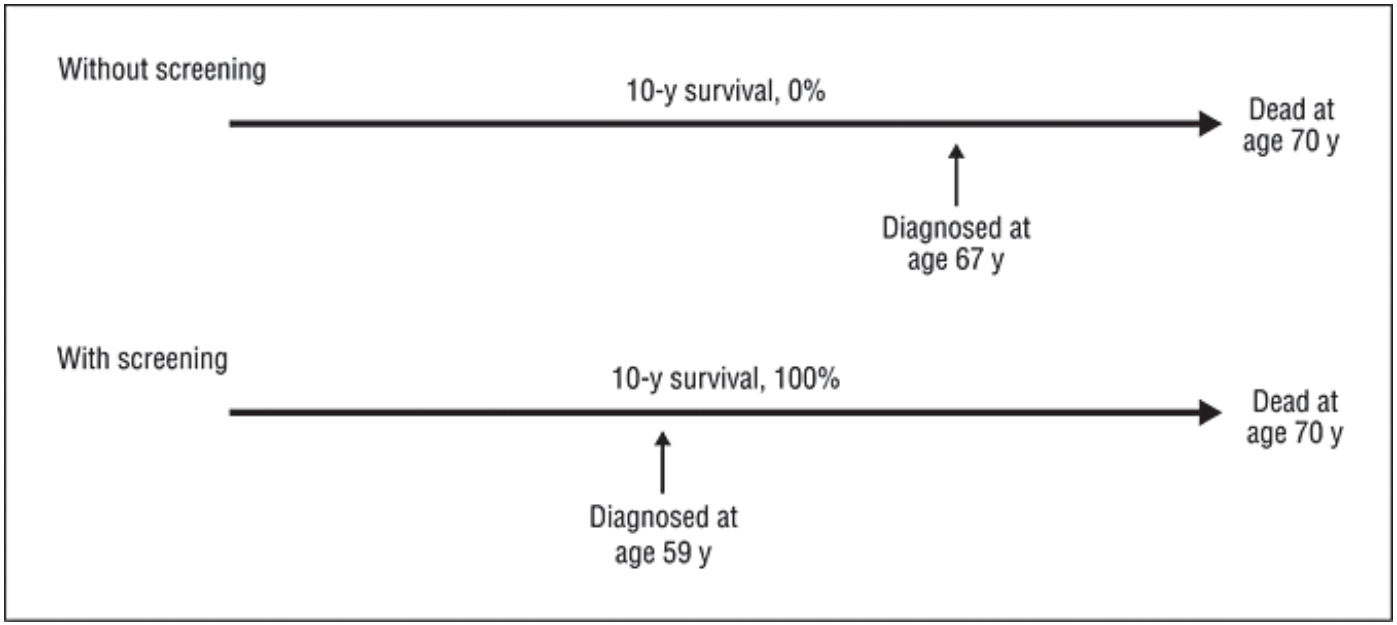
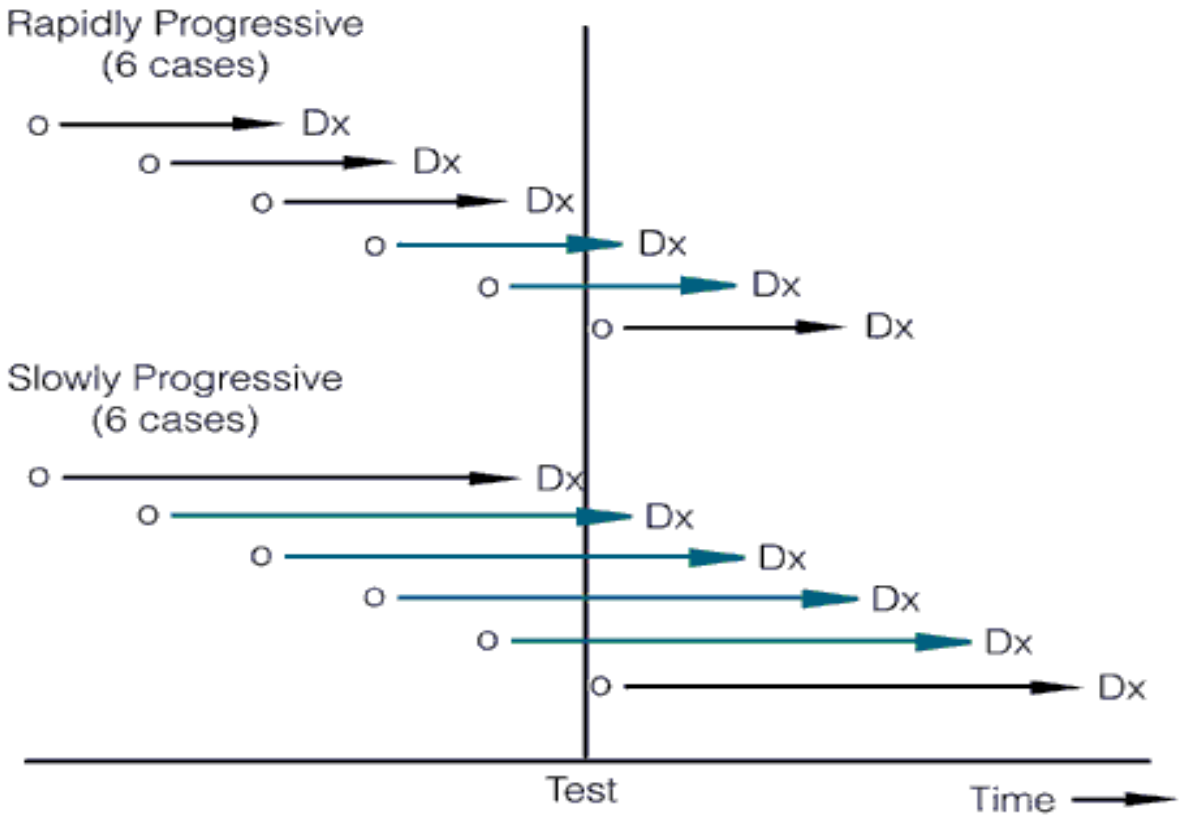
Lead-time bias



