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PREVENTIVE STRATEGIES FOR MENTAL HEALTH

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ABSTRACT

Current treatment modalities have shown a limited effect on the burden associated with mental disorders. We review promising universal, selective, and indicated preventive mental health strategies that may reduce the incidence of mental disorders or shift expected trajectories to less debilitating outcomes. Some of these interventions also seem to be cost-effective. In the transition to mental illness, the cumulative lifetime effect of multiple small-effect-size risk factors progressively increases vulnerability to mental disorders. This may inform different levels and stages of tailored interventions to lessen risk or increase protective factors and resilience, especially during sensitive developmental periods. Gaps between knowledge, policy, and practice need to be bridged. Future steps should include more emphasis on mental health promotion and improvement of early detection and interventions in clinical settings, schools, and the community, with essential support from society and policymakers.

Key words: child psychiatry, adolescents, community mental health, epidemiology, outcome studies, economics, prevention, promotion.

Key messages panel:

- There is increasing evidence supporting the efficacy of some universal and selective preventive interventions to promote mental wellbeing and prevent mental disorders throughout development.
- Indicated prevention in those showing sub-threshold manifestations of vulnerability can shift expected trajectories towards less debilitating outcomes or delay the onset of severe mental disorders.
- Ethical and safety considerations should guide the implementation of preventive interventions in mental health, especially in young people and at-risk populations.
- Mental health professionals should incorporate a focus on prevention into their daily practice and work in close cooperation with other specialties (primary care, obstetrics,

paediatrics) and sectors (education, social services) to increase awareness of the evidence base for preventive interventions in mental health.

Introduction

While there is increased interest in early detection to prevent progression to severe mental disorders such as schizophrenia and recurrent major depression, knowledge of risk factors and developmental trajectories has not yet been widely applied to clinical practice and public health.[1] Psychiatry has traditionally been based on treatment and prevention of progression and disability in individuals with established illness (i.e. tertiary prevention). Although a number of medical specialties have joined forces with public education and health associations to reduce risk factors for diseases such as myocardial infarction,[2] preventive initiatives in mental health have received far less attention. Scientific evidence gathered from other areas of medicine, along with increasing knowledge of developmental risk factors preceding psychiatric illness and preliminary findings supporting preventive interventions, indicate that our field could move toward the more ambitious goals of universal prevention of vulnerability, selective prevention in high-risk subgroups and indicated prevention of full or more severe expression of illness in those already showing early manifestations.[3] The reality is that, of all mental health research funding, less than 5% goes to prevention research, even in countries that have actually invested in prevention.[4]

In this narrative review, we will first summarize the various possibilities for mental health prevention throughout development and the evidence supporting them. We will then review the potential limitations currently associated with these approaches and potential ways to overcome them.

1. Prevention in mental health

Prevention in mental health aims at reducing the incidence, prevalence, and recurrence of mental disorders and their associated disability. Preventive interventions are based on modifying risk exposure and strengthening the coping mechanisms of the individual.[5] Effective interventions require identifying causal risk factors[6] and can target both generic risk factors,

which are likely to be shared by different disorders, and disease-specific factors. Most preventive programmes will likely involve a combination of strategies for reducing exposure to risk factors, enhancing protective factors, and targeting putative mediating causal mechanisms such as cognitive schemas or neurotransmitter imbalances. Primary preventive interventions in mental health are those targeting risk factors and promoting mental health in individuals without a clinically diagnosable mental disorder. Such interventions may target a whole population regardless of individual risk (universal prevention), a subpopulation known to be at increased risk for mental illness (selective prevention), or individuals already showing sub-threshold clinical manifestations (indicated prevention).[5] Table 1 provides an overview of the different kinds of preventive interventions in mental health with examples of each. This review will focus mostly on primary preventive interventions.

Risk factors increasing vulnerability to mental disorders

Mental disorders have different degrees of heritability, pathogenic genetic variation being a major risk factor for multiple mental disorders.[7] The cumulative effect of multiple common alleles of small effect or the relatively high impact of rare pathogenic variants, in interaction with environmental risk factors, increases the risk for development of mental disorders.[8] This is also true for environmental risk factors. Although some rare environmental risk factors might have large effect sizes, most environmental risk factors are characterized by small effect sizes and seem to increase susceptibility but are not sufficient to explain the occurrence of a disorder.[8] They include but are not limited to prenatal environment (e.g. poor nutrition, exposure to drugs or toxins, maternal infections or stress), birth complications, preterm delivery, brain trauma, social risks (e.g. socio-economic disadvantage and poverty, urbanicity, immigration, social isolation), trauma (e.g. parental neglect, physical, emotional, and sexual abuse, bullying), lack of stimulation, general adversity and stressful life events, and drug abuse (see Figure 1).[9-12] Many of these risk factors are interrelated and tend to cluster and have

synergistic effects. For example, immigration often co-occurs with urbanicity and social disadvantage,[13] while children who have been exposed to violence are at higher risk of repeated victimization.[14] Subjects with mental disorders or disabilities and those who have already been exposed to risk factors may be less capable of defending themselves and seem to be more often targeted by bullies and abusers.[15] Therefore, once vulnerable, it is more likely that further risk factors may lead to a vicious cycle. This "facilitation effect" is also supported by epigenetic changes found in the serotonin transporter and glucocorticoid receptor genes of victims of child trauma and their subsequent neuroendocrine alterations and changes in brain structure and function.[16] These neurobiological changes may lead to maladaptive responses to stress, thus increasing vulnerability to stress-related diseases and feeding lifetime revictimization.[16]

Identification of specific risk and protective factors for mental disorders is challenging because of person-environment interactions and correlations. Individuals are not passive recipients of events inasmuch as they process their experiences according to their personal history and social environment, and this influences their ability to adapt to these events and may modify how they interact with the environment to shape and select their future experiences.[17] Interaction with the environment is also subject to genetic influence; genetic factors may affect the sensitivity of the individual to particular environmental risks and contexts (i.e. gene-environment interactions)[8] and modulate exposure to certain risk and protective factors (i.e. gene-environment correlations).[19] Furthermore, exposure to the environment and life events, as well as interventions (both pharmacological and psychosocial), can induce biological changes at different levels (e.g. epigenetics, neurotransmitters, brain connectivity), thus modifying the ability to adapt to further stressors. This complicates the picture but also affords an opportunity for different levels of intervention (biological, psychological, family-related, social environment) at different developmental stages to lessen risk or increase protective factors.

