Both explained and unexplained physical symptoms reduce the effectiveness of treatment for depression in primary care
Abstract

**Aim:** to assess to what extent clinically significant concomitant physical symptoms influence the effect of treatment for major depression, and whether or not this relationship is explained by actual co morbid medical conditions.

**Method:** Pre-planned secondary data-analysis on a one-year cluster-randomized trial in primary care, comparing the effectiveness of collaborative care with care as usual (CAU). Depression was measured using the PHQ9. The number of physical symptoms was measured with the Physical Symptoms Questionnaire (PSQ) at baseline. Multilevel logistic regression models were used to test whether physical symptoms predicted lack of response to treatment, adding interaction terms to test differential effects on collaborative care versus CAU.

**Results:** Concomitant physical symptoms negatively influenced the response to treatment for collaborative care and care as usual, but the effect was the same for both conditions (there was no interaction). Therefore, collaborative care for depression is still more effective than CAU for patients with concomitant physical symptoms, but these patients have lower odds on response to treatment regardless of treatment condition. Specifically, physical symptoms predicted a lack of response in both treatment conditions at 3 (OR = 6.8, 95% CI = 1.3-36.8), 6 (OR = 4.1; 95% CI = 1.1-14.9), and 9 months follow-up (OR = 6.4; 95% CI = 1.6-24.8). The time to first treatment response was 4.3 months longer for the group suffering from concomitant physical symptoms. The results were not explained by the presence of chronic physical illness.

**Conclusion:** In this RCT, patients with MDD and concomitant physical symptoms benefited less from treatment for MDD in primary care, regardless of the type of treatment (either collaborative care or CAU). Whether or not these physical symptoms were due to a comorbid medical condition did not explain the results. Further research is needed to improve treatment for MDD with concomitant physical symptoms, but in the mean time there is no reason not to apply collaborative care for patients suffering from both depression and physical symptoms.

**Trial registration:** Dutch trial register ISRCTN15266438
Introduction

Patients under treatment for Major Depressive Disorder (MDD) often report concomitant physical symptoms. Indeed, 70% report physical instead of psychological symptoms during their first visit to a General Practitioner (GP) for what later turns out to be MDD. Moreover, epidemiological data indicate that MDD frequently co-occurs with both somatoform disorders and chronic medical conditions. However, there has not been much research into the topic of the possible influence of concomitant physical symptoms - especially if these are not due to an apparent chronic medical condition - on the effectiveness of treatment for MDD.

This is an important issue because there is ample room for improvement in terms of response and remission percentages for MDD in everyday care, even though efficacious treatments are available. In the usual care arm in the large IMPACT-trial, assessing the effectiveness of collaborative care in primary care, only 16.7% of the participating patients achieved remission after six months. One of the reasons why treatment for MDD appears to be suboptimal in everyday care may well be the high co-occurrence with physical symptoms. In the primary care setting, for instance, GPs are faced with competing demands, as physical symptoms and psychological symptoms are often presented simultaneously in the short time span of a consultation. This may interfere with effective treatment for MDD.

Studies into the possible influence of persistent physical symptoms on the outcome of MDD have so far focussed almost exclusively on pain. A systematic review and a recent study in primary care, however, showed that studies should also look at the wider spectrum of physical symptoms, such as fatigue, indigestion, dizziness, and fainting. Such physical symptoms in patients with MDD may be due to a chronic medical condition, may be considered a symptom dimension of the depression, or may remain medically unexplained. Concomitant physical symptoms might well be a relevant factor in course and treatment of MDD, regardless of their origin, but up until now we are not aware of any empirical research into the importance of the distinction between 'explained' and 'unexplained' physical symptoms with regard to the outcome of MDD. Unexplained physical symptoms are often operationalized by measuring them on a scale, but evidently this is not sufficient to be sure that there is no known underlying somatic pathology. Crombez and colleagues have called this 'the unbearable lightness of somatisation'.

