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ORIGINAL ARTICLE

An international risk prediction algorithm for the onset of generalized anxiety and panic syndromes in general practice attendees: predictA

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Background. There are no risk models for the prediction of anxiety that may help in prevention. We aimed to develop a risk algorithm for the onset of generalized anxiety and panic syndromes.

Method. Family practice attendees were recruited between April 2003 and February 2005 and followed over 24 months in the UK, Spain, Portugal and Slovenia (Europe4 countries) and over 6 months in The Netherlands, Estonia and Chile. Our main outcome was generalized anxiety and panic syndromes as measured by the Patient Health Questionnaire. We entered 38 variables into a risk model using stepwise logistic regression in Europe4 data, corrected for over-fitting and tested it in The Netherlands, Estonia and Chile.

Results. There were 4905 attendees in Europe4, 1094 in Estonia, 1221 in The Netherlands and 2825 in Chile. In the algorithm four variables were fixed characteristics (sex, age, lifetime depression screen, family history of psychological difficulties); three current status (Short Form 12 physical health subscale and mental health subscale scores, and unsupported difficulties in paid and/or unpaid work); one concerned country; and one time of follow-up. The overall C-index in Europe4 was 0.752 [95% confidence interval (CI) 0.724–0.780]. The effect size for difference in predicted log odds between developing and not developing anxiety was 0.972 (95% CI 0.837–1.107). The validation of predictA resulted in C-indices of 0.731 (95% CI 0.654–0.809) in Estonia, 0.811 (95% CI 0.736–0.886) in The Netherlands and 0.707 (95% CI 0.671–0.742) in Chile.

Conclusions. PredictA accurately predicts the risk of anxiety syndromes. The algorithm is strikingly similar to the predictD algorithm for major depression, suggesting considerable overlap in the concepts of anxiety and depression.

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Key words: Anxiety, prevention, primary care, risk algorithm.

Introduction

Anxiety disorders occur in between 6% and 12% of the general population (Alonso *et al*. 2004*a*; Andlin-Sobocki & Wittchen, 2005). Help seeking may mean that prevalence is somewhat higher in general practice attendees than the general population (Ansseau *et al*. 2005); however only about one-quarter of sufferers will contact a health service professional over any one year (Alonso *et al*. 2004*b*). The high prevalence and relapsing nature of anxiety disorders means that they account for at least 35% of all disability and sick leave days due to mental disorders (Andlin-Sobocki & Wittchen, 2005). Even subclinical anxiety states may have major impacts on quality of life (Andlin-Sobocki & Wittchen, 2005; Das-Munshi *et al*. 2008). Although there appear to be high indirect costs from the

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substantial burden of illness, direct treatment costs tend to be relatively low due to low recognition and low rates of treatment (Andlin-Sobocki & Wittchen, 2005). There are established, effective treatments for anxiety disorders (Deacon & Abramowitz, 2004; van Boeijen *et al*. 2005) but even when the disorders are recognized, treatment is often not provided adequately (Fernández *et al*. 2007). Research into prevention is much more limited (Schmidt & Zvolensky, 2007). The key challenge in prevention is to develop a clear understanding of the nature of risk factors and vulnerability processes underlying the development of anxiety disorders (Schmidt & Zvolensky, 2007). We aimed to develop a risk algorithm (predictA) for first onset or recurrence of generalized anxiety and panic syndromes in European general practice attendees and test its predictive power in external populations in Europe and in Chile. We modelled our approach on our earlier work to develop a predictD algorithm for onset of Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) major depression (King *et al*. 2006, 2008).

Method

Study setting and design

The cohort to be described in this paper was originally recruited with the aim of developing a risk model (predictD) for the onset of major depression (King *et al*. 2006). However, we also aimed to predict the onset of anxiety syndromes and how predictors of risk for anxiety might relate to those for the development of major depression. The study was approved by ethical committees and conducted in seven countries: (1) 25 general practices in the Medical Research Council's General Practice Research Framework (MRC GPRF), in the UK; (2) nine large primary care centres in Andalucía, Spain; (3) 74 general practices nationwide in Slovenia; (4) 23 general practices nationwide in Estonia; (5) seven large general practice centres near Utrecht, The Netherlands; (6) two large primary care centres in the Lisbon area of Portugal; and (7) 78 general practitioners in 10 health centres in Concepción and Talcahuano in the Eighth region of Chile. The practices covered urban and rural populations with substantial socio-economic variation.

In our original 12-month cohort for the predictD study, data on anxiety syndromes as possible risk factors for major depression were only collected at recruitment and the 6-month follow-up. However, when further funding became available for a 24-month follow-up of all participants in the UK, Spain, Portugal and Slovenia (hereafter referred to as Europe4 countries), we included a further evaluation of anxiety symptoms at this point in order to develop a predictA risk model for anxiety. To best use these data, we decided to construct the predictA risk model for anxiety over 6 and 24 months in the Europe4 countries and validate it over 6 months in three external populations, namely The Netherlands, Estonia and Chile.

Study participants

Consecutive attendees aged between 18 and 75 years in all seven countries were recruited, consented and interviewed between April 2003 and September 2004 and re-interviewed after 6 months. In the Europe4 countries all participants were once again re-interviewed at 24 months from April 2005 to November 2005. Exclusion criteria were an inability to understand one of the main languages involved, psychosis, dementia and incapacitating physical illness. Participants gave informed consent and undertook a research evaluation within 2 weeks.

