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Efficacy of an Internet- and Mobile-Based Intervention for Subclinical Anxiety and Depression (ICare Prevent) with Two Guidance Formats: Results from a Three-Armed Randomized Controlled Trial

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Keywords
Internet intervention · Transdiagnostic prevention · Subthreshold disorders · Subclinical anxiety · Subclinical depression

Abstract

Introduction: Limited research exists on intervention efficacy for comorbid subclinical anxiety and depressive disorders, despite their common co-occurrence. Internet- and mobile-based interventions (IMIs) are promising to reach individuals facing subclinical symptoms. ***Objective:*** This study aimed to evaluate the efficacy of a transdiagnostic and self-tailored IMI in reducing subclinical anxiety and depressive symptom severity with either individualized (IG-IMI) or automated (AG-IMI) guidance compared to a waitlist control group with care-as-usual access (WLC). ***Methods:*** Participants included 566 adults with subclinical anxiety (GAD-7 $\geq$ 5) and/or depressive (CES-D $\geq$16) symptoms, who did not meet criteria for a full-syndrome depressive or anxiety disorder. In a three-arm randomized clinical trial, participants were randomized to a cognitive behavioral 7-session IMI plus booster session with IG-IMI (n = 186) or AG-IMI (n = 189) or WLC (n = 191). Primary outcomes included observer-rated anxiety (HAM-A) and depressive (QIDS) symptom severity 8 weeks after randomization assessed by blinded raters via telephone. Follow-up outcomes at 6 and 12 months are reported. ***Results:*** Symptom severity was significantly lower with small to medium effects in IG-IMI (anxiety: d = 0.45, depression: d = 0.43) and AG-IMI (anxiety: d = 0.31, depression: d = 0.32) compared to WLC. No significant differences emerged between guidance formats in primary outcomes. There was a significant effect in HAM-A after 6 months favoring AG-IMI. On average, participants

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completed 85.38% of IG-IMI and 77.38% of AG-IMI. ***Conclusions:*** A transdiagnostic, self-tailored IMI can reduce subclinical anxiety and depressive symptom severity, but 12-month long-term effects were absent. Automated guidance holds promise for enhancing the scalability of IMIs in broad prevention initiatives.

Introduction

Subclinical anxiety and depressive symptoms that do not meet full diagnostic criteria are highly prevalent [1, 2] and increase the risk of developing full-syndrome disorders [3]. Similar to full-syndrome disorders, subclinical anxiety and depression symptoms often co-occur. Individuals with comorbid symptoms have been found to experience elevated distress, poorer functioning, increased treatment demand, elevated costs, and greater barriers to mental health services compared to those with singular anxiety or depressive symptoms [2, 4–6].

Comorbid subclinical anxiety and depressive disorders, even without meeting full diagnostic criteria, warrant attention due to their prevalence and associated impairment. Despite one-third of individuals with subclinical depression expressing an unmet need for help [7], attitudinal barriers, such as fear of stigmatization and a preference for self-help limit the use of psychological support services [8]. Furthermore, on-site interventions for subclinical symptoms are scarce and implementing traditional psychological treatments for these symptoms may be impractical due to resource constraints in healthcare systems [9]. Internet- and mobile-based interventions (IMIs) offer accessible, evidence-based solutions. Previous IMI prevention research, though mostly targeting one disorder in isolation, shows small effects on symptom reduction for either anxiety (d = 0.21, d = 0.31) or depressive (d = 0.25–0.35) symptom severity [10–12]. To address comorbidity, transdiagnostic and tailored IMIs, targeting common mechanisms, such as avoidance [13, 14], and individually self-tailored IMIs combining modules from different intervention packages based on preferences, characteristics, and symptom presentations [15, 16], need exploration. Limited data exist on the efficacy of these interventions, but a targeted IMI for transdiagnostic prevention (n = 1,047) showed small to medium between-group effects on anxiety disorders (d = 0.42) and depression (d = 0.58) in students at high risk for developing common mental disorders compared to an active control condition [17].

While accessible and scalable IMIs offer advantages, they also come with the risk of low adherence and dropout, especially among those with comorbid symptoms [18]. IMIs that incorporate human guidance have been associated with higher intervention adherence and better efficacy compared to unguided IMIs [19–22]. Human guidance is cost-intensive, posing a significant barrier to widespread dissemination [23]. Automated guidance, delivered by a software platform without human input, appears scalable, but early results vary in efficacy and adherence. Safety and treatment satisfaction outcomes are currently lacking [24–26].

Thus, the study aimed to evaluate the efficacy of a transdiagnostic and self-tailored IMI in reducing subclinical anxiety and depressive symptoms in an individualized (IG-IMI) and an automated guided (AG-IMI) version compared to a waitlist control group with access to care-as-usual (WLC). We hypothesized that (1) both IG-IMI and AG-IMI would be more effective than WLC, and (2) IG-IMI would show greater efficacy and acceptability over AG-IMI in observer-rated (primary outcomes) and self-reported (key secondary outcomes) anxiety and depression symptom severity and other secondary outcomes.

Materials and Methods

Study Design

This study is part of the ICare Prevent three-arm randomized controlled trial, detailed in a prior study protocol [27], investigating both prevention of disorder onset and symptom severity reduction in individuals with subclinical anxiety and depressive disorder. This study focuses on data from the German-speaking countries collected by the German-Swiss trial site, with data from other trial sites to be reported separately [28]. The study was preregistered (German Clinical Trial Registration DRKS00011099) and obtained ethical approval in Germany and Switzerland (Medical Ethics Committee, University of Erlangen-Nürnberg, Germany, reference No. 144_16 B; ethics commission of the Canton of Bern, Switzerland, reference No. 2016-01389).

Recruitment and Assessment of Eligibility

Recruitment was conducted both online (e.g., study website, Google AdWords, online magazines, targeted social media campaigns such as Facebook, Instagram) and offline (e.g., flyers, mail campaigns via health insurance companies), specifically addressing individuals exhibiting subclinical symptoms. Applicants for the study completed an online screening to verify eligibility, ensuring they: (1) were 18 years or older, (2) experiencing subclinical anxiety (Generalized Anxiety Disorder Scale [GAD-7] score ≥5 [29]) and/or depression (Center for Epidemiological Studies Depression Scale [CES-D] score ≥16 [30]). Exclusion criteria included (3) a history of psychosis, bipolar disorder, or dissociative symptoms, (4) elevated suicidal risk assessed in the diagnostic interview, (5) lack of internet access and language proficiency, or (6) no provision of informed consent, and (7)

current/past psychotherapy within 6 months or being placed on a waiting list for psychotherapy for depression and/or anxiety disorders. The Mini International Neuropsychiatric Interview Version 6.0 (MINI, [31]) was conducted, with exclusions for meeting full diagnostic criteria for (1) an anxiety disorder currently or in the previous 6 months, or (2) a major depression currently or in the previous 6 months and reporting a core symptom of major depression (i.e., dysphoria, anhedonia) in the previous 3 weeks.