A good opportunity to test the assumption that physical symptoms, regardless of their origin, interfere with treatment of MDD, would be a pre-planned secondary data-analysis on a trial assessing the effectiveness of enhanced treatment for MDD in primary care. If it is true that concomitant physical symptoms negatively influence the effect of treatment for MDD, this might be less pronounced if enhanced treatment reduces the burden of competing demands. If a specialised nurse is available to address psychosocial issues, this may enhance effectiveness of treatment for MDD even when concomitant physical symptoms are present. An example of a form of enhanced care for MDD that incorporates these elements is collaborative care.

We tested the assumption that concomitant physical symptoms influence the effectiveness of treatment for MDD in a recently completed RCT that evaluated the effectiveness of collaborative care in primary care in the Netherlands. Physical symptoms were measured at baseline (before the start of treatment) and the outcome in
terms of depression severity was determined at follow-up. We hypothesized (i) that the presence of concomitant physical symptoms at baseline has a generic negative effect on the lack of response to treatment for MDD at follow-up, (ii) that this effect may be stronger in CAU than in collaborative care, and (iii) that this effect is not explained by the presence of chronic physical illness. Thus, if hypothesis iii holds true, this implies that the results regarding hypothesis i and ii are still the same when the model is corrected for chronic physical illnesses.
Methods

Design and patients

We conducted a pre-planned secondary analysis of data from a cluster-randomized trial assessing the effectiveness of collaborative care for MDD in primary care in the Netherlands. The design of the study has been described in more detail elsewhere, but is summarized below.18 18 primary care centers (with a total of 82 GPs) were randomly assigned to either collaborative care (CC) or care as usual (CAU) by an independent statistician using a computer algorithm for cluster allocation.126 GPs in Primary care centers randomized to the CC condition received training in the collaborative care model, the use of a web-based tracking system, and cooperation with a consultant psychiatrist. Patients of the respective practices could enter the trial in two ways: either by screening or after identification by their GP. Screening was done as follows: all patients who had consulted their GP during the past 6 months received the PHQ9 by mail, regardless of the reason for prior consultation. The reason for this broad approach is that literature suggests that patients suffering from Major Depressive Disorder (MDD) are more likely to report miscellaneous somatic symptoms to their GP instead of the core symptoms of MDD.25;38

After informed consent patients were asked to return the questionnaire regardless of whether or not they still had any symptoms. At the moment of screening, patients were unaware of their allocation. Inclusion criteria were age > 17 years, PHQ9 score ≥ 10 and a classification of MDD according to the MINI neuropsychiatric interview, which was administered by telephone. Exclusion criteria were suicidality, psychosis, dementia drug or alcohol dependence, being already under specialty mental health treatment, or insufficient knowledge of Dutch to fill in the questionnaires.

The trial flowchart describing the randomization procedure and the percentages of patients who returned the follow-up-questionnaire at three, six, nine, and twelve months is presented in Figure 1 (next page). The patients who received collaborative care after identification by their GP were treated as a separate group in the flowchart (to provide insight in the inclusion process), but we will present results for the collaborative care group as a whole.

The collaborative care intervention is described in more detail elsewhere. Briefly, a GP, a depression care manager (for instance a specialised nurse), and a consultant psychiatrist operate as a team to provide optimised primary care for MDD based on a stepped care algorithm. Usual care could be any form of care that was available to a patient. The results of the trial were described elsewhere, and showed a better outcome in terms of treatment response for collaborative care compared to CAU.

Study oversight: This study was part of the Netherlands Depression Initiative, a national initiative aimed to improve depression treatment. The study was supervised by a steering committee and a supervisory board that met 4 times a year.
Figure 1 Flowchart of participants included in the analysis

18 Health care centers in primary care were randomized to CAU or Collaborative care.

9 Health care centers randomized to collaborative care

56 patients received collaborative care (CC) after direct referral by their GP.

