Omega-3 fatty acids in bipolar patients with a low omega-3 index and reduced heart rate variability: the “BIPO-3” trial

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Abstract

Background: Research suggests that a low omega-3 index may contribute to the low heart rate variability and the increased risk of cardiovascular morbidity and mortality in bipolar disorders. However, so far, no intervention trial with EPA and DHA has been conducted in bipolar patients attempting to increase their heart rate variability.

Methods: 119 patients with bipolar disorder according to DSM-IV were screened, with 55 euthymic bipolar patients—owing to inclusion criteria (e.g. low omega-3 index (< 6%), SDNN < 60 ms.)—being enrolled in a randomized, double-blind, 12-week parallel study design with omega-3 fatty acids (4 capsules of 530 mg EPA, 150 mg DHA) or corn oil as a placebo, in addition to usual treatment. Heart rate variability as well as the omega-3 index were measured at baseline and at the endpoint of the study.

Results: A total of 42 patients (omega-3: n = 23, corn oil: n = 19) successfully completed the study after 12 weeks. There was a significant increase in the omega-3 index (value at endpoint minus value at baseline) in the omega-3 group compared to the corn oil group (p < 0.0001). However, there was no significant difference in the change of the SDNN (value at endpoint minus value at baseline) between the treatment groups (p = 0.22). In addition, no correlation between changes in SDNN and change in the omega-3 index could be detected in the omega-3 group (correlation coefficient = 0.02, p = 0.94) or the corn oil group (correlation coefficient = −0.11, p = 0.91). Similarly, no significant differences between corn oil and omega-3 group regarding the change of LF (p = 0.19), HF (p = 0.34) and LF/HF ratio (p = 0.84) could be demonstrated.

Conclusions: In our randomized, controlled intervention trial in euthymic bipolar patients with a low omega-3 index and reduced heart rate variability no significant effect of omega-3 fatty acids on SDNN or frequency-domain measures HF, LF and LF/HF ratio could be detected. Possible reasons include, among others, the effect of psychotropic medication present in our trial and/or the genetics of bipolar disorder itself. Further research is needed to test these hypotheses.

Trial registration ClinicalTrials.gov, NCT00891826. Registered 01 May 2009—Retrospectively registered, https://clinicaltrials.gov/ct2/show/NCT00891826

Keywords: Bipolar disorders, Omega-3 fatty acids, Heart rate variability, omega-3 index, Randomised controlled trial

Introduction

Bipolar disorders are common diseases, with a lifetime prevalence of around 1–5%, depending on the definition applied (Merikangas et al. 2011) and are associated with substantial disability (Vos et al. 2012) and...
reduced life expectancy Kessing et al. 2015a, b). Most studies suggest that patients with bipolar disorders are at increased risk of cardiovascular morbidity and mortality (Goldstein et al. 2015a, b; Marsha et al. 2017; Prieto et al. 2014; Wulsin et al. 2018). A low heart rate variability (HRV) is thought to be a risk factor for cardiovascular morbidity and mortality (Huikuri and Stein 2013), specifically in patients with affective disorders and comorbid heart disease (Carney et al. 2005). Even when being euthymic, i.e. showing no significant symptoms, a substantial proportion of bipolar patients, possibly in particular those with more advanced stages of the disorder (Freyberg et al. 2020), have decreased heart rate variability compared to a control group, irrespective of specific pharmacological treatment, possibly indicating a shift of sympathovagal balance towards vagal tone predominance and a reduced sympathetic tone (Cohen et al. 2003). The reasons for this are still largely unclear (Drewery et al. 2017; Faurholt-Jepsen et al. 2017). Notwithstanding, the available data suggest that reduced heart rate variability could therefore contribute to the increased cardiovascular morbidity and mortality in patients with bipolar disorder.

