The effectiveness of essential fatty acid, B vitamin, Vitamin C, magnesium and zinc supplementation for managing stress in women: a systematic review protocol

Delia McCabe[1]

Marc Colbeck[1]

1. The Joanna Briggs Institute, Faculty of Health Sciences, University of Adelaide, Australia

Corresponding author:

Delia McCabe

delia.mccabe@adelaide.edu.au

Review question/objective

The objective of this systematic review is to identify the effectiveness of essential fatty acids (EFAs), B vitamins, Vitamin C, magnesium and zinc, consumed as supplements to the daily diet, for managing stress in women.

Background

The definition of stress has changed in the last few decades. It is no longer seen as only a natural physiological response to a life-threatening event, but also as a specific psychological experience.[1] Used colloquially, it is understood to be a negative state of mind, and can broadly be defined as the fear of not being able to cope with a situation that one faces.[2] "Time pressure" is another aspect related to the perception of stress today, and relates to the feeling that there is not enough time to accomplish tasks.[3] Continuously feeling unable to cope, coupled with ongoing time constraints in performing required tasks, may lead to chronic stress. Chronic stress has been linked to two specific mental health disorders, namely, severe anxiety and depression, due to stress hormone release impacting a number of brain regions, including those responsible for maintaining emotional equilibrium.[2,4] Therefore, although stress is not a mental health disorder, in and of itself, when experienced chronically, it may lead to anxiety disorders and depression, which are classified as mental health disorders.[2,5]

Although the rate at which men and women suffer from mental health disorders is similar, there are marked gender differences in the overall pattern of their mental illness.[6,7] Compared to men, women are 50% more susceptible to depression, generalized anxiety disorder, panic disorder, phobias and insomnia, hypothesized to be as a result of internalizing their feelings and emotions.[2,7,8] Men are more susceptible to externalizing their feelings and emotions, which result in alcoholism, aggression, and substance abuse.[2,7,8] Although there are a number of theories explaining why this gender disparity exists, such as neurobiological and neurochemical gender differences, sex steroids and psychosocial stressors, there is as yet no consensus.[8,9] Even though the reproductive cycle is considered to be an

important part of the physiological explanation for this gender disparity, psychosocial factors are seen to play an increasingly important role.[9,10] According to the World Health Organization (WHO), exposure to poverty, socioeconomic disadvantages, subordinate social rank and gender based violence and discrimination are other societal factors to take into account when assessing the disparity between the rates of depression experienced by women and men.[6]

The variety of social roles that women play in today's complex society, such as being wives, mothers, workers and, caretakers of elderly parents, and the growing strata of single-mothers, may be additional risk factors that increase feelings of psychological distress, such as anxiety, fear, confusion and depression, as well as mood-swings.[2,8] In addition, some research suggests that women spend more time performing household tasks, and perform a wider range of them than men do, placing additional demands on their time.[11,12] The juggling of these various roles, coupled with ongoing domestic tasks, expose women to multiple stressors which can lead to the experience of chronic stress.

Chronic stress has been linked to the development of depression, with a significant increase in rates of depression being observed when anxiety disorders are present too.[2,7] When stress is experienced, cortisol is one of a number of hormones produced, with high levels of circulating cortisol associated with high levels of stress.[2,13] The discovery that depression is also linked to high circulating levels of cortisol supports the findings of psychological research on stress and depression often co-existing.[2,7] Depression has been equated to an extreme reaction to chronic stress, indicating that chronic stress could be a catalyst for the development of depression.[2] However, more research has been conducted on gender differences in depression than on anxiety disorders.[2] The role that gender plays in the development of depression in the presence of anxiety is therefore not well understood. The 1996 Global Burden of Disease (GBD) Study predicted that clinical or unipolar depression would be the second most significant cause of disability burden in the world by 2020.[14] The 2004 updated GBD Study indicates that depression is the leading cause of disease burden for women in low, middle and high-income countries.[15] In contrast, it ranked fourth among the 15 leading causes in 1990, showing an adverse, steady increase.[14] Addressing ongoing stress may serve to prevent the development of depression in vulnerable women.

