

Evidence on the clinical effectiveness of selected nutritional supplements prescribed in the context of naturopathic practice for preventing and/or treating injury, disease, medical conditions, or pre-clinical conditions: Overview of Reviews

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Griffith University

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Dates

This evidence evaluation and accompanying technical report received approval from the National Health and Medical Research Council (NHMRC) Natural Therapies Working Committee (NTWC) on 20 November 2024.

The protocol for the evidence evaluation was approved by NTWC 15 December 2022 (PROSPERO: CRD42023410906).

History

NHMRC has been engaged by the Department of Health and Aged Care (the Department) to update the evidence underpinning the *2015 Review of the Australian Government Rebate on Natural Therapies for Private Health Insurance* (2015 Review) (1). The natural therapies to be reviewed are Alexander technique, aromatherapy, Bowen therapy, Buteyko, Feldenkrais, homeopathy, iridology, kinesiology, naturopathy, Pilates, reflexology, Rolfing, shiatsu, tai chi, western herbal medicine, and yoga. These therapies are among those excluded from the private health insurance rebate as of 1 April 2019.

To support NHMRC in their evidence review, the Centre for Applied Health Economics at Griffith University has been engaged to conduct an overview of the evidence of the clinical effectiveness of selected nutritional supplements prescribed in the context of naturopathic practice. This overview is designed to complement the systematic review of “*Whole system, multi-modal or single modal interventions delivered in the context of naturopathic practice, for preventing and treating health conditions*” (PROSPERO CRD42021266381), which will assess primary research as part of a review of whole system naturopathy.

This evidence evaluation was developed by the Centre for Applied Health Economics at Griffith University in conjunction with NHMRC, NTWC, and the Department of Health and Aged Care’s Natural Therapy Advisory Panel (NTREAP). It describes the main body of evidence related to the clinical effectiveness of selected nutritional supplements prescribed in the context of naturopathic practice. Supplementary information is provided in Appendices A to H. All associated materials have been developed in a robust and transparent manner in accordance with relevant best practice standards.

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Thank you to the members of the Department’s Natural Therapies Review Expert Advisory Panel and the National Health and Medical Research Council’s Natural Therapies Working Committee for their advice and comments throughout the creation of this document. PRACI data were provided by Dr Amie Steel at UTS.

Membership and other details of the Panel and Committee can be found at:

www.health.gov.au/committees-and-groups/natural-therapies-review-expert-advisory-panel

www.nhmrc.gov.au/about-us/leadership-and-governance/committees/natural-therapies-working-committee

Evidence Evaluation for the Clinical Effectiveness of Selected Nutritional Supplements Prescribed in Naturopathy: Overview of Systematic Reviews

Plain language summary

What was the aim of the review?

The aim of this overview review was to assess the best evidence for the use of certain nutritional supplements for conditions that are commonly seen by naturopaths in Australia (e.g. magnesium prescribed for anxiety). It is a companion review to the review of naturopathy as a system of health care. This overview was targeted for the Australian Government Department of Health and Aged Care (the Department) to assist in their Natural Therapies Review, which is designed to determine whether certain natural therapies, including naturopathy, have enough evidence of effectiveness to be considered re-eligible for private health insurance rebates. This overview is not designed to be a complete review of all nutritional supplements used in naturopathy, nor is it intended to inform decisions about whether an individual or practitioner should prescribe nutritional supplements in practice. This overview should be considered in context with the companion review.

Key messages

For the population/condition and supplement combinations assessed, some nutritional supplements can probably or may improve some key health outcomes. The evidence assessed in this overview provided moderate to low certainty.

What was studied in this review?

The overview identified systematic reviews using a planned literature search, with no limit to publication date. To ensure the overview was manageable, the overview only assessed certain conditions or groups of people and supplements. These priority conditions were decided based on Australian survey information about the kinds of conditions that people see naturopaths for. Information from courses in naturopathy about the supplements that are used for those conditions was then used to form specific population-supplement pairings. Assessment of cost effectiveness, safety and studies of healthy populations were not included in this overview.

Certainty in the evidence was assessed using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) framework. GRADE is a method used to assess how confident (or certain) systematic review authors can be that the estimates of the effect (reported in studies) are accurate. The assessment made by the reviewer is then described as either:

- high certainty – meaning the authors have a lot of confidence that the true effect is similar to the estimated effect.
- moderate certainty – meaning that the true effect is probably close to the estimated effect.
- low certainty – meaning the true effect may be very different from the estimated effect.
- very low certainty – meaning the true effect is probably markedly different from the estimated effect. Reviewers' confidence was so limited that interpretation was not provided.

What studies did we identify in this review?

Using a planned approach 7,335 unique articles from 5 databases were collected and examined across all 15 prioritised population-supplement pairs. In addition, 437 articles were provided

through the Department's public call for evidence or by other key stakeholders. One of the articles provided by the Department's call for evidence was included in the overview (identified in addition to database searching). After excluding ineligible articles, data were extracted for 97 reviews covering the 15 prioritised population-supplement pairs. The highest quality and most comprehensive review for each outcome was used to summarise findings (26 reviews).

What were the main results of the review?

The evidence provides moderate to low certainty that taking nutritional supplements is more effective than not taking supplements for some conditions in the overview. The evidence also provides moderate to low certainty that nutritional supplements have little (or no) benefit for some conditions assessed in this overview. There are some population-supplement pairs where the effect of the supplement is unknown.

The evidence provides **moderate certainty** that nutritional supplements probably **improve** some key health outcomes for people with or at-risk of four conditions:

- Probiotics **probably improves** the number of people with global symptom improvement for people with irritable bowel syndrome (IBS) although probiotics **may have little to no effect** on global IBS symptoms or response on average.
- Antioxidants (specifically CoQ10 and alpha-lipoic acid (ALA)) **probably reduce** global fatigue severity/burden for people with fatigue (including myalgic encephalomyelitis (ME) and Chronic Fatigue Syndrome (CFS)).
- Zinc **probably reduces** recurrent infections when measured by the number of episodes of infection per child per year in children with otitis media (although when recurrence is measured by the number of children with at least one episode of infection during follow-up, zinc **may have little to no effect** on recurrent infections in children with otitis media).
- Antioxidants (specifically CoQ10 and ALA) **probably improve** fasting blood glucose and glycaemic control in people with obesity at risk of Type II Diabetes Mellitus.

The evidence provides **low certainty** that nutritional supplements may **improve** some key health outcomes for people with four conditions:

- Magnesium + a naturopathy co-intervention **may improve** anxiety-related emotional functioning/mental health burden in people with anxiety.
- Probiotics **may improve** stool consistency and health-related quality of life, and **slightly improve** abdominal pain and stool frequency in people with IBS.
- Magnesium **may reduce** headache frequency and the number of days with migraine for people with headache and migraine.
- Omega-3 fatty acids **may slightly improve** systolic blood pressure for people with hypertension.

The evidence provides **moderate certainty** that nutritional supplements probably result in **little to no difference** for some key health outcomes for people with two conditions:

- Antioxidants **probably have little to no effect** on fasting blood glucose, glycaemic control, or diastolic blood pressure in people with Type II Diabetes Mellitus.
- Omega-3 fatty acids **probably have little to no effect** on depression-related emotional functioning/mental health burden in people at-risk of perinatal depression.

The evidence provides **low certainty** that nutritional supplements may result in **little to no difference** for some key health outcomes for people with and at-risk of four conditions:

- Omega-3 fatty acids **may have little to no effect** on the number of people with response (50% improvement) or remission (no or low depression) in people with depression.
- Omega-3 fatty acids **may have little to no effect** on diastolic blood pressure in people with hypertension.

The overview found only very low certainty evidence for the following pairings: magnesium (alone) for anxiety, magnesium for insomnia/sleep disorders, zinc for atopic disorders, and magnesium for fibromyalgia, and for some priority outcomes within the conditions listed above.

No relevant reviews were identified for: magnesium for stress (perceived, occupational), cruciferous indoles for dysmenorrhea, cruciferous indoles for premenstrual syndrome (PMS), and magnesium for arthritis/osteoarthritis.

Implications for health policy and research

This review assessed the evidence of selected nutritional supplements used for certain conditions in naturopathic practice in Australia to inform the Australian Government about health policy decisions for private health insurance rebates. The review is not designed to cover all the reasons that people use nutritional supplements and is not intended to inform individual choices about their use.

The results of this overview indicate that some of the supplements considered, probably or may result in improvements for some of the conditions for which they are prescribed. However, some supplements probably or may have no effect on the outcomes considered for the conditions for which they are prescribed. For most of the population-supplement pairs examined, the evidence has very low certainty, and further research is needed.

In considering the evidence on the overall effectiveness of naturopathy, this overview should be considered in context with the systematic review of whole-system naturopathic treatment (Naturopathy review A; PROSPERO CRD42021266381) and the overview of systematic reviews to assess the clinical effectiveness of Western herbal medicines for certain conditions and populations (PROSPERO CRD42021243337).

How up to date is this review?

Searches were conducted from the earliest date included in the databases until May 2023. Reviews published after this date are not included in this overview.

Executive Summary

Background

Naturopathic practice encompasses a variety of treatment methods, including nutritional supplementation. Naturopaths prescribe nutritional supplements to restore balance, to detoxify, and/or to treat or prevent a wide range of illnesses and disease.

In 2015, an overview of systematic reviews of naturopathy, as a health service, conducted for the Australian Government found no reliable evidence demonstrating its effectiveness in treating any clinical condition. This overview is a companion review to the systematic review of primary studies on the effects of whole system, multi-modal or single modal interventions delivered in the context of naturopathic practice, for preventing and treating health conditions. This overview provides a synthesis of evidence for the efficacy of nutritional supplements in naturopathy based on assessing the best available systematic reviews for the use of certain nutritional supplements for conditions that are commonly seen by naturopaths in Australia.

Objective

The objective of this overview was to summarise and interpret the evidence from systematic reviews that examine the clinical effectiveness of selected nutritional supplements (commonly prescribed in the context of naturopathic practice) in preventing and/or treating injury, disease, medical conditions, or pre-clinical conditions. This information will be used by the Australian Government, in combination with the companion reviews, to inform its decision about whether to reinstate naturopathy as eligible for private health insurance rebates after naturopathy was excluded in 2019. This review was not designed to assess all the reasons that people use supplements used by naturopaths, or the reasons practitioners prescribe naturopathy and is not intended to inform decisions about whether an individual should use naturopathy or a practitioner practise naturopathy.

Search methods

Literature searches for each priority population-supplement combination were conducted in Epistemonikos (which includes Cochrane, PubMed, Embase, CINAHL, PsycINFO, Campbell, JBI), AMED (OVID), Emcare (OVID), Natural Medicines Comprehensive Database, and PROSPERO from database inception to May 2023. The public was also invited by the Department of Health and Aged Care to submit references for published research evidence. There were no limits on language or date of publication in the searches.

Selection criteria

The overview prioritised 15 conditions/populations which are commonly seen by naturopaths in Australia, based on Australian survey data. The 15 conditions were paired with nutritional supplements for those conditions, based on courses on naturopathy taught in Australia. These are termed “priority population-supplement pairs” throughout the overview. Prioritisation was conducted by NTWC with input from NTREAP as part of scoping and before the protocol was finalised.

Systematic reviews of randomised controlled trials (RCTs) or quasi-randomised trials that examined the clinical effectiveness of any of the priority population-supplement pairs were

eligible for inclusion. This included both (a) treatment for populations with a confirmed diagnosis of a condition of interest, and (b) disease prevention in at-risk healthy populations. Eligible interventions were those that contained either the supplement of interest alone or with other ingredients (given nutritional supplements often have co-supplementation, e.g. multivitamins). Reviews were only included if they met a set of minimum quality criteria (i.e. were systematic). Two review authors independently conducted review screening and eligibility checking.

Data collection and analysis

A summarising (as opposed to re-analysis) approach was used for synthesis of findings, which involves extracting data as they were reported in the underlying systematic reviews and then reformatting and presenting in text, tables and/or figures, as appropriate. Per this approach, additional analysis or re-assessment of primary study risk of bias was not conducted. Presentation of results was divided according to type of population: those “with condition” and those “at risk of condition”, and type of intervention: “supplement only” and “supplement + naturopathy co-intervention”.

A blinded outcome prioritisation process was undertaken by NTCW (with input from NTREAP). The outcome prioritisation process was based on published core outcome sets, systematic reviews in the priority populations, and relevant Cochrane reviews. As part of the process NTCW (with advice from NTREAP) were asked to specify up to seven ‘critical’ or ‘important’ outcome domains for inclusion in the analysis and synthesis of the overview. For outcome domains, the NTCW applied the GRADE scoring of 0 (of limited importance for decision making) to 9 (critical for decision making). Adverse events and cost-effectiveness measures were out of scope.

Where there were no reviews which reported a prioritised outcome for a population-supplement pairing, this was noted as an evidence gap in the overview.

Data were collected into Endnote, Covidence and Excel. Review characteristics and results for each outcome were extracted. Reviews were assessed for risk of bias using the ROBIS tool. One reviewer completed data extraction and risk of bias assessment of reviews, which was independently confirmed by another reviewer.

