Researching the Effectiveness of *attexis*, a Digital Health Application for Adults with Attention Deficit Hyperactivity Disorder - a randomized controlled trial (READ-ADHD)

Clinical investigation report following ISO 14155:2020

Investigational device

attexis

Study design

- prospective
- randomized (simple randomization)
- controlled (two arms)
- online

Study population

337 patients, aged 18-65 years, with a diagnosis of ADHD and elevated levels of ADHD symptoms (score of ≥ 17 either on the inattention subscale or on the impulsivity/hyperactivity subscale of the ASRS v1.1).

Statement

This clinical investigation was performed in accordance with ISO 14155:2020 and the ethical principles in the Declaration of Helsinki.

Sponsor

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Study registration number

ClinicalTrials.gov ID: NCT06221930

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Version

2

Summary of the revision history

Version	Date	Changes
1.1	17.12.2024	● In version 1.1, the footer was updated to include the document title and document date.
2	07.07.2025	● The date of the last-patient-last-visit was updated ● Figure 1, Tables 3-5 were updated to include information on the participant flow ● Tables 4-18 were renumbered ● Table 6 was updated to report baseline characteristics of drop-outs and completers for each group separately ● Results of the analysis of T2 data and J2R analyses were added ● The discussion was extended to include results of the T2 data and J2R analyses, as well as a comparison of the original scale values and responder rates with published data

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1. Summary

1.1 Title of the clinical investigation

Researching the Effectiveness of *attexis*, a Digital Health Application for Adults with Attention Deficit Hyperactivity Disorder - a randomized controlled trial (READ-ADHD)

1.2 Introduction

ADHD is a neurological disorder affecting 2.58% to 6.76% of adults worldwide [1]. Most prominent symptoms of ADHD comprise attention deficit, hyperactivity and impulsive behavior. Persons with ADHD struggle massively with daily life and work productivity [2], suffer from higher risk for accidents and injuries over the life-span [3], diminished quality of life until old age [4], public stigma [5] and pose additional financial costs in health care [6].

Depression and anxiety disorders have been identified as widespread comorbidities [7], which pose further risk for diminished quality of life. Moreover, substance use disorders are quite common among persons with ADHD [8], possibly due to self-medication.

The gold standard of adult ADHD treatment comprises either psychosocial intervention, medication, or a combination of both according to the German S3 Clinical Guideline [9]. For pharmacological treatment, amphetamines can be identified as the first line intervention [10]. For non-pharmacological treatment, cognitive-behavioral therapy (CBT) should be chosen according to the German S3 Clinical Guideline [9], as it has been shown to be effective in treating ADHD [11]. Additionally, mindfulness-based strategies [12], [13] as well as physical exercise [14], especially exercise duration rather than intensity [15], have been demonstrated to be effective.

The availability of cognitive behavioral therapy is limited and waiting times exceed several months [16]. To combat this shortage and offer low-threshold help for patients, digital health applications have been developed successfully for other psychiatric conditions, e.g. depression [17] and anxiety [18]. To date, there are promising effects of digital interventions for ADHD in youth [19], [20] and preliminary evidence of their effectiveness in adults with ADHD [21], [22], [23], [24]. Nonetheless, the field of research is still underexamined and more studies, with better power, are needed [25].

The intervention at hand was developed on the basis of patient materials integrating cognitive behavioral methods and mindfulness-based interventions for adults with ADHD [26], which has been shown to be effective in the treatment of ADHD in adults [27].

The aim of the present pragmatic RCT was to investigate the effectiveness of the online intervention *attexis* to decrease ADHD symptoms in people with ADHD.

1.3 Purpose of the clinical investigation

The purpose of this clinical investigation was to assess the effectiveness of the self-guided digital health application *attexis* in adult patients with ADHD in terms of reducing the severity of ADHD symptoms.

1.4 Description of the clinical investigation population

The study population consisted of adult patients (18-65 years) with ADHD who reported elevated levels of ADHD symptoms (score of ≥17 either on the inattention subscale or on the impulsivity/hyperactivity subscale of the ASRS v1.1).

1.5 Clinical investigation method

Recruitment of patients was through an online campaign. Participants were then routed to a linked study website providing information about the trial and details about participation. First Patient First Visit was on 2024-03-11 and Last Patient Last Visit was on 2024-12-25.

1.6 Results of the clinical investigation

1.6.1 Primary endpoint

The intent-to-treat (ITT) analysis showed that after 3 months of using *attexis*, patients in the TAU + *attexis* intervention group had lower levels of ADHD symptoms than patients in the TAU-only control group: the estimated baseline-adjusted difference between the groups after 3 months was -5.0 points on the Adult ADHD Self-Report Scale v1.1 [ASRS] total score (95% CI = [-6.4, -3.6], $p < 0.001$; Cohen's $d = 0.85$). A similar picture emerged in the conservative jump-to-reference (J2R) sensitivity analysis (baseline-adjusted group difference in the ASRS total score = -4.4 points, 95% CI = [-5.7, -3.2], $p < 0.001$; Cohen's $d = 0.75$) and the per protocol (PP) analysis (baseline-adjusted group difference in the ASRS total score = -5.0 points, 95% CI = [-6.4, -3.6], $p < 0.001$; $d = 0.86$).

Results of the responder analysis based on a 30% reduction in the severity of ADHD symptoms from baseline to T1, as assessed by the ASRS total score, showed that more patients in the intervention group (11.6%) than in the control group (1.2%) achieved clinically relevant reductions in ADHD symptoms after 3 months ($\chi^2 = 15.67$, $p < 0.001$; Odds Ratio [OR] = 11.2, 95% CI = [2.6, 48.9]). In addition, the pre-specified safety analysis revealed that the use of *attexis* was associated with a significant reduction in the proportion of participants reporting a worsening of ADHD symptom severity after 3 months (IG: 10.7%, CG: 24%; $\chi^2 = 9.43$, $p = 0.002$; OR = 2.6, 95% CI = [1.4, 5.0]).

1.6.2 Secondary endpoints

All secondary endpoints were tested following a prespecified gatekeeping strategy. After 3 months, the ITT analysis showed significant improvements in the intervention group

compared to the control group for the secondary endpoint work-related and social-functioning (estimated baseline-adjusted group difference on the WSAS total score = -3.7 points, 95% CI = [-5.0, -2.3], $p < 0.001$; $d = 0.61$).
Similarly, there were significant reductions in depression (estimated baseline-adjusted group difference on the PHQ-9 total score = -1.1 points, 95% CI = [-1.8, -0.4], $p = 0.003$; $d = 0.32$) and significant improvements in self-esteem (estimated baseline-adjusted group difference on the Rosenberg Self-Esteem Scale [RSES] = 1.7 points, 95% CI = [0.9, 2.5], $p < 0.001$; $d = 0.48$) and health-related quality of life (estimated baseline-adjusted group difference on the Assessment of Quality of Life - 8 Dimensions [AQoL-8D] = 2.6 points, 95% CI = [1.3, 4.0], $p < 0.001$; $d = 0.44$). The PP analyses yielded highly comparable results.

Similarly, a significantly higher proportion of patients showed clinically relevant improvements in social and work-related functioning in the intervention (26.2%) compared to the control group (11.6%) after 3 months ($\chi^2 = 11.9$, $p < 0.001$; Odds Ratio [OR] = 2.7, 95% CI = [1.5, 4.9]). We also observed clinically relevant improvements in the intervention compared to the control group regarding depression (IG: 31.1%, CG: 19.7%; $\chi^2 = 5.85$, $p = 0.016$; Odds Ratio [OR] = 1.8, 95% CI = [1.1, 3.0]), self-esteem (IG: 20.1%, CG: 9.8%; $\chi^2 = 7.06$, $p = 0.008$; Odds Ratio [OR] = 2.3, 95% CI = [1.2, 4.3]) and health-related quality of life (IG: 21.3%, CG: 9.8%; $\chi^2 = 8.55$, $p = 0.003$; Odds Ratio [OR] = 2.5, 95% CI = [1.3, 4.6]) after 3 months.

After 6 months, the ITT analyses showed significant reductions in ADHD symptoms in the intervention group compared to the control group (estimated baseline-adjusted group difference on the ASRS total score = -4.5 points, 95% CI = [-6.2, -2.9], $p < 0.001$; $d = 0.61$). Similarly, there were significant improvements in the secondary endpoint work-related and social-functioning (estimated baseline-adjusted group difference on the WSAS total score = -3.1 points, 95% CI = [-4.6, -1.6], $p < 0.001$; $d = 0.47$), significant reductions in depression (estimated baseline-adjusted group difference on the PHQ-9 total score = -1.4 points, 95% CI = [-2.3, -0.5], $p < 0.001$, $d = 0.36$) and significant improvements in self-esteem (estimated baseline-adjusted group difference on the RSES = 1.9 points, 95% CI = [0.9, 2.9], $p < 0.001$; $d = 0.43$) and health-related quality of life (estimated baseline-adjusted group difference on the AQoL-8D = 3.6 points, 95% CI = [2.0, 5.3], $p < 0.001$; $d = 0.47$). The PP and J2R analyses yielded comparable results.

1.7 Conclusion

Results of this clinical investigation show that *attexis* in addition to TAU leads to significant and clinically relevant reductions in ADHD symptoms compared to TAU alone after 3 months in patients with ADHD. Moreover, *attexis* shows significant and clinically relevant intervention effects on social and work-related functioning, depression, self-esteem, as well as health-related quality of life after 3 months. At the 6-month follow-up, the intervention's significant positive effects were maintained, and some outcomes even showed further improvement, with all findings validated through conservative J2R sensitivity analyses. No adverse events linked to the use of *attexis* were observed. No adverse device effects were observed.

1.8 Date of the clinical investigation initiation

- First Patient First Visit: 2024-03-11

1.9 Completion date of the clinical investigation

- Last Patient Last Visit: 2024-12-25

2. Introduction

ADHD is a neurological disorder affecting 2.58% to 6.76% of adults worldwide [1]. Most prominent symptoms of ADHD comprise attention deficit, hyperactivity and impulsive behavior. Persons with ADHD struggle massively with daily life and work productivity [2], suffer from higher risk for accidents and injuries over the life-span [3], diminished quality of life until old age [4], public stigma [5] and pose additional financial costs in health care [6].

Depression and anxiety disorders have been identified as widespread comorbidities [7], which pose further risk for diminished quality of life. Moreover, substance use disorders are quite common among persons with ADHD [8], possibly due to self-medication.

The gold standard of adult ADHD treatment comprises either psychosocial intervention, medication, or a combination of both according to the German S3 Clinical Guideline [9]. For pharmacological treatment, amphetamines can be identified as the first line intervention [10]. For non-pharmacological treatment, cognitive-behavioral therapy (CBT) should be chosen according to the German S3 Clinical Guideline [9], as it has been shown to be effective in treating ADHD [11]. Additionally, mindfulness-based strategies [12], [13] as well as physical exercise [14], especially exercise duration rather than intensity [15], have been demonstrated to be effective.

The availability of cognitive behavioral therapy is limited and waiting times exceed several months [16]. To combat this shortage and offer low-threshold help for patients, digital health applications have been developed successfully for other psychiatric conditions, e.g. depression [17] and anxiety [18]. To date, there are promising effects of digital interventions for ADHD in youth [19], [20] and preliminary evidence of their effectiveness in adults with ADHD [21], [22], [23], [24]. Nonetheless, the field of research is still underexamined and more studies, with better power, are needed [25].

The intervention at hand was developed on the basis of patient materials integrating cognitive behavioral methods and mindfulness-based interventions for adults with ADHD [26], which has been shown to be effective in the treatment of ADHD in adults [27].

The aim of the present pragmatic RCT was to investigate the effectiveness of the online intervention *attexis* to decrease ADHD symptoms in a broad sample of people with ADHD.

3. Investigational device and methods

attexis is an interactive online program for independent use by patients with ADHD. It focuses on a treatment manual for adults with ADHD, integrating cognitive behavioral methods and mindfulness-based interventions, providing respective psychoeducation and psychotherapeutic exercises, methods and techniques (see table 1). Content is presented tailored to the user's reported needs and interests.

attexis has one main function and several supporting secondary functions. The main function consists of a "simulated dialogue". This means that *attexis* presents the user brief text passages, and users then select a response option that interests them most or best suits their individual situation. *attexis* then responds emphatically to this response and conveys the next piece of information, to which the user can then respond in turn, and so on. In this way, a communication dynamic evolves. Patients are also motivated to complete simple homework tasks. Users can pause *attexis* at any time and continue from the point where they left off. Users are reminded regularly to take breaks.

