Preventive psychiatry: a blueprint for improving the mental health of young people

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Preventive approaches have latterly gained traction for improving mental health in young people. In this paper, we first appraise the conceptual foundations of preventive psychiatry, encompassing the public health, Gordon's, US Institute of Medicine, World Health Organization, and good mental health frameworks, and neurodevelopmentally-sensitive clinical staging models. We then review the evidence supporting primary prevention of psychotic, bipolar and common mental disorders and promotion of good mental health as potential transformative strategies to reduce the incidence of these disorders in young people. Within indicated approaches, the clinical high-risk for psychosis paradigm has received the most empirical validation, while clinical high-risk states for bipolar and common mental disorders are increasingly becoming a focus of attention. Selective approaches have mostly targeted familial vulnerability and non-genetic risk exposures. Selective screening and psychological/psychoeducational interventions in vulnerable subgroups may improve anxiety/depressive symptoms, but their efficacy in reducing the incidence of psychotic/bipolar/common mental disorders is unproven. Selective physical exercise may reduce the incidence of anxiety disorders. Universal psychological/psychoeducational interventions may improve anxiety symptoms but not prevent depressive/anxiety disorders, while universal physical exercise may reduce the incidence of anxiety disorders. Universal public health approaches targeting school climate or social determinants (demographic, economic, neighbourhood, environmental, social/cultural) of mental disorders hold the greatest potential for reducing the risk profile of the population as a whole. The approach to promotion of good mental health is currently fragmented. We leverage the knowledge gained from the review to develop a blueprint for future research and practice of preventive psychiatry in young people: integrating universal and targeted frameworks; advancing multivariable, transdiagnostic, multi-endpoint epidemiological knowledge; synergically preventing common and infrequent mental disorders; preventing physical and mental health burden together; implementing stratified/personalized prognosis; establishing evidence-based preventive interventions; developing an ethical framework, improving prevention through education/training; consolidating the cost-effectiveness of preventive psychiatry; and decreasing inequalities. These goals can only be achieved through an urgent individual, societal, and global level response, which promotes a vigorous collaboration across scientific, health care, societal and governmental sectors for implementing preventive psychiatry, as much is at stake for young people with or at risk for emerging mental disorders.

Key words: Young people, prevention, mental disorders, preventive psychiatry, psychosis, bipolar disorder, anxiety, depression, evidence-based medicine, neurodevelopment, children, adolescents

(World Psychiatry 2021;20:200–221)

According to the latest World Health Organization (WHO) Global Burden of Disease study, about one billion people of the total global population (7.5 billion) are affected by any mental disorder[1], including psychotic, bipolar or common mental disorders such as depression and anxiety. Overall, about 50% of mental disorders start by the age of 14, and 75% start by the age of 24[2,3]. Young people account for 41% of the current global population (0-14 years: 25.4% and 15-24 years: 15.5%[4]). Justifiably, mental disorders have been called "the chronic diseases of the young"[5].

After their onset, mental disorders often persist, disrupting the capacity for young people to fulfil their potential[6,7], limiting access to mental[8] and physical[9-12] health care, and exposing them to poor education and reduced occupational opportunities[13], stigma, social isolation, discrimination, and violation of human rights[14-16]. Young individuals suffering from mental disorders have higher morbidity and mortality risks for any reason (including suicide[17]) than the general population, translating into a striking 10-20 years reduction in life expectancy[18].

The mental health of the younger generation, and indeed of our future, is already fragile and threatened by exceptional worldwide forces such as an ongoing pandemic, population migrations, economic uncertainties, the sustainability of ecosystems and climate changes[19]. An urgent individual, societal, and global level response is needed to reduce the incidence and burden of mental disorders in young people[6,20]. Preventive approaches in psychiatry lagged behind somatic medicine[21] and emerged only a few decades ago, increasingly gaining traction. At the same time, future advancements require ongoing efforts to identify and overcome their limitations.

This paper addresses these issues, with a focus on reducing the incidence of psychotic, bipolar and common mental disorders. We first summarize the conceptual foundations of preventive psychiatry and then appraise the evidence supporting

different preventive approaches in young people, as well as their current limitations. The knowledge reviewed is then used to develop a blueprint for future preventive research and practice to improve the mental health of young people.

DEFINING PREVENTIVE PSYCHIATRY

This section reviews core preventive psychiatry concepts and frameworks that hold relevance for assessing the evidence and limitations of prevention in young populations and informing future research.

Public health framework

"Possible measures of prevention"[22] for mental disorders have been advocated since the late 19th century. In the early 20th century, an individual with the lived experience of a mental disorder initiated the mental hygiene movement[23], which generated new community practices for preventing mental disorders in young people[24], establishing preliminary public health principles[25] of preventive psychiatry[26]. Therefore, historically, service users and the community have been key actors in the development of preventive psychiatry, a discipline which is closely intertwined with societal and cultural values.

Early work by Leavell and Clark (middle of 20th century) introduced a classification of prevention in medicine[27], which was tailored on the pre-pathogenesis (primary prevention: health promotion and specific protection) and pathogenesis (secondary and tertiary prevention) phases of syphilis[28]. Caplan, in 1964, classified prevention in mental health as follows: a) primary prevention, which "aims at reducing the incidence of new cases of mental disorder and disability in a population"; b) secondary prevention, which "aims at reducing the duration of cases (and therefore the prevalence) of mental disorders, which will inevitably occur in spite of the programs of primary prevention"; c) tertiary prevention, which "aims at reducing the community rate of residual defect, which is a sequel to acute mental illness"[29].

In 1978, Strasser introduced a fourth level of "primordial prevention" to denote activities that prevented the penetration and appearance of risk factors (risk factors increase the likelihood of clinical events, while protective factors decrease this likelihood) into the population itself, as opposed to primary prevention which addresses risk factors to prevent diseases[30]. Finally, Bradford Hill defined nine criteria that may be considered in navigating the difficult question of causation versus plain association: strength of association, consistency across different situations, specificity and temporality between exposure and outcomes, biological gradient, biological plausibility, coherence with present knowledge, experiment (in laboratory and randomized trials), and analogy with similar classes of exposures and outcomes[31,32].

Gordon's framework

The original formulation of the public health framework was disease-oriented, relying on mechanistic linearity of infectious diseases and identification of a clear-cut biological onset. It also ignored epidemiological knowledge on statistical associations between risk/protective factors and clinical events, as well as multifactorial aetiopathologies with a long period of latency[33]. Furthermore, several disorders may be risk factors for other disorders, so all treatments could potentially be labelled as preventive interventions.

In 1983, Gordon[33] addressed these issues in the context of physical illnesses, reserving the term prevention for those individuals who were not "suffering from any discomfort or disability from the disease or disorder to be prevented", thus excluding tertiary prevention as well as antecedents such as clinical high-risk syndromes (see below). Furthermore, Gordon noted that the public health definitions of prevention had little correspondence to interventions offered, and proposed an alternative threefold classification based on the costs and benefits of delivering the intervention: a) universal prevention, "a measure that is desirable for everybody", including actions for the general public which, in many cases, can be "applied without professional advice or assistance"; b) selective prevention, "a procedure [which] can be recommended only when the individual is a member of a subgroup of the population whose risk of becoming ill is above average"; c) indicated preventive measures, that "are advisable only for persons who, on examination, are found to manifest a risk factor, condition, or abnormality that identifies them, individually, as being at sufficiently high risk to require the preventive intervention"[33].

As illustrated in Figure 1, while targeted approaches (i.e., selective and/or

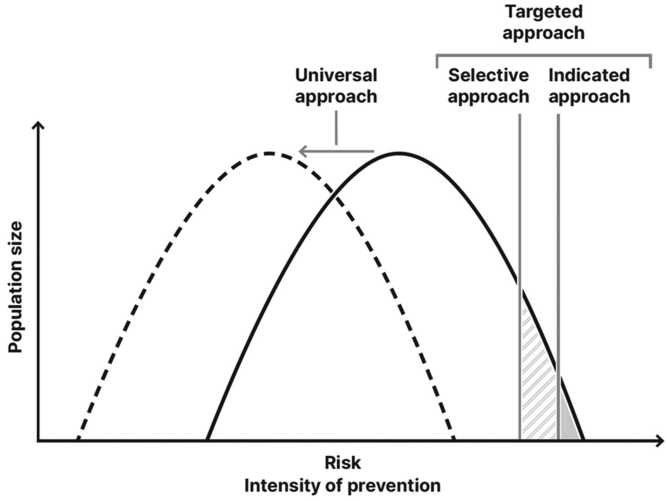

Figure 1 Universal, selective and indicated prevention. Selective and indicated approaches aim to reduce risk amongst those with the most to gain, and therefore reach a small proportion of the population. Universal approaches aim to shift the risk profile of the whole population.

indicated) aim to reduce risk among those with the most to gain, and therefore reach a small proportion of the population, universal approaches aim to shift the risk profile of the whole population.

US Institute of Medicine framework

Gordon's classification was not designed for use in mental disorders. In 1994, the US Institute of Medicine[34] noted that the definition of caseness is more difficult to establish in psychiatry than in somatic medicine, and that the presence of symptoms and dysfunctions is frequent even if diagnostic criteria (ICD/DSM) for mental disorder are not met. Prevention was thus refined as "reducing incidence, prevalence, recurrence of mental disorders, the time spent with symptoms, or the risk condition for a mental illness, preventing or delaying recurrences and also decreasing the impact of illness in the affected person, their families and the society"[34]. The Institute allowed indicated interventions to target antecedents of the disorder, such as clinical high-risk syndromes[34].