Opportunities for prevention during development

a) Mental disorders as "multiple-hit" developmental disorders

It is usually the cumulative effect of risk and lack of protective factors during development that leads to a transition from health to mental illness.[20] Even if early risk factors (e.g. genetic risk or early environmental factors such as severe deprivation) are present, in the absence of additional "hits", a disorder ultimately may not develop. This has been shown to be especially important in the development of disorders such as schizophrenia and bipolar disorder[21] and offers a unique opportunity for targeted prevention in high-risk individuals by reducing exposure to further risk factors and enhancing protective factors.[9] Among the possible additional risk factors, bullying victimization has been strongly associated with short- and long-term vulnerability to mental illness.[11] Interestingly, ceasing exposure to bullying and maltreatment during childhood has been shown to reduce the incidence of psychotic experiences after 12 months.[22] Effective strategies to reduce bullying such as school-based anti-bullying programmes have also proved effective in reducing subsequent aggression or internalizing problems in adolescents.[23] Similarly, strategies such as providing comprehensive educational and family support to economically disadvantaged children could be effective in preventing other risk factors such as child abuse, with one study reporting a reduction in its incidence among participants by 52%.[24]

Even when there is a "first hit" or further "hits", the effect could be lessened by enhancing protective factors such as family and social support and promoting resilience.[25] Resilience is a multidimensional construct that can be conceptualized as the ability to adapt well after experiencing adversity, trauma, or other stressors.[25] A number of effective interventions have been developed to promote resilience, especially in children and adolescents.[26] Their core elements include enhancing social and emotional competence skills and promoting self-efficacy, adaptability, and social connectedness in young people, as well as fostering positive parenting and facilitating family communication and problem-solving.[26] For instance, in children exposed to risk factors such as low birthweight or bullying, a positive family environment has been found to increase resilience to these risk factors.[27,28] Although the essential approach for bullying prevention entails intervening in community and school factors that foster bullying

behaviour, family interventions and other strategies to promote individual resiliency may be helpful in improving outcomes in those who have already been victimised.[29]

b) Developmental pathways of vulnerability to mental ill-health

From a developmental psychopathology perspective, mental disorders appear to be the result of a dynamic process of repeated environmental maladaptation leading to progressive deviation from normative development. Multiple pathways can lead to similar manifest outcomes, while the same deviant developmental pathway can lead to different psychopathological outcomes. Although change may be constrained to some extent by prior adaptation, especially during sensitive periods, the pluripotentiality of early trajectories of vulnerability suggests that change is possible at many points during development.[30] This is also compatible with a staging model similar to models developed in other areas of medicine, which suggests that severe mental disorders develop from at-risk preclinical states, then pass through undifferentiated general symptoms, followed by increasing clinical specificity and functional decline.[31]

Both perspectives lead to an optimistic outlook for a preventive approach, inasmuch as it would be possible to intervene in the developmental process of any mental condition or shift the psychopathological expression towards less debilitating disorders, by intervening in people with risk factors or already showing subtle abnormal development.[32] Early risk markers of developmental deviance that can precede severe disorders in adulthood include subtle language and motor delays, extreme temperament traits, irritability, sub-threshold hyperactivity and conduct problems, low cognitive performance, decline in IQ, and social difficulties in childhood.[33-35] These signs could help characterize subpopulations with increased developmental vulnerability to guide targeted intensive interventions.

There are several examples that suggest that it may be feasible to change trajectories toward a less severe mental disorder or a less severe form of a given disorder. Psychosocial interventions in subjects at clinical high risk (CHR) for psychosis, such as cognitive-behavioural therapy (CBT), may lead to a reduction in transition rates to psychosis or a delay of onset and

amelioration of debilitating symptoms.[36] Although based on a single study that warrants replication, there is also very preliminary evidence suggesting that early intervention in toddlers diagnosed with autism spectrum disorder may improve functionality and diminish core symptoms of the disorder.[37] Another example is attention deficit hyperactivity disorder (ADHD). Treatment with stimulants in childhood may improve or stabilize social functioning and academic performance in ADHD. Subsequently, the rate of secondary drug abuse, conduct disorders, and social problems may decrease in adolescence and adulthood, stopping a potential downward spiral.[38] Similarly, there is evidence suggesting that reducing the duration of anxiety or depressive episodes in young people may prevent the development of more severe mental disorders during adulthood.[39]

c) Sensitive periods for prevention in mental health

During a lifespan, there are sensitive periods where risk and protective factors may have greater impact and long-lasting consequences.[16,40] These periods include the prenatal period, childhood, and adolescence through early adulthood (see Figure 1). It may not be coincidental that the windows of vulnerability largely overlap with periods of major developmental brain changes, such as maturation of several receptors, myelination, pruning, and development of hub regions.[40] These periods are also crucial for development of secure attachment, basic schemas related to self, others, and the world, self-esteem and self-integrity, and finally the adult personality, and overlap with the peak incidence of major mental disorders.[41] Prevention focusing on these periods may be more effective and have long-lasting benefits.

There is emerging evidence that the prenatal environment may shape gene expression related to foetal brain development and thus affect the risk of mental disorders.[42] Therefore, providing appropriate screening and care for factors such as maternal nutrition and substance abuse including smoking, and parental mental disorders and stress during this period could considerably contribute to global prevention of mental disorders in children.[43,44] In the postnatal period and early childhood, exposure to stressors, such as child abuse, neglect, or malnutrition

may interfere with the development of brain regions critical to regulation of emotion and lead to poorer mental and physical health.[16] Thus, reducing child abuse rates and improving early family and social environments could decrease lifetime mental disorders.[45] During adolescence, strategies to prevent substance abuse and other risky behaviours, and to promote healthy lifestyles and positive coping mechanisms could be especially useful.[26,46]

Despite the numerous opportunities for prevention in mental health, there are some specific factors that may hamper the advancement of prevention in psychiatry and should be considered when designing and implementing interventions. Panel 1 shows an overview of these factors and potential ways to overcome some of these difficulties.

