Prevention: an achievable goal in personalized medicine

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In the past 15 years a considerable number of studies have found evidence that it may be possible to prevent the onset of some mental disorders. Most evidence is available for depressive disorders, but a growing number of studies have focused on anxiety disorders and psychotic disorders. This paper reviews the studies which have examined the effects of preventive interventions on the incidence of mental disorders in people who do not meet criteria for a mental disorder at baseline. More than 20 studies have examined prevention of depressive disorders, and they have found an overall reduction in the incidence of about 25% compared with control groups. The problem of identifying the most optimal target groups for preventive interventions is also illustrated. This is a problem because most risk indicators have a low specificity, and most people with a risk indicator do not develop a mental disorder. Finally, this paper will show how other statistics, such as the exposure rate, the attributable fraction, and the number needed to treat can help in identifying the most optimal target groups for preventive interventions.

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It has long been thought that it is not possible to prevent the onset of mental disorders, because the processes involved in the etiology are too complex and not yet sufficiently understood. In the past 15 years, however, the knowledge about identifying target groups for prevention and about the effects of preventive interventions has increased considerably. A growing number of randomized controlled trials has shown that it is possible in some cases to actually prevent or at least delay the onset of mental disorders, including depressive disorders and anxiety disorders, and some studies indicate that it may even be possible to prevent the onset of psychotic disorders in high-risk groups (see review below). Research on effective prevention programs is very important for several reasons. First, effective prevention programs may potentially contribute to the reduction of the enormous burden of mental disorders.[1] Mental disorders account for 22% of the total burden of disease in established market economies, as measured in disability-adjusted life years lost,[2] with the common mental disorders (depression, anxiety, and substance use disorders) accounting for three quarters of the burden of all mental disorders. At any given moment, 150 million people suffer from a depressive disorder, 90 million suffer from a substance-related disorder, and each year a million people commit suicide. Mental disorders are associated with huge losses in quality of life in patients and their relatives, with increased mortality and morbidity, with high levels of service use, and with enormous economic costs.[3,4]

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Selected abbreviations and acronyms

AF	*attributable fraction*
ER	*exposure rate*
NNT	*number needed to treat*
OR	*odds ratio*

It is estimated that only half of the burden of the common mental disorders can be averted with existing treatment methods (both psychological and pharmacological) given maximized coverage (the number of people seeking treatment), clinician competence, and patient compliance with treatment.[5] If we want to reduce the burden of mental disorders further, we can either develop new treatment methods that are considerably better than existing ones, or we can develop preventive interventions that result in reductions of new cases. The option for preventive interventions has not been examined very thoroughly, although it can be regarded as a promising way to reduce the burden of psychiatric diseases.[5] Another reason why this research is so important is that it may increase our knowledge of the etiology of mental disorders. Until now, most mental disorders have been thought to be caused by multiple factors on different levels (physical, social, psychological), and it is not possible to predict which individual is going to develop the disorder and who is not. If it proves to be possible to prevent new cases of mental disorders, the interventions must somehow change the basic mechanisms that lead to the occurrence of the disorder.

This review will first define exactly what prevention is. Then, the research on the effects of interventions on the prevention of the incidence of new cases of mental disorders will be summarized. Finally, the possibilities of developing personalized preventive interventions, using new epidemiological methods to identify the most important high-risk groups for prevention, will be described.

What is prevention?

In the definition of depression which is currently used by most researchers and practitioners, depression comprises all interventions which are conducted before subjects meet the formal criteria for a mental disorder (according to the *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed, *DSM-IV*).[6] Curative interventions are given to persons who suffer from acute disorders, and maintenance treatments are given to patients with chronic disorders. In this spectrum of interventions, three types of prevention can be distinguished:

- Universal prevention is aimed at the general population or parts of the general population, regardless of whether they have a higher-than-average risk of developing a disorder. The best-known examples of universal prevention include school programs aimed at all students, whether they have an increased risk of developing a mental disorder or not, and mass-media campaigns, aimed at the general population.
- Selective prevention is aimed at high-risk groups, who have not yet developed a mental disorder. High-risk groups include people who have recently experienced a stressful life event or who experience a chronic stressor, such as divorce, losing a family member through death, caring for an ill family member, and unemployment.
- Indicated prevention is aimed at individuals who have some symptoms of a mental disorder but do not meet diagnostic criteria. Indicated prevention is aimed at people who already suffer from some (depressive) symptoms.