Procedure

Once participants had given informed consent, trained clinical interviewers conducted the diagnostic interviews, and individuals who fulfilled all study inclusion and no exclusion criteria proceeded to complete the baseline assessment including the self-report online questionnaires. Subsequently, participants were randomized to one of the three study conditions (i.e., IG-IMI, AG-IMI, WLC).

Randomization and Blinding

Randomization was performed at an individual level in a 1:1:1 ratio (IG-IMI, AG-IMI, WLC) within three strata according to the presence of subclinical symptoms (subclinical anxiety, subclinical depression, and comorbid subclinical anxiety and subclinical depression) by an independent biostatistician who was not involved in the study administration. An automated computer-generated block-randomization algorithm with concealed block length was used for the randomization procedure. During the randomization process, participant assignment was concealed from study personnel, clinical interviewers, eCoaches, and participants. After the randomization process, participants of the IG-IMI were informed that they would receive feedback by an eCoach (details provided below), whereas participants of the AG-IMI did not receive further information. Clinical interviewers were not otherwise involved in the study and were blinded to participants' randomization status. If blinding was (accidentally) broken during the posttreatment or 6-month follow-up outcome interviews, the clinical interviewer was replaced by another blinded interviewer for the follow-up telephone assessments.

Internet-Based Intervention

Both intervention conditions were based on the same IMI and differed only regarding the guidance format. The IMI has been previously described in detail in the study protocol [27]. Transdiagnostic components of the 7-session IMI addressing both anxiety and depression included: need orientation, behavioral activation, psychoeducation, cognitive restructuring, problem-solving, and exposure and relapse prevention. There was an additional booster session 4 weeks after completion of the seventh session. In addition, there were eight transdiagnostic elective modules on rumination and worries, acceptance, relaxation, alcohol and affect regulation, self-worth, perfectionism, appreciation and gratitude, and sleep. Individual tailoring via conditional content within a session allowed participants to choose between different components of the intervention content (e.g., focus on problem-solving or exposure or both). Participants were also able to opt to receive additional motivational messages to their smartphones. Intervention content was interactive (i.e., free response fields and quizzes) with various presentation formats (i.e., text, audio, video). Participants could additionally use a diary on their smartphone.

Guidance Formats

Individual Guidance

Participants in the IG-IMI received manualized feedback on every completed treatment session individualized to the participant's input and overall progress. Each participant in the IG-IMI was sent feedback by a personal eCoach through the messaging function on the eHealth platform [32]. eCoaches had at least a bachelor's degree in Psychology and access to supervision when required. Coaching time spent, on average, per participant was 90 min (13 min on average per module). Individualized guidance additionally included treatment adherence monitoring with adherence reminders sent via email and text message if a session was not completed within 7 days.

Automated Guidance

Participants in the AG-IMI were automatically sent standardized manualized feedback on every completed treatment session through the eHealth platform without individualized adaptations by an eCoach. The goal of this standardized feedback was to encourage the participant to engage with the intervention. Automated guidance also included the same adherence monitoring procedure as in IG-IMI, except that for participants in the AG-IMI, due to technical constraints, the study team sent impersonalized emails manually, without engaging in personal communication.

Control Condition

The waitlist control group received intervention access following the 12-month study duration, while also having access to routine standard care during the study phase [33]. We assessed the potential utilization of care.

Outcomes

Study outcomes reported here were assessed at baseline (T1), posttreatment (8 weeks after randomization, T2), 6-month (T3) and 12-month (T4) follow-up. The primary outcomes of this study were observer-rated anxiety and depression symptom severity based on a structured clinical telephone interview by trained masters-level psychology students. All other measures were based on self-report and collected using a secured online-based assessment system (256-bit encrypted).

Sociodemographic Information, Intervention Experiences, and Expectations

The following sociodemographic and mental health-related information was collected: age, gender, country of residence, migration background, ethnic background, university degree, marital status, place of residence, prior mental disorder diagnoses, prior psychotherapy experience, prior experience with health promoting interventions (e.g., stress management), reasons for using an IMI, and guidance preference. Participants' intervention expectations were assessed with the Credibility/Expectancy Questionnaire (CEQ; 6 items) [34, 35], including the subscales for treatment credibility (3 items, $\alpha = 0.87$, score range: 3–27) and expectancy (3 items, $\alpha = 0.86$, score range: 3–27), with higher scores indicating greater credibility or expectancy regarding the forthcoming intervention, respectively.

Primary Outcomes

Observer-Rated Anxiety and Depression Symptom Severity

The primary outcomes were observer-rated anxiety and depression symptom severity at T2. Observer-rated anxiety symptom severity was assessed using the Hamilton Anxiety Rating Scale

(HAM-A) in combination with the Structured Interview Guide for the Hamilton Anxiety Scale (SIGH-A; 14 items, score range: 0–56, α = 0.77) [36]. Observer-rated depressive symptom severity was assessed by clinician ratings of the Quick Inventory of Depressive Symptomatology (QIDS-C; 16 items, score range: 0–27, α = 0.59), covering criteria such as sleep disturbance, sad mood, appetite/weight changes, concentration/decision making, self-view, thoughts of death or suicide, general interest, energy level, and restlessness/agitation [37]. Strong pairwise severity rating correlations were found between raters (Pearson's r = 0.98 for HAM-A and r = 0.92 for QIDS-C).

Key Secondary Outcomes

Self-Reported Anxiety and Depression Symptom Severity

Key secondary outcomes were self-reported anxiety and depression symptom severity at T2. Generalized anxiety disorder was measured by the Generalized Anxiety Disorder Assessment (GAD-7; 7 items, score range: 0–21; α = 0.76) [29]. Higher scores indicate greater anxiety symptoms (5–9: mild, 10–14: moderate, ≥15: severe). Self-reported depressive symptoms were assessed with the Center for Epidemiological Studies Depression Scale (CES-D; 20 items, score range: 0–60; α = 0.82) [30]. Higher scores indicate greater depressive symptoms (<16: none to mild, ≥16: moderate, ≥24: severe).

