Udvikling og validering af en ny risikomodel for lungecancer baseret på biokemi – CPH-Lung

Årsmøde for Dansk Lungecancer Gruppe, 2. september 2025

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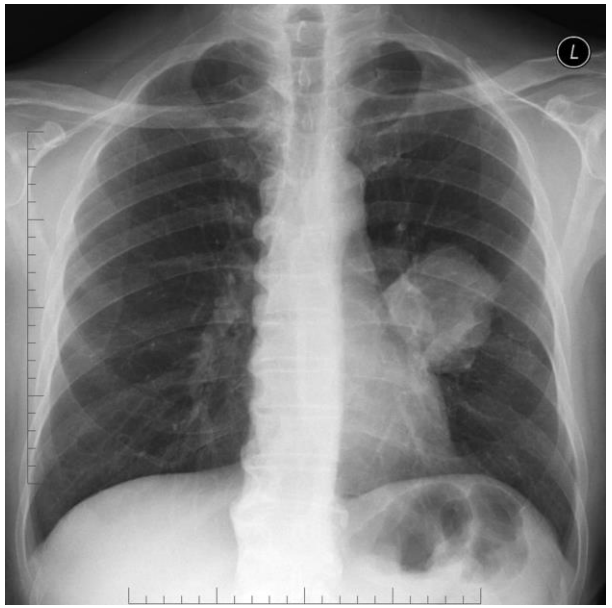
Hvem skal screenes for lungecancer?

- Lungekræft dræber ca. 3,500 danskere per år
- Screening med low-dose CT for lungekræft øger overlevelsen

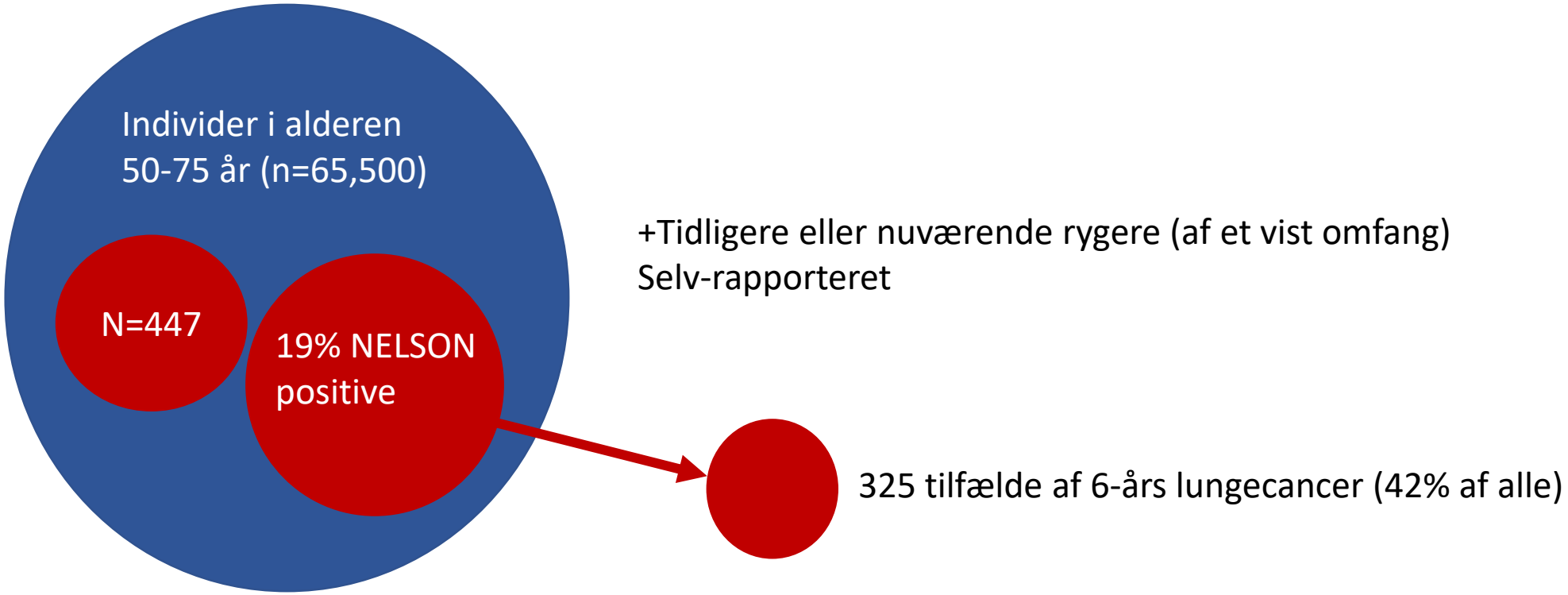


Hvem skal screenes for lungecancer?

Herlev-Østerbroundersøgelsen

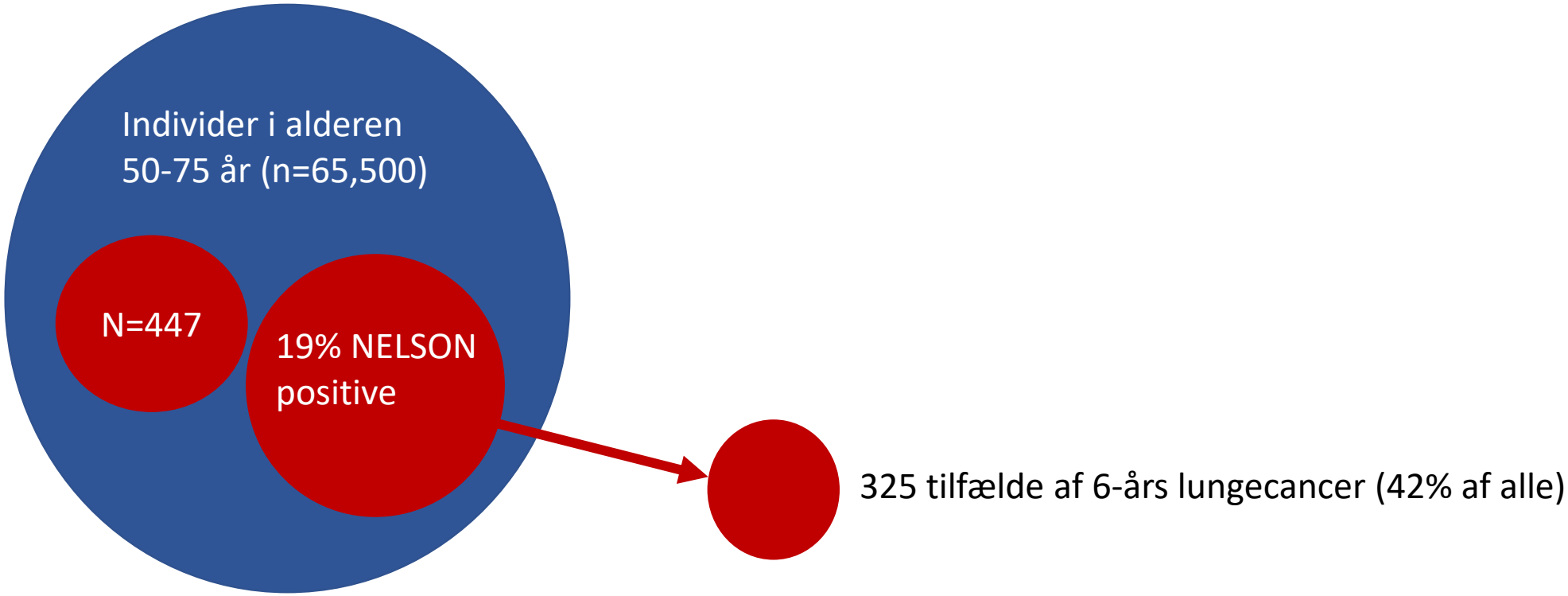
110.000 deltagere

772 tilfælde af 6-års lungecancer



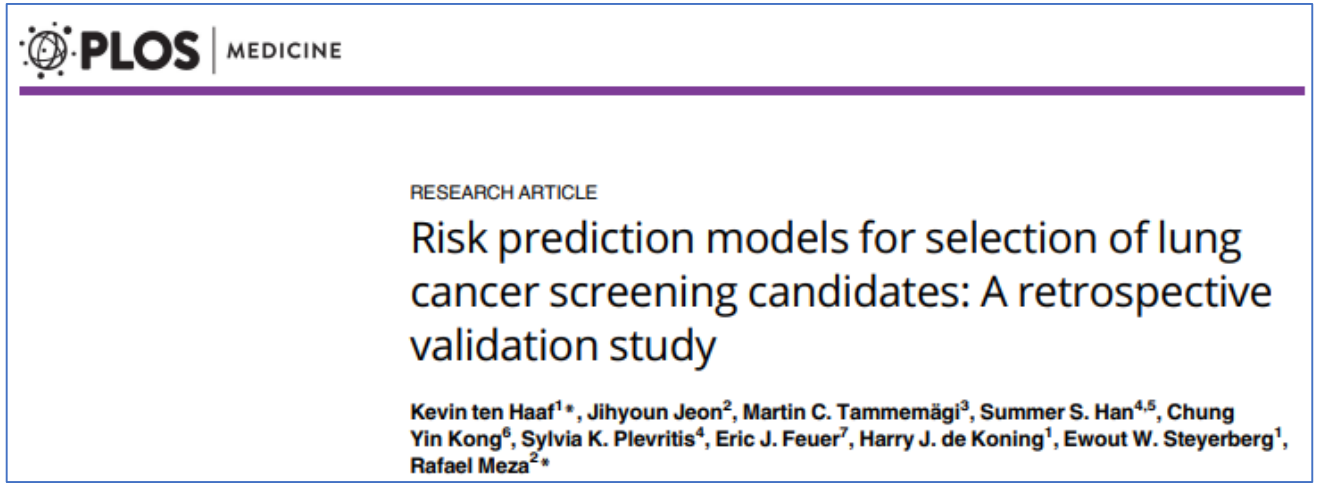
Hvem skal screenes for lungecancer?

Algoritmer udpeger 15-20% af befolkningen over 50 år som i risiko –
men overser 40-60% af de, der senere udvikler lungekræft
20% af befolkningen mellem 50-75 år = 360.000 personer



Hvem skal screenes for lungecancer?

Risikomodeller kan potentielt forbedre sensitivitet og cost-effectiveness af screening – fx PLCOm2012


PLOS | MEDICINE

RESEARCH ARTICLE

Risk prediction models for selection of lung cancer screening candidates: A retrospective validation study

Kevin ten Haaf[1]*, Jihyoun Jeon[2], Martin C. Tammemägi[3], Summer S. Han[4,5], Chung Yin Kong[6], Sylvia K. Plevritis[4], Eric J. Feuer[7], Harry J. de Koning[1], Ewout W. Steyerberg[1], Rafael Meza[2]*


ORIGINAL RESEARCH

Annals of Internal Medicine

Risk Model–Based Lung Cancer Screening

A Cost-Effectiveness Analysis

Iakovos Toumazis, PhD; Pianpian Cao, PhD*; Koen de Nijs, MSc*; Mehrad Bastani, PhD*; Vidit Munshi, PhD; Mehdi Hemmati, PhD; Kevin ten Haaf, PhD; Jihyoun Jeon, PhD; Martin Tammemägi, PhD; G. Scott Gazelle, MD, MPH, PhD; Eric J. Feuer, PhD; Chung Yin Kong, PhD; Rafael Meza, PhD; Harry J. de Koning, MD; Sylvia K. Plevritis, PhD; and Summer S. Han, PhD

Hvem skal screenes for lungecancer?

