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Preventive Medicine

Derivation and validation of a set of 10-year cardiovascular risk predictive functions in Spain: The FRESCO Study

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Funding

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Justification of primary prevention of coronary heart disease

- Greatest cause of death in developed countries

- In ~35% of cases its onset symptom is sudden death.

- Most cases are related to lifestyle & other modifiable factors, whose improvement results in reduced CHD incidence.

- An accurate risk estimation is the best tool to establish priorities in CHD primary prevention

Cardiovascular Risk Estimation

- Risk functions consist of risk estimation methods based on mathematical algorithms

- They aim at estimating the excess risk in individuals compared to the average population

- The prediction yields the proportion of population with the individual's combination of factors that will develop a CHD event at 10 years

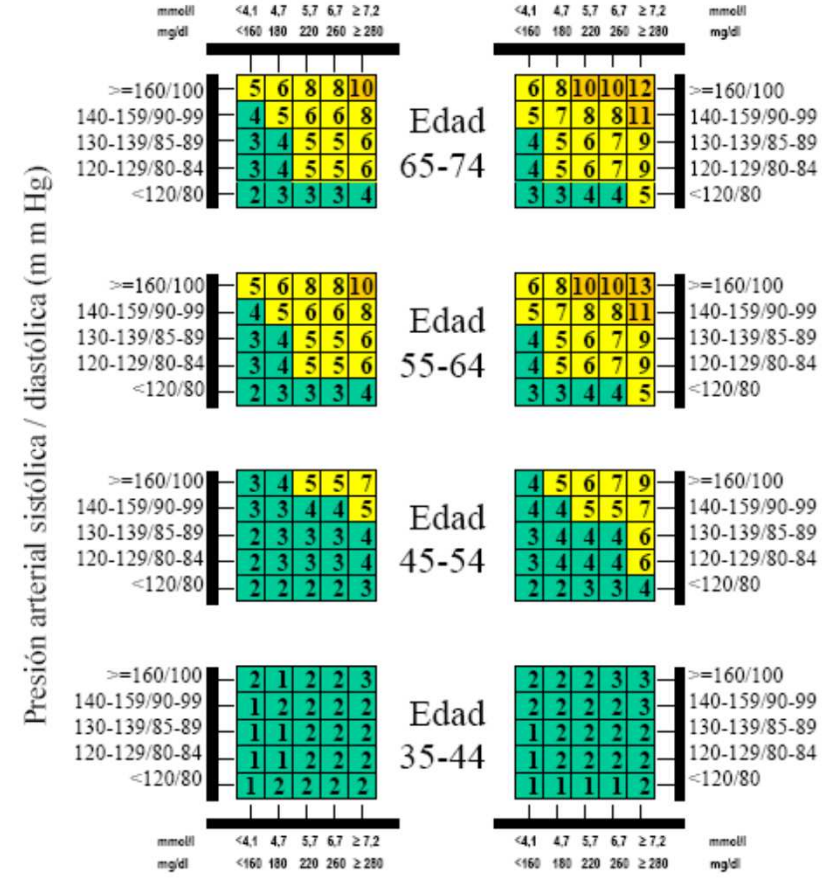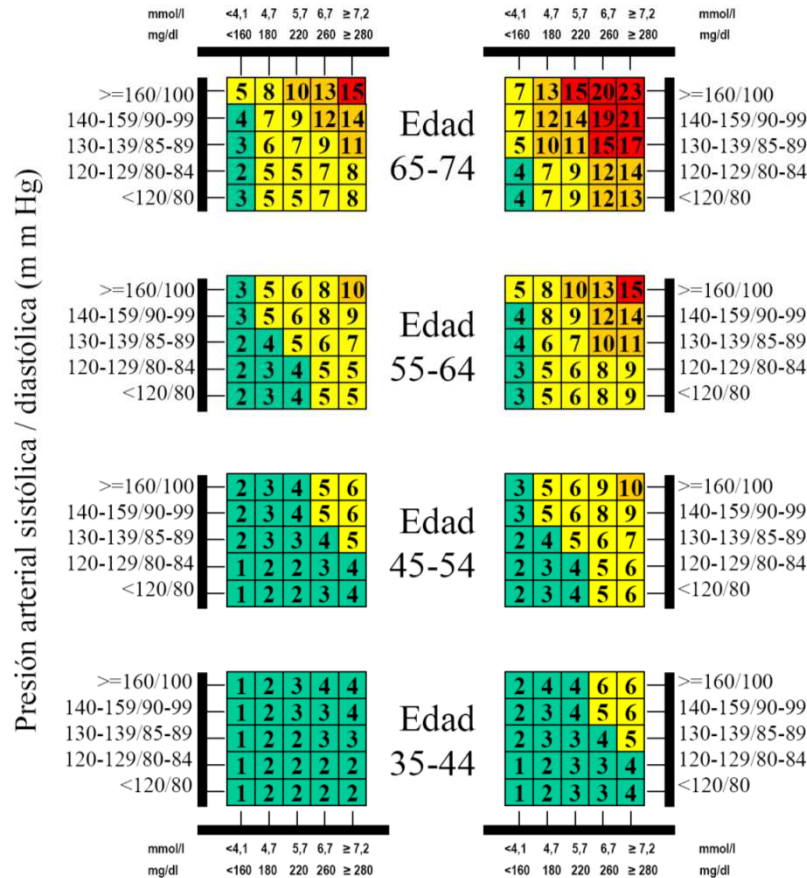# Framingham-REGICOR adapted version 2010
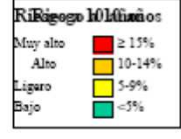