Anxiety syndromes and measured risk factors

Our main outcome of interest was anxiety and/or panic syndrome over the preceding 6 months as defined by the Patient Health Questionnaire (PHQ; Spitzer *et al*. 1999). These symptoms match exactly onto the DSM-IV criteria for generalized anxiety disorder and panic disorder but do not include other anxiety syndromes such as phobias and post-traumatic stress disorder. Where possible we used standardized measures of our chosen risk factors. Questions adapted from standardized questionnaires or developed for the study were evaluated for test–retest reliability in 285 general practice attendees recruited in all the European countries before the main study began (King *et al*. 2006). Each instrument or question not available in the relevant languages was translated from English and back-translated by professional translators (King *et al*. 2006). A total of 38 risk factors were assessed; each is numbered in square brackets and those assessed for test–retest reliability are in italics:

(*a*) Age[1], sex[2], occupation[3], educational level[4], marital status[5], employment status[6], ethnicity[7], owner occupier accommodation[8], living alone or with others[9], born in country of residence or abroad[10], satisfaction with living conditions[11] and long-standing physical illness[12].

(*b*) A DSM-IV diagnosis of major depression in the preceding 6 months was made using the Depression Section of the Composite International Diagnostic Interview (CIDI; Robins *et al*. 1988; World Health Organization, 1997)[13].

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(*c*) Lifetime depression was based on affirmative answers to both of the first two questions of the CIDI depression section[14] (Arroll *et al*. 2003).

(*d*) *Stress in paid and unpaid work in the preceding 6 months using questions from the job content instrument* (Karasek & Theorell, 1990). *Participants were categorized as feeling in control in paid*[*15*] *or unpaid work*[*16*]*; as experiencing difficulties without support in paid or unpaid work*[*17*]*; and experiencing distress without feeling respect for their paid or unpaid work*[*18*].

(*e*) Financial strain using a question used in UK government social surveys[19] (Weich & Lewis, 1998).

(*f*) Self-rated physical[20] and mental health[21] was assessed by the Short Form 12 (Jenkinson *et al*. 1997). The weights used to calculate scores are from version 1.

(*g*) Alcohol use in the preceding 6 months using the Alcohol Use Disorder Test (AUDIT)[22] (Barbor *et al*. 1989). We asked whether participants had ever had an alcohol problem or treatment for the same[23].

(*h*) *Whether participants had ever used recreational drugs using adapted sections of the CIDI*[24].

(*i*) *Questions on the quality of sexual*[*25*] *and emotional relationships*[*26*] *with partners or spouses* (Taylor *et al*. 1994).

(*j*) Presence of serious physical, psychological or substance-misuse problems, or any serious disability, in people who were in close relationship to participants[27].

(*k*) *Difficulties in getting on with people and maintaining close relationships*[*28*] (Tyrer, 1990).

(*l*) Childhood experiences of physical and/or emotional[29] and sexual abuse[30] (Fink *et al*. 1995).

(*m*) Holding religious and/or spiritual beliefs[31] (King *et al*. 1995).

(*n*) *History of serious psychological problems*[*32*] *or suicide in first-degree relatives*[*33*] (Qureshi *et al*. 2005).

(*o*) *Satisfaction with the neighbourhood*[*34*] *and perceived safety inside/outside of the home*[*35*] *using questions from the Health Surveys for England* (Sproston & Primatesta, 2003).

(*p*) Major life events in the preceding 6 months[36], using the List of Threatening Life Experiences Questionnaire (Brugha *et al*. 1985).

(*q*) *Experiences of discrimination*[*37*] *in the preceding 6 months on grounds of sex, age, ethnicity, appearance, disability or sexual orientation using questions from a European study* (Janssen *et al*. 2003).

(*r*) Adequacy of social support[38] from family and friends (Blaxter, 1990).

We emphasize that all participants were re-evaluated for anxiety and panic symptoms using the PHQ after 6 and 24 months in the Europe4 countries, whereas in The Netherlands, Estonia and Chile they were assessed again only after the 6-month follow-up.

Statistical analysis

All analyses and data imputation were performed using Stata release 10 (StataCorp. LP, USA).

Imputation

Multiple imputation was carried out for the dataset on which the model was built (Europe4) and for each of the external datasets (The Netherlands, Estonia and Chile). For each variable with missing data, imputation was conducted using other risk factors and outcome variables. In all four imputed datasets, the imputation model included 38 risk factors and the outcome measure at baseline, 6 and 24 months. In Europe4, the imputation model also included country. The imputation process was conducted 10 times to produce 10 imputed datasets. Parameter estimates were obtained by fitting models to each of the imputed datasets and then combining these estimates using Rubin's rules (Rubin, 1987).

Model selection

We employed standard methods for model building (Royston *et al*. 2009). Logistic models were fitted to each of the 10 imputed datasets only using participants without anxiety or panic syndromes at baseline. Robust standard errors were used to account for dependence between observations on the same individual at 6 and 24 months. There was negligible clustering within practices (intra-cluster correlation = 0.003) and thus standard errors were not adjusted for practice-level clustering. The initial model consisted of country, time, 38 risk factors, and interactions between each of the risk factors and time. Stepwise regression (backwards elimination) at a significance level of $p = 0.01$ was used to identify a parsimonious model with age, sex, country and time forced into the model. The backwards elimination consisted of two steps: (1) selection of interaction terms and (2) selection of main effects. In the first step, all main effects were forced into the model and backwards elimination was conducted on the interaction terms; this was done to avoid models in which interaction terms were present without their constituent main effects. In step (2) backward elimination was carried out on the main effects and interaction terms identified in (1). For the interaction terms identified as significant in (1), the risk factor was jointly tested with the interaction term.

Continuous variables were modelled using fractional polynomials of order 1.

Shrinkage

Parameter estimates were 'shrunk' using a method proposed by Copas (1983). According to this method, model coefficients are multiplied by a shrinkage factor to provide more accurate predictions when the risk algorithm is applied in new settings. The degree of shrinkage is related to the number of model parameters. We used the number of parameters in the original model (country, time, 38 risk factors, and interactions between time and risk factors), to compensate for over-fitting as a result of the model selection procedure.

