

## Research paper

## Does symptom severity matter in stepped and collaborative care for depression?

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## ARTICLE INFO

## Keywords:

Stepped care  
Collaborative care  
Outcome  
Depression  
Severity subgroups  
Treatment utilization

## ABSTRACT

**Background:** We investigated the differential effectiveness of a stepped and collaborative care model (SCM) vs. treatment as usual (TAU) for primary care patients with various depression severity degrees and explored whether subgroups received distinct evidence-based treatments.

**Methods:** Subgroup analyses of a RCT were calculated applying a multiple linear mixed model with the factors 1. group (SCM; TAU), 2. severity ((mild-moderate (MMD); severe depression (SD)) and their interaction, with PHQ-9 as primary outcome. Utilization of treatments was analyzed descriptively.

**Results:** For the 737 participating patients (SCM:  $n = 569$ ; TAU:  $n = 168$ ), availability of data substantially varies between subgroups at 12-month follow-up ranging between 37% and 70%. ITT-analysis (Last-observation-carried-forward) revealed a significant interaction for group  $\times$  severity [ $p = 0.036$ ] and a significant difference between groups in symptom reduction for MMD ( $-3.9$ ; [95% CI:  $-5.1$  to  $-2.6$ ,  $p < 0.001$ ;  $d = 0.64$ ] but not for SD ( $-1.6$ ; [95% CI:  $-3.4$  to  $0.2$ ,  $p = 0.093$ ;  $d = 0.27$ ]. Sensitivity analyses (multiple imputation, complete analysis, pattern mixture model) didn't confirm the interaction effect and showed significant effects for both severity groups with slightly higher effect sizes for MMD. Differences between SCM and TAU in the percentage of patients utilizing depression-specific treatments are larger for MMD.

**Limitations:** There was a high proportion of missing values among severely depressed patients, especially in SCM. **Conclusion:** SCM is effective for both MMD and SD. Utilization patterns might help explain the higher effects for MMD. Various strategies of replacement of missing values lead to slightly divergent results due to selective drop out between severity groups.

## 1. Introduction

Depression is one of the most common mental disorders. It is a very broad diagnostic category which can be divided into several subtypes of depression (DGPPN et al., 2015; Kessing, 2007; Kessler et al., 2003; NICE, 2010; Wittchen et al., 2000). The International Statistical Classification of Diseases and Related Health Problems (ICD-10) and the Diagnostic and Statistical Manual of Mental Disorders (DSM) differentiate mild, moderate and severe depression

(American Psychiatric Association, 2013; Dilling et al., 2014). The ICD-10 additionally distinguishes between recurrent disorders and single episodes (Dilling et al., 2014). The differentiation into the subtypes of depression with regard to severity, duration and course is not only important for how depression presents clinically, but also for guideline-adherent decision-making regarding evidence-based treatments (DGPPN et al., 2015; NICE, 2010): international guidelines recommend providing active monitoring to patients with subthreshold depression or patients with mild depression as first step. Patients with mild to

**Abbreviations:** SCM, Stepped and Collaborative Care Modell; TAU, Treatment as usual; RCT, Randomized controlled trial; MMD, mild to moderate depression; SD, severe depression; ITT, Intention to treat; CI, Confidence interval; ICD-10, International Statistical Classification of Diseases and Related Health Problems; DSM, Diagnostic and Statistical Manual of Mental Disorders; CBT, cognitive behavioral therapy; CCBT, computerized cognitive behavioral therapy; GP, General practitioner; LOCF, last-observation carried forward; MI, multiple imputation; AD, antidepressant treatment; PT, psychotherapeutic treatment

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<https://doi.org/10.1016/j.jad.2020.07.079>

Received 25 January 2020; Received in revised form 22 May 2020; Accepted 5 July 2020

Available online 21 July 2020

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moderate depression or persistent subthreshold depressive symptoms should be offered low intensity treatments like bibliotherapy, individual guided self-help based on the principles of cognitive behavioral therapy (CBT), computerized cognitive behavioral therapy (CCBT), or physical activity programs. Either medication or psychotherapy should be offered to patients with mild to moderate depression or persistent subthreshold depressive symptoms who did not benefit from low intensity treatments. For severely depressed patients, a combination of medication and psychotherapy is recommended. In cases of severe and complex depression, this combined treatment should be offered as standard, sometimes also in an inpatient treatment setting if patients do not improve in outpatient care (DGPPN et al., 2015; NICE, 2010).

As there are distinct recommendations for different groups of depressed patients which vary in treatment intensity, a systematic treatment selection applying a stepped and collaborative care approach is crucial. While stepped care focuses on treating patients with an adequate treatment of the lowest possible intensity while continuously monitoring progress, collaborative care aims to systematically integrate different care providers. Both health care models are often combined and recommended by international depression guidelines (DGPPN et al., 2015; Landelijke Stuurgroep, 2005; NICE, 2010).

However, guideline implementation is still insufficient. Often patients with mild depression are over-prescribed with antidepressant medication (Baer et al., 2013; Trautmann and Beesdo-Baum, 2017), while patients with severe depression often do not receive the intensity of care they would need (Melchior et al., 2014). For the patients' sake but also from a cost-effectiveness perspective it would be relevant to prevent inpatient treatment by offering adequate outpatient treatment options at an early stage of treatment. These health care issues are addressed by guidelines and stepped and collaborative care models (SCM).

