Matching depression management to severity prognosis in primary care: Results of the Target-D randomised controlled trial

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Abstract

Background: Mental health treatment rates are increasing but the burden of disease has not reduced. Tools to support efficient resource distribution are required.

Aim: To investigate whether a person-centred e-health platform matching depression care to symptom severity prognosis can improve depressive symptoms relative to usual care.

Design and setting: Stratified individually randomised controlled trial in 14 general practices in Melbourne, Australia (April 2016 to February 2019). 1868 participants (aged 18 – 65; current depressive symptoms; Internet access; no recent change to antidepressant; no current antipsychotic medication; no current psychological therapy) were randomised (1:1) via computer-generated allocation to intervention or usual care.

Methods: The intervention was an e-health platform accessed in the GP waiting room, comprising symptom feedback, priority-setting, and prognosis-matched management options (online self-help, online guided psychological therapy, or nurse-led collaborative care). Management options were flexible, neither participants nor staff were blinded, there were no substantive protocol deviations. Primary outcome: Depressive symptom severity (PHQ-9) at 3 months.

Results: In ITT analysis, the estimated between-arm difference in mean PHQ-9 scores at 3 months was -0.88 (95% CI: -1.45 to -0.31), favouring the intervention, and -0.59 at 12 months (95% CI: -1.18 to 0.01); standardised effect sizes of -0.16 (95% CI: -0.26 to -0.05) and -0.1 (-0.21 to 0.0002), respectively. No serious adverse events were reported.

Conclusions: Matching management to prognosis using a person-centred e-health platform improves depressive symptoms at 3 months compared to usual care and could feasibly be implemented at scale. Scope exists to enhance the uptake of management options.

Keywords: Mental health; primary health care; general practice; randomized controlled trial; clinical prediction rule

How this fits in

Depression is a leading contributor to the global burden of disease and a significant problem in primary care where it is typically identified and managed. Stepped care approaches are recommended but difficult to implement in routine care, due in part to a lack of effective tools to guide GPs in matching intervention intensity to patient need. This RCT showed that a person-centred clinical prediction tool and e-health platform matching management options to prognosis results in improvement in depressive symptoms at 3 months in depressive symptoms relative to usual care. This approach could be implemented in routine care to support more efficient and effective depression care without adding to GPs' workload.

Introduction

Despite significant investment in improving access to care,[1] depression remains a leading contributor to the burden of disease and constitutes a significant public health issue.[2] This in part reflects suboptimal targeting of care, with both over- and under-treatment occurring.[1 3] Treatment guidelines and policy initiatives have aimed to address this mismatch by encouraging provision of the least intensive intervention that is likely to be effective for an individual (an approach known as stepped care).[4 5] However, there is currently no consensus as to how the appropriate level of intervention intensity is identified. Therefore, building the evidence base to support the implementation of stepped care is key to reducing the time and resources currently required to identify an individual's mental needs and match them to care accordingly.[6-8]

Such evidence is particularly important for primary care, where the majority of depression care is delivered.[9 10] Currently, general practitioners (GPs) rely mostly on clinical judgement when allocating depression care, which can be a time-consuming and inconsistent process.[8] This is in contrast to other areas of medicine where a range of clinical prediction tools (CPTs) are available to streamline systematic decision making,[11-15] although there is increasing recognition that such tools must be user-friendly and action-oriented in order to be successfully translated in routine practice.[16] To address this gap we developed a CPT that uses self-reported biopsychosocial data to classify individuals into one of three prognostic groups based on the predicted severity of their depressive symptoms in three months' time (minimal/mild, moderate, or severe).[17] We then embedded this CPT into an e-health platform[18] (henceforth referred to as the Target-D platform) which was designed using the principles of motivational interviewing[19] and psychologically-driven goal modelling[20] to deliver a person-centred approach to depression care.[18] The Target-D platform provides patients with feedback on their responses, an opportunity to reflect on their mental health

priorities and motivation to change, and a management option matched to their severity prognosis.

In the Target-D randomised controlled trial (RCT), the primary aim was to investigate whether a complex intervention comprising the Target-D platform and matched management options for primary care patients with depressive symptoms improved depressive symptoms at 3-month follow-up, relative to usual care plus attention control. Secondary aims were to test for an intervention effect at 12 months overall, and within prognostic groups at both three and 12 months.