Other Secondary Outcomes

Drinking frequency, alcohol quantity, and episodic heavy drinking were measured with the Alcohol Use Disorders Identification Test alcohol screen (AUDIT-C; 3 items, score range: 0–12; α = 0.62) [38, 39]. Well-being was assessed by the Well-Being Index (WHO-5, score range: 0 [absent] – 25 [maximal]; percentage score range: 0 [absent] – 100 α = 0.85) [40]. Worry was measured by the ultra-brief Penn State Worry Questionnaire – Past Week (PSWQ-3; 3 items, score range: 0–18; α = 0.87) [41–43]. Sleep quality was assessed by the 1-item subscale of the Pittsburgh sleep quality index (PSQI; item range: 0 (very good) – 3 (very bad) [44]. Resilience was measured with the 10-item version of the Connor-Davidson Resilience Scale (CD-RISC 10; score range: 0 [poor resilience] – 40 [great resilience]; α = 0.87) [45]. Motivational incongruence was assessed by the short form of the Incongruence Questionnaire (K-INK; 23 items, score range: 1–5; α = 0.63) [46]. Behavioral activation was assessed by the short form of the Behavioral Activation for Depression Scale (BADS-SF; 9 items, score range: 0–54; α = 0.92) [47–49]. Quality of life was measured by the Assessment of Quality-of-Life Instrument (AqoL-8D; 35 items; range: 0–100, α = 0.89) [50–52] (see online suppl. material for further details; for all online suppl. material, see https://doi.org/10.1159/000536149). Additionally, intervention adherence and dropout was calculated, and intervention benefits and negative effects were assessed and analyzed (see online suppl. material).

Care-as-Usual Utilization

Participant's use of healthcare and self-help resources in the past 8–10 weeks, such as visit to a general practitioner, was assessed at T2 with two items developed by the authors. Additionally, the Attitudes toward Seeking Professional Psychological Help short form questionnaire (ATSPPH; 10 items, score range: 0 [disagree] – 30 [agree]; α = 0.77) gauged participants' attitudes toward seeking professional help [53, 54]. A higher sum score indicates a more positive attitude toward professional help seeking [55].

Sample Size

The trial's a-priori sample size estimation was based on planned analyses of the time to disorder onset [27], reported separately. The recruited sample size involved a total of 566 participants (IG-IMI n = 186, AG-IMI n = 189, WLC n = 191). The study had 80% power to detect a standardized effect size of d = 0.275 (or larger) using a t-test and an alpha-level of p = 0.025 (2-sided).

Data Analyses

All analyses are reported according to the CONSORT statements [56, 57]. Analyses were based on the intention-to-treat principle, encompassing all initially randomized participants. Missing data were imputed using predictive mean matching [58, 59] and aggregated according to Rubin's rule [60]. The prediction model for each imputed variable incorporated baseline characteristics, including age, height, weight, income, and initial scores of primary and secondary outcome variables. This approach ensures accurate estimations of potential follow-up scores. The use of predictive mean matching ensures the avoidance of generating implausible values enhancing the robustness of the imputation process. Sensitivity analyses included a study completer analysis and an intervention completer analysis. The latter is based on multiple imputed data and considered as a per-protocol analysis (see online suppl. material).

Linear mixed models assessed between-group differences at all time points, tested against T1 scores. Each model investigated the overall condition and time interaction in a first step to assess the efficacy of the IG-IMI and the AG-IMI in comparison to WLC. In the case of statistical significance, planned contrasts between study conditions at T2, T3, and T4 were reported as mean between-group differences and as Cohen's d effect sizes and their 95% confidence interval [61, 62]. To assess subclinically relevant improvement and deterioration in the primary outcomes, the number of participants who showed at least 30% symptom improvement or deterioration was determined via change scores using the equation $100\ x\ \frac{post-pre}{pre}$, from T1 to T2, T3, and T4 [63]. The rates were compared across conditions and in the predefined planned contrasts using contingency tables and χ^2 tests. Both intervention conditions were also tested for significant differences in terms of intervention adherence and negative effects. Only significant results are reported. For each of the analyses, the number needed to treat (NNT) and the 95% confidence interval to achieve one additional treatment response were calculated [64].

All analyses were performed with IBM SPSS (version 28) and SAS Software (version 9.4). All reported p values were two-sided. The family-wise error rate regarding the global significance level (α = 0.05) of the two primary hypotheses and the key secondary hypotheses were corrected using the Bonferroni-Holm method [65], while remaining outcomes were exploratorily with uncorrected significance levels (α = 0.05).

Results

Study Attrition

Between February 7th, 2017 and June 14th, 2019, 566 participants were randomized into the study (IG-IMI n = 186, AG-IMI n = 189, WLC n = 191). Figure 1 shows the