38 patients (67.9%) filled out the PSQ; 8 of these patients (21.1%) scored above the cut-off the PSQ.

20 patients returned the 3 month questionnaire (52.6%); return percentage in group above cut-off: 50.0%.

25 patients returned the 6 month questionnaire (65.8%); return percentage in group above cut-off: 50.0%.

24 patients returned the 9 month questionnaire (63.2%); return percentage in group above cut-off: 62.5%.

23 patients returned the 12 month questionnaire (60.5%); return percentage in group above cut-off: 50.0%.

45 patients received collaborative care (CC) after inclusion through screening.

37 patients (84.1%) filled out the PSQ; 8 of these patients (21.6%) scored above the cut-off the PSQ.

26 patients returned the 3 month questionnaire (78.4%); return percentage in group above cut-off: 75.0%.

33 patients returned the 6 month questionnaire (70.2%); return percentage in group above cut-off: 62.5%.

24 patients returned the 9 month questionnaire (64.9%); return percentage in group above cut-off: 75.0%.

27 patients returned the 12 month questionnaire (72.9%); return percentage in group above cut-off: 62.5%.

48 patients received Care as Usual (CAU) after inclusion through screening.

40 patients (83.3%) filled out the PSQ; 19 patients of these (47.5%) scored above the cut-off the PSQ.

33 patients returned the 3 month questionnaire (82.5%); return percentage in group above cut-off: 78.9%.

29 patients returned the 6 month questionnaire (82.5%); return percentage in group above cut-off: 78.9%.

26 patients returned the 9 month questionnaire (70.0%); return percentage in group above cut-off: 68.4%.

27 patients returned the 12 month questionnaire (72.5%); return percentage in group above cut-off: 68.4%.
Measures

Physical symptoms:

Physical symptoms were measured using the validated Physical Symptoms Questionnaire[^33] which participants filled out at baseline. It measures 51 physical symptoms, such as chest pain, headache, dizziness, seizures, intolerance to certain types of food, and shortness of breath. Symptoms are measured on a scale that ranges between 0 (not present in the past week) to 3 (often present in the past week) and are added up. When a patient scores 2 or higher on an item, this is counted as a physical symptom. According to Van Hemert and colleagues a score of 15 symptoms or higher is the average for severe physical symptoms in men suffering from anxiety or depression, and the same holds for a score of 17 symptoms or higher for women[^34]. We applied these means as cut-off scores for men and women in order to identify patients who were suffering from clinically significant concomitant physical symptoms.

Additionally, we also performed the analyses without the cut-off because such a score is always somewhat arbitrary even if it is based on cross-sectional data such as described by Van Hemert. A cut-off, however, is easier to apply in everyday clinical practice.

Chronic medical illness:

Information about chronic medical illness was obtained by using a self-report questionnaire developed by the Dutch Central Bureau for Statistics (the CBS list)^[196]. This list contains 28 chronic medical conditions, such as cancer, COPD, high blood pressure, and diabetes. Although an assessment of the medical status by a medical doctor at baseline—as opposed to our method of self-report—might have been preferable, results from a large cohort-study suggest that patients’ self-reports on chronic diseases are fairly accurate[^197]. This was also found by the National Center for Health Statistics in the USA, especially for well known chronic conditions such as diabetes and high blood pressure[^198].

