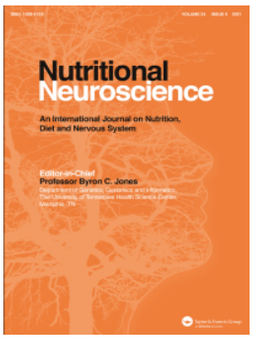

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Nutritional Neuroscience

An International Journal on Nutrition, Diet and Nervous System

ISSN: 1028-415X (Print) 1476-8305 (Online) Journal homepage: www.tandfonline.com/journals/ynns20

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To cite this article: Monique Aucoin, Laura LaChance, Inge van der Wurff, Meagan McLaren, Sasha Monteiro, Sean Miller, Andrew Jenkins, Elham Sabri & Kieran Cooley (2025) Dietary counseling plus omega-3 supplementation in the treatment of generalized anxiety disorder: results of a randomized wait-list controlled pilot trial (the 'EASe-GAD Trial'), Nutritional Neuroscience, 28:6, 635-648, DOI: 10.1080/1028415X.2024.2403901

To link to this article: https://doi.org/10.1080/1028415X.2024.2403901

NUTRITIONAL NEUROSCIENCE
2025, VOL. 28, NO. 6, 635–648
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Dietary counseling plus omega-3 supplementation in the treatment of generalized anxiety disorder: results of a randomized wait-list controlled pilot trial (the 'EASe-GAD Trial')

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ABSTRACT

Objectives: Clinical evidence suggests that nutrition interventions can significantly improve symptoms of major depressive disorder; however, the effect on clinical anxiety symptoms in individuals with anxiety disorders has not been studied. The primary objective of the present study was to assess the feasibility and acceptability of a nutrition intervention. The secondary objectives included assessing changes in anxiety symptom severity, diet quality, self-efficacy, mindful eating, quality of life, and biomarkers.

Methods: This study was a randomized, wait-list controlled pilot trial delivering a 12-week, biweekly dietary counseling intervention and omega-3 supplementation to 50 adult women with generalized anxiety disorder. Questionnaires and blood work were completed at baseline, after the waiting period, and after the intervention.

Results: 443 individuals expressed interest within eight months; 50 met the criteria for enrollment. The mean number of sessions attended was 6.4. Final questionnaires were completed by 46 participants. Eighty-four percent of participants strongly agreed with the statement 'My experience during this study was positive'. The mean anxiety symptom severity score in the intervention group was 26.2 (95% CI 22.94–29.48) at baseline and 11.0 (95% CI 8.05–13.87) at week 12. The mean diet quality score was 7.2 (95% CI 6.32–8.10) and 10.5 (95% CI 9.55–11.49) at baseline and week 12, respectively. Among the waitlist participants, the mean baseline anxiety score was 29.3 (95% CI 24.73–33.91) and 26.8 (95% CI 22.09–31.56) at week 12.

Discussion: This study was feasible and acceptable. Participation in the intervention was associated with a decrease in anxiety symptoms. These findings lay the foundation for large-scale studies. Trial registration: ClinicalTrials.gov NCT05573672.

KEYWORDS
Diet therapy; nutrition therapy; omega-3 fatty acids; anxiety disorders; anxiety; mental health; psychiatry; nutrition; diet counseling; diet counselling

Introduction

Generalized Anxiety Disorder (GAD) is a prevalent psychiatric disorder with a significant personal and societal cost. GAD is characterized by increased levels of worry and tension surrounding daily events occurring on most days of the week for at least 6 months [1]. Accompanying symptoms may include heightened motor tension, autonomic hyperactivity, and heightened vigilance [1]. Cross-national data from high-income countries suggest that 5% of adults experience symptoms of GAD at some point in their life [2]. Studies have shown that untreated or inadequately treated GAD can result in reduced productivity and impaired ability to work, as well as contributing to higher healthcare expenses and economic burden on individuals and society [3]. On a personal level, GAD can lead to impairment in quality of life and functioning, increased risk of comorbid mental health

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Trial registration: ClinicalTrials.gov identifier: NCT05573672.
Supplemental data for this article can be accessed online at https://doi.org/10.1080/1028415X.2024.2403901.

conditions, social isolation, increased personal health care cost, and lost income [4]. There are a number of treatment options available for GAD including psychosocial and pharmacological interventions; however, not all patients experience benefit from these treatments and additional barriers such as cost, availability, side effects and stigma further limit the potential for people to benefit from these treatments [5–7]. It is estimated that only 20–32% of patients receive appropriate and effective treatment for GAD [3], highlighting the need for alternative or adjunctive therapeutic approaches.

The Mediterranean diet has been thoroughly studied and adherence to this diet has been linked to numerous favorable health effects [8]. This diet is characterized by a high consumption of vegetables, fruits, whole grains, nuts, and olive oil, with a moderate intake of fish and poultry. There is a growing body of research that has shown a positive association between adherence to the Mediterranean diet and a reduced risk of depression in prospective cohort studies [9]. Additionally, five randomized controlled trials have been executed in which the Mediterranean diet was used as a treatment for people with major depressive disorder [10–14]. In these studies, a significant decrease in depressive symptoms was seen in the Mediterranean diet group compared to the control group. While the benefits of the Mediterranean diet are attributed to a range of dietary constituents, one of these is omega-3 fatty acids. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are essential polyunsaturated fatty acids found in large quantities in certain fish and seafood species; numerous physical and mental health benefits have been attributed to increased intake of these fatty acids. For depression, EPA seems to be especially important; a 2023 meta-analysis of randomized controlled trials showed that supplementation of omega-3 fatty acids containing EPA greater than 60% of total EPA plus DHA, in doses ranging from 200 to 2200 mg per day significantly reduced symptoms of depression compared to placebo [15]; however, an earlier Cochrane review published in 2021 concluded that effects of omega-3 fatty acids may not be sufficiently large to be clinically meaningful for reducing depression in adults and that there is a low degree of certainty in the evidence [16].