There is good evidence for the general effectiveness and partially also for the cost-effectiveness of SCM for depression (Archer et al., 2012; Firth et al., 2015; Goorden et al., 2014; Härter et al., 2018; Ho et al., 2016; van Straten et al., 2015; Von Korff et al., 1997). However, there is still little knowledge and evidence about differential effects of these models, i.e. whether there are characteristics of the patient or the type of the depression predicting the response to SCM. Since SCM comprises a complex intervention that is tailored individually for patients, in the differential analysis of effects treatment variables have also to be taken into account, i.e. the type of treatments actually received by patients. These analyses of individual treatment utilization and treatment pathways may help explain (variations in) outcome effects.

Even though it is known that depression severity degree is one of the best predictors of treatment response (Katon et al., 1994; Walker et al., 2000), only few studies report results of SCM referring to different severity subgroups. One SCM intervention showed a significant improvement in depressive symptoms after 6 and 28 months compared with usual care for the group of moderately depressed patients, but not for patients in the high severity group (Katon et al., 2002; Walker et al., 2000). In a SCM for depression in the Netherlands, Franx and colleagues found that patients in the non-severe depression group were treated according to the guideline oriented SCM protocol considerably more often than severely depressed patients. Furthermore, the adherence to the SCM improved during the study for the non-severe group, but not for the severe group. The authors concluded that special attention should be paid to the quality of care for severely depressed patients (Franx et al., 2009). However, another study reported that health care consumption increased significantly in both depressed patient groups (Gidding et al., 2014). In accordance with this, Unützer and colleagues did not find a significant interaction between intervention effect and depressive symptom severity (Unützer et al., 2002). In summary, no conclusive answer to this research question exists yet.

## 1.1. Aims of the study

Against this background, this article examines whether patients with different degrees of depression severity benefit differentially from stepped and collaborative care and whether they differ in the treatments received, taking into account severity degree. The general effectiveness of the model under investigation has been already reported elsewhere (Härter et al., 2018), while the present analyses combine subgroup analyses with the treatment utilization of the subgroups.

## 2. Methods

### 2.1. Study design

This parallel cluster-randomized controlled intervention trial assessed a consecutive sample of patients with depression from primary care with measurements at four time points (baseline and 3, 6 and 12 months after baseline). Randomization was conducted at the level of participating GP practices, dividing these into an intervention group and a control group in a 3:1 ratio. Patients recruited by GPs in the intervention group were treated in the stepped and collaborative care model (SCM), while patients recruited by GPs in the control group received treatment as usual (TAU). The process of randomization was conducted by a computer program using minimization based on practice size, practice location and income level of the practice's local district (Watzke et al., 2014).

Sample size calculation was based on the detection of a small to moderate effect (Cohen's *d* of 0.40) with a statistical power of 0.80 and a type I error rate of 0.05 (two sided) between SCM and TAU. After considering the clustered design with an assumed intra-cluster correlation of 0.05, the differential expected attrition rates between groups, and the plan to run further separate analyses for each of six treatment options, which are available in SCM (see section "2.5 Intervention"), we aimed to recruit a total of 860 patients. Expecting that every participating GP practice would recruit 15–25 patients, we planned to gain 40 practices for study participation (660 patients from 30 practices in SCM and 200 patients from 10 practices in TAU). In total, we recruited 49 practices: 36 practices were randomized to SCM and 13 practices to TAU (Watzke et al., 2014).

The study was approved by the Ethics Committee of the Hamburg Chamber of Psychotherapists and conducted according to the principles of the Declaration of Helsinki (2013 version). Written informed consent was obtained from all participants. The study was registered in ClinicalTrials.gov (registration number: NCT01731717; registration date: 11.12.2012).

### 2.2. Setting

The study "Health Network Depression" was embedded into the intersectoral research initiative *psychnet - The Hamburg Network for Mental Health* (2011–2015; funded by the German Federal Ministry of Education and Health) which consisted of 11 research and development projects on mental health care research in the metropolitan area of Hamburg (Germany) (Härter et al., 2012; Watzke et al., 2014). Patient assessment and treatment in SCM took place within a multi-professional, specially established and trained network of GP practices, psychotherapists, psychiatrists and inpatient clinic representatives implemented in routine care (Härter et al., 2015; Heddaeus et al., 2015), while assessment and treatment in TAU was conducted in GP practices as well as any facilities available in routine care.

### 2.3. Care providers

All GP practices, psychotherapists, psychiatrists of the greater Hamburg area were invited by mail via the Hamburg Chamber of Physicians to participate in the study. Inclusion criteria for

participation were willingness to participate in study procedures and to be working as a Statutory Health Insurance GP, psychotherapist or psychiatrist in an established practice. For inpatient institutions inclusion criteria were willingness to participate in study procedures and to have a license from the Association of Statutory Health Insurance.

## 2.4. Patients

Patient recruitment in SCM and TAU was carried out by the participating GPs and comprised three screening and assessment steps using checklists and the PHQ-9, successively (Watzke et al., 2014). Inclusion criteria were a minimum age of 18, five or more points on PHQ-9 and informed consent. Patients with insufficient knowledge of the German language or a health situation that did not allow questionnaire completion were excluded. Neither somatic nor mental comorbidities were exclusion criteria. Patients were only excluded if a mental disorder other than depression, e.g. a trauma-related disorder, was the main treatment focus. Patient inclusion took place from August 08, 2012 to March 31, 2014. Follow-up measurements took place between 2012 and 2015.

## 2.5. Interventions

### 2.5.1. Stepped and collaborative care model (SCM)

The SCM is a stratified stepped and collaborative care approach which has been described in detail elsewhere (Watzke et al., 2014). GPs of the intervention group, i.e. GPs offering their patients SCM, completed an ICD-10-based checklist and imparted psycho-education if patients fulfilled the study criteria (PHQ-9  $\geq$  5). Treatment interventions according to SCM were allocated by the GPs on the basis of the ICD-10 diagnosis following the evidence-based recommendations of the German National Clinical Practice Guideline “Unipolar Depression” (Watzke et al., 2014), i.e. criteria were: (1) depression severity and (2) patient preferences as result of a shared decision-making process.

