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ABSTRACT

Background Previous tools for stroke risk assessment have either been developed for specific populations or lack data on non-fatal events or uniform data collection. The purpose of this study was to develop a stepwise model for the estimation of 10 year risk of stroke in nine different countries across Europe.

Methods Using data from the MOnica Risk, Genetics, Archiving and Monograph (MORGAM) Project, sex-specific models estimating 10 year risk of stroke were developed using a Cox regression model stratified by country and including modelling of competing risks. Models were developed in a stepwise manner first using only data from questionnaires, and then adding data from physical examinations and finally data from blood samples.

Results During 1 176 296 years of observation, 2928 incident fatal and non-fatal events of stroke were registered. The developed model showed good calibration and accuracy of prediction. The discrimination of the model varied between sex and country but increased with increasing number of variables used (area under the receiver operating characteristic curve between 0.77 and 0.79 in men and between 0.75 and 0.80 in women).

Conclusion The present study shows that using a large multicountry cohort from nine European countries it is possible to develop a stepwise risk estimation model for 10 year risk of stroke tailored to different availability of risk factors and still obtain valid measures of risk even in the simplest form of the model, with increasing performance of the model following increasing complexity. The methods chosen which separate this model from previous models (competing risk and stepwise approach) should be considered for future risk estimation models.

INTRODUCTION

During the last two decades several risk appraisal tools have been developed for prevention of cardiovascular disease (CVD). Most of these were developed for coronary heart disease (CHD) or the combined end point CVD, but few have been developed for stroke only. The Framingham Heart Study was the first to develop a risk estimation tool for stroke,[1] a model which has since been used in several guidelines for CVD prevention.

Other stroke risk estimation tools have subsequently been developed,[2–6] but these models have been either developed for fatal non-CHD events only[2] or limited to one population.[3–6]

It has become evident that risk models developed using data from Framingham have poor predictive or discriminative ability in other populations.[7–9]

There is need for risk estimation models that are sensitive to the differences in absolute risk between countries. The development of such models requires a multicentre study across several populations with a uniform standardised data collection, as done in the MONICA populations.[10 11]

In order to be able to tailor models to clinical settings of diverse resources it could be useful to develop risk estimation models of increasing complexity using a stepwise approach. In this way it is possible to estimate risk based solely on data from questions, then based on questions and physical examinations and finally including data from blood samples. This approach has, to our knowledge, never been used before.

The purpose of this study was first to develop a risk model for the estimation of 10 year risk of fatal and non-fatal stroke in a stepwise approach, in nine different countries across Europe, and secondly to estimate the predictive and discriminative ability of the model in each of the steps and for each of the countries included.

METHODS

The present study used baseline and follow-up data on fatal and non-fatal stroke from 16 centres in nine different European countries from the MOnica Risk, Genetics, Archiving and Monograph (MORGAM) collaboration.[12] The cohorts included in the MORGAM study were either examined as part of the WHO MONICA Project or MONICA procedures were used at baseline. The three French PRIME cohorts only included men (table 1). Details of the cohorts have been described elsewhere.[13]

Data collection on risk factors at baseline and cardiovascular end points during the follow-up were harmonised according to the MONICA and MORGAM manuals, respectively.[14 15] Diabetes, use of antihypertensive drugs and daily smoking at baseline were self-reported. The data from the baseline physical examinations included body mass index (BMI), calculated as weight (kg) divided by the square of the height (m^2), and blood pressure, which was measured twice in the right arm in a sitting position after 5 min of resting using a standard mercury or the random-zero mercury sphygmomanometer,[11] except in the French PRIME cohorts where blood pressure was measured once using an automated device. In the present study,