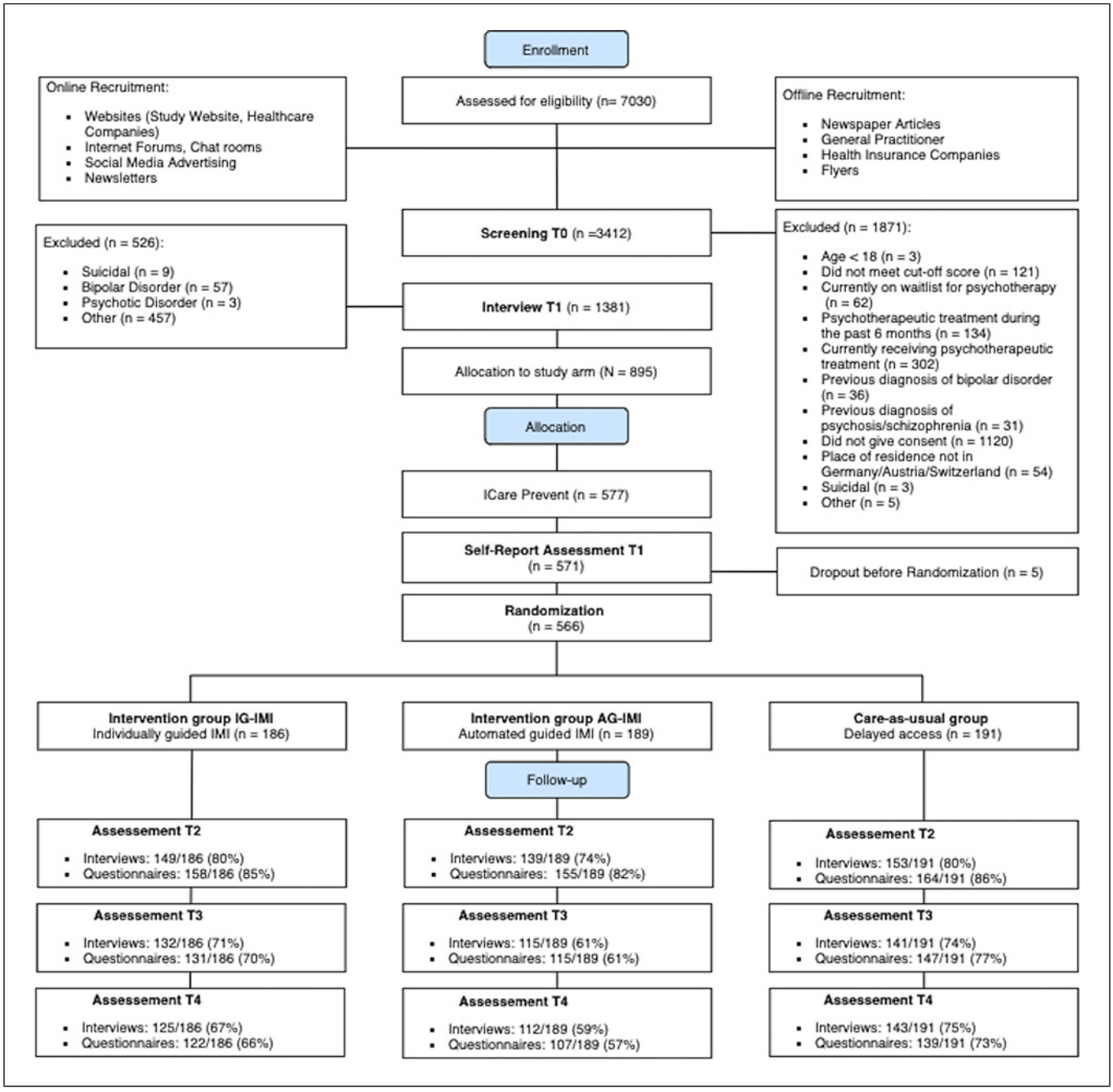

Fig. 1. Study Flow. Automated guided internet- and mobile-based intervention (AG-IMI) and individualized guided internet- and mobile-based intervention (IG-IMI). T1, baseline; T2, posttreatment 8 weeks after randomization; T3, 6-month follow-up; T4, 12-month follow-up.

study flow. At T2, 442 participants (78.09%) completed the interview (attrition 21.91%), and 477 participants (84.28%) completed the questionnaires (attrition 15.72%). At T3, 388 participants (68.55%) completed the interview (attrition 31.45%), and 393 participants (69.43%) completed the questionnaires (attrition 30.57%). At T4, 380 participants (67.14%) completed the interview (attrition rate 32.86%), and 368 participants (65.02%) the questionnaires (attrition 34.98%). Participants who discontinued the assessments at follow-up

showed higher resilience (T2: $\chi^2(1) = 7.41$, $p < 0.01$), lower behavioral activation (T2: $\chi^2(1) = 8.02$, $p < 0.01$), higher sleep quality (T3: $\chi^2(1) = 5.67$, $p = 0.02$), lower behavioral activation (T3: $\chi^2(1) = 20.19$, $p < 0.001$), lower motivational incongruence (T3: $\chi^2(1) = 7.71$, $p < 0.01$), and more prior experience with health interventions (T4: $\chi^2(1) = 8.58$, $p < 0.01$) at baseline.

Sociodemographic Information, Treatment Experience, and Expectations

Participant characteristics at T1 are shown in Table 1. Participants were, on average, 40 years old (*SD* = 14.02, range 18–81), predominately female (*n* = 410, 72.44%), living in Germany (*n* = 478, 84.45%), and Caucasian (*n* = 484, 85.51%). In total, 347 participants had a university degree (61.31%), 74 had a migration background (13.07%), 224 were single (39.58%), and 175 were living in a small town (30.92%). Of the 566 participants, 34.81% reported having received a diagnosis of a mental disorder in the past (*n* = 197). Nearly half of the participants had received psychotherapy at some point in their lives (47.53%, *n* = 269), but only 121 individuals (21.38%) endorsed experience with a health-promoting intervention prior to the study. The two most common reasons for wanting to participate in an IMI were a preference for self-help (*n* = 527, 93.11%) and finding IMIs appealing (*n* = 407, 71.91%). Over two-thirds of the participants had a preference to receive feedback during the intervention (*n* = 366, 64.66%), and around one-third had no preference regarding whether to receive guidance (*n* = 178, 31.45%). However, almost all participants wished to receive adherence reminders (*n* = 530, 93.64%). Treatment credibility scores ranged from 3 to 27 (M = 20.05, SD = 4.81), and the expectancy scores ranged from 3 to 27 (M = 16.52, *SD* = 5.45). Means and standard deviation for all outcomes are reported in Table 2.

Primary Outcomes

Observer-Rated Anxiety and Depression Symptom Severity

There was a statistically significant overall between-group difference in HAM-A scores in favor of the intervention groups ($F(6,1689) = 3.64$, $p = 0.001$), see Table 3. In direct comparison with WLC at T2, HAM-A scores were significantly lower with small effect sizes in both the IG-IMI ($b = -2.32$, $p < 0.01$, $d = 0.45$, 95% CI: 0.24–0.65; *NNT*: 2.91, 95% CI: 2.19–4.60) and the AG-IMI ($b = -3.19$, $p < 0.01$, $d = 0.31$, 95% CI: 0.11–0.51; *NNT*: 4.09, 95% CI: −2.74–8.47). A statistically significant overall between-group difference was also found in QIDS-C scores in favor of the intervention groups ($F(6,1689) = 3.76$, $p = 0.001$). In direct comparison with WLC at T2, QIDS-C scores were significantly lower with small effect sizes in both the IG-IMI ($b = -1.26$, $p < 0.01$, $d = 0.43$, 95% CI: 0.23–0.64; *NNT*: 2.86, 95% CI: 2.17–4.38) and the AG-IMI ($b = -1.67$, $p < 0.01$, $d = 0.32$, 95% CI: 0.12–0.52; *NNT*: 3.92, 95% CI: 2.67–8.09), respectively.

