Risk Prediction Models in Psychiatry:
Toward a New Frontier for the Prevention of Mental Illnesses

Francesco Bernardini, MD[a]; Luigi Attademo, MD[a]; Sean D. Cleary, PhD, MPH[b]; Charles Luther, MD[c]; Ruth S. Shim, MD, MPH[d,e]; Roberto Quartesan, MD[a,f]; and Michael T. Compton, MD, MPH[d,e,*]

ABSTRACT

Objective: We conducted a systematic, qualitative review of risk prediction models designed and tested for depression, bipolar disorder, generalized anxiety disorder, posttraumatic stress disorder, and psychotic disorders. Our aim was to understand the current state of research on risk prediction models for these 5 disorders and thus future directions as our field moves toward embracing prediction and prevention.

Data Sources: Systematic searches of the entire MEDLINE electronic database were conducted independently by 2 of the authors (from 1960 through 2013) in July 2014 using defined search criteria. Search terms included *risk prediction*, *predictive model*, or *prediction model* combined with *depression*, *bipolar*, *manic depressive*, *generalized anxiety*, *posttraumatic*, *PTSD*, *schizophrenia*, or *psychosis*.

Study Selection: We identified 268 articles based on the search terms and 3 criteria: published in English, provided empirical data (as opposed to review articles), and presented results pertaining to developing or validating a risk prediction model in which the outcome was the diagnosis of 1 of the 5 aforementioned mental illnesses. We selected 43 original research reports as a final set of articles to be qualitatively reviewed.

Data Extraction: The 2 independent reviewers abstracted 3 types of data (sample characteristics, variables included in the model, and reported model statistics) and reached consensus regarding any discrepant abstracted information.

Results: Twelve reports described models developed for prediction of major depressive disorder, 1 for bipolar disorder, 2 for generalized anxiety disorder, 4 for posttraumatic stress disorder, and 24 for psychotic disorders. Most studies reported on sensitivity, specificity, positive predictive value, negative predictive value, and area under the (receiver operating characteristic) curve.

Conclusions: Recent studies demonstrate the feasibility of developing risk prediction models for psychiatric disorders (especially psychotic disorders). The field must now advance by (1) conducting more large-scale, longitudinal studies pertaining to depression, bipolar disorder, anxiety disorders, and other psychiatric illnesses; (2) replicating and carrying out external validations of proposed models; (3) further testing potential selective and indicated preventive interventions; and (4) evaluating effectiveness of such interventions in the context of risk stratification using risk prediction models.

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[a]School of Psychiatry, University of Perugia, Perugia, Italy
[b]Department of Epidemiology and Biostatistics, The George Washington University Milken Institute School of Public Health, Washington, DC
[c]Department of Psychiatry, Southwest General Health Center, University Hospitals, Middleburg Heights, Ohio
[d]Department of Psychiatry, Lenox Hill Hospital, New York, New York
[e]Hofstra Northwell School of Medicine, Hempstead, New York
[f]Department of Medicine, Division of Psychiatry, Clinical Psychology and Psychiatric Rehabilitation, University of Perugia, Santa Maria della Misericordia Hospital, Perugia, Italy
**Corresponding author:* Michael T. Compton, MD, MPH, Lenox Hill Hospital, Department of Psychiatry, 111 E. 77th St, New York, NY 10075 (mcompton@northwell.edu).

Risk prediction models are statistical models used to estimate the probability that a currently unaffected individual will develop a condition in the future.[1] Specifically, such models, derived from large studies, estimate the risk of individuals developing future outcomes based on 1 or more underlying characteristics (risk factors or predictors).[2] Prognostic prediction models use combinations of predictors to estimate the absolute probability that a certain outcome will occur within a specific time period in an individual with a particular predictor profile.[3]

Although work toward developing risk prediction models is relatively nascent in psychiatry, other fields of medicine have carried out extensive research on such models. For example, to assess the risk of breast cancer in healthy women, one of the most widely used tools is the Gail model (also known as the Breast Cancer Risk Assessment Tool).[4] Initially developed in 1989, it was first validated in Caucasian women and then modified for different races and ethnicities (though even with the modifications, it underestimates risk in African American women and overestimates risk in Asian women).[5] It is used to estimate the 5-year risk of invasive breast cancer.[4] The original Gail model was based on follow-up of Caucasian women undergoing annual mammographic screening through the Breast Cancer Detection Demonstration Project.[6] It relied on 5 risk factors: age, age at menarche, the number of previous breast biopsies, age at first live birth, and the number of first-degree relatives with breast cancer. The National Surgical Adjuvant Breast and Bowel Project modified this model by precluding its use among women with a history of ductal carcinoma in situ and including the risk factor of atypical ductal hyperplasia on breast biopsy.[6]

Another commonly known risk prediction model produces the Framingham risk score (FRS) for the prediction of 10-year coronary event risk among individuals without previously diagnosed coronary heart disease (CHD).[7] Widely regarded as the gold standard in CHD risk assessment tools, the FRS was developed from the Framingham Heart Study[8] and has been validated in multiple populations.[9] The Framingham Heart Study is a long-term and ongoing cardiovascular study; it began in 1948 and has provided substantial insight into the epidemiology

of and risk factors for cardiovascular disease.[10] Two versions of the FRS are currently in use. The first version[8] was published in 1998 and includes age, sex, smoking history, blood pressure, cholesterol, high-density lipoprotein cholesterol, and blood glucose level or history of diabetes[7]; it evaluates CHD risk among individuals who are free of CHD at presentation.[9] The second version was published within the National Cholesterol Education Program Adult Treatment Panel III guideline and includes hypertension medication status among its inputs. Furthermore, its use is precluded among those with a diabetes diagnosis (because type 2 diabetes was considered to be a CHD "risk equivalent," having the same 10-year risk as individuals with prior CHD), thereby making the second version of the FRS applicable only to individuals without CHD or diabetes.[9] Several studies have reported factors that offer additional predictive value beyond what the FRS achieves; however, limited evidence on these modified models remains.[11]