Validation

C-indices and Hedges' g were computed for Europe4 and the three external countries; both are measures of the ability of the model to predict anxiety. For a discordant pair of individuals one anxious, the other not, the C-index is the probability that the anxious individual has the higher risk score. Hedges' g measures effect size: the difference between average logit transformed risk among individuals who became anxious compared with those who did not, standardized by an estimate of the pooled standard deviation. Both measures were computed separately for 6- and 24-month outcome data and using combined outcome data. For the combined 6- and 24-month data confidence intervals (CIs) for Hedges' g were obtained using robust standard errors for the estimate of the average difference in logit transformed risk; we did this to account for dependence between the repeat measures at 6 and 24 months on the same individual.

Model stability

The model selection procedure was conducted on each imputed dataset separately rather than on the combined estimates, obtained using Rubin's rules, described above. The variables selected in each imputed dataset were compared to assess the stability of the model. The fraction of missing information was used to quantify the uncertainty in each parameter estimate attributable to missing data; it is computed by estimating the proportion of the total variability of an estimate that is due to variability between imputations (Rubin, 1987; Schafer, 1999).

Sensitivity/specificity

In practice, the risk of panic/anxiety can only be assessed for individuals with complete covariate data. Sensitivity and specificity were estimated for a range of predictA cut-offs for individuals with complete covariate data using the imputed outcome data.

Results

A total of 10 045 people took part in the seven countries. Response to recruitment was high in Portugal (76%), Estonia (80%), Slovenia (80%) and Chile (97%) but lower in the UK (44%) and The Netherlands (45%). Ethical considerations prevented the collection of data on non-responders at baseline. The response to follow-up was 86.4% at 6 months and 66.9% at 24 months in the Europe4 countries and 92.6% at 6 months in Estonia, The Netherlands and Chile.

Numbers in the analysis

The model was built using 4905 individuals in Europe4 (UK, Spain, Slovenia and Portugal). They provide data on outcome (PHQ-defined anxiety and/or panic syndrome) at baseline, 6 and 24 months. Validation was carried out using 6-month outcome data from Estonia ($n=1094$), The Netherlands ($n=1221$) and Chile ($n=2825$). Demographic information on key variables for the whole sample is provided in Table 1. The amount of missing data in outcome and covariates is summarized in Table 2. For all countries there are few outcome data missing at baseline, but this increases significantly at 6 and 24 months. In Europe4 countries 14.7% are missing outcome at 6 months and this rises to 34.4% at 24 months. Taking the set of covariates as a whole, a large proportion of individuals were missing data in at least one covariate. In Europe4, 57.2% of individuals are missing data in at least one covariate. However, restricting the set of covariates to only those used in the final model, this proportion decreases to 5.2%.

Onset of anxiety and panic syndromes

We estimated that the incidence of either anxiety or panic syndrome or both at 6 months in Europe4 was 5.5% (95% CI 4.6–6.6). For the other countries, the incidence at 6 months was 3.1% (95% CI 2.2–4.3) in The Netherlands, 5.2% (95% CI 3.6–7.3) in Estonia and 8.6% (95% CI 7.2–10.2) in Chile. Occurrence of anxiety or panic syndrome at either 6 and/or 24 months in Europe4 was 10.7% (95% CI 9.0–12.6). We use the word occurrence here as the PHQ covered only the preceding 6 months, so strictly we cannot express the onset as an incidence rate at 24 months. It is also important to note that the figures given here vary very slightly from Table 1, as they are based on imputed data.

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Development of the predictA algorithm in the Europe4 countries

Non-linear transformations of continuous variables did not significantly improve the model fit. In addition to time, age, sex and country, five variables were retained after the backwards elimination procedure (Table 3). In the final model, four variables concerned past events or patient characteristics (sex, age, lifetime depression screen, family history of psychological difficulties); three current status (Short Form 12 physical health subscale score, Short Form 12 mental health subscale score, and unsupported difficulties in paid and/or unpaid work); one concerned country, and one concerned time of follow-up. None of the interactions with time was included in the final model. Examination of the predictA model developed in each of the 10 imputed datasets revealed that it was relatively stable in terms of the variables selected. Besides country, age and sex, four variables (family history of psychological difficulties, Short Form 12 physical health subscale score, Short Form 12 mental health subscale score and lifetime depression screen) were selected in all 10, while unsupported difficulties in paid and/or unpaid work were selected in eight imputed datasets. A number of variables not contained in the final predictA model nevertheless appeared in some imputed datasets as follows: discrimination appeared in seven, religious belief in seven, major depression in five and lack of control in paid or unpaid work in five datasets. Other variables not in the final model appeared in only one imputed dataset. A moderate amount of uncertainty in parameter estimates could be attributed to missing data. The fraction of missing (Table 3) information for the parameter estimates ranged from 0.126 (first-degree relative with an emotional problem) to 0.412 (unsupported difficulties in paid and unpaid work).

The ability of the predictA model to discriminate between those who became anxious, and those who did not was assessed through the C-index (Table 4) and the Hedges' *g* estimate of effect size (Table 5). In Europe4 the overall C-index was 0.752 (95% CI 0.724–0.780). The model was better able to discriminate anxiety status at 6 than 24 months. When fitted to 6-month data alone, the C-index was 0.775 (95% CI 0.743–0.807) compared with 0.729 (95% CI 0.685–0.774) when fitted to 24-month data alone. The model was most predictive in Slovenia and least predictive in the UK (Table 4).

The effect size (Hedges' *g*) for the difference in log odds of predicted probability between attendees in Europe4 who subsequently developed anxiety and/or panic syndromes at 6 or 24 months and those who did not was 0.972 (95% CI 0.837–1.107) (Table 5). Again, the model discriminated best in Slovenia (1.282) and least well in the UK (0.841).