2. Evidence supporting primary prevention in psychiatry

2.1. Universal preventive interventions

Universal prevention of mental disorders addresses generic risk and protective factors in the general population. Such interventions are likely to affect the global probability of developing psychiatric and other disorders in a non-specific fashion. A holistic approach to health, integrating psychosocial and physical aspects of wellbeing, may be especially valuable in this regard. A recent meta-analysis of 67 cluster trials reported that the World Health Organization (WHO) Health Promoting School framework, a school-based programme using this approach, has significant positive effects on physical activity, physical fitness, body weight, fruit and vegetable intake, tobacco use, and bullying. The authors' interpretation was that, despite the small effect sizes, these interventions could have public health benefits at the population level.[47] There are also data suggesting that promoting healthy lifestyles, including appropriate nutrition and regular exercise, could have positive effects on cognitive development, scholastic achievement, and mental health vulnerability.[5,48] Something as simple as eating dinner as a family may serve as a venue for parents to promote coping strategies that offset the impact of stressful environmental factors, such as cyber-bullying.[49]

Schools play a central universal prevention role in childhood and adolescence. There are a number of effective school-based anti-bullying programmes that reduce bullying rates, on average by ~20%,[50] and may reduce related mental health symptoms.[23] Universal school-based programmes may also be effective in improving social and emotional skills, attitudes, behaviour, and academic performance, as suggested by a meta-analysis assessing 213 programmes involving more than 270,000 students from kindergarten through high-school.[51] School-based programmes using self-regulation change techniques could also improve self-esteem and internalizing behaviour in adolescents, with small effect sizes (~0·20).[52]

Additional key targets for universal prevention include the prenatal and perinatal periods. Recent studies suggest that dietary phosphatidylcholine supplementation during the second and third trimesters may prevent cerebral inhibition deficits associated with schizophrenia and attention deficit disorder.[53] There is also evidence suggesting that vitamin D supplementation during pregnancy may reduce rates of low birthweight and preterm delivery,[54] which have been associated with attention deficits and increased risk for childhood behavioural and emotional disorders.[55,56]. Similarly, preliminary data suggest that vitamin D supplementation during the first year of life may reduce the incidence of schizophrenia in males.[57] Other strategies to improve maternal nutrition (fortification or supplementation) may be associated with reduced obstetric complication rates and improved behavioural outcomes in offspring.[58] Interventions to promote effective parenting in expectant or new parents can also have positive effects on the cognitive, social, and motor development and mental health of the child.[59]

There is evidence based on meta-analyses and systematic reviews that some psychosocial universal preventive interventions are effective for anxiety and depression,[60,61] eating disorders,[62] and substance use disorders in young people.[46] Restriction of access to lethal means and school-based awareness programmes have been found to significantly reduce suicidality.[63] There is also preliminary evidence suggesting that additional supplementation strategies (e.g. N-acetylcysteine, sulphoraphane, probiotics) constitute promising strategies for universal prevention in mental health that merit further research in the coming years.[64]

2.2 *Selective preventive interventions*

Children of parents with mental illness or substance use disorders represent one of the populations at highest risk for psychiatric problems.[65] In children at high familial risk for psychosis, about 10% will develop psychosis and 50% non-psychotic problems.[33,65] Similarly, offspring of depressed parents have a threefold higher risk of developing anxiety disorders, major depression, and substance dependence.[66] Genetic vulnerability aside, there are several studies that attribute childhood risk to parental mental health status, suggesting that successful management of parental psychopathology could improve outcomes in their offspring. A meta-analysis indicates that preventive interventions targeting mentally ill parents could reduce the risk of mental disorders in their offspring by 40%.[67]

Other at-risk populations include children with genetic disorders associated with an increased risk for early developmental deficits and psychiatric symptoms. In these at-risk populations, universal school- or community-based preventive interventions against bullying and abuse may be especially helpful to prevent mental disorders, by reducing exposure to these frequent risk factors. Selective preventive interventions in at-risk populations should target social stress and emotional problems, promote resilience, and facilitate early identification and access to services in those already in need of care.[9] Compensatory approaches to social and cognitive problems could provide additional benefits to interventions aimed at improving resilience in these populations.[68]

There is also evidence supporting the efficacy of some psychosocial selective interventions to prevent externalizing disorders in children reared in disadvantaged environments,[69] or exposed to violence within the family context,[70] post-traumatic stress disorder (PTSD) in children and adolescents exposed to traumatic events,[71] eating disorders in young people belonging to high-risk groups (e.g. female athletes or adolescents with body image issues),[62] postpartum depression,[72] and depression and/or anxiety disorders in young offspring of patients with depressive disorders[73] and other high-risk populations,[60,74] as well as of some pharmacotherapy

strategies (e.g. hydrocortisone) to prevent PTSD.[75] Most of the effective interventions had small to medium effect sizes relative to control conditions.