In bipolar patients, levels of the two omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have been found to be low in most (Faurholt-Jepsen et al. 2017; Freyberg et al. 2020), but not all cross-sectional studies (Voggt et al. 2015), including studies with individuals at risk of or with first-episode bipolar disorder (McNamara et al. 2015, 2016; Wulsin et al. 2018). Meta-analyses have demonstrated that EPA-predominant formulations improve symptoms of clinically diagnosed depression (Liao et al. 2019; Saunders et al. 2016), which prompted guidelines to adopt this approach (Guu et al. 2019). Furthermore, omega-3 fatty acids have been demonstrated to increase heart rate variability in many intervention trials in different patient populations (Rovere and Christensen 2015) and may reduce the risk of coronary death and coronary events (Abdelhamid et al. 2020; Zelniker et al. 2021). However, so far, no intervention trial with EPA and DHA has been conducted in bipolar patients attempting to increase their heart rate variability. Therefore, we tested the hypothesis that omega-3 fatty acids significantly improve heart rate variability (Severus et al. 1999), measured as standard deviation of the normal-to-normal interval (SDNN, ms), in a randomized, double blind controlled intervention trial in euthymic patients with bipolar disorders with a low omega-3 index (Harris and von Schacky 2004, 2007) and reduced heart rate variability.

Methods
Participant recruitment
Potential trial participants were screened in the inpatient and outpatient units of the Department of Psychiatry and Psychotherapy of the Ludwig-Maximilians-University, Munich. Potentially eligible patients were approached by one of the authors (MB) and informed about the study. If patients were interested in participating in this study, the following clinical inclusion and exclusion criteria were checked. Patients who were (1) diagnosed with bipolar disorders (I, II) in remission according to the Structured Clinical Interview (SCID) for the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV), (2) able to give written informed consent, (3) between 18 and 65 years of age, (4) on stable psychotropic medication for at least 2 weeks, (5) fluent in German or English to complete baseline and follow-up interviews met the clinical inclusion criteria. Clinical exclusion criteria were: (1) a diagnosis of current substance abuse (with or without substance dependence), (2) intake of omega-3 fatty acids was indicated according to recent treatment guidelines, (3) treatment with anticoagulants, (4) any acute or life-threatening comorbidity, such as collapse and shock, acute myocardial infarction, stroke, embolism, or disease seriously limiting life expectancy (5) current significant suicidal or homicidal risk in the investigator’s judgement, (6) low likelihood of compliance with the study protocol, (7) childbearing potential without a medically accepted method of contraception, pregnancy or breastfeeding.

If patients were eligible, they were asked to sign a written informed consent form. After signing, diagnosis was confirmed using the structured clinical interview for DSM-IV (Wittchen et al. 1997). A blood sample was drawn for determination of the omega-3 Index and heart rate variability was measured. A low omega-3-index (<6%), and a low SDNN (<60 ms) were inclusion criteria numbers 6 and 7. Patients fulfilling all inclusion and no exclusion criteria were recruited for the trial.

The present trial was approved by the ethics’ committee of the medical faculty of the Ludwig-Maximilians-University, Munich, registered at Clinicaltrials.gov (NCT00891826), and conducted between January 2009 and April 2012 according to the Guidelines laid down in the Declaration of Helsinki and Good Clinical Practice. Informed consent allowed analysis of all the clinical and laboratory data mentioned in the present report. The trial was initiated, designed, conducted, and evaluated by the investigators, and the sponsor had no role in study design, data acquisition, or evaluation or preparation of the manuscript.
**Trial design**

The present trial was a randomized, double-blind, single-center, 12-week parallel study comparison of omega-3 fatty acids vs. corn oil, in addition to usual treatment. The primary endpoint of the trial was a change in HRV, as assessed by SDNN in ms. Predefined secondary endpoints were a change in HRV, as assessed by a ratio of low frequency to high frequency (LH/HF ratio); new episodes of bipolar depression; and mood rating scales.

**Procedures**

Eligible patients were randomized to 4 capsules EPAX 6015 TG per day (2 in the morning, 2 in the evening), each containing 530 mg of EPA (eicosapentaenoic acid) and 150 mg of DHA (docosahexaenoic acid) as triglycerides or 4 matching capsules containing corn oil as placebo, to be taken with a meal to maximize bioavailability. Both products were produced and provided by EPAX AS: http://www.epax.com/. The placebo was matched to the study drug for taste, color and size. Patients were to continue with their pre-existing psychotropic medication, with adjustments as clinically indicated.