The use of both the Mediterranean diet and omega-3 supplements has been extensively studied in the treatment of depression; however, research on these interventions for the treatment of anxiety disorders is limited. A recent systematic review examined 17 studies investigating the impact of dietary modification on symptoms of either depression or anxiety [17]. Of these studies, 10 reported on anxiety outcomes. However, of these, nine evaluated changes in anxiety symptoms among individuals with physical illness or the general population. The remaining study enrolled participants with a major depressive episode and clinically significant anxiety symptoms based on the hospital anxiety and depression scale (HADS-A) [11]. Following a 12-week dietary counseling intervention, based on a modified Mediterranean diet, there was a signification reduction in the mean HADS-A score compared to the control group with a moderate effect size [11]. A recently conducted meta-analysis of studies measuring the impact of omega-3 supplementation on anxiety symptoms found a significant reduction in anxiety symptoms severity; however, there was a very low certainty of evidence [18]. In line with the diet change studies, none of the 23 included trials recruited participants with anxiety disorders. Overall, there is evidence to suggest that the Mediterranean diet and omega-3 supplementation may be useful therapeutic strategies in the treatment of anxiety disorders; however, clinical trials involving participants with anxiety disorders are needed. The *Eating and Supplementation for Generalized Anxiety Disorder* (EASe-GAD) pilot study is the first study to deliver such a combination intervention to participants diagnosed with GAD.

Methods

The protocol of this randomized, wait-list controlled open-label feasibility study has been published [19] and registered at ClinicalTrials.gov (Identifier: NCT05573672 https://clinicaltrials.gov/study/NCT05573672). Details of trial design and setting, participants, intervention and its development, sample size calculation, recruitment plan, screening, randomization and blinding, outcome measures, analytic methods and implementation are described therein. The study received approval and oversight from the research ethics board of the Canadian College of Naturopathic Medicine, and Health Canada. One minor change to the protocol was made prior to publication of the protocol regarding the eligibility of participants supplementing with vitamin D at baseline; no changes were made to the protocol following publication. The study objectives and methods are summarized here in accordance with the CONSORT extension on reporting pilot and feasibility trials [20].

Objectives

This study's primary objective was to assess the feasibility and acceptability of a diet counseling plus

supplementation intervention delivered to 50 adult women with GAD. This was measured by the ability to recruit and retain participants, and by participants uptake of the intervention. It was also assessed through a participant satisfaction questionnaire. Secondary objectives included changes in anxiety symptom severity (Beck Anxiety Index (BAI) [21]), diet quality (MEDI-LITE questionnaire [22]), quality of life (PROMIS-29 [23]), mindful eating behaviors (Mindful Eating Questionnaire [24]), self-efficacy (General Self Efficacy Scale [25]), and biomarkers aligned with dietary components of the intervention (OmegaScore (summation of %EPA, %docosapentaenoic (DPA) and %DHA of whole blood fatty acids) [26], hemoglobin A1c, fasting insulin, fasting glucose, and calculated HOMA-IR, vitamin C, beta-carotene, and C-reactive protein) during the intervention period as compared to during the waitlist control period. Additional data on demographics, physical activity (International Physical Activity Questionnaire [27]) and body weight were collected. Adverse events were tracked.

Recruitment and eligibility

Recruitment occurred through several avenues including advertisements on social media and public spaces (i.e. public transit), flyers sent to a variety of healthcare providers, clinics and patient groups, and word of mouth from participants. Participants were eligible to participate if they: were between the ages of 18 and 65 years; identified as a woman; were categorized as having moderate to severe anxiety as defined as a score of ≥22 on the BAI; had a low-quality diet as defined as a score of ≤8.5 on the MEDI-LITE questionnaire; had stable use of psychiatric medication, natural health products and psychotherapy for the past 4 weeks; had a primary health care provider for their mental health care; were able to tolerate the study product (i.e. swallow capsules); and were able to read in English and provide informed consent. Using DMS-5 criteria, a clinical interview with a psychiatrist confirmed diagnosis of GAD; participants were excluded if they met criteria for bipolar, eating, psychotic, obsessive-compulsive or substance use disorders or high suicidality (Columbia Suicide Severity Scale, suicidal ideation category 3 or higher). Other exclusion criteria included: severe food allergies, aversions or intolerances to components of study product (e.g. fish, non-medical ingredients such as bovine gelatin); current participation in a program, research study or treatment plan that involved diet or lifestyle modification; OmegaScore of >5% (i.e. adequate omega-3 fatty acid status). If eligible, participants were randomized to waitlist or intervention arms using an internet-based computer-generated randomization service using random permuted blocks.

Study intervention

The study intervention consisted of a 12-week program combining seven bi-weekly dietary counseling sessions and omega-3 supplementation. The program was designed using Social Cognitive Theory [28]. The dietary recommendations were based on the Mediterranean diet intervention with minor modification based on the results of a scoping review on the relationship between diet and anxiety [29]. The dietary counseling sessions included many strategies to support behavior change including personalized recommendations, motivational interviewing, goal-setting, and action planning. It included activities about mindful eating and managing non-hunger cravings for food. A naturopathic doctor with 10 years of experience provided the one-on-one, 30–60 min sessions in a combination of in-person and virtual visits. Participants were provided with a fish oil product (AquaOmega HighEPA capsules), and instructions to take four capsules daily – (3456 mg of omega-3 fatty acids: 2659 mg of EPA, 532 mg of DHA; and 800 IU of vitamin D). In addition, participants were provided shelf-stable food items that were aligned with recipes and dietary advice (such as olive oil, nuts and seeds, whole grains). Participant educational resources are available at www.ccnm.edu/anxiety. All concomitant medication, psychotherapy or natural health products were allowed.

Results

Recruitment

A total of 443 individuals contacted the study to express interest between July 2022 and April 2023. The most common ways that they reported learning about the study included the social media advertisement ($n = 154$), the public transit advertisement ($n = 95$) and the study flyer ($n = 47$). Additional sources included health care providers ($n = 33$), word of mouth ($n = 31$), the CCNM website ($n = 30$), other online postings ($n = 15$), professional newsletters ($n = 15$), and other or not stated ($n = 23$).