2.3. Indicated preventive interventions

Indicated preventive interventions are those conducted in individuals showing subthreshold manifestations of mental disorders. Interventions in these subgroups may be more efficient, since they minimize the number of individuals who need to be exposed to the intervention and target individuals who may already be in need of care. Some meta-analyses suggest that indicated interventions could have greater effect sizes than universal ones (e.g. programmes for eating disorders or depression),[61,62,76] although this is not a consistent finding, and several meta-analyses report no significant differences or even greater effect sizes for universal interventions.[60] Examples of effective indicated interventions supported by meta-analyses include parent management training to prevent externalizing disorders in children with high antisocial behaviour scores,[77] and to prevent depression and anxiety disorders in children showing early manifestations of internalizing disorders.[78] CBT in CHR subjects may lead to a reduction in transition rates to psychosis.[79] There is also evidence that CBT-based strategies may be effective for preventing chronic PTSD in patients showing early acute stress symptoms after exposure to a traumatic event[80] and eating disorders in young people showing subthreshold symptoms.[62] CBT and interpersonal therapy may be also effective for prevention of depression and/or anxiety in young people and adults presenting with subclinical symptoms.[76,81]

3. Is it worth investing in mental health prevention?

Despite mounting scientific data supporting the efficacy of early intervention and prevention in psychiatry, there still is a gap between research evidence and clinical and public health practices. Can this be attributed to economics? All in all, the accumulated evidence suggests that improving long-term outcomes and reducing some of the long-term adverse consequences

of poor mental health (e.g. secondary disorders, criminality, unemployment) make many early mental health interventions cost-effective for society,[9,82] especially in light of the high direct and indirect costs generated by neuropsychiatric disorders, which are responsible for 14% of the global burden of disease (disability-adjusted life years) worldwide.[83] Recently, the European Observatory on Health Systems and Policies, the Organization for Economic Co-operation and Development, and the WHO Regional Office for Europe have compiled data demonstrating that influencing risk behaviours for chronic non-communicable diseases, including mental disorders, is an efficient use of government money and that government policies can have a major impact on risk behaviours for mental disorders.[84]

For example, in the UK, it was calculated that for every US dollar spent on mental health promotion and prevention, ten-year total societal returns on investment, (including impacts on health and other sectors, such as education and the criminal justice system) were $83·73 for whole-school conduct disorder prevention and $10·27 for early detection services in people with prodromal symptoms of psychosis.[82] A recent estimate of the benefits of preventing bullying suggests a conservative return of between $10·67 and $16·79 per dollar invested by age 21 due to higher earnings and better educational outcomes, with other savings likely due to avoided adult depression.[85] Similarly, there could be substantial savings when investing in home-visiting programmes for disadvantaged pregnant women,[86] early intensive behavioural interventions in pre-school children with autism,[87] interventions to reduce truancy and school exclusion,[88] parenting interventions to prevent internalizing[89] or externalizing disorders in children,[77] and early intervention services for early-onset psychosis in children and adolescents.[90] There is also evidence supporting the cost-effectiveness of interventions to prevent the neuropsychiatric consequences of prenatal risk factors, such as folic acid fortification of enriched cereal-grain products for the prevention of neural tube deficits[91] and universal screening in pregnancy for subclinical hypothyroidism.[92] For conditions such as maternal depression and suicidal behaviour, there may be benefits to individuals, relatives, and society of improving the ability of professionals to detect and intervene in at-risk and early

stages.[93,94] The promotion of health literacy in routine educational settings may also be cost-effective for a wide range of health, educational, and social outcomes.[95] Table 2 provides a summary of the cost-effectiveness analysis of key examples of primary preventive interventions in psychiatry.

Compared with other medical conditions, savings in psychiatry may be greater. Debilitating mental disorders usually have a much earlier onset than many other chronic diseases, increasing the number of years that health and social welfare services and caregiver support will be needed, hence the potential savings from prevention. Whereas 50% of mental disorders start before 14 years of age and 75% before the age of 24,[41] the mean age at onset of diabetes is 53·8 years[96] and the average age of a first heart attack in US men is 65.[97] Therefore, it is reasonable to assume that the direct and indirect savings (e.g. higher rates of employment and higher earnings when employed) to society from early and long-lasting reduction of the burden of mental illness would be much higher than for many other chronic medical conditions. Furthermore, considering the bidirectional relationship between mental and physical health, influencing risk factors for psychiatric disorders could also help prevent other medical conditions in adulthood. For example, bullying victimization has been associated with an increased future risk of a number of inflammatory disorders.[11] Interventions to prevent bullying are likely to have an impact on the development of both psychiatric and medical disorders, as well as non-medical outcomes (e.g. educational attainment and societal benefits).

In light of this evidence, two recent initiatives in the US[98] and Europe[99] have included prevention among the top priorities for mental health research. The US group emphasizes that it is feasible to achieve these priorities in the next ten years, but only if funding begins immediately.[98] And the clock has already started ticking…

4. Current role of mental health professionals in mental health prevention

Some of the general factors that can potentially increase the risk for reduced psychological wellbeing and psychiatric disorders, such as social exclusion or economic inequality, cannot be directly addressed by psychiatrists. Universal interventions in the general population require a public mental health approach and will probably be delivered by other medical specialties such as obstetrics and general practice or other sectors such as education. We believe that it is the duty of mental health professionals to increase awareness among the general public, politicians, and policymakers about the importance of mental health prevention and promotion and about the evidence supporting cost-effective interventions. Mental health professionals should start incorporating an at-risk-oriented focus into our clinical practice by improving current definitions for early clinical stages, enhancing screening instruments, developing targeted interventions, and promoting training in prevention for all mental health professionals. The role of clinicians may be especially important for selective and indicated interventions, by providing care to those already at risk, in whom periodic specialized monitoring of subsequent mental problems may be especially useful. Strengthening the coordination between child/adolescent and adult psychiatric services targeting the same areas could be especially valuable to facilitate management of the offspring of patients with major mental disorders and to assist with the transition through services in other high-risk populations. This could be especially useful, considering the often large treatment gap during the transition from child/adolescent to adult services.[100] Improving access to care in those already in need may constitute an excellent secondary and tertiary preventive strategy, by reducing duration of untreated illness and its negative consequences. Considering the high comorbidity and bidirectional association of mental disorders with somatic conditions, coordination with primary care is also essential. Panel 2 provides specific details on some key areas of mental health prevention that we believe should be prioritized in the coming years.