In order to examine the fit of the model at 6 and 24 months, we divided the predictA risk score into deciles. Within each decile we plotted mean risk score, obtained using the model coefficients shown in Table 3, *versus* observed probability of anxiety (Fig. 1). Similar plots were also produced using 6- and 12-month data alone (Fig. 1). The average predicted risks within deciles of risk score are close to the observed risks for Europe4 countries (Fig. 1). The occurrence of anxiety or panic syndrome at 6 months in the highest decile of risk score in the Europe4 countries was almost 20% (Fig. 1) compared with the overall incidence of 5.5% in the imputed data.

External validation of the predictA algorithm in The Netherlands, Estonia and Chile

Table 1 shows the 6-month incidence rates for anxiety and panic syndromes in The Netherlands, Estonia and Chile. Predicted risks at 6 months for the external countries were obtained using shrunk coefficients. Since the risk model includes coefficients for the Europe4 countries in which it was built, the model for the external countries was modified by adding the average of the four shrunk coefficients arising from Europe4 (including the coefficient for the UK which is zero) to the shrunk intercept (see Tables 4 and 5 and Fig. 1). The predictA algorithm performed best in The Netherlands (C-index 0.811) and least well in Chile (C-index 0.707). This is demonstrated graphically in Fig. 1 where it can be seen that in The Netherlands and Estonia observed risks were in relatively good agreement with predicted risks, while in Chile agreement was less good. The weaker performance of predictA in Chile was possibly due to a higher incidence of panic and anxiety than in the European countries (Table 1), which means that risk is generally underestimated in Chile.

We give examples (Table 6) to illustrate the profiles of attendees at varying levels of risk (predicted probability of anxiety and panic syndromes on the predictA score algorithm). In order to demonstrate the potential impact of mutable factors (Short Form 12 physical health and mental health subscale scores, and unsupported difficulties in paid and/or unpaid work) on risk, we have recalculated scores in the last three examples after reducing or eliminating such factors.

Sensitivity and specificity

Estimates of sensitivity and specificity at 6 and 24 months for varying risk score cut-offs are shown in Table 7.

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Table 1. *Demographic characteristics of primary care attendees without anxiety or panic syndrome at baseline*

	UK (*n* = 1076)		Spain (*n* = 985)		Slovenia (*n* = 1014)		Estonia (*n* = 1073)		The Netherlands (*n* = 1007)		Portugal (*n* = 946)		Chile (*n* = 2533)		Total (*n* = 8634)	
Age, years																
18–29	93	(8.6)	134	(13.7)	134	(13.2)	275	(29.1)	154	(14.4)	126	(12.5)	401	(17.1)	1317	(15.6)
30–39	155	(14.4)	132	(13.5)	153	(15.1)	235	(24.8)	176	(16.4)	165	(16.4)	409	(17.5)	1425	(16.9)
40–49	195	(18.1)	173	(17.7)	222	(21.9)	136	(14.4)	191	(17.8)	169	(16.8)	452	(19.3)	1538	(18.2)
50–59	232	(21.6)	198	(20.2)	228	(22.5)	134	(14.2)	285	(26.6)	191	(19.0)	485	(20.7)	1753	(20.8)
60–69	270	(25.1)	228	(23.3)	198	(19.6)	106	(11.2)	188	(17.5)	228	(22.7)	410	(17.5)	1628	(19.3)
70–76	131	(12.2)	114	(11.6)	77	(7.6)	60	(6.3)	79	(7.4)	125	(12.5)	185	(7.9)	771	(9.1)
Total	1076	(100)	979	(100)	1012	(100)	946	(100)	1073	(100)	1004	(100)	2342	(100)	8432	(100)
Sex																
Female	707	(65.7)	661	(67.1)	633	(62.4)	683	(72.2)	672	(62.6)	652	(64.7)	1797	(70.9)	5805	(67.2)
Male	369	(34.3)	324	(32.9)	381	(37.6)	263	(27.8)	401	(37.4)	355	(35.3)	736	(29.1)	2829	(32.8)
Total	1076	(100)	985	(100)	1014	(100)	946	(100)	1073	(100)	1007	(100)	2533	(100)	8634	(100)
Married or living with partner																
No	267	(24.8)	296	(30.1)	303	(30.0)	318	(33.6)	279	(26.3)	271	(26.9)	1156	(45.6)	2890	(33.5)
Yes	808	(75.2)	688	(69.9)	708	(70.0)	628	(66.4)	781	(73.7)	735	(73.1)	1377	(54.4)	5725	(66.5)
Total	1075	(100)	984	(100)	1011	(100)	946	(100)	1060	(100)	1006	(100)	2533	(100)	8615	(100)
Education																
Above school	437	(41.3)	136	(13.8)	176	(17.4)	547	(57.8)	470	(45.0)	135	(13.4)	79	(3.1)	1980	(23.1)
Secondary	433	(40.9)	209	(21.2)	382	(37.7)	286	(30.2)	497	(47.6)	183	(18.2)	966	(38.2)	2956	(34.4)
Primary	23	(2.2)	639	(64.9)	223	(22.0)	112	(11.8)	78	(7.5)	659	(65.4)	1173	(46.3)	2907	(33.9)
Trade, other	165	(15.6)	1	(0.1)	232	(22.9)	1	(0.1)	0	(0)	30	(3.0)	314	(12.4)	743	(8.7)
Total	1058	(100)	985	(100)	1013	(100)	946	(100)	1045	(100)	1007	(100)	2532	(100)	8586	(100)
Employed/retired/other																
Employed	572	(53.2)	343	(34.9)	549	(54.5)	707	(74.7)	617	(59.2)	480	(47.7)	917	(36.2)	4185	(48.7)
Retired	299	(27.8)	179	(18.2)	367	(36.4)	136	(14.4)	142	(13.6)	297	(29.5)	270	(10.7)	1690	(19.7)
Other	205	(19.1)	462	(47.0)	91	(9.0)	103	(10.9)	284	(27.2)	229	(22.8)	1346	(53.1)	2720	(31.6)
Total	1076	(100)	984	(100)	1007	(100)	946	(100)	1043	(100)	1006	(100)	2533	(100)	8595	(100)
Professional																
No	303	(28.9)	100	(10.2)	160	(15.8)	278	(31.2)	379	(37.2)	99	(9.8)	30	(1.2)	1349	(15.9)
Yes	746	(71.1)	882	(89.8)	851	(84.2)	614	(68.8)	640	(62.8)	908	(90.2)	2501	(98.8)	7142	(84.1)
Total	1049	(100)	982	(100)	1011	(100)	892	(100)	1019	(100)	1007	(100)	2531	(100)	8491	(100)