In addition to the dialogues, which are at the core of the program, *attexis* offers a range of features including media such as audio recordings to guide therapeutic exercises or explain specific content in more detail and PDF-materials (worksheets and summary sheets), tailored motivational short text messages delivered as SMS (optional) or via email, as well as self-monitoring questionnaires to track target behaviors.

The content of *attexis* is presented in table 1.

Table 1 | Therapeutic areas of *attexis.*

Psychoeducation. Psychoeducation covers information on adult ADHD, treatment options, and a modern review of ADHD in the current debate concerning neurodiversity. Further topics are attention, impulsivity and physical exercise, and social competence, among others.
Exploration and self-reflection. Assessment of the symptomatic expression of ADHD, anamnestic exploration of problematic fields, exploration of attention deficits in daily life, reflection of (negative) self-image, identification of aspects hindering and sustaining attention, identification of key memories in childhood, guided reflection of impulsive behavior by using practical examples, identifying personal experience and psychological resources as individual resources.
Therapeutic interventions and techniques. Introduction of several techniques to sustain attention, schematherapeutic intervention to alter the impact of negative memories, intervention to strengthen cognitive reflection in typical situations, mental contrasting for implementing more physical exercise in daily life, updating the concept of "problem" as a challenge that can be overcome, introduction of active problem-solving strategies to overcome one obstacle (SMART goals) and multiple obstacles (Eisenhower matrix), cognitive restructuring to validate unconventional ways to attain a goal, intervention to not forget personal belongings.

3.2 Intended purpose

attexis is intended to provide therapeutic methods and exercises based on evidence-based psychological and psychotherapeutic therapies for patients with ADHD, to help them manage their ADHD symptoms.

attexis is intended as a self-application for patients 18 years of age or older.

attexis is neither intended to replace treatment provided by a health care provider nor to provide information which is used to make decisions with diagnosis or therapeutic purposes.

4. Clinical investigation plan

4.1 Clinical investigation objectives

The primary objective of this study was to evaluate the effectiveness of the self-guided digital health application *attexis* in reducing ADHD symptoms in patients with ADHD in addition to usual care. Moreover, the effects of *attexis* were examined in terms of improvements in social and work-related functioning, depression, self-esteem and health-related quality of life.

4.2 Clinical investigation design

- prospective
- randomized (simple randomization)
- controlled (two arms)
- online

4.3 Clinical investigation endpoints

4.3.1 Primary endpoint

- Severity of ADHD symptoms (assessed with the ASRS v1.1 total score [28]; validated German version in adults with ADHD [29])

4.3.2 Secondary endpoints

- Social and work-related functioning (assessed with the WSAS total score [30]; validated German version [31]; validated in adults with ADHD [32])
- Depression (assessed with the PHQ-9 total score [33], [34]); validated German version [35], [36]; used in German adults with ADHD [37])
- Self-esteem (assessed with the RSES total score [38]; validated German version [39], [40]; used in German adults with ADHD [41])
- Health-related quality of life (assessed with the AQoL-8D total score [42]; validated German version [43])

4.4 Control group

Participants in the control group received usual medical care in consultation with their respective treating team. Following the pragmatic study design, usual medical care was supposed to reflect the reality of care, and may therefore have comprised forms of outpatient care, including treatment by a primary care physician or specialist, psychotherapy (such as CBT), and no treatment at all [44], [45].

4.5 Ethical considerations

This study and its amendment was reviewed and approved by the ethics committee of the Medical Chamber Hamburg (reference number 2023-101052-BO-ff).

4.6 Data quality assurance

Data were collected online using a secure, internationally recognized survey software (LimeSurvey). The survey software was programmed such that valid possible responses and response ranges were predefined for every question. Quality of the data and procedures were checked every week (e.g., participants were contacted in time to complete the questionnaires). Regular record-checking took place using a codebook with appropriate metadata. In addition, a daily backup of the data was performed. These were stored in anonymized form after the study was completed. The data will be retained for 10 years.

4.7 Subject population for the clinical investigation

Inclusion criteria:

- women, men, non-binary
- age 18-65 years
- diagnosis of ADHD (assessed via DIVA-5 [46])[1]
- ADHD severity score (cut-off): score of ≥17 either on the inattention subscale *or* on the impulsivity/hyperactivity subscale of the ASRS v1.1, as used in previous studies on digital interventions for ADHD [21], [22]
- stable treatment (psychotherapy, medication, no treatment, …) for at least 30 days at the time of inclusion
- consent to participation
- sufficient knowledge of the German language

Exclusion criteria:

- diagnosis of another severe psychiatric disorder (severe affective disorder, autism spectrum disorder, psychotic disorder, Borderline personality disorder, antisocial personality disorder, substance use disorder, suicidality)
- plans to change treatment (psychotherapy, medication, …) in the upcoming three months after inclusion

4.8 Treatment allocation schedule

Simple randomization (no blocked randomization, no stratification) akin to a digital coin toss was performed automatically and concealed from study staff.

[1] The confirmation of the diagnosis was established through a semi-structured diagnostic interview (DIVA-5; Diagnostic Interview for ADHD in Adults), administered by trained psychological staff. This interview was conducted with individuals who had obtained a score ≥ 17 on one or both of the ASRS v1.1 subscales, suggesting a high likelihood for the presence of ADHD. Unclear cases were discussed in regular supervision meetings with PD Dr. Gitta Jacob. Inclusion was finalized following a thorough review of all data by the study physician.

4.9 Concomitant medications/treatment

All participants received usual medical care in consultation with their respective treating physician. Following the pragmatic study design, usual medical care should reflect the reality of care, and may therefore include forms of outpatient care, including treatment by a primary care physician or specialist, psychotherapy (such as CBT), and no treatment at all [44], [45].

4.10 Duration of follow-up

The total duration of follow-up was 6 months.

4.11 Statistical design

Analysis of intervention effects at the 3-month time point was performed by calculating an ANCOVA: the respective outcome at 3 months served as the dependent variable, the treatment condition (intervention vs. control group) as the independent variable, and the baseline values of the respective outcome as the covariate. Treatment effects (independent variable: treatment condition), i.e., baseline-adjusted mean group differences between the intervention and control group in the respective outcome variable at 3 months, are reported on the original scale, along with the corresponding 95%-CI. The corresponding *p*-value of the treatment effect from the ANCOVA was used to determine statistical significance of the results. Standardized effect sizes (Cohen's *d* [47], [48]) were calculated based on the difference in estimated marginal means (i.e., baseline-adjusted means) between the intervention and control groups at the 3-month time point, derived from the ANCOVA model, using the *R* package *emmeans* [49].

The primary analysis was performed as an ITT analysis with multiple imputation under 'missing at random' (MAR) assumption [50], [51]. The ITT analysis provides an estimation of the treatment effect for all subjects randomized [50]. In the ITT analysis, missing data points at the 3-month survey time point were imputed using the respective variable values at baseline as well as group membership and other sociodemographic and clinical variables planned for subgroup analyses and/or associated with dropout (age, sex, psychotherapy at baseline, treated by ADHD expert at baseline, intake of any psychotropic medication at baseline, ethnicity white, ethnicity middle eastern). The ITT analysis was implemented following a computationally efficient implementation for bootstrapped maximum likelihood multiple imputation by von Hippel and Bartlett (2021) [52] using the *R* packages *bootImpute* [52] and *mice* [53]. The relevant outcome variable was imputed using the *mice* package with default settings (i.e., using the predictive mean matching method with a pool of 5 candidate values drawn at random), as recommended.

These procedures were analogously employed in the per-protocol (PP) analysis, which encompassed all participants from the control group and those from the intervention group who had activated their voucher to use *attexis*.

As part of a conservative sensitivity analysis, these results were compared to a J2R imputation. Under reference-based imputation, patients who drop out of the intervention

group are assumed to no longer participate in the intervention and their outcomes from that point on are assumed to be the same as those of the control group [54], [55]. J2R sensitivity analysis was implemented with a computationally efficient implementation for bootstrapped maximum likelihood multiple imputation by von Hippel and Bartlett (2021) [56] using the *bootImpute* package in *R*.

For ITT, J2R and PP analysis, ANCOVA was performed on each imputed data set as described above and parameters of interest were aggregated by pooling [52], [57]. Standardized effect sizes were calculated analogously within the ITT, J2R and PP analyses for each imputed data set and then pooled as well [52], [57].

Analogously, all analyses (ITT, J2R and PP) were performed for the 6-month time point to assess the durability of effects.

Operationally, all results were considered statistically significant at the two-sided 5% level. This is equivalent to using a one-sided *p*-value (nominal $\alpha = 0.025$) and a one-sided 2.5% overall significance level [58]. No adjustments for multiplicity were needed, as a gatekeeping testing strategy was applied, meaning that significance on preceding endpoints was required before sequentially testing subsequent endpoints [59]. The ranks of secondary endpoints (listed in section 4.3.2) were pre-specified a priori for this approach.

Moreover, responder analyses were conducted using prespecified MCIDs or the reliable change index (RCI) in case that no MCID was reported in the literature. The RCI was calculated as the ratio of the difference between pre- and post-scores of an individual participant (numerator) and the standard error of measurement of the difference (denominator). RCI scores larger than 1.96 indicate that it is unlikely that the posttest score is not reflecting real change ($p < .05$), thus indicating that the participant is a responder [60]. If a specific MCID was specified for an endpoint, responder analyses were instead based on that value. Responders were defined as participants reaching this difference from T0 to T1. The proportion of responders between groups was compared using χ^2 tests. Moreover, the odds ratio was reported.

All analyses were performed with *R*, version 4.4.1 [61].

4.12 Amendments to the CIP

The CIP was amended on 2024-05-03, incorporating the following changes:

- Addition of additional clinical variables to assess treatment satisfaction at T1 and T2.
- Inclusion of a subgroup analysis examining the effectiveness of *attexis* in individuals with changes in concomitant treatment versus individuals without changes in concomitant treatment.

The amendment was acknowledged by the ethics committee of the Medical Chamber Hamburg on 2024-05-21. The ethics committee raised no objections to the continuation of the study.

5. Results

5.1 Clinical investigation initiation date

- First Patient First Visit: 2024-03-11

5.2 Clinical investigation completion/suspension date

- Last Patient Last Visit: 2024-12-25

5.3 Disposition of subjects

Recruitment of patients was through an online campaign. 2,058 people were screened for participation. Of these, 337 met all specified inclusion criteria and were randomized to the intervention (n = 164) und control group (n = 173). The investigational device *attexis* was provided free of charge by its developer and manufacturer, GAIA. The intervention group received access immediately after randomization, while the control group was offered access to *attexis* after 6 months. *attexis* is an Internet-based application that does not require any installation. However, Internet access and an up-to-date Internet browser are required to use *attexis*.

5.4 Accountability of subjects

Figure 1 summarizes the flow of participants through the study. In the ITT analysis, missing data points at the 3-month survey time point were imputed using the respective variable values at baseline as well as group membership and other sociodemographic and clinical variables planned for subgroup analyses and/or associated with dropout (age, sex, psychotherapy at baseline, treated by ADHD expert at baseline, intake of any psychotropic medication at baseline, ethnicity white, ethnicity middle eastern). The ITT analysis was implemented following a computationally efficient implementation for bootstrapped maximum likelihood multiple imputation by von Hippel and Bartlett (2021) [52] using the *R* packages *bootImpute* [52] and *mice* [53]. The relevant outcome variable was imputed using the *mice* package with default settings (i.e., using the predictive mean matching method with a pool of 5 candidate values drawn at random), as recommended.