Within the SCM, treatment options were available on four levels of intensity: *Step 1*) active monitoring; *2a*) bibliotherapy (Görlitz, 2010); *2b*) internet-based self-management (Meyer et al., 2009); *2c*) telephone-administered psychotherapy (9–13 sessions) (Steinmann et al., 2016); *3a*) outpatient cognitive-behavioral or psychodynamic psychotherapy (usually  $\leq$  25 sessions) as stand-alone treatment; *3b*) antidepressant pharmacotherapy as stand-alone treatment; and *4*) combination of psycho- and pharmacotherapy in either out- or inpatient setting. Therefore, there were six treatment options (step 2–4) within the SCM – considering Step 1 (“active monitoring”) as an antecedent option and not as actual treatment option.

Course of treatment and symptoms were monitored by care providers with the PHQ-9 in predefined intervals depending upon intervention and symptoms. If the PHQ-9 score had not improved by at least 20% since beginning a treatment, stepping up was recommended. A care provider network was built up to facilitate communication and prompt referral between primary and secondary care. To improve referral and to reduce waiting times, an online platform indicating available treatment capacities was implemented. All participating multi-professional providers obtained intensive training regarding the relevant guideline recommendations (DGPPN et al., 2015; NICE, 2004), the SCM and its related interventions. Quarter-yearly quality circles took place to assure the quality of the integrated care model and a stable adherence to clinical recommendations.

### 2.5.2. Treatment as usual (TAU)

Patients in the TAU received treatment as usual by their GP and within the regular German health care system, including potentially necessary referrals to psychotherapy and psychiatry in out- or inpatient care settings. Systematic screening was carried out in both SCM and TAU to ensure a comparable recruitment and inclusion process.

## 2.6. Outcomes

All outcomes were assessed by self-report questionnaires at four time points: The baseline (T0) assessment was handed out by the GP at study inclusion and filled out before any treatment began. The questionnaires 3 (T1), 6 (T2) and 12 months (T3) after baseline were sent to patients by mail. If a questionnaire was not returned within two weeks, up to two reminder letters were sent to the patient and one to the patient's GP within the following month to improve response rates.

Primary outcome was change in depressive symptoms assessed by the Patient Health Questionnaire-9 (PHQ-9) (Löwe et al., 2004) from baseline to 12 months (differential treatment outcome). Treatment utilization during the 12 months of study participation was assessed by patient self-report questionnaires at T1, T2 and T3. Patients retrospectively reported their use of different treatment options and consultation of various care providers.

## 2.7. Statistical analysis

The outcome analysis regarding change in PHQ-9 from baseline to T3 was based on the intention to treat (ITT) population. Only this time point was part of our analysis. In case of missing follow-up values, a last-observation carried forward (LOCF) imputation was performed using also the time points in between for the imputation (primary analysis) (Watzke et al., 2014). As dropouts were distributed unequally, three kinds of sensitivity analyses were performed: One model using the ITT population and the multiple imputation (MI) replacement method instead of LOCF and a second one without LOCF replacement but with only those cases who provided data for the main outcome at T3 (i.e. completer analyses). To account for a possible violation of the missing at random assumption, we used a pattern mixture model with control-based pattern imputation as a third sensitivity analysis (Ratitch et al., 2013).

For the subgroup analysis, we divided patients in both conditions into two groups of different depression severity: mild to moderate depression severity (averaged PHQ-9-score of less than 15) and severe depression severity (averaged PHQ-9-score of 15 or more). We calculated a multiple linear mixed model with group (SCM vs. TAU), depression severity (mild-moderate vs. severe), their interaction and education level as fixed effects (due to differences at baseline in this variable, cp. Table 1) and the general practice care unit as a random effect. We fitted a random intercept model with a scaled identity covariance matrix. We reported adjusted marginal means of the interaction term and their 95% confidence interval and p values. The significance level was set at 5% (two-sided).

The differential treatment utilization of the two groups was analyzed descriptively. The analysis of treatment utilization is based on the sample of patients for which T3 data (including information on treatment utilization during the whole observation period of 12 months) is available (see also 3.3.2). The following hypotheses regarding differences in treatment utilization were derived from the stepped care model: In both severity groups (MMD und SD) it was expected that SCM was associated with fewer patients being treated with nothing besides GP consultations, as well as with a higher utilization of depression-specific treatments. For MMD, SCM was expected to result in the utilization of low intensity treatments, more psychotherapeutic treatment, less antidepressant (AD) treatment (as AD is not the first line treatment for mild depression) and less inpatient treatment than TAU. For severe depression, SCM was expected to be associated with more psychotherapeutic treatment (PT), more AD treatment, and more combination of PT and AD.

All analyses were conducted with SPSS 23 and SAS 9.4.