Results from the systematic review that provided the “best” evidence for each outcome in each population-supplement pair were presented; these were termed “preferred reviews”. The preferred review was determined based on review risk of bias, comprehensiveness and recency.

Main results

Across all 15 population-supplement pairs, we identified 7,335 unique articles via database searching, and 437 articles were submitted through the Department’s public call for evidence. In total, 480 reviews were sought for full-text assessment. A total of 97 systematic reviews met criteria for inclusion in this overview and underwent data extraction. Results from the highest quality, and most relevant and comprehensive review (“preferred” reviews) for each outcome were presented (26 reviews contributing).

Findings were assessed using the GRADE framework for each outcome (Grading of Recommendations Assessment, Development and Evaluation). GRADE combines information to assess overall how certain systematic review authors can be that the estimates of the effect (reported across a study/s for each critical or important outcome) are correct. High certainty means the authors have a lot of confidence that the true effect is similar to the estimated effect.

Moderate certainty means that the true effect is probably close to the estimated effect. Low certainty means the true effect might be markedly different from the estimated effect. Very low certainty means the true effect is probably markedly different from the estimated effect.

This review evaluated 15 prioritised population-supplement pairs relevant to naturopathy in Australia on an outcome considered critical or important by NTWC.

There was **moderate certainty** evidence that nutritional supplements probably **improve** some key health outcomes for people with and at-risk of four conditions:

- Probiotics probably increases the number of people with global symptom improvement of 10-50% when assessed as a dichotomous outcome for people with irritable bowel syndrome (IBS), although probiotics **may have little to no effect** on global IBS symptoms or response on average (continuous scale).
- Antioxidants (specifically CoQ10 and alpha-lipoic (ALA)) probably reduce global fatigue severity/burden in people with fatigue (including myalgic encephalomyelitis and Chronic Fatigue Syndrome).
- Zinc probably reduces recurrent infections when measured by the number of episodes of definite infection per child per year in children with otitis media (although when recurrence is measured by the number of children with at least one episode of infection during follow-up, zinc may have little to no effect on recurrent infections in children with otitis media).
- Antioxidants (specifically CoQ10 and ALA) probably improves fasting blood glucose and HOMA-IR (glycaemic control) in people at risk of Type II Diabetes Mellitus due to obesity.

There was **low certainty** evidence that nutritional supplements may **improve** some key health outcomes for people with and at-risk of four conditions:

- Magnesium + a naturopathy co-intervention may improve anxiety-related emotional functioning/mental health burden in people with anxiety.
- Probiotics may improve stool consistency and health-related quality of life, and slightly improve abdominal pain and stool frequency in people with IBS.
- Magnesium may reduce headache pain frequency and the number of days with migraine in people with headache and migraine.
- Omega-3 fatty acids may slightly improve systolic blood pressure in people with hypertension.

There was **moderate certainty** evidence that nutritional supplements probably result in **little to no difference** for some key health outcomes for people with and at-risk of two conditions:

- Omega-3 fatty acids probably have little to no effect on depression-related emotional functioning/mental health burden in people at-risk of perinatal depression.
- Antioxidants (specifically CoQ10 and ALA) probably have little to no effect on fasting blood glucose and Hb1AC levels (glycaemic control), or diastolic blood pressure in people with Type II Diabetes.

There was **low certainty** evidence that nutritional supplements probably result in **little to no difference** for some key health outcomes for people with and at-risk of four conditions:

- Omega-3 fatty acids may have little to no effect on the number of people with response (50% improvement) or remission (no or low depression) in people with depression.
- Omega-3 fatty acids may have little to no effect on diastolic blood pressure in people with hypertension.

The overview found only very low certainty evidence for the following pairings: magnesium (alone) for anxiety, magnesium for insomnia/sleeping disorders, zinc for atopic disorders, magnesium for fibromyalgia, and for some priority outcomes within the conditions listed above.

No relevant reviews were identified for: magnesium for stress (perceived, occupational), cruciferous indoles for dysmenorrhea, cruciferous indoles for premenstrual syndrome (PMS), and magnesium for arthritis/osteoarthritis.

A summary of harms of supplements used in naturopathy is not possible, as it was out of scope of this review to assess adverse outcomes related to the practice of naturopathy.

Limitations

NTWC considered that the available evidence for naturopathy as a whole-system treatment is likely limited and sought two companion reviews to accompany the totality of the evidence for naturopathy for Government decision-making. This overview is the companion review on clinical effectiveness of certain nutritional supplements commonly utilised in naturopathic practice.

This overview is limited to the analysis of the 15 population-supplement pairs prioritised by NTWC and therefore this report may not cover all the reasons why people use or prescribe supplements in a naturopathic context. Given that the aim of this overview was to provide a broad summary of the 15 population-supplement pairs, results were presented exactly as they were reported in reviews. Additional analysis and assessment of risk of bias in primary studies was not conducted.

The overview did not find evidence for many outcomes identified as important for decision-making.

Conclusions

The evidence provides moderate to low certainty that taking nutritional supplements is more effective than not taking supplements for some population-supplement pairs assessed in the overview. The evidence also provides moderate to low certainty that nutritional supplements have little (or no) benefit for some population-supplement pairs assessed in this overview. There are some population-intervention pairs where the effect of the supplement is unknown.

Given the paucity of evidence across many outcomes important for decision-making in this overview, future work is needed. In addition, reviewing the most efficacious combinations of ingredients in promising interventions may be useful.

Contents

Plain language summary	4
Executive Summary	7
Contents	11
List of Tables	13
List of Figures	16
List of Appendices	17
1. Background	18
1.1. Description of condition and setting.....	18
1.2. Description of intervention	19
1.3. How the intervention might work.....	19
1.4. Why it is important to do this review.....	19
2. Objectives	20
2.1. Priority population-supplement pairs.....	20
3. Methods	22
4. Results	23
4.1. Anxiety (including post-natal), magnesium.....	23
4.2. Stress (perceived, occupational), magnesium.....	31
4.3. Irritable bowel syndrome, probiotics.....	34
4.4. Insomnia/sleeping disorders, magnesium.....	44
4.5. Depression (including post-natal), Omega-3	53
4.6. Dysmenorrhea, Cruciferous indoles (indole-3-carbinol, di-indolylmethane).....	64
4.7. Premenstrual syndrome (PMS), Cruciferous indoles (indole-3-carbinol, diindolylmethane)	67
4.8. Atopic disorders (including eczema, dermatitis, allergic rhinitis, allergies), Zinc	70
4.9. Fatigue (general) (including CFS and ME), antioxidants (specifically CoQ10 and alpha-lipoic acid)	77
4.10. Headache and migraine, magnesium.....	83
4.11. Arthritis/osteoarthritis, magnesium	89
4.12. Hypertension, Omega-3	92
4.13. Fibromyalgia, magnesium	98

4.14.	Recurrent infection/s (including urinary tract infections, cystitis, respiratory tract infection, otitis media in children), zinc	104
4.15.	Diabetes (Type II) (including metabolic syndrome), Antioxidants (specifically CoQ10 and ALA)	111
5.	Discussion.....	119
5.1.	Summary of main results.....	119
5.2.	Overall completeness and applicability of evidence	120
5.3.	Certainty of the evidence.....	121
5.4.	Potential biases in the overview process	121
5.5.	Agreements and disagreements with other studies or reviews	122
5.6.	Limitations.....	122
6.	Authors' conclusions	123
7.	Author contributions and declaration of interests.....	124
8.	References	125

List of Tables

Table 1. List of target population-supplement pairs by priority tier.	20
Table 2. List of prioritised outcomes – anxiety (including post-natal), magnesium (as assessed as part of the Outcome Prioritisation Exercise by NTWC).	24
Table 3. Summary of ROBIS assessments – anxiety (including post-natal), magnesium.	26
Table 4. Contributing reviews for each population and intervention/co-intervention combination – anxiety (including post-natal), magnesium.	26
Table 5. Magnesium compared to placebo/inactive control for people at risk of anxiety (including postnatal).	27
Table 6. Magnesium + naturopathy co-intervention compared to placebo/inactive control for anxiety	29
Table 7. List of prioritised outcomes – stress (perceived, occupational), magnesium (as assessed as part of the Outcome Prioritisation Exercise by NTWC).	32
Table 8. List of prioritised outcomes – irritable bowel syndrome, probiotics (as assessed as part of the Outcome Prioritisation Exercise by NTWC).	34
Table 9. Summary of ROBIS assessments – IBS, probiotics	37
Table 10. Contributing reviews for each population and intervention/co-intervention combination – IBS, probiotics.	38
Table 11. Probiotics compared to placebo/inactive control for IBS	39
Table 12. Probiotics + naturopathy co-intervention compared to placebo/inactive control for IBS	42
Table 13. List of prioritised outcomes – insomnia/sleeping disorders, magnesium (as assessed as part of the Outcome Prioritisation Exercise by NTWC).	45
Table 14. Summary of ROBIS assessments – Insomnia/sleeping disorders, Magnesium	46
Table 15. Contributing reviews for each population and intervention/co-intervention combination – insomnia/sleeping disorders, magnesium.	47
Table 16. Magnesium compared to placebo/inactive control for insomnia/sleep disorders	48
Table 17. Magnesium + naturopathy co-intervention compared to placebo/inactive control for insomnia/sleep disorders	51
Table 18. List of prioritised outcomes – Depression (including post-natal), Omega-3 fatty acids (as assessed as part of the Outcome Prioritisation Exercise by NTWC).	54
Table 19. Summary of ROBIS assessments – Depression (including post-natal), Omega-3 fatty acids.	55
Table 20. Contributing reviews for each population and intervention/co-intervention combination – Depression (including post-natal), Omega-3 fatty acids.	56

Table 21. Omega-3 fatty acids compared to placebo for depression (including postnatal)	58
Table 22. Omega-3 fatty acids compared to placebo for people at risk of depression (including postnatal).....	62
Table 23. List of prioritised outcomes – Dysmenorrhea, Cruciferous indoles (indole-3-carbinol, diindolylmethane) (as assessed as part of the Outcome Prioritisation Exercise by NTWC).....	64
Table 24. List of prioritised outcomes – Premenstrual syndrome (PMS), Cruciferous indoles (indole-3-carbinol, di-indolylmethane) (as assessed as part of the Outcome Prioritisation Exercise by NTWC).....	67
Table 25. List of prioritised outcomes – atopic disorders (including eczema, dermatitis, allergic rhinitis, allergies), zinc (as assessed as part of the Outcome Prioritisation Exercise by NTWC). ..	71
Table 26. Summary of ROBIS assessments – atopic disorders, zinc	72
Table 27. Contributing reviews for each population and intervention/co-intervention combination – atopic disorders, zinc	73
Table 28. Zinc compared to placebo/inactive control for atopic disorders.....	74
Table 29. List of prioritised outcomes – fatigue (general) (including CFS and ME), antioxidants (specifically CoQ10 and ALA) (as assessed as part of the Outcome Prioritisation Exercise by NTWC).	78
Table 30. Summary of ROBIS assessments – fatigue (general) (including CFS and ME), antioxidants (specifically CoQ10 and ALA).....	79
Table 31. Contributing reviews for each population and intervention/co-intervention combination – fatigue (general) (including CFS and ME), antioxidants (specifically CoQ10 and ALA)	80
Table 32. Antioxidants (specifically CoQ10 and ALA) compared to placebo/inactive control for fatigue (general) (including CFS and ME).....	81
Table 33. List of prioritised outcomes – Headache and migraine, magnesium (as assessed as part of the Outcome Prioritisation Exercise by NTWC).....	84
Table 34. Summary of ROBIS assessments – Headache and migraine, magnesium	85
Table 35. Preferred reviews for each population and intervention/co-intervention combination – headache and migraine, magnesium.....	86
Table 36. Magnesium compared to placebo/inactive control for headache and migraine.....	87
Table 37. List of prioritised outcomes – arthritis/osteoarthritis, magnesium (as assessed as part of the Outcome Prioritisation Exercise by NTWC).....	90
Table 38. List of prioritised outcomes – hypertension, omega-3 fatty acids (as assessed as part of the Outcome Prioritisation Exercise by NTWC).....	93
Table 39. Summary of ROBIS assessments – hypertension, omega-3 fatty acids	94
Table 40. Contributing reviews for each population and intervention/co-intervention combination – hypertension, omega-3 fatty acids.	95