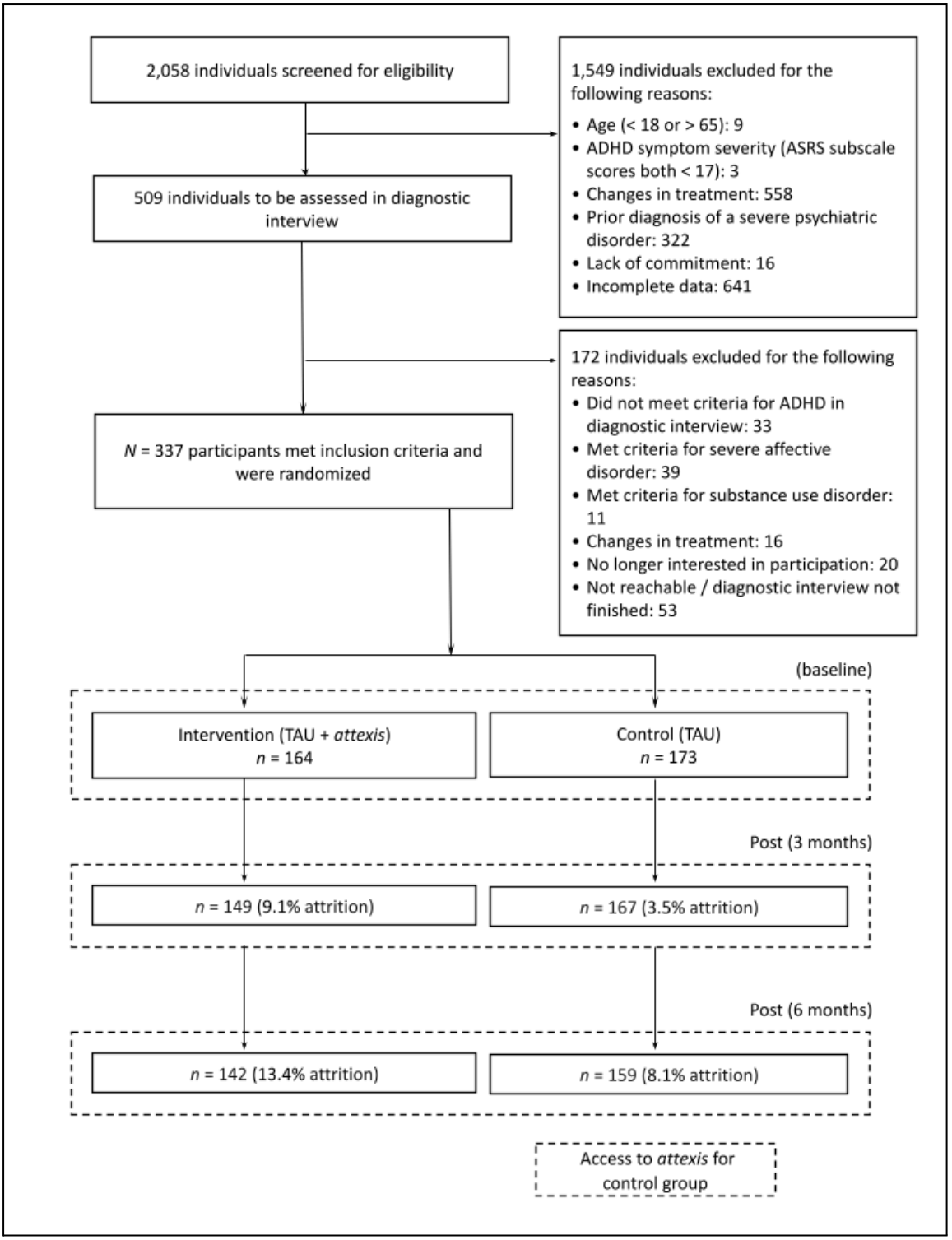

Figure 1 | Flow of participants through the study.

5.4.1 Subjects who did not pass the screening test

A total of 2,058 people were initially screened for eligibility. Of these, 1,549 had to be excluded in the online questionnaire for the following reasons:

- Age (< 18 or > 65): 9

- ADHD symptom severity (ASRS subscale scores both < 17): 3
- Changes in treatment: 558
- Positive screening for another severe psychiatric disorder (severe affective disorder, autism spectrum disorder, psychotic disorder, Borderline personality disorder, antisocial personality disorder, substance use disorder, suicidality): 322
- Lack of commitment: 17
- Incomplete data: 641

Thus, 509 persons were to be assessed for eligibility in a diagnostic interview conducted via telephone. Of these, 172 were excluded for the following reasons:

- Did not meet diagnostic criteria for ADHD in diagnostic interview: 33
- Met criteria for severe affective disorder in diagnostic interview: 39
- Met criteria for substance use disorder in diagnostic interview: 11
- Changes in treatment: 16
- No longer interested in participation: 20
- Not reachable / diagnostic interview not finished: 53

5.4.2 Subjects lost to follow-up

Table 2 | Number of patients lost to follow-up by T1 and study group.

Control	***attexis***
5	14

Table 3 | Number of patients lost to follow-up by T2 and study group.

Control	***attexis***
13	21

5.4.3 Subjects withdrawn from the clinical investigation

Table 4| Number of patients withdrawn from the clinical investigation by T1.

Control	***attexis***
1	1

Table 5 | Number of patients withdrawn from the clinical investigation by T2.

Control	***attexis***
1	1

5.4.4 Comparison of dropouts and completers

Table 6 | Comparison of baseline characteristics of dropouts and completers (up to T1).

	Control			*attexis*			Whole sample		
	Dropouts	**Completers**	**Statistical comparison**	**Dropouts**	**Completers**	**Statistical comparison**	**Dropouts**	**Completers**	**Statistical comparison**
	n = 6	n = 167		n = 15	n = 149		n = 21	n = 316	
Age	29.68 (4.62)	37.75 (9.91)	t = -3.96, p = 0.006	34.64 (10.04)	38.14 (9.21)	t = -1.30, p = 0.213	33.22 (9.01)	37.93 (9.57)	t = -2.31, p = 0.030
Sex (n [%])			X^2 = 0, p = 1			X^2 = 1.62, p = 0.203			X^2 = 0.88, p = 0.348
female	4 (66.7)	114 (68.3)		9 (60.0)	112 (75.2)		13 (61.9)	226 (71.5)	
male	2 (33.3)	53 (31.7)		6 (40.0)	37 (24.8)		8 (38.1)	90 (28.5)	
intersexual	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Family situation (n [%])			X^2 = 0.41, p = 0.815			X^2 = 1.77, p = 0.413			X^2 = 0.80, p = 0.670
never married	3 (50.0)	90 (53.9)		10 (66.7)	74 (49.7)		13 (61.9)	164 (51.9)	
married / registered civil partnership	3 (50.0)	69 (41.3)		4 (26.7)	66 (44.3)		7 (33.3)	135 (42.7)	
divorced / registered partnership annulled	0 (0.0)	8 (4.8)		1 (6.7)	9 (6.0)		1 (4.8)	17 (5.4)	
widowed / registered partner deceased	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Education (n [%])			X^2 = 3.11, p = 0.683			X^2 = 13.23, p = 0.021			X^2 = 4.06, p = 0.541

	Control			*attexis*			Whole sample		
	Dropouts	**Completers**	**Statistical comparison**	**Dropouts**	**Completers**	**Statistical comparison**	**Dropouts**	**Completers**	**Statistical comparison**
Hauptschulabschluss	0 (0.0)	3 (1.8)		1 (6.7)	0 (0.0)		1 (4.8)	3 (0.9)	
Realschulabschluss	0 (0.0)	12 (7.2)		2 (13.3)	7 (4.7)		2 (9.5)	19 (6.0)	
Fachhochschulreife	1 (16.7)	19 (11.4)		1 (6.7)	11 (7.4)		2 (9.5)	30 (9.5)	
Abitur (A-levels)	2 (33.3)	20 (12.0)		1 (6.7)	12 (8.1)		3 (14.3)	32 (10.1)	
completed vocational training	1 (16.7)	28 (16.8)		1 (6.7)	31 (20.8)		2 (9.5)	59 (18.7)	
completed university studies	2 (33.3)	85 (50.9)		9 (60.0)	88 (59.1)		11 (52.4)	173 (54.7)	
Employment (n [%])			$X^2 = 11.58$, p = 0.115			$X^2 = 9.59$, p = 0.213			$X^2 = 12.18$, p = 0.095
not employed	1 (16.7)	26 (15.6)		3 (20.0)	12 (8.1)		4 (19.0)	38 (12.0)	
employed irregularly	1 (16.7)	2 (1.2)		0 (0.0)	3 (2.0)		1 (4.8)	5 (1.6)	
marginal employment	0 (0.0)	5 (3.0)		1 (6.7)	6 (4.0)		1 (4.8)	11 (3.5)	
employed part-time	0 (0.0)	53 (31.7)		1 (6.7)	57 (38.3)		1 (4.8)	110 (34.8)	
employed full-time	4 (66.7)	67 (40.1)		10 (66.7)	61 (40.9)		14 (66.7)	128 (40.5)	
in vocational training	0 (0.0)	5 (3.0)		0 (0.0)	1 (0.7)		0 (0.0)	6 (1.9)	
on parental leave	0 (0.0)	6 (3.6)		0 (0.0)	6 (4.0)		0 (0.0)	12 (3.8)	
in re-training	0 (0.0)	3 (1.8)		0 (0.0)	3 (2.0)		0 (0.0)	6 (1.9)	
Ethnicity (multiple answers possible; n [%])									
White	4 (66.7)	158 (94.6)	$X^2 = 3.63$, p =	12 (80.0)	139 (93.3)	$X^2 = 1.73$, p =	16 (76.2)	297 (94.0)	$X^2 = 6.93$, p =

	Control			*attexis*			Whole sample		
	Dropouts	**Completers**	**Statistical comparison**	**Dropouts**	**Completers**	**Statistical comparison**	**Dropouts**	**Completers**	**Statistical comparison**
			0.057			0.189			0.008
Black	0 (0.0)	1 (0.6)	$X^2 = 0$, p = 1	0 (0.0)	3 (2.0)	$X^2 = 0$, p = 1	0 (0.0)	4 (1.3)	$X^2 = 0$, p = 1
Middle Eastern	2 (33.3)	5 (3.0)	$X^2 = 7.03$, p = 0.008	2 (13.3)	6 (4.0)	$X^2 = 0.93$, p = 0.334	4 (19.0)	11 (3.5)	$X^2 = 7.86$, p = 0.005
South East Asian	0 (0.0)	2 (1.2)	$X^2 = 0$, p = 1	0 (0.0)	1 (0.7)	$X^2 = 0$, p = 1	0 (0.0)	3 (0.9)	$X^2 = 0$, p = 1
Latin American	0 (0.0)	3 (1.8)	$X^2 = 0$, p = 1	1 (6.7)	3 (2.0)	$X^2 = 0.06$, p = 0.814	1 (4.8)	6 (1.9)	$X^2 = 0.01$, p = 0.920
Unknown	0 (0.0)	1 (0.6)	$X^2 = 0$, p = 1	0 (0.0)	0 (0.0)	n/a	0 (0.0)	1 (0.3)	$X^2 = 0$, p = 1
Prefer not to say	0 (0.0)	2 (1.2)	$X^2 = 0$, p = 1	0 (0.0)	1 (0.7)	$X^2 = 0$, p = 1	0 (0.0)	3 (0.9)	$X^2 = 0$, p = 1
Sick days (last 3 months; n [%])			$X^2 = 0.82$, p = 0.846			$X^2 = 0.91$, p = 0.823			$X^2 = 0.82$, p = 0.845
0 days	3 (50.0)	78 (46.7)		8 (53.3)	71 (47.7)		11 (52.4)	149 (47.2)	
1-5 days	2 (33.3)	41 (24.6)		3 (20.0)	42 (28.2)		5 (23.8)	83 (26.3)	
6-10 days	0 (0.0)	17 (10.2)		1 (6.7)	15 (10.1)		1 (4.8)	32 (10.1)	
10+ days	1 (16.7)	31 (18.6)		3 (20.0)	21 (14.1)		4 (19.0)	52 (16.5)	
Sick pay days (last 3 months; n [%])			$X^2 = 0.59$, p = 0.899			$X^2 = 1.30$, p = 0.728			$X^2 = 1.95$, p = 0.583
0 days	6 (100.0)	152 (91.0)		15 (100.0)	137 (91.9)		21 (100.0)	289 (91.5)	
1-5 days	0 (0.0)	6 (3.6)		0 (0.0)	5 (3.4)		0 (0.0)	11 (3.5)	
6-10 days	0 (0.0)	1 (0.6)		0 (0.0)	2 (1.3)		0 (0.0)	3 (0.9)	
10+ days	0 (0.0)	8 (4.8)		0 (0.0)	5 (3.4)		0 (0.0)	13 (4.1)	

