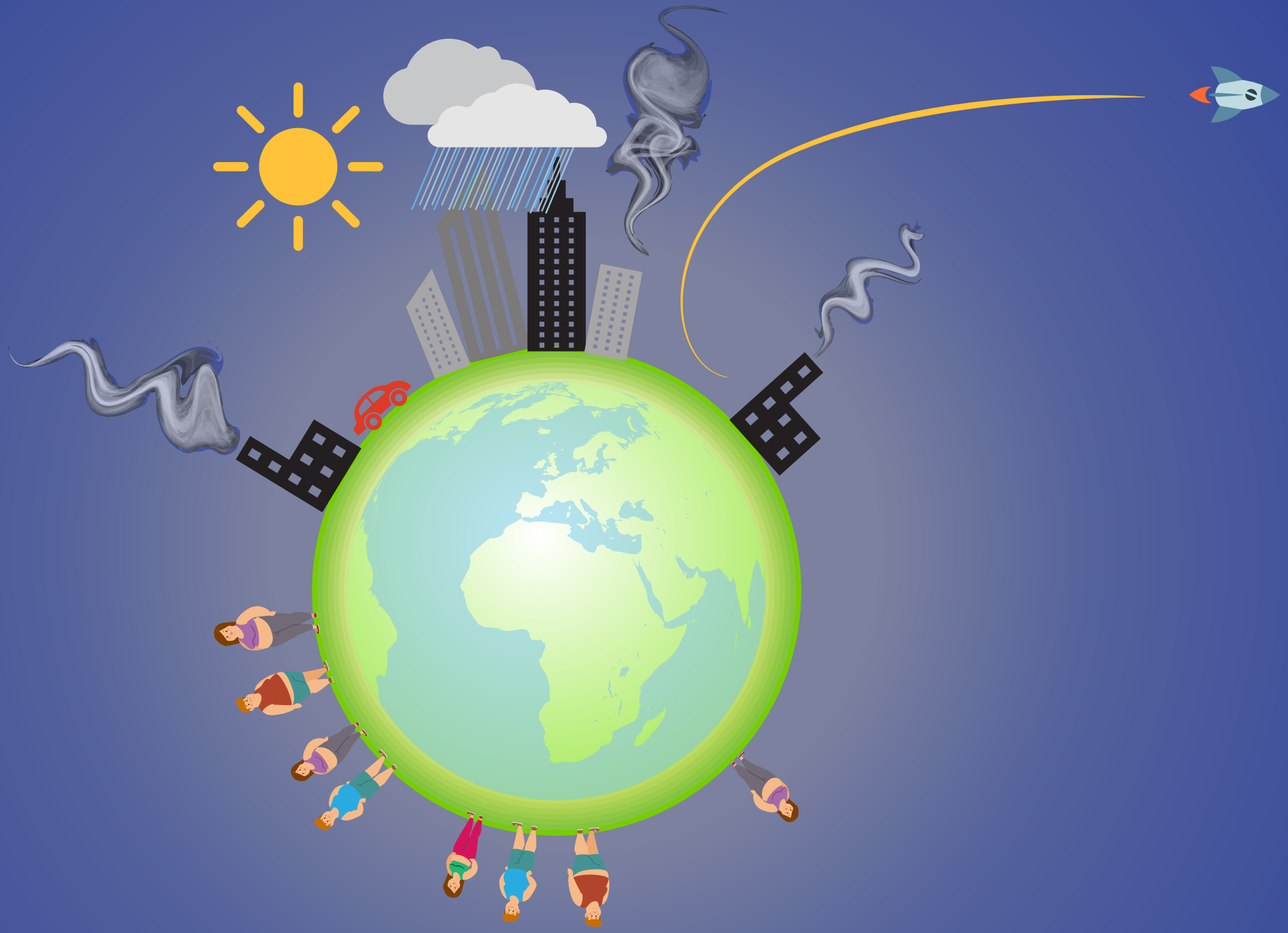
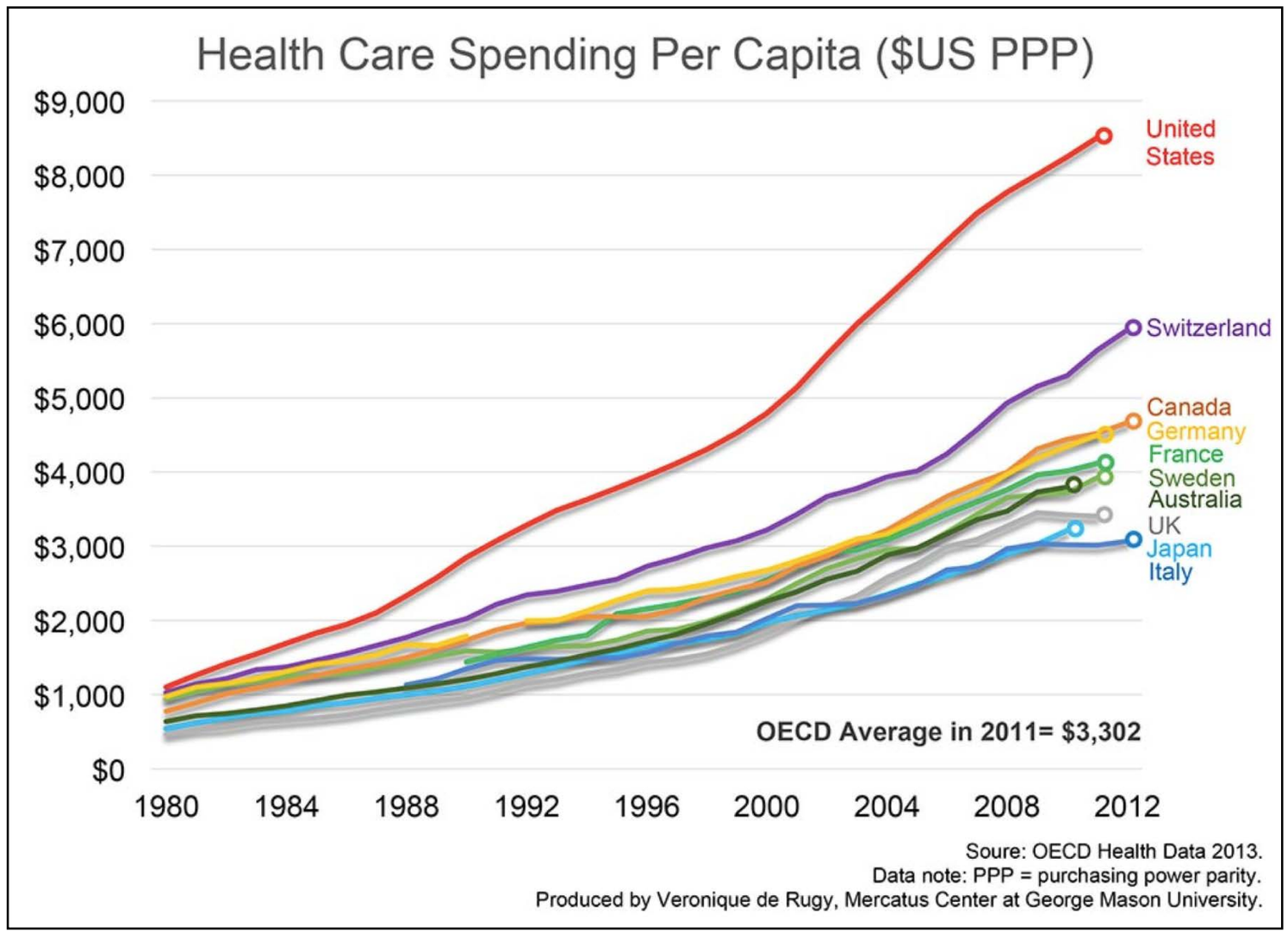
Screening Tests

Martina Steurer, MD MAS
Thomas Newman, MD MPH

October 13, 2016




Health Care Spending Per Capita ($US PPP)
$9,000
$8,000
$7,000
$6,000
$5,000
$4,000
$3,000
$2,000
$1,000
$0
1980
1984
1988
1992
1996
2000
2004
2008
2012
United States
Switzerland
Canada
Germany
France
Sweden
Australia
UK
Japan
Italy
OECD Average in 2011= $3,302
Soure: OECD Health Data 2013.
Data note: PPP = purchasing power parity.
Produced by Veronique de Rugy, Mercatus Center at George Mason University.

Definition of screening

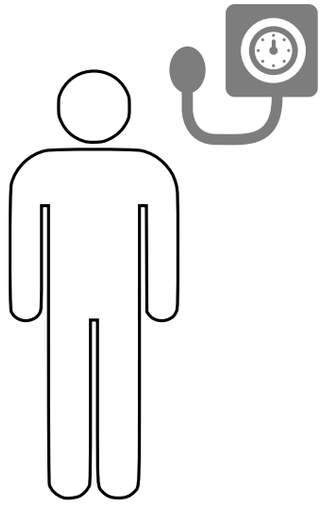
Common definition: testing to detect asymptomatic disease

Better definition*: application of a test to detect a potential disease or condition in people with no known signs or symptoms of that disease or condition.

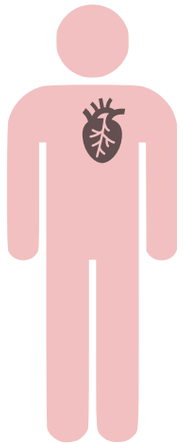
- Disease vs. condition
- Asymptomatic vs. no known signs or symptoms

**Common screening tests*. David M. Eddy, editor. Philadelphia, PA: American College of Physicians, 1991

Spectrum of screening



risk factor



presymptomatic disease

unrecognized symptomatic disease

recognized symptomatic disease

more people recognized and treated
harder to demonstrate benefit
more potential for harm

fewer labeled and treated
easier to demonstrate benefit
less potential for harm

hypercholesterolemia

neonatal hypothyroidism

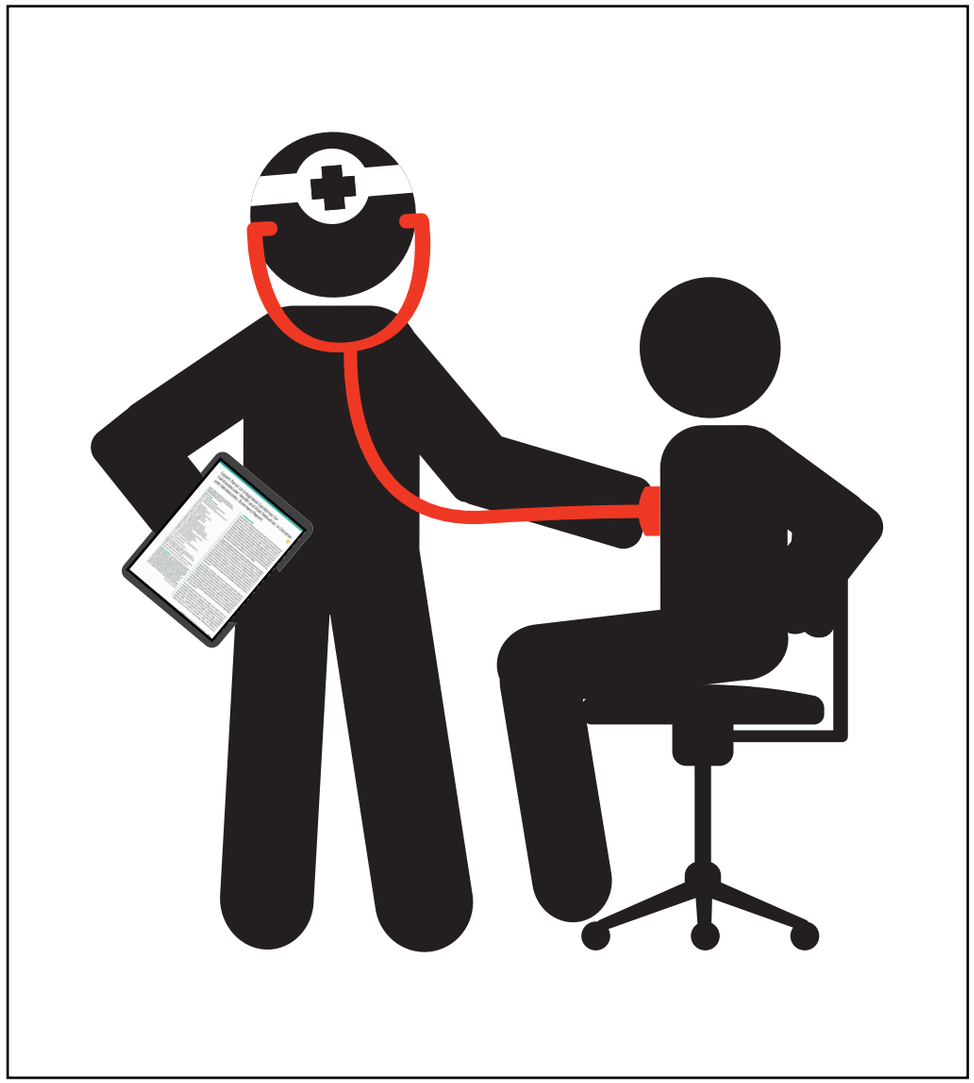
HIV

prostate cancer

iron deficiency anemia

vision and hearing problems in young children

Harm from screening?



Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: Summary Report

EXPERT PANEL ON INTEGRATED GUIDELINES FOR CARDIOVASCULAR HEALTH AND RISK REDUCTION IN CHILDREN AND ADOLESCENTS

ABBREVIATIONS

CVD—cardiovascular disease
NHLBI—National Heart, Lung, and Blood Institute
RCT—randomized controlled trial
PDAY—Pathobiological Determinants of Atherosclerosis in Youth
BP—blood pressure
HDL—high-density lipoprotein
DM—diabetes mellitus
CIMT—carotid intima-media thickness
LDL—low-density lipoprotein
T1DM—type 1 diabetes mellitus
T2DM—type 2 diabetes mellitus
TC—total cholesterol
AAP—American Academy of Pediatrics
DGA—*Dietary Guidelines for Americans*
NCEP—National Cholesterol Education Program
DASH—Dietary Approaches to Stop Hypertension
CHILD—Cardiovascular Health Integrated Lifestyle Die
FLP—fasting lipid profile
CDC—Centers for Disease Control and Prevention
AMA—American Medical Association
MCHB—Maternal and Child Health Bureau
FDA—Food and Drug Administration
AHA—American Heart Association

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FINANCIAL DISCLOSURE: Dr Daniels has served as a consultant for Abbott Laboratories, Merck, and Schering-Plough and has received funding/grant support for research from the National Institutes of Health (NIH); Dr Gidding has served as a consultant for Merck and Schering-Plough and has received funding/grant support for research from GlaxoSmithKline; Dr Gillman has given invited talks for Nestle Nutrition Institute and Danone and has received funding/grant support for research from Mead Johnson, Sanofi-Aventis, and the NIH; Dr Gottesman has served on the Health Advisory Board, Child Development Council of Franklin County, was a consultant to Early Head Start for Region 5B, has written for iVillage and taught classes through Garrison

(Continued on last page)

1. INTRODUCTION

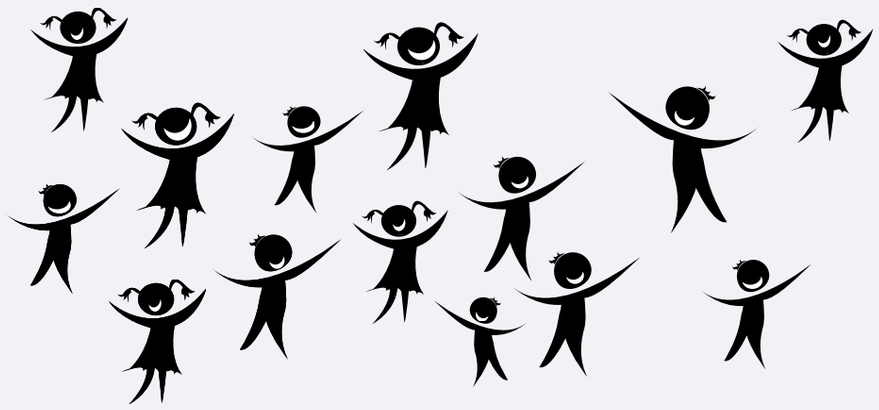
Atherosclerotic cardiovascular disease (CVD) remains the leading cause of death in North Americans, but manifest disease in childhood and adolescence is rare. By contrast, risk factors and risk behaviors that accelerate the development of atherosclerosis begin in childhood, and there is increasing evidence that risk reduction delays progression toward clinical disease. In response, the former director of the National Heart, Lung, and Blood Institute (NHLBI), Dr Elizabeth Nabel, initiated development of cardiovascular health guidelines for pediatric care providers based on a formal evidence review of the science with an integrated format addressing all the major cardiovascular risk factors simultaneously. An expert panel was appointed to develop the guidelines in the fall of 2006.

The goal of the expert panel was to develop comprehensive evidence-based guidelines that address the known risk factors for CVD (Table 1-1) to assist all primary pediatric care providers in both the promotion of cardiovascular health and the identification and management of specific risk factors from infancy into young adult life. An innovative approach was needed, because a focus on cardiovascular risk reduction in children and adolescents addresses a disease process (atherosclerosis) in which the clinical end point of manifest CVD is remote. The recommendations, therefore, need to address 2 different goals: the prevention of future CVD by effective management of identified risk factors (primary prevention).