Table 41. Omega-3 fatty acids compared to placebo/inactive control for people with hypertension	96
Table 42. List of prioritised outcomes – fibromyalgia, magnesium (as assessed as part of the Outcome Prioritisation Exercise by NTWC).	99
Table 43. Summary of ROBIS assessments – fibromyalgia, magnesium	100
Table 44. Contributing reviews for each population and intervention/co-intervention combination – fibromyalgia, magnesium.	101
Table 45. Magnesium + naturopathy cointervention compared to placebo for people with fibromyalgia	102
Table 46. List of prioritised outcomes – recurrent infections, zinc (as assessed as part of the Outcome Prioritisation Exercise by NTWC).	105
Table 47. Summary of ROBIS assessments – recurrent infections, zinc.....	106
Table 48. Contributing reviews for types of populations and interventions examined in each review – recurrent infections, zinc.....	107
Table 49. Zinc compared to placebo for recurrent infection/s	108
Table 50. List of prioritised outcomes – Diabetes (Type II) (including metabolic syndrome), antioxidants (specifically CoQ10 and ALA) (as assessed as part of the Outcome Prioritisation Exercise by NTWC).	112
Table 51. Summary of ROBIS assessments – Diabetes (Type II) (including metabolic syndrome), antioxidants (specifically CoQ10 and ALA).....	113
Table 52. Contributing reviews for types of populations and interventions examined in each review – Diabetes (Type II) (including metabolic syndrome), antioxidants (specifically CoQ10 and ALA)	114
Table 53. Antioxidants compared to placebo/inactive control for people with T2DM.....	115
Table 54. Antioxidants compared to placebo/inactive control for people at risk of T2DM	116

List of Figures

Figure 1. PRISMA flowchart – anxiety (including post-natal), magnesium.	25
Figure 2. PRISMA flowchart – stress (perceived, occupational), magnesium.....	33
Figure 3. PRISMA flowchart – irritable bowel syndrome, probiotics.	36
Figure 4. PRISMA flowchart – insomnia/sleeping disorders, magnesium.	46
Figure 5. PRISMA flowchart – Depression (including post-natal), Omega-3.....	55
Figure 6. PRISMA flowchart – Dysmenorrhea, Cruciferous indoles (indole-3-carbinol, di-indolylmethane)	65
Figure 7. PRISMA flowchart – Premenstrual syndrome (PMS), Cruciferous indoles (indole-3-carbinol, di-indolylmethane)	69
Figure 8. PRISMA flowchart – atopic disorders, zinc.....	72
Figure 9. PRISMA flowchart – fatigue (general) (including CFS and ME), antioxidants (specifically CoQ10 and alpha-lipoic acid).....	79
Figure 10. PRISMA flowchart – Headache and migraine, magnesium	85
Figure 11. PRISMA flowchart – Arthritis/Osteoarthritis, Magnesium.	91
Figure 12. PRISMA flowchart – hypertension, omega-3.	94
Figure 13. PRISMA flowchart – fibromyalgia, magnesium.....	100
Figure 14. PRISMA flowchart – recurrent infections, zinc.	106
Figure 15. PRISMA flowchart – Diabetes (Type II) (including metabolic syndrome), antioxidants (specifically CoQ10 and ALA).	113

List of Appendices

Appendix A	Searching, selection criteria and screening
Appendix B	Methods of data collection, appraisal and reporting
Appendix C	Citation details of reviews assessed at full text but not included
Appendix D	Characteristics of included reviews
Appendix E	Results of included reviews
Appendix F	ROBIS assessments
Appendix G	Differences between protocol and overview
Appendix H	How comments from methodological review were addressed

1. Background

In 2015, an overview of systematic reviews (overview) conducted for the Australian Government found no reliable evidence on the effectiveness of naturopathy as a health service (1). The 2015 overview included systematic reviews published in the English language between 2008 to May 2013. The 2015 overview informed the 2015 Review of the Australian Government Rebate on Private Health Insurance for Natural Therapies, which resulted in naturopathy, along with 15 other natural therapies, being excluded from private health insurance rebates (2).

In the 2015 overview, systematic reviews of components (or “tools of the trade”) of naturopathy were not eligible for inclusion. However, because naturopathy includes many different treatment methods (prescribed and used in varying ways in the Australian population), it was determined important to review the evidence for commonly used standalone naturopathy modalities, as well as the wider naturopathic practice. This overview of systematic reviews is a companion to the evidence evaluation for *“Whole system, multi-modal or single modal interventions delivered in the context of naturopathic practice, for preventing and treating health conditions”* (PROSPERO registration: CRD42021266381), which assessed the clinical effectiveness of individual and/or multi-modality treatments delivered by naturopaths as part of naturopathic whole-system practice. This overview examines the evidence for the clinical effectiveness of nutritional supplements (prescribed in the context of naturopathic practice) for preventing and/or treating specific conditions.

This overview focused on the populations and conditions commonly seen and treated by naturopaths in Australia and some of the core nutritional supplements taught to naturopaths in Australia for treating those populations and conditions. Prioritisation was by NHMRC’s Natural Therapies Working Committee (NTWC), with advice from the Department’s Natural Therapies Review Expert Advisory Panel (NTREAP) and was conducted as part of the protocol development. This overview is not intended to be an exhaustive review of all nutritional supplements prescribed by naturopaths; and the assessment of safety or cost effectiveness was considered out of scope of this overview.

1.1. Description of condition and setting

Naturopathy is a holistic treatment approach grounded in enabling and restoring a body’s natural healing abilities to prevent and treat a broad range of conditions (3). Naturopathy practice encompasses a variety of treatment methods and health management strategies. Some of the most common naturopathic modalities include lifestyle recommendations, nutritional supplementation, exercise prescription, and herbal medicine (3, 4). Naturopaths generally practice in a variety of settings, including in private practice, multi-modality clinical settings, and in collaboration with multi-disciplinary teams.

This overview focused specifically on prescription of nutritional supplementation in the context of naturopathy. To ensure this overview was manageable and most relevant to the Australian context, the target population, intervention, and conditions of interest were determined as those for which people seek treatment from naturopaths in Australia. The conditions included in this overview were pre-specified and ranked in order of relative importance by NTWC in collaboration with NTREAP. The list of target populations and conditions was derived using Tertiary Education Quality and Standards Agency (TEQSA) approved naturopathic curricula, in consultation with educational providers, and Australian survey data derived from the Practitioner Research and

Collaboration Initiative (PRACI) survey (4, 5) on conditions for which people seek treatment from naturopaths. The final list was priority ranked by NTWC, with advice from NTREAP.

1.2. Description of intervention

Naturopathy covers a wide range of modalities. The use of nutritional supplementation (sometimes termed “clinical nutrition”) is one of the most frequently used interventions in naturopathic practice (3); a survey conducted by PRACI identified that nutritional supplementation is prescribed by approximately 65% of Australian naturopaths surveyed (4). When prescribed in the context of naturopathic practice, nutritional supplements as an intervention are used to treat or prevent certain conditions (3). In prescribing nutritional supplements, naturopaths may consider nutrient adequacy, food quality, dietary behaviours, and lifestyle to develop an individualised nutrition care plan.

This overview focused on nutritional supplements commonly prescribed by naturopaths for certain populations and conditions in Australia. The list of nutritional supplements eligible for this overview were pre-specified by NTWC in consultation with NTREAP. Similarly to the list of target populations and conditions eligible for this overview, the list of nutritional supplements was derived using TEQSA approved naturopathic curriculums, in consultation with educational providers, and data derived from a PRACI survey (4). The final list was priority ranked by NTWC, with advice from NTREAP.

1.3. How the intervention might work

In addition to diet and nutrition being a core tenet of naturopathic philosophy in a holistic sense, nutritional supplements are also prescribed as a targeted intervention for certain conditions (3). Naturopaths prescribe nutritional supplements to restore balance, to detoxify, and/or to treat or prevent illnesses and disease (3).

Nutritional supplements are either naturally derived or synthetically manufactured single ingredients or compounds (e.g. vitamins, minerals, amino acids) which also naturally occur in foods (6). They are designed to mimic naturally occurring biochemical compounds within the body (3). The term ‘supplement’ refers to the use of these individual nutritional compounds to bolster or replace what is considered as missing from a person’s diet or that may be needed to treat certain conditions (such as providing the necessary nutritional building blocks for production of chemicals in the body) (3).

A paragraph on how the individual intervention might work for each intervention population match is included in the descriptions below.

1.4. Why it is important to do this review

In Australia, natural therapies, including naturopathy, are often used in conjunction with conventional medicine and other strategies for maintaining health and wellbeing, with over 6% of Australians consulting a naturopath annually (7). Nutritional supplements are one of the most used modalities in naturopathic clinical practice, with 65% of naturopaths in a PRACI survey reporting prescribing nutritional supplements (8). With the popularity of nutritional supplementation in the context of naturopathy, it is important to understand the most recent evidence for clinical effectiveness. This overview informs the wider Natural Therapies Review being undertaken by the Australian Government Department of Health and Aged Care, which is evaluating evidence of the clinical effectiveness of 16 natural therapies (including naturopathy).

As stated, the 2015 overview focussed on the evidence of naturopathy as a health service and did not assess the effectiveness of core modalities (or “tools of the trade”) used by naturopaths (1). To address this potential gap in synthesis, this update is formed by two companion evidence reviews. The first is a systematic review of primary studies on the effects of whole system, multi-modal or single modal interventions delivered in the context of naturopathic practice, for preventing and treating health conditions, which assessed the clinical effectiveness of individual and/or multi-modal treatments delivered by naturopaths as part of naturopathic whole-system practice (PROSPERO registration: CRD42021266381). The second (this overview) is an overview of systematic reviews that assessed the clinical effectiveness of one core modality of naturopathy (nutritional supplementation). In contrast to the review of whole-system naturopathy, this overview does not require the treatment to be delivered by a naturopath. This two-pronged approach was chosen to ensure that recommendations relating to the clinical effectiveness of naturopathy have considered the breadth of the therapy, including evaluation of evidence for core modalities utilised by practitioners. The overview of the clinical effectiveness of western herbal medicines for certain conditions and populations (PROSPERO CRD42021243337) should also be considered.

2. Objectives

The overall objective of this overview was to summarise the evidence from systematic reviews that examine the clinical effectiveness of selected nutritional supplements (prescribed in the context of naturopathic practice) in preventing and/or treating injury, disease, medical conditions, or pre-clinical conditions. The overview prioritised certain conditions or populations which are commonly seen by naturopaths in Australia, and supplements which naturopaths would commonly suggest to aid those conditions (henceforth “priority population-supplement pairs”). Healthy populations not at risk were excluded. Reviews that examined the treatment of populations of interest with a supplement where the patient was known to have a deficiency of that supplement were excluded, as per protocol.

The main comparator was placebo or inactive control, with or without a naturopathic co-intervention. Active comparators were excluded (e.g. an eligible supplement vs another supplement or an eligible supplement vs another intervention). Details of the comparisons can be found in Appendix A3.4.

2.1. Priority population-supplement pairs

Priority population-supplement pairs were ranked by NTWC (with Tier 1 being highest priority, and Tier 3 being lowest priority), with advice from NTREAP (presented in December 2021). These were developed prior to the overview protocol based on initial scoping. Following searches during the Evidence Evaluation, it was determined to only consider the Tier 1 combinations (15 highest priority) due to the volume of reviews.

Table 1. List of target population-supplement pairs by priority tier.

	Priority population (listed in order of priority)	Priority intervention (Tier 1)	Priority intervention (Tier 2) – not considered	Priority intervention (Tier 3) – not considered
1	Anxiety (including post-natal)	Magnesium	Vitamin B and mineral complex (B6, B12, folate – individually and in combination)	N-acetylcysteine (NAC)

2	Stress (perceived, occupational)	Magnesium	Vitamin B and mineral complex (B6, B12, folate – individually and in combination)	N-acetylcysteine (NAC)
3	Irritable bowel syndrome	Probiotics (see TGA list for specific strains)	Glutamine	Digestive enzymes (including betaine hydrochloride, papain, bromelain)
4	Insomnia/Sleeping disorders	Magnesium	5-HTP (5-hydroxytryptophan)	Palmitoylethanolamide (PEA)
5	Depression (including post-natal)	Omega-3 fatty acids	Vitamin B and mineral complex (B6, B12, folate – individually and in combination)	N-acetylcysteine (NAC)
6	Dysmenorrhea	Cruciferous Indoles (indole-3- carbinol, di-indolylmethane)	Magnesium	Vitamin B and mineral complex (B6, B12, folate – individually and in combination)
7	Premenstrual syndrome (PMS)	Cruciferous Indoles (indole-3- carbinol, di-indolylmethane)	Magnesium	Vitamin B and mineral complex (B6, B12, folate – individually and in combination)
8	Atopic disorders (including eczema, dermatitis, allergic rhinitis, allergies (e.g. hay fever))	Zinc	Prebiotics (including beta-glucan, guar gum and others listed on the TGA list)	Probiotics (see TGA list for specific strains)
9	Fatigue (general) (including myalgic encephalomyelitis (ME) and Chronic Fatigue Syndrome (CFS))	Antioxidants (specifically: CoQ10 and alpha-lipoic acid)	Vitamin B and mineral complex (B6, B12, folate – individually and in combination)	Magnesium
10	Headache and migraine	Magnesium	Vitamin B and mineral complex (B6, B12, folate – individually and in combination)	N-acetylcysteine (NAC)
11	Arthritis/Osteoarthritis	Magnesium	Omega-3 fatty acids	Vitamin D
12	Hypertension	Omega-3 fatty acids	Antioxidants (specifically: CoQ10 and alpha-lipoic acid)	Magnesium
13	Fibromyalgia	Magnesium	Omega-3 fatty acids	Vitamin D
14	Recurrent infection/s (including urinary tract infections, cystitis, respiratory tract infection, otitis media in children, etc.)	Zinc	Prebiotics (including beta-glucan, guar gum and others listed on the TGA list)	Probiotics (see TGA list for specific strains)
15	Diabetes (Type II) (including metabolic syndrome)	Antioxidants (specifically: CoQ10 and alpha-lipoic acid)	Chromium (specifically: chromium picolinate, chromium enriched brewers' yeast)	Inositol

Note: Glutathione, Vitamin B12 (including cyanocobalamin and methylcobalamin) and Vitamin C were also considered but were not identified as a priority for any of the target populations/conditions.