	Control			*attexis*			Whole sample		
	Dropouts	**Completers**	**Statistical comparison**	**Dropouts**	**Completers**	**Statistical comparison**	**Dropouts**	**Completers**	**Statistical comparison**
Prior ADHD diagnosis (n [%])	4 (66.7)	70 (41.9)	$X^2 = 0.61$, p = 0.433	9 (60.0)	67 (45.0)	$X^2 = 1.24$, p = 0.266	13 (61.9)	137 (43.4)	$X^2 = 2.74$, p = 0.098
Age at diagnosis (in individuals with prior ADHD diagnosis; in years)	28.00 (3.37)	33.14 (13.97)	t = -2.17, p = 0.052	28.56 (16.83)	34.18 (10.98)	t = -0.97, p = 0.355	28.38 (13.85)	33.65 (12.56)	t = -1.32, p = 0.208
Psychiatric diagnoses (Mini-DIPS) (multiple answers possible; n [%])									
Anxiety disorders									
Panic disorder	0 (0.0)	3 (1.8)	$X^2 = 0$, p = 1	0 (0.0)	4 (2.7)	$X^2 = 0$, p = 1	0 (0.0)	7 (2.2)	$X^2 = 0$, p = 1
Agoraphobia	0 (0.0)	4 (2.4)	$X^2 = 0$, p = 1	0 (0.0)	7 (4.7)	$X^2 = 0.04$, p = 0.851	0 (0.0)	11 (3.5)	$X^2 = 0.06$, p = 0.814
Specific phobia	1 (16.7)	15 (9.0)	$X^2 = 0$, p = 1	4 (26.7)	18 (12.1)	$X^2 = 1.40$, p = 0.237	5 (23.8)	33 (10.4)	$X^2 = 2.31$, p = 0.129
Social anxiety disorder	1 (16.7)	20 (12.0)	$X^2 = 0$, p = 1	2 (13.3)	16 (10.7)	$X^2 = 0$, p = 1	3 (14.3)	36 (11.4)	$X^2 = 0.00$, p = 0.961
Generalized anxiety disorder	0 (0.0)	6 (3.6)	$X^2 = 0$, p = 1	0 (0.0)	8 (5.4)	$X^2 = 0.08$, p = 0.771	0 (0.0)	14 (4.4)	$X^2 = 0.18$, p = 0.674
Mood disorders									
Bipolar disorder	0 (0.0)	0 (0.0)	n/a	0 (0.0)	1 (0.7)	$X^2 = 0$, p = 1	0 (0.0)	1 (0.3)	$X^2 = 0$, p = 1
Major depressive disorder	3 (50.0)	40 (24.0)	$X^2 = 0.94$, p = 0.332	1 (6.7)	46 (30.9)	$X^2 = 2.81$, p = 0.094	4 (19.0)	86 (27.2)	$X^2 = 0.32$, p = 0.572
Persistent depressive disorder	0 (0.0)	3 (1.8)	$X^2 = 0$, p = 1	0 (0.0)	1 (0.7)	$X^2 = 0$, p = 1	0 (0.0)	4 (1.3)	$X^2 = 0$, p = 1

	Control			*attexis*			Whole sample		
	Dropouts	**Completers**	**Statistical comparison**	**Dropouts**	**Completers**	**Statistical comparison**	**Dropouts**	**Completers**	**Statistical comparison**
Sleep-wake disorders									
Hypersomnia	2 (33.3)	3 (1.8)	$X^2 = 10.83$, p = 0.001	0 (0.0)	3 (2.0)	$X^2 = 0$, p = 1	2 (9.5)	6 (1.9)	$X^2 = 2.20$, p = 0.138
Insomnia	0 (0.0)	15 (9.0)	$X^2 = 0$, p = 0.976	0 (0.0)	9 (6.0)	$X^2 = 0.15$, p = 0.701	0 (0.0)	24 (7.6)	$X^2 = 0.76$, p = 0.383
Currently in psychotherapy (n [%])	3 (50.0)	40 (24.0)	$X^2 = 0.94$, p = 0.332	4 (26.7)	32 (21.5)	$X^2 = 0.02$, p = 0.892	7 (33.3)	72 (22.8)	$X^2 = 1.22$, p = 0.269
Number of psychotherapy sessions	2.00 (2.76)	1.46 (3.12)	t = 0.47, p = 0.654	1.07 (2.09)	1.42 (3.21)	t = -0.59, p = 0.559	1.33 (2.27)	1.44 (3.16)	t = -0.20, p = 0.841
Currently treated by ADHD specialist	1 (16.7)	4 (2.4)	$X^2 = 0.66$, p = 0.418	2 (13.3)	5 (3.4)	$X^2 = 1.33$, p = 0.249	3 (14.3)	9 (2.8)	$X^2 = 4.54$, p = 0.033
Ever in psychotherapy (n [%])	2 (33.3)	93 (55.7)	$X^2 = 0.44$, p = 0.507	8 (53.3)	95 (63.8)	$X^2 = 0.63$, p = 0.426	10 (47.6)	188 (59.5)	$X^2 = 1.15$, p = 0.284
Self-medicating (n[%])	0 (0.0)	13 (7.8)	$X^2 = 0$, p = 1	1 (6.7)	12 (8.1)	$X^2 = 0$, p = 1	1 (4.8)	25 (7.9)	$X^2 = 0.01$, p = 0.919
Currently taking any psychotropic medication[a] (n [%])	4 (66.7)	55 (32.9)	$X^2 = 1.62$, p = 0.203	8 (53.3)	55 (36.9)	$X^2 = 1.55$, p = 0.213	12 (57.1)	110 (34.8)	$X^2 = 4.25$, p = 0.039
Regular medication (multiple answers possible; n [%])									
Antipsychotics	0 (0.0)	1 (0.6)	$X^2 = 0$, p = 1	0 (0.0)	0 (0.0)	$X^2 = 0$, p = 1	0 (0.0)	1 (0.3)	$X^2 = 0$, p = 1
Anxiolytics	0 (0.0)	0 (0.0)	n/a	0 (0.0)	0 (0.0)	n/a	0 (0.0)	0 (0.0)	n/a

	Control			*attexis*			Whole sample		
	Dropouts	**Completers**	**Statistical comparison**	**Dropouts**	**Completers**	**Statistical comparison**	**Dropouts**	**Completers**	**Statistical comparison**
Hypnotics and sedatives	0 (0.0)	3 (1.8)	$X^2 = 0$, p = 1	0 (0.0)	0 (0.0)	n/a	0 (0.0)	3 (0.9)	$X^2 = 0$, p = 1
Antidepressants	1 (16.7)	14 (8.4)	$X^2 = 0$, p = 1	3 (20.0)	17 (11.4)	$X^2 = 0.31$, p = 0.579	4 (19.0)	31 (9.8)	$X^2 = 0.95$, p = 0.330
Psychostimulants	1 (16.7)	40 (24.0)	$X^2 = 0$, p = 1	7 (46.7)	45 (30.2)	$X^2 = 1.71$, p = 0.191	8 (38.1)	85 (26.9)	$X^2 = 1.24$, p = 0.266
Medication as needed (multiple answers possible; n [%])									
Antipsychotics	0 (0.0)	0 (0.0)	n/a	0 (0.0)	0 (0.0)	n/a	0 (0.0)	0 (0.0)	n/a
Anxiolytics	0 (0.0)	0 (0.0)	n/a	0 (0.0)	0 (0.0)	n/a	0 (0.0)	0 (0.0)	n/a
Hypnotics and sedatives	0 (0.0)	4 (2.4)	$X^2 = 0$, p = 1	0 (0.0)	0 (0.0)	n/a	0 (0.0)	4 (1.3)	$X^2 = 0$, p = 1
Antidepressants	0 (0.0)	1 (0.6)	$X^2 = 0$, p = 1	0 (0.0)	2 (1.3)	$X^2 = 0$, p = 1	0 (0.0)	3 (0.9)	$X^2 = 0$, p = 1
Psychostimulants	2 (33.3)	12 (7.2)	$X^2 = 2.39$, p = 0.122	2 (13.3)	3 (2.0)	$X^2 = 2.70$, p = 0.100	4 (19.0)	15 (4.7)	$X^2 = 5.12$, p = 0.024
ASRS v1.1 total score	57.5 (7.7)	52.6 (7.0)	t = 1.55, p = 0.178	57.1 (6.8)	51.7 (7.4)	t = 2.91, p = 0.010	57.2 (6.9)	52.2 (7.2)	t = 3.27, p = 0.003
WSAS total score	27.7 (8.9)	22.7 (7.1)	t = 1.51, p = 0.188	27.3 (8.1)	22.9 (7.1)	t = 2.06, p = 0.056	27.4 (7.9)	22.8 (7.1)	t = 2.65, p = 0.015
PHQ-9 total score	13.8 (5.1)	11.7 (4.4)	t = 0.99, p = 0.365	14.0 (6.3)	11.5 (4.9)	t = 1.52, p = 0.147	14.0 (5.8)	11.6 (4.6)	t = 1.81, p = 0.085
RSES total score	16.0 (4.8)	17.3 (5.8)	t = -0.64, p = 0.547	16.9 (6.2)	17.1 (5.9)	t = -0.12, p = 0.905	16.7 (5.7)	17.2 (5.8)	t = -0.42, p = 0.675
AQoL-8D total score	58.8 (11.0)	63.6 (9.4)	t = -1.04, p = 0.344	61.6 (13.7)	63.3 (9.7)	t = -0.46, p = 0.649	60.8 (12.8)	63.4 (9.5)	t = -0.92, p = 0.370

[a] ATC classification codes N05 / N06.

Abbreviations: AQoL-8D = Assessment of Quality of Life - 8 Dimensions; ASRS v1.1 = Adult ADHD Self-Report Scale v1.1; PHQ-9: Patient Health Questionnaire-9; RSES = Rosenberg Self-Esteem Scale; WSAS = Work and Social Adjustment Scale.

Among participants of the intervention group, the average number of hours spent in *attexis* was significantly higher in completers (mean = 11.5, SD = 6.5) than in dropouts (mean = 5.3, SD = 4.4; $t = -4.89$, $p < 0.001$) up to T1.

5.4.5 Per Protocol Dataset

In adherence to the predetermined criteria for inclusion in the PP analyses, 163 out of 164 participants, 99.4%) in the intervention group had activated the voucher to use *attexis*. Consequently, the PP dataset comprised a total of 336 participants, with 163 from the intervention group and all 173 participants from the control group.

5.5 Subject demographics and clinical characteristics

Table 7 summarizes key characteristics of the study participants. The average age was around 38 years, with the majority being women (roughly 71%) and living in partnerships or marriages. Most participants had completed higher education, with over half holding a university degree. Employment was common, with 42% working full-time and 33% part-time. In terms of ethnicity, the vast majority of participants identified as White (93%), with smaller proportions identifying as Middle Eastern (4.5%), Latin American (2.1%), and Black (1.2%).

Comorbid psychiatric diagnoses were notable: The diagnostic interview (Mini-DIPS) revealed that 27% of participants fulfilled the diagnostic criteria for major depressive disorder, and 12% for social anxiety disorder. Approximately 24% were currently in psychotherapy, with an average of 1.43 sessions attended in the last 3 months. In terms of medication, 36% of participants were taking psychotropic medication, with psychostimulants being the most frequently used on a regular basis (28%).

Table 7 | Subject demographics and clinical characteristics at baseline. Values represent mean (SD) unless stated otherwise.

	Control	**attexis**	**Total**
	n = 173	n = 164	n = 337
Age	37.47 (9.88)	37.82 (9.31)	37.64 (9.59)
Age category (n [%])			
18-25 years	13 (7.5)	15 (9.1)	28 (8.3)
26-35 years	63 (36.4)	49 (29.9)	112 (33.2)
36-45 years	66 (38.2)	67 (40.9)	133 (39.5)
46-55 years	19 (11.0)	22 (13.4)	41 (12.2)
56-65 years	12 (6.9)	11 (6.7)	23 (6.8)
Sex (n [%])			
female	118 (68.2)	121 (73.8)	239 (70.9)
male	55 (32.0)	43 (26.2)	98 (29.1)
intersexual	0 (0)	0 (0)	0 (0)

	Control	attexis	Total
Family situation (n [%])			
never married	93 (53.8)	84 (51.2)	177 (52.5)
married / registered civil partnership	72 (41.6)	70 (42.7)	142 (42.1)
divorced / registered partnership annulled	8 (4.6)	10 (6.1)	18 (5.3)
widowed / registered partner deceased	0 (0)	0 (0)	0 (0)
Education (n [%])			
Hauptschulabschluss	3 (1.7)	1 (0.6)	4 (1.2)
Realschulabschluss	12 (6.9)	9 (5.5)	21 (6.2)
Fachhochschulreife	20 (11.6)	12 (7.3)	32 (9.5)
Abitur (A-levels)	22 (12.7)	13 (7.9)	35 (10.4)
completed vocational training	29 (16.8)	32 (19.5)	61 (18.1)
completed university studies	87 (50.3)	97 (59.1)	184 (54.6)
Employment (n [%])			
not employed	27 (15.6)	15 (9.1)	42 (12.5)
employed irregularly	3 (1.7)	3 (1.8)	6 (1.8)
marginal employment	5 (2.9)	7 (4.3)	12 (3.6)
employed part-time	53 (30.6)	58 (35.4)	111 (32.9)
employed full-time	71 (41.0)	71 (43.3)	142 (42.1)
in vocational training	5 (2.9)	1 (0.6)	6 (1.8)
on parental leave	6 (3.5)	6 (3.7)	12 (3.6)
in re-training	3 (1.7)	3 (1.8)	6 (1.8)
Ethnicity (multiple answers possible; n [%])			
White	162 (93.6)	151 (92.1)	313 (92.9)
Black	1 (0.6)	3 (1.8)	4 (1.2)
Middle Eastern	7 (4.0)	8 (4.9)	15 (4.5)
Latin American	3 (1.7)	4 (2.4)	7 (2.1)
East Asian	0	0	0
South Asian	0	0	0
Unknown	1 (0.6)	0 (0.0)	1 (0.3)
Prefer not to say	2 (1.2)	1 (0.6)	3 (0.9)