Outcome measured with the PHQ9:

The primary outcome measure was treatment response in terms of at least 50% reduction in depression severity between baseline and follow-up after three, six, nine, and twelve months of treatment. This was measured with the PHQ9[^1], the depression subscale of the self-report Patient Health Questionnaire (PHQ).[^141] The PHQ9 consists of 9 items referring to the DSM IV criteria for MDD. Each item is scored from 0 (not at all) to 3 (nearly everyday). The total score thus varies between 0 and 27. Alternatively we also looked at the continuous PHQ9-total score, which was the secondary outcome measure in the trial.
We applied multilevel logistic regression analysis (MLA) to determine the association of physical symptoms measured at baseline with the dichotomous outcome measure response to treatment (a 50% reduction of the PHQ9-score between baseline and follow-up). The PHQ9 was administered 3, 6, 9, and 12 months after baseline. We used MLA since randomization had been done at the level of health care center. The levels used in the MLA-models were: health care center, GP, patient and occasion (number of days between baseline and completion of the follow-up questionnaire at three months). The analyses were conducted using MLwiN 2.0 multilevel software. Additionally propensity scores were added to the model in order to correct for the possibility of selection bias due to the cluster randomization. This is a commonly applied procedure in cluster randomized studies.

The determinant of focus to test the first hypothesis (that physical symptoms might have a generic negative effect on the outcome of treatment for MDD), was the dichotomized PSQ-score (cut-off score PSQ ≥ 15 for men and PSQ ≥ 17 for women). Additionally, a composite score was computed based on the first time point to achieve treatment response. We also performed the logistic regression analyses without the cut-off (thus determining odds ratios per point on the PSQ) given the fact that such a score is always arbitrary up to a certain extent. Differences between treatment groups on this score were also analyzed using MultiLevel Analysis.

To explore whether or not the hypothetical effect of physical symptoms was differential for the treatment conditions (collaborative care or CAU) the interaction term 'treatment condition times physical symptoms' (cut-off score PSQ ≥ 15 for men and PSQ ≥ 17 for women) was tested for statistical significance (P<.05).

The number of chronic physical conditions a patient reported at baseline was added to the model as an independent variable to explore whether or not the hypothetical effect of physical symptoms was in fact 'explained' by chronic medical conditions. 67% of our sample reported at least one chronic medical condition. 22% even reported three or more chronic medical conditions.
Results

Study population

149 patients participated in the trial: 101 in the collaborative care group (either selected through screening or through identification by the GP) and 48 in the Care as Usual group (CAU). Because we did not include a GP-identified CAU-group in the trial, the number of patients receiving collaborative care is almost twice as large as the number patients receiving CAU. As mentioned in the methods section and below in this section we corrected for this in the analyses.

For 115 patients (77.2 % of those who entered the trial) a baseline assessment based on the PSQ could be made as to whether they scored below or above the cut-off for clinically significant physical symptoms (PSQ≥15 for men and PSQ ≥ 17 for women). 75 of these patients were included in the collaborative care group (74.3% of the collaborative care patients in the trial), compared to 40 in the CAU group (83.3%). These percentages did not deviate significantly from each other (P=.365), which means that there is no evidence for selective bias with respect to patients who did and patients who did not fill out the PSQ.

Patients who scored above the cut-off on the PSQ did not differ significantly from patients who scored below this cut-off on key baseline variables such as age, civil status, gender, and their PHQ9-score. They did differ however with respect to treatment condition. Patients who scored above the cut-off on the PSQ were more likely to have received care as usual (CAU) than patients who scored below the cut-off (P=.004). We therefore corrected the MLA-models for the variable treatment condition. The baseline scores for all variables can be found in Table 1.

TABLE 1. Baseline characteristics, treatment (N=115)

<table>
<thead>
<tr>
<th></th>
<th>PSQ&lt;cut-off (N=80)</th>
<th>PSQ≥cut-off (N=35)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (sd)</td>
<td>48.1 (11.9)</td>
<td>52.1 (16.7)</td>
<td>.207</td>
</tr>
<tr>
<td>Gender (%male)</td>
<td>23.8%</td>
<td>28.6%</td>
<td>.584</td>
</tr>
<tr>
<td>Living alone (%)</td>
<td>48.8%</td>
<td>42.9%</td>
<td>.560</td>
</tr>
<tr>
<td>Non Dutch origin (%)</td>
<td>25.0%</td>
<td>21.2%</td>
<td>.668</td>
</tr>
<tr>
<td>PHQ9 at baseline (sd) CC (%)</td>
<td>14.8 (4.9)</td>
<td>16.2 (5.5)</td>
<td>.171</td>
</tr>
<tr>
<td>CAU (%)</td>
<td>52.5%</td>
<td>47.5%</td>
<td>.00*</td>
</tr>
</tbody>
</table>

