ioral problems below the threshold for referral to mental health care.

A stage-based screening and stratification approach[9] was set up in non-specialized school-based services, with the dual goal to identify: a) the target group of youths with common emotional and/or behavioral problems; and b) those with emerging/severe mental illnesses, e.g. psychosis, who were supported to seek specialized care. The common treatment elements were "distilled" from evidence-based single-disorder CBT programs and organized into modules, materials, video-based feedback, supervision and training of the therapists to help them tailor the treatment to the individual subject.

The flexible and modular transdiagnostic implementation of CBT outperformed MAU on multiple endpoints, including reduced impact of mental health problems on functioning in daily life at the end of treatment, corresponding to a Cohen's effect size of 0.60. Harms were low and non-differential by the end of treatment, but significantly lower with MMM versus MAU at follow-up[8].

All the above-mentioned levels of prevention should be integrated in a common strategy. Interventions at different levels should be regarded not as contradictory, but as synergistic. Therefore, it is sad to witness psychiatrists spending time discussing, for example, the discontinuation of early interventions for high-risk populations in order to prioritize efforts to reduce cannabis use[1]. Instead, we should be inspired by the synergistic approaches implemented in other areas of medicine. Would we see a similar fight in cancer (i.e., scientists attacking each other's efforts in smoking cessation initiatives or screening programs versus surgical or medical treatment for cancer)? Our approach should be that it is important to intervene at all levels depicted above, and that we need studies, and preferably controlled trials, to identify the most effective interventions.

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Characterizing transdiagnostic premorbid biotypes can help progress in selective prevention in psychiatry

Fusar-Poli et al's insightful paper[1] is a timely appraisal of the foundations of preventive psychiatry. It is a call to action for our field to mount an individual, societal and global response to improve the lives of people with and those at risk for mental disorders. The authors outline a series of ambitious next steps in preventive psychiatry. They seek to advance this goal by integrating universal and targeted frameworks and by advancing our epidemiological knowledge of the multifactorial causation of mental disorders. An additional important step is to use such data toward developing stratified and personalized approaches. However, a major challenge in tackling these ambitious goals is the enormous heterogeneity of mental disorders, at symptomatic, pathophysiologic and etiologic levels. In this light, several strategies deserve consideration toward a successful move forward with Fusar-Poli et al's suggested next steps.

Any effort at prevention should first clarify what we are planning to prevent. For this reason, an accurate and valid diagnosis is critically important. As the authors point out, caseness is difficult to determine in psychiatry, because the disorders are defined based on symptoms, not on biology. For this reason, psychiatric diagnostic systems currently lack validity[2]. A biomarker-based nosology is clearly a critical next step toward stratification of populations meaningfully separating more homogeneous entities.

In a biomarker-driven effort to address the heterogeneity of psychotic disorders, investigators in the Bipolar-Schizophrenia Network on Intermediate Phenotypes (BSNIP) consortium recently used a K-means clustering approach to parse alterations in cognition and electrophysiology (event-related potentials and eye tracking) across the three major psychotic disorders: schizophrenia, schizoaffective disorder, and psychotic bipolar disorder.

Three distinct "biotypes" were identified which seemed orthogonal to the DSM-based categories[3]. Biotype 1 is characterized by severe cognitive impairments, reduced neural response to salient stimuli, marked gray matter reductions, social function deficits, more frequent family history of psychosis, and prominent negative symptoms. Biotype 2 is marked by moderate cognitive and social impairments and gray matter reductions, and by enhanced neural reactivity. Biotype 3 shows few neurobiological differences from healthy controls. These observations point to the possibility that biomarker-derived classifications may potentially better distinguish subtypes within the psychotic spectrum.

However, having a disease-related biomarker is not sufficient for early identification and prevention purposes, unless the biomarker is demonstrated to be present at illness onset or even before overt clinical manifestations of the disorders. This points to the potential value of identifying premorbid biotypes. Interestingly, biotype

1 appears to identify the deficit syndrome, and premorbid adjustment and cognitive profile can distinguish the schizophrenia deficit subgroup with moderate accuracy[4]. It is noteworthy that biotype 1 is associated with higher frequency of family history of psychosis compared to the other biotypes. It is also of interest that cognitive impairment and family history of psychosis[5], as well as biomarkers characterizing biotype 1 such as decreased auditory P300 amplitudes[6], are together strong predictors of risk for conversion to psychosis among individuals at clinical high risk.

A testable prediction, therefore, is whether biotype 1 psychosis may be preceded by a biotype 1-like biomarker signature in the premorbid phase of the illness that is similar to the features seen later in this subtype. Likewise, it is possible that a biotype 1-like biomarker profile may predict impaired functional outcome in early course psychosis patients. Identifying such premorbid bio-signatures requires prospective longitudinal characterization in individuals at familial and clinical high-risk, and those in the early course of a psychotic illness.

Neurobiological entities seem to cut across psychiatric diagnostic categories. Consistent with this view, biotypes of depression[7] and autism[8] have been identified in studies examining the heterogeneity of these syndromes. Interestingly, similar to psychotic disorders, cognitive impairments may serve as valuable stratification markers in these populations as well.

It is useful to consider biomarker-driven approaches in the light of the traditional (primary vs. secondary vs. tertiary) and the more recent (US Institute of Medicine and World Health Organization) models of prevention outlined by Fusar-Poli et al. The identification of transdiagnostic premorbid biomarker signatures and biotypes may be of particular relevance to the field of selective prevention, though not for universal prevention. Biomarker-driven prediction is an aspirational goal for primary selective prevention (e.g., preventing psychosis in individuals at familial high risk for psychosis), though more work is needed in this area. On the other hand, there is emerging evidence in the literature supporting the possibility of predicting psychosis for indicated secondary prevention in individuals at clinical high risk for psychosis[6], and of predicting relapse and functional outcome for the purpose of tertiary prevention in patients in the early course of psychosis[9].

The steady expansion of new knowledge of brain function, and of new approaches, such as imaging, genetics, proteomic and metabolomic technologies, offers the possibility for developing predictive biomarkers in the near future. However, the complex multifactorial determination of mental illnesses and the enormous amount of the available "omics" data make this goal challenging. As Fusar-Poli et al rightly point out, advancing stratified approaches for prevention requires a multicausal, transdiagnostic, multifinal epidemiological knowledge at an individual level. Large multi-site studies, carefully characterized populations, and sophisticated computational approaches, including machine learning, are needed to generate and harness such "big" data sets toward the development of actionable biomarkers for personalized medicine.

In summary, I agree with Fusar-Poli et al's articulation of the need to urgently develop a blueprint for preventive strategies in psychiatry. First, a transdiagnostic view may be applicable not only to psychoses as outlined here, but to all of psychiatric disorders. Second, a neuroscience-based categorization of distinct subtypes in these disorders, as opposed to symptom-based categories, may improve our ability to predict outcome and treatment response. Finally, extending such a translational approach to clinical and familial high-risk states and to early course clinical populations may help identify early predictors of illness and enable individually tailored preventive interventions.

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