3. Methods

The methodologies for this overview are based on those reported in the Cochrane Handbook Chapter V: overviews of Reviews (9) and the Preferred Reporting Items for Overviews of Reviews (PRIOR) checklist (10). An overview of reviews was selected as the most appropriate methodology due to the likelihood of sufficient systematic reviews being available to cover the broad range of populations, interventions, and outcomes required to answer the research question. This was confirmed by an initial scoping review.

The methodology was pre-determined and endorsed by the NHMRC (registered as a protocol (PROSPERO 2023 CRD42023410906). Any deviations from, or clarifications to, the original protocol are presented in Appendix G. A full description of the overview methods is provided in Appendix A and B:

- Appendix A1 search methods
- Appendix A2 search strategy
- Appendix A3 eligibility criteria (types of review, types of participants, types of interventions, types of outcome measures)
- Appendix A4 selection of studies (inclusion decisions)
- Appendix B1 data collection
- Appendix B2 data analysis and synthesis
- Appendix B3 risk of bias of evidence in included reviews
- Appendix B4 certainty of evidence

Outcome prioritisation

As part of the overview process, an outcome prioritisation exercise was conducted with NTREAP and NTRWC to identify critical and important outcomes for each priority population-supplement pair. The outcome prioritisation exercise methodology is detailed in Appendix A3.5. The list of prioritised outcomes for each population-intervention is provided in each results section. Outcomes related to safety, patient experience and cost effectiveness were excluded as considered out of scope.

Selection of preferred reviews

The overview used a summarising approach, which involves choosing and presenting the best available evidence for each PICO (and not undertaking re-analysis) (9). Following outcome prioritisation and full-text assessment, the systematic review that provided the “best” evidence for each PICO was determined based on risk of bias of the review (assessed with ROBIS), comprehensiveness (meta-analysis with the most studies/participants) and recency (date review was published, date included primary studies were published) (11). These are termed “preferred reviews”. To be assessed, reviews had to meet a minimum criteria including conducting a comprehensive search, providing details of PICO and inclusion criteria, and assess risk of bias (RoB) or quality of primary studies (see Appendix A3.1 for details).

Rather than implementing rigid decision rules for use of the criteria to select “preferred reviews”, these were used as guiding principles for choosing the most relevant evidence (per advice from NTRWC and NTREAP). Further details are provided in Appendix A and B. Explanations for choosing the preferred review for each PICO are presented in the relevant results sections.

Data collection and analysis

Results are presented by population-supplement pairing, with separate information for populations “with condition” and “at risk of condition”. Separate comparisons are also presented for supplements delivered singularly or with a co-intervention.

Summary of Findings tables were developed, and results were reported for preferred reviews for outcomes rated as critical or important by the NTC. Summary of Findings tables included up to 7 critical and important outcome domains prioritised by NTC who were guided by the GRADE framework. Risk of bias for GRADE assessments were based on those completed by review authors and reported as part of reviews.

4. Results

4.1. Anxiety (including post-natal), magnesium

4.1.1. Description of condition

Anxiety disorders are a class of mental health conditions characterised by excessive and persistent fear, worry, and apprehension that significantly disrupt an individual's daily functioning (12, 13). While some level of anxiety experienced infrequently is normal, anxiety disorders involve responses that extend beyond typical adaptive reactions to stressors. Symptoms of anxiety disorders can be both psychological and physiological. Common psychological symptoms include persistent worry, restlessness, irritability, difficulty concentrating, and a sense of impending danger (13, 14). Physiological symptoms may include increased heart rate, sweating, trembling, shortness of breath, and muscle tension. These symptoms can significantly impair daily life, affecting relationships, work or academic performance, and overall well-being.

Anxiety disorders are prevalent in Australia, representing the most common class of mental health conditions. Recent data suggests approximately 17% of Australians have an anxiety disorder (15). Anxiety disorders also frequently co-occur with other mental health conditions, particularly depression and substance use disorders (12).

Mental health professionals diagnose anxiety disorders according to the criteria outlined in the Diagnostic and Statistical Manual of Mental Disorders (current version is DSM-5) (14). Specific diagnostic categories include generalised anxiety disorder (GAD), panic disorder, social anxiety disorder, and specific phobias (12, 14). Diagnosis involves a thorough clinical interview, medical history evaluation, and potentially the use of psychometric measures. Differential diagnosis is also crucial to exclude medical conditions that might mimic anxiety symptoms.

4.1.2. Description of the intervention

Magnesium (often abbreviated as its chemical symbol: Mg) is a naturally occurring mineral in the human body. It is an essential mineral playing numerous crucial roles in the human body, including enzymatic reactions, energy production, muscle function, and bone health (16, 17). Recent evidence suggests that magnesium levels in the body may be associated with some health conditions, including Diabetes Mellitus (Type II), cardiovascular disease, osteoporosis, and migraines (17).

It is thought that Magnesium may play a role in lowering abnormal levels of cortisol and regulate neurotransmitters in the brain (18). Cortisol, a stress hormone, can worsen anxiety when

chronically elevated, and magnesium may help reduce cortisol, thereby reducing anxiety. The proposed mechanism for this is that Magnesium blunts the release of the excitatory neurotransmitter glutamate and promotes the release of the inhibitory neurotransmitter GABA, helping keep anxiety in check.

The recommended dietary intake for magnesium varies depending on age and sex, typically ranging from 310-420 mg daily for adults (19). While it is a typical component of most diets, and is abundant in foods such as leafy vegetables, nuts, legumes, and grains, supplementation is available. Magnesium supplements come in several forms with varying bioavailability (absorption rates), including magnesium oxide, citrate, glycinate, or lactate (17).

Oral magnesium supplements are readily available without prescription and are sometimes sold in tandem with one or multiple other nutritional supplements. Magnesium supplements are generally safe for most people when taken at appropriate doses¹; though some medications may interact with magnesium (including antibiotics, diuretics and bisphosphonates) (17). Excess magnesium is usually excreted by the kidneys as urine, although very high amounts of magnesium from dietary supplements can result in diarrhoea, nausea and abdominal cramping (17).

4.1.3. Prioritised outcomes

Seven priority outcomes were identified by NTWC as part of the Outcome Prioritisation Exercise. These are listed below by order of priority. Outcomes were rated by their importance to decision-making, with those rated 7-9 being critical for decision-making.

Table 2. List of prioritised outcomes – anxiety (including post-natal), magnesium (as assessed as part of the Outcome Prioritisation Exercise by NTWC).

#	Priority population	Priority intervention	Priority outcomes	
			NTWC Rating*	Outcome domain
1	Anxiety (including post-natal)	Magnesium	9	Anxiety-related emotional functioning/mental health burden
			9	Physical function burden from anxiety (gastrointestinal disorders, loss of sexual desire, frequent upper respiratory tract and other infections)
			9	Improvement in clinical levels of anxiety
			8	Depression-related emotional functioning/mental health burden
			8	Stress-related emotional functioning/mental health burden
			8	Physiological symptoms of anxiety (heart rate, BP, adrenaline, skin conductance, weight gain, weight loss, cortisol levels)
			8	HRQoL

Abbreviations: BP = blood pressure; HRQoL= health-related quality of life; NTWC = Natural Therapies Working Group

*1-3 = of limited importance to decision making; 4-6 = important, but not critical, to decision making; 7-9 = critical for decision-making

4.1.4. Search findings

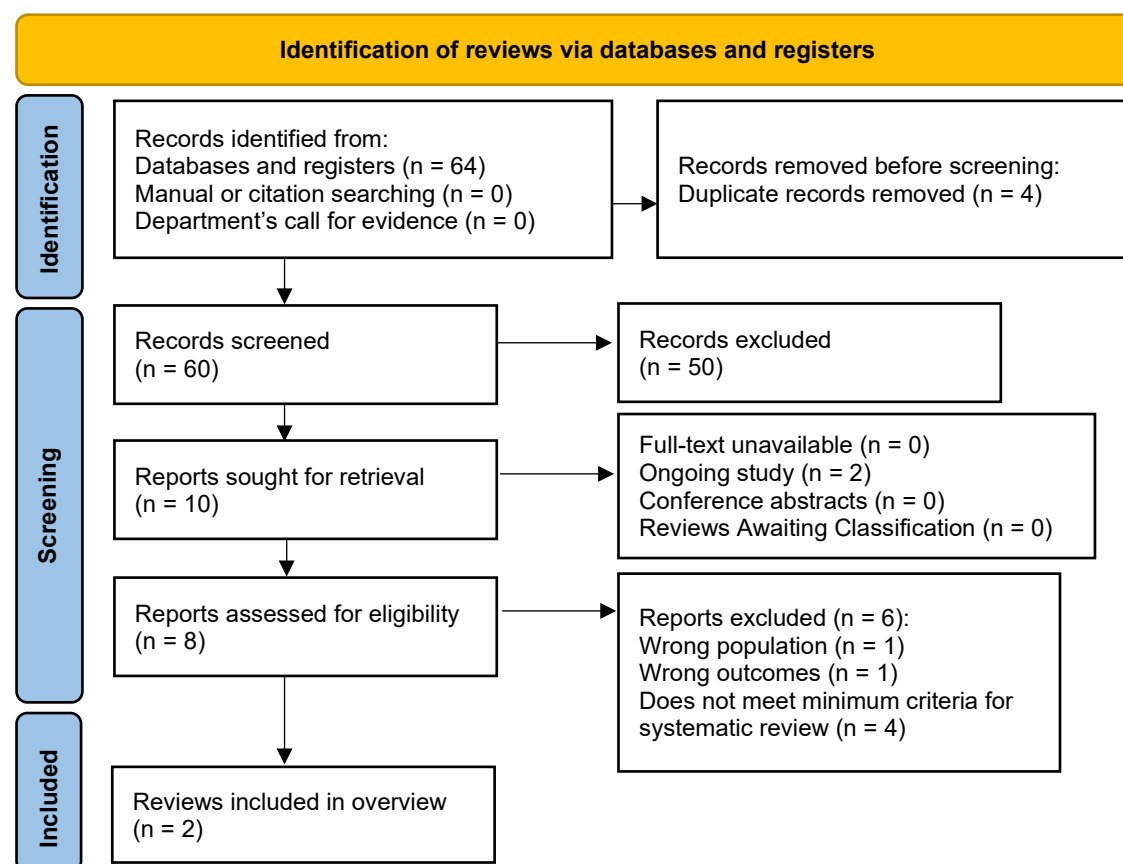
¹ The TGA has recently updated warning labels for supplements containing B6 due to over 30 reports of peripheral neuropathy (symptoms of which include tingling, burning and numbness). The TGA notes “In many cases, people reported they were not aware they had consumed vitamin B6, as the product they were taking was a magnesium supplement.” See [Why TGA made these labelling and use changes | Health supplements containing vitamin B6 can cause peripheral neuropathy | Therapeutic Goods Administration \(TGA\)](#)

In total, 60 reviews were identified in the searches after de-duplication and underwent screening. None of the reviews provided by the Department's call for evidence were relevant to this population-supplement pair. After title and abstract screening, 10 reviews were sought for retrieval for full-text screening:

- 2 reviews were ongoing (citation details recorded in Appendix C4)
- 6 reviews did not meet inclusion criteria (citation details and reasons for exclusion recorded in Appendix C)

Therefore, two reviews met the inclusion criteria. Characteristics of included reviews are presented in Appendix D. A full PRISMA flowchart is presented below.

Figure 1. PRISMA flowchart – anxiety (including post-natal), magnesium.



4.1.5. Description of included reviews

Two reviews were identified as eligible for inclusion (conducted in 2018 and 2023). Both were systematic reviews of randomised controlled trials (RCTs) and both included a meta-analysis. A detailed summary of characteristics of the included reviews are reported in Appendix D.

Barić et al.'s (2018) (20) review evaluated the clinical efficacy and safety of complementary and alternative medicine in the treatment of generalised anxiety disorder. Tsai et al.'s (2023) (21) review assessed the effectiveness of dietary interventions for the treatment of perinatal depression and/or anxiety (i.e. during pregnancy or within the first 12 months postpartum). Each review included one primary study which evaluated the impact of magnesium on outcomes of interest to this overview (anxiety-related emotional functioning/mental health burden or

depression-related emotional functioning/mental health burden). Tsai 2023 examined perinatal populations, but the relevant primary study evidence examined a postnatal population only (specifically, the first 8 weeks of the postpartum period).