Born in country of residence																
No	72	(6.7)	47	(4.8)	203	(20.1)	29	(3.3)	60	(5.6)	34	(3.4)	6	(0.2)	451	(5.3)
Yes	1001	(93.3)	936	(95.2)	807	(79.9)	863	(96.7)	1005	(94.4)	973	(96.6)	2524	(99.8)	8109	(94.7)
Total	1073	(100)	983	(100)	1010	(100)	892	(100)	1065	(100)	1007	(100)	2530	(100)	8560	(100)
European ethnicity																
Not European	34	(3.3)	11	(1.1)	2	(0.2)	1	(0.1)	67	(6.4)	15	(1.5)	2533	(100)	2663	(31.1)
European	1007	(96.7)	973	(98.9)	1011	(99.8)	945	(99.9)	981	(93.6)	992	(98.5)	0	(0)	5909	(68.9)
Total	1041	(100)	984	(100)	1013	(100)	946	(100)	1048	(100)	1007	(100)	2533	(100)	8572	(100)
Anxiety and/or panic syndrome at 6 months																
No	866	(94.9)	729	(93.0)	888	(96.1)	851	(95.4)	942	(97.2)	846	(95.1)	2113	(92.2)	7235	(94.4)
Yes	47	(5.1)	55	(7.0)	36	(3.9)	41	(4.6)	27	(2.8)	44	(4.9)	179	(7.8)	429	(5.6)
Total	913	(100)	784	(100)	924	(100)	892	(100)	969	(100)	890	(100)	2292	(100)	7664	(100)
Anxiety and/or panic syndrome at 24 months																
No	706	(94.0)	478	(92.3)	674	(96.7)	686	(94.6)	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	2544	(94.5)
Yes	45	(6.0)	40	(7.7)	23	(3.3)	39	(5.4)	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	147	(5.5)
Total	751	(100)	518	(100)	697	(100)	725	(100)	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	2691	(100)

Data are given as number (percentage). N.A., Not applicable.

Discussion

To our knowledge this is the first risk algorithm for anxiety and panic to be developed in a general medical setting and validated in external populations. The C-index is a standard method for comparing the discriminative power of risk models (Pepe *et al*. 2004). In terms of C-indices the predictA risk score compares favourably with our predictD score for onset of major depression (King *et al*. 2008) as well as for risk indices for cardiovascular events (Conroy *et al*. 2003). The risk model developed included a variable for time, which allows us to use it to predict risk at 6 and 24 months (risk at intermediate times can also be calculated by interpolation). However, time had only a weak non-significant effect on risk; thus, in practice, an individual's estimated risk is effectively the same at 6 and 24 months. Our shrinkage factor estimates degree of over-fitting in the Europe4 data and allows for its adjustment in estimating risk of anxiety in new settings. In risk-model development, external validation and shrinkage for over-fitting are often not undertaken (Moons *et al*. 2004). When the algorithm is applied in a country outside of the Europe4 countries we recommend that either the average Europe4 country coefficient (-0.073) be used or the coefficient for the European country that most closely matches the incidence of anxiety (if known) in the new setting (Table 3). If the algorithm is applied in one of the three external countries we suggest using the coefficient obtained by recalibration of the algorithm in this country (Table 3).

One strength of using data from a cohort that was established originally to develop a risk model for major depression (King *et al*. 2008) is that participants were unaware of the aim behind this risk modelling. When follow-up of the predictD cohort became possible beyond the 12 months envisaged originally in the Europe4 countries, we took the opportunity of measuring anxiety and panic syndromes as an outcome once again and this allowed us to develop a predictA model over 6 and 24 months in these four countries. One limitation was that anxiety disorders were only measured for the 6 months before each interview. Thus, although participants were followed up at 24 months in the Europe4 countries, the PHQ only enquired about anxiety symptoms in the 6 months preceding that follow-up point. Hence, we will not have captured any anxiety or panic syndromes that developed and resolved in the period 6 to 18 months after recruitment. Another limitation is the lower recruitment rates in the UK and The Netherlands, which possibly occurred because in these two countries researchers approached patients waiting for consultations, while in the other European countries doctors

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Table 2. *Missing data in outcome and covariates in Europe4[a] countries, Estonia, The Netherlands and Chile*

	Europe4[a] ($n=4905$)	Estonia ($n=1094$)	The Netherlands ($n=1221$)	Chile ($n=2825$)
Missing panic/anxiety at baseline				
No	4849 (98.9)	1093 (99.9)	1149 (94.1)	2822 (99.9)
Yes	56 (1.1)	1 (0.1)	72 (5.9)	3 (0.1)
Missing panic/anxiety 6 months				
No	4185 (85.3)	1025 (93.7)	1094 (89.6)	2559 (90.6)
Yes	720 (14.7)	69 (6.3)	127 (10.4)	266 (9.4)
Missing panic/anxiety 24 months				
No	3216 (65.6)	0 (0)	0 (0)	0 (0)
Yes	1689 (34.4)	1094 (100)	1221 (100)	2825 (100)
Missing data from any covariate				
No	2097 (42.8)	659 (60.2)	426 (34.9)	870 (30.8)
Yes	2808 (57.2)	435 (39.8)	795 (65.1)	1955 (69.2)
Missing data from covariates in the final model				
No	4738 (96.6)	1087 (99.4)	1142 (93.5)	2824 (100)
Yes	167 (3.4)	7 (0.6)	79 (6.5)	1 (0)

Data are given as number (percentage).
[a] Europe4 is the UK, Spain, Slovenia and Portugal combined.