It was also acknowledged that, although some people receiving indicated preventive interventions may already have comorbid mental disorders, if they are selected into the intervention based on having early symptoms, then the intervention is still considered preventive[34]. Kessler and Price[35] later refined the concept as primary prevention of secondary psychiatric comorbidities.

The Institute also defined prevention screening to identify risk exposure at population level (for universal prevention efforts, e.g. poverty, violence, lack of health care) or at-risk group/individual level (for selective prevention efforts, e.g. maternal depression or childhood abuse), or to identify core/distinctive characteristics in high-risk individuals (for indicated prevention, e.g. attenuated symptoms, functional impairment or early phenotypic features). Core requisites of prevention screening are identifiable risk/protective factors linked to a disorder, availability of a validated screening tool, an effective intervention to address the identified factors and improve outcomes, solid guidelines on care pathways following screening, wide acceptability to the population, and dynamic implementation of screening procedures[34].

WHO framework

In the current WHO framework (Table 1), universal, selective and indicated preventive interventions are all included within primary prevention[36], and indicated approaches are allowed to target antecedents/clinical high-risk syndromes (see below).

The WHO classifies the management of mental disorders as a continuum encompassing prevention (complementary universal, selective and indicated approaches), treatment (secondary prevention and early or standard treatment), and rehabilitation (tertiary prevention and long-term care). The conceptual boundaries between preventive "interventions" (in "individuals") and "treatments" (in "patients"), particularly in early management[37], are porous at times and associated with several empirical, ethical and societal aspects.

Prevention of mental disorders vs. promotion of good mental health

The WHO broadly defines good mental health as "a state of well-being in which the individual realizes his or her own abilities, can cope with the normal stresses of life, can work productively and fruitfully, and is able to make a contribution to his or her community"[36]. Therefore, mental health is much more than the absence of mental disorders.

Good mental health and mental disorder, although interrelated, are not on a one-dimensional continuum. For example, empirical evidence has associated individual levels of creativity with psy-

Table 1 World Health Organization's classification of preventive approaches for mental disorders[36]

Public health classification of prevention	Gordon's classification of prevention[33], modified by the US Institute of Medicine[34]
Primary prevention seeks to prevent the onset (incidence) of a disorder or illness.	
	Universal prevention is defined as those interventions that are targeted at the general public or a whole population group that has not been identified on the basis of increased risk.
	Selective prevention targets individuals or subgroups of the population whose risk of developing a mental disorder is significantly higher than average, as evidenced by biological, psychological or social risk factors.
	Indicated prevention targets high-risk people who are identified as having minimal but detectable signs or symptoms foreshadowing mental disorder, or biological markers indicating predisposition for mental disorders, but who do not meet diagnostic criteria for disorder at that time.
Secondary prevention seeks to lower the rate of established cases of the disorder or illness in the population (prevalence) through early detection and treatment of diagnosable diseases.	
Tertiary prevention includes interventions that reduce disability, enhance rehabilitation and prevent relapses and recurrences of the illness.	

chotic or bipolar disorders[38,39], and this association has recently been confirmed at a genetic level[40]. Conversely, individuals without mental disorders do not necessarily have good mental health. Normally developing young people can display reactive mild anxiety or depression as physiological adaptive strategies aimed at harm avoidance and extinction of maladaptive behaviours[41].

Therefore, mental health promotion can be implemented across all stages illustrated in Figure 2 (e.g., from healthy people to individuals affected with chronic mental disorders)[34], and not only during the pre-pathological phase (i.e., within primary preventive approaches, as suggested by Leavell and Clark[27]). Promotion of good mental health could also be enhanced by improving physical health, given the close relatedness between these two domains[42].

Neurodevelopmental prevention of mental disorders in young people

As noted by Clark[28], prevention "requires knowledge of the natural history" of a disease. Psychotic disorders are infrequent before the age of 14[43]; their incidence peaks in the age group of 15-35 and declines after the age of 35[44]. The average age of onset for bipolar disorder is 23 years, with a wide range (9 to 37)[45]. The median onset age is earlier for anxiety disorders (11 years of age) versus major depression (32 years)[2]. The range of the age of onset of depressive disorders is typically wider than for many other mental disorders[46].

The pathophysiology of psychotic disorders is generally understood to originate from several genetic and non-genetic risk/protective factors (and their interactions) that impact the neurodevelopment[7,47,48]. Early abnormalities of maturational changes appear from the ectodermal phase to the first year after birth (first-wave hits)[49]. A further phase of significant neurobiological changes is from mid-childhood through pubescence to mid-20s (second-wave hits)[47], when the risk of disorder onset is the highest. Similar neurobiological models have been investigated for bipolar disorder[50,51] and depression[52].

Clinical staging models[53] integrate these epidemiological and neurobiological findings (Figure 2)[47]. The clinical staging model for psychosis is the most established[54,55], but similar models have also emerged for bipolar[56-59], depressive[60,61] and anxiety[62-65] disorders. The premorbid stage starts during the perinatal period and is often asymptomatic and generally associated with preserved functioning (Figure 2). Accumulation of further risk factors from infancy to young adulthood could lead to the emergence of a clinical high-risk stage (Figure 2), characterized by attenuated symptoms that do not meet the diagnostic threshold for mental disorders but are typically associated with some degree of functional impairment. These attenuated symptoms can then progress to a fully symptomatic mental disorder, and then persist into adulthood, especially if treated sub-optimally, leading to a relapsing stage and eventually a chronic stage (Figure 2).

The period from the prenatal/perinatal phase to the onset of the first episode of the disorder may represent the most compelling window of preventive opportunity[7,55]. By integrating the preventive framework within a neurodevelopmentally sensitive clinical staging model, primary prevention (universal, selective and indicated) and promotion of good mental (and physical) health[7] emerge as core strategies to target this critical window (Figure 2).

EVIDENCE SUPPORTING PRIMARY PREVENTION AND MENTAL HEALTH PROMOTION IN YOUNG PEOPLE

This section reviews the evidence supporting indicated, selective and universal preventive interventions and promotion of good mental health, reflecting the in-

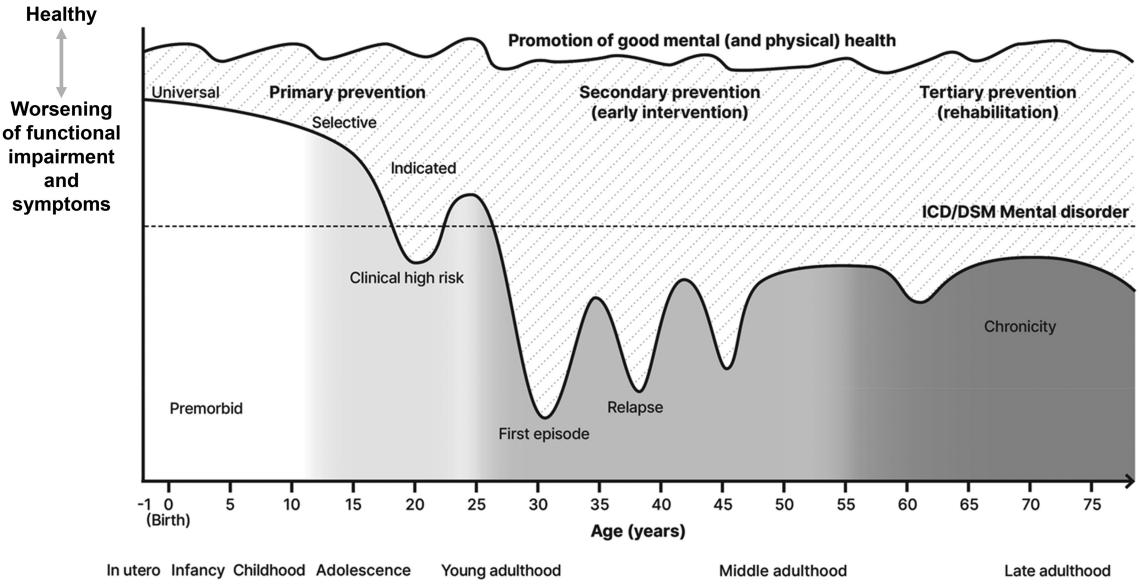

Figure 2 Neurodevelopmental continuum model for prevention of psychosis, bipolar disorder and common mental disorders, and promotion of good mental and physical health

creasing width of these approaches from relatively small subgroups to the wider population (Figure 1).

Indicated preventive interventions

The available evidence supporting indicated preventive interventions for psychotic, bipolar and common mental disorders is summarized in Table 2.

Psychosis

Indicated prevention of psychosis originated in Australia about twenty-five years ago[66] and subsequently gained traction globally, leading to the implementation of specialized services[67] taking care – according to a survey carried out in 2017-2018 – of over than 22,000 young individuals across Western Europe (51.1%), North America (17.0%), East Asia (17.0%), Australia (6.4%), South America (6.4%) and Africa (2.1%)[67]. The consolidation of this paradigm in clinical practice has impacted national[68] and international[69] clinical guidelines and diagnostic manuals (e.g., DSM-5 attenuated psychosis syndrome[70]), although not everywhere[71].

Young (typically 14-35 years old, mean age 21 years[72]) individuals at clinical high risk for psychosis (CHR-P)[73,74] accumulate several risk factors for the disorder[44,75,76], which can lead to functional impairments[77] and the emergence of attenuated psychotic symptoms[78] (which last on average 2 years[72]). Because of these problems, these individuals often seek help[79], including at specialized CHR-P clinical services when available[67,80,81].

Detection of CHR-P individuals is unsystematic and mostly based on referrals made on suspicion of psychosis risk by several agencies and idiosyncratic sampling strategies. This recruitment phase nevertheless leads to substantial risk enrichment in help-seeking samples[82]. Although several screening instruments for CHR-P have been tested, their validation is currently limited[83].

