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## A transdiagnostic model to prevention in mental and behavioral disorders: a comprehensive review and delineation of a new proposal

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# A transdiagnostic model to prevention in mental and behavioral disorders: a comprehensive review and delineation of a new proposal

Short title: Transdiagnostic model to mental health prevention

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## Abstract

**Introduction:** Current disease-specific models for prevention of mental disorders are challenged by the overlap of psychopathology, biological mechanisms, and risk factors. Moreover, mental disorders usually begin during childhood or adolescence, when symptoms fluctuate and are highly non-specific. **Discussion:** We propose a staging model that integrates three domains - psychopathology, functional impairment and risk factors-, in which prevention is defined as actions to avoid stage progression, irrespective of diagnosis. Thus, preventive interventions should be broadened to include mental health promotion and strategies of risk reduction performed individually, at any stage, even for non-symptomatic subjects (before current at-risk definitions) currently exposed to risk factors. **Conclusion:** The model features three innovations: a focus shift from disease conversion to stage progression, highlights

functionality as an independent target, and acknowledgment of risk factors in the staging. The model must be validated before implementation.

**Keywords:** mental health; prevention; clinical staging.

## Introduction

Sustained recovery and achievement of optimal functional outcomes remain major challenge for mental and substance use disorders (MDs)[1]. As the understanding of biological mechanisms involved of MDs increases, it becomes clearer that the phenotypic presentation by the time of the diagnosis is probably the late manifestation of an underlying process that started earlier in life[2]. Thus, diagnostic and therapeutic concerns have shifted from palliative treatment to early recognition and prevention. The development of at-risk criteria for schizophrenia and bipolar disorder[3,4], for instance, led to the first prevention programs in psychiatry, but a critical review of available evidence indicates need for changing paradigms[5]. In this paper, we review the limitations of current models and propose a transdiagnostic approach increasing the range of phenotypic and functional outcomes investigated.

## Challenges for prevention strategies in Mental Health

### *Taxonomy and pathophysiology – Common pathways for mental disorders*

Mental disorders are currently categorized and diagnosed as clinical syndromes with core features operationalized in a list of symptoms occurring in specific time ranges[6]. This structure significantly enhanced diagnostic reliability, but arguably lacks construct validity, since it relies on clinical observation rather than etiology or pathophysiology[7]. Hence, MDs display significant clinical heterogeneity, in which different or even opposing symptoms can be combined in numerous manners within each syndrome. For example, a person with depression can present insomnia, weight loss and psychomotor agitation, while another may contrarily manifest hypersomnia, weight gain and psychomotor retardation.

As a counterpoint to strictly categorical approaches in mental disorders, dimensional models have been proposed. Rather than a yes or no classification, the dimensional approach quantifies symptoms or characteristics thar are represented within numerical values or as a continuum. Two classical dimensions have emerged in the classification of child and adolescent mental disorders labelled as internalizing

and externalizing. Different propositions further advanced on the study of dimensional psychopathology[8]. The Research Domain Criteria (RDoc) initially proposed the existence of five distinct domains of human neurobehavioral functioning (negative valence systems, positive valence systems, cognitive systems, systems for social processes and arousal/regulatory systems) as a new framework for investigating mental disorders[9]. The Hierarchical Taxonomy of Psychopathology (HiTOP) is based upon empirical data of psychopathology structures combined into more homogeneous traits of individual signs and symptoms hierarchically structured[10]. Dimensional models significantly advance on the problems of reliability, heterogeneity and comorbidity of classical categorical classifications of mental disorders.

Furthermore, distinct disorders can feature similar characteristics since the same symptoms may be present in different syndromes. As a result, symptom overlap and comorbidity occurrence is rather the rule than the exception[11,12]. Diagnostic transition is also common among mental disorders – up to 36% of patients initially diagnosed with bipolar disorder I later receive a schizophrenia spectrum disorder diagnosis[13,14]. Issues regarding diagnostic stability and validity are particularly common during early developmental phases of MDs, weakening the applicability of preventive disease-specific interventions[15].