Method

Study design

A stratified individual RCT, enrolling primary care patients who screened positive for depressive symptoms (see protocol for details[21]). The intervention period lasted three months. No substantive changes to the published protocol were made.

Participants

Research assistants (RAs) recruited participants from the waiting rooms of 14 general practices in metropolitan Melbourne, Australia (Supplement 1 describes practice characteristics). Adults aged 18-65 were invited to complete an eligibility survey on an iPad, and were eligible if they reported: current depressive symptoms (≥2 on the 2-item version of the Patient Health Questionnaire [PHQ-2][22]); no self-reported change to antidepressant medication in the past month; access to the Internet; and sufficient written English to follow an Internet-based cognitive behavioural therapy (iCBT) program. Patients reporting current use of antipsychotic medication or receipt of psychological therapy (online or face-to-face) were ineligible.

Randomisation occurred after participants provided informed consent and completed baseline measures (including items required for the CPT), all integrated with the Target-D platform on a purpose-built website accessible on any internet-enabled device.

Interventions

All participants received an automated email encouraging them to speak with their GP if they had concerns about their mental health and providing contact details for community-based services (e.g., crisis support lines).

Intervention arm

Individuals received CPT feedback, set priorities, and received a management option matched to the prognostic group (Supplement 2). Briefly:

- Minimal/mild: myCompass online program,[23] a CBT-based self-help resource where participants could choose from 15 modules (e.g., Tackling Unhelpful Thinking, Communicating Clearly).
- Moderate: Worry and Sadness course of the This Way Up iCBT program[24] which required participants to work through 6 lessons in sequence.
- Severe: nurse-led collaborative care including up to eight contacts (over telephone or in person) with a trained research nurse to develop and implement a tailored depression management plan in conjunction with their GP.[25-29]

Control arm

Individuals received usual care plus attention control (UC+; telephone call from an RA about trial involvement and to seek views about research participation).

Randomisation and blinding

Participants were randomly assigned to trial arm (1:1, stratified by practice and prognostic group) using a computer-generated biased-coin algorithm with an imbalance intolerance of three embedded in the purpose-built website (See Supplement 3).

Due to the nature of the intervention, participants could not be blinded to their allocated management option. Staff involved in intervention delivery (RAs discussing management options, nurses delivering collaborative care) were also unblinded. GPs were notified only of participants allocated to collaborative care, with no emergency unblinding required. RAs responsible for contacting participants at follow-up were blinded to trial arm and prognostic group. All analyses were conducted and discussed while statisticians and study investigators remained blind to trial arm allocation.

Outcomes

Data were collected primarily via online survey at baseline and at three- and 12-months post-randomisation. At each time-point, non-responders received phone, text, and/or email reminders and were offered alternative options for completion (e.g., hard copy, phone). At trial enrolment, participants provided information on demographic (age, gender, education, and employment) and clinical characteristics relevant to trial exclusion criteria.

The primary outcome was depressive symptom scores at three months, assessed using the 9-item Patient Health Questionnaire (PHQ-9).[30]

Secondary outcomes included: depressive symptom severity at 12 months; and anxiety symptom severity (GAD-7),[31] mental health self-efficacy (MHSES),[32] and quality of life (AQoL-8D)[33] at three and 12 months.

Sample size

For the primary hypothesis, 1320 participants (660 per arm) provided 90% power at 5% significance two-tailed alpha) to detect a standardised mean difference (SMD) of 0.2 in depressive symptoms at three months, assuming 20% attrition over 12 months of the follow-up period. For secondary hypotheses, we had 80% power to detect a between-arm SMD of 0.2 in depressive symptoms in the minimal/mild group and 0.5 within the moderate and severe groups, respectively. Calculations assumed 70% (924) of participants would be in the minimal\mild group and 15% (198) in each of the moderate and severe groups.

Statistical methods

All analyses were pre-defined in the statistical analysis plan[34] and conducted using Stata (version 15). Main analyses employed an intention to treat (ITT) approach, where all participants were analysed in the trial arm to which they were allocated. Differences in mean outcomes between trial arms (intervention effect) were estimated with linear mixed-effects models, using restricted maximum likelihood with random intercepts for individuals. Stratification factors (practice, prognostic group) and time (baseline, three and 12 months) were included as fixed effects, with a two-way interaction between arm and time, except at baseline where trial-arm means were constrained to be equal. Similar mixed effects analysis was conducted for each prognostic group. Sensitivity analyses included random-effects for nurse in the severe group and assessed the robustness of the missing data assumption (Supplement 4). Complier average causal effect (CACE) analysis[35] used a two stage-least squares instrumental regression with trial arm used as the instrumental variable for adherence to treatment.[34]

