Part V
Prevention of depression: summary and general discussion

Chapter 5.1
Prevention of depression: summary of preceding chapters
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Summary of preceding chapters

5.1.1 Introduction

The aim of the previous chapters was to answer four questions about prevention of depression: (1) do we need it? (2) do we know where to start? (3) is it effective? (4) is it affordable? Here, in the Summary we will return to these questions, and address each of them.

5.1.2 Do we need it?

Chapter 1.1

Individual suffering, however severe, does not make a major public health problem. Here a second factor has to come into play. It is only when individual suffering is multiplied by the vast number of prevalent cases that a disorder attains the status of a major problem in the realm of public health. Indeed, both severity and prevalence have combined to make depression one of the disorders with the largest burden of illness, worldwide.

Although, depression is a condition that can be treated successfully, it has been shown in two studies (Andrews et al, 2004; Chisholm et al, 2004) that current curative interventions can only partially reduce the depression-related disease burden at population level. As a consequence there remains a formidable gap to be bridged between the needs of many and what treatment can offer. Therefore, we need to look for interventions other than curative treatment alone. In the formulation of Chapter 1.1, this major health problem has to be tackled along its width and breadth, and that is why prevention has to play an adjunctive role to treatment. This need is further underscored by the fact that the incidence of depressive disorder is very substantial relative to its prevalence: 49% of the prevalent cases are in fact new cases. Seen from a public health perspective, this calls for a reduction in the massive influx of new cases. Again, prevention may be the answer – provided that we know where to begin, that prevention is effective, and that it is affordable.

Chapter 1.2

The latter issue brings us to Chapter 1.2, which is a cost-of-illness study of the common mental disorders. Here we showed, by a conservative estimate, that the annual excess costs of depressive disorder amount to € 2,300 per capita, which gives us some idea of the potential cost-offset of successfully preventing new onsets. At population level, where the per capita costs have to be multiplied by the vast number of prevalent cases, the societal costs become staggering: depressive
disorder poses a formidable economic burden to society of more than €1,300,000,000 in the Dutch population aged 18 – 65 years, each year, every year. It stands to reason that a reduction in the incidence of depressive disorder will also bring about a reduction in the economic burden of the disorder. Thus Chapter 1.2 has two-fold take-home message. First, it might be worthwhile, from a strictly economic perspective, to further develop, evaluate, and implement preventive interventions in depression. Second, it holds the promise that prevention of mental disorder, in particular depressive disorder, is likely to become a cost-effective endeavour. This cost-of-illness study is in press at the Journal of Mental Health Policy and Economics.

5.1.3 Do we know where to start?

Background
Against the background sketched in Chapters 1.1 and 1.2, it becomes important to get clear-cut answers to the question, do we know where to begin with depression prevention?

The question is relevant, because far too many people are exposed to one or another possibly relevant risk factor; and, leaving ethic considerations aside, it would be a sheer impossibility, both logistically and economically, to provide all these people with selective prevention. Similarly, the number of people with some depressive symptoms who don’t meet the diagnostic criteria of depressive disorder can be very large too, depending, of course, on the exact definition of subthreshold depression. Moreover, vaguely defined groups, wherein the risk of actually becoming depressed may vary considerably, may give rise to justifiable ethical concerns with regard to the acceptability and appropriateness of offering preventive interventions. Hence, the relevance of the question, where to start?

Our approach to answering this question was to try to identify groups with a calculable ultra-high risk for the disorder. The idea was that ultra-high risk groups would at once be numerically small, and yet account for a large share of all the new cases of the disorder in the population. Furthermore, in small, ultra-high risk groups, with a large share in the incidence, prevention is likely to stand the best chance of becoming cost-effective. Expressed in epidemiological and statistical terms, we were looking for groups with a high incidence rate (IR) of depressive disorder, higher than the incidence rate in groups not exposed to certain risk factors. Hence, we were looking for groups with a high incidence rate ratio (IRR). At the same time, we would like these groups to be as small as possible, i.e. with a very low exposure rate (ER) of the risk factors. Both the exposure rate and the incidence rate ratio can be combined in another statistic, the population attributable fraction (AF). The AF is a useful statistic from a prevention perspective: it indicates by how many percent the incidence rate of the disorder in the population will be lowered, when the adverse effect of the risk factor can be completely blocked by some
preventive intervention. This makes the AF an index of potential health gain in a population under optimal preventive scenarios. It would not be realistic to assume that preventive interventions are completely successful in averting the impact of a risk factor. Therefore, it is readily understood that the AF puts an upper limit to the potential health gain. Nevertheless, the AF is a useful statistic when it comes to creating a hierarchy of risk factors that have value for prevention.