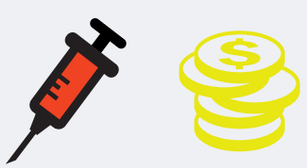
The evidence review also required an innovative approach. Most systematic evidence reviews include 1 or, at most, a small number of finite questions that address the impact of specific interventions on specific health outcomes, and a rigorous literature review often results in only a handful of in-scope articles for inclusion. Typically, evidence is limited to randomized controlled trials (RCTs), systematic reviews, and meta-analyses published over a defined time period. There is a defined format for abstracting studies, grading the evidence, and presenting of results. The results of the review lead to the conclusions, independent of interpretation.

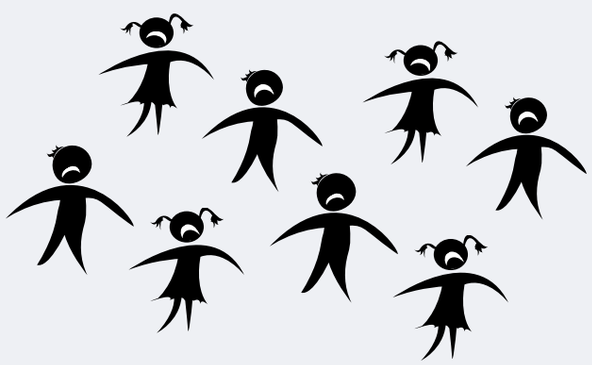
By contrast, given the scope of the charge to the expert panel, this evidence review needed to address a broad array of questions concerning the development, progression, and management of multiple risk factors extending from birth through 21 years of age, including studies with follow-up into later adult life. The time frame extended back to 1985, ~5 years before the review for the last NHLBI guideline addressing lipids in children published in 1992.[1] This evidence is largely available in the form of epidemiologic observational studies

Harm from screening:
Lipid screening in childhood



harm to those not tested ?





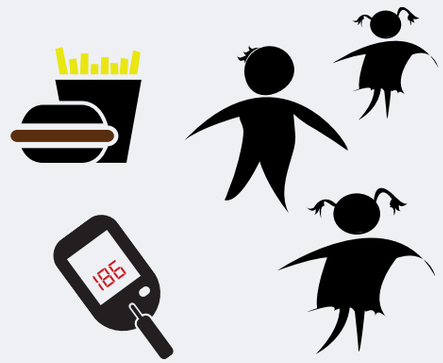
harm to all tested

cost

discomfort/pain

+ result

- result

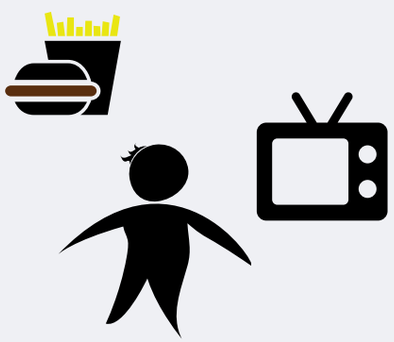


harm to those with positive results

follow up testing

harmful treatment

unnecessary treatment



harm to those with negative results

inappropriate reassurance leading to delay in diagnosis or unhealthy decisions

Harm from screening

Editorial | October 2016

LESS IS MORE

Lipid Screening in Children
Low-Value Care

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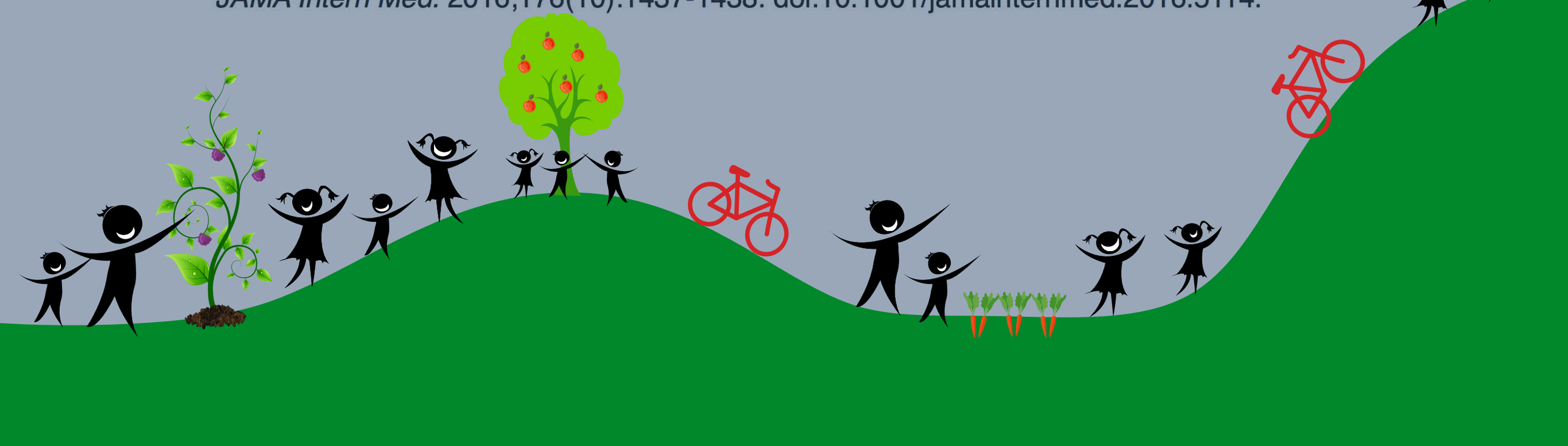
JAMA Intern Med. 2016;176(10):1437-1438. doi:10.1001/jamainternmed.2016.5114.



Excessive screening?

Nearly every body part susceptible to cancer now has an advocacy group, politician or athlete with a public awareness campaign to promote routine screening tests — even though it is well established that many of these exams offer little benefit for the general public.

The New York Times
FORTY YEARS' WAR; In Push for Cancer Screening, Limited Benefits
By NATASHA SINGER
Published: July 17, 2009

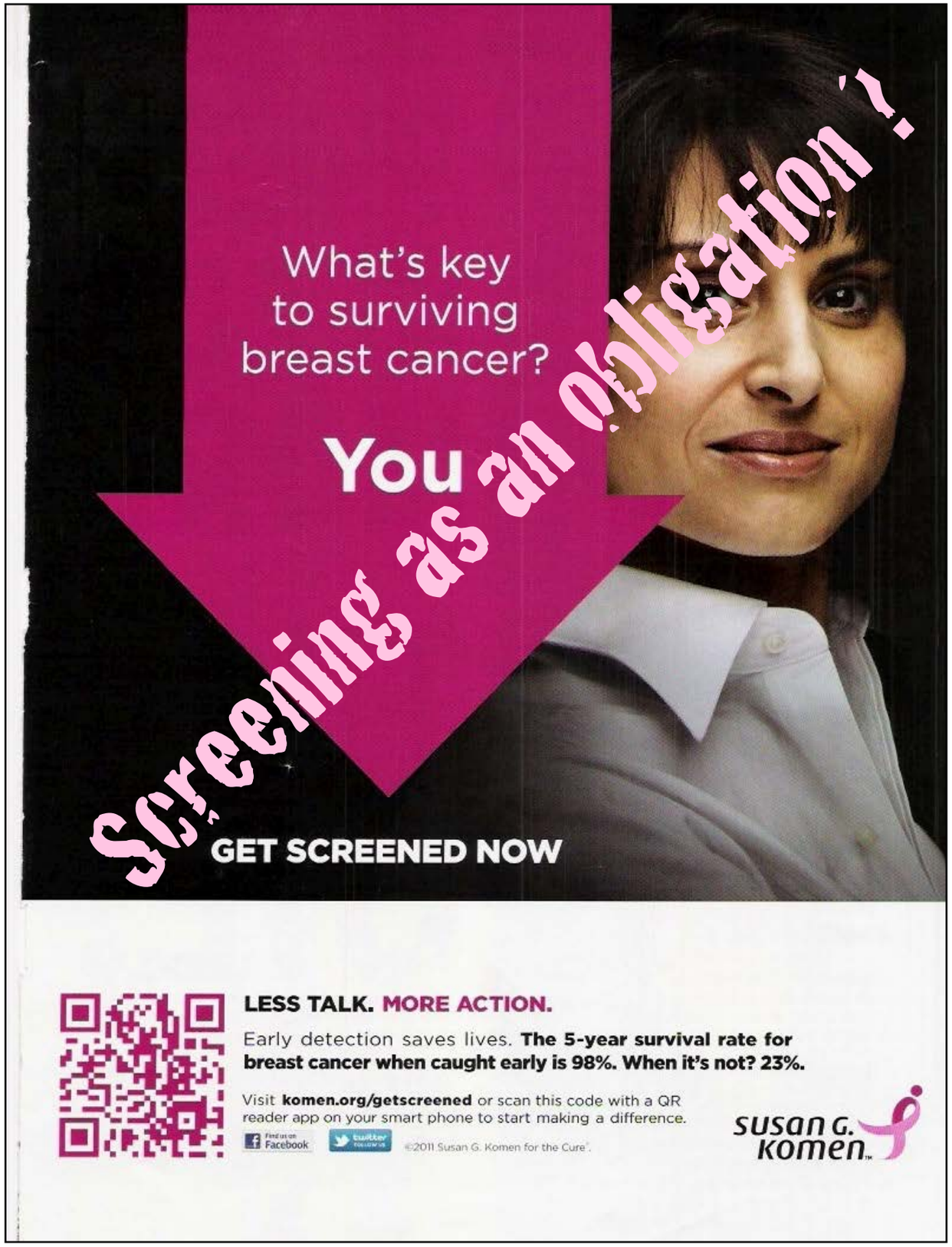
Forces behind excessive screening

- ✦ Companies selling instruments to do the test
- ✦ Companies selling the test itself
- ✦ Companies selling products to treat the condition
- ✦ Clinicians who treat the condition
- ✦ Politicians who are (or want to appear) sympathetic
- ✦ Disease research and advocacy groups
- ✦ Academics who study the condition
- ✦ Clinicians doing or interpreting the test
- ✦ Managed care organizations
- ✦ The public


LA ROCHE-POSAY
LABORATOIRE DERMATOLOGIQUE
IF YOU CARE FOR SOMEBODY,
CHECK THEIR BEAUTY SPOTS.


Remember to ask your doctor to check your neck for thyroid cancer.
Light of Life Foundation
checkyourneck.com


Concerned about lung cancer?
Lung cancer is by far the leading cause of cancer death among both men and women, and nearly half of all cases are in the most advanced stage at diagnosis. Fortunately, Carolinas Imaging Services now offers a lung cancer screening that can detect cancer before it becomes symptomatic. The National Comprehensive Cancer Network recommends the screening for individuals 55+ with a history of heavy smoking (at least 30 pack-years), and individuals 50+ with a 20-pack-year history coupled with another risk factor, such as asbestos exposure. The cost is only $250—well worth the peace of mind that comes with finally having answers.
Schedule your lung cancer screening today at 704.442.4390.
Carolinas Imaging Services


What's key
to surviving
breast cancer?
You
Screening as an obligation ?
GET SCREENED NOW
LESS TALK. MORE ACTION.
Early detection saves lives. The 5-year survival rate for breast cancer when caught early is 98%. When it's not? 23%.
Visit komen.org/getscreened or scan this code with a QR reader app on your smart phone to start making a difference.
Find us on Facebook
twitter
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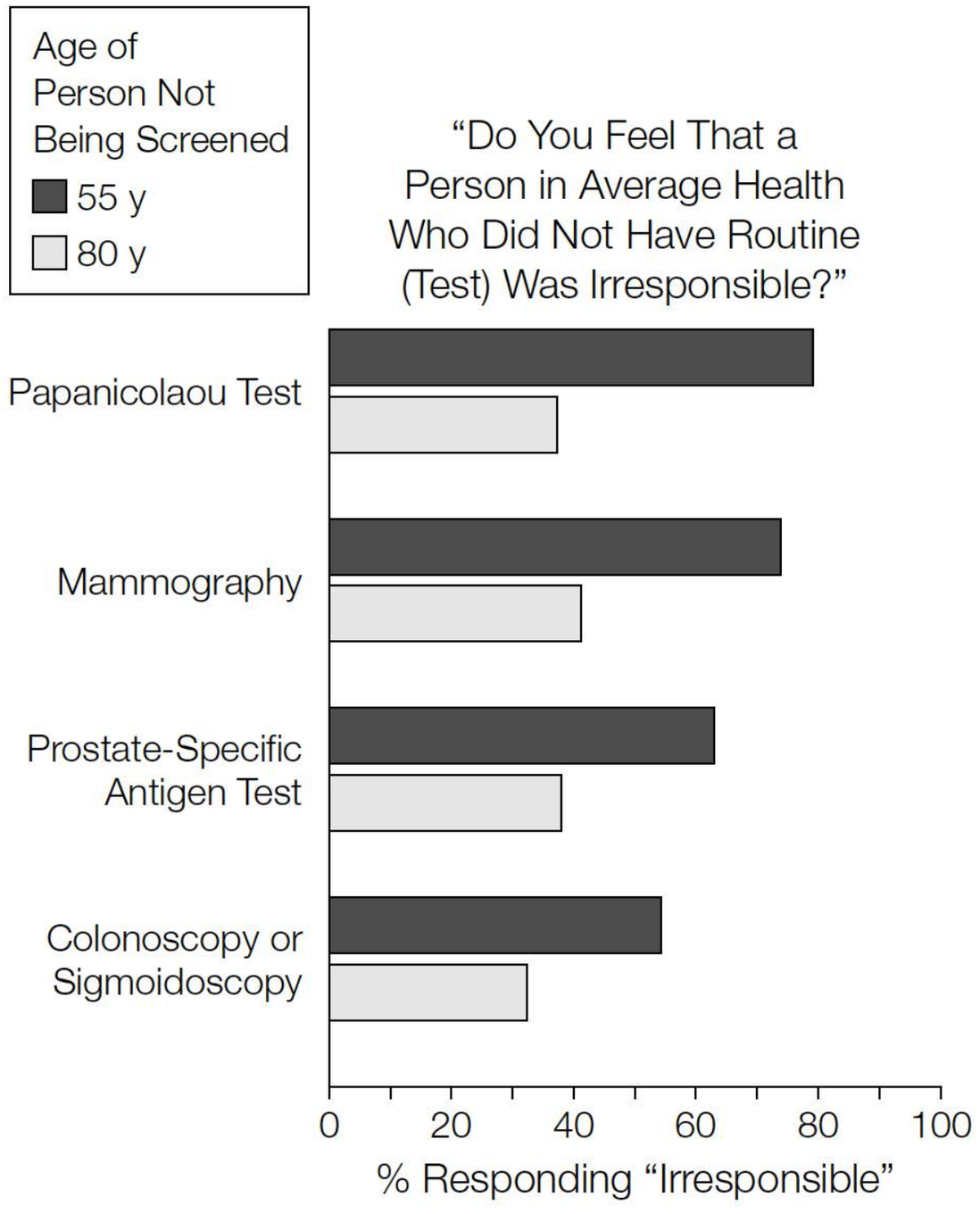
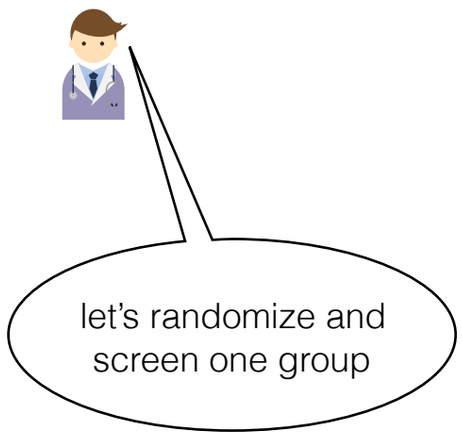
Screening as an obligation ?