Biological findings also suggest some concerns about current nosological categories in psychiatry. Recent studies on molecular genetics reinforce the liability overlap between schizophrenia and autism spectrum disorder (ASD); attention-deficit/hyperactivity disorder (ADHD) and ASD; bipolar disorder and schizophrenia, among others[16]. Neuroimaging studies found analogous abnormalities, both anatomical and functional, to be related to a broad range of MDs and at-risk states[17-19]. Additional findings from physiological stress and its role in neurotoxicity and inflammation also strengthen the hypothesis of shared biological mechanisms in MDs[20].

### *Non-specificity of risk factors*

Identification of risk factors is central to any preventive strategy. Most known environmental risk factors for mental disorders are reported indistinctly for different syndromes[21]. Preterm birth has been associated to increased rates of bipolar disorder, nonaffective psychosis, depressive disorder and eating disorders[22]. Traumatic events

exposure, a risk factor with large effect size to schizophrenia[23], also increases risk for depression, anxiety and other mental disorders[24]. The same occurs for perinatal complications, neglect and bullying[25,26]. There are associations deemed more specific, i.e., maternal tobacco smoking and ADHD[27] or cannabis use and schizophrenia[28]. However, even these links are not exclusive, since such risk factors can also increase liability for other disorders[29-31].

Studies including offsprings of patients with MDs suggest that even familial risk surpasses diagnostic boundaries, and although homotypic risks are higher, heterotypic familial transmission is also significant[32]. Apart from non-specificity, risk factors are highly interrelated and produce substantial pleiotropic effects, as they tend to cluster further boosting vulnerability[33]. The cumulative effect of intertwined risk factors also contributes to nonadaptive patters of behaviors, thus increasing the probability of developing a mental disorder[34].

***Limited clinical utility of available At-Risk Criteria***

In the last two decades, several studies support the idea of psychosis high-risk state characterized by three clinical syndromes[4]. Later results, though, indicate that only 10 to 15% of those considered at-risk for schizophrenia will convert to a first episode psychosis (FEP)[35], and 10% will develop an affective psychosis, stressing limitations on specificity[36]. Moreover, less than 20% of those referred to screening actually fulfill at-risk criteria[37,38]. This means that to find one at-risk person, about fifty to one hundred referrals must be assessed. A recent investigation found that only under 5% of FEP individuals had been previously evaluated by prodromal services[39]. Also, studies estimate that 30 to 50% of individuals with FEP do not present prodromal symptoms prior to onset[40,41].

From a public health perspective, “a large number of people at a small risk may give rise to more cases of disease than the small number who are at a high risk”[42]. This paradigm suggests that even small reductions in risk factors in the whole population would produce a larger decrease of the targeted disorder than focusing solely on high-risk individuals. Therefore, it is imperative to develop population-based mental health prevention strategies in addition to high-risk strategies.

**New framework for preventing MDs**

Clinical staging establishes a set of characteristics for each specific phase across the continuous of illness progression. The concept emerged in other areas of medicine from the necessity of defining the best treatment through the course of disease, including prevention-focused interventions[43-45]. The TNM (Tumor-Nodes-Metastasis) clinical staging model for cancer defines a specific therapeutic for each patient, with a general outline that is adapted for specific cancer types, and it has revolutionized oncologic treatment[46]. We used the TNM frame as a model to delineate our new staging approach to prevention.

In our model, prevention is defined as avoiding stage progression, from early to late stages. Some argue that the term prevention should be reserved to measures designed to reduce the occurrence of a disorder[47]. This framework clearly is based on a broader notion of prevention encompassing three levels: primary, secondary, and tertiary prevention[48,49]. Although secondary and tertiary prevention consist mainly of optimizing treatment and early access to care, this proposed clinical staging model reinforces the necessity of incorporating concepts of neuroprogression in mental disorders, to diminish the cumulative burden. Advancing on Leavell and Clark's classification[48], the current model includes a decision tree diagram to optimize clinical practice.