ARCHIVES OF INTERNAL MEDICINE

Welch HG et al. Arch Intern Med 2007;167:2289-2295.

Length bias



o = Time of disease onset.
Dx = Time when disease is clinically obvious without testing.

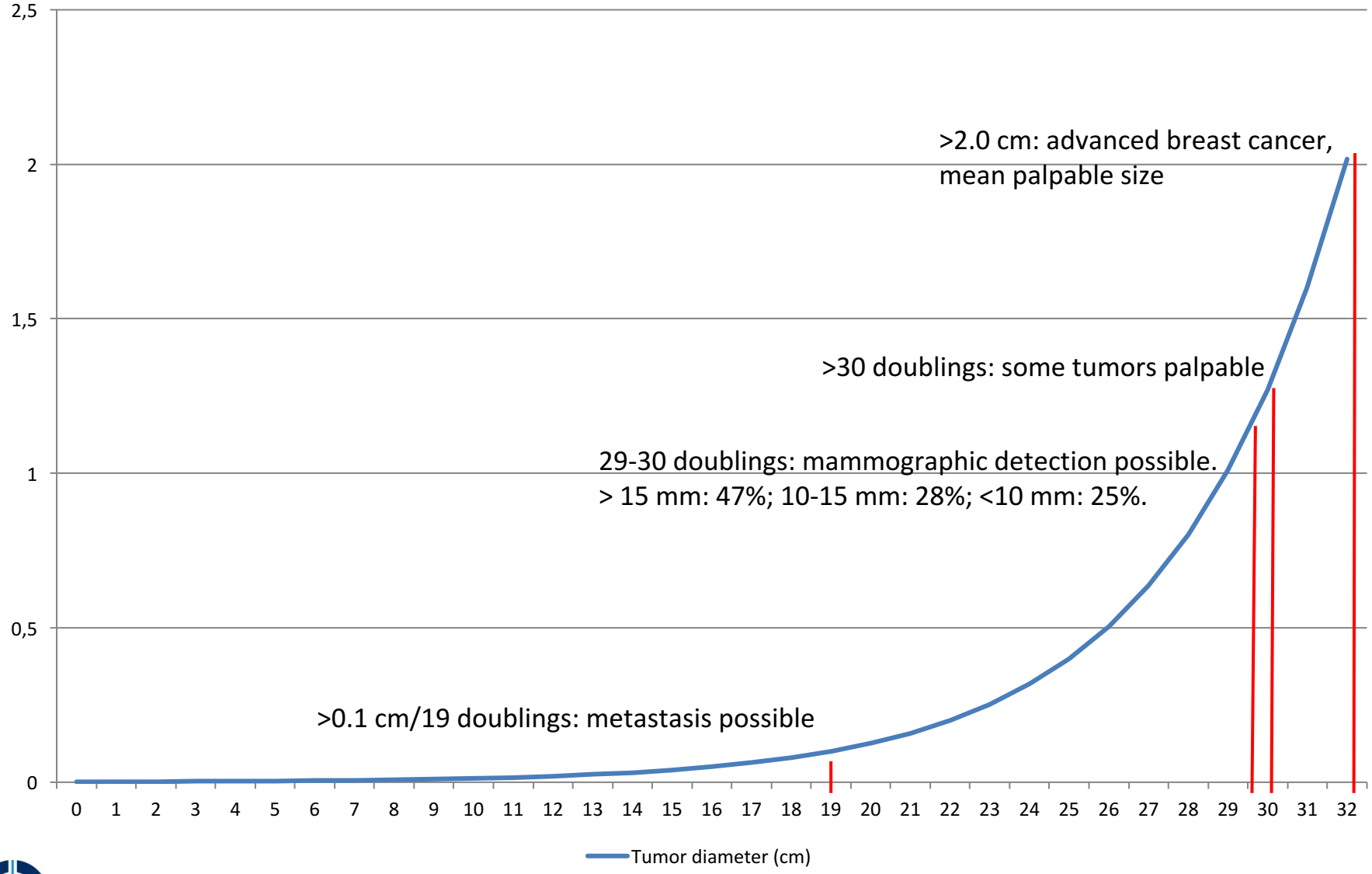
Welch HG et al. Arch Intern Med 2007;167:2289-2295.

