MRC Epidemiology Unit

UNIVERSITY OF CAMBRIDGE

Principles of screening and should we screen for diabetes?

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Professor of General Practice

Cambridge Diabetes Seminar, Clare College, Wednesday 3 April 2019

Wellcome Trust – MRC IMS Institute of Metabolic Science

Cambridge Institute of Public Health

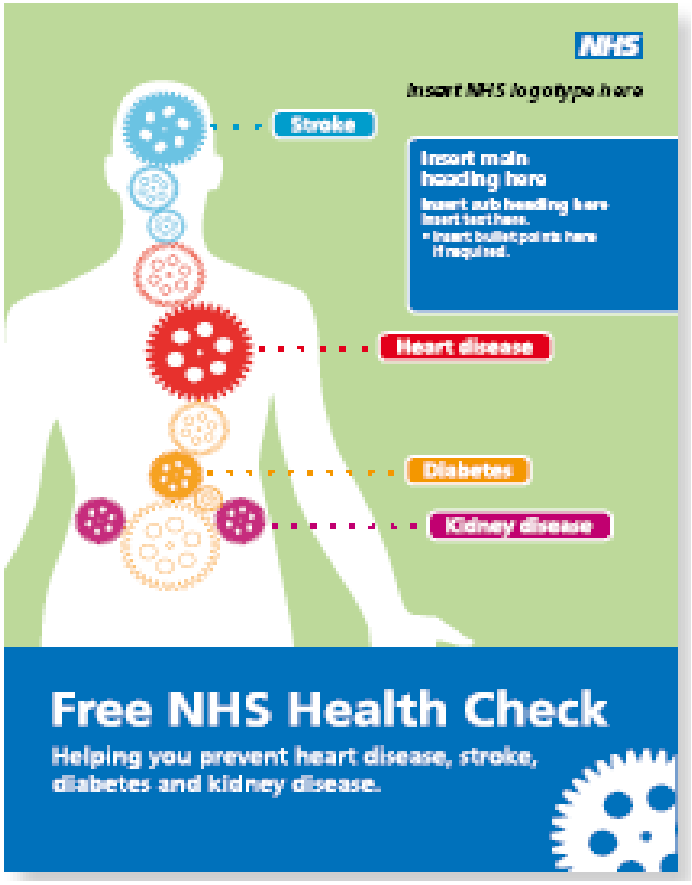
Definition of Screening

'The systematic application of a test or inquiry, to identify individuals at sufficient risk of a specific disorder to warrant further investigation or direct preventive action, amongst persons who have not sought medical attention on account of symptoms of that disorder'

National Screening Committee, Department of Health, 1998

Screening for what?

- **Prevalent undiagnosed type 2 diabetes**
- **High risk of**
  - **incident diabetes**
  - **incident cardiovascular disease**
  - **kidney disease**
  - **dementia**



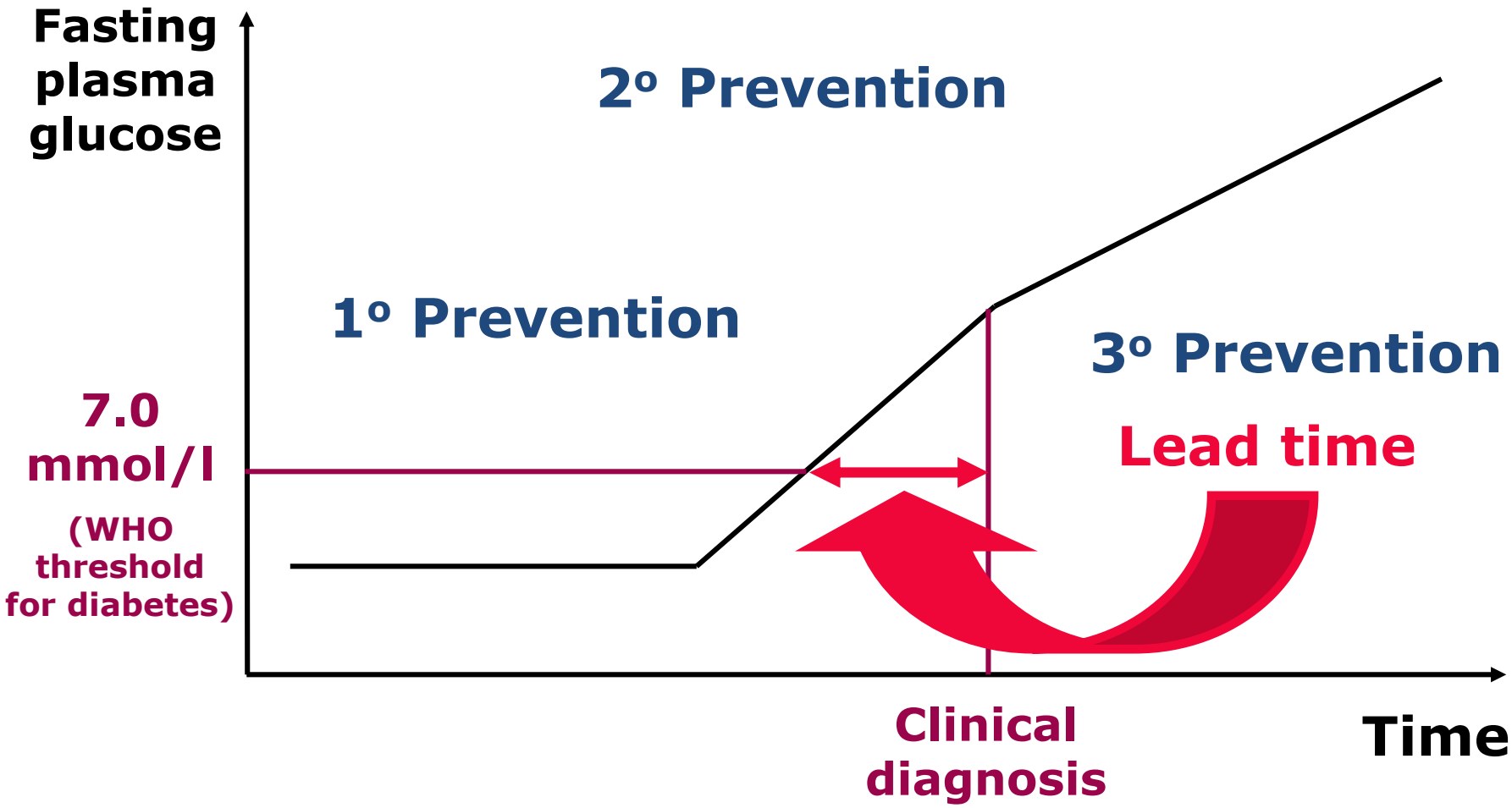
Ethical Difference Between Medical Practice and Screening

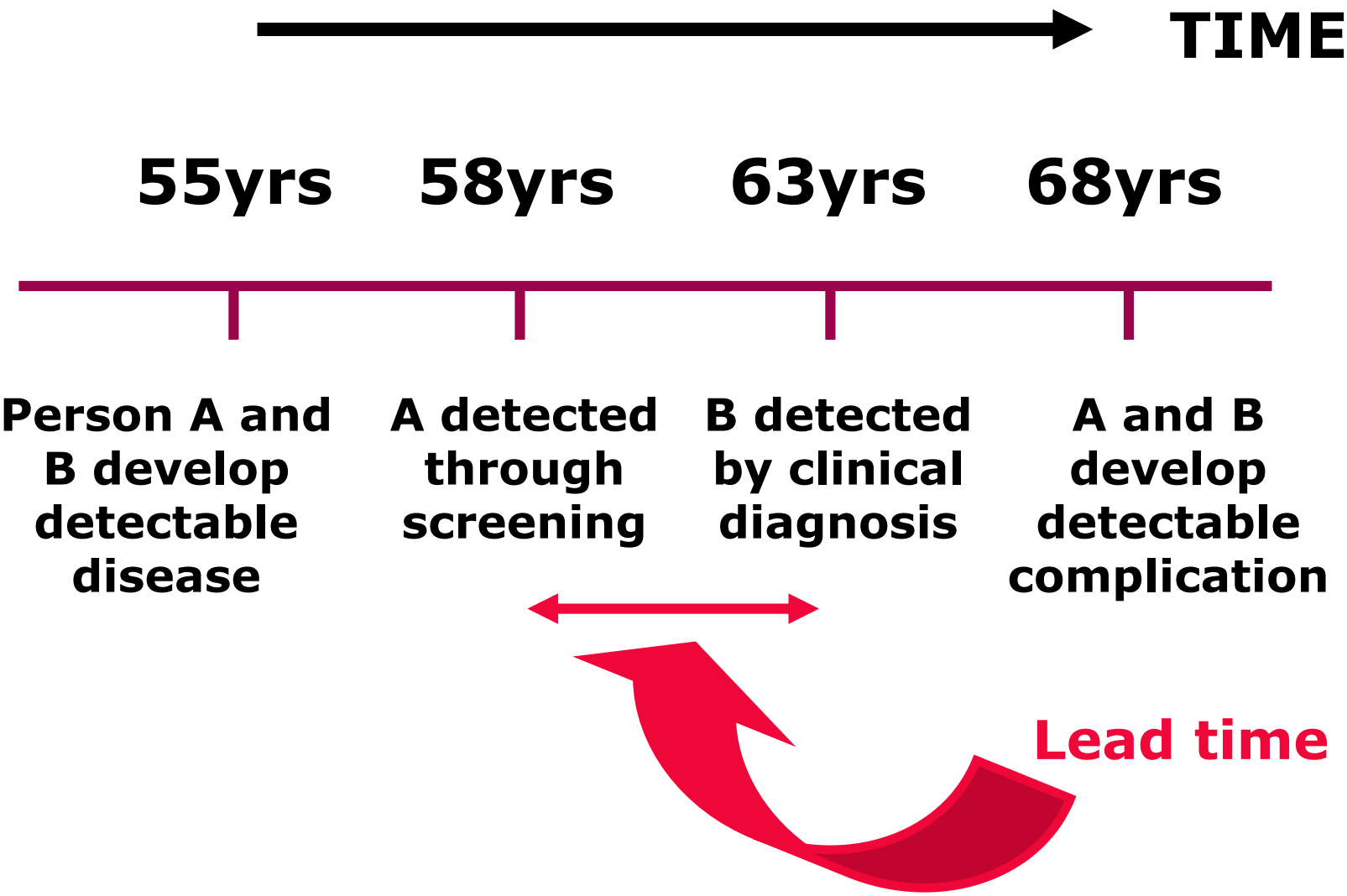
"If a patient asks a medical practitioner for help, the doctor does the best he can. He is not responsible for defects in medical knowledge.

If screening is initiated, he should have conclusive evidence that screening can alter the natural history of the disease in a significant proportion of those screened."

Cochrane and Holland 1971

The benefits of screening: treatment in the lead time

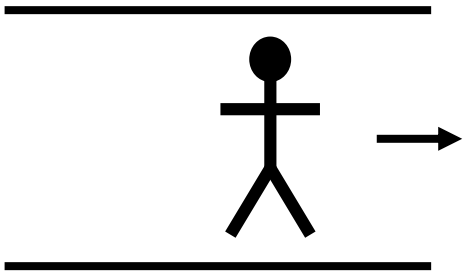


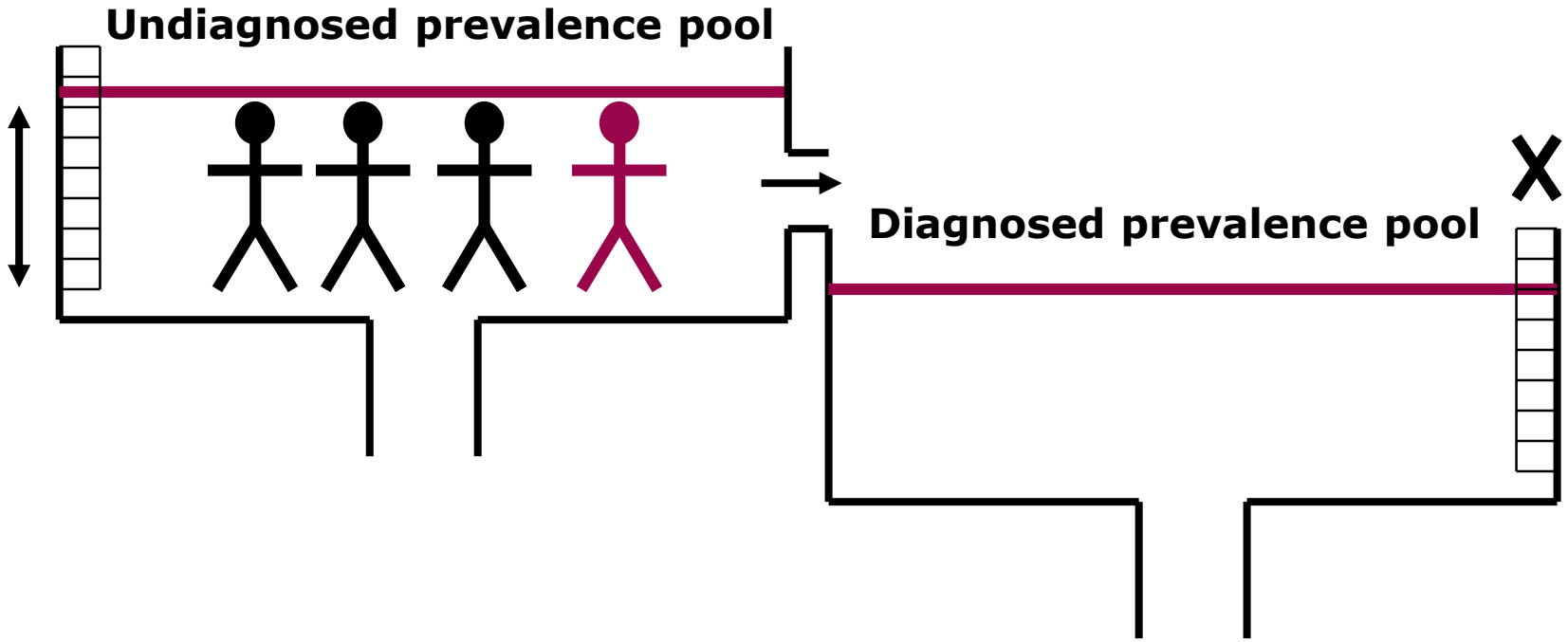

TIME
55yrs
58yrs
63yrs
68yrs
Person A and B develop detectable disease
A detected through screening
B detected by clinical diagnosis
A and B develop detectable complication
Lead time