Is prevention of mental disorders effective?

In the past few decades, several hundred controlled studies have examined the effects of mental health programs aimed at preventing mental health problems at school,[7,8] substance use and abuse at school,[9] work-related stress,[10] distress among caregivers for the elderly,[11,12] child abuse,[13–15] and many other conditions. This considerable body of research has shown that some prevention programs in mental health are capable of strengthening protective factors, such as social skills, problem-solving skills, stress-management skills, prosocial behavior, and social support; that these programs can reduce the consequences of risk factors, psychiatric symptoms, and substance use; and that they may have positive economic effects.

However, only a small proportion of these studies have focused on possibilities for actually preventing the onset of new cases of mental disorders.[6] In recent years, a growing number of studies have examined whether prevention programs are actually capable of reducing the incidence of cases of mental disorders as defined by diagnostic criteria. In these studies a standardized diagnostic interview at baseline is used to exclude the pretest presence of a full-blown depressive disorder and to

examine the incidence of depressive disorders at follow-up (again with a diagnostic interview). In the following, we will review these studies.

Prevention of depressive disorders

Most research has focused on the prevention of depressive disorders. Following the first studies conducted in the 1990s,[16-18] the number of studies has increased rapidly since 2000. We recently conducted a meta-analysis of these studies,[19] and found a total of nineteen studies in which subjects with a depressive disorder according to DSM criteria at baseline were excluded, and only subjects with no formal depressive disorder were included. All these studies examined whether the incidence rate of mental disorders was reduced in the recipients of preventive interventions compared with subjects who did not participate in such an intervention. We found that the overall incidence rate ratio was 0.78 (95% CI: 0.65~0.93). The incidence rate ratio is the incidence rate of developing a depressive disorder in experimental subjects relative to the incidence rate in control subjects. An incidence rate ratio of 0.78 indicates a reduction of the risk of developing a depressive disorder in the next year of about 22% compared with people in the control groups. This study indicates that prevention of new cases of depressive disorders is indeed possible, and could be a realistic strategy to reduce the enormous burden of these disorders, next to treatment of existing depressive disorders. Preventive interventions have been developed in several settings, including the school setting, prevention of postpartum depression in pregnant women, and prevention of depression in general medical disorders.

A considerable number of studies has examined the possibilities of prevention in the school setting.[20,21] However, most of these have only examined whether school programs are capable of reducing the overall level of depressive symptoms in students. Although this is interesting in its own right, and positive effects may be indicative of effects on depressive disorders, the results of these studies do not result in clear evidence of a preventive effect of these interventions on depressive disorders. Until now, only four studies have examined preventive interventions aimed at the reduction of the incidence of depressive disorders at school.[17,22-24] Two studies used a universal intervention aimed at all students, regardless of whether they had an increased risk of developing a depressive disorder.[25,26] In both studies, no significant effect on the onset of depressive disorders was found. In three studies, the effects of an indicated intervention were used examined,[17,22,24] and these had mixed results, with one study finding strong and significant effects on the incidence of new depressive disorders at 1-year follow-up.[17] Most interventions in the school setting, both universal and indicated, have used cognitive behavioral group interventions.

There is also a considerable number of studies that have examined the possibilities of preventing postpartum depression (PPD),[27,28] but again most of these studies did not use diagnostic criteria at pretest and post-test, to exclude women who already had a depressive disorder at pretest, and to examine the effects of prevention on the incidence. Most studies have used self-report measures, and have only examined whether the level of depressive symptoms have decreased in the prevention groups compared with control groups. Many of these studies used cognitive behavioral interventions,[29-30] although other studies used psychoeducational interventions,[31] debriefing,[32] and interpersonal psychotherapy.[33,34] A recent meta-analysis of studies on prevention of PPD did not find clear evidence that preventive interventions during pregnancy may reduce the incidence of postpartum depression.[27] This meta-analysis did not, however, focus on studies in which women who met diagnostic criteria for a depressive disorder were excluded at pretest, and in which the incidence of depression in treatment and control groups were established according to diagnostic criteria. In the earlier described meta-analysis, seven randomized controlled in which diagnostic instruments were used, could be included. These resulted in an incidence rate ratio of 0.65 (95% CI: 0.41~1.05; P<0.1).