Healthy Screenee effect.

"The screenees are the healthy, well-educated, affluent, physically fit, fruit and vegetable eating, non-smokers with long-lived parents."

J. A. Muir Gray, former Programmes Director, National Screening Commitee, UK.

Tumor diameter (cm) vs. cell doublings



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effect of Three Decades of Screening Mammography on Breast-Cancer Incidence

Archie Bleyer, M.D., and H. Gilbert Welch, M.D., M.P.H.

ABSTRACT

BACKGROUND

To reduce mortality, screening must detect life-threatening disease at an earlier, more curable stage. Effective cancer-screening programs therefore both increase the incidence of cancer detected at an early stage and decrease the incidence of cancer presenting at a late stage.

METHODS

We used Surveillance, Epidemiology, and End Results data to examine trends from 1976 through 2008 in the incidence of early-stage breast cancer (ductal carcinoma in situ and localized disease) and late-stage breast cancer (regional and distant disease) among women 40 years of age or older.

RESULTS

The introduction of screening mammography in the United States has been associated with a doubling in the number of cases of early-stage breast cancer that are detected each year, from 112 to 234 cases per 100,000 women — an absolute increase of 122 cases per 100,000 women. Concomitantly, the rate at which women present with late-stage cancer has decreased by 8%, from 102 to 94 cases per 100,000 women — an absolute decrease of 8 cases per 100,000 women. With the assumption of a constant underlying disease burden, only 8 of the 122 additional early-stage cancers diagnosed were expected to progress to advanced disease. After excluding the transient excess incidence associated with hormone-replacement therapy and adjusting for trends in the incidence of breast cancer among women younger than 40 years of age, we estimated that breast cancer was overdiagnosed (i.e., tumors were detected on screening that would never have led to clinical symptoms) in 1.3 million U.S. women in the past 30 years. We estimated that in 2008, breast cancer was overdiagnosed in more than 70,000 women; this accounted for 31% of all breast cancers diagnosed.

CONCLUSIONS

Despite substantial increases in the number of cases of early-stage breast cancer detected, screening mammography has only marginally reduced the rate at which women present with advanced cancer. Although it is not certain which women have been affected, the imbalance suggests that there is substantial overdiagnosis, accounting for nearly a third of all newly diagnosed breast cancers, and that screening is having, at best, only a small effect on the rate of death from breast cancer.

From the Quality Department, St. Charles Health System, Central Oregon, and the Department of Radiation Medicine, Oregon Health and Science University, Portland (A.B.); the University of Texas Medical School at Houston, Houston (A.B.); and the Dartmouth Institute for Health Policy and Clinical Practice, Geisel School of Medicine at Dartmouth, Hanover, NH (H.G.W.). Address reprint requests to Dr. Bleyer at 2500 NE Neff Rd., Bend, OR 97701, or at ableyer@gmail.com.