Results

Figure 1 shows the trial profile. 1868 participants (1270 women and 598 men; mean [SD] age 35.5 [12.1] years). The CPT classified 1357 (72.6%) participants to the minimal/mild group, 288 (15.4%) to the moderate group and 223 (11.9%) to the severe group. Some differential attrition was evident, with retention higher in the control arm overall (and within the minimal/mild and moderate prognostic groups. In the severe group, retention was higher in the intervention arm. Participants in the two trial arms were similar, overall and within prognostic groups (Table 1, Supplementary Table 3).

Primary outcome

The estimated difference in mean depressive scores at three months was 0.88, favouring the intervention arm (95% CI: -1.45 to -0.31) (Table 2), equivalent to a SMD of -0.16 (95% CI: -0.26 to -0.05). Findings were robust to different missing data assumptions (Supplementary Figure 2).

Secondary outcomes

At 12 months, weak evidence supported a smaller intervention effect on depressive symptoms at 12 months overall (Figure 2, Table 2), but no evidence for a difference in mean anxiety symptom severity between trial arms (Table 3, Supplementary Table 4). Mean mental health self-efficacy was 1.39 points higher in the intervention arm compared to the control arm (95% CI: 0.31 to 2.50). There was no evidence of an overall difference in mean quality of life between trial arms, although within the moderate group, mean scores were 0.05 points higher in the intervention arm (95% CI: 0.01 to 0.09) compared to control arm.

Adherence-adjusted analyses

Five (<1%) of 679 intervention participants in the minimal/mild group completed at least one myCompass module, and eight (6%) of 143 participants in the moderate group completed the

Worry and Sadness course in full (Supplementary Table 5, Supplementary Figure 3). Given the few completers in these groups, no further planned analyses were conducted.

In the severe group, 64 participants (58%) attended at least one collaborative care appointment and 30 (27%) of 111 participants attended eight (Supplementary Figure 3). Participants who completed all eight collaborative care appointments had a 5.2-point greater reduction in mean PHQ-9 at three months (95% CI: -10.9 to 0.44) compared to their control arm counterparts, equivalent to a SMD of -1.4 (95% CI: -3.0 to 0.12).

Discussion

Summary

Development of revolutionary new treatments for depression is considered unlikely.[36] Instead, efforts to reduce the burden of disease have focused on better tailoring of existing interventions, leading to the development and testing of a range of stepped care approaches. This is the first RCT of a person-centred e-health platform supporting prognosis-based allocation of depression management in primary care. For our primary outcome, results favoured the intervention overall, although the effect size was small. Pre-specified adherence-adjusted analysis identified greater improvements associated with completion of collaborative care in the severe group. The intervention effect on depressive symptoms had diminished by 12 months, and few differences were observed on secondary outcomes.

Strengths and limitations

Strengths include: individual randomisation and a primary outcome measure that allows comparison with international studies; successful recruitment to target with a balance of baseline characteristics between trial arms; primary outcome completion rates comparable to previous stepped depression care trials in primary care;[37-42] and a pragmatic design that tested a model of care designed for scalability. However, low uptake of online management options

limited our ability to complete planned analyses, and the wide availability of depression care in Australian primary care[43] (see Supplement 5) may have reduced the potential for our intervention to improve upon usual care. Our focus on depression may reduce generalisability to other mental health conditions and we did not assess symptom duration at enrolment, although we set a low threshold for eligibility and interventions were not disorder specific. We observed greater attrition than anticipated and finally, our approach was limited to initial allocation only and intervention intensity was not adjusted according to participant response.