Table 1 Characteristics of the MORGAM populations included in the analyses

Country	Population	Type of cohorts* (no. of cohorts)	Age range at baseline	Survey period	Years of follow-up	No. of subjects†	Total years of observation	No. of all strokes, fatal and non-fatal		
								♂	♀	Total
Denmark	DEN-GLO Glostrup	MONICA centre (3)	30, 40, 50, 60	1982–1992	9–19	6483/4978	96232	162	127	289
Finland	FIN-EAS Eastern Finland and Oulu	MONICA centre and MONICA procedures (4)	25–64, 25–74‡	1982–1997	11–26	16347/12055	270549	464	385	849
	FIN-WES Turku-Loimaa and Helsinki	MONICA centre and MONICA procedures (4)	25–64, 25–74	1982–1997	11–26	10257/7204	161514	241	182	423
Sweden	SWE-NSW Northern Sweden	MONICA centre (3)	24–65, 24–74	1986–1994	5–14	4804/1525	43883	50	42	92
Poland	POL-WAR Warsaw	MONICA centre (3)	34–65	1983–1993	2–11	4691/2174	27473	25	11	36
Lithuania	LTU-KAU Kaunas	MONICA centre (3)	33–65	1983–1993	5–11	3908/2781	35506	44	32	76
Russia	RUS-NOV Novosibirsk	MONICA centre and MONICA procedures (4)	24–65	1983–1995	3–16	5391/2748	37125	25	16	41
France	FRA-LIL Lille	PRIME (MONICA procedures), men only (1)	49–64	1991–1993	10	2336/2336	22411	38	0	38
	FRA-STR Strasbourg	PRIME (MONICA procedures), men only (1)	49–60	1991–1993	10	2342/2342	22343	24	0	24
	FRA-TOU Toulouse	PRIME (MONICA procedures), men only (1)	49–60	1991–1993	10	2423/2423	23176	22	0	22
Italy	ITA-BRI Brianza	MONICA centre (4)	25–66	1986–1994	9–16	4520/3057	55141	39	21	60
	ITA-PAM Pamela	MONICA procedures (1)	25–75	1990–1993	9–12	1888/1888	20207	24	14	38
	ITA-ROM Rome and area Latina	MONICA centre and MONICA procedures (4)	19–77	1983–1995	8–19	8561/6643	124970	115	98	213
Scotland	UNK-EDI Edinburgh	MONICA procedures (1)	25–64	1986	19	1233/1233	22472	36	23	59
	UNK-GLA Glasgow	MONICA centre (4)	25–64, 25–75	1986–1995	10–19	4770/4770	62689	130	117	247
	UNK-SHH Nationwide	MONICA procedures (1)	39–59	1984–1987	18–21	8336/8336	150605	248	173	421
All MORGAM cohorts						88290/66493	1176296	1687	1241	2928

*MONICA centre refers to populations included in the original MONICA study. MONICA procedures refer to populations not included but using MONICA procedures.
†No. of subjects used in the analyses/no. of subjects used for model validation.
‡Three cohorts use the age range 25–64, while one cohort use the age range 25–74.

the mean of the two measurements has been used. Total serum cholesterol and high-desity lipoprotein (HDL) cholesterol were measured from blood samples.[11]

Each member of the different MORGAM cohorts was followed-up for fatal and non-fatal stroke and death from any cause. Fatal stroke cases were identified by national or regional health information systems. Non-fatal strokes were identified by a linkage to a specific population-based stroke register, the hospital discharge registers or by contacting the cohort members. Most centres validated the end point events using the original WHO MONICA diagnostic criteria based on clinical presentation rather than imaging technique.[16] There was an upper age limit of follow-up for non-fatal stroke in Poland (65 years), Lithuania (65 years), Russia (75 years) and Sweden (75 years). These age limits were applied for all follow-up in these cohorts in this analysis. Details of the baseline and follow-up procedures used in each cohort, and the quality of the data have been published elsewhere.[17]

Statistics

Subjects with documented or self-reported history of myocardial infarction or stroke at baseline or missing information on one or several of the included variables were excluded. All included subjects were used when developing the model, but only those cohorts with a minimum follow-up of 10 years were used in validating the model.

All analyses were conducted separately for men and women. Risk estimation models for 10 year risk of stroke were developed using a Cox regression model with age as underlying time scale and a similar Cox regression model for the competing risk of dying without preceding stroke events. The two developed models were then combined to give a model for the absolute risk.[18] In this way it is possible to estimate the risk of an event given that you do not die before the event. The Cox regression models were stratified by country—that is, the baseline hazard varies between countries but the effects of the covariates are the same. Possible interaction terms between country and the covariates were included one by one to test whether the effect of the covariate depended on country. Significant interactions were observed in women for smoking. Continuous variables were modelled using quadratic effects or restricted cubic splines with knots at 5, 35, 65 and 95% when deviations from linearity were observed.