In CHR-P clinics, help-seeking individuals undergo a semi-structured psychometric assessment with validated instruments, which deliver a group-level estimate for predicting psychosis (i.e., at risk vs. not at risk)[74]. The CHR-P criteria are robustly associated with psychosis onset (odds ratio, OR=9.32)[44] within high-risk clinical sam-

Table 2 Level of evidence for available indicated interventions to prevent (reduce the incidence) of psychotic, bipolar and common (depression/anxiety) mental disorders in young people

	Psychotic disorders	Bipolar disorder	Depression/Anxiety disorders
Target	Clinical high risk for psychosis (CHR-P)[72]****	Bipolar at-risk states[97,105]*, bipolar prodrome[103,104]*	Not available
Detection			
Referral, risk enrichment	On suspicion of psychosis risk, 15% at 3 years[82]***	On suspicion of bipolar risk	Screening in schools, universities or primary care[114,115]***
Screening instruments (sensitivity, specificity, positive predictive value, negative predictive value)	Several, but poor validation (67-100%, 39-100%, 24-100%, 58-100%)[83]**	BPSS-AS-P (data not available)[103]*	Some, but none validated (data not available)[114]***
Duration of attenuated symptoms	709 days[72]****	107.9 months[98]***	Not available
Mean age (SD) or range	21 (3.2) years[72]****	16-23 years[103-105]*	18-25 years[113]***
Prognosis			
Assessment instruments (accuracy)	CAARMS[287]***, SIPS[288]***, DSM-5 APS [288]*** (0.90 pooled at 38 months)[74]*** Not recommended outside clinical samples[74]***	BPSS-FP (data not available)[104]*, SIBARS (0.7 at 18 months)[105]* Used in clinical samples only[104,105]*	Not available
Transition risk	17% at 1 year; 22% at 3 years (BLIPS>APS>GRD)[88]***	14% at 1 year[289]*; 23% at 2 years[105]*	Not available
Intervention			
Type of intervention (efficacy)	Needs-based interventions, psychotherapy, pharmacotherapy, combinations (no evidence for superior efficacy in preventing psychosis or improving other outcomes)[93,94]***,[72,251]****	Family-focused therapy (reduced time to recovery, no effect on incidence of bipolar disorder)[106]* Individual psychotherapy (no efficacy on affective symptoms)[107]*	Psychotherapy/psychoeducation (reduced severity of depressive/anxiety symptoms[113,115]***, but not with digital psychoeducation[119]*** and not in humanitarian settings[120]***; no evidence of effect on incidence of depressive/anxiety disorders[113,115]***)

* single study, ** systematic review, *** meta-analysis, **** umbrella review. APS – attenuated psychotic symptoms, BLIPS – brief limited intermittent psychotic symptoms, BPSS-AS-P – Bipolar Prodrome Symptom Scale - Abbreviated Screen for Patients, BPSS-FP – Bipolar Prodrome Symptom Interview and Scale-Full Prospective, CAARMS – Comprehensive Assessment of At Risk Mental States, GRD – genetic risk and deterioration syndrome, SIBARS – Semistructured Interview for Bipolar At Risk States, SIPS – Structured Interview for Psychosis-Risk Syndromes.

ples (but not in the general population[84]), while they cannot predict new cases of bipolar or common mental disorders[85,86].

In CHR-P samples, most (~85%) individuals present with attenuated psychotic symptoms (APS), ~10% with short-lived frank psychotic symptoms (brief and limited intermittent psychotic symptoms, BLIPS), and ~5% with schizotypal traits or a relative affected with psychosis coupled with functional decline (genetic risk and deterioration, GRD)[72]. Since most (68%) individuals with BLIPS also meet ICD-10 criteria for an acute and transient psychotic disorder[87], interventions in CHR-P people extend beyond primary indicated prevention (for APS and GRD) into secondary prevention (for BLIPS). The overall risk of developing psychosis (22% at 3 years) differs across these three subgroups[88].

Transition to psychosis is associated with clinically meaningful real-world outcomes[89] and is modulated by baseline levels of attenuated positive psychotic (OR=2.56) and negative (OR=2.68) symptoms, while good functioning reduces the risk (OR=0.59)[44].

Indicated prevention implemented in CHR-P services (the NICE-recommended intervention is cognitive behavioural therapy[68]) has the potential to ameliorate presenting symptoms, delay or prevent the onset of psychosis, reduce health care access and duration of untreated psychosis (secondary prevention)[55,90]. Furthermore, CHR-P services routinely incorporate comprehensive needs-based interventions focusing on psychosocial, vocational and familial requirements, as well as several public health initiatives such as outreach campaigns in collaboration with the local community (e.g., non-governmental organizations, youth centres, schools, colleges, faith groups; low-income, racial/ethnic, sexual and gender minorities) to foster mental health literacy (e.g., reducing illicit substances use, enhancing self-coping strategies) and promote good mental (e.g., resilience, positive lifestyle behaviours) and physical health[72].

Earlier meta-analyses of randomized controlled trials suggested a significant preventive effect for psychological interventions[91,92]. However, the most updated network meta-analysis[93] found no robust evidence to favour any of these indicated interventions compared to each other or needs-based interventions. A second independent pairwise meta-analysis by the Cochrane group confirmed these findings, concluding that "there was no convincing unbiased, high-quality evidence" to suggest that any type of intervention is more effective than others, including needs-based interventions[94] (another meta-analysis was recently published[95], but used older data than the above-mentioned ones[93,94]).

Bipolar disorder

Indicated prevention in bipolar disorder was developed, following the CHR-P template, only fifteen years ago[96,97], and is rapidly emerging[98-101]. The supporting evidence lags behind that for CHR-P[99,102].

Detection of a symptomatic clinical high risk for bipolar disorder is complicated by its inherent episodicity, long duration and the complex nature and definition of the disorder[98]. Individuals at clinical risk for bipolar disorder are represented by young help-seeking clinical samples[97] (mean age 16-23 years[103-105]), including a subset of CHR-P individuals[105], who present with attenuated bipolar-risk features (which last on average 9 years[98]). Self-administered screening instruments have been developed, but require further validation[103].

With respect to assessment, early manifestations – such as sleep disturbance, anxiety, irritability, cyclothymic features, manic or hypomanic symptoms, and depression – are non-specific[100]. Emerging semi-structured interviews can rate sub-threshold manic, depressive and general symptoms[104] to define high-risk subgroups in clinical samples: sub-threshold mania, depression and cyclothymic features, genetic risk and depression, genetic risk and cyclothymic features, sub-threshold mixed episode, mood swings[105]. The prospective validity of these instruments awaits validation, despite some promising pilot findings[105].

Interventional research is in its infancy. Two randomized controlled trials conducted in young people presenting with genetic risk for (schizo)affective disorder and attenuated affective symptoms suggested a potential beneficial effect of family-focused and cognitive behavioural therapy on time to recovery from attenuated symptoms[106], but no efficacy in terms of reducing the severity of affective symptoms[107] or preventing the onset of bipolar disorder[106].

Common mental disorders

Indicated prevention of depression and anxiety disorders in young people still represents a "blind spot in health care"[108-110] and has been less investigated than selective/universal approaches[111]. There is also some degree of overlap with indicated prevention for bipolar disorder, because subthreshold/frank depressive episodes (especially the atypical phenotype) and cyclothymic features or genetic risk for depression coupled with bipolar-like features are already subsumed in the clinical criteria for bipolar risk[112].

Young people[113] at clinical high risk for depression/anxiety disorders have been detected through psychometric screening for sub-threshold symptoms in schools, universities or primary care[114,115], typically following selective/universal screening[116]. However, results do not suggest that such screening is ready for wider use. Beyond these attempts, there are no established clinical high-risk criteria to assess young people with an increased risk of depression (without bipolar risk features) or anxiety disorders and predict their outcomes.

Early meta-analyses not focusing on young individuals showed that indicated psychological interventions, generally based on cognitive behavioural therapy, can reduce the incidence of depression[114,117], and that these interventions can be effectively delivered digitally in middle-aged adults[118]. However, the most recent meta-analysis focusing on young people with baseline sub-threshold depression (along with selective/universal approaches) found that none of the included psychological intervention studies measured the incidence of emerging depression[113]. Another recent meta-analysis confirmed that there is no evidence favouring digital psychoeducation over no intervention to

improve depressive symptoms in young people[119].

Meta-regression analyses showed that psychological/psychoeducational interventions might be effective in reducing the severity of some anxiety symptoms in young people, but no conclusion could be drawn concerning prevention of the onset of anxiety disorders[115]. A meta-analysis showed that indicated psychological/social interventions are not effective to prevent anxiety/depression in people living in low- and middle-income countries affected by humanitarian crises[120].

Selective preventive interventions

Selective preventive interventions in the premorbid stage of psychotic, bipolar and common mental disorders (summarized in Table 3) would require screening and reducing the exposures to identified detrimental factors in at-risk groups before symptoms and help-seeking behaviour manifest[76].

This approach would require robust aetiopathological knowledge of the association between specific genetic and non-genetic factors and incidence of these disorders (and effective interventions). However, comprehensive explanatory pathophysiology is not established in psychiatry, and no singular putative causal factor fully meets Bradford Hill criteria, so that current diagnostic manuals (ICD-11/DSM-5) refer to mental syndromes (i.e., disorders) and not pathophysiological processes (i.e., diseases).