	Control	attexis	Total
Sick days (last 3 months; n [%])			
0 days	81 (46.8)	79 (48.2)	160 (47.5)
1-5 days	43 (24.9)	45 (27.4)	88 (26.1)
6-10 days	17 (9.8)	16 (9.8)	33 (9.8)
10+ days	32 (18.5)	24 (14.6)	56 (16.6)
Sick pay days (last 3 months; n [%])			
0 days	158 (91.3)	152 (92.7)	310 (92.0)
1-5 days	6 (3.5)	5 (3.0)	11 (3.3)
6-10 days	1 (0.6)	2 (1.2)	3 (0.9)
10+ days	8 (4.6)	5 (3.0)	13 (3.9)
Prior ADHD diagnosis (n [%])	74 (42.8)	76 (46.3)	150 (44.5)
Age at diagnosis (in individuals with prior ADHD diagnosis; in years)	32.86 (13.65)	33.51 (11.82)	37.64 (9.59)
Psychiatric diagnoses (Mini-DIPS) (multiple answers possible; n [%])			
Panic disorder	3 (1.7)	4 (2.4)	7 (2.1)
Agoraphobia	4 (2.3)	7 (4.3)	11 (3.3)
Specific phobia	16 (9.2)	22 (13.4)	38 (11.3)
Social anxiety disorder	21 (12.1)	18 (11.0)	39 (11.6)
Generalized anxiety disorder	6 (3.5)	8 (4.9)	14 (4.2)
Bipolar disorder	0 (0.0)	1 (0.6)	1 (0.3)
Major depressive disorder	43 (24.9)	47 (28.7)	90 (26.7)
Persistent depressive disorder	3 (1.7)	1 (0.6)	4 (1.2)
Hypersomnia	5 (2.9)	3 (1.8)	8 (2.4)
Insomnia	15 (8.7)	9 (5.5)	24 (7.1)
Currently in psychotherapy (n [%])	43 (24.9)	36 (22.0)	79 (23.4)
Number of psychotherapy sessions	1.47 (3.10)	1.39 (3.12)	1.43 (3.11)
Currently treated by ADHD specialist	5 (2.9)	7 (4.3)	12 (3.6)

	Control	attexis	Total
Ever in psychotherapy (n [%])	95 (54.9)	103 (62.8)	198 (58.8)
Self-medicating (n[%])	13 (7.5)	13 (7.9)	26 (7.7)
Currently taking any psychotropic medication [a] (n [%])	59 (34.1)	63 (38.4)	122 (36.2)
Regular medication (multiple answers possible; n [%])			
Antipsychotics	1 (0.6)	0 (0.0)	1 (0.3)
Anxiolytics	0 (0.0)	0 (0.0)	0 (0.0)
Hypnotics and sedatives	3 (1.7)	0 (0.0)	3 (0.9)
Antidepressants	15 (8.7)	20 (12.2)	35 (10.4)
Psychostimulants	41 (23.7)	52 (31.7)	93 (27.6)
Medication as needed (multiple answers possible; n [%])			
Antipsychotics	0 (0.0)	0 (0.0)	0 (0.0)
Anxiolytics	0 (0.0)	0 (0.0)	0 (0.0)
Hypnotics and sedatives	4 (2.3)	0 (0.0)	4 (1.2)
Antidepressants	1 (0.6)	2 (1.2)	3 (0.9)
Psychostimulants	14 (8.1)	5 (3.0)	19 (5.6)
ASRS v1.1 total score	52.7 (7.1)	52.2 (7.4)	52.5 (7.3)
WSAS total score	22.9 (7.1)	23.3 (7.3)	23.1 (7.2)
PHQ-9 total score	11.8 (4.4)	11.7 (5.0)	11.8 (4.7)
RSES total score	17.2 (5.7)	17.1 (5.9)	17.2 (5.8)
AQoL-8D total score	63.3 (9.5)	63.1 (10.1)	63.2 (9.8)

[a] ATC classification codes N05 / N06.

Table 8 | Relevant treatment characteristics over the course of the clinical investigation.

	Control	*attexis*	Statistical comparison
T1	n = 167	n = 149	
Currently in psychotherapy (n [%])	40 (24.0)	31 (20.8)	$\chi^2 = 0.45$, p = 0.503
Currently taking any psychotropic medication[a] (n [%])	55 (32.9)	53 (35.6)	$\chi^2 = 0.24$, p = 0.622

	Control	*attexis*	Statistical comparison
Regular medication (multiple answers possible; n [%])			
Antipsychotics	0 (0)	0 (0)	n/a
Anxiolytics	0 (0)	0 (0)	n/a
Hypnotics and sedatives	2 (1.2)	0 (0.0)	$\chi^2 = 0.40$, p = 0.529
Antidepressants	12 (7.2)	17 (11.4)	$\chi^2 = 1.69$, p = 0.194
Psychostimulants	44 (26.3)	43 (28.9)	$\chi^2 = 0.25$, p = 0.618
Anti-dementia drugs	1 (0.6)	0 (0)	$\chi^2 = 0$, p = 1
Medication as needed (multiple answers possible; n [%])			
Antipsychotics	0 (0)	0 (0)	n/a
Anxiolytics	0 (0)	0 (0)	n/a
Hypnotics and sedatives	5 (3.0)	1 (0.7)	$\chi^2 = 1.20$, p = 0.272
Antidepressants	2 (1.2)	1 (0.7)	$\chi^2 = 0$, p = 1
Psychostimulants	9 (5.4)	3 (2.0)	$\chi^2 = 1.62$, p = 0.203
Anti-dementia drugs	0 (0)	0 (0)	n/a

[a] ATC classification codes N05 / N06.

Table 9 | Changes in treatments (regular medication or psychotherapy) over the course of the clinical investigation until T1, including both uptake and discontinuation of treatment.

	Control	*attexis*
T1	n = 167	n = 149
Any treatment change since T0 (n [%])	31 (18.6)	22 (14.8)
Changes in any regular psychotropic medication since T0 (n [%])	18 (10.8)	14 (9.4)
Changes in regular psychotropic medication since T0 (multiple answers possible; n [%])		
Antipsychotics	1 (0.6)	0 (0.0)
Anxiolytics	0 (0)	0 (0)
Hypnotics and sedatives	1 (0.6)	0 (0.0)
Antidepressants	4 (2.4)	10 (6.7)
Psychostimulants	12 (7.2)	6 (4.0)
Anti-dementia drugs	1 (0.6)	0 (0)
Changes in psychotherapy since T0 (n [%])	16 (9.6)	11 (7.4)

[a] ATC classification codes N05 / N06.

5.6 CIP compliance

The CIP was complied with throughout the duration of the investigation.

5.7 Analysis

The means at T1 and T2 presented in tables 10-14 are unadjusted for baseline.

5.7.1 Primary endpoint

- ADHD symptom severity (assessed with the ASRS v1.1 total score)

Table 10 | Results of the primary endpoint ADHD symptom severity.

Time		Control			*attexis*			ANCOVA			
		n	mean	SD	n	mean	SD	Treatment effect (95% CI)[a]	*p*-value	Partial η^2	Cohen's *d* (95% CI)[b]
ITT	T0	173	52.7	7.1	164	52.2	7.4	-	-	-	-
	T1	173	50.0	7.6	164	44.6	8.4	-5.0 (-6.4, -3.6)	< .001	0.15	0.85 (0.62, 1.08)
	T2	173	48.5	8.5	164	43.7	8.7	-4.5 (-6.2, -2.9)	< .001	0.09	0.61 (0.39, 0.83)
J2R	T0	173	52.7	7.1	164	52.2	7.4	-	-	-	-
	T1	173	49.9	7.5	164	45.1	8.7	-4.4 (-5.7, -3.2)	< .001	0.13	0.75 (0.55, 0.95)
	T2	173	48.5	8.4	164	44.6	8.9	-3.6 (-5.1, -2.2)	< .001	0.06	0.49 (0.3, 0.69
PP	T0	173	52.7	7.1	163	52.3	7.4	-	-	-	-
	T1	173	49.9	7.6	163	44.6	8.4	-5.0 (-6.4, -3.6)	< .001	0.16	0.86 (0.63, 1.08)
	T2	173	48.5	8.5	163	43.6	8.7	-4.6 (-6.2, -2.9)	< .001	0.09	0.62 (0.39, 0.84)

[a] between-group difference on original scale 3 months after baseline, adjusted for baseline scores.
[b] based on baseline-adjusted means; positive values show effects in favor of the intervention group.

5.7.2 Secondary endpoints

- Responder Rate: ADHD symptom severity (assessed with the ASRS v1.1 total score)

Statistical comparison of the number of responders (defined as a reduction in ADHD symptoms, assessed with the ASRS v1.1 total score, of at least 30% from baseline to T1 [62]) in the ITT population showed that clinically relevant effects on ADHD symptoms were more frequent in the intervention group than in the control group: 19/164 patients (11.6%, Clopper-Pearson 95 % CI = [7.1%, 17.5%]) in the intervention group versus 2/173 (1.2%,

Clopper-Pearson 95 % CI = [0.1%, 4.1%]) patients in the control group were classified as responders, respectively (χ^2 = 15.67, p < 0.001; OR = 11.2, 95% CI = [2.6, 48.9]).

- Social and work-related functioning (assessed with the WSAS total score)

Table 11 | Results of the secondary endpoint social and work-related functioning.

Time		Control			*attexis*			ANCOVA			
		n	mean	SD	n	mean	SD	Treatment effect (95% CI)[a]	*p*-value	Partial η^2	Cohen's *d* (95% CI)[b]
ITT	T0	173	22.9	7.1	164	23.3	7.2	-	-	-	-
	T1	173	23.0	7.0	164	19.5	7.3	-3.7 (-5.0, -2.3)	< .001	0.09	0.61 (0.38, 0.84)
	T2	173	21.3	7.4	164	18.4	7.8	-3.1 (-4.6, -1.6)	< .001	0.05	0.47 (0.24, 0.7)
J2R	T0	173	22.8	7.1	164	23.3	7.3	-	-	-	-
	T1	173	22.9	7.1	164	19.9	7.5	-3.3 (-4.6, -2.1)	< .001	0.07	0.55 (0.34, 0.76)
	T2	173	21.3	7.2	164	18.7	7.9	-2.8 (-4.1, -1.5)	< .001	0.05	0.43 (0.23, 0.62)
PP	T0	173	22.8	7.1	163	23.2	7.2	-	-	-	-
	T1	173	22.9	7.0	163	19.5	7.2	-3.7 (-5.0, -2.4)	< .001	0.09	0.62 (0.39, 0.85)
	T2	173	21.3	7.4	163	18.3	7.7	-3.2 (-4.7, -1.7)	< .001	0.06	0.48 (0.26, 0.7)

[a] between-group difference on original scale 3 months after baseline, adjusted for baseline scores.
[b] based on baseline-adjusted means; positive values show effects in favor of the intervention group.

To assess the clinical significance of the findings, we conducted a prespecified analysis to identify responders at the 3-month time point (T1). A change in the WSAS of 8 points has been considered as minimal clinically important difference (MCID) in patients [63]. We therefore used this threshold (i.e., reduction in the WSAS total score from baseline to T1 of at least 8 points) to identify responders to treatment in terms of social functioning. ITT-results showed that 43/164 patients (26.2%, Clopper-Pearson 95 % CI = [19.7%, 33.6%]) in the intervention group versus 20/173 (11.6%, Clopper-Pearson 95 % CI = [7.2%, 17.3%]) patients in the control group were classified as responders, respectively (χ^2 = 11.9, p < 0.001; OR = 2.7, 95% CI = [1.5, 4.9]). Thus, the responder analysis confirmed that the additional use of *attexis* was more likely to result in clinically relevant improvements in social and work-related functioning compared with TAU alone.

- Depression (assessed with the PHQ-9 total score)

Table 12 | Results of the secondary endpoint depression.