Comparison with existing literature

While overall effect size at three months (-0.16) was lower than that reported in a stepped care meta-analysis (-0.34),[44] our confidence intervals included the clinically relevant value of -0.24 proposed by Cuijpers and colleagues.[45] Importantly, our effect was achieved through delivery of a minimally time- and resource-intensive intervention in a routine setting across a large number of practices. Further, the meta-analysis by Cuijpers and colleagues[45] assessed the effectiveness of stepped care in people meeting diagnostic criteria for depression whereas our effect was observed in a heterogenous sample reflecting real-life primary care.[46]

Within prognostic groups, our observed effect was smaller than that reported in previous RCTs of myCompass[32] and This Way Up[47 48] but similar to iCBT effect sizes in primary care settings.[49 50] This is further compounded by the low rates of program completion, although even if all participants completed their recommended program, they had limited room for symptom improvement. Within the severe group, our estimated effect size was consistent with previous trials of collaborative care,[25 51-54] contributing to the growing literature showing that nurse-delivered collaborative care is both effective and acceptable in the management of depression.[55] Participants who completed the full course of collaborative care reported substantial improvements, the effect size comparing favourably to that associated with antidepressants.[56] Analysis of the characteristics of completers and their tailored management

plans is underway to refine the intervention to enhance uptake and completion (publication forthcoming).

Our novel, theory-driven approach provides not only assessment but a prompt to reflect on priorities and motivation, aiming to empower patients to take ownership of their mental healthcare. Patients are triaged to care according to their predicted severity of depressive symptoms in three months' time, rather than severity when first assessed. This approach incorporates broader determinants of poor mental health (e.g., financial and physical health difficulties), which are critical to delivering comprehensive primary care, and recognises that mild and transitory depressive symptoms are prevalent and will often resolve without formal intervention. Current policy aims to redirect the minimal/mild group away from face-to-face services and towards lower intensity (including online) interventions, in line with clinical guidelines.[4 5] However, our findings suggest simply recommending these interventions, even when designed to activate patients towards uptake,[18] was insufficient to encourage their use. Our experience is not unique; research and policy interest in online interventions has not yet translated into their widespread use (and the multifaceted reasons for this are discussed elsewhere).[57-61] This is a rapidly evolving field and emerging health, social, and economic levers may improve acceptability of online interventions, and thus the potential for an approach like Target-D to serve as an effective conduit. For instance, public health crises such as the COVID-19 pandemic may necessitate greater engagement with online programs[62] due to overburdened health systems and a pressing need to efficiently triage people to mental health care without lengthy consultation in general practice.

Implications for research and practice

Mental health remains the predominant issue managed in primary care,[63] despite substantial and sustained investment. Worldwide, health systems face the challenge of ensuring that investments are well targeted to optimise patient outcomes and experiences of care. It is

likely that improvements in mental health care will be incremental and gained by ongoing optimisation of promising approaches. Our person-centred, e-health platform which can quickly and easily triage and tailor depression care to severity prognosis is a promising component of stepped mental health care. We present the cost-effectiveness of this approach in a separate paper.[64] While the trial was not set up to test the effectiveness of the Target-D platform and matched management options in preventing disorder onset, this may be an avenue for future research. Alternatively, an option for implementation may be to offer the Target-D platform to all patients but provide matched management options only to the moderate and severe groups where the potential for improvement is greater. Findings also support further research into how to optimise uptake, particularly of low intensity services.

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Ethical approval

Approval was provided by the Human Research Ethics Committee at the University of Melbourne (ID: 1543648)

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Competing interests

None to declare.