Lead time bias

… could occur if early detection increased complication-free interval or survival only because detection is earlier not because treatment is effective in delaying or preventing morbidity or death

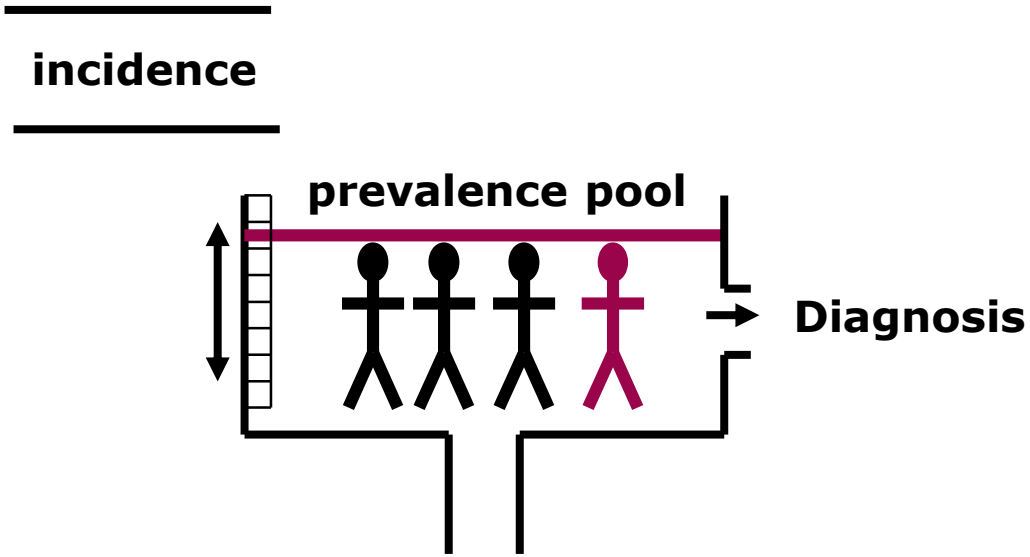
Incidence



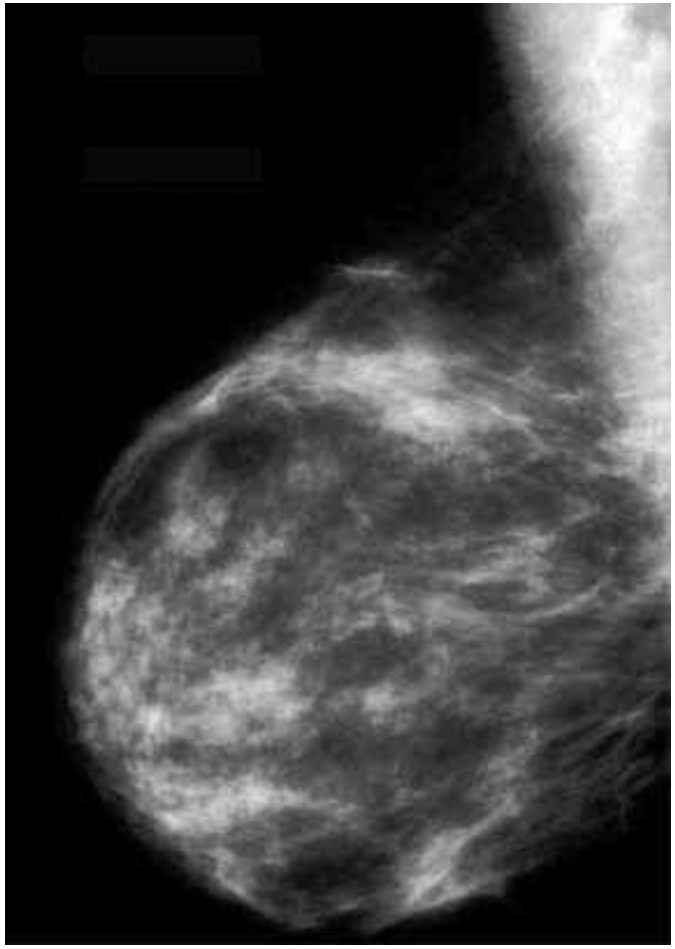


Length-time bias

… could occur if individuals identified through screening have a longer pre-clinical phase, milder disease or lower morbidity and mortality regardless of when the disease is detected



The screening paradox



Screening is only worthwhile if the effectiveness of treatment for people diagnosed without screening is limited

Positive public perception of screening

- 'A stitch in time saves nine'
- 'Prevention is better than cure'
- Inflated sense of the benefits and discounted sense of the harms of mammography, cervical smears and PSA screening.

JAMA Intern Med 2015;175:274-87

Screening is a public health intervention

- Most individuals do not benefit
- A large benefit to the minority of individuals with screen-detected disease may be outweighed by a small harm to the majority with negative screening tests

Screening influences our cause of death but may not reduce our risk of death

- Some (3/10) trials of cancer screening demonstrate reductions in disease-specific mortality rates but none showed reductions in overall mortality
- Studies are underpowered
- Screening can increase mortality due to conditions other than the cancer targeted by the screening test

BMJ 2016;352:h6080

Screening is always associated with harm, sometimes it is also associated with benefit

- Screening tests may be harmful
- Screening tests are imprecise leading to false positives and false negatives
- Diagnostic tests may be harmful
- Diagnostic tests are imprecise leading to false positives and false negatives
- Treatment may have adverse effects

Screening for Hypertension

- **Screening and diagnosing hypertension in Canadian steel workers:**
  - significantly increased subsequent absenteeism from work (5.2 days, $p<0.025$)

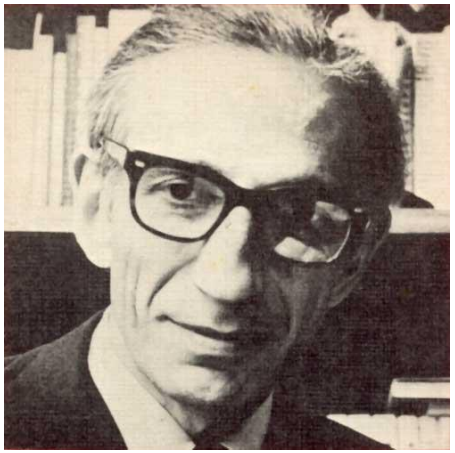
    Haynes et al NEJM 1978:741-44
  - significantly decreased subsequent annual income ($1093)

    Johnston ME et al J Chron Dis 1984;37:417-23

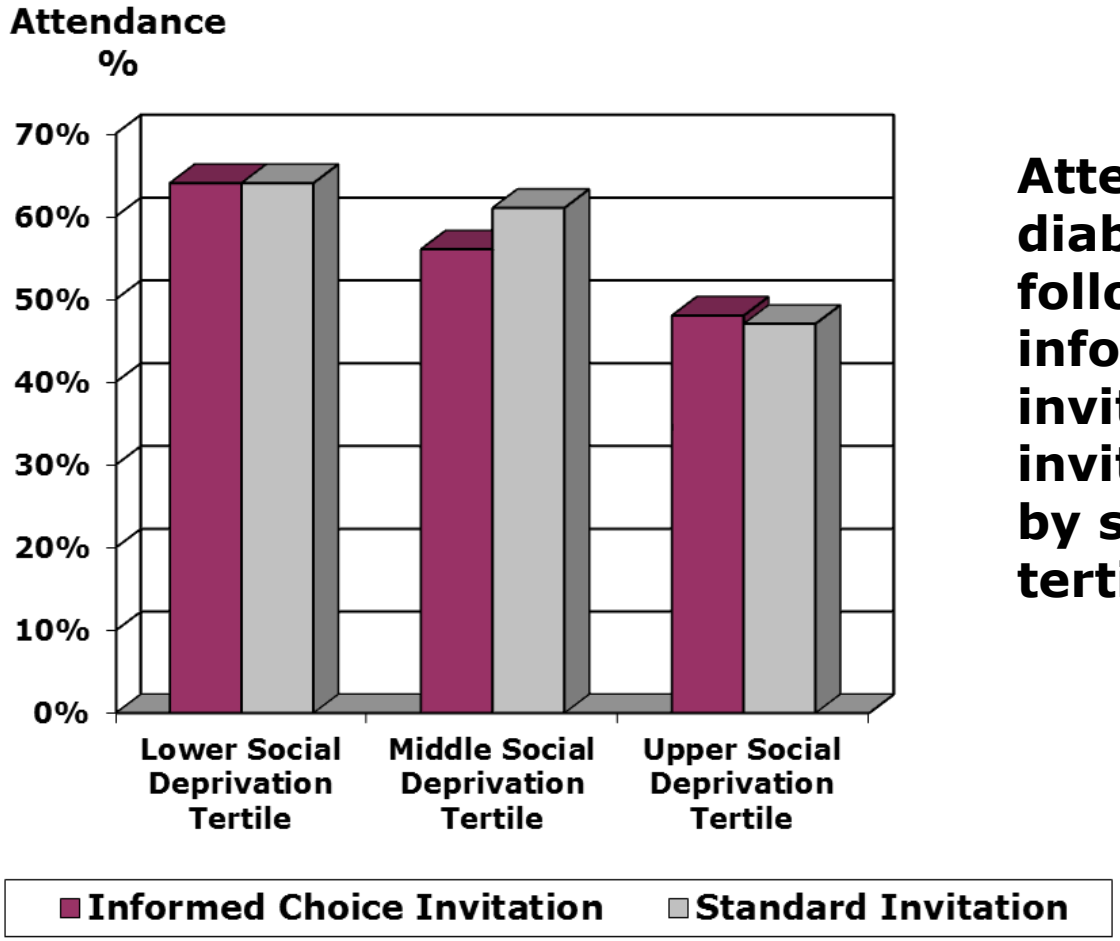
Screening is always associated with harm, sometimes it is also associated with benefit

"Medical science has made such tremendous progress that there is hardly a healthy human left."
Aldous Huxley

"The medical establishment has become a major threat to health..."
Ivan Illich



Attendance for screening: social patterning and informed choice

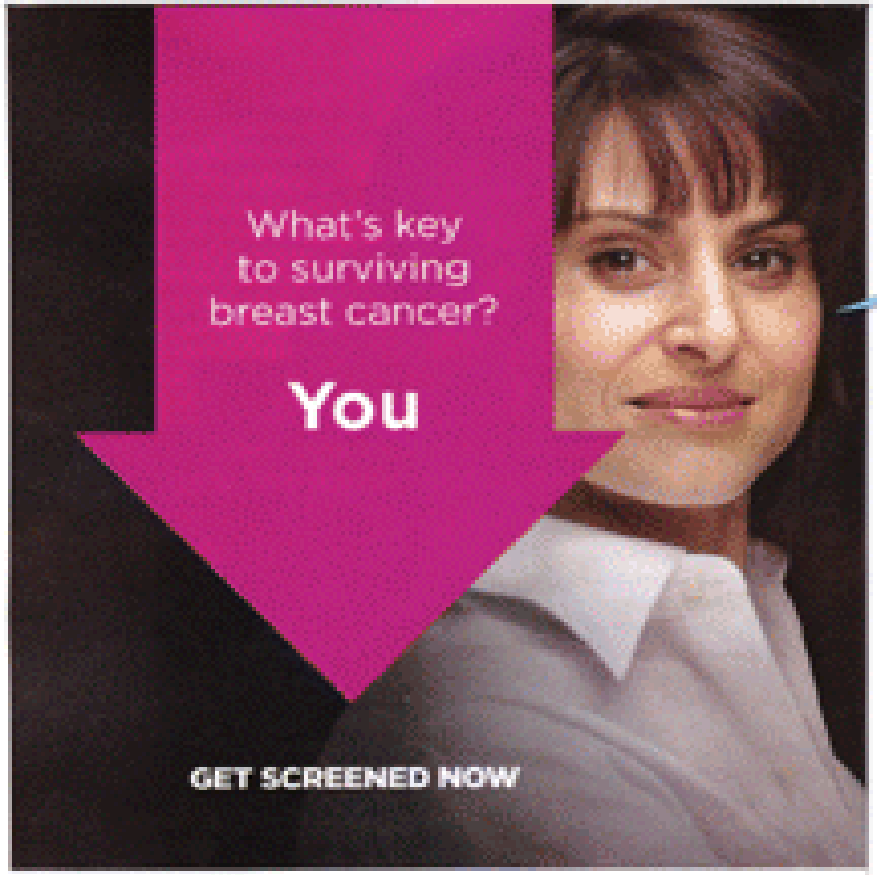


Attendance (%) at diabetes screening following receipt of an informed choice invitation or a standard invitation, grouped by social deprivation tertiles

***BMJ* 2010;340:c2138**

Overdiagnosis and overtreatment

TOO MUCH MEDICINE



Not so

Screening mammography does not guarantee that a woman will "survive" breast cancer. The best evidence indicates that it decreases the chance that a 50 year old woman will die from breast cancer in the next 10 years roughly from 0.53% to 0.46%—a difference of 0.07 percentage points. Because breast cancer treatments are much more effective now than when trials of screening were done, some experts question whether screening mammography has any benefit.

Not so

The five year survival for early and late stage cancers tells you nothing about the benefit of screening. Because of biases caused by lead time (the time from diagnosis by screening to when a tumour can be felt) and overdiagnosis, five year survival can improve regardless of whether cancer mortality is increased, decreased, or unchanged by screening

SHORTCUTS
BLOG
A SIDEWAYS LOOK AT THE NEWS

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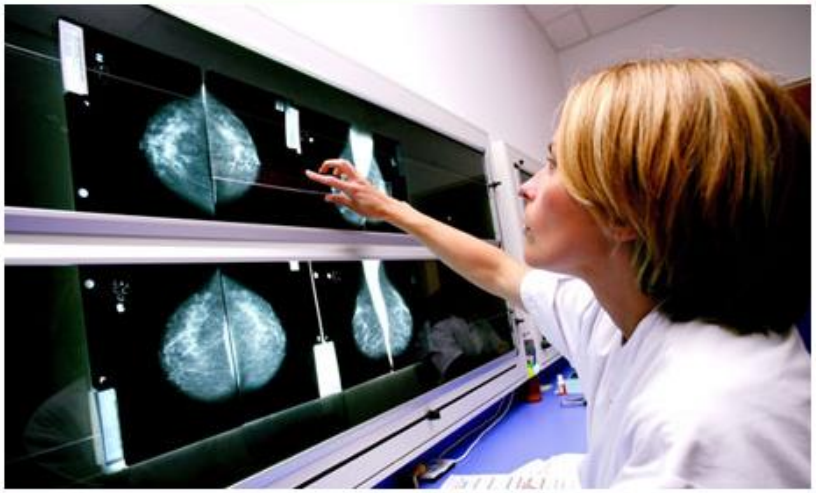
Breast cancer screening: should you, shouldn't you?

