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The impact of a multimodal intervention on physical health factors and lifestyle in patients with affective disorders – results from a randomized controlled trial

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ABSTRACT

Background: Traditional treatment for affective disorders primarily focuses on symptom management through pharmacotherapy and psychotherapy and rarely addresses co-existing physical impairments.
Methods: This randomized controlled trial assessed the impact of a six-month multimodal intervention (AWARE) on physical health in patients with bipolar and unipolar depressive disorders. A total of 103 patients, median age 40.75 years (65 % female), were randomized into the AWARE group (n = 50) or treatment as usual (TAU) group (n = 53). The AWARE intervention included five modules focused on activities of daily living, mood management, social relations, physical health, and cognition, with participants receiving approximately 12 sessions. TAU involved standard psychiatric care, Health outcomes were evaluated on sleep, metabolic markers, substance use, medication side effects, and perceived physical health. Statistical analyses used logistic regression for group comparisons and analysis of covariance for continuous outcomes.
Results: The AWARE group had significant improvements in sleep onset latency and reported reduced physical pain affecting daily work compared to TAU. However, no statistically significant differences were found in other physical health outcomes, such as metabolic markers, substance use, medication side effects, or perceived physical health. Study limitations include a modest sample size and a relatively short intervention duration.
Conclusion: While the AWARE intervention improved sleep and pain management, it did not significantly affect other health markers. Future research should involve longer intervention periods, larger sample sizes, and a comprehensive approach to both mental and physical health.

1. Introduction

Patients with unipolar depressive disorder and bipolar disorder (affective disorders) often experience physical health implications of their illness such as obesity, cardiovascular problems, and early mortality [1]. These patients have impaired functioning and poorer overall health compared with the general population [2]. The average years of potential life lost for individuals with unipolar depressive disorders are 12.8 years, and 12.5 years for those with bipolar disorder [3]. This significant reduction in lifespan can only partly be attributed to unnatural causes, such as suicide [4]. The majority of the decreased life expectancy is due to natural causes [4], as individuals with mental health disorders have a higher prevalence of physical diseases [5], particularly cardiovascular diseases [6,7]. Several studies have shown that the higher prevalence of physical illnesses among people with mental health disorders is partly due to their more sedentary lifestyle and disrupted circadian rhythm [8]. Therefore, it is essential to explore interventions targeting these underlying factors to improve the physical health of this patient group.

Traditional treatment for affective disorders primarily focuses on symptom management through pharmacotherapy and psychotherapy [9,10] and rarely addresses co-existing physical impairments and

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comorbidities [11]. Neuromodulation techniques such as electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), and deep brain stimulation have shown promise in alleviating affective symptoms [12–14]. While these interventions primarily target affective symptoms, they do not directly address the physical health challenges that individuals with affective disorders often face. A comprehensive understanding of these diverse treatment options and their interactions is crucial for optimizing patient outcomes, particularly concerning the limitations of conventional treatments.

Recognizing the limitations of conventional treatments, there is a growing interest in the potential benefits of comprehensive lifestyle interventions that address the broader health challenges faced by patients with affective disorders [1]. While earlier studies showed mixed results with lifestyle interventions [15,16], the present research includes a wider array of physical health measures. In addition to assessing traditional factors like BMI and cardiovascular risks, it examines sleep patterns, physical activity, smoking and alcohol habits, medication side effects, and subjective health perceptions. This comprehensive approach aims to provide a broad evaluation of how multimodal interventions may enhance overall health in individuals with affective disorders. Furthermore, patients with mental health conditions seek greater attention to their physical health as part of their treatment, emphasizing the importance of integrated care that addresses both physical and mental well-being [17]. However, studies integrating multimodal lifestyle interventions for patients with affective disorders still need to be expanded [18].

To address this unmet need, the present study, "Affective disorders: eliminate WArning signs and REstore functioning" (the AWARE study), investigated the efficacy of a multimodal intervention aimed at improving the functioning of individuals diagnosed with unipolar depressive disorder or bipolar disorder [19]. The primary outcome was overall functioning assessed using an observer-based measure of daily function evaluating differences in the Assessment of Motor and Process Skills (AMPS) from baseline to the endpoint between the intervention and control group, which showed no statistically significant difference between the treatment as usual (TAU) and AWARE groups [20]. However, we did observe a statistically significant improvement in secondary outcomes of patient-reported functioning, perceived stress, and cognition. The study further collected data on several secondary and tertiary physical health outcomes, which can provide valuable insights into the physical health of these patients.

Given the multidimensional nature of physical health challenges in affective disorders, a structured multimodal intervention may offer a more targeted approach to addressing these factors. Unlike previous studies focusing primarily on symptom relief in affective disorders, this study explicitly examines a multimodal intervention's broader physical health effects. The aim of the present paper is, hence, to explore whether the AWARE intervention had any impact on lifestyle and physical health in patients with affective disorder. We hypothesized that patients with affective disorders receiving the AWARE intervention would significantly improve physical health outcomes, including sleep, metabolic health markers, smoking, alcohol habits, physical activity, medication side effects, and perceived health, compared to those receiving TAU.

2. Methods

2.1. Study design

The AWARE study was a randomized, controlled, parallel-group clinical trial conducted in an outpatient setting in the Capital Region of Denmark (Psychiatric Centre Northern Zealand and Psychiatric Centre Copenhagen) from February 2021 to July 2023. Study design and outcome measures are described in detail in Schwarz et al., 2022 [19].

2.2. Study participants

The participants were 103 outpatients who met the eligibility criteria. Initially, the goal was to include 120 eligible outpatients; however, achieving this sample size proved challenging despite intensive recruitment efforts spanning three COVID-19 lockdowns. Therefore, 103 outpatients were ultimately included. Statistical power analysis indicated that a sample size of 103 was sufficient to study the primary outcome measures [20].

The inclusion criteria were age 18–65 years, diagnosed with bipolar disorder or unipolar depressive disorder by the diagnostic criteria of the WHO's International Classification of Diseases, 10th edition (ICD-10) [21], verified using The Mini-International Neuropsychiatric Interview (M.I.N.I) [22]. Participants should be in full or partial remission, defined as scores of $\leq$14 on the 17-item Hamilton Depression Rating Scale (HDRS-17) [23] and the Young Mania Rating Scale (YMRS) [24]. Additionally, impaired functioning was defined as a score of $\geq$11 on the Functioning Assessment Short Test (FAST) [25]. To be eligible, participants also had to commit to attending at least two-thirds of the planned intervention visits/sessions.