Genetic factors

Many genetic variants have been identified that modulate the risk for psychotic,

Table 3 Level of evidence for at-risk group exposures and available selective interventions to prevent (reduce the incidence) of psychotic, bipolar and common (depression/anxiety) mental disorders in young people

	Psychotic disorders	Bipolar disorder	Depression/Anxiety disorders
At-risk group exposures (association with the disorder)	**Genetic risk/protective factors:** 22q11.2 deletion syndrome (prevalence 10-41%[132]*, risk 37% at 32 months[135]*) Offspring (RR=7.54)[121]*** Twins (monozygotic concordance rate 40%)[123]* First-degree relatives (one proband: OR=7.69; two probands: OR=11.11)[127]*** **Non-genetic risk/protective factors:** Black-Caribbean ethnicity in England (OR=4.87)[44]**** Ethnic minority in low ethnic density area (OR=3.71)[44]**** Second-generation immigrants (OR=1.68)[44]**** Trait anhedonia (OR=4.41)[44]**** Minor physical anomalies (OR=5.30)[44]**** Premorbid IQ (OR=0.47)[44]**** Olfactory identification ability (OR=0.19)[44]**** Several prenatal/perinatal factors (OR=0.86 to 3.05)[150]*** Physical activity (OR=0.728)[235]**** Smoking (OR=1.99)[235]**** **Peripheral biomarkers** Decreased pyridoxal (vitamin B6) levels (data not available)[147]****	**Genetic risk/protective factors:** Offspring (RR=4.06)[121]*** Twins (monozygotic concordance rate 45%)[124]* First-degree relatives (one proband: RR=6.10, two probands: RR=29.1)[128]* **Non-genetic risk/protective factors:** Irritable bowel syndrome (OR=2.48)[144]**** Childhood adversity (OR=2.86)[144] **** Physical activity (OR=0.49)[235]**** Smoking (OR=1.46)[235]**** Poor sleep (OR=1.79)[235]**** **Peripheral risk/protective biomarkers:** Elevated awakening cortisol levels (g=0.25)[147]****	**Genetic risk/protective factors:** Offspring (depression: RR=2.38[121]***; anxiety: RR=1.76 [122]***) Twins (monozygotic concordance rate – depression: 46%[126]*; anxiety: 13-73%[125]*) First-degree relatives (anxiety: OR=4.1-6.1[129]*; depression: one proband OR=2.14, two probands OR=3.23[130]***) **Non-genetic risk/protective factors:** Sedentary behaviour (RR=1.25)[145]**** Sexual dysfunction (OR=2.71)[145]**** Four or five metabolic risk factors (OR=2.06)[145]**** Obesity (OR=1.35)[145]**** Job strain (OR=1.77)[145]**** Physical abuse in childhood (OR=1.98)[145]**** Early physical trauma (OR=2.59)[146]**** Physical activity (OR=0.837)[235]**** Smoking (OR=1.73)[235]**** Healthy diet (OR=0.77)[235]**** Poor sleep (OR=2.27)[235]****
Type of intervention (efficacy)	Screening for family history of psychotic disorder (data not available)[132]* Screening pregnant/postnatal women for emerging psychopathology (data not available)[148]***	Psychoeducation for young people at risk (improved affective symptoms but no evidence of effect on incidence of bipolar disorder)[155]***	Screening for family history of depression and psychoeducation (improved depressive symptoms and reduced incidence of depression in offspring)[136]*** Screening for post-partum depression and psychoeducation/psychotherapy (inconclusive evidence)[152]*** Psychological interventions in women disclosing partner violence (improved anxiety but not depression)[153]*** Psychological/psychoeducation (improved anxiety symptoms[115]***, but not as school-based interventions[156]*** and not in humanitarian settings[120]***; no evidence of effect in preventing depression/anxiety disorders[115]***) Physical exercise in at-risk youths (reduced severity of depression[157]*** and incidence of anxiety[174]***)
	Behavioural counselling to prevent illicit substance use in at-risk adolescents and young adults (no evidence of efficacy)[154]***		

* single study, ** systematic review, *** meta-analysis, **** umbrella review. OR – odds ratio, RR – risk ratio

bipolar or common mental disorders, but almost all of them have very small, and thus clinically unclear, effects for selective screening. Polygenic risk scores have been developed to overcome these limitations by analyzing genetic variants *en masse*[48], but the variance explained is still too small for implementation in selective prevention and does not provide singular neurobiological targets.

For example, offspring of patients affected with psychosis, bipolar disorder or depression have a greater risk of developing these disorders (32% by adulthood)[121,122]. Monozygotic twins[123-126] and first-degree relatives (depending on the number of probands)[127-130] also have an increased likelihood of developing these disorders. However, only 17.4% of the association between family history of psychosis and the disorder is mediated through a modelled polygenic risk score[131]. The only molecular risk factor for psychosis that may have a preventive relevance is the 22q11.2 deletion syndrome, which is characterized by high rates of schizophrenia (prevalence from 10% in adolescents to 41% in young adults)[132].

Overall, familial vulnerability (along with 22q11.2 deletion syndrome) represents the most implementable target for selective screening intervention in health care[133]. It is more established for psychosis[134], but it is emerging for bipolar disorder. One possible intervention could be monitoring and psychometric assessment for a CHR-P/bipolar-risk state when symptoms or functional disability develop[135].

The associated preventive capacity is, however, limited: while a meta-analysis found that selective psychoeducational interventions may have a small effect on reducing the severity and incidence of depression in the offspring of patients[136], the preventive efficacy of other psychosocial interventions in young individuals with a familial vulnerability for psychotic[137], bipolar[138] or anxiety disorders is currently unknown.

Non-genetic factors

Similarly, non-genetic factors have not yet entered selective screening[139,140]. This situation is mostly due to the intrinsic complexity of the psyche itself[141], and conflicting research findings that are characterized by several biases such as high heterogeneity, excess significance, selective reporting of statistically significant (i.e., "positive") results and no adjustment for multiple confounders[142,143]. Table 3 lists non-genetic factors, along with their meta-analytic strength of association (according to established criteria to classify the evidence) with psychotic[44], bipolar[144], depressive[145] and anxiety[146] disorders.

Among 733,316 measurements on 162 different peripheral biomarkers for psychosis, bipolar disorder and depression, only two were found to be reliably associated with these disorders[147](see Table 3). Studies targeting inflammatory biomarkers using anti-inflammatory therapies like aspirin[148] or targeting individual nutrients such as vitamin D[149] to prevent depression have not turned out to be effective approaches, at least in adults, dampening hopes in youth[133].

Within risk/protective factors listed in Table 3 (their distinction from biomarkers may be challenging without clear pathophysiological knowledge), the majority exert their role before the age of 25 years, and some are potentially modifiable in vulnerable groups. For example, the evidence concerning several prenatal/perinatal risk factors laid the rationale for screening pregnant/postnatal women for emerging psychopathology in order to detect an incipient risk of psychosis or post-partum depression[150,151]. However, the risk may not be high enough to make such screening clinically useful. Furthermore, a meta-analysis investigating psychological/ psychoeducational selective interventions (along with universal/indicated ones) to prevent post-partum depression in pregnant/postnatal women[151] found considerable cost-effectiveness uncertainty[152].

Women disclosing current or recent intimate partner violence exposure represent another vulnerable group. A meta-analysis found that selective psychological interventions can reduce their anxiety (but not depression) even in in low/middle-income countries[153].

Another potentially modifiable risk factor selectively targeted across psychotic, bipolar and common mental disorders has been the initiation of illicit and non-medical drug use among adolescents and young adults. However, a recent meta-analysis by the US Preventive Service Task Force found no evidence to favour selective (as well as population-level/universal) behavioural counselling[154].

Selective psychological/social interventions are not effective to prevent anxiety/depression in humanitarian settings[120], and there is scarce preventive research in other vulnerable subgroups such as racial/ethnic, sexual and gender minorities.

Selective approaches have also been tested in various subgroups of at-risk youths. A recent meta-analysis reviewed the efficacy of selective (along with universal) interventions for young people (across different settings), finding that psychoeducation may be the most effective preventive intervention for improving affective symptoms (Hedges' g=0.6), but there was no efficacy on the incidence of mood disorders[155]. Another meta-regression analysis showed that selective (as well as universal) psychological/psychoeducational interventions delivered across different settings (e.g., community schools and colleges, primary care clinics) might be effective in reducing some anxiety symptoms in young people, although findings were inconclusive regarding prevention of depression/anxiety disorders[115]. Recent sensitivity (network) meta-analyses found little evidence that selective (and universal/indicated) school-based educational interventions are effective for the prevention of common mental disorders in young people[156].

Importantly, a recent umbrella review has documented that an exercise intervention may be effective in reducing depressive symptoms in at-risk youths[157]. However, even the possible benefits at the level of symptoms may be due to selective reporting and other biases for what are largely subjective outcomes in unmasked trials.