It's a matter of what makes you feel most comfortable, in this doctor's opinion



Posted by
Ann Robinson
Tuesday 30 October
2012 18.01 GMT
The Guardian

Jump to comments (80)

Article history

Society

17 October 2012 Last updated at 01:02

General health check-ups 'offer no benefit'

Visiting a doctor for a general check-up is unlikely to lead to a condition needing treatment being identified, but may cause undue stress, say experts.

Health MoTs check things like blood pressure and cholesterol

The Danish researchers that carried out the latest review, which involved more than 180,000 patients, say doctors should stop offering such check-ups.

Health MoTs did not reduce deaths overall or deaths from cancer and heart disease, according to their review.

In England, people aged 40-74 are offered a free health check.

The initiative, launched in 2009, is designed to spot conditions such as heart disease, stroke and diabetes by looking for silent risk factors such as high blood pressure and cholesterol.

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Over 40s 'missing heart checks'

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Executive meltdown
Are the rewards worth the excessive stress?

"Governments seem to be promoting this against good evidence. Health Checks are pulling in an awful lot of people who have nothing wrong with them. And the very people you would want to be dragging in do not attend. We should be focusing on the hard-to-reach groups instead and policies like plain packaging for cigarettes and minimum pricing for alcohol."

RCGP Royal College of General Practitioners

Dr Clare Gerada
RCGP Chair

"Far from being useless, there is good evidence that, if properly implemented, it could prevent thousands of cases of Type 2 diabetes a year, as well as having a positive impact for heart disease, kidney disease and stroke."

Barbara Young
Chief Executive Diabetes UK

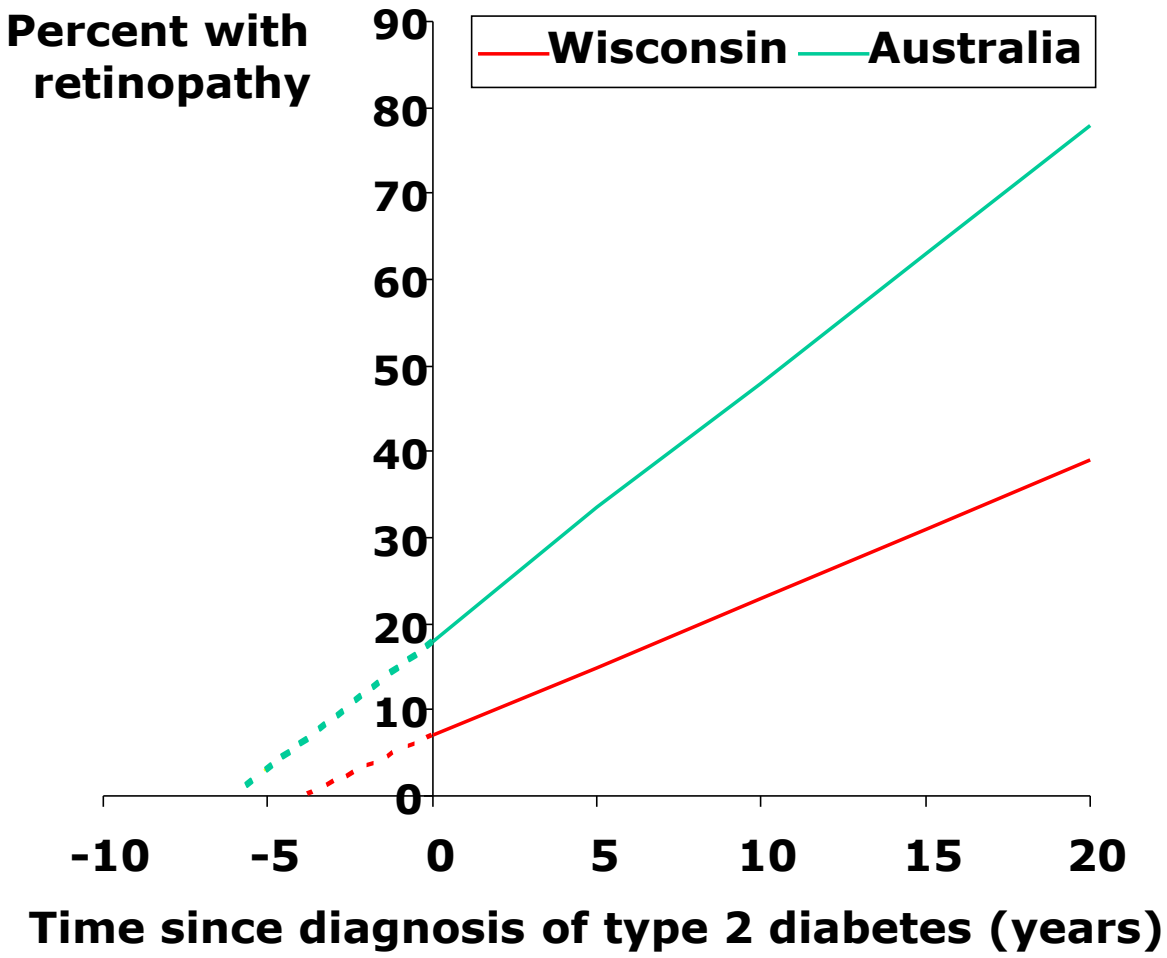

Mounds
Pit (dis)
Pit (dis)
Pit (dis)
Pit (dis)
Enclosure
269
271
272
Carbon Down
Earthwork
Resr
Moral High Ground
BS
Gallop
Resr
CND Hill
Pits (dis)
Pit (dis)
Pits (dis)
Vegetarian Bungalow
Resr
Tumulus

Screening Criteria

- ✓ **A well defined disorder with a known prevalence**
- ✓ **A burdensome disease with a long detectable pre-clinical phase**

Wilson JGM, Jungner G. Geneva: WHO, 1968
BMJ 2001;322:986-988

The Delay Between Disease Onset and Diagnosis May Be up to 10 Years



Harris et al. *Diabetes Care* 1992;15:815-8.

Screening Criteria

- ✓ A well defined disorder with a known prevalence
- ✓ A burdensome disease with a long detectable pre-clinical phase
- ✓ **A simple, safe, accessible, feasible, sensitive/specific screening test/programme**

Wilson JGM, Jungner G. Geneva: WHO, 1968
BMJ 2001;322:986-988

Screening questionnaires and scores

TYYPIN 2 DIABE
SAIRASTU

Rengasta oikea vaihtoeh

1. Ikä
   0 p. Alle 45 v.
   2 p. 45 – 54 v.
   3 p. 55 – 64 v.
   4 p. Yli 64 v.

2. Painoindeksi
   (katso taulukosta kääntöp
   0 p. Alle 25 kg/m²
   1 p. 25 – 30 kg/m²
   3 p. Yli 30 kg/m²

3. Vyötärönympärys m
   alapuolelta (yleensä

   MIEHET

   0 p. Alle 94 cm
   3 p. 94 – 102 cm
   4 p. Yli 102 cm

4. Sisältyykö jokaiseen p
   puoli tuntia liikuntaa
   ns. arkiliikunta muka

   0 p. Kyllä
   2 p. Ei

5. Kuinka usein syöt kas
   tai marjoja?

   0 p. Päivittäin
   1 p. Harvemmin kuin jo

Testin suunnittelu: Professori Jaakko Tuo

MRC | Medical

Diabetes Risk Test

Complete the questionnaire below to find out if you are at risk of developing type 2 diabetes.

	Answer	Tick appropriate box	Score
1. How old are you?	44 & under	☐	0
	45-49	☐	7
	50-54	☐	13
	55+	☐	18
2. What sex are you?	Male	☐	4
	Female	☐	0
3. What is your Body Mass Index (BMI)?	24 & under	☐	0
	25-29	☐	7
	30+	☐	15

Use your height and weight to work out your Body Mass Index (BMI) using the graph below: e.g. 4 ft10 ins 11 stone = obese class 1, i.e. BMI is over 30 therefore score 15.

	Answer	Tick appropriate box	Score
4. Have you been diagnosed with high blood pressure?			
	Yes	☐	10
	No	☐	0
5. Are you physically active in your leisure life? *e.g. 30 minutes of moderate physical activity, such as brisk walking, at least 5 days a week*			
	Yes	☐	0
	No	☐	6
6. Are either of your parents diabetic?			
	Yes	☐	7
	No	☐	0
		TOTAL (max 60)	

SCORE RANGES
If you have a total score of 31 or more you may be at increased risk of having undiagnosed diabetes. Please consider following the advice below and overleaf to arrange a simple blood sugar test at a local pharmacy, or discuss the result with your practice nurse.

Identify diabetes early

Diabetes causes elevated levels of sugar in the blood and may run in families. Untreated diabetes may cause damage to the heart, eyes, kidneys and feet. Early diagnosis and treatment can reduce the risk of complications.

Some of the signs of diabetes include always feeling tired, being irritable, being thirsty, passing urine excessively and getting infections and numbness in the feet.

See overleaf

Screening Criteria

- ✓ A well defined disorder with a known prevalence
- ✓ A burdensome disease with a long detectable pre-clinical phase
- ✓ A simple, safe, accessible, feasible, sensitive/specific screening test/programme
- **Absence of significant harm associated with screening**
- **An efficient intervention that is more effective earlier in the disease process**
- **Trial evidence of cost-effectiveness of screening**
- ~~**All primary prevention interventions should be in place**~~
- ~~**Clinical management of the condition should be optimised prior to screening**~~

Wilson JGM, Jungner G. Geneva: WHO, 1968
BMJ 2001;322:986-988

What determines the cost-effectiveness of diabetes screening?

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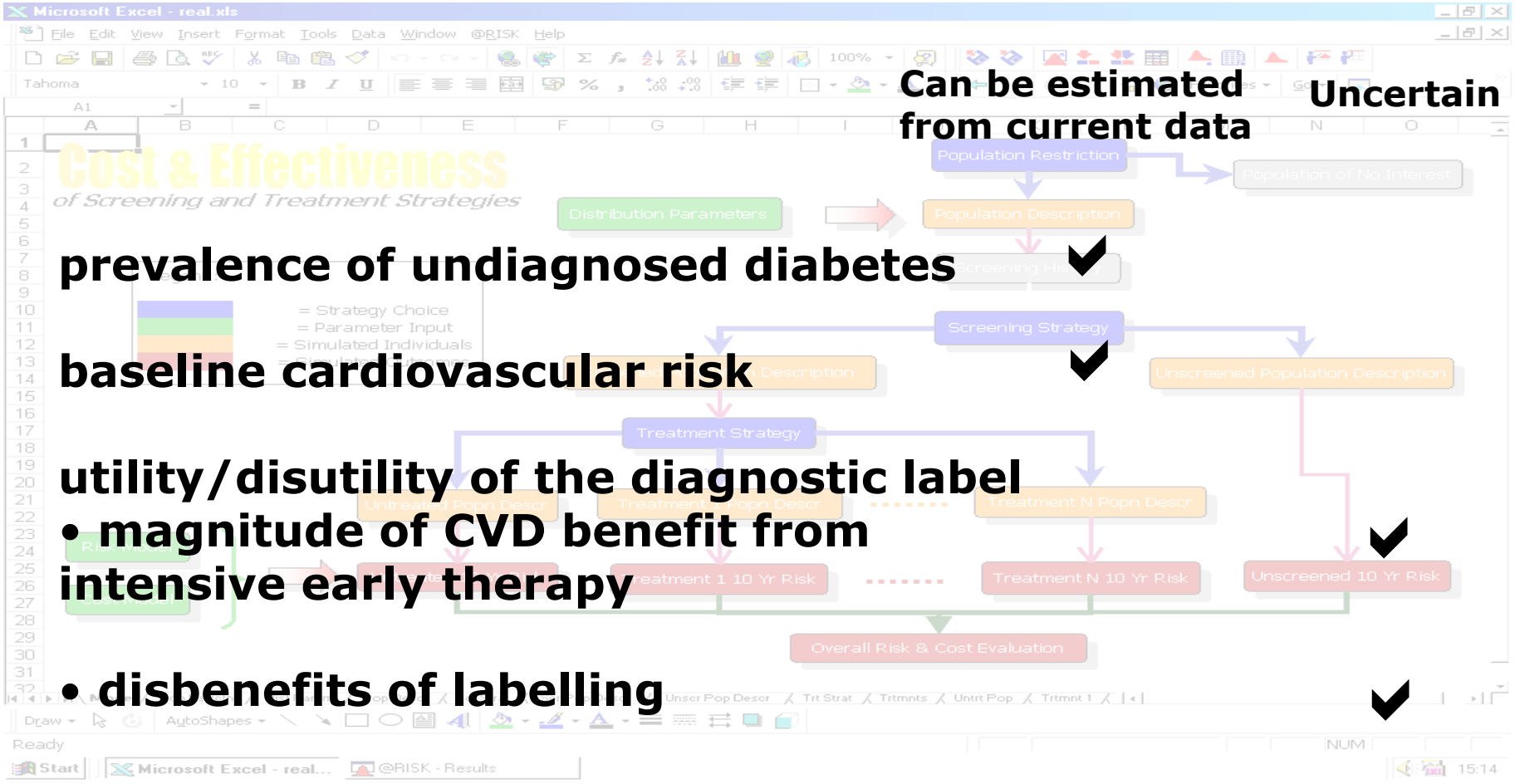