To ensure the generalizability (external validity) of the trial's findings, only a limited number of exclusion criteria were applied. These included ongoing alcohol or substance abuse, recent electroconvulsive therapy (within three months prior to inclusion), dementia, or any other condition that would prevent cooperation with the study, including the inability to speak or read Danish [20].

2.3. Recruitment

Patients were recruited from the outpatient clinic at Psychiatric Centre Northern Zealand and Psychiatric Centre Copenhagen and referred to the study by the patients' consultant psychiatrist. Patients interested in participating underwent a brief telephone screening. Those likely to meet the inclusion criteria were invited to an in-person meeting, where research staff thoroughly explained the trial's purpose and nature, assessed the inclusion/exclusion criteria, and answered patients' questions. There was a reflection period of a few days between the oral and written information provided and obtaining written informed consent.

2.4. Randomization

The randomization method was block randomization within strata with block sizes randomly varied between 2, 4, and 6, and the treatment order within each block randomly assigned in a 1:1 ratio. Stratification was done by age (18–34 years vs 35–65 years), sex (men vs women), and diagnosis (bipolar disorder vs unipolar depressive disorder). Randomization was performed in Research Electronic Data Capture (REDCap).

2.5. Blinding

The trial was an open-label, outcome assessor blinded study. The REDCap coding file for the allocation sequence was inaccessible to the therapist responsible for the allocation, the rater (baseline and endpoint), or any other personnel involved in the trial. However, the study was performed as an open-label study as participants and clinicians providing the intervention were not blinded to the group allocation.

2.6. Treatment as usual - TAU

The TAU group received the standard care provided for bipolar disorder or unipolar depressive disorder according to Danish guidelines. These guidelines, developed by the Danish Health Authority, outline treatment typically administered by general practitioners, psychiatrists, and psychologists. Standard care may involve pharmacological

treatment with antidepressants, mood stabilizers, or antipsychotics, depending on the patient's diagnosis and symptom profile [26]. In addition, patients may receive psychotherapy, which can include cognitive behavioral therapy (CBT), interpersonal therapy (IPT), or psychodynamic therapy, among others, depending on individual needs and clinician preferences [27]. Psychoeducation is also commonly offered, either in individual or group formats, with a focus on illness management, relapse prevention, and coping strategies [26,27]. However, the exact composition and intensity of treatment within TAU varies based on clinical judgment and resource availability, meaning that patients in this group may receive different combinations of these interventions.

2.7. The intervention - AWARE

The AWARE intervention is a comprehensive, multimodal, individualized program developed to target known mediators of patient functioning. Based on the International Classification of Functioning (ICF) Brief Core Set [28,29], a five-pillar model of possible focus areas for the intervention was established, encompassing (1) ADL ability as part of carrying out daily routines, (2) mood symptoms, medication, and side effects, (3) social relationships, including relatives and networks, (4) physical health, such as body mass index (BMI), biomarkers, and exercise, and (5) cognition, circadian rhythm (e.g., sleep quality), and stress reduction (coping) [19]. An individualized intervention profile with one to three specific focus areas from this model was selected in collaboration with each patient [19].

The practical implementation of the intervention involved a mean of 12 sessions (standard deviation = 4, range 6–18) [20] between the patient and relevant healthcare professionals, such as medical doctors, occupational therapists, and nurses. During the first appointment, feedback on the baseline assessments was provided, and the individualized intervention profile was created. In the final appointment, the patient evaluated the intervention and assessed the progress of the goals and focus areas. The sessions in-between focused on the intervention, targeting the individual focus areas, and were conducted either in the clinic or at the patient's home. A medical doctor or an occupational therapist guided these intervention sessions.

2.8. Outcome measures

Data were collected at baseline (pre-allocation, day 0) and after 6 months through interviews, questionnaires, observations, cognitive performance tests, and measurements on metabolic health markers [19]. The primary analyses have been presented in a previous paper [20]. The study was outcome assessor-blinded, and all outcome assessors were external assessors masked for allocation who did not participate in the treatment of participants or conducting the trial. Patients were carefully instructed not to disclose any information concerning their treatment allocation during endpoint assessments. FAST was the only outcome measure assessed unblinded (blinding of FAST was initially planned, but was, due to practical reasons, not possible).

Depressive and manic/hypomanic symptoms were assessed with the HDRS-17 [23] and YMRS [24], respectively. Partial remission was defined as a total score between >7 and ≤ 14, and full remission was defined as a total score of ≤7 on both the HDRS and YMRS. Cognition was objectively measured with SCIP (Screen for Cognitive Impairment in Psychiatry) [30].

Functioning was measured using different methods, the observer based primary outcome was change in Activities of Daily Living (ADL) motor and process ability from baseline to endpoint according to endpoint according to scores on the AMPS [20,31].

Secondary outcomes were the self-reported using WHO Disability Assessment Schedule (WHODAS 2.0) [32] and Functioning Assessment Short Test (FAST) [25]. The FAST is a semi-structured interview of functioning with higher scores reflecting poorer functional capacity. Scores>11 indicate functional impairment (12–20 = mild impairment; 21–40 = moderate impairment; >40 = severe impairment) [33].

The Pittsburgh Sleep Quality Index (PSQI) was used to assess changes in sleep quality among participants. The PSQI provides a comprehensive measure of sleep disturbances across multiple domains, allowing for a detailed evaluation of any improvements in sleep patterns [34]. Height was measured lightly dressed and without shoes to the nearest millimeters on a rigid stadiometer at the baseline visit. At all visits, weight was measured to the nearest 0.1 kg using a calibrated floor scale. Body Mass Index (BMI) is a proxy for assessing changes in body composition throughout the intervention. Metabolic syndrome was assessed by measuring the indicators hemoglobin A1C, non-HDL cholesterol level, blood pressure, and medicinal treatment [35]. Blood samples were taken as part of the daily clinic and analyzed using standardized methods and blinded regarding participant allocation status for all parts of collection, handling, processing, and analyzing.

The International Physical Activity Questionnaire (IPAQ) was administered to quantify the level of physical activity among participants [36].