Chapter 2.1
This approach was taken in Chapter 2.1 in a somewhat explorative fashion. We made use of a population-based psychiatric cohort study, Nemesis, and calculated exposure rates (ERs), incidence rate ratios (IRRs), and population attributable fractions (AFs) for a large set of putative risk factors assumed to be predictive of first-ever onset of depressive disorder in people aged 18 – 65 years. For each risk factor we also calculated the number-needed-to-be-treated (NNT) as an index of the potential efficiency of a preventive intervention when it is successful in blocking the adverse effect of that particular risk factor. Using this methodology, we began to see the numerically small, high-risk groups, where prevention was likely to generate the largest health gains, in the most efficient way, for the fewest costs. This study was published in the Journal of Affective Disorders (Smit et al, 2004), and ended on a note to the effect that future research should compute the indices for health gain (IRR, AF) and effort (ER, NNT) not for a single risk factor at a time, but for multivariate sets of risk factors, such that these indices are maximised and minimised in their respective desired directions.

Chapter 2.2
It was precisely this multivariate approach that we took in Chapter 2.2. Here, we evaluated the effects of joint exposures on the indices of health gain and effort in another large population-based psychiatric cohort study of people aged 55 – 85 years, the Longitudinal Aging Study Amsterdam (LASA). This approach enabled us, in a much better way, to identify the ultra-high risk groups, that were numerically small, that accounted for the bulk of new cases of depressive disorder, and where prevention stood the best chance of being efficient and cost-effective. We also performed an ante hoc economic evaluation, demonstrating that prevention of late-life depression was indeed likely to be a cost-effective venture. The corresponding study was published in the Archives of General Psychiatry (Smit et al, 2006a), and ended with the observation that the new methodology employed in this study needed cross-validation in a further study.

Chapter 2.3
This cross-validation is contained in the last chapter of Part II of this study. Use was made of yet another psychiatric cohort study, viz., the Amsterdam Study of the Elderly (the Amstel study). It is worth noting that in this study depression was ascertained in a different way, and slightly different definitions of the putative risk
factors were used. We also made use of a different method of identifying ultra-high risk groups. This method is known as Classification and Regression Tree (CART) analysis. The “tree” in the name refers to the tree-like diagrams that are produced to systematically trace the effect of adding new risk factors in terms of ER, IRR, AF and NNT. The procedure of adding risk factors helps to ascertain what combinations help optimise the health gain and efficiency, and minimise the effort of generating these health gains.

It was interesting to see that this approach yielded near identical results to those found in Chapter 2.2: indicated prevention in later life is best directed at people who (-) have some depressive symptoms, (-) have a chronic somatic illness, (-) experience disability (-) are living alone, and (-) are female. There was one exception: in the Amstel study we found widowhood to be a significant predictor, while in the LASA study we did not. However, it should be noted that in the LASA study widowhood was defined as “ever widowed” (without reference to a specific time-frame), whereas in the Amstel study it was more accurately described as “recent widowhood” (in the last 6 months). Thus, the different definitions may account for the single difference in the studies’ outcomes.

On account of the overall congruence of both study outcomes, we are tempted to conclude that we may say with some confidence that we now do see where to begin: indicated prevention in groups that have some depressive symptoms offers the best start, and can be improved on when the target group is further selected with help of the afore-mentioned risk factors. The study also indicates that selective prevention may be an alternative; it offers the additional benefit that the corresponding target group can be easily identified in the primary care setting with help of a brief checklist based on a small set of easy-to-recognise risk factors, such as recent widowhood, medical illness, disability and female gender. It is these risk indicators, and in this combination, that carry the promise that prevention may yield substantial health gains in an efficient and presumably cost-effective way. This study, by Schoevers, myself and colleagues, has been published in the American Journal of Psychiatry (Schoevers et al, 2006).

