

Study title: Dietary counselling plus omega-3 supplementation in the treatment of generalized anxiety disorder (EASe-GAD)

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**Dietary counselling plus omega-3 supplementation in the treatment of
generalized anxiety disorder: Protocol for a randomized wait-list controlled pilot
trial (the “EASe-GAD Trial”)**

Monique Aucoin* (1,2), Laura LaChance (3, 4), Inge van der Wurff (5), Sean Miller (6), Umadevi Naidoo (7, 8), Andrew Jenkins (9), Kieran Cooley (1, 10, 11, 12)

1. Canadian College of Naturopathic Medicine
2. University of Guelph
3. McGill University
4. St. Mary's Hospital
5. Health Psychology, Faculty of Psychology, Open University of the Netherlands
6. Peer Connections Manitoba
7. Massachusetts General Hospital
8. Harvard Medical School
9. Lipid Analytical Laboratory
10. Southern Cross University
11. University of Technology Sydney
12. Pacific College of Health and Science

*Corresponding author, maucoin@ccnm.edu 1255 Sheppard Ave E, Toronto ON, Canada, M2K 1E2

Abstract

Background: Anxiety disorders are prevalent and disabling conditions involving excessive worry and tension. Generalized anxiety disorder (GAD), the most common anxiety disorder, affects 5% of individuals from high-income countries and many individuals report that treatment options are not accessible, effective, or tolerable. Clinical evidence suggests that nutrition interventions, based on the Mediterranean diet and supplementation of omega-3 fatty acids, can significantly improve symptoms of depression; however, the effect of nutrition interventions on anxiety symptoms has not been studied in a clinical population. The primary objective of the present study is to assess the feasibility and acceptability of a dietary counselling and omega-3 fatty acid supplementation intervention delivered to adult women with GAD. The secondary objectives include assessing changes in anxiety symptom severity, assessing changes in quality of life, assessing changes in biomarkers and evaluation of the components of the program.

Methods: This study is a randomized, wait-list controlled pilot trial delivering a 12-week, dietary counseling intervention and omega-3 supplementation to 50 adult women with GAD. Participants will complete seven individual counselling sessions which include education, personalized recommendations, mindful eating techniques, motivational interviewing, and goal setting. They will be provided with recipes, instructional videos, and food items. The intervention is designed based on the Social Cognitive Theory and previous research that has been done by the author team to identify dietary constituents with the most evidence to support their use in the treatment of anxiety disorders. Questionnaires and blood work will be completed at baseline, after the wait period (for those in the waitlist group) and after the intervention.

Discussion: Results from this study will lay the foundation for future large-scale studies in this area and may provide preliminary evidence of the role of diet counselling and omega-3 supplementation in the

management of GAD. Research on the role of nutrition in psychiatric care has been identified as a priority by a number of international organizations. The present trial directly addresses the call for the research that is most needed to advance the field. This protocol was registered at Clinicaltrials.gov on October 10, 2022; NCT05573672; <https://clinicaltrials.gov/ct2/show/NCT05573672>.

Key Words: Nutrition, Diet, Anxiety, Psychiatry, Mental Health, Lifestyle, Omega-3

Background

Generalized Anxiety Disorder (GAD) is a common psychiatric disorder involving high levels of worry or tension. The symptoms are persistent and distressing and they interfere with an individual's functioning(1). Cross-national data suggest that 5% of adults from high income countries are affected by symptoms compatible with GAD in their lifetime(2), and that the illness exerts a large negative impact on quality of life(3). Available treatment options include pharmacotherapy and psychotherapy; however, due to adverse effects, high cost and incomplete resolution of symptoms, many patients report that these options are inaccessible, ineffective or intolerable(4) and the percentage of patients adequately treated is estimated to be as low as 20 to 32%(5). The result is a large personal and social cost and a need for alternative or adjunctive therapeutic options.

There is growing evidence that nutrition is an important modifiable risk factor for many illnesses, including psychiatric illnesses. While the field of nutritional psychiatry research is rapidly expanding, research of anxiety disorders lags behind research related to depression. Observational evidence shows an association between poor diet quality and high prevalence/severity of anxiety disorders(6-8). Recently, several randomized, controlled trials involving participants with depressive disorders have reported significant improvement in depression symptoms following dietary interventions aimed at improving diet quality and increasing consistency with the Mediterranean diet (9-12) alone or in combination with omega-3 fatty acid supplementation(13). A recent systematic review identified 17 studies that assessed the effect of diet modification on depression and anxiety symptoms(14). Of these, ten assessed anxiety outcomes; however, only one of these studies enrolled participants with clinically diagnosed anxiety disorders(10), the remaining assessed changes in anxiety symptoms in patients with physical illnesses such as cardiometabolic illness or healthy participants. In this single study(10), participants were included if they met criteria for a major depressive episode; however, the mean

anxiety severity rating score was consistent with the presence of clinically significant anxiety. Following a 12-week diet counselling intervention, the mean anxiety score decreased significantly compared with the control intervention(10). The low or absent baseline levels of anxiety symptoms in the remaining studies may have precluded the detection of a change. Additionally, findings from studies involving non-psychiatric populations have unclear applicability to psychiatry populations. Overall, the effect of diet modification on anxiety symptoms in clinical populations are unknown. There have been multiple calls for clinical research that modifies the dietary patterns of individuals with anxiety disorders(14, 15).

The Mediterranean Diet is the pattern of food traditionally consumed by individuals from the Mediterranean region. It includes high intake of vegetables, fruit, whole grains, legumes, olive oil, seafood and water, moderate intake of poultry, cheese and yoghurt, and low intake of meats and sweetened foods. The Mediterranean diet has been extensively researched and higher levels of consistency with this diet pattern have been associated with a large number of positive health outcomes including decreased risk of cancer(16), cardiovascular disease(17), and all-cause mortality(18). Early clinical research using diet interventions in the treatment of depression has used a version of the Mediterranean diet(10, 12, 13). Omega-3 fatty acids are important dietary factors related to mental health. A recent meta-analysis found an association between omega-3 supplementation and a reduction in anxiety symptoms scores in clinical trials(19).