N Engl J Med 2012;367:1998-2005.
DOI: 10.1056/NEJMoa1206809

BMJ

BMJ 2013;346:f1064 doi: 10.1136/bmj.f1064 (Published 26 February 2013)

RESEARCH

Overdiagnosis in screening mammography in Denmark: population based cohort study

OPEN ACCESS

Sisse Helle Njor *statistician*[1], Anne Helene Olsen *statistician*[2], Mogens Blichert-Toft *professor emeritus*[3], Walter Schwartz *chief physician*[4], Ilse Vejborg *chief physician*[5], Elsebeth Lynge *professor*[1]

[1]Department of Public Health, University of Copenhagen, Østre Farimagsgade 5, DK 1014 Copenhagen K, Denmark; [2]Institute of Community Medicine, University of Tromsø, Tromsø, Norway; [3]Danish Breast Cancer Cooperative Group, 2100 Copenhagen Ø, Denmark; [4]Mammography Screening Clinic, University Hospital Odense, 5000 Odense, Denmark; [5]Diagnostic Centre, University Hospital Copenhagen, Blegdamsvej, 2100 Copenhagen Ø, Denmark

Abstract

Objective To use data from two longstanding, population based screening programmes to study overdiagnosis in screening mammography.

Design Population based cohort study.

Setting Copenhagen municipality (from 1991) and Funen County (from 1993), Denmark.

Participants 57 763 women targeted by organised screening, aged 56-69 when the screening programmes started, and followed up to 2009.

Main outcome measures Overdiagnosis of breast cancer in women targeted by screening, assessed by relative risks compared with historical control groups from screening regions, national control groups from non-screening regions, and historical national control groups.

Results In total, 3279 invasive breast carcinomas and ductal carcinomas in situ occurred. The start of screening led to prevalence peaks in breast cancer incidence: relative risk 2.06 (95% confidence interval 1.64 to 2.59) for Copenhagen and 1.84 (1.46 to 2.32) for Funen. During subsequent screening rounds, relative risks were slightly above unity: 1.04 (0.85 to 1.27) for Copenhagen and 1.14 (0.98 to 1.32) for Funen. A compensatory dip was seen after the end of invitation to screening: relative risk 0.80 (0.65 to 0.98) for Copenhagen and 0.67 (0.55 to 0.81) for Funen during the first four years. The relative risk of breast cancer accumulated over the entire follow-up period was 1.06 (0.90 to 1.25) for Copenhagen and 1.01 (0.93 to 1.10) for Funen. Relative risks for participants corrected for selection bias were estimated to be 1.08 for Copenhagen and 1.02 for Funen; for participants followed for at least eight years after the end of screening, they were 1.05 and 1.01. A pooled estimate gave 1.040 (0.99 to 1.09) for all targeted women and 1.023 (0.97 to 1.08) for targeted women followed for at least eight years after the end of screening.

Conclusions On the basis of combined data from the two screening programmes, this study indicated that overdiagnosis most likely amounted to 2.3% (95% confidence interval −3% to 8%) in targeted women. Among participants, it was most likely 1-5%. At least eight years after the end of screening were needed to compensate for the excess incidence during screening.

Introduction

The purpose of screening mammography is to reduce mortality from breast cancer without increasing mortality from other diseases. Preventive measures in healthcare might, however, also have unintended negative side effects, and the occurrence of these should be closely monitored. In screening mammography, the most serious concern is the risk of overdiagnosis—that is, diagnosis of breast cancer that would in the absence of screening not have led to clinically manifest disease in the woman's lifetime.[1] Overdiagnosis cannot be identified biologically, as distinguishing between progressive and non-progressive or slowly progressive cancers is not possible with current diagnostic tools. Overdiagnosis can therefore be investigated only epidemiologically.

Screening affects the incidence rate. Assuming a three year advancing of time of diagnosis (lead time) and screening of all women during a two year period, a doubling of the incidence rate is expected during the first round of screening.[2] As screening continues, the incidence rate should go down to the level before screening, apart from an increase caused by the artificial aging—that is, breast cancer diagnosed at age 55 in the absence of screening will during screening be diagnosed, for example, at age 52. A complementary dip in the incidence rate is expected after women leave the screening programme.[3 4] Overdiagnosis occurs if the cumulative incidence some years after the end of