Can be estimated from current data ✓ **Uncertain**

prevalence of undiagnosed diabetes ✓

baseline cardiovascular risk ✓

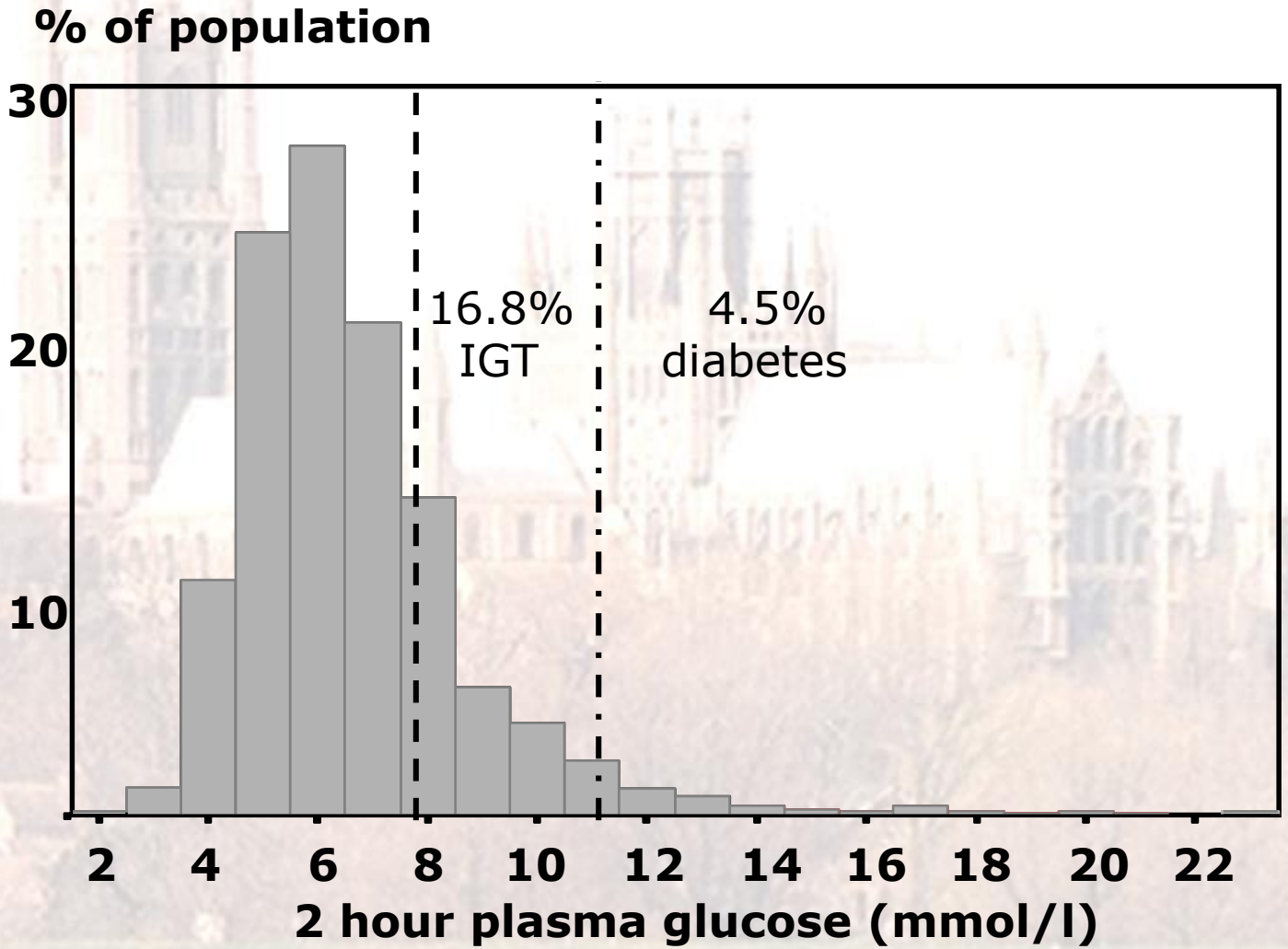
utility/disutility of the diagnostic label

- **magnitude of CVD benefit from intensive early therapy** ✓
- **disbenefits of labelling** ✓

Diabetologia 2006;49:1536-1544
BMJ 2001;322:986-988

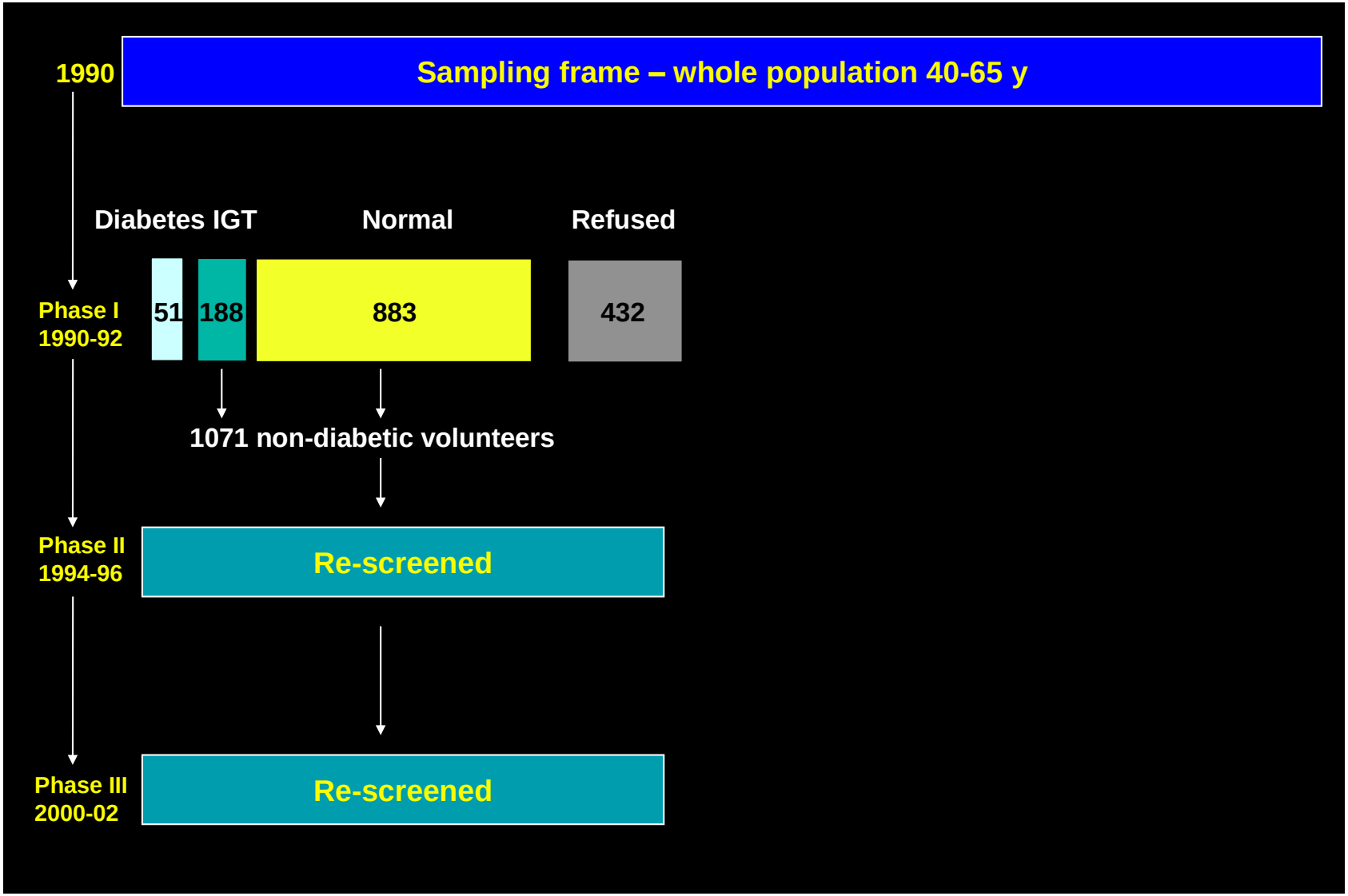
Ely Retrospective Study

Population Distribution of 2-Hour Glucose in a Previously Unscreened Population: Ely Study

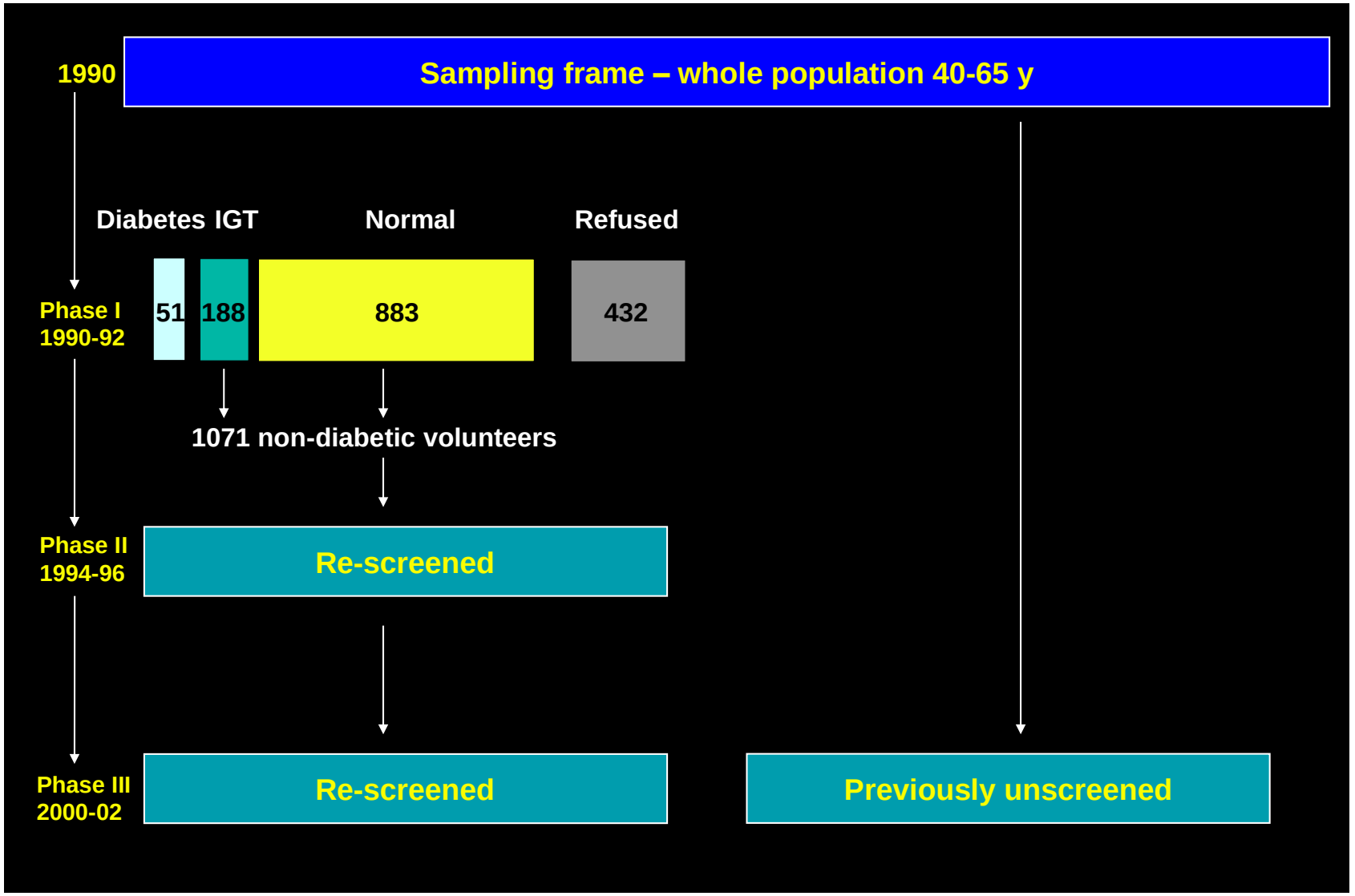


Williams DRR, Wareham NJ et al. *Diabetic Med* 1995;12:30-5

Ely Retrospective Study Design



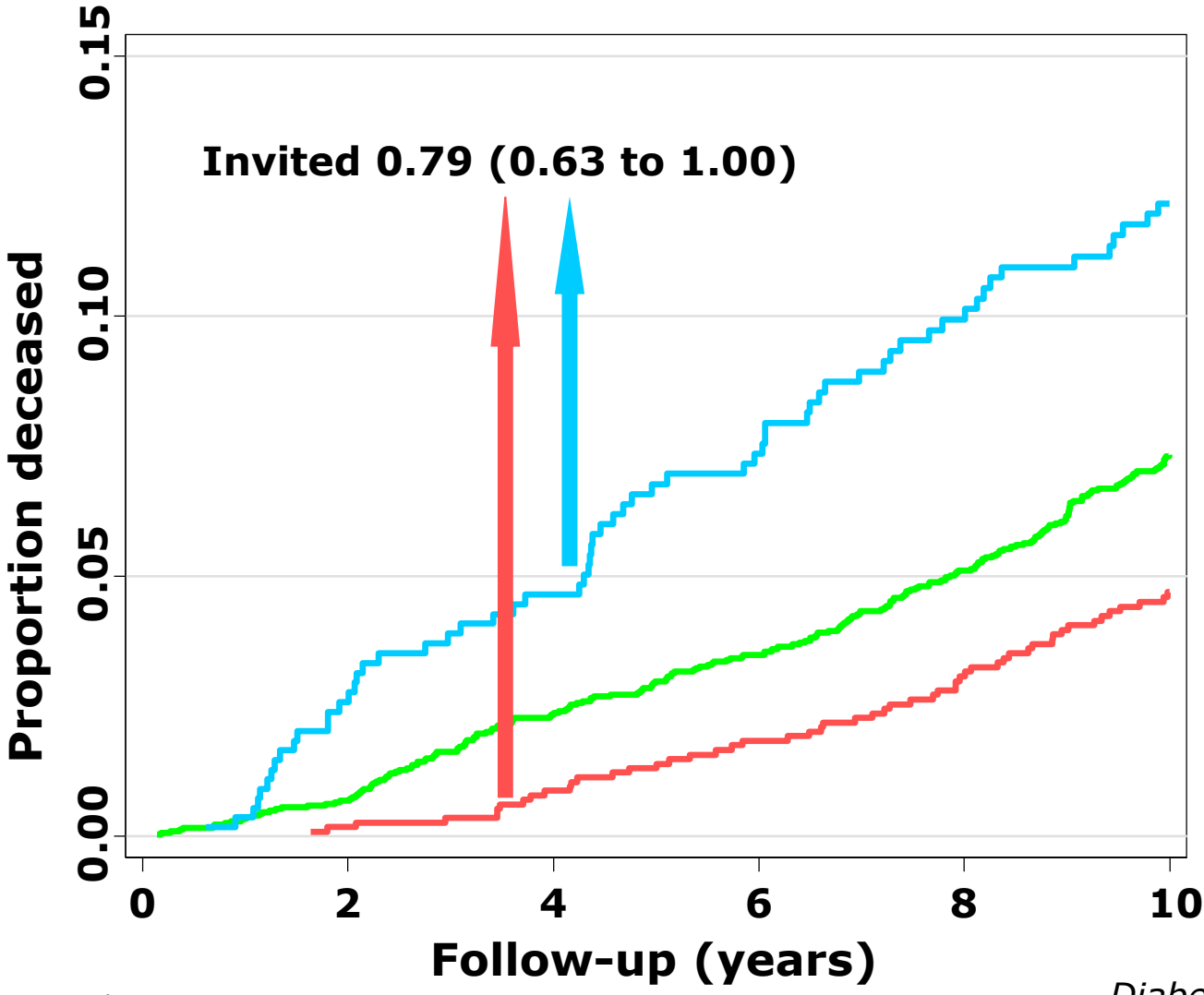
Ely Retrospective Study Design



Results

- **68% initial attendance**
- **Non-attenders were more likely to be male ($p<0.001$) and more deprived ($p=0.005$)**
- **345 deaths over a median of 10 years**

