Suffering in silence: studies on screening for major depressive disorder in primary care
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General Discussion
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In primary care, major depressive disorder (MDD) often is not detected. Many patients suffering from MDD do not seek help for their psychological complaints (soberness, loss of interest, or other), but instead consult their GP with non-specific physical complaints, leading to under-recognition in up to 50% of patients suffering from MDD.\(^1,2\) Screening on MDD is proposed to improve recognition in primary care. However, until present, evidence for effectiveness of screening for MDD in primary care is lacking. As stated in the introduction, two measures might augment screening effectiveness and improve patient outcomes: (1) increasing the pre-test prevalence of MDD by selecting a population at high-risk for MDD; and (2) embedding screening into a disease management program including diagnosis and treatment.\(^3,4\) These two measures were subject of our study in which we selected three high-risk groups in primary care and invited these patients for a disease management program including three steps: screening, diagnosis and (free-of-charge) treatment for MDD.

This thesis consists of three parts in which we studied three main subjects concerning this disease management program for MDD in primary care: the target population for screening (part I); the Patient Health Questionnaire as screening instrument (part II), and the feasibility of the screening program for MDD (part III). The main finding of our study is that although the prevalence of MDD indeed was higher in the selected population than in the unselected primary care population, and the test-characteristics of the PHQ were acceptable, screening for MDD in primary care proved to be not feasible. Before exploring the background of this outcome, we will discuss the findings of the first and second part of this thesis: the target population for screening and the screening instrument.

Part I: The high-risk population

As stated in the introduction, screening for MDD in the unselected primary care population seems not efficient because of relatively low prevalence of MDD, leading to low positive predictive value of a MDD screening test, despite acceptable sensitivity and specificity. Screening a pre-selected high-risk population with a corresponding higher positive predictive value of the screener as a logical consequence, could lead to improved screening efficiency.\(^3\) This reasoning led to the research questions of the first part of this thesis, 1) which patients are at high-risk for MDD in primary care?, and 2) what is the prevalence of psychiatric disorders in this high-risk population?
Different primary care patient groups at high-risk for MDD have been described, including the three high-risk groups, used for the present study: frequent attenders (FA), patients with unexplained somatic complaints (USC), and patients with mental health problems (MHP) like stress, sleeping problems, financial problems or other psychological or social problems. Also other groups have been described like patients with MDD in the past and patients with disabling somatic illnesses. The last two groups were based on consensus (and not on epidemiological data) and were recommended by the NICE-guideline just after the start of our study in which we had decided to select the three high-risk groups described above.\(^3\) We did not regard patients with disabling somatic diseases as a separate high-risk group, as most of these patients attend their GP on a regular scheme for their chronic illnesses or for prescriptions of medication; these patients are embedded in the frequent attenders group. Patients with MDD in the past are certainly at risk for a new episode, but because of their earlier experience with psychiatric symptoms, recognition of a relapse might be less of a problem both to the patient as well as for the general practitioner.

The selected high-risk groups were screened with four modules of the PHQ: major depressive disorder (MDD), panic disorder (PD), other anxiety disorder (OAD) and undifferentiated somatoform disorder (USD). Diagnoses of the three disorders MDD, PD and USD and one group of disorders (OAD) were defined according to the strict DSM-IV criteria operated with the SCID-I. Patients suffering from anxiety disorders like phobic disorder, obsessive-compulsive disorder, posttraumatic stress disorder, generalized anxiety disorder or anxiety disorder not otherwise specified were categorized as OAD.

The main finding after this screening procedure was that 26.1% of all patients suffered from any of these four psychiatric disorders. MDD was present in 12.6% of all patients, PD in 5.7%, OAD in 11.1% and USD in 8.0% of all patients. Patients with unexplained somatic complaints had the highest prevalence of any of these four disorders (43.1%). Of the frequent attenders 25.5% was suffering from any disorder and of the patients with mental health problems 31.3%.

The finding that more than a quarter of our high-risk patients suffered from MDD, AD, PD or USD, could be a strong motivation to screen for psychiatric disorders. In this part of the study we did not analyse the proportion of patients with psychiatric disorders that remained undetected by GPs, but different studies reported detection rates of MDD of 50%.\(^1,2\) In the Netherlands, the Nemesis-2 study reported that only 50.5% of all patients with MDD in the past year were treated for MDD.\(^5\) Patients from the high-risk groups in this thesis have an increased health care consumption compared to other patients because of frequent (frequent attendant) and/or time-consuming visits (unexplained somatic complaints or mental health problems). In case of unexplained somatic complaints the doctor-patient
relation could be difficult and strained.\footnote{6} Although under-detection and under-treatment are more related to mild depressive disorders than to severe MDDs, attention to and treatment of hidden psychiatric disorders could have a positive effect not only on psychiatric symptoms, but also on health care consumption and on the doctor-patient relationship.\footnote{7,9} Moreover, when patients from this high-risk population suffer from a chronic somatic disease, successful treatment of co-morbid psychiatric disorder improves treatment compliance and the course of somatic diseases.\footnote{10-12}

