
بسم الله الرحمن الرحيم

Determining a national risk function

to predict

CVD mortality

using the pooled data of

population-based cohort studies in

Iran

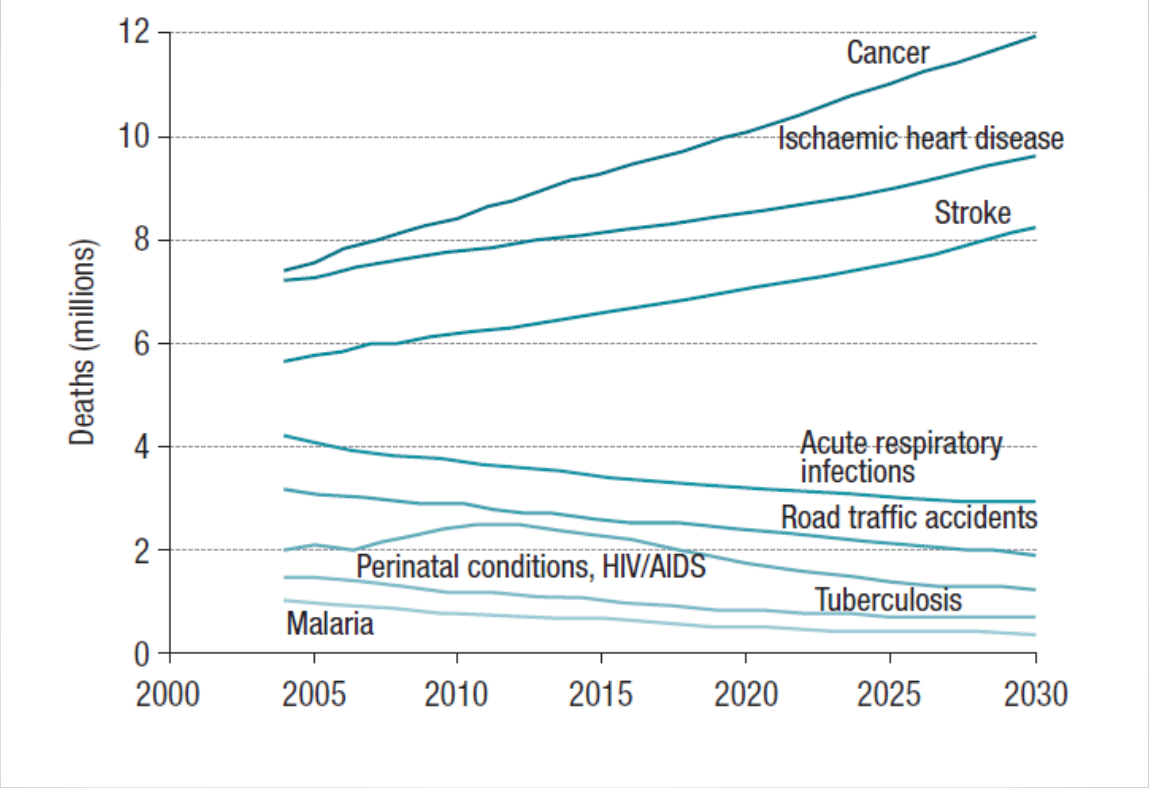
Cardiovascular Mortality

17.9 million people die each year from CVDs, an estimated 31% of all deaths worldwide

>75% of CVD deaths occur in low-income and middle-income countries

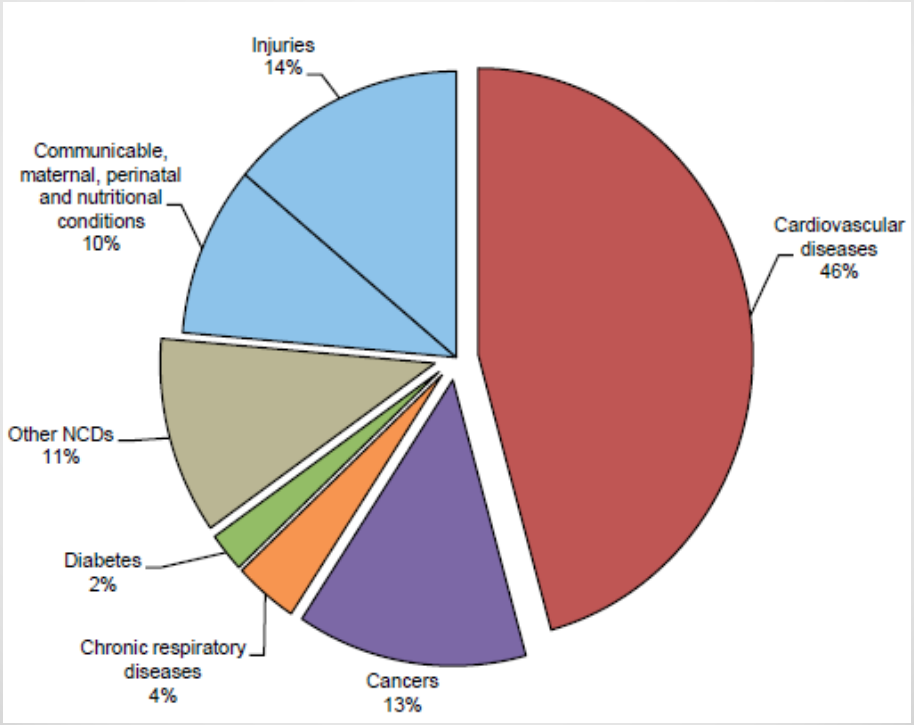
While

80% of CVD mortalities are preventable



Projected global death,2004-2030

In Iran: CVD is the first cause of mortality (~46%)



World Health Organization, *Non-communicable Diseases (NCD) Country Profiles*, 2014

Two approaches to identify high risk individuals:

- Old approach (considers each risk factor, separately)
- New approach (considers model-based CVD risk which currently use in most treatment guidelines)

Prediction Models

Type of studies:

- Developing a new model
- Validating an existing model
- Updating an existing model

Using an existing model is preferred if ..