Of the 443 individuals who expressed interest, 257 were ineligible after screening, 134 did not complete all of the screening activities (either because the

expressed that they were no longer interested, were lost to follow up or study recruitment had completed) and two were eligible but declined to participate. The reasons for ineligibility are listed in Table 1. One barrier that the study staff encountered was the time delay associated with assessment of baseline omega-3 status during eligibility screening. The kits were mailed to interested individuals who collected the blood sample at home and mailed the kit to the lab for analysis. Several prospective participants were lost to follow-up in this process. The most common reasons for ineligibility were high baseline diet quality ($n = 151$), low baseline anxiety severity ($n = 103$) and other psychiatric diagnoses ($n = 49$).

Figure 1 presents a CONSORT flow chart. One participant withdrew prior to providing baseline data. Two participants provided baseline data and withdrew prior to starting the intervention. One participant experienced a recurrence of a medical illness during the study period and was subsequently lost to follow-up. Baseline demographics of the enrolled participants are presented in Table 2. The two groups were similar in terms of many baseline demographics; however, it is noted that food insecurity was higher in the waitlist control group and physical activity levels were higher in the immediate start group.

Primary outcome: feasibility and acceptability

The time required to recruit 50 eligible participants was eight months. The mean number of sessions attended by study participants was 6.4 out of 7 (SD 1.72), including three participants who withdrew prior to attending any sessions.

With respect to data collection, baseline questionnaires were completed by 49 out of 50 participants. The end of waitlist questionnaires were completed by 23 of 25 (92%) waitlist participants and the end of the intervention questionnaires were completed by 46 of 50 (92%) participants.

The supplement bottles were returned for estimation of compliance by 44 of the 47 (94%) participants who received them. Four participants experienced adverse reactions which limited their dose of the supplement. Among the remaining participants ($n = 40$), compliance was estimated to be 88.6%.

Participant responses to the multiple-choice questions on the satisfaction survey are presented in Table 3. One hundred percent of the participants agreed with the statement 'Overall, my experience during this study was positive' with 84% of participants strongly agreeing. Ninety-three percent agreed that the recommendations were easy to follow up and 91% agreed that their health and well-being improved during the study program. The themes that emerged from participant responses to the open-text questions are presented in Figure 2. Overall, participants expressed a high level of appreciation for the program ('Overall excellent program, and truly had a positive impact on our family's health!').

Participants expressed that the strategies to support behavior change were most helpful ('Custom goals that felt achievable', 'It felt good to have some accountability and to have someone check on you. If it was just me, having discipline would have been difficult', '[the program was] non-judgmental. The goals felt realistic and like things I could actually accomplish', 'I liked that it was individualized and catered to my specific needs. I not only understood the science behind the diet changes, but also felt motivated by how easy it was to implement the changes due to the [food] we received. Convenience,

Table 1. Reasons for ineligibility.

Reason for ineligibility	Number of participants (%)
Diet quality score was too high	151 (34.1)
Anxiety severity score was too low	103 (23.2)
Other psychiatric diagnosis (or diagnoses)	49 (11.1) (some individuals had multiple diagnoses) Obsessive-compulsive disorder: 19 Eating disorder: 16 Bipolar disorder: 12 Substance use disorder: 4 Psychosis: 3
Vitamin D supplementation >4000IU per day	36 (8.1)
No current health care provider	35 (7.9)
Current dietary restriction	13 (2.9)
Current involvement in diet counseling	7 (1.5)
Did not identify as a woman	5 (1.1)
Recent change in medication	4 (0.9)
Did not meet criteria for GAD during psychiatric interview	3 (0.1)
Age	2 (0.1)
Fish allergy	2 (0.1)
Omega-3 score >5%	2 (0.1)