Kaplan-Meier Curves for the Ely cohort 1990-1999 by Attendance at Screening (adjusted for age, gender and social class)



Invited but did not attend
1.36 (1.01 to 1.82)

Not invited

Invited and attended
0.54 (0.40 to 0.74)

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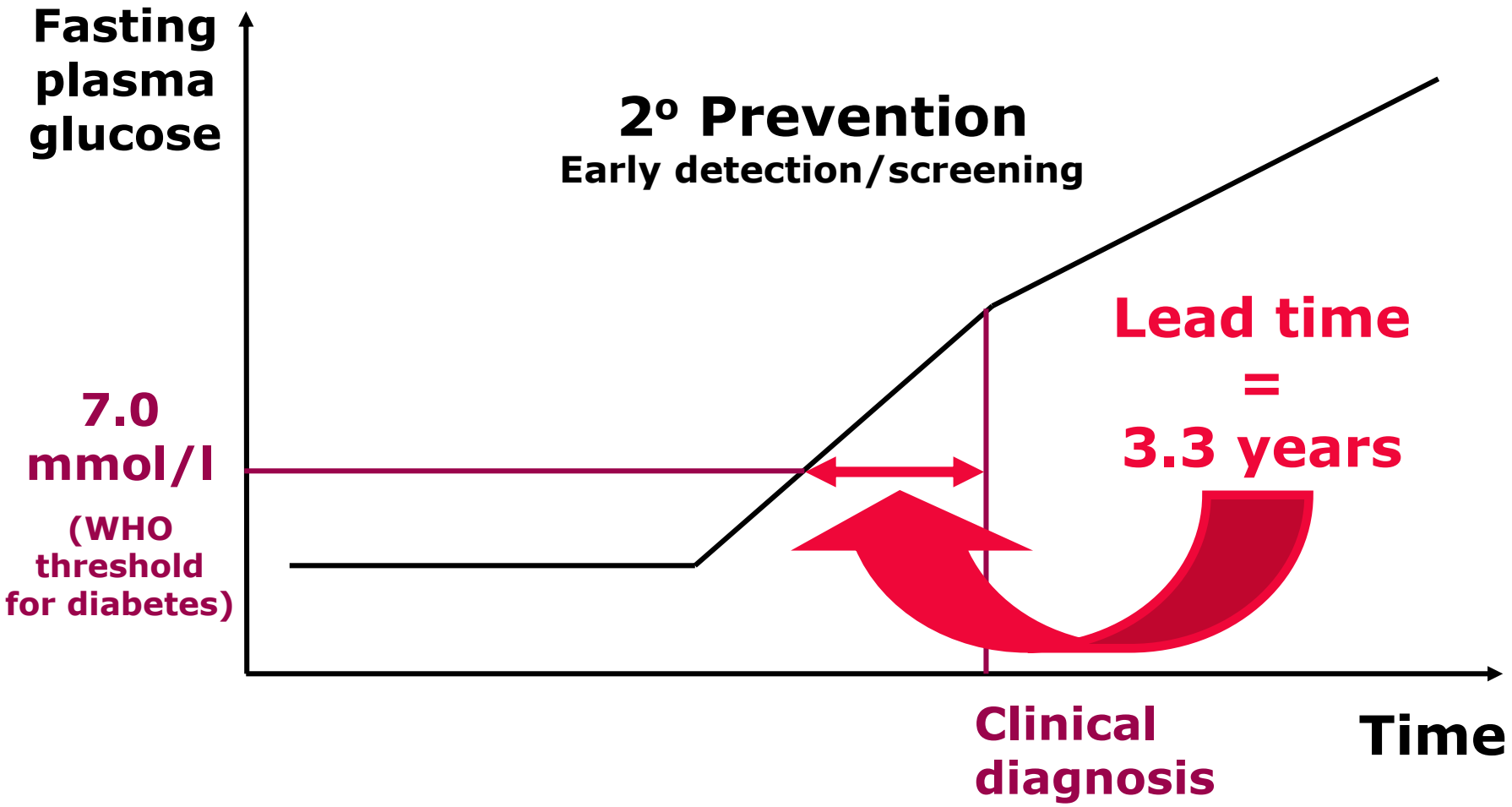
Diabetologia 2011;54:312–319.

Duration of lead time



A Randomised Trial of Screening for Diabetes: Effects on Anxiety

1200 people aged 40-69 yrs without known diabetes

354 in the top 30 % of risk for having undiagnosed diabetes

116 Invited

238 Not Invited

After 6 weeks postal questionnaires:
SF-Spielberger Anxiety, Self Perceived Health

70% response rate

BMC Public Health 2008;8:350.

Results

	Invited Mean (SD)	Not Invited Mean (SD)	p-value (MWU test)
Anxiety	37.6 (12.2)	34.1 (12.1)	0.015
Self perceived health	3.03 (0.86)	3.05 (0.87)	0.998

- **Mean anxiety score in the 6 new patients was 46.7**
- **ICD-10 threshold for 'clinical anxiety' is 42**
- **Mean anxiety score in pregnant women who have just received an abnormal test result for Down's syndrome/Spina Bifida screening is 46.4**

BMC Public Health 2008;8:350.

ADDITION-Cambridge Study Design

60 practices in the Eastern Region

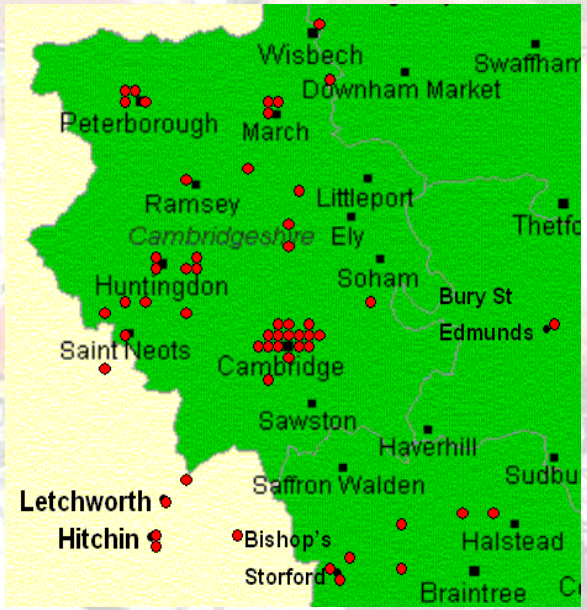
28 practices screening and intensive target driven management of risk factors

27 practices screening and routine care

5 control practices

1 year — **Assessment of CVD risk among screen-detected diabetic patients**

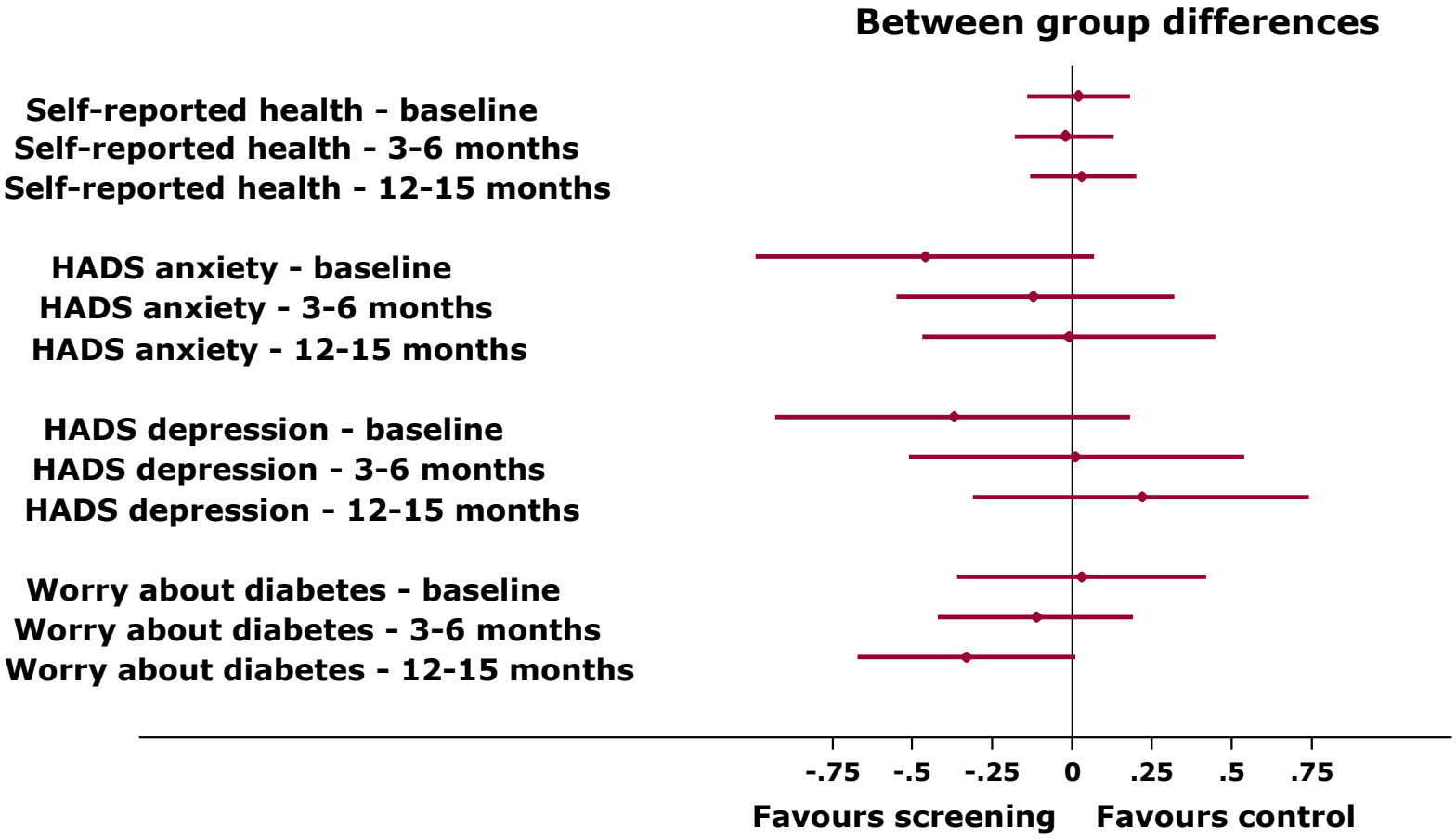
5 years — **Assessment of CVD events and mortality among screen-detected diabetic patients**



BMC Public Health 2009;9:136.

No Evidence of Harmful Effects of Screening For Type 2 Diabetes

- Parallel group cohort study in 10 screening and five control practices
- Questionnaires sent to 6416 invited for screening and 964 controls



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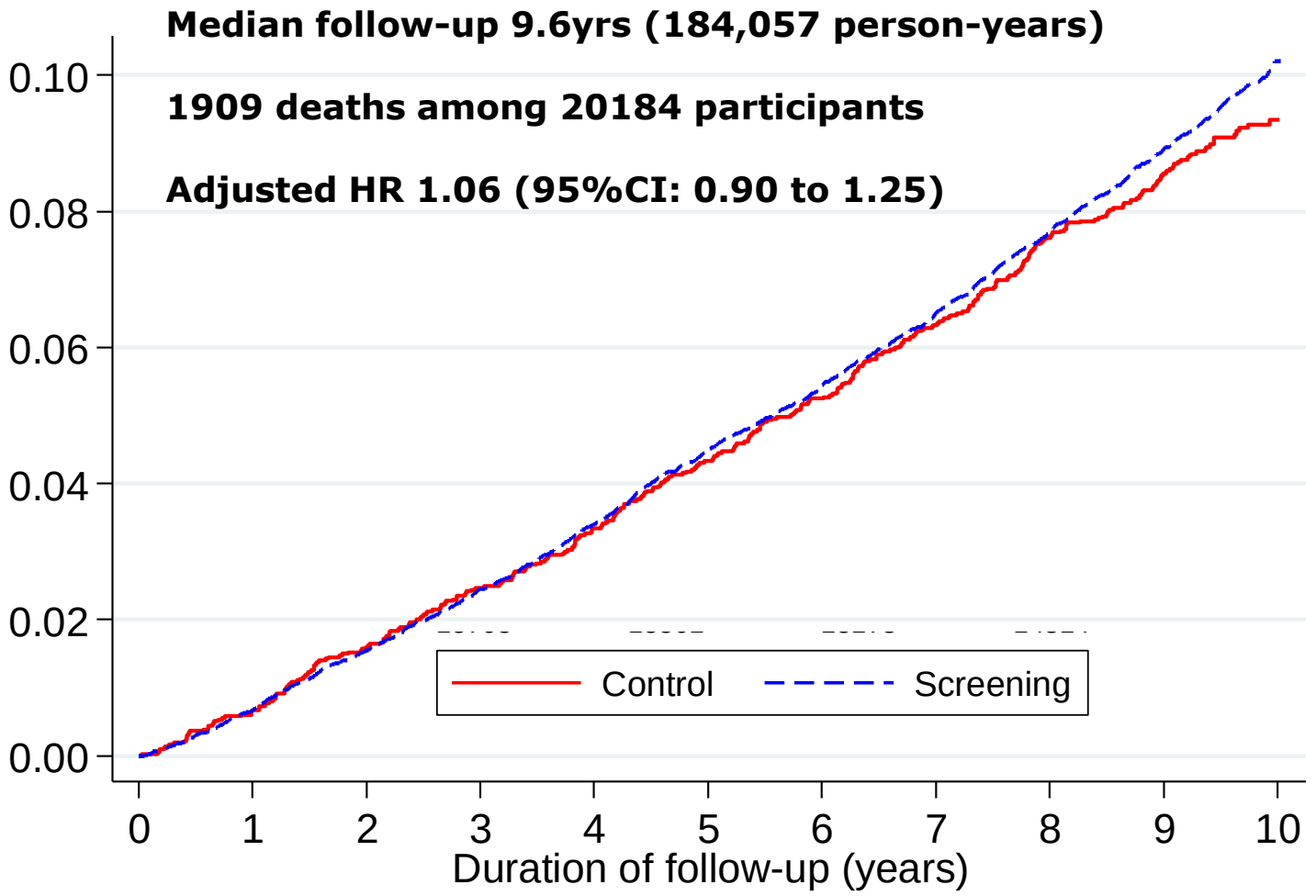
BMJ 2007;335:486-489.