High blood pressure (hypertension) may also be an indicator of increased stress levels.[3] When associated with stress, blood pressure increases due to raised heart muscle activity, the narrowing of blood vessels (vasoconstriction), and increased blood flow to the heart and muscles, in anticipation of imminent physical danger. During the stress response, the sympathetic nervous system (SNS) is activated, which stimulates adrenal activity, consequently increasing blood pressure too.[13] Although there are other physiological symptoms of stress, such as reduced immunity, gastrointestinal challenges, changes in weight and increased fatigue, measuring blood pressure may be a simple, quick and efficient way to confirm the presence of stress.[3,13] As mentioned above, circulating cortisol levels, measured in either blood or saliva, also provide a good indication of stress levels.[2,3,13]

The body and brain are reliant on optimal nutrient supply for structure and function.[16,17] Various key nutrients are critical for cognitive functioning, hormone and neurotransmitter synthesis, and stress response regulation. Stress inducing thoughts or experiences stimulate a biochemical cascade that activates the flight-or-flight response, via the hypothalamus, pituitary and adrenal (HPA) axis.[1,2,18] Many of the B vitamins, as well as vitamin C, magnesium and zinc are used to regulate the stress response and synthesize hormones necessary for increased physical activity, such as adrenaline and cortisol.[1] In

contrast, the synthesis of the calming neurotransmitter serotonin also requires many of the same nutrients.[17] As the stress response is a survival mechanism, it takes precedence over the synthesis of hormones and neurotransmitters that regulate mood, induce calm and precede sleep. Therefore, being exposed to chronic stress has the potential to deplete the body and brain of these nutrients, and reduce the capacity to synthesize other important hormones and neurotransmitters.[1] Likewise, the ability to return to homeostasis after experiencing stress may be severely compromised when a deficiency in these nutrients exists.[1] A downward spiral of increased stress levels and depression may result, with women being more susceptible to this trend because of their exposure to multiple stressors.

Although essential fatty acids (EFAs) are not directly involved in the stress regulation process, they are critically important nutrients required for optimal cellular functioning.[19] The presence of EFAs in cell membranes improves oxygen and nutrient assimilation to facilitate cellular energy production, and improves membrane flexibility and permeability, which are important aspects of cellular, and specifically, neuronal functioning.[19] There are two classes of EFAs, omega 3 and omega 6, which have to be supplied by the diet because humans lack the enzymes to synthesize them.[19] The brain, comprising 60% fat at dry weight, is particularly susceptible to a lack of EFAs due to the variety of critical roles they play in neuronal and synaptic membrane structure and function. It is estimated that approximately 20% of the 60% is made up of EFAs.[19] Essential fatty acids are also precursors to eicosanoids, which play important roles in a variety of neural activities.[19] Over the last five or six decades the consumption of omega 3 has been declining in the general population due to a variety of reasons, leading to a general deficiency in this critically important nutrient.[20,21]

Supplementing with the following key nutrients, which are vital for the synthesis of hormones linked to the stress response and its regulation, may be useful when ongoing stress is present:

• Essential fatty acids are involved in both neuronal membrane structure and neurotransmitter release.[19] A deficiency in these important nutrients is linked to cognitive functioning deficits, which may affect the ability to cope with stress effectively.[19,22]

• Specific B vitamins are used as co-factors during the stress response to synthesize adrenaline, and they are also used to synthesize neurotransmitters, such as serotonin and dopamine.[1,16] B vitamins are also used during glucose metabolism in the brain.[15] The role they play in cognitive functioning is therefore critical, and a deficiency may affect the ability to cope with stress effectively.[17]

• Vitamin C has an important antioxidant role to play in the brain, in addition to being a co-factor in adrenalin and neurotransmitter synthesis. The brain and adrenal glands are the organs with the highest concentration of this critically important nutrient.[16, 23] A lack of this vitamin will therefore affect cognitive functioning, and may impact on the ability to cope effectively with stress.[17]

• The micronutrient magnesium is involved in neuronal cell metabolism and is an important co-factor in adrenalin and neurotransmitter synthesis.[1,24] Magnesium deficiency will therefore influence cognitive functioning, and may impact on the ability to cope with stress effectively.[25]

• The micronutrient zinc is involved in neuronal cell structure and metabolism, and plays an important role as a co-factor in adrenalin and neurotransmitter synthesis.[26,27] Zinc deficiency will therefore influence cognitive functioning, and may impact on the ability to cope effectively with stress.[26]

• In addition, B vitamins, Vitamin C, magnesium and zinc are co-factors in converting plant based omega 3 EFAs to the highly unsaturated fatty acid (HUFA) metabolites.[19] A lack of these metabolites in brain tissue is associated with a variety of mental health challenges.[19] A lack of these EFAs may therefore impact on the ability to cope with stress effectively.[19]

Research has clearly shown that these nutrients are required for hormone and neurotransmitter synthesis.[1,17,19,24,26] During ongoing stress these nutrients become depleted because they are used on an ongoing basis to synthesize stress hormones, which takes precedence over other important physiological functions also requiring these nutrients.[1,17,28] Furthermore, the absorption of some of these nutrients is also hampered during ongoing stress, and increased excretion of others occurs.[1]

A number of studies have examined the role that some of these nutrients play in mental health, generally, either in various combinations or alone.[28-34] There is however a lack of evidence to support the use of nutrient supplementation for the management of stress, even though supplementation to ameliorate the symptoms of stress is widespread.[35] The aim of this systematic review is therefore to investigate whether EFAs, B vitamins, Vitamin C, magnesium and zinc are capable of reducing levels of stress experienced by women.