**Table 1**  
Baseline characteristics on patient level in SCM<sub>1</sub> and TAU<sub>2</sub>.

Baseline characteristics	Group Mild-moderate SCM <sub>1</sub> (n = 383)	TAU <sub>2</sub> (n = 113)	Severe SCM <sub>1</sub> (n = 186)	TAU <sub>2</sub> (n = 55)
Age (M (Standard Deviation))	43.4 (13.9)	48.9 (16.4)	39.4 (12.2)	38.9 (10.8)
Female gender (% (n))	75.2 (288)	77.9 (88)	66.7 (124)	72.7 (40)
Education level (% (n))				
Secondary general school <sub>3</sub>	18.8 (72)	32.7 (37)	23.7 (44)	23.6 (13)
Intermediate secondary school <sub>4</sub>	29.0 (111)	23.0 (26)	24.7 (46)	32.7 (18)
High school <sub>5</sub>	25.8 (99)	23.9 (27)	23.7 (44)	18.2 (10)
University or technical college degree	17.5 (67)	10.6 (12)	7.5 (14)	9.1 (5)
No school degree	1.6 (6)	3.5 (4)	3.2 (6)	1.8 (1)
Missing	7.3 (28)	6.2 (7)	17.2 (32)	14.5 (8)
Employment status (% (n))				
No employment	22.7 (87)	25.7 (29)	32.8 (61)	40.0 (22)
Minor employment	3.1 (12)	4.4 (5)	3.2 (6)	1.8 (1)
Part-time employment	20.9 (80)	16.8 (19)	14.0 (26)	14.5 (8)
Full-time employment	44.4 (170)	38.9 (44)	35.5 (66)	34.5 (19)
Missing	8.9 (34)	14.2 (16)	14.5 (27)	9.1 (5)
Living in partnership (% (n))	58.2 (223)	52.2 (59)	45.7 (85)	52.7 (29)
Missing	7.0 (27)	8.0 (9)	14.0 (26)	9.1 (5)
PHQ-9 at baseline (M (SD))	13.3 (3.9)	11.8 (4.0)	19.5 (3.1)	18.7 (3.2)

<sup>1</sup> SCM = Stepped collaborative care model (intervention group); <sup>2</sup>TAU = Treatment as usual (control group); <sup>3</sup>German: Hauptschule (9 years of education); <sup>4</sup>German: Realschule (10 years); <sup>5</sup>German: Gymnasium (13 years).

### 3. Results

#### 3.1. Participant flow

Fig. 1 shows the participant flow. 737 patients were included (SCM:  $n = 569$  vs. TAU:  $n = 168$ ), with data available for 60% of SCM patients and 64% of TAU patients after 12 months. In SCM, 67% of patients ( $n = 383$ ) had a PHQ-9 score of less than 15 points (mild to moderate depression (MMD)). In TAU this was the case for 67% ( $n = 113$ ). The severe depression group (SD) in SCM consisted of  $n = 186$  (33%) and in TAU of  $n = 55$  patients (33%). After baseline assessment, 46% of SD patients in SCM and 31% in TAU dropped out. For MMD, this rate was lower, with 11% of patients in SCM and 14% in TAU dropping out. At T3, 70% of the data of the MMD group were available in both SCM and TAU. In the SD group, 53% of the data were available in TAU and 37% in SCM.

#### 3.2. Sample

Table 1 shows the baseline characteristics of patients in the four subgroups.

#### 3.3. Differential treatment outcome

##### 3.3.1. Primary analysis

The LOCF-analysis of the adjusted PHQ-9 mean reduction from baseline to 12 months revealed a significant interaction between group and depression severity [ $p = 0.036$ ] (Table 2). Symptom reduction on the PHQ-9 for MMD was  $-6.2$  points in the SCM and  $-2.4$  points in TAU. For SD, symptom reduction on the PHQ-9 was  $-2.6$  in SCM and  $-1.0$  points in TAU. With a difference of 3.9 points in the PHQ-9, the MMD group in SCM showed a significantly greater reduction in PHQ-9 scores than patients in TAU [95% confidence interval (CI):  $-5.1$  to  $-2.6$ ,  $p < 0.001$ ; Cohen's  $d = 0.62$ ]. For the SD group, the difference between SCM and TAU (a symptom reduction of 1.6 points) was not significant [95% CI:  $-3.4$  to  $0.3$ ,  $p = 0.093$ ; Cohen's  $d = 0.25$ ].

##### 3.3.2. Sensitivity analyses

Table 2 also summarizes the results of the three different model calculations for the sensitivity analyses (ITT analyses with MI replacement method and completer analyses and pattern mixture model with

control-based pattern imputations). For all forms of analyses, an interaction between group and severity was not confirmed. The difference in symptom reduction between SCM and TAU was significant in both severity groups, but with higher effect sizes for MMD than for SD.

#### 3.4. Differential treatment utilization

Table 3 summarizes the observed proportions of treatments patients received during the 12 months of study participation and the comparison between SCM and TAU in total and differentiated for severity groups.