No Evidence of False Reassurance

- Parallel group cohort study in 10 screening and five control practices
- 964 controls and 4370 screening attenders were sent questionnaires
- No significant differences between controls and screen negatives for perceived personal risk, behavioural intentions, or self-rated health after first appointment, at 3-6 months or 12-15 months later

BMJ 2009;339:b4535.

Cumulative incidence of death in the screening and no-screening control groups (ADDITION-Cambridge trial)



Lancet 2012;380:1741-1748

Screen-detected patients have high but potentially modifiable CVD risk

- **18.5% had pre-existing CVD**
- **85.8% had hypertension (BP≥135/85)**
  - **35% not prescribed drugs**
  - **42.0 % were sub-optimally treated**
- **72.5% had dyslipidemia (tot chol>5.0mmol/l)**
  - **67.9% not prescribed medication**
- **20.0% had microalbumiuria**
- **18.1% were smokers**
- **Median 10-year CVD risk**
  - **UKPDS: 34.0% in men and 21.5% in women**
  - **Framingham: 38.6% in men and 24.6% in women**
- **Numbers needed to treat* were 11-20 and 10-19**

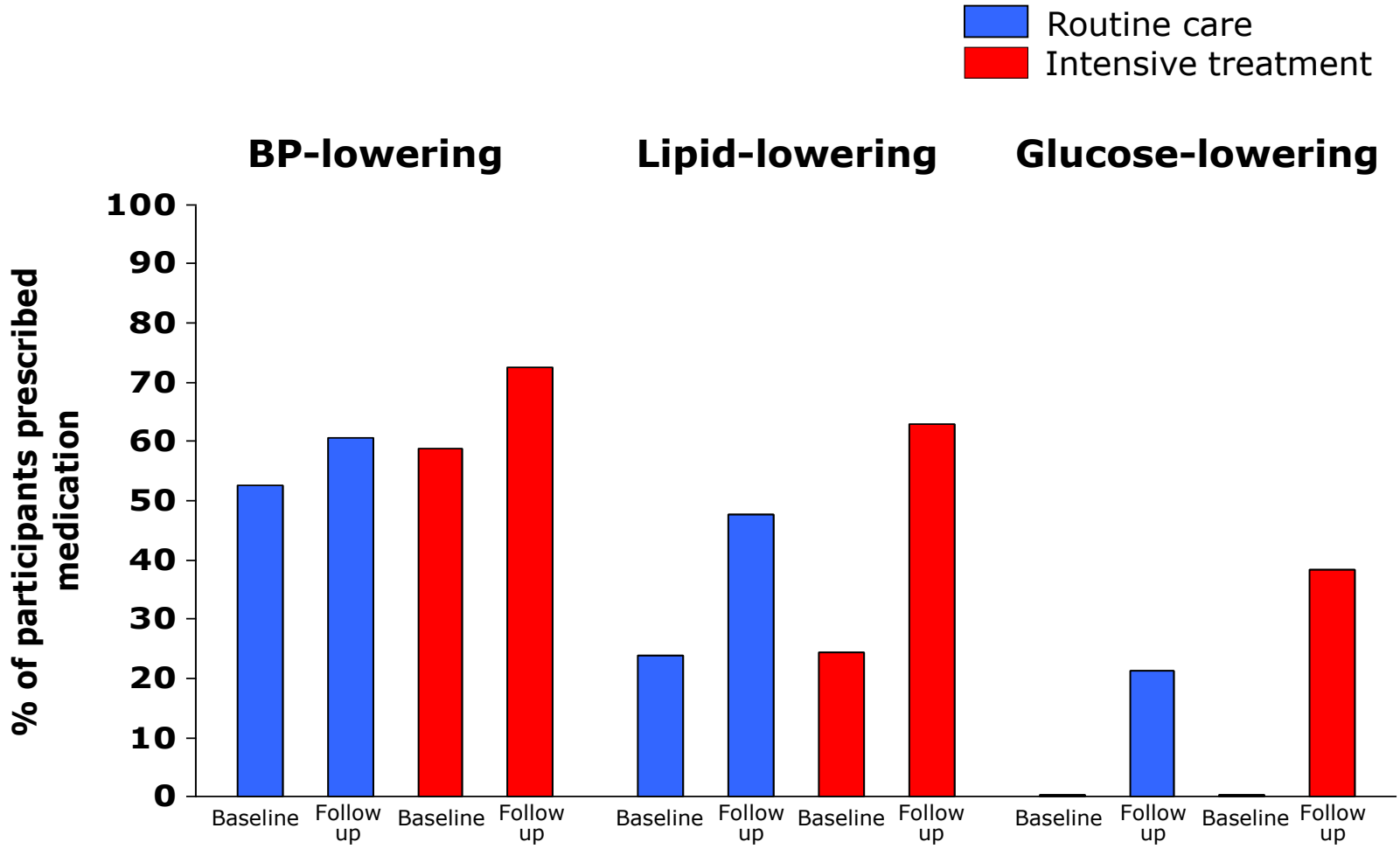
*** Conservative scenario (no additive effect of therapies)**

Adapted from *Diabet Med 2008;25:1433–1439.*

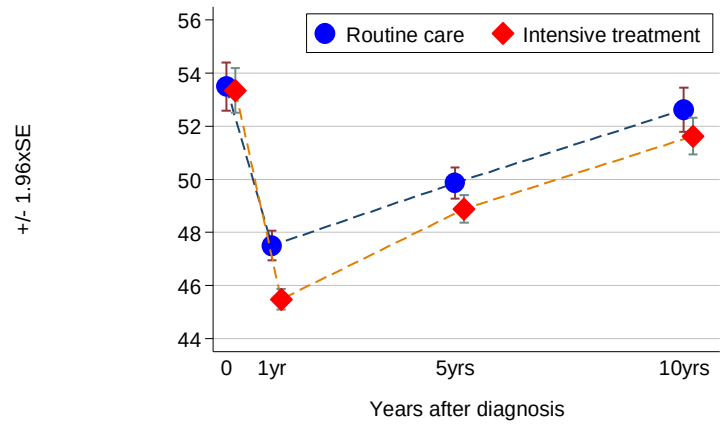
Change in Outcomes Over 1 Year Among Screen-detected Routine Care Participants

	Baseline Mean (SD)	One Year Mean (SD)
HbA1c (%)	**7.33 (1.65)**	**6.62 (0.95)**
BMI kg/m^2	**33.6 (5.9)**	**32.6 (6.0)**
Systolic BP (mmHg)	**142.1 (20.0)**	**138.0 (18.6)**
Diastolic BP (mmHg)	**81.4 (10.3)**	**79.6 (9.9)**
Cholesterol (mmol/l)	**5.42 (1.18)**	**4.74 (0.96)**

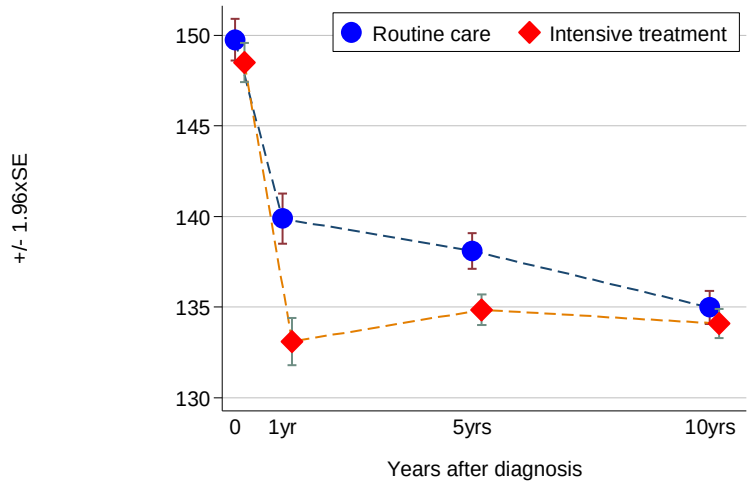
Prescribed treatment at baseline and 1yr follow-up



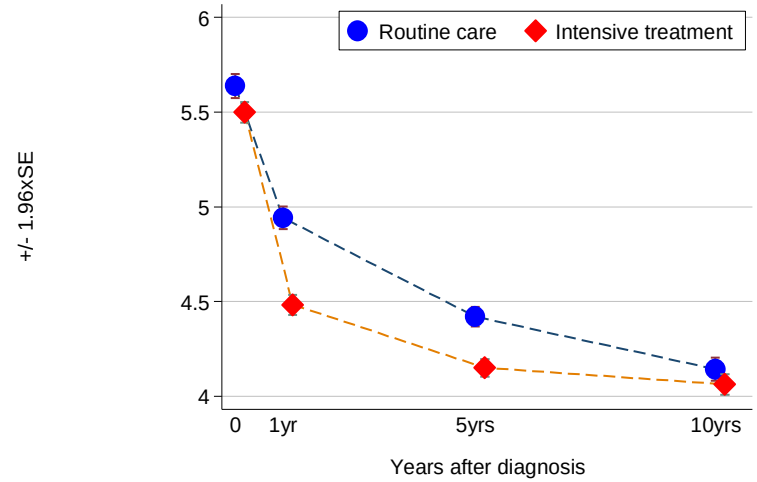
Change in CVD risk factors in the 10 years following diagnosis by screening



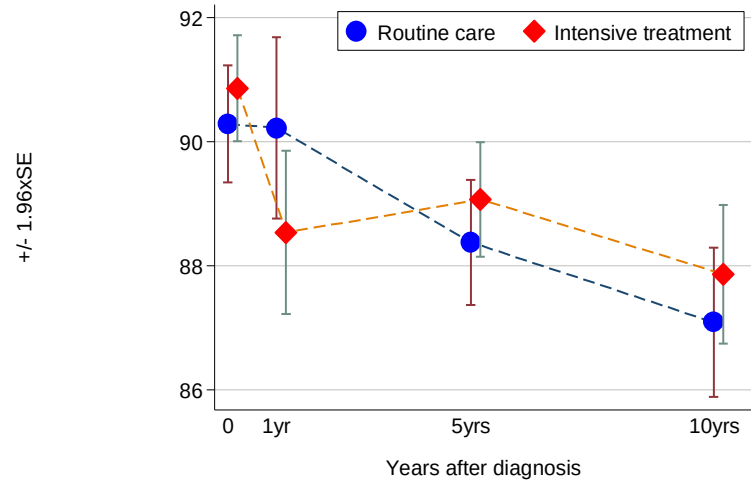
Routine Care	1298	1202	1226	954
Intensive Treatment	1591	1547	1514	1162