Table 3. *Regression coefficients before and after shrinkage in Europe4[a] countries*

Prognostic factors	Levels in factor	Coefficient	(S.E.)	p	Missing information	Coefficient after Copas shrinkage
Constant		0.116	(0.517)	0.822	0.295	−0.560
Time	Months	0.007	(0.006)	0.201	0.208	0.005
Age	Years	0.001	(0.004)	0.810	0.156	0.001
Sex	Male					
	Female	0.219	(0.144)	0.130	0.272	0.163
Difficulties in paid and unpaid work	No difficulties or often supported					
	Difficulties without support	0.509	(0.165)	0.002	0.412	0.380
Mental health	SF12 subscale score	−0.044	(0.005)	0.000	0.187	−0.033
Physical health	SF12 subscale score	−0.039	(0.006)	0.000	0.295	−0.029
First-degree relative with emotional problem	No					
	Yes	0.407	(0.119)	0.001	0.126	0.304
Lifetime depression	No					
	Yes	0.511	(0.128)	0.000	0.173	0.382
Country	UK					
	Spain	0.134	(0.162)	0.407	0.251	0.100
	Slovenia	−0.381	(0.180)	0.034	0.155	−0.285
	Portugal	−0.144	(0.175)	0.410	0.221	−0.108
	Four country average					−0.073[b]
	The Netherlands					−0.636[c]
	Estonia					−0.388[c]
	Chile					0.397[c]

S.E., Standard error; SF12, Short Form 12.
[a] Europe4 is the UK, Spain, Slovenia and Portugal combined.
[b] The Europe4 country average is (0 + 0.1–0.285–0.108)/4.
[c] The coefficients for external countries were obtained by recalibrating in these countries.

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Table 4. *C-indices for all participating countries*[a]

	6 months		24 months		6 and 24 months	
Country	C-index[b]	(95% CI)	C-index	(95% CI)	C-index	(95% CI[c])
Europe4[d]	0.78	(0.74–0.81)	0.73	(0.68–0.77)	0.75	(0.72–0.78)
UK	0.69	(0.62–0.76)	0.74	(0.67–0.81)	0.72	(0.67–0.77)
Spain	0.77	(0.71–0.83)	0.72	(0.63–0.80)	0.74	(0.69–0.79)
Slovenia	0.83	(0.76–0.90)	0.79	(0.70–0.87)	0.81	(0.76–0.86)
Portugal	0.80	(0.74–0.86)	0.64	(0.55–0.73)	0.72	(0.66–0.78)
Estonia	0.73	(0.65–0.81)				
The Netherlands	0.81	(0.74–0.89)				
Chile	0.71	(0.67–0.74)				

CI, Confidence interval.

[a] The C-index is similar to the area under the relative operating characteristic curve of sensitivity against 1 – specificity. A perfect test has a C-index of 1.00 while a test that performs no better than chance has a C-index of 0.5 (Cooper & Hedges, 1994).

[b] Average C-index over 10 imputed datasets.

[c] This CI is calculated assuming that observations collected at 6 and 24 months are independent.

[d] Europe4 is the UK, Spain, Slovenia and Portugal combined.

Table 5. *Hedges' g effect size estimates*[a]

	6 months		24 months		6 and 24 months	
Country	*g*	(95% CI)	*g*	(95% CI)	*g*	(95% CI)
Europe4[b]	1.08	(0.93–1.24)	0.87	(0.68–1.06)	0.97	(0.84–1.11)
UK	0.71	(0.42–1.00)	0.94	(0.64–1.24)	0.84	(0.62–1.06)
Spain	1.05	(0.78–1.31)	0.77	(0.44–1.10)	0.90	(0.68–1.12)
Slovenia	1.44	(1.07–1.81)	1.14	(0.75–1.52)	1.28	(0.98–1.58)
Portugal	1.22	(0.91–1.53)	0.54	(0.18–0.90)	0.86	(0.58–1.13)
Estonia	0.89	(0.56–1.22)				
The Netherlands	1.27	(0.88–1.65)				
Chile	0.76	(0.60–0.91)				

CI, Confidence interval.

[a] Predicted probabilities were logarithmically transformed and compared between depressed and non-depressed individuals over the subsequent 6 and 24 months and both time periods. Hedges ' g is preferred to Cohen's *d* where the sizes of each group (depressed/non-depressed) are markedly unequal. The risk score was computed using unshrunk estimates in Europe and shrunk estimates in Chile.

[b] Europe4 is the UK, Spain, Slovenia and Portugal combined.

first introduced the study before contact with the research team. However, most importantly, response to follow-up in all countries was high, ensuring high internal validity of these findings. Although our risk factors are based on self-report, we used standardized instruments where possible and unstandardized questions were tested for reliability (King *et al*. 2006). There is a moderate uncertainty in the parameter estimates due to missing data as measured by the fraction of missing information. This is principally due to missing outcome data at 24 months. However, in all cases the fraction of missing information is below 50%, the value at which Ruben (2003) questions the usefulness of multiple imputation. Finally, we stress that we have only considered generalized anxiety and panic disorders as defined by the PHQ. Our data do not concern other anxiety disorders such as post-traumatic stress disorder or phobic anxiety disorders.