Explanatory variables were added to the model in a stepwise approach simulating the clinical setting, starting with data obtainable through questions: diabetes (dichotomised (yes/no)), treatment for high blood pressure (dichotomised (yes/no)) and smoking (dichotomised (yes/no)); followed by data from

physical examinations: BMI (modelled as a restricted cubic spline for men, with quadratic effect for women) and systolic (SBP) (linear) and diastolic blood pressure (DBP) (linear); ending with data only obtainable from blood samples: total serum cholesterol (linear) and HDL cholesterol (modelled as a restricted cubic spline). Furthermore, the predictive and discriminative ability of a model consisting only of data from blood samples and a model consisting of data from blood samples and physical examinations were determined.

Evaluating the ability of the model

In the validation of the stroke risk model only the cohorts with a minimum of 10 years of follow-up were used, excluding 21 797 individuals (24.7%) from the validation (table 1). The validation of the model was determined by assessing both the predictive ability and the discrimination of the model.

The predictive ability of the model was determined comparing observed and predicted events using the Hosmer–Lemeshow test of goodness of fit and the Brier score. The Spiegelhalter test was used to test whether adding variables from another step to the model significantly improved the Brier score.

The discriminative ability of the model was assessed using the area under the receiver operating characteristic curve (AUC). The AUC was calculated for every model in each of the steps and tested for significant differences using the SAS macro ROC.[19] Furthermore, the integrated discrimination improvement (IDI) and net reclassification index (NRI) were calculated.[20]

In order to prevent the model from being too optimistic and sensitive to changes in data, the developed stratified stroke risk models including competing risk were validated using bootstrap sampling methods with 1000 repetitions, allowing us to estimate slope shrinkage (a measure of relative calibration) for the Cox regression models, and the mean of the 1000 Brier scores and AUC measures, which were compared with the original estimates.

All analyses were conducted using the statistical software program SAS version 9.2 (SAS Institute, Cary, North Carolina, USA) with a statistical significance level of 5%, except for the Hosmer–Lemeshow χ^2 test where a significance level of 1% is used.

RESULTS

During 1 176 296 person-years of observation 2928 fatal and non-fatal events of stroke were registered (table 1). The HRs of the included variables of the risk model are seen in table 2, with the most important risk factors being diabetes, treatment for hypertension, smoking and SBP. For women, a positive interaction was seen between country and smoking on the risk of stroke. The restricted cubic splines are difficult to interpret, but were used since deviations from linearity were observed. Graphical presentations showed the expected relationship between the risk factors and risk of stroke (j-shaped curve illustrating the relationship between BMI and risk of stroke and decreasing risk with decreasing HDL cholesterol—figures not shown).

Table 2 HRs for the risk of stroke for men and women

	HR	95% CI
Men		
Diabetes	1.971	1.636 to 2.373
Treatment for hypertension	1.285	1.121 to 1.473
Smoking	1.689	1.528 to 1.868
Systolic BP (mm Hg)	1.016	1.013 to 1.019
Diastolic BP (mm Hg)	1.004	0.999 to 1.010
BMI	0.892	0.843 to 0.945
BMI1*	1.002	1.001 to 1.004
BMI2*	0.994	0.989 to 0.998
Total cholesterol (mmol/l)	1.027	0.985 to 1.072
HDL cholesterol (mmol/l)	0.382	0.221 to 0.662
HDL1†	6.300	0.873 to 45.464
HDL2†	0.017	0.000 to 4.696
Women		
Diabetes	2.051	1.661 to 2.511
Treatment for hypertension	1.629	1.410 to 1.878
Smoking×Denmark‡	2.231	1.557 to 3.228
Smoking×Finland	1.615	1.294 to 1.997
Smoking×Sweden	1.171	0.554 to 2.299
Smoking×Poland	6.549	1.881 to 30.023
Smoking×Lithuania	4.841	1.419 to 12.572
Smoking×Russia§	–	–
Smoking×Italy	1.681	0.859 to 3.007
Smoking×Scotland	2.214	1.766 to 2.779
Systolic BP (mm Hg)	1.011	1.008 to 1.015
Diastolic BP (mm Hg)	1.007	1.001 to 1.014
BMI	0.910	0.853 to 0.978
BMI×BMI¶	1.001	1.000 to 1.003
Total cholesterol (mmol/l)	0.983	0.937 to 1.031
HDL cholesterol (mmol/l)	0.368	0.224 to 0.616
HDL1**	2.284	0.560 to 9.186
HDL2**	0.257	0.003 to 26.124

*BMI as a restricted cubic spline (knots at 5, 35, 65 and 95%).
†HDL cholesterol as a restricted cubic spline (knots at 5, 35, 65 and 95%).
‡Interaction between smoking and country.
§No estimate from Russia since there are no smokers among the stroke cases.
¶BMI squared.
**HDL cholesterol as a restricted cubic spline (knots at 5, 35, 65 and 95%).
BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein.