Considering the challenges stated above, feasibility of assessment and the need to inform interventions, we decided to include 3 factors to identify clinical staging**:** **R**isk Factors**, C**linical staging, **F**unctional impairment (RCF model – Figure 1). A step-by-step assessment will guide clinicians' decision while also tackling disease progression. The proposed evaluation, including rational and supporting evidence, will be explained in the following paragraphs.

***Assessing Risk Factors***

The first step is the assessment of risk factors. Risk factors can influence progression at any stage – including those asymptomatic or without functional impairment – and are largely excluded from current at-risk definitions[24,26]. This assessment may be done in different settings, including primary care.

Risk factors are defined as conditions or variables associated with a lower likelihood of positive outcomes and a higher likelihood of negative or socially

undesirable outcomes[50]. The probability of developing a MD and functional impairment increases with the number, duration and "toxicity" of the risk factors encountered[51]. The risk factors stratification (R) includes main clusters with adding effect. Ideally, a risk stratification should rely on individual odds ratio for each risk factor to predict the likelihood of developing a MD[52]. In the lack of empirical data to support the combination of risk factors, we propose to group them in three broad categories adapted from an ecological framework: individual, interpersonal and society/community[53]. This ecological framework tackles the interrelation between an individual and the environment throughout developmental trajectories (Figure 3). The individual cluster includes personal characteristics and conditions such as temperament and cognitive styles, and socioeconomic status. Individual risk factors include gestational factors (such as obstetric complications[54], preterm birth[55]; exposure to drugs and medications[56,57]), socio-demographic factors (such as sex[58], socioeconomic status[59], and educational level[60]), intelligence quotient level[61], substance misuse[62], difficult temperament[63] (such as higher negative emotionality and low effortful control), urbanicity[64] and physical health problems (e.g.: diabetes[65], cancer[66]). The interpersonal cluster includes factors that emerge from the individual's relationships with other people (social interactions) such as family, friends, and other contexts. Interpersonal risk factors include traumatic life events[67], bullying[68], family conflict or instability[67,69] and parental mental illness[70,71]. Finally, the society/community cluster refers to a broader setting including structural factors and public policy. Society/community risk factors include air pollution[72], discrimination and stigma[73] and economic recession and inequality[74,75].

Risk (R) factors would be classified by counting the number of clusters each person scores. For example, a person exposed to traumatic events and family conflict would be considered R1, since both risk factors are considered interpersonal factors. There is a large overlap between risk factors' exposure. Adversity is usually related to a higher propensity to several risk factors. For instance, those who have lower economic status will be at increased risk of violence and deprivation. Risk factors' impact on the probability of developing a disorder is highly heterogeneous and it is unlikely that all risk factors carry the same weight. To account for that, in addition to determining the number of clusters, risk factor is also separated into "a" and "b". Classification "a" include low-frequency and/or low-impact risks and classification "b"

include high-frequency and/or high-impact risks. For example, a person who suffered from physical abuse would be considered R1b and a person born in urban areas should be considered R1a.

These different aspects of risk factors, such as variations in impact and frequency, are important to delineate possible intervention. For example, Adverse Childhood Experiences (ACEs) encompass potentially traumatic events occurring during childhood, such as experiencing or witnessing violence, abuse, or neglect, or growing up in environments characterized by instability due to substance misuse, mental health issues, or the incarceration of a family member. Studies have shown that ACEs are strongly associated with increased risks for a variety of health problems, including mental health disorders like depression and anxiety, substance abuse, and chronic diseases such as cardiovascular issues and obesity[76]. Due to its complex etiology, interventions to prevent ACE more likely include multiple components such as strengthening economic supports for families[77,78]; promoting social norms that protect against violence[79]; early childhood programs such as high-quality preschool and home visiting programs[80,81]; teaching prosocial skills through social-emotional learning[82]. Targeted interventions may also be crucial to lessen the harms of ACEs for children who have already experienced adversity such as victim-centered services that address the specific needs of children affected by trauma and support healing and recovery, reducing the risk of continued harm from past ACEs[83]. On the other hand, urbanization usually affects mental health through social, economic, and environmental factors. Therefore, intervention targeting individuals who live in urban areas to prevent mental disorders could aim to specific factors according to each individual including programs to improve social security[84].