The UKU Side Effect Rating Scale (UKU-SERS) was used to evaluate the occurrence and severity of medication side effects throughout the study period. This scale provides a standardized method for quantifying and comparing adverse effects across medications, categorizing side effects into four subgroups - psychic, neurological, autonomic, and other [37].

Finally, the participants' perceived self-rated health, including fitness, dietary habits, physical pain, and fatigue, was assessed through self-reported questionnaires using the "Health of the Danes" survey [38].

2.9. Statistical analyses

Data collection spanned from baseline to dropout or endpoint (after six months of intervention). Analyses were conducted unadjusted and adjusted for covariates, including baseline value, age, sex, diagnosis (unipolar and bipolar), and number of affective episodes. Descriptive statistics are presented with numbers and percentages for categorical data and median [interquartile range] for quantitative data.

Differences in secondary and tertiary endpoints were analyzed between the intervention and control group using an analysis of covariance (ANCOVA) model both using only the baseline value of the endpoint as a covariate, and adjusted with sex, age, diagnosis, and number of affective episodes as covariates. Binary outcomes were evaluated using binary logistic regression. Outcome mean differences, 95 % confidence intervals, and p-values are provided. In addition, sensitivity analyses were conducted according to the level of affective symptoms and the severity of impaired functioning and cognition. Finally, we conducted three sensitivity analyses to explore potential effects that may have been masked in the primary analyses. First, in line with the primary outcome analyses [20], the sample was divided according to whether the participants were in full remission (HDRS-17 $\leq$ 7) or partial remission (HDRS-17 > 7). Second, the sample was divided according to whether the participants exhibited objective cognitive impairment, defined as SCIP scores <70. Third, since perceived stress, as a secondary outcome, differed significantly between the AWARE and TAU groups, the sample was divided based on the participant reported perceived stress levels. Statistical significance was set at $p < 0.05$. Statistical analysis was performed in IBM SPSS Statistics Version 29.0.1.0.

2.10. Ethics

All patients were provided oral and written information about the trial before signing informed consent. All patients were informed that they were free to withdraw their participation at any time without this having any consequences on their course of treatment afterwards. The study was conducted according to all relevant institutional committees in Denmark and to the Declaration of Helsinki of 1975. The study

protocol for the AWARE study was approved by The Regional Ethics Committee in the Capital Region of Denmark (protocol number H-20029748). The study was registered at clinicaltrials.gov (NCT04701827) in January 2021, and two minor protocol amendments about inclusion criteria (age range) and target sample size were sent to the database in February 2022.

3. Results

3.1. Participant characteristics

One hundred three patients were included in the study, with 50 allocated to the AWARE intervention and 53 to the TAU group. Both groups had a low dropout rate. Specifically, 2 % (one out of 50 patients) dropped out from the AWARE group, while 9.4 % (five out of 53 patients) dropped out from the TAU group. The sociodemographic characteristics of the two groups were broadly similar, as summarized in Table 1. Regarding clinical characteristics, both groups had comparable ages of illness onset and the distribution of unipolar versus (vs) bipolar diagnoses. The median number of previous affective episodes was slightly higher in the AWARE group than in the TAU group. The participants in the AWARE group had a slightly higher rate of prior psychiatric hospitalizations (62.0 % vs. 45.3 % TAU). Psychiatric comorbidities were prevalent across both groups (20.0 % AWARE vs. 24.5 % TAU). The prevalence of medical comorbidities was comparable (56.0 % AWARE vs. 41.5 % TAU). In terms of medication use, both groups had similar patterns, with the most common medications including lithium, antipsychotics, antidepressants, and anticonvulsants. Use of benzodiazepines was somewhat higher in the AWARE group (32.0 % vs. 20.8 % TAU) (for a detailed presentation [20]).

Other characteristics for both groups are detailed in Table 1, which provides baseline and follow-up measures on sleep, metabolic health markers, alcohol and tobacco, physical activity, medication side effects, and perceived health. The adjusted and unadjusted ANCOVA analyses of these outcomes are presented in Tables 2 and 3.

3.2. Sleep

As seen from Table 2, using the Pittsburgh Sleep Quality Index (PSQI) there was no statistically significant differences between the AWARE and TAU groups for overall sleep quality in either the unadjusted or adjusted models (the unadjusted mean difference is −0.277 ((p = 0.668), and the adjusted mean difference is −0.429 (p = 0.509)) (Table 2). However, the likelihood of falling asleep within 30 min, was significantly increased in the AWARE group compared with the TAU group (adjusted beta-coefficient B = 1.298, p = 0.029, Table 3). Before the intervention, the odds ratio (OR) for falling asleep within 30 min in the AWARE group compared to the TAU group was 2.02 (95 % CI = 0.95–4.30). After the intervention, the odds ratio increased to 3.92 (95 % CI = 1.44–10.59), indicating a greater likelihood of faster sleep onset in the AWARE group relative to the TAU group (Fig. 1). Numerically, the overall sleep quality improved in the AWARE group, although it did not reach statistical significance (B = 0.749, p = 0.170, Table 3).

3.3. Metabolic health markers

No statistically significant differences were found between the AWARE and TAU groups in weight, BMI and waist circumference in the unadjusted or adjusted models (Table 2). Likewise, when comparing the fulfilment of the criteria for metabolic syndrome before and after the interventions, there were no significant differences between the two groups (Table 3). Similarly, biomarker analyses, including hemoglobin A1c, triglycerides, LDL, and HDL did not reveal any significant findings, though CRP revealed a trend (adjusted mean difference = 1.251, p = 0.081) (Table 2).

Table 1
Characteristics and health factors of the included patients with bipolar or unipolar disorders according to treatment group.