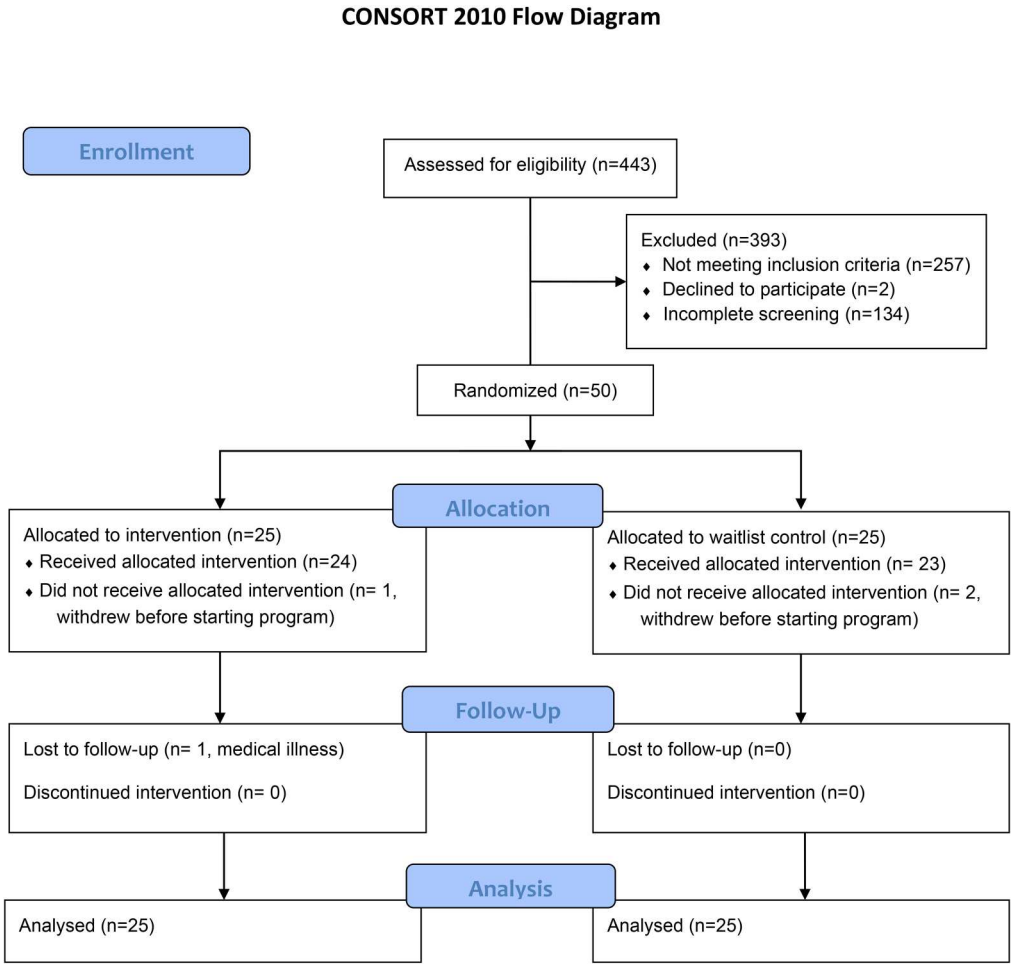

Figure 1. CONSORT flow chart. Note: Available data from all 50 participants were used in analysis. Baseline and/or final data were missing from four participants (3 withdrew, 1 lost to follow up).

accessibility, and affordability are key factors that contributed to my success in this study.'). Many reported appreciation for the food items provided ('enjoyed sampling the food items provided that I would not have otherwise purchased and tried', 'I really loved being given food that fit with the diet – This helped with affordability, and also encouraged me to eat foods in alignment with the diet.') In terms of the intervention deliverer, the qualities that were most valued by the participants included effective listening and practical suggestions ('I liked feeling heard and seen by the healthcare professionals. My doctor really helped me by listening deeply and then providing valuable solutions that were do-able and practical'), and warmth ('[intervention deliverer] was quick to remember me and made the experience very warm and inviting.'). Participants appreciated the one-on-one delivery ('I enjoyed the individual sessions') and regular follow-up visits. They enjoyed trying new things ('The chance to try foods and recipes I wouldn't normally', 'Becoming creative with the meals I eat').

Participants shared that they gained significant knowledge ('I gained volumes of knowledge'), created new habits ('It improved my eating habits a lot. Fruits added, protein added, gave up pop', 'Long term habits have been formed') and improved their mental health ('seeing how my mental health is impacted by food') and overall health ('[The best thing was] the health benefits, I felt better').

Participants reported that many resources were helpful including the handouts, recipes, goal setting worksheets educational materials and website 'The recipe website was very useful to me. I will continue using it', 'The recipes, the handouts, goal setting sheets'); however, some did not access the website and would have preferred that all materials were available in printed form.

They attributed a range of benefits to taking the omega-3 supplement ('I think they helped in lowering my inflammation', 'My eyes seemed less dry, my nails and hair improved. My mood was fairly stable', 'I think it improved my overall health status.').

Table 2. Baseline demographics of study participants.

	Immediate $n = 24$	Waitlist $n = 25$
Demographics		
Age *(SD)*	39 (14)	35 (10)
Sex-assigned at birth		
Female	24	25
BMI *(SD)*	29.03 (7.20)	28.35 (7.25)
Psychiatric medications		
Taking	10	9
Not taking	14	14
Missing data	1	2
Psycotherapy		
Past or active counseling	12	10
No psychotherapy	12	13
Missing data	1	2
Marital status		
Single	11	11
Married/common law	11	9
Divorced	2	2
Prefer not to answer	0	3
Employment status		
Employed full-time	16	15
Employed part-time	1	2
Self-employed	2	1
Student	4	2
Unemployed	1	3
Retired	0	1
Prefer not to answer	0	1
Ethnicity		
Black	2	4
East/Southeast Asian	3	0
First Nations/Indigenous/Metis	1	0
Latino	2	1
Middle Eastern	1	0
South Asian	1	3
White	13	14
Another race	1	2
Do not know	0	1
Education		
No certificate, diploma, or degree	0	0
High school diploma or equivalency	2	1
Apprenticeship or trades certificate or diploma	1	0
College or other non-university certificate or diploma	2	5
University diploma or certificate below bachelor level	0	1
University certificate, diploma, or degree at bachelor level or above	19	18
Income		
$10,000 or less	0	1
$10,001–$20,000	2	2
$20,001–$30,000	0	0
$30,001–$40,000	0	2
$40,001–$50,000	2	3
$50,001–$60,000	1	4
$60,001–$70,000	2	0
$70,001–$80,000	3	3
$80,001–$90,000	4	2
$90,001–$100,000	3	1
Greater than $100,000	7	7
Smoking status		
Yes	0	1
No	24	24
Alochol inatake per week		
Do not drink	0	0
1–2	10	11
3–4	10	10
5–6	2	3
6–7	2	1
7+	0	0
Beck Anxiety Inventory *(SD)*	26.2 (8.17)	29.32 (11.71)
Food security		
Food secure	15	12
Marginal food insecurity	5	4
Moderate food insecurity	2	6
Food insecure	1	3
International Physical Activity Questionnaire		
Low activity	5	11
Moderate activity	6	9
High activity	13	5

SD: Standard deviation.

The components of the program that the participants found most challenging, least beneficial, or less enjoyable were the size and number of omega-3 supplement capsules, adverse events attributed to the omega-3 supplement, commuting to the study visits, and the standardized allotment of food provided ('Offer selection for foods. Some of the foods given to me were foods I would not eat'). There was an interest in having the option to choose between capsule and liquid fish oil supplements.

Regarding the study's conduct, participants expressed a range of views about the in-person and online components of the program. The most common comment was an appreciation for the hybrid delivery format ('I liked that the 'in person' visits were limited, it was a lot easier to schedule virtual visits and made it easier to participate').

Although not part of the formal data collection plan, participants informally provided feedback to the intervention deliverer that seemed meaningful for future follow-up study design. Many participants commented on eating less processed, packaged and restaurant foods and cooking at home more often; however, this was not captured in the pilot study data collection. Several participants commented on the impact of study participation on the cost of eating. Some reported eating less take-out and restaurant food, which had a beneficial impact on their total spending. Even though it was not a goal of the intervention, a significant number of participants commented on a desire to lose weight during the intervention, often these comments occurred during the study visits where weight was measured by study personnel.

