Journal of Affective Disorders 180 (2015) 52–61

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research report

Multiple risk factors predict recurrence of major depressive disorder in women

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ARTICLE INFO

Article history:
Received 31 December 2014
Received in revised form
12 March 2015
Accepted 25 March 2015
Available online 2 April 2015

Keywords:
Major depressive disorder
Prediction
Recurrence
Women

ABSTRACT

Background: It is difficult to predict recurrence of depressive episodes in patients with major depression (MD): evidence for many risk factors is inconsistent and general prediction algorithms are lacking. The aim of this study was to develop a prediction model for recurrence of depressive episodes in women using improved methodology.

Methods: We used prospective data from a general population sample of female twins with a last-year MD episode ($n=194$). A rich set of baseline predictors was analyzed with Cox proportional hazards regression subject to elastic net regularization to find a model predicting recurrence of depressive episodes. Prediction accuracy of the model was assessed in an independent test sample ($n=133$), which was limited by the unavailability of a number of key predictors.

Results: A wide variety of risk factors predicted recurrence of depressive episodes in women: depressive and anxiety symptoms during the index episode, the level of symptoms at the moment of interview, psychiatric and family history, early and recent adverse life events, being unmarried, and problems with friends and finances. Kaplan Meier estimated survival curves showed that the model differentiated between patients at higher and lower risk for recurrence; estimated areas under the curve were in the range of 0.61–0.79.

Limitations: Despite our rich set of predictors, certain potentially relevant variables were not available, such as biological measures, chronic somatic diseases, and treatment status.

Conclusions: Recurrence of episodes of MD in women is highly multifactorial. Future studies should take this into account for the development of clinically useful prediction algorithms.

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1. Introduction

Patients with major depression (MD) differ considerably in their course of illness: most patients have recurrent episodes, but others suffer only one single depressive episode during their lifetime (Eaton et al., 2008; Hardeveld et al., 2010; Solomon et al., 2000). These course differences complicate clinical decisions concerning monitoring and long-term treatment, and can result in both under- and overtreatment of patients (Patten, 2013).

In order to differentiate between MD patients with distinct course types, a number of prior studies have sought to identify predictors of relapse and recurrence. Although some predictors have been found to consistently increase the risk of recurrence – the number of previous episodes, the level of residual symptoms, and childhood maltreatment (Hardeveld et al., 2010; Nanni et al., 2012) – evidence for other predictors is inconsistent (Hardeveld et al., 2010). Moreover, general prediction algorithms, which quantify risk for recurrence based on a combination of risk factors that can be applied in clinical practice, are lacking (Hardeveld et al., 2010; Patten, 2013). Such instruments might guide clinical decision making, comparable to instruments in for instance cardiology (Antman et al., 2000; Granger et al., 2003). This makes it difficult to discriminate between patients with a benign course versus those with recurrent episodes (Hardeveld et al., 2010; Monroe and Harkness, 2011; Mueller et al., 1999), and personalize treatments in order to prevent future episodes.

However, research on prediction algorithms for psychiatry is growing. Several recent studies have investigated multivariate prediction algorithms for MD onset (King et al., 2008; Wang et al., 2013), MD treatment resistance (Perlis, 2013), suicide (Kessler et al., 2015; Tran et al., 2014), and persistence and severity of course of MD (van Loo et al., 2014; Wardenaar et al., 2014). One study developed a multivariate prediction model for recurrence of MD, which resulted in an algorithm with 19 unique factors and a C-statistics of 0.72 in

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http://dx.doi.org/10.1016/j.jad.2015.03.045
0165-0327/© 2015 Published by Elsevier B.V.

independent test data (Wang et al., 2014). Our aim was to contribute to the development of prediction algorithms by studying recurrence of MD in a female sample from the general population. We did this from a novel perspective using a rich set of predictors in a regularized multivariate prospective design, focusing on maximizing prediction accuracy in cross-validation instead of model fit, and testing our model in an independent validation sample.

2. Methods

2.1. Samples

The data for this study consisted of subsamples of female–female twin pairs from the Virginia Adult Twin Study of Psychiatric and Substance Use Disorders (VATSPSUD), a population-based longitudinal study of Caucasian twins (for details, see Kendler and Prescott (2006)). We studied female–female twin pairs because their follow up included four interview waves. Moreover, studying females and males separately might lead to more accurate prediction models because risk factors can be sex-dependent, which has been shown for episodes of MD (Kendler and Gardner, 2014). Female–female twin pairs born during 1933–1972 were initially contacted by a mailed questionnaire, the response to which was 64% ($n=2435$). Participants were then interviewed face-to-face in 1988–1989 (FF1 interview), at which time the refusal rate was 12%. These twins completed three more telephone interviews in 1990–1991 (FF2), 1992–1994 (FF3), and 1995–1997 (FF4), with cooperation rates ranging from 85% to 93%. All participants provided written informed consent for face-to-face interviews and verbal consent prior to all telephone interviews; the study was approved by the Office of Research Subjects Protection at Virginia Commonwealth University.