Risikomodeller kan potentielt forbedre sensitivitet og cost-effectiveness af screening – fx PLCOm2012

PLOS | MEDICINE

Variable	Odds Ratio (95% CI)	P Value	Beta Coefficient
Age, per 1–yr increase†	1.081 (1.057–1.105)	<0.001	0.0778868
Race or ethnic group‡			
White	1.000		Reference group
Black	1.484 (1.083–2.033)	0.01	0.3944778
Hispanic	0.475 (0.195–1.160)	0.10	–0.7434744
Asian	0.627 (0.332–1.185)	0.15	–0.466585
American Indian or Alaskan Native	1		0
Native Hawaiian or Pacific Islander	2.793 (0.992–7.862)	0.05	1.027152
Education, per increase of 1 level†§	0.922 (0.874–0.972)	0.003	–0.0812744
Body-mass index, per 1-unit increase†	0.973 (0.955–0.991)	0.003	–0.0274194
Chronic obstructive pulmonary disease (yes vs. no)	1.427 (1.162–1.751)	0.001	0.3553063
Personal history of cancer (yes vs. no)	1.582 (1.172–2.128)	0.003	0.4589971
Family history of lung cancer (yes vs. no)	1.799 (1.471–2.200)	<0.001	0.587185
Smoking status (current vs. former)	1.297 (1.047–1.605)	0.02	0.2597431
Smoking intensity¶			–1.822606
Duration of smoking, per 1-yr increase†	1.032 (1.014–1.051)	0.001	0.0317321
Smoking quit time, per 1-yr increase†	0.970 (0.950–0.990)	0.003	–0.0308572
Model constant			–4.532506

Annals of Internal Medicine

ni, PhD*; Vidit Munshi, PhD; Mehdi Hemmati, PhD; Kevin ten Haaf, PhD; Jihyoun Jeon, PhD; Martin Tammemägi, PhD; G. Scott Gazelle, MD, MPH, PhD; Eric J. Feuer, PhD; Chung Yin Kong, PhD; Rafael Meza, PhD; Harry J. de Koning, MD; Sylvia K. Plevritis, PhD; and Summer S. Han, PhD

Mål

At udvikle en mere sensitiv risikomodel for 6-års lungecancer i nuværende og tidligere rygere baseret på kliniske, biokemiske og epigenetiske risikomarkører

Metode

- Udvikling af risikomodel i **Herlev-Østerbroundersøgelsen**
  - Nested case-control studie inkluderende nuværende og tidligere rygere
  - 689 cases med 6-års lungecancer matchet 1:3 med 1924 kontroller
  - 26 kliniske og biokemiske variable testet for association med 6-års lungecancer
  - Inklusiv en epigenetisk markør for rygning – *AHRR* metylering

- Validering i **Østerbroundersøgelsen**
  - 2001-2003 visit
  - Kohorte inkluderende nuværende og tidligere rygere med alder ≥50 år
  - 68 tilfælde af 6-års lungecancer blandt 3195 individer

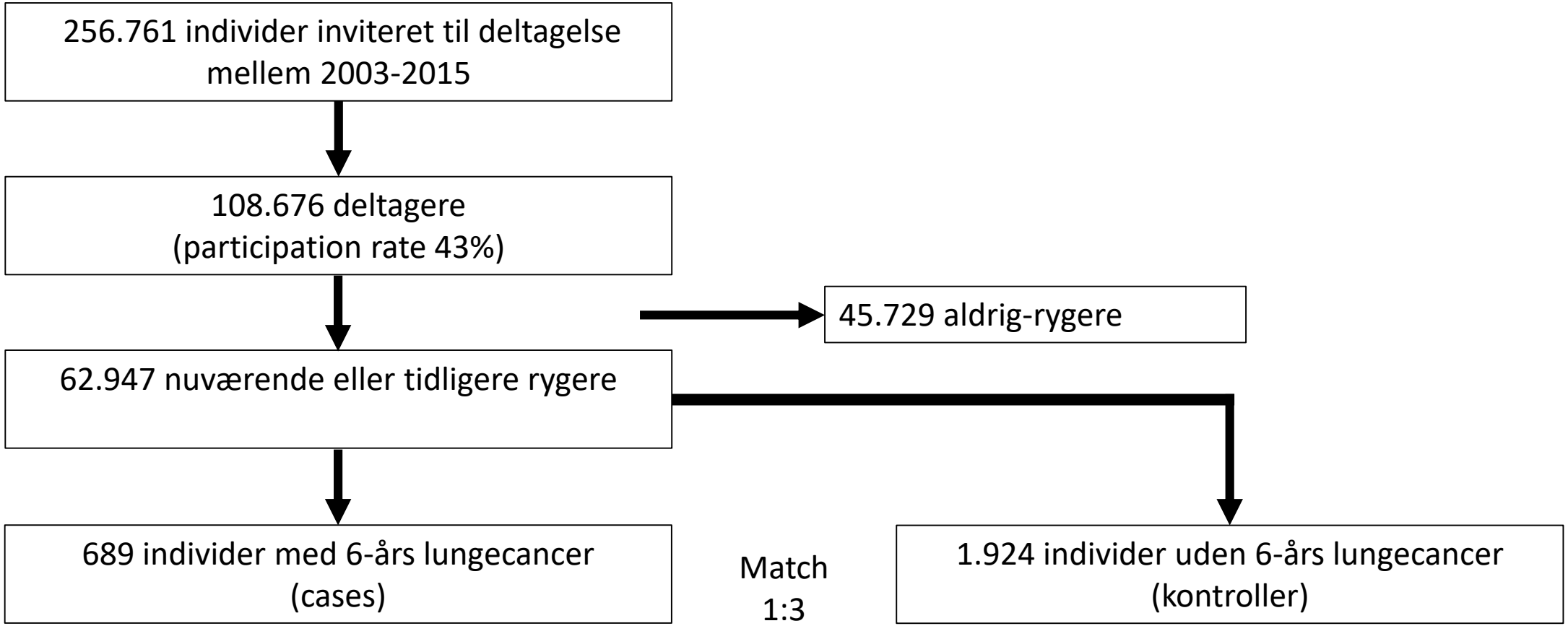
- Sammenligning med **PLCOm2012 modellen**
  - Udregning af 6-års lungecancer risiko baseret på alder, race, uddannelse, BMI, KOL diagnose, tidligere kræft, lungekræft i familien, rygestatus, rygeintensitet, varighed af rygning og tid siden rygeophør.

Herlev Østerbroundersøgelsen
110.000 deltagere
2003-2015

Østerbroundersøgelsen
6.200 deltagere
2001-2003 (fjerde visit)

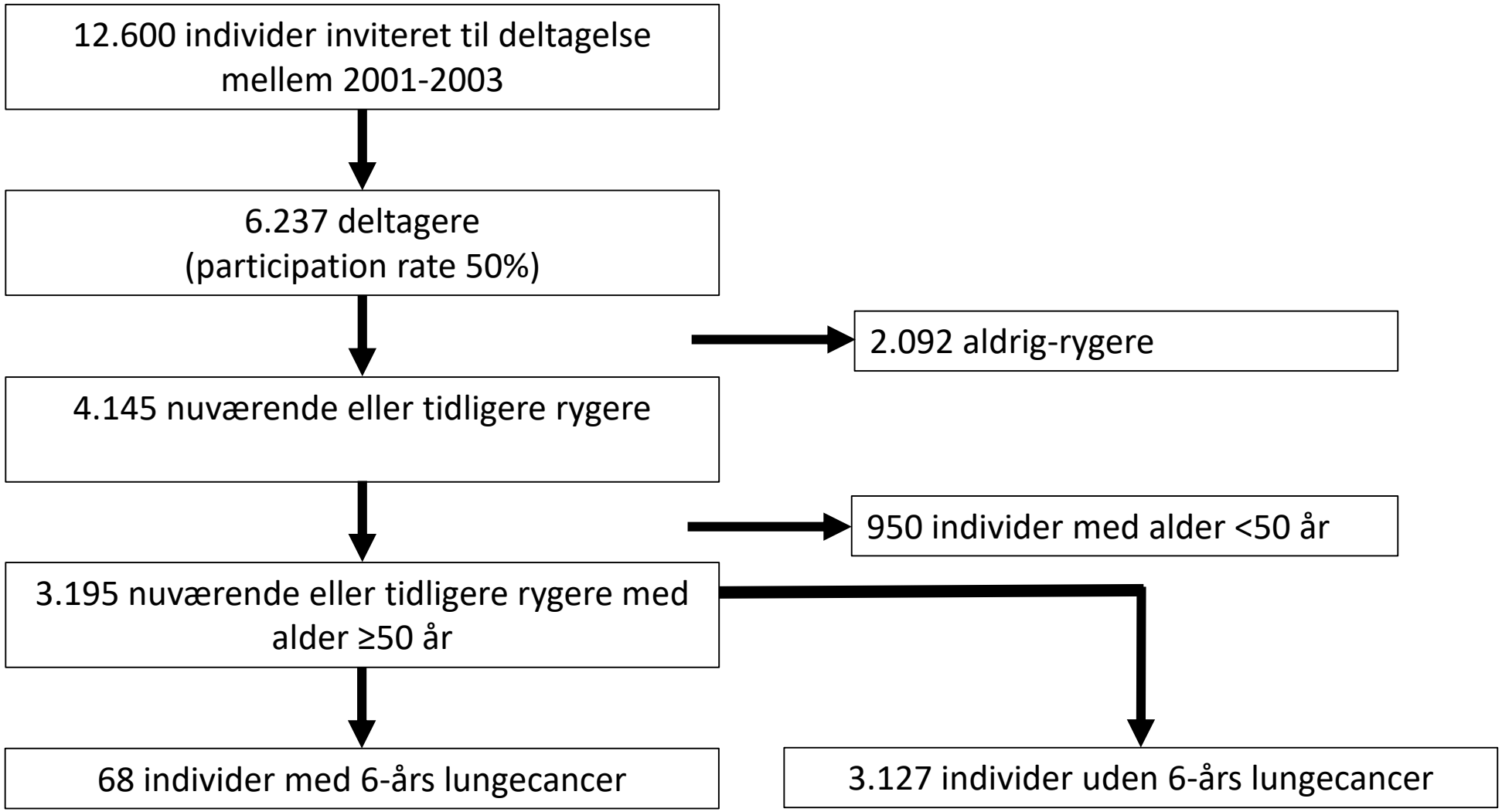
Generelle befolkningsundersøgelser
Baseline undersøgelse med klinisk undersøgelse, spørgeskemaer, blodprøver
Follow-up i nationale registre

Herlev-Østerbroundersøgelsen



Udvikling af case-kontrol design

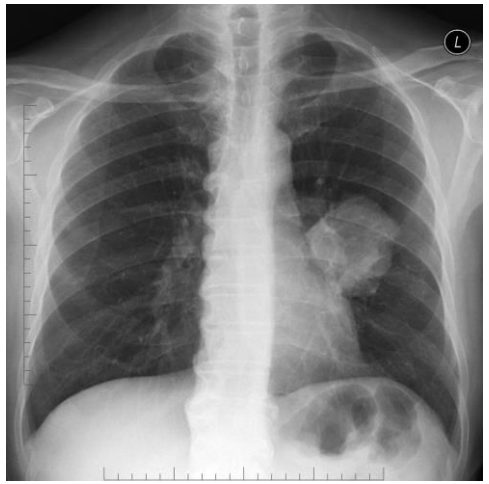
Østerbroundersøgelsen



Validering i kohortedesign

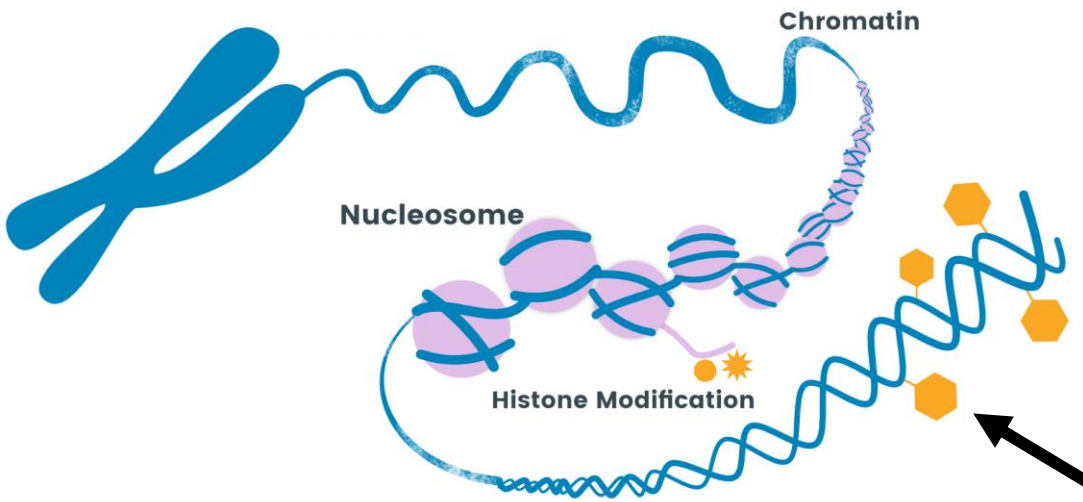
AHRR methylering

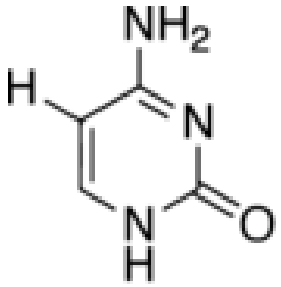
AHRR methylering



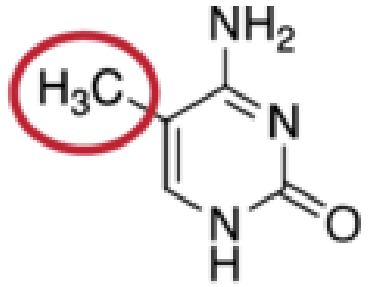
AHRR methylering

Kromosom 5





Cytosine



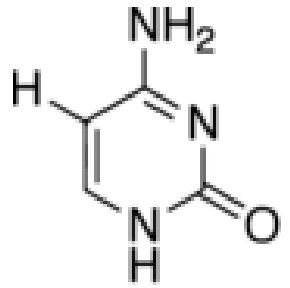
methylated Cytosine

CpG site (cg05575921)