Hombres

Mujeres

Cardiovascular risk functions timeline

Anderson KM. Am Heart J. 1991
1st version Framingham risk function

D'Agostino RB. JAMA. 2001
Calibration method for Framingham adaptation

Conroy RM. Eur Heart J. 2003
SCORE Risk function for European population

Wilson PW. Circulation.1998
2nd version Framingham risk function

Hense HW. Eur Heart J. 2003
PROCAM Risk function for German population

Liu J. JAMA.2004
Framingham adaptation to Chinese population

Hippisley-Cox J. BMJ. 2007
Q Risk function based on electronic medical records

D'Agostino RB. Circulation. 2008
Framingham general cardiovascular risk function

Marrugat J. JECH. 2003
Framingham adaptation to Spanish population

Marrugat J. JECH. 2007
Validation of Framingham REGICOR risk function

Risk Estimation and the South European Paradox

- The gradual aging process increases the average cardiovascular risk

- CHD is the main cause of death in Spain
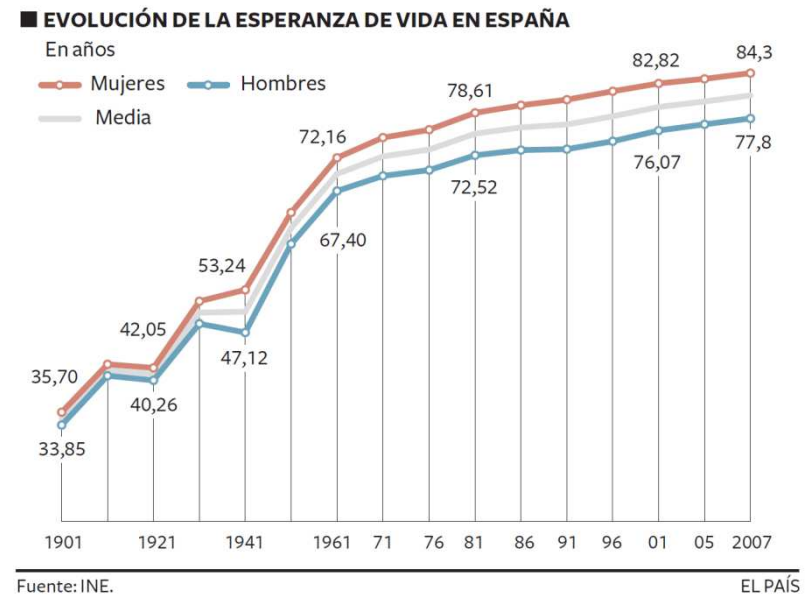
- Spain has shown a high prevalence of classic cardiovascular risk factors together with an unexpectedly low incidence of CHD

EVOLUCIÓN DE LA ESPERANZA DE VIDA EN ESPAÑA
En años
Mujeres   Hombres
Media

84,3
82,82
78,61
77,8
76,07
72,16
72,52
67,40
53,24
47,12
42,05
40,26
35,70
33,85

1901 1921 1941 1961 71 76 81 86 91 96 01 05 2007

Fuente: INE.   EL PAÍS

Characteristics of the ideal risk function in Spain

- Based on data from a Spanish population cohort

- Applicable to individuals aged 35 to 79 years

- Large sample size to produce accurate estimations

- Allowing to estimate the CHD and stroke risk, separately

- Applicable to diabetic patients

The FRESCO Project: Aims

Función de Riesgo ESpañola de acontecimientos Coronarios y Otros
Spanish Risk function of coronary and other cardiovascular events

- To create and validate a set of coronary, stroke and cardiovascular risk functions in the Spanish population

- This set of functions should work in an automated environment of electronic medical records

- The functions may suit different situations of risk factor measurement availability

The FRESCO Project: Methodology

- Pooled analysis of individual data from 11 population cohorts from 7 Spanish regions

- Participants aged 35 to 79 years

- 50,408 eligible subjects followed a median time of 9.3 years (447,516 person-years)

- The occurrence of fatal and non-fatal CHD and stroke was registered

- The prevalence of major CV risk factors was registered by standard methods

Derivation of FRESCO risk function

- 60% of the pooled cohort

- Cox proportional hazard models stratified by sex and adjusted for potential confounders for three end-points

  - CHD (myocardial infarction or angina)

  - Stroke

  - Combined end-point (myocardial infarction, angina or stroke)

- A "frailty term" was used to control inter-centre variability

Validation of FRESCO risk function

- 40% of the pooled cohort

- Accuracy or calibration
  - The number of events predicted in a population are compared to those observed at follow-up
  - Nam-D'Agostino goodness of fit

- Reliability or discrimination
  - Capacity for classifying individuals in the cohort in relation to whether an event will or will not occur in the period under study
  - C statistic