No included reviews reported results for the following outcomes: physical function burden from anxiety, improvement in clinical levels of anxiety, stress-related emotional functioning/mental health burden, physiological symptoms of anxiety (heart rate, BP, adrenaline, skin conductance, weight gain, weight loss, cortisol levels), health-related quality of life.

4.1.6. Assessment of risk of bias of included reviews

Risk of bias assessments of the included reviews, as appraised using the ROBIS tool, are presented below. Full assessments are reported in Appendix F.

Table 3. Summary of ROBIS assessments – anxiety (including post-natal), magnesium.

Review ID	ROBIS Domains				Overall risk of bias
	Domain 1: Study eligibility criteria	Domain 2: Identification and selection of studies	Domain 3: Data collection and study appraisal	Domain 4: Synthesis and findings	
Barić 2018	Low	Unclear	Low	Low	Low risk
Tsai 2023	Low	Unclear	Low	Low	Low risk

4.1.7. Results

There was no cross-over of PICO; one review included magnesium alone, where the other included a co-intervention, and so both Barić 2018 and Tsai 2023 were considered preferred reviews, and all reported results were presented.

Table 4. Contributing reviews for each population and intervention/co-intervention combination – anxiety (including post-natal), magnesium.

	With anxiety (including post-natal)	At risk of anxiety (including post-natal)
Magnesium VS placebo/inactive control	-	Tsai 2023
Magnesium + naturopathy co-intervention VS placebo/inactive control	Barić 2018	-

4.1.8. Summary of findings and evidence statements

Table 5. Magnesium compared to placebo/inactive control for people at risk of anxiety (including postnatal)

Patient or population: **At risk of anxiety (including postnatal)**
Intervention: **Magnesium**
Comparison: **Placebo/inactive control**

NTWC Rating*	Outcomes	Contributing review	Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
	Anxiety-related emotional functioning/mental health burden					
9	Condition: At-risk of postnatal anxiety Population: First 8 weeks postpartum Dose: 64.6mg per day Assessed with: STAI Follow up: 8 weeks after baseline	Tsai 2023#	SMD = -0.34 (-0.83, 0.15)^	31 (1)	⊕○○○ VERY LOW ^a	The evidence is very uncertain about the effect of magnesium on anxiety-related emotional functioning/mental health burden for people at risk of anxiety.
9	Physical function burden from anxiety	-	-	-	-	No reviews found. The effect of magnesium on improvement in physical function burden from anxiety for people at risk of anxiety is unknown.
9	Improvement in clinical levels of anxiety	-	-	-	-	No reviews found. The effect of magnesium on improvement in clinical levels of anxiety for people at risk of anxiety is unknown.
	Depression-related emotional functioning/mental health burden					
8	Condition: At-risk of post-natal anxiety Population: First 8 weeks postpartum Dose: 64.6mg per day Assessed with: EPDS Follow up: 8 weeks after baseline	Tsai 2023#	SMD = 0.20 (-0.29, 0.69)^	31 (1)	⊕○○○ VERY LOW ^a	The evidence is very uncertain about the effect of magnesium on depression-related emotional functioning/mental health burden for people at risk of anxiety.
8	Stress-related emotional functioning/mental health burden	-	-	-	-	No reviews found. The effect of magnesium on improvement in stress-related emotional functioning/mental health burden for people at risk of anxiety is unknown.
8	Physiological symptoms of anxiety (heart rate, BP, adrenaline, skin conductance, weight gain, weight loss, cortisol levels)	-	-	-	-	No reviews found. The effect of magnesium on improvement in physiological symptoms of anxiety for people at risk of anxiety is unknown.
8	Health-related quality of life	-	-	-	-	No reviews found. The effect of magnesium on improvement in health-related quality of life for people at risk of anxiety is unknown.

*Ratings 1-3 = of limited importance to decision making; 4-6 = important, but not critical, to decision making; 7-9 = critical for decision-making

#Absolute risk differences measured using STAI and EPDS were not presented.

^SMDs of 0.2, 0.5, and 0.8 are considered small, medium, and large, respectively (22)

Abbreviations: BP=blood pressure, CI=Confidence Interval, EPDS= Edinburgh Postnatal Depression Scale, STAI=State Trait Anxiety Inventory, SMD=Standardised Mean Difference

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Risk of bias was rated by review authors as “some concerns” (no change for risk of bias). Population in the included review was restricted to pregnant women at risk of postnatal anxiety only (downgraded one for indirectness). Wide CI to where point estimate is uninterpretable; CI appreciably crosses the threshold(s) of interest (SMD = 0.2) (downgraded 3 for very serious imprecision). No inconsistency due to singular study (no change for inconsistency). Publication bias not assessed due to insufficient number of studies (no change for publication bias).

Table 6. Magnesium + naturopathy co-intervention compared to placebo/inactive control for anxiety

Patient or population: **Anxiety**

Intervention: **Magnesium + naturopathy co-intervention**

Comparison: **Placebo/inactive control**

NTWC Rating*	Outcomes	Contributing review	Absolute risk difference	Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
9	Anxiety-related emotional functioning/mental health burden Condition: GAD Dose: 2x Magnesium 75mg + Cratageus oxyacantha 75mg + Eschscholtzia californica 20mg, twice per day Assessed with: HAM-A Follow up: 12 weeks	Barić 2018	Difference in reduction in HAM-A score: -1.7 (-1.8 to -1.6)	RR = 1.41 (1.04 to 1.93)^	264 (1)	⊕⊕○○ LOW ^a	Magnesium + naturopathy co-intervention may improve anxiety-related emotional functioning/mental health burden for anxiety.
9	Physical function burden from anxiety	-	-	-	-	-	No reviews found. The effect of magnesium on improvement in physical function burden from anxiety for anxiety is unknown.
9	Improvement in clinical levels of anxiety	-	-	-	-	-	No reviews found. The effect of magnesium on improvement in clinical levels of anxiety for anxiety is unknown.
8	Depression-related emotional functioning/mental health burden	-	-	-	-	-	No reviews found. The effect of magnesium on improvement in depression-related emotional functioning/mental health burden for anxiety is unknown.
8	Stress-related emotional functioning/mental health burden	-	-	-	-	-	No reviews found. The effect of magnesium on improvement in stress-related emotional functioning/mental health burden for anxiety is unknown.
8	Physiological symptoms of anxiety (heart rate, BP, adrenaline, skin conductance, weight gain, weight loss, cortisol levels)	-	-	-	-	-	No reviews found. The effect of magnesium on improvement in physiological symptoms of anxiety for anxiety is unknown.
8	Health-related quality of life	-	-	-	-	-	No reviews found. The effect of magnesium on improvement in health-related quality of life for anxiety is unknown.

*Ratings 1-3 = of limited importance to decision making; 4-6 = important, but not critical, to decision making; 7-9 = critical for decision-making.

^aThere are no published MCID estimations for HAM-A. A 20% relative risk difference (i.e., risk ratio ≤ 0.8 or ≥ 1.2) was therefore considered as a minimal clinically important difference (MCID) (23).

Abbreviations: CI=Confidence Interval, GAD=generalised anxiety disorder, HAM-A=Hamilton Anxiety Scale, BP=blood pressure, EPDS=Edinburgh Postnatal Depression Scale, RR=risk ratio

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Low risk of bias was rated by review authors (no change for risk of bias). Population in the included review was restricted to GAD only, however given this is one of the most common anxiety disorders, this is considered to directly address the population of interest (no change for indirectness). CI boundaries suggest very different inferences based on MCID (RR = 1.2) (downgraded two for serious imprecision). No inconsistency due to singular study (no change for inconsistency). Publication bias not assessed due to insufficient number of studies (no change for publication bias).

4.2. Stress (perceived, occupational), magnesium

4.2.1. Description of condition

Stress is the body's natural reaction to perceived challenges or threats. It involves a complex interplay of physiological and psychological responses designed to aid survival and adaptation. However, when stress becomes chronic or overwhelming, it can have adverse effects on mental and physical well-being (24). Stress is distinguished from formal psychiatric diagnoses like anxiety and mood disorders, but it is a significant risk factor for their development (25).

Stress manifests in various ways. Common physiological symptoms include increased heart rate, rapid breathing, muscle tension, headaches, and digestive upset (26). People who experience stress may also experience symptoms such as irritability, difficulty concentrating, restlessness, worry, and sleep disturbances (26). Prolonged or chronic levels of stress can contribute to a range of health problems, including psychological conditions, cardiovascular disease, weakened immune function, and gastrointestinal disorders (25, 27).

Stress is a highly prevalent experience in Australia. Recent data reported that a significant portion of the population reports experiencing stress on a regular basis, with 37% reporting stress as having moderate to very strong impact on their mental health (28). Key drivers of stress can include financial, health, and family issues, and evidence suggests that people who are stressed are more likely to participate in risky health behaviours like gambling, consuming alcohol, smoking cigarettes, and taking recreational drugs (28). While there is no formal diagnostic process for "stress" itself, healthcare professionals may assess stress levels using self-report measures (such as the Perceived Stress Scale (29)) or evaluate physiological markers.

4.2.2. Description of the intervention

Magnesium (often abbreviated as its chemical symbol: Mg) is a naturally occurring mineral in the human body. It is an essential mineral playing numerous crucial roles in the human body, including enzymatic reactions, energy production, muscle function, and bone health (16, 17). Recent evidence suggests that magnesium levels in the body may be associated with some health conditions, including Diabetes Mellitus (Type II), cardiovascular disease, osteoporosis, and migraines (17).

The recommended dietary intake for magnesium varies depending on age and sex, typically ranging from 310-420 mg daily for adults (19). While it is a typical component of most diets, and is abundant in foods such as leafy vegetables, nuts, legumes, and grains, supplementation is available. Magnesium supplements come in several forms with varying bioavailability (absorption rates), including magnesium oxide, citrate, glycinate, or lactate (17). As described above, it is thought that Magnesium may play a role in lowering abnormal levels of cortisol (stress hormone that) and reduce stress levels.

Oral magnesium supplements are readily available without prescription and are sometimes sold in tandem with one or multiple other nutritional supplements. Magnesium supplements are

generally safe for most people when taken at appropriate doses²; though some medications may interact with magnesium (including antibiotics, diuretics and bisphosphonates) (17). Excess magnesium is usually excreted by the kidneys as urine, though very high amounts of magnesium from dietary supplements can result in diarrhea, nausea and abdominal cramping (17).

4.2.3. Prioritised outcomes

Seven priority outcomes were identified by NTWC as part of the Outcome Prioritisation Exercise. These are listed below by order of priority. Outcomes were rated by their importance to decision-making, with those rated 7-9 being critical for decision-making.

Table 7. List of prioritised outcomes – stress (perceived, occupational), magnesium (as assessed as part of the Outcome Prioritisation Exercise by NTWC).

#	Priority population	Priority intervention	Priority outcomes	
			NTWC Rating	Outcome domain
2	Stress (perceived, occupational)	Magnesium	9	Improvement in clinical levels of stress
			9	Improvement in clinical levels of occupational stress/burnout
			8	Anxiety burden from stress
			8	Physiological symptoms of anxiety (heart rate, BP, adrenaline, skin conductance, weight gain, weight loss, cortisol levels)
			8	Quality of life
			7	Depression burden from stress
			7	Absenteeism

Abbreviations: BP=blood pressure; HRQoL=health-related quality of life; NTWC=Natural Therapies Working Group

*1-3 = of limited importance to decision making; 4-6 = important, but not critical, to decision making; 7-9 = critical for decision-making