*Statistically significant (P<0.05), chi square test for dichotomous variables and T-test for continuous variables; CC=Collaborative Care. There are significantly more patients who score above the PSQ cut-off in the CAU-group. We controlled for this variable (condition) in the model in Table 2.
The available 115 patients were followed and included in the analysis. Follow-up data were obtained on a minimum of 76 (66.1%) patients at T3 to a maximum of 84 (73.0%) patients at T2, as shown in the flowchart. There was no evidence of selective non-response to the questionnaires. Only 4.3% of the patients did not return any of the follow-up questionnaires. These patients were not included in the analyses. They were evenly distributed over both groups: the group scoring above the cut-off on the PSQ and the group scoring below the cut-off (P=.64).

**Effect of physical symptoms on the effectiveness of collaborative care**

Overall, concomitant physical symptoms did exert a negative effect on response for collaborative care and care as usual, but the effect was the same for both conditions. There was no interaction effect, which in combination with a substantial main effect, shows that collaborative care works for these patients as well (although less well than for patients not suffering from concomitant physical symptoms, but this problem is also present for patients in the CAU-group).

The MLA revealed a generic negative effect of physical symptoms (PSQ≥15 for men and PSQ≥17 for women, yes/no) on response to treatment (*hypothesis i*). This effect was statistically significant even after correction for treatment condition after three (T1), six (T2), and nine months (T3), but not at after 12 months (T4). The outcome in terms of odds ratios for response to treatment (a decrease of at least 50% on the PHQ9 between baseline and follow-up) is displayed in Table 2.

<table>
<thead>
<tr>
<th></th>
<th>OR PSQ≥cut-off (CI)</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Three months (T1)</td>
<td>6.83 (1.27-36.81)**</td>
<td>82</td>
</tr>
<tr>
<td>Six months (T2)</td>
<td>4.05 (1.10-14.92)**</td>
<td>84</td>
</tr>
<tr>
<td>Nine months (T3)</td>
<td>6.38 (1.64-24.80)**</td>
<td>76</td>
</tr>
<tr>
<td>Twelve months (T4)</td>
<td>1.93 (.57-6.57)</td>
<td>79</td>
</tr>
</tbody>
</table>

OR= Odds ratio; CI=Confidence Interval
*Corrected for treatment condition (CAU or CC)
**P<.05

The group without concomitant physical symptoms had a higher odds (6.83; 95%CI: 1.27 to 36.81) on response after three months than the group with such symptoms. The OR after six months for response was 4.05 (CI: 1.10-14.92), and the OR after nine months was 6.38 (CI: 1.64-24.80). Time to first response was also 4.3 months longer for the group suffering from clinically significant concomitant physical symptoms. The logistic regression analyses without the PSQ cut-off revealed significant ORs on
response (on the PHQ9) per point on the PSQ at T1 and T3. The OR per point at T1 was 1.12 (CI: 1.02-1.23), and at T3 it was 1.10 (CI: 1.02-1.19). The results at T2 and T4 pointed in the direction of a negative effect of a higher PSQ score, but were non significant (P=.12 at T2; P=.06 at T4).

The more negative course of MDD for the group that scores above the cut-off for clinically significant concomitant physical symptoms on the PSQ is also shown in Figure 2.