At baseline, demographics, clinical history and medication were assessed by means of the Network Enrolment Questionnaire as previously used by the Stanley Foundation Bipolar Network (Suppes et al. 2001). At baseline and at 12 weeks, HRV and the omega-3 Index and other blood parameters were measured, as was the pathological state using standardized rating scales: Young Mania Rating Scale (YMRS), Hamilton Rating Scale for Depression, [HAMD (Hamilton 1967)], Montgomery-Åsberg Depression Rating Scale [MADRS (Montgomery and Asberg 1979)], Beck Depression Inventory [BDI (Beck et al. 1961)] and Clinical Global Impressions Scale for Bipolar Illness [CGI (Spearing et al. 1997)].

**Heart rate variability**

HRV was assessed as recently described in more detail (Voggt et al. 2015). A slightly darkened room was used which had a comfortable room temperature. Participants were asked to relax and stay awake during the test period. Careful considerations were made to ensure subjects were not disturbed by noise. Recordings took place at the same time of the day, commonly between 10 am and 2 pm, with few exceptions being equally distributed between verum and placebo groups. A ProSciCard III (CPS medical, Tyler, TX, USA), was used to continuously record electrocardiograms (ECG) in a supine position, during normal breathing, after a short rest during a 30 min interval. The RecordProSciCard computer system (ProSciCard III) was installed for analysing HRV. By using the recorded NN intervals, the standard deviation of the NN interval (SDNN) (as a statistical time domain measure) was calculated (CPS GmbH 2009). The system’s intern check of the data was performed by Task Force Analysis, artefacts were marked. Before elimination of the artefacts, it was double-checked if the artefacts set by the software were correct and if overlooked by the software artefacts could be marked by the investigator (CPS GmbH 2009). Artefacts were defined as a fluctuation range of more than 15% of the RR-Intervals. Using power spectrum analysis frequency domain parameters of HRV were derived with high-frequency power (HFP; defined as 0.15–0.40 Hz) and low-frequency power (LFP; defined as 0.04–0.15 Hz) expressed in normalized units adjusting for changes in total power (which is related to HR).

**Omega-3 index**

Erythrocyte fatty acid composition was analysed according to the HS-Omega-3 Index® methodology as previously described (Harris and von Schacky 2004). Results are given as EPA plus DHA expressed as a percentage of total identified fatty acids after response factor correction. The coefficient of variation for EPA plus DHA was 5%. Analyses were quality-controlled according to DIN ISO 15189 (Rovere and Christensen 2015).

**Statistical analyses**

The power calculation is based on Cohen et al. (2003), in combination with our own data, the statement of the taskforce (Heart rate variability 1996) and the usual assumptions (alpha = 5%, power = 80%): the primary outcome parameter was defined as standard deviation of all normal RR intervals (SDNN, in ms.). Based on the assumption that SDNN will increase by 10 ms on average in the omega-3 fatty acid group, 23 patients per group were needed; a total of 46 patients. Furthermore, as we expected approximately 10% of our patients to drop out prematurely due to a variety of reasons, we planned to recruit a total number of 51 patients.

Data analysis was carried out using the statistical program R 2.9.0 (Hornik 2012). For categorical data, Fisher’s Exact test was used, and Wilcoxon rank sum test for metric variables. In the case of HRV, baseline and endpoint values of SDNN, low frequency (LF), high frequency (HF), LF/HF ratio were compared both within and between groups.

Linear mixed models with random intercept were calculated unadjusted, and adjusted for age and gender, as it has been shown in previous studies that HRV measures decline with advancing age (Bigger et al. 1995; Liao et al. 1995; Zulfiqar et al. 2010), and supplementation with omega-3 fatty acids seems to have a beneficial effect on HRV especially in men (Christensen and Schmidt 2007). Linear regression models that explain
heart rate variability (SDNN, LF, HF, LF/HF ratio) best were created: In order to explain the dependent variable group affiliation and omega-3 index were integrated as independent variables. As a next step the change/difference (value at endpoint minus value at baseline) was illustrated. This was calculated for SDNN, omega-3 index, LF, HF and LF/HF ratio. First univariate tests, using Wilcoxon signed-rank test, on differences between placebo and verum group were performed. In addition, unadjusted and adjusted (age, gender) linear mixed models on the changes of SDNN were calculated with group affiliation and change in omega-3 index as independent variables. Furthermore, Pearson correlation coefficients with changes in SDNN were calculated for the change of omega-3 index. For all statistical calculations the significance level was set 5% (p < 0.05).