The relationship between diet and mental health is complex and bidirectional. While prospective trials assessing baseline diet and mental health outcomes at follow-up suggest that poor diet quality may play a role in the development of mental illness(6), there is also evidence suggesting that the presence of psychiatric symptoms may influence diet choices. Animal studies have reported that a highly palatable diet decreases behavioural and neuroendocrine markers of anxiety(20) and human data also suggest a connection between anxiety symptoms and “emotional eating” or “comfort eating”, defined as the

consumption of food in response to negative affect in an effort to mitigate emotional symptoms(21). This typically includes an increase in the amount of food and an increase in food with higher levels of calories, sugar and fat(21, 22). This pattern of eating behaviour contributes negatively to the diet quality of individuals with mental illness(23). Individuals affected by anxiety experience more sweet cravings(24) and observational studies show increased eating as a response to difficult emotions may decrease levels of perceived stress(25). The results of numerous studies suggest that sex and/or gender may play a role in comfort eating and that women may be more susceptible to this phenomenon(23, 26, 27). One large observational study found that women were nearly three times as likely as men to eat something as a coping strategy in response to emotional stress(28). Human and animal studies have found an effect of estrogen and progesterone cycles on comfort eating behaviours(20, 29). Factors related to gender, such as eating restraint and disinhibition(23, 26), may also mediate this relationship. One approach that has been shown to improve emotional eating behaviour is called “mindful eating”, defined as “an approach to food that focuses on individuals’ sensual awareness of the food and their experience of the food” (30). Participants in pilot trials using mindful eating interventions have reported improved eating behaviours (31).

Observational evidence suggests that food consumption and diet choices impact mental wellbeing. Preliminary clinical evidence suggests that diet modification intervention and omega-3 supplementation can improve symptoms of depression. The impact of these interventions on anxiety symptoms, among individuals with GAD, has not been assessed to date in a clinical trial. This protocol is for the *Eating and Supplementation for Generalized Anxiety Disorder study (“EASe-GAD”)*, a randomized, wait-list controlled, pilot trial aimed at assessing the feasibility and acceptability of a dietary counselling and omega-3 supplementation intervention delivered to women with GAD. This protocol was prepared using the SPIRIT checklist (Supplemental file 1).

Methods

Objectives

The primary objective of the proposed pilot clinical trial is to assess the feasibility and acceptability of delivering a diet counselling plus supplementation intervention to adult women with generalized anxiety disorder (GAD) as measured by recruitment, retention, and intervention uptake. The secondary objectives are to evaluate changes in anxiety symptom severity, quality of life, diet quality, mindful eating behaviours, self-efficacy, and biomarkers, over the intervention period as compared to the waitlist control period. This trial will lay critical groundwork for a larger, adequately powered clinical trial, designed to assess the effectiveness of dietary counselling in the management of GAD.

Trial Design and Setting

This pilot intervention study will recruit 50 adult women with moderate to severe GAD and provide a dietary counselling intervention in combination with an omega-3 supplement that also contains vitamin D. A randomized, waitlist-controlled design will be used (Figure 1). The waitlist-control design was selected to allow for random allocation to a non-treatment condition while still allowing all participants to complete the intervention. Waitlist-control designs have been suggested to improve rigor and preserve ethical considerations for studies where participant blinding is difficult(32). Twenty-five participants will be randomized to begin the intervention immediately and twenty-five participants will be randomized to observe a 12-week waitlist period before completing the intervention. This trial will take place at a single site. The study setting is the community clinic in the Canadian College of Naturopathic Medicine in Toronto, Canada. The study has been reviewed by the Research Ethics Board of the Canadian College of Naturopathic Medicine (CCNMREB040.Aucoin). Any amendments to this protocol will be communicated to the Research Ethics Board and Health Canada (the regulatory

authority for clinical trials in Canada) and modified on the trial registry. The design of this study involved participation from people with expertise in nutrition, psychiatry, research methods, laboratory testing, culinary education, behaviour changes, and lived experience with mental illness.