Until 2013, more than 363 CVD prediction models were developed

CVD prediction models:

Laboratory-based

- Total CVD (CHD- CVD)
- CVD mortality

Non laboratory-based

- Total CVD (CHD- CVD)
- CVD mortality

The aim of the project in three steps:

- To pool data from the selected cohorts.
- To validate and recalibrate the selected lab-based prediction models
- To drive a new office-based model

Among existing models, two models were selected:

- **SCORE**
- **Globorisk**

The reasons to select these models include:

- Outcome is CVD mortality
- Derived from pooled cohorts
- Variables are available

Four cohorts were included:

1-Tehran Lipid and Glucose Study (**TLGS**)

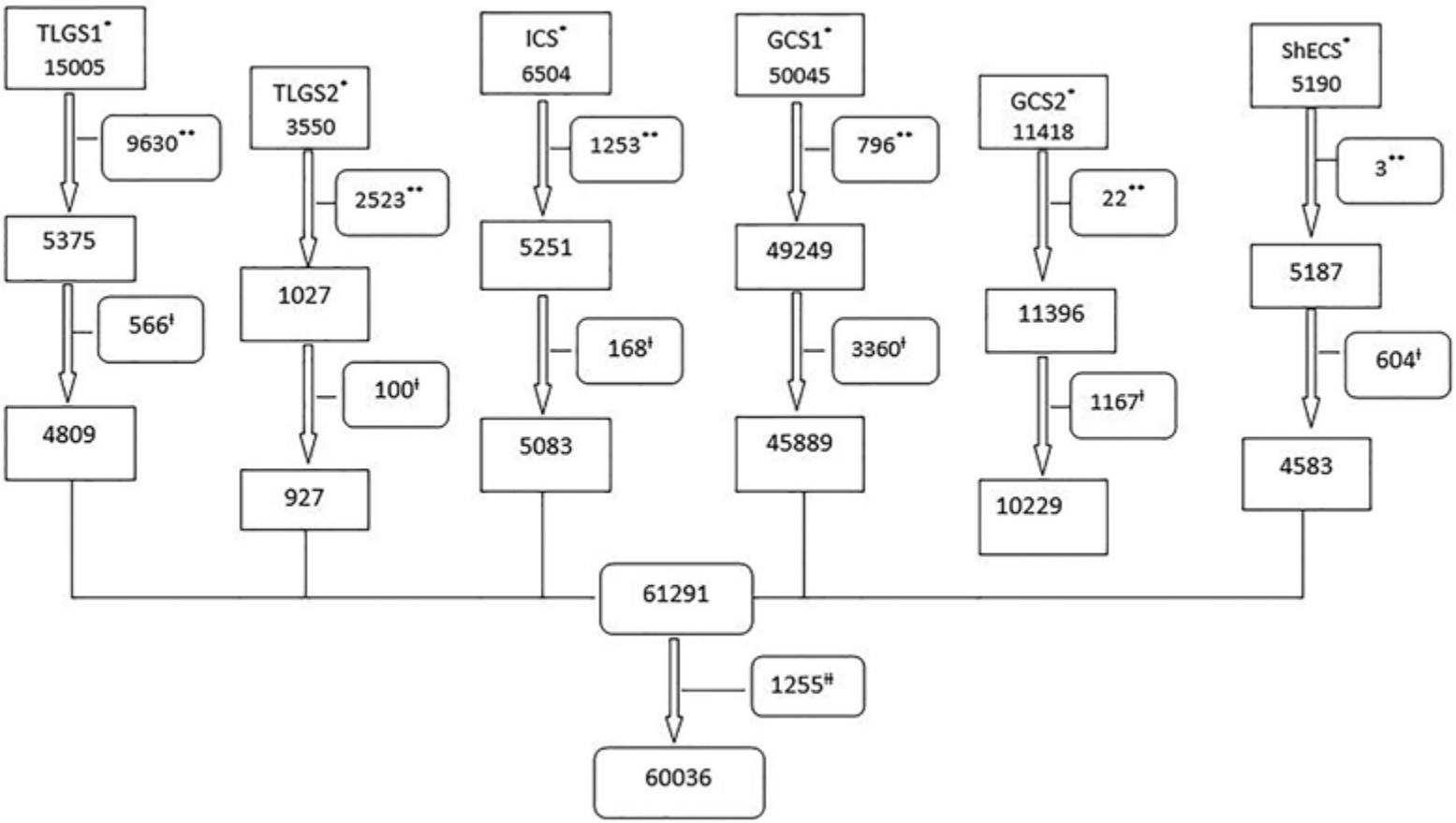
2- Isfahan Cohort Study (**ICS**)

3- Golestan Cohort Study (**GCS**)

4- Shahroud Eye Cohort Study (**ShECS**)

Phase 1

- Data Harmonization
- Data description



Supplementary Figure 1: Study participants' entry

*Excluded because of age<40 or age>80

**Excluded because of CVD history at baseline

† Loss to any follow up

Table 1 Characteristics of the Iranian cohort studies included in the pooling project to define prediction models for CVD mortality

	TLGS1	TLGS2	ICS	GCS1	GCS2	ShECS
Study baseline	1999	2002	2001	2004	2010	2009
Study population	Urban	Urban	Urban–Rural	Urban–Rural	Urban–Rural	Urban
Location	Tehran	Tehran	Isfahan, Najafabad, Arak	Gonbad, Kalaleh, Ag-Qala	Gonbad, Kalaleh, Ag-Qala	Shahroud
Age range, years	≥3	≥3	≥35	40–75	45–80	40–64
Baseline cohort size, n	15005	3550	6504	50045	11418*	5190
Rural population, %	–	–	27.52	76.10	81.14	–
Women, n (%)	55.94	50.54	51.29	57.57	52.46	58.55
Included in the current study†	4809	927	5083	45889	10229	4583
Women, n (%)	2723 (56.6)	449 (48.4)	2605 (51.3)	26378 (57.5)	5412 (52.9)	2726 (59.5)
Median follow-up (IQR), years	14.1 (13.6–14.6)	9.6 (9.0–9.9)	11.3 (10.9–12.3)	9.1 (8.0–10.0)	4.5 (3.9–5.0)	5.0 (4.8–5.2)
No follow-up, n	476	21	703	52	0	0‡

Table 2 General characteristics of the individuals included in the pooling project at baseline of the cohorts

	TLGS*	ICS	GCS1	GCS2	ShECS
Continuous variables as mean (SD)					
Age, years	53.6 (9.8)	53.7 (10.4)	51.9 (8.7)	55.3 (7.9)	50.8 (6.2)
Body mass index, kg/m^2	27.9 (4.6)	26.8 (4.5)	26.6 (5.4)	27.0 (5.3)	28.4 (4.9)
Waist circumference, cm	92.7 (11.2)	95.1 (12.2)	95.1 (13.7)	94.1 (13.8)	–
Hip circumference, cm	101.8 (9.7)	101.7 (10.1)	99.4 (9.3)	98.9 (8.9)	–
Serum cholesterol, mmol/L	5.7 (1.2)	5.6 (1.4)	–	5.3 (1.1)	–
Ln serum triglyceride, mmol/L†	2.2 (0.5)	2.3 (0.5)	–	1.9 (0.5)	–
Serum HDL, mmol/L	1.1 (0.3)	1.2 (0.3)	–	1.6 (0.4)	–
Serum LDL, mmol/L	3.7 (1.0)	3.4 (1.4)	–	3.0 (0.9)	–
Categorical variables as n (%)					
Education, diploma and higher	1802 (31.4)	831 (16.4)	3854 (8.4)	1067 (10.4)	1906 (41.6)
Current smoking	865 (15.1)	793 (15.6)	5045 (11.0)	869 (8.5)	508 (11.1)
Diabetes‡	784 (13.7)	481 (9.5)	–	1250 (12.3)	528 (11.5)
Self-reported diabetes§	765 (13.3)	621 (12.2)	2902 (6.3)	999 (9.8)	508 (11.1)
Hypertension¶	1926 (33.6)	1610 (31.7)	18823 (41.0)	3858 (37.7)	1843 (40.2)
Family history of CVD	944 (16.5)	485 (9.5)	–	–	–
Family history of diabetes	1624 (28.3)	517 (10.2)	–	–	–