Finally, a linear regression model within the patient group taking omega-3 as well as the control group taking corn oil was calculated in order to explain SDNN change over time. Explaining variables were EPA change, DHA change and omega-3 index at baseline. Age, gender and diagnosis of bipolar disorder were further co-variables in the model.

Results
Study population
Of 119 patients with Bipolar I/II Disorder screened, 55 patients met the inclusion criteria, and were willing to participate. Of those, 27 were randomized to omega-3 fatty acids, and 28 patients to corn oil. A total of 42 patients (omega-3 fatty acids: n = 23, corn oil: n = 19) completed the study, while 13 did not (omega-3 fatty acids: n = 4, corn oil: n = 9). The reasons were as follows: 6 patients were excluded from the study due to non-adherence to the study protocol, 6 patients withdrew consent, 1 patient was no longer accessible (Fig. 1: Flow Diagram). Demographic and clinical characteristics of study completers are shown in Table 1. No statistical significant differences could be demonstrated.

The psychotropic medication taken by the bipolar patients in the omega-3 group and in the corn oil group is shown in Table 2. With few exceptions with regard to the dose of the medication prescribed, equally distributed between treatment groups, psychotropic medication was stable during the study period.

Standardized rating scales
At baseline there was a significant difference in terms of the total score of the 21-item HAMD scale. According to this scale, patients in the omega-3 group were more depressed (6.9 ± 6.50) than those in the corn oil group (3.1 ± 3.25) (p = 0.019), though still not meeting the criteria for a depressive episode.

At end of study, in none of the standardized rating scales a significant difference between patients in the omega-3-group and the corn oil group was found. Endpoint and baseline scores were not significantly different (Table 3).

SDNN
At baseline mean SDNN in patients in the omega-3 group was 34.4 ± 13.30 ms, and in the corn oil group 32.2 ± 16.65 ms (n.s.) (Table 4). At endpoint mean SDNN in patients in the omega-3 group was 39.8 ± 12.25 ms, and in the corn oil group 33.89 ± 17.24 (n.s.) (Table 5). The change in SDNN (value at endpoint minus value at baseline) was 1.8 ± 14.35 ms in the corn oil group and 5.4 ± 18.19 ms. in the omega-3 group. There was no significant difference in the change of SDNN (in comparison of baseline and endpoint) between groups (Table 6). In addition, no correlation between changes in SDNN and change in the omega-3 index in the omega-3 group was detected (correlation coefficient = 0.02, p = 0.94). The same was true for the corn oil group (correlation coefficient = − 0.11, p = 0.91).

Linear mixed models with random intercept were created, initially unadjusted (Tables 7, 8), then adjusted for age and gender (Tables 9, 10). Unadjusted as well as adjusted for age and gender no significant effect of group affiliation (unadjusted: p = 0.5873, adjusted: p = 0.8270) and the omega-3 index (unadjusted: p = 0.8143, adjusted: p = 0.8377) on SDNN were observed.

In addition, linear models on the SDNN change were calculated including group affiliation and change of omega-3 index as predictors. Neither for group (unadjusted: p = 0.4445, adjusted: p = 0.4447) nor for change of omega-3 index (unadjusted: p = 0.6462, adjusted: p = 0.6241) statistically significant effects were found.

However, in the intervention group, but not in the control group, the result of the regression model, with explaining variables EPA change, DHA change and omega-3 index at baseline and age, gender and diagnosis of bipolar disorder as further co-variables in the model, indicates a positive association of the omega-3 index at baseline with an increase of SDNN during the study (p = 0.04). In addition, the change of DHA shows a positive association with concurrent change of SDNN in the study (i.e. increasing the concentration of DHA goes along with increasing SDNN, (p = 0.01), while the change of EPA shows a negative association with SDNN (i.e. increasing concentration of EPA goes along with decreasing SDNN, p = 0.01).

LF, HF und LF/HF
In terms of the absolute values of HF, LF, and the LF/HF ratio, no significant differences between the corn oil
and the omega-3 group were found at baseline and at the end of the study period (Tables 4, 5). Linear mixed models were created including group affiliation and omega-3 index as predictors. Neither for group (LF \( p = 0.5535 \), HF \( p = 0.4579 \), LF/HF ratio \( p = 0.4654 \)) nor for omega-3 index (LF \( p = 0.3810 \), HF \( p = 0.7065 \), LF/HF ratio \( p = 0.5564 \)) significant influence on frequency parameters were shown.