5.1.4 Is it effective?

Background
The third part of the thesis addresses the question concerning the effectiveness of preventive interventions in avoiding new onsets of depressive disorder. To put this in context, the effectiveness of preventive interventions has been evaluated in literally hundreds of randomised trials, but the outcome was nearly always a reduction in symptom level, and only very rarely a reduction of incidence. Thus in effect, next to nothing was known about primary prevention of depression. The reason for this apparent omission is clearly explained in Cuijper’s 2003 article in the American Journal of Psychiatry where it was demonstrated that due to the often
very low incidence rates of mental disorders, differences in the incidence rates across experimental and control conditions can only be evaluated in trials that are based on astronomically large sample sizes. Logistic and financial constraints preclude this as a viable option. However, the sample size problem can be circumvented by conducting trials in high-risk groups with correspondingly high incidence rates.

Chapter 3.1
We followed this strategy in the study described in Chapter 3.1. This study was designed as a pragmatic randomised prevention trial in two parallel groups. The trial participants were general practice patients, who were recruited while waiting to see their doctor. They were eligible for inclusion in the trial if a number of criteria were met; the most important of these were having at least one depressive core symptom plus one, two, or three additional symptoms, not meeting the diagnostic criteria for DSM-IV depressive disorder as ascertained with the CIDI. Exclusion criteria were presence of full-blown DSM axis-I disorders, such as dysthymia and bipolar disorder. On the basis of the scientific literature we expected the risk of depressive disorder to be close to 20% per year in this population. We hypothesised that this risk could be lowered by one third if in addition to care-as-usual an adjunctive preventive cognitive-behavioural self-help intervention was offered with minimal guidance. To power the trial to detect such an effect, we needed to enrol 200 participants in each condition; a number sufficiently large to also compensate for some expected loss-to-follow-up. The central end-point of this trial was CIDI/DSM-IV depression status after 12 months.

Analyses were conducted while adhering to the intention-to-treat principle. For this, missing observations at follow-up were imputed. The analyses also accounted for a clustering effect in the data, which was induced by the fact that some patients were recruited from the same general practice. In total, 107 consenting participants were randomised to the intervention and 109 to the care-as-usual group.

The results were as follows. In the care-as-usual group the incidence rate of depressive disorder was 18%; and this was 12% in the treatment group, implying a reduction by 33%. The unidirectional 0-hypothesis that adjunctive self-help combined with care-as-usual is inferior to care-as-usual alone, had to be rejected at $P<0.05$ in a one-sided test, thus lending credibility to the idea that self-help as an adjunct is superior to primary care as usual alone.

This was good news, but there were two problems: recruitment had proved to be a difficult process, and the participation and completion rates in the intervention were low. This reflected unfavourably on the acceptability of the intervention, and may call for more stringent selection criteria of the participants, for example on the basis of the risk factors as identified in Chapters 2.1, 2.2 and 2.3, and especially with regard to the participants’ own perceived need to enrol in such an intervention.
The outcomes of the prevention trial were published in the British Journal of Psychiatry (Willemse et al, 2004).

Chapter 3.2
Our prevention trial (see Chapter 3.1) was one of the seven that ascertained the effectiveness of a psychological intervention in actually preventing the onset of full-blown depressive disorder in people with subthreshold depression. In Chapter 3.2 we pooled the outcomes of all seven studies meta-analytically.

Two types of outcomes were considered. The first is the reduction in depressive symptom level, and the corresponding effect size is Cohen’s d, which indicates by how many standard units the experimental group is removed from the control group in terms of health gain. The second outcome is the reduction in the risk of becoming a case of depressive disorder in the experimental group relative to the control group, which was ascertained with an outcome technically known as the incidence density ratio.