Figure 2. Negative effect of physical symptoms score PSQ on the course of depression for the whole group (N=115)

However, no differential effect of concomitant physical symptoms could be demonstrated on one of the treatment conditions (hypothesis ii). There was no significant interaction between treatment condition (either collaborative care or CAU) and physical symptoms (P at three months=.22 ; P at six months=.88 ; P at nine months=.34 ; P at twelve months =.94) with respect to the outcome measure response to treatment. Interaction was also not found in the logistic model without the cut-off on the PSQ.
Adding the number of chronic medical conditions to the model did not have an effect on the outcome (hypothesis iii). When looking at the results as a whole, the conclusion is that the correction for medical conditions did not influence the results, and that the effect of concomitant physical symptoms remained statistically significant after this correction. Furthermore the correction for chronic medical conditions did also not influence the results for time to first treatment response.

As data were available on care given by the care managers in the collaborative care arms of the trial, it was possible to explore the possibility that the negative effect of concomitant physical symptoms was perhaps due to lower adherence to the protocol. In that case one would expect that it was less likely that care had been initiated when patients scored above the cut-off on the PSQ and that these patients had received less sessions. We could not demonstrate this conclusively: although 37.5% of the patients with concomitant physical symptoms in the collaborative care groups did not go to a care manager at all or only went to the first appointment, as opposed to 20.3% without, this difference was not significant (P=.154). The same was true for the number of appointments with a care manager: patients with concomitant physical symptoms in the collaborative care groups had less sessions, on average 4.9 (SD=3.8) appointments as opposed to 6.4 (SD=3.7) in the group with no extra physical symptoms, but again this finding was not significant (P=.174).
Discussion

Our hypothesis that physical symptoms might have a generic negative effect on the outcome of treatment for MDD was confirmed. Patients in the group suffering from clinically significant concomitant physical symptoms responded on average 4.3 months later than patients in the group that scored below the cut-off on the PSQ. Our second hypothesis was not confirmed. No differential effect for type of treatment (collaborative care or care as usual) could be demonstrated. Treatment for MDD in primary care thus appears to be less successful for all patients (regardless of treatment condition) who are suffering from clinically significant concomitant physical symptoms, but they can benefit from collaborative care anyway. The association of physical symptoms with lack of response remained significant after three, six, and nine months; and after the models were corrected for the presence of chronic medical illnesses (e.g. COPD or Diabetes).

Whether the physical symptoms a patient experiences concomitant to a depression are explained by a chronic medical disorder or not, apparently is not relevant to the effect of these symptoms on the course of MDD and the outcome of treatment for this disorder. This is an important issue: comorbidity of MDD with chronic medical illnesses is high, but so is the comorbidity with somatoform disorders where the underlying pathology is not explained. Minsky and colleagues report that the presence of 3 or more physical symptoms is a significant predictor of mental health service use, and that whether or not these symptoms are explained by a known medical disorder is not particularly relevant in that respect.

By asking patients at baseline about the medical conditions they were suffering from, we were able to explore this issue. In our current sample the distinction indeed appeared to be irrelevant when looking at the relationship with the outcome of MDD. Replication in a study where the physical symptoms are assessed by a medical doctor at baseline is advisable, even though results from a large cohort-study suggest that patients' self-reports on chronic diseases are fairly accurate.

Limitations

A first limitation of this study is the percentage of patients who did not return a questionnaire at one or more of the time points of on average 30.2% (ranging from 27.0% at six months to 33.9% at nine months). There was no evidence of selective non-response to the questionnaires at any of the time points. Other studies with dropout percentages below 20%, have also found a negative association of concomitant physical symptoms with MDD, which implies that there is little reason to doubt the finding that concomitant physical symptoms predict a more negative course of MDD. More research seems necessary though regarding the hypothesis that there might be interaction of physical symptoms with the type of treatment that was provided (hypothesis ii). Our study may have been underpowered to detect this.

