



# Research into Overdiagnosis and Overtreatment

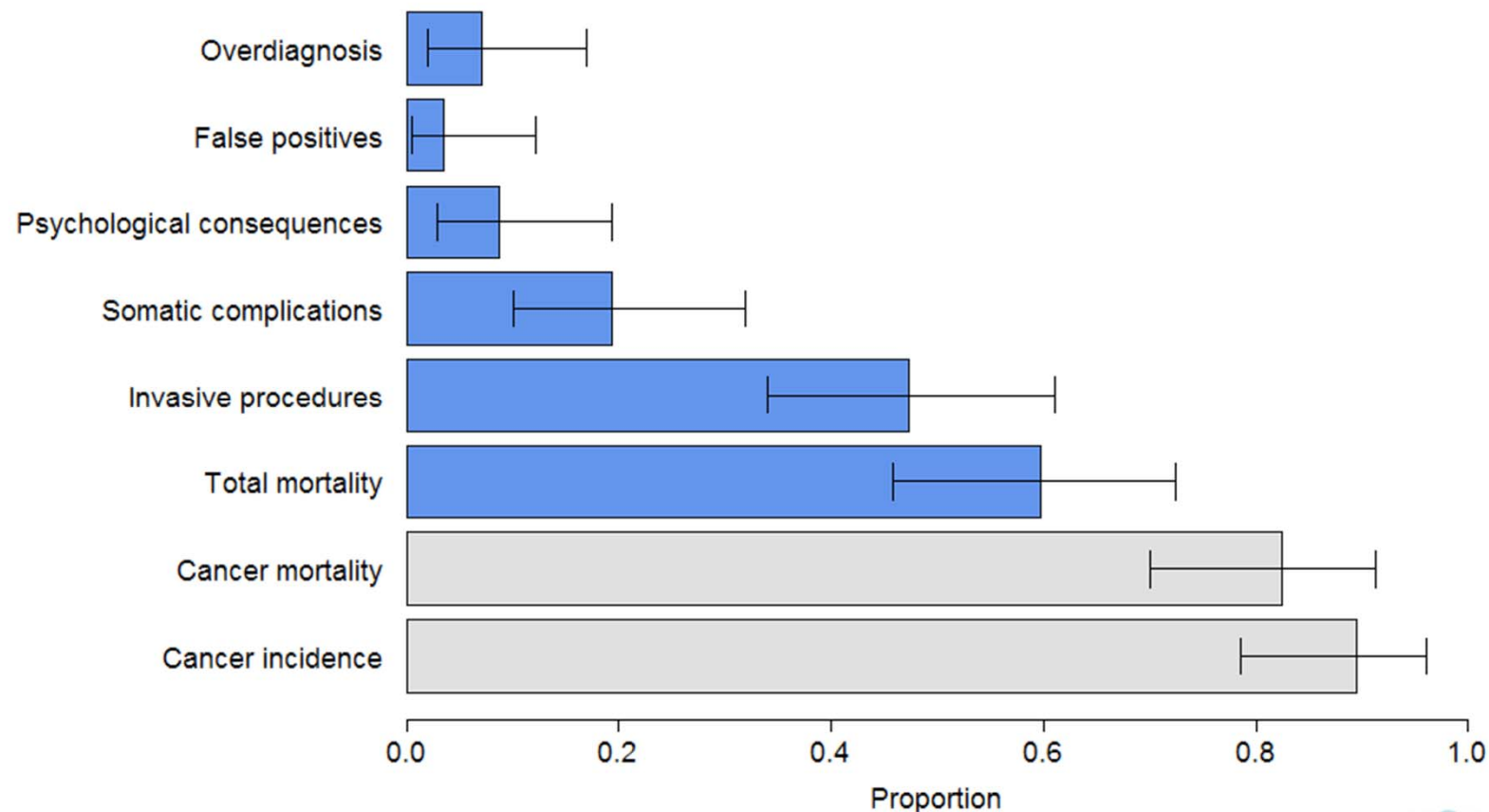
John Brodersen

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Primary Health Care Research Unit, Zealand Region

# Is it important to do research in these topics?



B. Heleno, M. F. Thomsen, D. S. Rodrigues, K. J. Jørgensen, J. Brodersen. Quantification of harms in cancer screening trials: literature review. *BMJ*. 347:f5334, 2013.



# Content of presentation

- Defining overdiagnosis
- Types of overdiagnosis
- Experiences of being overdiagnosed
- The degree of overdiagnosis
- Consequences of overdiagnosis
- Drivers to overdiagnosis



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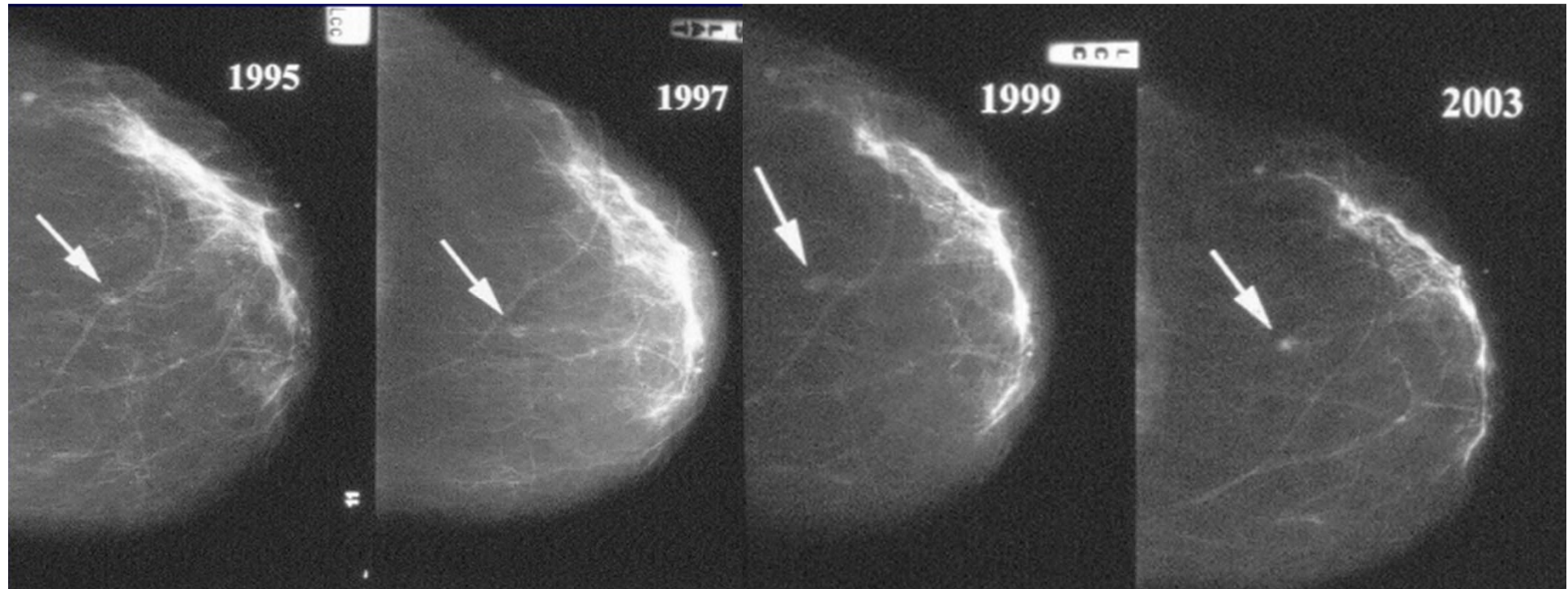


# What is overdiagnosis?

Talk 2 & 2 for 2 minutes

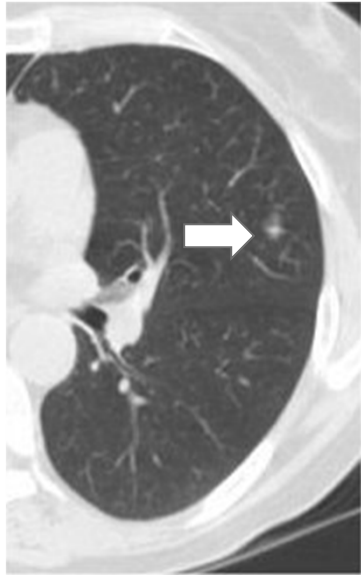


# Mammography screening

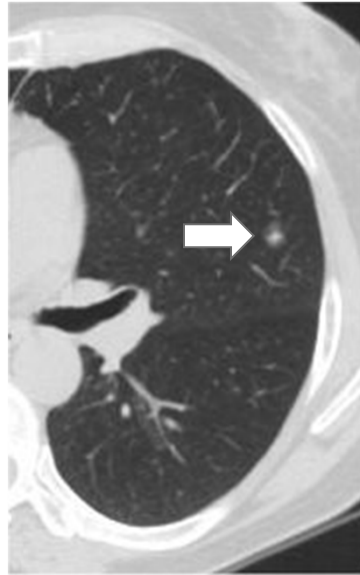


# Lung cancer screening with CT

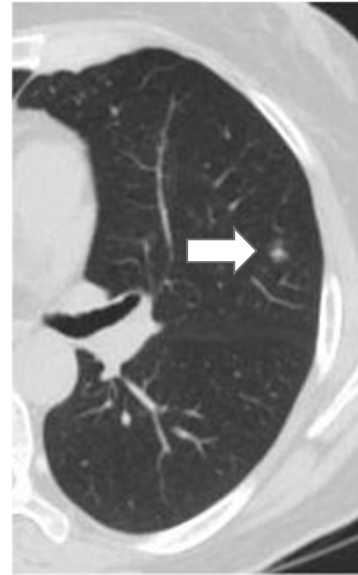
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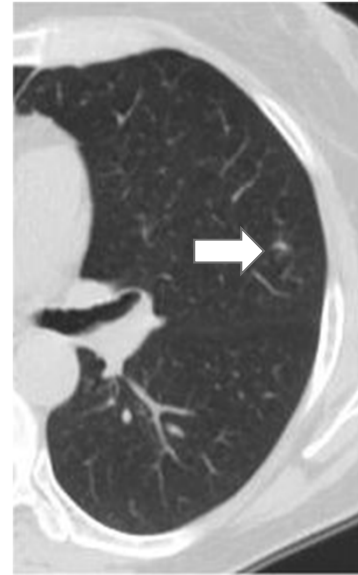
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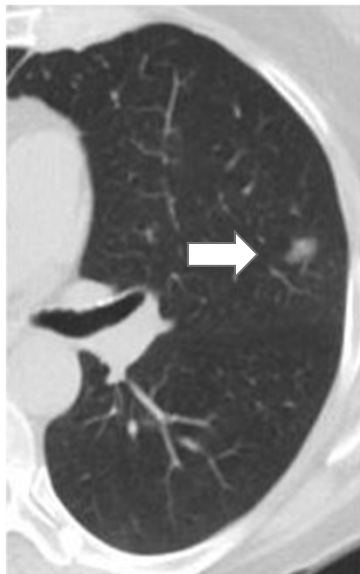
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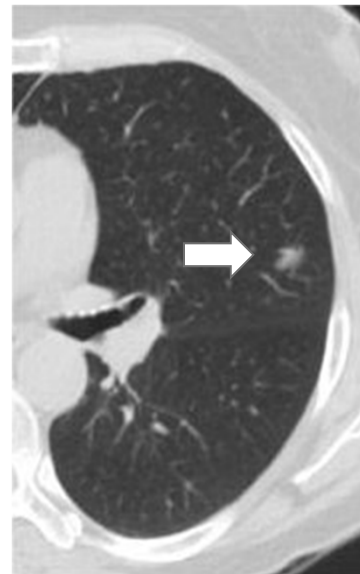
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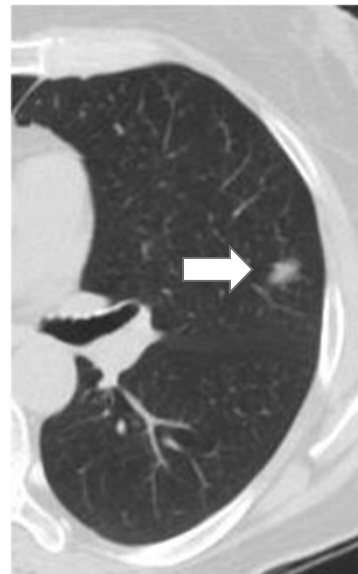
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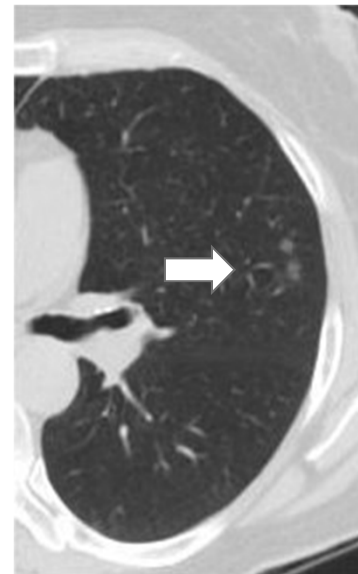
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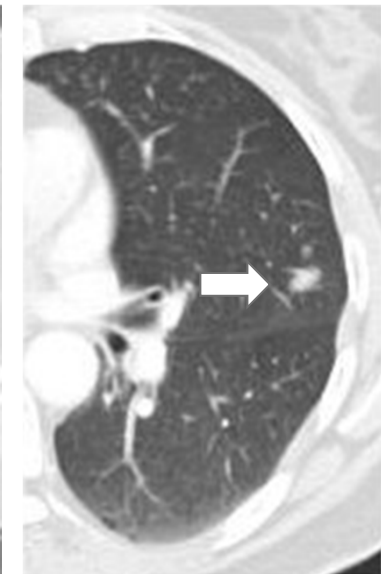
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17.08.09



## Overdiagnosis - definition

“Overdiagnosis is the diagnosis of ‘illnesses’ that would never have caused patients harm but potentially exposes them to treatments where the risks outweigh the benefits.”

Doust & Glasziou. Is the problem that everything is a diagnosis? *Australian Family Physician* 42:856-859, 2013.

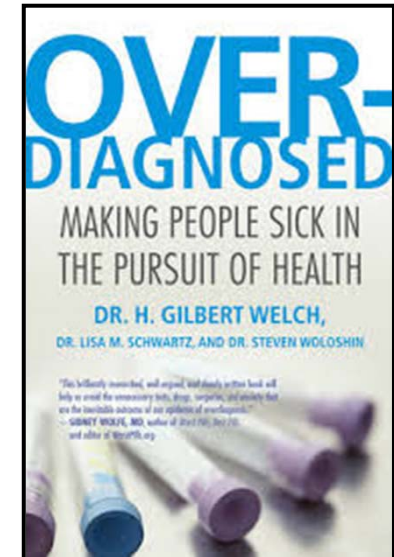




## Overdiagnosis - description

“Overdiagnosis occur when individuals are diagnosed with conditions that will never cause symptoms or death.”

“...the ultimate criterion for overdiagnosis: at the end of life, if the person never developed a problem from her condition, she has been overdiagnosed.”



Welch, Schwartz, Woloshin. *Overdiagnosed. Making People Sick in the Pursuit of Health*, Boston: Beacon Press, 2011.



## Overdiagnosis – my own definition

Overdiagnosis is the diagnosis of deviations, abnormalities, risk factors and/or pathology that never in itself will: cause symptoms (applies only to risk factors and pathology), lead to morbidity or be the cause of death.



## Overdiagnosis – Søren Kierkegaard

*"Life can only be understood backwards; but it must be lived forwards"*

Søren Kierkegaard  
(Danish philosopher 1813-55)



## Overdiagnosis – therefore

- Individual level: never sure when the patient is actually overdiagnosed
- At the end of life the GP can be certain if the diagnosis was correct or iatrogenic



# What is overtreatment?

- Treatment of overdiagnosed conditions is one category of overtreatment
- Another type of overtreatment is when best available external evidence shows that the treatment has no beneficial effect on the diagnosed condition



# Content of presentation

- Defining overdiagnosis
- **Types of overdiagnosis**
- Experiences of being overdiagnosed
- The degree of overdiagnosis
- Consequences of overdiagnosis
- Drivers to overdiagnosis



# Types of overdiagnosis

- Overdetection – screening
- Disease mongering
- Expanding disease definitions or changing disease boundaries



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# How is it to be overdiagnosed?

- Subjects: Conditions and diagnoses where the likelihood of overdiagnosis is large
- Material & Methods: Interviews, observational field work, documents etc.



# Osteoporosis 1

16 healthy women with no chronic or disabling conditions and who had been (over)diagnosed with osteoporosis via a population-based cohort study

Reventlow SD, Hvas L, Malterud K. Making the invisible body visible. Bone scans, osteoporosis and women's bodily experiences. Soc Sci Med 2006 Jun;62(11):2720-31.



## Osteoporosis 2

- appeared to take the scan literally
- planned their lives accordingly
- believed that the 'pictures' revealed some truth
- interpreted the scan result to mean bodily fragility, which they incorporated into their bodily perception

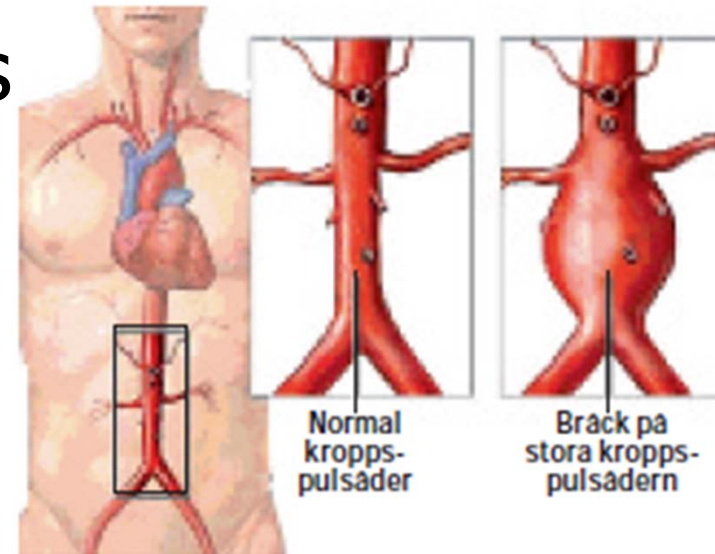
Reventlow SD, Hvas L, Malterud K. Making the invisible body visible. Bone scans, osteoporosis and women's bodily experiences. Soc Sci Med 2006 Jun;62(11):2720-31.



“A ticking bomb inside your stomach”

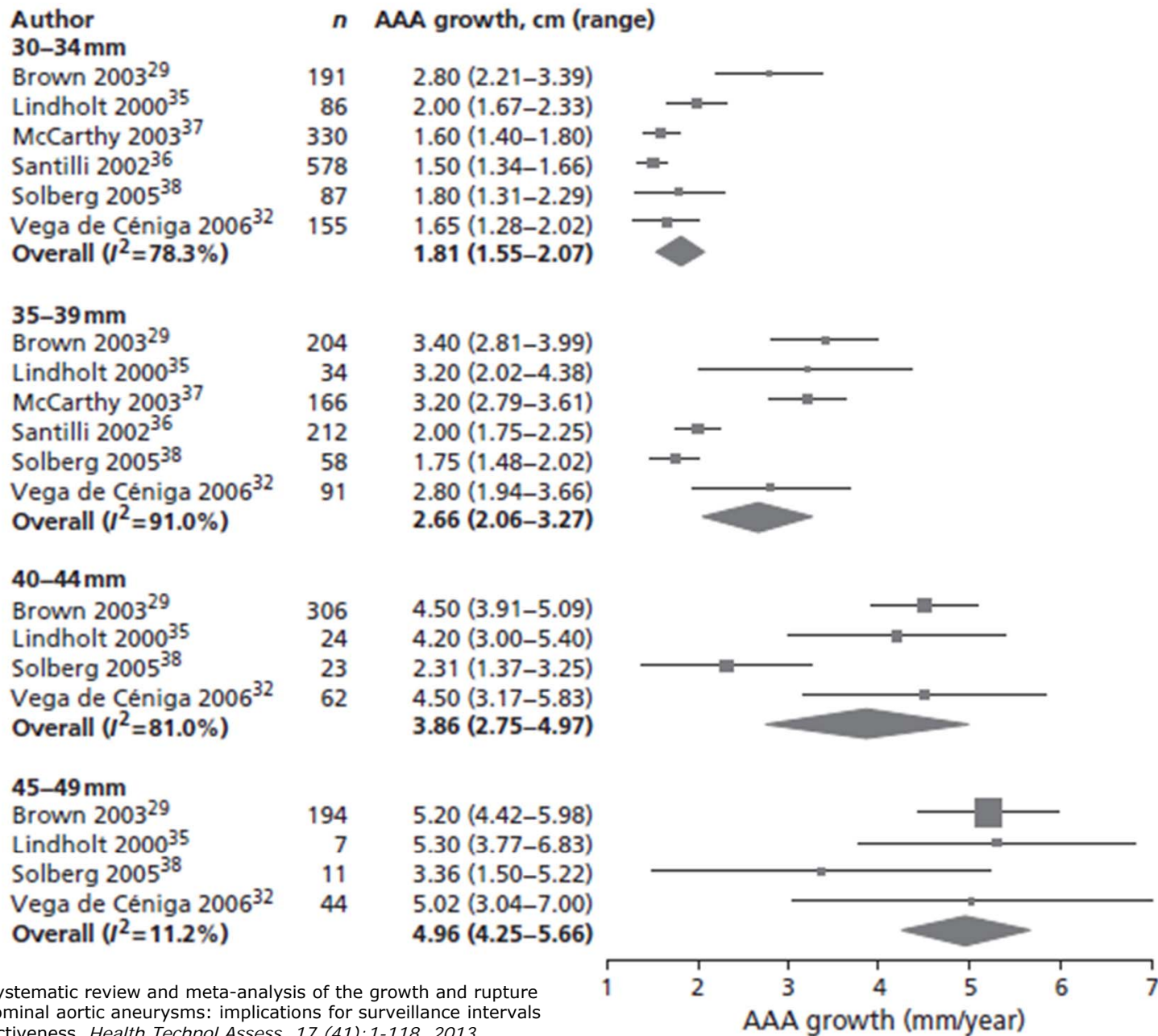
## 15 men (over)diagnosed

- median aortic diameter: 32 mm
- 15 single interviews
- 3 group interviews  
one year later