Routine Care	1346	642	1205	879
Intensive Treatment	1617	682	1518	1100



Routine Care	1300	1134	1226	950
Intensive Treatment	1593	1377	1524	1149



Routine Care	1344	585	1192	789
Intensive Treatment	1615	636	1491	1019

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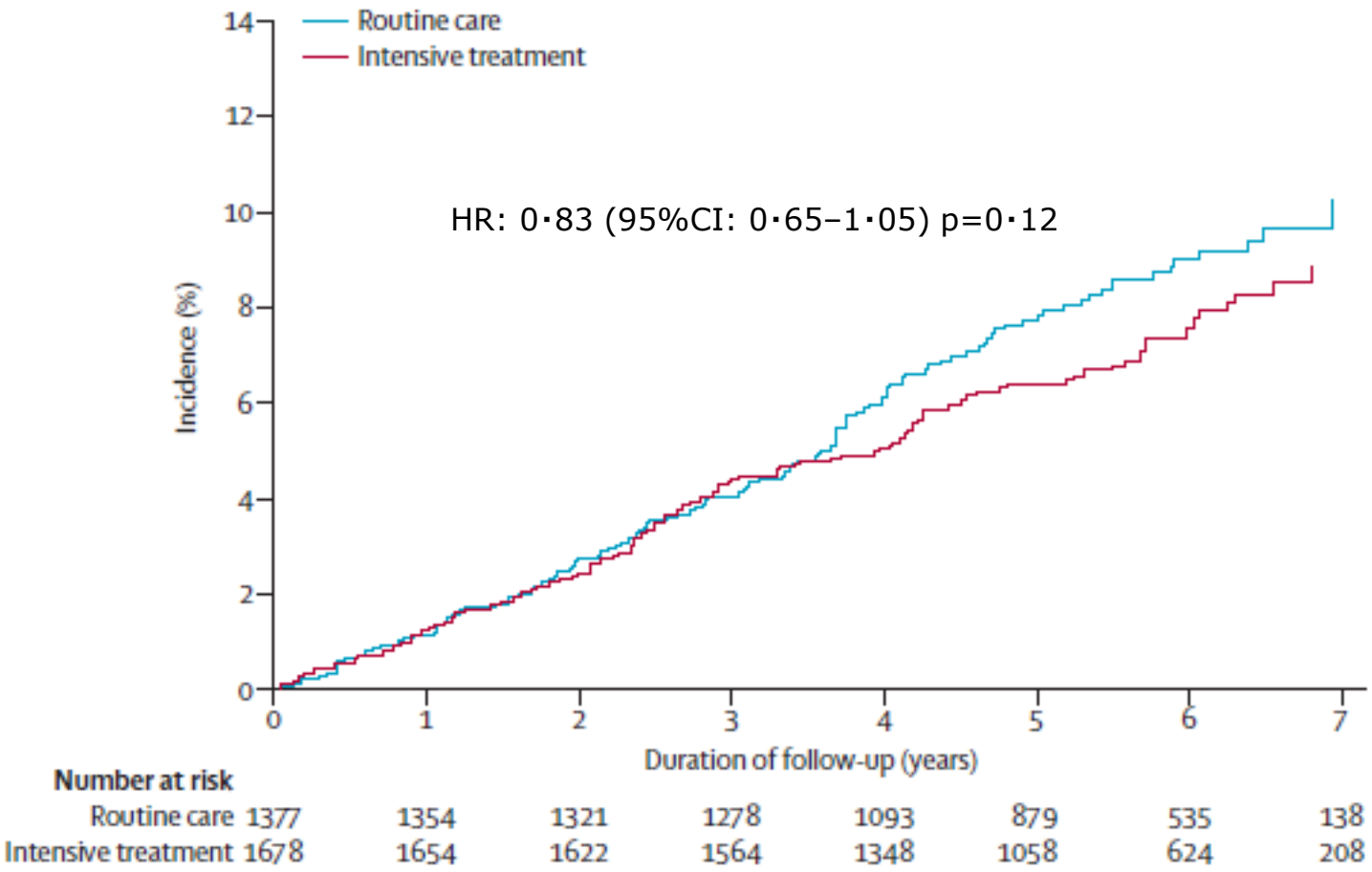
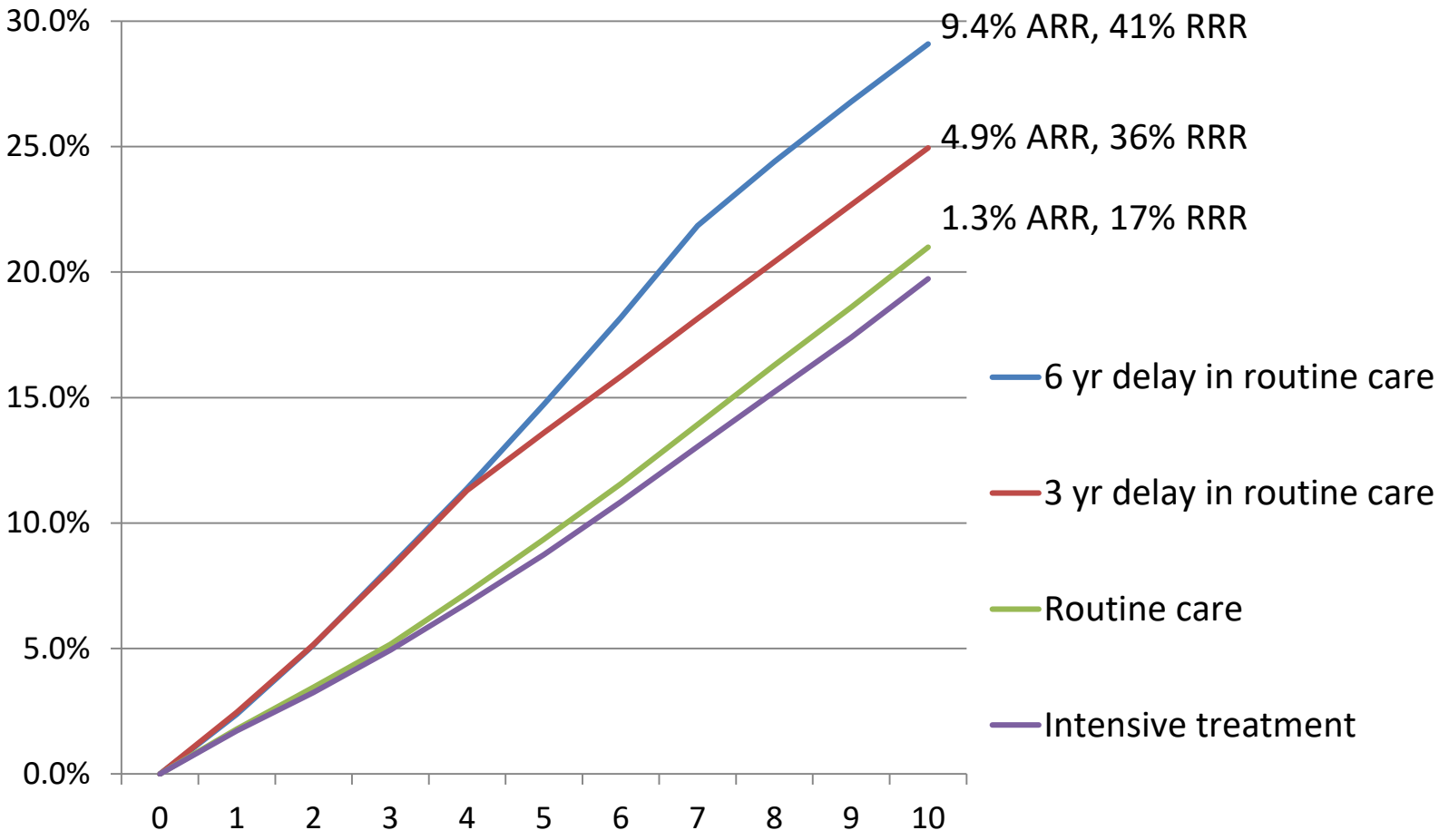
Under review *Lancet Diabetes Endocrinol*

Cumulative incidence of composite cardiovascular endpoint



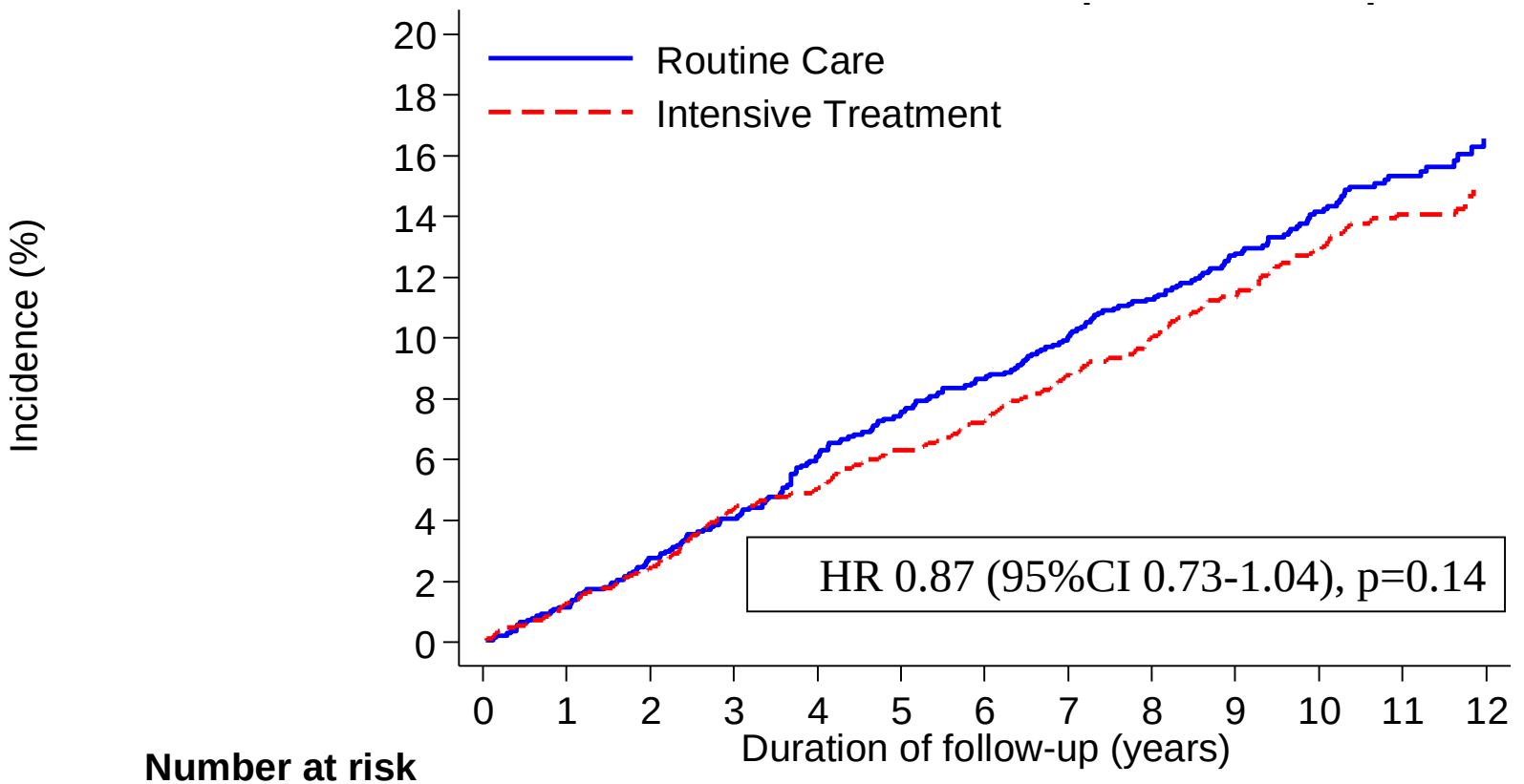
Lancet 2011;378:156-167.

Michigan model simulation of incidence of the composite CVD outcome by treatment group with and without delays in diagnosis and treatment in the *ADDITION-Europe* trial



Diabetes Care 2015;38:1449-1455.

Cumulative incidence of composite cardiovascular endpoint



Number at risk

Routine Care	1379	1322	1255	1185	1091	786	261
Intensive Treatment	1678	1623	1543	1474	1391	1001	309

ADDITION-Denmark study design

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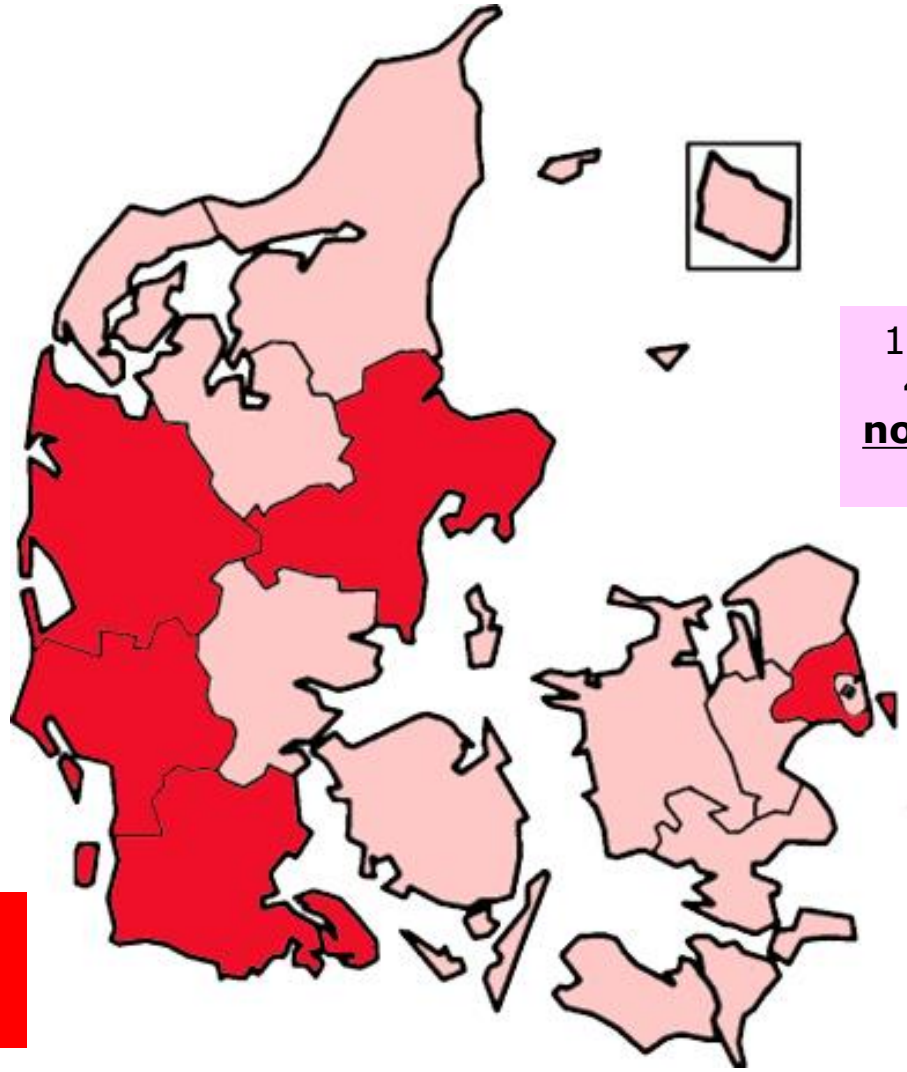

1,759,285 people aged 40-69 years in 2,247 **no-screening (control)** practices

153,107 people aged 40-69 years in 181 **screening** practices

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Intervention: invitation to screening for diabetes and CVD risk

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HAR DU FORØGET RISIKO FOR SUKKERSYGE?

Du kan se om din risiko for at have sukkersyge er højere end normalt ved at besvare de følgende 7 spørgsmål. Ved hvert spørgsmål kan du skrive dit point-tal i kolonnen til højre og til sidst lægge alle pointene sammen. Hvis du har 5 point eller mere, er din risiko for at have sukkersyge forøget, og du opfordres til at bestille tid ved din læge til undersøgelse for sukkersyge.