Enthusiasm for Cancer Screening in the US, Schwartz LM et al, JAMA 2004

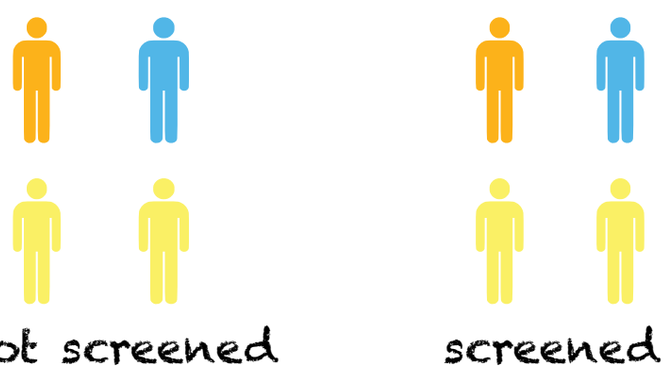


Evaluating studies of screening

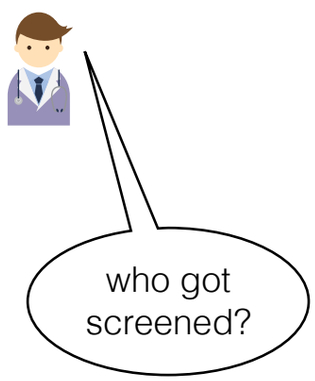
Ideal study

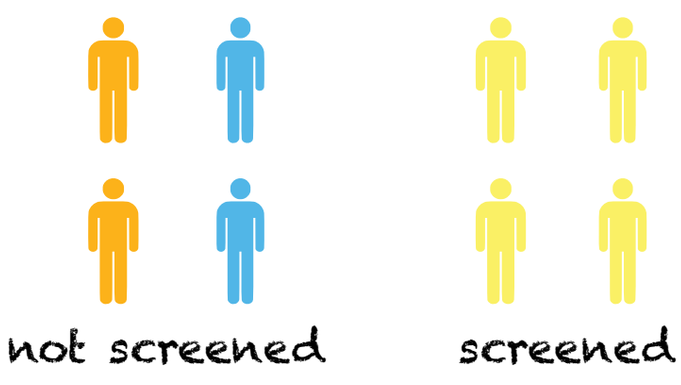


randomization guarantees that groups are exchangeable



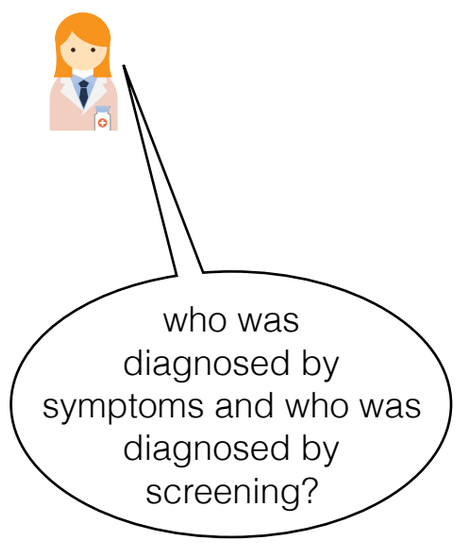
compare mortality of ENTIRE screened group and ENTIRE NOT screened group

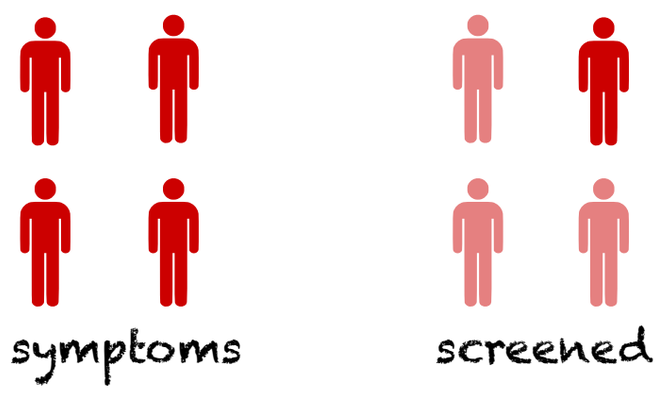




compare mortality between those screened and those not screened

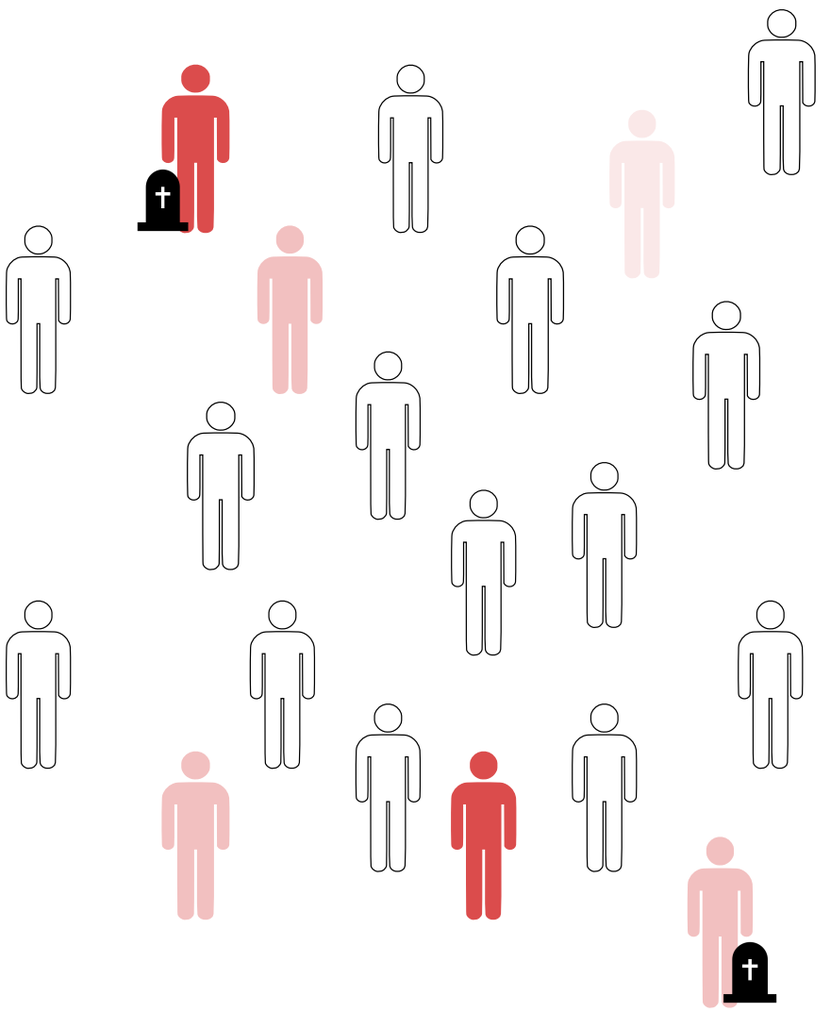
Observational study





compare mortality between those diagnosed by screening and those diagnosed by symptoms

Mortality versus Survival

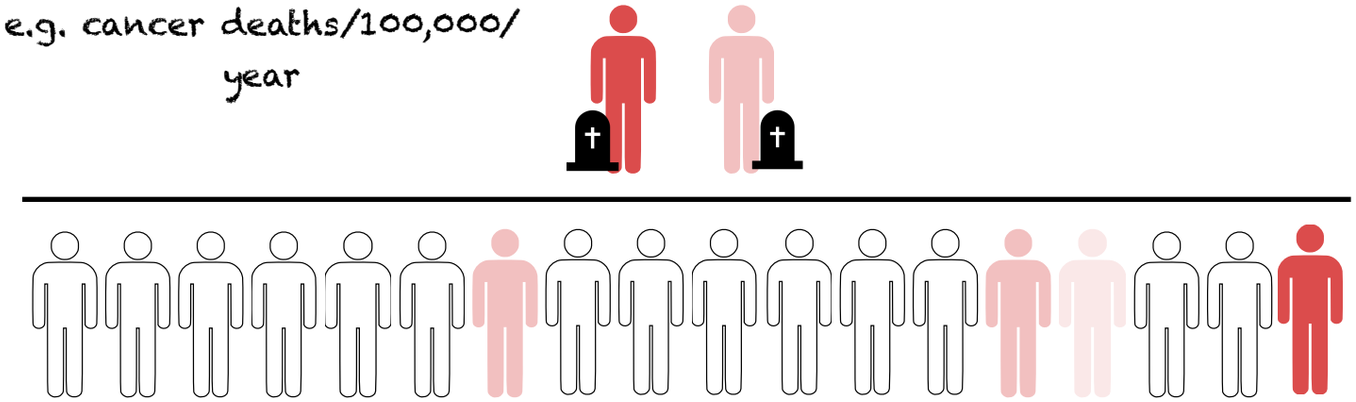


Population

Denominator is a POPULATION, most of whom never get the disease

e.g. cancer deaths/100,000/ year

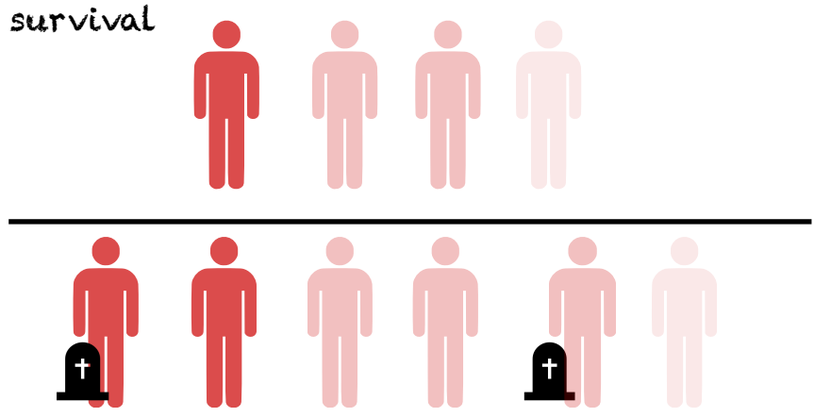
Mortality



Denominator is patients with the disease

e.g. 66% 5 year survival

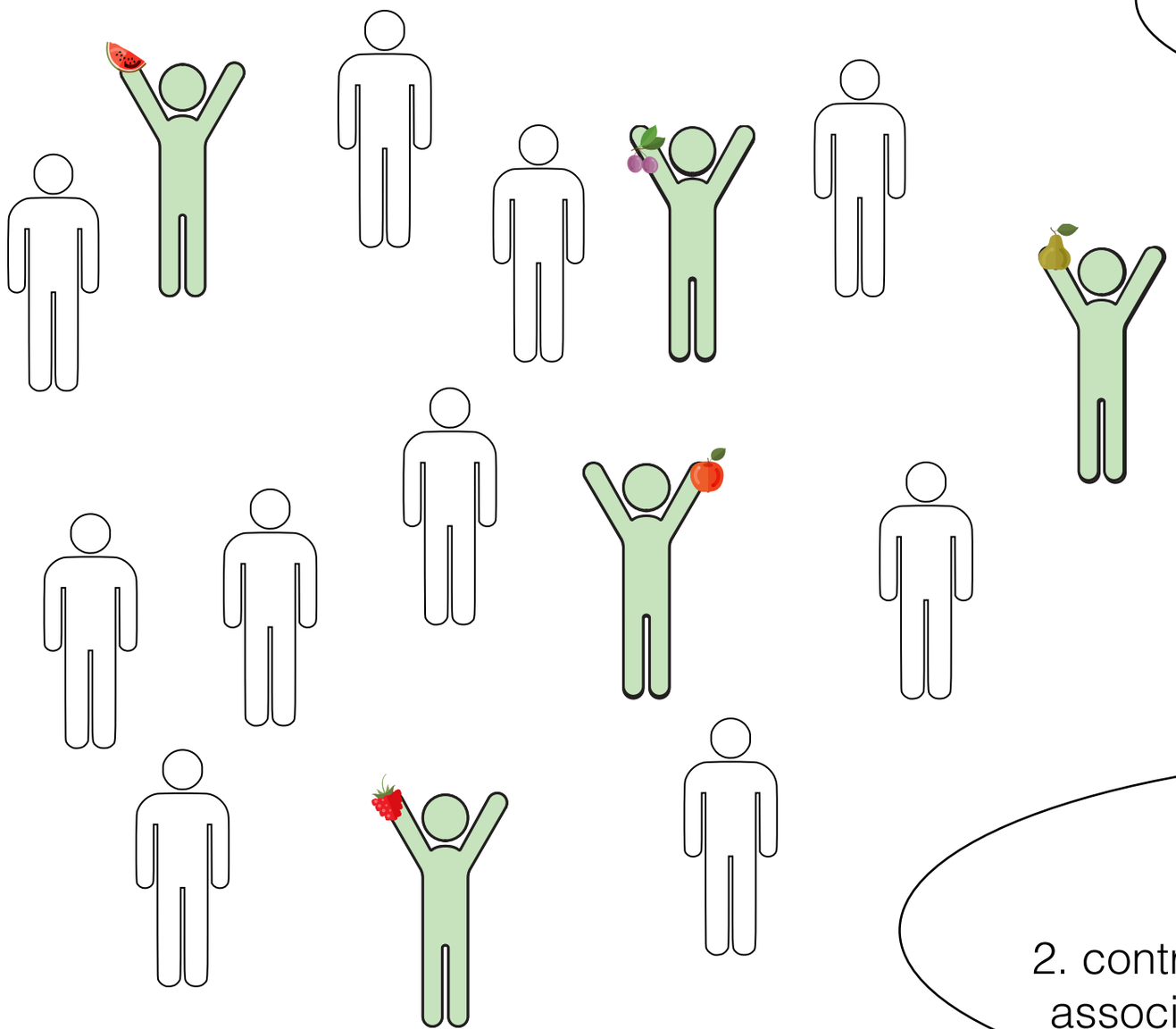
Survival



Possible Biases in Observational Studies of Screening Test

- ✦ Volunteer bias
- ✦ Lead time bias
- ✦ Length time bias
- ✦ Stage migration bias
- ✦ Pseudodisease

Volunteer Bias



who volunteers to get a mammogram

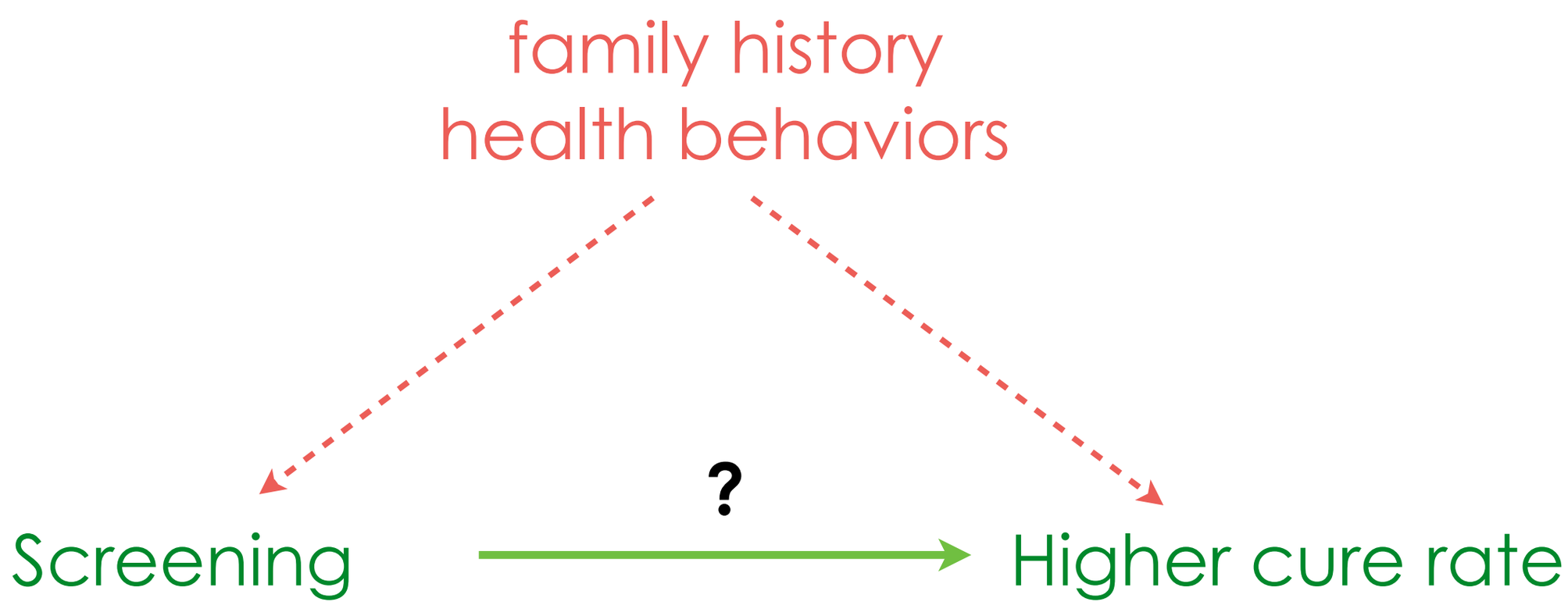
people who volunteer might be more educated, more interested, healthier, etc., this group is not representative of the population

e.g. woman who volunteer for mammograms have lower heart disease rates

avoid volunteer bias:
1. randomize or
2. control for known factors (confounders) associated with screening and outcome