	Baseline		Follow-up	
Randomization group	AWARE (n = 50)	TAU (n = 53)	AWARE (n = 48)	TAU (n = 44)
Sociodemographic:				
Age, mean (s.d.)	41.64 (12.75)	39.92 (12.29)	Not collected	Not collected
Sex, female, n (%)	33 (66.00)	34 (64.15)	Not collected	Not collected
Education years, mean (s.d.)	13.61 (2.40)	13.83 (2.75)	Not collected	Not collected
Marital status "married/widowhood", n (%)	15 (30.00)	14 (26.42)	Not collected	Not collected
Employment status "employed" n (%)	11 (22.00)	15 (28.30)	Not collected	Not collected
Disability pension, n (%)	4 (8.00)	3 (5.66)	Not collected	Not collected
Student, n (%)	4 (8.00)	9 (16.98)	Not collected	Not collected
Clinical characteristics:				
Unipolar, n (%)	15 (30.00)	17 (32.08)	14 (29.17)	14 (31.82)
Bipolar, n (%)	35 (70.00)	36 (67.92)	34 (70.83)	30 (68.18)
Age at illness onset, mean (s.d.)	20.38 (8.30)	20.34 (8.57)	Not collected	Not collected
HDRS-17 total score, mean (s.d.)	9.48 (3.41)	9.75 (2.85)	9.55 (6.43)	9.88 (5.82)
YMRS total score, mean (s.d.)	2.40 (2.29)	2.98 (2.51)	2.02 (2.45)	2.15 (2.99)
FAST total, mean (s.d.)	37.76 (10.06)	35.53 (10.22)	31.04 (12.97)	36.05 (13.86)
Psychiatric comorbidity, n (%)	10 (20.00)	13 (24.53)	10 (20.83)	11 (25.00)
Medical comorbidity, yes, n (%)	28 (56.00)	22 (41.51)	27 (56.25)	18 (40.91)
Previous episodes (all – depressive, hypomanic, and manic), n, [IQR]	22 [38]	20 [25]	Not collected	Not collected
Previous hospitalization, n (%)	31 (62.00)	24 (45.28)	30 (62.50)	20 (45.45)
Hospitalizations, n, median [IQR]	1 [3]	0 [2]	1 [3]	0 [2]
Sleep:				
PSQI, mean (s.d.)	7.98 (2.81)	8.21 (3.03)	8.36 (3.73)	8.87 (3.89)
Global PSQI score less than 5 (indicating good sleep), n (%)	9/50 (18.0)	11/53 (20.8)	13/47 (27.7)	9/46 (19.6)
Falling asleep takes 30 min or less, n (%)	37/50 (74.0)	31/53 (58.5)	39/47 (83.0)	27/46 (58.7)
Metabolic health markers:				
Weight, mean (s.d.)	85.75 (19.05)	86.31 (22.27)	84.61 (19.60)	85.31 (22.74)
BMI, mean (s.d.)	29.01 (6.89)	29.01 (6.90)	28.74 (7.12)	28.90 (6.86)
Waist circumference, mean (s.d.)	99.26 (16.52)	96.44 (18.34)	98.33 (18.04)	97.92 (18.60)
Metabolic syndrome criteria met, n (%)	15/44 (34.10)	13/48 (27.10)	14/38 (36.80)	11/26 (42.30)
Haemoglobin A1c, mean (s.d.)	35.03 (9.46)	35.30 (9.38)	30.48 (15.03)	31.71 (14.65)
Triglycerides, mean (s.d.)	1.80 (1.38)	1.65 (1.28)	1.67 (1.04)	1.71 (1.25)
LDL, mean (s.d.)	2.81 (1.07)	2.53 (0.66)	2.76 (0.98)	2.65 (0.89)
HDL, mean (s.d.)	1.41 (0.37)	1.43 (0.47)	1.31 (0.30)	1.34 (0.48)
CRP, mean (s.d.)	4.37 (4.03)	4.92 (5.14)	5.14 (4.00)	4.27 (4.22)
Substance use:				
Smoking status "yes", n (%)	11/50 (22.0)	14/52 (26.9)	12/48 (25.0)	14/44 (31.8)
Alcohol consumption of more than 5 drinks at	2/50 (4.0)	4/53 (7.5)	3/48 (6.3)	7/44 (15.9)

(continued on next page)

Table 1 (*continued*)

Randomization group	Baseline		Follow-up	
	AWARE (n = 50)	TAU (n = 53)	AWARE (n = 48)	TAU (n = 44)
least once a week, n (%)				
Physical activity:				
IPAQ total score in MET-minutes mean, (s.d.)	2287.98 (2679.19)	2578.11 (3134.91)	2125.06 (2425.11)	2155.37 (2651.24)
Weekly calories burned through physical activity mean, (s.d.)	3141.10 (3587.40)	3496.81 (4127.96)	2968.77 (3373.94)	3133.30 (3908.42)
Medication side effects:				
UKU, psychic side effects mean, (s.d.)	1.28 (0.45)	1.34 (0.43)	1.00 (0.51)	0.99 (0.38)
UKU, neurological side effects mean, (s.d.)	0.34 (0.23)	0.24 (0.21)	0.53 (0.31)	0.55 (0.25)
UKU, autonomic side effects mean, (s.d.)	0.50 (0.32)	0.40 (0.24)	0.48 (0.37)	0.40 (0.26)
UKU, other side effects mean, (s.d.)	0.24 (0.14)	0.19 (0.16)	0.14 (0.14)	0.17 (0.20)
UKU, all side effects mean, (s.d.)	0.59 (0.23)	0.54 (0.19)	0.53 (0.25)	0.53 (0.17)
Perceived health:				
Self-rated overall health as “good”, “very good”, or “excellent”, n (%)	19/50 (38.0)	27/53 (50.9)	22/48 (45.8)	27/44 (61.4)
Self-rated fitness as “good” or “very good”, n (%)	4/50 (8.0)	8/53 (15.1)	8/48 (16.7)	8/44 (18.2)
Self-rated dietary habits as “relatively healthy”, “healthy” or “very healthy”, n (%)	29/50 (58.0)	34/53 (64.2)	35/48 (72.9)	30/44 (68.2)
Physical pain to an extent that it impairs daily work, n (%)	32/50 (64.0)	32/53 (60.4)	24/48 (50.0)	29/44 (65.9)
Very troubled by fatigue, n (%)	25/50 (50.0)	31/53 (58.5)	18/48 (37.5)	21/44 (47.7)
Perceives their weight as too high, n (%)	41/50 (82.0)	40/53 (75.5)	40/48 (83.3)	32/44 (72.7)

AWARE, Affective disorders: eliminate WArning signs And REstore functioning; TAU, Treatment as Usual; IQR, Interquartile Range; HDRS-17, The 17-item Hamilton Depression Rating Scale; YMRS, Young Mania Rating Scale; ECT, Electroconvulsive Therapy; FAST, Functioning Assessment Short Test; WHO Qol, WHO Quality of Life; BMI, Body Mass Index; LDL, Low Density Lipoprotein cholesterol; HDL; High Density Lipoprotein cholesterol; CRP, C-reactive Protein; PSQI, Pittsburg Sleep Quality Index; UKU, The UKU Side Effect Rating Scale; IPAQ, International Physical Activity Questionnaire; MET minutes, Metabolic Equivalent of Task minutes; n, number; s.d., standard deviation.