The behavior change techniques and study materials used in the intervention sessions were individualized to the needs and preferences of the study participants. These included motivational interviewing (used in 229 of 312 study visits) and goal setting worksheets (used in 219 study visits). For a full list

Table 3. Responses to multiple choice questions about satisfaction.

Prompt	Strongly disagree	Disagree	Neutral	Agree	Strongly agree
I enjoyed the foods I ate during this program	0	0	1	21	24
The recommendations were easy to follow	0	0	3	13	30
I felt hungry while following the program recommendations	15	22	3	5	1
I missed some of the foods that I used to eat while following these recommendations	9	16	11	7	3
I think I will be able to follow these eating recommendations long-term	0	0	0	23	23
Eating according to the recommendations is affordable, compared to my usual eating habits	1	2	17	18	8
I believe my overall health and well-being improved because of changing my eating habits	0	0	4	25	17
When dining out, it was easy to find foods on the menu that fit with the recommendations	0	9	11	22	4
The recipes provided to me were helpful	0	1	7	22	16
The educational materials provided to me were helpful	0	0	1	23	22
The amount of time I spent preparing foods was reasonable	0	1	1	29	15
My interaction with the research staff was professional	0	0	0	2	44
I was comfortable and had time to discuss my thoughts, questions and concerns	0	0	0	2	44
I felt as if my treatment plan was individualized to my goals, personal beliefs, values and cultural background	0	0	5	5	36
I felt that it was easy to schedule appointments	0	0	2	4	40
E-mails and phone calls were responded to in a timely manner	0	0	0	2	44
I would recommend a family member or friends to participate in this study	0	0	1	3	42
I was satisfied with the Omega-3 supplement	0	2	5	8	31
I would recommend the Omega-3 supplement to a friend or family member	0	2	6	9	29
Overall, my experience during this study was positive	0	0	0	5	41

of behavioral change techniques used, please refer to supplemental file 1.

Secondary outcomes

The mean score in anxiety symptoms severity, QOL, mindful eating, diet quality and self-efficacy at baseline and 12 weeks are reported in Table 4. Mean anxiety and diet quality scores are also presented in Figure 3.

The *a priori* statistical analysis plan for BAI data described in the study protocol was completed. The between-group difference in BAI score at 12 weeks was calculated using least square mean difference and 95% confidence intervals using ANCOVA analysis adjusting for the baseline score. A statistically significant difference in score at 12 weeks was observed between the two groups when adjusted for baseline score, – 13.72 (−18.54,−8.90), p-value < 0.0001. This difference remained statistically significant after adjusting for other baseline characteristics of patients (age, income, education, food insecurity, smoking status, body mass index, alcohol consumption and physical activity level), – 12.27 (−17.27,−8.28), p-value < 0.0001. The second stage of analysis, aimed at increased precision of the effect estimate, assessed the change in anxiety score from just prior to the 12-week intervention to just afterwards for all patients, waitlisted or not. The mean change, 95% confidence interval and p-value were – 12.1 (−15.1, – 9.0), p-value <0.001.

While formal analysis of the other secondary outcomes was not part of the *a priori* plan, an informal comparison by observing the remaining secondary variables at baseline and 12 weeks, as provided in Table 4, suggest an increase for diet quality, mindful eating and global self-efficacy and an improvement in the Anxiety, Depression, Fatigue and Social Participation quality of life subscales of the PROMIS-29; however, formal analysis is needed in the future full scale study for conclusions to be made.

Lab data

Baseline lab data was collected for 47 participants. Lab data from the end of the waitlist was collected for 22 of 25 (88%) participants. Final lab data were collected for 43 of 50 (86%) participants. The reasons for not collecting lab data included: withdrawn from the study (n = 3), travel (n = 1), and did not have time to visit the lab (n = 3). The mean lab values are presented in Table 5. The mean lab values did not appear to change during the intervention period. Seventy-three percent of the lab reports included one or more abnormal findings; with participants' permission, these were reported to the participants' primary healthcare provider.

The baseline whole blood dry blood spot OmegaScore was completed by all participants during screening. End of waitlist testing was completed for 23 of 25 (92%) participants and end of intervention testing was completed for 43 of 50 (86%) participants. A summary