- Reclassification capacity
  - To assess whether the inclusion of new variables to a reference model improves the classification of individuals
  - Net reclassification index

Models adjusted stratified sex

	Model 1
Derivation cohort	
Age	/////
Smoker	/////
Body mass index	/////
Diabetes	/////
Systolic blood pressure	
Total cholesterol	
HDL cholesterol	
Hypertension treatment by SBP>120 mmHg	
Age by smoking	
Age by systolic blood pressure	

*Used in models for CHD and composite end-point

Designed for individual
risk self-estimation

Models adjusted stratified sex

	Model 1	Model 2
Derivation cohort		
Age	▨	▨
Smoker	▨	▨
Body mass index	▨	
Diabetes	▨	▨
Systolic blood pressure		▨
Total cholesterol		▨
HDL cholesterol		▨
Hypertension treatment by SBP>120 mmHg		▨
Age by smoking*		▨
Age by systolic blood pressure*		▨

*Used in models for CHD and composite end-point in men

Designed to estimate risk in a clinical setting

Flow chart of participant selection
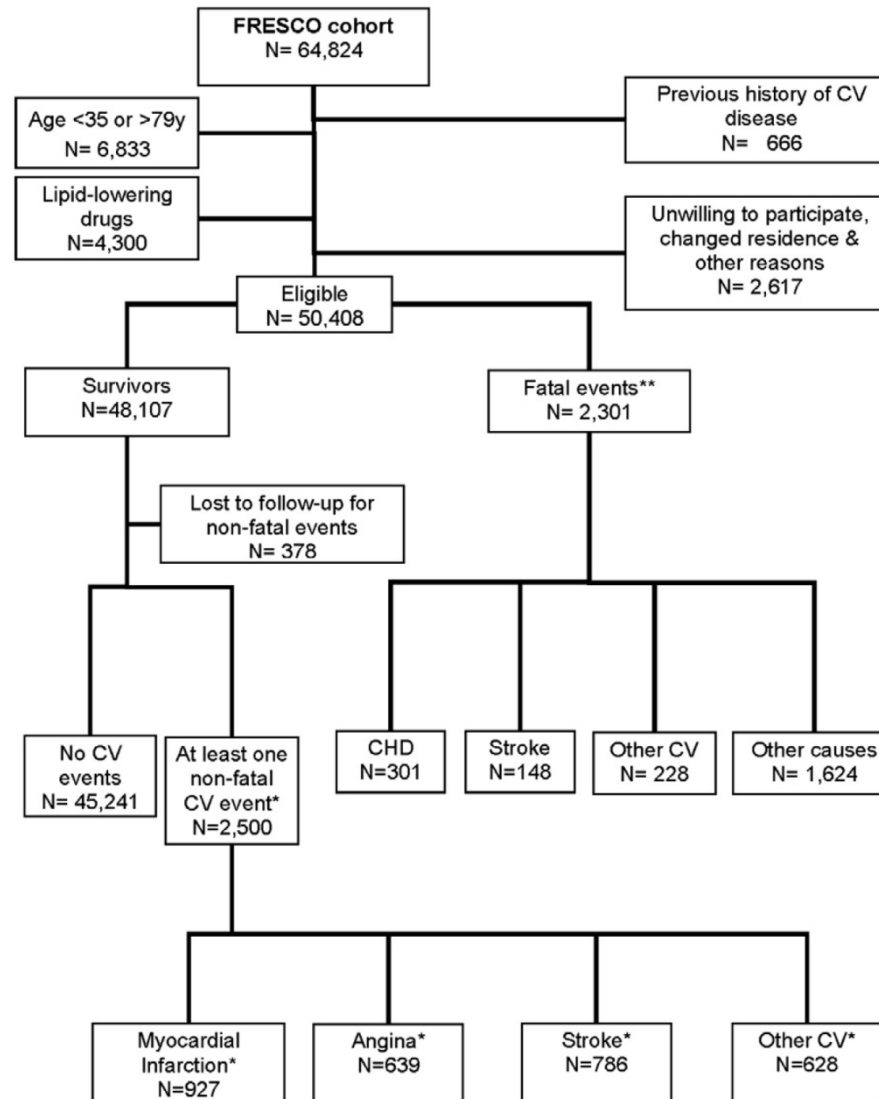
* Participants may have presented more than one event
** Fatal events considered in participants without previous non-fatal events alone

Participant characteristics of the FRESCO Study

	Derivation cohort		Validation cohort	
	Men	**Women**	**Men**	**Women**
	N = 14,090	**N = 16,180**	**N = 9,199**	**N = 10,939**
Age	56 (12)	56 (12)	56 (12)	56 (12)
Total cholesterol	219 (40)	223 (41)	219 (40)	223 (40)
HDL cholesterol	50 (13)	59 (15)	50 (13)	59 (14)
Systolic blood pressure	137 (18)	133 (21)	137 (19)	132 (21)
Diabetes	17%	12%	17%	13%
Body mass index	27.7 (3.7)	27.9 (5.0)	27.7 (3.8)	27.8 (4.9)
Smoker	30%	13%	30%	14%
Median follow up [1Q-3Q] years	8.9 [7.1;10.0]	9.3 [7.6;10.0]	9.0 [7.3;10.0]	9.3 [7.6;10.0]
Angina	1.7%	0.9%	1.8%	0.9%
Acute myocardial infarction	2.8%	1.0%	2.9%	1.1%
Stroke	2.0%	1.2%	2.1%	1.2%
Causes of death in fatal cases				
Coronary heart disease	14.8%	11.0%	13.7%	11.1%
Stroke	6.4%	7.3%	5.2%	7.0%
Other cardiovascular	7.9%	12.7%	7.8%	14.0%
Other non-cardiovascular	70.5%	68.4%	73.0%	67.9%