people who volunteer for screening differ from those who do not

Volunteer Bias



Volunteer Bias

Observational study

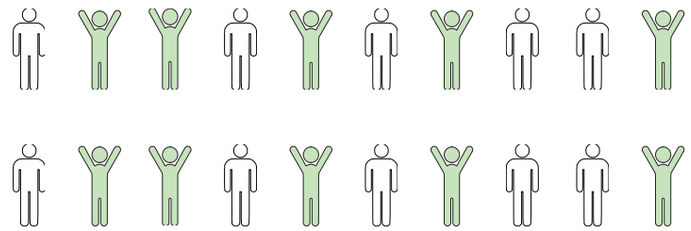
who volunteers to get a mammogram

people who volunteer are different from people who do not
VOLUNTEER BIAS

sometimes also referred to as volunteer bias

lack of generalizability of internally valid results to other population

RCT

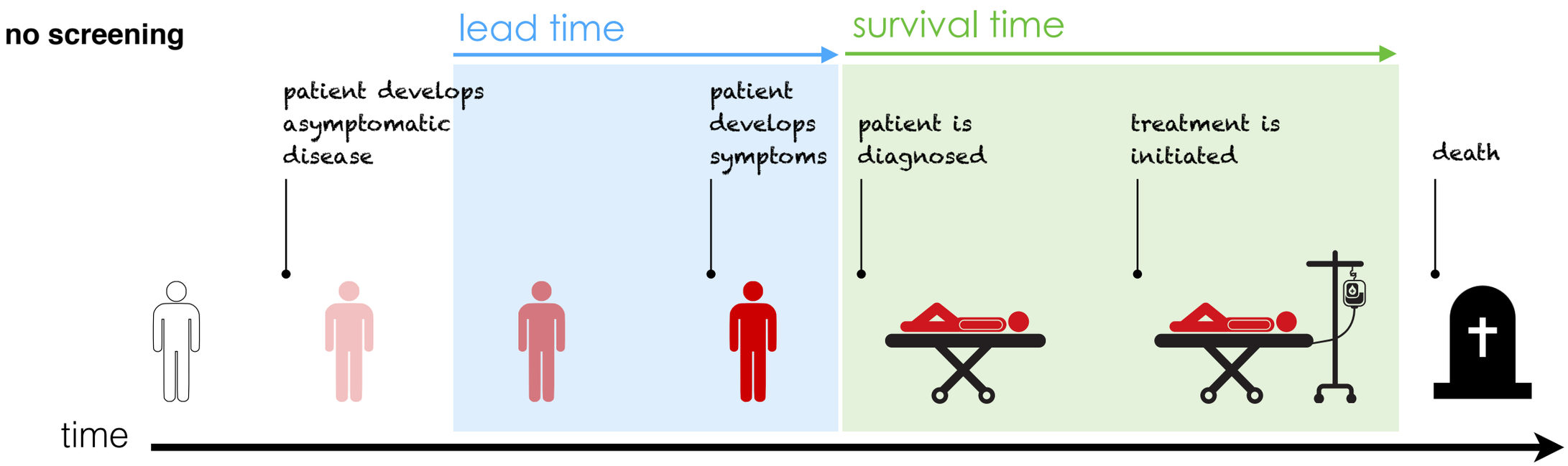


who volunteers to be in this RCT

result internally valid

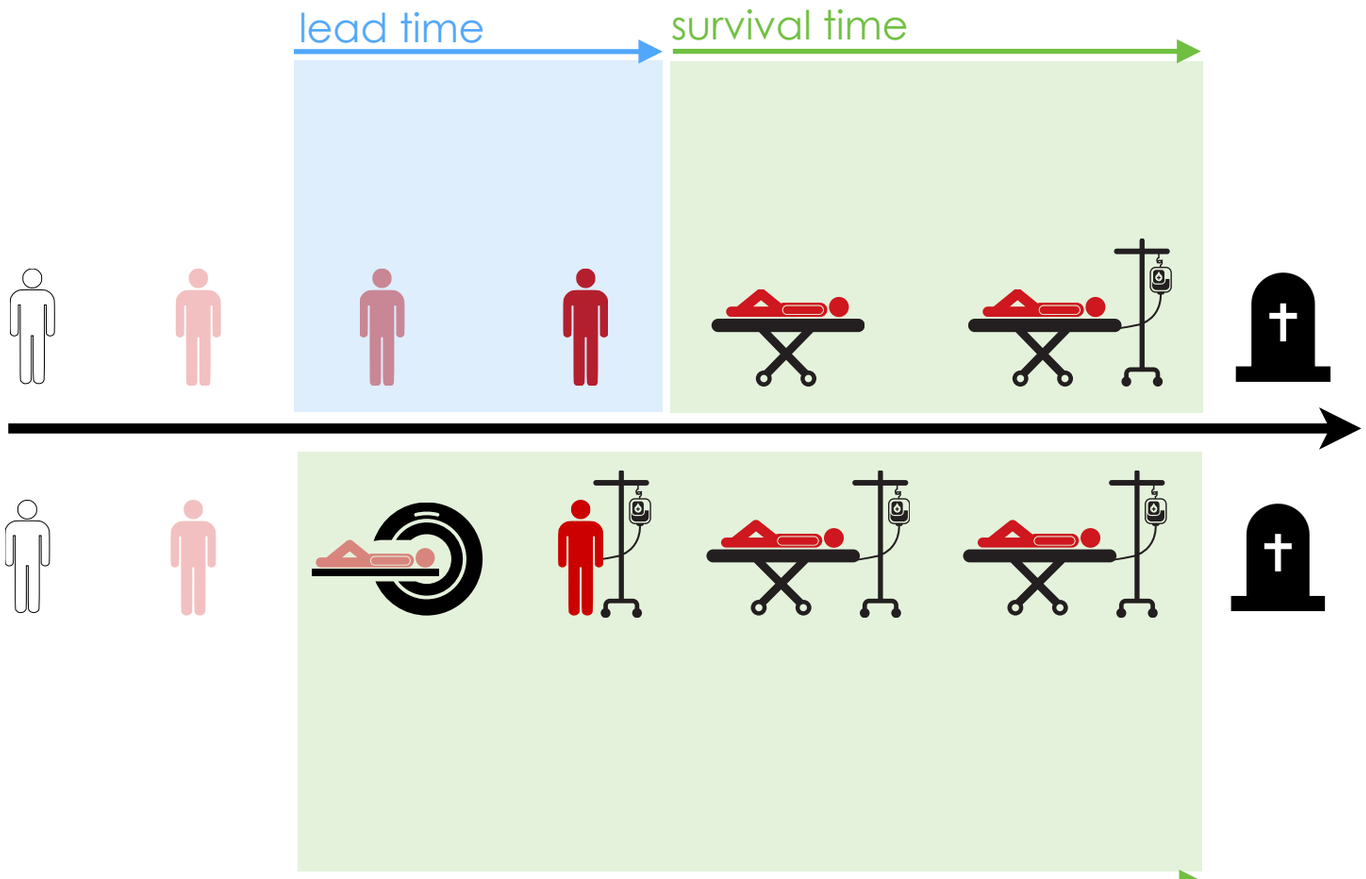
randomization

Lead Time Bias



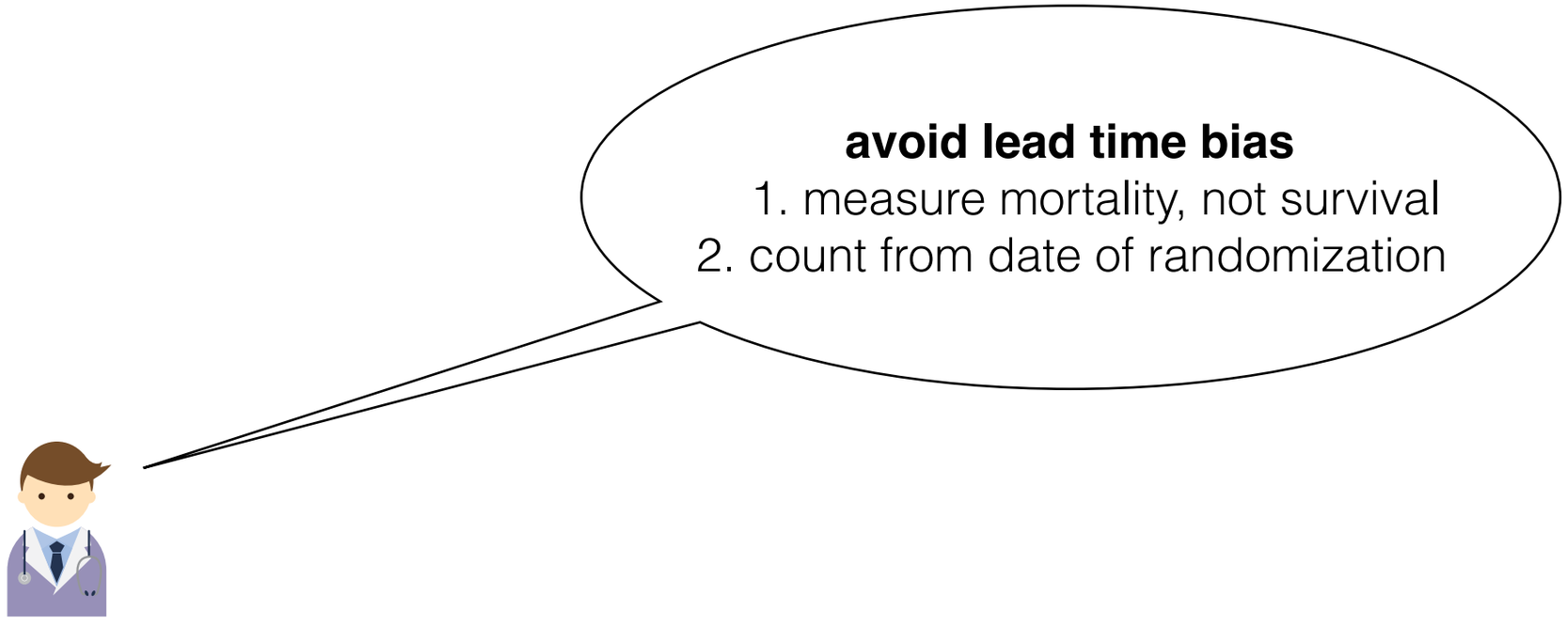
Screening identifies disease during a latent period before it becomes symptomatic. If survival is measured from time of diagnosis, screening will always improve survival even if there is no benefit of early diagnosis

Lead Time Bias

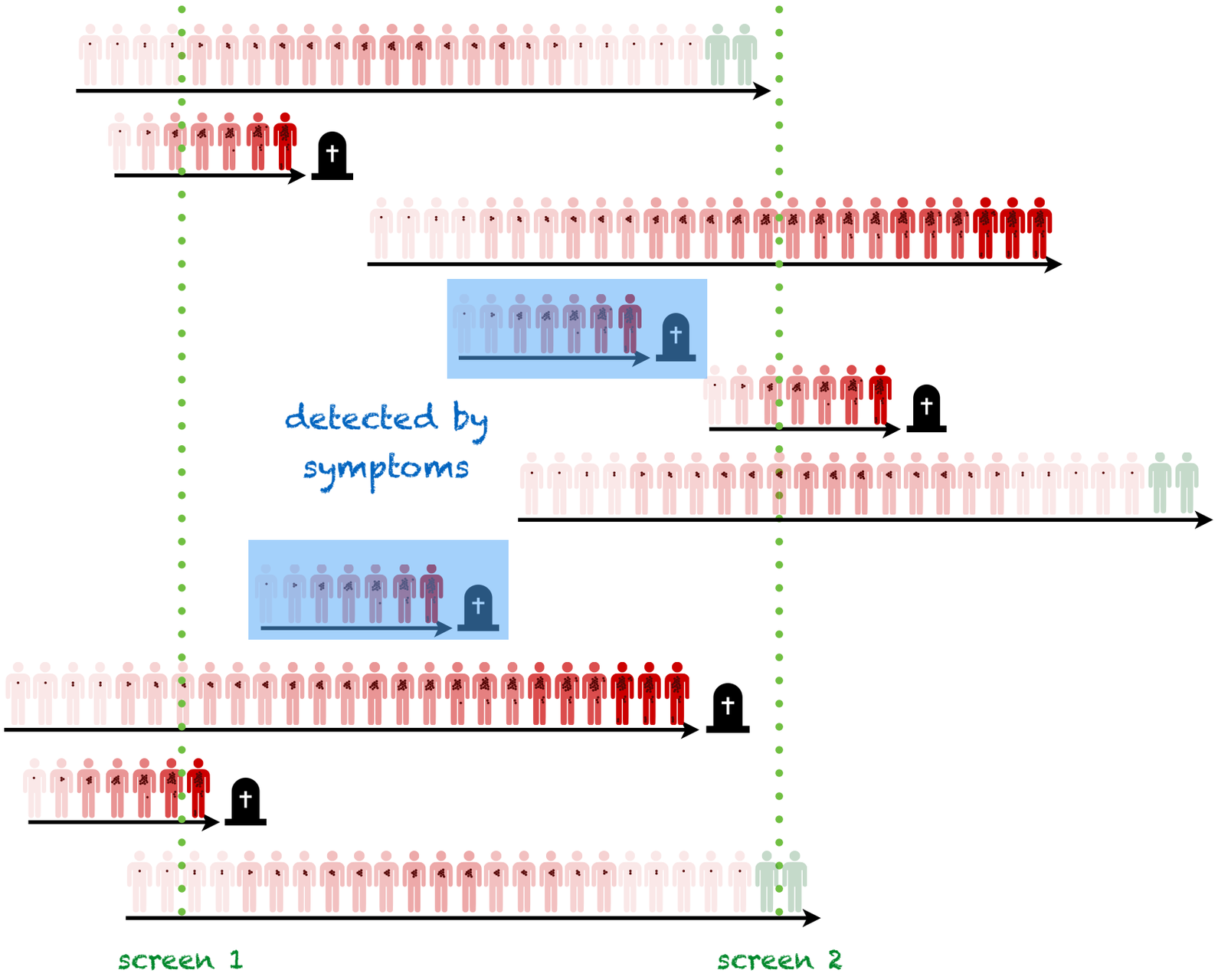


Lead time bias is only present when survival from diagnosis compared between diseased persons

- screened vs. not screened
- diagnosed by screening vs. by symptoms
- diagnosed at different stages



Length Bias



Prevalence = incidence x duration

Slower growing tumors have greater duration in the pre-symptomatic phase, therefore greater prevalence

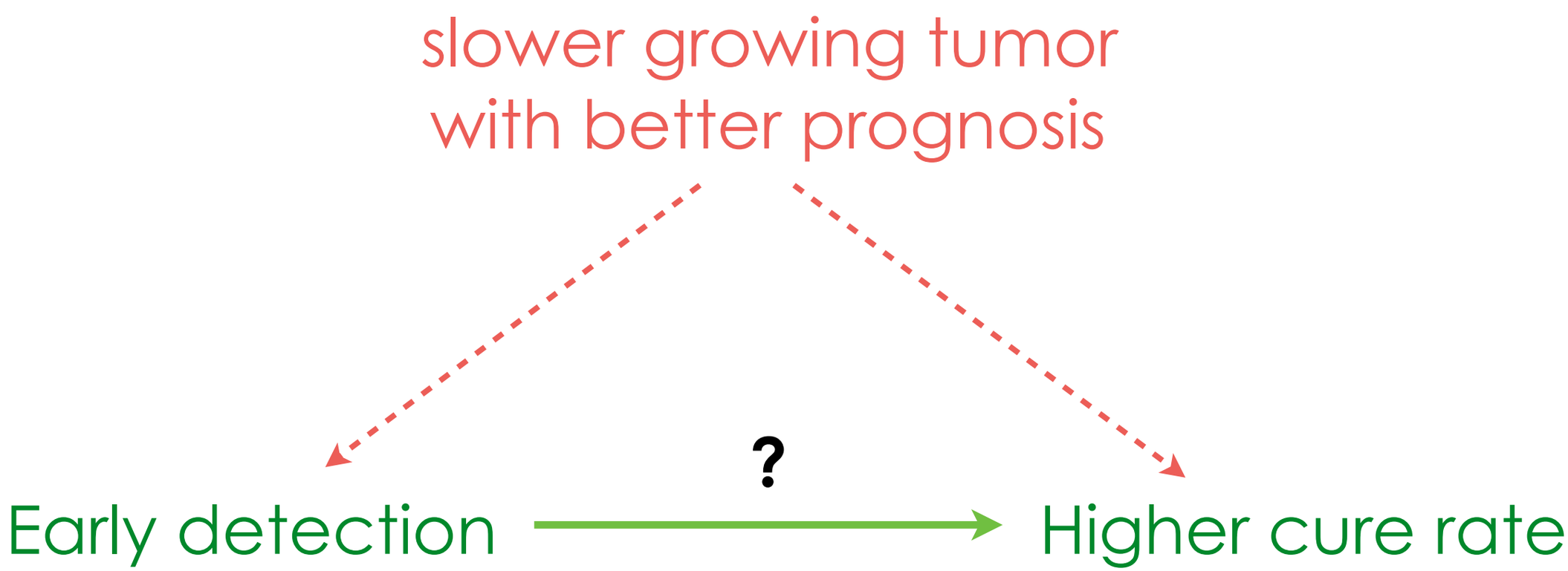
Screening picks up *prevalent* cases, which therefore will be disproportionately slower growing

Screen 1 and screen 2 detect a total of 8 tumors: 5/8 have a good prognosis, 3/8 have a bad prognosis.