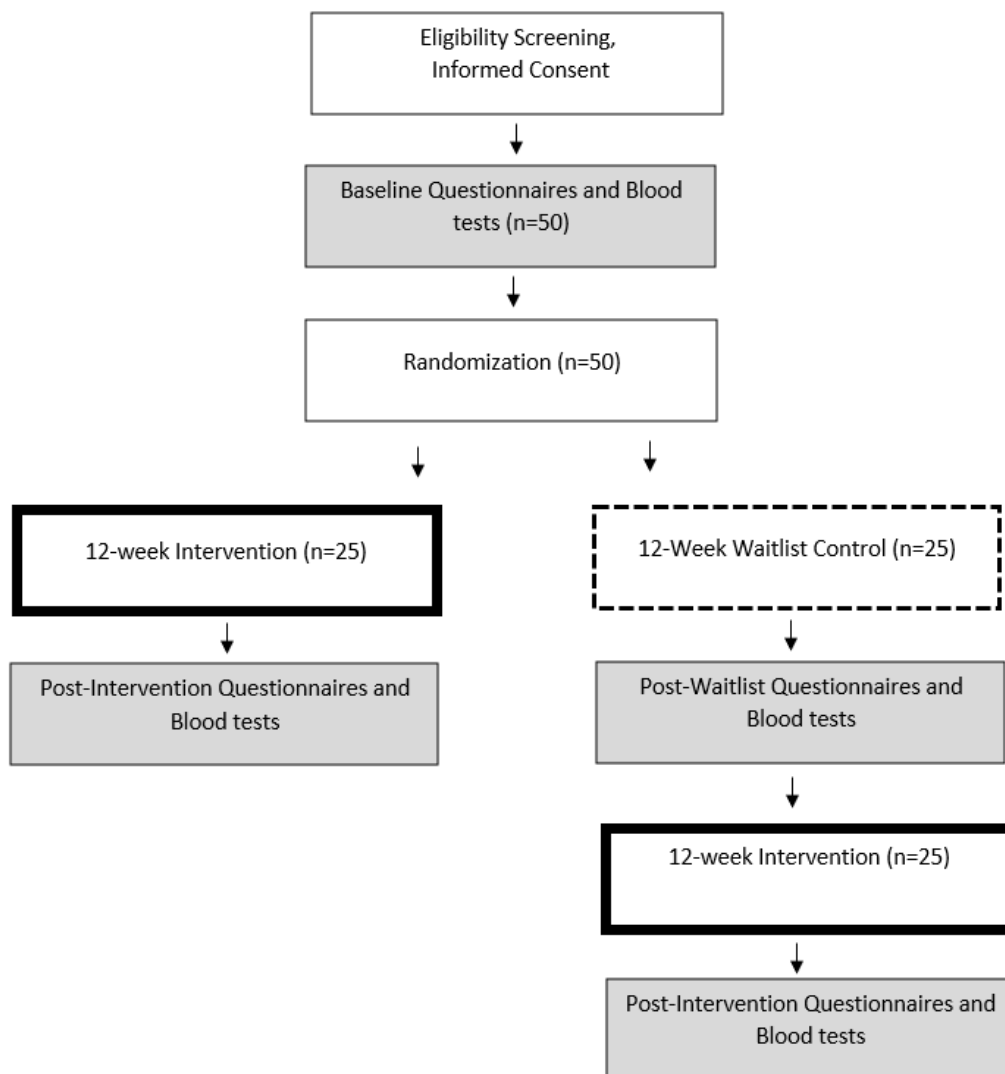


Figure 1: Diagram of participant flow through the trial

Participants Eligibility

Inclusion criteria:

1. A person aged 18-65 years who currently identifies as a woman.
2. Primary diagnosis of generalized anxiety disorder based on a clinical interview with a psychiatrist using the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria.
3. Moderate to severe anxiety as defined as a Beck Anxiety Inventory score of 22 or higher.
4. Low quality diet as defined as a score of 8.5 or less on the MEDI-LITE tool.
5. All psychiatric medication, psychotherapy, and natural health products stable for the past four weeks.
6. Established therapeutic relationship with a family doctor, psychiatrist, or clinical psychologist as their primary source of mental health care.
7. Ability to swallow capsules.
8. Ability to read in English and provide informed consent.

Exclusion Criteria:

1. Currently meets DSM-5 criteria for obsessive-compulsive disorder, bipolar disorder, a psychotic disorder, an eating disorder, or substance use disorder based on clinical interview with a psychiatrist.
2. Current high level of suicidality assessed by trial psychiatrist using the Columbia Suicide Severity Scale.
3. Starting or changing the dose of a psychiatric medication, psychotherapy, or natural health products in the past four weeks.
4. Severe food allergies, intolerances or aversions that would prevent the individual from modifying their diet (includes aversion to bovine gelatin which is a component of the fish oil supplement).

5. Current participation in a program, research study or treatment plan involving diet or lifestyle modification.
6. Baseline Omega Score of >5% (suggesting adequacy of omega-3 fatty acids).
7. Supplementation of greater than 4000IU of vitamin D daily for at least one month in the previous six months.
8. Allergy to fish or any of the non-medicinal ingredients in the study product.

Participants who are assigned to the waitlist control, who do not meet one or more of the criteria at the time of starting the intervention will still be permitted to participate. This data will be included in the analysis. If a participant begins a new medication or psychotherapy, or adjusts the dosage, during the waitlist period, this new treatment must be stable for four weeks prior to beginning the treatment phase of the study, even if this requires extending the waitlist period by up to four weeks.

The inclusion and exclusion criteria were designed with the intention of recruiting a sample of participants who are likely to be good candidates for the proposed intervention. Assessment of baseline diet quality, and inclusion of individuals with low quality at baseline, was completed in a similar trial(10); similarly, trials utilizing omega-3 supplementation have highlighted the importance of including participants with sub-optimal baseline levels(33). The participants are also similar with respect to non-modifiable factors that might influence the impact of the intervention. For example, there is evidence that emotional eating behaviours, which many influence the eating habits of people experiencing anxiety and depression, may be influenced by sex and/or gender and that women may be more affected(23). In the absence of clear evidence differentiating the respective roles of sex and gender, we have elected to include participants who presently identify as women. We recognize that this may introduce greater heterogeneity within the sample with respect to hormonal status, however, we acknowledge that the sample of adult women will include variation in hormonal status related to hormonal birth control, menstrual and hormonal cycle irregularities and disorders, and medically

induced or natural menopause. We have included a question in the demographic questionnaire about sex assigned at birth. This will be used to characterize the study participants. If a significant number of participants respond with an answer other than female, sub-analysis may be undertaken. Future studies can be undertaken to assess the impact of diet on men or people of other genders who experience anxiety disorders.

Participants with co-morbid depression will be eligible to participate in the intervention because of the high level of comorbidity with GAD(34). The criterion related to recent high dose vitamin D supplementation is included to identify potential participants who would exceed the maximum recommended daily allowance of vitamin D if they began taking the study product. Initially, this exclusion criterion was “Supplementation of greater than 1700IU of vitamin D daily [...]”; however, early results from screening identified a high number of interested individuals who were ineligible because of this criterion and an amendment was made to make the study more inclusive without compromising on participant safety. In order to ensure that participants have access to adequate care, should they experience a serious worsening of their psychiatric illness during the study period, an established therapeutic relationship with a mental health professional is required.

Sample Size and Recruitment Plan

Because of the pilot nature of the present trial, a formal sample size calculation was not completed. No intervention study has attempted to deliver a dietary intervention to participants with GAD and thus, the expected effect is unclear. The results of this pilot trial will inform the sample size calculation for a full-scale trial.

Participants will be recruited through multiple strategies. Letters will be mailed to local mental health service providers including psychiatrists, counsellors, psychotherapists, and psychologists. The clinicians will be provided with a poster to display in their office and fliers to distribute directly to clients.

Additional recruitment strategies will include online advertising through Facebook and other social media sites. This will include posts in existing, local anxiety/mental health groups and paid advertisements. If needed, newspaper advertisements may be used.