Time		Control			*attexis*			ANCOVA			
		n	mean	SD	n	mean	SD	Treatment effect (95% CI)[a]	*p*-value	Partial η^2	Cohen's *d* (95% CI)[b]
ITT	T0	173	11.8	4.4	164	11.7	5.0	-	-	-	-

	T1	173	10.4	4.1	164	9.2	4.1	-1.1 (-1.8, -0.4)	0.003	0.03	0.32 (0.10, 0.54)
	T2	173	10.5	4.6	164	9.1	4.2	-1.4 (-2.3, -0.5)	0.002	0.03	0.36 (0.14, 0.57)
J2R	T0	173	11.8	4.4	164	11.7	5.0	-	-	-	-
	T1	173	10.4	4.1	164	9.3	4.1	-1 (-1.7, -0.3)	0.005	0.02	0.29 (0.08, 0.49)
	T2	173	10.6	4.5	164	9.2	4.3	-1.3 (-2.1, -0.5)	0.001	0.03	0.32 (0.13, 0.51)
PP	T0	173	11.8	4.4	163	11.7	5.0	-	-	-	-
	T1	173	10.4	4.1	163	9.3	4.1	-1.1 (-1.8, -0.3)	0.004	0.03	0.31 (0.09, 0.53)
	T2	173	10.6	4.6	163	9.1	4.2	-1.5 (-2.4, -0.6)	0.001	0.04	0.36 (0.14, 0.59)

[a] between-group difference on original scale 3 months after baseline, adjusted for baseline scores.
[b] based on baseline-adjusted means; positive values show effects in favor of the intervention group.

To evaluate the clinical significance of the findings, we performed a prespecified analysis of responders at the 3-month time point (T1) using an MCID of 5 points in the PHQ-9 total score to define responders [64]. ITT-results showed that 51/164 patients (31.1%, Clopper-Pearson 95 % CI = [24.1%, 38.8%]) in the intervention group versus 34/173 (19.7%, Clopper-Pearson 95 % CI = [14.0%, 26.4%]) patients in the control group were classified as responders, respectively ($\chi^2 = 5.85$, $p = 0.016$; OR = 1.8, 95% CI = [1.1, 3.0]). Thus, the responder analysis confirmed that the additional use of *attexis* was more likely to result in clinically relevant reductions in depressive symptoms compared with TAU alone.

- Self-esteem (assessed with the RSES total score)

Table 13 | Results of the secondary endpoint self-esteem.

Time		**Control**			***attexis***			**ANCOVA**			
		n	mean	SD	n	mean	SD	Treatment effect (95% CI)[a]	*p*-value	Partial η^2	Cohen's *d* (95% CI)[b]
ITT	T0	173	17.2	5.7	164	17.1	5.9	-	-	-	-
	T1	173	17.6	5.6	164	19.2	5.6	1.7 (0.9, 2.5)	< 0.001	0.06	0.48 (0.25, 0.70)
	T2	173	18.1	6.0	164	19.9	5.9	1.9 (0.9, 2.9)	< .001	0.05	0.43 (0.21, 0.65)
J2R	T0	173	17.2	5.7	164	17.1	5.9	-	-	-	-
	T1	173	17.6	5.6	164	19.1	5.6	1.5 (0.8, 2.3)	< .001	0.05	0.42 (0.21, 0.63)
	T2	173	18.1	5.9	164	19.8	6.0	1.8 (0.9, 2.7)	< .001	0.04	0.42 (0.22, 0.61)
PP	T0	173	17.2	5.7	163	17.0	5.9	-	-	-	-
	T1	173	17.6	5.6	163	19.2	5.6	1.7	< .001	0.06	0.48

								(0.9, 2.6)			(0.24, 0.71)
	T2	173	18.1	6.0	163	19.9	5.9	1.9 (0.9, 2.9)	< .001	0.05	0.43 (0.2, 0.66)

[a] between-group difference on original scale 3 months after baseline, adjusted for baseline scores.
[b] based on baseline-adjusted means; positive values show effects in favor of the intervention group.

To evaluate the clinical significance of the findings, we performed a prespecified analysis of responders at the 3-month time point (T1) using the psychometric criterion of the reliable change index [43], given the lack of published MCID for the RSES. ITT-results showed that 33/164 patients (20.1%, Clopper-Pearson 95 % CI = [14.3%, 27.1%]) in the intervention group versus 17/173 (9.8%, Clopper-Pearson 95 % CI = [5.8%, 15.3%]) patients in the control group reached this criterion, respectively (χ^2 = 7.06, p = 0.008; OR = 2.3, 95% CI = [1.2, 4.3]). Thus, the responder analysis confirmed that the additional use of *attexis* was more likely to result in clinically relevant improvements in self-esteem compared with TAU alone.

- Health-related quality of life (assessed with the AQoL-8D total score)

Table 14 | Results of the secondary endpoint health-related quality of life.

Time		**Control**			***attexis***			**ANCOVA**			
		n	mean	SD	n	mean	SD	Treatment effect (95% CI)[a]	*p*-value	Partial η^2	Cohen's *d* (95% CI)[b]
ITT	T0	173	63.3	9.5	164	63.1	10.0	-	-	-	-
	T1	173	64.2	9.1	164	66.7	9.9	2.6 (1.3, 4.0)	< .001	0.05	0.44 (0.22, 0.66)
	T2	173	64.8	10.3	164	68.3	10.1	3.6 (2.0, 5.3)	< .001	0.06	0.47 (0.26, 0.69)
J2R	T0	173	63.3	9.5	164	63.1	10.0	-	-	-	-
	T1	173	64.3	9.0	164	66.5	9.9	2.4 (1.2, 3.6)	< .001	0.04	0.40 (0.2, 0.6)
	T2	173	64.6	10.2	164	67.8	10.4	3.3 (1.8, 4.8)	< .001	0.05	0.44 (0.25, 0.63)
PP	T0	173	63.3	9.5	164	63.0	10.0	-	-	-	-
	T1	173	64.2	9.1	164	66.7	9.9	2.6 (1.3, 4.0)	< .001	0.05	0.44 (0.21, 0.68)
	T2	173	64.7	10.3	164	68.3	10.2	3.8 (2.1, 5.4)	< .001	0.06	0.49 (0.27, 0.7)

[a] between-group difference on original scale 3 months after baseline, adjusted for baseline scores.
[b] based on baseline-adjusted means; positive values show effects in favor of the intervention group.

To evaluate the clinical significance of the findings, we performed a prespecified analysis of responders at the 3-month time point (T1) using the psychometric criterion of a reliable change index [43] for the AQoL-8D, given the lack of published MCID for the AQoL-8D. ITT-results showed that 35/164 patients (21.3%, Clopper-Pearson 95 % CI = [15.3%, 28.4%]) in the intervention group versus 17/173 (9.8%, Clopper-Pearson 95 % CI = [5.8%, 15.3%]) patients in the control group reached this criterion, respectively (χ^2 = 8.55, p = 0.003; OR = 2.5, 95% CI = [1.3, 4.6]). Thus, the responder analysis confirmed that the additional use of

attexis was more likely to result in clinically relevant improvements in health-related quality of life compared with TAU alone.

- Use of *attexis*

Virtually all patients in the intervention group (163/164, 99.4%) registered to use *attexis*. Registered patients spent an average of 10.9 hours (SD = 6.5) in the program up to T1, and an average of 13.3 hours (SD = 6.9) up to T2.

- User Satisfaction

After 3 and 6 months of access to *attexis*, participants were asked how likely they were to recommend the program to a friend or colleague with ADHD [65]. User satisfaction was assessed with a 11-point Numerical Rating Scale ranging from 0 = "I definitely do not recommend the program" to 10 = "I definitely recommend the program". The mean rating was 6.1 (SD = 2.9) at T1 and 5.9 (SD = 3.3) at T2, indicating that the program was, on average, more likely to be recommended than not.

Subjective improvement of ADHD symptoms in the last 3 months (from T0 to T1) was evaluated with the Patient Global Impression of Change scale [66]. At T1, the intervention group reported an average score of 4.3 (SD = 0.9), significantly higher than the control group's mean of 3.8 (SD = 0.8; t = -4.92, $p < 0.001$; d = 0.56, 95% CI = [0.34, 0.79]), indicating that participants receiving the intervention were more likely to perceive symptom improvement. Similarly, the intervention group reported a greater subjective improvement in the impact of ADHD on daily activities from T0 to T1, with an average score of 4.4 (SD = 0.9) compared to the control group's mean of 3.8 (SD = 0.8; t = -5.74, $p < 0.001$; d = 0.66, 95% CI = [0.43, 0.88]). In a binary assessment of significant improvement in daily functioning, 36.5% of participants in the intervention group reported meaningful improvements from T0 to T1, as opposed to only 9.6% in the control group ($\chi^2 = 32.9$, $p < 0.001$).

The same items, reflecting improvements over the past three months, were also evaluated at T2. The intervention group achieved an average score of 4.3 (SD = 0.9), which was significantly higher than the control group's mean of 3.8 (SD = 1.0; t = -4.80, p < .001; d = 0.55, 95% CI = [0.32, 0.79]), indicating greater perceived symptom improvement among participants receiving the intervention. Similarly, the intervention group reported greater subjective improvements in the impact of ADHD on daily activities from T0 to T1, with a mean score of 4.4 (SD = 1.0) compared to the control group's 3.8 (SD = 0.9; t = -5.38, p < .001; d = 0.63, 95% CI = [0.39, 0.86]). Additionally, 40.1% of participants in the intervention group reported significant improvements in daily functioning from T1 to T2, compared to only 17.6% in the control group ($\chi^2 = 18.8$, $p < 0.001$).

In sum, these findings underscore the effectiveness of *attexis* in promoting both ADHD symptom reduction and enhanced daily functioning, as judged by patients themselves.

5.7.3 Adverse events and adverse device effects

Monitoring of adverse events (operationalized as unplanned and emergency outpatient and inpatient treatments in the last 3 months) showed that a comparable proportion, 13 of 167

participants in the control group (7.8%) and 8 out of 147 participants in the intervention group (5.4%), reported such events (χ^2 = 0.69, *p* = 0.407) at T1. A similar pattern of results was observed at T2, with 10 out of 159 participants in the control group (6.3%) and 6 out of 142 participants in the intervention group (4.2%) reporting such events, with no significant difference between the groups (χ^2 = 0.63, *p* = 0.426).

No adverse events were linked to the use of *attexis*. No adverse device effects were observed.

Symptom worsening, a pre-specified safety endpoint, was evaluated by comparing the proportion of participants who reported a higher total ASRS score at T1 compared to T0 (i.e. T1-T0 > 0) with the proportion of participants who reported no worsening. Results showed that 16/149 patients (10.7%) in the intervention group versus 40/167 (24%) patients in the control group reported a worsening of ADHD symptoms, respectively (χ^2 = 9.43, *p* = 0.002; OR = 2.6, 95% CI = [1.4, 5.0]). Thus, the analysis confirmed that the additional use of *attexis* was less likely to lead to a worsening of ADHD symptoms compared with TAU alone.

5.8 Device deficiencies and serious adverse events

Device deficiencies or serious adverse events were not observed.

5.9 Subgroup analyses for special populations

5.9.1 Subgroup analyses

Subgroup analyses were performed on multiply imputed data following the ITT-principle for the primary endpoint severity of ADHD symptoms (ASRS v1.1. total score) for the subgroup analyses presented in tables 15-18. Results are also summarized as a forest plot in figure 4.

- Sex

Table 15 | Subgroup analysis based on sex for the primary endpoint ADHD symptom severity at T1.

	Time	**Control**			***attexis***			**ANCOVA**		
		n	mean	SD	n	mean	SD	Treatment effect (95% CI)[a]	*p*-value	Cohen's *d* (95% CI)[b]
Women (n = 239)	T0	118	52.9	6.7	121	52.7	7.0	-	-	-
	T1	118	50.1	7.1	121	45.4	8.3	-4.5 (-6.1, -3.0)	< 0.001	0.81 (0.55, 1.07)
Men (n = 98)	T0	55	52.2	7.7	43	51.0	8.3	-	-	-
	T1	55	49.6	8.5	43	42.4	8.2	-6.3 (-9.0, -3.6)	< 0.001	1.01 (0.59, 1.44)

[a] between-group difference on original scale 3 months after baseline, adjusted for baseline scores.
[b] based on baseline-adjusted means; positive values show effects in favor of the intervention group.

- Psychotherapy status

Table 16 | Subgroup analysis based on psychotherapy status at baseline for the primary endpoint ADHD symptom severity at T1.