Considering patients from the USC-group, recognition of psychiatric disorders might prevent unnecessary tests and ineffective treatments. If these patients present themselves with physical symptoms, GPs often focus on excluding somatic illnesses. The arguments of GPs to order somatic tests for patients with low pre-test probability of disease, are to reassure patients or to rule out a somatic cause of the physical symptoms and make psychosocial causes more plausible for patients.\footnote{13,14} However, the reassuring effect of a negative test result is doubtful; multiple tests increases the risk of false positives and rarely, somatic testing provides a good basis for discussing psychological problems.\footnote{15,16} The high prevalence of psychiatric disorders in our high-risk groups underscores the necessity to attentively explore the possibility of one or more psychiatric problems in these high-risk patients.

Part II: The Screener: the Patient Health Questionnaire

The second part of this thesis consists of studies about three different sections of PHQ: the depression scale (PHQ-9), the panic scale (PHQ-PD) and the somatic symptom severity scale (PHQ-15). Validation of the other anxiety scale (OAD) is difficult because this module represents a group of disorders instead one specific disorder. Recently, the developers of PHQ presented a modified screening scale for generalized anxiety disorder (GAD-7), but this scale is not yet part of the PHQ.\footnote{17} The studies in this thesis aimed to investigate psychometric properties and validity of the three PHQ-scales as screenings instruments. The main conclusion considering the PHQ-9 is that when the cut off score of $\geq 10$ is used, its test characteristics proved to be adequate with a high sensitivity (0.93) and negative predictive value (0.99). The other two scales had lower test characteristics. Sensitivity and specificity of the PHQ-PD were 0.71 and 0.83 while corresponding values of the PHQ-15 were 0.78 and 0.71 respectively. All three scales could be used for screening when followed by formal diagnostic procedures. Conversely, the developers claimed that PHQ-9 could also be used as diagnostic instrument when the algorithm (based on DSM-IV, for details see appendix 1)
instead of sum score (≥10) is used to indicate a positive case, but our data do not support that statement. We found a sensitivity and specificity for this algorithm of 0.68 and 0.95 respectively. In our sample with a prevalence of 12.3% MDD, this generated a positive predictive value of 0.67 and negative predictive value of 0.96. Such positive predictive value is too low to be useful in a clinical setting, as this will lead to 30% false-positives. These diagnostic limitations are even more applicable to the panic module (PPV 0.30) and the somatoform module (PPV 0.20). Consequently, PHQ is not suitable for diagnosis of psychiatric disorder in populations with a disease prevalence of around 15% or lower, like for instance in primary care populations. If PHQ is used in these samples, this instrument, which only suggests “possible” disorder in patients with a positive test score, should definitively be followed by further diagnostic processes.

Recently, the developers of PHQ (Kroenke, Spitzer & Lowe) systematically reviewed the PHQ-literature. Their review was more positive than our studies and concluded that the depression, panic and somatic symptom scales of PHQ are adequate for screening, but also for diagnostic purposes. However, only sensitivity and specificity data were reported. Compared to other depression screeners like the Beck Depression Inventory (BDI) or others (see general introduction), the sensitivity and specificity of PHQ-9 are indeed high, but the authors did not comment on the risk of misclassification, possibly resulting in overdiagnosis or underdiagnosis.

From the second part of this thesis we conclude that PHQ (mood, panic and somatoform module) is useful for screening, but an additional diagnostic procedure is required to prevent patients from being over-diagnosed as suffering from a psychiatric disorder.

Part III: The screening program

In the third part of this thesis we investigated the feasibility of screening embedded in a disease management program for MDD in primary care. The main conclusion is that this disease management program was not feasible in general practice. Initial participation to screening was about 50%. Of the 780 participants, screening disclosed a considerable amount of patients with MDD (n=71, 9.1%), but treatment initiation was reached for only 17 (23.9%) patients. This is partly caused by the fact, that of the patients with a ‘hidden depression’, about 50% was already treated for another psychiatric or psychological problem and another 25% refused treatment. The number needed to screen to treat one additional patient with MDD was 118. Considering a treatment effect of about 20% this means that almost 600 patients should be screened and if positive also treated to effectively improve outcome in one patient. The effort to detect these patients was high and participating GPs experienced intrusion in their daily practice by the screening procedure.
The main finding that screening on MDD is not feasible can be explained by two factors that are both related to acceptability of screening:

1. Low participation rate of the target population.
2. Withdrawal after the screening procedure and before treatment.

In the following paragraphs these two factors are further explored.