Evidence suggests that effects of risk factors can be prevented or reduced by proper interventions[85-87]. As an example, the Triple P-Positive Parenting Program is a multilevel system of parenting aiming to prevent behavioral problems in children and includes both universal and targeted interventions[88]. Targeted intervention using the Triple P-Positive Program has been developed to specific risk factors such as parents with mental disorders, parents with low income, socially disadvantaged neighborhoods, and parents with marital problems among others. Other programs improve mental health outcomes by targeting social determinants, such as cash transfer programs[89]. Thus, assessing risk factors offers different targets for preventing

mental disorders. The model could benefit from improvements by adding biological risks for mental disorders, such as polygenic risk scores[90]. Since study of biological mechanisms are still incipient, we chose not the include them at this point.

Figure 1 – RCF clinical staging mode

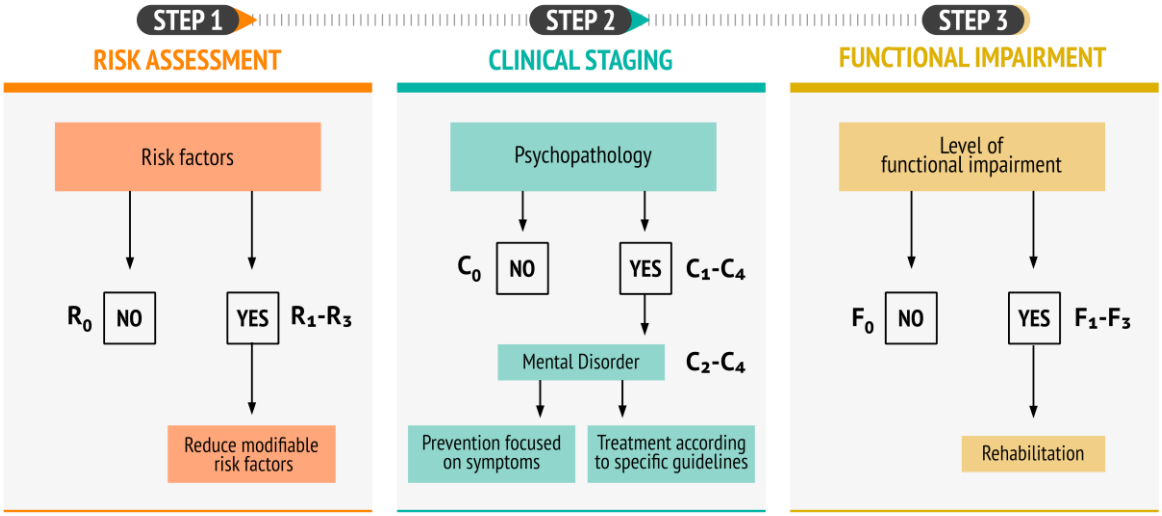



Table 1 – Clusters of risk factors

Table 1 – Clusters of risk and protective factors

| | Risk factors |
|---|---|
| Society/ Community | **Air pollution**[74] |
| | **Discrimination and stigma**[75] |
| | **Economic recession and inequality**[76,77] |
| Interpersonal | **Traumatic life events**[69] |
| | **Bullying**[70] |
| | **Family conflict or instability**[63,71] |
| | **Parental mental illness**[72,73] |
| Individual | **Gestational: obstetric complications**[56]**; preterm birth**[57]**; exposure to drugs and medications**[58,59] |
| | **Socio-demographic factors**[60,61,62] |
| | **Low IQ**[62,63] |

| | |
|---|---|
| | **Substance misuse**[64] |
| | **Difficult temperament**[65] |
| | **Urbanicity**[66] |
| | **Physical health problems**[67,68] |

In the absence of risk factors, individuals should be continuously assessed in routine primary care to monitor dynamic risk factors. In the presence of risk factors, individuals should be referred to existing evidence-based interventions and monitoring.