4.2.4. Search findings

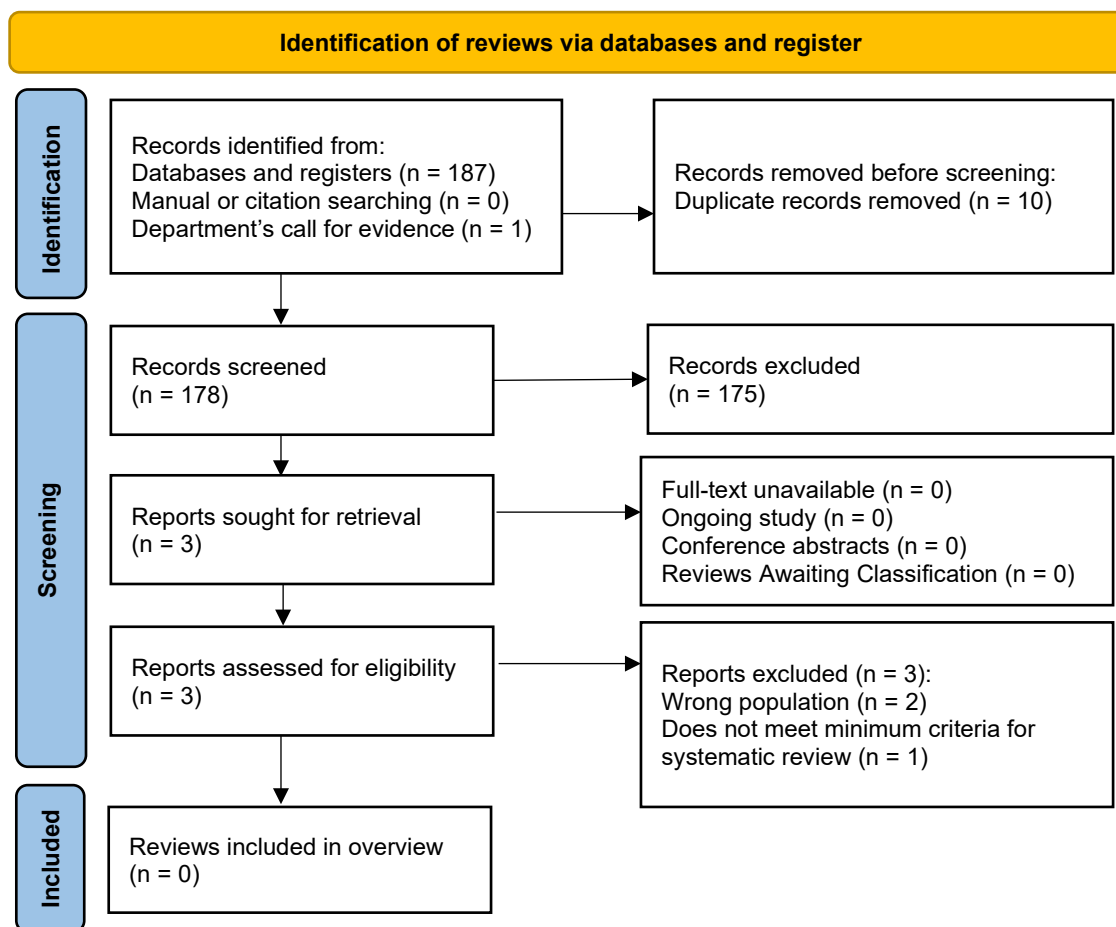
In total, 178 reviews were screened following de-duplication. One review provided by the Department's call for evidence was relevant to this population-supplement pair, which was already identified in database searching and excluded as a duplicate (see Appendix C2). After title and abstract screening, 3 reviews were assessed for eligibility at full-text screening:

- 3 reviews did not meet inclusion criteria (citation details and reasons for exclusion recorded in Appendix C)

Following assessment, no reviews met the inclusion criteria. A full PRISMA flowchart is presented below.

² The TGA has recently updated warning labels for supplements containing B6 due to over 30 reports of peripheral neuropathy (symptoms of which include tingling, burning and numbness). The TGA notes "In many cases, people reported they were not aware they had consumed vitamin B6, as the product they were taking was a magnesium supplement." See [Why TGA made these labelling and use changes | Health supplements containing vitamin B6 can cause peripheral neuropathy | Therapeutic Goods Administration \(TGA\)](#)

Figure 2. PRISMA flowchart – stress (perceived, occupational), magnesium.



4.2.5. Description of included reviews

No reviews met inclusion criteria.

4.2.6. Assessment of risk of bias of included systematic reviews

No reviews met inclusion criteria.

4.2.7. Results

No reviews met inclusion criteria.

4.2.8. Summary of findings and evidence statements

The effect of magnesium on improvement in clinical levels of stress, improvement in clinical levels of occupational stress/burnout, anxiety burden from stress, physiological symptoms of anxiety (heart rate, BP, adrenaline, skin conductance, weight gain, weight loss, cortisol levels), quality of life, depression burden from stress or absenteeism in people with stress (perceived, occupational) is unknown.

4.3. Irritable bowel syndrome, probiotics

4.3.1. Description of condition

Irritable bowel syndrome (IBS) is a gastrointestinal disorder characterised by symptoms such as abdominal pain, bloating, altered bowel habits (diarrhea, constipation, or both), and other gastrointestinal symptoms (30). Symptoms can vary significantly between individuals, making diagnosis and management challenging. Estimates of prevalence are varied, though IBS likely affects around 1 in 10-20 people globally (31, 32). IBS can significantly affect quality of life, leading to emotional distress, anxiety, and social limitations (33). IBS also frequently co-occurs with some mental health conditions, such as anxiety and depression (33), which can complicate management and may point patients towards seeking a holistic approach that considers both gut and mental health aspects of IBS.

Diagnosing IBS is primarily based on clinical criteria, such as Rome IV Diagnostic Criteria for IBS, as there is no single definitive test for IBS. Rome IV criteria must be fulfilled for at least 2 months prior to diagnosis and includes criteria related to abdominal pain, change in frequency of stool, change in form (appearance) of stool, or after appropriate evaluation symptoms cannot be fully explained by another medical condition (34). Other investigations, such as blood tests, stool analysis, and imaging, may be performed to rule out other medical conditions with similar symptoms.

4.3.2. Description of the intervention

Probiotics are microorganisms that support the intestinal microbiome, which includes the bacteria, viruses, and protozoa that populate the gastrointestinal tract (35, 36). They are found naturally in some foods (e.g. fermented foods like kimchi, sauerkraut or kombucha) and are also available as dietary supplements in capsules, tablets, powders, and beverages (36). The specific bacterial strains used in probiotic products vary; some of the most common types include *Lactobacillus*, *Bifidobacterium*, and *Saccharomyces* (36).

Probiotics may assist in maintaining gut health by balancing the gut flora. They may strengthen the intestinal barrier, support the immune system in removing harmful bacteria, and aid in nutrient breakdown. These mechanisms may improve the symptoms of IBS (37).

Probiotics supplements are available without prescription; some are sensitive to heat or light and may require refrigeration. The recommended dosage and frequency of intake for probiotics can vary depending on the specific product and the intended health benefit.

4.3.3. Prioritised outcomes

Seven priority outcomes were identified by NTWC as part of the Outcome Prioritisation Exercise. These are listed below by order of priority. Outcomes were rated by their importance to decision-making, with those rated 7-9 being critical for decision-making.

Table 8. List of prioritised outcomes – irritable bowel syndrome, probiotics (as assessed as part of the Outcome Prioritisation Exercise by NTWC).

#	Priority population	Priority intervention	Priority outcomes	
			NTWC Rating*	Outcome domain

3	Irritable bowel syndrome (IBS)	Probiotics (see TGA list for specific strains)	9	Global improvement of IBS
			8	Abdominal pain burden
			8	Health-related quality of life
			8	Number of recurrent episodes
			7	Functioning
			7	Stool frequency, bowel transit time
			7	Stool consistency

Abbreviations: BP=blood pressure; HRQoL=health-related quality of life; NTWC=Natural Therapies Working Group

*1-3 = of limited importance to decision making; 4-6 = important, but not critical, to decision making; 7-9 = critical for decision-making

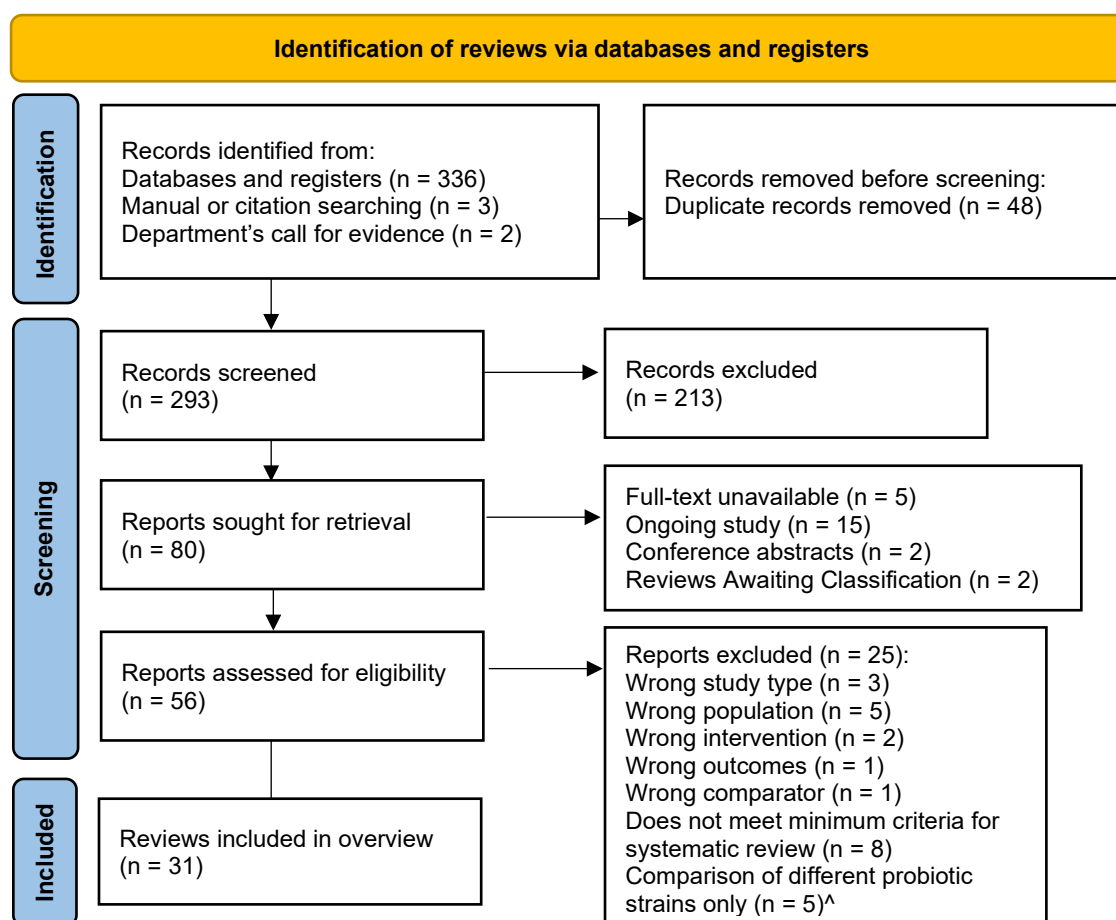
4.3.4. Search findings

In total, 293 reviews were screened following de-duplication. Two reviews provided through the Department's call for evidence were relevant to this population-supplement pair; both were already identified in database searching so were excluded as duplicates (see Appendix C2). After title and abstract screening, 80 reviews were sought for retrieval for full-text screening:

- 9 reviews did not have full-text copies able to be retrieved (citation details recorded in Appendix C3)
- 13 reviews were ongoing (citation details recorded in Appendix C4)
- 2 reviews were published in languages other than English (citation details recorded in "Reviews awaiting classification" table in Appendix C3)
- 25 reviews did not meet inclusion criteria (citation details and reasons for exclusion recorded in Appendix C1)

A final 31 reviews met the inclusion criteria. Characteristics of included reviews are presented in Appendix D. A full PRISMA flowchart is presented below.

Figure 3. PRISMA flowchart – irritable bowel syndrome, probiotics.



[^]Where reviews only presented comparisons of different strains, these were excluded at full-text review and listed as “Comparison of different probiotic strains only” as reason for exclusion. Further details are listed in Appendix G: Differences between protocol and review.

4.3.5. Description of included reviews

Thirty-one reviews were identified as eligible for inclusion (conducted between 2008 and 2023) (38-68). Most of the reviews (n = 29) only included randomised controlled trials, and most included a meta-analysis (n=24). A detailed summary of characteristics of the included reviews are reported in Appendix D.

Most reviews aimed to measure the efficacy and/or safety of probiotics alone for treatment of irritable bowel syndrome, aligning directly with the overview’s PICO (n = 30). Only one review examined the effect of co-supplementation of probiotics (with Vitamin D) (68). Reviews examined a variety of probiotic formulas, including specific strains or combinations of strains of probiotics. Some specifically reported strains evaluated, where others did not specify and termed “probiotics” as a general intervention. Where a review reported results for both probiotics as a general intervention and specific strains/formulas of probiotics, only general results were extracted (as per protocol evaluating the comparative efficacy of probiotic strains is out of scope of this overview).

Most reviews specified the population as adult patients with IBS. Many specified that IBS diagnosis needed to be based on meeting specific diagnostic criteria (e.g. Manning or Rome I, II,

III, IV). Three reviews looked at specific types of IBS: two examined IBS-C (41, 44) and one examined IBS-D (42). Five reviews included a range of gastrointestinal disorders or symptoms, and examined IBS as a subpopulation (45, 56, 58, 61, 64).

Most reviews (n = 18) limited their included population to adults, either ≥15, 16 or 18 years of age. Six reviews examined paediatric populations (40, 56, 59, 61, 63, 64). Seven reviews included both adult and paediatric populations (38, 45, 49, 51, 60, 66, 68).

4.3.6. Assessment of risk of bias of included systematic reviews

Risk of bias assessments of the included reviews, as appraised using the ROBIS tool, are presented below. Full assessments are reported in Appendix F.