1. Participation to screening

First, participation of the target population to our screening program was 49%. Other screening programs for MDD reported similar participations of 40% (primary care waiting room patients) to 70% (patients attending a general medicine clinic). This could be regarded as indication of low acceptability for screening on MDD, but these figures are not unique to MDD screening. Studies about screening programs for somatic illnesses have reported variable participation rates: chlamydia 16%; online cardiometabolic risk test 33% and 75%; prostate cancer 52%; colorectal cancer 55%; cervical cancer 69%; breast cancer 74% and 80% in the Netherlands. Although many of these screening programs have already been implemented in practice, these figures point out that the willingness to participate in screening of the different target populations varies widely but is never above 80%.

Divergent explanations for a low participation to screening have been reported of which some are also applicable to our method of MDD screening: kind of illness (negative public opinion and little knowledge about illness, low lethality, behavior related illness, stigma of psychiatric diagnosis and characteristics of MDD: loss of interests and feelings of hopelessness), screening procedure (long lists, time-consuming or burdensome examination) and characteristics of invitees (low social status, unhealthy behavior, foreign ethnicity). A systematic review on participation obstacles for psychiatric research reported fear, suspicion and/or distrust of researchers, concerns about confidentiality, severity of illness, lack of financial reward, inconvenience, fear of relapse as a result of participation, and the stigma of mental illness.

Selection bias

A problem of low screening participation is the risk of selection bias, or the so-called ‘healthy screenee effect’. Participants (or the ‘worried well’) in somatic screening programs (breast-, prostate-, colon-, and lungcancer) are often healthier than non-participants. Compared to participants, non-participants more often belong to lower social-economic classes, are less likely to be married and employed, and less likely to be well educated. Non-participants tend to describe their general health in less favourable terms and are more likely to be smokers. The prevalence of MDD might be higher among non-participants because the
characteristics of nonparticipants (unmarried, non-employed, lower educated, smoking) have also been mentioned as risk factors for MDD. In addition, symptoms of MDD (like apathy, concentration problems and fatigue) probably hinder participation to screening because patients are asked to read study information and to fill in questionnaires. Although this selection bias has not been studied in screening on MDD, one study on schizophrenia reported that more non-participants were suffering from severe schizophrenia compared to participants. This selection bias would implicate that a screening program for MDD might not reach the complete target population.

2. Withdrawal after screening
A second explanation for the low efficiency of screening was the high withdrawal of patients after initial being screened positive and further diagnosed as suffering from MDD. In our study about the effect of screening GPs did exclude all patients with known MDD before the start of the screening program. Nevertheless, about half of the patients that were detected by the screening program as suffering from MDD were already following some kind of mental health treatment for their complaints. We have not analysed the indications for these treatments, but probably other disorders related to MDD, like adjustment and anxiety disorders or other psychosocial indications, were present before starting treatment. Theoretically, some of these patients may have been diagnosed with MDD by his/her GP and started with treatment just after we had selected the high-risk population and before the screening procedure. However, this is unlikely because of the small time window of 4 weeks between our screening procedure and the start of treatment.

From all detected untreated patients with MDD, 45% refused treatment. Similar to our study, screening studies for cardiovascular disease and renal failure reported high withdrawal of patients after being screened positive of an illness or risk factor (cardiovascular risk: 34% to 64%; renal failure 75%). The reported explanations for the low uptake of the screening results were related firstly to the method and setting of screening program, and secondly to the target disorder. Screening for renal failure was not part of regular GP care. The authors stated that if screening was embedded into GP care patients would be better informed about the consequences of the test and would be more motivated to participate in follow up consultations. Our screening program was partly embedded into GP care and some of the above explanations for the low uptake, are probably also applicable to our screening program. The invitation for screening was sent by GPs, but the screening consisted of a self-report questionnaire followed by a diagnostic interview of 45 minutes by telephone administered by researchers. If patients were diagnosed as suffering from MDD, PD, OAD or USD patients were informed by letter and they were invited to consult their GP to discuss the diagnosis and to start
treatment. The diagnosis and information about the test-results were not part of regular GP care and this procedure could therefore not be adapted to individual patient' requirements. The treatment options consisted of regular GP-care or free-of-charge cognitive behavioral treatment by psychologists.