Table 4 CVD mortality rates per 100 000 person-years in four population-based cohort studies in Iran, ages 40–65 years

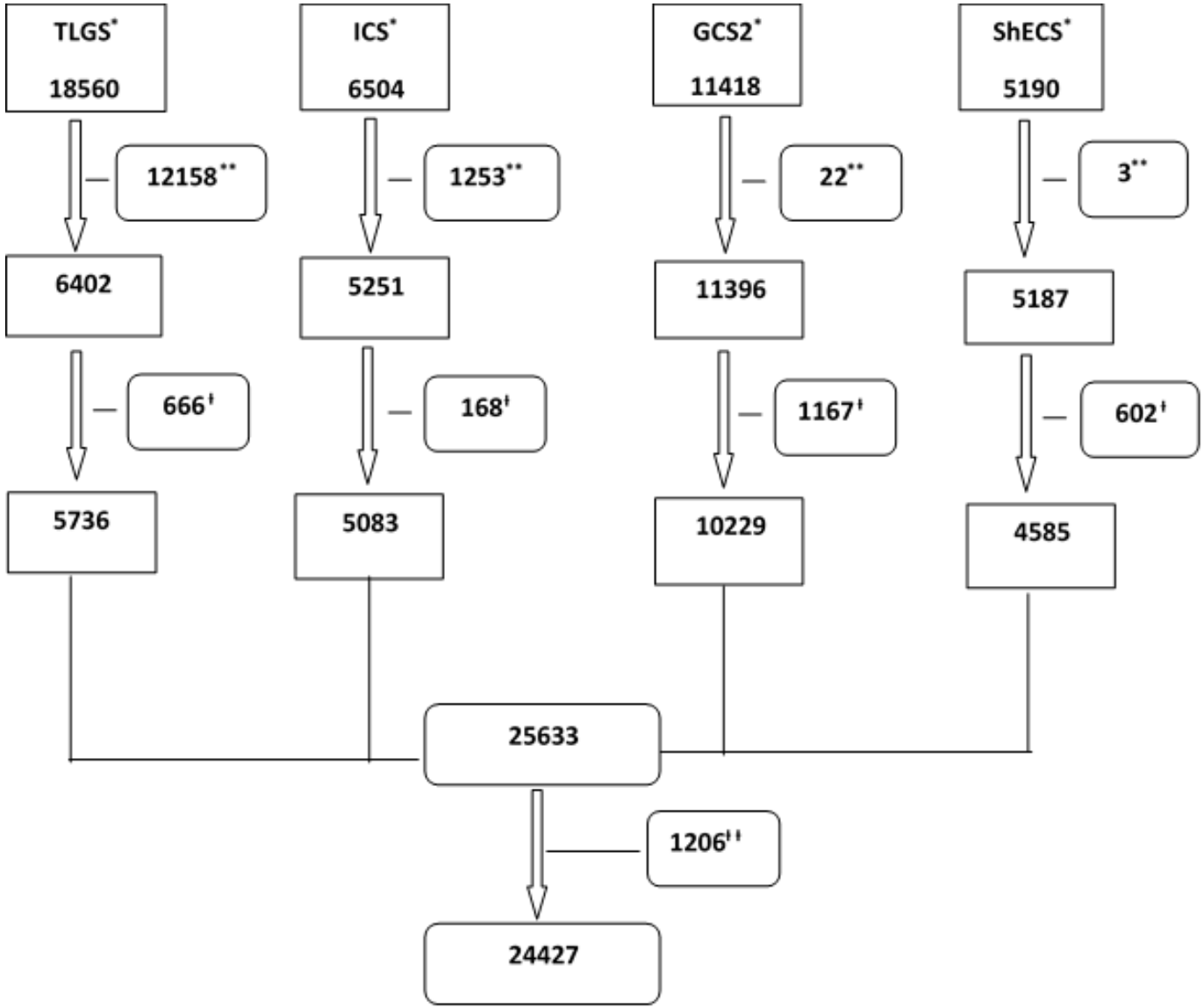
	10-year CVD mortality, n	Person-years	Crude mortality rate (95% CI)	Direct standardised mortality rate (95% CI)*	Direct standardised mortality rate (95% CI)†	Multivariable adjusted HRs‡	P values
Total							
TLGS	66	42 787	158 (125 to 202)	153 (115 to 191)	183 (139 to 228)	1	–
ICS	56	32 223	178 (137 to 231)	173 (127 to 218)	196 (144 to 249)	1.17 (0.82–1.67)	0.394
GCS	1080	361 418	303 (285 to 321)	324 (304 to 344)	366 (343 to 389)	2.30 (1.79–2.96)	<0.001
ShECS	27	22 744	119 (82 to 174)	118 (72 to 163)	133 (81 to 184)	0.85 (0.54–1.34)	0.477
Women							
TLGS	24	24 314	101 (68 to 150)	95 (57 to 134)	118 (71 to 165)	1	–
ICS	20	16 641	123 (79 to 191)	121 (68 to 175)	131 (72 to 190)	1.27 (0.70–2.29)	0.434
GCS	540	213 755	256 (235 to 278)	274 (251 to 298)	316 (288 to 344)	3.03 (2.01–4.59)	<0.001
ShECS	11	13 566	81 (45 to 147)	76 (31 to 121)	87 (34 to 139)	1.02 (0.49–2.09)	0.963
Men							
TLGS	42	18 473	235 (174 to 318)	211 (146 to 276)	251 (175 to 328)	1	–
ICS	36	15 582	236 (170 to 327)	222 (148 to 296)	262 (175 to 349)	1.09 (0.70–1.71)	0.693
GCS	540	147 663	371 (341 to 404)	374 (342 to 406)	426 (388 to 463)	1.92 (1.38–2.63)	<0.001
ShECS	16	9178	175 (107 to 285)	145 (74 to 215)	173 (87 to 259)	0.76 (0.42–1.36)	0.353

Phase 2

- Assessment and Recalibration of the models and assessment of the model performance

- Discrimination
- Calibration
- Sensitivity, Specificity, PV, LR (using Bootstraping methods)
- Clinical usefulness

- Model Agreements


TLGS*
18560
12158**
6402
666†
5736
ICS*
6504
1253**
5251
168†
5083
GCS2*
11418
22**
11396
1167†
10229
ShECS*
5190
3**
5187
602†
4585
25633
1206††
24427

Clinical Usefulness

- Through calculating net benefits and decision curves

$$\text{Net Benefit} = (TP - w\,FP) / N$$

$$w = \text{harm} / \text{benefit} = P_{treatment} / (1 - P_{treatment})$$

In 154,522 person-year of follow-up, 437 cardiovascular deaths (280 men) occurred.