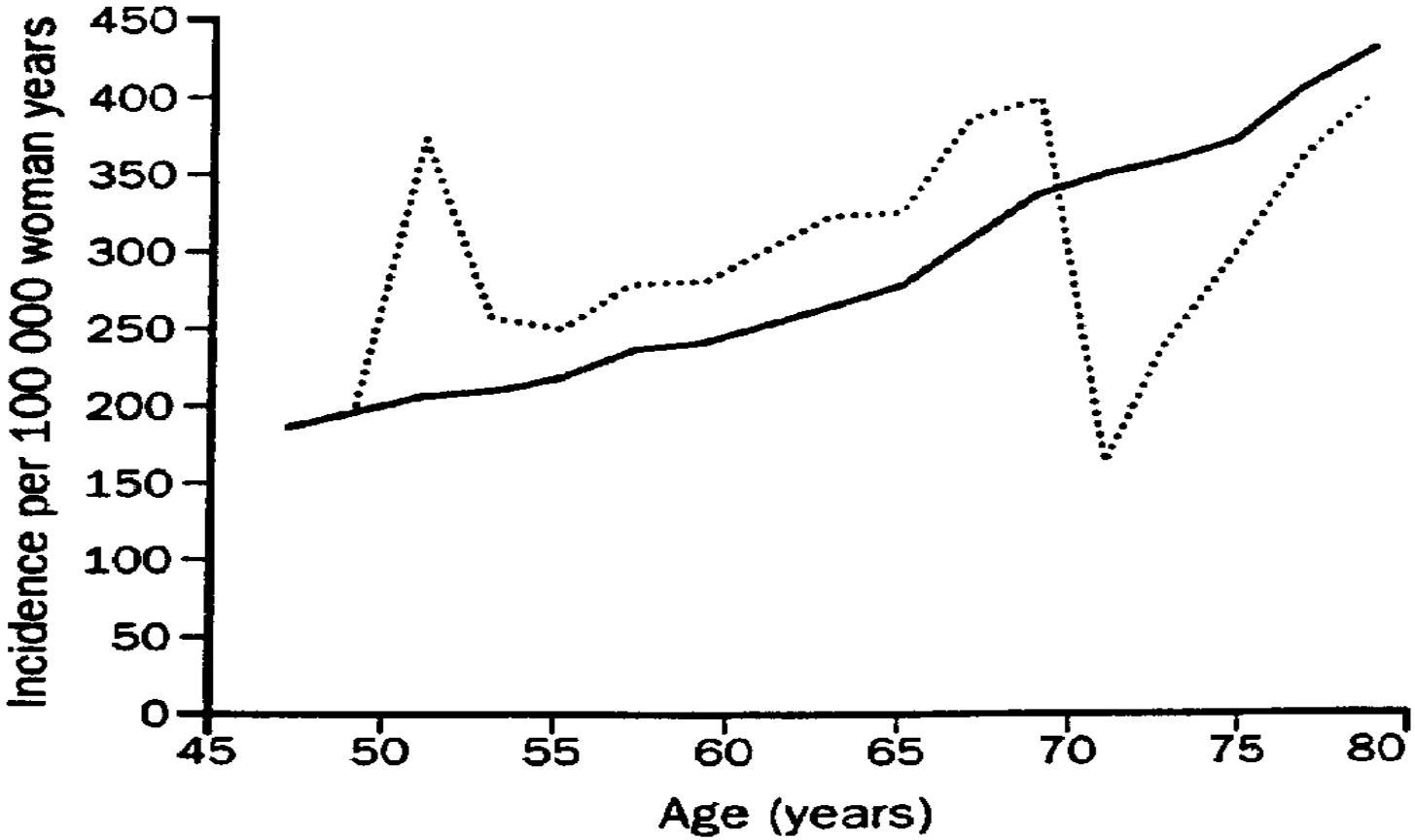
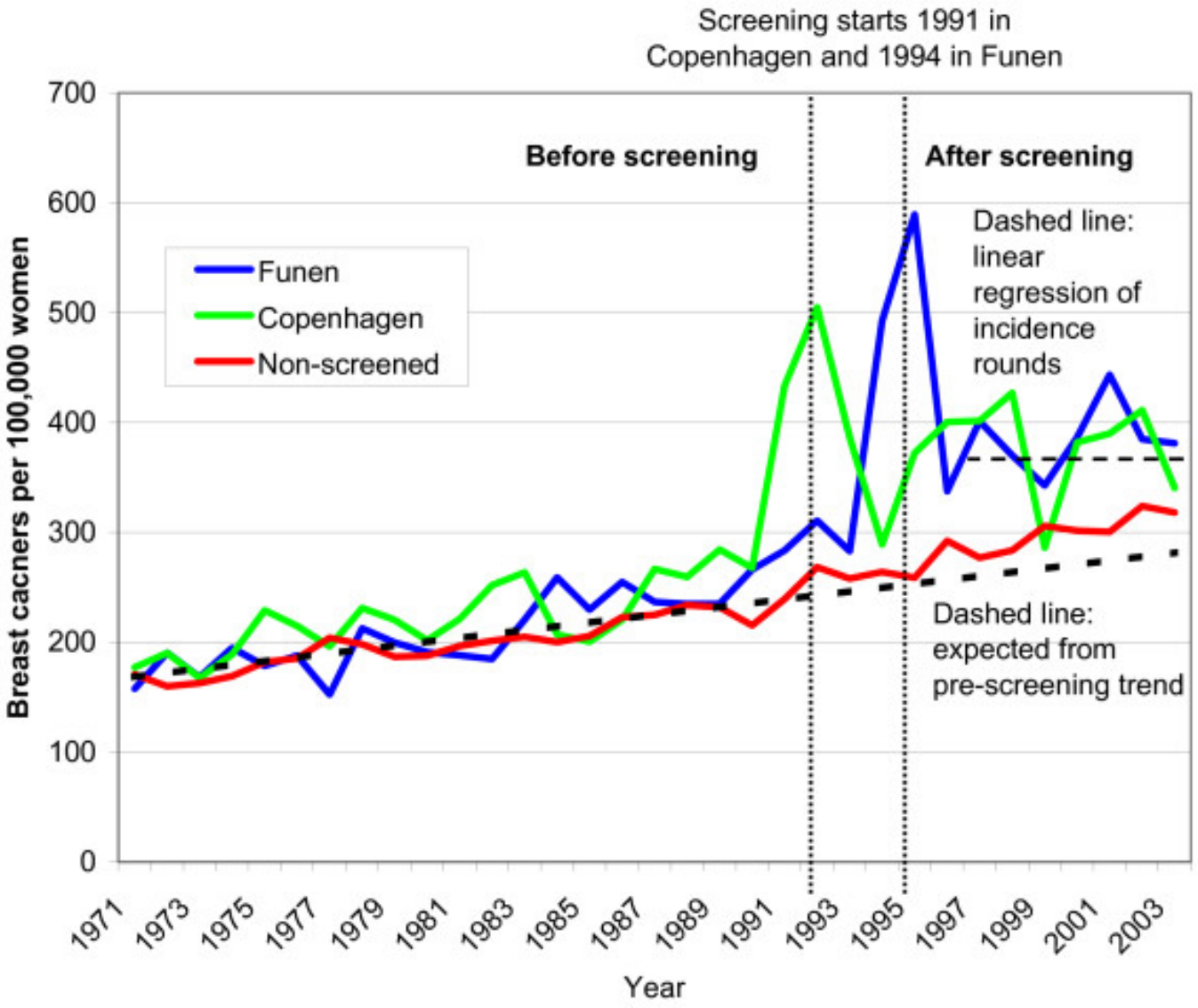