Table 9. Summary of ROBIS assessments – IBS, probiotics

Review ID	ROBIS Domains				Overall risk of bias
	Domain 1: Study eligibility criteria	Domain 2: Identification and selection of studies	Domain 3: Data collection and study appraisal	Domain 4: Synthesis and findings	
Abboud 2020	Low	Low	Low	Low	Low risk
Asha 2020	High	Unclear	Unclear	Unclear	High risk
Connell 2018	Low	Unclear	Low	Low	Low risk
Corbitt 2018	High	High	Unclear	Unclear	High risk
Ding 2019	Low	High	Unclear	Unclear	High risk
Fatahi 2022	Low	Low	Low	Low	Low risk
Ford 2014	Low	Low	Low	Low	Low risk
Horvath 2011	Low	Low	Low	Unclear	Unclear risk
Hoveyda 2009	Low	Unclear	Low	Low	Unclear risk
Huertas-Ceballos 2009	Low	Low	Low	High	High risk
Hungin 2018	Low	Unclear	Unclear	High	High risk
Konstantis 2023	Low	Low	Low	Low	Low risk
Kortierink 2014	Low	Low	Low	High	High risk
Le Morvan 2021	Low	Low	Unclear	Unclear	Unclear risk
Li 2020	Low	Unclear	Low	Low	Low risk
Liang 2019	Low	Unclear	Low	Low	Low risk
McFarland 2008	Low	Low	Low	Low	Low risk
McFarland 2021	Low	Low	Low	Unclear	Unclear risk
Moayyedi 2010	Low	Low	Low	Unclear	Unclear risk
Nikfar 2008	Low	Low	Low	Low	Low risk
Niu 2020	Low	Unclear	Low	Low	Low risk
Ortiz-Lucas 2013	Low	Unclear	Unclear	High	High risk
Pratt 2020	Low	Low	Low	High	High risk
Ritchie 2012	Low	Unclear	Unclear	Low	Unclear risk
Shang 2022	Low	Unclear	Low	Low	Low risk
Sun 2020	Low	Low	Low	High	High risk
Wang 2022	Low	Low	Low	Low	Low risk
Wen 2020	Low	Unclear	Low	Low	Low risk
Xu 2021	Low	Unclear	Low	Unclear	Unclear risk
Yuan 2017	Low	Unclear	Unclear	Unclear	Unclear risk
Zhang 2016	Low	Unclear	Low	Unclear	Unclear risk

4.3.7. Results

Evidence from the lowest risk of bias, relevant, and/or comprehensive review was chosen for each outcome. Contributing reviews for each population and intervention combination are listed in the matrix in Table 10.

Table 10. Contributing reviews for each population and intervention/co-intervention combination – IBS, probiotics.

	With IBS	At risk of IBS
Probiotics VS placebo/inactive control	Li 2020 Wen 2020 Le Morvan 2021 Ding 2019	-
Probiotics + naturopathy co-intervention VS placebo/inactive control	Abboud 2020	-

4.3.7.1. Probiotics versus placebo/inactive control for IBS

Li et al. (2020) (54) was the preferred review for probiotics versus placebo/inactive control for people with IBS (assessed as having a low risk of bias and providing the largest meta-analysis with most recent findings). The authors reported global improvement in IBS symptoms as both continuous (29 RCTs including 3,726 patients) and dichotomous outcomes (35 RCTs including 4,392 patients), and abdominal pain burden (38 RCTs including 4,579 patients).

Stool frequency and consistency were measured in five and seven reviews, respectively. The preferred review for these outcomes was Wen et al. (2020) (41) (lowest risk of bias with the most comprehensive meta-analysis). The population of interest in Wen's review was IBS-C (constipation sub-type). Pooled analysis of 10 RCTs including 11 comparisons assessed number of bowel movements per week (where increased bowel movements are beneficial given the constipation sub-type). Meta-analysis of 9 trials including 10 comparisons examined stool consistency.

Twelve reviews examined the effect of probiotics alone versus placebo on health-related quality of life in IBS. The preferred review for this outcome was Le Morvan et al. (2021). Despite unclear risk of bias relating to data collection and extraction methods, and the possibility of publication bias, Le Morvan et al. (2021) was assessed as providing by far the most recent and comprehensive results (including 11 trials and 1501 participants in meta-analysis).

Ding et al. (2019) was the only review which examined functioning as an outcome (64). This was a rapid systematic review with no meta-analysis. No effect sizes were reported; instead, the authors reported results narratively.

4.3.7.2. Probiotics + naturopathy co-intervention versus placebo/inactive control for IBS

Abboud et al. (2020) was the only review that examined evidence of probiotics plus a naturopathy co-intervention (Vitamin D) (68). The only outcome assessed was global improvement of IBS. No effect sizes were reported; the authors reported results narratively.

4.3.8. Summary of findings and evidence statements

Table 11. Probiotics compared to placebo/inactive control for IBS

Patient or population: IBS Intervention: Probiotics Comparison: Placebo/inactive control							
NTWC Rating*	Outcomes	Contributing review	Absolute effect (95% CI)	Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
9	Global improvement of IBS						
	Global IBS symptoms scores						
	Population: 18 years or older Dose: Range of probiotic strains and dosage amounts Assessed with: IBS-SSS, Subject's Global Assessment, GSS, GSRS, GSRS-IBS, Likert scale, IBS SSI, VAS, Birmingham IBS Symptom Questionnaire Follow-up: 4 weeks to 6 months	Li 2020	NR	SMD = -0.18 (-0.30 to -0.06) ^a	3726 (35 comparisons from 29 trials)	⊕⊕○○ LOW ^a	Probiotics may result in little to no difference in global IBS symptoms or response (as a continuous outcome) for people with IBS.
8	Symptoms improvement or response as a dichotomous outcome						
	Population: 18 years or older Dose: Range of probiotic strains and dosage amounts Assessed with: 10%-50% improvement compared to baseline; other Follow-up: 4 weeks to 6 months	Li 2020	RD = 0.17 (0.14 to 0.20) [#]	RR = 1.53 (1.33, 1.77) [#]	4650 (39 comparisons from 35 trials)	⊕⊕⊕○ MODERATE ^b	Probiotics probably result in an improvement in global IBS symptoms or response (of 10 to 50% improvement when assessed as a dichotomous outcome) for people with IBS.
8	Abdominal pain burden						
	Population: 18 years or older Dose: Range of probiotic strains and dosage amounts Assessed with: Likert scale, VAS, numerical scale, GSRS, IBS-SSS Follow-up: 4 weeks to 6 months	Li 2020	NR	SMD = -0.22 (-0.33 to -0.11) ^a	4579 (44 comparisons from 38 trials)	⊕⊕○○ LOW ^c	Probiotics may result in a slight improvement in abdominal pain burden for people with IBS.

Health-related quality of life							
8	Population: Adults Dose: Range of probiotic strains and dosage amounts Assessed with: IBS-QOL questionnaire Follow-up: 4-24 weeks	Le Morvan 2021	NR	SMD = 0.36 (0.07, 0.64) [^]	1501 (11)	⊕⊕○○ LOW ^d	Probiotics may result in an improvement in health-related quality of life for people with IBS.
8	Number of recurrent episodes	-	-	-	-	-	No reviews found. The effect of probiotics on improvement in number of recurrent episodes for people with IBS is unknown.
Functioning							
7	Population: Children aged 0-18 years Dose: Range of probiotic strains and dosage amounts Assessed with: FDI, Functional scale by LS3, Family life disruptions by caregiver's report, School absenteeism Follow up: 4-12 weeks	Ding 2019	NR	Three of four studies found a positive result for probiotic usage.	242 (4)	⊕○○○ VERY LOW ^e	The evidence is very uncertain about the effect of probiotics on functioning for children aged 0 to 18 years with IBS.
Stool frequency							
7	Population: Patients with IBS-C (constipation sub-type), aged 16 years or older Dose: Range of probiotic strains and dosage amounts Assessed with: Bowel movements (BMs) per week Follow-up: 2-12 weeks	Wen 2020	NR	MD = 1.29 BMs/week (0.69 to 1.89) [‡]	1139 (11 comparisons from 10 trials)	⊕⊕○○ LOW ^f	Probiotics may result in a slight improvement in stool frequency for people with IBS.
Stool consistency							
7	Population: Patients with IBS-C, aged 16 years or older Dose: Range of probiotic strains and dosage amounts Assessed with: Bristol Stool Form Scale or modified versions, other Follow-up: 2-12 weeks	Wen 2020	NR	SMD = 0.55 (0.27 to 0.82) [^]	NR (10 comparisons sets from 9 trials)	⊕⊕○○ LOW ^g	Probiotics may result in an improvement in stool consistency for people with IBS.

*Ratings 1-3 = of limited importance to decision making; 4-6 = important, but not critical, to decision making; 7-9 = critical for decision-making

^No absolute risk differences were reported. SMDs of 0.2, 0.5, and 0.8 are considered small, medium, and large, respectively

#A 5% absolute risk difference and 20% relative risk difference (i.e., risk ratio ≤ 0.8 or ≥ 1.2) was considered as a minimal clinically important difference (MCID) (23).

‡MD of ≥ 1.3 -1.6 times mean weekly bowel movement frequency considered MCID (69).

Abbreviations: ARD=absolute risk difference; BM=bowel movements, CI=confidence interval, GSRS=Gastrointestinal Symptom Rating Scale, GSS=Global symptoms score, IBS=Irritable bowel syndrome, IBS-SSS=IBS symptom severity scale, IBS-SSI=IBS Symptom Severity Index, FDI=Functional Disability Inventory, IBS-C=Constipation-Predominant Irritable Bowel Syndrome, MD=mean difference, NR=Not reported, RD=risk difference, RR=risk ratio, SMD=standardised mean difference, VAS=visual analogue scale

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

- a. Most studies for most domains were indicated as low risk of bias, except for unclear risk of selection bias in most studies due not describing allocation concealment. On balance, this is unlikely to impact results (no change for risk of bias). High I^2 values and statistically significant heterogeneity, point estimates indicated different directions of effect, CIs have limited overlap (downgrade one for inconsistency). CI boundaries suggest different inferences based on MCID (SMD = 0.2), with lower bound approaching the threshold for effect (downgrade one for imprecision). Publication bias unlikely supported by non-significant Egger test and visual inspection of funnel plot (no change for publication bias).
 - b. Most studies for most domains were indicated as low risk of bias, except for unclear risk of selection bias in the majority of studies due not describing allocation concealment. On balance, this is unlikely to impact results (no change for risk of bias). High I^2 values and statistically significant heterogeneity, point estimates varied somewhat, though the majority favoured the intervention (no change for inconsistency). Pooled effect confidence intervals were within threshold for MCID for absolute risk difference (ARD = 5%) and crossed MCID for relative estimates of effect, but only just (RR = 20%); lower bounds of CIs still suggested an appreciable effect (no change for imprecision). Possible publication bias supported by significant Egger test and visual inspection of funnel plot (downgraded one for publication bias).
 - c. Most studies for most domains were indicated as low risk of bias, except for unclear risk of selection bias in the majority of studies due not describing allocation concealment. On balance, this is unlikely to impact results (no change for risk of bias). High I^2 values and statistically significant heterogeneity, point estimates indicated different directions of effect, CIs have limited overlap (downgrade one for inconsistency). CI boundaries suggest different inferences based on MCID (SMD = 0.2) (downgraded one for imprecision). Publication bias unlikely, supported by non-significant Egger test and visual inspection of funnel plot (no change for publication bias).
 - d. Most primary studies assessed at low risk of bias (no change for risk of bias). High I^2 values and statistically significant heterogeneity, point estimates indicated different directions of effect, inconsistency not explained by subgroup analysis of duration of treatment (downgrade one for inconsistency). CI boundaries suggest different inferences based on MCID (SMD = 0.2), with lower bound approaching the threshold for effect (downgraded one for imprecision). Publication bias not assessed by review authors; unable to confirm if potential for missing studies (no change for publication bias).
 - e. Most studies for most domains were indicated as low risk of bias (no change for risk of bias). Population included children only (downgrade one for indirectness). Small sample size raising concerns about optimal information size, no effect estimates provided (downgrade two for serious imprecision). Five of six studies sponsored by pharmaceutical companies which may suggest publication bias (downgrade one for publication bias).
 - f. Most studies for most domains were indicated as low or unclear risk of bias, with no assessments of high risk of bias (no change for risk of bias). High I^2 values and statistically significant heterogeneity, though most point estimates and upper and lower bounds of CIs were above the threshold for change in effect (no change for inconsistency). Population included IBS-C subtype only (downgrade one for indirectness). CI boundaries suggest different inferences based on MCID (BM/week = 1.3 – 1.6) (downgraded one for imprecision). Publication bias unlikely supported by non-significant Egger test and visual inspection of funnel plot (no change for publication bias).
 - g. Most studies for most domains were indicated as low or unclear risk of bias, with no assessments of high risk of bias (no change for risk of bias). High I^2 values and statistically significant heterogeneity, though most point estimates and upper and lower bounds of CIs were above the threshold for change in effect with relative overlap of CIs (no change for inconsistency). Population included IBS-C subtype only (downgrade one for indirectness). CI boundaries suggest different inferences about the magnitude of benefit based on MCID (SMD = 0.2), however lower boundary still falls about the MCID threshold (downgraded one for imprecision). Publication bias unlikely supported by non-significant Egger test and visual inspection of funnel plot (no change for publication bias).
-

Table 12. Probiotics + naturopathy co-intervention compared to placebo/inactive control for IBS

Patient or population: **IBS**

Intervention: **Probiotics + naturopathy co-intervention**

Comparison: **Placebo/inactive control**

NTWC Rating*	Outcomes	Contributing review	Absolute effect (95% CI)	Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
Global improvement of IBS							
9	Dose: Probiotics (Lactobacillus acidophilus, CUL60, CUL21, Bifidobacterium bifidum CUL20 and Bifidobacterium animalis subsp. lactis CUL34 2.5 × 10 ¹⁰ CFU per capsule; Vitamin D3 (3000 IU) Assessed with: Questionnaire Follow-up: 12 weeks	Abboud 2020	NR	Effect sizes NR^	51 (1)	⊕○○○ VERY LOW ^a	The evidence is very uncertain about the effect of probiotics + naturopathy co-intervention on global improvement of IBS for people with IBS.
8	Abdominal pain burden	-	-	-	-	-	No reviews found. The effect of probiotics + naturopathy co-intervention on improvement in abdominal pain burden for people with IBS is unknown.
8	Health-related quality of life	-	-	-	-	-	No reviews found. The effect of probiotics + naturopathy co-intervention on improvement in HRQoL for people with IBS is unknown.
8	Number of recurrent episodes	-	-	-	-	-	No reviews found. The effect of probiotics + naturopathy co-intervention on improvement in number of recurrent episodes for people with IBS is unknown.
7	Functioning	-	-	-	-	-	No reviews found. The effect of probiotics + naturopathy co-intervention on improvement in functioning for people with IBS is unknown.
7	Stool frequency, bowel transit time	-	-	-	-	-	No reviews found. The effect of probiotics + naturopathy co-intervention on improvement in stool frequency for people with IBS is unknown.