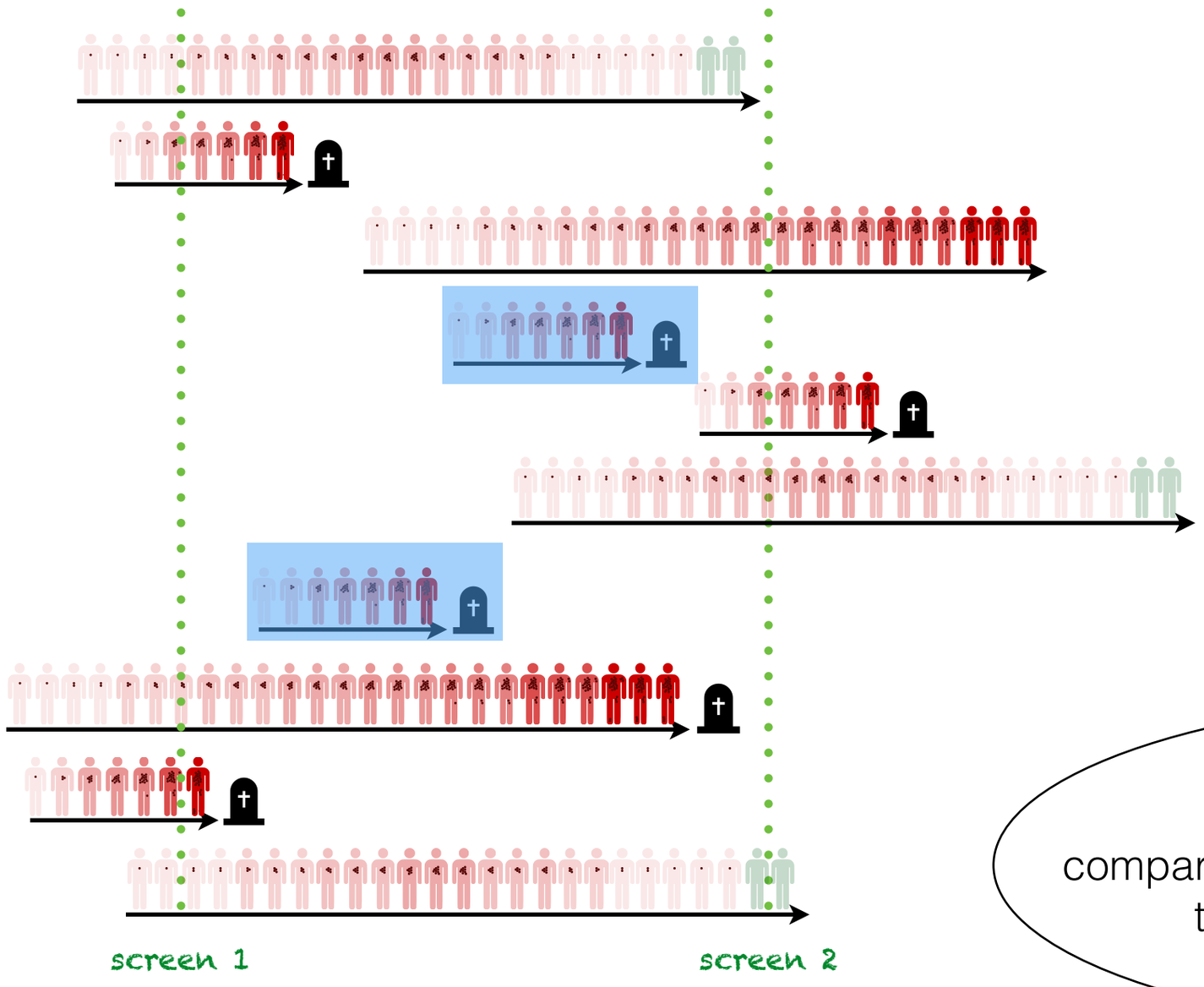
Symptoms lead to detection of 2 tumors - both of them had a bad prognosis.

Screening picks up prevalent disease, benign courses of disease have a greater prevalence

Length Bias


slower growing tumor
with better prognosis
?
Early detection
Higher cure rate

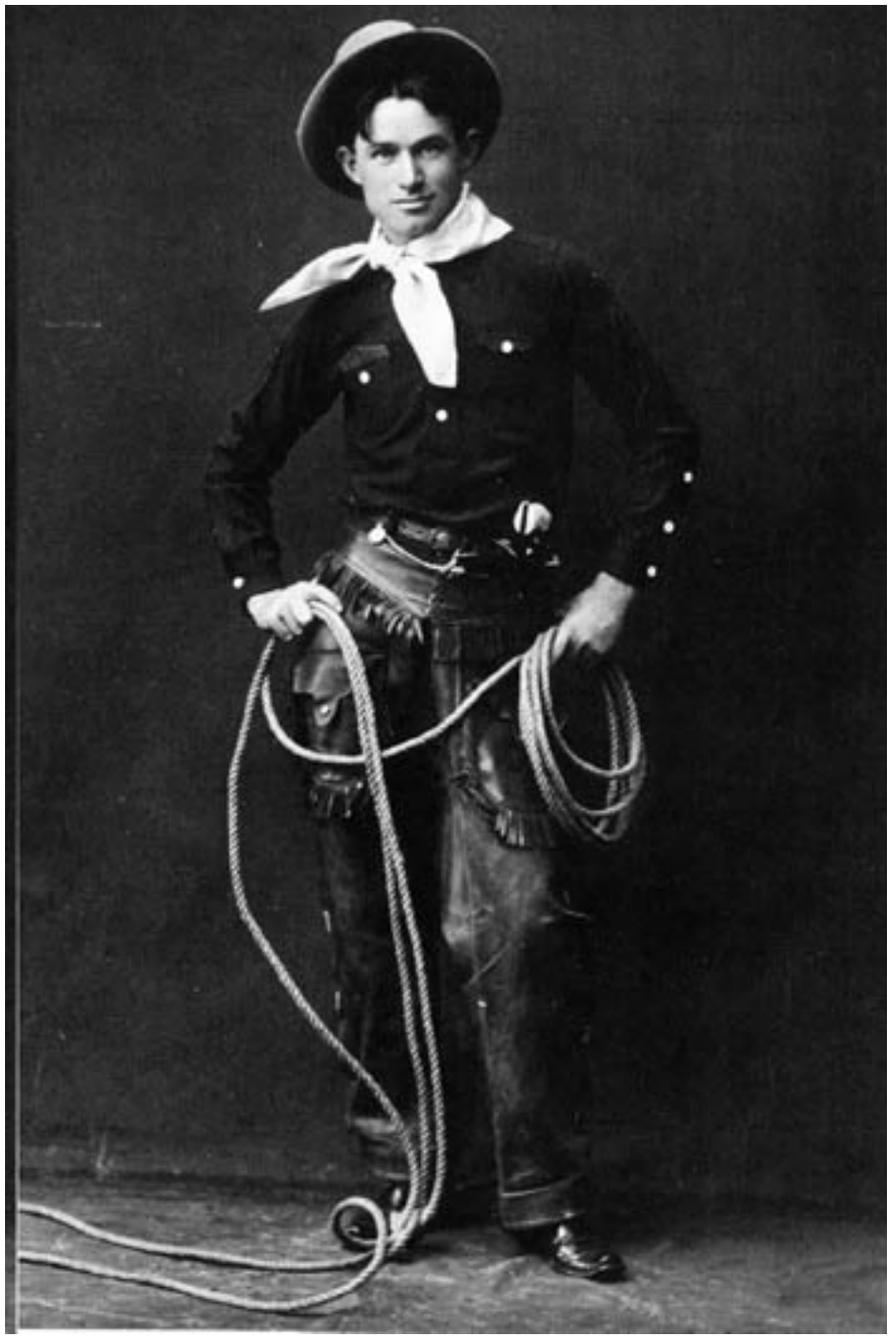
Length Bias



length bias is only present when survival from diagnosis is compared AND disease is heterogeneous

lead time bias usually present as well

avoiding length bias:
compare mortality in the ENTIRE screened group to the ENTIRE unscreened group



“Even if you are on the right track, you will get run over if you just sit there”

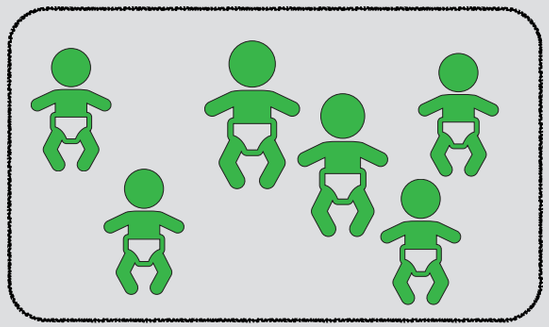
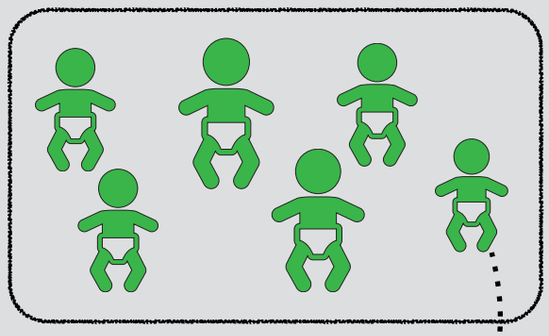
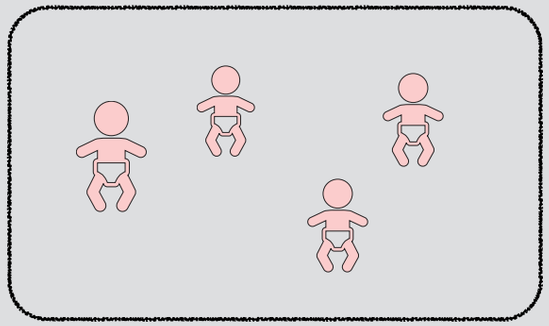
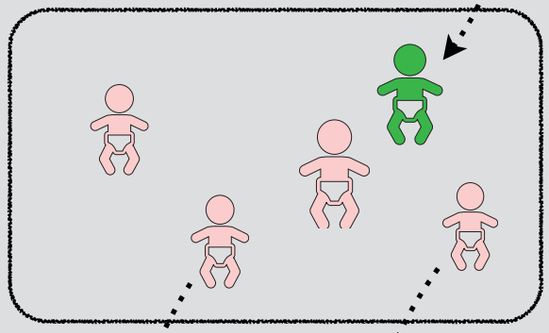
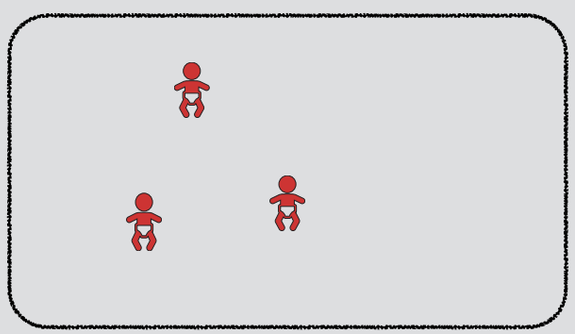
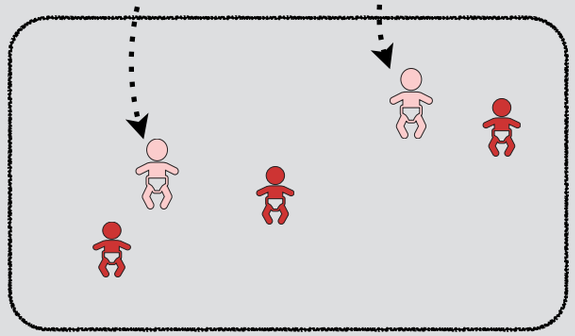
Will Rogers Phenomenon

The Will Rogers phenomenon: Stage migration and new diagnostic techniques as a source of misleading statistics for survival in cancer, Feinstein AR et al, NEJM 1985

When the Okies left Oklahoma and moved to California, they raised the average intelligence level in both states.

- Will Rogers

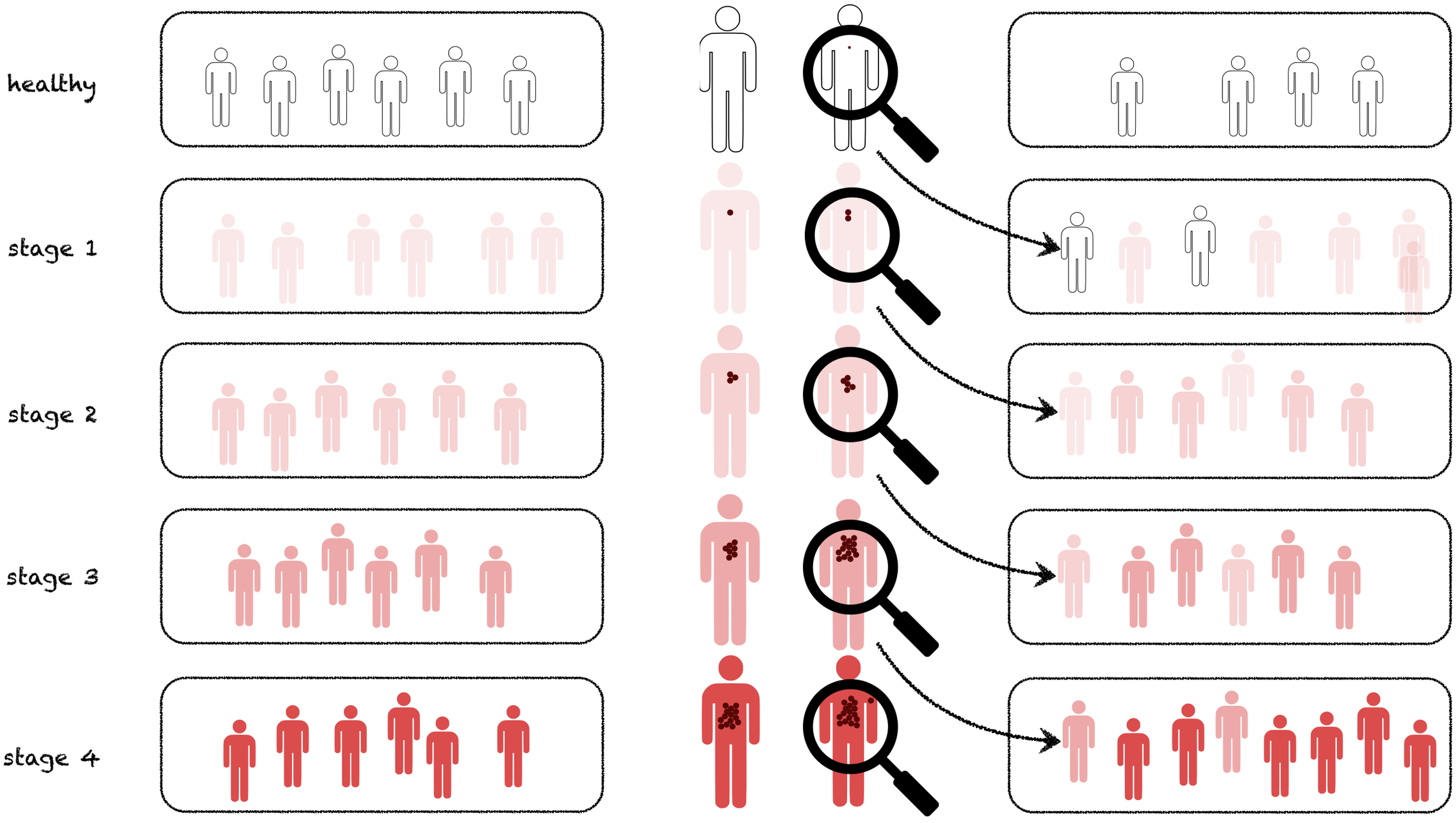
Birth weight strata and Factor X

BW strata	Factor X absent		Factor X present	
Normal birth weight		Mortality 1%		Mortality 0.5%
Low birth weight		Mortality 3%		Mortality 2%
Very low birth weight		Mortality 5%		Mortality 4%

What happened? Is factor X good or bad?

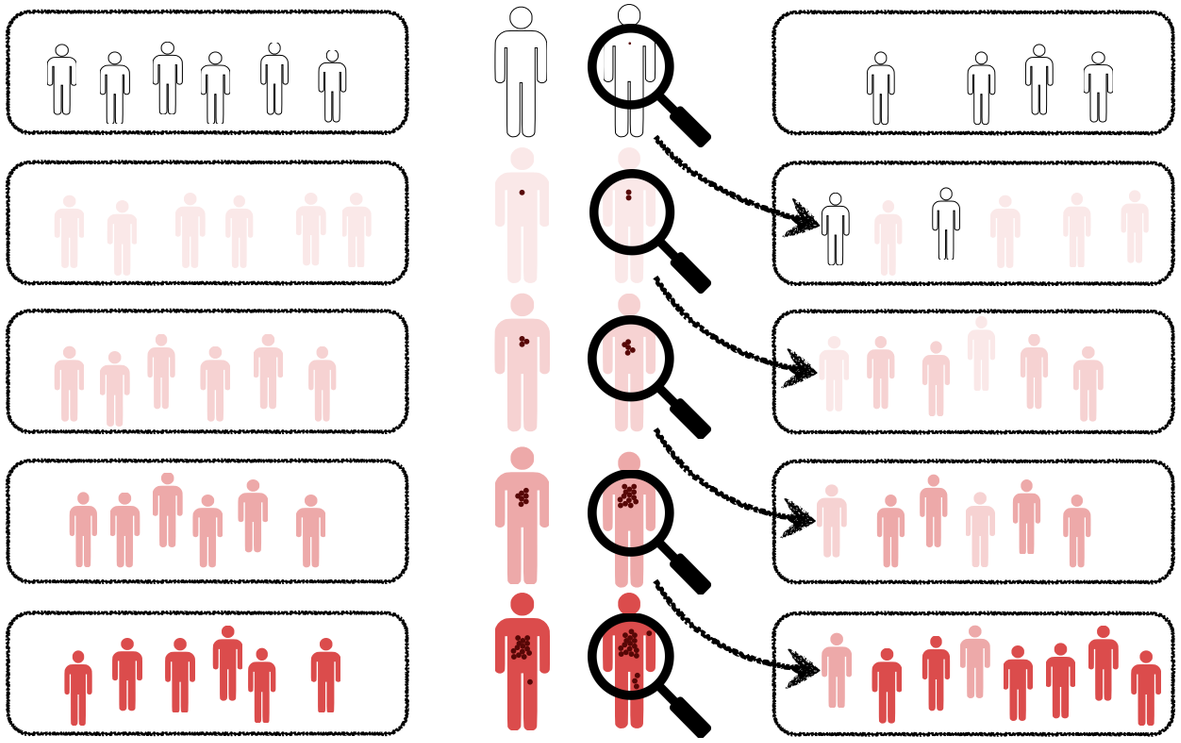
Mortality numbers are mock up numbers

Stage Migration Bias



Newer tests classify people into more advanced stages. Stage specific survival improves.

