

SCORE2 models allow consideration of sex-specific CVD risks by region

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SCORE2 is a risk algorithm developed to estimate 10-year cardiovascular disease (CVD) risk in men and women from four different risk regions of Europe¹, which is now recommended for use by the 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice². We agree with Kimenai et al [ref comment] on the need for consideration of sex differences in cardiovascular disease risk in both basic, clinical and translational research and prevention guidelines. Indeed, our development of the SCORE2 algorithm recognised this, with all steps of model development performed separately for each sex. This has resulted in accurate and externally validated prediction algorithms for both men and women, with further research validation and clinical application facilitated by different translational tools already provided (or in progress), including: easy-to-use risk charts (main paper **Figure 3**), statistical software program --score2risk-- (<https://www.phpc.cam.ac.uk/ceu/erfc/programs/>).

Furthermore, all relevant sex-specific model parameters were included in the Supplementary materials, in particular: **Supplementary Table 7** (for beta coefficients and baseline hazards) and **Supplementary Methods Table 2** (for recalibration scales)¹. We do, however, recognize the relevance of making all model parameters available to a greater precision in order to facilitate

appropriate usage. Therefore, we have included with this comment an additional table of sex-specific model coefficients and recalibration scales (**Table 1**) rounded to four decimal places. To make these parameters as easily accessible as possible, these table have been included in the updated version of the article supplement.

Table 1: Model coefficients, baseline survival and recalibration scales of the SCORE2 algorithm

A) Model coefficients:					
Risk factor (units)	Transformation equation	Log HR		HR	
		Male	Female	Male	Female
Age (yrs)	cage = (age - 60)/5	0.3742	0.4648	1.45	1.59
Smoking (current vs. other)	current=1, other=0	0.6012	0.7744	1.82	2.17
Systolic blood pressure (SBP, mm Hg)	csbp = (sbp - 120)/20	0.2777	0.3131	1.32	1.37
Diabetes* (yes vs. no)	yes=1, no=0	0.6457	0.8096	1.91	2.25
Total cholesterol (mmol/L)	ctchol = (tchol - 6)/1	0.1458	0.1002	1.16	1.11
HDL cholesterol (mmol/L)	chdl = (hdl - 1.3)/0.5	-0.2698	-0.2606	0.76	0.77
Smoking x age interaction	cage x smoking	-0.0755	-0.1088	0.93	0.90
SBP x age interaction	cage x csbp	-0.0255	-0.0277	0.98	0.97
Total cholesterol x age interaction	cage x ctchol	-0.0281	-0.0226	0.97	0.98
HDL cholesterol x age interaction	cage x chdl	0.0426	0.0613	1.04	1.06
Diabetes* x age interaction	cage x diabetes	-0.0983	-0.1272	0.91	0.88
Baseline survival		0.9605	0.9776		
10-year risk estimate (un-calibrated) = 1-baseline survival $\exp(\text{linear predictor}^{**})$					
B) Recalibration scales					
Risk region		Male		Female	
		Scale1	Scale2	Scale1	Scale2
Low risk region		-0.5699	0.7476	-0.7380	0.7019
Moderate risk region		-0.1565	0.8009	-0.3143	0.7701
High risk region		0.3207	0.9360	0.5710	0.9369
Very high risk region		0.5836	0.8294	0.9412	0.8329
Calibrated 10-year risk = $1 - \exp(-\exp(\text{scale1} + \text{scale2} \times \ln(-\ln(1 - \text{un-calibrated 10-yr risk})))$					

*Diabetes mellitus was included in the modelling since this was necessary for the recalibration approach, which relies on data from the whole population, including those with diabetes. However, SCORE2 is not intended for use in individuals with diabetes and has not been validated in this population. For risk prediction in the target population of individuals without diabetes this risk factor will always be 0, meaning the coefficient can effectively be ignored.

** linear predictor= $\sum(\text{transformed risk factor value} \times \log \text{HR})$

Final estimate should be multiplied by 100 in order to express as a percentage rather than a probability

1. Hageman S, Pennells L, Ojeda F, et al. SCORE2 risk prediction algorithms: new models to estimate 10-year risk of cardiovascular disease in Europe. *Eur Heart J.* 2021;42(25):2439-2454.
2. Visseren FLJ, Mach F, Smulders YM, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J.* 2021;42(34):3227-3337.