3.4. Tobacco and alcohol habits

There were no statistically significant differences between the groups for smoking status or alcohol habits (Table 3) at endpoint. For smoking status B = −0.260, p = 0.776. Numerically, the participants in the AWARE group were less likely to drink more than five drinks at least once a week, although this finding was not statistically significant (B = −1.184, p = 0.165). Finally, the number of affective episodes was significantly related to smoking (B = −0.055, p = 0.025).

3.5. Medication side effects

Across all domains including the four subdomains on the UKU Side Effect Rating Scale no significant differences were found between the AWARE and TAU groups (Table 2).

3.6. Perceived physical health

No statistically significant differences were found between the AWARE and TAU groups for most self-rated health measures (Table 3). However, a significant difference was identified regarding physical pain affecting daily work, where participants in the AWARE group were less likely to report such pain at follow-up (B = −1.656, p = 0.014). Before the intervention, the odds ratio (OR) for experiencing physical pain that impaired daily work was 1.17 in the AWARE group compared to the TAU group (95 % CI = 0.53–2.59). After the intervention, the odds ratio decreased to 0.52 (95 % CI = 0.22–1.20), indicating a reduced likelihood of pain impairing daily work in the AWARE group compared to the TAU group (Fig. 2).

3.7. Sensitivity analyses

First, the dataset was stratified by baseline HDRS scores, dividing participants into those with HDRS scores <7 (n = 84) and those ≥7 (n = 19). No significant or near-significant findings emerged among participants with HDRS scores <7. However, for those with HDRS scores ≥7, we found a borderline significant reduction in waist circumference in the AWARE group compared to the TAU group = −2.774 cm (95 % CI: 5.787 to 0.239, p = 0.070).

Second, the dataset was stratified using baseline SCIP scores, with participants categorized into those scoring <70 (n = 51) and those ≥70 (n = 52). In the cognitively impaired group, a significant reduction in waist circumference was found in the AWARE group compared to the TAU group on −4.496 cm (95 % CI: 8.081 to −0.911, p = 0.016). Additionally, we observed a trend toward a significant reduction in alcohol consumption (B = −2.865, p = 0.072) and global PSQI scores (B = −2.373, p = 0.097). In the cognitively unimpaired group, no significant findings were noted.

Third, the dataset was stratified using baseline perceived stress scale (PSS) scores. Participants with PSS scores <27 (n = 78) reported "low" or "moderate stress," while those with scores ≥27 (n = 25) reported "high stress" [39]. For participants with low or moderate stress, a statistically significant reduction in physical pain impairing daily work was observed in the AWARE group compared to the TAU group (B = −3.214, p = 0.005). For participants with high perceived stress levels, a borderline significant improvement in self-rated overall health was found at follow-up in the AWARE group (B = 2.964, p = 0.059).

4. Discussion

This randomized open label outcome assessor blinded clinical trial study investigated the effects of a multimodule individualized six months intervention on functioning in 103 patients with unipolar depressive disorder and bipolar disorder. The aim was to analyze health factors to gain insights into the intervention’s potential impact on physical health as secondary and tertiary outcome measures in the AWARE trial. Two key findings emerged: The AWARE group showed significantly better outcomes in falling asleep faster and experiencing less physical pain which impaired daily work compared to the TAU group. The improvements were evident in the odds ratios, demonstrating the intervention’s effectiveness. The odds ratio of falling asleep within 30 min nearly doubled, increasing from 2.02 to 3.92 after the intervention. Additionally, the AWARE group’s odds ratio of reporting pain impairing daily work decreased from 1.17 to nearly half 0.52 after the intervention.

Despite the positive findings, the intervention did not significantly affect other physical health outcomes, including weight, BMI, waist circumference, metabolic syndrome, medication side effects, smoking behavior, alcohol habits, weight, BMI, waist circumference, metabolic syndrome, and the metabolic biomarkers hemoglobin A1c, triglycerides, LDL, HDL, or CRP.

4.1. Comparison with findings from other studies

Regarding sleep, there was a statistically significant increase in the number of participants in the AWARE group who managed to fall asleep

Table 2
Results of the secondary and tertiary outcome measures at 6-months follow up (endpoint) in patients with bipolar or unipolar disorders according to treatment group.

	Model 1			Model 2		
Outcome	Difference between AWARE and TAU	95 % CI	p	Difference between AWARE and TAU	95 % CI	p
Sleep:						
PSQI	−0.277	−1.556; 1.002	0.668	−0.429	−1.716; 0.858	0.509
Metabolic health markers:						
Weight	0.225	−1.788; 2.237	0.825	0.165	−1.920; 2.251	0.875
BMI	0.53	−0.617; 0.722	0.876	0.035	−0.659; 0.728	0.921
Waist circumference	−1.479	−4.290; 1.331	0.298	−1.697	−4.568; 1.174	0.243
Haemoglobin A1c	0.919	−5.399; 7.238	0.772	0.469	−6.017; 6.956	0.885
Triglycerides	0.043	−0.455; 0.542	0.862	0.100	−0.404; 0.604	0.692
LDL	0.169	−0.350; 0.687	0.517	0.095	−0.420; 0.611	0.711
HDL	−0.085	−0.204; 0.034	0.156	−0.088	−0.204; 0.029	0.136
CRP	1.232	−0.270; 2.734	0.106	1.251	−0.158; 2.661	0.081
Physical activity:						
IPAQ total score in MET-minutes	−38.860	−1030.742; 953.022	0.938	183.995	−740.615; 1108.604	0.693
Weekly calories burned through physical activity	−345.710	−1814.263; 1122.843	0.641	−77.969	−1498.254; 1342.316	0.913
Medication side effects:						
UKU, psychic side effects	0.077	−0.124; 0.278	0.450	0.044	−0.158; 0.246	0.663
UKU, neurological side effects	0.088	−0.208; 0.033	0.152	−0.096	−2.18; 0.026	0.121
UKU, autonomic side effects	0.011	−0.106; 0.128	0.853	0.011	−0.107; 0.128	0.857
UKU, other side effects	−0.038	−0.113; 0.037	0.322	−0.041	−0.118; 0.036	0.293
UKU, all side effects, mean	−0.034	−0.116; 0.048	0.895	−0.041	−0.124; 0.041	0.322