The outcomes of the meta-analysis were as follows. All seven studies examined a total of 700 subjects, with 343 subjects in the experimental conditions, and 357 in the control conditions. In six studies, the control condition was care-as-usual, and in one study it was a waiting list with unrestricted access to care-as-usual. Because heterogeneity was virtually absent, and outcomes of random effect models and fixed effect models were quite similar, we reported only the outcomes of the more simple fixed effect models. Symptom reduction was achieved by 0.42 standard units, in favour of the psychological interventions, and as measured immediately after the intervention. This effect size represents an effect of medium size as compared to what is found as the median of all effect sizes in the field of behavioural and psychotherapeutic interventions. However, we also noticed a drop in the effect size over time: after one year it had shrunk to a small effect of 0.16 standard units, which only bordered on statistical significance at P= 0.08, two-sided. The second outcome, which captured the relative risk reduction of becoming depressed, indicated that psychological interventions help to reduce the incidence of new cases by 30%, which was marginally significant at P= 0.07 in a two-sided test.

Our appreciation of these results is as follows. In clinical terms the effect sizes are in an order of magnitude that is in line of what may be expected from relatively low-key psychological interventions, but the observation that effects diminish over time must be seen as an important issue. The time-decay may indicate the need for booster sessions, and may further alert us that we have to understand prevention of mental disorders not in terms of a single-shot, magic-bullet, sort of approach, but rather more like safety belts in cars that need to be used every time we drive. In the same vein, the risk reduction of 30% looks good from the clinical perspective, but leaves one wondering whether this effect will survive over time. From the statistical point of view we are not overly concerned with P-values that were only bordering on significance, because the P-values would have been significant in an one-sided test, while, in this context, the use of a one-sided test can
be justified by the unidirectional hypothesis based on the idea that adjunctive interventions added to care-as-usual are almost certainly superior to care-as-usual alone. But not wishing to jump to conclusions prematurely, we suggest that all we have now are “indications” that preventive interventions of a psychological nature can be successful in preventing full-blown depressive disorder in people suffering from subthreshold depression. It is also clear that more prevention trials are required, because we need to know what groups in what settings benefit from what interventions and for how long.

5.1.5 Is it affordable?

Chapter 4.1
We conducted a cost-effectiveness analysis alongside the same prevention trial that was described in Chapter 3.1. In the economic evaluation we took the societal perspective. To this end, the following costs were considered. Direct medical costs arise in connection with the uptake of all types of health services, including this intervention. Direct non-medical costs include the patients’ out-of-pocket costs that are made when travelling to health services, paying for parking, plus the cost of the patients’ time while travelling, waiting and receiving treatment. Furthermore, we included the indirect non-medical costs, that is, the costs related to production losses in paid work due to work loss days and work cutback days, plus the costs of production losses in the domestic sphere. Costs were calculated for one year, and were therefore neither discounted nor corrected for inflation, as per the Dutch guideline for health economic evaluation.

The results were as follows. The adjunctive self-help intervention with minimal guidance combined with care-as-usual in primary care was 33% more successful in avoiding onsets of depressive disorder than care-as-usual alone (cf. Chapter 3.1). The mean integral costs are € 6,766 per capita per annum in the experimental group, which compares favourably with the sum of € 8,614 in the control condition. The incremental cost-effectiveness ratio indicated that offering the adjunctive self-help results in a modest cost saving of € 288.75 per depression-free survival year. However, the latter outcome was surrounded by a considerable degree of stochastic uncertainty.

A probabilistic approach, based on 2,500 bootstraps, indicated that adjunctive self-help had a 70% probability of being more acceptable from a cost-effectiveness perspective than routine primary care alone, even in the conservative scenario that there is no willingness to pay for the health gain of a depression-free survival year. A sensitivity analysis showed that production losses were the main cost-drivers. Excluding these costs, and thus limiting the economic evaluation to direct costs only, showed that adjunctive self-help has a 47% probability of dominating routine primary care in terms of the incremental cost-effectiveness ratio at a willingness to pay equal to zero. Raising the willingness to pay to a ceiling of €
30,000 per depression-free survival year resulted in a 72% probability that the adjunctive self-help intervention is more acceptable than routine primary care alone as seen from a cost-effectiveness point of view.