Pre-study Screening, Randomization and Baseline Evaluation

Interested participants who contact the study will complete a virtual screening visit. A member of the research team will administer the MEDI-LITE Score, and the Beck Anxiety Inventory and review the additional inclusion and exclusion criteria by phone or secure video call. If the participant meets these criteria, they will complete the clinical interview and Columbia Suicide Severity Scale with the trial psychiatrist by secure video platform. Following the completion of a verbal consent process, the participant will be mailed a kit for collecting a blood spot sample at home and will return the sample by mail for analysis of baseline omega-3 status.

Individuals who meet all study inclusion criteria will be contacted and invited to enroll in the study. There is no predetermined time between screening and baseline; as soon as all screening requirements are complete, enrollment and baseline data collection can begin. The baseline activities and data collection will take place through a combination of virtual and in-person activities. In an enrollment video call with the study coordinator, participants will complete the informed consent process by reviewing the informed consent form and asking questions. Following enrollment, baseline data collection will involve the completion of several questionnaires through a secure online platform (Supplemental File 2). If the participant does not have access to an internet enabled device, they will be mailed a paper copy of the baseline questionnaires. Baseline assessment will also include the provision of a fasting blood sample. Following baseline data collection, participants will attend an in-person study visit. At this time, baseline height and weight will be measured, and the participants will be randomized. Randomization will be completed by the trial coordinator using a computer-generated internet-based

randomization service provider using random permuted blocks. Following assignment, the trial coordinator, intervention deliverer, and participants will be aware of allocation. Outcome assessors will be blind to allocation when measuring height and weight. Measurement of the omega-3 samples and interpretation of the data will be completed by a research team member who is blind to allocation. Data analysts will be blind to allocation; they will be provided with data from two groups of participants labelled group 1 and 2.

For participants randomized to the waitlist control group, the baseline visit will conclude with instructions for the waitlist period. Participants randomized to the immediate start group will immediately begin the first dietary counselling session. There is no predetermined time between baseline data collection and commencement of the intervention; once all baseline electronic data are collected, participants may schedule the first in-person visit which will include the collection of the remaining baseline data and the first intervention session.

The Intervention

The intervention will consist of seven dietary counselling sessions delivered over 12 weeks (one session every two weeks). Three visits (the first, fourth, and seventh) will take place in person and the remaining will take place by secure video platform. If participants do not have access to a computer or the internet, they may complete all sessions in person. In the event that COVID-19 restrictions change during study delivery, the number of virtual sessions may be altered in order to comply with local restrictions. The sessions will be 45 to 60 minutes in length.

Intervention Development

The dietary recommendations are based on the Mediterranean diet⁽³⁵⁾ with minor modifications based on the results of a recent scoping review which identified and collated all of the existing research on diet

factors and anxiety(36). The Mediterranean diet has been studied extensively; a meta-analysis has demonstrated an association between greater adherence to the Mediterranean diet and reduced risk of depression(37) and this diet has served as the intervention in other clinical trials where diet was used in the treatment of depression(10, 12, 13), with positive outcomes. The scoping review additionally suggested that the following dietary components were important for people with GAD: limitation of caffeine intake, inclusion of culinary herbs and spices, green tea and herbal teas, dietary factors that support microbiome health and an emphasis on adequate protein and lower glycemic index foods(36). The Canadian Food Guide (2019) was utilized as a reference for national dietary recommendations and culturally relevant foods(38). Because we expected the study participants to reflect the multicultural nature of Canada, we intentionally included foods and recipes reflecting a range of cultural backgrounds. Lastly, the dietary interventions and resources used in nutritional psychiatry studies that have previously reported benefit were reviewed in order to guide the design of the present intervention(39).

Use of Theory

The behavioural change component of the intervention was guided by Social Cognitive Theory which posits a role of environmental, individual, and behavioural factors on behaviour(40). Environmental factors influencing eating habits will be addressed through provision of recommended foods during the study period, prompts to consider individuals in the participants' life who could support them in their goals, and instruction to modify the physical environment. With respect to individual factors, we will increase knowledge about nutrition, food preparation, and the role of diet in mental health as well as increasing knowledge about participants' own eating habits through self monitoring. We will increase self-efficacy and confidence through motivational interviewing (41). Regarding behaviour, participants will be provided with educational videos in order to improve their skills and ability to perform the

desired behaviours (i.e., preparing nutritious food for themselves). We will also address habitual behaviours that are known to influence food choices in this population such as comfort eating.

Educational Material and Resources

A set of educational handouts were developed for use in the EASe-GAD study (Table 1).

Table 1: EASe-GAD Educational Handouts

Handouts to be provided at the first Diet counselling session	Handouts to be provided as indicated
-EASe-GAD Diet Recommendations and Rationale -Meal Ideas	-Caffeine and Beverages -Mindful Eating -Managing Cravings -Shopping List Template -Tracking Log

A collection of recipes was assembled as well as a collection of videos demonstrating recipe preparation, food preparation skill, and food safety videos. Participants will also receive shelf-stable food items at the first and fourth (in-person) visits in order to encourage adherence to the recommendations and decrease barriers to change.

Dietary Counselling

The dietary counselling sessions will be conducted by a licensed Naturopathic Doctor with more than 10 years of experience providing dietary counselling to individuals with mental health concerns and a certificate in motivational interviewing. The counselling sessions will aim to focus on the benefits of the recommended foods, highlighting the advantages of following the recommendations rather than the risks of following alternative diet patterns in order to maintain a positive message. The emphasis of the intervention will be on changes to dietary patterns; participants will be advised to consume the diet *ad libitum* with no restrictions on caloric intake.