### *Clinical staging operationalization*

The next step is to evaluate psychopathology. The clinical presentation is not disease specific to accommodate the huge symptom overlap during neurodevelopment. If a mental disorder is already diagnosed during the first contact with the patient, adequate treatment must be readily provided according to functional impairment and risk factors associated. Our proposal includes symptom/ psychopathology assessment – clinical staging (C) – ranging from healthy to severe MDs. Stage C0 includes healthy individuals with no signs of psychopathology with minimal or no impairment. Stage C1 includes subthreshold symptoms of any mental disorder necessarily representing a change from previous status where new signs and symptoms emerge. Stages C2 to C4 consist of individuals with full blown psychiatric disorders progressing from a single first episode to treatment-resistant MDs. Stage C2a refers to individuals with a first episode of non-psychotic mental disorders and stage C2b to individuals with a first episode of psychotic mental disorders. Psychotic symptoms are markers of disease severity associated with poorer outcome[91], and thus are classified separately from other MDs. First-episode psychosis (stage C2b) includes individuals with a diagnosis of schizophrenia, schizophreniform, or schizoaffective disorder, as well as affective psychotic disorders or other diagnosis in which psychosis is severe enough to become a focus of treatment. Stage C3 includes both chronic MDs and relapsed MDs that are still responsive to treatment. Finally, stage C4 refers to persistent unremitted and treatment-resistant MDs.

Asymptomatic individuals may be the target for primary prevention and mental health promotion focusing on ameliorate risk factors. Symptom management should follow specific evidence-based guidelines, also acknowledging associated risk factors and considering additional interventions focused on functional recovery.

***Functional impairment***

The final step is to evaluate the level of functional impairment, which may be present even in the absence of a full-blown syndrome, for individuals with subthreshold symptoms. Functional impairment is a distinct feature, usually not fully explained by symptoms, and a main reason patients seek professional help[92,93]. Real-world functional performance is frequently impaired in individuals with severe mental disorders regardless of symptom remission[94]. In at-risk populations, even for those among non-converters with significant improvement in psychopathology, disability may persist for longer periods[95]. Poor functional outcome in individuals in clinical high risk for psychosis is significant and not entirely dependent on the development of psychosis, but also associated to functional impairments at baseline[96].