Another group of studies has focused on the prevention of depression in general medical disorders. Several groups of general medical patients have been examined in prevention studies, including adolescents with newly diagnosed epilepsy and subthreshold depression (but no major depressive disorder),[35] older patients with neovascular macular degeneration,[36] and stroke patients.[37] Three studies have examined the possibility of preventing depressive disorders in primary care.[16,38,39] Most studies in this field used cognitive behavior therapy[16,35,38] or problem-solving therapy as intervention.[36,37]

One of the studies in primary care used a stepped-care intervention. Such stepped-care interventions are inter-

esting because they seem to have larger effects than single interventions (with a reduction of the incidence of 50%),[39] and because they devote most intervention time to those who need it most. In such a stepped-care approach, the first step is watchful waiting. This means that no specific intervention is conducted for 6 to 8 weeks, because many subclinical depressive symptoms recover spontaneously without intervention. In the second step, a guided self-help intervention is provided to patients. Guided self-help has been proven to be effective in the reduction of depressive symptoms,[40] and may be sufficient for some patients. If the guided self-help is not sufficient and patients continue to have depressive symptoms, a brief psychological intervention is provided, such as problem-solving therapy, or a brief cognitive-behavioral intervention. When this is not enough, patients are referred to specialized mental health care where they receive intensive treatment with antidepressant medication.

Prevention of other mental disorders

Although most research has examined the effect of prevention on the incidence of depressive disorders, a growing number of studies has examined the possibilities of preventing the onset of anxiety disorders and psychotic disorders in high-risk populations.

A considerable number of studies has examined the possibility of preventing the onset of post-traumatic stress disorder (PTSD) with debriefing interventions.[41] Unfortunately, many of these studies did not use diagnostic instruments to establish the presence of PTSD at follow-up. However, the studies that have been conducted seem to indicate that debriefing increases the risk of developing PTSD, instead of decreasing this risk.[41,42]

Several other studies have examined the possibilities of prevention of other anxiety disorders. In an early study among patients with panic attacks who visited the emergency room of a hospital, it was found that exposure therapy had better outcomes than reassuring them that there was no physical illness.[43] In a more recent study among persons with high levels of anxiety sensitivity, it was found that preventive training consisting of psychoeducation and behavioral exercises significantly reduced the risk of developing an anxiety disorder in the following 2 years.[44] In another study, it was found that the incidence of panic disorder in people with subthreshold panic attacks is lower at 6 months' follow-up in those who attended a 1-day preventive workshop compared with those on a waiting list.[45]

In recent years, several studies have examined the effects of preventive interventions on the onset of psychotic disorders.[46-49] In these studies, patients with subthreshold symptoms of psychotic disorders (without meeting full diagnostic criteria) are randomized to cognitive behavior therapy or a control condition. These studies show significant reductions of transition to psychotic episodes in those who have received the preventive interventions, compared with those in the control groups, although the longer-term effects are not so clear.[47,48]

Problems in identifying target groups for preventive interventions

In the preceding paragraphs it was shown that a considerable number of recent studies have examined the effects of preventive interventions on the incidence of mental disorders, and, when taken together, with considerable success. However, the success of these interventions depends very much on the selection of the right target populations. The first step in every intervention is to select a target population which has an increased risk of developing a mental disorder within the coming months or year. In the following paragraphs, we will explain why this selection of high-risk groups is very complicated, and present some recently developed methods in epidemiology to solve the problems in the selection of target groups.

In the past few decades, an enormous body of research has shown that many biological, psychological, and psychosocial risk indicators are associated with the onset of mental disorders. These include genetic factors, characteristics of personality, social economic status, stress and burden, urbanization, loneliness, life events, and somatic factors, such as complications during pregnancy, developmental disorders, neuroendocrinological factors, and general medical disorders. Note that we define these variables as risk indicators, and not as risk factors, as risk factors suggest that these are causally associated with the onset of depressive disorders. Risk indicators only indicate that there is an association between the variable and the onset, while no causal association is assumed. In principle, these risk indicators can be used to identify target groups for preventive interventions. In the next part of this paper, we will show that several groups of interventions actually have focused on such high-risk groups.