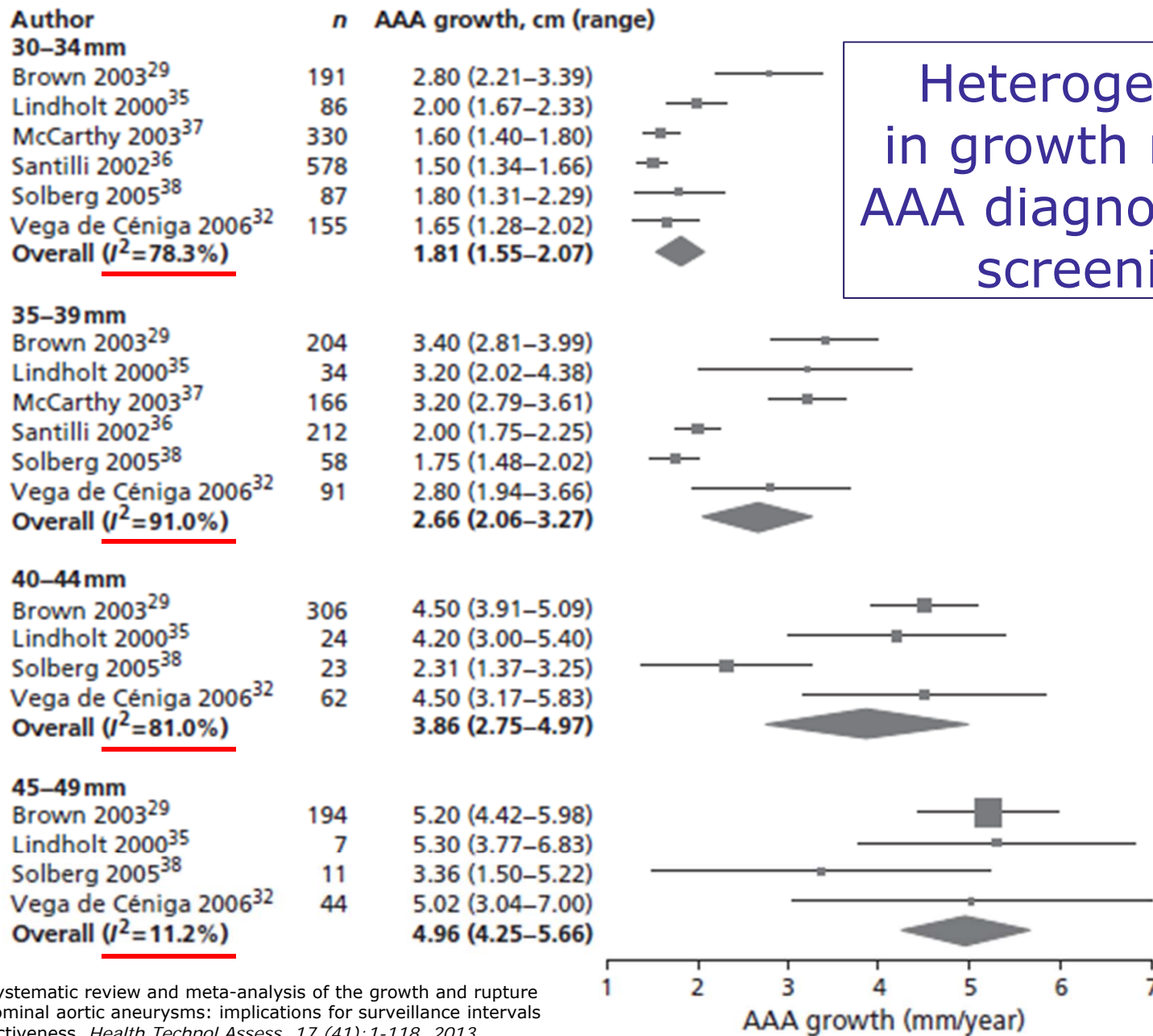
A. Hansson, J. Brodersen, S. Reventlow & M. Pettersson. Opening Pandora's box: The experiences of having an asymptomatic aortic aneurysm under surveillance. *Health, Risk & Society* 14 (4): 341-359, 2012.





Thompson et al. Systematic review and meta-analysis of the growth and rupture rates of small abdominal aortic aneurysms: implications for surveillance intervals and their cost-effectiveness. *Health Technol. Assess.* 17 (41):1-118, 2013.

**FIGURE 3** Aneurysm growth rate by 5-mm size ranges of baseline aneurysm diameter: random-effect meta-analyses conducted within subgroups.

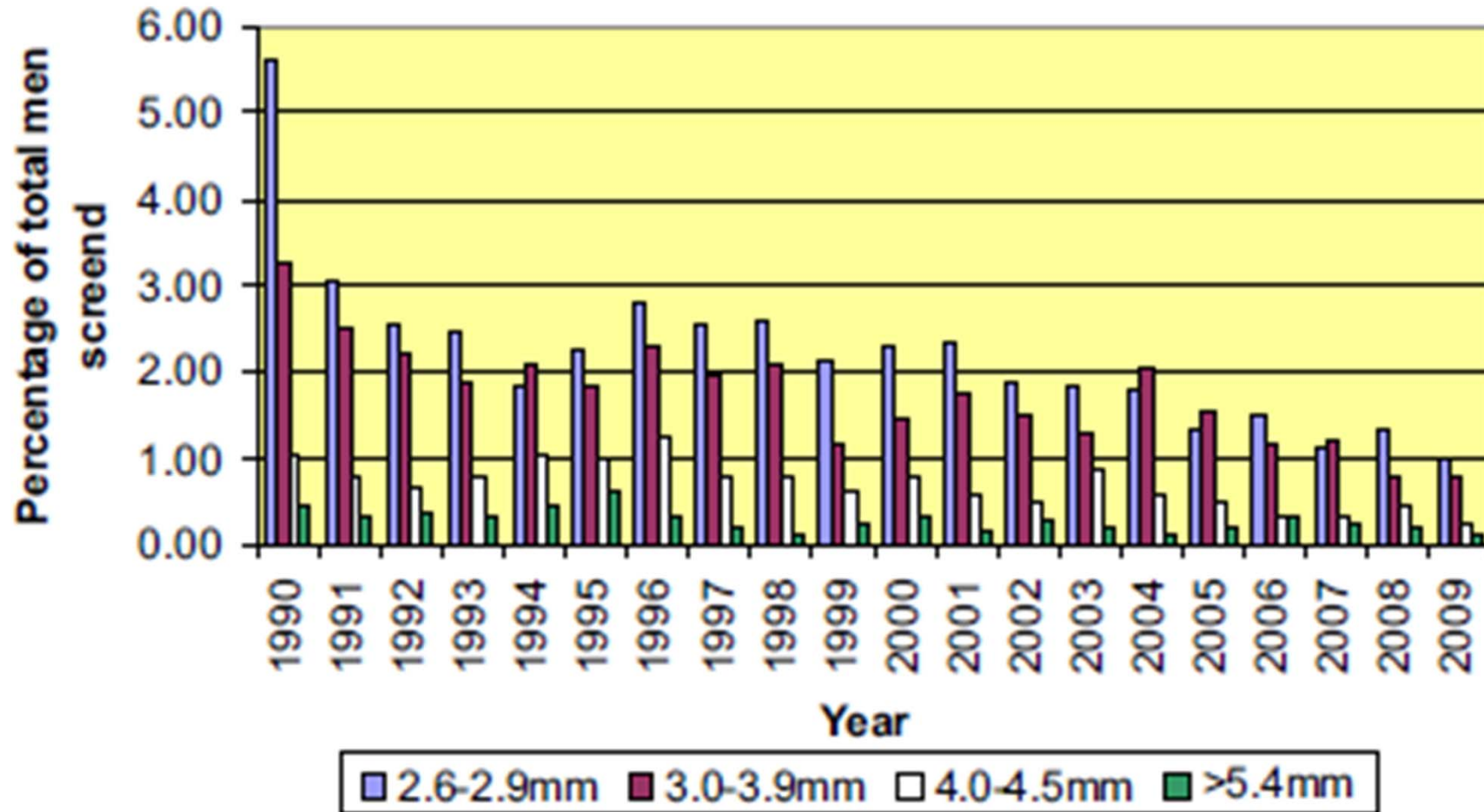


Heterogeneity in growth rate in AAA diagnosed via screening

Thompson et al. Systematic review and meta-analysis of the growth and rupture rates of small abdominal aortic aneurysms: implications for surveillance intervals and their cost-effectiveness. *Health Technol. Assess.* 17 (41):1-118, 2013.

**FIGURE 3** Aneurysm growth rate by 5-mm size ranges of baseline aneurysm diameter: random-effect meta-analyses - conducted within subgroups.

# Drop in incidens of AAA: 77%



Darwood et al. Twenty-year review of abdominal aortic aneurysm screening in men in the county of Gloucestershire, United Kingdom. *J.Vasc.Surg.* 56 (1):8-13, 2012.



# Opening Pandora's box

The men expressed ambivalence towards the diagnosis:

*"they appreciated having the knowledge but it was accompanied by worry, feelings of anxiety and existential thoughts about the fragility and finiteness of life"*

A. Hansson, J. Brodersen, S. Reventlow & M. Pettersson. Opening Pandora's box: The experiences of having an asymptomatic aortic aneurysm under surveillance. *Health, Risk & Society* 14 (4): 341-359, 2012.





# COS-AAA, part I

- Anxiety
- Sense of dejection
- Negative impact on behaviour
- Negative impact on sleep
- Change in body perception
- Guilt
- Fear and powerlessness
- Negative experiences from the examination
- Negative emotional reactions
- Change in lifestyle
- Better not knowing
- Fear of rupture
- Negative impact on sexuality
- Lack of information
- Stigmatised
- Self-blame for smoking
- Still regretful smoking

Brodersen, Johansson, Hansson, Siersma, Langenskiöld Monica Pettersson. Consequences of Screening in Abdominal Aortic Aneurysm: Development and Dimensionality of a Questionnaire. Paper in progress.



## COS-AAA, part II

- More or less relaxed/calm
- Social relationship
- Existential values
- Empathy
- Impulsivity

Brodersen, Johansson, Hansson, Siersma, Langenskiöld Monica Pettersson. Consequences of Screening in Abdominal Aortic Aneurysm: Development and Dimensionality of a Questionnaire. Paper in progress.



# To what degree and for how long?

- Subjects: Conditions and diagnoses where people are overdiagnosed for at shorter period of time and/or the likelihood of overdiagnosis is large
- Material & Methods: Survey



# Cumulative risk of false-positive screening mammography

Country	Age Group	Cumulative risk
US	40-49 y	61.3% (10 rounds in 10 years)
US	40-69 y	49.1% (10 rounds in 10 years)
US	40-69 y	43.1% (9 rounds in 9 years)
Australia	50-69 y	37.5% (10 rounds in 20 years)
Spain	50-69 y	32.4% (10 rounds in 20 years)
Norway	50-69 y	20.8% (10 rounds in 20 years)
Denmark	50-69 y	8.1-21.5% (10 rounds in 20 years)

# Focus groups: content validity

Examinations	Ultrasound & clinical mammography	Plus needle biopsy	Plus surgical biopsy
No. of women	5	7	7
Examinations	Plus early recall	Plus needle biopsy	Plus surgical biopsy
No. of women	5	5	7

*J. Brodersen and H. Thorsen. Consequences Of Screening in Breast Cancer (COS-BC): development of a questionnaire. Scand.J Prim.Health Care 26 (4):251-256, 2008.*



# COS-BC part I

## Psychosocial consequences of abnormal false-positive screening mammography

- Anxiety
- Negative impact on behaviour
- Sense of dejection
- Negative impact on sleep
- Breast examination
- Negative impact on sexuality
- 2 single items

*J. Brodersen, H. Thorsen, S. Kreiner. Validation of a condition-specific measure for women having an abnormal screening mammography. Value in Health 10 (4):294-304, 2007.*

*J. Brodersen & H. Thorsen. Consequences Of Screening in Breast Cancer (COS-BC): development of a questionnaire. Scand.J Prim.Health Care 26 (4):251-256, 2008.*



## COS-BC part II

### Long-term psychosocial consequences of false-positive screening mammography

- Anxious about/belief in (not) having breast cancer
- More or less relax
- Social relationship
- Existential values

*J. Brodersen. Measuring psychosocial consequences of false-positive screening results - breast cancer as an example, Department of General Practice, Institute of Public Health, Faculty of Health Sciences, University of Copenhagen: Månedsskrift for Praktisk Lægegering, Copenhagen. ISBN: 87-88638-36-7, 2006.*  
*J. Brodersen and H. Thorsen. Consequences Of Screening in Breast Cancer (COS-BC): development of a questionnaire. Scand.J Prim.Health Care 26 (4):251-256, 2008.*



# Longitudinal survey

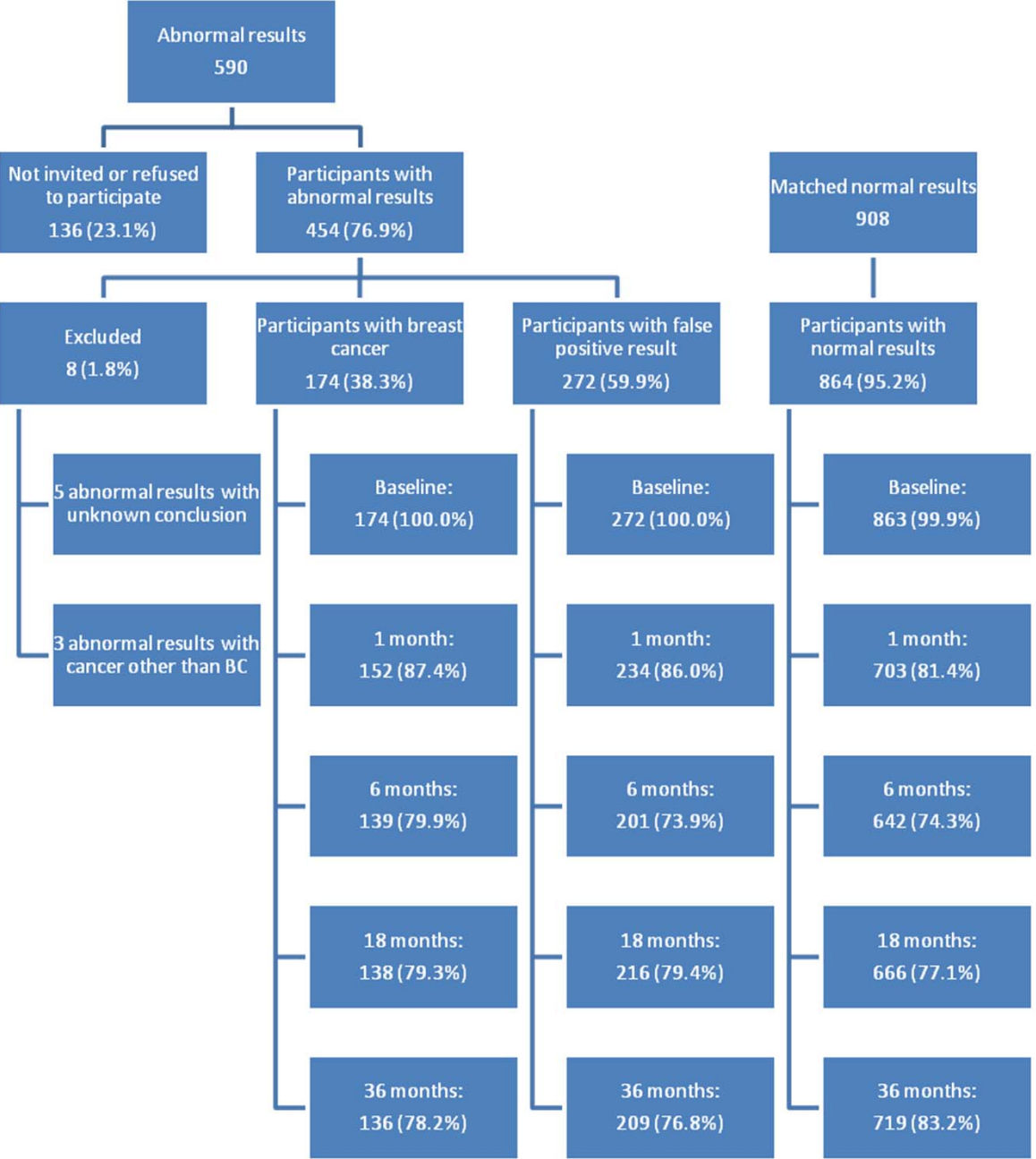
- 3 June 2004 - 2 June 2005
- 1,318 women consecutively recruited
- 2 screening centres
- 5 assessments: 0, 1, 6, 18 & 36 months after screening/diagnosis
- COS-BC:
  - 12 psychosocial outcomes

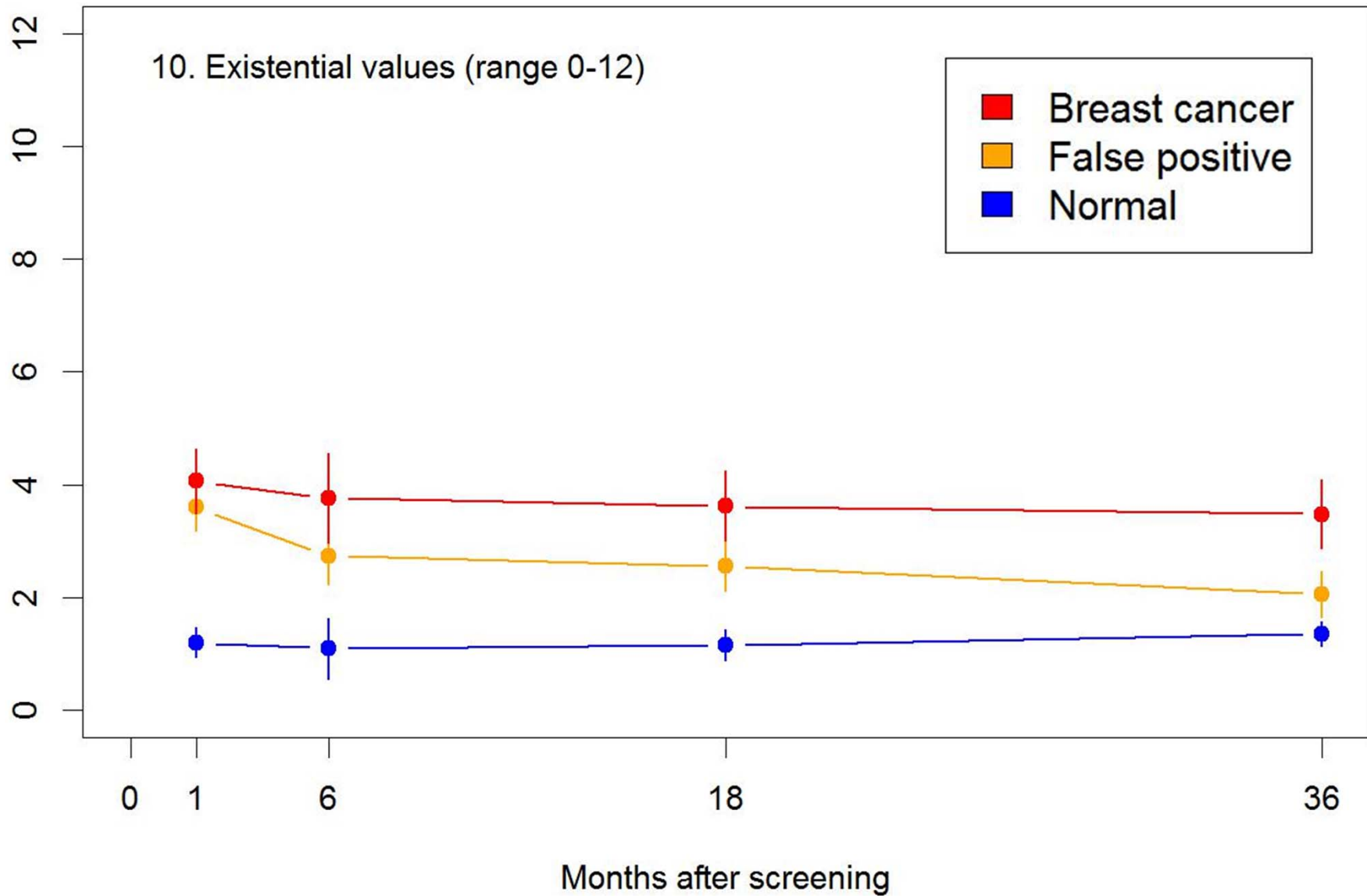
J. Brodersen & V. Siersma. Long-term psychosocial consequences of screening mammography. *Annals of Family Medicine*.11(2):106-115, 2013.