Stage Migration Bias



the harder you look for disease, and the more advanced the technology the higher the prevalence, the higher the stage, and the better the (apparent)outcome for the stage

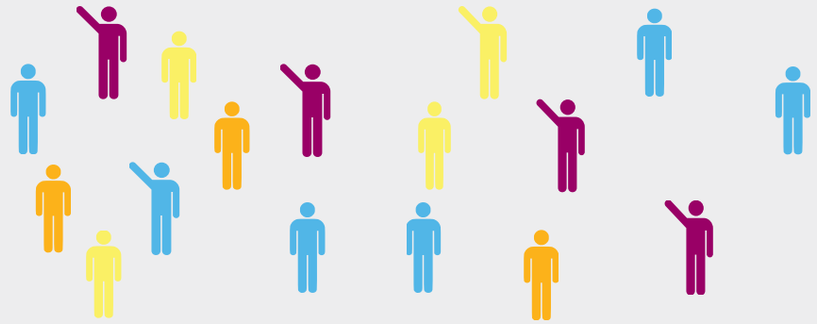
avoid stage migration bias

1. beware of stage migration in any stratified analysis: check OVERALL survival in screened vs. unscreened group
2. more generally do not stratify on factors distal in a causal pathway to the factor you wish to evaluate

Summary

Volunteer bias

people who volunteer for screening differ from those who do not

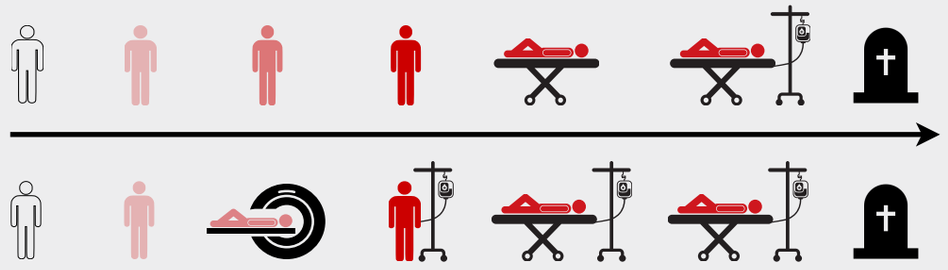


how to avoid

- ✳ randomize people to screened and unscreened
- ✳ otherwise, try to control for factors (confounders) associated with both screening and outcome

Lead time bias

screening identifies disease during a latent period before it becomes symptomatic - screening appears to improve survival

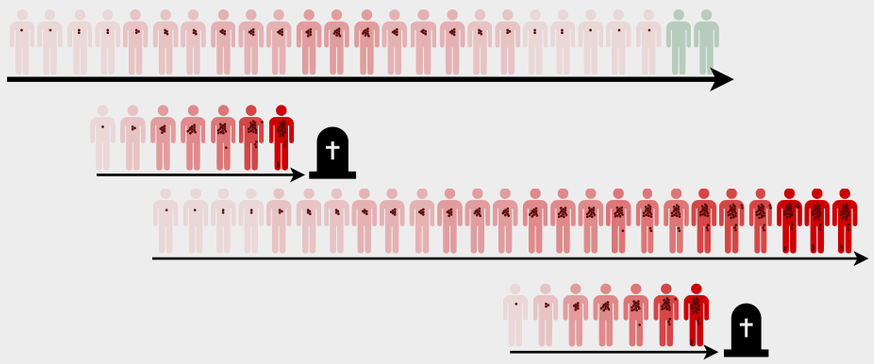


how to avoid

- ✳ measure mortality and not survival
- ✳ count from date of randomization

Length bias

screening picks up prevalent disease and benign courses of disease have a greater prevalence

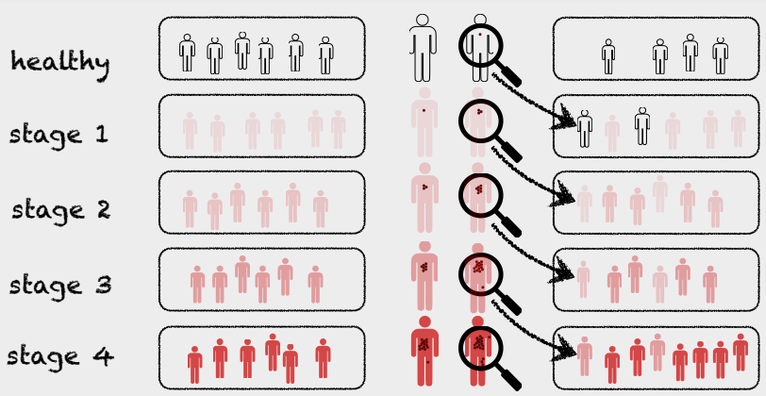


how to avoid

- ✳ compare mortality in the ENTIRE screened group to the ENTIRE unscreened group

Stage migration bias

newer tests classify people into more advanced stages - stage specific survival improves.



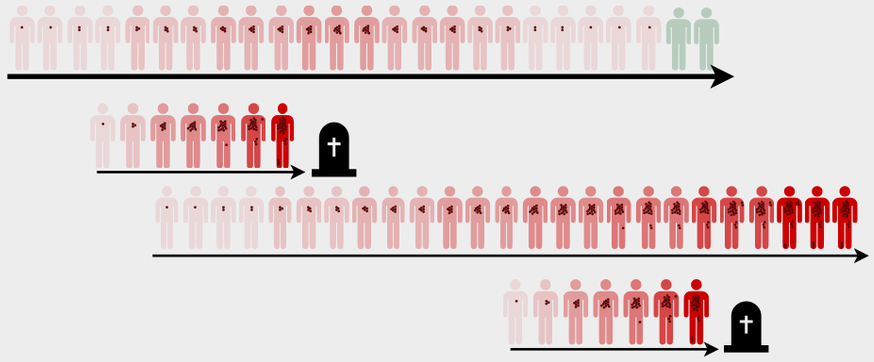
how to avoid

- ✳ beware of stage migration in any stratified analysis
- ✳ check OVERALL survival in screened vs. unscreened group

A special case of Length Bias!

Length bias

screening picks up prevalent disease and benign courses of disease have a greater prevalence



how to avoid

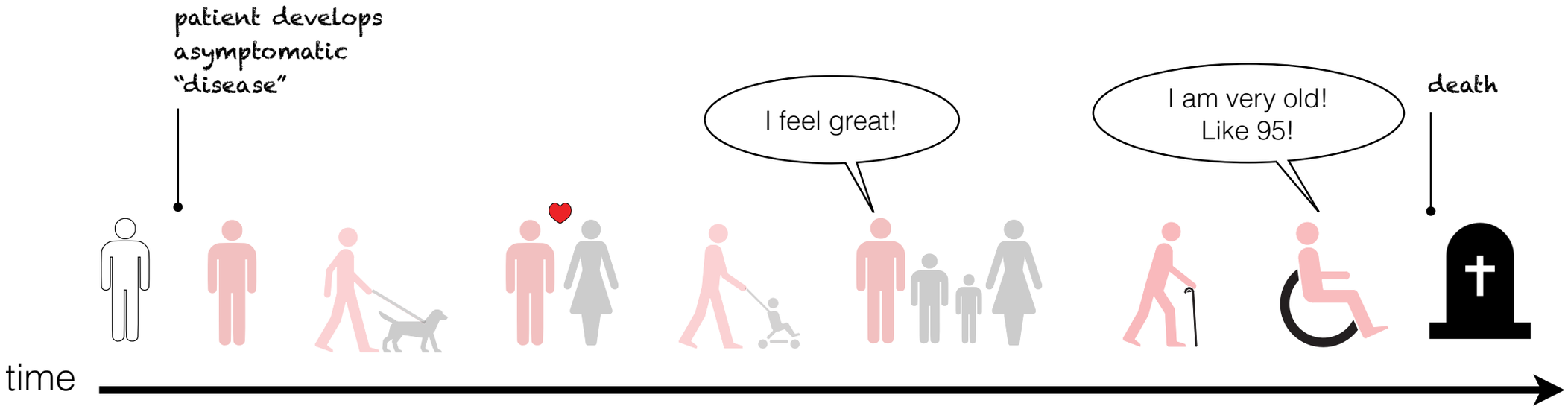
- compare mortality in the ENTIRE screened group to the ENTIRE unscreened group

Pseudodisease or Overdiagnosis

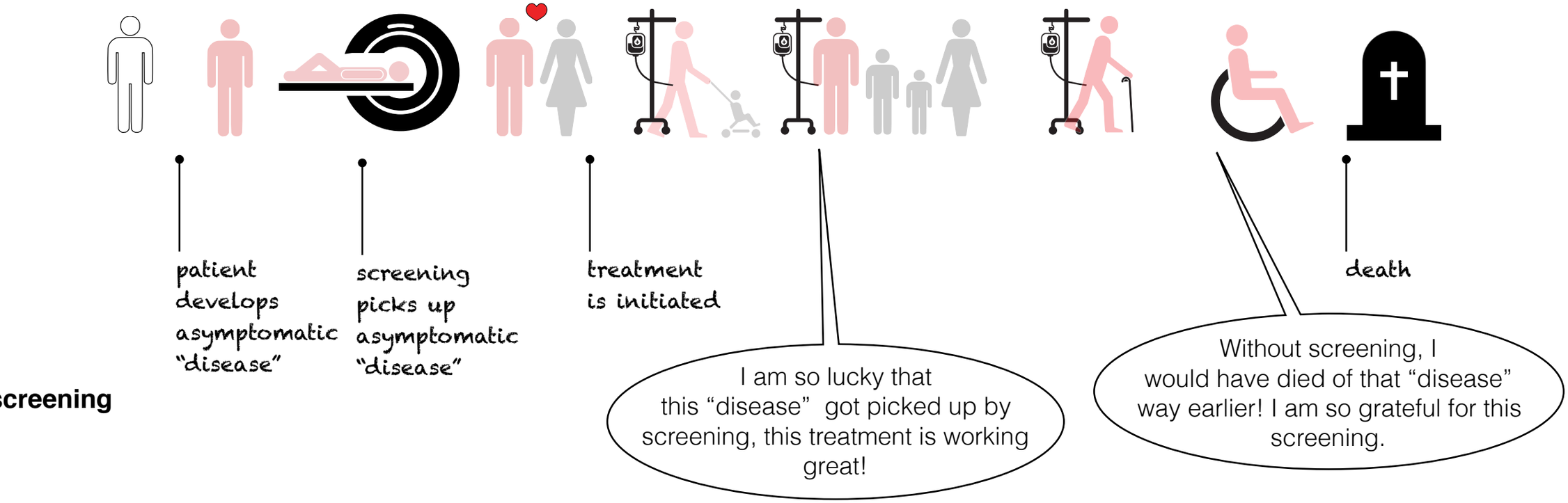
Overdiagnosis is sort of like length bias. That is, the disease would NEVER have become symptomatic if it had not been diagnosed by screening.

Pseudodisease or Overdiagnosis

no screening

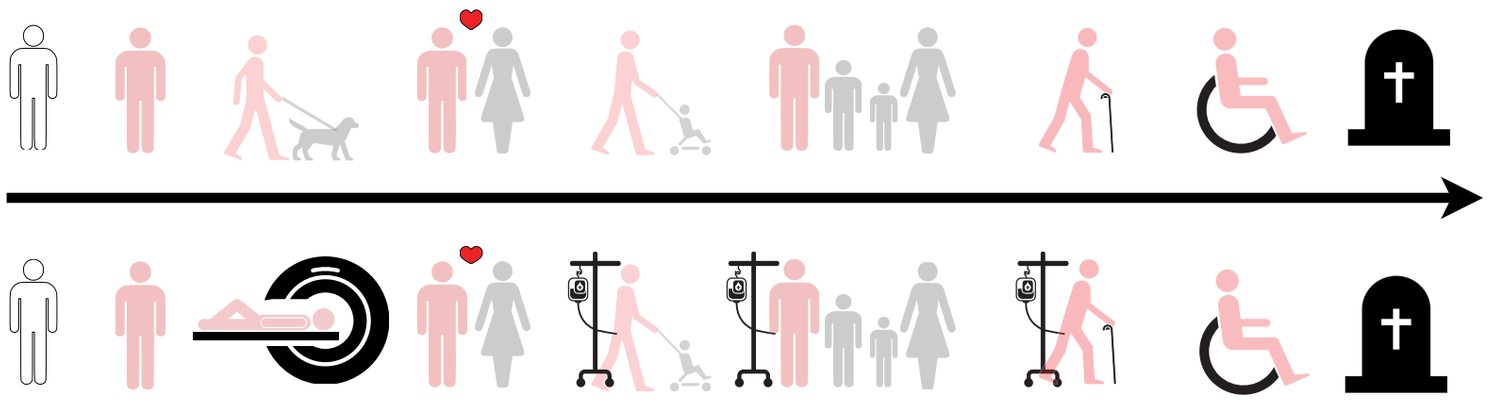


screening



Pseudodisease is a condition that looks just like the disease, but never would have bothered the patient

Pseudodisease or Overdiagnosis



two types of pseudodisease:

Type 1: disease which would never cause symptoms
Type 2: preclinical disease in people who will die from another cause before disease presents

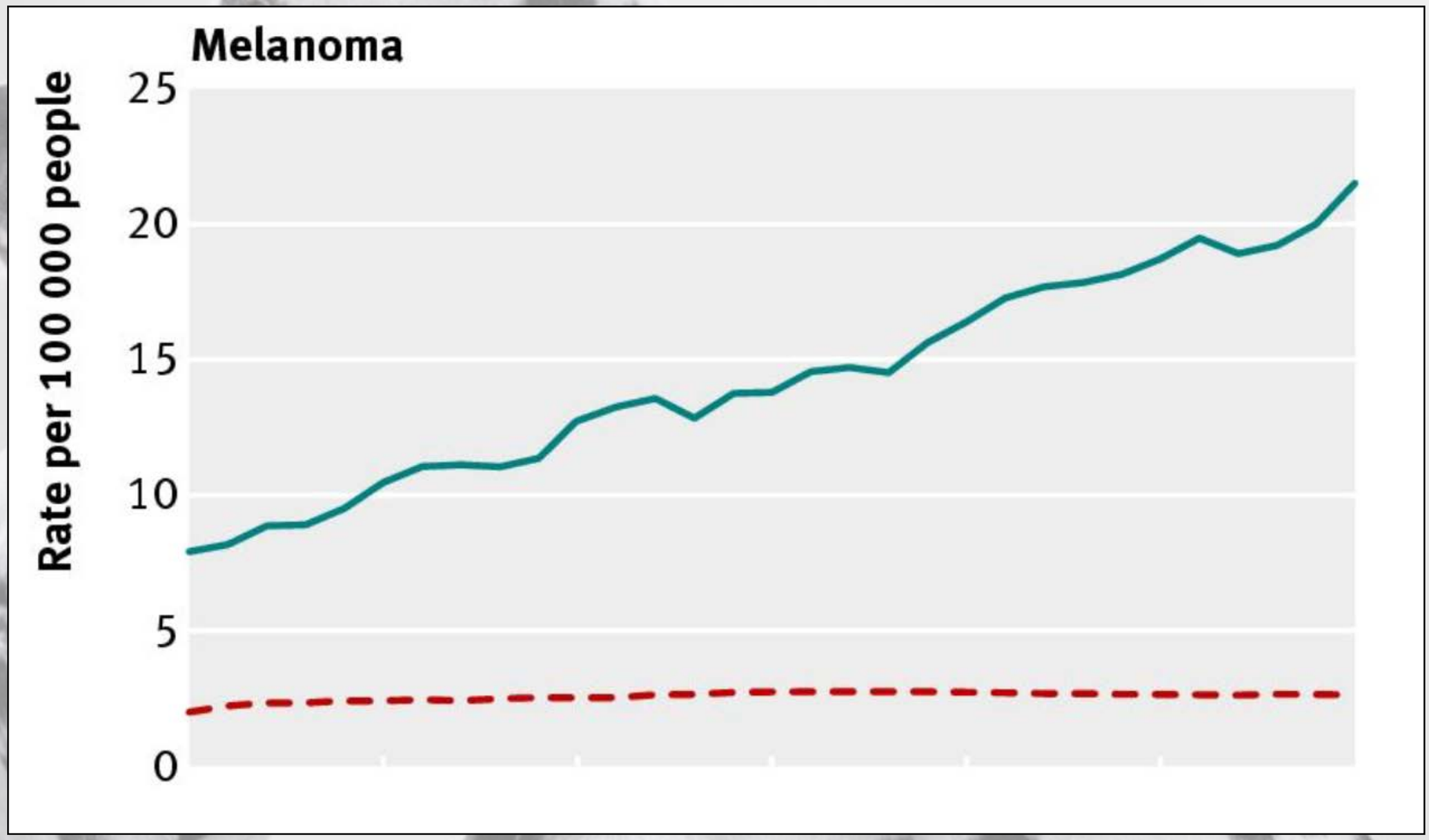
in an INDIVIDUAL TREATED PATIENT
it is IMPOSSIBLE to distinguish pseudo disease from successfully treated asymptomatic disease

