Dear Dr Weber,

We sincerely thank the reviewer for the detailed comments, which were of help in revising the manuscript.

Below you will find the comments from the reviewer, our response, and the changes we have made accordingly.

Yours sincerely,

Johanna Damen

Reviewer: 1

Recommendation:

Comments:

The authors have addressed all the reviewer points to my satisfaction. I have two extremely minor further observations.

1. Page 15 line 435 includes three citations with full names that can be omitted.

AUTHOR RESPONSE: We thank the reviewer for this suggestion and have made the following adjustment:

"Several prediction models have been developed using data from Asia (e.g. Asia Pacific Cohort studies (2007),⁴⁴ Liu et al. (2004),⁵¹ Wu et al. (2006)⁵²) but none of these models have yet been externally validated by independent researchers."

2. The last line of Table 4 gives the range of observed/expected ratios. Including the median as well would be useful.

AUTHOR RESPONSE: We thank the reviewer for this comment and agree that including the median in Table 4 would be useful. See below the changes we have made to Table 4.

Table 4: Description of study populations and design characteristics used to validate the seven most often (i.e. >10 times, see Table 3) validated models.

		Framingham Wilson 1998 ⁵	Framingham Anderson	SCORE Conroy	Framingham D'Agostino	Framingham ATP III 2002 ³⁷	Framingham Anderson	QRISK Hippisley-Cox
		n=89	1991a n=73	2003 11=63	2008 n=44	n=51	19910 N=30	2007 h=12
	[. ·	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Location	Asia	9 (10%)	3 (4%)	2 (3%)	8 (18%)	2 (6%)	2 (7%)	0 (0%)
	Australia	0 (0%)	12 (16%)	4 (6%)	2 (5%)	1 (3%)	2 (7%)	0 (0%)
	Europe	34 (38%)	52 (71%)	47 (75%)	20 (45%)	6 (19%)	18 (60%)	12 (100%)
	North America	46 (52%)	6 (8%)	10 (16%)	14 (32%)	22 (71%)	8 (27%)	0 (0%)
Age	Same age range as development study*	2 (3%)	21 (29%)	4 (6%)	5 (11%)	0 (0%)	0 (0%)	12 (100%)
	Young people (<50)	3 (3%)	6 (8%)	4 (6%)	3 (7%)	3 (10%)	1 (3%)	0 (0%)
	Elderly (>60)	5 (6%)	7 (10%)	4 (6%)	3 (7%)	10 (32%)	0 (0%)	0 (0%)
	Other	79 (89%)	39 (53%)	51 (81%)	33 (25%)	18 (58%)	29 (97%)	0 (0%)
Gender	Men	38 (43%)	30 (41%)	23 (37%)	11 (25%)	10 (32%)	16 (53%)	6 (50%)
	Women	29 (33%)	25 (34%)	23 (37%)	11 (25%)	10 (32%)	13 (43%)	6 (50%)
	Men and women	22 (25%)	18 (25%)	17 (27%)	22 (50%)	11 (35%)	1 (3%)	0 (0%)
		Median (range),	Median	Median	Median	Median	Median	Median
		n‡	(range), n	(range), n	(range), n	(range), n	(range), n	(range), n
Number of participants		2,716 (100- 163,627), n=87	2,423 (262- 797,373), n=71	8,025 (262- 44,649), n=63	2,661 (272- 542,987), n=44	3,029 (534- 36,517), n=31	3,573 (331- 542,783), n=30	536,400 (301,622- 797,373), n=12
Number of events		146 (8-24,659),	128 (1-42,408),	224 (16-1,722),	164 (15-	415 (35-2,343),	188 (4-26,202),	29,057 (18,027-
		n=65	n=59	n=54	26,202), n=35	n=29	n=28	42,408), n=6
		Range, n‡	Range, n	Range, n	Range, n	Range, n	Range, n	Range, n
C-statistic		<u>0.71 (</u> 0.57-0.92 <u>)</u> ,	<u>0.75 (</u> 0.53-	<u>0.75 (</u> 0.62-	<u>0.77 (</u> 0.58-	<u>0.66 (</u> 0.60-	<u>0.75 (</u> 0.63-	<u>0.79 (</u> 0.76-
		n=61	0.99 <mark>)</mark> , n=46	0.91 <u>)</u> , n=28	0.84 <mark>)</mark> , n=28	0.84 <mark>)</mark> , n=21	0.78 <mark>)</mark> , n=6	0.81 <u>)</u> , n=12
Observed/expected		<u>0.59 (</u> 0.37-1.92 <u>)</u> ,	<u>0.68 (</u> 0.18-	<u>0.68 (</u> 0.28-	<u>0.80 (</u> 0.62-	<u>0.47 (</u> 0.47-	<u>0.71 (</u> 0.32-	<u>0.94 (</u> 0.87-
ratio		n=14	2.60 <mark>)</mark> , n=42	1.50 <mark>)</mark> , n=26	0.96 <mark>)</mark> , n=3	0.47 <mark>)</mark> , n=1	3.92 <mark>)</mark> , n=14	1.00 <mark>)</mark> , n=4

* Age range in development studies: 30-74 (Framingham Wilson 1998, Framingham Anderson 1991, Framingham D'Agostino 2008, Framingham ATP III 2002, Framingham Anderson 1991 Circulation), 40-65 (SCORE Conroy 2003), 35-74 (QRISK Hippisley-Cox 2007).

† n indicates the number of times this model was externally validated.

‡ n indicates the number of models for which this information was reported.