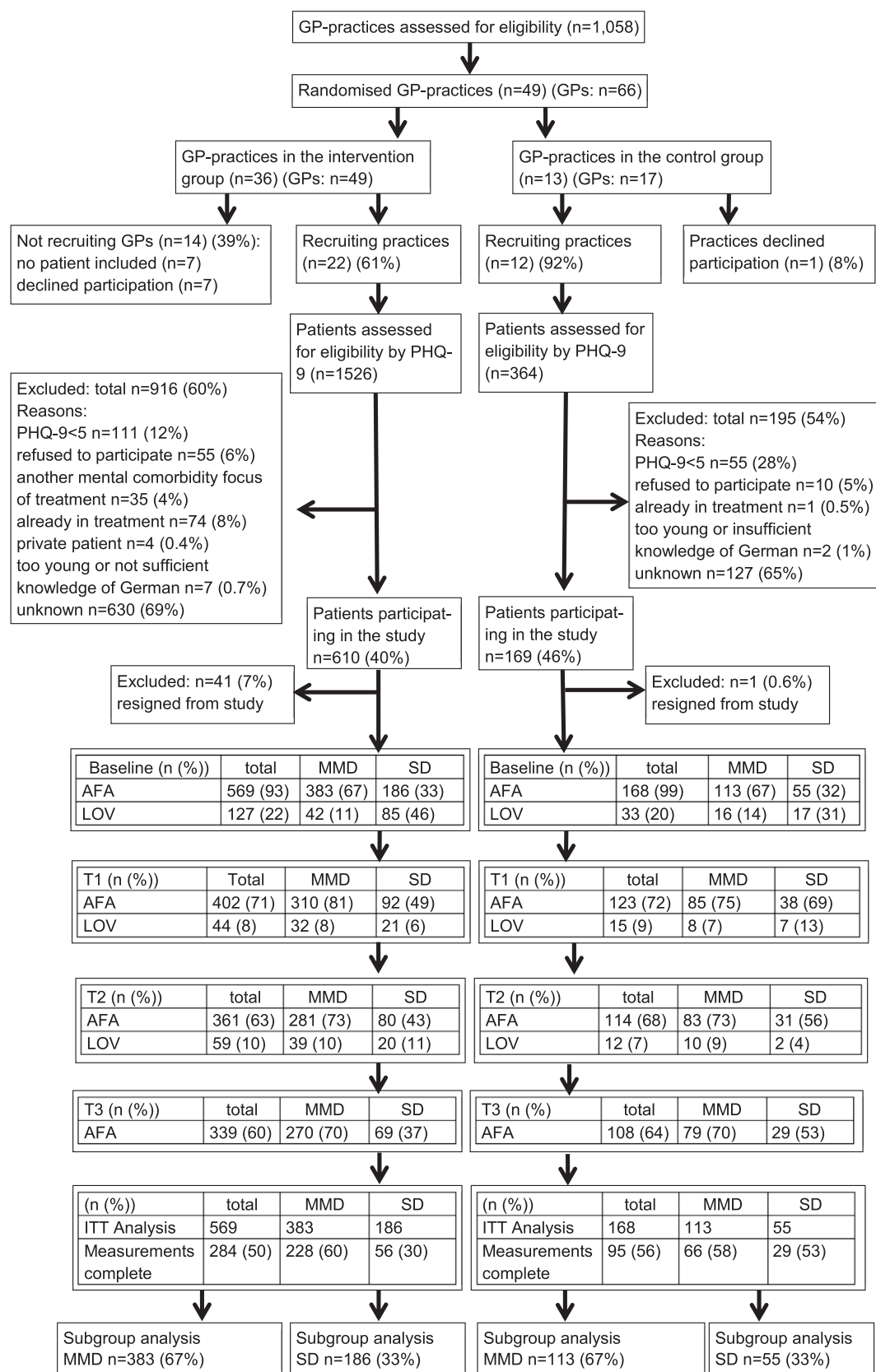
**GP consultation.** As recruitment took place in primary care, nearly all patients in SCM and TAU were seen by their GP (90.6% and 96.3% respectively). However, patients with TAU more often received nothing besides GP consultation, compared to patients in SCM (20.4% vs. 3.5%). Differentiated by severity subgroups, it becomes clear that this difference can be traced to the MMD group (25.3% TAU patients vs. 3.7% SCM patients with GP consultation only), whereas for the SD group the percentage is low in both conditions.

**Any outpatient depression-specific treatment.** The utilization of outpatient depression-specific interventions (a global category summarizing low intensity-treatments, psychotherapy and pharmacotherapy) is in line with this. Here, there is a different utilization pattern of 16.9% between TAU and SCM. Differentiated by severity groups, this difference can also be traced to the MMD group (72.2% TAU patients vs. 94.4% SCM patients with depression-specific treatment), whereas for the SD group more than 93% of the patients in both conditions received this kind of treatment. This pattern results in a 20% greater difference between SCM and TAU for MMD than for SD (22.2% vs. 2.6%).

**Low intensity treatments.** Low intensity treatments which were only offered in SCM (telephone psychotherapy, internet self-help, and bibliotherapy) were utilized by more than 40% of SCM patients (43.7% in MMD and 30.4% in SD). 20.7% of MMD patients utilized this form of intervention exclusively, i.e. without receiving a more intensive treatment in addition. In the SD group, there is a percentage of 15.9% of patients utilizing only low intensity treatments.

**Psychotherapy.** For the global category, i.e. psychotherapy alone or in combination, there is a difference in utilization of 13.4% between TAU and SCM. Differentiating for severity groups, this difference is higher for MMD (16.6%) than for SD (6.0%): Accordingly, psychotherapy is initiated for 45.6% of MDD patients in TAU, while in the





**Fig. 1.** Participant flowchart according to the cluster-randomized CONSORT statement (40). Legend: GP: General practitioner; MMD: mild to moderate depression; SD: severe depression; AFA: available for analysis; LOV: last observed value; ITT: Intention-to-treat.

**Table 2**  
Results of the primary and sensitivity analyses on differential treatment outcome of SCM<sub>1</sub> at T3.