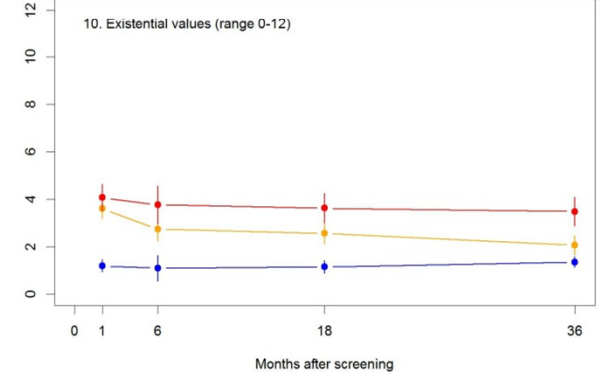
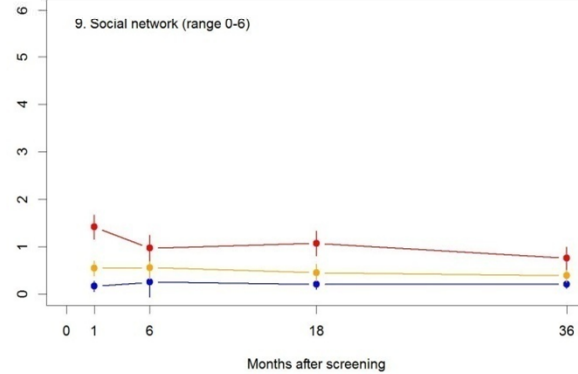
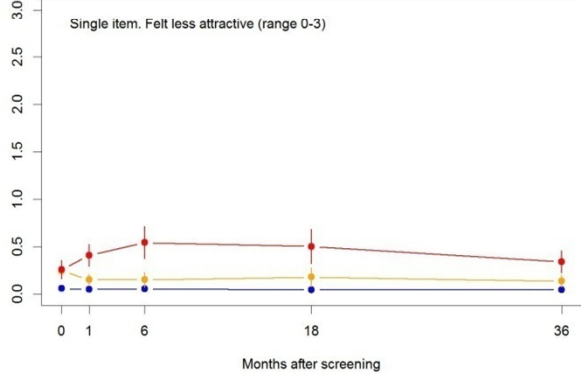
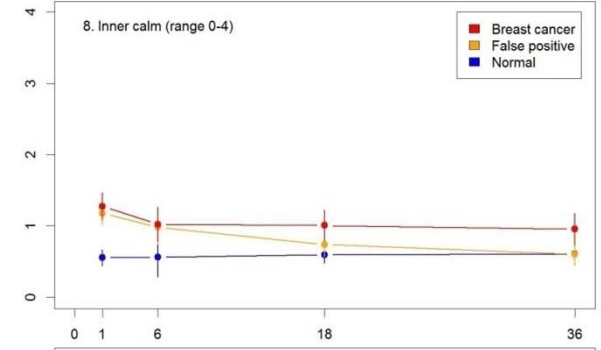
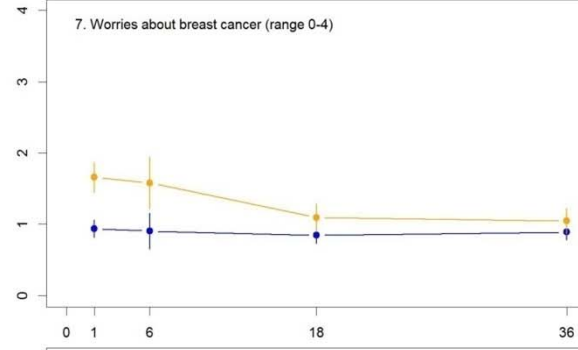
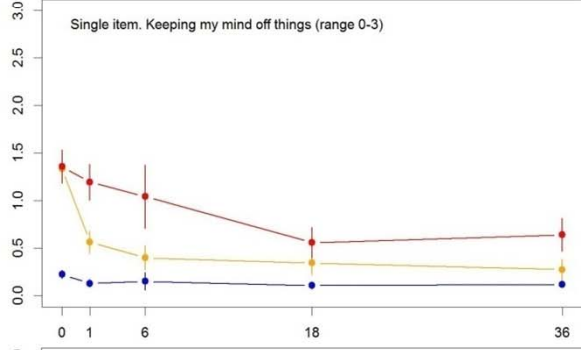
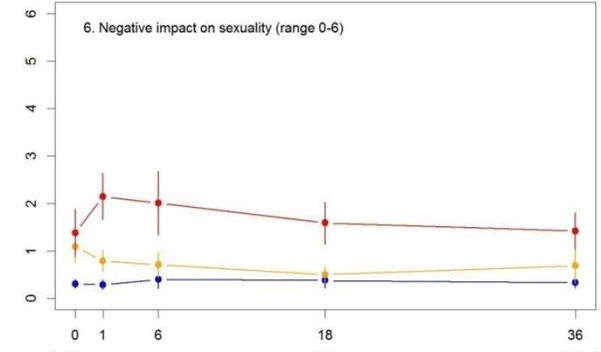
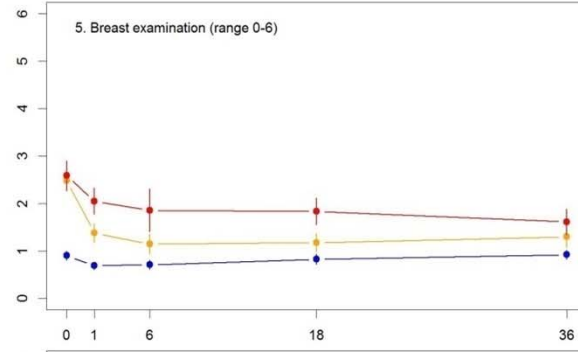
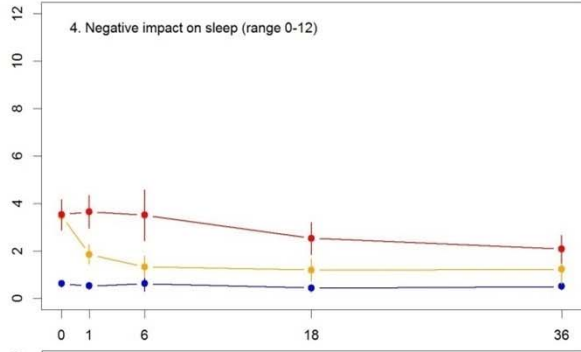
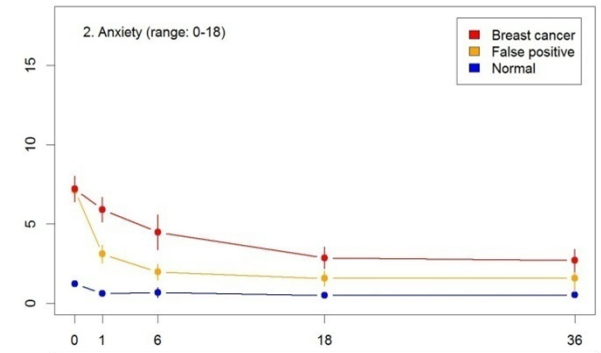
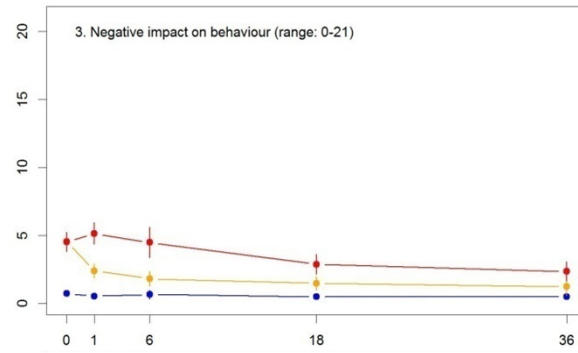
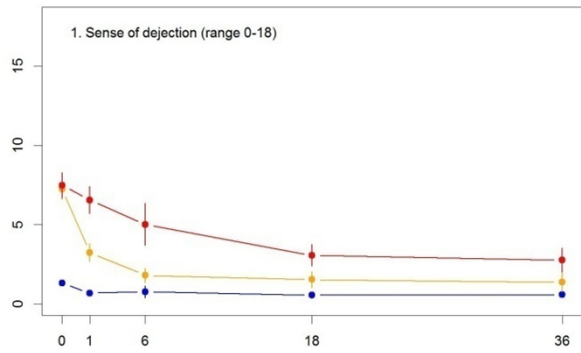


**Population screened in 1 year**  
Approx. 30,000

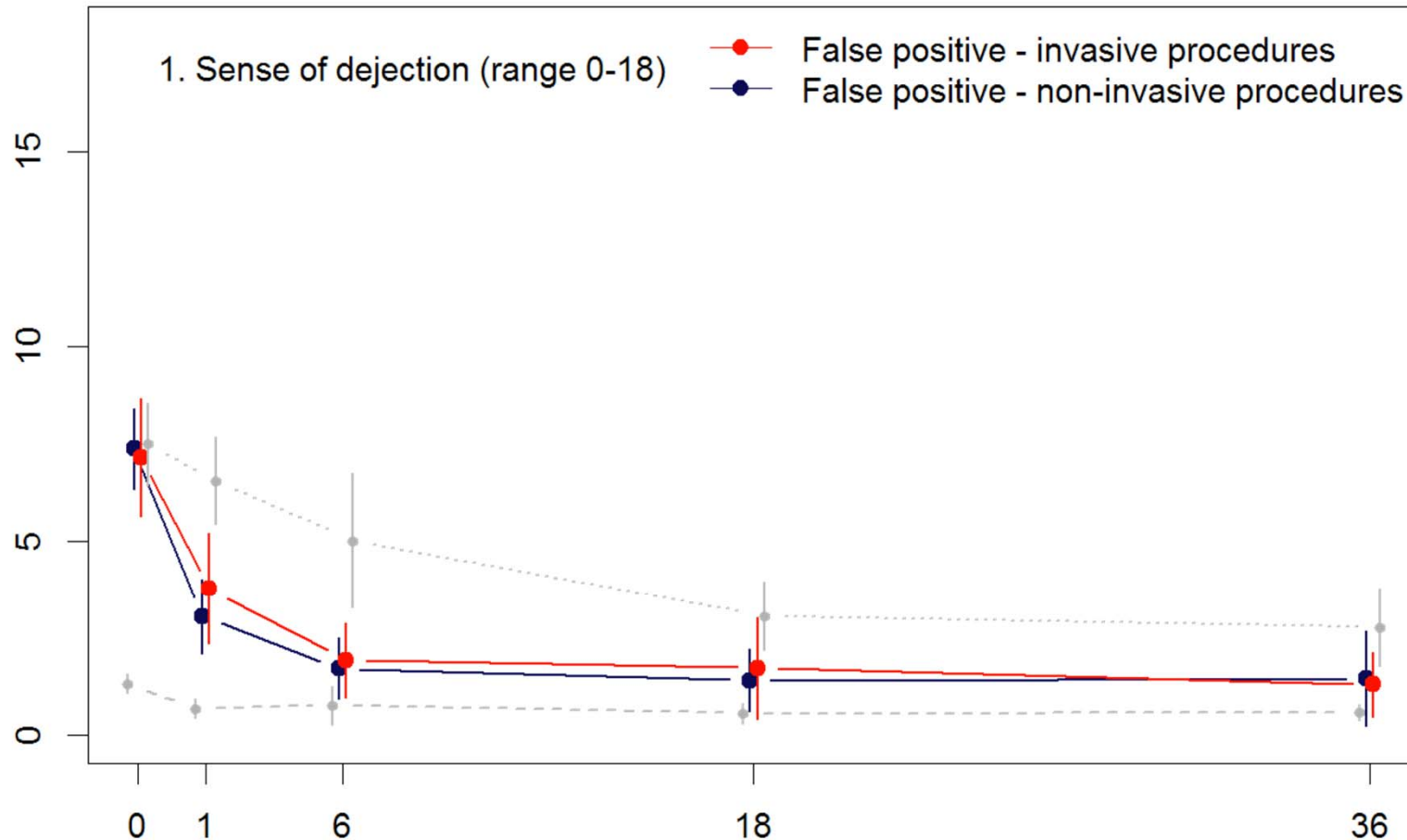




J. Brodersen & V. Siersma. Long-term psychosocial consequences of screening mammography. *Annals of Family Medicine*. 11 (2):106-115, 2013.

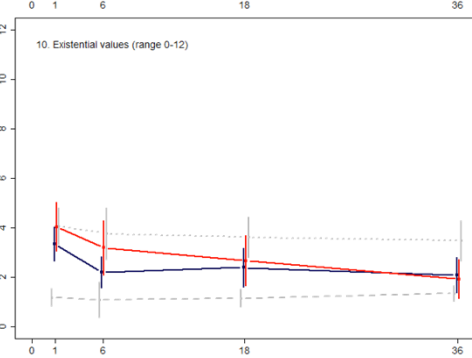
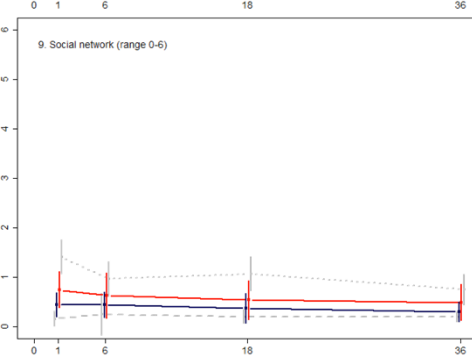
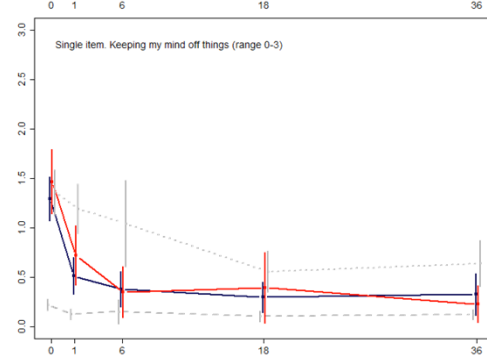
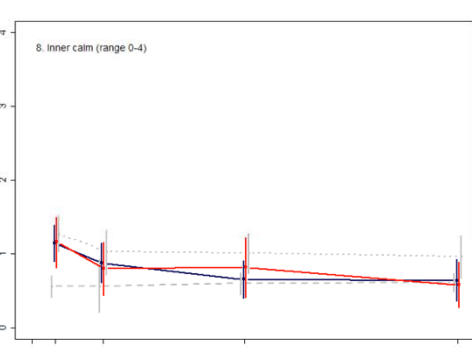
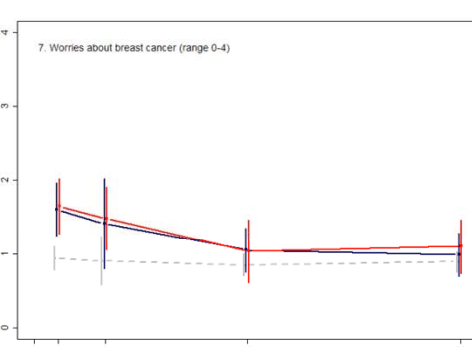
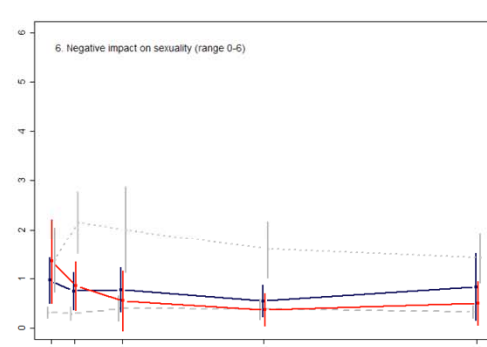
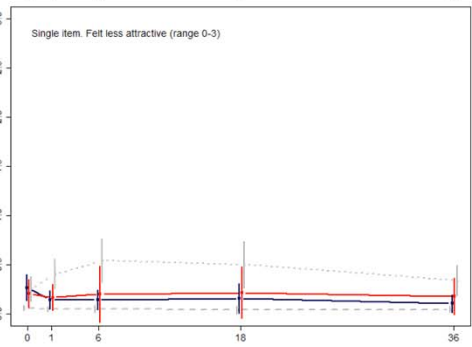
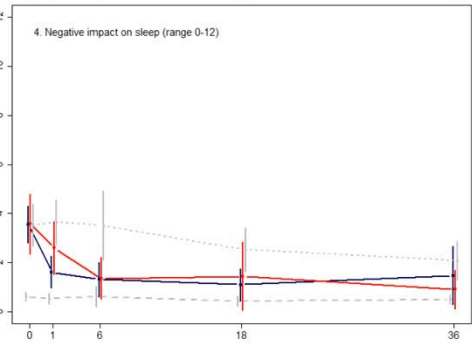
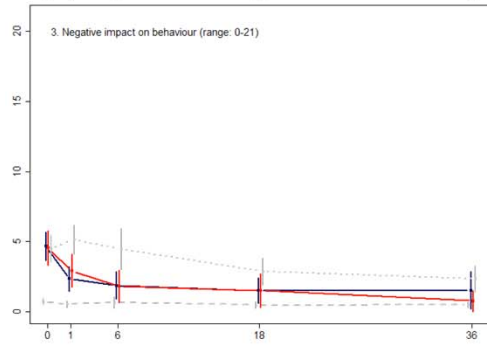
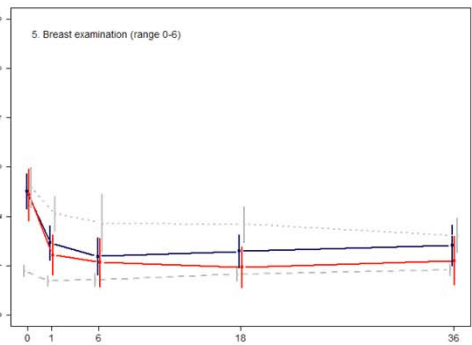
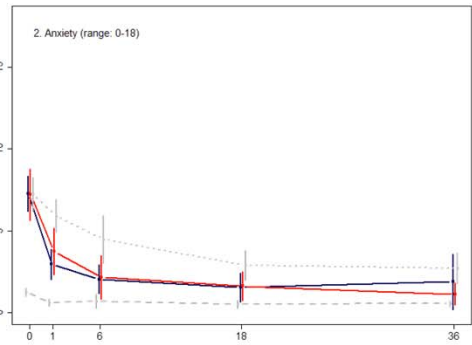
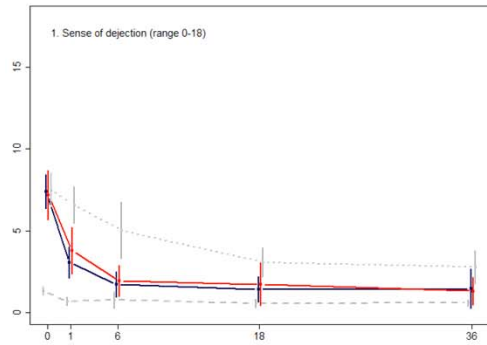


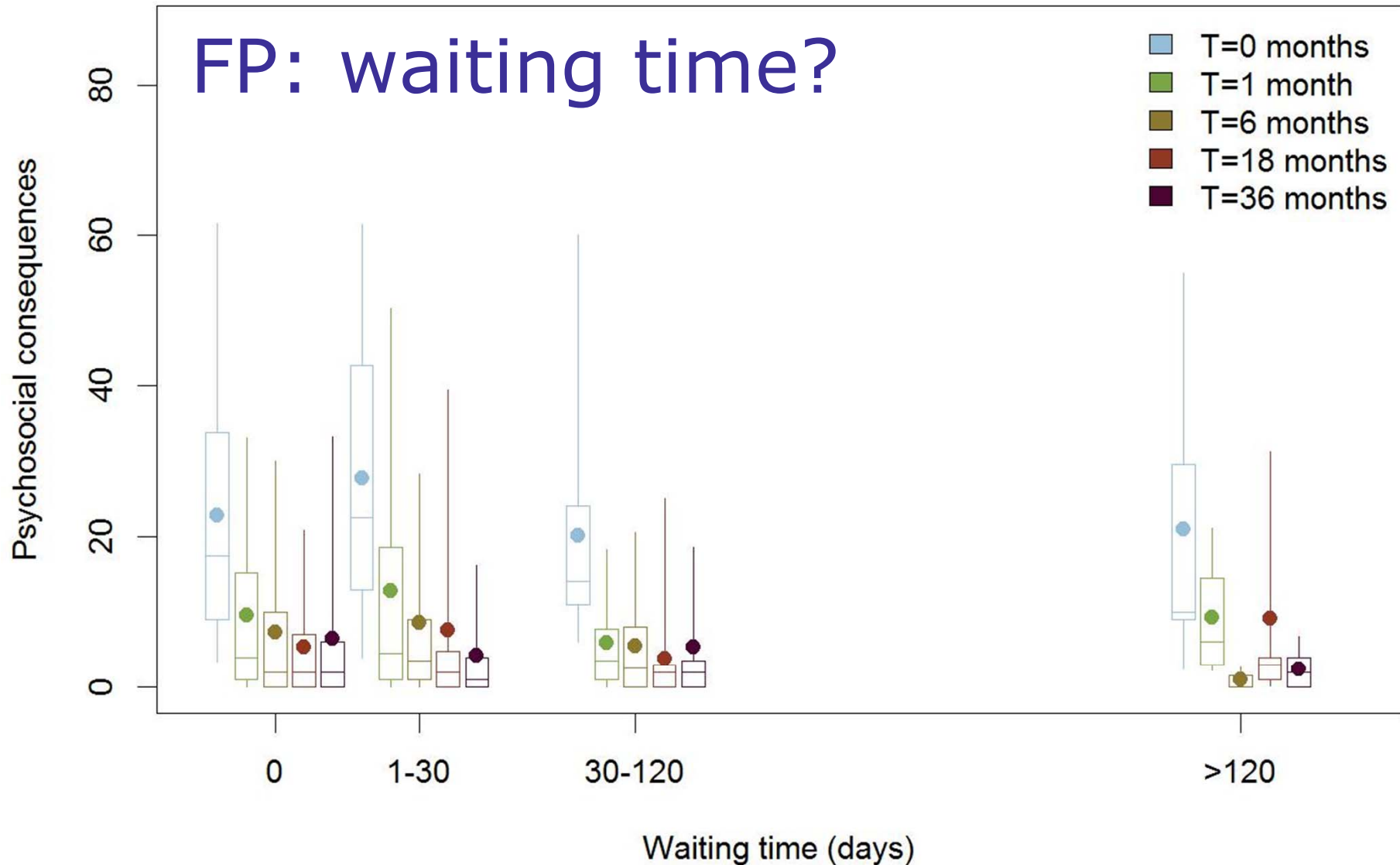
# False Positives: invasiveness?