Interestingly, online screening for cardiovascular disease was in fact part of GP care, but also suffered from a high withdrawal rate after screening. Only 36% of patients with a positive test result (increased risk of cardiovascular disease) consulted the GP. The study that used a written screening test reported lower withdrawal rates; 66% of patients with positive test result consulted the GP. Screening for cardiovascular disease is targeted at symptomless risk factors for future disease instead of current disease. In part, this could explain the withdrawal. Both authors speculated that the withdrawal could further be explained by the fact that the target disorder was highly related to behavior aspects (smoking, obesitas). Patients were aware of their unhealthy lifestyle and did not appreciate contacting their GP for this behavior because they felt guilty or hopeless (probably because of former failed attempts to change their behavior). In addition, these authors suggested that some patients probably were not ready or did not want to change their behavior.

Screening for MDD is comparable to screening for cardiovascular disease because many patients with MDD also suffer from feelings of guilt about their behavior. The characteristics of MDD itself (apathy, feelings of failure and fatigue) might refrain patients with MDD from starting treatment. Additionally, patients that participated in our qualitative study had doubts about the efficacy of psychotherapy or medication because they felt that external factors and their own reaction to these factors had caused their depressive symptoms. The fact that patients (and probably also GPs) rather focus on external problems is supported by earlier studies (not in a screening setting). In their causal way of thinking it are psychosocial problems that cause MDD and not vice versa. Patients expressed the need for help to solve these psychosocial problems themselves instead of being treated for MDD with psychotherapy or medication. They interpreted their inability to solve these problems as a weakness instead as a consequence of MDD. The personal histories of three patients were described between the three parts of this thesis (page 10, 27 and 92) as an illustration of the complexity of the problems patients were struggling with. All patients in this study expressed the need for help for their external problems and were positive about being actively approached for screening because now they could ventilate their emotional distress. At the same time their perception of MDD and of the therapeutic consequences of such psychiatric label did not meet their needs. As has been reported before, patients are not convinced of the necessity and effectiveness of antidepressant or psychological treatment, especially when contextual problems are clearly connected to MDD.
From the point of view of a GP, the opinion of these patients is highly understandable. If these patients would consult the GP with their emotional distress and psychosocial problems, GPs probably would not focus on the depressive symptoms or MDD, but instead encourage them to search for solutions that could change their situation, also called problem-solving therapy. This normalizing attributional style is common in general practices and one study reported that this behavior is an important cause of the under-detection of MDD. We can conclude that the applied psychiatric screening procedure, in which we labeled patients with the diagnosis MDD and asked them to consult the GP for treatment, does not suit the target population. Patients that were willing to participate to screening experienced MDD as a severe psychiatric label and they thought the consequences of this label did not properly suit their needs.

The Wilson & Jungner screening criteria

As stated in the introduction of this thesis, the Wilson and Jungner criteria were developed to ensure a positive net effect of screening programs. We stated that four of these ten criteria required further research of which we addressed three criteria in this thesis: (1) the validity of the screenings instrument, (2) the acceptability of the screening program to the target population, and (3) the effectiveness of the screening program. Although our instrument proved not to be ideal, the first criterion, the validity of the screening instrument, is met. However, as we discussed in the above section, the instrument is not adequate for diagnosis of MDD because of a too low positive predictive value and many patients would erroneously be diagnosed as suffering from MDD. This is in contradiction to results from former studies that recommended PHQ as a screener as well as diagnostic instrument.

Clearly, criteria two and three are not met. The low participation and high withdrawal rate during the screening program suggest that screening for MDD is insufficiently acceptable to the target population. Despite the fact that we could not formally evaluate cost-effectiveness, the very high number needed to screen suggests a very low cost-effectiveness of the complete disease management program including screening, diagnosis and treatment.

The possible health gain that could have been achieved by the treatment of the 17 patients with newly detected MDD who accepted treatment is limited. This can be explained by two factors. First, 50% of patients with MDD in primary care recover without specific treatment within three months. Secondly, the effectiveness of treatment for MDD is limited; the number needed to treat with antidepressants is between six and ten and recent papers even suggest insufficient evidence to
support the prescription of antidepressant medication to individuals other than the most severely depressed.\textsuperscript{56,57} For patients with mild depressive disorder, a watchful waiting period of three months before starting treatment is recommended.\textsuperscript{58} As a result we conclude that treatment of these 17 participants would have resulted in low health gain in comparison with conventional care; annual screening of 10% of one GP-practice of 2000 patients would result in one successfully treated extra patient in every five year. Based on these figures we conclude that the cost-effectiveness Wilson & Jungner criterion could not be achieved.