In addition to providing education about nutrition, there will be significant efforts to support behaviour change (Supplemental File 3: Summary of Behaviour Change Techniques). There will be an emphasis on providing encouragement, communicating that diet changes are possible among individuals experiencing mental illness and evoking past behaviour change successes. Goal setting will include a focus on setting measurable, specific, and realistic goals that are generated through a guided discussion with the participants and specific action planning related to the goal. Additionally, participants will be guided in identifying barriers to the achievement of the goal and strategies to overcome barriers. Participants will be instructed to modify their physical environment so that the encouraged foods are easy to access and require limited preparation and discouraged foods are less accessible. Because comfort eating is recognized as a driver of diet choices among the study population, participants will complete exercises related to mindful eating (ex. the raison exercise) and review strategies for managing non-hunger cravings to eat such as grounding, acknowledging feelings, and engaging in enjoyable or distracting activities. The dietary counselling activities to be completed at each study visit are listed in Table 2.

Table 2: Dietary counselling activities to be completed at each study visit

Study Visit	Dietary Counselling Activities
First Dietary Counselling Session	<ul style="list-style-type: none"> -inquiry about usual meals, beverages, aversions, preferences, cultural influences on eating -presentation of EASe-GAD recommendations and rationales -affirmation of aspects of diet that are already aligned with recommendations -guided discussion where participant identifies an opportunity for improvement without judgement -creation of a goal, identification of possible barriers and ways to navigate these barriers
Follow-up Dietary Counselling Sessions	<ul style="list-style-type: none"> -participant queried about previous goal -if achieved, affirmations -if not achieved, discussion of obstacles or challenges, generation of problem-solving strategies while maintaining positive message -presentation of new material (educational handouts, resources) as appropriate -creation of a new goal or adjustment of previous goal

Final Dietary Counselling Session	-discussion about achievements made during the program and affirmations -discussion of long-term goals and strategies to maintain
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Dietary Supplement

During the 12-week study period, participants will be supplied with an omega-3 capsule supplement (AquaOmega High EPA) and instructed to take a dose of four capsules, once daily (containing a total of 3456 mg of omega-3 fatty acids: 2659mg of Eicosapentaenoic acid (EPA), 532mg of docosahexaenoic acid (DHA), and 800IU of Vitamin D), with a meal. Significantly more trials have been completed using omega-3 supplementation in the treatment of depressive disorders than anxiety disorders(42). Recent guidelines recommend a daily dose of 1-2g of EPA with a ratio of EPA:DHA of at least 2:1 for the treatment of depression(43). Due to the lack of specific recommendations on dose of omega-3 use for anxiety, our intervention will draw inference from these guidelines on depression to employ a dose that has been shown to be beneficial in other psychiatric disorders. We have selected a high dose, high EPA formula in order to maximize the likelihood of detecting a signal of effect in the present pilot trial.

Concomitant Therapies

All concomitant medication, psychotherapy or natural health products will be allowed during this trial. In order to minimize the risk of adverse events related to hypervitaminosis D, participants who are supplementing 1701 to 4000IU of vitamin D daily at the time of screening will be eligible to participate if they agree to decrease their vitamin D supplementation to 1700 so that their total daily intake of vitamin D, including the study product, is 2500IU. Participants will be encouraged to continue all other previous treatments at the same dose for the duration of the trial, if possible, but allowed to make changes if recommended by their mental health care provider. Participants will be queried at baseline

and at each follow up visit about their use of medication, psychotherapy or natural health products and any changes will be recorded, analyzed, and reported.

Safety and Criteria for Withdrawal

As rescue medicine, participants will be advised to take the over-the-counter product, diphenhydramine (Benadryl), in the event of an allergic reaction to the study product or any of the new foods that they consume, as recommended on the product label. Diphenhydramine will be provided to participants with the study product. Participants will be queried about use of the rescue medication and asked to return any unused product at the end of the trial. The use of rescue medication for an allergic reaction will be recorded. Participants will be instructed to contact the study coordinator immediately if they experience a negative reaction to the study product or a serious worsening of their health. They will be provided with an email and phone number for this purpose. The qualified investigator will assess the patient and recommend a course of action. If the participant requires medical visits or medications that are not reimbursed by the Ontario Health Insurance Plan (OHIP), these costs will be reimbursed by the study sponsor, the Canadian College of Naturopathic Medicine. At each study visit, participants will be asked if they have experienced any negative effects since beginning the study product. Participants will be withdrawn from the study if they experience an allergic response, or other serious adverse event, as a result of the study product. These participants will be referred to their primary health care provider or a walk-in clinic for management. Participants will also be withdrawn if the trial psychiatrist deems the participant not adequately stable to continue to participate in the trial. This includes the presence of severe suicidal ideation or symptoms of psychosis. At each follow up visit, participants will be asked by the intervention deliverer if they have experienced a significant worsening in their mental health since the previous visit. If they report symptoms related to suicidal ideation, the Ask Suicide-Screening Questionnaire (ASQ) will be completed(44). If the participant screens positive, they will be referred to

the study psychiatrist for a complete assessment. If they screen acute positive, they will be referred directly to a crisis center or the hospital emergency room. If they report any symptoms related to psychosis (any report of hallucinations, delusions, or disordered thinking), the participant will be referred to the study psychiatrist for assessment. If they meet criteria for withdrawal, they will be referred to their current mental healthcare provider for appropriate assessment and treatment. If a participant reports a significant worsening in symptoms of anxiety or depression, they will be permitted to remain enrolled in the study. They will be encouraged to contact their primary mental health care provider for assessment and management. If the mental health care provider suggests that psychiatric rescue medication is needed, this clinician will recommend the treatment to the participant. If rescue medication is used for mental health symptoms, participants will be allowed to continue participating in the study. The use of rescue medication will be queried at each study visit and recorded. Given that the primary objective is feasibility and acceptability, participants with poor compliance with the study intervention will not be withdrawn from the study.

Expected adverse events for this study product include fishy aftertaste, bad breath, heartburn, nausea, or loose stools, atrial fibrillation, increased bleeding. All adverse events will be recorded, and these records will be maintained for 15 years. The clinical trial sponsor will inform the Natural and Non-prescription Health Product Directorate of Health Canada of any serious expected or unexpected adverse events related to the study product immediately if possible and no later than seven days after becoming aware of the information. Serious adverse events will also be reported to the Research Ethics Board that has reviewed the study protocol.