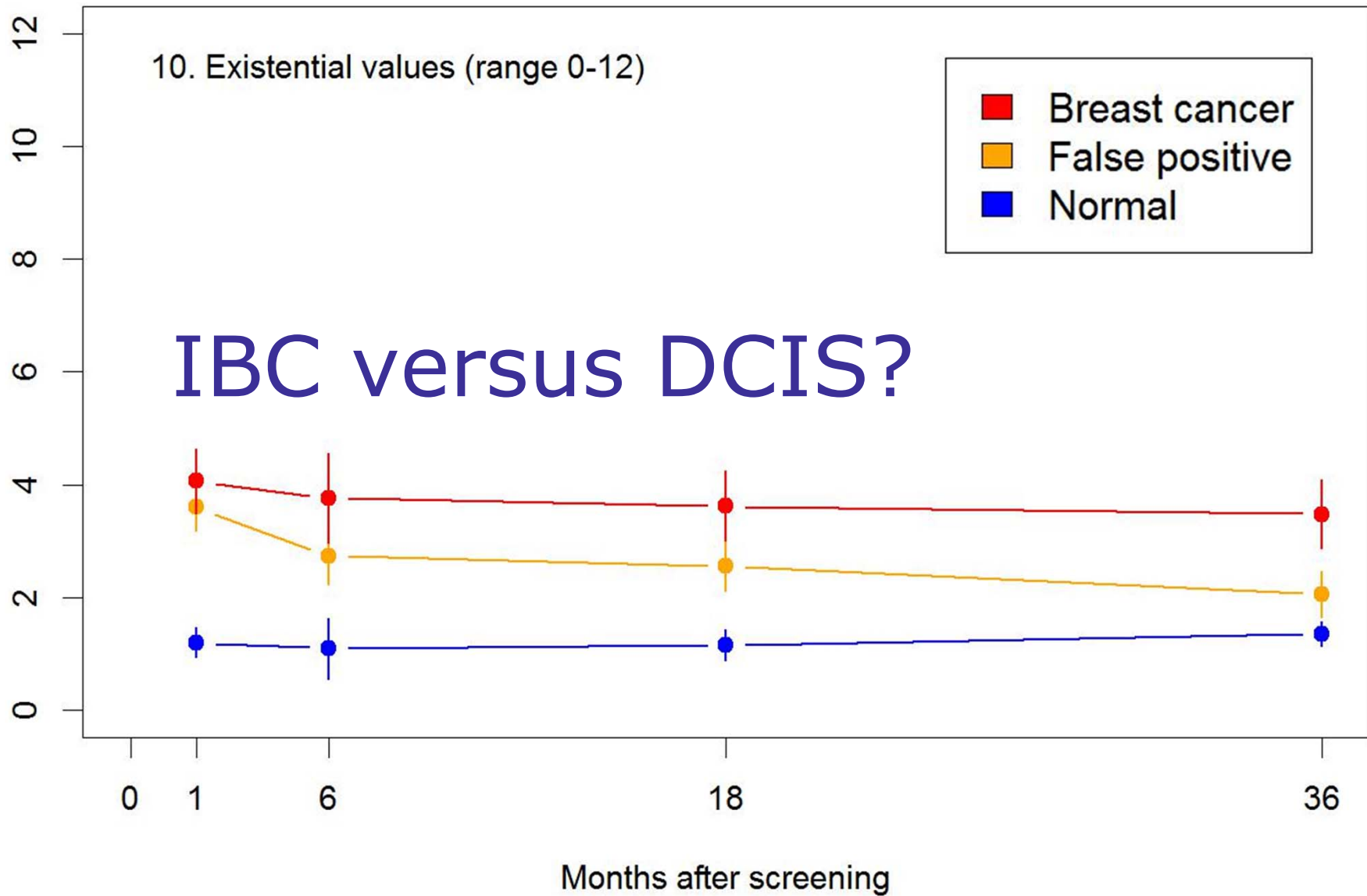
B. Heleno, V. D. Siersma, J. Brodersen. Diagnostic invasiveness and psychosocial consequences of false-positive mammography. *Ann.Fam.Med.* 13 (3):242-249, 2015.







B. Heleno, V. Siersma, J. Brodersen. Waiting time and the psychosocial consequences of false-positive mammography: cohort study. *J Negat. Results Biomed.* 14(1):8,2015.



J. Brodersen & V. Siersma. Long-term psychosocial consequences of screening mammography. *Annals of Family Medicine*. 11 (2):106-115, 2013.

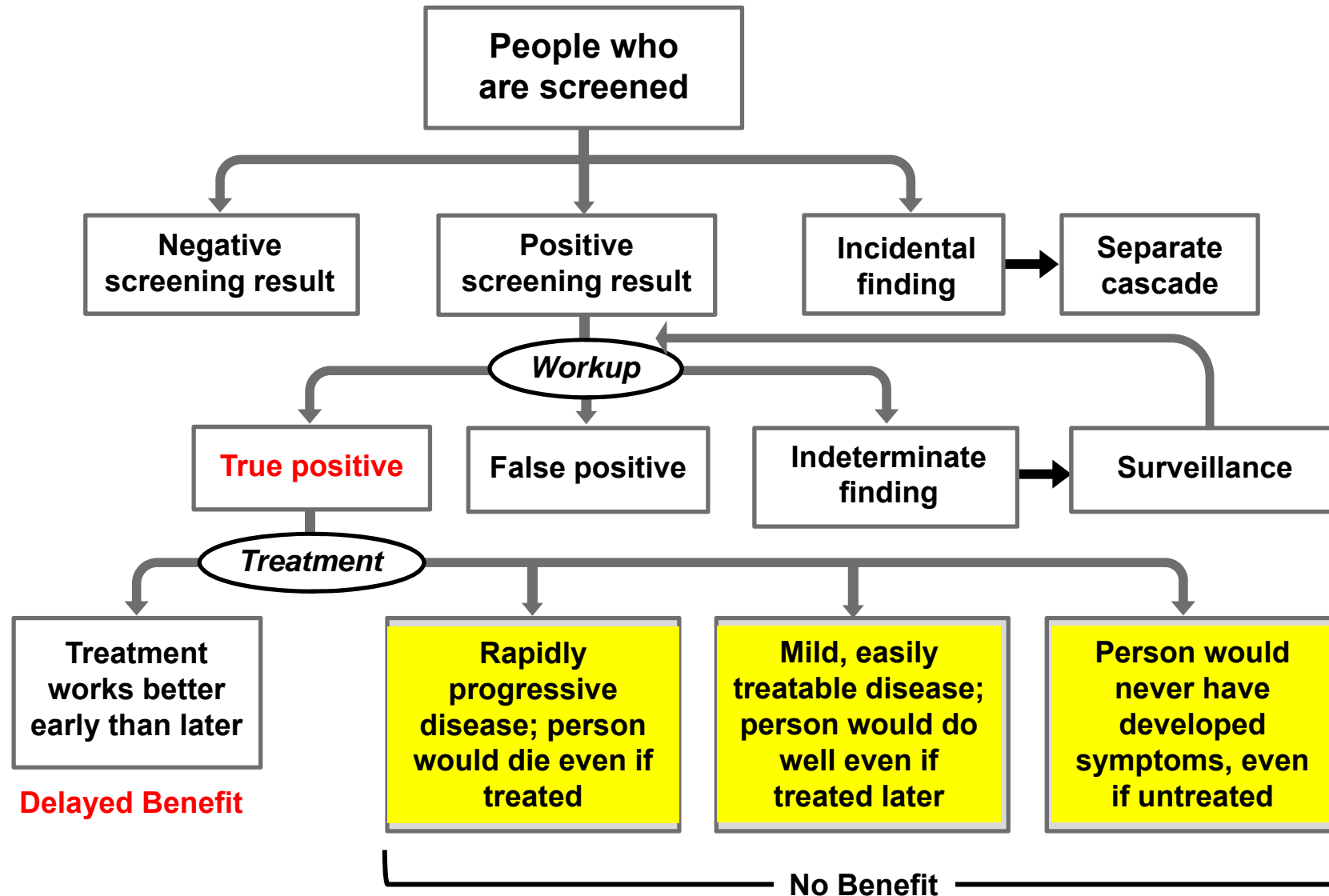
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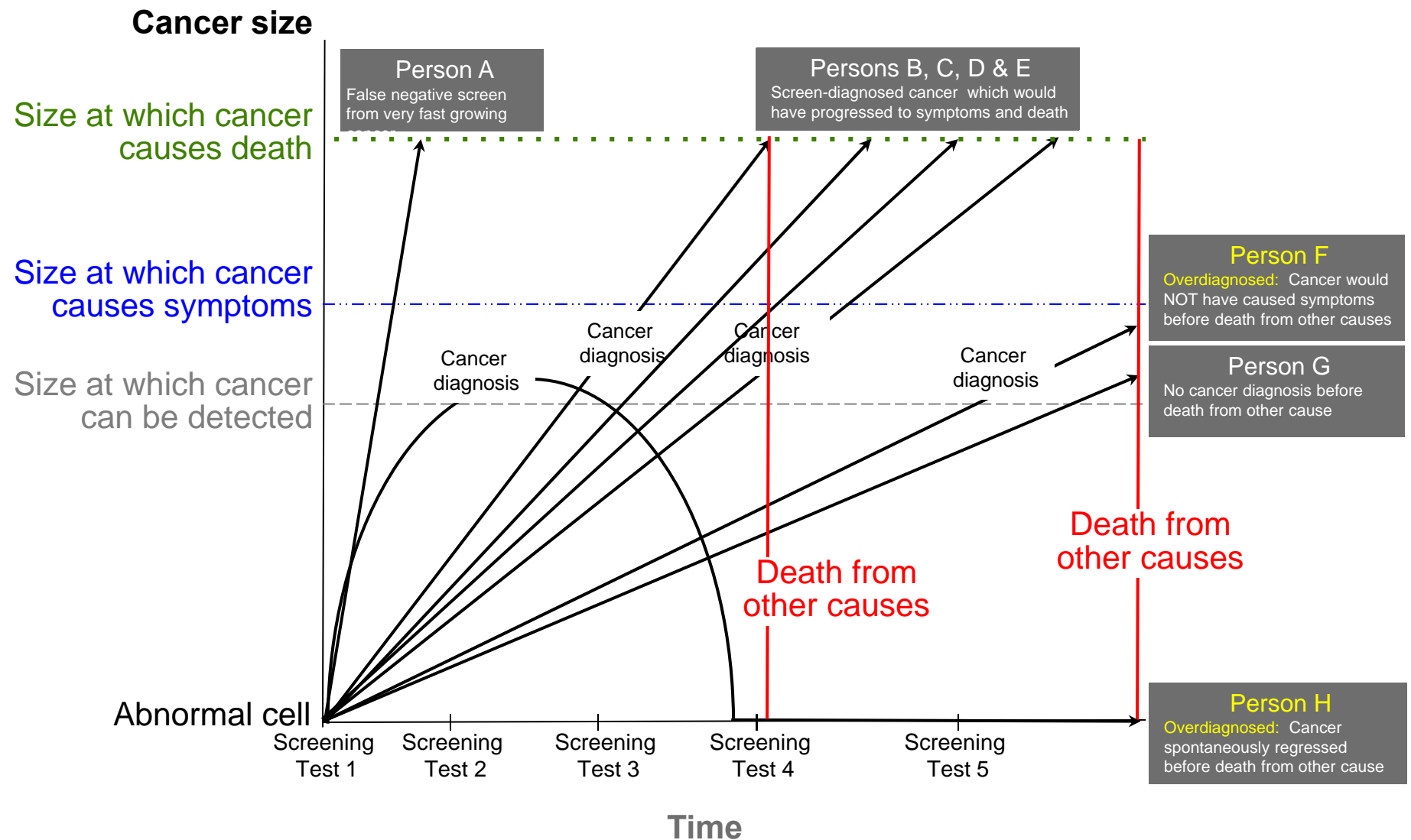


# The Screening Cascade



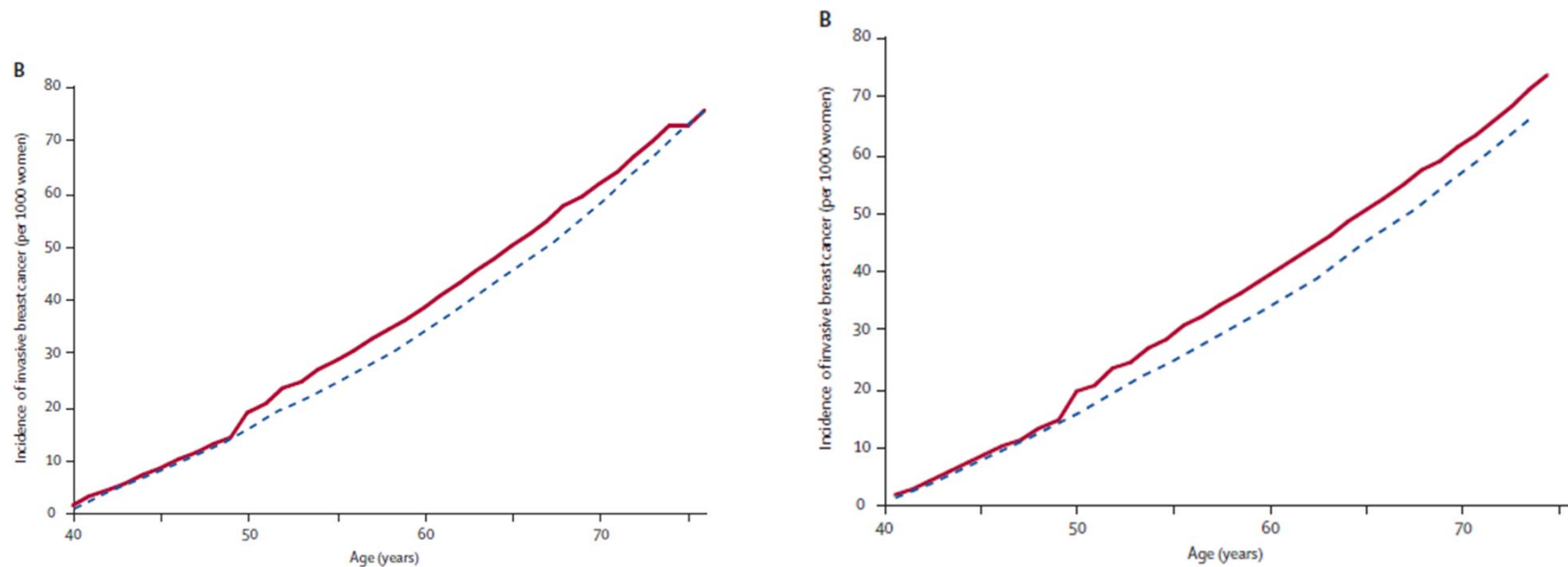
*Modified slide: Professor Russ Harris*

# Model: what happens at cancer screening?



Brodersen J., Schwartz L.M., Woloshin S. *Overdiagnosis: How cancer screening can turn indolent pathology into illness.* APMIS 122, 2014.

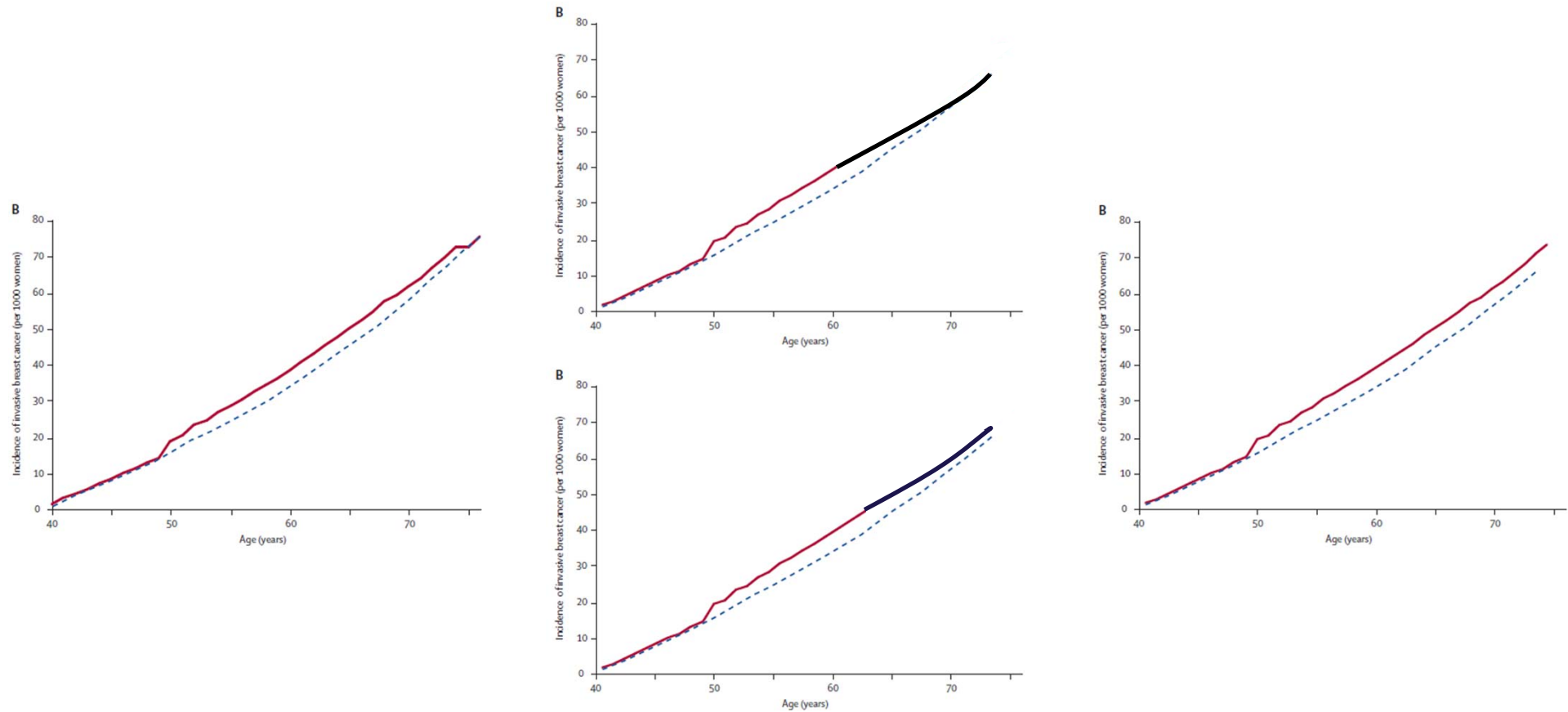
# Overdiagnosis in RCT



C. Biesheuvel, A. Barratt, K. Howard, N. Houssami, and L. Irwig.  
Effects of study methods and biases on estimates of invasive  
breast cancer overdetected with mammography screening: a  
systematic review. *Lancet Oncol.* 8 (12): 1129-1138, 2007.

