Chapter 1

General Introduction
Introduction

Currently, major depressive disorder (MDD) is the single most important cause of non-fatal disease burden (1). Approximately 1 in 5 women and 1 in 8 men will experience a major depressive episode during their lifetime (2). MDD is projected to be the leading cause of premature mortality and disability in high-income countries by 2030 accounting for almost 10% of the overall disease burden (3). The disease burden due to depression has also substantial economic ramifications. Depressive disorders account for vast costs in the health care sector. However, costs associated with production losses are assumed to exceed these costs by a factor of four (4).

However, it is estimated that only about one third of the disease burden caused by MDD can be averted assuming the hypothetical scenario of 100% coverage and full adherence to evidence-based treatments (5, 6). In fact, less than half of depressed patients are recognised and treated (7). Moreover, approximately one third of those patients receiving treatment do not respond, and over half of those experiencing a first onset of a major depressive episode will experience one or more recurrences (8). Not surprisingly, attention has increasingly been focused on the prevention of MDD.

Three types of prevention

Gordon suggested a threefold classification of prevention: Universal preventive interventions that are targeted at the general population regardless of any risk profile; selective preventive interventions that are aimed at high risk groups due to shared characteristics; and indicated interventions that are focused on individuals who show already detectable signs of the disorder but who do not yet meet the diagnostic criteria for the full-blown disorder (i.e. subthreshold depression) (9).

In each case, preventive interventions aim to reduce the incidence of the targeted disorder; that is, reducing the influx of new cases. Treatment rather aims at reducing prevalence. In other words, to reduce the number of existing cases of the disorder. Notably, by reducing the number of new cases, one necessarily reduces also the total number of cases of the disorder. Figure 1 graphically represents the different types of prevention and their interrelation with treatment.
Strategies to prevention

Rose proposed two strategies to prevention: a population-based strategy targeting an entire population regardless of individual differences in risk profiles; and an individual-based strategy targeting “high risk” individuals (10). It is absolutely possible that universal preventive efforts as a population-based strategy may have the highest payoff in terms of reducing population-wide incidence in the long-run. However, no studies are yet available showing that population-based strategies actually reduce the incidence of depressive disorder.

For both ethical and efficiency reasons, preventive efforts aiming to reduce the incidence of depression should target individuals with a high a priori risk pointing to selective and indicated prevention (11). Indicated prevention has been suggested to be more “efficient” than selective prevention (12). “Efficiency” is here defined in terms of “impact” (i.e., the number of cases that would be prevented if the targeted risk indicator were fully blocked in the population) and “effort” (i.e., the number-needed-to-treat to prevent one new case of major depression). From a clinical point of view, indicated prevention and thereby concentrating on subthreshold depression is worthwhile for several reasons.
Subthreshold depression
Subthreshold depression is commonly defined by the presence of clinically relevant depressive symptoms in the absence of a full-blown depressive disorder (13). Clinically relevant depressive symptoms are either defined as scoring above a certain cut-off score on a self-rating depression scale, as having a depressed mood with one or more additional symptoms of major depression, or as meeting the DSM-IV criteria of minor depression (14). In this thesis, clinically relevant depressive symptoms are defined as scoring above 16 on the Centre for Epidemiologic Studies Depression Scale (CES-D) (15).

Subthreshold depression is highly prevalent (14, 16), associated with poorer quality of life (17, 18), increased mortality (19), increased levels of health care service use (20), and with substantial economic costs (21). Additionally, subthreshold depression has been identified as a significant predictor of major depression (22). The clinical significance of subthreshold depression stems from its heterogeneous nature. Subthreshold depression can be seen in people having a transiently reduced (dysphoric) or lowered mood (i.e., dysthymia), but also refer to people on their way to become full-blown cases of major depression, which then might be followed by any of the disease sequela of depression. However, subthreshold depression could just as well refer to people who have partially recovered from a previous episode but linger on with residual symptoms.

Effectiveness of depression prevention
Emerging evidence shows that prevention of major depression seems feasible. A meta-analysis of 19 randomised controlled trials evaluating preventive interventions in mixed-age samples revealed a pooled incidence rate ratio of 0.78 (95% CI 0.65 - 0.93). This corresponds to a reduction in incidence of major depression of 22% over one year (23). These trials examined the effectiveness of psychosocial interventions, such as preventive cognitive-behavioural therapy, interpersonal psychotherapy, problem-solving therapy, or bibliotherapy. Results show that prevention in conjunction to treatment might contribute to a further reduction of the disease burden and economic costs related to depressive disorders.