The review author has conducted a preliminary search of the JBI COnNECT+ database, Embase, Prospero, CINAHL and MEDLINE via PubMed databases, using the keywords below, and no prior or progressing systematic reviews addressing the effectiveness of EFAs, B vitamins, Vitamin C, magnesium and zinc on stress levels in women have been found.

Keywords

Women, stress; psychological stress; mental fatigue; resilience; burnout; anxiety; omega 3 fatty acids; polyunsaturated fatty acids; micronutrients; dietary supplements; vitamins; B vitamins; Vitamin C; magnesium; zinc

Inclusion criteria

Types of participants

The systematic review will consider studies that include all women over the age of 18 years. Studies that include pregnant women will also be considered.

Studies that have included both genders will be considered where it is possible to extract data for female participants.

Women taking prescription medication for anxiety or depression will be excluded, as will hospitalized women or women suffering from eating disorders.

Types of intervention(s)

This review will consider studies that evaluate the effectiveness of supplementation with EFAs, specifically Omega-3; B Vitamins, specifically vitamin B3, B5, B6, B9 (folic acid) and B12; Vitamin C, magnesium and zinc at any dose/frequency for managing stress or anxiety being experienced by women. Supplements delivered in any oral form, including capsules, tablets, caplets, chewables, powders and liquids, at any dosage and for a duration of 14 days or longer will be considered. The supplementation of these nutrients will be investigated, whether used individually or in any combination.

This review will not consider interventions that have used a combination of herbal and EFA, B vitamin, vitamin C, magnesium and zinc supplementation, either alone with the herbal supplement, or in combination with the herbal supplement.

Types of comparators

Essential fatty acid, B vitamin, Vitamin C, magnesium and zinc supplementation, either alone, or combined, will be compared with either no intervention or placebo. This review will include studies that compare the named nutrients to each other, either in individual combinations or in a variety of combinations.

Types of outcomes

The systematic review will consider studies that include the following outcomes:

• Stress, as measured by any validated tool or measure, for example the Perceived Stress Scale (PSS) or the Perceived Stress Questionnaire (PSQ). Self- or observer reports will be considered.

• Anxiety, as measured by any validated tool or measure, for example, the Beck Anxiety Inventory (BAI) or the State-Trait Anxiety Inventory (STAI). Self- or observer reports will be considered.

• Measurements using validated tools, or physiological measures of stress, such as increased blood pressure or cortisol levels in blood or saliva will be considered. The presence of stress related symptoms, including, but not limited to, insomnia, irritability, headaches, fatigue, tense muscles, frequent upper respiratory tract and other infections, weight gain, weight loss, gastrointestinal disorders, such as irritable bowel syndrome (IBS) and loss of sexual desire will be considered. Self- or observer reports will be considered.

Types of studies

This review will consider experimental studies, including randomized controlled trials, non-randomized controlled trials and quasi-experimental studies. The review will also consider observational studies, series and case control studies and descriptive cross sectional studies. Any of the studies that investigate the use of any of the named supplements, either alone or in any combination, will be included.

Search strategy

The search strategy aims to find both published and unpublished studies. A three-step search strategy will be utilized in this review.

An initial limited search of MEDLINE via PubMed and Embase will be undertaken followed by an analysis of the text words contained in the title and abstract, and of the index terms used to describe the article.

A second search using all identified keywords and index terms will then be undertaken across all included databases.

Thirdly, the reference list of all identified studies and articles will be searched for additional studies.

Studies published in English will be considered for inclusion in this review.

No date limits are stipulated in this review.

The following databases will be searched:

MEDLINE (via PubMed)

Embase

Scopus

CINAHL

PsycINFO

In addition, the search for unpublished studies will include the following databases:

MedNar

PsycARTICLES

National Institute of Mental Health

International Association for Women's Mental Health.

Initial keywords

women, woman, female, gender, anxiety, psychological stress, psychological distress, psychological resilience, emotional stress, mental health, mental fatigue, essential fatty acids, polyunsaturated fatty acids, B vitamins, Vitamin C, magnesium, zinc, dietary supplements, micronutrient.

Assessment of methodological quality

Papers selected for retrieval will be assessed by two independent reviewers for methodological validity prior to inclusion in the review using standardized critical appraisal instruments from the Joanna Briggs Institute Meta-Analysis of Statistics Assessment and Review Instrument (JBI-MAStARI) (Appendix I). Any disagreements that arise between the reviewers will be resolved through discussion, or with a third reviewer.