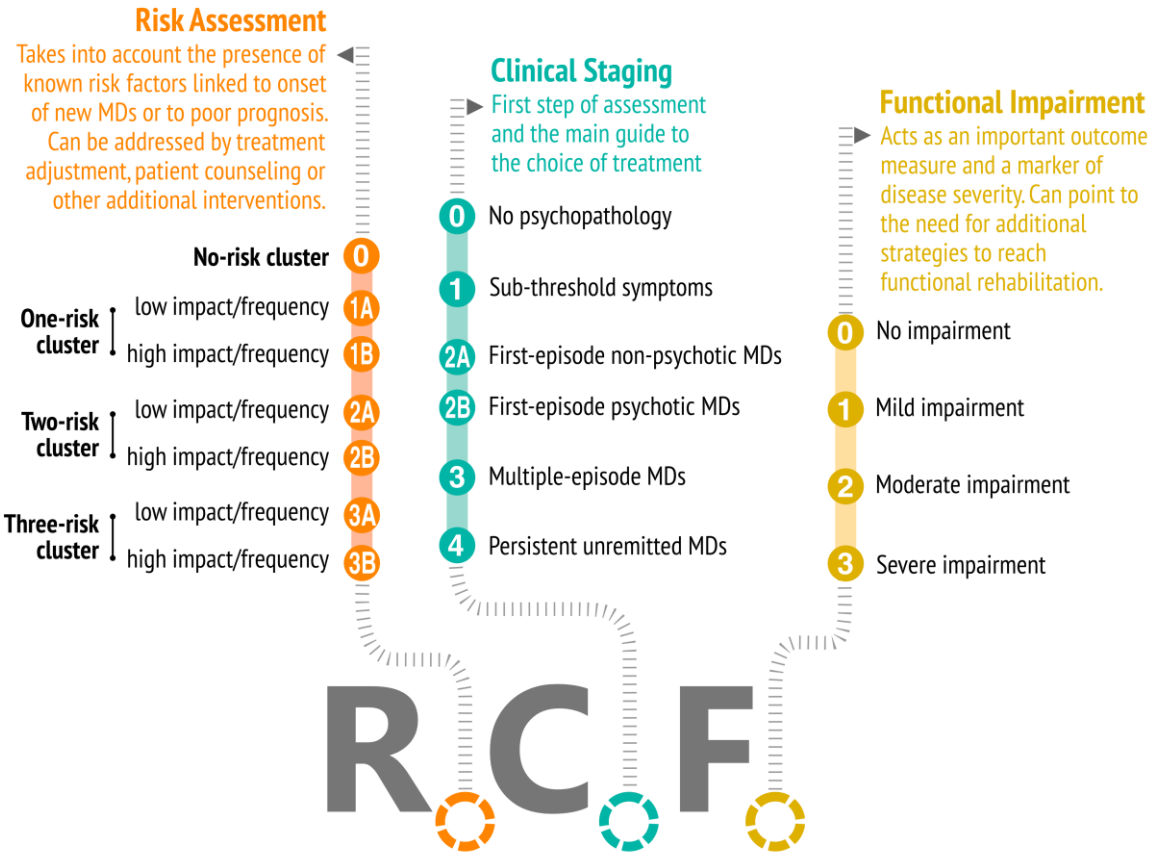
Additionally, functional performance is strongly predicted by functional capacity, including abilities related to social, occupational and practical activities, in individuals with schizophrenia and bipolar disorder[90]. Functional impairment acts both as an important outcome measure and a marker of disease severity, including underlying neurobiological mechanisms[97,98]. Assessing functional impairment continuously in parallel with symptomatology changes the focus from remission to recovery.

Functional impairment (F) encompasses four stages, varying from no impairment to severe impairment. The first stage (F0) includes individuals with no impairment, meaning good functioning in different areas such as everyday life activities and participation, social engaging and interpersonal relationships, occupational and school functioning. Mild impairment (F1) includes individuals with small difficulties in some or all areas or with moderate difficulties in only one area. Moderate impairment (F2) comprises individuals with moderate difficulties in more than one area or with major difficulties in only one area. Individuals with major impairments in several areas or inability to function in significant areas such as everyday life activities and participation should be classified as having severe impairment (F3). Since functional impairment represents a crucial target to

rehabilitation strategies, additional strategies to functional rehabilitation must be considered according to different levels of impairment (Figure 2).

The functional impairment classification helps the clinician improve the rationale for developing the treatment plan, even for individuals within the same clinical stage, such as an individual with schizophrenia classified as C3. While the majority of individuals with schizophrenia experience significant and enduring functional impairment, the degree and nature of this impairment vary between individuals[99], suggesting the necessity of a better classification of severity[100]. This intersubject variability is influenced by a combination of biological, cognitive, and environmental factors that shape each patient's unique experience with the disorder[101-103]. Notably, some patients show moderate functional stability and relatively good outcomes (classified as F1 in the RCF model), while others experience a severe decline in their ability to perform daily activities, maintain employment, and build social relationships (classified as F3 in the RCF model)[99,103]. Cognitive impairments, especially in executive function, memory, and attention, are consistently associated with poorer functional outcomes in schizophrenia[104]. Since cognitive impairments are not homogeneous among individuals with schizophrenia, interventions targeting cognitive deficits could be individually tailored to improve functional impairments[105].