Predictive ability

The Hosmer–Lemeshow test of goodness of fit showed that the model was well calibrated in all steps and for all sex- and country-specific variations (two-sided $p>0.01$).

When comparing observed and predicted number of events for all countries combined we saw that for men the model predicted extremely well, with a slight tendency towards overestimating the risk of stroke (table 3). When looking at the countries individually, we saw a slight overestimation for Denmark, Sweden, Lithuania and Scotland, whereas for Finland there was a tendency towards an underestimation.

For women the model with all countries combined had a tendency to overestimate the risk of stroke (table 4). When looking at the countries individually, we observed a small overestimation in Denmark, a slight underestimation for Finland and a very large overestimation of stroke risk for Lithuania, explaining the overestimation of events in the model with countries combined. For the rest of the countries events were predicted with great accuracy.

When using the Brier score as a measure of predictive ability there were generally very low scores, indicating good predictive ability for all sex- and country-specific models (tables 3 and 4). No significant differences in Brier scores were observed between the different steps in the model, neither in total nor within each country.

Discriminative ability

Discriminative ability measured as the AUC varied between country- and sex-specific models.

For men, the model combining all countries showed an increasing AUC when adding another group of variables to the

Table 3 Predictive and discriminative ability of the model for men

Country	N	Model*	Observed†	Predicted‡	Brier§	p Value¶	AUC**	p Value††	IDI‡‡	p Value§§
Nordic countries										
Denmark	2466	Q	50	60.72	0.0196		0.690			
		Q+E	50	60.80	0.0195	0.99	0.724	0.01	0.0051	0.05
		Q+E+B	50	60.98	0.0195	0.99	0.729	0.16	0.0026	0.19
		B	50	60.97	0.0198		0.682			
		B+E	50	60.77	0.0196	0.98	0.718	0.20	0.0066	0.03
		B+E+Q	50	60.98	0.0195	0.98	0.729	0.27	0.0069	0.05
Finland	9217	Q	233	214.51	0.0237		0.812			
		Q+E	233	211.61	0.0236	0.82	0.824	0.02	0.0057	<0.01
		Q+E+B	233	212.50	0.0235	0.99	0.826	0.13	0.0011	0.05
		B	233	215.87	0.0239		0.803			
		B+E	233	212.42	0.0237	0.80	0.821	<0.01	0.0068	<0.01
		B+E+Q	233	212.50	0.0235	0.87	0.826	0.12	0.0048	<0.01
Sweden	763	Q	13	16.47	0.0161		0.833			
		Q+E	13	16.41	0.0162	0.99	0.851	0.41	<0.0001	0.96
		Q+E+B	13	16.38	0.0163	0.99	0.845	0.36	−0.0039	0.11
		B	13	16.31	0.0166		0.745			
		B+E	13	16.31	0.0166	0.99	0.787	0.28	0.0023	0.42
		B+E+Q	13	16.38	0.0163	0.99	0.845	0.03	0.0136	0.08
Eastern European countries										
Poland	1066	Q	15	14.22	0.0136		0.685			
		Q+E	15	14.25	0.0135	0.99	0.766	<0.01	0.0054	<0.01
		Q+E+B	15	14.25	0.0135	0.99	0.766	0.99	−0.0002	0.35
		B	15	14.24	0.0137		0.590			
		B+E	15	14.29	0.0136	0.99	0.743	<0.01	0.0054	<0.01
		B+E+Q	15	14.25	0.0135	0.99	0.766	0.21	0.0019	0.07
Lithuania	1390	Q	28	36.67	0.0198		0.593			
		Q+E	28	35.31	0.0196	0.99	0.707	0.01	0.0079	0.03
		Q+E+B	28	35.34	0.0195	0.99	0.726	0.17	0.0018	0.10
		B	28	37.28	0.0198		0.607			
		B+E	28	35.80	0.0195	0.99	0.718	0.02	0.0095	0.01
		B+E+Q	28	35.34	0.0195	0.99	0.726	0.72	<−0.0001	0.94
Russia	1483	Q	13	13.44	0.0085		0.817			
		Q+E	13	13.38	0.0084	0.99	0.859	0.14	0.0078	0.02
		Q+E+B	13	13.36	0.0084	0.99	0.856	0.45	0.0002	0.85
		B	13	13.50	0.0086		0.803			
		B+E	13	13.34	0.0085	0.99	0.853	0.01	0.0071	0.02
		B+E+Q	13	13.36	0.0084	0.99	0.856	0.82	0.0048	0.14
Middle and Southern European countries										
France	7094	Q	84	84.36	0.0116		0.651			
		Q+E	84	84.25	0.0115	0.99	0.689	0.04	0.0034	<0.01
		Q+E+B	84	84.36	0.0115	0.99	0.699	0.12	0.0003	0.18
		B	84	84.40	0.0116		0.625			
		B+E	84	84.39	0.0116	0.99	0.682	0.01	0.0034	<0.01
		B+E+Q	84	84.36	0.0115	0.99	0.699	0.22	0.0037	<0.01
Italy	5548	Q	85	84.34	0.0148		0.820			
		Q+E	85	84.48	0.0146	0.95	0.831	0.11	0.0072	<0.01
		Q+E+B	85	84.74	0.0146	0.99	0.831	0.91	<0.0001	0.94
		B	85	85.14	0.0148		0.818			
		B+E	85	85.66	0.0146	0.93	0.835	0.04	0.0091	<0.01
		B+E+Q	85	84.74	0.0146	0.98	0.831	0.39	−0.0006	0.66
UK										
Scotland	7080	Q	161	168.22	0.0218		0.719			
		Q+E	161	169.33	0.0217	0.91	0.730	0.24	0.0061	<0.01
		Q+E+B	161	167.70	0.0217	0.99	0.732	0.51	−0.0006	0.21
		B	161	166.84	0.0219		0.698			
		B+E	161	168.29	0.0218	0.94	0.715	0.13	0.0059	<0.01
		B+E+Q	161	167.70	0.0217	0.95	0.732	<0.01	0.0031	<0.01