As a next step the change of LF, HF, LF/HF ratio (value at endpoint minus value at baseline) was illustrated. Using Wilcoxon signed-rank test no significant differences between the corn oil and the omega-3 group regarding the change of LF (\( p = 0.19 \)), HF (\( p = 0.34 \)) and LF/HF ratio (\( p = 0.84 \)) were demonstrated (Table 6).

Linear models on the change of LF, HF, LF/HF ratio were calculated including group affiliation and change of omega-3 index as predictors, initially unadjusted, then adjusted for age and gender. Neither for group (unadjusted: LF \( p = 0.53 \), HF \( p = 0.54 \), LF/HF ratio \( p = 0.39 \); adjusted: LF \( p = 0.76 \), HF \( p = 0.66 \), LF/HF ratio \( p = 0.57 \)) nor for change of omega-3 index (unadjusted: LF \( p = 0.47 \), HF \( p = 0.50 \), LF/HF ratio \( p = 0.63 \); adjusted: LF
### Table 1 Demographic and clinical variables of the study population: mean ± sd [missing values]

|                   | Omega-3 (n = 23) | Corn oil (n = 19) | p-value |
|-------------------|------------------|-------------------|---------|
| Age (years)       | 46.6 ± 13.25     | 42.1 ± 10.75      | 0.33    |
| Gender (m/f)      | 11/12            | 8/11              | 0.76    |
| Bipolar (I/II)    | 12/5             | 8/5               | 0.71    |
| Bipolar NOS       | 6                | 6                 | 0.74    |
| Age at onset depression (years) | 22.7 ± 10.25     | 24.2 ± 6.75      | 0.62    |
| Age at onset mania (years) | 29.0 ± 18.00      | 25.1 ± 7.25      | 0.36    |
| Number depressive episodes | 9.5 ± 7.00         | 9.9 ± 9.00     | 0.74    |
| Number manic episodes | 5.0 ± 4.00         | 8.3 ± 4.00      | 0.86    |
| Episodes mania/depression | 0.2 ± 0.25         | 0.2 ± 0.00      | 0.76    |
| Hospitalisation depression | 2.1 ± 1.75         | 2.9 ± 1.00      | 0.77    |
| Hospitalisation mania | 1.4 ± 2.00         | 1.5 ± 2.00      | 0.62    |
| Hospitalisation mania/depression | 0.6 ± 1.00          | 0.6 ± 1.00     | 0.69    |
| MADRS LOCF        | 6.06|0 (9.53) | 7.45|5 (8.24) | 0.6485 |
| MADRS change      | 3.2|0 (6.5)  | 2.22|0 (5.08) | 0.7031 |
| HAMD LOCF         | 5.56|2 (7.7)  | 6.45|5 (6.16) | 0.7105 |
| HAMD change       | 2.44|0 (5.11) | 0.16|0 (5.44) | 0.1558 |
| HAMD-17 LOCF      | 4.25|1 (6.77) | 5.25|3 (5.24) | 0.6308 |
| HAMD-17 change    | 1.69|0 (4.69) | 0.21|0 (4.96) | 0.3726 |
| CGI MANIA LOCF    | 1.27|0 (0.59) | 1.35|0 (0.81) | 0.7282 |
| CGI MANIA change  | 0.36|0 (0.74) | 0.44|0 (1.04) | 0.7843 |
| CGI depression LOCF | 1.67|1 (1.11) | 2.1|1.5 (1.33) | 0.3031 |
| CGI depression change | 0.21|0 (0.89) | 0.11|0 (1.02) | 0.7631 |
| CGI bipolar LOCF  | 1.67|1 (1.11) | 2.05|2 (1.1)  | 0.3187 |
| CGI Bipolar change | 0.14|0 (1.23) | 0.11|0 (0.83) | 0.5144 |
| YMRS LOCF         | 2.06|0 (3.82) | 1.2|1 (1.54) | 0.4063 |
| YMRS change       | 0.12|0 (3.4)  | 0.94|0 (1.59) | 0.2631 |