AWARE, Affective disorders: eliminate WArning signs And REstore functioning; TAU, Treatment As Usual; CI, Confidence Interval; PSQI, Pittsburg Sleep Quality Index; BMI, Body Mass Index; LDL, Low Density Lipoprotein cholesterol; HDL, High Density Lipoprotein cholesterol; CRP, C-reactive Protein; IPAQ, International Physical Activity Questionnaire; MET, Metabolic Equivalent of Task; UKU, The UKU Side Effect Rating Scale.
Model 1: Analysis of Covariance, unadjusted (only adjusted for baseline value).
Model 2: Analysis of Covariance, adjusted for age, sex, diagnosis, and number of affective episodes (and adjusted for baseline value).

within 30 min at follow-up compared to baseline, an improvement that was significantly greater than what was observed in the TAU group (see Table 1). Furthermore, participants in the AWARE group reported less physical pain impairing daily work than those in the TAU group. However, no statistically significant differences were found between the groups regarding overall sleep quality, consistent with the findings in a recent review [1]. This systematic review did not find improvements in general sleep disturbances in individuals with bipolar disorder, despite targeting sleep as a lifestyle domain. These findings suggest that while specific aspects of sleep, such as sleep onset latency, may be responsive to interventions, broader improvements in sleep quality remain elusive. An upcoming study [40] describes a randomized controlled trial aiming to improve sleep quality in individuals with depression and bipolar disorder using a transdiagnostic approach that combines cognitive behavioral therapy for insomnia and chronotherapy. Similar to the AWARE study, the intervention includes individualized sessions addressing sleep disturbances and incorporates occupational therapy to address functional challenges in daily life. The study evaluates both overall sleep quality and specific parameters, such as sleep onset latency, through a lifestyle-focused intervention. Here, the sensitivity analyses showed that the subgroup of the cognitively impaired AWARE participants reported a trend towards improving global sleep scores. These results align with the primary analyses that also revealed that the AWARE subgroup with cognitive impairment significantly improved overall observer-rated functioning [20]. Findings that clinically point to that the patients with impaired function and co-existing cognitive impairment benefited more from the intervention.

The AWARE study showed no changes in physical health markers such as BMI, weight, and waist circumference between the groups. These results are consistent with another randomized study [15], which also reported no significant changes in BMI following their lifestyle intervention aimed at reducing cardiovascular disease risk in 134 patients with bipolar disorder. However, other studies have produced more favorable outcomes in terms of lifestyle. One study [16] targeting 402 patients with a diagnosis of bipolar disorder, schizophrenia, or major depression investigated the effects of a psychosocial group intervention on BMI, body weight and waist circumference and found a significant reduction in BMI (32.17–30.60, $p < 0.001$) and waist circumference (108.65 cm–105.89 cm, $p < 0.01$). The intervention focused solely on lifestyle factors such as diet, physical activity, smoking habits, and medication adherence, with group discussions and goal-setting activities in contrast to the AWARE study's primary aim targeting global functioning in patients with affective disorders with impaired functioning. Regarding metabolic blood markers, the AWARE intervention did not result in significant changes. These findings are consistent with another studies [41], who also reported no significant changes in HDL, LDL cholesterol, or triglycerides.

While the present AWARE intervention did not find significant improvements in physical activity levels measured by IPAQ, one study [42] demonstrated a statistically significant increase in the total metabolic equivalent of task minutes (MET minutes), with participants in the intervention group being nearly eight times more likely to increase their total MET (OR: 8.02, $p < 0.001$). This discrepancy could be due to the latter intervention's more structured and motivational approach provided for all participants, which incorporated regular walking sessions and a strong focus on behavioral change. Even though it was possible to target the AWARE intervention on regular walks and to increase the number of daily steps, the individualized approach used in the present study needs to be applied to all participants to generate measurable improvements in physical activity. These mixed results suggest that more focused interventions targeting physical health behaviors and metabolic markers may be necessary for significant improvements.

4.2. *Strengths and limitations*

One strength was the comprehensive assessment of physical health using a range of metrics, which the study captures, providing a broad and nuanced picture of the participants' health. Additionally, the use of both physical measurements and self-reported questionnaires adds depth to the assessment. Combining objective and subjective measures helps to provide a fuller understanding of physical health. One limitation is the relatively short duration of the intervention. A six-month

Table 3
Binary logistic regression models examining the influence of intervention group (AWARE vs. TAU), gender, age, diagnosis, and number of affective episodes on physical health parameters at follow-up compared to baseline.