Conclusions

Increasing evidence suggests that there are feasible and safe preventive interventions in psychiatry that could translate into a broader focus on prevention in our field. Many preventive interventions in mental health may be cost-effective or even cost-saving. There is evidence supporting the efficacy of some universal, indicated, and selective prevention strategies for improving psychological wellbeing or preventing mental disorders throughout development. The search for further scientific evidence on the efficacy and cost-effectiveness of preventive interventions is warranted. Nevertheless, despite incomplete evidence for some universal interventions, there are public health prevention strategies in other areas of medicine for which evidence was acquired only after universal adoption (e.g. folic acid supplementation, fluoride treatment, and measles vaccine). These set the example for moving forward with safe interventions for which there is initial evidence for efficacy in advance of empirical proof of mental disorder prevention, especially considering the potential two-decade gap between implementation of early preventive strategies and emergence of mental disorders.

Investigation of early stages of mental disorders integrating different dimensions (genetic, transcriptomic, neurobiological, psychological, socio-economic), including their complex interactions throughout early developmental periods, is needed. Further evidence should be gathered on the optimization of different intervention strategies based on developmental timing, while also factoring in potential short- and long-term benefits beyond mental health outcomes (educational, functional, societal). As there is a need to prioritize these interventions, we propose that implementation in the area of mental health could start in children with factors known to increase the risk for developing a mental disorder (e.g. children of parents with major mental disorders, children with genetic risks known to increase incidence of mental disorders) or those showing nonspecific symptomatic manifestations of the early stages of mental disorders or indicators of early developmental deviation. To achieve these goals, the support of

society and public policymakers is essential. Disseminating the potential societal benefits of evidence-based findings may increase community awareness and stimulate inclusion of cost-effective prevention programmes for mental disorders in political agendas.

Search strategy and selection criteria

References for this narrative, critical review were identified through PubMed searches for articles and previous reviews published through December 2016 using the key terms "prevention", "high-risk", "risk factors", "promotion", "resilience", "development", "staging", and "early intervention" in combination with the terms "psychiatry", "mental health", and "psychopathology". Articles identified by these searches that related to the main topics covered in the manuscript and relevant references cited in those articles were selectively reviewed. We conducted an additional systematic PubMed search from inception through November 2017 to identify meta-analyses assessing primary preventive interventions for specific mental conditions [i.e. mood disorders (depression, bipolar disorder), anxiety disorders, post-traumatic stress disorder, externalizing disorders (disruptive behaviour disorders (i.e. conduct disorders, oppositional-defiant disorder), attention-deficit hyperactivity disorder), eating disorders, psychotic disorders, autism spectrum disorders, and suicidal behaviour] (see Supplemental Material for additional details). These references were systematically reviewed and the most recent or comprehensive meta-analyses supporting universal, selective, or indicated preventive interventions for each disorder were included in the manuscript. Complementary searches were performed in Google Scholar and PubMed to identify examples of cost-effectiveness studies on preventative interventions in psychiatry.

Contributors

All authors contributed to the conceptualization of the paper. C. A., C.D.-C., and E.S.-D. performed the literature search and the selection of references, wrote the first draft of the manuscript, and were involved in the design of the tables and figure. All authors contributed to the critical review of the scientific literature, revised the manuscript, and approved the final version.

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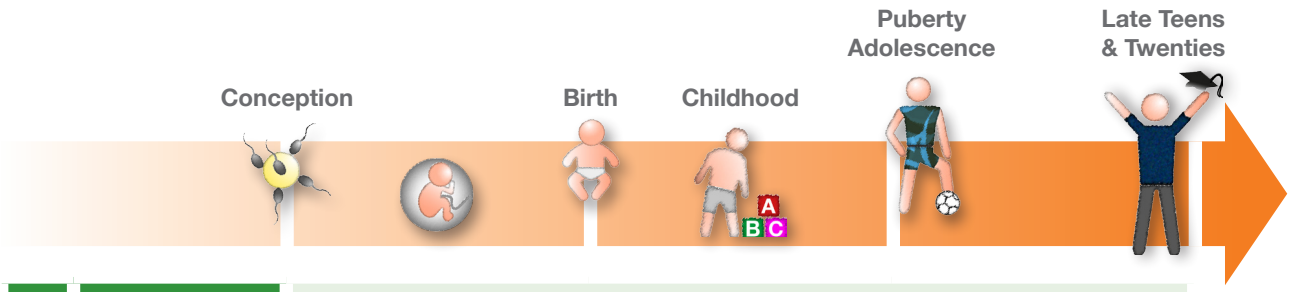
Figure 1: Risk factors for mental disorders in sensitive periods of intervention

Abbreviations: ADHD: attention deficit hyperactivity disorder; ASD: autism spectrum disorders; CBT: cognitive-behavioural therapy; HR: high risk; IPT: interpersonal therapy; IQ: intelligence quotient; SNV: single nucleotide variant; CNV: copy number variation



Risk Factors

Genetic

- Positive family history of mental disorders (65, 66)
- Clinically significant SNV or CNV such as 22q11.2 deletion (101)

Biological

- Maternal infection (102)
- Preterm birth and obstetric complications (55, 103)
- Poor nutrition (43)
- Exposure to drugs & medications (44)
- Brain trauma (104)
- Physical health (105)
- Epigenetic changes in serotonin and glucocorticoid transporters, changes in brain structure and function (16)
- Brain & hormonal changes (106)
- Substance abuse (107)
- Physical health (105)

Family-related

- Perinatal depression (108)
- Parental neglect (10)
- Child maltreatment (10, 45)
- Parental mental illness (65, 66)

Society

- Bullying and other forms of abuse (11)
- Lack of proper stimulation (109)
- Bullying and other forms of abuse (11)
- Social adversity: socio-economic disadvantage, stressful urban environments, immigration, social isolation (12, 13, 110)
- Stigma (111)