Data extraction

Data will be extracted from papers included in the review using the standardized data extraction tool from JBI-MAStARI (Appendix II). The data extracted will include specific details about the interventions, populations, study methods and outcomes of significance to the review question and specific objectives.

Data synthesis

Quantitative data will, where possible be pooled in statistical meta-analysis using JBI-MAStARI. All results will be subject to double data entry. Effect sizes expressed as odds ratio (for categorical data) and weighted mean differences (for continuous data) and their 95% confidence intervals will be calculated for analysis. Heterogeneity will be assessed statistically using the standard Chi-square and also explored using subgroup analyses based on the different study designs included in this review, if considered useful and appropriate. Where statistical pooling is not possible the findings will be presented in narrative form, including tables and figures, to aid in data presentation. Subgroup analyses on the basis of participant age will be conducted if this information is available.

Conflicts of interest

The authors declare no competing interests in relation to this systematic review.

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Appendix I: Appraisal instruments

MAStARI appraisal instrument

JBI Critical Appraisal Checklist for Randomised Control / Pseudo-randomised Trial

Reviewer _____ Date _____

Author _____ Year _____ Record Number _____

	Yes	No	Unclear	Not Applicable
1. Was the assignment to treatment groups truly random?	☐	☐	☐	☐
2. Were participants blinded to treatment allocation?	☐	☐	☐	☐
3. Was allocation to treatment groups concealed from the allocator?	☐	☐	☐	☐
4. Were the outcomes of people who withdrew described and included in the analysis?	☐	☐	☐	☐
5. Were those assessing outcomes blind to the treatment allocation?	☐	☐	☐	☐
6. Were the control and treatment groups comparable at entry?	☐	☐	☐	☐
7. Were groups treated identically other than for the named interventions	☐	☐	☐	☐
8. Were outcomes measured in the same way for all groups?	☐	☐	☐	☐
9. Were outcomes measured in a reliable way?	☐	☐	☐	☐
10. Was appropriate statistical analysis used?	☐	☐	☐	☐
	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info. ☐

Comments (Including reason for exclusion)

JBI Critical Appraisal Checklist for Descriptive / Case Series

Reviewer _____ Date _____

Author _____ Year _____ Record Number _____

	Yes	No	Unclear	Not Applicable
1. Was study based on a random or pseudo-random sample?	☐	☐	☐	☐
2. Were the criteria for inclusion in the sample clearly defined?	☐	☐	☐	☐
3. Were confounding factors identified and strategies to deal with them stated?	☐	☐	☐	☐
4. Were outcomes assessed using objective criteria?	☐	☐	☐	☐
5. If comparisons are being made, was there sufficient descriptions of the groups?	☐	☐	☐	☐
6. Was follow up carried out over a sufficient time period?	☐	☐	☐	☐
7. Were the outcomes of people who withdrew described and included in the analysis?	☐	☐	☐	☐
8. Were outcomes measured in a reliable way?	☐	☐	☐	☐
9. Was appropriate statistical analysis used?	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

JBI Critical Appraisal Checklist for Comparable Cohort/ Case Control

Reviewer _____ Date _____

Author _____ Year _____ Record Number _____

	Yes	No	Unclear	Not Applicable
1. Is sample representative of patients in the population as a whole?	☐	☐	☐	☐
2. Are the patients at a similar point in the course of their condition/illness?	☐	☐	☐	☐
3. Has bias been minimised in relation to selection of cases and of controls?	☐	☐	☐	☐
4. Are confounding factors identified and strategies to deal with them stated?	☐	☐	☐	☐
5. Are outcomes assessed using objective criteria?	☐	☐	☐	☐
6. Was follow up carried out over a sufficient time period?	☐	☐	☐	☐
7. Were the outcomes of people who withdrew described and included in the analysis?	☐	☐	☐	☐
8. Were outcomes measured in a reliable way?	☐	☐	☐	☐
9. Was appropriate statistical analysis used?	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info. ☐

Comments (Including reason for exclusion)

Appendix II: Data extraction instruments

MAStARI data extraction instrument

JBI Data Extraction Form for Experimental / Observational Studies

Reviewer _____ Date _____

Author _____ Year _____

Journal _____ Record Number _____

Study Method

RCT ☐ Quasi-RCT ☐ Longitudinal ☐

Retrospective ☐ Observational ☐ Other ☐

Participants

Setting _____

Population _____

Sample size

Group A _____ Group B _____

Interventions

Intervention A _____

_____

Intervention B _____

_____

Authors Conclusions:

_____

_____

_____

Reviewers Conclusions:

_____

_____

_____

Study results

Dichotomous data

Outcome	Intervention ( ) number / total number	Intervention ( ) number / total number

Continuous data

Outcome	Intervention ( ) number / total number	Intervention ( ) number / total number