Universal preventive interventions

As shown in Figure 1, universal preventive strategies (summarized in Table 4)

Table 4 Level of evidence for population-level exposures and available universal interventions to prevent (reduce the incidence) of psychotic, bipolar and common (depression/anxiety) mental disorders in young people

	Psychotic disorders	Bipolar disorder	Depression/Anxiety disorders
Population-level exposures (association with the disorder)	**Surrogate markers**: psychotic experiences (risk of psychosis 0.5-1 per year)[290]***	**Surrogate markers**: K6/10 (data not available)[163]*	**Surrogate markers**: K6/10 (data not available)[163]*
	Neurodevelopmental biomarkers (data not available)[164,165,167]*		
	Social determinants of mental disorders (data not available)[173]**** Demographic (community diversity, population density, longevity, survival) Economic (economic recessions, economic inequalities, macroeconomic policy) Neighbourhood (infrastructure, neighbourhood deprivation, built environment settings) Environmental events (natural/industrial disasters, war or conflict, climate change, forced migration) Social/cultural (community social capital, social stability, culture)		
Type of intervention (efficacy)	Screening for psychotic experiences (data not available)[161]*	Screening for bipolar experiences (data not available)[163]*	Screening for depressive/anxiety experiences (data not available)[163]*
	Perinatal phosphatidylcholine (modulated biomarkers of neonatal brain development[164]*; fewer attention problems and less social withdrawal[165]*); perinatal folate acid (improved executive functioning)[167]*; vitamin D, polyunsaturated fatty acids (inconclusive evidence)[166]**	Psychoeducation for young people (improved affective symptoms but no evidence of effect on incidence of bipolar disorder)[155]***	Psychological/psychoeducation (improved anxiety symptoms[115]***, but not as school-based interventions[156]*** and not in humanitarian settings[120]***; no evidence on preventing depression/anxiety disorders[115]***) Public health strategies on school climate (improved depressive symptoms)[171]* Physical exercise (reduced incidence of anxiety disorders)[174]***
	Reduction of gender-based violence, child maltreatment, racial discrimination and xenophobia; basic income grants and improved employment; safe neighbourhoods; reductions in violence; early response to environmental events; action on protecting vulnerable ecosystems; improved education (data not available)[173]****		
	Behavioural counselling to prevent illicit substance use in adolescents and young adults (no evidence of efficacy)[154]***		

* single study, ** systematic review, *** meta-analysis, **** umbrella review. K6/10 – Kessler Distress Scale 6- or 10-item

would theoretically allow a population-wide reduction in incidence/burden of psychosis, bipolar and common mental disorders in young people, producing wider societal-level benefits compared to indicated/selective measures.

Universal strategies may take the form of a safe intervention that: a) decreases exposures to population-level risk factors (most of the at-risk group exposures listed in Table 3 could be, in principle, considered as well for population-level universal approaches) and/or b) increases exposure to population-level protective factors. However, pathophysiological knowledge is limited, and there is a lack of methods to readily assess the efficiency of such interventions.

In line with Gordon's observations, psychosis and bipolar disorder are characterized by a low incidence and long latency between exposures and the manifestation of the disorders (the latter point also applies to common mental disorders). Demonstrating an impact on the incidence of these disorders would be, if at all feasible, long and expensive[158].

Decreasing exposures to population-level risk factors

A possible avenue may be to use surrogate population-level markers that may predict the effect of universal interventions on the incidence of disorders and that are convenient to measure. For example, "psychotic experiences"[159] are relatively frequent at the population level (prevalence about 8% in young adults aged 24[160]) and can be measured through self-administered questionnaires (e.g., Prodromal Questionnaire, PQ)[161]. These mostly transitory sub-threshold manifestations are not to be conflated with clinical psychotic symptoms (see below)[162], but could represent a potential surrogate marker of psychosis (risk of psychosis: 0.5-1% per year[160]). Other self-administered instruments, such as the Kessler Psychological Distress Scale (6 or 10 items, K6/10)[163], could theoretically be used as surrogate markers for bipolar, depressive and anxiety disorders. However, to date, there is no preventive capacity associated with these surrogate markers.

Similarly, neurodevelopmental surrogate biomarkers have been used to test dietary phosphatidylcholine supplementation in healthy pregnant women[164]. Phosphatidylcholine is an agonist at alpha-7 nicotinic receptors, which are involved in the final maturation of GABA inhibitory synapses before birth, and have been implicated in schizophrenia[164]. A first randomized controlled trial confirmed the effect of perinatal phosphatidylcholine on an electrophysiological biomarker of foetal development[164]. A subsequent study demonstrated that, at 40 months, phosphatidylcholine impacted neurocognitive biomarkers, leading to fewer attention problems and less social withdrawal compared with the placebo group, thus potentially altering the risk of later development of psychosis[165].

Another dietary intervention involved folic acid supplementation in pregnancy (folate is important in neurogenesis, cell growth and proliferation, and myelination), which has become one of the most important public health advances in medi-

cine[166]. A randomized controlled trial demonstrated that folate supplementation could improve some neurocognitive biomarkers in children 8.5 years later[167]. Other compounds for use in pregnancy (vitamin D[168], polyunsaturated fatty acids[166]) have been suggested, but no randomized controlled trials have been conducted, and the overall evidence is inconclusive[166].

Several other compounds have demonstrated hints of efficacy on experimental neurodevelopmental biomarkers (e.g., neonatal N-acetylcysteine[62], sulphoraphane[169], modulation of microbiota[170]) and are under investigation in humans (not listed in Table 3). However, these surrogate markers have not been well validated, and thus it is unknown whether they would indeed translate to preventive benefits. Furthermore, it is important to have fully preregistered protocols, including details on which biomarkers will be collected and how/when they will be analyzed. The large number of markers and analytical options allows for a situation where spurious "positive" results may emerge/be more likely published.

Beyond surrogate markers, universal psychoeducation and psychological interventions [115,155,156] have been frequently tested (blended with selective interventions, Table 3) for young people. Psychological interventions may improve affective symptoms[155], while psychotherapy/psychoeducation may improve some anxiety symptoms[115] (but not as school-based education intervention[156]). Multi-component public health and youth engagement strategies impacting the overall school climate (rather than individual behaviour change) may improve depressive symptoms (along with physical health outcomes)[171,172]. However, there is no evidence that they can impact the incidence of depression/anxiety disorders[115]. As noted above, universal interventions were not effective to prevent illicit substance use in the general adolescent and young adult population[154], or to prevent common mental disorders in humanitarian settings[120].

To date, the most established population-level exposures encompass social determinants of mental disorders, which have become the cornerstone of public health prevention. A large umbrella review has summarized about 300 (mostly observational) papers on social determinants of psychotic, bipolar and common mental disorders, and empirically linked them with the Sustainable Development Goals promoted by the United Nations Member States in 2015 (demographic, economic, neighbourhood, environmental events, social and cultural domains)[173]. For example, there is strong evidence that adverse social and economic circumstances – including poverty, income inequality, interpersonal and collective violence, and forced migration – are key risk determinants of psychotic disorders[173].

The umbrella review identified several interventions that lie at the interface between universal, primordial and promotion approaches and could potentially lead to high benefit for young people: reduction of gender-based violence, child maltreatment, racial discrimination and xenophobia, basic income grants and improved employment, safe neighbourhoods, reductions in violence, early response to environmental events, action on protecting vulnerable ecosystems, and improved education[173]. However, the review acknowledged that future trials should demonstrate the direct effect of these interventions on psychotic, bipolar or common mental disorders; furthermore, many implementation challenges remain unresolved[173].

Increasing exposures to population-level protective factors

Current evidence is mostly limited to the promotion of good mental health (reviewed below). Other approaches have focused on universal physical exercise interventions in young people, to foster resilience and additionally relieve the associated physical health burden. A recent umbrella review has demonstrated that an exercise intervention may be potentially effective in reducing the incidence of anxiety[174] in the general young population. Universal exercise interventions have also been suggested for psychotic[175] and bipolar[176] disorder. Interventions promoting positive lifestyle behaviours are under development (see below). However, there is not yet solid evidence demonstrating that these interventions can prevent psychotic, bipolar or common mental disorders (see below).

Promotion of good mental health

Promotion of good mental health (not summarized in Tables 2-4) has received less research attention than prevention of mental disorders, mostly because operationalization of outcomes have been fragmented[41]. Mental health promotion is also highly sensitive to different systems, cultures or clinical practices that differ in values. However, core domains of good mental health have been empirically proposed[177], encompassing mental health literacy, attitude towards mental disorders, self-perceptions and values, cognitive skills, academic/occupational performance, emotions, behaviours, self-management strategies, social skills, family and significant relationships, physical health, sexual health, meaning of life, and quality of life[41].

The consistency and magnitude of available interventions to promote good mental health in young people are similarly patchy and conflicting, comprising psychoeducation (including parent training)[178,179], psychotherapy[180,181], and less frequently physical therapy[182], pet[183] or art[184] therapy.

A meta-analysis appraised the efficacy of these interventions aimed to promote good mental health in asymptomatic young people[185]. Compared to controls, available interventions significantly improved mental health literacy (Hedges' g=0.685), emotions (g=0.541), self-perceptions and values (g=0.490), quality of life (g=0.457), cognitive skills (g=0.428), social skills (g=0.371), physical health (g=0.285), sexual health (g=0.257), academic/occupational performance (g=0.211) and attitude towards mental disorders (g=0.177)[185]. Another recent umbrella review showed that positive psychology could increase subjective well-being[186]. Although several interventions could be effective, evidence was of modest quality, and it is unknown whether these interventions can later impact the incidence of psychotic, bipolar or common mental disorders.

FUTURE DIRECTIONS OF RESEARCH AND PRACTICE

In this section, we integrate the conceptual frameworks with the evidence reviewed and suggest ten core ways toward advancing research and practice to prevent psychotic, bipolar and common mental disorders in young people.

Universal or targeted? Integrating preventive frameworks

An intense debate has lately centred on the antithesis between targeted and universal interventions for young people. Some authors[187] have split the field into proponents[188-190], opponents[191-193], and those with ambivalent attitudes[194] towards targeted interventions. A frequent criticism is that indicated prevention implemented in CHR-P clinics should be replaced by universal/public health approaches, aimed for example to decrease cannabis use (an environmental risk factor for psychosis) in young people[195]. Similar criticisms are emerging for the indicated prevention of clinical high-risk states for bipolar disorder[196,197]. The overarching supporting argument is that targeted interventions represent a "prevention paradox"[187], because they can only benefit a small minority of young people[198].