Early Detection & Risk Markers

- Screening for family history of mental disorders (65, 66)
- Screening for maternal psychiatric disorders (108)
- Screening for genetic variants associated with increased risk for neurocognitive and /or psychiatric phenotypes (101)
- Screening for postnatal depression or parental psychiatric illness (108)
- Screening and surveillance of developmental trajectories (112)
- Delayed or altered develop-mental milestones (33, 112): cognitive, language, psychomotor, social, academic performance
- Chronic irritability and hyperactivity (34, 35)
- Cognitive decline (9)
- Altered social behaviour or poor academic performance (33)
- Psychotic-like experiences (9)
- Brain and blood biomarkers (113): accelerated loss of frontal cortical grey matter and greater expansion of third ventricle, inflammation and oxidative stress

Preventive Interventions

General Population

- Reducing income inequality and unemployment (114)
- Improving education and child care (24, 115)
- Reducing social stigma (111)
- Increasing societal and professional awareness (116)
- Pregnancy care (86)
- Nutrition (43)
- Phosphatidylcholine supplementation (53)
- Promotion of bonding (117)
- Informative genetic counselling (118)
- Proper stimulation for developmental stage (119)
- Family dinners (49)
- School academic achievement, social climate, resiliency skills (24, 26)
- Anti-bullying interventions in schools (23, 50)
- Nutrition and physical exercise (48)
- Having dinner with minors (49)
- School academic achievement, social climate, resiliency skills (24, 26)
- Anti-bullying interventions in schools (23, 50)
- Nutrition and physical exercise (48)
- Prevention of substance use (46)

At-Risk Population

- Improving support for disadvantaged adolescents pregnant for the first time (86)
- Maternal mental illness: close monitoring of physical and mental state, substance and medication use (108, 120)
- Improving parental mental state (67)
- Early intensive intervention for ASD (37)
- Parent training for externalizing and internalizing problems (77, 78)
- Secondary prevention with stimulants of ADHD complications (38)
- Psychological interventions (e.g. CBT, IPT, other) for indicated prevention in young people with subclinical symptoms (76, 78-81)
- Cognitive remediation and improving social skills for selective prevention in some HR groups (9, 68)

Table 1: Definitions of preventive interventions in mental health

	Target population	***Aims***	***Examples***
Mental health promotion interventions	General public or whole population	• *Promote psychological wellbeing and increase the ability to achieve developmental milestones* • *Strengthen abilities to adapt to adversity and build resilience and competence*	*School-based programmes to foster healthy eating or positive coping skills*
Universal primary preventive interventions	General public or whole population, regardless of individual risk factors	• *Target risk factors in the whole population to prevent the development of one or more conditions* • *Interventions should be effective, safe, and associated with low costs.*	*School-based programmes to prevent bullying*
Selective primary preventive interventions	Individuals or subpopulation with a significantly higher than average risk of developing mental disorders The identification of these risk groups may be based on biological, psychological, or social risk factors	• *Target risk factors and strengthen abilities in these individuals or subpopulations to prevent the development of one or more conditions* • *Interventions should be effective and associated with low risk of adverse events and moderate costs.*	*Interventions in the offspring of patients with severe mental disorders*
Indicated primary preventive interventions	Individuals at high-risk showing early minimal but detectable clinical manifestations but currently not meeting diagnostic criteria	• *Treat subclinical manifestations to prevent transition to the full-blown disorder* • *Target risk factors and strengthen abilities in these individuals to promote resilience* • *Interventions may be associated with higher costs and some risks can be accepted.*	*Interventions in subjects at clinical high-risk for psychosis (i.e. showing attenuated psychotic symptoms and a recent decline in functioning)*
Secondary preventive interventions	Individuals meeting diagnostic criteria in the early stages of illness	• *Early detection and intervention in patients already meeting diagnostic criteria for a specific mental disorder* • *Provide adequate treatment, improve satisfaction with treatment, reduce substance use and prevent relapses*	*Interventions to improve early detection and access to services in patients with depression to reduce duration of untreated depression*
Tertiary preventive interventions	Individuals with established illness	• *Treat established disease to prevent deterioration, disability, and secondary conditions*	*Interventions for smoking cessation and cognitive remediation in patients with schizophrenia* *Prevention of suicide with lithium in patients with bipolar disorder*

It should be noted that there is some overlap between indicated primary preventive interventions and secondary preventive interventions. Universal primary preventive interventions will frequently employ mental health promotion strategies.

Table 2: Key examples of primary preventive interventions in mental health

Intervention	Sources of evidence	Efficacy results	Cost-effectiveness data (2016 US dollars)
Preventive strategies for postpartum depression	Meta-analysis Systematic review RCTs	~20% reduction in rates of maternal depression during the first months after birth[72] Improvement in mother-infant interaction and child developmental functioning Reduction of child abuse and neglect[120] Universal preventive interventions found to be most effective in reducing 12-month depression scores (Edinburgh Postnatal Depression Scale) were midwifery redesigned postnatal care, person-centred approach interventions, and cognitive behavioural therapy-based interventions[121]	In the UK, home health interventions were associated with cost of ~$7,281 to $7,928 per quality-adjusted life year gained as compared with routine care.[82,94] In Canada, trained telephone peer support had a 95% chance of a cost per case of averted maternal depression of less than $17,446.[122] These examples are conservative since long-term impacts on child, siblings and fathers are not considered. A more recent study in Australia suggests that psychoeducation may also be cost-effective in preventing postpartum depression and anxiety.[123]
Parent training for prevention of behavioural disorders	Meta-analysis Systematic review RCTs	Reduction in child conduct problems[77] Improvement in parental mental health, reduction in negative and harsh parenting practices[77]	60% of program investment recovered due to costs averted within 2 years and 100% in 5 years[77] Cost savings after 8 years and total savings over 25 years of at least $15,028 from public purse and societal perspective[82]
School-based interventions to prevent bullying	Meta-analysis Systematic review RCTs	~20% reduction in rates of peer victimization[50] Reduction in aggression and internalizing symptoms[23]	In the UK, a universal programme would show cost savings after 3 years and generate expected mid-term return on investment through reduced health costs, improved education outcomes, and likely higher earnings of $10.67 to $16.79 per dollar invested per pupil by age 21. Further savings due to likely reduced rate of adulthood depression.[85]