One notable finding is the overlap in the nature of the risk factors between the predictD model for major depression (King *et al*. 2008) and predictA for anxiety

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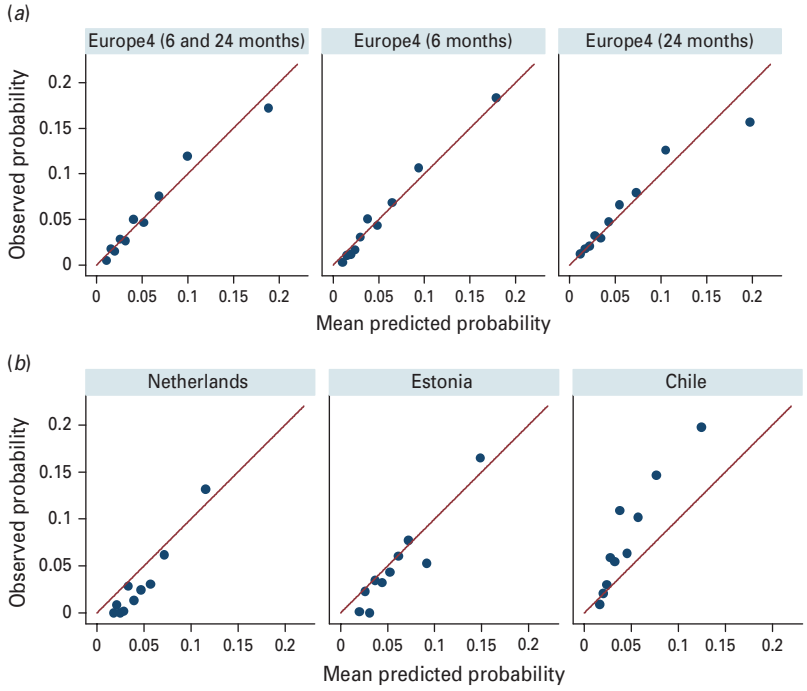

Fig. 1. Mean risk score plotted against observed probability within deciles of the risk score. (*a*) Estimates of risk for individuals in Europe4 (UK, Spain, Portugal and Slovenia) were produced using the unshrunk coefficients found in Table 3. (*b*) Risk scores at 6 months for the external datasets (The Netherlands, Estonia and Chile) were obtained using the average intercept of the four countries in Europe4 and the shrunk coefficients in Table 3.

disorders. Although their contribution to risk was different (in terms of regression coefficients), risk factors common to both disorders were lifetime depression screen, family history of psychological difficulties, Short Form 12 physical health subscale score, Short Form 12 mental health subscale score, and unsupported difficulties in paid and/or unpaid work. Sex, age and country were forced into both models (predictA and predictD). Two additional risk factors in the predictD algorithm for major depression (level of education and recent discrimination) were absent from the predictA model. However, recent discrimination appeared in seven of the 10 imputed datasets, suggesting it was close to inclusion. This similarity between the two risk algorithms may be due at least in part to the close correlation (co-morbidity) of depressive and anxiety/panic disorders (Gorman, 1996). Recent calls have been made for not separating these disorders into separate DSM/International Classification of Diseases (ICD) chapters (Goldberg *et al*. 2009). Moreover, other data have suggested that a core psychopathology of neuroticism is common to both anxiety disorders and depression (Griffith *et al*. 2010). In our study, however, it must be emphasized that the populations in each of our analyses were substantially different; in the predictD analysis, only participants without major depression at recruitment were included, while for predictA, only those without anxiety syndromes were analysed. Furthermore, although lifetime depression was a risk factor in the predictA algorithm for onset of anxiety, major depression at baseline was not a predictor of anxiety any more than an anxiety syndrome at baseline was a predictor of major depression in predictD. An alternative explanation to co-morbidity is the possibility that depressive and anxiety disorders are expressions of a broader latent pathological process (Tyrer *et al*. 1992; Middeldorp *et al*. 2005; Krueger & Markon, 2006; Mennin *et al*. 2008).

As we have noted previously (King *et al*. 2008), our results do not address how the risk algorithms predictA and predictD might best be implemented in general practice. However, their potential role in prevention is clear. Our results expressed by the C-index and effect sizes for predictA demonstrate a clear difference in risk between participants who developed anxiety and or panic syndromes and those who did not. In showing a number of thresholds for sensitivity and specificity (Table 7) we have emphasized specificity at the cost of reduced sensitivity. We would recommend setting 6-month specificity at 80–85% (risk score between 0.07 and 0.08 or greater in Europe4 countries), in order to minimize the workload resulting from false positives, despite the obvious risk of

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Table 6. *Examples of a range of predicted probabilities of anxiety and/or panic syndrome at baseline in Europe4*[a] *countries*

Risk score[b]	Profile
2% and 2%	A woman of 35 years living in the UK
	No difficulties or supported in paid or unpaid work
	SF12 mental scale score 55.2[c]
	SF12 physical scale score 55.1[c]
	No personal history of depression
	No family history of psychological difficulties
6% and 6% (3% and 3%)[d]	A woman of 70 years living in Slovenia
	Difficulties and unsupported in paid or unpaid work
	SF12 mental scale score 37.8
	SF12 physical scale score 46.0
	No personal history of depression
	No family history of psychological difficulties
11% and 12% (5% and 5%)[d]	A woman of 51 years living in Portugal
	No difficulties or supported in paid or unpaid work
	SF12 mental scale score 35.5
	SF12 physical scale score 29.7
	Personal history of depression
	No family history of psychological difficulties
14% and 15% (6% and 7%)[d]	A man of 47 years living in the UK
	Difficulties and unsupported in paid or unpaid work
	SF12 mental scale score 20.9
	SF12 physical scale score 57.9
	Personal history of depression
	Family history of psychological difficulties

SF12, Short Form 12; S.D., standard deviation.