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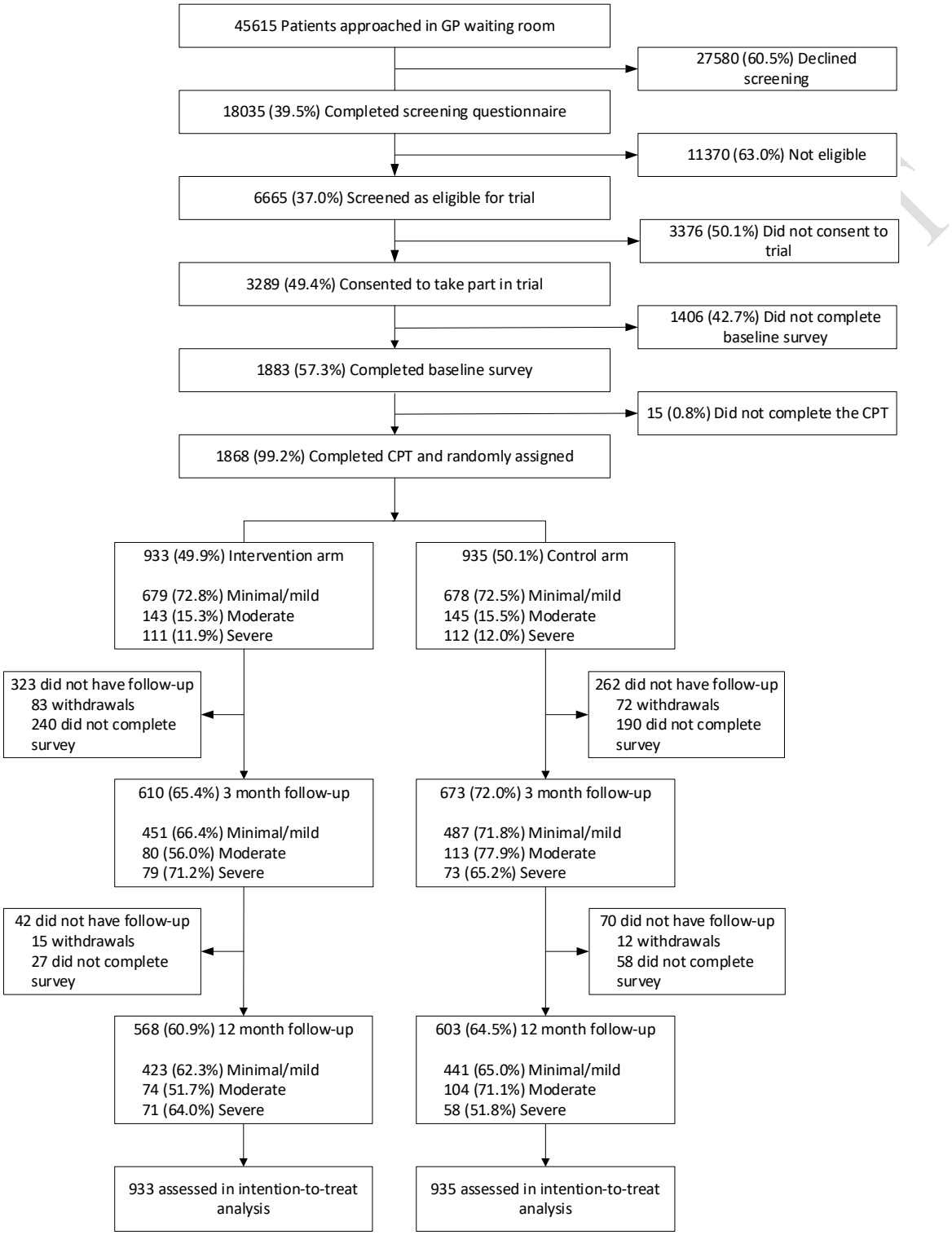
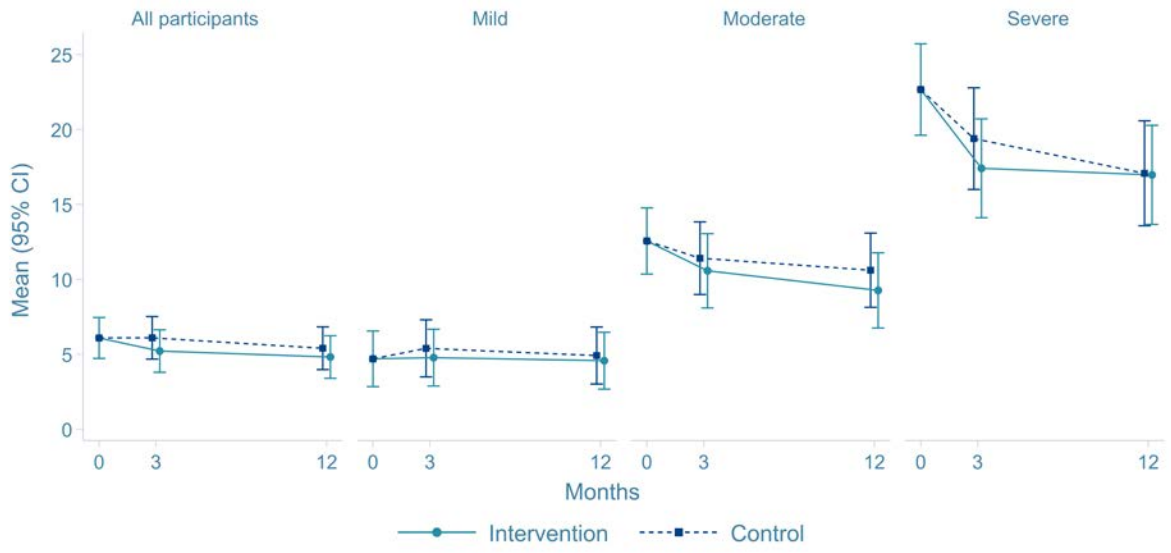
Figures and tables

Figure 1. Participant flow through the trial



Note: Denominators used to calculate retention at 3- and 12-month follow-up are the total number of participants randomised overall and within each prognostic group; All participants randomised (933 in intervention arm and 935 in the control arm) were included on the intention-to-treat analysis for the primary outcome; none of the withdrawals requested that their data be withdrawn prior to the statistical analysis.