Continued

Table 3 Continued

Country	N	Model*	Observed†	Predicted‡	Brier§	p Value¶	AUC**	p Value††	IDI‡‡	p Value§§
Total										
	36107	Q	682	692.93	0.0181		0.771			
		Q+E	682	689.82	0.0180	0.31	0.789	<0.01	0.0057	<0.01
		Q+E+B	682	689.62	0.0180	0.97	0.791	0.01	0.0005	0.09
		B	682	694.55	0.0182		0.759			
		B+E	682	691.28	0.0180	0.26	0.782	<0.01	0.0064	<0.01
		B+E+Q	682	689.62	0.0180	0.58	0.791	<0.01	0.0036	<0.01

*Q, data from questionnaires, E, data from physical examinations; B, data from blood samples.
†Observed number of events within 10 years.
‡Predicted number of events within 10 years.
§Brier score: average discrepancy between observed disease state after 10 years and the estimated risk.
¶Comparison of Brier scores between the current and the preceding model.
**Area under the curve.
††Test of difference between AUC from previous and actual model.
‡‡Integrated discrimination improvement. Gained discrimination from previous to present step.
§§Test whether IDI differs from 0.

model. Adding data from blood samples led to a significant yet minimal increase in discrimination (table 3). The lowest AUC was seen in the model containing only data from blood samples (AUC=0.759) and highest in the model containing all three steps (AUC=0.791). When looking at the country-specific models, a large AUC close to or above 80% was seen for Finland, Sweden, Russia and Italy, and all the country-specific models had acceptable discriminative ability, with France and Lithuania as the lowest with an AUC of ~70% (table 3). Using IDI, there was an increasing discrimination with an increasing number of steps. However, including a third step in a model already containing data from physical examinations did not result in significant increases in IDI for several countries (table 3), and for several countries very small increases or even a decrease in IDI was seen (Sweden, Poland, Lithuania, Russia, France, Italy and Scotland—table 3). Reclassification using NRI showed similar results (table 5A). Adding physical examinations to the model significantly increases classification by 8%; however, no improvements are seen when adding a third step.

For women, a similar picture was seen, although the lack of increasing discriminative ability when adding data from blood samples was even clearer using both the IDI and AUC. The model combining all countries showed an AUC between 0.753 for the model containing data from blood samples alone and 0.801 for the full model (table 4). The same AUC could be obtained using only data from questionnaires and physical examinations. When looking at the countries individually, we see that the models discriminate better for women than for men, except for Finland and Sweden. The countries where the models discriminated the best were Poland, Russia and Italy, with an AUC close to 90% (table 4). When NRI was calculated, only modest changes were seen in classification (table 5B).