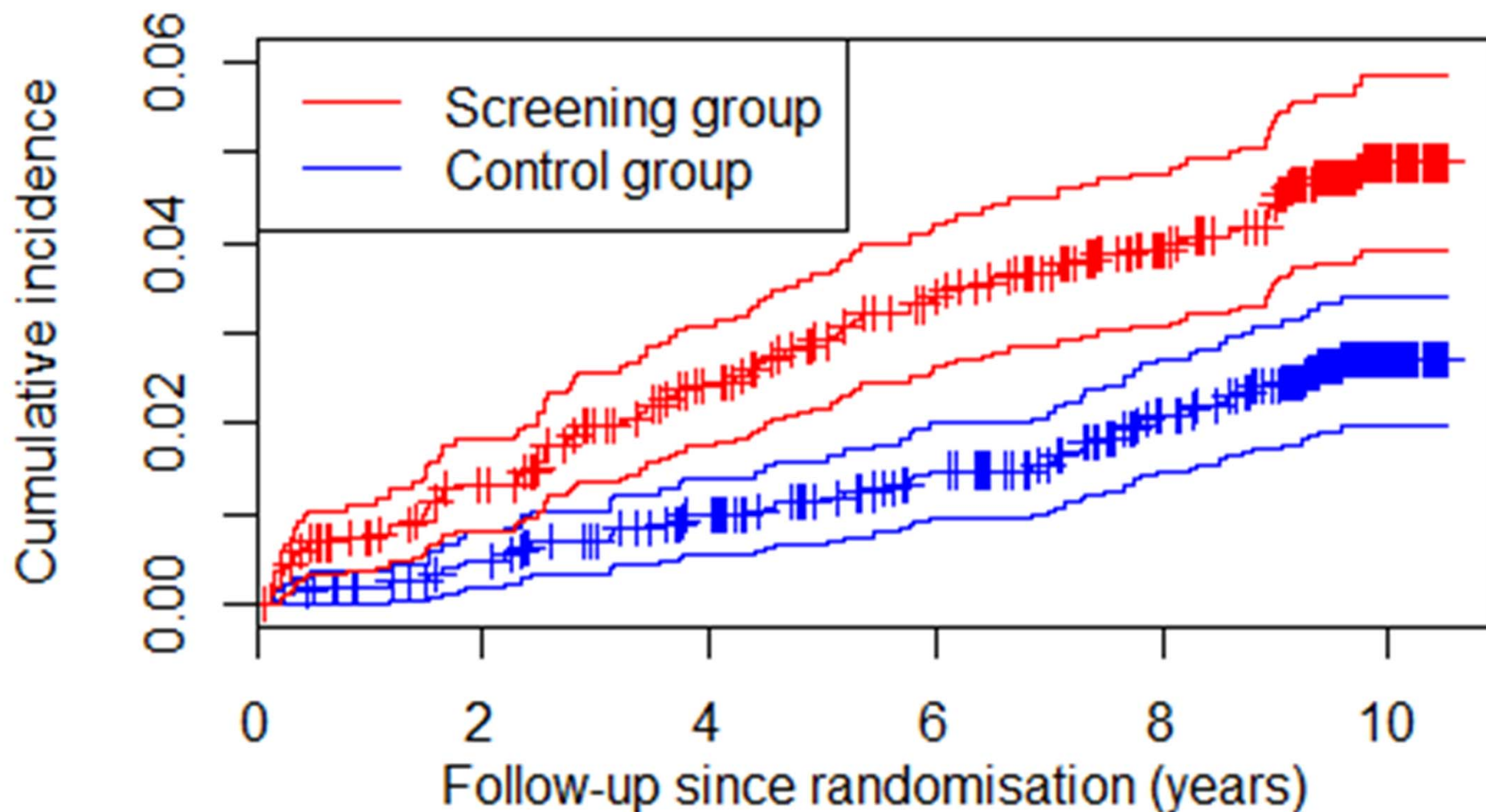


# Overdiagnosis in RCT



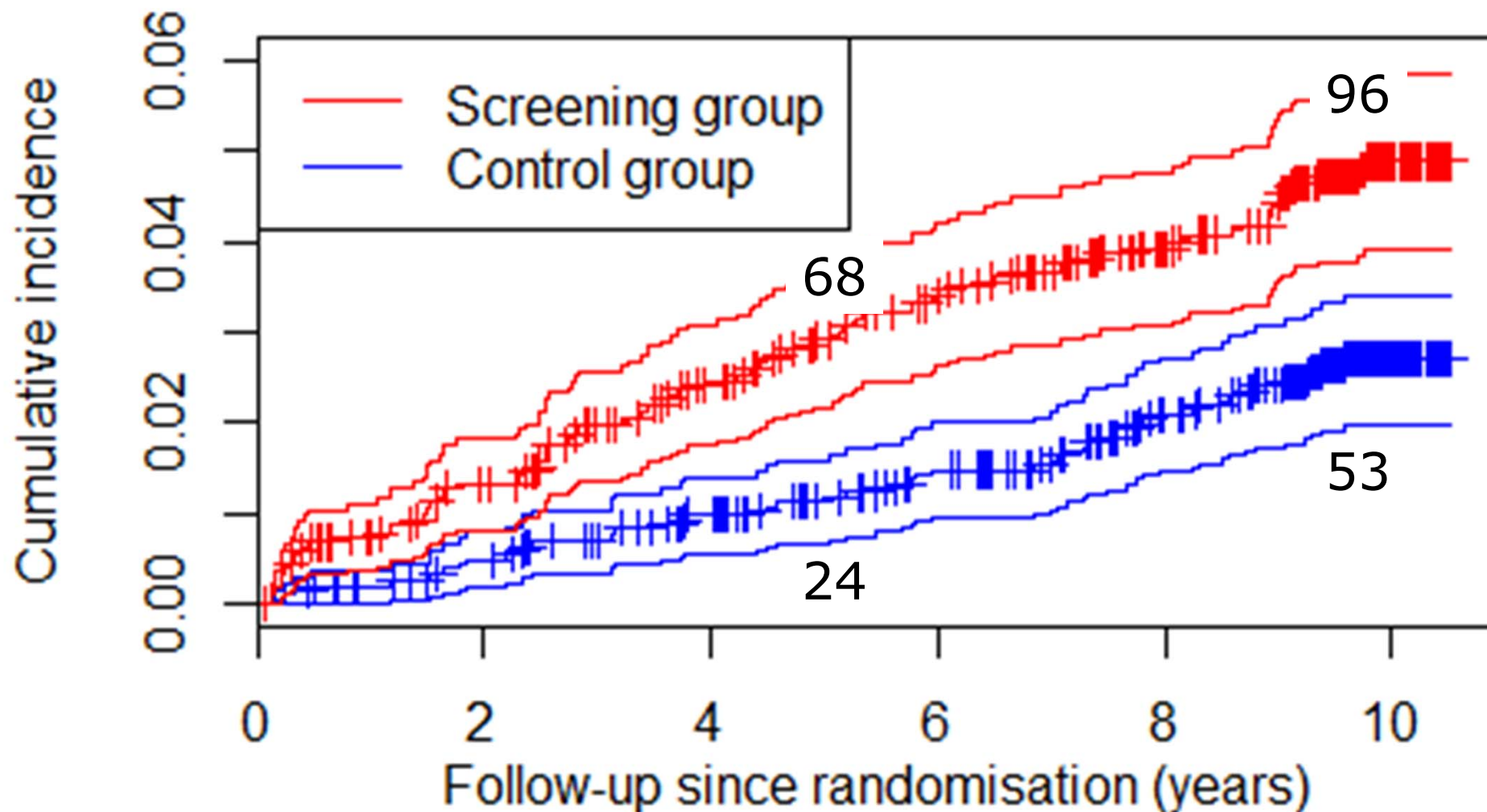
# Overdiagnosis in DLCST at 5 year follow-up

## Cumulative incidence of lung cancer



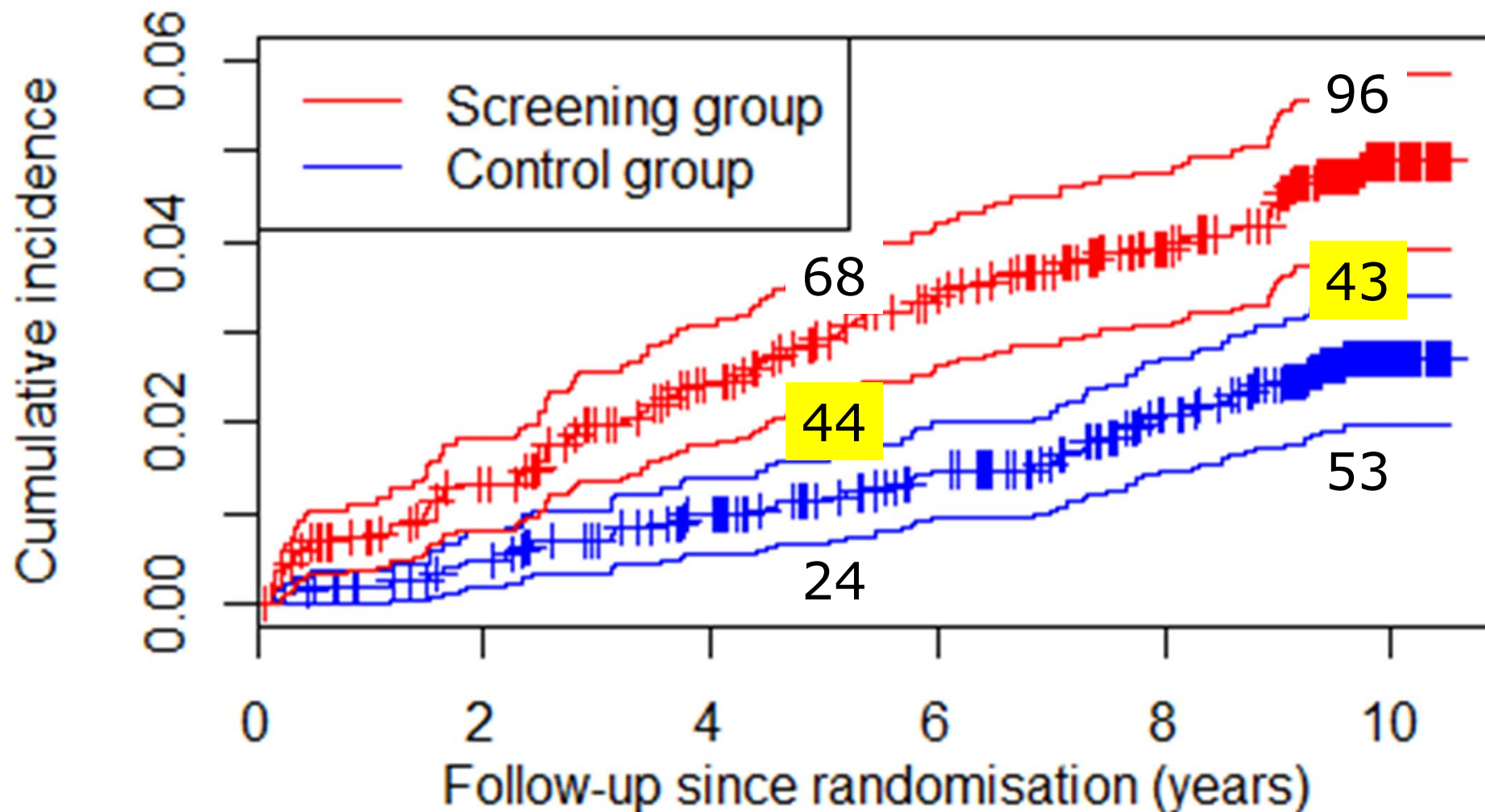
# Overdiagnosis in DLCST at 5 year follow-up

## Cumulative incidence of lung cancer



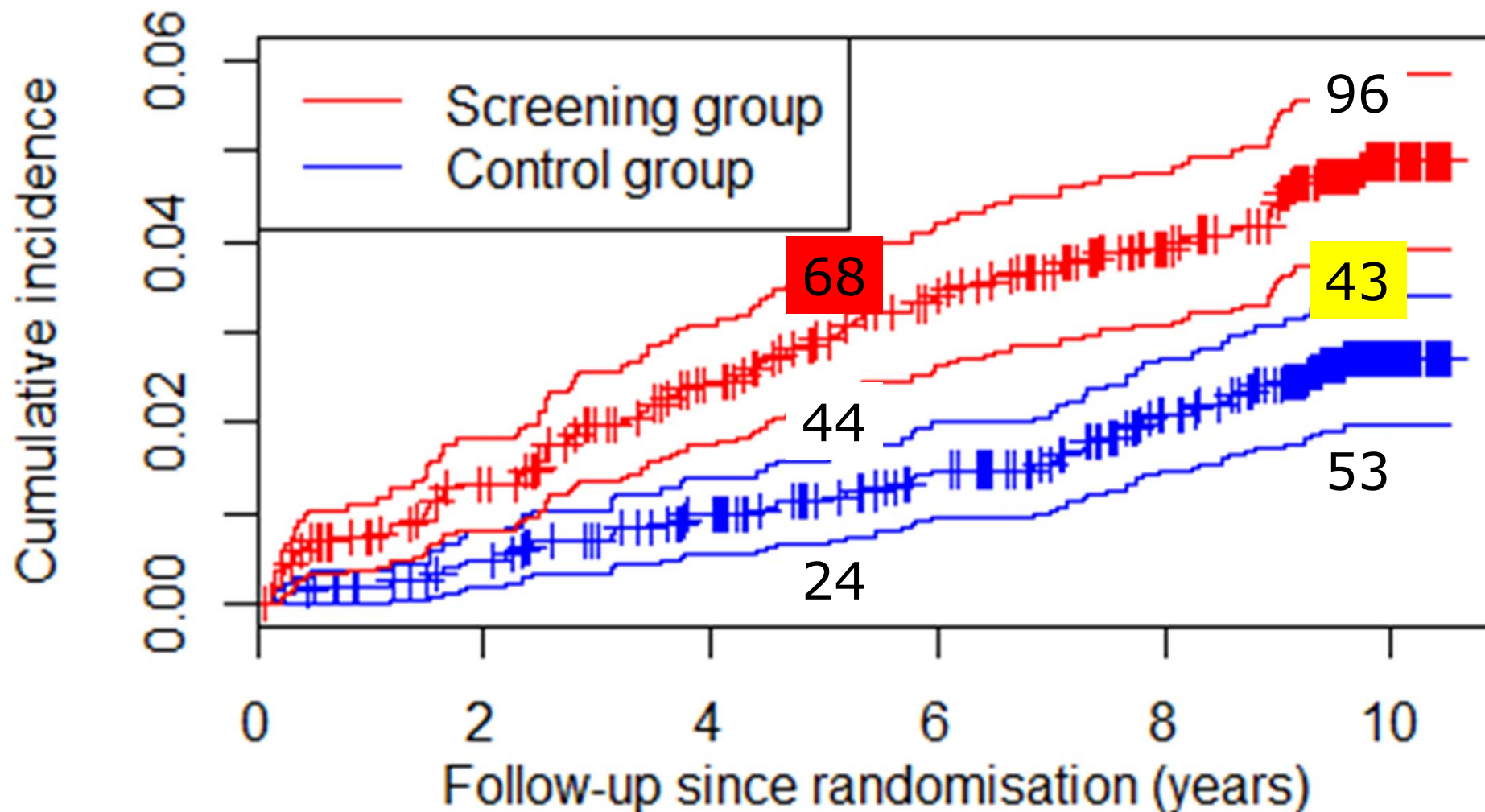
# Overdiagnosis in DLCST at 5 year follow-up

## Cumulative incidence of lung cancer



# Overdiagnosis in DLCST at 5 year follow-up

## Cumulative incidence of lung cancer





## Overdiagnosis in DLCST at 5 year follow-up

- Extra number of LC: 43 (96-53)
- ODX:  $43/68 = 63\%$  [95% CI; 33%-88%]

Wille et al. Results of the Randomized Danish Lung Cancer Screening Trial with Focus on High-risk Profiling. *Am.J Respir. Crit Care Med.*, 2015.



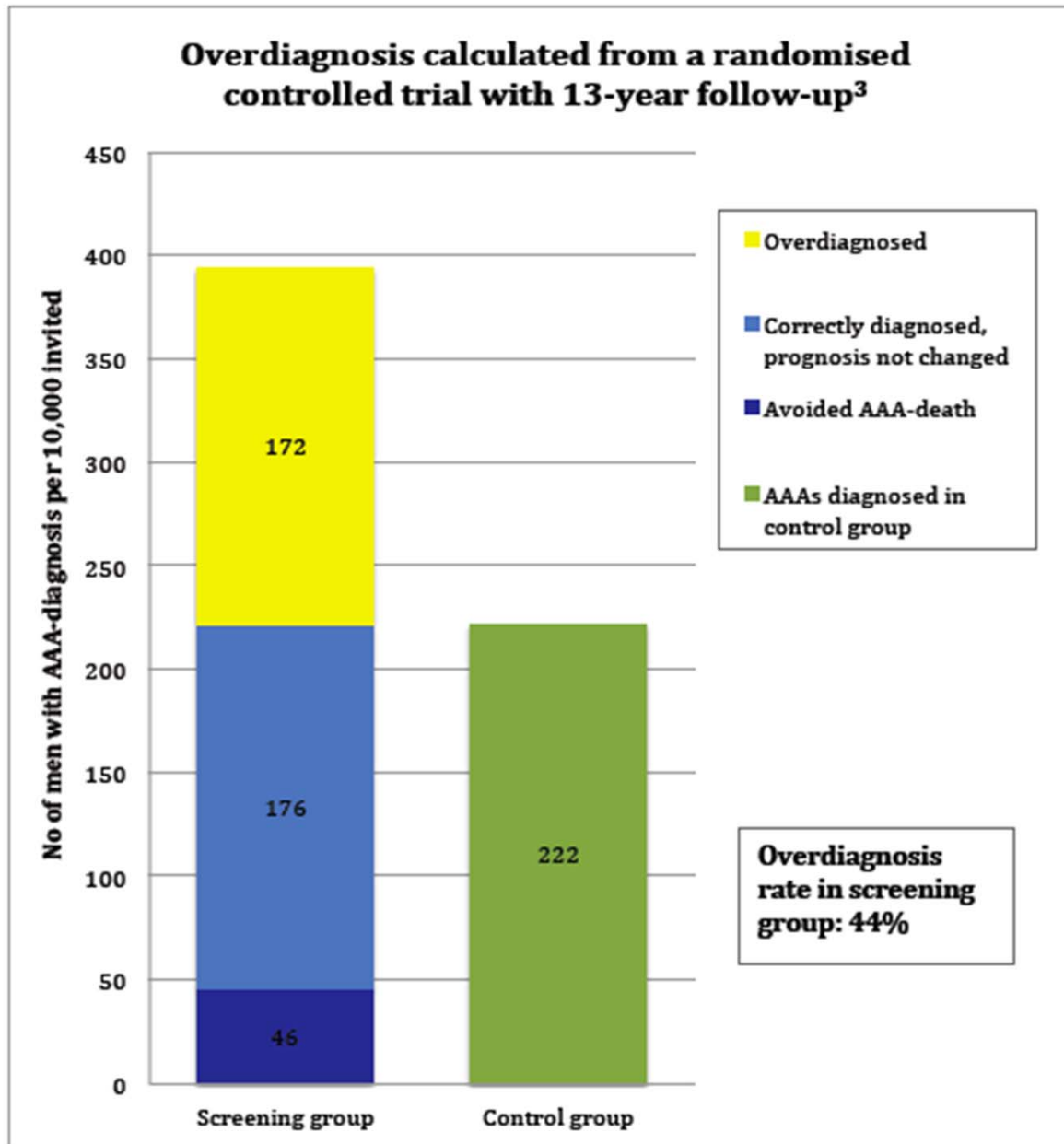
# Strength & limitations

- No screening in control group
- Minor contamination in control group
- Participation bias in DLCST?
- Too short follow-up?
- Uneven distribution of high risk heavy smokers after randomisation?

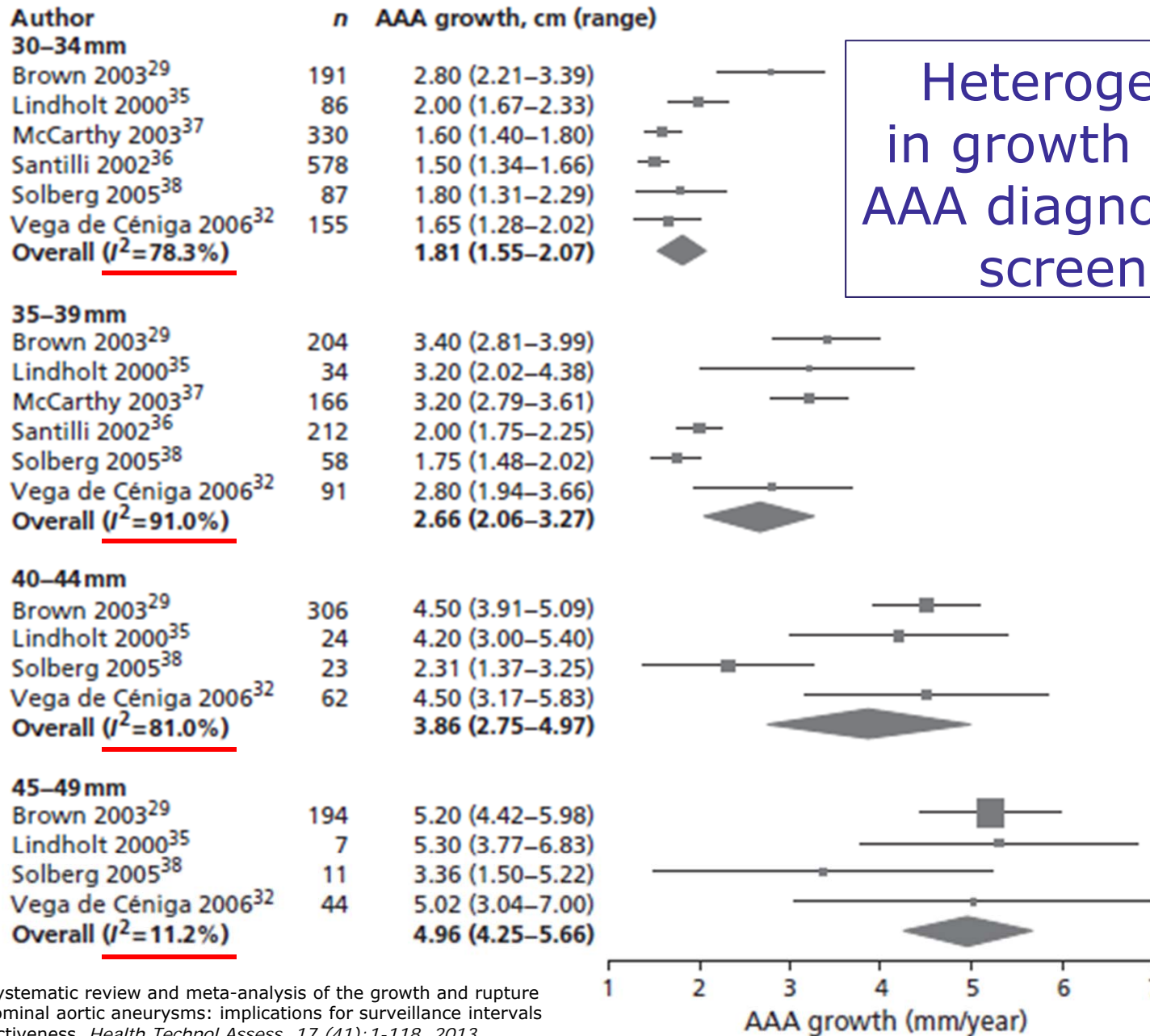
Wille et al. Results of the Randomized Danish Lung Cancer Screening Trial with Focus on High-risk Profiling. *Am.J Respir.Crit Care Med.*, 2015.



# AAA screening: 38-44% ODx



M. Johansson, A. Hansson, and J. Brodersen. Estimating overdiagnosis in screening for abdominal aortic aneurysm: could a change in smoking habits and lowered aortic diameter tip the balance of screening towards harm? *BMJ* 350:h825, 2015.