Although evidence suggests that preventive face-to-face interventions are effective, some challenges remain. These include: (a) difficulties in delivering preventive interventions to the community en masse due to constraints in the workforce and health care resources (24, 25), (b) limited availability of interventions and clinicians in routine practice, especially in rural areas, and (c) low participation rates even if access to those interventions is at little or no costs (26). Thus, innovative approaches are needed to increase the impact of preventive interventions.
Prevention via the Internet
A new development that might be of relevance and importance for depression prevention is the introduction of e-health to overcome some of the limitations of face-to-face preventive services (27, 28). The Internet might provide easy access to preventive depression interventions. For example, in 2014, 89% of the German population had access to the Internet (29).

E-health is here defined as “the use of information and communication technologies to improve psychological care” (30). Treatments of (mental) health problems provided via the Internet are also called web-based interventions. We define web-based interventions as “treatments, typically behaviourally based, that are operationalized and transformed for delivery via the Internet. Usually, they are highly structured; self-guided or partly self-guided; based on effective face-to-face interventions; personalised to the user; interactive; enhanced by graphics, animations, audio, and video; and tailored to provide follow-up and feedback” (31).

Web-based interventions do have several advantages: (a) they are accessible at any time and place reducing travel time and costs for both clinicians and participants, (b) participants can work at their own pace and go through materials as often as they want, (c) there is a great potential for the integration of learned techniques in daily life routine due to an emphasis on participants’ active role in (guided) self-help interventions, (d) anonymity is possible if participants want to avoid stigmatisation. Finally, (f) web-based interventions are easily scalable. Scalability refers to the ability of the intervention shown to be effective in a research setting to be expanded under real world conditions. To reach a greater proportion of the eligible population while retaining effectiveness, only a small increase in therapeutic resources is required. Thus, the marginal cost per additional user get lower via an economies-of-scale effect. Economies of scale refer to the reduction in the cost per treatment of an intervention as a result of increasing the number of clients. Economies of scale arise because many of the costs associated with the web-based intervention are fixed and not dependent on the number of clients (i.e., hosting the intervention on a server) and thus increasing the intervention output reduces the fixed cost per treatment. Economies of scale might also reduce variable costs (i.e., therapist’s support per participant) because therapists become more efficient through better organisation and experience.

Nowadays, several web-based interventions are available and well accepted by participants (32, 33). There is meta-analytic evidence that such interventions are effective in reducing depressive symptoms (34) and in the acute treatment of major depression (35).
Research questions

From the information above, we can conclude that prevention of depression is feasible. However, despite the effectiveness of psychological interventions and new developments in e-mental health care, several open questions in depression prevention remain unanswered.

(1) In an earlier meta-analysis, only 19 trials were included that examined the effects of preventive interventions and their quality was not in all cases optimal (23). However, in recent years more high quality studies have been conducted in the field of depression prevention. Hence, it is possible to estimate the overall effect size of preventive interventions with more precision. Besides, the greater statistical power also allows to investigate subfields of prevention in more detail, such as prevention of post-partum depression or depression in people with somatic diseases.

(2) Although several web-based interventions are labelled as preventive interventions (i.e. Colour your life) (36, 37), no study has yet investigated whether a web-based guided self-help intervention could actually prevent the onset of diagnosed major depressive disorders.

(3) Web-based interventions are assumed to be cost-effective. However, no randomised controlled trial has investigated the cost-effectiveness of such an intervention to prevent the onset of major depressive disorder.

(4) Guidance constraints scaling up web-based interventions. However, it is not known whether a web-based intervention with minimal guidance (i.e., adherence-focused guidance) is effective in treating subthreshold depression.

This leads to the following research questions addressed in this thesis:

- What is the effectiveness of preventive interventions in reducing the incidence of major depressive disorder?
- Is a web-based guided self-help intervention a promising approach
  - to restore health in people with subthreshold depression?
  - to prevent the onset of major depressive disorder?
- Does such a web-based intervention represent good value for money?
- Does adherence-focused guidance result in clinically meaningful outcomes?
Web-based guided self-help intervention