### Table 2 Psychotropic medication

|                   | Omega-3 (n = 23) | Corn oil (n = 19) |
|-------------------|------------------|-------------------|
| Quetiapine        | n = 13           | n = 13            |
| Olanzapine        | n = 4            | n = 1             |
| Risperidone       | n = 1            | n = 0             |
| Haloperidol       | n = 0            | n = 1             |
| Aripiprazole      | n = 2            | n = 1             |
| Melperone         | n = 1            | n = 0             |
| Prothipendyl      | n = 1            | n = 0             |
| Lithium           | n = 5            | n = 5             |
| Valproate         | n = 4            | n = 7             |
| Lamotrigine       | n = 4            | n = 9             |
| Lorazepam         | n = 2            | n = 1             |
| Diazepam          | n = 1            | n = 0             |
| Zopiclone         | n = 3            | n = 0             |
| Venlafaxine       | n = 0            | n = 4             |
| Mirtazapine       | n = 0            | n = 1             |
| Escitalopram      | n = 0            | n = 2             |
| Sertraline        | n = 1            | n = 0             |
| Fluoxetine        | n = 1            | n = 0             |
| Trimipramine      | n = 0            | n = 1             |
| Agomelatine       | n = 1            | n = 0             |
| Citalopram        | n = 1            | n = 0             |
| Duloxetine        | n = 1            | n = 0             |
| Doxepin           | n = 1            | n = 0             |
| Pregabalin        | n = 1            | n = 0             |
| No medication     | n = 2            | n = 0             |
| No data           | n = 3            | n = 0             |

### Table 3 Standardized rating scales endpoint and change from baseline, respectively: mean/median (SD) [missing values]

|                   | Omega-3 (n = 23) | Corn oil (n = 19) | p-value |
|-------------------|------------------|-------------------|---------|
| SDNN (ms)         | 34.4|32.1 (13.30) | 32.2|28.3 (16.65) | 0.45    |
| LF (ms²)          | 0.23|0.18 (0.17)  | 0.3|0.28 (0.22)  | 0.2379  |
| HF (ms²)          | 0.11|0.11 (0.07)  | 0.14|0.08 (0.13)  | 0.3873  |
| LF/HF ratio       | 2.84|1.96 (2.61)  | 2.2|2.02 (1.19)  | 0.2995  |
| Omega-3 index (%)| 4.7|4.8 (0.69)   | 4.6|4.8 (1.35)   | 0.67    |
p = 0.49, HF p = 0.47, LF/HF ratio p = 0.63) statistically significant effects on any of these variables was found.

### Omega-3-index

The mean omega-3 index at baseline was 4.6 ± 1.35% in the corn oil group, compared to 4.7 ± 0.69% in the omega-3 group (n.s.), (Table 4), the mean omega-3 index at endpoint was 4.23 ± 0.87% in the corn oil group, compared to 9.69 ± 2.35% in the omega-3 group (p < 0.0001) (Table 5). The change of omega-3 index after 12 weeks (value at endpoint minus value at baseline) was −0.4 ± 1.06% in the corn oil-group, compared to 5.0 ± 1.94% in the omega-3 group (p < 0.0001) (Table 6).

### Mood ratings, new episodes

In the omega-3 group, 3 patients experienced a depressive episode, but none in the placebo group. There were no significant differences in change from baseline to endpoint in any of the standardized rating scales (Table 3).

### Discussion

In our randomized, controlled intervention trial, comparing the effects of 2120 mg EPA plus 600 mg DHA per day with a corn oil placebo in euthymic bipolar patients with a low omega-3 index and reduced heart rate variability no significant effect of omega-3 fatty acids on SDNN or frequency-domain measures HF, LF and LF/HF ratio could be detected. In light of the positive effects of omega-3 fatty acids on parameters of HRV in cardiovascular patients (Harris et al. 2006) this is a perplexing finding.

Was our trial inadequately designed or conducted to detect an effect? As discussed in the introduction, our trial had a high likelihood of detecting a beneficial effect of EPA and DHA on HRV in bipolar patients. By selecting bipolar patients with low baseline levels of EPA and DHA, and with a low SDNN, we selected a population for our trial likely to benefit from our intervention. The trial design we used has been suggested for all trials with omega-3 fatty acids with cardiovascular endpoints (Rice 2003).