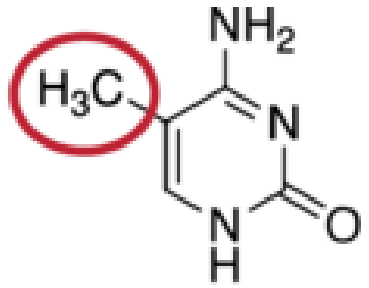
Aryl hydrocarbon receptor repressor gen (*AHRR*)

AHRR methylering = objektiv rygemarkør

Høje værdier er gode og indikerer lav rygebelastning
Lave værdier er dårlige og indikerer høj rygebelastning

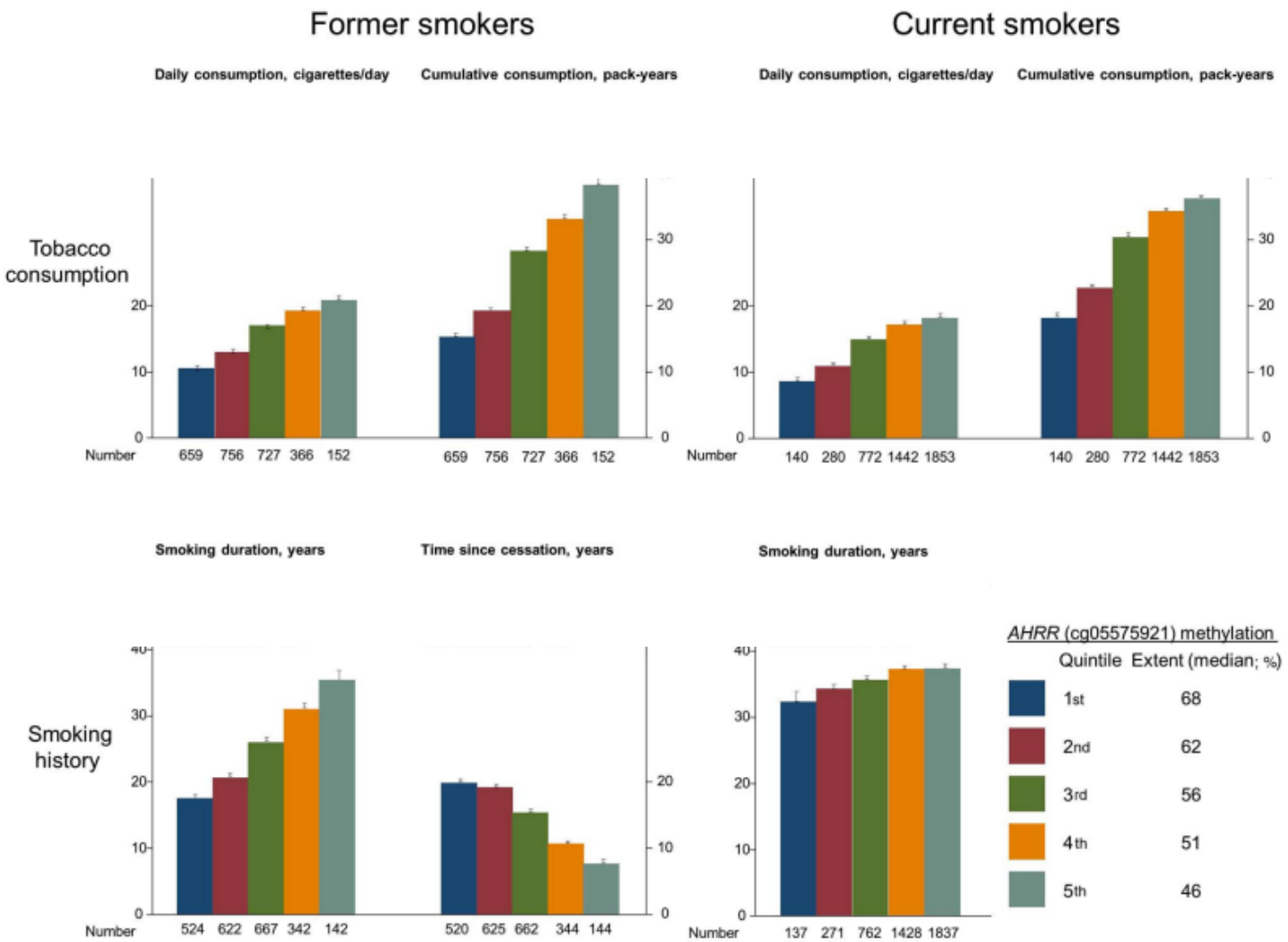


Cytosine



methylated Cytosine

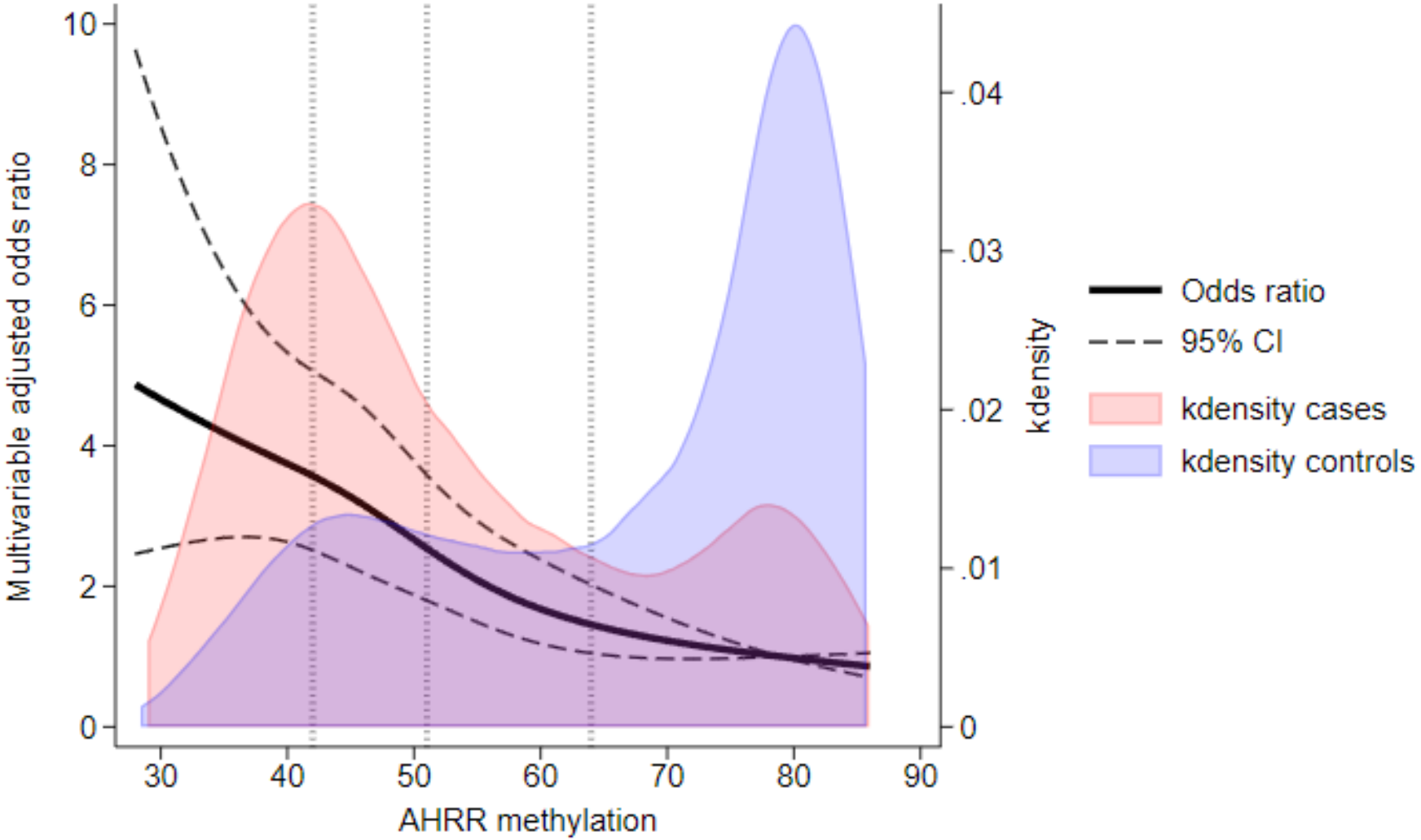
AHRR methylering



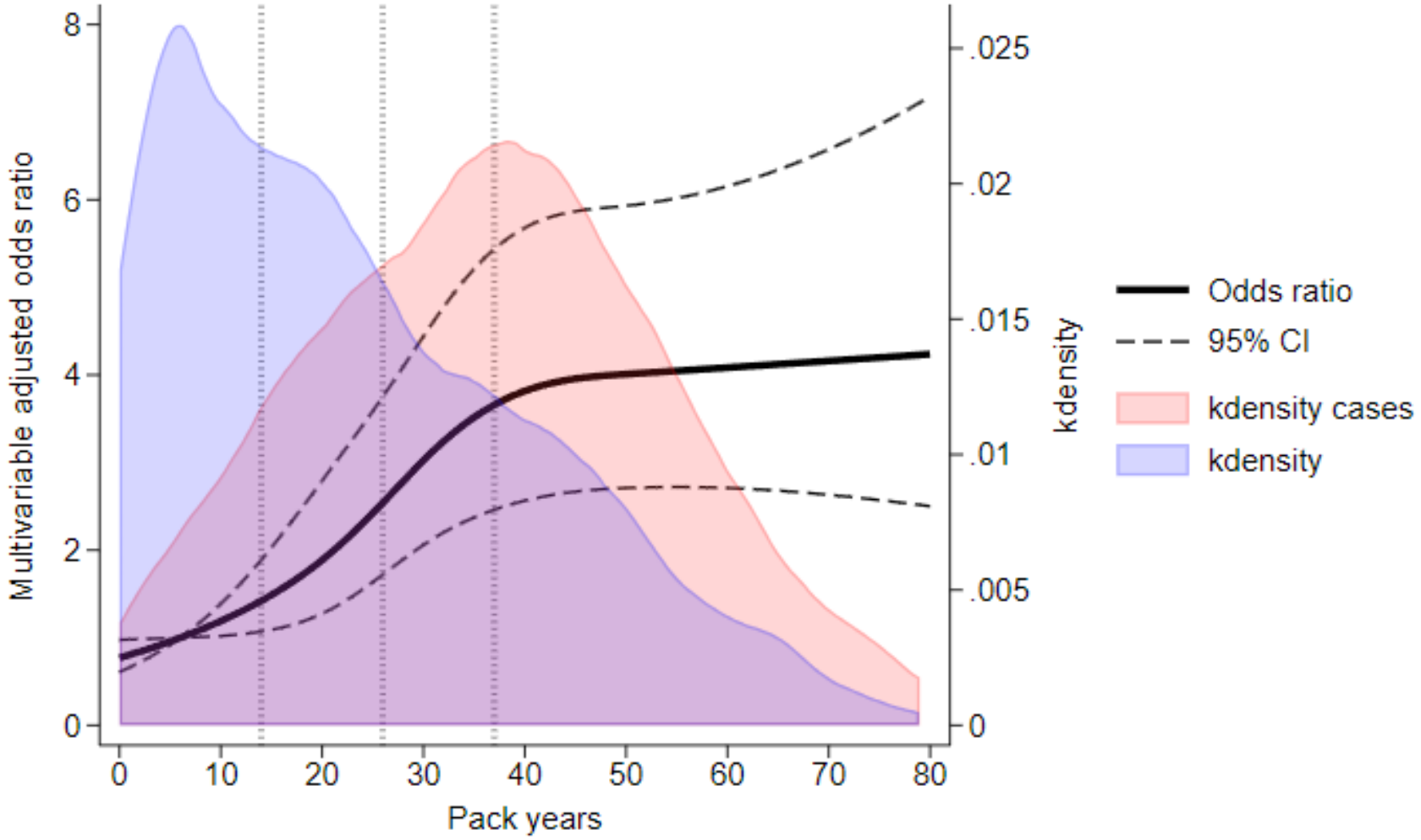
Bojesen SE, *et al*. *Thorax* 2017;**72**:646–653. doi:10.1136/thoraxjnl-2016-208789