[a] Europe4 is the UK, Spain, Slovenia and Portugal combined.

[b] Risk (predicted probability of anxiety) is for the intervals 0–6 and 18–24 months.

[c] Mean SF12 scores for Europe4 were: mental 48.9 (S.D. = 10.6); physical 44.1 (S.D. = 11.0). High scores indicate good health/well-being.

[d] Scores in parentheses correspond to removing work difficulties and correcting SF12 physical and mental health scores to the European mean (see text).

missing a proportion of those truly at risk of anxiety syndromes.

Recognition of those at risk in family practice may be helpful when it leads to watchful waiting or active support, such as re-starting treatment in patients with a history of anxiety. Advising patients on the nature of anxiety or on brief cognitive behaviour or problem-solving strategies they might undertake to reduce their risk could also be envisaged. Although efforts to reduce incidence of new or recurrent anxiety disorders might address factors such as physical health problems and work stress, this does not mean that when immutable factors (such as a family history of psychological disorders) predominate there can be no recourse to prevention. The effectiveness of a number of interventions for prevention of generalized anxiety disorders has been evaluated. These include self-help, problem-solving therapy (Hoek *et al*. 2009), online delivery of cognitive behaviour skills (Christensen *et al*. 2010) for adolescents, and stepped care incorporating psycho-education and problem-solving skills in people aged 75 years and over (van 't Veer-Tazelaar *et al*. 2006). Further evaluation of the effectiveness of prevention of anxiety and panic disorders in general adult populations is required, regardless of the risk factors implicated.

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Table 7. *Sensitivity, specificity, likelihood ratio of the predictA model at 6 and 24 months using different cut-offs of the risk score*

	6 months				24 months			
Country	Risk	Sensitivity % (95% CI)	Specificity % (95% CI)	Likelihood ratio (95% CI)	Risk	Sensitivity % (95% CI)	Specificity % (95% CI)	Likelihood ratio (95% CI)
Europe4[a]	0.071	58 (51–65)	80 (79–82)	2.9 (2.6–3.3)	0.077	53 (46–61)	80 (78–81)	2.6 (2.3–3.0)
	0.081	50 (43–58)	85 (84–86)	3.4 (2.9–3.9)	0.089	44 (36–51)	85 (84–86)	3.0 (2.5–3.5)
	0.099	39 (32–46)	90 (89–91)	4.0 (3.3–4.7)	0.110	29 (22–35)	90 (89–91)	2.9 (2.3–3.6)
UK	0.076	45 (31–59)	80 (78–83)	2.3 (1.6–3.1)	0.080	54 (41–68)	80 (77–82)	2.7 (2.1–3.5)
	0.085	39 (25–53)	85 (83–87)	2.6 (1.8–3.7)	0.091	48 (34–62)	85 (83–87)	3.2 (2.4–4.2)
	0.103	27 (15–39)	90 (88–92)	2.7 (1.7–4.3)	0.107	35 (22–48)	90 (88–92)	3.5 (2.4–5.1)
Spain	0.094	50 (38–63)	80 (77–83)	2.5 (1.9–3.2)	0.103	44 (31–58)	80 (77–83)	2.2 (1.6–3.0)
	0.105	47 (34–59)	85 (82–87)	3.1 (2.3–4.0)	0.116	34 (21–47)	85 (83–88)	2.3 (1.6–3.4)
	0.121	40 (28–53)	90 (88–92)	4.0 (2.9–5.4)	0.135	26 (14–37)	90 (88–92)	2.6 (1.7–4.0)
Slovenia	0.052	69 (54–84)	80 (78–83)	3.5 (2.8–4.4)	0.057	62 (44–80)	80 (77–83)	3.1 (2.3–4.2)
	0.060	63 (48–79)	85 (83–87)	4.2 (3.3–5.3)	0.066	53 (35–71)	85 (82–87)	3.5 (2.5–4.9)
	0.069	50 (34–66)	90 (88–92)	4.9 (3.6–6.8)	0.077	40 (23–57)	90 (88–92)	4.1 (2.7–6.3)
Portugal	0.068	63 (49–77)	80 (78–83)	3.2 (2.6–4.0)	0.075	43 (28–57)	80 (77–82)	2.1 (1.5–3.0)
	0.075	58 (44–72)	85 (82–87)	3.8 (3.0–4.9)	0.085	33 (19–47)	85 (83–87)	2.2 (1.5–3.4)
	0.089	52 (37–66)	90 (88–92)	5.2 (3.9–6.9)	0.106	21 (9–34)	90 (88–92)	2.1 (1.2–3.9)
Estonia	0.076	47 (31–62)	80 (77–83)	2.3 (1.7–3.2)				
	0.087	44 (29–59)	85 (82–87)	2.9 (2.0–4.1)				
	0.106	34 (19–48)	90 (88–92)	3.4 (2.2–5.2)				
The Netherlands	0.061	68 (51–85)	80 (77–82)	3.4 (2.6–4.3)				
	0.069	57 (39–74)	85 (83–87)	3.9 (2.8–5.3)				
	0.079	50 (32–68)	90 (88–92)	5.1 (3.6–7.4)				
Chile	0.062	45 (37–52)	80 (79–82)	2.2 (1.9–2.6)				
	0.072	37 (30–45)	85 (84–87)	2.5 (2.1–3.1)				
	0.086	27 (21–34)	90 (89–91)	2.7 (2.1–3.4)				

CI, Confidence interval.

[a] Europe4 is the UK, Spain, Slovenia and Portugal combined. Estimates were obtained using individuals with complete covariate data.

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Declaration of Interest

None.

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