It is true that CHR-P clinics can currently detect only a minority of individuals who will later develop psychosis[199] (similarly, early intervention services can only detect about half of first episode cases[200]), but research innovations to overcome this limitation are under development[198,201]. Notably, this criticism overlooks the fundamental conceptual point illustrated in Figure 1: targeted approaches are expected *a priori* to target the tip of the iceberg of the population-level risk, and are thus complementary and not antithetical to universal approaches. Furthermore, mainstreaming universal approaches to reduce cannabis abuse holds only theoretical foundation, because these approaches are not empirically effective in children, adolescents and young adults[154].

Future research and clinical practice should better incorporate the continuum model for preventive psychiatry illustrated in Figure 2, which integrates universal, selective and indicated approaches to synergistically and complementarily maximize their efficiency in young people, and indeed across the age spectrum. For example, school-based interventions to prevent anxiety and depression in children and young people are conceived as multilevel, systems-based interventions[156] that encompass different modalities. Another example concerns the quest for effective suicide prevention initiatives in young people, where no single strategy clearly stands above the others, and combinations of individual- and population-level strategies have been recommended[202]. A further example may be the implementation of a stepped or sequential assessment framework encompassing face-to-face CHR-P or bipolar-risk assessment (indicated prevention) following universal screening with self-assessment instruments (e.g., PQ, K6/10)[203], and the enhancement of public health approaches already partially implemented by CHR-P services in the local community. Available meta-analyses show that targeted and universal interventions can be blended together in young people to help preventing postnatal depression[152] or anxiety[115].

In line with these arguments, the Lancet Commission on Global Mental Health called for a joint global initiative on preventive psychiatry integrating public health/universal and targeted approaches[173]. However, if single interventions are not effective, it is yet unclear how exactly their combination could be optimally effective.

Advancing multivariable, transdiagnostic, multi-endpoint epidemiological knowledge

As noted by Leavell and Clark[27], robust genetic and environmental epidemiological knowledge is required to inform evidence-based preventive approaches. We have demonstrated above that this knowledge is currently limited, and several advancements are needed.

To date, non-genetic factors have been mostly measured in univariate analyses that cannot control for their intercorrelation. Future epidemiological studies are required to augment polygenic risk prediction by collecting multiple non-genetic exposures in the same individuals, using poly-environmental risk scores (e.g., psychosis poly-risk score, PPS) recently developed[204], and exploring their interaction with lifestyle behaviours (see below).

Environmental exposures can be measured with digital health technologies (electronic medical records, mobile apps)[205], but pose more challenges to measure massively: for example, measurement error, missing data and selection biases may be prominent, and operational definitions of environmental exposures may vary across and even within datasets. Collaborative harmonization efforts should mitigate these obstacles and integrate polygenetic and poly-environmental information to better map the complex pathophysiology of psychotic, bipolar and common mental disorders.

Another area of future research is the identification of protective and resilience factors. To date, the disease-centric model of research has inhibited the investigation of resilience factors that predict good outcomes (and that, therefore, cannot simply be defined as the inverse of risk factors). Shared definitions of good outcomes should also be developed, in particular with respect to promotion of good mental health, which is currently too fragmented. For example, in the CHR-P field, there is a current refocus on good outcomes beyond psychosis onset (e.g., functional status, remission, quality of life[206]). Importantly, these outcomes hold transdiagnostic potential to accommodate multi-endpoint numerators across psychotic, bipolar and common mental disorders (as well as across physical health disorders) that are essential to justify the denominator of preventive (universal/selective/indicated) effort and cost. For example, social functioning is a shared domain across schizophrenia, depression and neurodegenerative disorders such as Alzheimer's disease[207].

Transdiagnostic approaches have been suggested to complement current psychiatric nosography[208], which is intrinsically limited, in particular in young people[209,210], by integrating clinical staging models and optimizing preventive efforts. However, to date, transdiagnostic approaches have been limited by several methodological

caveats that should be addressed by future research.

First, there are frequently reporting inconsistencies (e.g., definition of the gold-standard DSM/ICD diagnoses, outcome measures, and type of transdiagnostic approach) and low quality of studies, with few findings externally replicated[211]. Future studies could use the TRANSD recommendations, that may help improving the reporting of transdiagnostic research[212]. Second, while psychotic, bipolar and common mental disorders exhibit both multifinality (the same aetiological agents can result in different mental health disorders) and equifinality (multiple agents can lead to the same disorder), knowledge into shared risk/protective factors (Table 3) is still limited. The latter are mostly limited to social determinants of mental disorders, childhood adversity and familial vulnerability (and physical health/lifestyle behaviours discussed below). For example, risk of mood disorders is significantly increased among offspring of parents with schizophrenia (relative risk, RR=1.62), while the risk of schizophrenia is significantly increased in offspring of parents with bipolar disorder (RR=6.42)[121]. However, there is also evidence for diagnostic specificity: machine learning reclassification studies demonstrated a distinction between schizophrenia and mood disorders[213]; treatment requirements and outcomes also differ[55]. Similarly, while early neurocognitive functioning has been suggested as a promising transdiagnostic biomarker[214], some studies suggest that it is more specific to psychosis than to common mental disorders[215].

No convincing evidence supports the existence of a truly transdiagnostic biomarker[147]. Evidence supporting a transdiagnostic clinical staging model that cuts across psychotic, bipolar and common mental disorders[216,217] is similarly limited to a few studies[218], with scarce empirical validation[219]. There are also concerns that the natural course of bipolar[220] and depressive[221] disorders does not necessarily or consistently follow a clinical staging model. However, future research in this field is expected. For example, pervasively reduced neocortical thickness was recently found to be shared across psychotic and common mental disorders, representing a potentially transdiagnostic marker of general psychopathology (termed "p factor")[222]. Thus, universal prevention of all these disorders may, in theory, overlap greatly.

Synergically preventing common and infrequent mental disorders

Refined transdiagnostic preventive approaches could facilitate targeting more prevalent common mental disorders to synergistically prevent the more infrequent psychotic and bipolar disorders, whose incidence may have been progressively declining[198], although not everywhere[223]. Notably, the notion that psychotic symptoms are not infrequent but rather common among young individuals is caused by the trivialization of their contextual significance and operationalization, resulting in non-specificity[224]. For example, surrogate markers, such as psychotic experiences, are frequently conflated with the APS of the CHR-P state[225] (without explaining what makes a symptom truly "psychotic"[225]). Unlike self-assessed psychotic experiences, APS require detection by an experienced and trained clinician to distinguish pathological from non-pathological phenomena[226], and they are neither common features nor distributed continuously in the general population, accounting for only 0.3% of individuals[227].

Overall, 66% of the incidence of clinical psychosis in the population is accounted for by preceding mood disorders[187]. This finding is not new: Conrad's phenomenological clinical-stage model of psychosis onset[228] established early mood dysregulation as the underlying core feature. At the same time, a substantial proportion (37%) of the population-level incidence of psychosis is explained by the CHR-P stage, independently from mood disorders[187]. The majority of CHR-P individuals have comorbid non-psychotic mental disorders (which do not increase the risk for psychosis but tend to persist over time[229]), mostly common mental disorders: 41% depressive disorders and 15% anxiety disorders[72,230]. These findings demonstrate that the CHR-P state is already partially transdiagnostic (some cases of psychosis may originate outside it[198]), potentially capturing a psychosis dimension that emerges from anxiety or depressive disorders.

These considerations may inform the future configuration of preventive health care services. Conventional mental health services are not generally engineered to detect and prevent psychosis onset from anxiety or depressive disorders, as claimed by some authors[195,231]. Young people at risk for psychosis or bipolar disorder typically present with blurred and unspecific symptoms that are too mild to fulfil the entry criteria of conventional mental health services. An alternative approach may be to enhance the transdiagnostic potential of current preventive (e.g., CHR-P) services, implementing the detection of emerging bipolar and depressive (and anxiety) disorders and better integrating them with primary care to facilitate the prevention of physical health burden[3]. Such initiatives are emerging[232].

Furthermore, the needs-based support and the public health campaigns routinely offered by CHR-P services could be expanded to better address the social determinants of psychotic and common mental disorders at the population level[233]. CHR-P services also represent a successful global template for transitional mental health services and applied clinical research[232] that fully integrate between adolescence and young adulthood[67]. This overcomes the historical paediatric-adult bifurcation, in which children and adolescent mental health services are usually cut at the age of 15 or 18 (the transitional period), when young people are most liable to mental disorders. This current two-tier clinical research system is developmentally inappropriate (psychopathology and brain maturation see no abrupt transition among adolescence and early adulthood) to advance preventive psychiatry for young individuals, and leads many of them to fall through cracks.

To overcome these issues, broader youth-friendly mental health services that ensure low-threshold entry into pathways to care are currently advocated, but solid effectiveness evidence is still needed[3], and caution is advised to not over-pathologize the potentially non-specific or transient occur-

rence of common mental health problems in young people[234].

Preventing physical and mental health burden together

Despite the interconnectedness between mental and physical health problems (e.g., several shared risk factors)[42], the severe physical health burden associated with emerging mental disorders in young people is not yet systematically incorporated in preventive approaches. A recent umbrella review of the top-tier evidence has demonstrated that some lifestyle behaviours – such as low levels of physical activity, sleep disturbances, adverse dietary patterns, and tobacco smoking – are associated with an increased risk of psychotic, bipolar and depressive/anxiety disorders[235]. Future research could employ the TRANSD criteria to ascertain the transdiagnostic potential of lifestyle behaviours: for example, poor sleep is associated with bipolar disorder and depression/anxiety but not psychosis, while poor diet is associated with depressive disorders only[235].