Resultater

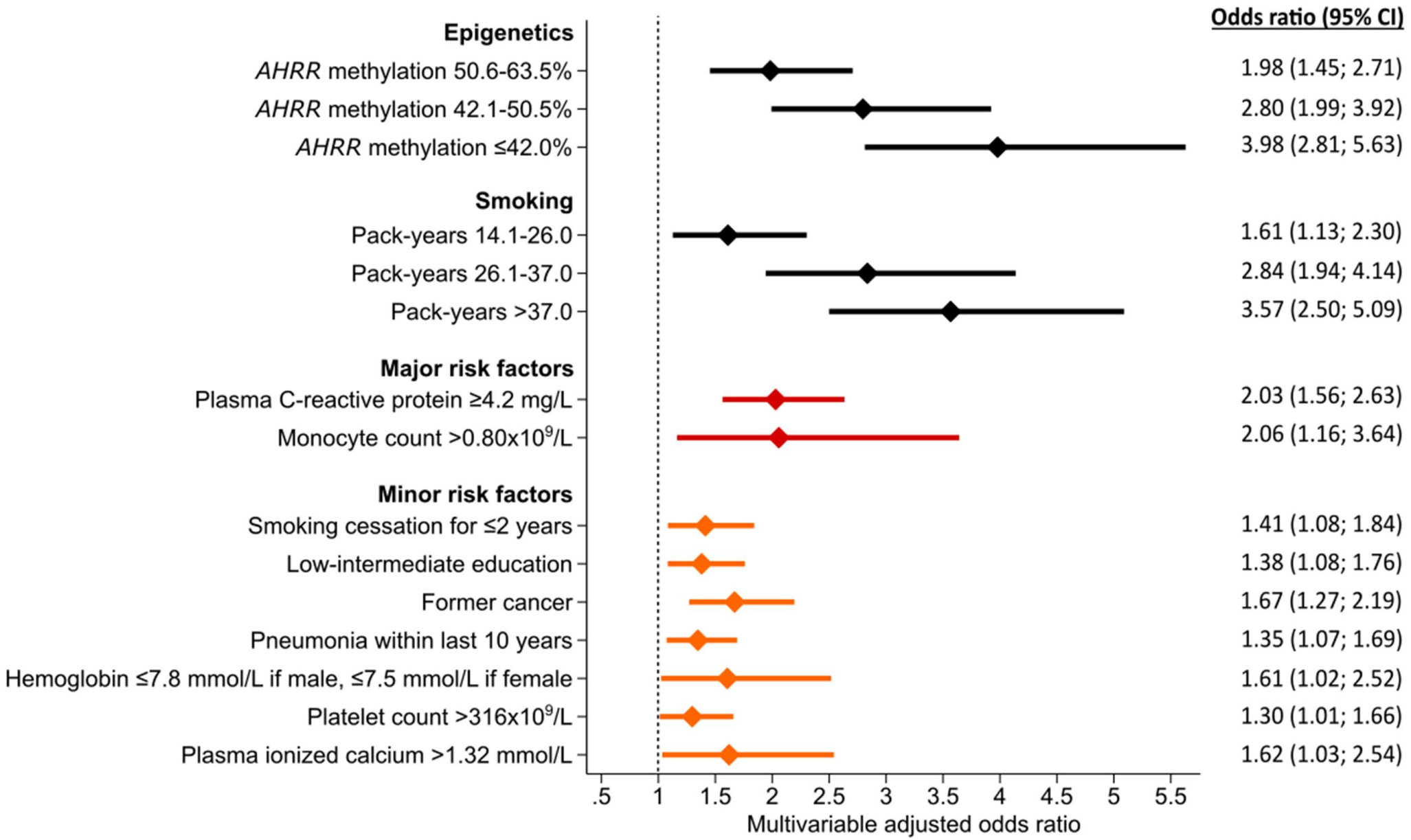
AHRR methylering og 6-års lungekræft



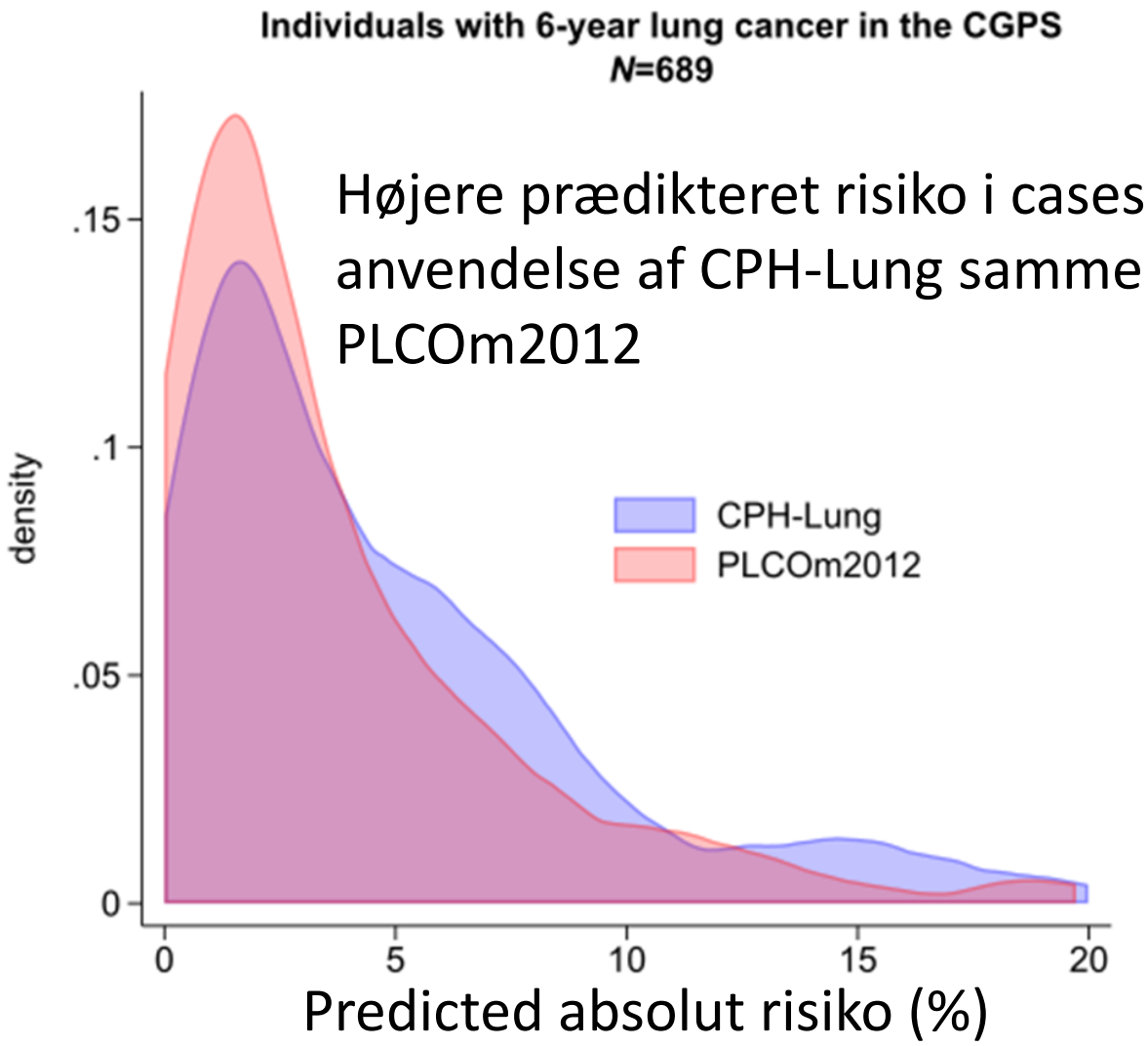
Antal pakkeår og 6-års lungekræft



Multivariable justerede odds ratioer for risikofaktorer inkluderet i CPH-Lung

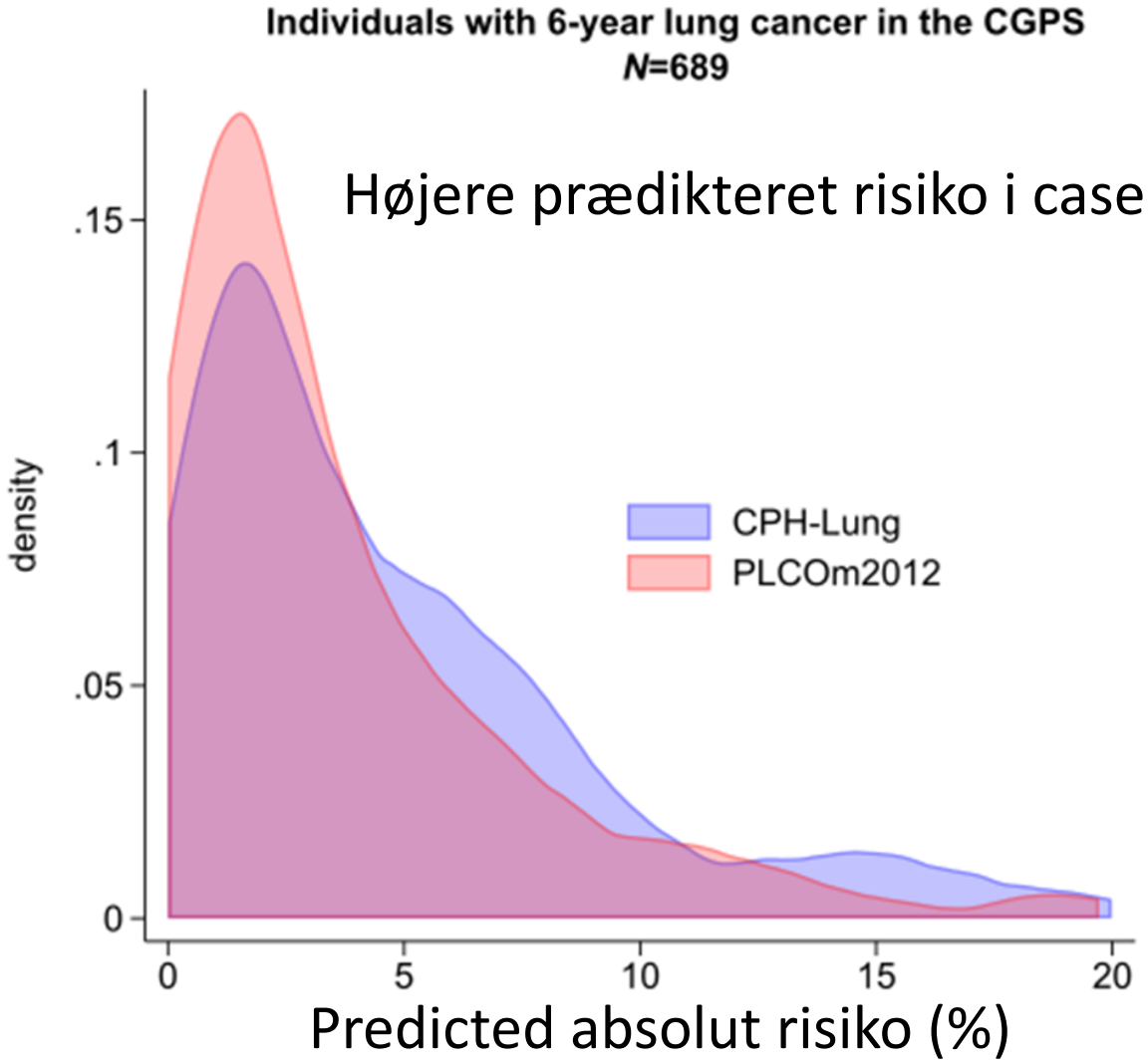


Prædikteret risiko i cases: CPH-Lung vs. PLCOm2012

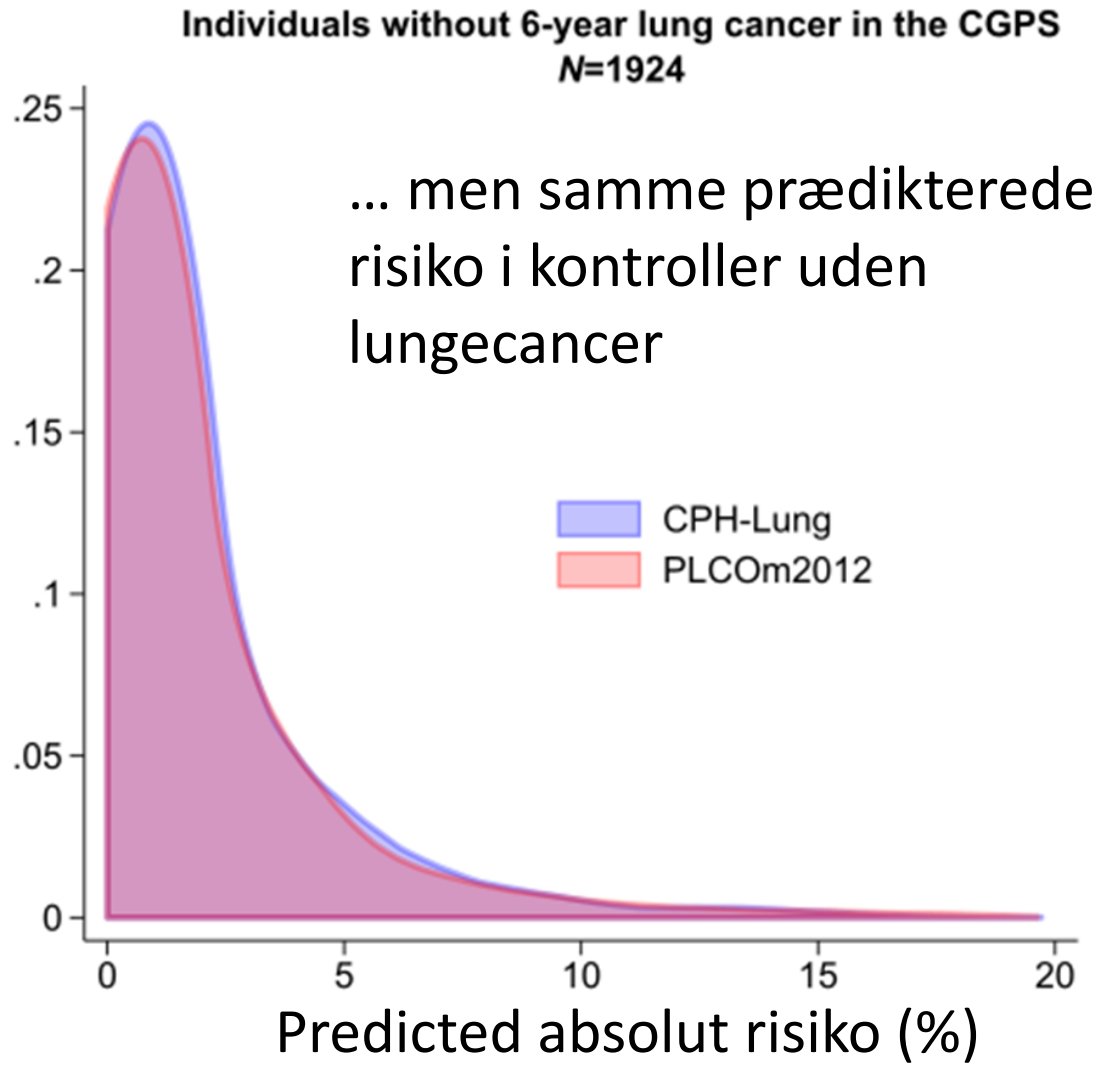


Højere prædikteret risiko i cases ved anvendelse af CPH-Lung sammenlignet med PLCOm2012