Mild-Moderate Depression (PHQ-9 <15)					Severe Depression (PHQ-9 ≥ 15)					Between groups difference: p-value		Effect size (Cohen's d)		Group x severity degree interaction	
SCM	TAU <sub>2</sub>	Adjusted mean change	95% CI	Between group difference (95% CI)	Between groups difference: p-value	Effect size (Cohen's d)	SCM	Adjusted mean change	95% CI	TAU	Adjusted mean change	95% CI	Between group difference (95% CI)	Effect size (Cohen's d)	Group x severity degree interaction
Replacement of missing values with Last-observation-carried-forward															
-6.23	-7.03; -5.43	-2.36	-3.53; -1.19	-3.87 (-5.13; -2.61)	<0.001	0.62	-2.60	-3.61; -1.60	-1.04			-2.70; 0.615	-1.56 (-3.38; 0.26)	0.25	0.036
Analysis of complete cases															
-7.89	-9.08; -6.70	-3.41	-5.06; -1.76	-4.48 (-6.12; -2.84)	<0.001	0.61	-5.00	-6.72; -3.29	-2.00			-4.34; 0.33	-3.00 (-5.67; -0.33)	0.47	0.339
Replacement of missing values with Multiple Imputation															
-7.07	-7.75; -6.38	-3.01	-4.18; -1.85	-4.05 (-5.39; -2.72)	<0.001	0.66	-4.43	-5.50; -3.36	-1.48			-3.16; 0.19	-2.95 (-4.92; -0.97)	0.47	0.332
Replacement of missing values with pattern mixture model															
-7.42	-8.69; -6.16	-2.92	-4.49; -1.34	-4.50 (-5.71; -3.30)	<0.001	0.51	-5.30	-6.83; -3.76	-1.76			-3.83; 0.31	-3.54 (-5.60; -1.48)	0.49	0.340

<sup>1</sup> SCM: Stepped and collaborative care; <sub>2</sub> TAU: Treatment as usual.

**Table 3**  
Treatment utilization for different patient groups in SCM<sub>1</sub> or TAU<sub>2</sub> within 12-month study participation.

Intervention% (n) [confidence interval]	Total sample SCM n = 349	TAU n = 98	MMD <sub>5</sub> (PHQ-9 < 15) SCM n = 270	TAU n = 79	SD <sub>6</sub> (PHQ-9 ≥ 15) SCM n = 69	TAU n = 29
No intervention	1.5 (5) [0;3]	0.9 (1) [0;5]	1.9 (5) [1;4]	1.3 (1) [0;7]	0.0 (0) [0;5]	0.0 (0) [0;12]
GP only	3.5 (12) [2;6]	20.4 (22) [13;29]	3.7 (10) [2;7]	25.3 (20) [16;36]	2.9 (2) [0;10]	6.9 (2) [1;23]
GP consultation (alone or in combination)	90.6 (307) [87;93]	96.3 (104) [91;99]	90.4 (244) [86;94]	96.2 (76) [89;99]	91.3 (63) [82;97]	96.6 (28) [82;100]
Psychotherapy (alone or in combination)	63.4 (215) [58;69]	50.0 (54) [40;60]	62.2 (168) [56;68]	45.6 (36) [34;57]	68.1 (47) [56;79]	62.1 (18) [42;79]
Treatment with antidepressant pharmacotherapy (alone or in combination)	54.6 (185) [49;60]	62.0 (67) [52;71]	49.6 (134) [44;56]	54.4 (43) [43;66]	73.9 (51) [62;84]	82.8 (24) [64;94]
Antidepressant pharmacotherapy only	6.2 (21) [4;9]	19.4 (21) [12;28]	5.9 (16) [3;9]	20.3 (16) [12;31]	7.2 (5) [2;16]	17.2 (5) [6;36]
Psychotherapy only	11.8 (40) [9;16]	9.3 (10) [5;16]	13.0 (35) [9;18]	10.1 (8) [4;19]	7.2 (5) [2;16]	6.9 (2) [1;23]
Psychotherapy and antidepressant pharmacotherapy	39.2 (133) [34;45]	36.1 (39) [27;46]	35.9 (97) [30;42]	29.1 (23) [19;40]	52.2 (36) [40;64]	55.2 (16) [36;74]
Low-intensity treatment (telephone psychotherapy, internet self-help, bibliotherapy) (alone or in combination)	41.0 (139) [36;46]	n.a. <sub>3</sub>	43.7 (118) [38;50]	n.a. <sub>3</sub>	30.4 (21) [20;43]	n.a. <sub>3</sub>
Low-intensity treatment only	19.8 (67) [16;24]	n.a. <sub>3</sub>	20.7 (56) [16;26]	n.a. <sub>3</sub>	15.9 (11) [8;27]	n.a. <sub>3</sub>
Any outpatient depression-specific treatment <sub>4</sub>	94.7 (321) [92;97]	77.8 (84) [69;85]	94.4 (255) [91;97]	72.2 (57) [61;82]	95.7 (66) [88;99]	93.1 (27) [77;99]
Inpatient in total	15.0 (51) [11;19]	25.0 (27) [17;34]	8.9 (24) [6;13]	21.5 (17) [13;32]	39.1 (27) [28;52]	34.5 (10) [18;54]
no information (missing data)	23 (128)	20 (33)	12 (46)	14 (16)	44 (82)	31 (17)

<sup>1</sup> SCM: Stepped and collaborative care; <sub>2</sub> TAU: Treatment as usual; <sub>3</sub> n.a.: not assessed; <sub>4</sub> Any outpatient depression-specific treatment: low-intensity and/or psychotherapy and/or antidepressant pharmacotherapy; <sub>5</sub> MMD: mildly to moderately depressed patients; <sub>6</sub> SD: severely depressed patients; **bold numbers**: confidence intervals that do not overlap between SCM and TAU within the total sample and within each severity group.

other three groups the utilization rate is 62% or higher. However, confidence intervals for these comparisons (total and MMD patients) overlap slightly.

For the subgroup of patients receiving psychotherapy only and for the subgroup receiving psychotherapy and antidepressant medication, no differences in utilization between groups was found. Since there is no difference for these treatment utilization patterns, it can be concluded that the difference for the global category (psychotherapy alone or in combination) is due to the use of psychotherapy in combination with low-intensity treatments.