Figure 2. Estimated mean depressive symptom severity (PHQ-9) with 95% confidence intervals for each trial arm, in total and by prognostic group and time-point



Note: Means and confidence intervals estimated using linear mixed-effects regression with random intercepts for individuals and adjusted for baseline outcome measure, general practice, time and prognostic group (for all participants only). Mean outcome at baseline was constrained to be equal.

Table 1. Baseline characteristics of participant according to study arm, in total and stratified by prognostic group (N=1868) [1]

	All participants (n=1868)		Prognostic group					
			Minimal / mild (n=1357)		Moderate (n=288)		Severe (n=223)	
	Intervention (n=933)	Control (n=935)	Intervention (n=679)	Control (n=678)	Intervention (n=143)	Control (n=145)	Intervention (n=111)	Control (n=112)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Age (years)	35.5 (12.1)	35.6 (12.1)	35.2 (11.7)	35.5 (11.8)	36.0 (13.1)	35.5 (12.5)	36.3 (13.4)	36.5 (13.1)
Depressive symptom severity (PHQ-9)	9.2 (5.8)	9.3 (5.7)	6.4 (3.4)	6.6 (3.4)	14.2 (2.3)	13.9 (2.4)	19.7 (3.5)	19.6 (3.6)
Anxiety symptom severity (GAD-7)	8.6 (5.3)	8.7 (5.1)	6.7 (4.2)	7.0 (4.2)	11.6 (4.1)	11.4 (4.5)	15.9 (3.7)	14.8 (4.7)
Mental health self-efficacy (MHSES)	38.1 (12.2)	37.4 (12.1)	42.2 (10.5)	41.4 (10.5)	30.2 (9.3)	30.5 (9.0)	24.4 (9.8)	23.1 (8.8)
Quality of life (AQoL-8D)	0.6 (0.2)	0.6 (0.2)	0.6 (0.2)	0.6 (0.2)	0.4 (0.1)	0.4 (0.1)	0.3 (0.1)	0.3 (0.1)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Gender								
Male	313 (33.5)	277 (29.6)	225 (33.1)	191 (28.2)	52 (36.4)	45 (31.0)	36 (32.4)	41 (36.6)
Female	617 (66.1)	653 (69.8)	453 (66.7)	485 (71.5)	90 (62.9)	98 (67.6)	74 (66.7)	70 (62.5)
Other	3 (0.3)	5 (0.5)	1 (0.1)	2 (0.3)	1 (0.7)	2 (1.4)	1 (0.9)	1 (0.9)
Highest level of education completed								
Year 11 or less	109 (11.7)	112 (12.0)	65 (9.6)	68 (10.0)	21 (14.7)	20 (13.8)	23 (20.7)	24 (21.4)
Year 12 or equivalent	136 (14.6)	146 (15.6)	93 (13.7)	94 (13.9)	22 (15.4)	31 (21.4)	21 (18.9)	21 (18.8)
Certificate/Diploma	211 (22.6)	230 (24.6)	140 (20.6)	169 (24.9)	35 (24.5)	30 (20.7)	36 (32.4)	31 (27.7)
Bachelor's degree or higher	477 (51.1)	447 (47.8)	381 (56.1)	347 (51.2)	65 (45.5)	64 (44.1)	31 (27.9)	36 (32.1)
Employment status								
Employed/working for profit or pay	686 (73.5)	667 (71.3)	513 (75.6)	509 (75.1)	99 (69.2)	89 (61.4)	74 (66.7)	69 (61.6)
Unemployed	92 (9.9)	119 (12.7)	64 (9.4)	66 (9.7)	17 (11.9)	30 (20.7)	11 (9.9)	23 (20.5)