We developed the GET.ON Mood Enhancer Prevention intervention that aims to prevent depression. It consists of 6 30-minute interactive sessions. The duration of sessions might, however, vary among users. Sessions include video clips explaining theoretical frameworks in a user-friendly way, text, exercises, and testimonials supporting participants to work through the exercises. The intervention is based on elements from behaviour therapy (BT) and problem-solving therapy (PST). In BT, a strong focus rests on daily positive activity scheduling that is integrated in each session. Participants are also asked to keep a mood diary. In our intervention, PST is based on three elements: (1) to list important things in life and to plan activities on how to strengthen these important things in life, (2) to list and distinguish personal problems in “manageable” and “unmanageable”, and (3) a 6-step procedure that is meant to assist in solving “manageable” problems. In addition to the BT and PST elements, participants are offered three elective modules targeting sleep hygiene, relaxation techniques, and dealing with worrying thoughts. In the final session, participants are asked to reflect on the techniques that were introduced during the intervention and to evaluate which of these techniques were particularly helpful in improving their mood. In a final step, participants develop a plan for the future on how they will integrate these techniques routinely in their daily life without assistance.

A strong focus of the intervention lies on transfer tasks (homework assignments) to integrate newly acquired skills and techniques into daily life. In the beginning of each subsequent session, participants are invited to reflect on their practical experiences with these techniques. As an optional component, participants can choose to receive a set of about 42 standardised text-messages supporting them to integrate the learned techniques into their everyday life. An example of such a text-message would be “Everyone has his own strategies to vanquish the inner temptation. What helps you?”

During the intervention, participants are supported by an online-trainer who provides written feedback after each session. This feedback focusses on supporting participants to work through the exercises and online-trainer do not provide any therapeutic advice. Participants can only move on to the following session after having read the feedback. We trained trainees in psychotherapy and Master level students to provide guidance.
Design of the randomised controlled trials

The first trial
We conducted a two-armed randomised controlled trial (N = 406) to compare the GET.ON Mood Enhancer Prevention intervention with enhanced usual care (web-based psychoeducational intervention). All participants had unrestricted access to care-as-usual. Measurements were taken at baseline, post-treatment (6 weeks; only self-report questionnaires), 6-, and 12-month follow-up (self-report questionnaires, SCID interviews).

Study participants were recruited from the general population via a large German health insurance company (BARMER GEK), through newspaper articles, on-air media, and related websites. Applicants self-identifying with a diminished mood were assessed for eligibility. We included adults (age ≥ 18) with subthreshold depression (Centre for Epidemiologic Studies Depression Scale (CES-D) ≥ 16) but who did not meet DSM-IV criteria for a major depressive episode. Interested individuals were excluded if they met DSM-IV criteria for a bipolar disorder or a psychotic disorder. Additional exclusion criteria were: a history of a major depressive disorder in the past six months, current psychotherapy, being on a waiting list for psychotherapy, psychotherapy in the past six months, and showing a notable suicidal risk.

The primary outcome was time to onset of MDD within the 12-month follow-up period. Time to onset of MDD was assessed by means of life charts. Secondary outcomes included changes on various indicators of depressive symptom severity, anxiety and quality of life. Additionally, an economic evaluation based on a societal and public health care perspective was conducted.

The second trial
In addition, we conducted a second two-armed, pragmatic randomised controlled clinical trial to compare the GET.ON Mood Enhancer Prevention intervention with an adherence-focused guidance concept with a waitlist control condition (N = 204). The recruitment strategy as well as in- and exclusion criteria were the same as in the first trial.

Assessments took place at baseline (diagnostic interviews, online questionnaires), at post-treatment (7 weeks; diagnostic interviews, online questionnaires), and at 3-month follow-up (online questionnaires only). The primary outcome was the reduction in observer-rated depressive symptom severity as measured with the Quick Inventory of Depressive Symptomatology at post-treatment.
Outline of the thesis
As all chapters are written as separate articles for publication in scientific journals, they can be read independently. Chapters 3 to 6 present results from one randomised controlled trial and have therefore some overlap.

Chapter 2 reports on the results of a meta-analysis examining the effectiveness of preventive interventions for depression. Chapter 3 describes the design of the randomised controlled trial that evaluates our web-based guided self-help intervention as compared to enhanced usual care. Chapter 4 presents the findings regarding the clinical effectiveness of the intervention in treating subthreshold depression. Chapter 5 reports on the effects of the intervention in preventing the onset of diagnosed major depressive disorder over one year. Chapter 6 contains the economic evaluation dealing with both cost-effectiveness and cost-utility analyses. Chapter 7 describes the findings of the second randomised controlled trial, in which we evaluated the same intervention, but with an adherence-focused guidance concept. In chapter 8, the dissertation concludes with a general discussion including a critical discussion of clinical implications and directions for future research. Finally, a summary in English, German, and Dutch is provided in chapter 9.
References