For this report, we used two independent samples from the full dataset to find an optimal prediction model (training sample – model selection) and to evaluate its performance (test sample – model assessment). The goal was to obtain estimates of prediction accuracy: if a prediction model is overfitting the training data (i.e. the modeling process capitalizes on "noise" in the training data), the training data will give an overly optimistic estimate of prediction accuracy. Thus, new data are needed to get an estimate of the prediction accuracy and generalizability of the model (Hastie et al., 2009; James et al., 2013).

The training sample – used for model selection – included 194 twins who reported a DSM-III MD episode in the year prior to FF1 interview and who completed at least the subsequent FF2 interview. To minimize recall bias, we used twin reports of a depressive episode in the last year rather than those reported for a lifetime episode. Of 2163 twins interviewed at FF1, 217 females reported a MD-episode in the year prior to FF1, of whom 196 completed at least the subsequent FF2 interview. In addition, we excluded two twins who reported a chronic episode lasting from the year prior to FF1 up to the first follow up interview (FF2), so as to focus on the prediction of MD recurrence instead of chronicity. Thus, all 194 twins included in our training sample had a depression-free period between the first episode in the year prior to FF1 and the interview at FF2.

The independent test sample – used for model assessment – included 133 twins who reported a DSM-III MD episode in the year prior to FF2 interview, and who completed at least the subsequent FF3 interview. Of 2002 twins interviewed at the subsequent FF2 interview, 200 females reported a MD-episode in the year prior to FF2, of whom 182 completed at least the subsequent FF3 interview. A female who had not recovered from this episode at the time of the FF3 interview was excluded, again to focus on MD recurrence instead of chronicity. From this sample of 181 twins, we excluded 48 additional twins who also reported an episode at FF1 interview to keep the training sample independent. Due to this selection procedure, all subjects in the test sample were by definition depression-free for a period (i.e., the year preceding FF1) unlike the training sample. We were unable to draw two random mixed samples from the total 327 females because the design of the FF1 and FF2 interview diverged too much: many relevant predictors that were expected to be predictors of recurrence of MD were not assessed at the FF2 interview, as this interview focused more on parent–child relationships. A flow chart of the selection of both samples is shown in additional Table 1.

2.2. Assessment of major depression

At all interview waves, participants were asked about all the depressive symptoms in the 12 months prior to interview by a structured psychiatric interview based on the Structured Clinical Interview for DSM-III-R (SCID) (Spitzer and Williams, 1985). If depressive symptoms occurred, respondents were asked if they clustered together temporally into a syndrome and then when they occurred and the months of their onset and remission. The diagnosis of major depression was based on the DSM-III-R criteria,

Table 1
Baseline characteristics.

	Mean training data ($n=194$)	(SD)	Mean test data ($n=133$)	(SD)	t-test[a]	p-Value
Demographics						
Age at interview (years)	30.7	(7.1)	32.4	(7.1)	−2.1	0.04
Unmarried	53%		47%		1.06	0.29
Number of years of education	13.2	(1.9)	13.5	(2.2)	−1.28	0.20
Psychiatric history						
Age at MD onset (years)	22.1	(9.4)	26.1	(9.5)	−3.74	0.00
History of MD	63%		44%		3.34	0.00
Number of episodes (if history of MD is present)	10.1	(20.0)	5.1	(9.1)	2.33	0.02
History of early anxiety	58%		53%		0.87	0.39
Episode prior to FF1 (training data)/FF2 (test data)						
Sum of 9 MD criteria	6.3	(1.2)	6.4	(1.1)	−0.95	0.34
Duration of longest episode previous (months)	2.7	(3.0)	2.7	(2.8)	0.19	0.85
Number of episodes in year prior to interview	2.3	(2.0)	2.4	(2.3)	−0.47	0.64
Adverse life events (early and recent)						
Number of lifetime traumas	2.3	(1.8)	2.0	(1.6)	1.81	0.07
Number of stressful life events past year	4.0	(2.4)	2.7	(2.0)	5.16	0.00

[a] Welch's t-test.

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