Risk prediction has 2 different objectives. One is to assign to each individual in the population sampled a score based on some combination of baseline factors, which can be translated into an estimate of that individual's probability of having onset of a specific disorder in a subsequent period of time. The FRS is such a score, applicable (in its original form) to a community population of those without previously diagnosed CHD. The outcome is onset of CHD in the subsequent 10 years (eg, a score of 12% means that 12 of 100 people with the particular level of risk based on the predictor values will have a heart attack in the next 10 years). The predictors, all measured at the time of entry into the study, included age, sex, smoking history, etc, and the model assigned weights to those predictors to derive a score. The other objective is to classify each individual as "high risk" or "low risk," a binary classification, based on a certain cut point, usually done to identify those high-risk individuals who warrant a particular preventive intervention (eg, therapeutic lifestyle changes and possibly a low-density lipoprotein (LDL)–lowering drug for those with a 10-year risk > 20% who have an LDL level above the target).

Assessing a risk prediction model's validity consists of 2 main phases: model development (including internal validation using the same data or data source) and external validation (using new data from a different source). Validation requires demonstrating that the model is accurate in the population for whom it is intended. This process must ascertain the model's ability to distinguish between individuals with different outcomes ("discrimination") and show the level of agreement between predicted and observed risks in groups of individuals with similar risk predictions ("calibration").[2] Several statistical approaches and machine learning algorithms are used to develop predictive models. When the number of predictors being examined is relatively small relative to the sample size, the typically used statistical approaches to developing predictive models include Cox regression, logistic regression, and classification and regression trees (CART). When the number of predictors is large relative to the sample size, a commonly used method is the support vector machine (SVM).[12] The SVM is a supervised machine classifier, widely used in many domains because it performs well on high dimensional data (ie, those with more variables included)[12]; it is able to classify individuals into predefined groups. In recent years, the SVM approach has been successfully applied to disease diagnosis, prediction of transition from latent to overt disease, and treatment prognosis.[13]

The choice of statistical methods has implications for the accuracy and interpretation of the model. For a thorough discussion of each, including strengths and weaknesses, see Ahmed et al,[2] Strobl et al,[12] and Wu and Lee.[14] CART-derived risk prediction models are fit with bootstrap aggregating (bagging) and boosting (bias reduction for a single tree) techniques.[15] Using these methods allows for more flexible regression model fitting by permitting selection of covariates without predefined (parametric or nonparametric) relationships with the outcomes. In some instances, these models have been shown to be superior to other regression models, particularly with complex datasets.[16,17]

The traditional statistical approach is to quantify how close predictions are to the actual outcome using measures such as explained variation and the Brier score. Performance can be quantified further in terms of calibration (ie, Do approximately *X* of 100 patients with a risk prediction of *X*% have the outcome?) using a goodness-of-fit test. Furthermore, discrimination is essential (ie, Do patients who have the outcome have higher risk predictions than those who do not?), which can be quantified with measures such as sensitivity, specificity, and the area under the curve (AUC), or *concordance* statistic, the latter indicating the discriminative ability of generalized linear regression models. For a binary outcome, the concordance is identical to the AUC, which plots the sensitivity against the false-positive rate (or 1 – specificity), for consecutive cutoffs for the probability of an outcome.[18] Thus, AUC is defined as the probability that the predicted probability of a randomly selected diseased subject will exceed that of a randomly selected nondiseased subject plus half the probability of a tie. The AUC is a value between 0.5 and 1.0, with a higher value indicating better prediction performance. A prediction model with an AUC value of 0.5 is no better than tossing a

Clinical Points

- The development and validation of risk prediction models, which are crucial to the goal of prevention, have been largely neglected to date for many psychiatric illnesses.
- Risk prediction models for psychiatric disorders are feasible and could ultimately provide clinicians with valuable information regarding the level of risk for onset of a specific condition within a particular time frame. Proven preventive interventions could then be provided in a targeted fashion.
- Although much more research is clearly needed, risk prediction models hold promise for accurately stratifying risk and targeting interventions to avert the onset of psychiatric disorders.

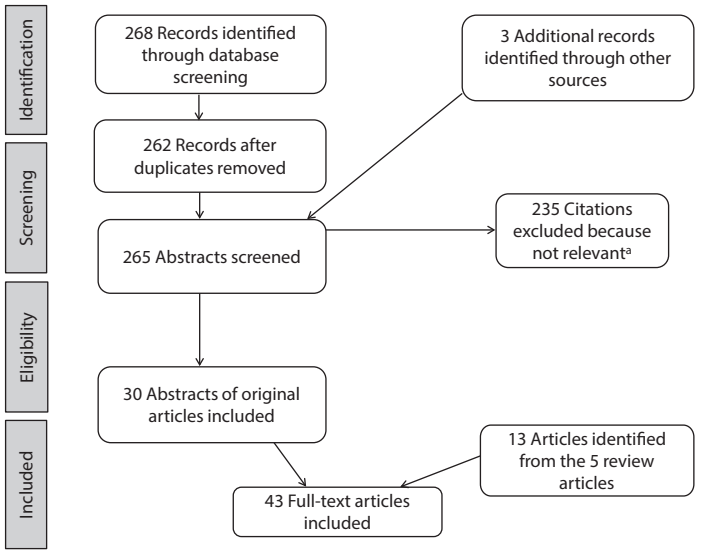
coin, and at the other extreme, a model with an AUC value of 1.0 is a perfect model, with 100% accurate predictions.[14] For systematic reviews, the success rate difference (SRD), a generalized version of the AUC, is commonly reported. The SRD is defined as the difference between the probability that a diseased person has a higher predicted probability of occurrence than a nondiseased person and the probability that a nondiseased person has a higher predicted probability of disease occurrence than a diseased person.[19,20] The SRD corresponds to an effect size defined by Cohen *d*, and for binary outcomes and ordinal predictors, is equivalent to Kendall τ. Traditional measures for binary and survival outcomes include the Brier score to indicate overall model performance, the concordance statistic for discriminative ability (AUC), and goodness-of-fit statistics for calibration.[18]