**Treatment with antidepressant pharmacotherapy.** AD as global category, i.e. alone or in combination, differences in utilization between groups cannot be confirmed. Approximately half of the patients with MMD received AD (54.4% in TAU and 49.6% in SCM), whereas more than 2/3 of patients with SD received AD (82.8% in TAU and 73.9% in SCM).

For the subgroups of patients receiving AD only there is a difference in utilization between TAU and SCM: This difference is similar across severity groups (MMD: 20.3% TAU vs. 5.9% SCM; SD: 17.2% TAU vs. 7.2% SCM patients with AD only). However, due to the large and overlapping confidence interval in the SD group the difference is reliable only for the MMD group.

**Inpatient treatment.** Inpatient care was initiated 12.6% less frequently in SCM than in TAU (21.5% TAU vs. 8.9% SCM patients with inpatient treatment). For the SD group, approx. 1/3 of patients in both conditions received inpatient care (39.1% TAU and 34.5% SCM patients).

## 4. Discussion

### 4.1. Differential treatment outcome

This subgroup analysis of a cluster-randomized controlled intervention trial suggests that SCM is effective for patients of different severity groups. Our primary strategy for data analysis (ITT analysis with replacement of missing values by the LOCF method) shows a significant effect regarding depressive symptom reduction for SCM in mildly to moderately depressed patients but not in severely depressed patients. However, the sensitivity analyses (ITT-analysis with MI replacement, the completer analysis and the pattern mixture model with control-based pattern imputation) do not confirm this result: According to these three sensitivity analyses, there are significant effects for SCM in both severity groups. However, effect sizes for SCM are higher for mildly to moderately depressed patients compared to severely depressed patients. Given these slightly divergent results, a relevant proportion of the differential effect of SCM for different severity groups in the LOCF analysis might be due to the high rate of selective dropouts in the group of severe depression patients, i.e. especially those treated in the SCM. A closer look at the dropouts in severely depressed patients reveals that most of them left the study immediately after study inclusion and did not contribute any other data except baseline assessment - neither regarding the patient questionnaires nor the documentation data of their GPs. Replacing missing values by LOCF, i.e. by the baseline score, for a substantial percentage (46%) within the severely depressed patients in SCM might have led to an underestimation of effectiveness for this subgroup. Therefore, defining LOCF as primary strategy of replacement of missing values when designing the study turns out to be unfavorable in the course of the trial revealing the (unexpected) selective drop out between severity groups. Accordingly, when changing the replacement strategy and choosing MI replacement or pattern mixture model, SCM is also effective for severe depression. The differential effect sizes of stepped and collaborative care models with larger effects for mild to moderate patients are in line with those few outcome studies taking into account symptom severity of depression (Katon et al., 2002; Walker et al., 2000). Interestingly, this differential effect points in the reverse direction compared to results of meta analyses on placebo-

controlled antidepressant trials suggesting an effect of AD only with increasing severity of depression symptoms (Fournier et al., 2010; Khan et al., 2002; Rabinowitz et al., 2016). However, this is not contradictory to the results of our study as we have not investigated a single treatment options such as antidepressant medication but a whole care model aiming at tailoring treatments to patients – and relying the treatment selection on guideline recommendations which are exactly based on the evidence on differential effects of antidepressant medication (among others). This has led to the algorithm within the SCM that in mild to moderate depression the first line treatment was (low intensity) psychological treatment - and not antidepressant medication.

What might have caused the selective dropout in the severely depressed group in our study? We do not have any information about the reasons for this. The severity of these patients' depression and the associated symptom burden may have impeded their participation in data collection and staying in continuous contact with the responsible care providers, as SCM recommends. Franx et al. report similar difficulties in adherence for patients with severe depression participating in stepped care (Franx et al., 2009). When severely depressed patients joined the SCM and were treated according to its concept, they benefitted significantly more from treatment in SCM than patients in TAU, as shown in the completer analysis.

However, even when taking into account the methodical uncertainty caused by the selective dropout, we did find - at least slightly - lower effect sizes for severely depressed patients in both SCM and TAU implicating that this group profits less from treatment than mildly to moderately depressed patients. This could be confirmed by all analyses (again with variation across primary analysis on the one hand and sensitivity analyses on the other hand) and is in line with findings of other studies that report better outcomes for non-severely depressed patients than for severely depressed patients (Franx et al., 2009; Katon et al., 2002; Walker et al., 2000).

### 4.2. Differential treatment utilization

The analysis of treatments received by patients during 12-month study participation provides important information for understanding the results of the differential outcomes and allows an insight into which treatments and interventions were actually implemented in SCM and routine care in the different subgroups. Overall, the results of the treatment utilization analysis are consistent with those of the effectiveness analysis: they help explain the higher benefit of the SCM for mildly to moderately depressed patients in terms of adequate treatment allocation. The hypothesis that patients in SCM more often receive depression-specific treatment and less often GP consultation only was confirmed. Additionally, a higher difference in these treatment utilization patterns and therefore a higher impact of the SCM on utilization was observed for mildly to moderately depressed patients in comparison to severely depressed patients. This finding can partly be explained by the successful implementation of low intensity approaches as stand-alone treatment for mildly to moderately depressed patients. These treatments were additional intervention options GPs in SCM could use. However, this stand-alone application of low intensity treatments is adherent to the SCM concept only for mildly to moderately depressed patients, but not for severely depressed patients. However, the latter were also provided with only this treatment in 16% of the cases. Thus, these severely depressed patients were not treated in line with the SCM rational and with guidelines, and it can be assumed that they were undersupplied: for this group, the low intensity treatment did not facilitate the access to more intense treatments by introducing them into the health care system and motivating them for further treatment (vs. approx. 14% severely depressed patients who received an additional specific treatment, i.e. for whom the low intensity treatment succeeded in serving as “door opener”). This may explain the lower effect size of the effectiveness analysis in the SCM for the subgroup of severely depressed patients, at least to a certain degree. The hypothesis of reduced