Although many risk indicators are known to be associated with the onset of mental disorders, most of them have a low specificity. This low specificity implies that most subjects who are exposed to the risk factor do not develop the disorder, and that one such risk factor by itself is not sufficient to bring the disorder into being.[50,51] Furthermore, most risk indicators are related to lifetime risk, while target populations for preventive interventions must have an increased risk at the shorter term. Suppose, for example, that the risk of developing a major depressive disorder in the general population is 2.5% in 1 year.[52,53] If a high-risk group has a relative risk of developing a depressive disorder of 4.00, this will be highly significant (if the research population is large enough). However, this means that still only about 10% of the high-risk group will actually develop a depressive disorder, and about 90% will not.

Many epidemiological researchers are satisfied after finding a highly significant relative risk of 4.00, but from the point of view of prevention this is clearly not enough. A high-risk group will probably be difficult to motivate for participation in a preventive program if only 10% eventually will develop the disorder, apart from the question of whether it is ethically acceptable to identify such a population as being "at risk" when most are in fact not at risk, or to intervene in such a population when for the vast majority of participants the intervention is not needed, and thus the time they spend on it is, in a sense, wasted. Furthermore, such an intervention is probably not very efficient or cost-effective, because the majority will never develop a disorder and the intervention has no preventive effect in this majority.

From the perspective of preventive intervention research, this low specificity is also problematic because very large numbers of subjects are needed to provide sufficient statistical power for these intervention studies.[51] Suppose, for example, that we would be able to motivate people from the high-risk group (10% of whom will develop a mental disorder in the following year) to participate in a preventive intervention. In order to show that such an intervention is capable of reducing the incidence from 10% to 5% (a risk reduction of 50%), we would need about 950 persons in a controlled trial (assuming a statistical power of 0.80; alpha level 0.05; calculations in STATA/SE 8.2). Trials of this size are logistically complex, expensive, and have a high risk of failure.

Towards an improved method of identifying target groups for prevention

As previously stated, traditional indicators of the strength between a risk indicator and the incidence of a mental disorder are not sufficient when we want to identify the best target populations for preventive interventions and to develop personalized interventions. Improvements can be made by selecting target groups while using indices other than odds ratios (ORs), relative risks (RRs) or incidence rate ratios (IRRs) alone, and in particular by studying the cumulative effect of joint exposures to several risk indicators rather than the effect of a single risk indicator. The proposed method can be carried out in several steps.

First, a set of significant risk indicators is identified such that each of them has a statistically significant impact on the likelihood that the disorder will develop. To do this any of the available measures of association for binary outcomes (OR, RR or IRR) can be used.

Second, if an OR can be calculated, then it is also possible to say how many people are exposed to that risk indicator. Call this measure "exposure rate" (ER). For prevention the ER is important, because it tells us how many people have to be targeted by the preventive intervention. Clearly, smaller groups (smaller ER) are associated with less effort and hence lower costs of delivering the intervention.

Third, with the OR and ER in hand one can calculate the population attributable fraction (AF). The AF indicates by how many percent points the current incidence rate of the mental disorder in the population could be reduced when the adverse effect of the risk indicator is completely blocked.[54-56] This equals the maximum possible health gain of a completely successful preventive intervention.

Fourth, if the OR can be calculated, then it is also possible to obtain the risk difference (eg, under a linear probability model) and its inverse: the number needed to treat (NNT). In the context of these analyses the NNT can be interpreted as the number of people who should be the recipients of a preventive intervention to avoid the onset of the disorder in one person. Again we have to assume that the preventive intervention is completely successful in containing the adverse effect of the risk factor. This assumption is not realistic, but the NNT may still help to create a hierarchy of risk indicators to be targeted in prevention.

Now comes the most important part of the method. We want to maximize the health gain (large AF) and minimize the effort to generate this health gain by targeting the smallest possible group (small ER) in the most efficient way (small NNT). Best values overall can be found by looking at combinations of risk indicators. That is, we can see what combinations of exposures (joint exposures) help to minimize and maximize the indices, such that a target group is selected where prevention is most likely to become cost-effective.