Key Secondary Outcomes

Self-Reported Anxiety and Depression Symptom Severity

There was a statistically significant overall between-group difference in GAD-7 scores in favor of the intervention groups ($F(6,1689) = 3.51$, $p < 0.01$), see Table 3. In direct comparison with WLC at T2, GAD-7 scores were significantly lower with small effect sizes in both the IG-IMI ($b = -1.47$, $p < 0.01$, $d = 0.37$, 95% CI: 0.16–0.57; *NNT*: 3.76, 95% CI: 2.64–7.13) and the AG-IMI ($b = -1.45$, $p < 0.01$, $d = 0.34$, 95% CI: 0.14–0.54; *NNT*: 4.28, 95% CI: 2.86–8.89). A statistically significant overall between-group difference was also found in CES-D scores in favor of the intervention groups ($F(6,1689) = 4.00$, $p = 0.001$). In direct comparison with WLC at T2, CES-D scores were significantly lower with small effect sizes in both the IG-IMI ($b = -3.04$, $p = 0.01$, $d = 0.38$, 95% CI: 0.18–0.59; *NNT*: 3.84, 95% CI: 2.67–7.13) and the AG-IMI ($b = -3.82$, $p < 0.01$, $d = 0.31$, 95% CI: 0.11–0.51; *NNT*: 4.60, 95% CI: 3.00–10.45), respectively.

Treatment Responses

Observer-Rated Anxiety Symptom Severity

A 30% symptom improvement from T1 to T2 in HAM-A scores was seen in significantly more participants in the IG-IMI (*n* = 92/186, 49.46%) and the AG-IMI (*n* = 90/188, 47.87%) compared to WLC (*n* = 56/190, 29.47%; $\chi^2(2) = 19.12$, $p < 0.001$). Both, participants in the IG-IMI ($p < 0.001$; *OR* = 2.34, 95% CI: 1.53–3.58; *NNT*: 4.78, 95% CI: 3.31–9.44) and the AG-IMI ($p < 0.001$; *OR* = 2.20, 95% CI: 1.44–3.35; *NNT*: 5.15, 95% CI: 3.46–11.09) were more likely to experience a 30% symptom improvement in HAM-A compared to WLC. A 30% symptom deterioration from T1 to T2 in HAM-A was seen in significantly less participants in the IG-IMI (*n* = 19/186, 10.22%) and the AG-IMI (*n* = 34/188, 18.09%) compared to WLC (*n* = 40/190, 21.05%; $\chi^2(2) = 8.54$, $p = 0.01$). Specifically, participants in the IG-IMI ($p < 0.01$; *OR* = 0.43, 95% CI: 0.24–0.43; *NNT*: 7.56, 95% CI: 5.34–20.76) were less likely to experience a 30% symptom deterioration in HAM-A compared to WLC. Participants in the IG-IMI were also less likely to experience a 30% symptom deterioration in HAM-A compared to those in the AG-IMI ($p = 0.03$; *OR* = 1.94, 95% CI: 1.06–3.55; *NNT*: 6.80, 95% CI: 83.54–3.37).

Table 1. Sociodemographic information, treatment experience, and expectations at T1

	IG-IMI (n = 186)		AG-IMI (n = 189)		WLC (n = 191)		Total (N = 566)	
Sociodemographic data								
Age, M (SD)	40.61	14.33	38.67	13.68	41.13	13.99	40.14	14.02
Range	19–75		19–81		18–77		18–81	
Female, n (%)	140	75.27	134	70.90	136	71.20	410	72.44
Germany as country of residence, n (%)	152	81.72	161	85.19	165	86.39	478	84.45
Migration background, n (%)	25	13.44	27	14.29	22	11.52	74	13.07
Caucasian, n (%)	157	84.41	163	86.24	164	85.86	484	85.51
University degree, n (%)	112	60.22	117	61.90	118	61.78	347	61.31
Single, n (%)	72	38.71	71	37.57	81	42.41	224	39.58
Place of residence (<20,000 residents)	60	32.26	61	32.28	54	28.27	175	30.92
Mental health treatment experience								
Prior diagnosis of mental disorder, n (%)	62	33.33	71	37.57	64	33.51	197	34.81
Prior psychotherapy experience, n (%)	93	50.00	85	44.97	91	47.64	269	47.53
Prior experience with health trainings, n (%)	38	20.43	32	16.93	51	26.70	121	21.38
Reason for participation in IMI								
No other contact point found	7	3.76	12	6.35	15	7.85	34	6.01
No access to psychotherapy on site	5	2.69	5	2.65	2	1.05	12	2.12
Fear of stigmatization with psychotherapy on site	17	9.14	15	7.94	17	8.90	49	8.66
Waiting times for psychotherapy too long	28	15.05	25	13.23	20	10.47	73	12.90
Not getting into psychotherapy	8	4.30	6	3.17	4	2.09	18	3.18
Preference for self-help	178	95.70	179	94.71	170	89.01	527	93.11
Digital intervention as appealing option	137	73.66	131	69.31	139	72.77	407	71.91
Other reasons	38	20.43	39	20.63	37	19.37	114	20.14
Treatment expectations								
Guidance preference, n (%)								
Wish to receive feedback	119	63.98	132	69.84	115	(60.21)	366	64.66
No guidance preference	60	32.26	50	26.46	68	(35.60)	178	31.45
Wish to receive adherence reminders	172	92.47	179	94.71	179	(93.72)	530	93.64
Treatment credibility (CEQ), M (SD)	20.09	4.91	19.97	4.63	20.09	(4.91)	20.05	4.81
Treatment expectation (CEQ), M (SD)	16.25	5.38	16.63	5.29	16.66	(5.67)	16.52	5.45

M, mean; SD, standard deviation; n, number; IMI, Internet- and mobile-based interventions; CEQ, Credibility/Expectancy Questionnaire (3–27); IG-IMI, individually guided; AG-IMI, automated guided; WCG, waitlist control group.

Observer-Rated Depression Symptom Severity

A 30% symptom improvement from T1 to T2 in QIDS-C scores was seen in significantly more participants in the IG-IMI (n = 102/180, 56.67%) and the AG-IMI (n = 91/184, 49.46%) compared to WLC (n = 60/187, 32.09%; $\chi^2(2) = 23.71$, $p < 0.001$). Both, participants in the IG-IMI ($p < 0.001$; OR = 2.77, 95% CI: 1.81–4.24; NNT: 4.17, 95% CI: 3.14–6.86) and the AG-IMI ($p < 0.001$; OR = 2.07, 95% CI: 1.36–3.16; NNT: 5.64, 95% CI: 3.76–13.09) were more likely to experience a 30% symptom improvement in QIDS-C scores compared to WLC. A 30% symptom deterioration from T1 to T2 in QIDS-C scores was seen in significantly less participants in the IG-IMI (n = 32/180, 17.78%) and the AG-IMI (n = 35/184, 19.02%) compared to WLC (n = 57/187, 30.48%; $\chi^2(2) = 10.41$, $p < 0.01$). Participants in the IG-IMI ($p < 0.01$; OR = 0.49, 95% CI: 0.30–0.81; NNT: 6.23, 95% CI: 4.03–19.29) and the AG-IMI ($p < 0.01$; OR = 0.54, 95% CI: 0.33–0.87; NNT: 6.97, 95% CI: 4.29–28.91) were less likely to experience a 30% symptom deterioration in QIDS-C scores compared to WLC.