1. Treating pseudo disease will always be successful
2. Treating pseudo disease can only cause harm

LA ROCHE-POSAY
LABORATOIRE PHARMACEUTIQUE

Pseudodisease or Overdiagnosis

Moynihan et al., BMJ 2012;344:e3502



Pseudodisease or Overdiagnosis

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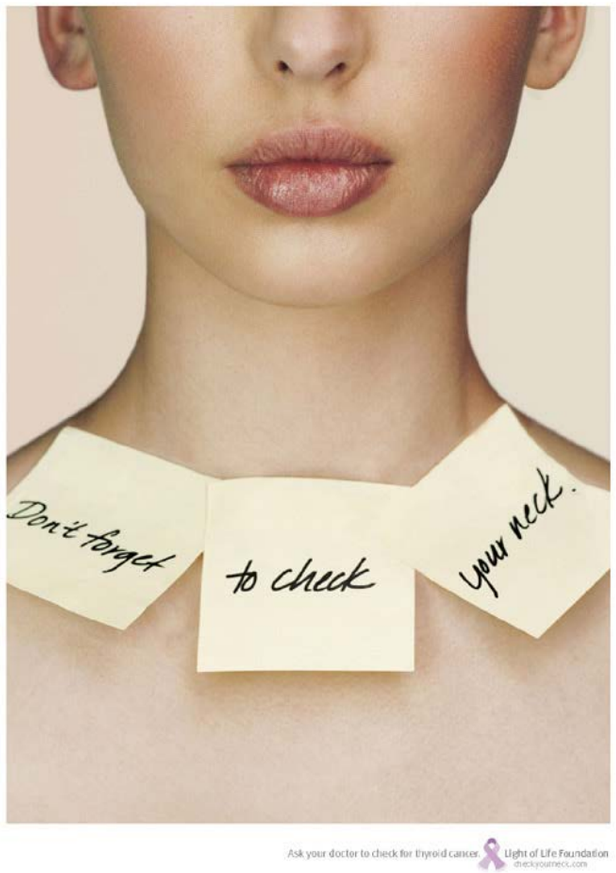
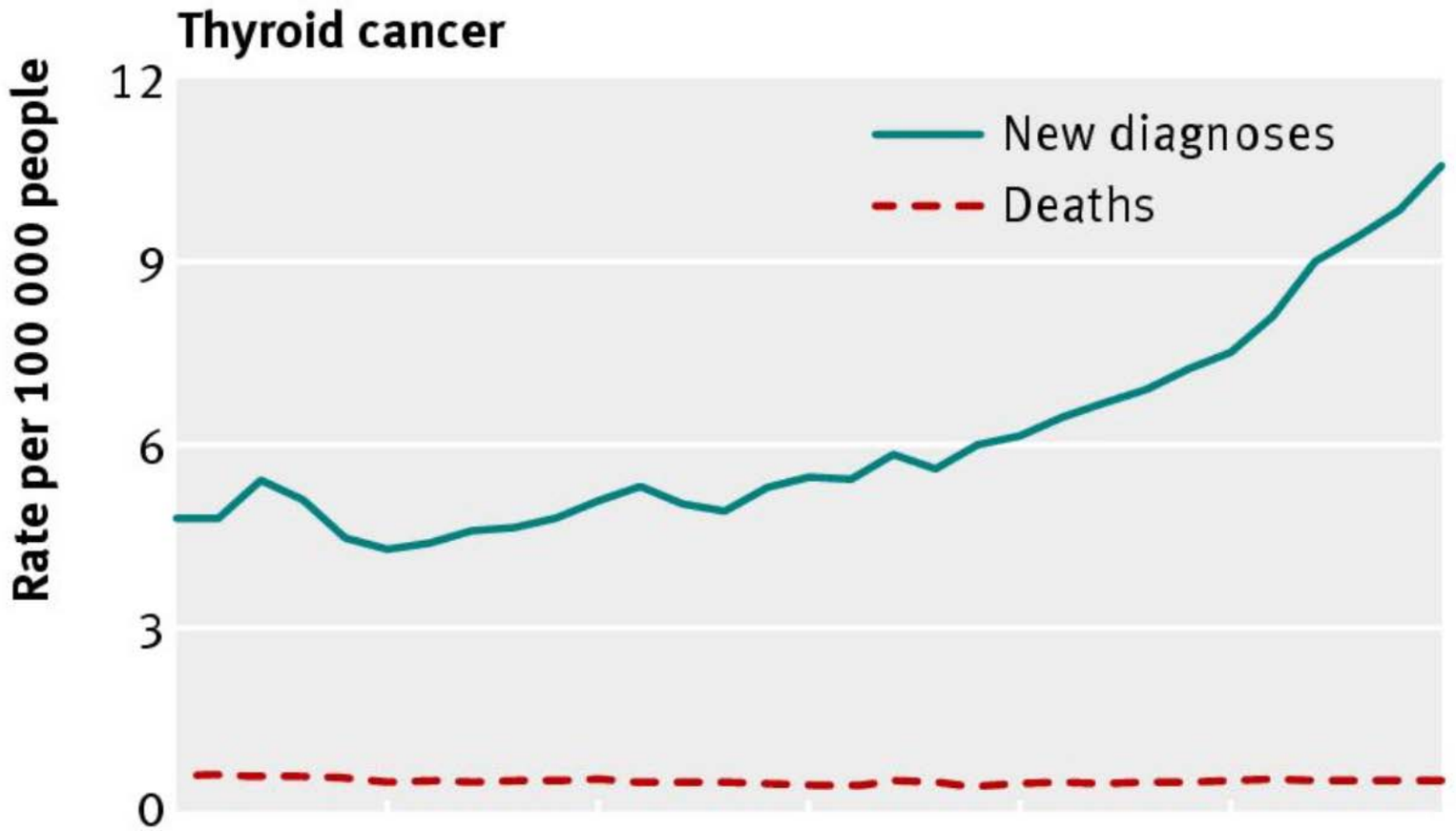
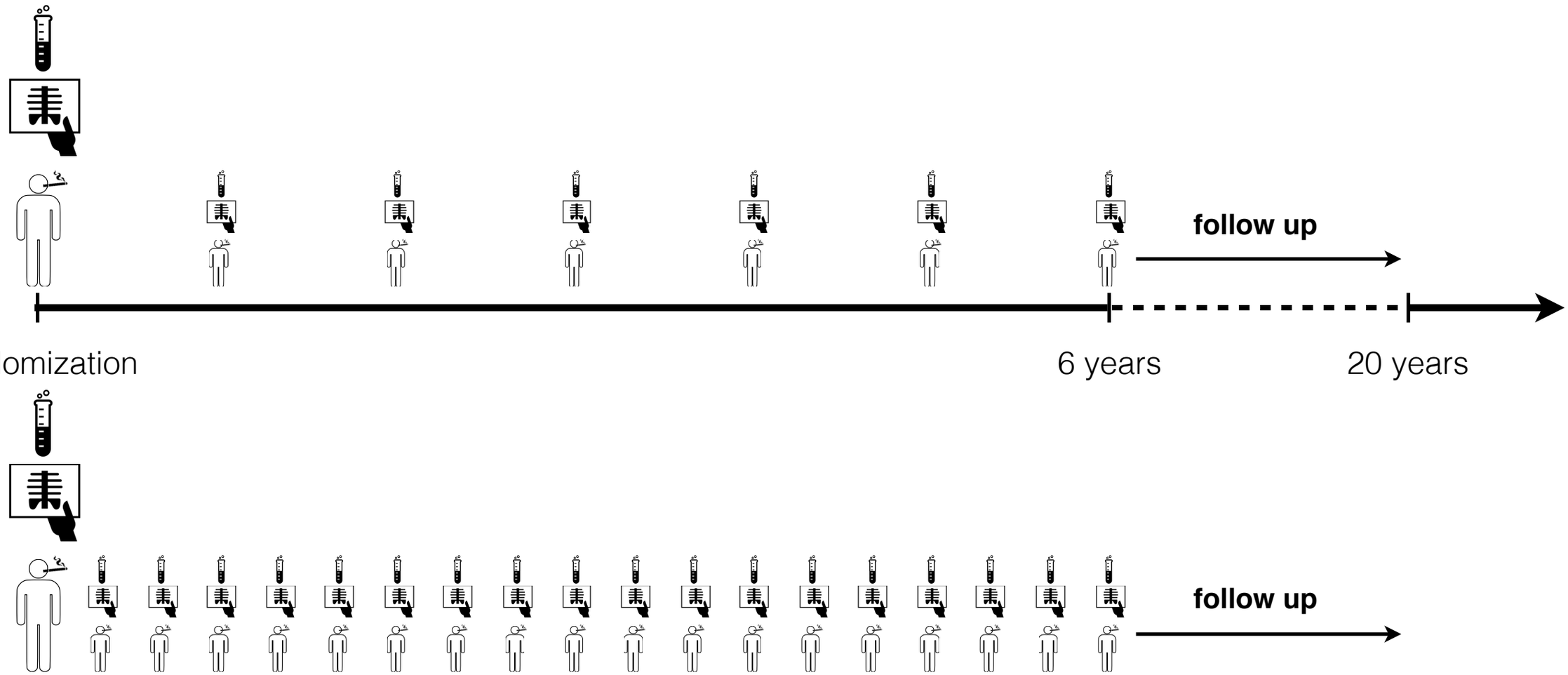




Mayo Lung Project: an RCT

Marcus et al., JNCI 2000;92:1308-16

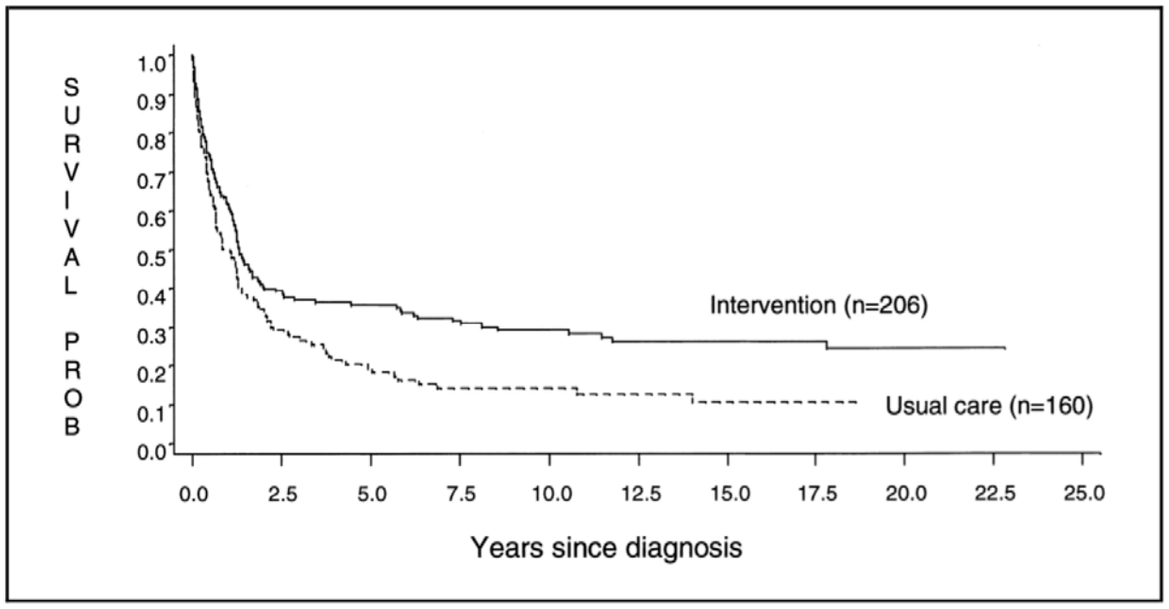
standard group

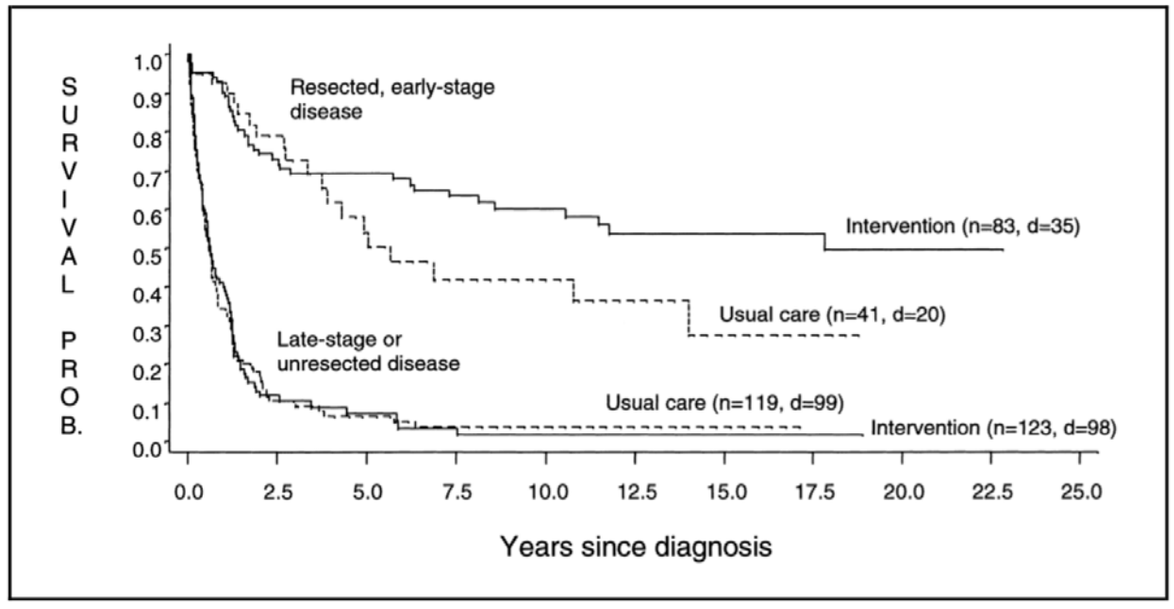


intervention group

Mayo Lung Project: Results

Marcus et al., JNCI 2000;92:1308-16

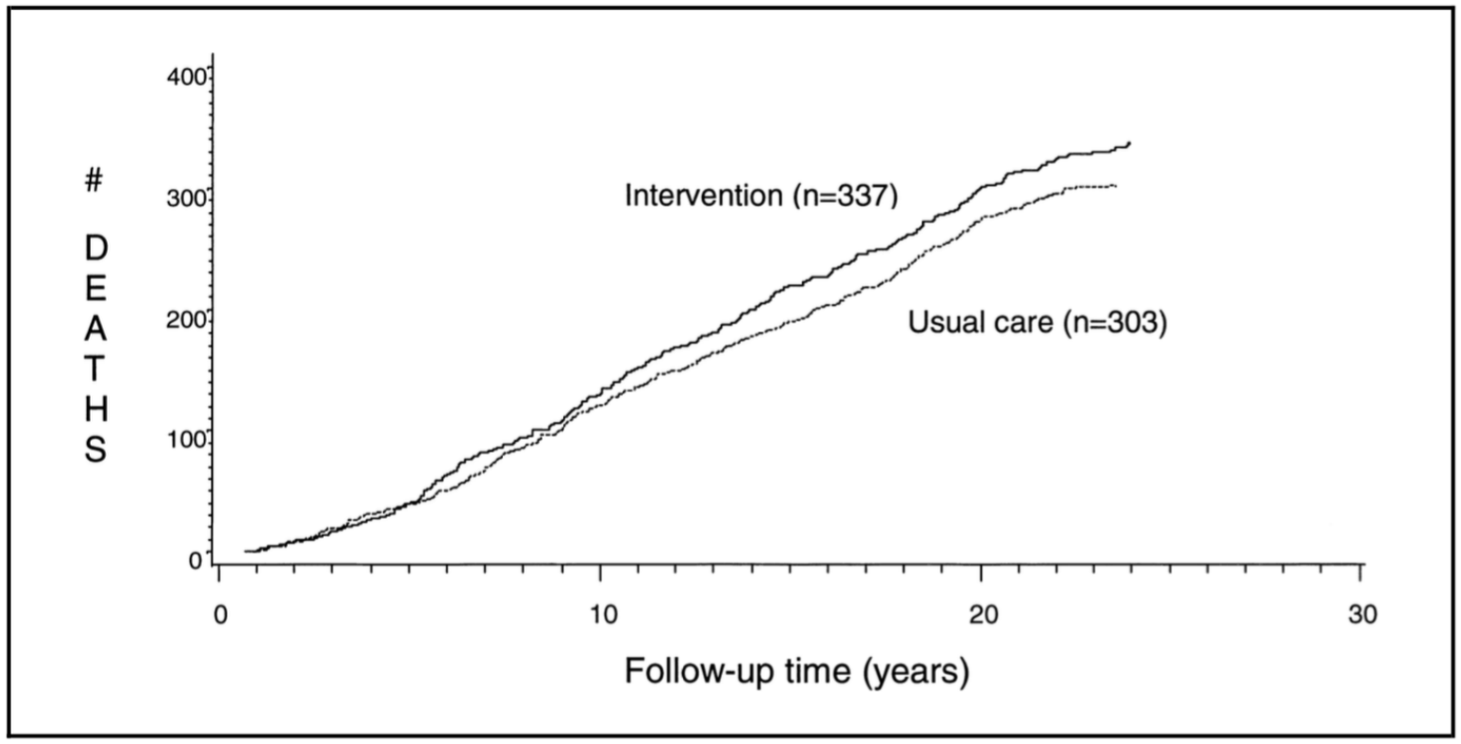




What happened?