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**Table 5** Endpoint values: mean/median (SD)

| Omega-3 (n = 23) | Corn oil (n = 19) | p-value |
|------------------|-------------------|---------|
| SDNN (ms)        | 39.8 ± 40.27 (12.25) | 33.8 ± 31.55 (17.24) | 0.21    |
| LF (ms²)         | 0.43 ± 0.24 (0.43)  | 0.39 ± 0.16 (0.5)   | 0.8046  |
| HF (ms²)         | 0.16 ± 0.14 (0.13)  | 0.16 ± 0.06 (0.24)  | 0.9625  |
| LF/HF ratio      | 4.38 ± 2.76 (4.31)  | 3.08 ± 2.89 (1.58)  | 0.1871  |
| Omega-3 Index (%)| 9.69 ± 9.96 (2.35)  | 4.23 ± 4.13 (0.87)  | < 0.0001 |

**Table 6** Change endpoint vs. baseline: mean/median (SD)

| Omega-3 (n = 23) | Corn oil (n = 19) | p-value |
|------------------|-------------------|---------|
| SDNN (ms)        | 5.4 ± 5.8 (18.19)  | 1.8 ± 0.0 (14.35) | 0.22    |
| LF (ms²)         | 0.2 ± 0.0 (0.42)   | 0.1 ± 0.0 (0.22)  | 0.19    |
| HF (ms²)         | 0.0 ± 0.0 (0.14)   | 0.0 ± 0.0 (0.04)  | 0.34    |
| LF/HF ratio      | 1.5 ± 0.8 (2.31)   | 0.9 ± 0.6 (1.74)  | 0.84    |
| Omega-3 Index (%)| 5.0 ± 5.3 (1.94)   | −0.4 ± 0.3 (1.06) | < 0.0001 |

**Table 7** Effect of Omega-3 Index on SDNN, unadjusted

| p-value |
|---------|
| Intercept | 10.698–59.239 | 0.0032 |
| Omega-3 index | −5.453–4.735 | 0.8143 |
| Time | −27.714–24.799 | 0.8161 |
| Omega-3 x time | −4.389–6.206 | 0.6382 |

**Table 8** Effect of group on SDNN, unadjusted

| p-value |
|---------|
| Intercept | 26.469–38.012 | 0.0000 |
| Group verum | −5.841–9.783 | 0.5873 |
| Time | −6.225–9.587 | 0.6114 |
| Group verum x time | 7.122–14.500 | 0.4422 |

**Table 9** Effect of Omega-3 Index on SDNN, adjusted for age and sex

| p-value |
|---------|
| Intercept | 0.0490–67.3953 | 0.0419 |
| Age | −0.2779–0.2875 | 0.9953 |
| Gender | −8.3393–3.5283 | 0.4163 |
| Omega-3 index | −5.4301–6.3270 | 0.8377 |
| Time | −27.1000–33.2260 | 0.8107 |
| Omega-3 x time | −6.0341–6.0408 | 0.9955 |

**Table 10** Effect of group on SDNN, adjusted for age and sex

| p-value |
|---------|
| Intercept | 22.0956–56.2707 | 0.0001 |
| Age | −0.3337–0.2395 | 0.7813 |
| Gender | −9.2594–2.6153 | 0.4067 |
| Group Verum | −7.4779–8.8112 | 0.8270 |
| Time | −6.6198–10.0832 | 0.6169 |
| Group Verum x time | −7.1723–15.5608 | 0.3089 |
This page discusses the measurements of heart rate variability (HRV) and the impact of omega-3 fatty acids on it. The study measured low-frequency (LF), high-frequency (HF), and the LF/HF ratio. Changes in HRV were assessed using various parameters such as standard deviation of normal-to-normal intervals (SDNN) and the proportion of RR intervals that differ more than 50 ms (pNN50). The trial aimed to improve heart rate variability and prevent changes in omega-3 status in the intervention group. The results showed a significant difference in omega-3 status between the intervention and control groups.