Beta coefficients and models performance for CHD

	Model A		Model B	
	Men	**Women**	**Men**	**Women**
Derivation cohort	N = 13,240	N = 15,311	N = 12,075	N = 13,935
Number of events	466	215	425	189
Age (1 year)	0.053***	0.080***	0.241***	0.066***
Smoker	0.466***	0.776**	2.453***	0.784**
Body mass index	0.331**	0.217		
Diabetes			0.528***	0.778***
Systolic blood pressure (10 mmHg)			0.888***	0.038
Total cholesterol (10 mg/dl)			0.061***	0.077***
HDL cholesterol (10 mg/dl)			-0.211***	-0.272***
Hypertension treatment by SBP >120 mmHg			0.519***	0.133
Age by smoking			-0.034**	
Age by systolic blood pressure			-0.013***	
	Men	**Women**	**Men**	**Women**
Validation cohort	N = 7,955	N = 9,481	N = 7,955	N = 9,481
Number of events	263	147	263	147
C-statistic [95% CI]	66 [63;69]	70 [66;73]	71 [68;74]***	74 [70;78]***
Nam-D'Agostino goodness of fit	18.2	10.7	13.1	12.7
Net Reclassification Index†	Ref.	Ref.	11 [3;19]	8 [1;16]

*p <0.05; **p<0.01; ***p<0.005; †Risk categories: <5%; 5-9.9% and ≥10%

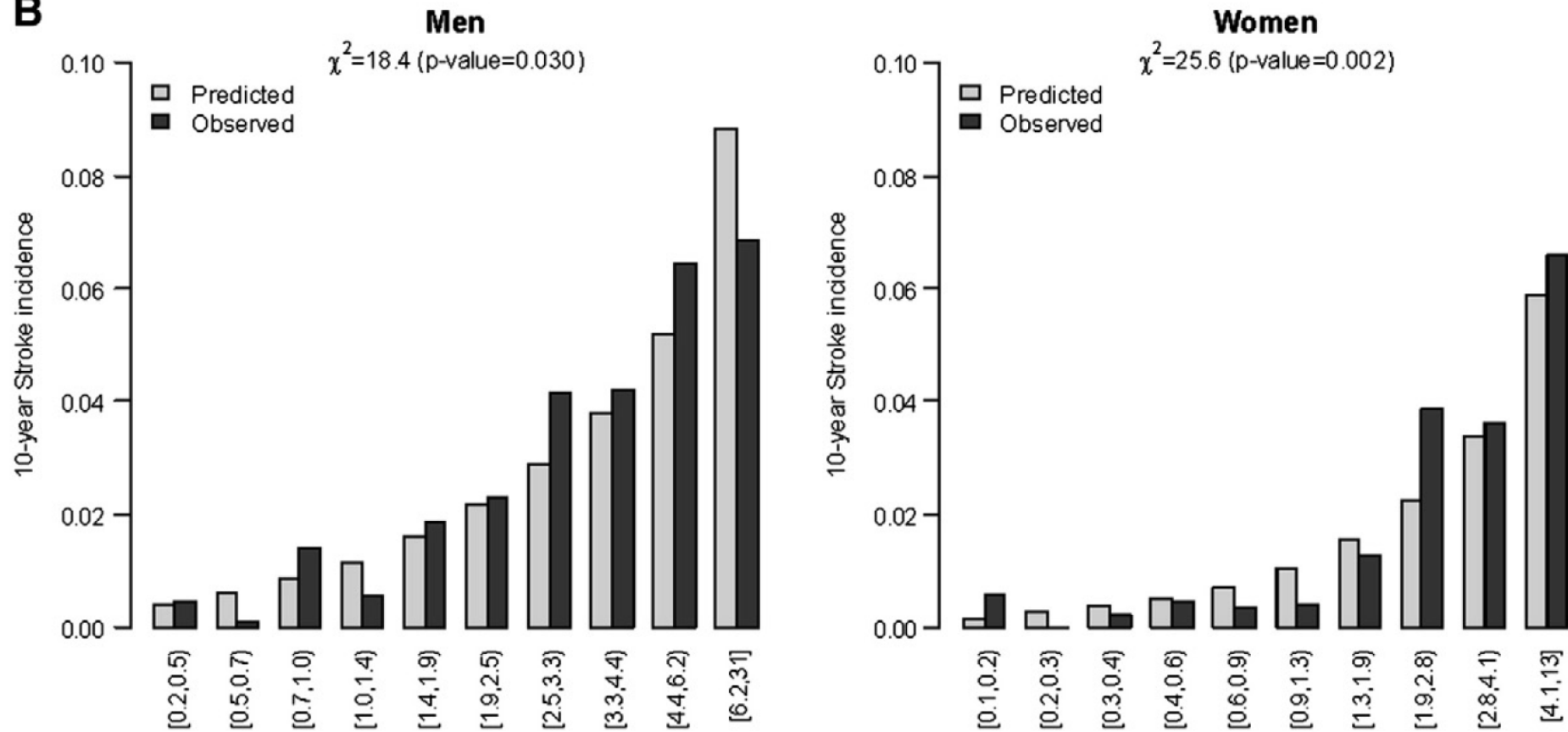# Observed incidence and CHD event prediction in the validation cohort
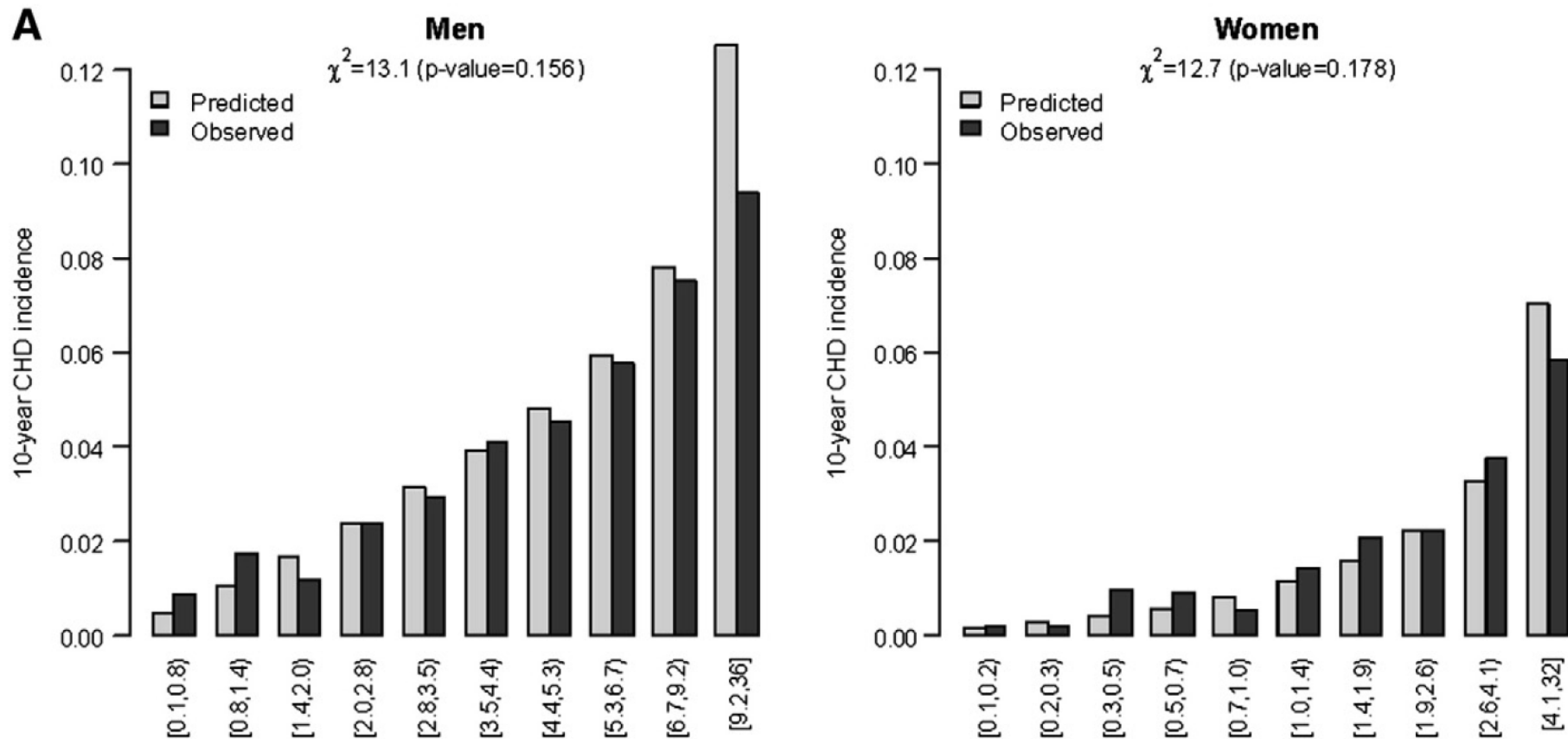
Beta coefficients and models performance for stroke