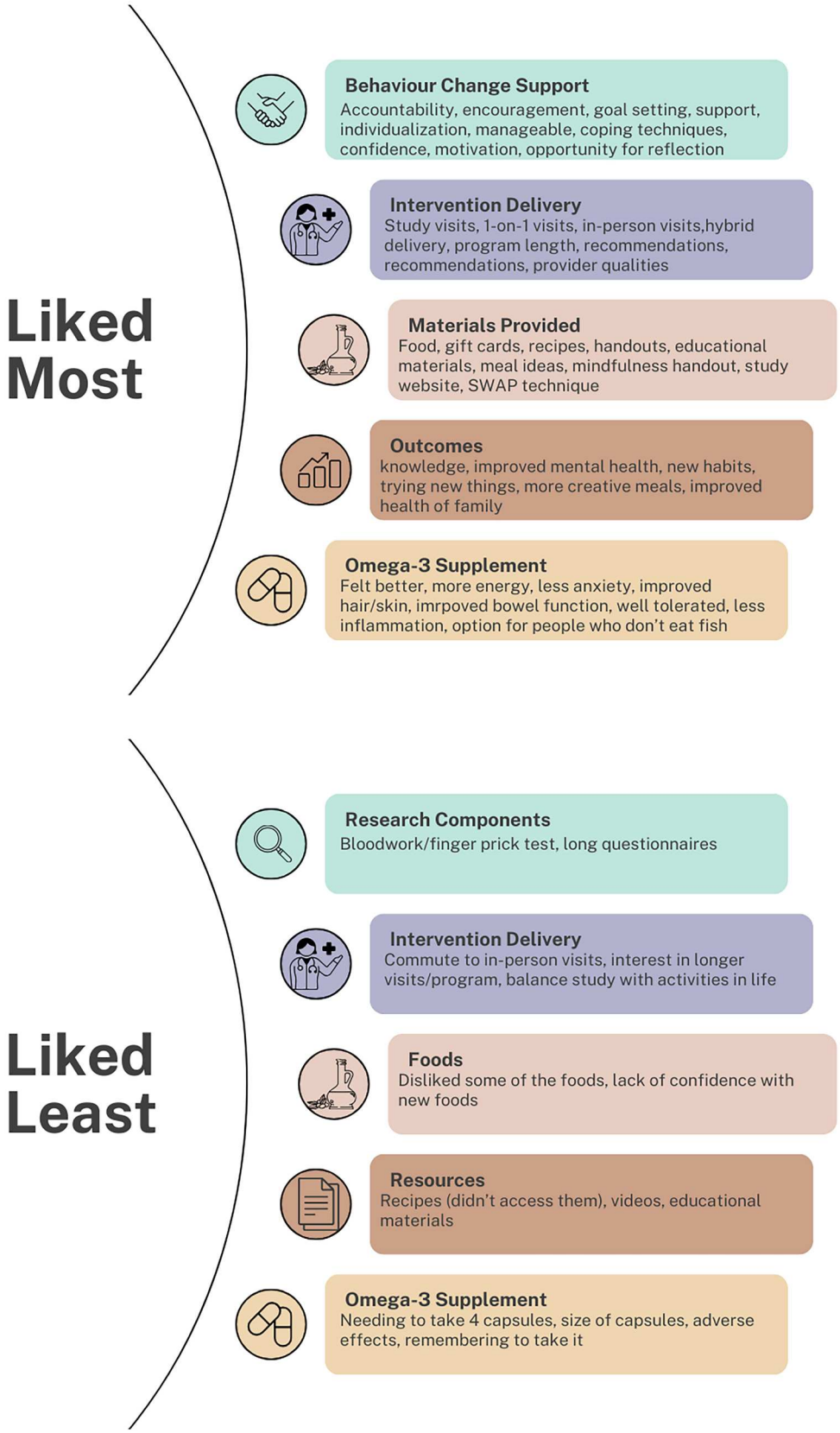

Figure 2. Themes from participant responses to the open-text questions: Components that the participants liked most and least.

Table 4. Mean baseline and week 12 secondary outcomes data (Mean and 95% CI).

	Baseline intervention group	End of intervention	Baseline waitlist group	End of waitlist
Beck Anxiety Inventory	26.2 (22.94–29.48)	11.0 (8.05–13.87)	29.3 (24.73–33.91)	26.8 (22.09–31.56)
MEDI-LITE	7.2 (6.32–8.10)	10.5 (9.55–11.49)	7.1 (6.33–7.91)	6.9 (6.17–7.74)
Mindful Eating Questionnaire	2.5 (2.38–2.73)	2.88 (2.73–3.03)	2.6 (2.46–2.77)	2.5 (2.37–2.69)
Global Self Efficacy	28.9 (27.24–30.59)	32.3 (30.70–33.91)	28.2 (26.20–30.20)	28.2 (26.49–29.95)
PROMIS-29				
Physical	4.54 (4.29–4.79)	4.79 (4.61–4.97)	4.28 (3.93–4.63)	4.20 (3.82–4.56)
Anxiety	3.42 (3.18–3.65)	2.16 (1.81–2.52)	3.55 (3.29–3.81)	3.25 (2.92–3.58)
Depression	2.59 (2.11–3.07)	1.72 (1.37–2.08)	2.48 (2.03–2.95)	2.27 (1.83–2.72)
Fatigue	3.78 (3.45–4.12)	2.75 (2.32–3.18)	3.69 (3.35–4.03)	3.53 (3.09–3.97)
Social Participation	2.83 (2.38–3.28)	3.79 (3.31–4.28)	2.81 (2.45–3.17)	3.14 (2.66–3.62)
Pain	2.09 (1.59–2.59)	1.57 (1.19–1.96)	2.24 (1.73–2.75)	2.14 (1.62–2.66)

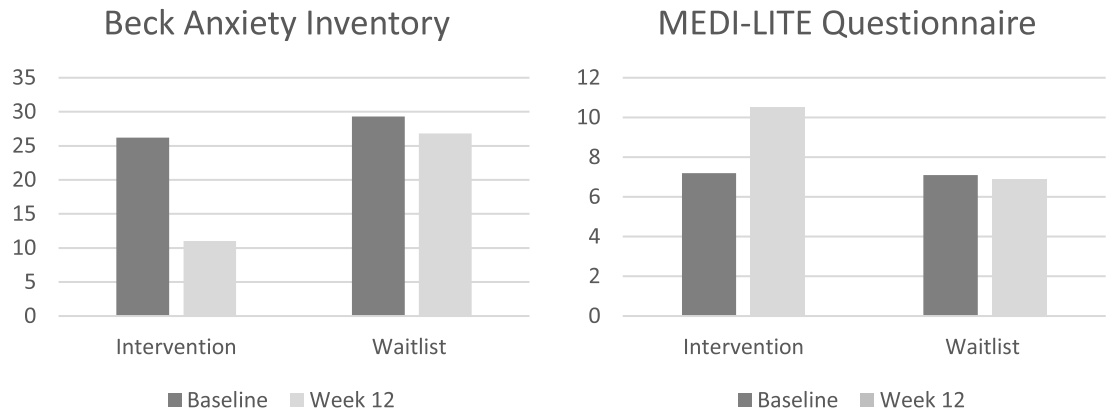

Figure 3. Changes in Beck Anxiety Inventory and MEDI-LITE scores.

Table 5. Mean baseline and week 12 lab values and fatty acids (Mean and (95% CI).