Longer Term Effects

Observer-Rated Anxiety and Depression Symptom Severity

There was a statistically significant between-group difference in HAM-A scores favoring the AG-IMI at T3 in comparison to WLC (b = –2.98, $p < 0.01$, d = 0.28, 95% CI: 0.08–0.48; NNT: 6.37, 95% CI: 3.74–22.36).

Table 2. Means and standard deviations for the primary and key secondary outcomes and assessment points based on the ITT sample

Treatment outcomes	Group	*n*	T1		T2		T3		T4	
			M	SD	M	SD	M	SD	M	SD
HAM-A										
	IG-IMI	186	16.04	7.03	11.73	7.13	11.78	7.75	11.20	7.18
	AG-IMI	189	14.59	7.44	11.14	7.08	10.95	6.50	10.23	6.12
	WLC	191	15.29	7.07	14.16	6.54	14.01	7.87	12.56	7.56
QIDS-C										
	IG-IMI	186	6.72	3.45	4.47	2.99	5.25	3.89	4.41	3.58
	AG-IMI	189	6.16	3.60	4.32	3.21	4.81	3.55	4.03	2.72
	WLC	191	6.42	3.78	5.84	3.20	5.74	4.30	5.37	3.90
GAD-7										
	IG-IMI	186	9.20	3.56	5.73	3.32	5.49	3.16	5.78	3.85
	AG-IMI	189	9.11	3.82	5.63	3.97	5.34	3.17	5.57	3.27
	WLC	191	9.31	3.81	7.30	3.88	6.96	3.91	6.86	3.81
CES-D										
	IG-IMI	186	24.95	8.13	15.77	8.74	15.28	8.34	16.32	9.73
	AG-IMI	189	23.96	8.09	15.58	9.28	13.94	7.34	14.72	8.26
	WLC	191	24.27	7.63	18.92	8.99	18.64	9.77	17.96	9.49

n, sample size; M, mean; SD, standard deviation; ITT, intention-to-treat; IG-IMI, individually guided; AG-IMI, automated guided; WLC, treatment as usual; HAM-A, Hamilton Anxiety Rating Scale; QIDS-C, Quick Inventory of Depressive Symptomatology; GAD-7, General Anxiety Disorder Measurement; CES-D, Center for Epidemiological Studies Depression Scale.

Self-Reported Anxiety and Depression Symptom Severity

There was a statistically significant between-group difference in GAD-7 scores favoring the IG-IMI ($b = -1.42$, $p = 0.01$, $d = 0.34$, 95% CI: 0.14–0.54; *NNT*: 5.26, 95% CI: 3.36–12.68) and the AG-IMI ($b = -1.35$, $p = 0.02$, $d = 0.35$, 95% CI: 0.15–0.55; *NNT*: 5.12, 95% CI: 3.30–11.84) at T3 compared to WLC. There was a statistically significant between-group difference in CES-D scores favoring the IG-IMI ($b = -4.39$, $p < 0.01$, $d = 0.41$, 95% CI: 0.21–0.61; *NNT*: 4.38, 95% CI: 3.00–8.47) and the AG-IMI ($b = -4.03$, $p < 0.01$, $d = 0.44$, 95% CI: 0.23–0.64, *NNT*: 4.09, 95% CI: 2.86–7.74) at T3 compared to WLC.

Other Secondary Outcomes

At T2, there were statistically significant between-group effects for all other secondary outcomes favoring IG-IMI ($d = 0.33$–0.60) and AG-IMI ($d = 0.33$–0.61) except for the AUDIT-C (see online suppl. material). At T3, there were statistically significant small to moderate between-group effects for all other secondary outcomes favoring the IG-IMI ($d = 0.25$–0.50) and the AG-IMI ($d = 0.33$–0.71) in comparison to WLC except for AUDIT-C and PSQI. At T4, there were also statistically significant between-group effects for all other outcomes favoring the IG-IMI except for AUDIT-C and PSQI ($d = 0.21$–0.39) and in the AG-IMI except for AUDIT-C, PSWQ-3, PSQI, and BADS-SF ($d = 0.42$–0.46). On average, participants in the IG-IMI completed 6.84 modules (SD = 2.02, 85.38% of the intervention), and participants in the AG-IMI completed 6.19 modules (SD = 2.40, 77.38% of the intervention) of the 8 sessions ($Z = -2.72$, $p = 0.01$). Detailed results on other secondary outcomes as well as study and intervention completer results are displayed in the online supplementary material.

Care-as-Usual Utilization

Of all the study participants, 68 out of 476 (14.29%) reported that they were receiving support from other sources (e.g., additional health interventions, seeing a physician, psychotherapist) within the 8–10 weeks following the start of the study (IG-IMI: 15.92%; AG-IMI: 11.61%; WLC: 15.24%). There was a statistically significant overall between-group difference in attitudes toward seeking professional psychological help at T2 in favor of the intervention groups ($F(2, 563) = 6.32$, $p = 0.002$). In direct comparison with WLC, patients' attitude toward seeking professional help were significantly more positive

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Table 3. Mixed model analyses with between-group effect sizes based on the ITT sample