The validation using bootstrap sampling methods showed slope shrinkage close to 1 for all sex- and country-specific models (highest 1.0078 and lowest 1.00034), strongly indicating that the original developed models were robust and not sensitive to change in data. In the same way, the mean AUC and mean Brier scores were almost identical to the scores from the original models.

DISCUSSION

A recent paper from the MORGAM project deals with RR of stroke in different populations.[21] In the present study the absolute risk of stroke is investigated. It is worth noting that even the simple model containing only information from either questions or blood samples had good predictive ability and that there were no significant increases in predictive ability with increasing steps. However, the discriminative ability of the model varied between countries and increased when adding further steps to the model. It is worth noting that the step including physical examinations seemed to have most influence on the discriminative ability, which is not surprising since it contains BMI and, more importantly, SBP and DBP. When using the AUC, the combined model for all countries had similar or even higher discriminative ability than previous models (0.79 for men and 0.80 for women).[4 5] These results show that it is possible to develop risk estimation models that can be tailored for different countries and different settings according to data and resources available. This is of real public health importance since it is possible to develop simple models with acceptable performance and use these in low resource healthcare settings.

The strengths of this study lie in the use of data from the MORGAM collaboration. The use of large cohort studies from nine countries with a uniform baseline data collection following the WHO MONICA protocol and the registration of both fatal and non-fatal stroke cases with strict diagnostic criteria ensures comparable data for stroke risk estimation. Still some limitations have to be noted. In this study we do not separate ischaemic and haemorrhagic strokes since stroke subtype definition was not possible in all cases or populations. In some populations, CT scanners were not available, especially in the first years of registration, or autopsy rates were low in patients dying outside hospital. Other limitations are the limited number of risk factors used in the model. Possible risk factors such as alcohol consumption, physical activity or triglycerides were not available from all cohorts. The use of diabetes at baseline in the model results in an exclusion of two Russian cohorts since they have no information on self-reported diabetes. For the included cohorts from Russia and Lithuania, 10% and 9%, respectively, are excluded due to missing data on HDL cholesterol. This may result in selection bias if the data are not missing at random.

Adding the measure of the competing risk to the developed model is an important strength of this study. Previous tools for risk prediction/estimation work under the assumption that during the period of prediction (eg, 10 years) there are only two possible disease states. Either you are disease free or you are an incident case. This is a false assumption since it is possible to die of a competing event in the same time period. By including the risk of a competing event, the predictive accuracy of the risk model will increase. In a recent publication, this approach has been suggested to be applied to cardiovascular risk estimation.[22]

The choice of variables included in the model was made a priori. The model includes diabetes as in several models of risk