Participants will be withdrawn from the study if their baseline serum levels of 25-hydroxy-vitamin-D is greater than 120 nmol/L, as this level has been associated with safety concerns⁽⁴⁵⁾. These individuals will be instructed to contact their primary health care provider for assessment and management. In the event that the baseline or final blood work assessment suggests the presence of an undiagnosed

medical condition, the participant will be notified immediately that there is an abnormal finding and told to contact their primary healthcare provider for appropriate assessment and treatment. With the participants' permission, the lab reports will be sent to the healthcare provider. The participant will be allowed to continue to participate in the study.

Outcomes Measured

As the intervention is a pilot study, process evaluation (feasibility and acceptability) will be the primary outcome, helping to inform a future full-scale trial. The time to recruit 50 participants will be evaluated as part of assessment of feasibility. In order to assess acceptability, the number of sessions attended will be counted. All participants will be asked to complete a brief satisfaction survey concerning the participant's level of satisfaction with the program, the aspects which were helpful or unhelpful, and opportunities for improvement (Supplemental File 4: Outcome Assessment). A sub-sample will be recruited to participate in a brief focus group in order to obtain more detailed qualitative responses about the participant experience and participant satisfaction. We will aim to recruit 8-18 participants to run 2-4 focus groups, each having 4-6 participants. After the second focus group, we will complete a brief data analysis and run additional focus groups if data saturation has not been achieved. The focus groups will be conducted using a semi-structured qualitative interview methodology. The sessions will be audio recorded and transcribed. Transcripts will be analyzed using thematic analysis(46).

Additionally, we will assess the fidelity of the intervention by comparing the intervention protocol with the intervention delivery. The frequency of use of each questionnaire and resource will be counted. At baseline, a brief demographic questionnaire will capture information related to age, sex at birth, marital status, employment status, ethno-racial background, income, smoking status, and alcohol consumption (Supplemental File 4: Outcome Assessment). Assessment of physical activity levels and food insecurity will also be completed using the International Physical Activity Questionnaire(47) and Canadian Community Health Survey Household Food Security Survey Module(48), respectively. Height and weight

will be measured before and after the waitlist period and the intervention period. Body mass index and change in weight during the intervention and control period will be calculated. These data will characterize the study participants and allow for assessment of confounding factors.

In order to assess changes in anxiety symptom severity, the Beck Anxiety Inventory, a validated, 21-item self-report inventory for measuring the severity of anxiety in participants with psychiatric illness, will be administered(49). The impact on quality of life will be assessed using PROMIS-29(50). In order to assess the impact of the intervention on behaviour change and qualitatively assess the acceptability of the intervention, questionnaires related to mindful eating and diet quality will be administered before and after the intervention. Mindful eating behaviours will be measured using Mindful Eating Questionnaire (MEQ) which has been validated for use in a diverse adult population(51). Changes in diet quality will be measured using the MEDI-LITE score, a concise tool for measuring consistency with the Mediterranean diet, which has been validated for use in adult populations(52). Changes in self-efficacy will be assessed using the General Self-Efficacy Scale(53). Changes in diet quality will also be assessed objectively through blood tests. Omega-3 fatty acids levels will be assessed using the dried blood spot test, Omega Score(54), which represents summed EPA, DHA and Docosapentaenoic acid as a percentage of the total fatty acids in whole blood. Analysis will be completed by Lipid Analytical Laboratories. Additional assessment will be completed to measure fasting serum cholesterol panel, markers of blood sugar levels and regulation (Hemoglobin, fasting insulin, fasting glucose and calculated HOMA-IR(55, 56)), vitamin C, beta-carotene, and C-Reactive Protein. These analyses will be completed by LifeLabs. Completion of the questionnaires and blood tests will be done at baseline, at the end of the waitlist control period (for participants assigned to this group) and at the end of the intervention. Participants who do not attend all of the scheduled visit but have not withdrawn will be contacted to complete the questionnaires and blood tests. See Supplemental File 4 for a summary of assessments on participant demographics, satisfaction with the dietary intervention, the research program, and participant experience.

Compliance with the supplement will be assessed at the final visit. Participants will be instructed to bring back all study product bottles containing any remaining capsules. The remaining capsules will be counted and recorded by a member of the study team. Compliance with the supplement will be reported as a percentage based on calculating the amount of pills consumed in comparison to the amount expected according to instructions.

Statistical Analysis

Since the pilot study is not powered to demonstrate efficacy, analysis of the pilot study results will be strictly descriptive. Baseline demographics and outcome measures will be summarized by group as means and confidence intervals, medians and interquartile ranges, or percentages and confidence intervals as appropriate. Process evaluation will be described both quantitatively (percent screened positive for inclusion, percent of eligible patients who consent to participate, percent with significant protocol violations, etc.) and qualitatively (e.g., reasons for failing inclusion criteria, reasons for refusing to participate, participant impressions of the intervention, etc.). All participants will be analyzed in the group to which they were randomized. Missing data will be carefully documented to inform the design of the larger trial. Participants who complete the treatment but do not report a satisfaction level will be treated as 'unsatisfied.' No interim analysis will be undertaken. The study will be considered feasible if 50 participants are recruited within two years, and participants in the intervention group take at least 60% of the study product and attend at least 60% of the diet counselling sessions. The study will be considered acceptable if at least 70% of participants report that they were satisfied with the intervention. The statistical analysis plan for the full-scale trial is included in Supplemental file 5.

Data management

The collection and storage of data will be done according to Good Clinical Practice Guidelines. All study staff involved in the collection or entry of data will be trained by the trial coordinator and will complete

ethical conduct of research training (Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans 2). Data from potential and enrolled participants will be stored in the secure platform, Research Electronic Data Capture (REDCap) and a password protected database on a secure server managed by the Canadian College of Naturopathic Medicine. Data collected at each study visit will be captured using an electronic case report form which will be entered into the database. Questionnaire completion will be done by the study participants through REDCap. Laboratory data will be entered into the database and double checked for accuracy by a team member blind to participant allocation. An audit of the data will be completed by a senior member of the research team who is not involved in data collection after 10 participants are enrolled or three months of time, whichever comes first. All information obtained during the trial will be kept in a locked cabinet or on a password protected computer and destroyed (deleted or shredded) after 15 years.