	Model A		Model B	
	Men	**Women**	**Men**	**Women**
Derivation cohort	N = 13,248	N = 15,307	N = 12,085	N = 13,934
Number of events	258	184	235	168
Age (1 year)	0.075***	0.097***	0.058***	0.088***
Smoker	0.116	0.864**	0.095	0.775*
Body mass index	0.091	-0.192		
Diabetes			0.519***	0.513**
Systolic blood pressure (10 mmHg)			0.176***	0.030
Total cholesterol (10 mg/dl)			0.009	-0.020
HDL cholesterol (10 mg/dl)			-0.005	-0.038
Hypertension treatment by SBP >120 mmHg			-0.027	0.054
Age by smoking				
Age by systolic blood pressure				
	Men	**Women**	**Men**	**Women**
Validation cohort	N = 7,956	N = 9,482	N = 7,956	N = 9,482
Number of events	170	120	170	120
C-statistic [95% CI]	72 [69;75]	77 [73;81]	73 [70;77]	78 [74;82]
Nam-D'Agostino goodness of fit	21.7*	16.7	18.4*	25.6*
Net Reclassification Index	Ref.	Ref.	5 [-5;14]	-1 [-9;8]

*p <0.05; **p<0.01; ***p<0.005; †Risk categories: <5%; 5-9.9% and ≥10%

Observed incidence and stroke prediction in the validation cohort

Beta coefficients and models performance for CVD

	Model A		Model B	
	Men	**Women**	**Men**	**Women**
Derivation cohort	N = 13,251	N = 15,310	N = 12,088	N = 13,937
Number of events	702	391	639	349
Age (1 year)	0.061***	0.089***	0.198***	0.077***
Smoker	0.345***	0.856***	1.913***	0.826***
Body mass index	0.251**	0.011		
Diabetes			0.519***	0.684***
Systolic blood pressure (10 mmHg)			0.728***	0.038
Total cholesterol (10 mg/dl)			0.045***	0.032*
HDL cholesterol (10 mg/dl)			-0.139***	-0.168***
Hypertension treatment by SBP >120 mmHg			0.330***	0.119
Age by smoking			-0.026**	
Age by systolic blood pressure			-0.010***	
	Men	**Women**	**Men**	**Women**
Validation cohort	N = 7,958	N = 9,482	N = 7,958	N = 9,482
Number of events	420	257	420	257
C-statistic [95% CI]	68 [66;71]	72 [69;75]	71 [68;73]*	75 [72;78]***
Nam-D'Agostino goodness of fit	24.8*	22.6*	10.2	14.4
Net Reclassification Index	Ref.	Ref.	3 [-4;10]	6 [-3;14]

*p <0.05; **p<0.01; ***p<0.005; †Risk categories: <5%; 5-9.9% and ≥10%

# Observed incidence and CVD event prediction in the validation cohort
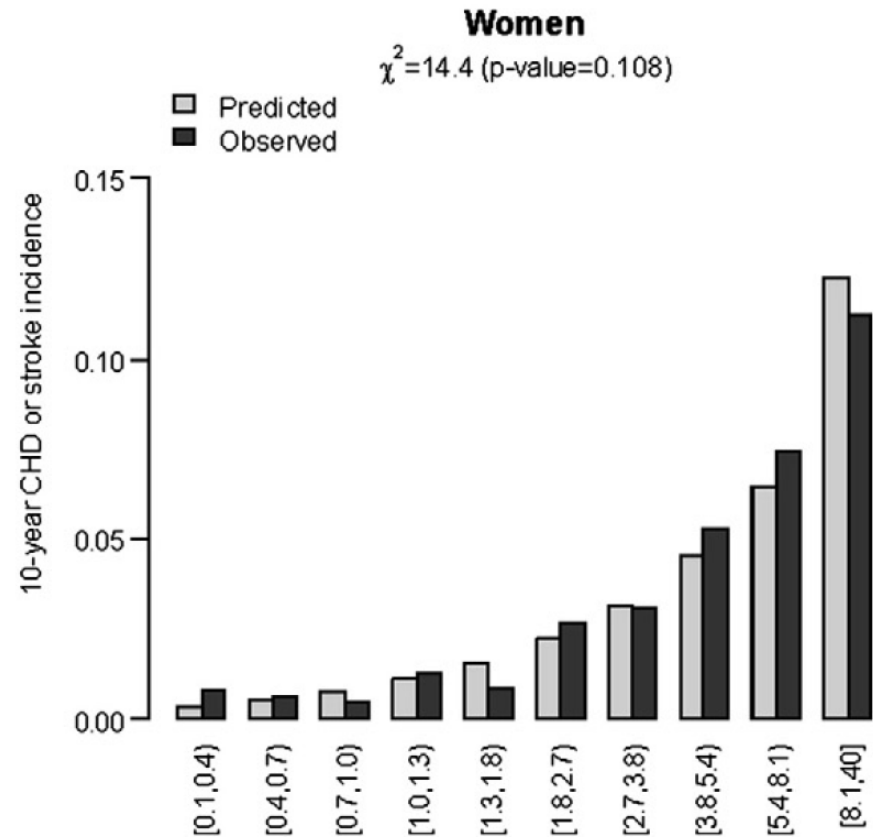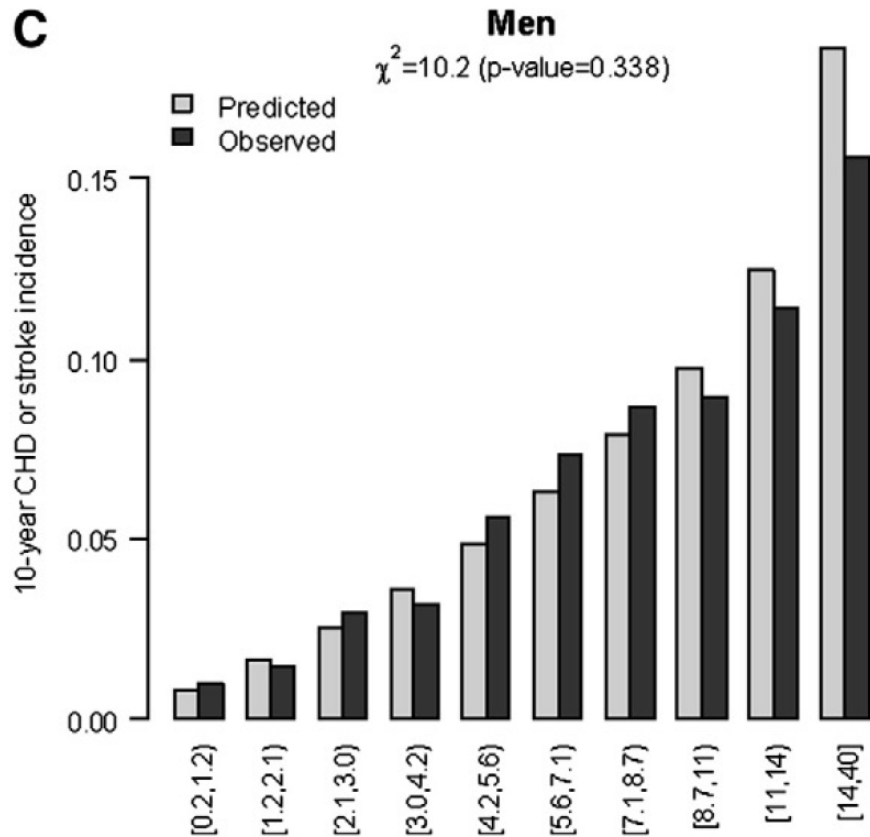
The FRESCO Project: Secondary analysis