For binary classification, where the classes are often called positive and negative classes, different classification outcomes include true positive, true negative, false positive, and false negative, according to what the predicted class and true underlying class were. The simplest and often most relevant performance measure in a classification task is the percentage of correctly made classifications. This classification performance is called *accuracy* and is defined simply as the ratio of correct classifications to all classifications. While classification performance measures the overall accuracy of the classifier, it loses information about the distribution of true and false positives and negatives. Different performance measures have been developed for measuring different types of errors. Four basic measures are sensitivity, or true-positive rate; specificity, or true-negative rate; positive predictive value (PPV), or precision; and negative predictive value (NPV). Sensitivity and specificity are often used together to assess the distribution of correctly made positive and negative classifications.[21]

The accuracy of the classification is indicated by the PPV (the probability that a "high-risk" individual subsequently has onset in the specified time period) and NPV (the probability that a "low-risk" individual remains free of onset in the specified time period). PPV and NPV have meaning only in relation to each other, or in relation to the incidence of onset during the specified time period. PPV + NPV – 1 must be greater than 0 for nonrandom decision making.

In recent years, there have been increased research efforts focused on reducing the incidence of mental disorders, and there is now substantial cause for optimism regarding the opportunities for prevention.[22] Risk prediction models are key to advancing the goals of prevention. Despite the evidence for the effectiveness and cost-effectiveness of a number of preventive interventions within the mental health field, research focused on the prediction of mental disorders remains insufficient. Improving prevention will require better predictive capabilities as well as effective interventions to prevent mental illnesses.

Figure 1. PRISMA Diagram for the Systematic Review



[a]The 235 citations were excluded for the following reasons: review articles on the topic (5), original articles on the topic written in languages other than English (4), original articles on the topic but describing prediction of subdiagnostic symptomatology (4), articles about prediction of conditions/diseases other than psychiatric (115), articles about prediction of psychiatric conditions/diseases off our topic (83), and other articles (24).

Given that accurate prediction of risk is a first step toward successful prevention within psychiatry and allied disciplines, we conducted a systematic review of risk prediction models designed and tested for a number of major psychiatric disorders: depression, bipolar disorder, generalized anxiety disorder, posttraumatic stress disorder, and schizophrenia and other primary psychotic disorders. Our goal was to summarize the literature to date on risk prediction models for these 5 disorders and give recommendations for future research directions as our field moves toward embracing prediction and prevention.

METHODS

Systematic searches of the MEDLINE electronic database (from 1960 through 2013) were conducted independently by the first 2 authors in July 2014. The year 1960 was selected as the start date for the search partly because it was only in the second half of the twentieth century that the science of risk prediction models was developed. Search terms included *risk prediction*, *predictive model*, or *prediction model* combined with *depression*, *bipolar*, *manic depressive*, *generalized anxiety*, *posttraumatic*, *PTSD*, *schizophrenia*, or *psychosis*. As depicted in Figure 1, we compiled articles that (1) were published in English, (2) provided empirical data (as opposed to reviews or commentaries), and (3) presented results pertaining to developing or validating a risk prediction model in which the outcome was the diagnosis of 1 of the 5 aforementioned mental illnesses. The titles and

abstracts of all identified citations were screened based on the defined inclusion criteria. All references within included studies and those of any previous pertinent reviews were carefully reviewed to identify additional relevant studies. Any articles published after the search date that became known to the investigative team were also included. Consensus was then derived, resulting in a final set of articles that would be reviewed and summarized. Based on the above search terms and criteria, 268 articles were initially identified. From this list, we selected 30 original research reports. Additionally, 13 original research articles were identified from 5 review articles.[12,23–26] Four non-English articles,[27–30] though potentially relevant to the review, were excluded. The 2 independent reviewers then abstracted 3 types of data elements (sample characteristics, variables included in the model, and reported model statistics) and again came together to reach consensus regarding any discrepant abstracted information. Table 1 summarizes findings, including only the 21 articles developing a prognostic score (risk prediction) or binary classification (classification for preventive intervention). For risk prediction models, when data were available, the calculation SRD = (2 × AUC) – 1 was included; effect sizes equivalent to Cohen *d* "small," "medium," and "large" are SRDs of 11%, 28%, and 43%, respectively. For binary classification models, we included 2 indicators: PPV + NPV – 1 and sensitivity + specificity – 1. Due to dichotomization, prediction indicators will almost always be higher than classification indicators. Select studies are described below. Otherwise informative articles are summarized in Table 2.

RESULTS

With regard to models developed for the prediction of major depressive disorder, we identified 12 relevant reports.[31–35,52–58] Among them, 5 focused on samples of patients with medical disorders (specifically, rheumatoid arthritis,[52] traumatic brain injury,[31] intracerebral hemorrhage,[34] prior history of depression,[56] and stroke[35]), only 2 involved individuals in the general population,[33,58] and 5 focused on specific demographic groups (eg, adolescents,[32] new mothers,[53] older adults,[55,57] spouses of women with breast cancer[54]). Regarding the former type of study, the best-performing predictive model was developed among 382 patients recently hospitalized for stroke; it demonstrated PPV, NPV, AUC, and SRD of 94%, 33%, 78%, and 56%, respectively.[35] Regarding the other studies pertaining to depression, the most informative study[32] described a model developed using data from 4,791 adolescents, which demonstrated PPV, NPV, AUC, and SRD of 64%, 89%, 80%, and 60%, respectively.