There are several ways of finding specific combinations of risk indicators, whether genetic or environmental, that meet the above criteria, including sophisticated statistical techniques, such as classification and regression trees (CART) analysis, and bootstrap aggregation (bagging).[57,58] The most straightforward method, which we use here for illustrative purposes, is to select significant predictors of incidence (with standard techniques such as logistic regression) after which all possible combinations of these significant risk indicators are explored in terms of maximizing the OR and AF, and minimizing ER and NNT associated with each of the joint exposures. We used this approach in a population-based sample of older adults,[54] and found that subjects with (subclinical) depressive symptoms, functional limitations, a small social network, and female gender comprised only 8% of the total population (ER) while 24.2% of the new incident cases could be attributed to this group (AF). The number of subjects from this population that would have to receive a preventive intervention in order to prevent one incident case (NNT) was 4 (assuming that the intervention is 100% successful).

There is little doubt that these methods will help to identify the best target groups for preventive interventions in the near future and to develop personalized interventions. However, at this moment these methods have not yet been applied in intervention studies.

Conclusion

This paper is intended to illustrate why prevention of mental disorders is important. Reasons for its importance include its very high prevalence, incidence, disease burden, and its huge economic costs of depression. It is also important because current treatments can reduce the disease burden only to a limited extent, even when only evidence-based treatments are given and all patients receive such an intervention.

In the past 15 years a growing number of studies has shown that interventions to prevent the onset of depressive disorders are probably effective, and can reduce the incidence by about one quarter. Prevention of anxiety disorders and psychotic disorders may also be effective, although the number of studies in these areas are lower. It is not clear whether these preventive interventions have actually prevented the onset of mental disorders altogether, or only delayed the onset. In both cases, however, the health benefits of preventive interventions are considerable.

In the next few years, the internet will probably provide new opportunities for the broad implementation of preventive interventions, because access is easy, cheap, and effective. Another important development is stepped-care interventions, which are interesting because they may have stronger effects than individual interventions and spend most resources on those who need it most.

It has also been shown that traditional epidemiological research can not identify the best target populations for prevention. Relatively simple statistics, such as the exposure rate, the population attributable fraction, and the number needed to treat can be used to select those high-risk groups which are as small as possible, but explain as many of the new incident cases as possible. These methods will probably help in the further development of personalized preventive interventions. ❑

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La prevención: un objetivo alcanzable en la medicina personalizada

En los últimos quince años numerosos estudios han encontrado evidencias de que puede ser posible prevenir la aparición de algunos trastornos mentales. Si bien la mayor evidencia de que se dispone corresponde a los trastornos depresivos, existe un número creciente de estudios focalizados en los trastornos de ansiedad y psicóticos. Este artículo revisa los estudios que han examinado los efectos de las intervenciones preventivas en la incidencia de los trastornos mentales en personas que no cumplen con los criterios de un trastorno mental en el estado basal. Más de veinte estudios han examinado la prevención de los trastornos depresivos, y han encontrado una reducción global de la incidencia de alrededor del 25% comparado con los grupos control. También se ilustra el problema de la identificación de los grupos blanco más específicos para realizar intervenciones preventivas. Esto es un problema porque la mayoría de los indicadores de riesgo tienen una baja especificidad, y la mayor parte de las personas con un indicador de riesgo no desarrolla un trastorno mental. Por último, este artículo muestra cómo otras variables (frecuencia de exposición, fracción atribuible y número necesario para tratar) pueden ayudar a identificar los grupos blanco más específicos para las intervenciones preventivas.

La prévention : un objectif accessible pour la médecine personnalisée

Un nombre important d'études a montré au cours de ces 15 dernières années qu'il pourrait être possible de prévenir la survenue de certains troubles mentaux. La plupart des résultats concernait les troubles dépressifs mais de plus en plus d'études se sont intéressées aux troubles anxieux et psychotiques. Cet article passe en revue les études qui ont examiné les effets des actions de prévention sur l'incidence des troubles mentaux chez des sujets qui ne présentaient pas initialement les critères de pathologies psychiatriques. Dans plus de 20 études analysant la prévention des troubles dépressifs, l'incidence a globalement diminué d'environ 25 % comparée aux groupes témoins. Il est difficile d'identifier les meilleurs groupes cibles pour les actions préventives car la plupart des indicateurs de risque ont une faible spécificité et la plupart des personnes ayant un indicateur de risque ne développent pas de maladie mentale. Enfin, cet article se propose de montrer comment d'autres variables statistiques, comme le taux d'exposition, la fraction attribuable et le nombre de sujets ayant besoin d'être traités peuvent aider à identifier les cibles les plus adaptées des interventions de prévention..

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