The c-index of the models:

- Men: 0.784 (0.756-0.812) for SCORE
  0.793 (0.766-0.820) for Globorisk

- Women: 0.780 (0.744-0.815) for SCORE
  0.793 (0.757-0.829) for Globorisk

The deviation of the calibration slopes from one, reflected a need for recalibration.

The 10-year observed risks:

Men: 0.042 (95%CI: 0.037-0.048)

Women: 0.021 (0.018-0.025)

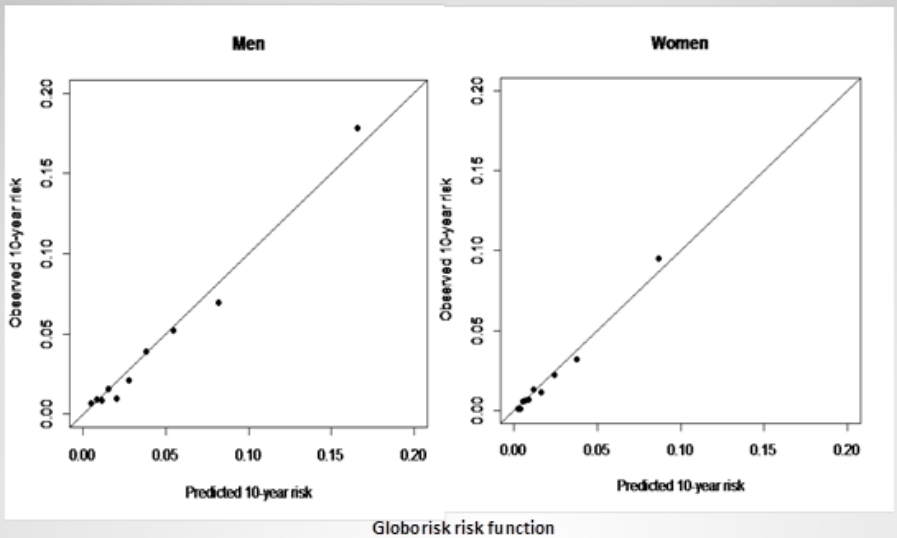
The 10-year Predicted risks:

Men: 0.0426 for SCORE

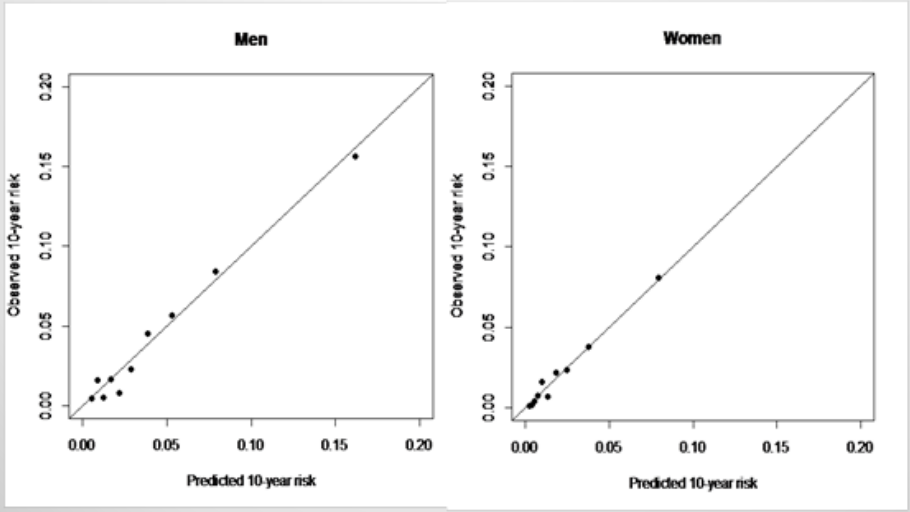
0.0427 for Globorisk

Women: 0.0202 for SCORE

0.0203 for Globorisk



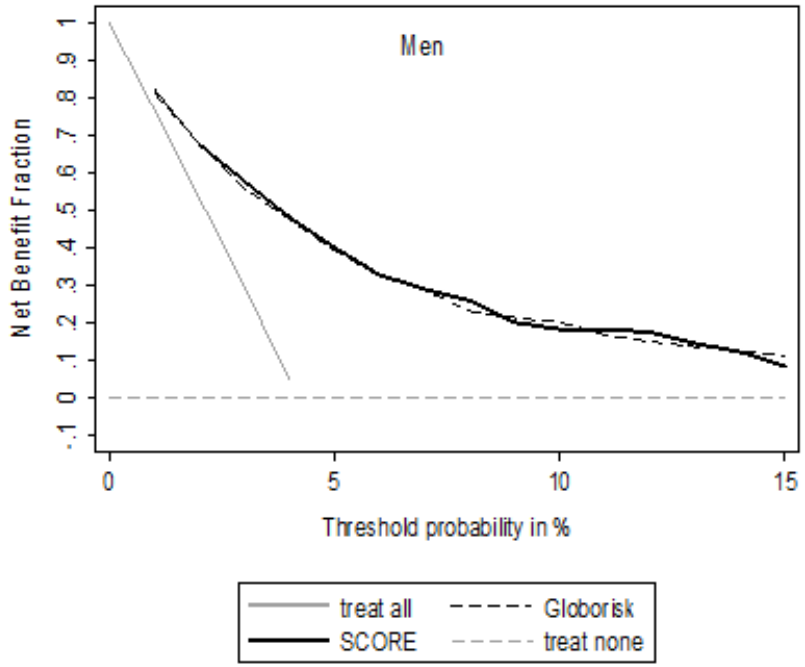
Globorisk risk function

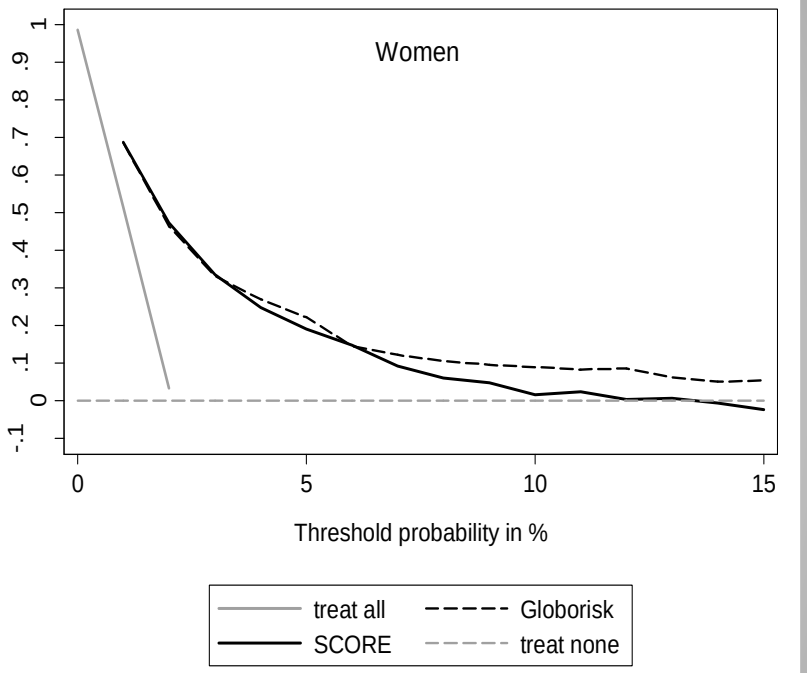


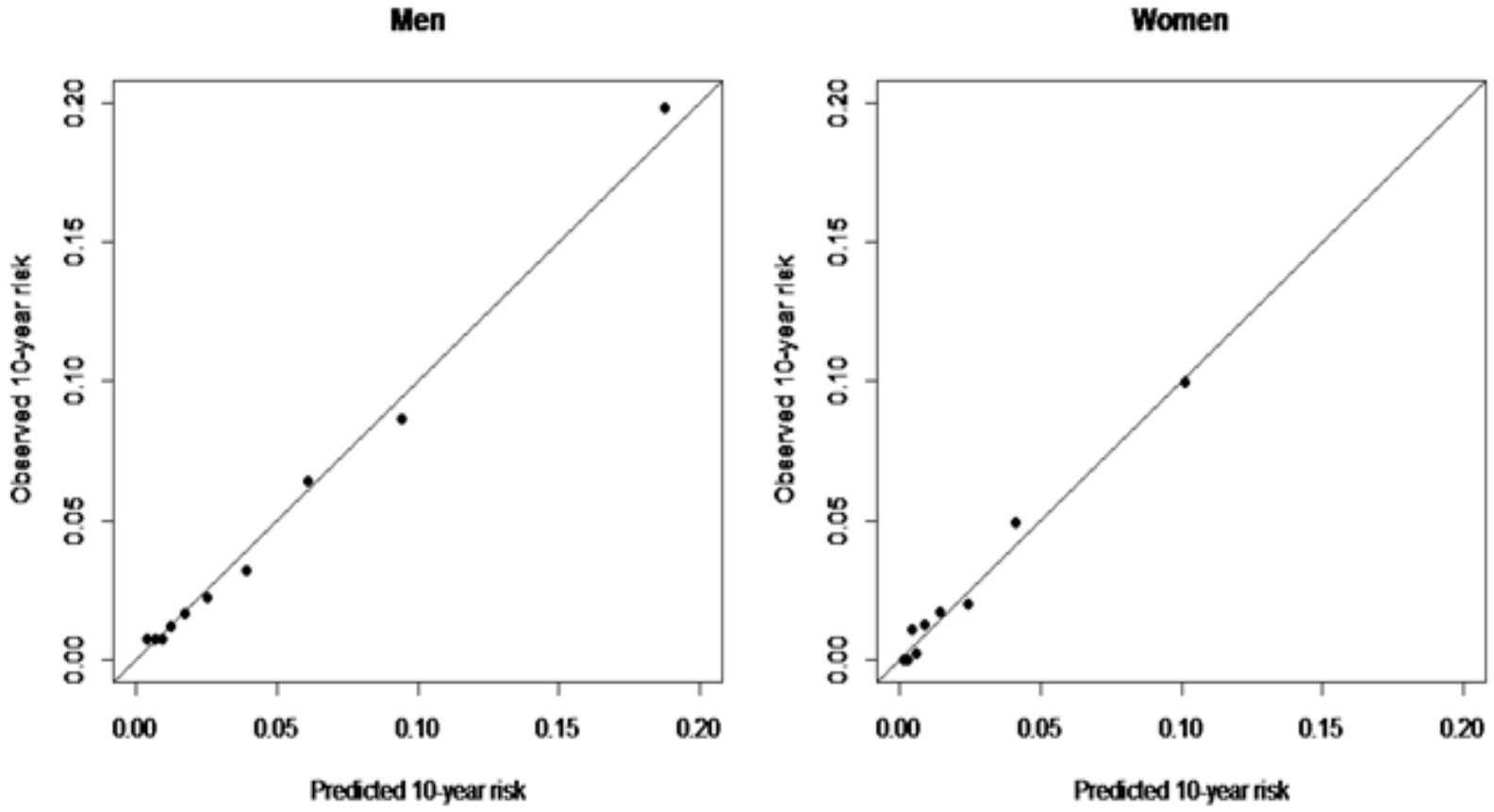
SCORE risk function (Without multiplication for diabetes)

Calibration plots of the recalibrated models, Globorisk and SCORE risk functions, by sex

Clinical Usefulness



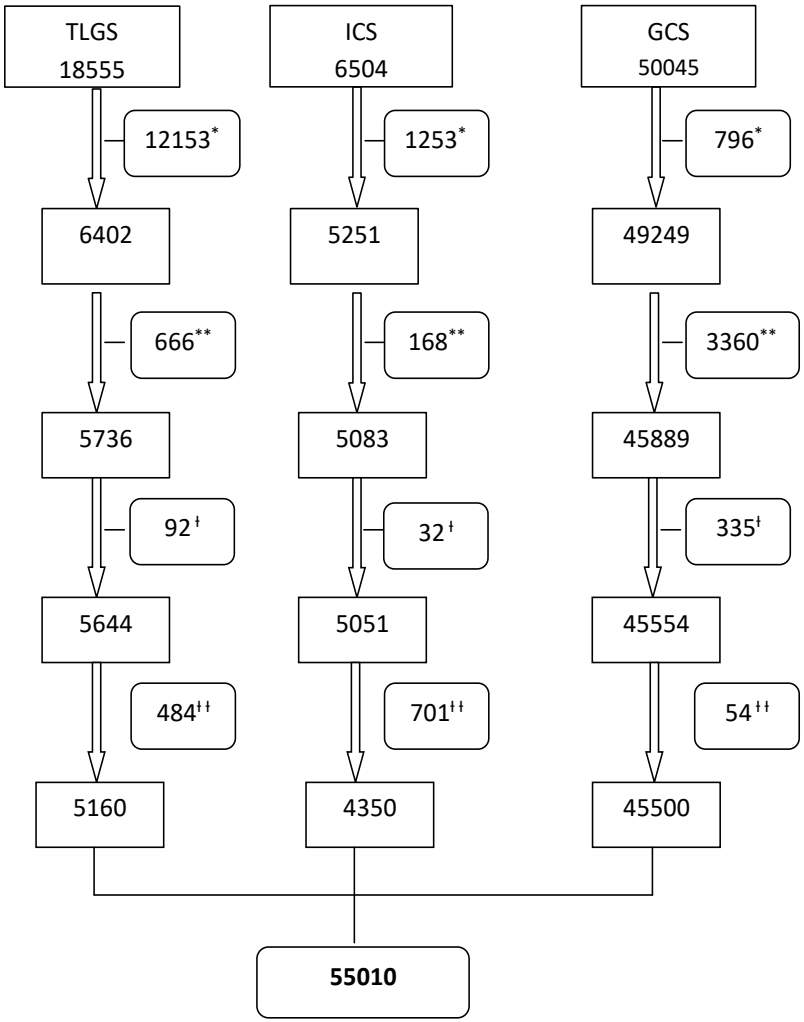




Calibration plot of the recalibrated "Globorisk" risk function, using CVD mortality coefficients in two cohorts with more than 10-year of follow-up (TLGS and ICS)