In terms of models for the prediction of bipolar disorder, we found only 1 relevant report.[36] It was developed using data from 268 Chinese patients with a major depressive episode and demonstrated PPV, NPV, AUC, and SRD of 87%, 67%, 85%, and 70%, respectively, with significant predictors ($P < .001$) including age at first onset, maximum duration of depressive episodes, somatalgia, hypersomnia, diurnal variation of mood, and irritability.[36]

We identified 2 relevant reports on the development of prediction models for generalized anxiety disorder.[37,59] The best-performing predictive model was derived using data from 271 participants (60 with lupus, 50 with gout, 100 with rheumatoid arthritis, and 61 healthy controls) and demonstrated PPV, NPV, AUC, and SRD of 81%, 85%, 90%, and 80%, respectively.[37]

Our search revealed 4 reports[38–40,60] on risk prediction models for PTSD. The largest-sample study included 25,478 people, ages 16 years and older, affected by the 1998 floods in Hunan, China, and demonstrated PPV, NPV, AUC, and SRD of 23%, 98%, 85%, and 71%, respectively.[38] The study conducted by Boscarino et al[39] among 2,368 New York City residents after the September 11, 2001, World Trade Center attacks demonstrated PPV, NPV, AUC, and SRD of 34%, 99%, 94%, and 89%, respectively. Russo et al[40] conducted a study analyzing electronic medical record data of 878 hospitalized injury survivors, demonstrating PPV, NPV, AUC, and SRD of 58%, 78%, 72%, and 44%, respectively.

With regard to models developed for the prediction of schizophrenia and other primary psychotic disorders, we identified 24 relevant reports,[41–51,61–73] primarily focused on samples of "at-risk," "ultra-high risk," or presumably "prodromal" young people. We will briefly review only 2 of the studies[48,51] that appear to be most impactful in this rapidly evolving field. Perhaps the best-performing predictive model related to 179 subjects and demonstrated PPV, NPV, AUC, and SRD of 83%, 87%, 81%, and 62%, respectively.[48] Significant predictors ($P < .001$) included psychopathology and life functioning. Another study[51] included 58 clinical high-risk subjects and demonstrated PPV, NPV, AUC, and SRD of 70%, 94%, 91%, and 82%, respectively.

For all models in the systematic review, assumption of nonrandomness was never violated based on our calculation. In addition, AUC and SRD values were all high, indicating that the risk prediction models reviewed have acceptable levels of discrimination. Several other studies[74–77] were identified pertaining to the prediction of subdiagnostic symptomatology (eg, depressive symptoms following stroke, depressive symptoms in children), which are not reviewed herein.

DISCUSSION

Although the field of risk prediction in mental health lags behind other areas of medicine (eg, breast cancer, cardiovascular disease), a number of promising studies have been conducted to begin to ascertain the operative combinations of risk factors for a number of psychiatric disorders. These models must be successfully replicated and validated in multiple samples external to the one used for the model development phase. This often takes many years to achieve. The use of risk prediction models must be thoroughly evidence based, with research demonstrating that the model is reliable and applicable to the intended populations of individuals.[78]

Table 1. Summary of the 21 Most Informative Articles on Developing a Prognostic Score (risk prediction) or Binary Classification (for preventive intervention)

Article	Sample Characteristics	Variables in the Model	Statistical Model	Risk Prediction Statistics	Classification Statistics	Validation
Major depressive disorder						
Levin et al, 2005[31]	N = 129; prospective cohort of adult patients with mild traumatic brain injury followed up at 3-mo postinjury Proportion of the outcome = 11.6% (n = 15)	Higher 1-wk CES-D score, older age, computed tomographic scans of intracranial lesions	Logistic regression	SRD = 0.720 AUC = 0.860	SEN + SPE − 1 = 0.550 SEN = 93% SPE = 62%	Training data used for the model
Van Voorhees et al, 2008[32]	N = 4,791 US adolescents The study included a baseline survey in 1995 and a 1-y follow-up survey in 1996	Baseline risk factors (social and cognitive vulnerability and mood)	Boosted regression	SRD = 0.600 AUC = 0.800	PPV + NPV − 1 = 0.528 SEN + SPE − 1 = 0.515 PPV = 0.636 NPV = 0.892 SEN = 75% SPE = 76.5%	Internal cross-validation
King et al, 2008[33]	N = 5,216 general practice attendees in European countries who were not depressed at recruitment, followed-up at 6 and 12 mo Proportion of the outcome = 7.7%	Patient characteristics or past events (sex, age, education, results of lifetime depression screen, family history for psychological difficulties), current status (discrimination, physical health and mental health, unsupported difficulties in paid or unpaid work), country	Logistic regression	SRD = 0.580 AUC = 0.790		External validation
Christensen et al, 2009[34]	N = 596 patients assessed at day 90 after intracerebral hemorrhage Proportion of the outcome = 20%	Patient characteristics (comorbidities, neurologic impairment, physical disability, female gender)	Logistic regression	SRD = 0.460 AUC = 0.730		Training data used for the model
de Man-van Ginkel et al, 2013[35]	n = 382 consecutive stroke patients who were able to communicate adequately, assessed within the first week after stroke Proportion of the outcome = 14.1% (n = 54)	Medical history of depression or other psychiatric disorder, hypertension, angina pectoris, Barthel Index of Activities of Daily Living dressing item	Logistic regression	SRD = 0.560 AUC = 0.780	PPV + NPV − 1 = 0.270 SEN + SPE − 1 = 0.480 PPV = 0.940 NPV = 0.330 SEN = 73% SPE = 75%	Internal cross-validation
Bipolar disorder						
Gan et al, 2011[36]	N = 344 patients with current major depressive episodes, with 268 completing 1-y follow-up Proportion of the outcome = 63% (n = 169)	Age at first onset, maximum duration of depressive episodes, somatalgia, hypersomnia, diurnal variation of mood, irritability	Logistic regression	SRD = 0.700 AUC = 0.850	PPV + NPV − 1 = 0.540 SEN + SPE − 1 = 0.580 PPV = 0.870 NPV = 0.670 SEN = 75% SPE = 83%	Internal cross-validation
Generalized anxiety disorder						
Mak et al, 2011[37]	N = 60 with systemic lupus erythematosus Proportion of the outcome = 38%	Higher damage accrual, higher cumulative glucocorticoid dose, depression, and fewer regular medications	Logistic regression	SRD = 0.800 AUC = 0.900	PPV + NPV − 1 = 0.656 SEN + SPE − 1 = 0.631 PPV = 0.810 NPV = 0.846 SEN = 73.9% SPE = 89.2%	Internal cross-validation
Posttraumatic stress disorder (PTSD)						
Huang et al, 2010[38]	N = 25,478 individuals aged ≥ 16 y affected by the 1998 floods in Hunan (China) Cross-sectional survey carried out in 2000 Proportion of the outcome = 9.2% (n = 2,336)	Patient characteristics (age, gender, education, mental status before flood) and characteristics of the flood (type, severity), flood experience	Logistic regression	SRD = 0.706 AUC = 0.853	PPV + NPV − 1 = 0.212 SEN + SPE − 1 = 0.562 PPV = 0.234 NPV = 0.978 SEN = 84.0% SPE = 72.2%	Internal cross-validation