Panel 1: Factors that hamper the advancement of prevention in psychiatry

a. Limitations of using diagnoses of specific mental disorders as outcome measures of preventive interventions

There do not seem to be silos of risk or protective factors for current clinical diagnoses. Whether at the level of aetiology[7] or pathophysiology,[124] these factors seem to increase or decrease vulnerability to many mental disorders. Even in genetic conditions such as 22q11.2 deletion syndrome, there is remarkable pleiotropy, and the outcome is highly variable in terms of functionality, intellectual disability, and psychiatric diagnosis. This is true for almost all copy number variations associated with psychiatric conditions.[101] Therefore, there do not seem to be fixed pathways leading to each specific DSM or ICD defined disorder.[30,32] Although some interventions may be more specific (e.g. some indicated interventions), this implies that many public health interventions, whether population-wide or in a high-risk subgroup, may have low specificity and reduce incidence or improve outcomes across disorders. Quantification of the effectiveness of such interventions should therefore be reflected by global measures of disorders and include other kinds of outcomes (education, wellbeing, social and legal services, etc.). For mental illness, in many instances, there is the additional problem of a two-decade delay from birth to emergence of a specific disorder.

b. Barriers to identification and care in those at-risk

In the absence of reliable biomarkers for mental disorders, it is very difficult to predict future illness in individuals and reliably identify subpopulations at risk for specific disorders. The difficulties involved in identifying those at highest risk are exacerbated by the fact that families most in need of intervention (e.g. disadvantaged) may have the least access to care. Further research should be done on the early stages of mental disorders with the aim of identifying potential psychological, biological, and social risk markers.

c. Methodological and ethical challenges of preventive interventions

Preventive strategies are associated with some intrinsic difficulties such as the high number of potentially false positive treatments and the high costs that can be associated with interventions in larger populations. Considering the potential for ineffective or even iatrogenic interventions, it is crucial to conduct rigorous research on preventive interventions. Since a high proportion of the population that is not necessarily at risk could be exposed to these kinds of interventions, safety should guide the implementation of primary universal interventions. In this concern, strategies to promote mental wellbeing, healthy eating, and physical activity, reduce bullying and other forms of child abuse, and improve workplace conditions are associated with very low risks and could be prioritized. Supplementation strategies (e.g. vitamin D) during pregnancy or the neonatal period should be further studied considering their potential risks. However, increasing evidence suggesting an association of reduced vitamin D during pregnancy and the neonatal period with neurodevelopmental disorders,[125] with preliminary data suggesting a beneficial effect of vitamin D supplementation on birth outcomes in the offspring,[54] and low risk of side effects[54], indicate that they could be carefully implemented, at least in high-risk subpopulations (i.e. pregnant women or neonates with vitamin D levels in the lowest percentiles). Low sensitivity to identify those with subthreshold symptoms could also limit indicated preventive interventions. For instance, it has been estimated that well-established clinical high-risk (CHR) services may miss 95% of those who will develop a psychotic disorder.[64]

Implementing early-stage detection and intervention strategies in a clinical context for indicated and selective prevention has clear ethical implications. It seems feasible (and critically important) to identify people at high risk for whom health systems are equipped to provide proper care (e.g. young people showing mild symptoms or behaviours suggestive of CHR and healthy individuals with known genetic risk). While disclosure in these instances may be beneficial for both patient and family, by providing understanding and perspective and offering advice for reducing risk, promoting resilience,

and orienting future actions in case of progression, this process may also be stressful and raise concerns regarding stigma. Disclosure should be done with great caution not to decrease self-esteem and hopes or aims for the future. Rather, interventions in at-risk individuals should be framed as encouragement for a better future. Safety should guide clinical decision-making in those identified as being at risk, and lower-risk interventions should be prioritized, especially in young people.

d. Long-term benefits do not seem to motivate health authorities or political decisions

Lack of awareness of the significant economic savings from preventive interventions for mental disorders, the need for an initial investment in training and investment of time by professionals, often with no short-term return, and stigma partly explain the lack of interest in mental health prevention as compared with other areas of medicine. It may take more time to realize the benefits of investing in prevention in mental health than in other areas of medicine (e.g. oncology or cardiovascular disease). This is problematic when politicians need to prioritize their health actions based on what can be communicated to future voters in four- to five-year election cycles. A focus on prevention and public health requires a long-term view, which is sometimes not possible for politicians due to their short terms in office and frequent shifts in priorities and main lines of intervention in health and education when a different party comes to power, sometimes without regard for the beneficial effect of previous approaches. National and international funding agencies could play an essential role in providing the required long-term support to appropriately evaluate and implement preventive interventions. In addition, prevention and early detection of mental disorders may be perceived as more complex than in other areas of medicine, as there is a false perception that mental disorders are not associated with mortality, and resources are more easily directed toward health conditions that are considered fatal, especially in the short term. To overcome these difficulties, politicians and the society should become aware of the high morbidity and mortality associated with mental disorders[126] and the economic return on investment of mental health research, which is similar to research in cardiovascular disease.

Some preventive interventions may be delivered by sectors other than healthcare. Support and funding from other institutions, including education authorities, may be required for improving health literacy and developing interventions targeting children and adolescents, especially in schools. An economic argument can be made to employers to try to motivate them to proactively intervene to reduce stress and improve working environments in their companies. This means that information and research on potential short-term benefits of interventions needs to look beyond impacts on the health system (e.g. for school-related outcomes such as academic achievement, reduced truancy, and teacher stress, or potential employer benefits of improved worker mental health) to involve these additional sectors in this process, which also opens opportunities for additional sources of funding and support.

e. Challenge of rebalancing investment in prevention and treatment of mental disorders

Even though the costs associated with some preventive interventions are not necessarily high, in a context of tight healthcare budgets, choices and trade-offs are required between investment in prevention and investment in treatment of existing conditions. This is where mid- to long-term cost-effectiveness arguments could be made. This is also applicable to other areas of medicine where effect sizes and cost-effectiveness data have not been more robust than for mental health. Multi-sectorial investment also becomes feasible if economic benefits to other sectors, e.g. education, can also be identified.