Phase 3

To develop a non-laboratory based prediction model



*age younger than 40 or older than 80

**history of cardiovascular diseases at baseline or unknown history

ǂ BMI>60 or BMI<16 or SBP>270 mmHg or SBP<60 mmHg

ǂǂ no follow up information

- During a 506889 person-year of follow-up, 2080 (1152 in men) CVD deaths occurred.

- The 10-year CVD mortality risks were
  0.052 (95%CI: 0.048-0.055) in men and
  0.032 (95%CI: 0.029-0.033) in women.

The Coefficients of CVD mortality risk factors in non-laboratory based model in Iranian cohorts, by sex

Men	Coefficients	95% CI*		P-value
Age, year	0.1509	0.0356	0.1837	<0.001
SBP ǂ, mm Hg	0.0500	0.3543	0.0643	<0.001
Smoking, yes	0.4883	0.5885	0.6222	<0.001
Self- reported diabetes, yes	0.7609	0.0022	0.9332	<0.001
Waist Circumference, cm	0.0070	0.1181	0.0117	0.004
Education, levels 0-4	-0.1398	-0.2017	-0.0779	<0.001
Age* SBP ‡	-0.0006	-0.0008	-0.0003	<0.001
Women	**Coefficients**	**95% CI***		**P-value**
Age, year	0.1270	0.0908	0.1632	<0.001
SBP ǂ, mm Hg	0.0345	0.0196	0.0494	<0.001
Smoking, yes	0.8493	0.4494	1.2493	<0.001
Self- reported diabetes, yes	0.9078	0.7475	1.0680	<0.001
Waist Circumference, cm	0.0215	0.0112	0.0318	<0.001
Education, levels 0-4	-0.3217	-0.4934	-0.1500	<0.001
Body Mass Index, kg/m^2	-0.0723	-0.0985	-0.0461	<0.001
Age* SBP ‡	-0.0003	-0.0006	-0.0001	0.011

*CI: Confidence interval, ǂSBP: Systolic blood pressure, ‡Age*SBP: Shows the interaction between age and systolic blood pressure

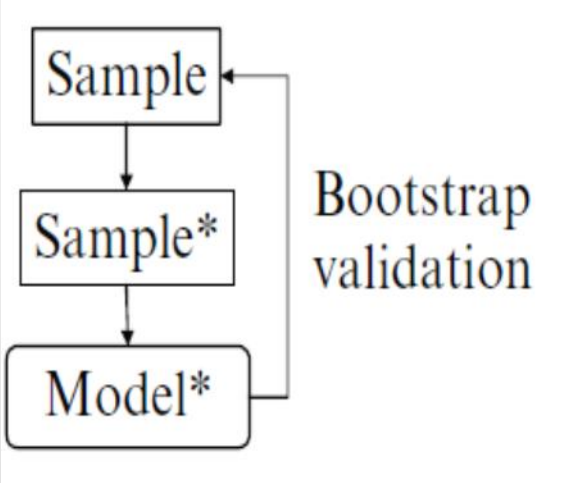
Model C-index:

Men: 0.776 (0.762-0.790)
Women: 0.799 (0.782-0.813)

But many developed mode suffers from Overfitting

To avoid this problem:

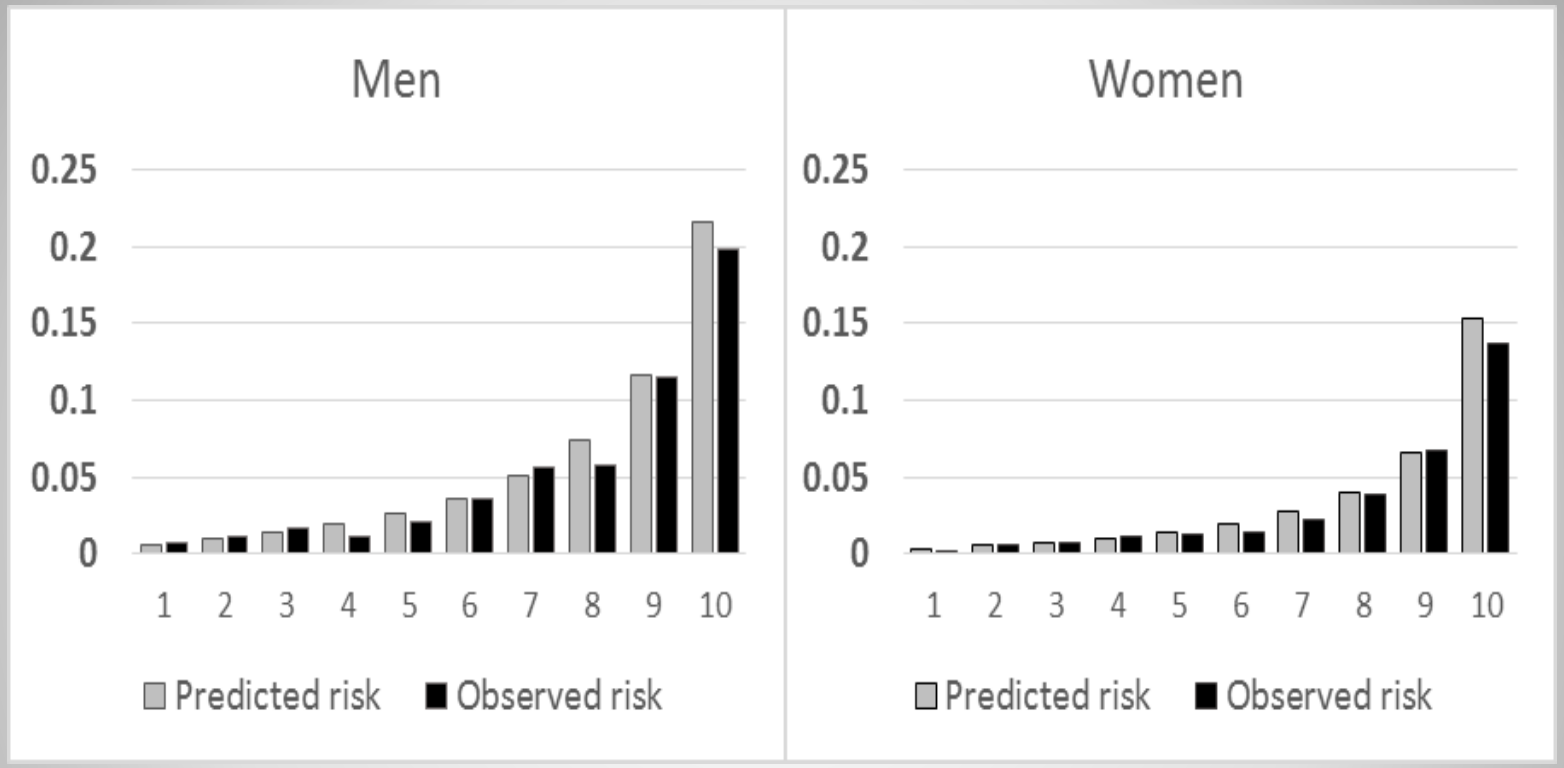
- We estimated the values of optimism and calculated the 'Optimism corrected performance'