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Article	Sample Characteristics	Variables in the Model	Statistical Model	Risk Prediction Statistics	Classification Statistics	Validation
Posttraumatic stress disorder						
Boscarino et al, 2011[39]	n = 2,368 adult New York City residents interviewed by telephone 1-year after the September 11, 2001, attack. A follow-up interview was conducted 1 y later Proportion of the outcome = 7.3% (n = 174)	Primary Care PTSD Screen, psychosocial risk factors	Logistic regression	SRD = 0.886 AUC = 0.943	PPV + NPV − 1 = 0.333 SEN + SPE − 1 = 0.788 PPV = 0.339 NPV = 0.994 SEN = 93% SPE = 86%	External validation
Russo et al, 2013[40]	n = 878 randomly selected adult hospitalized injury trauma survivors between April 2006 and September 2009 Proportion of the outcome = 3.6% (32)	Electronic medical record data (in particular, PCL-C risk cutoff of 3)	Logistic regression	SRD = 0.440 AUC = 0.720	PPV + NPV − 1 = 0.360 SEN + SPE − 1 = 0.370 PPV = 0.580 NPV = 0.780 SEN = 71% SPE = 66%	External validation
Schizophrenia or other primary psychotic disorders						
Carter et al, 2002[41]	N = 212 high risk subjects (family history of schizophrenia) assessed when the subjects average age was 15 y, and 25 y later Proportion of the outcome = 16.3% (n = 32)	Family history (interaction of genetic risk with rearing environment), life functioning (disruptive school behavior)	Discriminant function analysis		PPV + NPV − 1 = 0.350 SEN + SPE − 1 = 0.390 PPV = 0.530 NPV = 0.820 SEN = 66% SPE = 73%	Internal cross-validation
Yung et al, 2003[42]	n = 49 high-risk subjects (family history of psychotic disorder, schizotypal personality disorder, subthreshold psychotic symptoms, or brief transient psychotic symptoms) assessed and followed up monthly for 12 mo or until psychosis onset Proportion of the outcome = 40.8% (n = 20)	Psychopathology, life functioning (long duration of prodromal symptoms, poor functioning at intake, low-grade psychotic symptoms, depression and disorganization)	Cox regression		PPV + NPV − 1 = 0.740 SEN + SPE − 1 = 0.770 PPV = 0.800 NPV = 0.940 SEN = 86% SPE = 91%	Training data used for the model
Yung et al, 2004[43]	n = 104 UHR young subjects (family history of psychotic disorder combined with some functional decline or the presence of subthreshold or self-limiting psychotic symptoms) assessed at intake and at 6 and 12 mo Proportion of the outcome = 34.6% (n = 36)	Psychopathology, life functioning (poor functioning, long duration of symptoms, high levels of depression and reduced attention)	Cox regression		PPV + NPV − 1 = 0.630 SEN + SPE − 1 = 0.530 PPV = 0.810 NPV = 0.820 SEN = 60% SPE = 93%	Training data used for the model
Job et al, 2006[44]	n = 65 at FHR of schizophrenia subjects from the EHRS sample who had 2 MRI scans a mean of 1.52 years apart Proportion of the outcome = 12.3% (n = 8)	Voxel gray matter (significant predictors: right cerebellum, left uncus, left inferior temporal gyrus)	Linear regression with voxel masking		PPV + NPV − 1 = 0.520 SEN + SPE − 1 = 0.340 PPV = 0.600 NPV = 0.920 SEN = 38% SPE = 96%	Training data used for the model
Lencz et al, 2006[45]	n = 38 clinical high risk young patients with attenuated (subpsychotic) schizophrenia-like positive symptoms assessed at baseline and with clinical follow-up data of at least 6 mo duration (when available) Proportion of the outcome = 36.3% (n = 12)	Positive symptoms, neurocognition (in particular, verbal memory deficits)	Logistic regression		PPV + NPV − 1 = 0.570 SEN + SPE − 1 = 0.680 PPV = 0.690 NPV = 0.880 SEN = 82% SPE = 79%	Internal cross-validation

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Table 1 (continued). Summary of the 21 Most Informative Articles on Developing a Prognostic Score (risk prediction) or Binary Classification (for preventive intervention)