	Time	Control			*attexis*			ANCOVA		
		n	mean	SD	n	mean	SD	Treatment effect (95% CI)[a]	*p*-value	Cohen's *d* (95% CI)[b]
In psycho-therapy (n = 79)	T0	43	52.6	7.0	36	50.4	7.0	-	-	-
	T1	43	49.0	7.1	36	42.0	8.3	-5.3 (-8.0, -2.6)	< 0.001	0.98 (0.48, 1.47)
Not in psycho-therapy (n = 258)	T0	130	52.8	7.1	128	52.8	7.4	-	-	-
	T1	130	50.3	7.7	128	45.4	8.2	-4.9 (-6.5, -3.3)	< 0.001	0.83 (0.58, 1.09)

[a] between-group difference on original scale 3 months after baseline, adjusted for baseline scores.
[b] based on baseline-adjusted means; positive values show effects in favor of the intervention group.

- Psychotropic medication

Table 17 | Subgroup analysis based on psychotropic medication at baseline for the primary endpoint ADHD symptom severity at T1.

	Time	Control			*attexis*			ANCOVA		
		n	mean	SD	n	mean	SD	Treatment effect (95% CI)[a]	*p*-value	Cohen's *d* (95% CI)[b]
On medication[c] (n = 122)	T0	59	52.8	6.8	63	51.6	7.5	-	-	-
	T1	59	49.6	7.5	63	44.6	8.5	-4.1 (-6.4, -1.8)	< 0.001	0.69 (0.30, 1.08)
Not on medication[c] (n = 215)	T0	114	52.7	7.2	101	52.6	7.3	-	-	-
	T1	114	50.1	7.6	101	44.6	8.3	-5.5 (-7.1, -3.8)	< 0.001	0.96 (0.68, 1.23)

[a] between-group difference on original scale 3 months after baseline, adjusted for baseline scores.
[b] based on baseline-adjusted means; positive values show effects in favor of the intervention group.
[c] ATC classification codes N05 / N06.

- Changes in treatment

Please note that due to the nature of the analysis, only participants with complete observations were included in the subgroup analysis of changes in treatment from T0 to T1 below.

Table 18 | Subgroup analysis based on changes in treatment from baseline to T1 for the primary endpoint ADHD symptom severity at T1.

	Time	Control			*attexis*			ANCOVA		
		n	mean	SD	n	mean	SD	Treatment effect (95% CI)[a]	*p*-value	Cohen's *d* (95% CI)[b]

Changes in treatment (n = 53)	T0	31	53.5	6.6	22	51.2	5.8	-	-	-
	T1	31	50.3	7.5	22	43.7	7.1	-4.5 (-7.3, -1.7)	< 0.001	0.93 (0.33, 1.52)
No changes in treatment (n = 263)	T0	136	52.3	7.1	127	51.8	7.6	-	-	-
	T1	136	49.7	7.6	127	44.4	8.6	-4.9 (-6.4, -3.5)	< 0.001	0.82 (0.56, 1.07)

[a] between-group difference on original scale 3 months after baseline, adjusted for baseline scores.

[b] based on baseline-adjusted means; positive values show effects in favor of the intervention group.

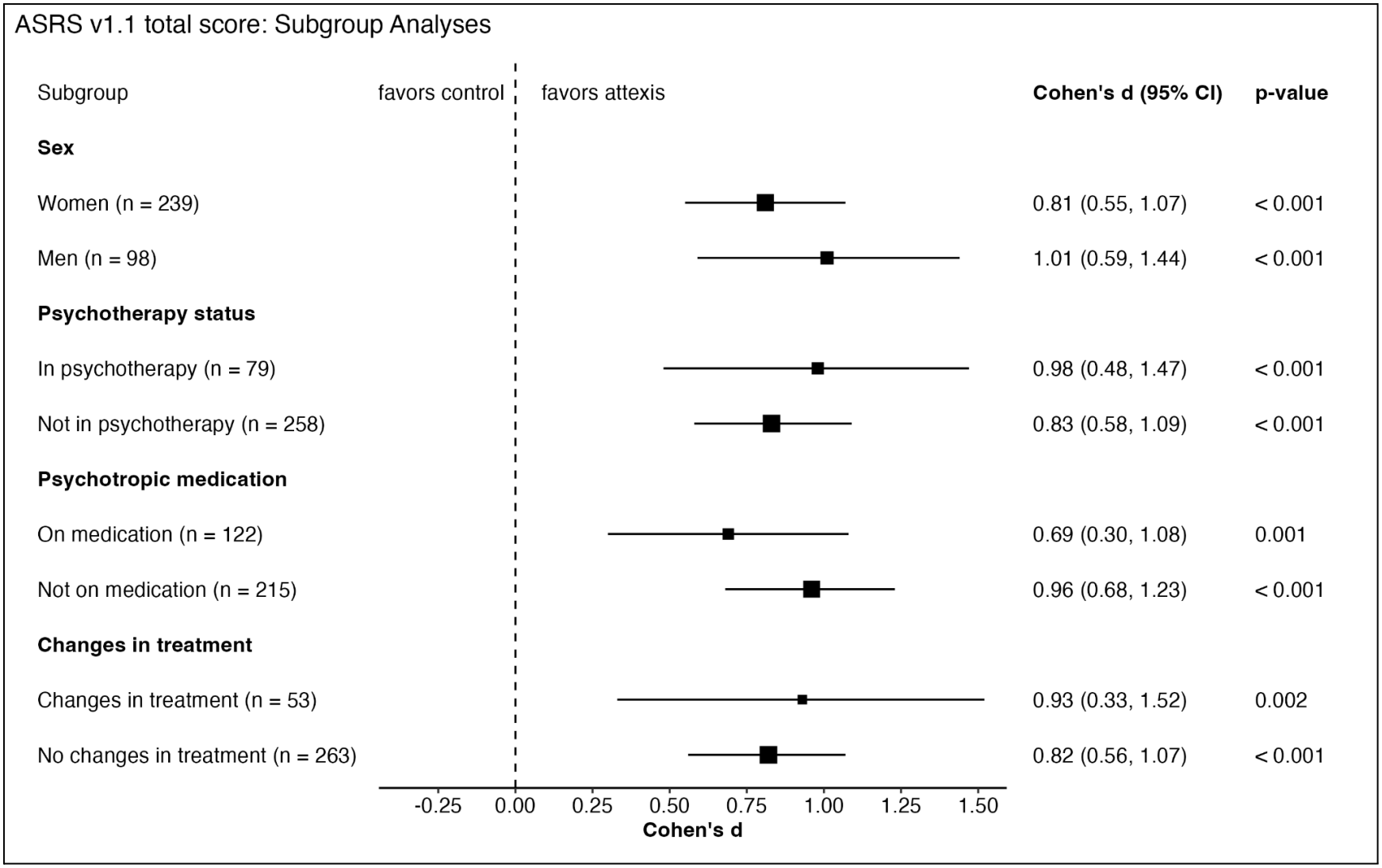

Figure 4 | Forest plot of effect sizes (Cohen's *d*) for the primary endpoint ADHD symptom severity, assessed with the ASRS v1.1 total score. *p*-values come from the ANCOVA.

5.10 Listings of deaths and reasons for deaths

Deaths and reasons thereof were not recorded during this clinical investigation.

6. Discussion and overall conclusions

6.1 Clinical performance, effectiveness and safety results

After 3 months, the *attexis* intervention group displayed a significantly lower severity of ADHD symptoms than the control group. Responder analyses verified the clinical significance of these reductions. In addition, there were significant and clinically relevant effects of *attexis* on social and work-related functioning, depression, self-esteem, as well as health-related quality of life. Results were confirmed in conservative J2R sensitivity analyses, supporting the robustness of the findings. Participants in the intervention group reported subjectively greater improvements in ADHD symptoms and daily functioning up to T1 compared to those in the control group, highlighting the program's effectiveness from a patient perspective. All effects were maintained or further enhanced at the 6-month follow-up, underscoring the long-term effectiveness of *attexis*.

6.2 Assessment of benefits and risks

This clinical investigation report demonstrates that the use of *attexis* alongside TAU is more effective in alleviating ADHD symptoms in patients with ADHD compared to TAU alone. The intervention also showed positive effects on social and work-related functioning, depression, self-esteem, as well as health-related quality of life. At the same time, there was no evidence of group differences in adverse events (operationalized as unplanned and emergency outpatient and inpatient treatments), and no adverse events were linked to the use of *attexis*. Additional pre-specified safety analyses revealed that a significantly higher proportion in the control than in the intervention group reported a worsening of ADHD symptoms from T0 to T1. This suggests that the benefits of *attexis* pertain not only to a clinically significant improvement in ADHD symptom severity but also to a marked reduction in symptom worsening compared to the control group. Consequently, the benefit-risk ratio is favorable.

6.3 Discussion of the clinical relevance of the results

ADHD is a common neurodevelopmental disorder that affects between 2.58% to 6.76% of adults worldwide [1] and which is associated with impairment across multiple domains of functioning and with increased risk for psychiatric comorbidity [67]. The German S3 Clinical Guideline recommends psychosocial (including psychotherapeutic) interventions in adults with ADHD to improve everyday functioning, reduce symptoms of ADHD and alleviate commonly co-occurring symptoms such as depression and low self-esteem [9]. Psychosocial interventions are also recommended in case of difficulties to accept the diagnosis, contraindications to drug treatment, persistent symptoms or impairments on drug treatment as well as in case of an informed decision against commencing medication or difficulties with medication adherence [9]. Among different psychological interventions, CBT interventions stand out as particularly effective in terms of reducing ADHD symptom severity, its associated functional impairments and psychological comorbidities [67], [68], [69], [70], [71]. However, psychological treatments for ADHD are still not broadly available and waiting times

exceed several months [16]. In addition, there is a lack of expertise on ADHD in adults amongst clinicians [72]. This is also evidenced by participants in the present study of whom only 3.6% were treated by a therapist with expertise in ADHD at baseline. Digital interventions have been shown to successfully narrow down this treatment gap for a range of psychological disorders [73], [74]. In adult ADHD, to date, four RCTs specifically addressed the efficacy of digital interventions on ADHD symptom severity, with effect sizes ranging between *d* = 0.42 to *d* = 1.21 [21], [22], [23], [24]. Although these studies have yielded promising results, a major limitation is their small sample size (between 13 and 61 participants per treatment arm). The RCT reporting the largest effect size had some additional shortcomings [22]: The effect size of *d* = 1.21 only pertained to the ASRS-Inattention subscale whereas virtually no between-group effect was found for the ASRS-Hyperactivity subscale (*d* = 0.19). Analyses for the ASRS total score were not reported. In addition, participants with a probable but not confirmed diagnosis of ADHD were included in the study. The intervention also included a coaching component delivered through human interaction. These issues make it difficult to disentangle the effects of the intervention and the human coaching component. Another study testing a digital intervention for adults with ADHD in Germany is currently ongoing, with quality of life after 3 months as the primary endpoint (DRKS00033320); however, results have not yet been published.

The present RCT - which is based on a 5-times larger sample size - complements and extends the findings of the above-discussed studies on digital interventions in adult ADHD: Following a 3-month utilization of *attexis*, the intervention group exhibited significantly lower levels of ADHD symptom severity in comparison to the control group, corresponding to a large effect of *d* = 0.85. Responder analyses verified the clinical significance of these reductions. Moreover, following the prespecified gatekeeping strategy, we were able to confirm significant intervention effects for all secondary endpoints, i.e., social and work-related functioning, depression, self-esteem and health-related quality of life were observed. All effects remained significant at the 6-month follow-up.

The average ASRS score at baseline (*M* = 52.5) is highly consistent with those reported in three of the four aforementioned RCTs on digital ADHD interventions, which ranged from 47.5 to 51.2[2] [21], [22], [23]; one RCT did not use the ASRS to assess ADHD symptom severity [24]. Although these studies showed slightly larger mean group differences (5.7 to 7.7 points[3]), this variation is likely due to the smaller sample sizes [75], [76]. Consequently, the observed reduction in ADHD symptom severity in our study falls squarely within the established range for digital interventions targeting adult ADHD.

The intervention group's responder rate was notably 10.0 times higher than the control group's, a ratio comparable to a previous study (8.33[4]) [23] and considerably exceeding those typically reported in pharmacological trials [77].

[2] One study [22] did not report analyses or mean values for the ASRS total score. Therefore we estimated the within-group means of the ASRS total score based on the reported sub-scales' means for this comparison.
[3] Mean group differences were estimated based on the difference in within-group changes which were computed based on the provided average scores for each group at baseline and follow-up.
[4] Estimated based on the reported responder rates in the intervention and control groups.

These findings, although highly promising, should be considered within the broader context of available treatment options, specifically CBT and pharmacotherapy. We will discuss them separately for each confirmatory outcome.