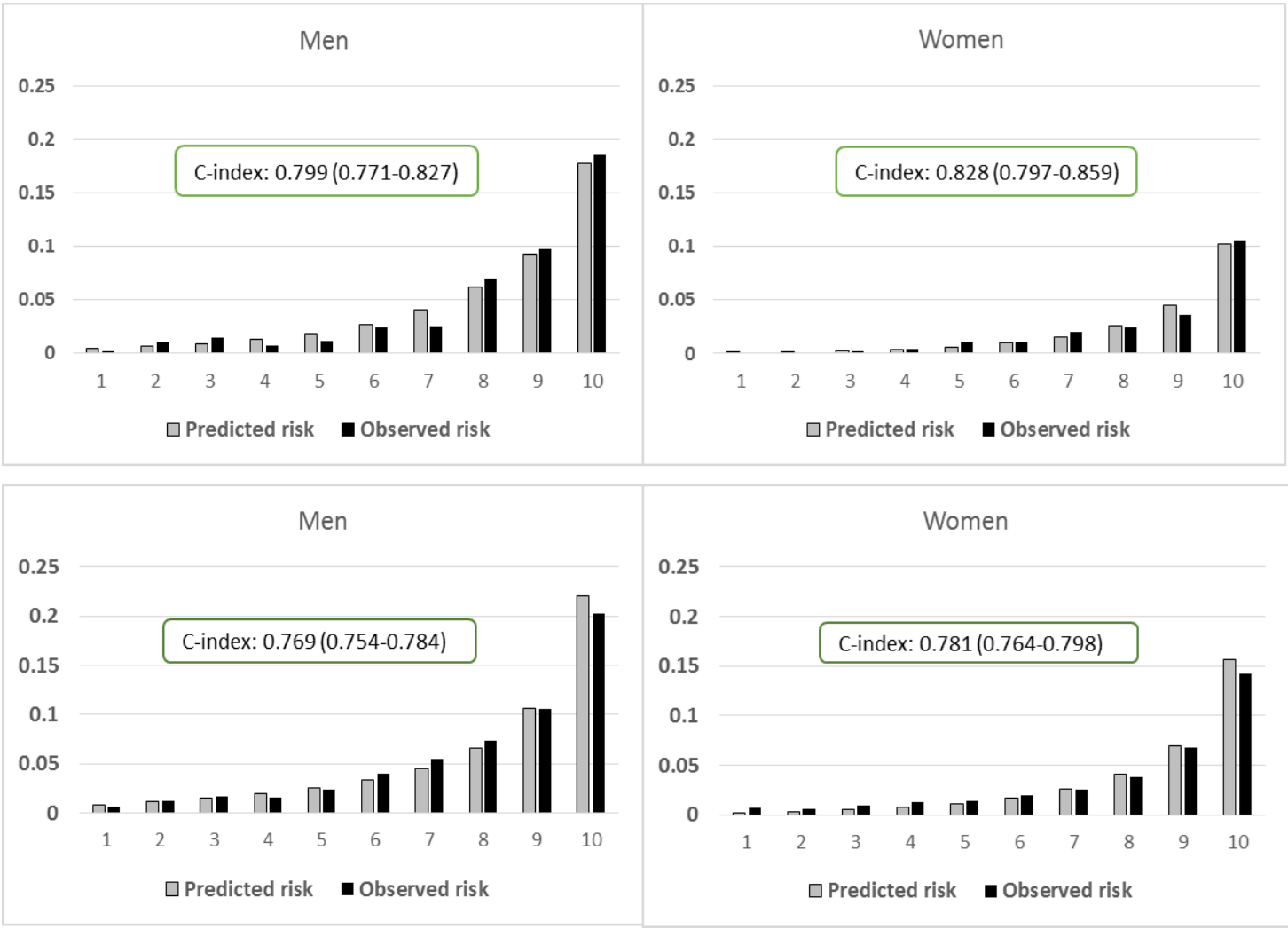
Other indices of model performance were estimated:

- Calibration (interexternal-
- Sensitivity, Specificity, PV, LR (using Bootstrapping methods)
- Clinical usefulness

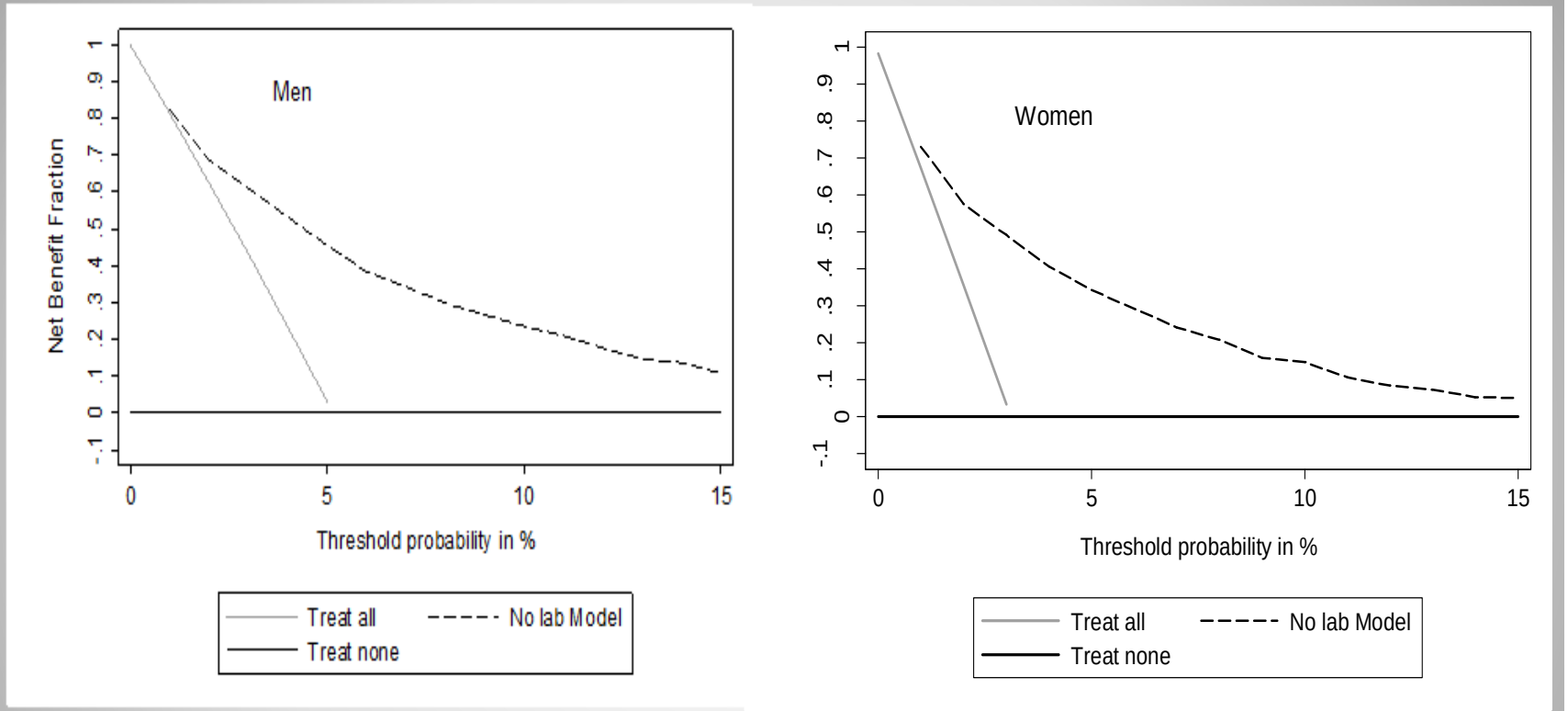
To account for the effect of **competing risks**, all steps were repeated using Fine and Gray approach as well