1. Er du mand eller kvinde?

		Skriv point
Mand giver	**1 point**	
Kvinde giver	0 point	

2. Hvor gammel er du?

		Skriv point
Yngre end 45 år giver	**0 point**	
Imellem 45 og 49 år giver	1 point	
Imellem 50 og 54 år giver	**2 point**	
Imellem 55 og 59 år giver	3 point	
60 år og ældre giver	**4 point**	

3. Har du tidligere haft sukkersyge, som svandt igen?

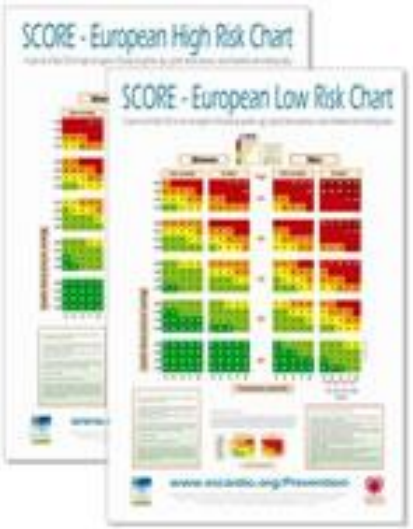
		Skriv point
Ja giver	**2 point**	
Nej giver	0 point	

4. Har eller havde dine forældre eller søskende sukkersyge?

		Skriv point
"Ingen af mine søskende eller forældre har/havde sukkersyge" giver	**0 point**	
"En af mine søskende eller en af mine forældre har/havde sukkersyge" giver	1 point	
"2 eller flere af mine søskende eller forældre har/havde sukkersyge" giver	**2 point**	
"Ved ikke" giver	0 point	

5. Har du nogensinde fået at vide, at du har haft højt eller forhøjet blodtryk?

		Skriv point
Ja giver	**2 point**	
Nej giver	0 point	
Ved ikke giver	**0 point**	



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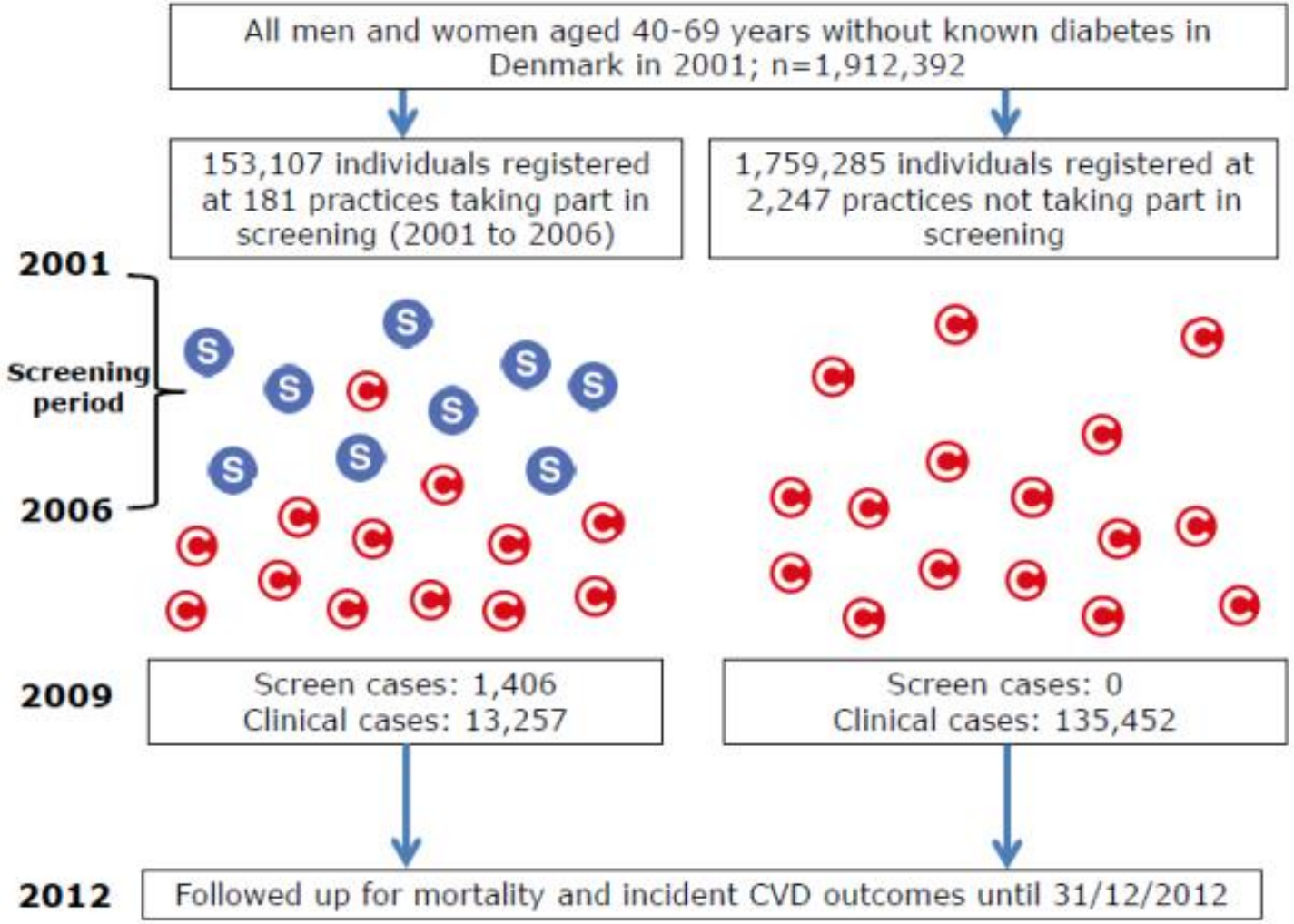
Effect of screening on risk of cardiovascular disease and mortality among 150,115 individuals with diabetes in Denmark



Cumulative incidence of death among people with diabetes in the screening and no-screening control groups

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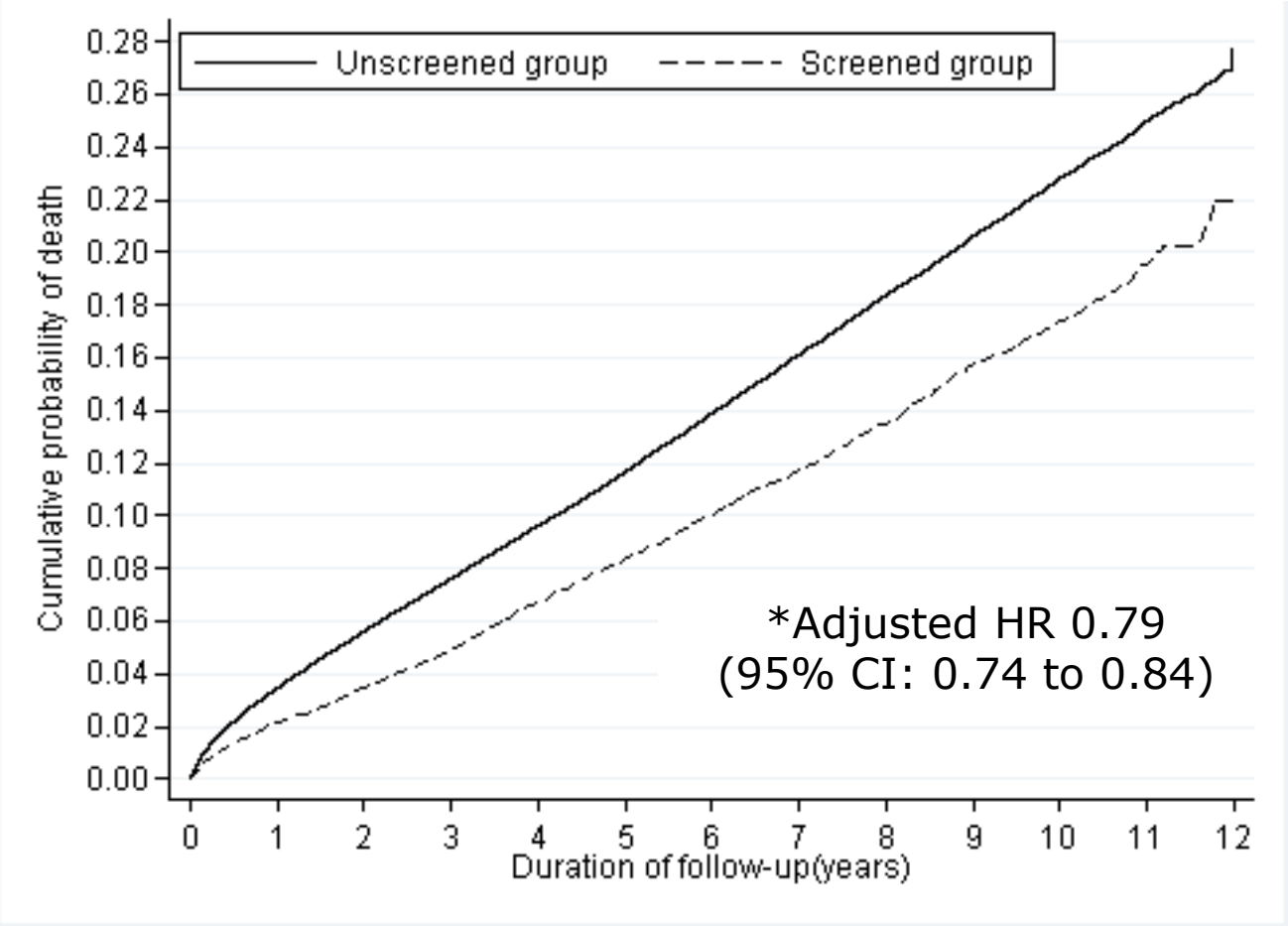
Control: 22,132 deaths in 865,994pyrs = 25.6/1000pyrs
Screening: 1,890 deaths in 102,126pyrs = 18.5/1000pyrs



*Adjusted for age, sex, education, and prevalent chronic disease (IHD, stroke, cancer); baseline hazards were stratified by county

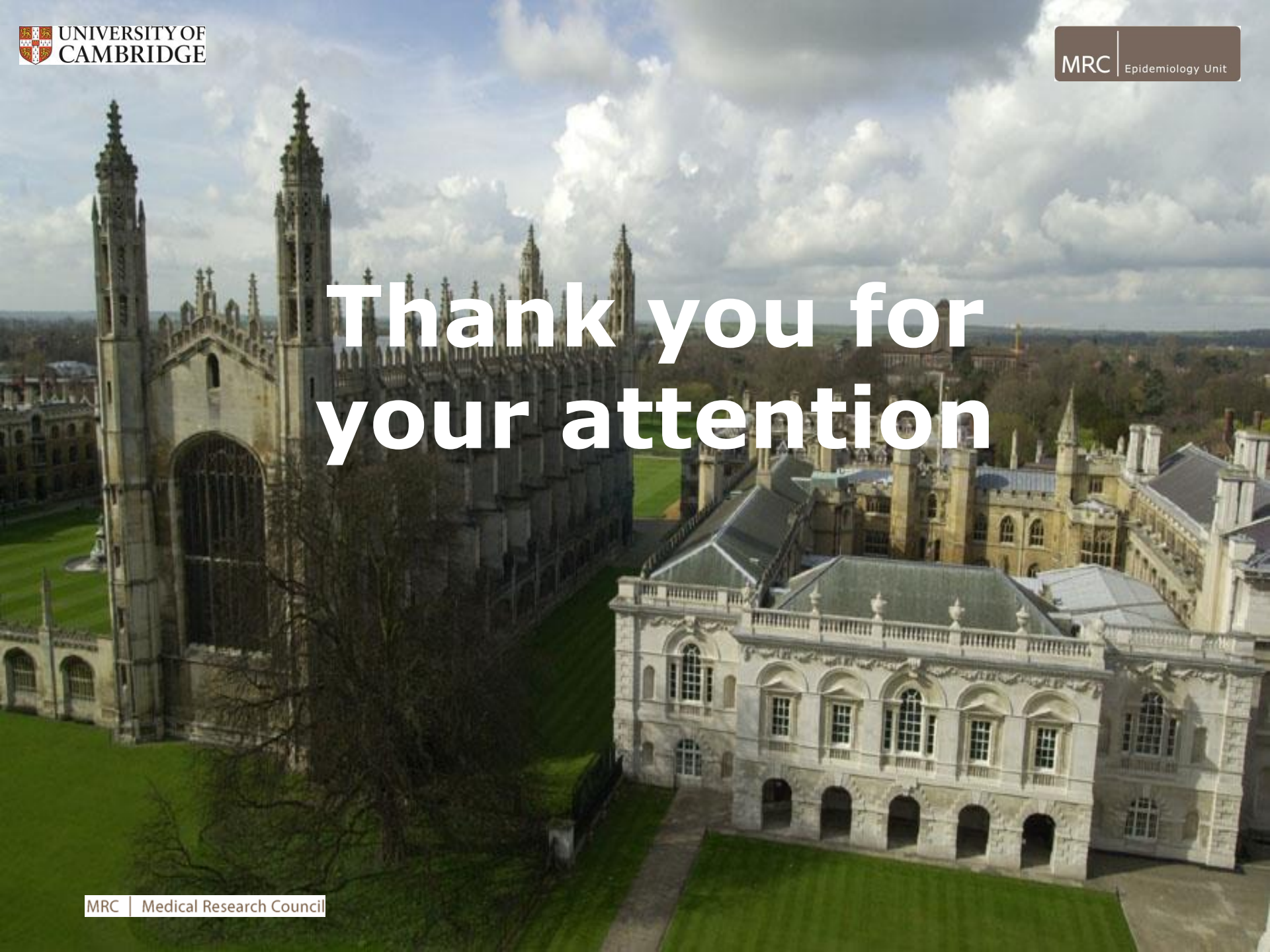
Diabetologia 2017;60:2192–2199.

Take home messages: early detection of people with diabetes

- **Population-based screening for type 2 diabetes is probably feasible…..just**
- **Screening identifies individuals with high but modifiable cardiovascular risk which is reduced following diagnosis, particularly by early intensive treatment**
- **The harmful effects of screening appear to be minimal**
- **The benefits of detection of diabetes and treatment earlier in the disease trajectory appear to outweigh the harms**

However….

- **Uncertainties remain, particularly concerning cost-effectiveness**
- **Screening does not reduce overall population mortality but may reduce mortality in those with undiagnosed diabetes**
- **Given the uncertainties screening should be targeted at those at increased risk**
- **If screening for diabetes is undertaken it should be combined with screening for other CVD risk factors and prevention among those at risk of diabetes**
- **Data are from high income countries, the benefits and costs of screening may be different in low income countries with higher prevalence of undiagnosed diabetes**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Thank you for your attention
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