Neither working nor looking for work	155 (16.6)	149 (15.9)	102 (15.0)	103 (15.2)	27 (18.9)	26 (17.9)	26 (23.4)	20 (17.9)
Receiving benefit or disability support	100 (11.6)	133 (15.4)	49 (7.9)	79 (12.7)	24 (17.1)	30 (21.9)	27 (26.2)	24 (22.6)
History of depression	582 (62.4)	593 (63.4)	341 (50.2)	348 (51.3)	130 (90.9)	137 (94.5)	111 (100.0)	108 (96.4)
Long term illness	245 (26.3)	270 (28.9)	124 (18.3)	129 (19.0)	56 (39.2)	70 (48.3)	65 (58.6)	71 (63.4)
Self-rated health								
Excellent/Very good/Good	732 (78.5)	729 (78.0)	596 (87.8)	589 (86.9)	94 (65.7)	94 (64.8)	42 (37.8)	46 (41.1)
Fair/Poor	201 (21.5)	206 (22.0)	83 (12.2)	89 (13.1)	49 (34.3)	51 (35.2)	69 (62.2)	66 (58.9)
Live alone	130 (13.9)	109 (11.7)	80 (11.8)	62 (9.1)	30 (21.0)	26 (17.9)	20 (18.0)	21 (18.8)
Manage on available income								
Easily / Not too bad / Difficult some of the time	832 (89.2)	817 (87.4)	643 (94.7)	640 (94.4)	121 (84.6)	111 (76.6)	68 (61.3)	66 (58.9)
Difficult all the time / Impossible	101 (10.8)	118 (12.6)	36 (5.3)	38 (5.6)	22 (15.4)	34 (23.4)	43 (38.7)	46 (41.1)
Number of times visited a psychologist/counsellor (past 12 months)								
0 times	549 (58.8)	529 (56.6)	436 (64.2)	428 (63.1)	64 (44.8)	55 (37.9)	49 (44.1)	46 (41.1)
1-6 times	292 (31.3)	312 (33.4)	187 (27.5)	198 (29.2)	57 (39.9)	65 (44.8)	48 (43.2)	49 (43.8)
7 times or more	92 (9.9)	94 (10.1)	56 (8.2)	52 (7.7)	22 (15.4)	25 (17.2)	14 (12.6)	17 (15.2)
Current use of antidepressants	190 (20.4)	226 (24.2)	92 (13.5)	120 (17.7)	54 (37.8)	58 (40.0)	44 (39.6)	48 (42.9)
Frequency of internet use								
Daily	904 (96.9)	910 (97.3)	662 (97.5)	661 (97.5)	139 (97.2)	142 (97.9)	103 (92.8)	107 (95.5)
Less than daily	29 (3.1)	25 (2.7)	17 (2.5)	17 (2.5)	4 (2.8)	3 (2.1)	8 (7.2)	5 (4.5)

n = Count; Mean= Sample mean; SD = Standard deviation

[1] Denominators may vary due to missing data

Table 2. Depressive symptom severity (PHQ-9) score according to trial arm, in total and stratified by prognostic group

	All participants		Prognostic group					
			Minimal / mild		Moderate		Severe	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
3 months								
Intervention	594	8.26 (6.02)	439	6.59 (5.04)	80	11.64 (5.51)	75	14.40 (6.39)
Control	668	9.16 (6.51)	483	7.29 (5.60)	112	12.69 (5.62)	73	16.10 (6.49)
12 months								
Intervention	563	7.77 (5.85)	421	6.33 (5.01)	74	10.53 (5.68)	68	13.69 (6.11)
Control	602	8.44 (6.19)	441	6.82 (5.26)	103	12.10 (6.14)	58	14.28 (6.64)
Total analysed	*1,868*		*1,357*		*288*		*223*	
		p-value		**p-value**		**p-value**		**p-value**
3 months								
Difference in mean outcome between arms(95% CI)[1]	-0.88 (-1.45 to -0.31)	0.003	-0.62 (-1.21 to -0.03)	0.04	-0.84 (-2.40 to 0.72)	0.29	-1.98 (-4.00 to 0.04)	0.06
Sensitivity analysis[2]	-0.87 (-1.43 to -0.30)	0.003	-0.62 (-1.21 to -0.04)	0.04	-1.08 (-2.66 to 0.49)	0.18	-2.16 (-4.20 to -0.12)	0.04
Sensitivity analysis[3]	n/a		n/a		n/a		-1.98 (-4.00 to 0.04)	0.06
CACE analysis[4]	n/a		n/a		n/a		-5.23 (-10.9 to 0.44)	0.07
SMD[1,5]	-0.16 (-0.26 to -0.05)		-0.18 (-0.36 to -0.01)		-0.36 (-1.02 to 0.31)		-0.56 (-1.12 to 0.01)	
12 months								
Difference in mean	-0.59 (-1.18 to 0.01)	0.05	-0.35 (-0.94 to 0.25)	0.26	-1.35 (-3.02 to 0.32)	0.11	-0.10 (-2.29 to 2.08)	0.93