- To compare the performance of the FRESCO functions and the validated Framingham-REGICOR function in the subset of population aged 35 to 74 years

    - Nam-D'Agostino goodness of fit

    - Coefficient of determination (R^2)

    - Intraclass correlation coefficient

Observed incidence and CHD event prediction in the validation cohort by deciles of Framingham-REGICOR risk
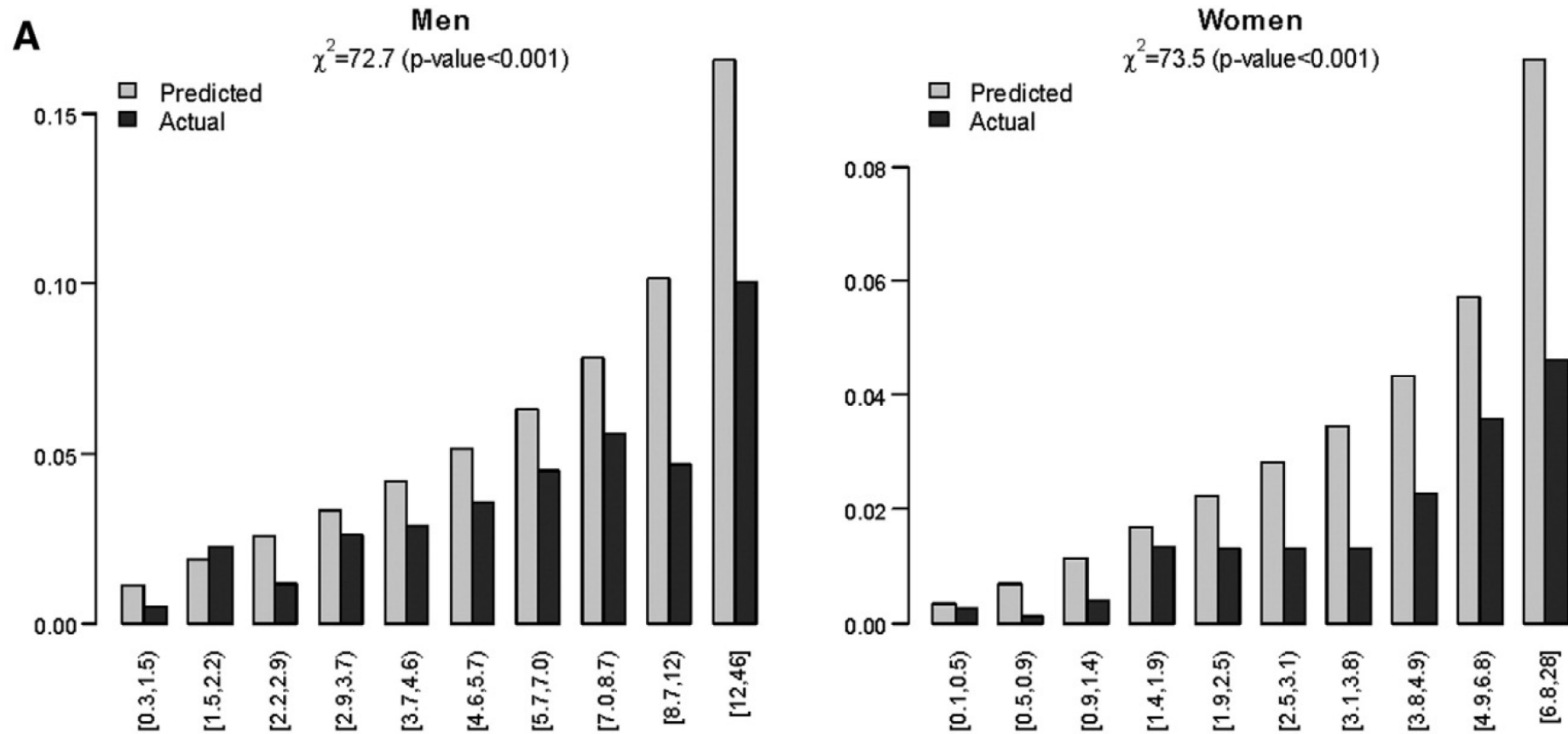
Coefficient of determination (R2) and intraclass correlation coefficient of Framingham-REGICOR and FRESCO functions