The study also considered potential confounders, such as patient population, dose, intervention duration, and type of placebo. The findings suggest that omega-3 fatty acids may improve HRV and prevent changes in omega-3 status.
low frequency [VLF (p = 0.009)], and for heart rate (HR (p = 0.03)). However, the interactions for all secondary HRV indices were not significant [in HF (p = 0.12), in LF (p = 0.11), in ultra low frequency (ULF (p = 0.23))]. SDNN was not measured. In the second place, in our study, in the intervention group, but not in the control group, there was a positive association of the omega-3 index at baseline with an increase of SDNN during the study (p = 0.04). This may indicate that in the presence of psychotropic drugs such as antidepressants or quetiapine a higher omega-3 index at baseline (or possibly a larger dose of omega-3 fatty acids) is needed to bring about a significant increase in SDNN in the intervention group. Interestingly, in the aforementioned trial our study best compares with (Carney et al. 2009, 2010), in the intervention but not in the control group, baseline red blood cells (RBC) levels of EPA + DHA were significantly higher among those whose depression subsequently remitted compared with those whose depression did not remit (Carney et al. 2016) while there was no significant difference between the treatment groups as a whole in the study in question (Carney et al. 2009) and a more recent trial (Carney et al. 2019). This suggests that a similar mechanism might exist regarding the antidepressant effects of omega-3 fatty acids in the presence of psychotropic drugs such as antidepressants (Guu et al. 2019).

It has recently been suggested that omega-3 fatty acids increase HRV via alterations in intrinsic pacemaker rate rather than via changes in cardiac autonomic neural regulation (Billman 2013). This would be in keeping with an earlier observation in patients with a cardiac transplant, a situation with no or little parasympathetic control of cardiac rhythm. Dietary omega-3 fatty acids appeared to alter electrophysiological properties of the heart itself (Harris et al. 2006). Bipolar disorder has a genetic component, with a striking number of the calcium channel gene superfamily being involved, among many other genes (Xin et al. 2013; Zelniker et al. 2021). Taken together, one might speculate, that in bipolar disorder, a genetically defined variant of a calcium channel of the intrinsic cardiac pacemaker might be resistant to the effects of EPA and DHA. Clearly, however, this speculation needs to be substantiated by further research.

This study could not detect any significant difference between number of new affective episodes or change in mood ratings between the study groups. This is not surprising given that the study was not powered to detect such changes—and the current evidence (McPhilemy et al. 2020). The numerically higher number of mood episodes in the omega-3 group might be a result of patients in the omega-3 group being more depressed at baseline.

Conclusions
In our randomized, controlled intervention trial, comparing the effects of 2120 mg EPA plus 600 mg DHA per day with a corn oil placebo in euthymic bipolar patients with a low omega-3 index and reduced heart rate variability no significant effect of omega-3 fatty acids on SDNN or frequency-domain measures HF, LF and LF/HF ratio could be detected. Given the positive evidence of omega-3 fatty acids on parameters of HRV in cardiovascular patients this was an unexpected finding with, among others, the effect of psychotropic medication present in our trial or the genetics of bipolar disorder itself being possible culprits. Clearly further research is urgently needed to better understand the underlying mechanisms.

Abbreviations
BDI: Beck Depression Inventory; CGI-BP: Clinical Global Impressions Scale for Bipolar Illness; DHA: Docosahexaenoic acid; DSM-IV: Statistical Manual of Mental Disorders Fourth Edition; ECG: Electrocardiogram; EPA: Eicosapentaenoic acid; HAMD: Hamilton Rating Scale for Depression; HF: High frequency; HFP: High frequency power; HR: Heart rate; HRV: Heart rate variability; LF: Low frequency; LF/HF ratio: A ratio of low frequency to high frequency; LFP: Low frequency power; MADRS: Montgomery– Åsberg Depression Rating Scale; pNN50: Proportion of RRIs that differ more than 50 ms; RBC: Red blood cells; RMSSD: Root mean square of normal to normal interval differences; SCID: Structured Clinical Interview; SDNN: Standard deviation of the normal-to-normal interval; ULF: Ultra low frequency; VLF: Very low frequency; YMRS: Young Mania Rating Scale.

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Authors’ contributions
MO, MR, CVs AND ES were responsible for the conception and design of this study. MB, AV, FFK and AL were responsible for the acquisition of the data. MB, FS, AV, MO, CVs. AND ES drafted the work. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations
Ethics approval and consent to participate
The present trial was approved by the ethics committee of the medical faculty of the Ludwig-Maximilians-University, Munich. The trial is registered at ClinicalTrials.gov, number NCT00891826.

Consent for publication
Not applicable.

Competing interests
MB, FS, AV, MO, FFK, AL, MR, ES: no competing interests. CVs: operates Omegametrix, a laboratory for fatty acid analyses. CVs received honoraria for consulting and/or speaking from BASF/Pronova, Huntsworth Medical, EPAX, and Norsan.
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