Article	Sample Characteristics	Variables in the Model	Statistical Model	Risk Prediction Statistics	Classification Statistics	Validation
Schizophrenia or other primary psychotic disorders						
Eack et al, 2008[46]	N = 86 at-risk young first- and second-degree relatives of schizophrenia probands followed for an average of 3 y Proportion of the outcome = 6% (n = 5)	Psychopathology, total brain volume, neurocognition	Structural equation modeling		PPV + NPV − 1 = 0.540 SEN + SPE − 1 = 0.420 PPV = 0.710 NPV = 0.830 SEN = 50% SPE = 92%	Training data used for the model
Koutsouleris et al, 2009[47]	n = 45 subjects with at-risk mental state regularly followed-up for 4 y Proportion of the outcome = 45.5% (n = 15)	Voxel gray matter, white matter (first 17 principal components)	Support vector machine		PPV + NPV − 1 = 0.630 SEN + SPE − 1 = 0.630 PPV = 0.830 NPV = 0.800 SEN = 83% SPE = 80%	External validation
Ruhrmann et al, 2010[48]	N = 179 at-risk individuals (UHR or cognitive disturbances) with a total follow-up time of 18 mo Proportion of the outcome = 19% (n = 34)	Psychopathology, life functioning	Cox regression	SRD = 0.616 AUC = 0.808	PPV + NPV − 1 = 0.703 SEN + SPE − 1 = 0.396 PPV = 0.833 NPV = 0.870 SEN = 41.7% SPE = 97.9%	Training data used for the model
Koutsouleris et al, 2012[49]	n = 37 at-risk mental state subjects Proportion of the outcome = 43.2% (n = 16)	Voxel gray matter (principal components after supervised feature selection)	Support vector machine		PPV + NPV − 1 = 0.680 SEN + SPE − 1 = 0.690 PPV = 0.780 NPV = 0.900 SEN = 81% SPE = 88%	External validation
Koutsouleris et al, 2012[50]	n = 35 at-risk mental state subjects assessed at baseline and after 4-y follow-up Proportion of the outcome = 42.8% (n = 15)	Neurocognition	Support vector machine		PPV + NPV − 1 = 0.540 SEN + SPE − 1 = 0.550 PPV = 0.830 NPV = 0.710 SEN = 80% SPE = 75%	External validation
Nieman et al, 2014[51]	N = 58 clinical high-risk subjects assessed at baseline and after 36 mo Proportion of the outcome = 31% (n = 18)	Premorbid adjustment (social adjustment), reduced parietal P300 amplitude	Logistic regression	SRD = 0.820 AUC = 0.910	PPV + NPV − 1 = 0.640 SEN + SPE − 1 = 0.714 PPV = 0.700 NPV = 0.940 SEN = 88.9% SPE = 82.5%	Internal cross-validation

Abbreviations: AUC = area under the curve, CES-D = Center for Epidemiologic Studies Depression Scale, EHRS = Edinburgh High Risk Study, FHR = familial high risk, MRI = magnetic resonance imaging, NPV = negative predictive value, PCL-C = PTSD Checklist-Civilian Version, PPV = positive predictive value, SEN = sensitivity, SPE = specificity, SRD = success rate difference, UHR = ultra-high risk.

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Table 2. Summary of the 22 Other Articles Identified

Article	Sample Characteristics	Variables in the Model	Notes, Findings, and Model Statistics
Major depressive disorder			
Covic et al, 2003[52]	N = 157; a study of prediction of depression and pain in rheumatoid arthritis patients	Helplessness, passive coping, physical disability	Helplessness and passive coping were significant mediators of the relationship between the physical disability and future depression and pain Cross-sectionally, the predictive model accounted for 52%–94% of variance in pain and 37%–71% of variance in depression Longitudinally, the predictive model explained 29%–43% of variance in pain and 21%–33% of variance in depression
Dennis et al, 2004[53]	N = 594 females at 1-wk postpartum Proportion of the outcome = 29.4% (n = 144)	Immigration within the past 5 y, history of depression independent of childbirth, diagnosis of pregnancy-induced hypertension, vulnerable personality style, stressful life events, lack of perceived support, lack of readiness for hospital discharge, dissatisfaction with infant feeding method	Probability of exhibiting depressive symptomatology ≥ 50%: SEN = 43.6%; SPE = 90.3%; SEN + SPE − 1 = 0.339
Lewis et al, 2008[54]	N = 206 males; spouses of women with nonmetastatic breast cancer Proportion of the outcome = 19% (n = 39)	Patient characteristics or past events (age, education, age when married, reported heightened fears over the wife's well-being, job performance preoccupation, uncertainty about the future, adjustment of the marriage)	Correct classification = 89.2%
Shin et al, 2009[55]	N = 299 community-dwelling older adults Proportion of the outcome = 31.2% (n = 93)	Patient characteristics (gender, income, education, activities of daily living, somatic symptoms)	Variance in depression explained = 28%
Ten Doesschate et al, 2010[56]	N = 172 remitted, recurrently depressed patients over 5.5-y follow-up Proportion of the outcome = 79% (n = 135)	Higher number of previous episodes, more residual symptoms, lower levels of positive refocusing	Explained variance = 29%
Okamoto et al, 2011[57]	N = 754 noninstitutionalized people aged ≥ 65 y Proportion of the outcome = 27.3% (n = 206)	Patient characteristics (hearing problem, less appetite, less financial leeway, low emotional support, less subjective usefulness)	SEN = 78.2%; SPE = 80.2%; SEN + SPE − 1 = 0.584
Bellon et al, 2011[58]	n = 11,891 nondepressed adults	Patient characteristics or past events (sex, age, sex × age interaction, education, physical child abuse, and lifetime depression) and current status (SF-12 physical score, SF-12 mental score, dissatisfaction with unpaid work, number of serious problems in very close persons, dissatisfaction with living together at home, and taking medication for stress, anxiety, or depression)	C-index of the predictD-Spain risk algorithm = 82%
Generalized anxiety disorder			
King et al, 2011[59]	N = 10,045 among different countries Proportion of the outcome = 5.5% in Europe4 countries (United Kingdom, Spain, Portugal, and Slovenia)	In the algorithm, 4 variables were fixed characteristics (sex, age, lifetime depression screen, family history of psychological difficulties); 3 pertained to current status (SF-12 physical health subscale and mental health subscale scores, and unsupported difficulties in paid and/or unpaid work); 1 concerned country; and 1, time of follow-up	The overall C-index in Europe4 countries was 0.75 (95% CI, 0.72–0.78) The effect size for difference in predicted log odds between developing and not developing anxiety was 0.97 (95% CI, 0.84–1.11) The validation of predictA resulted in C-indices of 0.73 (95% CI, 0.65–0.81) in Estonia, 0.81 (95% CI, 0.74–0.89) in The Netherlands, and 0.71 (95% CI, 0.67–0.74) in Chile
Posttraumatic stress disorder			
Roberge et al, 2010[60]	N = 389 subjects aged ≥ 18 y with diagnosis of myocardial infarction Proportion of the outcome = 4.1% (n = 13)	Psychological variables (perceived threat to life during the myocardial infarction, feeling of fear, helplessness or horror, intensity of depressive symptoms), psychological history (history of referral to psychologist or psychiatrist), sex (female)	Explained variance = 38.6%
Schizophrenia or other primary psychotic disorders			
Davidson et al, 1999[61]	n = 509, apparently healthy males who had their first hospitalization for schizophrenia 1 year or more after testing, compared to n = 9,215 nonpatients Proportion of the outcome = 5.2% (n = 509)	Social functioning, organizational ability, intellectual functioning	Patients compared to matched nonpatients: SEN = 75%; SPE = 100%; PPV = 72%; rate of correct classification = 87.5%; SEN + SPE − 1 = 0.750 Model applied to the entire healthy population: SEN = 74.7%; SPE = 99.7%; PPV = 42.7%; SEN + SPE − 1 = 0.744