Outcome measures	Time	Condition	Condition × Time	Contrasts	Posttreatment (T2)						6-month follow-up (T3)						12-month follow-up (T4)					
					estimate	SE	*p* value	d	CI	NNT (95% CI)	estimate	SE	*p* value	d	CI	NNT (95% CI)	estimate	SE.	*p* value	d	CI	NNT (95% CI)
HAM-A	*F*(3, 1,689) = 45.75, *p* < 0.0001	*F* (2, 563) = 9.50, *p* < 0.0001	*F*(6, 1,689) = 3.64, *p* = 0.0014	IG-IMI versus WLC	−2.32	0.72	<.01[1]	0.45	0.24–0.65	2.91 (2.19–4.60)	−2.36	0.89	.05[1]	0.36	0.15–0.56	4.98 (3.25–11.60)	−1.63	0.96	0.54[1]	0.25	0.05–0.46	7.13 (3.95–34.45)
				AG-IMI versus WLC	−3.19	0.73	<.01[1]	0.31	0.11 to 0.51	4.09 (2.74–8.47)	−2.98	0.89	<.01[1]	0.28	0.08 to 0.48	6.37 (3.74–22.36)	−2.11	0.97	0.17[1]	0.20	0.00 to 0.40	8.89 (−724.89–4.48)
				IG-IMI versus AG-IMI	−0.86	0.73	0.24	0.12	−0.09 to 0.32	10.45 (−29.55 to 4.49)	−0.62	0.89	0.49	0.08	−0.13 to 0.28	22.17 (−13.65 to 6.37)	−0.48	0.97	0.62	0.06	−0.14 to 0.27	29.55 (−12.68 to 6.6)
QIDS-C	*F*(3, 1,689) = 41.88, *p* < 0.0001	*F*(2, 563) = 8.97, *p* = 0.0001	*F*(6, 1,689) = 3.76, *p* = 0.0010	IG-IMI versus WLC	−1.26	0.40	<.01[1]	0.43	0.23–0.64	2.86 (2.17–4.38)	−0.67	0.47	.91[1]	0.18	−0.03 to 0.38	9.87 (−59.09 to 4.72)	−1.08	0.50	0.18[1]	0.28	0.08–0.48	6.37 (3.76–22.17)
				AG-IMI versus WLC	−1.67	0.40	<.01[1]	0.32	0.12 to 0.52	3.92 (2.67–8.09)	−0.79	0.47	.56[1]	0.15	−0.05 to 0.36	11.84 (−35.46–4.98)	−1.25	0.50	0.07[1]	0.25	0.04 to 0.45	7.13 (4.01–44.32)
				IG-IMI versus AG-IMI	−0.41	0.40	0.30	0.03	−0.17 to 0.23	11.84 (−17.74 to 4.49)	−0.12	0.47	0.80	0.04	−0.16 to 0.24	44.32 (−11.1 to 7.42)	−0.17	0.50	0.73	0.08	−0.12 to 0.28	22.17 (−14.79 to 6.37)
GAD-7	*F*(3, 1,689) = 146.13, *p* < 0.0001	*F*(2, 563) = 11.98, *p* < 0.0001	*F*(6, 1,689) = 3.51, *p* = 0.0019	IG-IMI versus WLC	−1.47	0.38	<.01[1]	0.37	0.16–0.57	3.76 (2.64–7.13)	−1.42	0.46	.01[1]	0.34	0.14 to 0.54	5.26 (3.36–12.68)	−1.08	0.50	0.18[1]	0.23	0.03–0.43	7.74 (4.19–59.09)
				AG-IMI versus WLC	−1.45	0.38	<.01[1]	0.34	0.14–0.54	4.28 (2.86–8.89)	−1.35	0.46	.02[1]	0.35	0.15–0.55	5.12 (3.30–11.84)	−0.96	0.50	0.33[1]	0.27	0.06–0.47	6.60 (3.84–29.55)
				IG-IMI versus AG-IMI	0.01	0.38	0.98	0.00	−0.20 to 0.21	/	0.07	0.46	0.89	0.02	−0.19 to 0.22	88.63 (−9.36–8.09)	0.12	0.50	0.81	0.03	−0.17 to 0.23	59.09 (−10.45–7.74)
CES-D	*F*(3, 1,689) = 151.53, *p* < 0.0001	*F*(2, 563) = 12.22, *p* < 0.0001	*F*(6, 1,689) = 4.00, *p* = 0.0006	IG-IMI versus WLC	−3.04	0.97	.01[1]	0.38	0.18 to 0.59	3.84 (2.67–7.13)	−4.39	1.15	<.01[1]	0.41	0.21 to 0.61	4.38 (3.00–8.47)	−2.93	1.21	0.10[1]	0.22	0.02 to 0.43	8.09 (4.19–88.63)
				AG-IMI versus WLC	−3.82	0.98	<.01[1]	0.31	0.11 to 0.51	4.60 (3.00–10.45)	−4.03	1.16	<.01[1]	0.44	0.23–0.64	4.09 (2.86–7.74)	−2.31	1.22	0.35[1]	0.32	0.11–0.52	5.59 (3.49–16.13)
				IG-IMI versus AG-IMI	−0.79	0.98	0.42	0.08	−0.12 to 0.28	22.17 (−11.84 to 5.95)	0.36	1.16	0.75	0.04	−0.16 to 0.24	44.32 (−11.10 to 7.42)	0.62	1.22	0.61	0.06	−0.14 to 0.27	29.55 (−12.68 to 6.60)

SE, standard error; *p*, *p*-value; *d*, Cohens' d effect size; *CI*, confidence interval; *NNT*, number needed to treat; *ITT*, intention-to-treat; T2, posttreatment (8 weeks after randomization); *T3*, 6-month follow-up; *T4*, 12-month follow-up; IG-IMI, individually guided; AG-IMI, automated guided; WLC, treatment as usual; HAM-A, Hamilton Anxiety Rating Scale; QIDS-C, Quick Inventory of Depressive Symptomatology; GAD-7, General Anxiety Disorder Measurement; CES-D, Center for Epidemiological Studies Depression Scale. [1]Bonferroni adjusted.

in both the IG-IMI (b = 0.81, p = *0.01*, d = 35, 95% CI: 0.01–0.41) and the AG-IMI (b = 1.10, $p < 0.001$, d = 0.35, 95% CI: 0.07–0.48), with small effect sizes.

Discussion

The study aimed to evaluate the efficacy of a transdiagnostic and self-tailored cognitive behavioral IMI for individuals with subclinical anxiety and depression symptoms. Both intervention groups demonstrated small to moderate significant effects in observer-rated anxiety and depression symptom severity compared to WLC at post-treatment, confirming our primary hypothesis. Small significant effects were also identified in self-reported anxiety and depression symptom severity. Approximately half of all participants showed a 30% symptom improvement in anxiety and depressive symptoms. High intervention adherence rates were reported, indicating good acceptability. Contrary to our second hypothesis, no differences emerged between the individualized and automated guided IMI regarding observer-based and self-reported anxiety and depression symptoms. No significant deterioration rates were observed overall. On the contrary, the IMI contributed to fewer people deteriorating in anxiety symptom severity compared to WLC. The IMI also increased well-being, resilience, and behavioral activation, and reduced worry and motivational difficulties with small to medium effects. In terms of longer term efficacy, small effects were present for self-reported anxiety and depression and observer-based anxiety after 6 months. While effects were maintained in the intervention groups, significant differences in most secondary outcomes, except primary outcomes, emerged after 12 months compared to WLC.