	Baseline intervention	End of intervention	Baseline Waitlist	End of Waitlist
Fasting Glucose (mmol/L)	4.90 (4.70–5.10)	4.94 (4.72–5.16)	5.32 (4.49–6.15)	5.32 (4.79–5.85)
Hemoglobin A1c (%)	5.35 (5.23–5.46)	5.36 (5.24–5.48)	5.52 (5.15–5.88)	5.57 (5.16–5.97)
Triglycerides (mmol/L)	1.13 (0.93–1.32)	0.88 (0.69–1.06)	1.02 (0.89–1.15)	0.88 (0.74–1.03)
Cholesterol (mmol/L)	4.72 (4.24–5.19)	4.62 (4.11–5.13)	4.80 (4.30–5.30)	4.75 (4.32–5.18)
HDL Cholesterol (mmol/L)	1.58 (1.40–1.75)	1.55 (1.37–1.73)	1.50 (1.34–1.66)	1.49 (1.32–1.67)
Non-HDL Cholesterol (mmol/L)	3.14 (3.61–2.67)	3.07 (2.59–3.55)	3.30 (2.87–3.74)	3.26 (2.90–3.62)
LDL Cholesterol (mmol/L)	2.63 (2.20–3.05)	2.67 (2.21–3.57)	2.84 (2.42–3.26)	2.86 (2.50–3.21)
Chol/HDL ratio	3.15 (2.75–3.55)	3.13 (2.69–3.14)	3.32 (2.94–3.69)	3.34 (2.96–3.72)
Fasting Insulin (pmol/L)	77.88 (57.71–98.04)	76.52 (53.33–99.72)	98.00 (72.45–123.55)	128.27 (42.05–214.49)
HOMA-IR	2.94 (2.01–3.87)	2.92 (1.89–3.95)	4.05 (1.86–6.25)	4.81 (0.93–8.69)
C-Reactive Protein (mg/L)	3.11 (1.97–4.26)	4.06 (2.27–5.85)	6.60 (2.77–10.43)	7.49 (2.78–12.19)
Vitamin D (nmol/L)	60.70 (50.52–70.87)	84.26 (70.11–98.41)	54.10 (41.57–66.62)	77.82 (66.50–89.14)
Vitamin C (umol/L)	49.00 (41.55–56.45)	50.90 (43.17–58.64)	41.36 (33.99–48.74)	42.25 (35.24–49.26)
Beta-carotene (umol/L)	0.53 (0.38–0.67)	0.66 (0.49–0.83)	0.40 (0.29–0.52)	0.44 (0.32–0.57)
Fatty Acid Testing				
OmegaScore	3.58 (3.29–3.87)	7.18 (6.35–8.01)	3.43 (3.23–3.62)	3.47 (3.10–3.85)
ALA	0.61 (0.50–0.73)	0.57 (0.48–0.65)	0.60 (0.52–0.69)	0.53 (0.45–0.60)
EPA	0.53 (0.41–0.65)	2.88 (2.22–3.53)	0.51 (0.44–0.58)	0.60 (0.38–0.81)
DHA	1.98 (1.71–2.24)	2.55 (2.40–2.71)	1.94 (1.78–2.10)	1.85 (1.60–2.09)
DPA	1.07 (0.91–1.23)	1.75 (1.56–1.94)	0.97 (0.92–1.03)	1.03 (0.91–1.15)
Omega-6/ Omega-3 ratio	4.24 (2.65–5.84)	3.64 (2.98–4.30)	4.28 (2.62–5.94)	7.48 (6.28–8.68)
AA/EPA ratio	43.15 (6.82–79.48)	3.90 (2.57–5.23)	30.82 (1.41–60.22)	36.55 (6.07–67.02)
% saturated fat	36.25 (34.61–37.89)	38.51 (37.89–39.13)	38.66 (36.95–40.37)	38.33 (38.11–39.66)

HDL: high-density lipoprotein LDL: low-density lipoprotein HOMO-IR: Homeostatic Model Assessment for Insulin Resistance; ALA: alpha-linolenic acid; EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid; DPA: docosapentaenoic acid; AA: arachidonic acid.

of the mean baseline and week 12 fatty acid composition is reported in Table 5. An informal comparison suggests an increase in OmegaScore, EPA, DHA and a decrease in arachidonic acid/EPA ratio.

Body mass index, medications or other interventions and exercise

Participant BMI did not change over the course of participating in the study. The mean BMI at baseline, end

of the waitlist and end of the intervention was 28.8 (7.15), 28.5 (7.20) and 28.4 (6.90), respectively.

At the baseline visit, seven participants were supplementing more than 1700IU per day of vitamin D; all agreed to reduce their vitamin D dose to 1700IU so that their total intake did not exceed 2500IU per day including the study product. No participants reported a change in psychotherapy during the study. Four participants in the immediate start group and six in the waitlist group began supplementation with vitamin D based on recommendations from their primary care providers who received a copy of their baseline blood work report. Two participants in each group started or increased their dose of an antidepressant or anti-anxiety medication. No participants stopped or decreased these medications. There was no change in exercise during the study period (Supplemental file 2).

Adverse events

Among the immediate start participants, a total of 21 adverse events were reported during the intervention period. No adverse events were reported during the waitlist period. The most common adverse events reported were gastro-intestinal in nature, including belching ($n = 5$), diarrhea ($n = 5$), gastroesophageal reflux ($n = 3$), bloating ($n = 3$), nausea ($n = 2$) and constipation ($n = 1$). One participant reported pruritis (itching). Two participants reported symptoms of palpitations which may have been related to atrial fibrillation, a known adverse reaction to high-dose omega-3 supplementation. In both cases, the symptoms began within the first two days of taking the supplement and resolved within one day of terminating the supplement. Two other participants decreased their use of the supplement based on adverse events; one participant experienced diarrhea, the other experienced gastroesophageal reflux. These symptoms also resolved with the modified dose.

Discussion

The EASe-GAD pilot study enrolled the target number of participants within the set time limit and achieved a high level of data collection, study visit attendance and dietary supplement compliance. A high level of satisfaction was reported by participants. Findings are suggestive of a reduction in anxiety symptom severity in the intervention group as compared to waitlist control. Because the time to recruit, supplement compliance, session attendance and reported participant satisfaction all exceeded the pre-defined criteria, the study was considered both feasible and acceptable.