Prædikteret risiko i cases: CPH-Lung vs. PLCOm2012

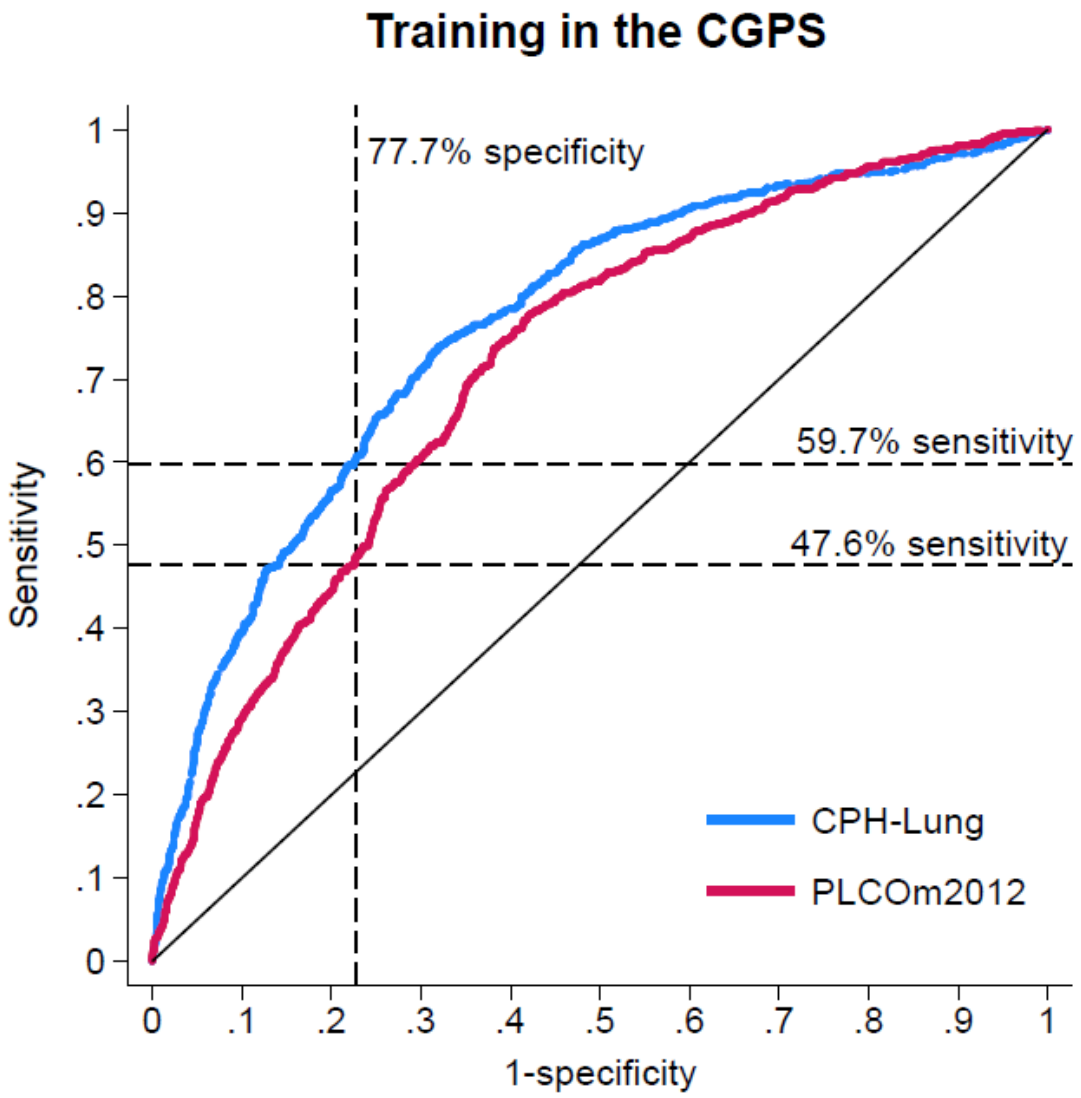


Højere prædikteret risiko i cases



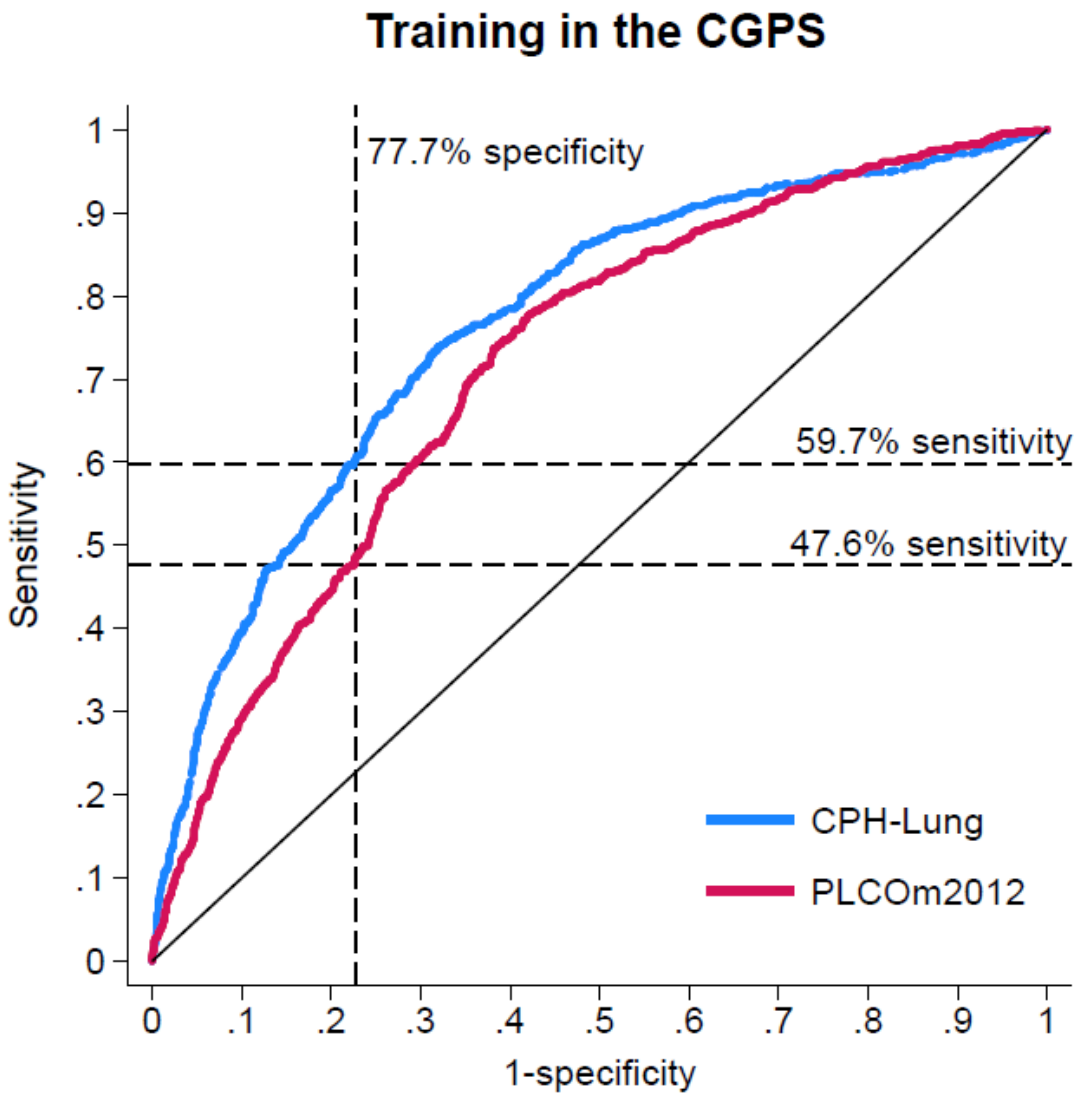
… men samme prædikterede risiko i kontroller uden lungecancer

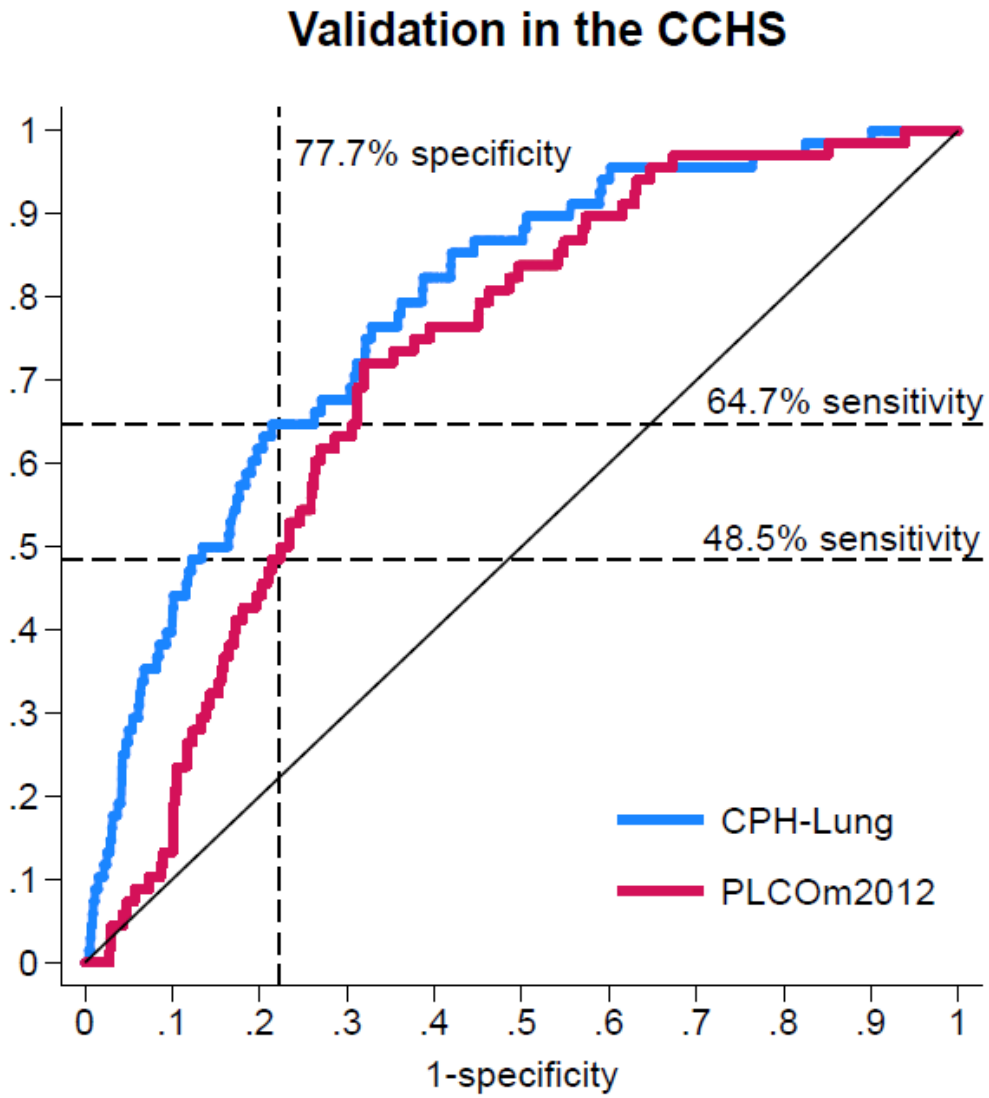
Diskrimination: CPH-Lung vs. PLCOm2012



Væsentlig højere sensitivitet ved 77% specificitet (samme specificitet som NELSON kriterier)