AD use in SCM for mildly to moderately depressed patients in general could not be confirmed. The reason for this might be that the group of mild to moderate depression does not only consist of mildly but also of moderately depressed patients, for whom it would be adequate to apply AD treatment as alternative treatment option to PT. However, there were less mildly to moderately depressed patients in SCM who received nothing but AD treatment, i.e. these patients received additional psychological support or used a self-help approach. The hypothesis of a reduced proportion of inpatient treatments for mildly to moderately depressed patients in SCM was confirmed, as admission rates in SCM were less than half of those in TAU (9% vs. approx. 22%). This shows that the SCM offers the potential to avoid this intensive and also cost-intensive care form for patients with non-severe depression, while at the same time improving the outcome of this group, as effectiveness analysis show.

The utilization data suggests that the focus of the GP in TAU lay on severely depressed patients while mildly to moderately depressed patients were more likely overlooked. This was different in SCM and implicates that SCM holds potential to detect and improve the under-supply of mildly to moderately depressed patients.

Again, as we refer to the same assessment in the analysis of utilization as in the outcome analyses (assessment at T3), the data base for utilization is broader for the mildly to moderately depressed group than for the severely depressed group, given the larger dropout rate of the latter. Therefore, comparisons within the severe depression group are less reliable due to the relatively small sample size and the associated larger confidence intervals. However, referring to the patients who participated the whole study period of 12 months (completers) we were able to robustly report patterns of utilization.

The major limitation of these outcome and utilization analyses is the aforementioned high proportion of missing values in the subgroup of severely depressed patients. Therefore, our analyses are more robust for the mild to moderate than for the severely depressed group. In order to respond to this limitation and to take into account this circumstance we conducted extensive sensitivity analyses. A limitation of the analysis of utilization is that due to the kind of data assessment (i.e. retrospectively assessed utilization data reported by patients) it is not possible to deduce statements about the exact temporal sequence of treatments, stepping-up pattern and – especially important – the quality of the treatments patients received, e.g. the quality of type, dose and frequency of medication in pharmacotherapy.

#### 4.3. General discussion

As both the differential outcome analyses with lower effect sizes for severely depressed patients in SCM and the treatment utilization analysis show, the particular challenge is to improve the care of severely depressed patients and to ensure more guideline-based care. Cases of severe depression are more complex and need more effort to implement guideline-adherent treatment. The results of our study suggest that certain interventions of the SCM especially for severe depression (e.g. combination of PT and AD) have not yet been implemented sufficiently and that there is need to improve the implementation of the SCM in line with its concept. A prior study analyzing the SCM patients of the same trial regarding treatment decisions and initial treatments reported consistent results: guideline-adherent treatment initiation was highest for mildly depressed patients and lowest for severely depressed patients, and the latter more often did not receive the treatment decided upon with their GP (Heddaeus et al., 2018).

The higher barriers in care delivery for severely depressed patients might be due to their higher symptom burden, which may affect treatment implementation. For example, the challenge to call a psychotherapist for an appointment may be higher for a severely depressed patient than for a mildly depressed patient who suffers from less symptoms of social withdrawal and hopelessness. Patients in severe crises might also be more ambivalent towards treatments and decide

against a selected treatment even before beginning it, due to doubts and negative expectations and emotions. One implication of this finding for the improvement of depression care could be the comprehensive implementation of closer systematic monitoring by the main care provider to check whether the patient receives the agreed-upon treatment and whether this leads to relevant symptom reduction or must be adapted. Another option would be the introduction of an even more systematic case management, which tracks and accompanies the patient throughout his or her treatment pathway. The conception of stepped and collaborative care imply this kind of support – however, implementing this properly within the complex intervention remains a crucial task.

## 5. Conclusions

In conclusion, access to treatment, triage and the coordination of pathways remains an area with challenges for which stepped care promises to offer a means of improvement for different severity levels of depression. An adequate implementation of the approach demands much effort by providers, patients and stakeholders (the latter for creating the adequate conditions and incentives within the health care system) and appears to be crucial for ensuring processes and – by this – improved outcome for patients.

## 6. Contributors

BW, DH and MH conceptualised and designed the analyses and were responsible for its conduct. BW and MH were responsible for the overall supervision. AD and KW contributed to specific methodical issues. DH, BW, AD, MS and AD were actively involved in the analysis and interpretation of data. All authors contributed, read and approved the final manuscript.

## Data availability statement

The datasets generated and analyzed during the current study are available from the study center on reasonable request.

## Declaration of Competing Interest

None.

## Acknowledgements

The study was funded within the larger project psychenet – The Hamburg Network for Mental Health. psychenet was a project network funded by the German Federal Ministry of Education and Research (funding code 01KQ1002B) in the region of Hamburg which consists of more than 80 scientific and medical institutions, counseling centers, the Senate and the Chamber of Commerce of the Free and Hanseatic City of Hamburg, companies, as well as patients' and relatives' associations (2011 – 2015; [www.psychenet.de](http://www.psychenet.de)). We would like to thank all care providers and patients who participated in this study.

Funding: This work was supported by the German Federal Ministry of Education and Research (grant number 01KQ1002B).

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.jad.2020.07.079](https://doi.org/10.1016/j.jad.2020.07.079).

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