Access to Data and Dissemination

All personal health information will be kept confidential and only accessed by the research team, unless required by law. This includes audit by CCNM Research Ethics Board or Health Canada Natural and Non-prescription Health Products Directorate. All data will be maintained on password protected, secure servers or locked filing cabinets for the required length of time. Following this time, data will be destroyed securely by deleting the digital files or shredding paper documents. No identifying information from any participant will be used in the dissemination of study results. Dissemination of the study findings will occur through publication. Study participants will have the option to be notified of the study findings.

Discussion

Given the increasing attention to the importance of nutrition in mental wellbeing being communicated to the general public by the popular media, we expect that participants will be interested in the trial and

that it will be feasible and acceptable. Given the abundance of observational data suggesting an important role of food choices in the development and progression of psychiatric disorders, in conjunction with the positive findings from recent intervention studies in depression, we expect that participation in the intervention will result in improvement of anxiety symptoms.

At this present time, attention to the role of diet and lifestyle in guidelines for the prevention and treatment of psychiatric disorders is significantly lacking. This trial will build the foundation for larger, adequately powered studies which will add to the expanding evidence base attesting to the importance of nutrition in mental health care. This type of evidence is creating a rationale for the inclusion of nutrition professionals in mental health care teams and use of dietary counselling in the treatment of mental illness. It will open the door to shifting policy and increasing access. Nutrition interventions can be low in risk, acceptable to patients, cost effective(10) and may have additional benefits to overall health. Nutritional counselling may be a way for nutrition professionals to contribute to meeting the needs of a patient population who report that presently available treatment options are often not accessible, effective, or tolerable, resulting in a decreased personal and social burden of GAD(4).

List of Abbreviations:

GAD: generalized anxiety disorder, EPA: Eicosapentaenoic acid, DHA: Docosahexaenoic acid, REDCap: Research Electronic Data Capture, EASE-GAD: Eating and Supplementation for Generalized Anxiety Disorder study, PROMIS: Patient Reported Outcomes Measurement Information System

Declarations

Ethics approval and consent to participate: The study has been reviewed by the Research Ethics Board of the Canadian College of Naturopathic Medicine (CCNMREB040.Aucoin). All participants will provide written informed consent. All research will be conducted in accordance with the Declaration of Helsinki and all other relevant guidelines and regulations.

Consent for publication: Not applicable

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

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Competing Interests: The authors report no conflicts of interest.

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Authors Contributions: Conceptualization: MA, LL, KC, Methodology: MA, LL, KC, lvdW, SM, UN, AJ, Writing-original: MA, Writing- review and editing: KC, LL, lvdW, Funding acquisition: MA, KC, LL

Trial Sponsor: The Canadian College of Naturopathic Medicine, 1255 Sheppard Ave E, Toronto, ON M2K 1E2, 416-498-1255

Steering Committee: Composed of MA, LL, KC, lvdW, SM, UN, AJ. The committee meets monthly to oversee the trial.

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Supplemental File 2

SPIRIT Figure: The schedule of enrolment, interventions, and assessments.

		STUDY PERIOD									
	Enrolment	Allocation	End of Wait List	Post-allocation							Close-out
TIMEPOINT (Days)	<i>Prior to allocation</i>	0	85	1 or 86	15 or 100	29 or 114	43 or 128	57 or 142	71 or 156	85 or 160	85+ or 160+
ENROLMENT:											
Eligibility screen	X										
Structured Clinical Interview administered by a psychiatrist	X										
Omega Score	X										
Informed consent	X										
Allocation		X									
INTERVENTIONS:											
<i>Dietary Counselling</i>				X	X	X	X	X	X	X	
<i>Omega-3 Supplement</i>											
ASSESSMENTS:											
<i>Satisfaction Survey</i>											X
<i>Attendance</i>				X	X	X	X	X	X	X	
<i>MEDI-LITE score</i>		X	W								X

Beck Anxiety Inventory		X	W									X
Omega Score		X	W									X
Mindful Eating Questionnaire		X	W									X
PROMIS-29		X	W									X
International Physical Activity Questionnaire		X	W									X
Food Security Assessment		X										
General Self-Efficacy Scale		X	W									X
Adverse Events				X	X	X	X	X	X	X	X	X
Height and Weight		X	W									X
Lipid panel, Hemoglobin A1C, fasting insulin, fasting glucose, vitamin C, beta-carotene, C-reactive protein		X	W									X
Compliance												X

X: All participants W: participants allocated to the waitlist arm

Supplemental File 3: Summary of Behaviour Change techniques used and coding according to Behaviour Change Techniques (BCT) Taxonomy Version 1

Grouping	Behaviour Change Technique	Intervention Component
Goals and Planning	1.1 Goal setting (behaviour)	Participants will set goals based on diet recommendations (ex. Eat fish twice per week)
	1.2 Problem solving	Discussion of barriers that may interfere and strategies to overcome the barriers
	1.4 Action Planning	Facilitator will guide participant in selecting meal ideas and recipes based on goal and set

		a plan to consume those meals on certain days of the week
	1.7 Review behaviour goal(s)	Follow up visit will involve a review of the previous week's goals and based on the outcome, future goals will be generated or modified
Feedback and Monitoring	2.3 Self-monitoring of behaviour	Participants will be given a form to record their intake of the recommended foods on a daily/weekly basis. This exercise will be optional.
Social Support	3.1 Social support (unspecified)	Participants will be encouraged to identify a person in their life that could assist them in achieving the goal
Shaping Knowledge	4.1 Instruction on how to perform a behaviour	Facilitator will explain cooking techniques or recipes that the participant is not familiar with. Provision of access to videos on food preparation skills
	4.2 Information about antecedents	Discussion of how emotions can lead to eating behaviours
	4.4 Behavioural Experiments	Ask participants to try soothing or distracting activities when experiencing non-hunger food cravings
Natural Consequences	5.6 Information about emotional consequences	Facilitator will present evidence suggesting a relationship between better quality diet and better mental health
Comparison of behaviour	6.1 Demonstration of the behaviour	Provision of access to videos demonstrating cooking skills and recipe preparation
Associations	7.1 Prompts/cues	Instructions to place recommended food items in visible locations in their kitchen
Repetition and substitution	8.4 Habit reversal	Instructions to prepare meals at home rather than purchasing take out
Comparison of outcomes	9.2 Pros and cons	Encourage participant to consider the pros and cons of current dietary habits if there is ambivalence to change
Reward and Threat	10.4 Social Reward	Congratulate participant on achieving goals
Regulation	11.2 Reduce negative emotions	Teach self-regulation and relaxation techniques for use during non-hunger cravings
	11.3 Conserving mental resources	Advise to prepare food in bulk, pre-portion meals or snacks, pre-plan meals or grocery lists