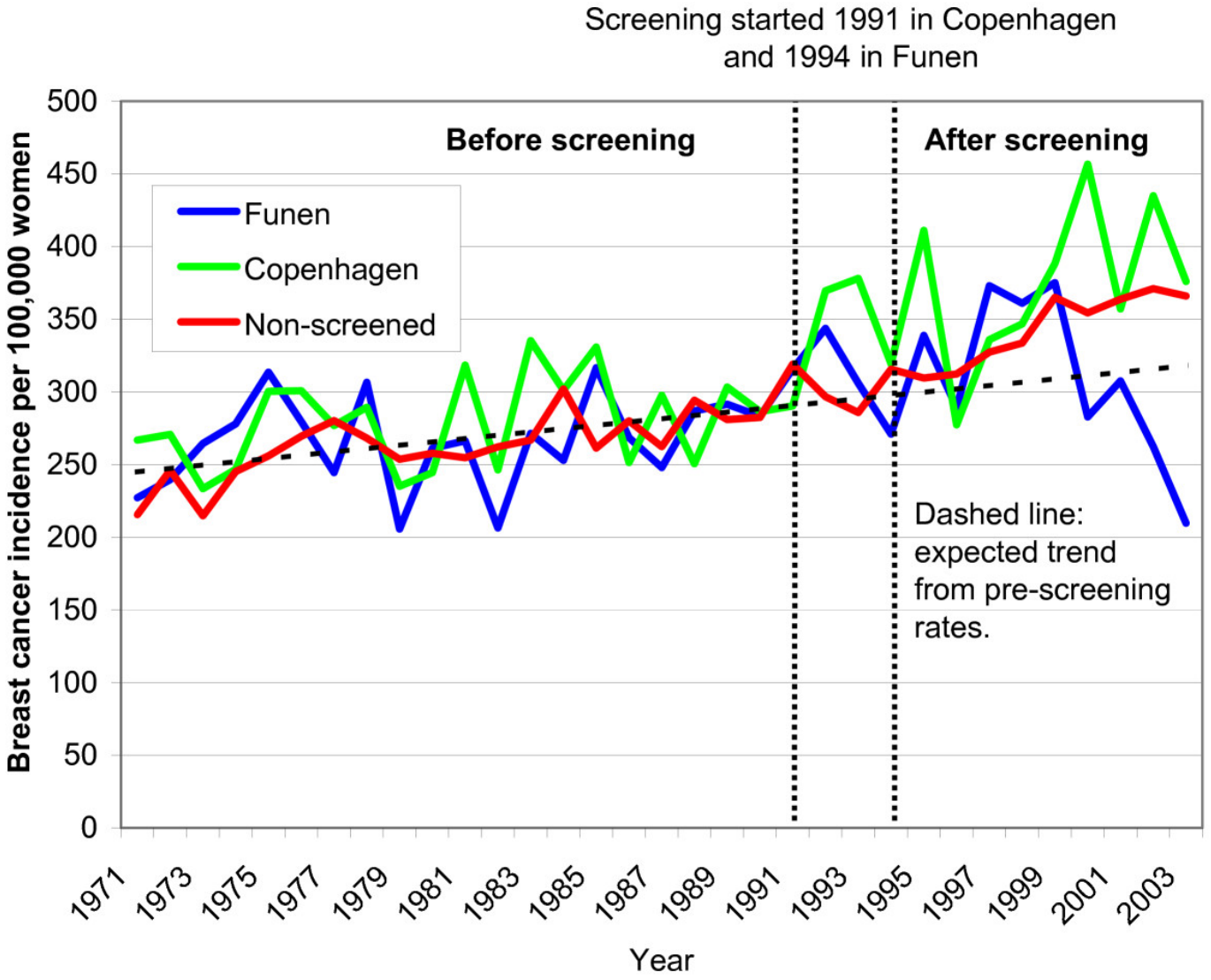