The outcomes of the study show that from a health economic point of view, adding the cognitive behavioural self-help intervention with minimal guidance to routine primary care has the benefit of producing health gains while at the same time it generates cost-offsets that compensate for the outlay involved in providing the self-help intervention in the first place. Thus, offering this intervention in the primary care setting appears to be an attractive option. Nevertheless, and as was pointed out before, we need to know more about the acceptability of the intervention, and its long term outcomes, before we can confidently recommend its broader implementation.

At the time when we wrote this paper, we were, to the best of our knowledge, the first to conduct an economic evaluation alongside a primary prevention trial in depressive disorder. However, before our paper appeared in print in the British Journal of Psychiatry (Smit et al, 2006), Lynch and colleagues published another cost-effectiveness study in the same research field, which appeared in the Archives of General Psychiatry, in 2005. In their paper they reached a similar conclusion to ours: a brief intervention to prevent depressive disorder in at-risk teens aged 13 to 18 years, was economically affordable given a variety of thresholds for the willingness to pay for a depression-free day. To summarise, we begin to see the first evidence that primary prevention of depression is an economically viable option. Nevertheless, there is a clear need to conduct more studies of this type, in order to better understand the outcomes of different interventions in different groups, and over longer time periods. We also need more in-depth efficacy studies to better understand what components of the intervention do really matter in producing the desired health effects. This knowledge can than be used to do a better job in designing cost-effective interventions.

Chapter 4.2

Many of the key concepts from the previous chapters were re-introduced in the last chapter, and brought together in a somewhat different framework. Again, the focus was on costs and risk factors, but this time we studied the costs of risk factors, thus putting an epidemiological slant on health economics. In so doing, we wanted to draw attention to the very roots of mental illness, disability, and the ensuing societal costs. In addition, we wanted to evaluate how the relationship between risk factor and costs was modified by a protective factor, mastery, which can be defined as the sense of being in control over one’s life. The idea was that an intact sense of mastery would help to cushion the adverse economic and health effects of being exposed to a risk factor. If this is indeed the case, then it may be of interest to pursue the concept of strengthening one’s sense of mastery as a strategic research topic.
For the analysis, we revisited the large population-based psychiatric cohort study, Nemesis, conducted among 5,618 people aged 18 – 65 years (cf. Chapters 1.2 and 2.1). The risk factors were measured at baseline and describe parental depression and parental anxiety as well as exposure to childhood abuse and emotional neglect before the respondents had reached the age of sixteen. These “early” risk factors are known to be predictive for the later onset of mental disorders. To facilitate etiological inference, the costs were measured one year later and encompass the integral medical and non-medical costs related to health care uptake, and the costs of production losses in both paid work and in the domestic sphere (cf. Chapter 1.2).

The results were as follows. The risk factors were associated with excess costs in the order of 2,000 – 3,000 US$ per exposed person per annum. Given the exposure rates of the selected risk factors in the population, the costs fall between 170 – 770 million US$ in every one million people. The effect of low versus high levels of mastery was in the hypothesised direction, with higher costs in exposed people with below average levels of mastery, and lower costs in exposed people who had above average mastery. In fact, the costs of the risk factors were down to roughly one-third of the average costs when people had an intact sense of mastery.

The results show that the selected risk factors are associated with formidable costs, even many years after exposure. The excess costs are incurred, year after year, and remain virtually the same when the effect of demographics variables is accounted for in multivariate analysis. This suggests that prevention directed at these risk factors may be economically rewarding. Still, it is difficult to see how prevention could help to contain the adverse effects of some of the selected risk factors, although strengthening mastery might prove to be the option we are looking for: it helps to reduce the costs associated with the risk factors to one-third of the original mean costs. However, at this point a word of caution is needed. One would much like to see analyses that show how a change in mastery is later followed by a change in costs, but these analyses could not be performed using the available data. Currently we are collecting longitudinal trial data on both mastery and costs, and we foresee that the proper analyses can be conducted in the near future. That research can now be guided by a new working hypothesis: with help of preventive interventions we may be able to induce a change in mastery, which, in turn, might be followed by changes in risk status and changes in the down-stream costs of mental disorder.