A second limitation could be that not all patients completed the PSQ at baseline (77.2% did), as some patients found the questionnaires too time consuming. As mentioned in the results section, there was no evidence for selective bias with respect to patients who did and patients who did not fill out the PSQ. It may, however, also (like the loss to follow-up) have influenced statistical power, and this might explain the lack of effect of concomitant physical symptoms at T4.
Finally, a third limitation of our current study, although it only refers to hypothesis iii as stated in the introduction (the hypothesis that the effect of concomitant physical symptoms is not explained by the presence of an underlying chronic physical illness), might have been the absence of the assessment of the concomitant physical symptoms by a medical doctor at baseline. The result is that it still remains somewhat unclear whether or not the physical symptoms were medically explained or not. By asking patients at baseline about the medical conditions they were suffering from, we were able to explore this issue however. In our current sample the distinction appeared to be irrelevant when looking at the relationship with the outcome of MDD. Replication in a study where the physical symptoms are assessed by a medical doctor at baseline is advisable, even although results from a large cohort-study suggest that patients' self-reports on chronic diseases are fairly accurate.197

**Implications for research and clinical practice**

Our analyses identify a group of patients whose condition -MDD with concomitant physical symptoms according to a self report questionnaire- shows a substantially less favourable treatment response. Apparently the presence of clinically significant physical symptoms as experienced by a patient and not the medical nature, i.e. explained by a medical condition or not influences the outcome of treatment (both collaborative care and care as usual).

Such levels of physical symptoms perhaps point to deeper rooted negative cognitions that the patient is not aware of yet, or might be considered as anxiety equivalents with the subsequent avoidance behaviour, but such considerations remain speculative. In any case, these patients are frequent visitors to their GP and are generally high service utilizers.200;201 Integrated treatment in primary care is therefore a logical way forward. Another possible explanation might be that these symptoms should be considered expressions of MDD or comorbid anxiety conditions, i.e. mixed anxiety-depression, that often occur in primary care as well.202

Although more research into the specific characteristics of this group is necessary, an important question for the future will be: how can we identify and treat patients suffering from depression accompanied by a high level of physical symptoms successfully? Our results support the increasing use in primary care of multidimensional symptom indicators such as the PHQ9, PHQ15, and PSQ.33;34 The PHQ15 and the PSQ were designed specifically to detect clinically significant physical symptoms in patients suffering from mental disorders.

Both collaborative care and care as usual for MDD are less effective for this group. The good news is that clinically significant concomitant physical symptoms do not appear to be a contraindication for collaborative care (since we did not find interaction with type of treatment). Nevertheless these symptoms do predict a more negative course of MDD, even if collaborative care is applied. Our data on the actual care that was delivered in the collaborative care arms of the trial suggest that patients suffering from concomitant physical symptoms received less sessions (4.9 vs. 6.4 on average) and that it was somewhat less likely that care had been initiated. These results were not statistically significant however. Nevertheless it might be worthwhile to invest more time and energy to convince this group that treatment for depression might be beneficial for them. After
all, collaborative care is still more effective than care as usual for patients suffering from clinically significant concomitant physical symptoms (but relatively less effective compared with the group that does not meet these criteria).

Promising results in this respect, were found in previous research for an adapted version of the collaborative care model for patients who were suffering from medically unexplained physical symptoms in which a consultant psychiatrist saw the patients together with the general practitioner in the primary care center. This was not common practice in the collaborative care model in our current study, in which the consultant psychiatrist had a less proactive role: the psychiatrist provided consultation advice if a patient was not responding to treatment after a certain amount of time. Another option may be to add a psychosomatic physiotherapist to the collaborative care team. These physiotherapists have been trained to recognize and influence the complex relationship between motor function, mental function, and psychosocial context, which might be helpful in the treatment of patients who suffer from both physical and mental problems. For patients suffering from comorbid chronic somatoform disorders referral to a psychotherapist or specialized mental health care may be worthwhile. In view of the negative influence on treatment response, research is warranted to improve the treatment model for patients with MDD with concomitant physical symptoms in primary care.