Prevention for these risk factors is currently driven by initiatives siloed in other non-communicable disorders, such as cancer and obesity. However, these factors are also common across physical disorders: pursuing physical health and positive lifestyle behaviours is a tantalizing population-level strategy for universal prevention, making sense for concurrently reducing the risk of many other physical diseases[42]. The numerator of cost and risk is thus offset by a denominator of multiple psychiatric and physical disease endpoints[236].

Experience from smoking prevention suggests that similar public health population-level interventions are far more effective than individual-level approaches. However, current preventive capacity is limited[235] (e.g., selective/universal physical exercise may prevent common mental disorders[157,174], but these findings need to be consolidated), and future research should establish the most effective physical health/lifestyle interventions in young people.

Implementing stratified/personalized prognosis

Modern advancements in the field of individualized prediction modelling aim to consolidate stratified (tailored to subgroups) or precision (tailored to the individual subject) preventive psychiatry in young people[237]. Several individualized risk prediction models for forecasting the onset of psychosis, bipolar and depression/anxiety in young people[238] (see Table 5) have been externally validated in terms of prognostic accuracy, which is an essential step to address the extent to which predictions can be generalized to the data from plausibly related settings.

Despite these progresses, prognostic accuracy for most of these models is not sufficient to prove clinical utility and implementability across different scenarios[239]. In fact, a systematic review has found that only about 5% of the total pool of risk prediction models published in psychiatry is externally validated, and that only 0.2% are being considered for implementation (most models may not cross the implementation threshold, as they would not improve outcomes), highlighting a profound replication and translational gap[240]. For example, across all prognostic models reviewed in Table 5, only the transdiagnostic risk calculator has been piloted for real-world implementation in clinical practice[241].

To overcome these limitations, the next generation of research should prioritize further refinements and replications of existing algorithms. Given their complexity, the weighting of the predictors may vary considerably with context (e.g., adolescent vs. young adult, geographic contexts). For those models that may reach higher levels of proof for clinical utility, the implementation pathway is a perilous journey undermined by several obstacles, related to individuals involved (e.g., making their data available or accepting the outputs of the risk calculators), clinicians (e.g., adherence to the recommendations made by prediction models, communicating risks), providers (e.g., confidentiality of data, interpretability of outputs) and funders/organizations (implementing standard prediction procedures)[238].

Implementation science itself is contested and complex, and there is no solid general implementation framework and practical guidance for preventive psychiatry. The next generation of research in this field should develop a coherent and pragmatic implementation framework and associated international infrastructures[177].

The latter necessitate collaborative data sharing efforts and international, large-scale, harmonized and multimodal (e.g., psychopathological, neurobiological, neurocognitive) clinical research databases, integrated with digital technologies (e.g., electronic medical records), as well as specific support from funders and stakeholders[237]. Harmonization is likely to be most successful for future datasets that are prospectively collected. However, efforts should also be made to standardize (to the extent possible) existing datasets that already include large amounts of data.

Establishing evidence-based preventive interventions

Another area of future research is the development of evidence-based preventive interventions to overcome the current divergence between "political" literature, which tends to deliver an overoptimistic message, and evidence-based literature, which emphasizes methodological biases and the inconsistency of the available findings. For example, two independent meta-analyses found no evidence (as opposed to evidence of absence) to favour specific interventions for preventing psychosis in CHR-P individuals[93,94]. Without providing any meta-analytical counter-evidence, some authors have complained that evidence needs to be contextualized, because the "potential for improvement is a key message for patients, families, and practitioners"[242]. The Cochrane authors replied that their meta-analysis was not a criticism of the valuable preventive aims, but only scientific grading of the available evidence[243].

Along these lines, Caplan first noted that, although there was little empirical evidence to support primary prevention and little knowledge of the aetiology of mental disorders, "there appears to be validity to

Table 5 Externally validated, individualized prognostic models for forecasting the onset of psychotic, bipolar (BD), and major depressive (MD)/generalized anxiety (GAD) disorders in young people

	Outcome	Predictors	Development sample size (mean age, location); performance (measure)	External validation sample size (mean age, location); performance (measure)
Cannon et al[291]	Psychosis onset in CHR-P	Age, family history, unusual thoughts and suspiciousness, lower verbal learning and memory performance, slower speed of processing, decline in social functioning	596 (18.5, US); 0.71 (C-index)[291]	176 (16.6, US); 0.79 (AUC)[292] 199 (19.1, China); 0.63 (AUC)[293] 68 (18.59, US); 0.71 (AUC)[294]
Zhang et al[295]	Psychosis onset in CHR-P	Functional decline, positive symptoms, negative symptoms, general symptoms	349 (20.4, China); 0.744 (AUC)[295]	100 (age not available, China); 0.804 (AUC)[295] 68 (18.59, US); 0.65 (AUC)[294]
Fusar-Poli et al[199]	Transdiagnostic psychosis onset in secondary mental health care patients	Age, sex, ethnicity, age by gender, ICD-10 index diagnosis	33,820 (34.4, UK); 0.80 (C-index)[199]	54,716 (32.0, UK); 0.79 (C-index)[199] 13,702 (40.9, UK); 0.73 (C-index)[296] 33,710 (22.7, UK), 0.79 (C-index)[297] 2,430,333 (34.2, US); 0.68 (C-index)[298]
		Refined version including 14 symptoms extracted with natural language processing	28,297 (34.8, UK); 0.86 (C-index)[299]	63,854 (33); 0.85 (C-index)[299]
King et al[300]	MD onset in primary care	Age, sex, country educational status, difficulties in work, history of depression in first-degree relatives, experience of discrimination, lifetime major depression episode, mental quality of life, physical quality of life	5,216 (48.9, UK, Spain, Slovenia, Portugal, The Netherlands); 0.79 (C-index)[300]	1,732 (47.0, Chile); 0.71(C-index)[300] 29,621 (43.8 US); 0.71(AUC)[301]
King et al[302]	GAD and MD onset in primary care	Age, sex, country, difficulties in paid and unpaid work, history of depression in first-degree relatives, follow-up period, lifetime major depression episode, mental quality of life, physical quality of life	4,905 (age not available, UK, Spain, Slovenia, Portugal); 0.75 (C-index)[302]	5,140 (age not available, Netherlands, Estonia, Chile); 0.71-0.81 (C-index)[302] 24,626 (age not available, US); 0.62 (AUC)[303]
Birmhaer et al[304]	Onset of BD-I or BD-II from sub-threshold BD symptoms	Age, sex, mania, depression, anxiety, emotional lability, functioning, duration of BD, ethnicity, family history of BD	140 (11.9, US); 0.71 (AUC)[304]	58 (11.9, US); 0.75 (AUC)[304]
Raket et al[201]	Onset of psychosis (schizophrenia) from primary and secondary care	Demographics and dynamic medical events (diagnoses, prescriptions, procedures, encounters and admissions, observations, and laboratory test results)	102,030 (42, US); 0.856 (AUC)[201]	4,770 (age not available, US); 0.799 (AUC)[201]

CHR-P – clinical high risk for psychosis, AUC – area under the curve

the assumptions"[244] of primary prevention, which ought not to be suspended while awaiting the results of evidence-based medicine. This tension extends beyond the CHR-P paradigm: other evidence-based syntheses have disconfirmed initial promising findings relating to the indicated/selective/universal prevention of anxiety and depression[113,115,156] or reduction of substance abuse in young people[154], and these debates are even more pronounced for public health approaches targeting social determinants of mental disorders. The goal to prevent psychotic, bipolar and common mental disease is noble, but this alone does not justify the use of interventions where there is no demonstrated effectiveness. Preventive breakthroughs that do not show cost-effectiveness (see below) are also unlikely to be implemented in health care systems and in the general population, and this would be for good reasons. Future research is also needed to better customize the effectiveness of preventive interventions to several vulnerable groups such as refugees, prisoners, persons in humanitarian contexts; lesbian, gay, bisexual and transgender persons; persons who are being bullied or exposed to violence, and those who have recently been bereaved.

Future research should also explore methodological innovations. The lack of evidence to favour several preventive interventions[113,115,154,156] may indicate that a one-size-fits-all approach is not effective and obfuscates the efficacy for specific subgroups of individuals. Future individual-participant data level network meta-analyses are under planning[245] and may help deconstructing the effect of different individual- or subgroup- level factors. As new interventions in this field are being tested at a rapid pace, living meta-analyses may be particularly useful to update the emerging evidence. However, subgroup effect claims have a notoriously poor record of validation across medicine[246,247]. Moreover, even if present, they would require very large sample sizes to be able to document and validate them in a rigorous fashion. Even large individual-level meta-analyses may not identify effect modification in most medical interventions[248].

Subgroup effects and intervention effect heterogeneity require rigorous documentation and validation before being adopted[249,250].

Another explanation for the lack of evidence may be that dilution of risk enrichment and infrequent events may have led to reduced statistical power to find a difference between a preventive intervention and a control group (e.g., more than 2,000 CHR-P individuals are needed to detect a 50% reduction in risk to psychosis[251]). Stratification algorithms to control for risk enrichment and inform trial recruitment are under development[252], and harmonization of large-scale datasets within international research consortia is expected to increase the statistical power.