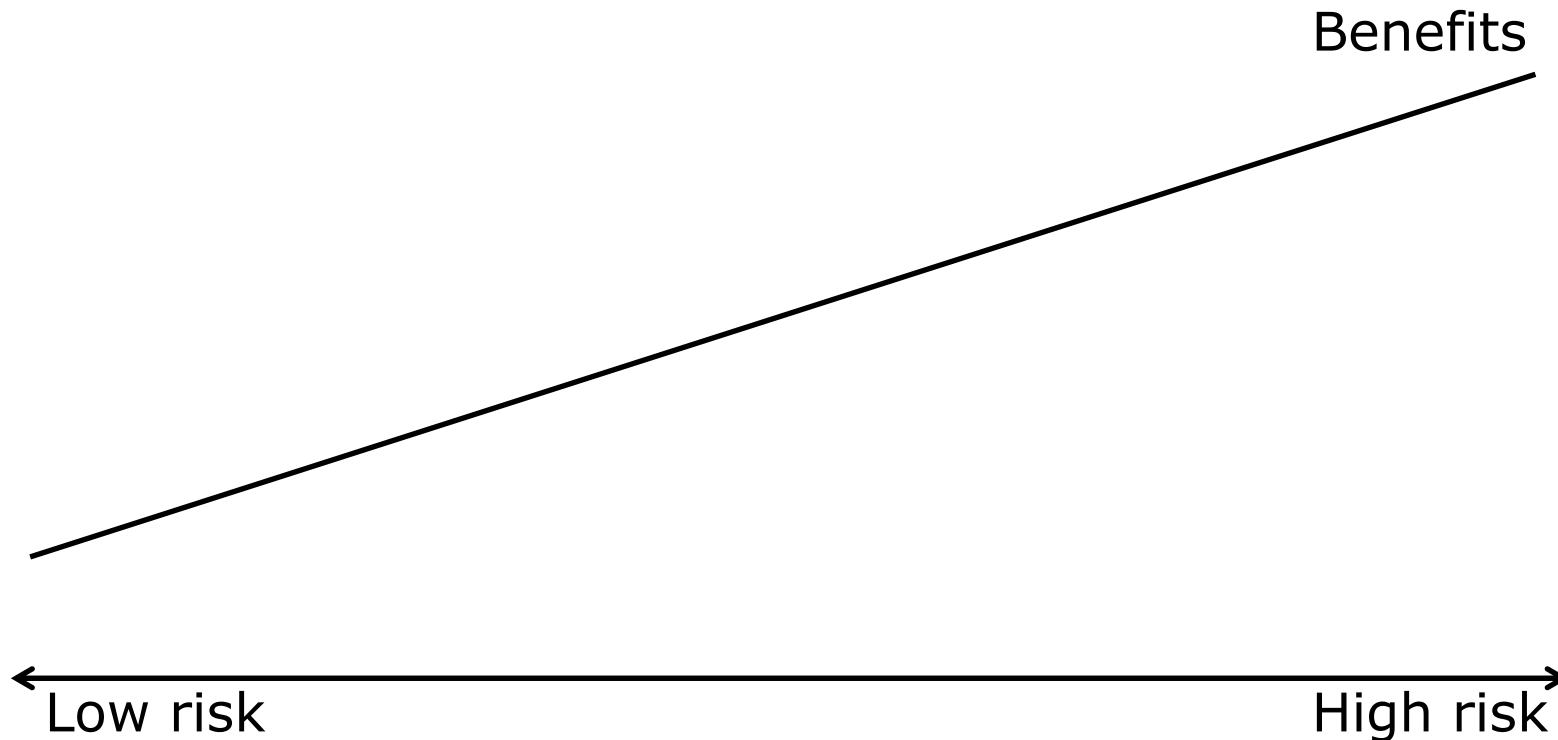


Heterogeneity  
in growth rate in  
AAA diagnosed via  
screening

Thompson et al. Systematic review and meta-analysis of the growth and rupture rates of small abdominal aortic aneurysms: implications for surveillance intervals and their cost-effectiveness. *Health Technol. Assess.* 17 (41):1-118, 2013.

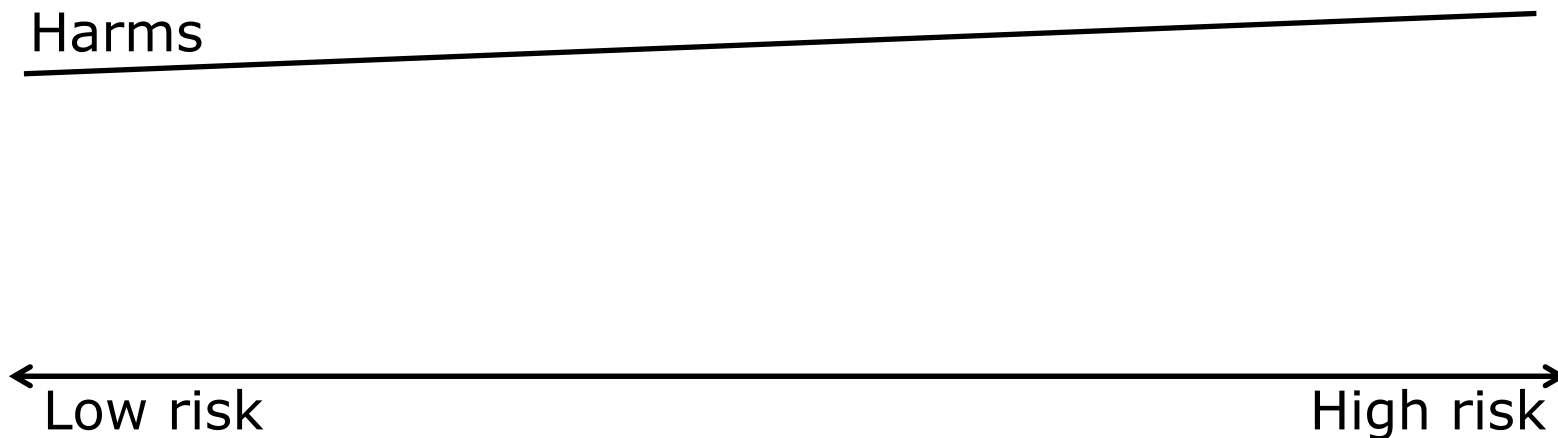
**FIGURE 3** Aneurysm growth rate by 5-mm size ranges of baseline aneurysm diameter: random-effect meta-analyses - conducted within subgroups.

# Any medical intervention: Balance of benefits & harms

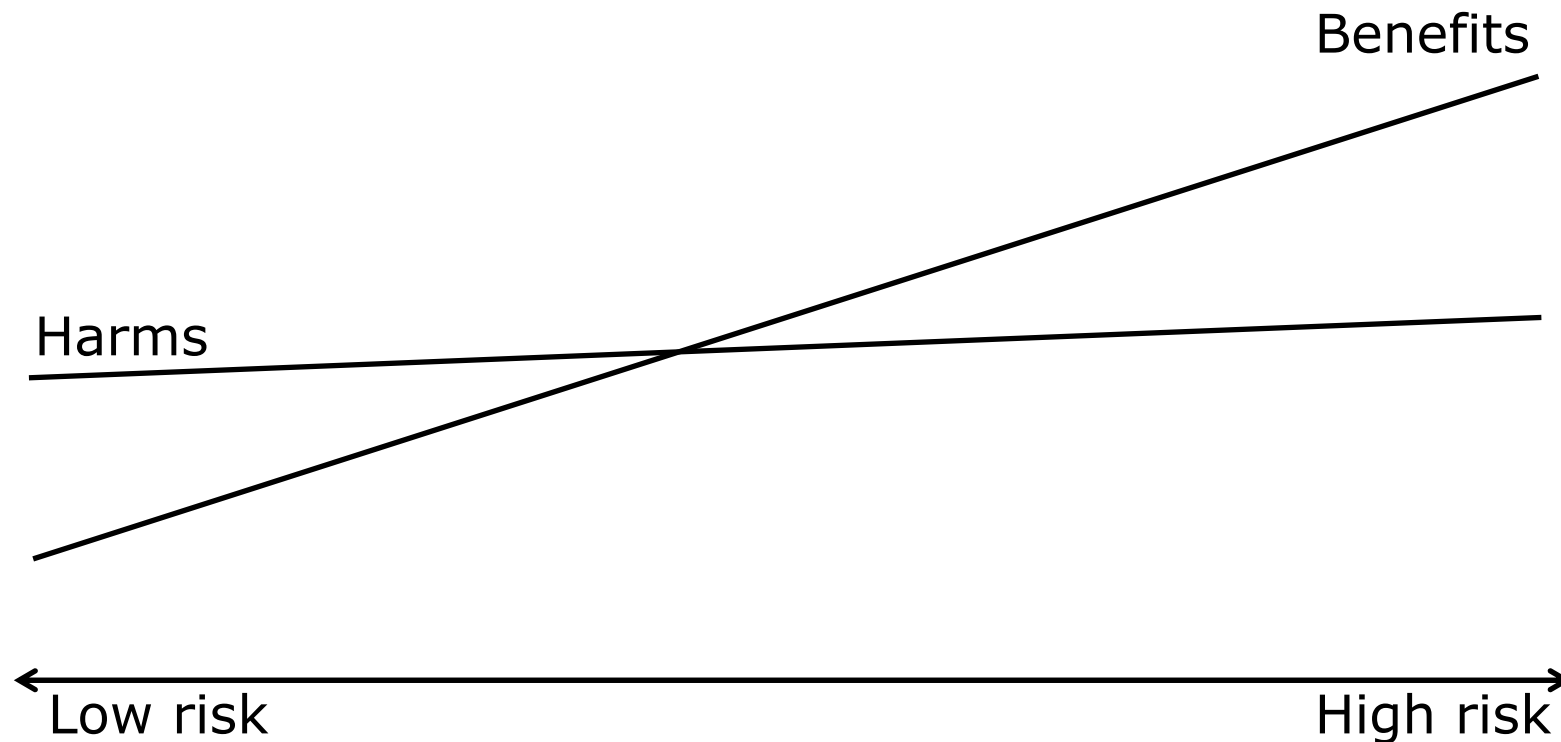


# Any medical intervention: Balance of benefits & harms

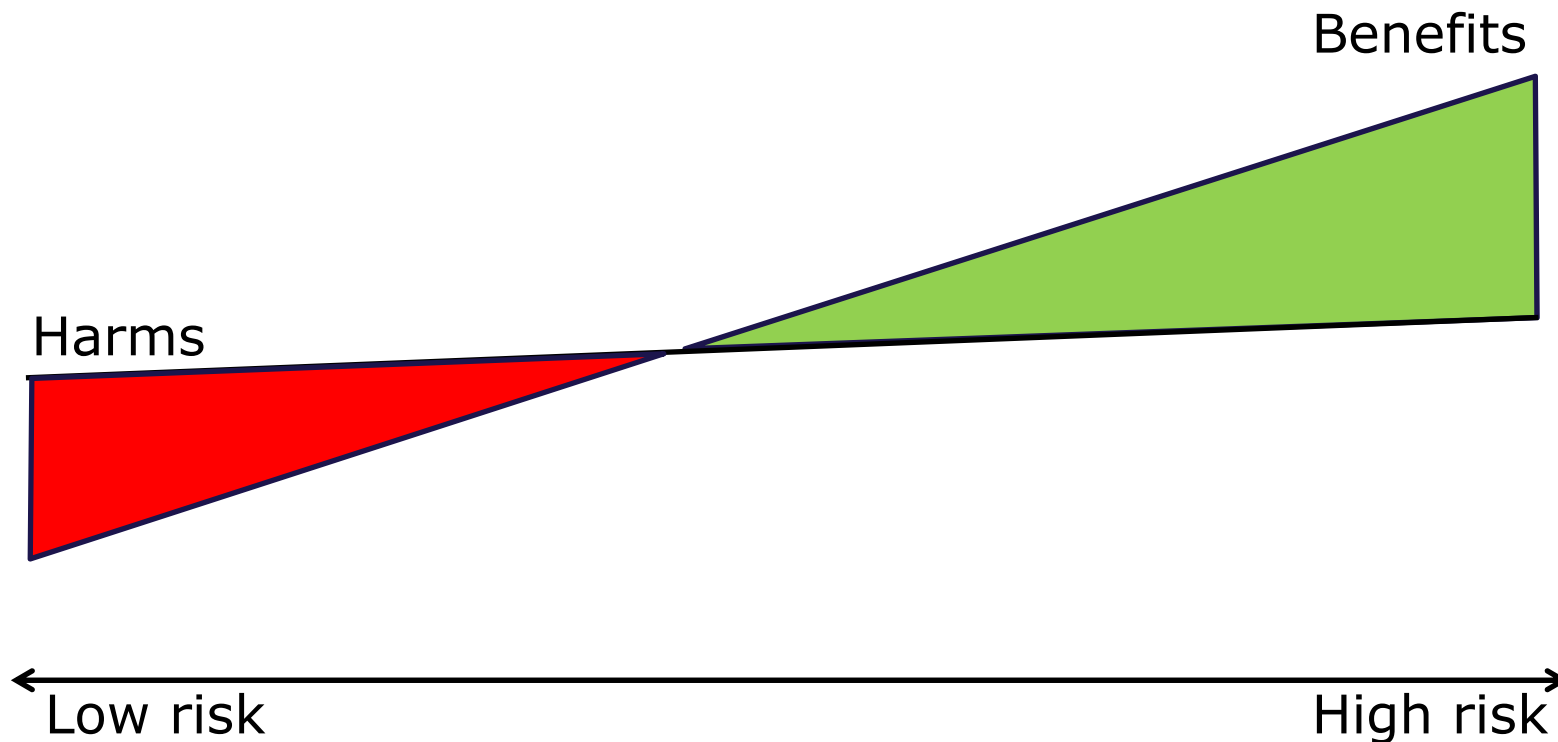
Harms



# Any medical intervention: Balance of benefits & harms



# Any medical intervention: Balance of benefits & harms



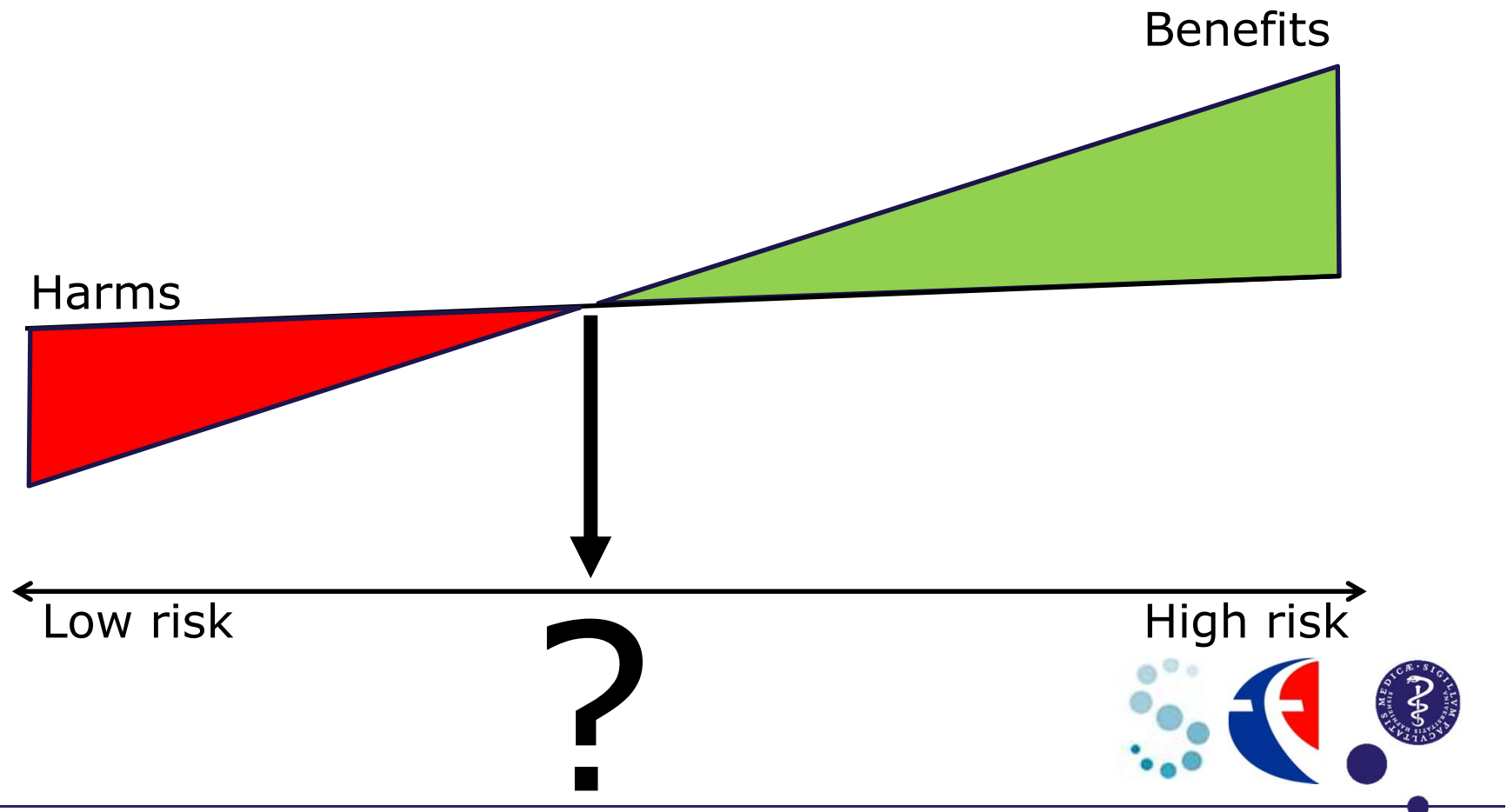


# AAA screening: 38-44% ODX

<http://www.bmj.com/content/350/bmj.h825/infographic>



# Any medical intervention: Balance of benefits & harms



# PSA-screening

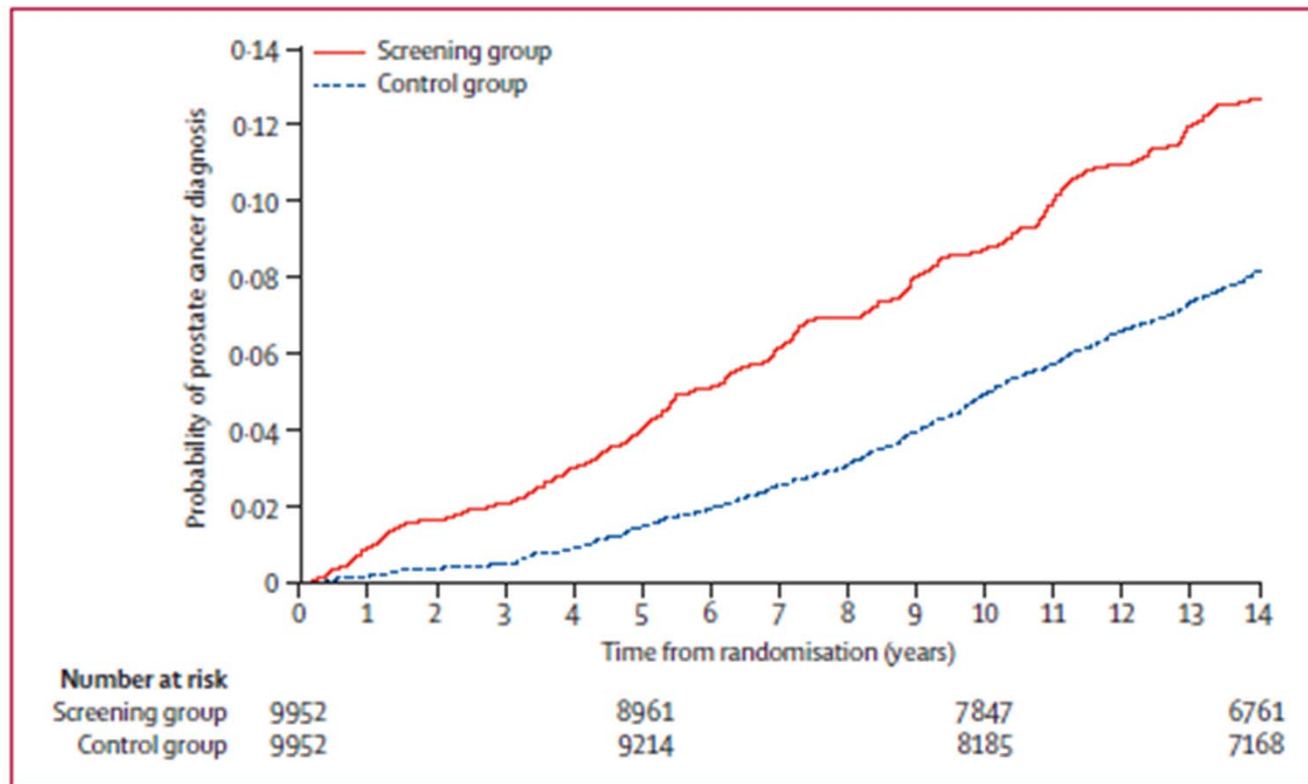


Figure 2: Cumulative incidence of prostate cancer in the screening group and in the control group

Hugosson J et al. Mortality results from the Göteborg randomised population-based prostate-cancer screening trial. [www.thelancet.com/oncology](http://www.thelancet.com/oncology) Published online July 1, 2010



# NORCCAP: 7 years follow-up

BMJ

RESEARCH

## Risk of colorectal cancer seven years after flexible sigmoidoscopy screening: randomised controlled trial

Geir Hoff, professor,<sup>1,2</sup> Tom Grotmol, professor,<sup>1</sup> Eva Skovlund, professor,<sup>3</sup> researcher,<sup>1,4</sup> for the Norwegian Colorectal Cancer Prevention Study Group

Results:

Participation rate: 63%

Incidence: HR 1.02 [95% CI 0.83-1.25]