(continued)

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Table 2 (continued). Summary of the 22 Other Articles Identified

Article	Sample Characteristics	Variables in the Model	Notes, Findings, and Model Statistics
Schizophrenia or other primary psychotic disorders			
Amminger et al, 2006[62]	n = 86 UHR subjects (presence of subthreshold and/or self-limiting psychotic symptoms and/or a family history of psychotic disorder combined with functional decline) Proportion of the outcome = 25.6% (n = 22)	Psychopathology, life functioning, gender	Age at onset (< 18 y) of psychiatric symptoms is the single most important factor associated with conversion to nonaffective psychosis Independent significant predictors of affective psychosis were poor functioning, female sex, and the presence of a combination of intake criteria at baseline
Cannon et al, 2008[63]	N = 291 at-risk subjects meeting Structured Interview for Prodromal Syndromes criteria Proportion of the outcome = 28.2% (n = 82)	Family history, psychopathology (unusual thought content, suspicion/paranoia), social functioning, substance abuse	SEN = 8%–80%; SPE = 43%–98%; PPV = 41%–81%
Riecher-Rössler et al, 2009[64]	n = 53 subjects with at-risk mental state Proportion of the outcome = 34% (n = 21)	Psychopathology, TAP Go/No Go (significant predictors: suspiciousness, SANS anhedonia/asociality, and TAP Go/No Go false alarm)	SEN = 83%; SPE = 79%; SEN + SPE − 1 = 0.620; overall predictive accuracy = 81%
Seidman et al, 2010[65]	n = 304 clinical high risk subjects; 52 persons not at clinical high risk with a family history of psychosis in first- or second-degree relatives (family high-risk group); and 193 normal controls with neither a family history of psychosis nor a clinical high-risk syndrome	Neuropsychological deficits	Tests of processing speed and verbal learning and memory were most sensitive in discriminating clinical high risk individuals from controls Neuropsychological functioning did not contribute uniquely to the prediction of psychosis beyond clinical criteria, but worse verbal memory predicted more rapid conversion
Walker et al, 2010[66]	n = 56 subjects aged 12–18 y, schizotypal personality disorder and/or attenuated positive symptoms Proportion of the outcome = 25% (n = 14)	HPA activity (in particular, salivary cortisol elevations)	At-risk subjects who subsequently developed psychosis showed significantly higher cortisol at the first follow-up, a trend at the 1-y follow-up, and a significantly larger area under the curve when compared to those who did not convert
Dragt et al, 2011[67]	N = 72 UHR subjects followed up for 36 mo Proportion of the outcome = 26.4% (n = 19)	Sociodemographic variables, Premorbid Adjustment Scale scores	Urbanicity, social-sexual aspects of premorbid adjustment, and social-personal adjustment significantly predicted development of psychosis
Mechelli et al, 2011[68]	N = 182 UHR subjects Proportion of the outcome = 26.4% (n = 48)	Voxel gray matter	SEN = 68%; SPE = 66%; SEN + SPE − 1 = 0.340; average accuracy = 67%; reduced left parahippocampal volume was specifically associated with the later onset of psychosis
Ayalew et al, 2012[69]	n = 3,322 subjects with schizophrenia, 3,587 controls	Top candidate genes for schizophrenia	Translational convergent functional genomics study using polyevidence scoring and pathway analyses to identify top genes that can be used to generate a genetic risk prediction score with predictive ability
Lin et al, 2012[70]	n = 120 subjects with schizophrenia, n = 76 healthy controls	Electroencephalography during auditory oddball paradigm (mismatch negativity at electrode FCz), neurocognition	The model performed well in differentiating patients from healthy subjects (percentage of concordant pairs: 90.5%)
Bicikova et al, 2013[71]	n = 22 drug-naive participants with schizophrenia; n = 47 healthy subjects	Steroid metabolome	The use of multivariate OPLS model distinguished schizophrenia status in males with 95% sensitivity and 100% sensitivity in females
Schultze-Lutter et al, 2014[72]	n = 246 no lifetime diagnosis of psychosis, no diagnosis of cognitive disorders, no general medical conditions Proportion of the outcome = 32.9% (n = 81)	UHR criteria and basic symptom criterion "cognitive disturbances"	Patients who met UHR criteria and cognitive disturbance (n = 127) at baseline had a significantly higher risk of conversion at month 48, and a shorter time to conversion, than patients who met only UHR criteria (n = 37) or only cognitive disturbance (n = 30)
Michel et al, 2014[73]	N = 97 at-risk patients Proportion of the outcome = 45.4% (n = 44)	At-risk criteria (attenuated psychotic symptoms, basic symptom criterion "cognitive disturbances"), processing speed deficit (digit symbol test)	The final prediction model included at-risk criteria and processing speed deficit The model was stratified into 4 risk classes, with hazard rates between 0.0 (both predictors absent) and 1.29 (both predictors present)

Abbreviations: HPA = hypothalamic-pituitary-adrenal, OPLS = orthogonal projections to latent structures, PPV = positive predictive value, SANS = Scale for the Assessment of Negative Symptoms, SEN = sensitivity, SF-12 = Short Form 12, SPE = specificity, TAP = Testbatterie zur Aufmerksamkeitsprüfung, UHR = ultra-high risk.