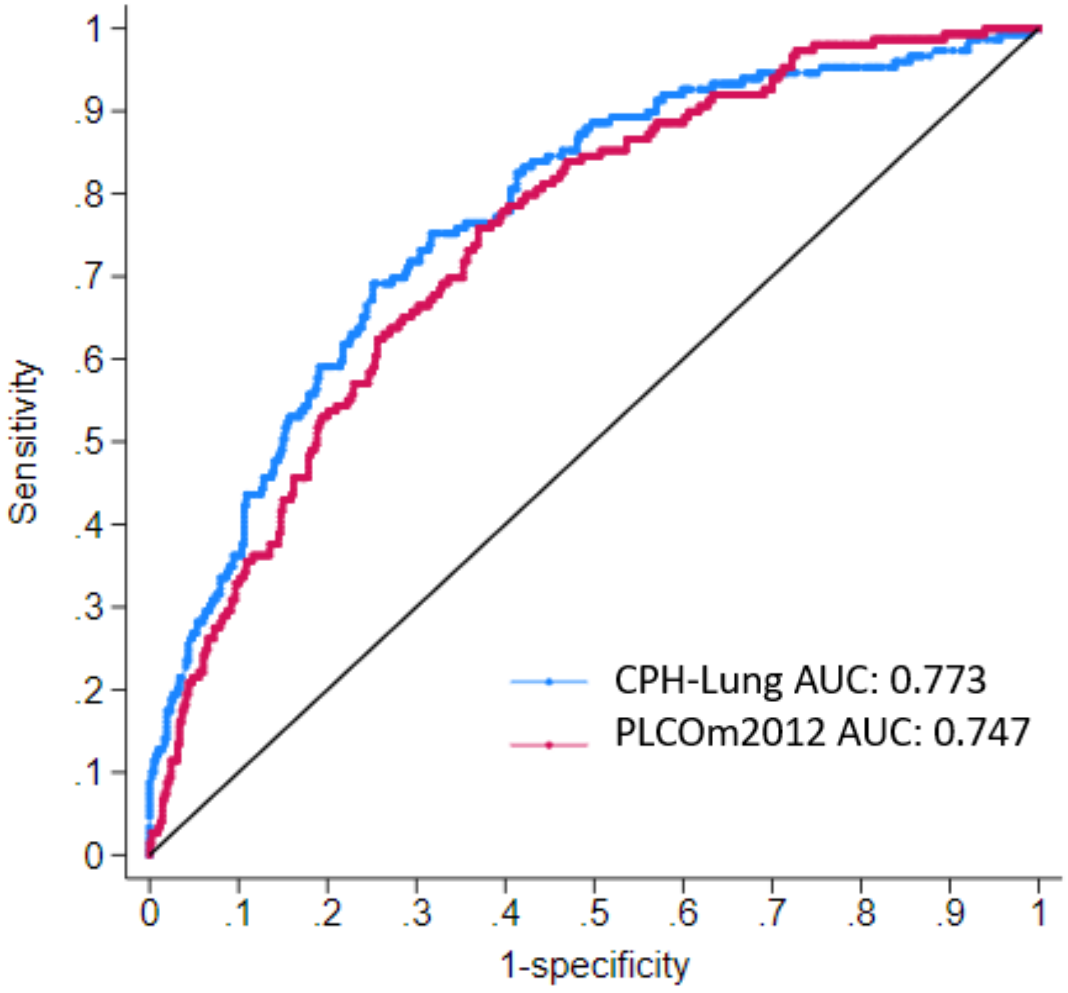
Diskrimination: CPH-Lung vs. PLCOm2012



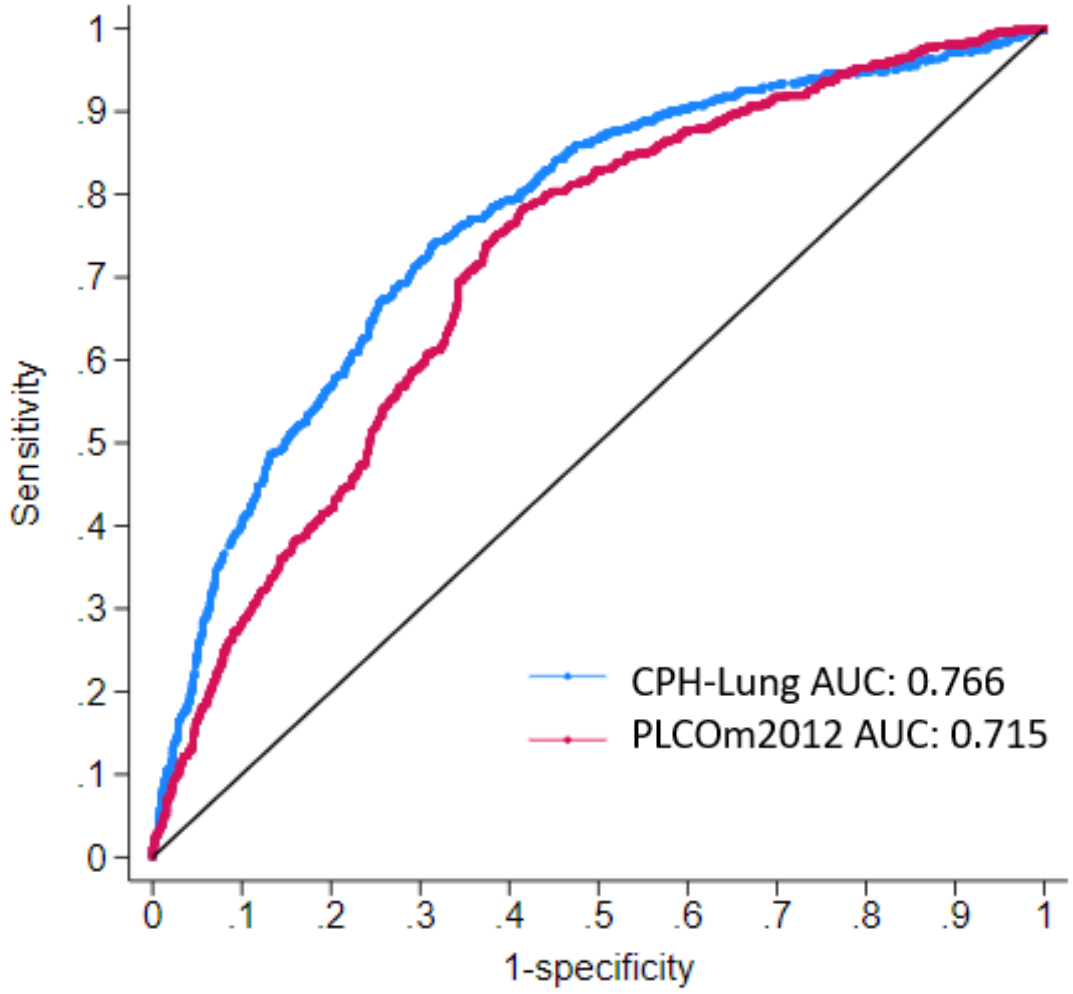


Tidlige og sene stadier af lungecancer

Stage I+II lung cancers (n=149)



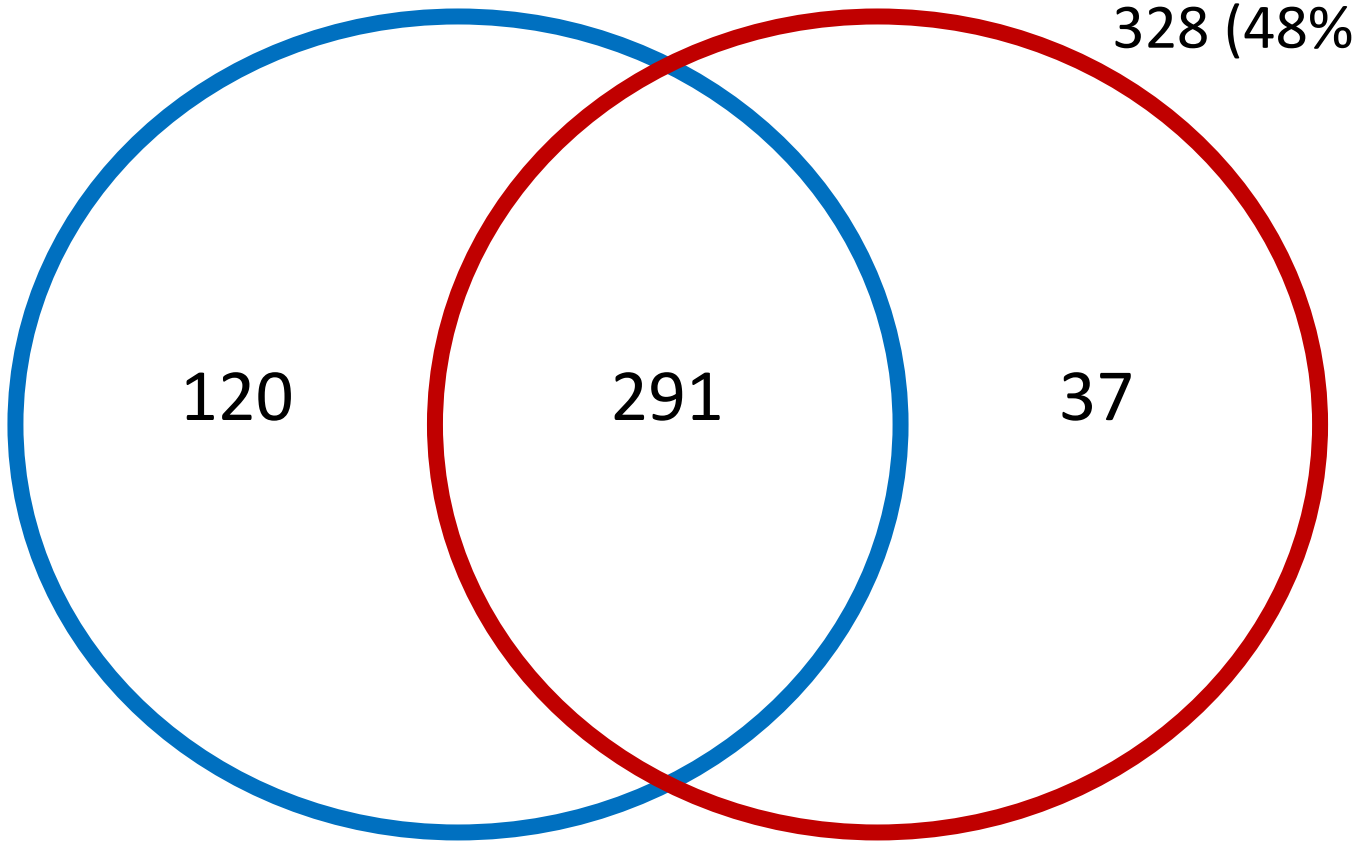
Stage III+IV lung cancers (n=484)



Lungekræft-tilfælde identificeret

CPH-Lung model detection:
411 (60%)

PLCOm2012 detection:
328 (48%)