Table 4 Predictive and discriminative ability of the model for women

Country	N	Model*	Observed†	Predicted‡	Brier§	p Value¶	AUC**	p Value††	IDI‡‡	p Value§§
Nordic countries										
Denmark	2512	Q	36	41.29	0.0140		0.779			
		Q+E	36	41.39	0.0139	0.99	0.801	0.04	0.0039	0.02
		Q+E+B	36	41.59	0.0138	0.99	0.804	0.47	0.0039	0.06
		B	36	42.91	0.0139		0.739			
		B+E	36	42.71	0.0138	0.99	0.772	0.01	0.0049	0.01
		B+E+Q	36	41.59	0.0138	0.99	0.804	0.02	0.0024	0.33
Finland	10041	Q	158	146.16	0.0152		0.748			
		Q+E	158	145.78	0.0152	0.99	0.759	0.05	0.0015	0.09
		Q+E+B	158	147.10	0.0151	0.99	0.763	0.13	0.0022	<0.01
		B	158	148.34	0.0153		0.730			
		B+E	158	147.58	0.0152	0.97	0.748	0.01	0.0034	<0.01
		B+E+Q	158	147.10	0.0151	0.92	0.763	<0.01	0.0057	<0.01
Sweden	762	Q	8	10.00	0.0104		0.704			
		Q+E	8	9.93	0.0103	0.99	0.778	0.17	0.0044	0.06
		Q+E+B	8	9.90	0.0103	0.99	0.779	0.97	0.0026	0.25
		B	8	9.91	0.0103		0.666			
		B+E	8	9.79	0.0102	0.99	0.780	0.19	0.0051	<0.01
		B+E+Q	8	9.90	0.0103	0.99	0.779	0.97	−0.0022	0.26
Eastern European countries										
Poland	1074	Q	7	7.45	0.0063		0.865			
		Q+E	7	7.39	0.0062	0.99	0.886	0.26	0.0059	0.16
		Q+E+B	7	7.38	0.0062	0.99	0.904	0.02	0.0010	0.35
		B	7	7.47	0.0063		0.722			
		B+E	7	7.42	0.0063	0.99	0.838	0.06	0.0048	<0.01
		B+E+Q	7	7.38	0.0062	0.99	0.904	0.25	0.0107	0.14
Lithuania	1391	Q	18	36.60	0.0132		0.736			
		Q+E	18	36.31	0.0131	0.99	0.754	0.35	0.0084	<0.01
		Q+E+B	18	36.02	0.0131	0.99	0.746	0.18	−0.0001	0.97
		B	18	38.84	0.0136		0.681			
		B+E	18	38.29	0.0134	0.97	0.722	0.05	0.0111	<0.01
		B+E+Q	18	36.02	0.0131	0.98	0.746	0.31	0.0117	0.31
Russia	1265	Q	13	13.64	0.0099		0.896			
		Q+E	13	13.54	0.0098	0.99	0.905	0.20	0.0068	0.12
		Q+E+B	13	13.50	0.0097	0.99	0.907	0.63	0.0045	0.32
		B	13	13.63	0.0098		0.897			
		B+E	13	13.54	0.0097	0.99	0.910	0.36	0.0071	0.16
		B+E+Q	13	13.50	0.0097	0.99	0.907	0.65	0.0052	0.42
Southern European country										
Italy	6038	Q	50	50.87	0.0080		0.856			
		Q+E	50	50.28	0.0080	0.99	0.878	0.01	0.0037	0.06
		Q+E+B	50	50.58	0.0080	0.99	0.882	0.18	0.0012	0.20
		B	50	50.56	0.0080		0.844			
		B+E	50	50.31	0.0080	0.99	0.878	0.02	0.0043	0.05
		B+E+Q	50	50.58	0.0080	0.99	0.882	0.57	0.0032	0.19
UK										
Scotland	7259	Q	116	115.07	0.0154		0.761			
		Q+E	116	115.57	0.0154	0.99	0.781	0.03	0.0015	0.46
		Q+E+B	116	113.64	0.0154	0.99	0.769	0.02	−0.0006	0.40
		B	116	113.58	0.0156		0.669			
		B+E	116	114.10	0.0155	0.98	0.713	<0.01	0.0026	0.14
		B+E+Q	116	113.64	0.0154	0.94	0.769	<0.01	0.0058	<0.01
Total										
	30342	Q	406	421.08	0.0130		0.785			
		Q+E	406	420.19	0.0129	0.96	0.801	<0.01	0.0026	<0.01
		Q+E+B	406	419.71	0.0129	0.94	0.801	0.79	0.0014	<0.01
		B	406	425.24	0.0130		0.753			
		B+E	406	423.73	0.0130	0.77	0.778	<0.01	0.0039	<0.01
		B+E+Q	406	419.71	0.0129	0.65	0.801	<0.01	0.0053	<0.01

*Q, data from questionnaires; E, data from physical examinations; B, data from blood samples.
†Observed number of events within 10 years.
‡Predicted number of events within 10 years.
§Brier score: average discrepancy between observed disease state after 10 years and the estimated risk.
¶Comparison of Brier scores between the current and the preceding model.
**Area under the curve.
††Test of difference between AUC from previous and actual model.
‡‡Integrated discrimination improvement. Gained discrimination from previous to present step.
§§Test whether IDI differs from 0.