**Implications for primary care and implications for further research**

*Active approach by GPs*

Data of this thesis suggest one cannot recommend implementing MDD screening in high-risk primary care groups. On the other hand, the second chapter of this thesis confirms a high prevalence of psychiatric disorders (including MDD, anxiety disorders and somatoform disorders) in this high-risk population: 26.1\% of all patients were suffering from at least one of the above mentioned psychiatric disorders according to the strict DSM-IV criteria operated with the SCID-I. In addition, participants expressed their appreciation for being actively approached by their GP for exploration of emotional distress. Therefore, regularly monitoring of these groups of high-risk patients by their GP may be recommended. GPs are probably aware of the possibility of underlying psychiatric morbidity in these groups, but an active approach should be advocated.

A recent qualitative study about the reasons of patients for not disclosing their depression to the GP pointed out that the most important reason was patient’s concern that the GP would recommend antidepressants.\textsuperscript{59} Additional reasons were that some patients felt that depression falls outside the purview of primary care; fear of being stigmatized by MDD; and feelings of failure. These findings are similar to our qualitative study and support our conclusion that GPs should actively bring up the subject of emotional distress by exploring psychosocial wellbeing and functioning. Beside GPs, practice nurses could also be involved in the detection of emotional distress because they have regular contacts with patients with chronic diseases (diabetes, COPD) that are included in our frequent attenders groups. Questionnaires as the PHQ or the Four-Dimensional Symptom Questionnaire (4DSQ) could be helpful in bringing up the subject of emotional distress.\textsuperscript{60} However, discussing emotional distress should fit to the perception of individual patients. More research is needed to find out how GPs can implement the active approach to detect emotional problems among high-risk patients in their daily practice.
Commonalities of disorders

A combined use of the depression module, the anxiety module, the panic module and the somatoform module would be interesting. Many patients in primary care are suffering from a combination of different psychiatric disorders.\(^{61}\) At one moment the symptoms of a specific patient could lead to the diagnosis of anxiety disorder. Later, the symptoms may have changed and a depressive disorder is diagnosed.\(^{62}\) Moreover, recent literature suggested that the commonalities of the disorders seen in primary care patients supersede their differences.\(^{62,63}\) Some studies concluded that the DSM-IV classification system is not well applicable to primary care patients because psychiatric symptoms of these patients are very heterogenic, overlapping and also instable over time. Some symptoms still are preclinical and some are self-limiting and could be seen as a normal transient reaction to a stressful event.\(^{62,64}\) Probably, a screening program detects many patients with symptoms that are in an early stage that could develop into different psychiatric disorders or have a favourable natural course. Labelling patients with one psychiatric disorder while they are (still) suffering from instable symptoms might be less useful and could even be stigmatising. Probably the diagnosis could be postponed while an approach adapted to the severity of suffering has already been started.

Stepped care approach

A recent meta-analysis reported that Dutch GPs are good at detecting severe MDDs.\(^{65}\) Under-recognition of MDD is more related to mild depressive disorder than to moderate or severe MDD.\(^{7-9}\) This finding implies that the abovementioned active approach to discuss emotional distress, is targeted at a population with relatively mild and heterogenic psychiatric symptoms (severe disorders have already been detected by GPs). For these patients, the diagnostic procedure could probably be postponed, meanwhile monitoring these patients with regular contacts and for instance ‘problem solving’ therapy. After a specific period of time (for instance three months) the course of emotional distress should be evaluated. For patients with unfavourable course a psychiatric diagnosis could then be considered. Patients with a psychiatric disorder that are willing to be treated could be referred for specific psychiatric treatment.

The updated multidisciplinary guideline for depression links up with this idea, except for the moment of diagnosis that is not postponed.\(^{58}\) This guideline advises to postpone psychotherapy or medication until three months after the diagnosis of MDD (except for moderate to severe MDDs), and to monitor these patients regularly and to provide psycho-education and motivation to structure their daily activities. Although this guideline is confined to MDD and other multidisciplinary guidelines (anxiety disorders, somatoform disorders) do not advice this stepped-care approach (yet), this stepped care principle with a watchful-waiting approach in
the first three months might be applicable to many of our high-risk patients with (all combinations of) common mental disorders. Within these three months patients with favourable natural course of symptoms are protected from medicalization of symptoms, stigmatization (when the moment of diagnosis is also postponed) and from unnecessary treatments. Patients with a more severe course of symptoms are being monitored regularly and the risk of under-detection and under-treatment will be minimized. However this stepped-care approach for other disorders than MDD is not recommended yet. Further research is required to investigate this stepped-care approach for anxiety and somatoform disorders.
References