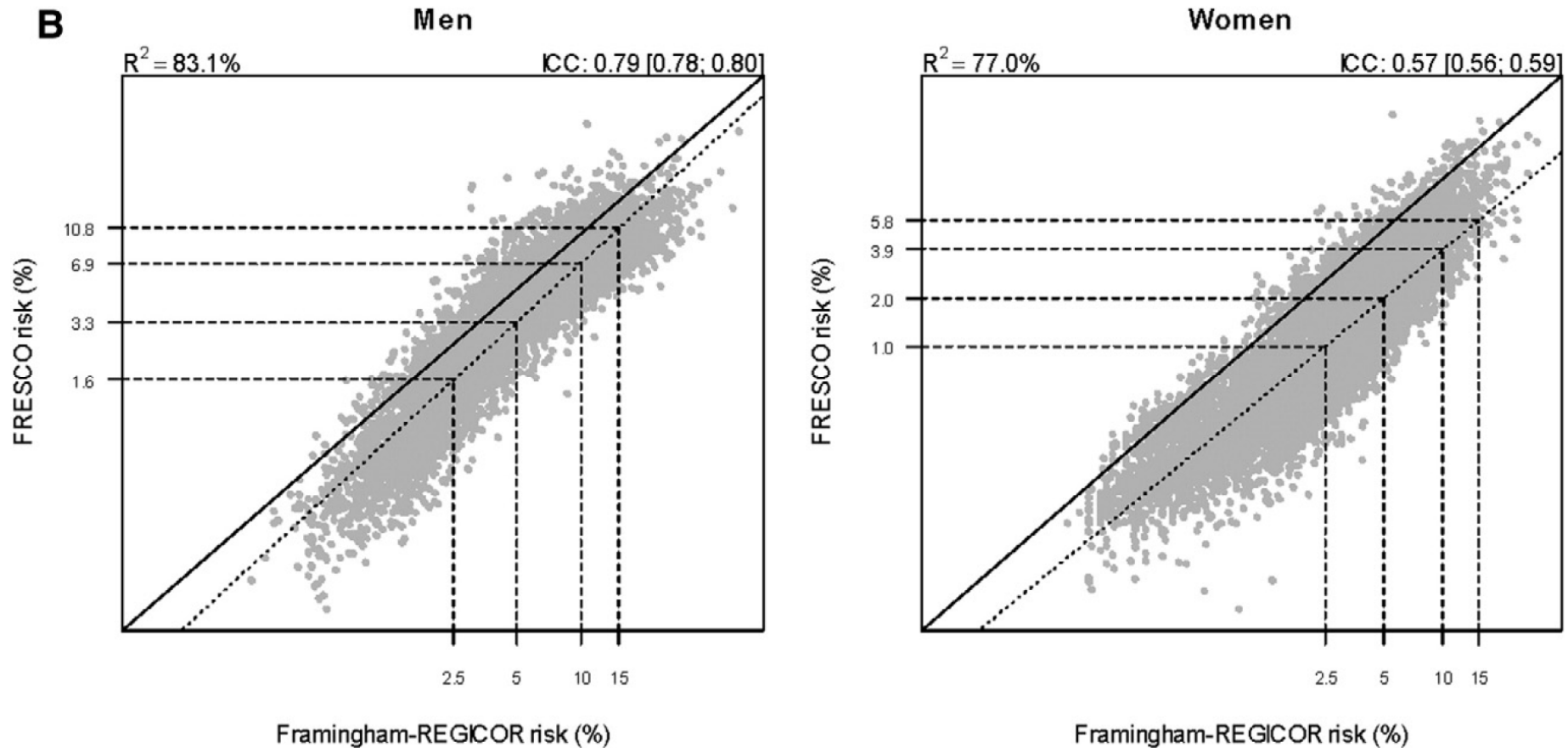
Conclusions

- The FRESCO set of functions are accurate and precise in the 10-year stroke and CHD risk, separately or combined, in the Spanish population aged 35 to 79 years.

- In population aged 35 to 74 years, the new CHD functions discriminate as well as the Framingham-REGICOR risk function.

- The Framingham-REGICOR risk function tended to systematically overestimate CHD risk.

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