Our study results are in line with overall small effects found for preventive IMIs regarding either anxiety (d = 0.21, d = 0.31) or depressive (d = 0.25–0.35) symptom severity [10–12], as well as small meta-analytic effects found on subclinical anxiety (d = –0.31) and depression (g = 0.35) after face-to-face psychological interventions [66, 67]. The results also align with findings reducing subclinical depression in older adults with multimorbidity (d = 0.29) [68]. The small effects found in the current transdiagnostic study are, however, below those identified in a comparable IMI solely focusing on subclinical depression in comparison to WLC (d = 0.69) [69]. The two studies shared similar sample characteristics, except for the baseline depression symptom severity, which was two points lower on average in our study. A study on a targeted IMI for transdiagnostic prevention (n = 1047) also showed slightly larger small to medium between-group effects on anxiety (d = 0.42) and depression (d = 0.58) in students at high risk for developing common mental disorders compared to an active control condition [17]. The small significant effects found at 6-month follow-up were in line with those of preventive IMIs in the general population [10]. A different study found that while an IMI prevented relapse in partially remitted depression after 2 years, it did not significantly impact anxiety and depressive symptoms during follow-up [70]. Limited data exist regarding the long-term effects of unguided preventive IMIs on anxiety and depression, mainly due to studies including follow-up periods of less than 3 months [12]. In this study, despite the lack of significant effects at 12 months, a pattern of improvement from T1 to T2 was seen in all three conditions, with gains maintained at follow-ups. Reasons for symptom severity reduction in WLC may include spontaneous recovery, regression to the mean, potential self-improvement in motivated participants, study participation prompting positive social support, and enhanced problem awareness, leading to self-initiated help seeking as well as questionnaire and interview assessments serving as sufficient intervention [71, 72].

The absence of significant differences between guidance formats aligns with previous studies on IMIs comparing automated versus individualized guidance for anxiety and depression [25, 73–75]. Approximately one-third of participants preferring no guidance might have found well-designed automated messages sufficient. For individuals with anxiety symptoms, an IMI's appeal may lie in limited human interaction [76]. Notably, participants in this study received some human contact through telephone-based diagnostic interviews and could reach out to the study team [77]. One could also argue that the differences between the two guidance formats were too minimal to alter the intervention's efficacy, as shown in previous studies [78, 79]. Although participants in the individualized guided condition may have expected more personalized support, this contradicts the high treatment adherence observed in this group. In contrast to efficacy results, individualized guidance was associated with higher intervention adherence rates (7 vs. 6 modules), consistent with findings favoring more individualized guidance compared to fully standardized feedback in reducing attrition [25].

This study has several limitations. First, the sample consisted of self-selected middle-aged, highly educated, and predominately female sample, typical for IMIs [80]. Additionally, approximately one-third of participants reported a history of mental disorder diagnosis, while nearly half had previous experience with psychotherapy, limiting generalizability to other populations. IMIs might also be specifically suitable for individuals with a preference for self-help. Idiographic outcomes for each individual were not analyzed,

making it unclear who benefited from increased human interaction. Second, in the automated study conditions, it should be noted that the study team sent standardized emails to remind people to participate in the intervention. However, there was no personal contact with the study participants. Third, this study was powered for the primary analysis on the time to disorder onset, not for differences in symptom severity measures and guidance formats. A replication with a sufficiently large sample size is essential to directly compare the efficacy of both guidance formats. Fourth, missing data ranged from 19% to 43%, and despite multiple imputation strategies, this should be considered when interpreting findings. Fifth, the IMI's tailoring component depended on participants' self-selection, lacking module allocation based on symptom assessments or characteristics.

This study demonstrates the efficacy of a transdiagnostic psychological intervention in reducing the severity of subclinical anxiety and depression symptoms, with enduring effects after 6 months. The automated standardized guidance format showed comparable efficacy to more individualized guidance, suggesting scalability, resource-efficiency and potentially cost-effectiveness to widely disseminate preventive interventions. However, the (cost-) effectiveness of the IMI in both guidance formats under routine conditions requires further investigation. These findings also set the stage to consider individual characteristics when determining the appropriate guidance format, addressing adherence, satisfaction, risk for symptom deterioration, negative effects, and contextual factors. Additionally, the variety of the comorbidity's presentations might also affect the individual requirements for the fit of an intervention [81]. The findings that almost 80% of study participants had no prior experience with health interventions and that over 50% had no prior experience with psychotherapy, suggest that this low-threshold intervention might meet the early-stage treatment needs of those without access to other face-to-face therapeutic resources. The outcomes highlight that the IMI effectively diminishes symptom severity both in the short term up to 6 months and mitigates the likelihood of full-syndrome disorder emergence. Beyond its impact on symptom severity, the intervention also enhances quality of life, general well-being, and resilience. Thus, the IMI has the potential to reduce the burden of anxiety and depression, decreasing the risk of developing full mental disorders at an earlier stage. Future studies should investigate the processes and mechanisms of digital interventions and their optimization and integration into a stepped model for mental health prevention and treatment.

In conclusion, this study shows that an IMI for subclinical anxiety and depression is effective with small effects. Even provided solely with automated guidance, IMIs might be a suitable, effective, and scalable solution to aid in the treatment of subclinical symptoms and the prevention of common mental disorders.

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Statement of Ethics

The study protocol was reviewed and approved by the Medical Ethics Committee of the Friedrich-Alexander-Universität Erlangen-Nürnberg, approval No. 144_16 B, and the ethics commission of the Canton of Bern, Switzerland, reference No. 2016-01389.

Conflict of Interest Statement

A.C.Z. reports to have received fees for lectures or workshops and for expert videos for an internet-based intervention. D.D.E. and M.B. are stakeholders of the GET.ON Institute/HelloBetter, which aims to implement scientific findings related to digital health interventions into routine care. M.B. is a scientific advisor of mentalis GmbH and GET.ON Institute/HelloBetter, both providers of digital mental healthcare products and services and a co-founder of mentalis GmbH. D.D.E. has served as a consultant to/on the scientific advisory boards of Sanofi, Novartis, Minddistrict, Lantern, Schoen Kliniken, Ideamed, and German health insurance companies (BARMER, Techniker Krankenkasse) and a number of federal chambers for psychotherapy. K.K.W., T.B., T.K., M.P.S., and D.G. have no conflicts of interest to declare.

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Author Contributions

D.D.E., M.P.S., T.B., and C.J. obtained funding for this study. A.C.Z., K.K.W., T.B., T.K., M.P.S., D.G., and D.D.E. developed the design of the study. A.C.Z., K.K.W., and T.K. conducted the study. D.G. conducted the analyses. A.C.Z. and K.K.W. drafted the manuscript. A.C.Z., K.K.W., T.B., T.K., M.P.S., M.B., D.G., and C.J. provided critical revision of the article and approved the final manuscript.

Data Availability Statement

Data can be requested from the corresponding author.

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