Although this study is the first to offer dietary counseling and omega-3 supplementation to individuals with a primary anxiety disorder, the findings with regards to changes in symptom severity are directionally consistent with similar studies that recruited participants with major depressive disorder [10–14]. Incidence of adverse events related to the omega-3 supplement were also similar to those previously reported [30].

The results of this study suggest that the participants' anxiety levels decreased during participation in a complex intervention with several possible underlying mechanisms. As purported by the fields of nutritional psychiatry and naturopathic medicine, the Mediterranean dietary pattern may improve mental health due to positive changes in micronutrient and macronutrient availability, gut microbiome, inflammation, and glycemic control [31]. Previous omega-3 supplementation studies conducted in patients with major depressive disorder have reported an association between change in EPA and DHA concentration and treatment response [32]. Psychological mechanisms may also have contributed to the observed effects. Behavior activation and change techniques such as motivational interviewing, goal setting and action planning may have contributed the observed improvements in self-efficacy in the intervention group [33, 34]. Mindful eating strategies may have contributed to improved mood regulation and coping with anxiety [35]. While it is not possible to determine which intervention components were responsible for the apparent improvement in anxiety symptoms, multi-component interventions are the norm in clinical care for patients with anxiety disorders.

The study findings suggest that further research on the effects of nutrition on GAD is warranted. The conduct of the present pilot study provided an opportunity to reflect on design elements that enhanced or hindered feasibility. We created an exclusion criterion related to adequate omega-3 status at baseline to avoid recruiting individuals who were already supplementing with omega-3 and less likely to benefit from the intervention; however, the process of mailing the collection kits, having the prospective participant collect the sample and mail it to the lab for analysis created a delay in the recruitment process that resulted in many prospective participants being lost to follow up. Additionally, 70 of the 72 participants who completed the omega-3 test were found to have sub-optimal levels, meaning that the criterion had limited impact on the composition of the participant sample. Baseline vitamin D supplementation was also found to be a barrier to recruitment early in the study and the allowable

baseline vitamin D intake was increased to facilitate recruitment. The laboratory testing yielded a relatively high proportion of abnormal findings which, for ethical reasons, were reported to the participants primary health care provider. This process may have resulted in contamination as participants and their providers were being alerted to abnormal lab values (such as vitamin deficiencies, glucose dysregulation and elevated cholesterol) which may have resulted in changes in diet, lifestyle or other recommendations. Given that this occurred in both the immediate start and the waitlist groups, the effect is likely to have been balanced between the groups. It may, in part, explain the small reduction in anxiety symptoms severity during the waitlist period. Future studies could consider the risks and benefits of not testing baseline omega-3, using an omega-3 supplement that does not contain vitamin D or limiting the use of blood tests.

Based on the feedback from participants, additional considerations for a future study include adding an assessment of changes in food spending and intake of ultra-processed foods. Measurement of body weight appeared to have the unintended consequence of communicating to the patient that weight was an important outcome in the study when the goal was to improve diet quality independent of weight change. The aspect of the study the participants most often reported disliking was the size and number of capsules of the omega-3 supplement. Several participants suggested giving participants the option of liquid or capsule delivery which could be considered. Because the secondary outcome data was only collected at baseline and the end of the intervention, it is not known how quickly the changes may have occurred or the duration of the effect. Inclusion of a midway or follow-up assessment could be considered in a future study focused on assessing the intervention impact.

This trial had several strengths and limitations. The study used randomization with the goal of creating two groups that were balanced at baseline; because of the relatively small sample size, there were some small differences between the two groups at baseline including higher food insecurity and lower physical activity in the waitlist group. Another strength is that the study assessed for changes in potential covariates. No changes in weight or exercise were seen during participation suggesting that these factors, known to impact mental health [36, 37], were unlikely to be responsible for the changes in anxiety that were observed. Changes in medication use were similar between the two groups.

One limitation of the study was the waitlist control design. During the waitlist period, participants received no treatment or interaction with study personnel. As a result, the non-specific effects of the bi-weekly meetings were not delivered to these participants. However, the waitlist control design allowed us to offer the intervention to all of the participants who enrolled. This study design appeared to have been highly acceptable to study participants as no participants withdrew following assignment to either arm; this resulted in a high level of data collection. The provision of shelf-stable food items appeared to be important to participants for increasing compliance; however, it is possible that this benefit contributed to the participants' level of satisfaction with the program. Given that involvement in the study was voluntary and based on expression of interest, it is possible that some level of selection bias influenced the high level of satisfaction. The satisfaction level reported by the study participants may not generalize to all groups of patients but rather reflects the satisfaction level of individuals who self-selected to take part in a nutrition program. Again, this intervention delivery is reflective of clinical practice whereby patients are selectively offered a treatment modality based on factors other than efficacy alone such as feasibility, patient preference and motivation. Lastly, the study was designed as a pilot study meant to primarily assess feasibility and acceptability. Although the findings suggest that the intervention delivered an anti-anxiety effect, further, large-scale studies are needed to confirm such an effect.

The EASe-GAD pilot study was found to be highly feasible and acceptable. Participation in the intervention was associated with an improvement in anxiety symptom severity. Further research is warranted to fully understand the anti-anxiety effects of a combination dietary counseling and omega-3 supplementation intervention.

Acknowledgements

We wish to acknowledge Umadevi Naidoo (Harvard Medical School) for participation in the steering committee and Wegdan Rashad (University of Toronto) for assistance with data extraction. Statistician Tim Ramsay (University of Ottawa, Ottawa Hospital Research Institute) advised on the statistical analysis plan.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This study received funding or gifts in kind from Ekhagastiftelsen, AquaOmega, Mitacs Accelerate, Lipid Analytical

Laboratories and Sobeys Inc. Trial funders had no role in the design of the study. A research team member from Lipid Analytical completed the omega-3 analysis for blinded samples and assisted with interpretation of blinded data. The other funders had no role in the interpretation of findings. The funders had no role in writing the manuscript.

Data availability statement

Data are available on reasonable request.

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