Figure 2 – Diagram for assessing CRFstaging model




To advance in the implementation of this model and determine which risk factors should be assessed in general, a thorough literature review is required. Some examples of risk factors ate listed in table 1, but this list is not exhaustive. A list of variables which are simple to obtain should be the goal to facilitate the implementation of the model in real world settings. Such strategy has been successfully used in a model to evaluate the risk of depression in adolescence[106].

From the perspective of the general population, it makes sense to start evaluation by assessing risk factors. Individuals referred to mental health services would probably be receiving a mental exam first, but assessing risk factors is an important step to consider and should done regardless of this order. When assessing clinical stage, stage C0 individuals presenting with risk factors may benefit of preventing strategies according to their risk classification. Individuals with subthreshold symptoms may benefit from indicated interventions. In symptomatic

individuals receiving proper treatment for mental disorders, prevention should rather focus on risk assessment and functional improvement. In this case, understanding risk factors may facilitate choice of treatment or indicate close monitoring (as in siblings of parents with schizophrenia or bipolar disorder presenting with depression). Although it may seem obvious that optimal treatment should include functional outcome, current treatment options as discussed frequently improve symptoms with little effect on functionality. So, a more thorough assessment of functional impairment is required. This is particularly true for individuals presenting with subthreshold symptoms who may not receive traditional treatment, but still require attention.

## Implications and future directions

### *Impacts in clinical practice*

If validated by empirical data, the RCF stratification can be used as a novel tool to systematically delineate the course of action when assessing mental disorders while considering preemptive interventions. When a specific mental disorder can be diagnosed, treatment should be determined according to proper guidelines, but risk factors should be assessed to consider any additional intervention. When no interventions are available, the only increment should be offering information about modifiable risk factors, such as psychoeducation to encourage the reduction of substance use in an individual with no psychopathology but with multiple interpersonal and individual risk factor. In some cases, risk assessment may result in changes of the treatment. For example, an adolescent with major depression disorder and a family history of bipolar disorder may be considered a candidate to receive atypical antipsychotics rather than antidepressants[107].

Hartmann and colleagues proposed a broader clinical staging classification for severe mental disorders, the Clinical high at-risk mental state (CHARMS), to assess help-seeking individuals with distress[108]. Despite CHARMS representing a step further on widening possibilities of at-risk syndromes, it is still based on transition to specific, clearly defined and non-overlapping syndromes. Recent studies further advances on a model of clinical staging for MDs validating the concept of progression from one stage to another with a large cohort[109,110]. However, the model proposed by Iorfino et al. focuses exclusively on early stages of disorders and only individuals with subthreshold and attenuated symptoms are included. The RCF offers the possibility

of evaluating both asymptomatic individuals and those with more severe syndromes across a wide age range.

The RCF model also advances on current dimensional classification proposals for mental health disorders. One of the primary challenges of RDoC in clinical settings is its limited applicability to everyday psychiatric practice[111]. RDoC is research-oriented and lacks diagnostic criteria that are practical for clinicians. The RDoC framework primarily focuses on neuroscientific research and requires specialized measurement tools that may not be widely available in clinical settings[112]. Additionally, the dimensional model of RDoC itself has been criticized, especially for major mental illnesses[113]. Although HiTOP dimensions are based on descriptions of clinical phenomena and more closely related to clinical practice[114], the systems is more focused on clinical syndromes and does not reflect research on prevention in mental health. Beyond the possible clinical utility of the RFC model, it also includes more clearly aspects of disease progression and prevention.