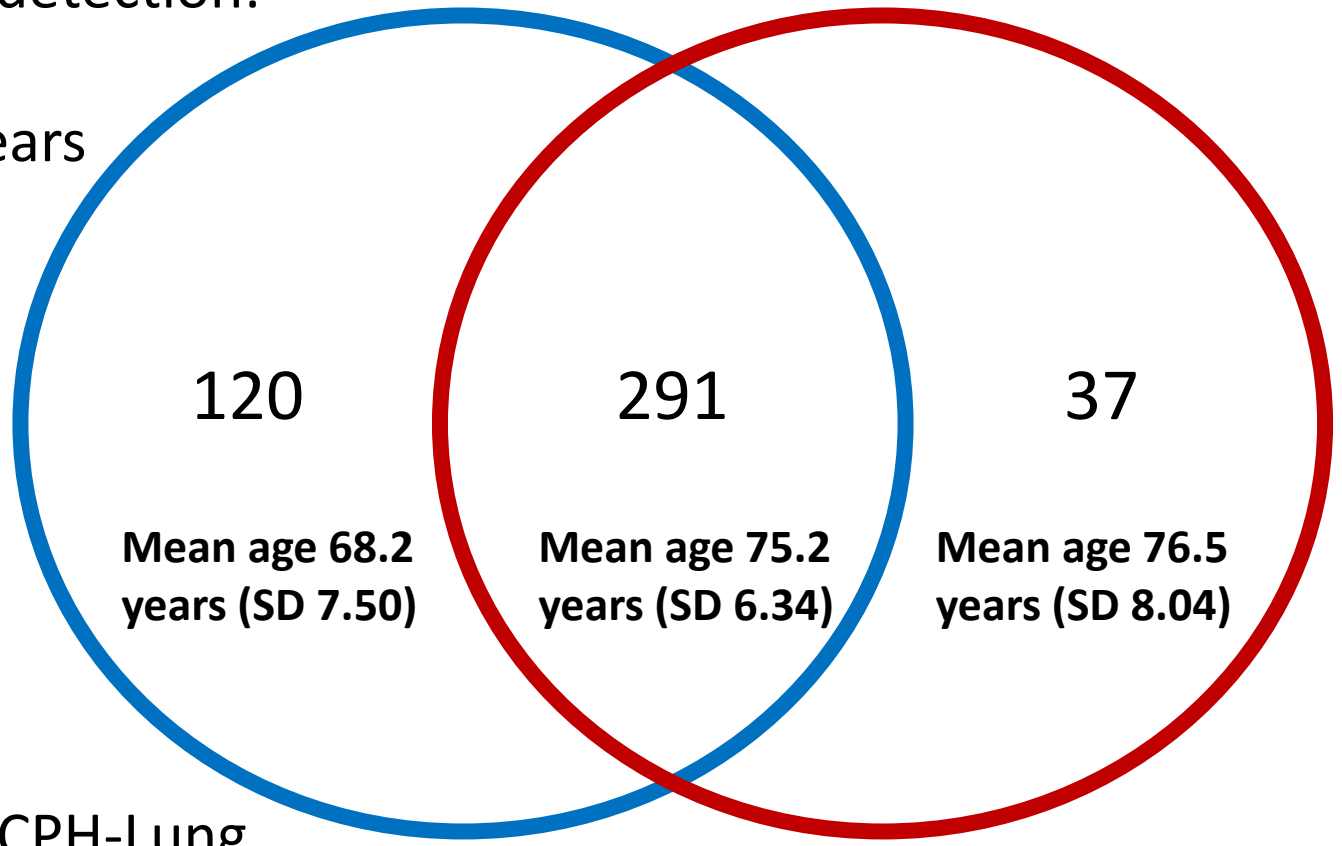
Total antal tilfælde: N=689

Not detected by any model: 241 (35%)
Cut-off at 77.7% specificity for each model

Alder ved diagnose

CPH-Lung model detection:
411 (60%)
Mean age 73.1 years
(SD 7.42)

PLCOm2012 detection:
328 (48%)
Mean age 75.4 years
(SD 6.57)



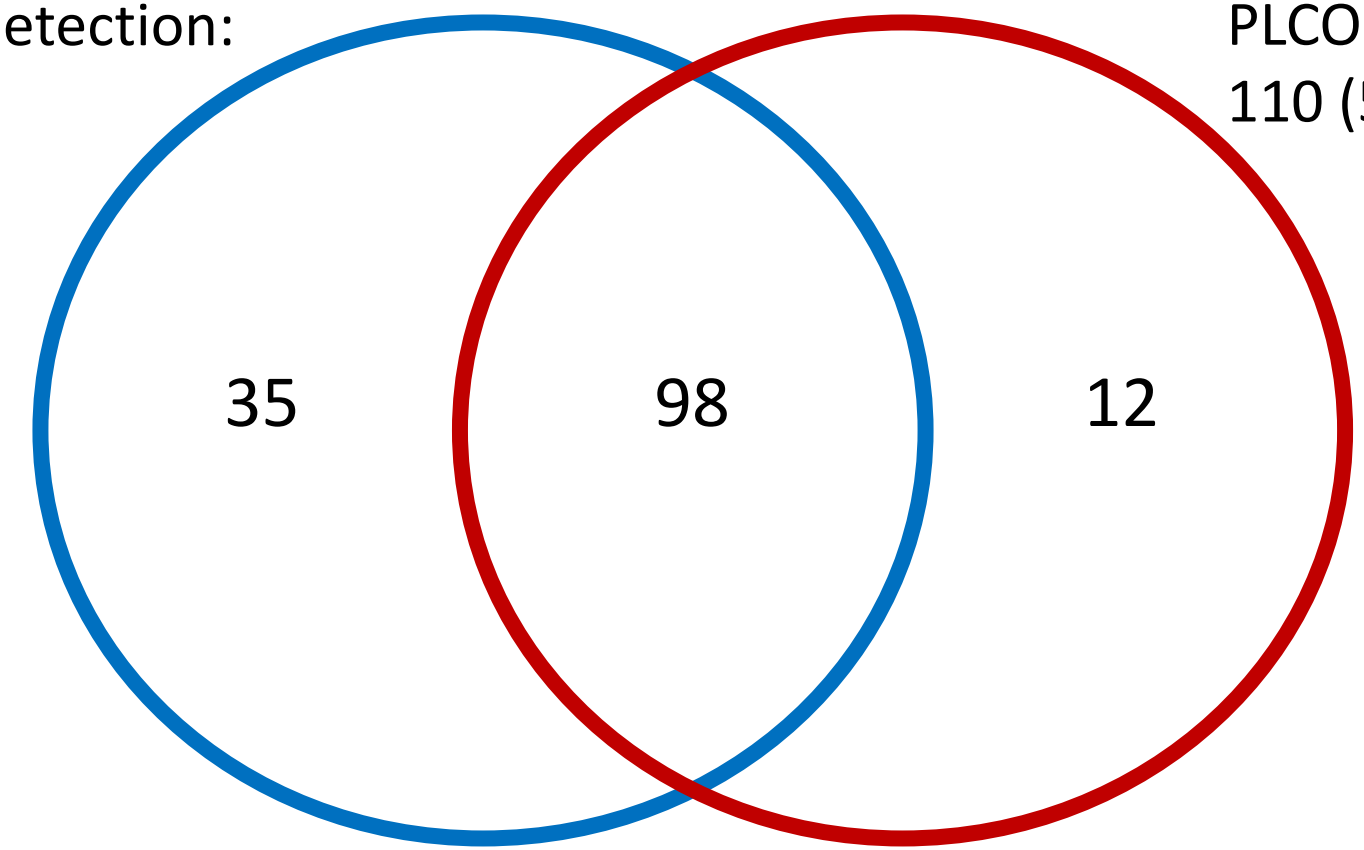
Cases fundet af CPH-Lung modellen alene er yngre

All lung cancers: 689
Not detected by any model: 241 (35%)
Cut-off at 77.7% specificity for each model

Lungekræft-tilfælde fundet <2 år fra undersøgelse

CPH-Lung model detection:
133 (62%)

PLCOm2012 detection:
110 (52%)



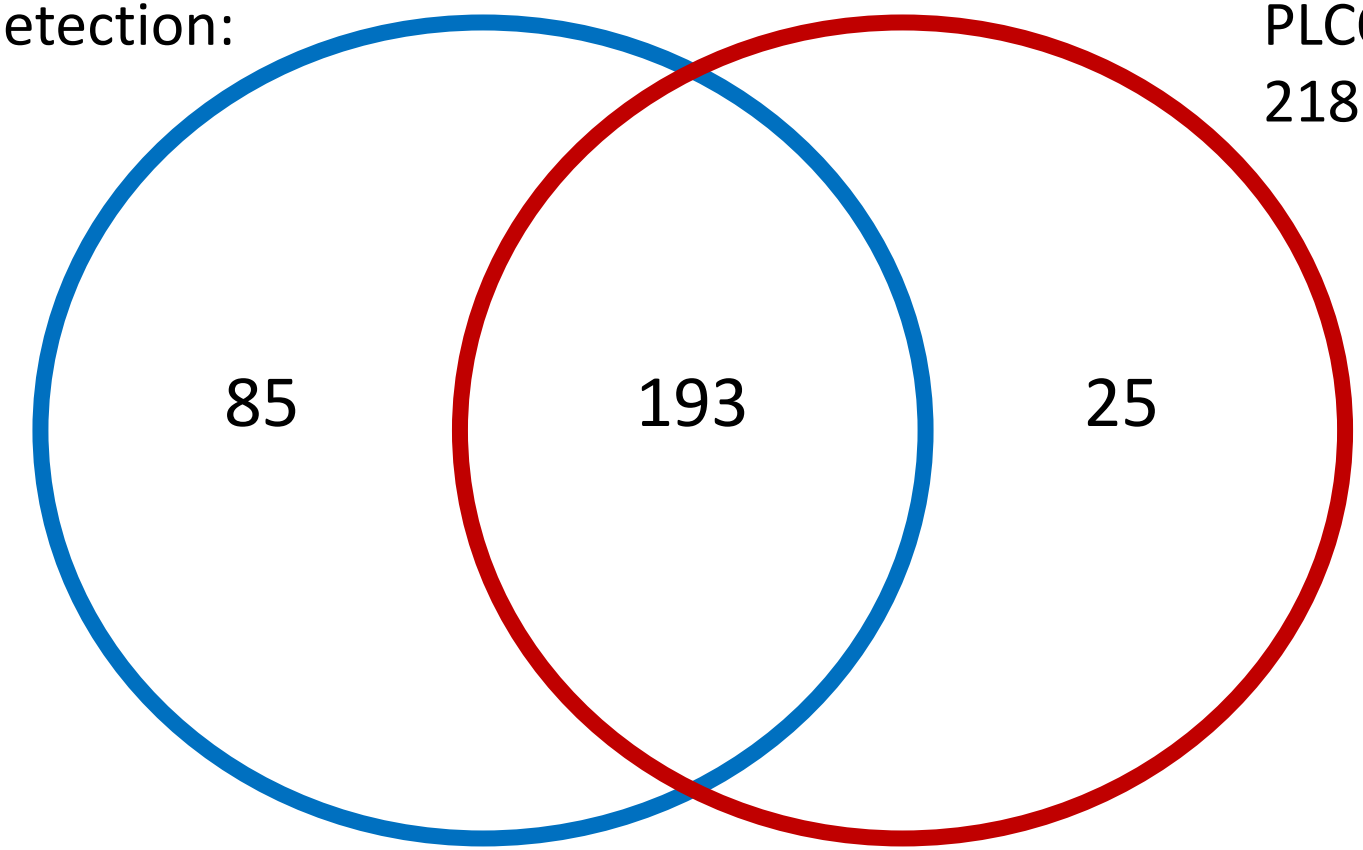
N=214

Not detected by any model: 69 (32%)
Cut-off at 77.7% specificity for each model

Lungekræft-tilfælde fundet 2-6 år fra undersøgelse

CPH-Lung model detection:
278 (59%)

PLCOm2012 detection:
218 (46%)