Meta-analytic evidence suggests that face-to-face CBT yields effect sizes between *d* = 0.71 and *d* = 0.98 in terms of reducing self-reported ADHD symptoms compared to control groups in RCTs [70], [71], [78]. Notably, effect sizes in the four reviewed digital interventions and *attexis* fall within the range of those for face-to-face CBT, suggesting that CBT may effectively reduce ADHD symptom severity, regardless of delivery format. A meta-analytic moderator analysis supports this conclusion, showing no significant differences in effect sizes across treatment formats, including individual therapy, group therapy with and without supportive contacts, and digital interventions [67].

The average ASRS total score at baseline in this RCT is comparable to those reported in face-to-face CBT studies, where ASRS values ranged from 37.5 to 50.8 [79], [80], [81]. The lowest value (37.5) stems from a study focusing on the inattentive subtype of ADHD [81], explaining the lower baseline values. Furthermore, the 5-point mean group difference on the ASRS total score found in our study is consistent with the reported effects of face-to-face CBT, which range from 2.3 to 7.7 points [79], [80], although one study found no significant between-group difference [81].

Licensed ADHD medications, such as methylphenidate and amphetamines, demonstrate heterogeneous meta-analytic effect sizes in reducing core ADHD symptoms, ranging from *d* = 0.37 to *d* = 1.06 [10], [82], [83], [84], [85]. Meta-analytic evidence indicates that combining pharmacotherapy with CBT may lead to improved treatment outcomes in adult ADHD compared to pharmacotherapy alone [78]. However, it is important to consider that ADHD pharmacotherapy has been linked to undesirable effects such as appetite suppression, headaches, sleep issues, and mood changes, along with increases in pulse and blood pressure compared to placebo [9], [10], [82], [83], [85].

Given the substantial challenges in accessing face-to-face CBT and undesirable effects linked to ADHD pharmacotherapy, our study findings thus underscore the crucial role of self-guided, digital interventions such as *attexis* in order to optimize the treatment results in adults with ADHD.

Adults with ADHD commonly experience functional impairments in managing their daily responsibilities, at work, and with family and friends [56]. However, only few studies have assessed the effects of CBT-based interventions on this outcome domain [86]. The limited available data on digital interventions have yielded mixed results: two studies reported small effects (*d* = 0.33 and *d* = 0.45, respectively [22], [23]), one study found no significant effect on functioning in ADHD [24], and another did not examine functioning as an outcome [21]. In studies where CBT was primarily conducted face-to-face, meta-analytic evidence suggests a moderate effect size of *d* = 0.51 for self-reported functioning [67]. Turning to pharmacotherapy, reported effect sizes in the literature are often non-significant, small and range from *d* = 0.14 to 0.41 [87].

These numbers align with a recent meta-analysis [88] that focused on work-related outcomes for adults with ADHD, and reported larger effect sizes for psychosocial (*d* = .56) than for pharmacological interventions (*d* = .19) on functioning.

Average WSAS total scores at baseline were highly consistent with the ones reported in a previous RCT [89] (IG: *M* = 20.0, *SD* = 8.2; CG: *M* = 21.8, *SD* = 8.0). Notably, patients in this RCT were directly recruited from a clinic specialized in adults with ADHD, indicating that online recruitment did not affect the severity of functional impairments. While the RCT reported a relatively large group difference of about 6.6 points (assessed after 30 weeks), it was also considerably more resource-intensive, involving 15 face-to-face CBT sessions by trained clinical or counseling psychologists with experience in ADHD [89].

Our results, conversely, show that participants using *attexis* achieved significant improvements in less than half the time (after 12 weeks). This positions *attexis* as a less resource-intensive and highly efficient alternative or bridging strategy to face-to-face CBT for improving psychosocial functioning in adults with ADHD.

Responder analysis for the WSAS (based on a MCID of 8 points) confirmed that *attexis* led to clinically significant improvement in 25.2% of all participants in the intervention group compared to 11.6% in the control group. These responder rates are consistent with the participant's self-assessment of significant improvements in their daily functioning, which 36.5% of participants in the intervention group confirmed, as opposed to only 9.6% in the control group.

Thus, demonstrating a significant and clinically relevant effect of moderate size on work and social functioning, *attexis* has potential to improve these important outcomes more effectively than existing treatment options.

Most adult ADHD trials to date have not included depression measures, leaving a gap in understanding the impact of existing ADHD treatment options on comorbid depressive symptoms, despite their high prevalence in the disorder [90]. Results regarding the reduction of depressive symptoms in adult ADHD have been heterogeneous among available digital interventions: Two studies reported small to moderate effects (*d* = 0.23 and *d* = 0.6, respectively [22], [23]), while another study found no significant effect [24], and one study did not assess depressive symptoms as an outcome [21]. Meta-analytic evidence suggests a small effect of face-to-face CBT on depression in adults with ADHD, with effect sizes ranging between *d* = 0.27 and *d* = 0.40 [71], [78]. Considering pharmacotherapy, existing evidence indicates that stimulant medications, such as methylphenidate, are generally ineffective for managing comorbid affective symptoms, such as depression and anxiety, in adults with ADHD [91]. Similarly, the literature shows limited impact of amphetamines on depressive symptoms in ADHD, with meta-analytic findings based on two studies indicating only a small and non-significant difference between amphetamine and placebo groups [83]. Analogous to core ADHD symptoms, meta-analytic evidence suggests that combining pharmacotherapy with CBT could be more effective than pharmacotherapy alone in reducing comorbid depression [78]. In this context, *attexis* demonstrates a significant and clinically relevant effect on depressive symptoms (*d* = 0.32), indicating its potential to address these comorbid

symptoms as effectively as face-to-face CBT, and more effectively than ADHD pharmacotherapy.

Self-esteem is a critical outcome for patients with ADHD, as it significantly influences their overall psychosocial functioning and well-being [26], [92]. However, to date, the examination of self-esteem as an outcome has been very limited in both non-pharmacological and pharmacological research. Notably, none of the four available studies on digital interventions in adult ADHD examined self-esteem as an outcome, leaving their effectiveness in this outcome domain unclear [21], [22], [23], [24]. In the context of traditional CBT-based interventions, a recent meta-analysis, including 4 studies, reported a *d* = 0.38, suggesting a small effect of CBT in improving self-esteem [71].

Out of these 4 studies, three used the RSES to assess self-esteem, with baseline scores ranging from 15.95 to 18.37 [93][5], [94][5], [95]. Estimated mean differences for these studies ranged between 0.72 to 1.08 points[6], indicating that participants using *attexis* - while starting with baseline RSES levels comparable to those in the reviewed studies - showed greater improvements, underscoring the effectiveness of *attexis* in boosting self-esteem.

For pharmacological interventions, our literature search indicates that to date, no RCT has investigated their effectiveness on self-esteem in adults with ADHD. This gap may arise from the notion that self-esteem is not an obvious target for medication. In this context, the observed effect size of *d* = 0.48 for *attexis* in enhancing self-esteem among a large sample of adults with ADHD is a promising finding: *attexis* has the potential to improve self-esteem to a significant and clinically relevant extent, thereby contributing to the overall well-being of individuals with ADHD.

Quality of life, much like functional impairment, reflects the real-world impact of ADHD on patients' daily lives [87]. Among the limited body of only four studies on digital interventions, the available data presents an overall inconclusive picture: Two studies indicate small to medium effects in improving quality of life [21], [23] while another found no significant effect [24], and one study did not assess quality of life as an outcome [22]. Meta-analytic evidence on the effects of predominantly face-to-face CBT on quality of life in adults with ADHD is mixed, with heterogeneous effect sizes (*d* = 0.21 to *d* = 0.39) [71], [78], [86]. Similarly, available evidence indicates a wide variability in the effectiveness of pharmacotherapy for enhancing quality of life in adults with ADHD, with effect sizes ranging from *d* = 0.12 to 0.92 [87], [96]. This variability may be attributed in part to a lack of consensus on assessments, with many different quality of life outcome measures in use in the field [87]. Given the available evidence, the significant and clinically relevant effect of *attexis* on quality of life (*d* = 0.44) is a positive result that aligns well with existing literature.

The results of our subgroup analyses demonstrate significant effectiveness of *attexis* across all tested subgroups, with large effect sizes observed in all but one subgroup. This

[5] Note that the reported average RSES scores were originally based on an item scale range of 1-4 and therefore transformed to match the item scale range used in the present study (0-3).

[6] In case group differences were not reported, they were estimated based on the difference in within-group changes which were computed based on the provided average scores for each group at baseline and follow-up.

homogeneous pattern of effectiveness suggests that *attexis* is a digital health application that can benefit a broad range of individuals with ADHD.

At the 6-month follow-up, the results showed sustained effects of *attexis* on ADHD symptoms, functional impairment, and self-esteem, alongside further improvements in depressive symptoms and quality of life. The findings suggest that as core ADHD symptoms decrease, individuals may be able to engage more fully with their environment and daily activities, leading to continued improvements in their well-being. This aligns with CBT models of adult ADHD, which suggest that the long-term integration of adaptive coping strategies can reduce comorbid internalizing conditions [86] and the functional impairment caused by neurobiological deficits [97]. Overall, the 6-month data underscore the sustained and evolving long-term effectiveness of *attexis* in addressing ADHD symptoms and associated patient-relevant outcomes.

In summary, *attexis* stands out favorably when compared to other interventions for ADHD in adults: its effect sizes on ADHD symptoms and associated impairments closely align with effect sizes reported in meta-analyses for face-to-face CBT interventions while offering the advantages of digital solutions (less resource-intensive, easier access, self-paced etc.). In comparison to pharmacotherapy, *attexis* was also associated with significant improvements in social-and work-related functioning, depressive symptoms, self-esteem and health-related quality of life that were considerably larger than reported for pharmacotherapeutic studies, and this without side effects, underscoring its multifaceted benefits for patients. Notably, the use of *attexis* was also associated with a significant reduction in the proportion of participants reporting symptom worsening in the intervention compared to the control group, suggesting that an additional benefit of *attexis* lies in its stabilizing effects on ADHD symptom severity.

Moreover, the considerable sample size in the effectiveness trial enhances the robustness of *attexis*' evidence, consolidating its position as a promising, scalable solution for managing ADHD core symptoms.

6.4 Specific benefits or special precautions required for individual subjects or groups considered to be at risk

Using *attexis* in addition to TAU was found to be more effective in reducing ADHD symptom severity compared to TAU alone. *attexis* should only be used as an adjunct to usual care, not as a substitute for it.

6.5 Implications for the conduct of future clinical investigations

This clinical investigation affirms the feasibility of online studies assessing the efficacy of fully automated interventions for ADHD. Future studies might explore whether certain patient profiles or care settings yield greater benefits from *attexis*.

6.6 Limitations of the clinical investigation

Slight differences in dropout rates emerged between the intervention and control group. It is conceivable that some participants in the intervention group used *attexis* until they perceived sufficient benefits, subsequently opting out of further study involvement—a phenomenon extensively documented as the "good enough" effect in psychotherapy research [98], [99]. Notwithstanding this limitation, dropout rates can overall be considered small, and our study establishes that *attexis* reduces ADHD symptom severity and other relevant secondary outcomes significantly and to a clinically relevant extent. Moreover, although planned treatment stability was a prerequisite for inclusion, treatment changes were reported by 16.8% of all participants (this number is at the lower end compared to [22], [23], [24]). However, as demonstrated by the subgroup analysis, even in those participants, treatment outcome was similar to those participants without treatment changes.

7. Abbreviated terms and definitions

ANCOVA	analysis of covariance
AQoL-8D	Assessment of Quality of Life - 8 Dimensions
ASRS v1.1	Adult ADHD Self-Report Scale v1.1
CC	complete case
CI	confidence interval
CIP	clinical investigation protocol
DiGA	“Digitale Gesundheitsanwendung”
ITT	intent to treat
J2R	jump to reference
MCID	Minimal Clinically Important Difference
NPS	Net Promoter Score
NRS	Numeric Rating Scale
PDF	Portable Document Format
PHQ-9	Gesundheitsbogen für Patienten - 9 Items
PP	Per Protocol
RCI	Reliable Change Index
RCT	randomized controlled trial
RSES	Rosenberg Self-Esteem Scale
SD	standard deviation
SE	standard error
SMS	Short Message Service
TAU	treatment as usual
WSAS	Work and Social Adjustment Scale

8. Ethics

This study and its amendment was reviewed and approved by the ethics committee of the Medical Chamber Hamburg (reference number 2023-101052-BO-ff). The clinical investigation was conducted in accordance with the ethical principles in the Declaration of Helsinki. Prior to participation, detailed patient information was provided and informed consent was obtained online.

9. Investigators and administrative structure of clinical investigation

This clinical investigation was primarily conducted as an online trial without a traditional physical investigation site. Study management including patient recruitment and data acquisition was conducted by the sponsor. No funding was provided by the sponsor.

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