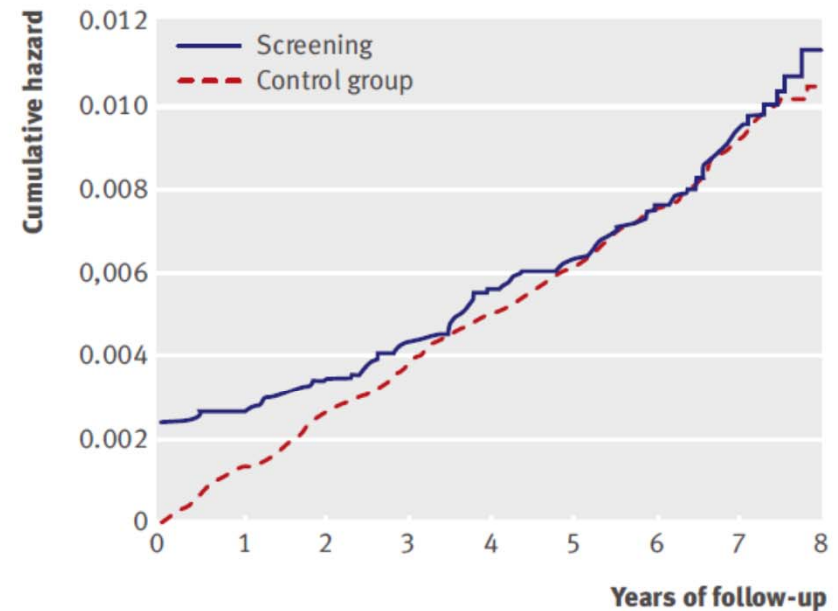


Fig 2 | Cumulative hazard for colorectal cancer in screening and control groups

# NORCCAP: 11 years follow-up

Original Investigation

JAMA August 13, 2014 Volume 312, Number 6

## Effect of Flexible Sigmoidoscopy Screening on Colorectal Cancer Incidence and Mortality A Randomized Clinical Trial

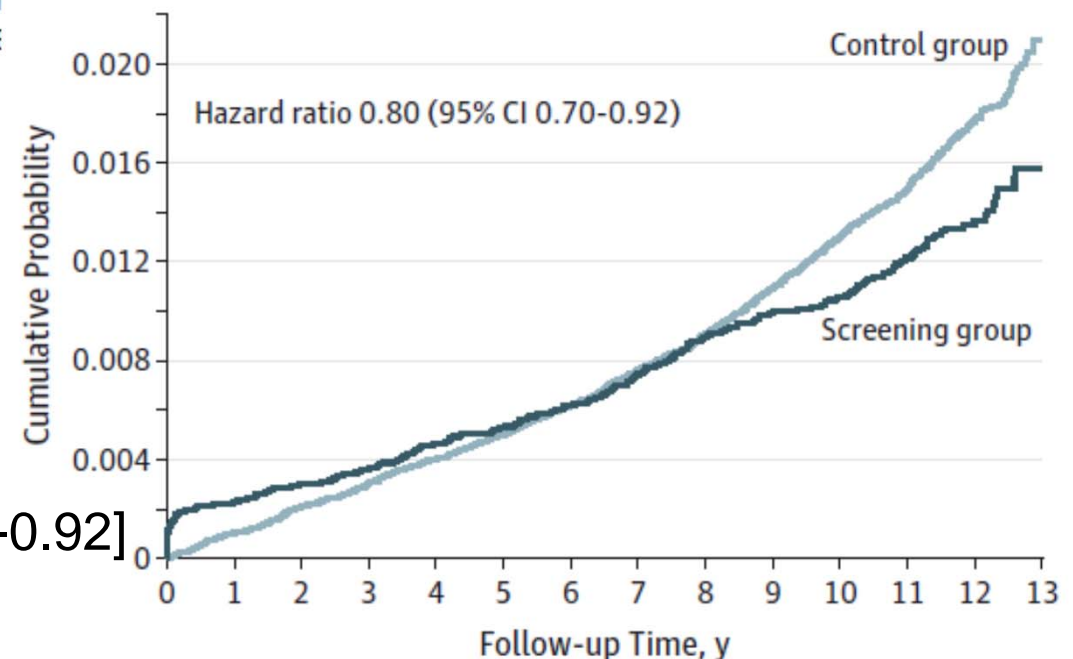
Øyvind Holme, MD; Magnus Løberg, MD; Mette Kalager, MD, PhD; I Miguel A. Hernán, MD, DrPH; Eline Aas, PhD; Tor J. Eide, MD, PhD; E Kjell Magne Tveit, MD, PhD; Geir Hoff, MD, PhD

Results:

Participation rate: 63%

Incidence: HR 0.80 [95% CI 0.70-0.92]

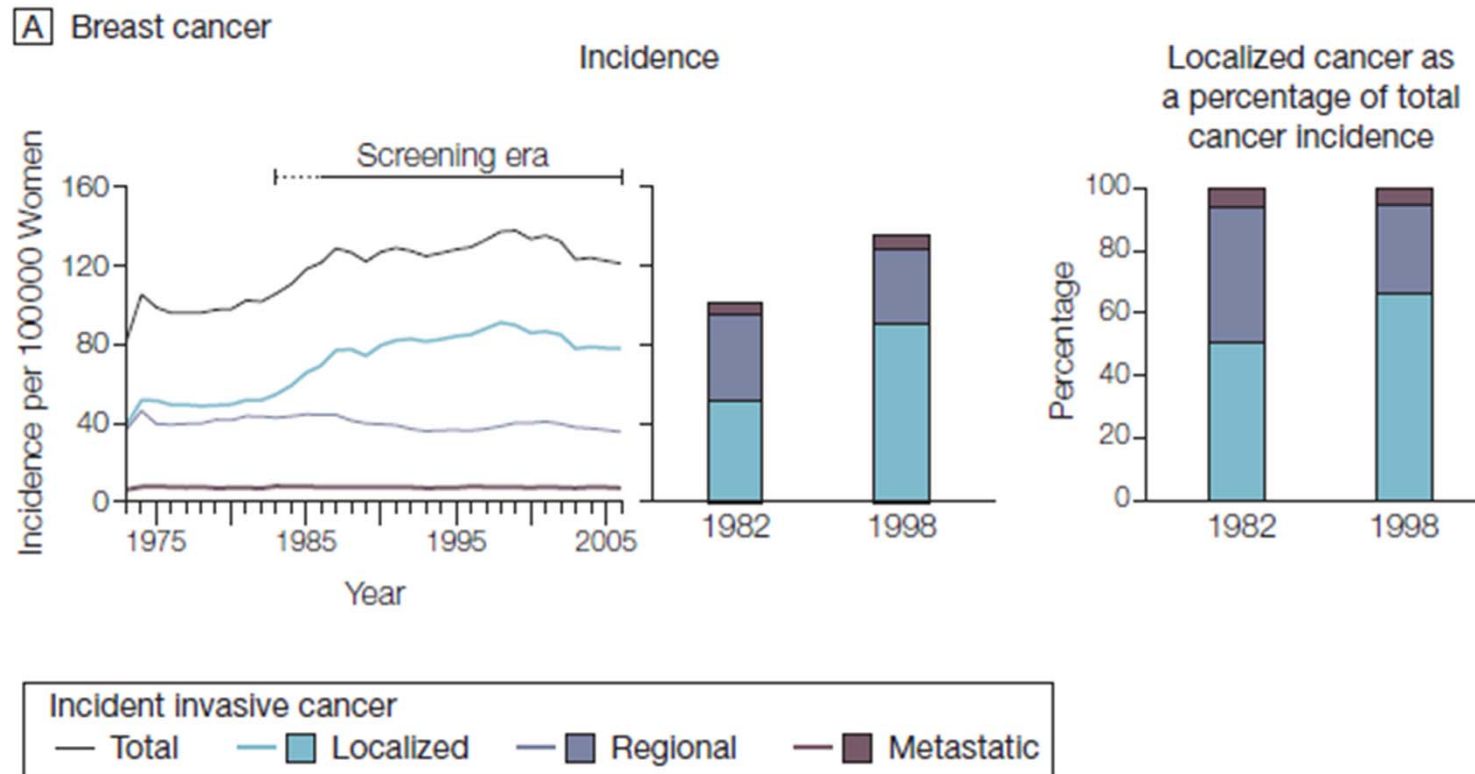
A Overall colorectal cancer incidence



# ODx in observational studies



# ODx in observational studies

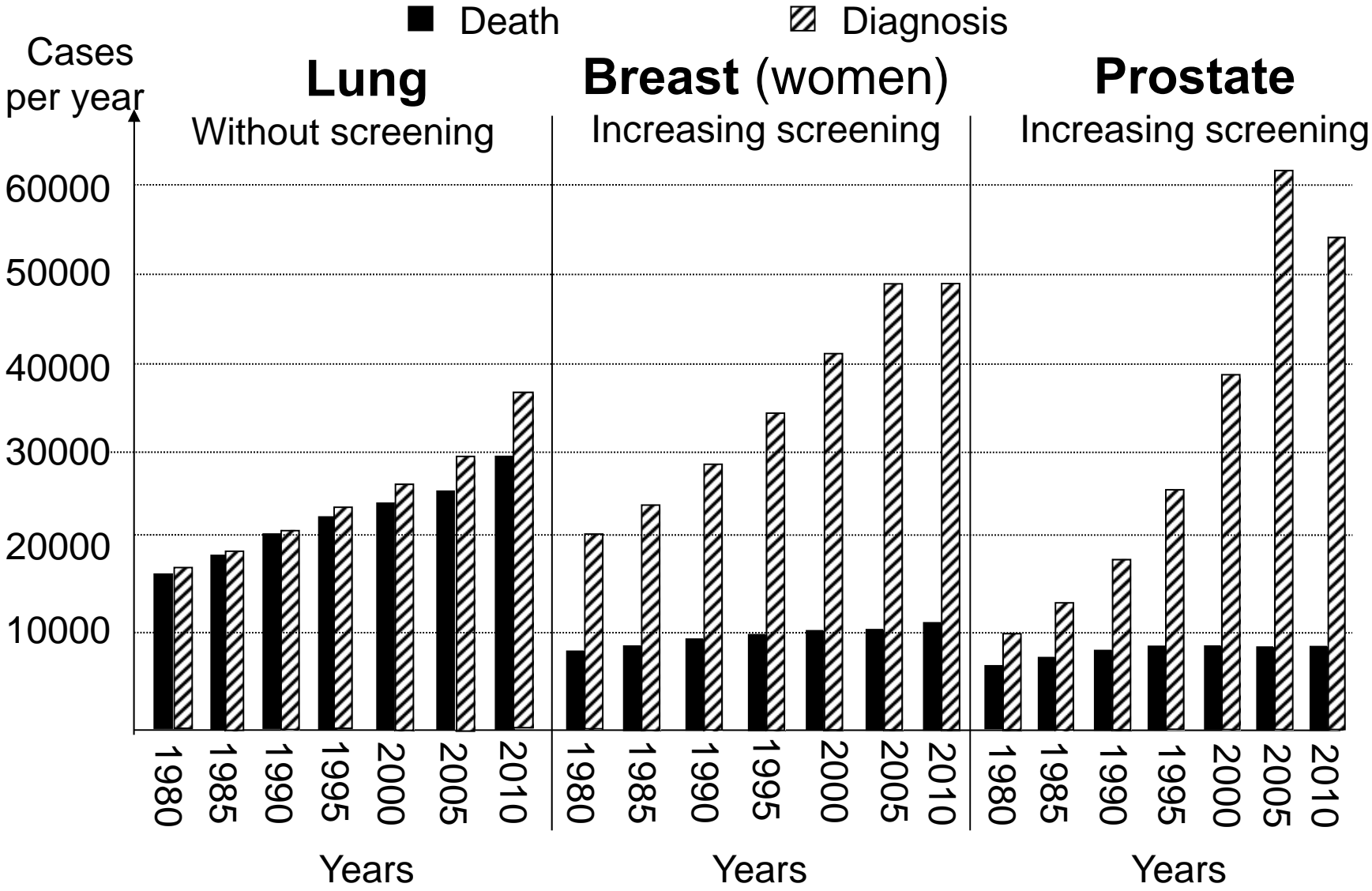


Esserman L., Shieh Y., & Thompson I.  
*Rethinking Screening for Breast Cancer and Prostate Cancer.*  
*JAMA: 302 (15):1685-1692, 2009.*



# Cancer death and invasive cancer diagnosis with and without screening

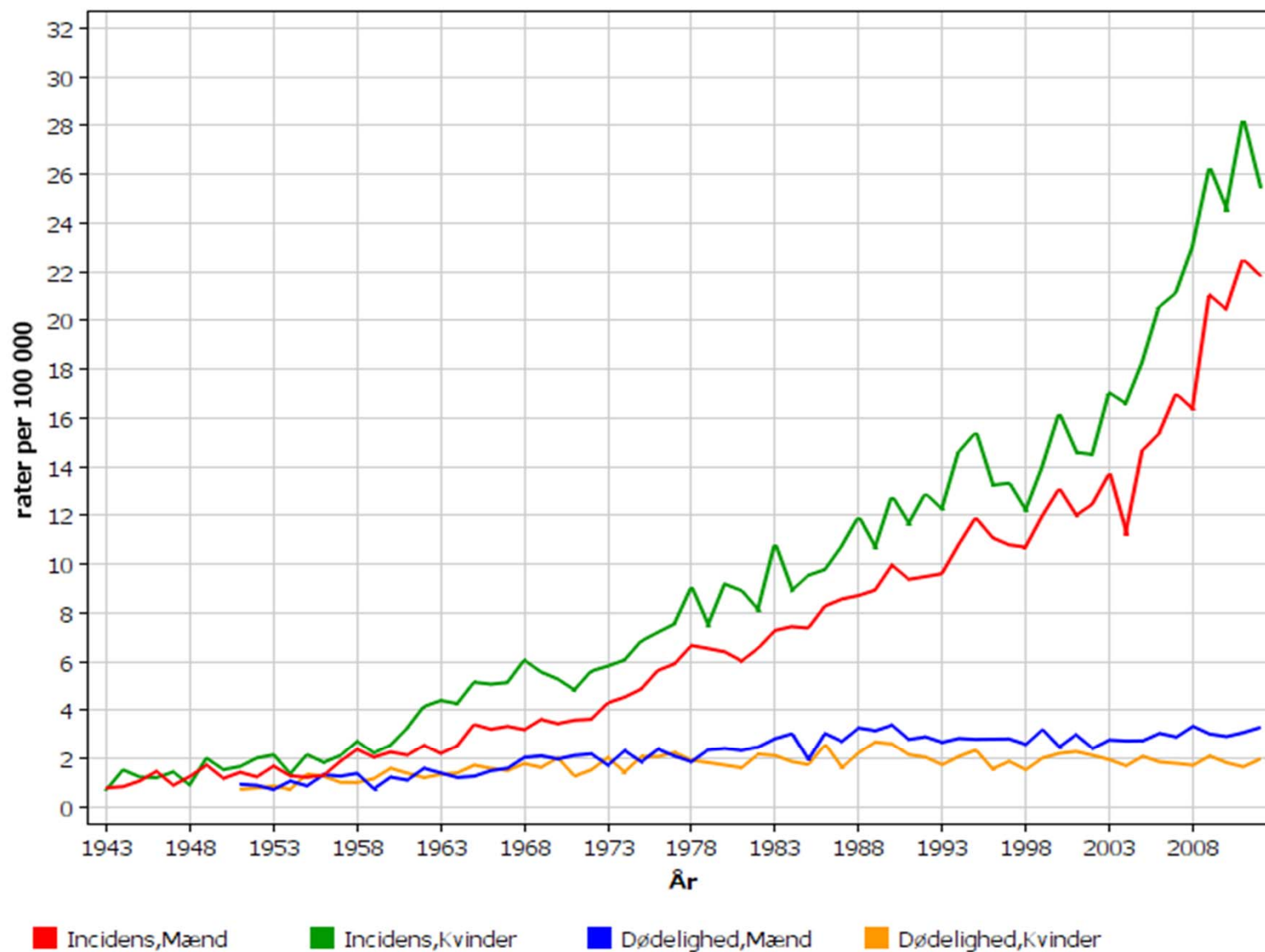
*Lung, breast and prostate. France 1980-2010*





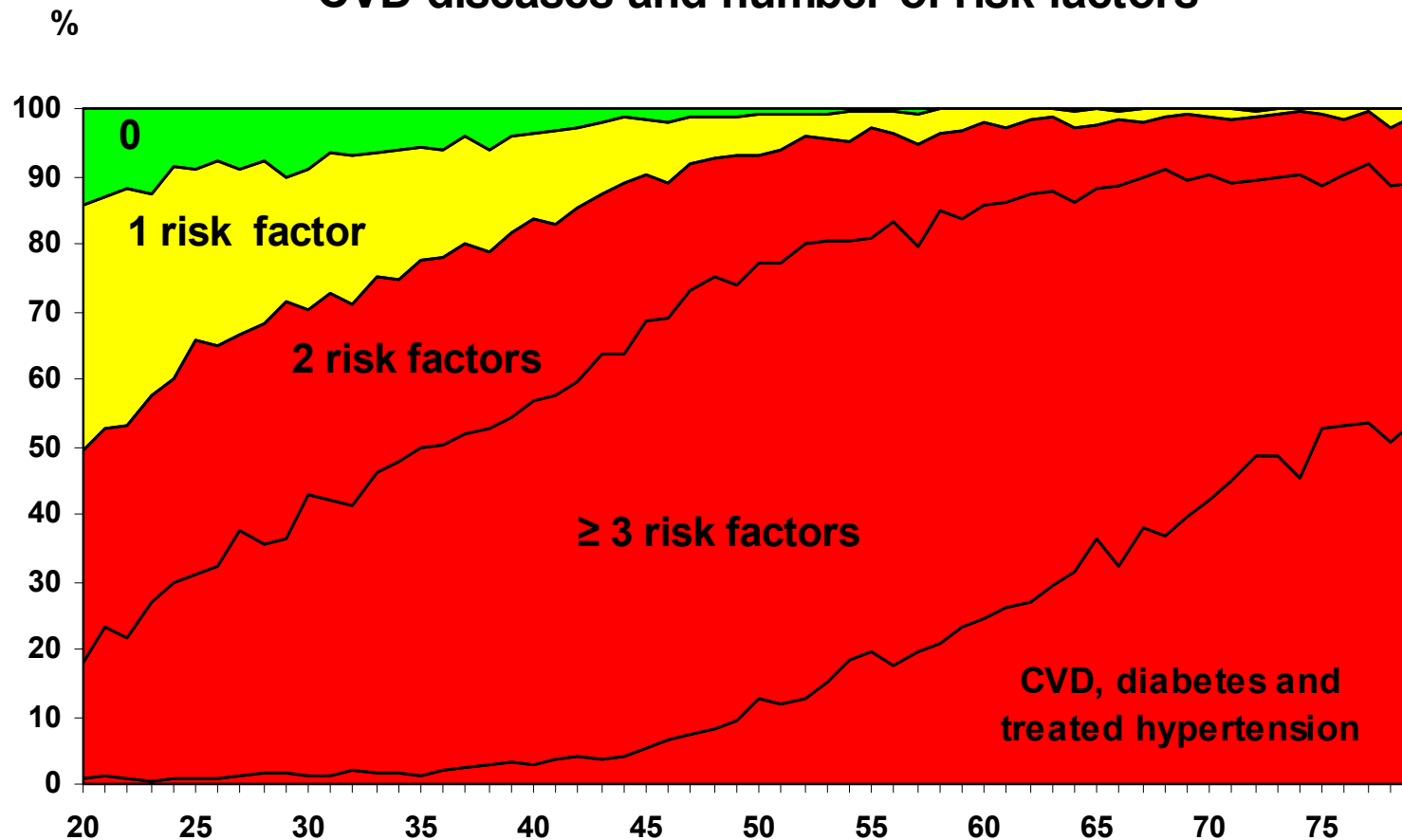
Danmark  
Modermærkekræft, hud  
ASR (W) alder 0-85+

# Malignant melanoma in DK



# Cardio-vascular Overdiagnosis

## CVD diseases and number of risk factors



H. Petursson et al. Can individuals with a significant risk for cardiovascular disease be adequately identified by combination of several risk factors? *J.Eval.Clin.Pract.* 15 (1): 103-109, 2009.