Future meta-analytical approaches could also exclude low-quality studies instead of pooling all available data (which has frequently been advocated[242]), most of which may be of insufficient quality[253-255]. Future interventional studies should investigate the efficacy of emerging preventive compounds (e.g., oxytocin, N-acetylcysteine, cannabinoids), screening procedures (e.g., maternal screening, bipolar risk screening, screening in low/middle-income countries) or refined psychoeducation interventions (e.g., for asymptomatic bipolar familial risk, reduction of alcohol and illicit substance abuse). Innovative adaptive trial designs[256] that integrate with stepped preventive care should also be considered.

Developing an ethical framework for preventive psychiatry

Preventive medicine in young people brings some ethical challenges. For example, the potential cost, inconvenience, social stigma and other harms of a false-positive designation in young people may be high[257]. These concerns are corroborated by lack of valid biomarkers of risk (remarkably, there are no approved biomarkers in all of psychiatry) and adverse effects of antipsychotics[258,259] or other psychotropic agents. Antipsychotics are not recommended for preventing psychosis[68], and these molecules are likely to be inappropriately prescribed to young people at risk outside preventive programmes[260]. Psychological/psychosocial interventions may also be associated with adverse effects. Population interventions to prevent substance abuse in children or common mental disorders in humanitarian settings have been shown to worsen outcomes[261] and to be not more acceptable than the waiting-list condition[120]. Notably, similar ethical issues have been raised in preventive medicine: for example, handling pre-diabetes (intermediate hyperglycaemia) has been challenged for the risk of false positives, as many people do not progress to diabetes[262].

Another question is the extent to which sharing a risk designation with young people and their families may produce harmful stigma (non-maleficence: first do no harm) or offer benefits (beneficence: helping the youth) and autonomy[263]. One perspective is that, in the absence of solid evidence for effectiveness and with potential for harm, preventive services may be seriously questioned. However, evidence shows that stigma is lower in service users than in their health care professionals[264], and caused by the service user's experience of symptoms rather than induced by the clinician's designation[265]. Stigma seems also associated with at-risk features even when no at-risk label is attached[266], and level of stigma in preventive services is comparable to that associated with depression[267]. Thus, sharing an at-risk designation may not only be helpful (beneficence), but honour the ethical principle that young people have the right to receive information relevant to their health (autonomy)[268], in particular given the very real morbidity (e.g., functional impairments of CHR-P individuals[77]), risks (e.g., up to 40% risk of developing persistent psychosis at 2 years for BLIPS[269]), and their active help-seeking behaviours.

A counter-argument is that, if no effective preventive intervention can be provided, then knowing in advance may not be helpful outside clinical monitoring (which can reduce the duration of untreated disorder[90]). However, young people accessing preventive (e.g., CHR-P) services benefit from an integrated package of vocational, psychosocial and familial support interventions which would otherwise not be available to them. Prognostic communication in these services is nuanced, tailoring it to each individual, illustrating the varying outcomes that might be possible (remission/response, persistence, worsening), and that currently there is no certain way to distinguish those possibilities for any given individual[263]. Furthermore, service user groups are actively involved in designing dissemination materials and advising on service delivery[3]. The effectiveness of these approaches needs better study but, in principle, they may help young people endorse the need for several precision/preventive psychiatry concepts, including how testing may lead to tailored interventions[270].

Future collaborative research should set up an ethical framework for implementing preventive psychiatry in young people, involving health care workers, policy makers, service users and their families, and putting emphasis on the subjective experience of the youth[271]. This call would realize the vision of predictive, preventive, personalized and participatory ("P4") psychiatry and help ensure that future progresses occur in an ethically acceptable manner that optimizes benefits and minimizes harms for young people[268].

Improving prevention through education and training

The recent systematic development of science-based prognosis and prevention for young people should be reinforced by a comprehensive educational action targeting several stakeholders. Editors and reviewers of scientific journals should become aware that improving reproducibility standards is needed to maximize the efficiency and trustworthiness of preventive research for young people[237]. Power and other statistical issues need to be considered when interpreting the results of studies.

Another problem is that the current division of medical training leads to often contrasting approaches among adolescent versus adult health care workers, enhancing the cultural divide among the specialities. Innovative curricula could be developed to train new "transitional" health care workers, which could also incorporate core conceptual and methodological issues pertaining to the science of prognosis and preventive in-

terventions (for example, universal/public health approaches may require economic or social understanding that extends beyond medical knowledge[33]).

Future curricula should also rectify the ongoing erosion of psychiatric training on psychopathology and phenomenology, boosted by checklist and algorithmic approaches in the context of pressured health care, to avoid blurring the borders between pathology (e.g., psychotic symptoms) and variants of the normal (e.g., psychotic experiences)[272] in young people.

Furthermore, knowledge and resources in the prevention of mental disorders and mental health promotion in young people are unevenly distributed around the world, and global training initiatives are needed to support countries that are still lacking capacity and expertise. This goal could be achieved through international networks of collaborating research centres[273]. Finally, policy makers should be educated on the achievements and limitations surrounding the prevention of mental disorders in young people, and funders supported to design preventive calls.

Consolidating the cost-effectiveness of preventive psychiatry

Due to high health care cost and impaired ability to work, psychotic, bipolar and common mental disorders in young people lead to a huge economic burden, estimated at US$ 16.3 trillion by 2030 (including neurological and substance use disorders), exceeding cardiovascular disease, chronic respiratory disease, cancer and diabetes, and accounting for more than half of the global economic burden attributable to non-communicable diseases[274]. However, the current global median expenditure on mental health is low (only US$ 2.5 per person annually, accounting for less than 2% of government health expenditure globally[275]), and this may be a major reason for the wide gap between young people's mental health needs and the provision of preventive interventions[275].

Cost-effectiveness of preventive interventions is essential to avoid adding pressure on already overstretched health care budgets. Available evidence indicates that cost-effective preventive interventions may include perinatal screening-plus-intervention programmes[276], stepped care for the prevention of anxiety (but not depression)[277], and prevention of psychosis in CHR-P individuals (savings of US$ 844 per prevented psychosis[278]). However, economic evaluations of preventive approaches in young people remain relatively neglected[279]. Moreover, these cost-effectiveness estimates may also be biased in favour of the tested interventions for various reasons (e.g., involvement of authors who are supportive of the interventions and/or practice them themselves, uncertain and inflated estimates of effectiveness, lack of reasonable estimates on most of the potential harms, difficulty to translate some harms, such as stigma, into quantitative parameters).

Future research should try to remedy some of these shortcomings and address economic evidence gaps in perinatal bipolar or anxiety disorders[275], adolescent mental health[280], interventions in low-resource settings (cost-effectiveness evidence may not be transferable across different countries) and youth mental health services[275]. Future economic preventive studies should also consider a long-term time horizon, in the light of the potentially progressive nature of these disorders and the wider familial and societal impact outside health care. Finally, the interconnectedness of socio-economic, religious, cultural, ethnic inequalities and cost-effectiveness[275] should be better addressed.

Decreasing inequalities to prevent mental disorders

Prevention of mental disorders in young people has not yet solidified as global research or programmatic focus[281]. We have demonstrated above that universal public health approaches targeting the social determinants of mental disorders hold the greatest potential for reducing the risk profile of the whole population. For example, the wide adoption of neo-liberal economic policies and globalization has increased wealth inequality (e.g., in the US, the top 10% of the population averages nine times as much income as the bottom 90%), which is robustly associated with psychotic and depressive disorders[282].

Effective actions may include reducing income inequality, such as progressive taxation policies and a basic universal income, in combination with promotion of good mental health and provision of packages of care with demonstrated effectiveness[283]. However, the effectiveness of poverty alleviation strategies is uncertain and requires further research; conversely, selective or indicated approaches in subgroups with mental health issues have the potential to improve economic outcomes[284].

Future public health research will also require advancements in epidemiologic methods of causal inference, improvements in data quality and availability[233], robust randomized controlled trials to demonstrate specific effectiveness on psychotic, bipolar and mental disorders, qualitative research to customize interventions around context/culture, and mixed-method implementation science to assess the scaling up of interventions[173].

Future public health approaches require committed and sustained efforts to address a range of other barriers, a strong health sector responsibility, and a vigorous leadership role in bringing society-wide attention and cross-government actions together. This point is particularly critical, given the experience of smoking prevention, whose success was predicated on successive hard-fought public policy battles.

Governments should tackle unacceptable inequalities in young people's mental health[285], and invest on improving the social determinants of their mental health: education, employment, social care, housing, criminal justice, poverty alleviation, social security/welfare benefits, community development, and immigration[275]. These inequalities are likely to increase with the current COVID-19 pandemic, which will force to change mental health services, focusing even more on flexible systems that include prevention[286].

Addressing these inequalities should be the shared responsibility of professionals across systems of care, representing the fundamental pillar of an individualized approach to youth mental health[233]. Such

primordial-like type of prevention argues for universal health care coverage and parity between physical and mental health[275]. It is hoped that more progress in this direction can be achieved in the decade to come, as much is at stake for young people at risk for and with emerging psychotic, bipolar and common mental disorders.

ACKNOWLEDGEMENTS

P. Fusar-Poli is supported by the European Union Seventh Framework Program (PSYSCAN project), US National Institute of Mental Health (ProNET project) and Wellcome Trust (STEP project). M. Berk is supported by an Australian National Health and Medical Research Council (NHMRC) Senior Principal Research Fellowship (grant no. 1156072). C. Arango is funded by the Spanish Ministry of Science and Innovation (grant nos. SAM16PE07CP1, PI16/02012, PI19/024), co-financed by European Regional Development Funds from the European Commission (grant no. B2017/BMD-3740 AGES-CM-2), European Union Seventh Framework Program (EU-GEI, PSYSCAN and METSY projects); and European Union H2020 Program (PRISM and AIMS-2-TRIALS projects).

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DOI:10.1002/wps.20869