		B	SE	P-value	Model 1 95 % CI	B	SE	P-value	Model 2 95 % CI
Sleep:									
Global PSQI score equal to or less than 5 (indicating good sleep)	Intercept	1.638	0.574	0.004	1.668; 15.857	1.625	0.591	0.006	0.062; 0.628
	Group	0.602	0.528	0.254	0.195; 1.540	0.749	0.545	0.170	0.162; 1.377
	Gender					0.190	0.617	0.758	0.247; 2.769
	Age					0.013	0.022	0.541	0.945; 1.030
	Diagnosis					−0.583	0.709	0.411	0.446; 7.195
	N episodes					0.024	0.022	0.269	0.935; 1.019
It takes 30 min or less to fall asleep	Intercept	2.115	0.533	<0.001	2.916; 23.553	2.423	0.605	<0.001	3.449; 36.902
	Group	1.122	0.544	**0.039**	0.112; 0.947	1.298	0.596	**0.029**	0.085; 0.878
	Gender					−0.729	0.679	0.283	0.548; 7.846
	Age					0.019	0.024	0.442	0.936; 1.029
	Diagnosis					−0.757	0.729	0.299	0.510; 8.906
	N episodes					0.002	0.021	0.926	0.958; 1.039
Metabolic syndrome:									
Metabolic syndrome criteria met	Intercept	−2.423	0.655	<0.001	0.025; 0.320	−2.166	0.722	0.003	0.028; 0.472
	Group	−0.695	0.657	0.290	0.138; 1.808	−0.786	0.674	0.244	0.122; 1.708
	Gender					0.487	0.748	0.515	0.375; 7.056
	Age					0.025	0.029	0.400	0.968; 1.086
	Diagnosis					−0.066	0.835	0.937	0.182; 4.809
	N episodes					−0.008	0.021	0.722	0.952; 1.035
Substance use:									
Smoking status "yes"	Intercept	5.119	0.902	<0.001	28.531; 979.228	6.051	1.200	<0.001	40.389; 4461.417
	Group	−0.158	0.846	0.852	0.228; 6.149	−0.260	0.912	0.776	0.217; 7.740
	Gender					0.013	0.041	0.740	0.911; 1.068
	Age					0.857	1.067	0.422	0.052; 3.439
	Diagnosis					0.258	1.346	0.848	0.055; 10.800
	N episodes					−0.055	0.025	**0.025**	1.007; 1.109
Alcohol consumption of more than 5 drinks once a weak or often	Intercept	3.217	0.984	0.001	4.032; 176.388	3.649	1.215	0.003	3.554; 415.969
	Group	−0.934	0.806	0.247	3.624; 171.767	−1.184	0.852	0.165	0.615; 17.355
	Gender					0.945	1.100	0.390	0.045; 3.358
	Age					−0.046	0.038	0.225	0.972; 1.127
	Diagnosis					1.097	1.106	0.321	0.038; 2.919
	N episodes					−0.042	0.024	0.074	0.996; 1.093
Perceived health:									
Self-rated overall health as "good", "very good", or "excellent"	Intercept	1.835	0.481	<0.001	2.442; 16.085	2.134	0.565	<0.001	2.791; 25.552
	Group	0.505	0.466	0.278	0.665; 4.132	0.374	0.503	0.457	0.256; 1.845
	Gender					−0.132	0.593	0.824	0.274; 2.801
	Age					−0.051	0.022	**0.022**	0.910; 0.993
	Diagnosis					0.990	0.660	0.134	0.738; 9.820
	N episodes					0.023	0.017	0.186	0.946; 1.011
Self-rated fitness as "good" or "very good"	Intercept	−3.000	0.752	<0.001	0.011; 0.217	−3.068	0.834	<0.001	0.009; 0.238
	Group	0.404	0.669	0.547	0.403; 5.558	0.422	0.680	0.535	0.402; 5.783
	Gender					0.169	0.703	0.810	0.298; 4.699
	Age					0.007	0.029	0.810	0.951; 1.066
	Diagnosis					0.855	0.914	0.350	0.392; 14.104
	N episodes					−0.002	0.020	0.939	0.960; 1.039
Self-rated dietary habits as "relatively healthy", "healthy" or "very healthy"	Intercept	2.260	0.542	<0.001	3.316; 27.720	2.349	0.560	<0.001	3.494; 31.416
	Group	0.563	0.533	0.291	0.200; 1.619	0.641	0.546	0.241	0.181; 1.538
	Gender					0.162	0.580	0.780	0.273; 2.652
	Age					0.011	0.022	0.618	0.947; 1.033
	Diagnosis					0.085	0.703	0.904	0.232; 3.641
	N episodes					0.009	0.017	0.611	0.958; 1.026
Physical pain to an extent that it impairs daily work	Intercept	−2.977	0.616	<0.001	0.015; 0.170	−2.751	0.686	<0.001	0.017; 0.245
	Group	−1.445	0.607	**0.017**	0.072; 0.775	−1.656	0.673	**0.014**	0.051; 0.714
	Gender					−1.009	0.621	0.104	0.108; 1.232
	Age					0.066	0.026	**0.012**	1.014; 1.125
	Diagnosis					−0.905	0.793	0.254	0.086; 1.915
	N episodes					−0.005	0.018	0.786	0.960; 1.031
Very troubled by fatigue	Intercept	−1.465	0.463	0.002	0.005; 0.536	−1.427	0.476	0.003	0.094; 0.610
	Group	0.332	0.451	0.461	0.191; 2.125	0.360	0.461	0.436	0.580; 3.539

(*continued on next page*)

Table 3 (*continued*)

		B	SE	P-value	Model 1 95 % CI	B	SE	P-value	Model 2 95 % CI
	Gender					−0.098	0.526	0.852	0.323; 2.542
	Age					−0.001	0.019	0.939	0.962; 1037
	Diagnosis					0.217	0.612	0.723	0.374; 4.127
	N episodes					0.006	0.016	0.682	0.976; 1.038
Perceives their weight as too high	Intercept	3.969	0.732	<0.001	12.612; 222.014	4.976	1.158	<0.001	14.986; 1401.462
	Group	0.561	0.734	0.444	0.135; 2.403	1.186	0.932	0.203	0.049; 1.896
	Gender					1.763	0.989	0.074	0.025; 1.190
	Age					−0.065	0.042	0.118	0.984; 1.157
	Diagnosis					3.122	1.552	**0.044**	0.002; 0.922
	N episodes					0.012	0.032	0.712	0.928; 1.052

AWARE, Affective disorders: eliminate WArning signs And REstore functioning; TAU, Treatment as Usual; N episodes, Number of Affective episodes; PSQI, Pittsburgh Sleep Quality Index; B, beta-value, SE, Standard Error; CI, Confidence Interval.
Model 1: unadjusted. Model 2: adjusted for gender, age, diagnosis, and number of affective episodes.