Mayo Lung Project: Results

Marcus et al., JNCI 2000;92:1308-16



Bias of screening tests in RCT

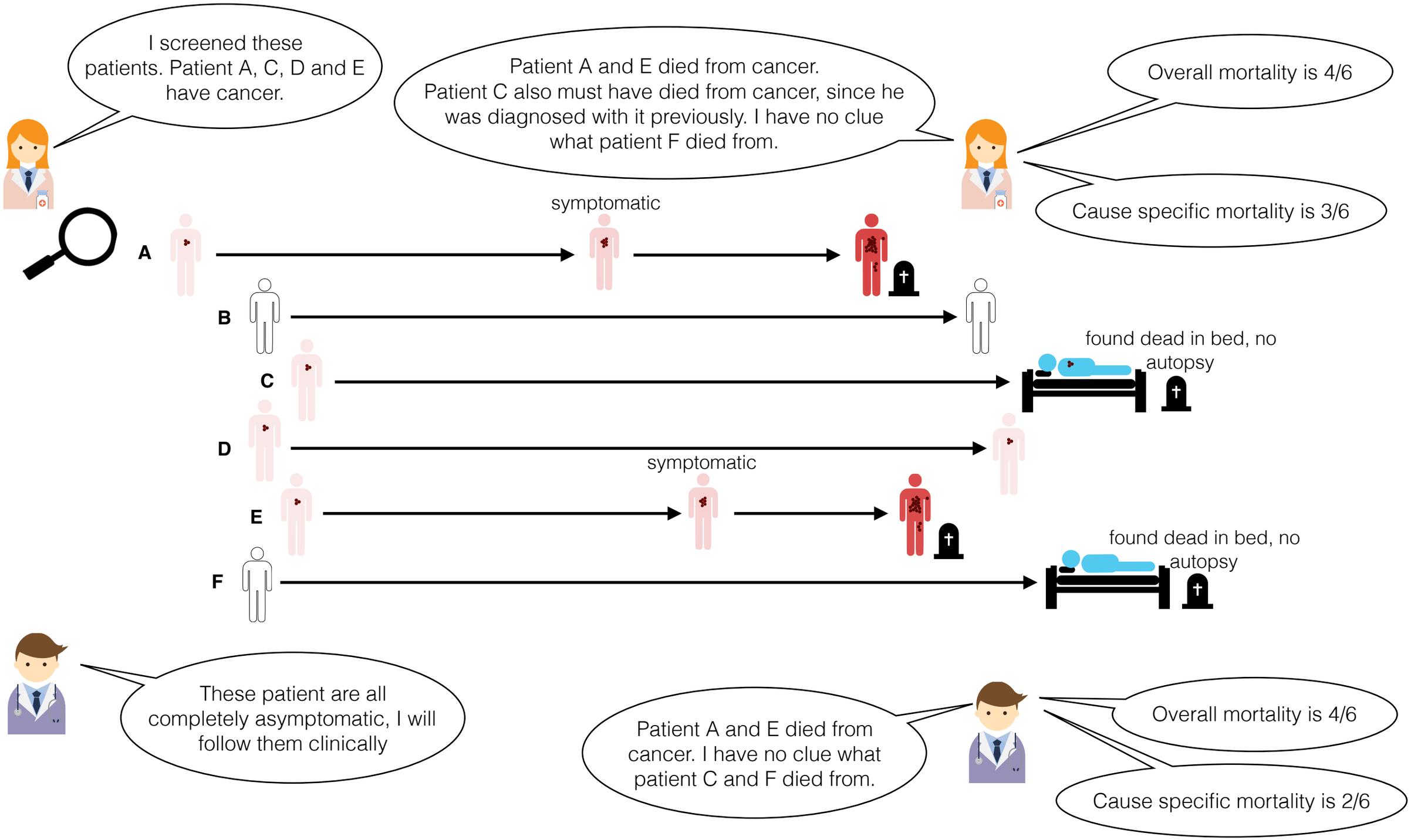
- ✦ Poor quality of randomization
- ✦ Poor choice of outcome variable: cause specific mortality

Poor quality of randomization

Edinburgh Trial
Br J Cancer. 1994 September; 70(3): 542–548

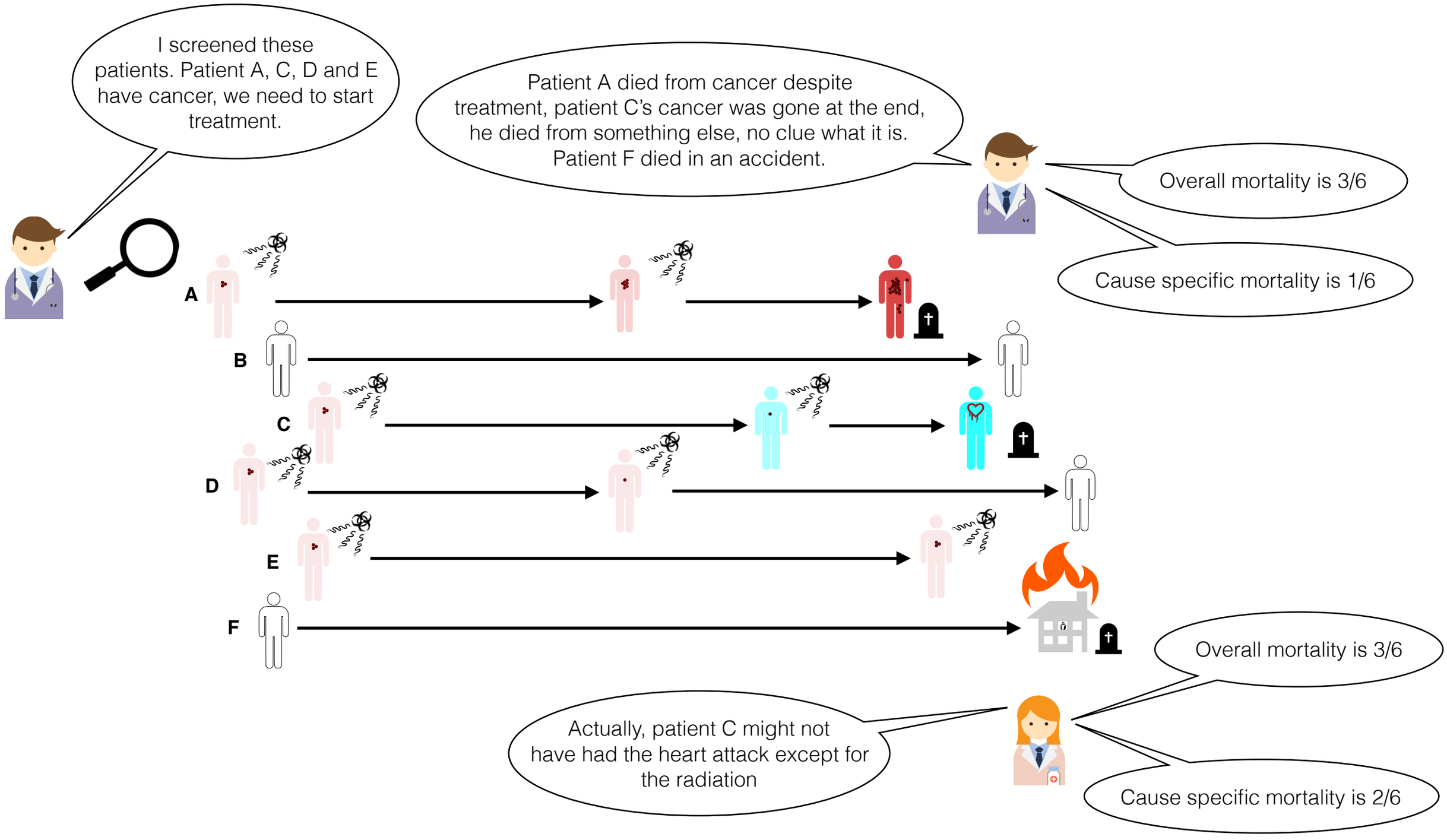
- Randomization by *practice* (N=87?), not by woman
- 7 practices changed allocation status
  - Highest SES
    - 26% of women in control group
    - 53% of women in screening group
  - 26% reduction in cardiovascular mortality in mammography group

Cause-specific mortality: Sticky diagnosis bias



Overestimation of cause-specific mortality due to incorrect assignment of cause of death. Can be avoided by measuring all cause mortality.

Cause-specific mortality: Slippery linkage bias



Underestimation of cause-specific mortality due to incorrect assignment of cause of death. Late deaths due to complications of screening or treatment will not be counted in cause-specific mortality. Can be avoided by measuring all cause mortality.

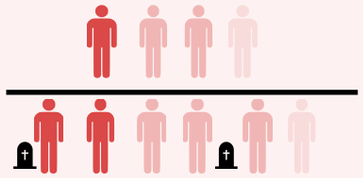
Cause-specific mortality: Slippery linkage bias

Early Breast Cancer Trialists Collaborative Group
Meta-analysis of radiotherapy for early breast cancer
Lancet 2000;355:1757

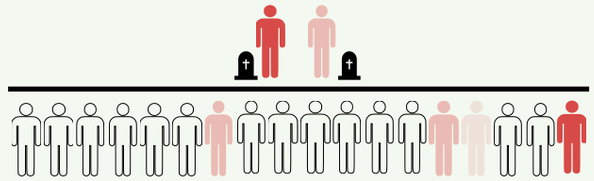
- Meta-analysis of 40 RCTs
- Central review of individual-level data; N = 20,000
- Breast cancer mortality reduced (20-yr absolute risk reduction 4.8%; P = .0001)
- Mortality from other causes increased (20-yr absolute risk **increase** 4.3%; P = 0.003)

Summary: Outcome variable and biases

survival



mortality

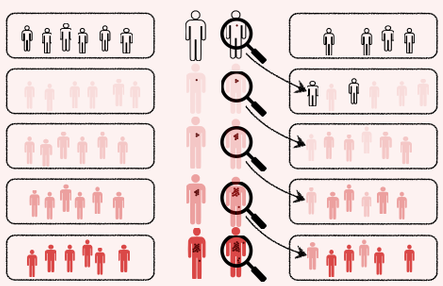


stratified survival

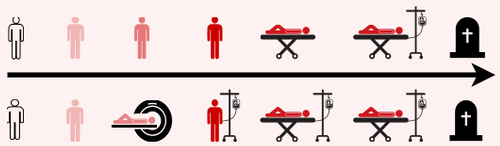
overall survival

cause-specific mortality

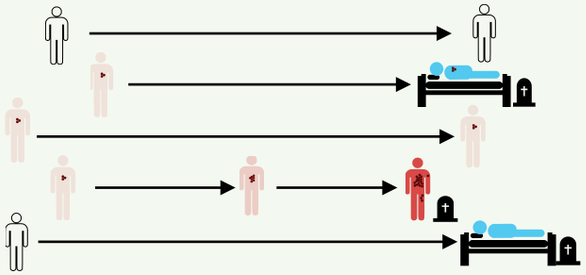
overall mortality



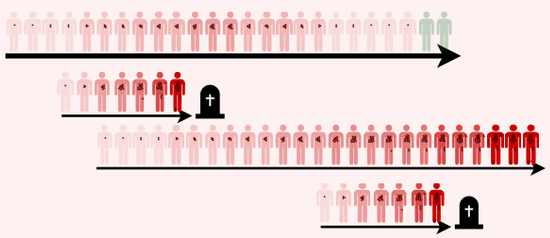
stage migration bias



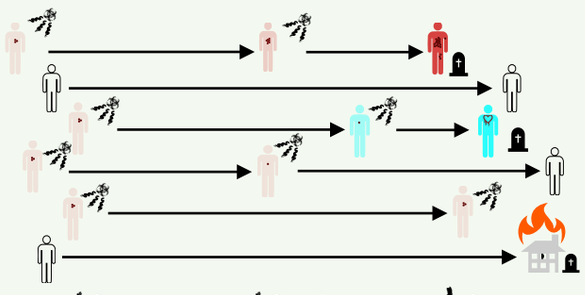
lead time bias



sticky-diagnosis bias



length bias



slippery-linkage bias

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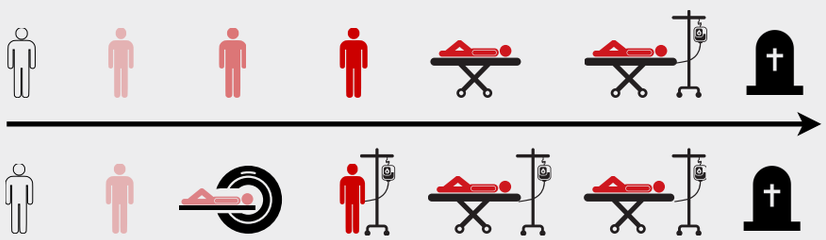
condition that looks just like the disease, but never would have bothered the patient

Lead time bias

screening identifies disease during a latent period before it becomes symptomatic - screening appears to improve survival



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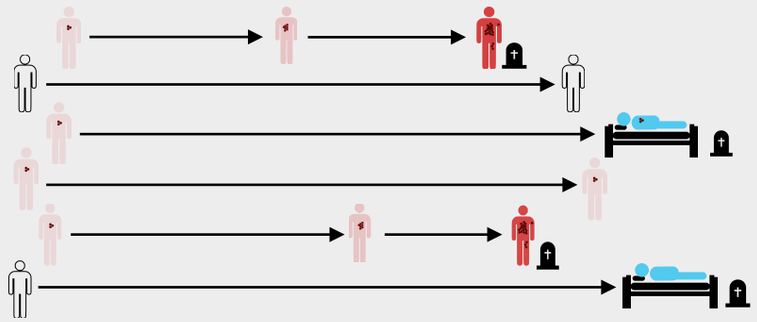
overestimation of cause-specific mortality due to incorrect assignment of cause of death



Length bias

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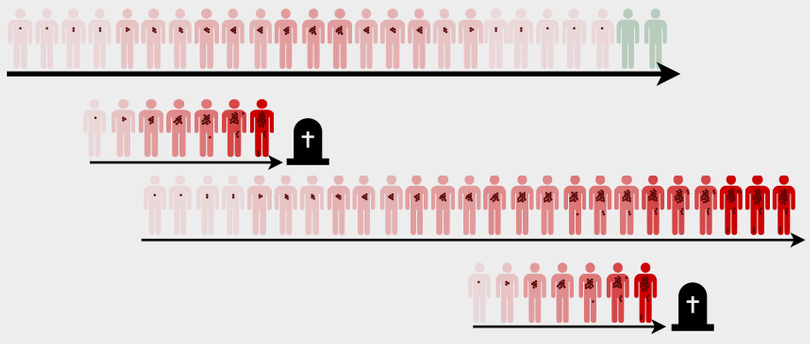

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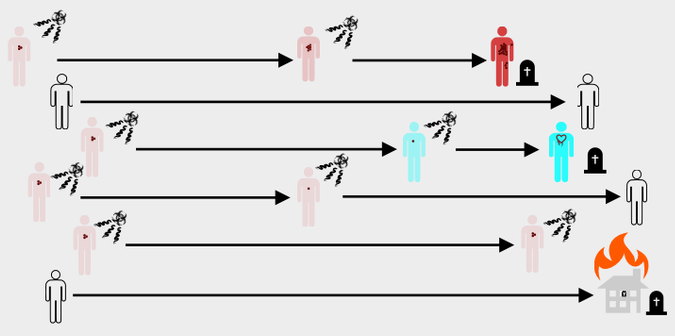

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