outcome between arms (95% CI)[1]								
Sensitivity analysis[2]	-0.57 (-1.16 to 0.02)	0.06	-0.34 (-0.93 to 0.25)	0.26	-1.47 (-3.14 to 0.21)	0.09	-0.19 (-2.43 to 2.04)	0.87
Sensitivity analysis[3]	n/a		n/a		n/a		-0.10 (-2.29 to 2.08)	0.93
CACE analysis[4]	n/a		n/a		n/a		-1.65 (-7.61 to 4.31)	0.59
SMD[1,5]	-0.10 (-0.21 to 0.002)				-0.58 (-1.29 to 1.14)		-0.03 (-0.64 to 0.58)	

n = Count; Mean= Sample mean; SD = Standard deviation; CI = Confidence interval; SMD = Standardised mean difference

[1] Estimated difference in mean outcome between intervention and control arms using linear mixed-effects regression with random intercepts for individuals and adjusted for baseline outcome measure, general practice, time and prognostic group (for all partcipants only); Mean outcome was constrained to be equal at baseline.

[2] Same as 1, adjusted for factors associated with non-response at 3 and 12 months (age, gender, highest level of education, current employment status, hold a health care care, long term illness, live alone, number of times visited a psychiatrist or counsellor in past 12 months and current use of antidepressants)

[3] Same as 1, adjust for imposed clustering by nurse in the intervention arm in the severe prognostic group only; 6 nurses (Cluster size (range) 1 to 31, median = 14 patients): Estimated intra-cluster correlation for imposed clustering was zero.

[4] Adherence-adjusted analysis for severe group only (adherence=completed all 8 sessions)

[5] SMD was calculated as the difference in means between arms and divided by the pooled standard deviation at baseline for all participants (SD=5.71); minimal/mild (SD=3.39); moderate (SD=2.34) and severe (SD=3.56) group.

Table 3. Estimated difference in mean between study arms (95% CI)[1] for secondary outcomes, in total and stratified by prognostic group

	All participants		Prognostic group					
			Minimal/mild		Moderate		Severe	
		p-value		p-value		p-value		p-value
Anxiety symptom severity (GAD-7)								
Total analysed	*1,780*		*1,285*		*278*		*217*	
3 months	-0.43 (-0.99 to 0.12)	0.13	0.10 (-0.50 to 0.70)	0.74	-1.17 (-2.63 to 0.28)	0.11	-1.18 (-2.99 to 0.63)	0.20
12 months	-0.17 (-0.78 to 0.45)	0.59	0.0005 (-0.66 to 0.66)	0.99	0.13 (-1.55 to 1.80)	0.88	-0.13 (-2.19 to 1.94)	0.91
Mental health self-efficiency (MHSES)								
Total analysed	*1,779*		*1,284*		*278*		*217*	
3 months	1.39 (0.31 to 2.46)	0.01	1.06 (-0.15 to 2.27)	0.09	2.35 (-0.22 to 4.91)	0.07	1.55 (-2.10 to 5.20)	0.41
12 months	0.87 (-0.43 to 2.17)	0.19	0.49 (-0.88 to 1.86)	0.48	1.10 (-2.53 to 4.73)	0.55	1.20 (-3.62 to 6.02)	0.63
Quality of life (AQoL-8D)								
Total analysed	*1,761*		*1,270*		*277*		*214*	
3 months	0.011 (-0.005 to 0.027)	0.16	0.0005 (-0.017 to 0.019)	0.96	0.047 (0.007 to 0.088)	0.02	0.033 (-0.010 to 0.075)	0.13
12 months	0.013 (-0.007 to 0.033)	0.19	0.010 (-0.013 to 0.033)	0.39	0.014 (-0.039 to 0.067)	0.60	0.028 (-0.037 to 0.093)	0.40

CI = Confidence interval

[1] Estimated using linear mixed-effects regression with random intercepts for individuals and adjusted for baseline outcome measure, general practice, time and prognostic group (for all partcipants only); Mean outcome is constrained to be equal at baseline.