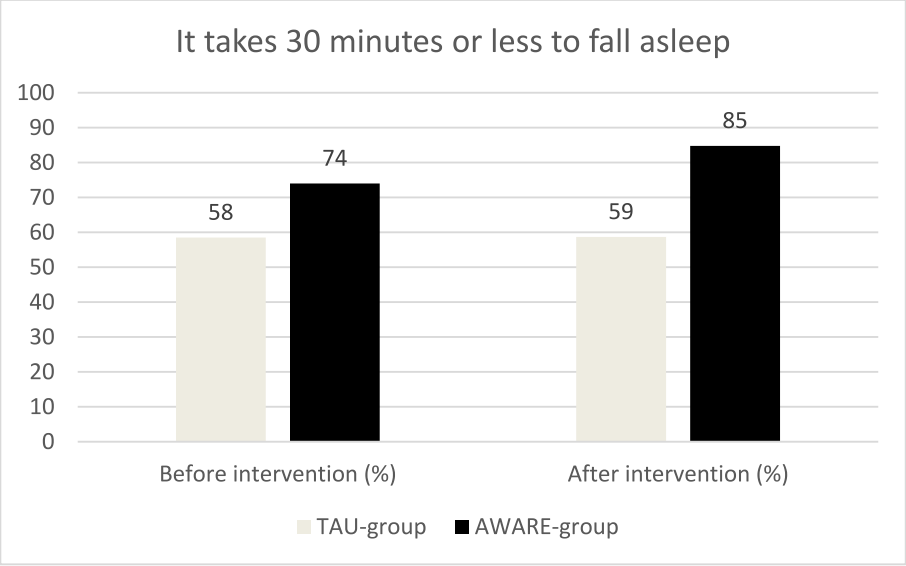

Fig. 1. The percentage of participants who fell asleep within 30 min in both the TAU group (TAU: Treatment as Usual) and the AWARE group (AWARE: AWARE intervention) before and after the intervention.

period may be insufficient to observe long-term changes in physical health outcomes, as meaningful improvements in these measures often require a more extended timeframe [43]. Further, due to the impaired functioning of the included patients, many had difficulties complying with the recommendations for fasting and smoking abstinence before blood tests and they were not strictly followed.

Furthermore, the intervention sessions were primarily conducted by a limited range of healthcare professionals, including occupational therapists, physicians, and nurses. The absence of other cross-disciplinary specialists such as physiotherapists or dietitians may have impacted the effectiveness of the intervention in areas such as physical activity, weight management, and dietary adjustments. Finally, the study's power calculations were based on the primary outcome measure, rather than the secondary and tertiary outcomes. Consequently, the sample size was not optimized to detect clinically meaningful changes in these additional health markers.

4.3. Clinical and research perspectives

Despite the negative results in most outcomes, this study provides valuable insights for future clinical research. Although multimodal interventions might show varied effects, they offer holistic benefits by simultaneously addressing multiple aspects of physical health. Rather than viewing these effects as a limitation, future studies could focus on optimizing multimodal designs to enhance overall physical health. Increasing the sample size would also improve statistical power, allowing for more precise detection of intervention effects. Extending the duration of the intervention and follow-up periods is essential, as changes in physical health markers often require more time to manifest. Furthermore, the results underscore the need for a broader range of healthcare professionals in the intervention process. Engaging specialists such as physiotherapists and dietitians could enrich the intervention, potentially leading to more substantial improvements. By building on the findings from this study, future research may refine multimodal interventions and develop more effective, tailored strategies for enhancing both mental and physical health outcomes in patients with affective disorders and impaired functioning.

4.4. Conclusion

The AWARE study demonstrates that a six-month multimodal intervention significantly improved sleep onset and daily pain management (as secondary outcome measures) in patients with affective disorders. However, no improvements were observed in other secondary

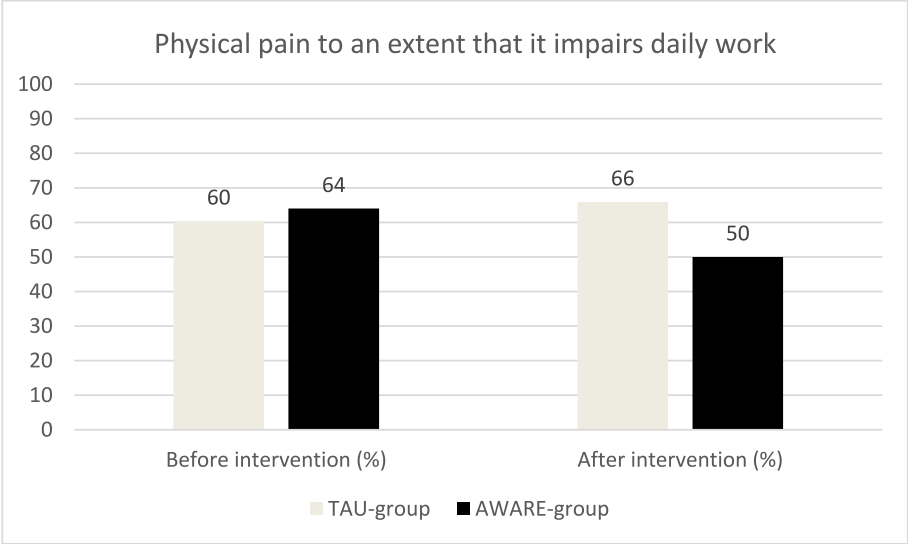

Fig. 2. The percentage of participants who reported physical pain to an extent that it impairs daily work in both the TAU group (TAU: Treatment as Usual) and the AWARE group (AWARE: AWARE intervention) before and after the intervention.

physical health markers, likely due to the study's limited sample size and duration. These findings underscore the complexity of addressing physical health in this patient group, particularly among individuals with functional impairments. Importantly, the results emphasize the need for clinicians to integrate a focus on physical pain perception in the management of affective disorders.

Given the challenges in achieving broad physical health improvements within a six-month period, future research should explore longer intervention durations, personalized treatment adaptations, and a more interdisciplinary approach involving healthcare professionals from multiple fields. Further refinement of multimodal interventions is relevant to effectively enhance both physical and mental health outcomes. The AWARE study provides valuable insights that can inform the design of future interventions, ultimately improving the quality of care for individuals with affective disorders.

CRediT authorship contribution statement

Ida Schou Ipsen: Writing – original draft. **Rasmus Schwarz:** Writing – original draft. **Lars Vedel Kessing:** Writing – original draft. **Kamilla M. Miskowiak:** Writing – original draft. **Maj Vinberg:** Writing – original draft.

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Declaration of competing interest

ISI has nothing to declare.

RS has within the last three years been a speaker/consultant for Lundbeck. After initiation of this work, RS has been employed by Novo Nordisk A/S; Novo Nordisk A/S is not involved in this project.

KWM has received honoraria from Lundbeck, Gideon Richter and Angelini in the past three years.

LVK has within the last three years been a consultant for Lundbeck and Teva.

MV has within the last three years been a speaker/consultant for Lundbeck and Janssen-Cilag.

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