Men:	C-index: 0.776 (0.762-0.790), optimism-corrected c-index: 0.774
Women:	C-index: 0.799 (0.782-0.813), optimism-corrected c-index: 0.798



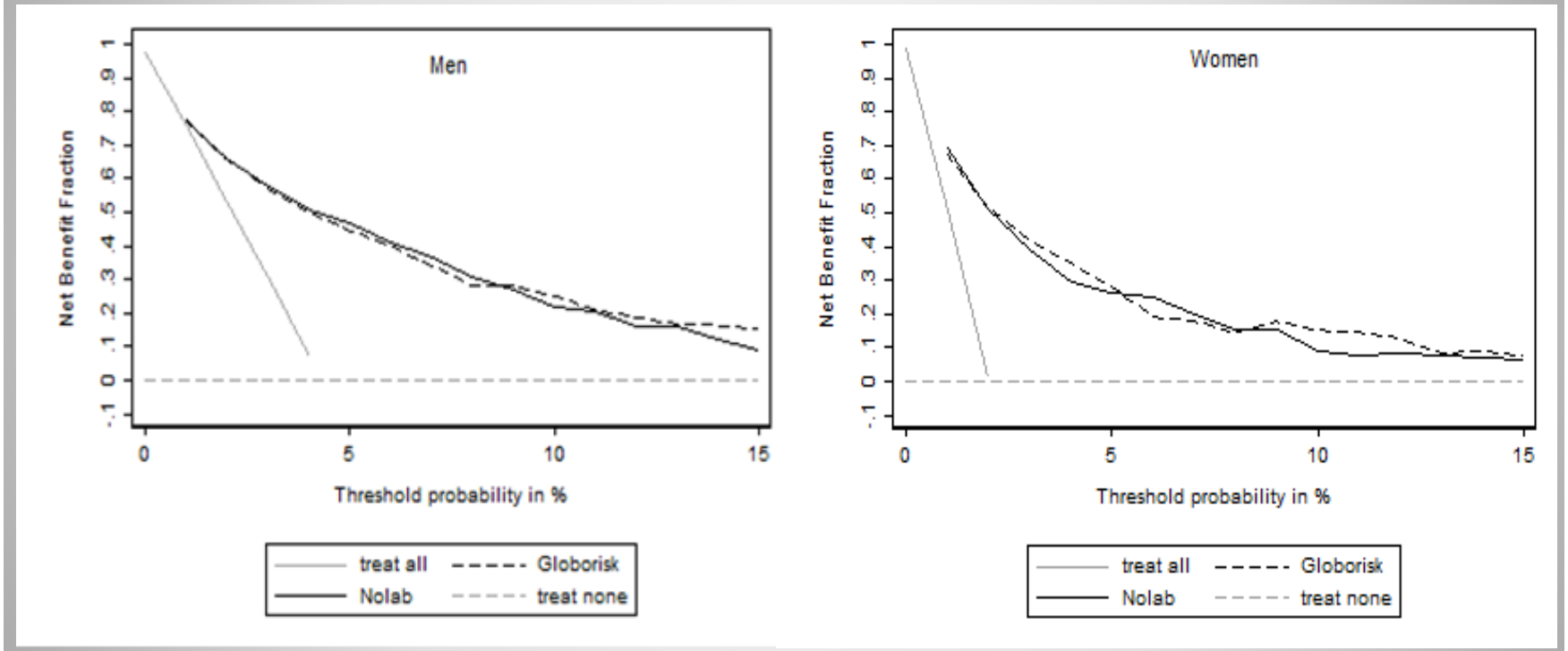
Performance of the cross validated non-laboratory models in men and women.
Upper graphs indicates the performance of the model developed in the TLGS and ICS, and validated in GCS. In lower graphs, the model was developed in GCS and validated in TLGS and ICS.



Decision curve for the predicted probabilities of the non-laboratory based model in different thresholds.

"Treat none" indicates no prediction and no treatment and, thus, no benefit; "treat all" means treating all subjects regardless of any prediction.

The comparison of lab-based and no-lab models in TLGS and ICS



- CVD mortality incidence in Iran is high.
- The Globorisk and SCORE models have good discrimination in the Iranian population but recalibration was needed.
- After recalibration, these models can be used for CVD mortality prediction with slightly better performance for Globorisk in women.
- Non-laboratory model can make risk assessment simpler in situations where laboratory testing is unavailable or expensive. High risk detected population may need more assessment and follow up.

Publications:

- Cardiovascular Mortality in a Western Asian Country: Results from the IRAN Cohort Consortium (Accepted)

- Prediction of cardiovascular disease mortality in a Western Asian country: performance of the Globorisk and SCORE functions in four population-based cohort studies of Iran (submitted)

- An office-based model to predict 10-year CVD mortality risk as a first step for screening: result from three prospective cohorts in a Western Asian country (drafting)

Abstracts in International clinical decision making congress

- Score Risk Function to Predict Cardiovascular Disease Mortality in a Population Outside of Europe: Performance and Challenges

- Consistency between Score and Globorisk Prediction Models for Cardiovascular Disease Mortality in a Western Asian Country


از حسن توجه شما سپاسگزارم