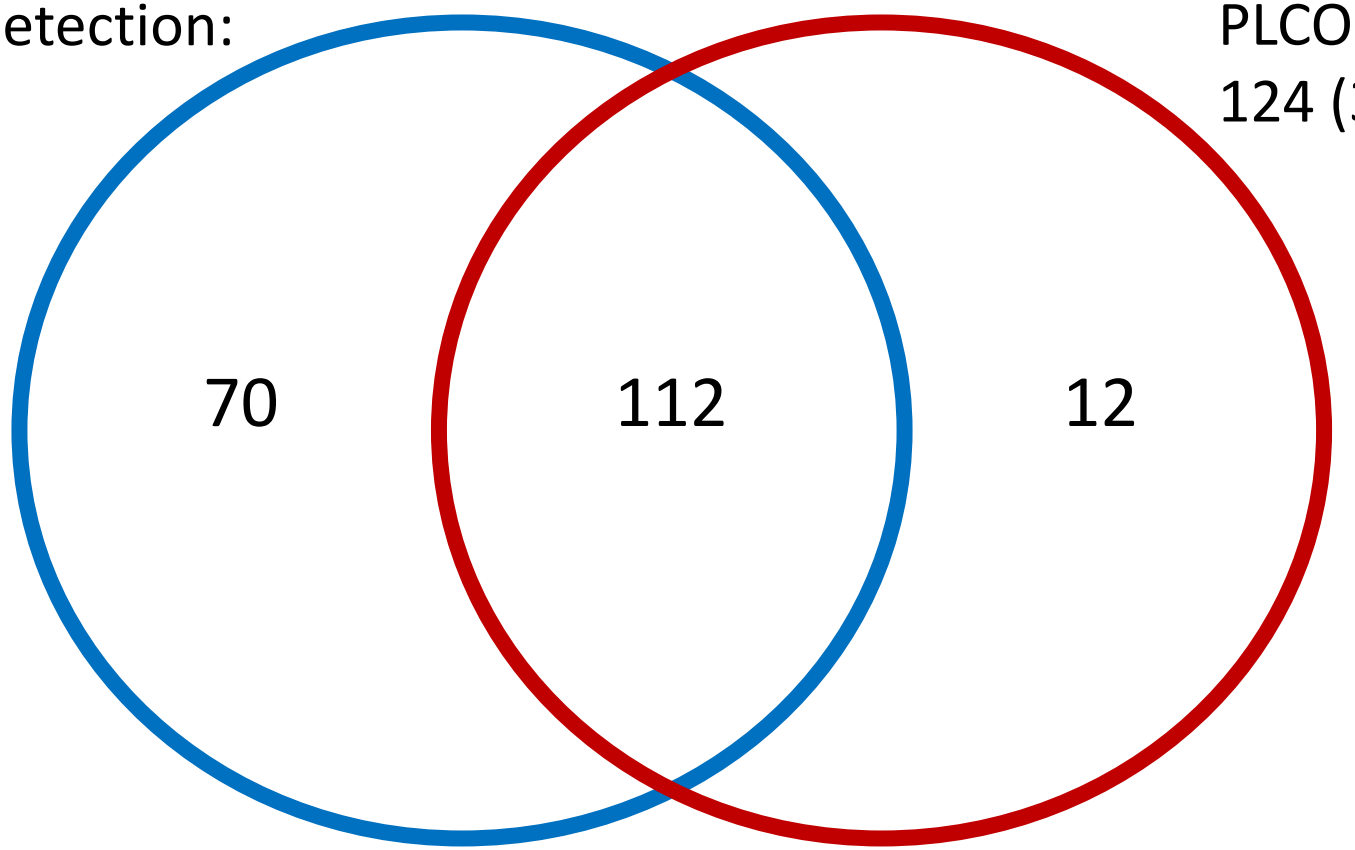


N=475

Not detected by any model: 172 (36%)
Cut-off at 77.7% specificity for each model

Lungekræft-tilfælde i kvinder

CPH-Lung model detection:
182 (58%)



PLCOm2012 detection:
124 (39%)

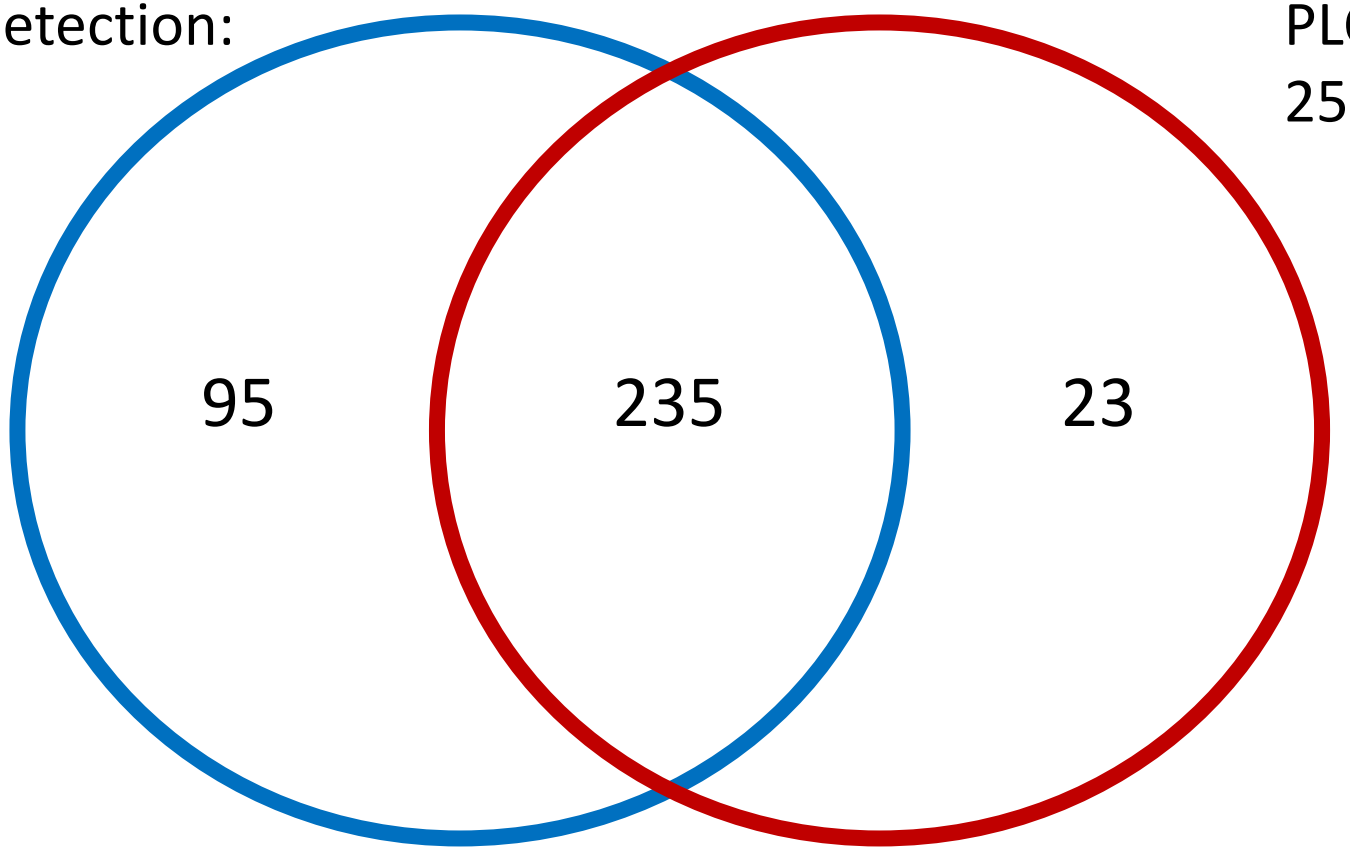
N=316

Not detected by any model: 122 (39%)
Cut-off at 77.7% specificity for each model

Lungekræft-tilfælde i lav-middel uddannelse

CPH-Lung model detection:
330 (64%)

PLCOm2012 detection:
258 (50%)



N=515

Not detected by any model: 162 (31%)
Cut-off at 77.7% specificity for each model

6-year lung cancer risk

Male 50-55 years

***AHRR* methylation**

	High >63.5%			High-Intermediate 50.6% to 63.5%			Low-Intermediate 42.1% to 50.5%			Low <42.1%		
	Number of major risk factors											
	0	1	2	0	1	2	0	1	2	0	1	2
Low <14.1												
Number of minor risk factors 0	<0.1	0.1	0.1	0.1	0.1	0.2	0.1	0.2	0.3	0.1	0.2	0.5
1	<0.1	0.1	0.2	0.1	0.2	0.4	0.1	0.3	0.5	0.2	0.4	0.7
2	0.1	0.1	0.3	0.1	0.3	0.5	0.2	0.4	0.8	0.3	0.5	1.1
3	0.1	0.2	0.4	0.2	0.4	0.8	0.3	0.6	1.1	0.4	0.8	1.6
4	0.2	0.3	0.6	0.3	0.6	1.2	0.4	0.9	1.7	0.6	1.2	2.5
5	0.2	0.5	0.9	0.5	0.9	1.8	0.6	1.3	2.6	0.9	1.8	3.7
6	0.4	0.7	1.4	0.7	1.4	2.7	1.0	1.9	3.8	1.4	2.8	5.5
7	0.5	1.1	2.1	1.0	2.0	4.1	1.4	2.9	5.8	2.1	4.1	8.3
Low-Intermediate 14.1 to 26.0												
0	0.0	0.1	0.2	0.1	0.2	0.4	0.1	0.3	0.5	0.2	0.4	0.8
1	0.1	0.1	0.3	0.1	0.3	0.6	0.2	0.4	0.8	0.3	0.6	1.2
2	0.1	0.2	0.4	0.2	0.4	0.9	0.3	0.6	1.2	0.4	0.9	1.7
3	0.2	0.3	0.7	0.3	0.6	1.3	0.5	0.9	1.8	0.7	1.3	2.6
4	0.2	0.5	1.0	0.5	1.0	1.9	0.7	1.4	2.7	1.0	2.0	3.9
5	0.4	0.7	1.5	0.7	1.4	2.9	1.0	2.0	4.1	1.5	2.9	5.9
6	0.6	1.1	2.2	1.1	2.2	4.3	1.5	3.1	6.1	2.2	4.4	8.8
7	0.8	1.7	3.3	1.6	3.2	6.5	2.3	4.6	9.2	3.3	6.6	13.2
Pack-years												
High-Intermediate 26.1 to 37.0												
0	0.1	0.2	0.4	0.2	0.3	0.7	0.2	0.5	1.0	0.3	0.7	1.4
1	0.1	0.3	0.5	0.3	0.5	1.0	0.4	0.7	1.4	0.5	1.0	2.1
2	0.2	0.4	0.8	0.4	0.8	1.5	0.5	1.1	2.2	0.8	1.6	3.1
3	0.3	0.6	1.2	0.6	1.1	2.3	0.8	1.6	3.2	1.2	2.3	4.7
4	0.4	0.9	1.8	0.9	1.7	3.4	1.2	2.4	4.9	1.7	3.5	7.0
5	0.7	1.3	2.7	1.3	2.6	5.2	1.8	3.6	7.3	2.6	5.2	10.5
6	1.0	2.0	4.0	1.9	3.9	7.7	2.7	5.5	10.9	3.9	7.9	15.7
7	1.5	3.0	6.0	2.9	5.8	11.6	4.1	8.2	16.4	5.9	11.8	>20
High >37.0												
0	0.1	0.2	0.4	0.2	0.4	0.9	0.3	0.6	1.2	0.4	0.9	1.8
1	0.2	0.3	0.7	0.3	0.6	1.3	0.5	0.9	1.8	0.7	1.3	2.6
2	0.3	0.5	1.0	0.5	1.0	1.9	0.7	1.4	2.7	1.0	2.0	3.9
3	0.4	0.8	1.5	0.7	1.5	2.9	1.0	2.1	4.1	1.5	3.0	5.9
4	0.6	1.1	2.3	1.1	2.2	4.4	1.5	3.1	6.2	2.2	4.4	8.9
5	0.8	1.7	3.4	1.6	3.3	6.5	2.3	4.6	9.3	3.3	6.7	13.3
6	1.3	2.5	5.1	2.5	4.9	9.8	3.5	7.0	13.9	5.0	10.0	20.0
7	1.9	3.8	7.6	3.7	7.4	14.7	5.2	10.4	>20	7.5	15.0	>20.0

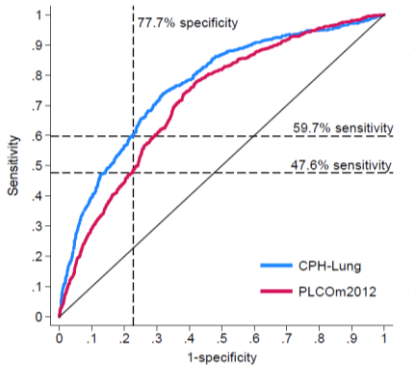
Major risk factors

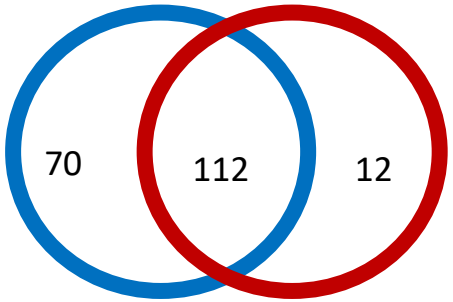
- CRP ≥4.20 mmol/L
- Monocyte count ≥0.81 x10^9/L

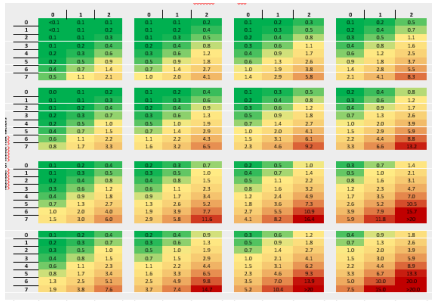
Minor risk factors

- Low-intermediate educational level
- Smoking cessation for ≤2 years (current smokers have 0 years)
- Pneumonia within last 10 years
- Former cancer (any type)
- Hemoglobin ≤7.8 mmol/L if male, ≤7.5 mmol/L if female
- Platelet count ≥317 x10^9/L
- Ionized calcium ≥1.33 mmol/L

Konklusion







- CPH-Lung sensitivitet 12 procentpoint højere ved acceptabelt niveau af specificitet
- CPH-Lung har især højere sensitivitet blandt
  - Yngre individer
  - Kvinder
  - Individer med lavt uddannelsesniveau
- AHRR-methylering hjælper med at skelne mellem lav og meget høj 6-års risiko for lungekræft

Tak for jeres opmærksomhed

Spørgsmål?