Figure: **Expected breast cancer incidence in 2-year age categories**

Solid line = not screened, dotted line = screened.



Jørgensen KJ, Zahl PH, Gøtzsche PC. BMC Women's Health 2009 **9**:36


Screening started 1991 in Copenhagen
and 1994 in Funen
Before screening
After screening
Funen
Copenhagen
Non-screened
Dashed line:
expected trend
from pre-screening
rates.
Breast cancer incidence per 100,000 women
500
450
400
350
300
250
200
150
100
50
0
1971
1973
1975
1977
1979
1981
1983
1985
1987
1989
1991
1993
1995
1997
1999
2001
2003
Year

Flexible sigmoidoscopy versus faecal occult blood testing for colorectal cancer screening in asymptomatic individuals (Review)

Holme Ø, Bretthauer M, Fretheim A, Odgaard-Jensen J, Hoff G

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- Reduced incidence carries great weight
- Mechanism of effect differs fundamentally between programmes
- Which screening programmes we use is as much about timing and politics as about science and the benefit/harm balance

General health checks in adults for reducing morbidity and mortality from disease (Review)

Krogsbøll LT, Jørgensen KJ, Grønhøj Larsen C, Gøtzsche PC

THE COCHRANE COLLABORATION®

A Department of Health representative told BBC News: "By spotting people who are at risk of heart attacks, diabetes, stroke and kidney disease we can help prevent them. The NHS Health Check programme is based on expert guidance."[1]

"…I have put our original suggestion of systematic health checks on ice. Because it did not have the desired effect."
Astrid Krag, Danish Minister of Health[2]

1: http://www.bbc.co.uk/news/health-19964600
2: Journal of the Danish Medical Association, October 24th 2012

New UK leaflet - improvements

- Clearly states that there is a choice
- Clear presentation of the most important harm
- No direct encouragement to attend
- No indication that breast screening reduce the risk of mastectomy

New UK leaflet – pending improvements

- Remaining harms must also be clearly presented using absolute numbers
- The importance and long-term consequences of false positive findings must be clearly stated
- Harms are not risks
- Pre-assigned appointments must be abandonned

Conclusions on Marmot-report:

- The benefit was overestimated and not based on an observed effect in the UK, but extrapolations.
- The major harm is clearly visible in UK statistics, but was underestimated.
- Improved treatment is the major cause of observed reductions in breast cancer mortality in the UK.
- An improvement in all cause or all cancer mortality has never been demonstrated.

How was the benefit estimated?