Antecedents	12.1 Restructuring the physical environment	Advise to keep food that is meant to be eaten less often in location that is inconvenient to access.
Self-belief	15.1 Verbal persuasion about capability	Tell participant that they can successfully modify their diet despite barriers such as mental health symptoms
	15.3 Focus on past success	Encourage participant to describe occasions where they have been able to eat healthy foods

Supplemental File 4: Outcome assessment

Demographic Questionnaire

Age: (enter age in years)

Sex assigned at birth:

- Female
- Male
- Other

Marital status:

- Single
- Married/common-law
- Divorced
- Widowed
- Prefer not to answer

Employment status

- Employed full-time
- Employed part-time
- Self-employed
- Student
- Unemployed
- Retired
- Prefer not to answer

Ethnic Background

- Black (African, Afro-Caribbean, African Canadian descent)
- East/Southeast Asian (Chinese, Korean, Japanese, Taiwanese, Filipino, Vietnamese, Cambodian, Thai, Indonesian descent)

- Indigenous (First Nations, Metis, Inuk/Inuit descent)
- Latino (Latin American, Hispanic descent)
- Middle Eastern (Arab, Persian, Afghan, Egyptian, Iranian, Lebanese, Turkish, Kurdish descent)
- South Asian (East Indian, Pakistani, Bangladeshi, Sri Lankan, Indo-Caribbean descent)
- White (European descent)
- Another race category
- Do not know
- Prefer not to answer

Education: Please indicate your highest level of education completed

- No certificate, diploma or degree
- Highschool diploma or equivalency
- Apprenticeship or trades certificate or diploma
- College or other non-university certificate or diploma
- University diploma or certificate below bachelor level
- University certificate, diploma or degree at bachelor level or above

Income: Please indicate the range that includes your total annual household income.

- \$10,000 or less
- \$10,001 to \$20,000
- \$20,001 to \$30,000
- \$30,001 to \$40,000
- \$40,001 to \$50,000
- \$50,001 to \$60,000
- \$60,001 to \$70,000
- \$70,001 to \$80,000
- \$80,001 to \$90,000
- \$90,001 to \$100,000
- Greater than \$100,000

Smoking status

- Have you smoked cigarettes in the past year? Yes (If yes, 2 questions below)
- No

On the days that you smoke, how soon after you wake up do you have your first cigarette?

- Within 5 minutes
- 6- 30 minutes
- 31-60 minutes
- After 60 minutes

How many cigarettes do you typically smoke per day?

- A. 10 or fewer
- B. 11-20
- C. 21-30
- D. 31 or more

Alcohol consumption

- Average number of alcoholic beverages per week: _____

Satisfaction Survey

Diet Satisfaction

	Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree
I enjoyed the foods I ate during this program.					
The recommendations were easy to follow					
I felt hungry while following the program recommendations.					
I missed some of the foods that I used to eat while following these recommendations.					
I think I will be able to follow these eating recommendations long-term.					
Eating according to the recommendations is affordable, compared to my usual eating habits.					
I believe my overall health and well-being improved because of changing my eating habits.					
When dining out, it was easy to find foods on the menu that fit with the recommendations.					
The recipes provided to me were helpful.					
The educational materials provided to me were helpful.					
The amount of time I spent preparing foods was reasonable.					

Program Satisfaction

	Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree
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My interactions with the research staff were professional.					
I was comfortable and had time to discuss my thoughts, questions and concerns.					
I felt as if my treatment plan was individualized to my goals, personal beliefs, values and cultural background.					
I felt that it was easy to schedule appointments.					
E-mails and phone calls were responded to in a timely manner.					
I would recommend a family member or friend to participate in this study.					
I was satisfied with the Omega-3 supplement.					
I would recommend the Omega-3 supplement to a friend or family member.					
Overall, my experience during this study was positive.					

Open text questions:

1. What did you like most about participating in this study?
2. What did you not like, or like least, about participating in this study?
3. Which resources were most helpful? (examples: recipes, handouts, educational materials, videos etc.)
4. Which resources were least helpful?
5. Do you feel that your expectations were met during this study? Please explain.
6. Do you have any further comments related to the how the study was conducted? (ex. the processes, the questionnaires, etc.)
7. Were there any things that you liked about taking the Omega-3 supplement?
8. Were there any things that you did not like about taking the Omega-3 supplement?
9. How can we make this study better in the future?
10. Any other comments, concerns, or suggestions?

Supplemental File 5: Statistical analysis plan for the full-scale trial

For the full-scale trial, the primary outcome (Beck Anxiety Inventory) will be analyzed in a two-stage manner. All participants will be analyzed in the group to which they were randomized. First, the change

in anxiety will be compared between the active group and the waitlisted controls at the completion of the 12-week intervention for the active group. Between-group differences will be tested using an ANCOVA analysis that compares 12-week anxiety measures between groups while controlling for baseline anxiety measure. The change in anxiety score from just prior to the 12-week intervention to just afterwards will be summarized for all patients, waitlisted or not, who do receive the dietary intervention. This will permit a more precise estimate (smaller confidence interval) for the magnitude of the benefit while preserving the rigor of the randomized controlled trial. As a secondary analysis, the ANCOVA analysis will be repeated adjusting for age, income, education, food insecurity, smoking, body mass index, alcohol consumption and physical activity level.