f. Stigma

General stigmatisation of mental illness implies an underestimation of the need for prevention in psychiatry on the part of the general population. The risk of a heart attack seems plausible to most of us, but many will not believe they need to be protected against suicide or self-harm. Personal and community stigma and lack of insight could also hinder indicated prevention in people with early manifestations of mental illness to a greater extent than in other medical conditions by delaying help-seeking behaviour and care due to anticipated discrimination.[111] Evidence-based interventions to tackle stigma and improving access to care in those already experiencing mental distress should be

prioritized.

g. Additional factors

Additional factors include: i) limited insurance coverage in some countries, ii) the need for multilevel and multi-sectorial intervention when services are usually compartmentalized, iii) low perception of risk when early manifestations of mental ill-being are subtle, especially in children and adolescents, iv) high variability of behavioural manifestations during infancy and adolescence, and v) paucity of validated screening tools and treatment for conditions first evident in infants. These factors should be considered when designing preventive interventions (see Panel 2)**.**

Panel 2: Takeaways for prevention of mental disorders

1. *Translating scientific evidence about cost-effective preventive interventions into public health initiatives, clinical practice, and service delivery systems.*

2. *Increasing social, professional, and political awareness about advancements and the importance of mental health prevention and promotion.*

   This includes social education campaigns about early signs, risk and protective factors, and consequences of mental disorders. Claims for societal health investment in preventive psychiatry should be based on personal, family, health, education, and social benefits of reducing mental illness burden, as well as on long-term and indirect economic savings of mental health prevention programmes by reducing disability.

3. *Moving clinical practice toward at-risk-oriented detection and intervention*.

   a. *Need for clearer and more specific definitions of early clinical stages* incorporating neuroimaging, neurocognitive, and biochemical markers into the description of cases, which may help monitor possible trajectories and detect new therapeutic targets.

   b. *Providing standardized and cost-effective screening measures for the accurate detection of at-risk populations at early stages of development* such as perinatal mental illness, developmental disorders, subjects at high risk for psychosis, and children of parents with severe mental illness. There is particularly a need to develop screening tools with high sensitivity, specificity, and positive predictive value for toddlers and pre-schoolers.

   c. *Procuring standardized and cost-effective preventive interventions* such as caring for pregnant adults and adolescents, parental training programmes, cognitive-behaviour therapy and other psychosocial interventions (for high-risk subjects).

   d. *Promoting proper training in standardized and cost-effective preventive interventions for professionals.* Since professionals will detect the risk, they should acquire skills for communicating probability and managing related stress in parents and patients facing uncertainty. In this regard, any decision-making should be based on evidence regarding risks and benefits.

4. *Providing interventions designed for each developmental stage aimed at minimizing the impact of risk factors*.

5. *Promoting interventions with a multidisciplinary and multi-level (psychological, social, familial, legal) approach.* This will require improving coordination among different institutions.

6. *Promoting healthy life styles including nutrition and exercise.*

7. *Encouraging school interventions (targeting children, parents, and education professionals)* for:
   a. Early detection of deviation from normal psychomotor development, language delays, abnormal social behaviour, and poor academic performance
   b. Reduction of bullying
   c. Protection and promotion of resilience to peer victimization and abuse in the vulnerable and assistance for victims, abusers, and bystanders
   d. Prevention of health risk behaviours, including substance abuse and suicidality, and related burden
   e. Promotion of mental and physical health

SUPPLEMENTAL MATERIAL

Supplemental Methods

A complementary systematic search of meta-analyses assessing primary preventive interventions for specific mental disorders [i.e. mood disorders (depressive disorders, bipolar disorder), anxiety disorders, post-traumatic stress disorder, externalizing disorders (disruptive behaviour disorders (i.e. conduct disorders, oppositional-defiant disorder), attention-deficit hyperactivity disorder (ADHD)), eating disorders, psychotic disorders, autism spectrum disorders, and suicidal behaviour] was conducted in PubMed from inception through 6 November 2017. A list of the search terms is provided below. We reviewed meta-analyses reporting pooled data for preventive interventions for specific mental disorders, not within a medical condition or targeting specific professional groups. We incorporated into the manuscript the most recent or comprehensive references for each kind of preventive intervention (universal, selective or indicated) for each specific mental disorder. Studies assessing both therapeutic and preventive interventions were reviewed only if they provided separate statistical data for the preventive interventions. Studies assessing general mental health outcomes (such as wellbeing or resilience) were not included in this review, but if relevant, their results were incorporated into the general manuscript. With respect to suicidality, we did not review interventions for the secondary prevention in people with mental disorders (e.g. lithium in patients with mood disorders, antidepressants in patients with major depression). No specific meta-analyses were found assessing primary preventive interventions in ADHD, obsessive-compulsive disorder, autism spectrum disorders or bipolar disorder.

Disorder	Mental disorder terms	Prevention terms
Depression	Depression Depress* Internalizing	Prevention Preventive Preventative Universal Indicated Selective
Bipolar disorder	Bipolar disorder Affective psychosis	
Anxiety disorders	Anxiety Phobia Anxi* Obsessive Compulsive OCD Panic Agoraphobia Internalizing	
Post-traumatic stress disorder	PTSD Post-traumatic stress disorder Posttraumatic stress disorder Acute stress disorder	
Psychotic disorders	Psychosis Schizophrenia	
ADHD	ADHD Attention-deficit/ hyperactivity disorder Attention deficit hyperactivity disorder ADD Attention deficit disorder	

	Attention-deficit hyperactivity disorder	
Other externalizing disorders	Conduct disorder Disruptive behaviour disorder Callous Antisocial Oppositional defiant Externalizing	
Suicidality	Suicide Suicid* Self-harm	
Eating disorders	Eating disorder Bulimia Anorexia	
Autism spectrum disorders	Autism Austist* Asperger	