Our model may expand the population considered at risk, increasing the demand for health attention. In this context, stratifying risk assessment is an important step to discriminate which population may benefit of each intervention and how to allocate resources to different individuals or scenarios. One person with subthreshold symptoms (C2), low socioeconomic status and exposure to physical abuse (R2) probably requires more attention than others with no psychopathology (C0) and obstetric complications during birth (R1). As such, interventions should be planned according to clinical stage (Figure 2). In addition, cost-effectiveness studies must be implemented to determine those interventions that may reduce economic and social burden in the long-term.

Our proposition faces some limitations. The first is to expand the concept of risk to a great range of factors. This may difficult assessment in the general population, which may impact on the worth of our model for epidemiological purposes. Secondly, the low specificity of most risk factors makes it a challenge to implement preventive strategies since most prevention programs are currently designed to specific disorders. The focus on risk assessment independent from diagnosis doesn't mean there are no specific risks factors. How to balance specificity and non-specificity of risk factors may depend on a deeper knowledge on neurobiology and prediction rates. Although the simplicity of the model gives an advantage in a broader variety of health

systems, such as primary care, it is possible, and rather probable, that in specific setting, such as specialized mental health centers, the model would have to consider the specificity of mental disorders. Therefore, the clinical utility of the model in primary care settings could be that of close monitoring and mor comprehensive mental health promotion orientations. In specialized mental health services, the clinical utility would depend on further expanding the classification to accommodate characteristics of specific mental disorders. Although protective factors should also be considered in the context of mental health prevention and promotion, investigations on protective factors are yet scarce, hindering a more robust classification and the inclusion in this framework. Additionally, to translate the model to clinical practice, defining which risks should be assessed and selecting instruments to assess each step is necessary. In investigating risk factors, further analysis of the clusters proposed must be conducted as well as determining with the cluster aggrupation may oversimplify the model by ignoring the strength of specific risks (such as exposition to trauma or parental history of mental illness) or of having multiple risk factors in the same cluster. Lastly, we still lack empiric data to test this concept, so extensive research is necessary to confirm if our model for clinical staging and risk assessment can benefit both asymptomatic and chronic patients.

### *Ethical considerations*

Ethical implications must be considered before implementing a stratification risk assessment for mental disorders. Studies show that psychosis risk status is associated with higher rates of stigma and diminished well-being[115]. But it is still unclear if such negative outcome is related to the label itself, since having psychotic experiences is related to higher perceived social stigma. In fact, the quality and amount of information provided during the diagnostic process impacts directly the emotions associated with it[116]. One study found that with a planned and careful approach during the “labeling process”, shame and discrimination are more related to the symptoms and that the label itself educe positive emotions such as sense of belonging and being understood[117].

Potential stigma associated with MDs may be attached to labeling individuals at risk. However, expanding the discussion about risk and the population included may also have the opposite effect, reducing stigma and raising awareness about your own

mental health. Additionally, individuals could feel discouraged towards risky behaviors in fear of triggering a mental disorder. Since this classification implicates in an increase of risk recognition, these ethical concerns are particularly important. The amount of information provided must be tailored to each person[118], considering patients' autonomy and their right to be informed about his health condition.

## Conclusion

The RCF model presents risk stratification and clinical staging independent of specific disorders. The proposed structure advances on current models by including functional assessment and incorporating knowledge about risk factors into the clinical practice. It allows for a fast and simple assessment that may inform clinicians to delineate prevention strategies. By also considering functionality, individuals with severe impairment will more likely receive specific interventions to prevent additional decline. In this regard, our staging model considers the relevance of pharmacological and non- pharmacological interventions for both general and disease-specific risk factors. The validity and utility of the suggested model must be validated with empirical data in follow-up studies.

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**Compliance with Ethical Standards**

Research involving Human Participants and/or Animals: this article does not contain any studies with human participants performed by any of the authors.



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