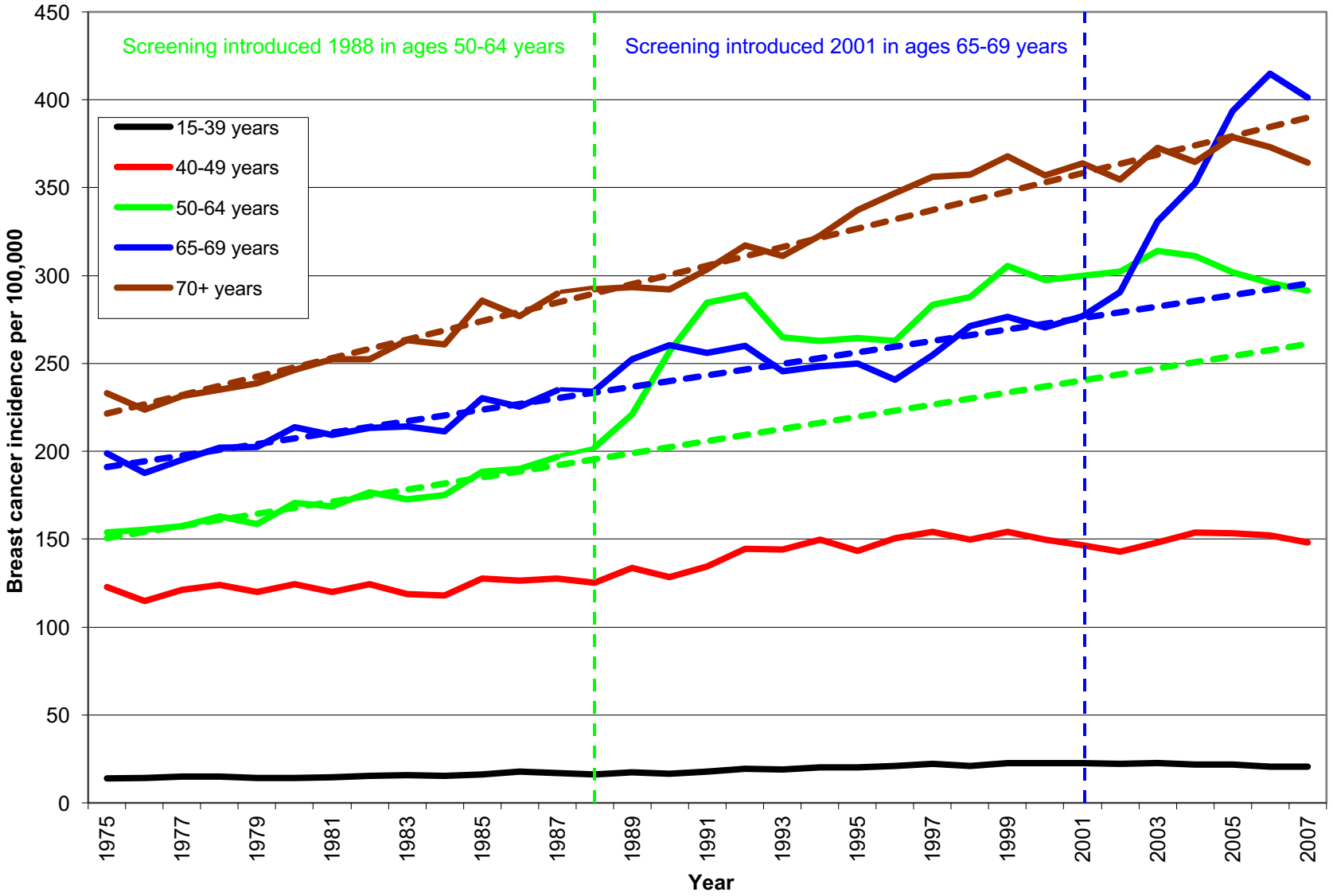
- ***Assumption 1:*** The randomised trials are equally reliable.
- ***Assumption 2:*** The effect can be extrapolated as unchanged 8-17 years beyond trial duration.
- ***Assumption 3:*** Identical effect today as then.
- ***Assumption 4:*** The effect remains unchanged 10 years beyond the screening age.
- ***Calculation:*** 20% fewer breast cancer deaths today than without screening in the age group 55-79 years (5843[1]) = 1461 fewer breast cancer deaths.

1: Average no. breast cancer deaths per year 2008-10: http://www.cancerresearchuk.org/cancer-info/cancerstats/types/breast/mortality/uk-breast-cancer-mortality-statistics

How was overdiagnosis estimated?

- Modelling based on observed invasive breast cancer incidence in the UK.
- 2250 linear and Poisson regression models applied to data from 1975-2004 with various assumptions.
- Most model results estimated ~3000 overdiagnosed invasive breast cancers per year.
- 50-69 years: 23,297 invasive, 3,931 CIS. 19% ODX = 5,920 cases per year in the UK.[1]

1: http://www.cancerresearchuk.org/cancer-info/cancerstats/types/breast/incidence/



Jørgensen KJ, Keen J, Gøtzsche PC. Radiology 2011; 260: 621-627