# Content of presentation

- Defining overdiagnosis
- Types of overdiagnosis
- Experiences of being overdiagnosed
- The degree of overdiagnosis
- **Consequences of overdiagnosis**
- Drivers to overdiagnosis



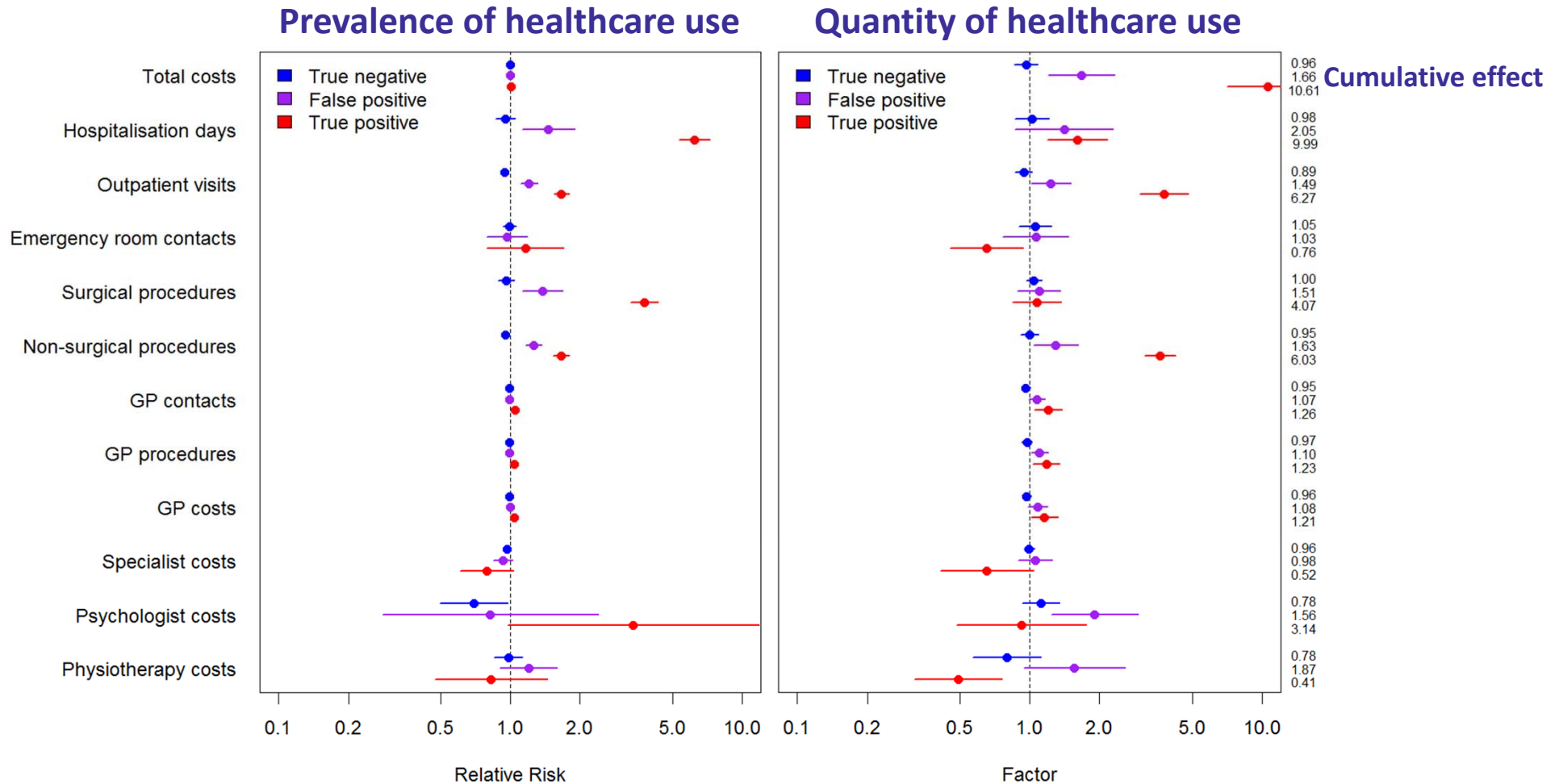
## Harmful consequences of ODx

- financial strain
- hassles/inconveniences
- medical costs
- opportunity costs
- physical harms
- psychological harms
- societal costs
- + work-related costs

Harris R.P. et al. The Harms of Screening: A Proposed Taxonomy and Application to Lung Cancer Screening, JAMA 2014

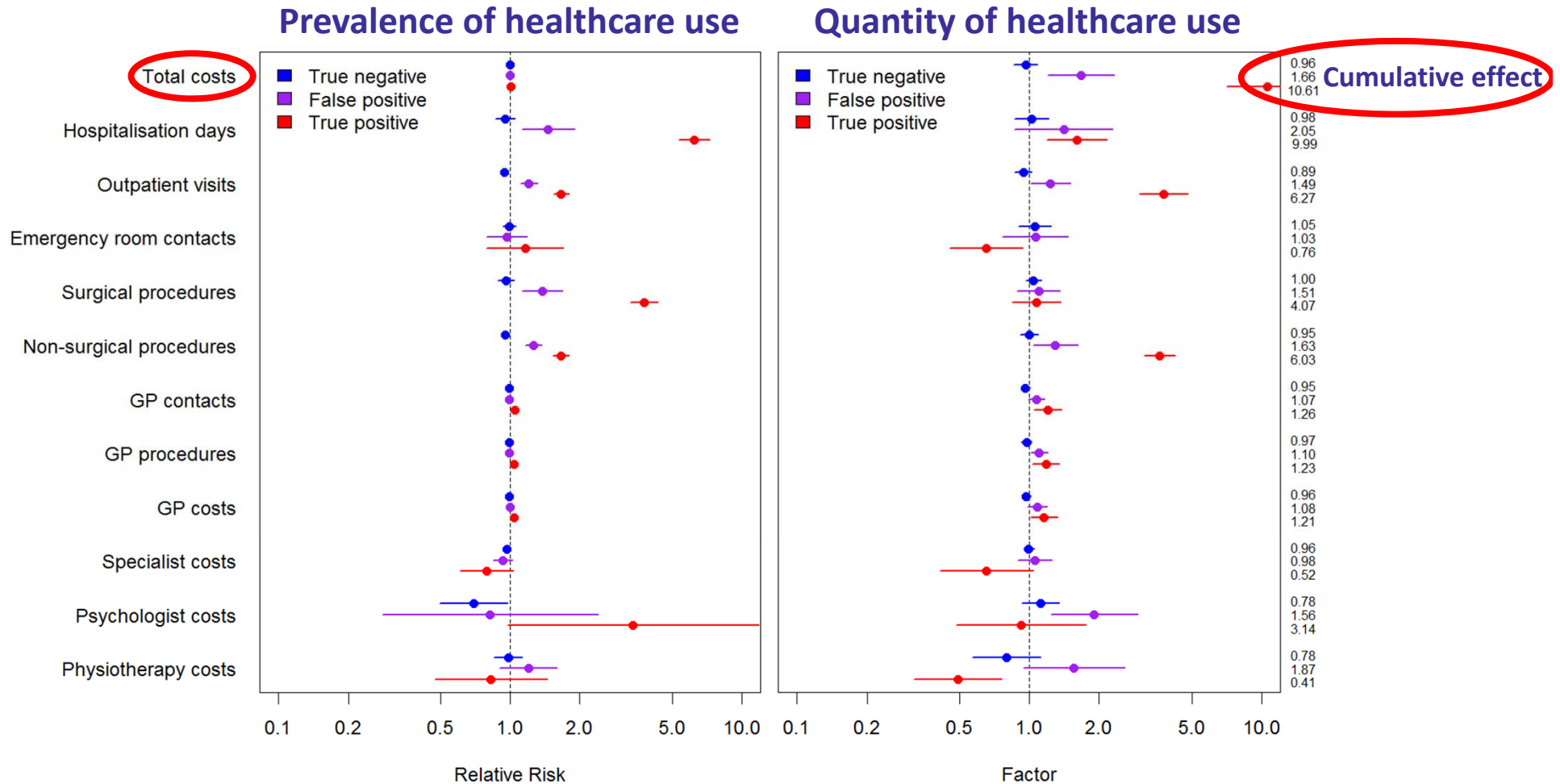


# Costs in the DLCST



J. F. Rasmussen, V. Siersma, J. H. Pedersen, B. Heleno, Z. Saghir, and J. Brodersen. Healthcare costs in the Danish randomised controlled lung cancer CT-screening trial: A registry study. *Lung Cancer* 83 (3):347-355, 2014.

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# Costs in the DLCST

Diagnostic groups	Cumulative effect
Controls	1.00
True negative	0.96
False positive	1.66
True positive	10.61

*J. F. Rasmussen, V. Siersma, J. H. Pedersen, B. Heleno, Z. Saghir, and J. Brodersen. Healthcare costs in the Danish randomised controlled lung cancer CT-screening trial: A registry study. Lung Cancer 83 (3):347-355, 2014.*



# Costs in the DLCST

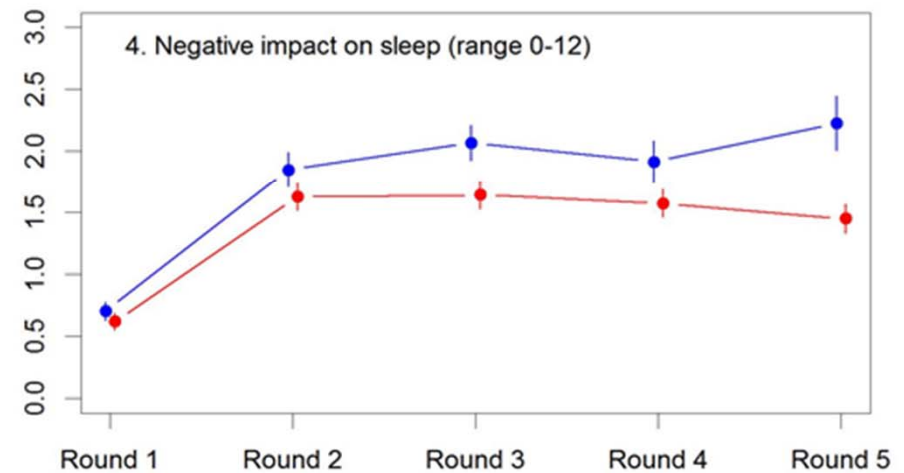
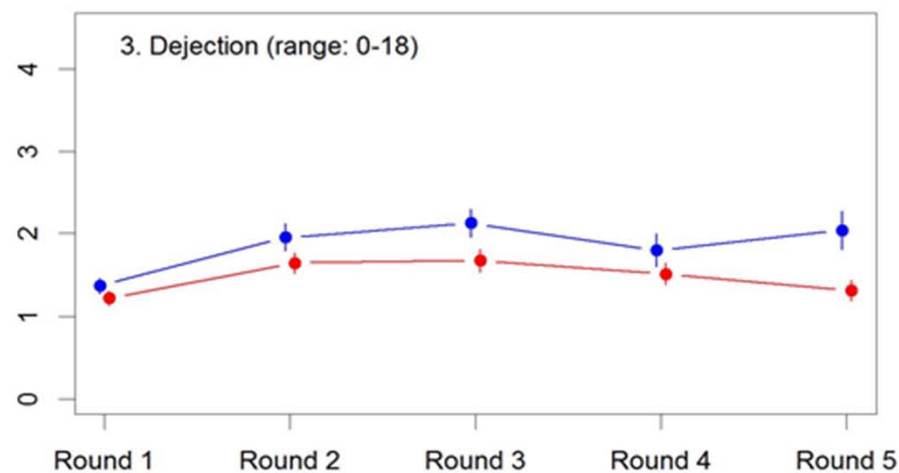
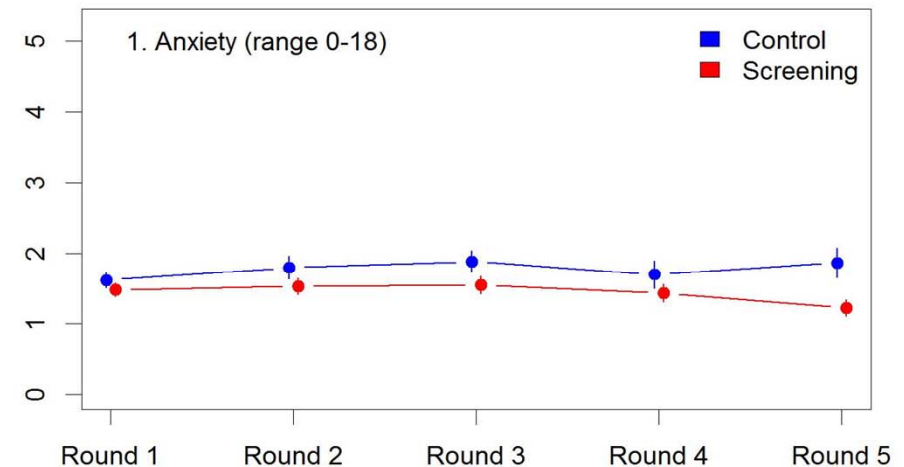
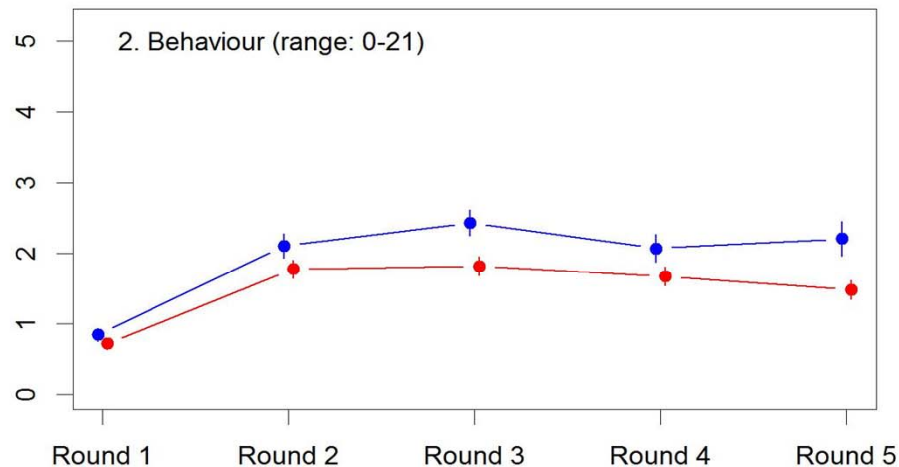
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# Psychosocial consequences of lung cancer screening



*J.F. Rasmussen, V. Siersma, J.H. Pedersen, J. Brodersen.  
Psychosocial consequences in the DLCST. Lung Cancer 87  
(1):65-72, 2015.*



# Participation bias in DLCST



Contents lists available at ScienceDirect

2011

Lung Cancer

journal homepage: [www.elsevier.com/locate/lungcan](http://www.elsevier.com/locate/lungcan)



Participation bias in a randomised trial of screening for lung cancer

Mie Sara Hestbech<sup>a,\*</sup>, Volkert Siersma<sup>b</sup>, Asger Dirksen<sup>c</sup>, Jesper H. Pedersen<sup>d</sup>, John Brodersen<sup>b</sup>

Conclusion:...substantial socio-demographic and psychosocial participation bias...

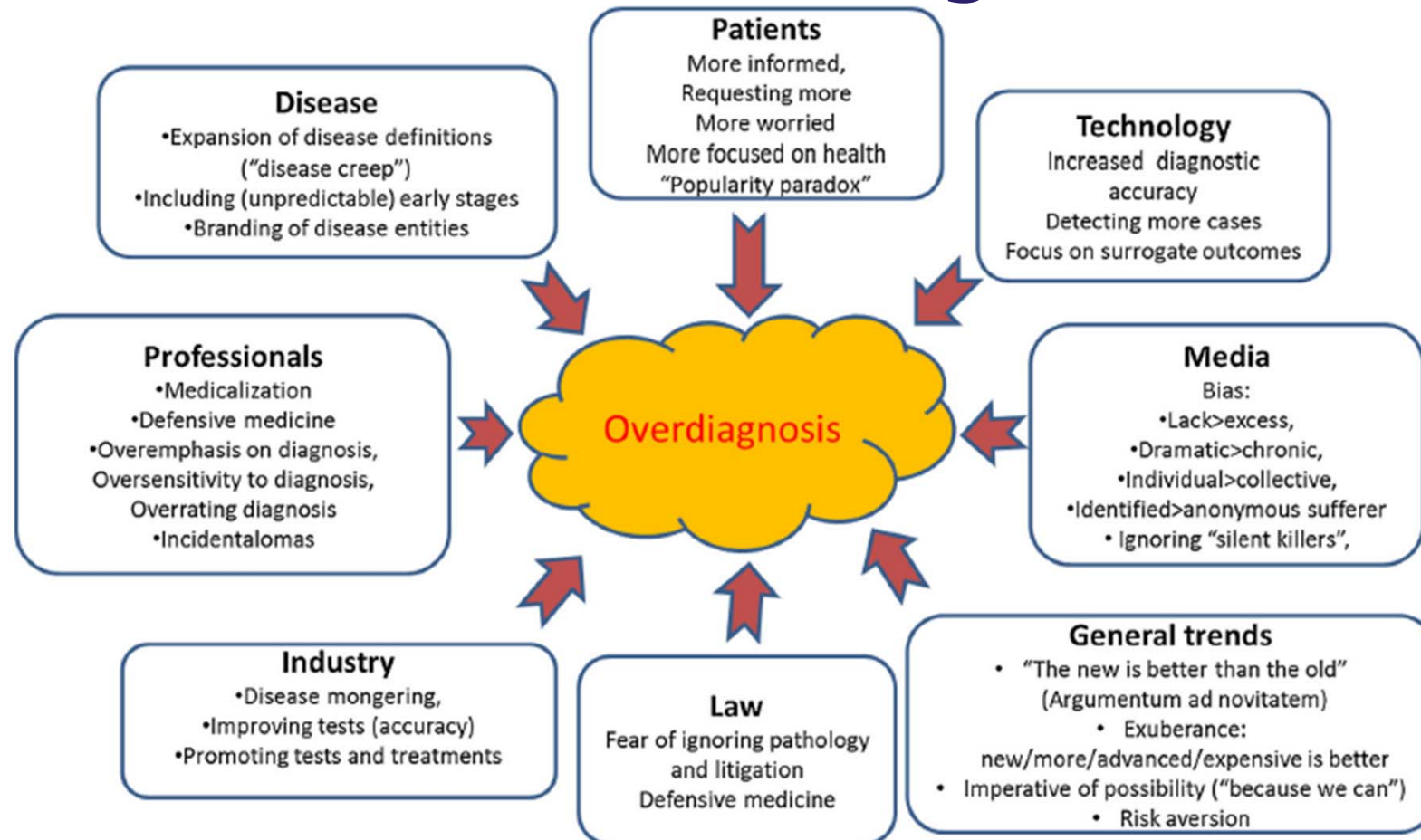


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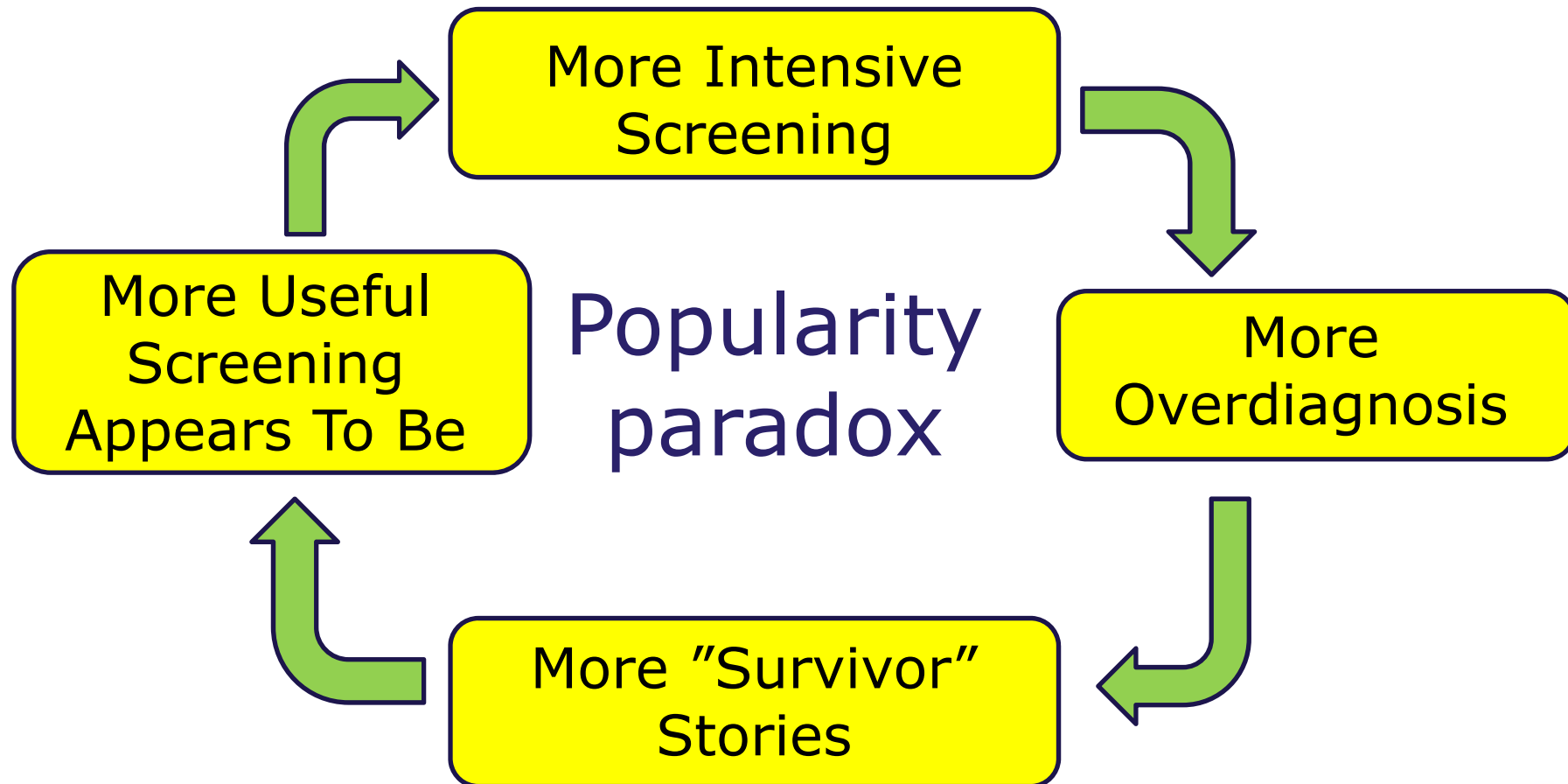
# Drivers of Overdiagnosis



B. Hofmann. Diagnosing overdiagnosis: conceptual challenges and suggested solutions. *Eur.J Epidemiol.* 29 (9):599-604, 2014.



# Survivors stories drive screening towards more overdiagnosis





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## BARCELONA 2016 – 20th to 22nd September 2016

Following successful conferences in Dartmouth in 2013, the University of Oxford in 2014 and the NIH in 2015, we are pleased to announce the dates for the 2016 international Preventing Overdiagnosis conference, to be held in Barcelona. Please let your colleagues and networks know about the announcement of these dates, and that abstract submission and registration will be open soon. Innovations to ... [Read More....](#)

September 2017: Quebec, Montreal

September 2018: Denmark, Copenhagen?