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Concerning major depressive disorder, bipolar disorder, and generalized anxiety disorder, our review found that there is not a well-established group of predictive variables. Future investigations should try to increase prediction accuracy using sociodemographic, environmental, neuropsychological, and biologic variables in different samples of at-risk individuals.

Among the psychiatric disorders we examined, the greatest progress appears to be in the area of psychotic disorders. This is probably because several clinical prodromal states have been defined (eg, attenuated psychotic symptoms syndrome, brief and intermittent psychotic symptoms) and there are now specific research diagnostic criteria for these prodromal syndromes. Efforts to establish a prevention approach to schizophrenia have focused on developing and validating criteria for identifying individuals at risk for imminent onset of psychosis (ie, clinical high-risk or prodromal adolescents and young adults) and following them over time.[63] The identification and refinement of prodromal states (and prodrome research consortia) for other psychiatric conditions (eg, generalized anxiety disorder) would bring greater attention to prediction and prevention of such psychiatric conditions. It is likely that the method with greatest success will employ, depending on the proportion of the outcome in the population (see Table 2), a 2-step approach: one step aimed at the identification of individuals who appear to be prodromal or at elevated risk (who could be offered "selective preventive interventions") and another step that seeks to further stratify risk so that "indicated preventive interventions" can be given to those in the highest risk stratum in an even more targeted and intensive fashion.

Validation is extremely important in developing risk prediction models. To be useful for clinicians, a prediction model must provide accurate estimates of the risks, and the use of those estimates should improve management and therapeutic decision making and, consequently, (relevant) individuals' outcomes and cost-effectiveness of care. Validation studies are crucial because the performance of most developed and internally validated prediction models, when applied to new individuals, is poorer than the performance seen in the sample in which it was developed.[3] The lack of internal and external validation of the models given in Table 1 indicates that the science of risk prediction models in psychiatry is nascent.

As noted by Paulus,[79] psychiatry needs to pragmatically address prediction as an alternative focus for testing hypotheses about clinically relevant issues in the field. One possible obstacle to developing risk prediction models in psychiatry is the prominent lack of availability of biological markers of disease. Another obstacle may be the misperception among clinicians and journal reviewers that a particular discrimination value (eg, an AUC threshold of 0.80) is required before clinical adoption. In most prediction algorithms, including those pertaining to the FRS, the AUC often ranges from 0.75 to 0.80.[80]

However, risk prediction is only as helpful as the preventive interventions available. That is, risk prediction models are useful only if those identified as high risk can be provided an effective preventive intervention. For example, in the field of cardiovascular disease, the FRS can be easily used by primary care physicians to help in deciding on the best approach to risk reduction (eg, recommending and facilitating lifestyle modifications such as smoking cessation and blood pressure and lipid monitoring and control), thereby ultimately reducing morbidity and mortality. Despite the availability of several validated risk prediction algorithms, their use has lagged in primary care.[81] If valid predictive models are developed, then just as much work needs to be done on figuring out how to make them easily applicable and useful for clinicians. In fact, the final step toward implementation of a validated prediction model is the quantification of its impact in clinical care. Although this final step is important to improve health care, literature shows that impact studies are even less frequently performed than validation studies.[82]

As research on risk prediction models advances in our field, so must the discovery of preventive interventions. In the area of psychosis, for example, in addition to tertiary prevention[83]—from pharmacotherapy to prevent relapse, to psychosocial and family-based strategies,[84] which prevent some of the worst consequences of the illness, such as suicide[85]—true primary preventive strategies must be developed. One such potential preventive intervention (an "indicated preventive intervention" for those deemed to be at ultra-high risk) that is being studied for preventing the transition from a high-risk state to frank psychosis is the use of omega-3 fatty acids that are thought to be neuroprotective.[86,87] All such preventive interventions will ultimately need to be studied in randomized controlled trials, with replications being performed in independent samples. The 2 areas of research on risk prediction and preventive intervention development must work hand in hand to make the prevention of mental disorders a realistic goal.

Several methodological limitations of our systematic, qualitative review must be acknowledged. First, to make the review feasible, we chose to focus on risk prediction models for only 5 types of psychiatric illnesses, excluding other behavioral disorders (eg, Alzheimer's disease, obsessive-compulsive disorder, substance use disorders). Second, we excluded articles published in languages other than English. Third, given the relative scarcity of research on this topic to date, and the variability across studies, we were not able to conduct a quantitative systematic review or meta-analysis. Meta-analytic results would be useful to provide important information regarding common predictors and the predictive power of existing models, but these are infeasible at present given the very limited state of research in this neglected area of clinical psychiatry.

In summary, risk prediction models can be feasibly developed for diverse psychiatric disorders just as they have been for chronic medical conditions. Measures of discrimination and calibration of risk prediction models reported to date have been reasonable, and our calculations revealed that the assumption of nonrandomness was

never violated among the models reported in Table 1 and that SRD values indicate that the models reviewed have acceptable levels of discrimination. The initial identification of a potentially accurate model must be followed by external validation and further refinements, which has not yet been done for these models. Validation research is needed. Ultimately, for such models to be useful in clinical settings, the predictor variables must be readily available and easy to assess, and those individuals deemed to be at high risk must be offered preventive interventions that are effective and present a low risk of adverse events. As such, additional research on effective selective and indicated preventive interventions is necessary. The initial steps toward risk prediction and risk stratification have been taken, especially for psychotic disorders. Now our field must advance further so that effective prediction and prevention will be feasible.

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