Table 5 Risk reclassification

(A) Reclassification of risk in men						
Risk estimated using only questions	Risk estimated using questions and simple examinations					
Individuals developing stroke within 10 years of follow-up (n=682)	<5%	5–10%	10–20%	>20%	No. up*	No. down†
<5%	381	76	2	0		
5–10%	46	110	30	1	112	56
10–20%	0	10	22	3		
>20%	0	0	0	1		
Individuals not developing stroke within 10 years of follow-up (n=35451)						
<5%	31692	774	36	2		
5–10%	848	1610	246	6	1071	950
10–20%	1	100	128	7		
>20%	0	0	1	0		
Net reclassification 0.079; p<0.0001						
Risk estimated using questions and simple examinations	Risk estimated using questions, simple examinations and blood samples					
Individuals developing stroke within 10 years of follow-up (n=682)	<5%	5–10%	10–20%	>20%	No. up	No. down
<5%	411	16	0	0		
5–10%	12	174	10	0	26	19
10–20%	0	7	47	0		
>20%	0	0	0	5		
Individuals not developing stroke within 10 years of follow-up (n=35451)						
<5%	32343	198	0	0		
5–10%	203	2233	48	0	250	244
10–20%	0	38	369	4		
>20%	0	0	3	12		
Net reclassification 0.010; p=0.3057						
(B) Reclassification of risk in women						
Risk estimated using only questions	Risk estimated using questions and simple examinations					
Individuals developing stroke within 10 years of follow-up (n=406)	<5%	5–10%	10–20%	>20%	No. up*	No. down†
<5%	288	20	0	0		
5–10%	23	43	9	1	30	26
10–20%	0	1	19	0		
>20%	0	0	2	0		
Individuals not developing stroke within 10 years of follow-up (n=29954)						
<5%	28233	306	2	0		
5–10%	363	754	79	1	393	431
10–20%	0	61	135	5		
>20%	0	0	7	8		
Net reclassification 0.011; p=0.5468						
Risk estimated using questions and simple examinations	Risk estimated using questions, simple examinations and blood samples					
Individuals developing stroke within 10 years of follow-up (n=406)	<5%	5–10%	10–20%	>20%	No. up	No. down
<5%	304	7	0	0		
5–10%	6	47	11	0	20	9
10–20%	0	3	25	2		
>20%	0	0	0	1		
Individuals not developing stroke within 10 years of follow-up (n=29954)						
<5%	28406	190	0	0		
5–10%	192	872	57	0	253	242
10–20%	0	46	171	6		
>20%	0	0	4	10		
Net reclassification 0.027; p=0.0442						

*Individuals moving to higher risk category.
†Individuals moving to lower risk category.

assessment,[1 4 6 23] treatment of hypertension as in, for example, the Framingham Stroke model,[24] and the QRISK[25] and smoking as in all risk estimation models. From physical examinations, BMI, SBP and DBP are obtained. Few models include DBP, but recent studies from the Framingham Heart Study suggest that using both SBP and DBP results in models superior to its single components.[26] From blood samples, total and HDL cholesterol are obtained. The Framingham stroke model[1] did not include lipids, but several models for CVD risk estimation include total cholesterol[2 27] and some include HDL cholesterol.[23 27]

The purpose of the stepwise approach to risk estimation was to imitate the clinical setting and to be able to tailor risk estimation models to different settings and still obtain valid estimations of risk. Previously the EUROSTROKE study developed

a model in three steps—that is, patient history, blood pressure and fibrinogen—and concluded that stroke events could be predicted using only patient history and simple examinations,[28] a conclusion which is supported by the findings from the present study. Work from the Framingham Heart Study and the NHANES have assessed the usefulness of a non-laboratory model substituting serum cholesterol with BMI with good results,[29 30] although the models were developed for CVD and not for stroke in particular.

A possible limitation of this study is the lack of socioeconomic status (SES) as a factor in the risk model. Both the ASSIGN and the QRISK score models have included measures of SES.[25 27] Since there is a social gradient in CVD, neglecting SES might result in a situation where risk of stroke is overestimated in the higher social groups but underestimated in the lower social groups.

For the three French PRIME cohorts, the model predicted with great accuracy but the discrimination was the lowest among the countries, with an AUC between 0.625 and 0.699. These findings persisted when looking at the three French cohorts separately (data not presented). The most likely explanation is the narrow age range of the French cohorts at baseline (table 1). The strong effect of age range of the studied population on the AUC is a limitation if evaluation of a model is based solely on the AUC.

Diabetes is used self-reported, and the fact that the definition of diabetes has changed over time together with the knowledge that up to 50% of examinees are not aware of their diabetic status means that the effect of diabetes might be under-reported.

A general limitation of any risk estimation model is that exposures or risk factor status are only measured once and may change from baseline and during follow-up. Therefore, some countries might have experienced a fall in, for example, blood pressure or smoking, while others have experienced a rise. This might explain the significant interaction between country and smoking for women seen in table 2.

The present study shows that using a large multicountry cohort from nine European countries it is possible to develop a stepwise risk estimation model for 10 year risk of stroke tailored to different availability of risk factors and still obtain valid measures of calibration and discrimination even in the simplest form of the model, with increasing performance of the model following increasing complexity. The methods chosen which separate this model from previous models (competing risk and stepwise approach) should be considered for future risk estimation models.

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