7	Stool consistency	-	-	-	-	No reviews found. The effect of probiotics + naturopathy co-intervention on improvement in stool consistency for people with IBS is unknown.
<p>*Ratings 1-3 = of limited importance to decision making; 4-6 = important, but not critical, to decision making; 7-9 = critical for decision-making</p> <p>^Outcome measure not reported in review, so MCID undeterminable.</p> <p>Abbreviations: CI=confidence interval, IBS=Irritable bowel syndrome</p> <p>GRADE Working Group grades of evidence</p> <p>High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.</p> <p>Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.</p> <p>Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.</p> <p>Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.</p> <p>Explanations</p> <p>a. Low risk of bias across all assessed domains for primary study (no change for risk of bias). Study questionnaire not provided, therefore cannot be sure if aligns with outcome (downgrade one for indirectness). Very small sample size raising concerns about optimal information size, no effect estimates provided (downgraded 3 for very serious imprecision). No inconsistency due to singular study (no change for inconsistency). Publication bias not assessed due to insufficient number of studies (no change for publication bias).</p>						

4.4. Insomnia/sleeping disorders, magnesium

4.4.1. Description of condition

Sleep disorders are a broad category of conditions that disrupt sleep patterns, quality, and duration. Common sleep disorders include insomnia, obstructive sleep apnoea, and movement-related sleep disorders (e.g. restless legs syndrome) (70, 71). Estimates of prevalence of these conditions vary; recent cross-sectional results have reported between 13.0% to 42.3% of Australian participants have at least one sleep disorder (72, 73). Sleep disorders cause significant impairment in social, occupational, educational, and behavioural function. Sleep disorders are also associated with an increased risk of other health conditions, including heart disease, hypertension, diabetes, stroke, and mental health conditions (74).

Insomnia is one of the most common sleep conditions, with symptoms of non-restorative sleep, difficulty initiating or maintaining sleep, early morning awakenings, and excessive daytime sleepiness (70). Symptoms are experienced regularly (e.g. at least 3 nights per week, for at least 3 months), and continue despite adequate opportunities for sleep (70). Other sleep disorders like sleep apnoea, restless legs syndrome, and narcolepsy present with other distinct symptoms.

Diagnosing sleep disorders typically involves a clinical evaluation, sleep history, and potential sleep studies. Diagnostic criteria include The International Classification of Sleep Disorders, Third Edition (ICSD-3), the Sleep Disorders section of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), or the International Classification of Diseases, Tenth Edition (ICD-10) (70). Polysomnography is a type of sleep study monitoring brainwaves, muscle activity, and other physiological parameters, and can aid in diagnosing specific sleep disorders like apnoea.

4.4.2. Description of the intervention

Magnesium (often abbreviated as its chemical symbol: Mg) is a naturally occurring mineral in the human body. It is an essential mineral playing numerous crucial roles in the human body, including enzymatic reactions, energy production, muscle function, and bone health (16, 17). Recent evidence suggests that magnesium levels in the body may be associated with some health conditions, including Diabetes Mellitus (Type II), cardiovascular disease, osteoporosis, and migraines (17).

It is thought that Magnesium may play a role in lowering abnormal levels of cortisol and regulate neurotransmitters in the brain (18). Cortisol, a stress hormone, can worsen anxiety when chronically elevated, and magnesium may help reduce cortisol, thereby reducing anxiety. The proposed mechanism for this is that Magnesium blunts the release of the excitatory neurotransmitter glutamate and promotes the release of the inhibitory neurotransmitter GABA, helping keep anxiety in check.

The recommended dietary intake for magnesium varies depending on age and sex, typically ranging from 310-420 mg daily for adults (19). While it is a typical component of most diets, and is abundant in foods such as leafy vegetables, nuts, legumes, and grains, supplementation is available. Magnesium supplements come in several forms with varying bioavailability (absorption rates), including magnesium oxide, citrate, glycinate, or lactate (17).

Oral magnesium supplements are readily available without prescription and are sometimes sold in tandem with one or multiple other nutritional supplements. Magnesium supplements are

generally safe for most people when taken at appropriate doses³; though some medications may interact with magnesium (including antibiotics, diuretics and bisphosphonates) (17). Excess magnesium is usually excreted by the kidneys as urine, though very high amounts of magnesium from dietary supplements can result in diarrhea, nausea and abdominal cramping (17).

4.4.3. Prioritised outcomes

Seven priority outcomes were identified by NTWC as part of the Outcome Prioritisation Exercise. These are listed below by order of priority. Outcomes were rated by their importance to decision-making, with those rated 7-9 being critical for decision-making.

Table 13. List of prioritised outcomes – insomnia/sleeping disorders, magnesium (as assessed as part of the Outcome Prioritisation Exercise by NTWC).

#	Priority population	Priority intervention	Priority outcomes	
			NTWC Rating	Outcome domain
4	Insomnia/ Sleeping disorders	Magnesium	9	Improvement in clinical levels of insomnia
			8	Global improvement in sleep quality or quantity (subjective)
			8	Global improvement in sleep quality or quantity (objective)
			8	Improvement in individual sleep parameters (Sleep onset latency, Total sleep duration, Total wake-time, Wake after sleep onset (WASO), Nocturnal and early morning waking, Sleep efficiency (ratio of time asleep to time in bed), parasomnias)
			8	Quality of life
			7	Daytime functioning
			7	Fatigue

Abbreviations: BP=blood pressure; HRQoL=health-related quality of life; NTWC=Natural Therapies Working Group

*1-3 = of limited importance to decision making; 4-6 = important, but not critical, to decision making; 7-9 = critical for decision-making

4.4.4. Search findings

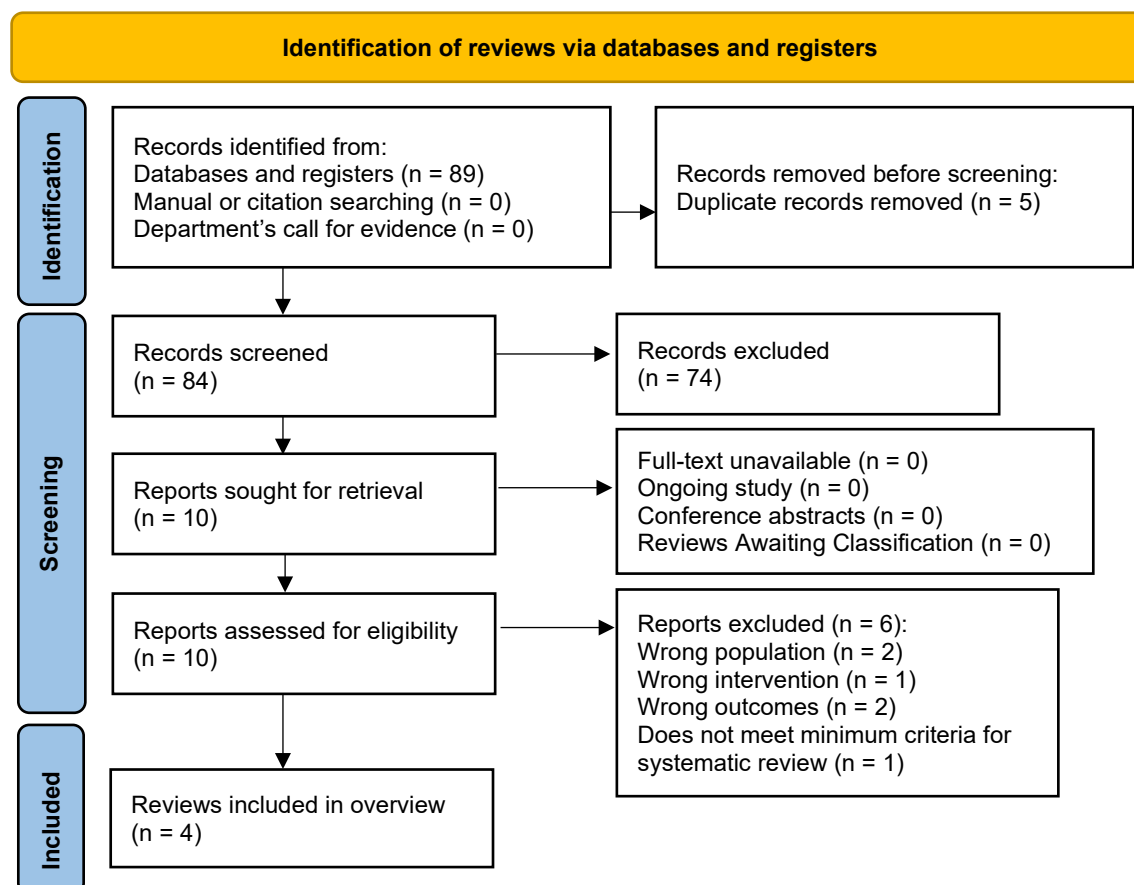
In total, 84 reviews were identified in the searches after de-duplication and underwent screening. None of the reviews provided by the Department's call for evidence were relevant to this population-supplement pair. After title and abstract screening, 10 reviews were sought for retrieval for full-text screening:

- 6 reviews did not meet inclusion criteria (citation details and reasons for exclusion recorded in AppendixC1)

Therefore, a final 4 reviews met the inclusion criteria. Characteristics of included reviews are presented in Appendix D. A full PRISMA flowchart is presented below.

³ The TGA has recently updated warning labels for supplements containing B6 due to over 30 reports of peripheral neuropathy (symptoms of which include tingling, burning and numbness). The TGA notes "In many cases, people reported they were not aware they had consumed vitamin B6, as the product they were taking was a magnesium supplement." See [Why TGA made these labelling and use changes | Health supplements containing vitamin B6 can cause peripheral neuropathy | Therapeutic Goods Administration \(TGA\)](#)

Figure 4. PRISMA flowchart – insomnia/sleeping disorders, magnesium.



4.4.5. Description of included reviews

Four reviews were identified as eligible for inclusion (75-78). Two reviews were a systematic review and meta-analysis (76, 78); one was a systematic review and network meta-analysis (75) and one was only a network meta-analysis (77). Reviews were conducted between 2020 and 2023, and all only included randomised controlled trials. A detailed summary of characteristics of the included reviews are reported in Appendix D.

One review specifically sought to assess oral magnesium supplementation in people (older adults specifically) with insomnia (76). The other three reviews aimed to summarise efficacy for a range of treatments for insomnia (75), narcolepsy (77) and general improvement in sleep quality (78).

4.4.6. Assessment of risk of bias of included systematic reviews

Risk of bias of the assessments of the included reviews, as appraised using the ROBIS tool, are presented below. Full assessments are reported in Appendix F.

Table 14. Summary of ROBIS assessments – Insomnia/sleeping disorders, Magnesium

Review ID	ROBIS Domains				Overall risk of bias
	Domain 1: Study eligibility criteria	Domain 2: Identification and selection of studies	Domain 3: Data collection and study appraisal	Domain 4: Synthesis and findings	

Chan 2021	Low	Unclear	Low	High	High risk
Mah 2021	Low	Unclear	Low	Unclear	Unclear risk
Samara 2020	Low	Low	Low	Unclear	Unclear risk
Zhan 2023	Low	Unclear	Low	High	Unclear risk

4.4.7. Results

The three reviews assessed at unclear risk of bias (rather than high risk) were preferred. As all reviews were assessed as at unclear or high risk of bias, evidence from the most relevant and/or comprehensive review was chosen for each outcome. Preferred contributing reviews are listed in the population-intervention matrix in Table 15.

Table 15. Contributing reviews for each population and intervention/co-intervention combination – insomnia/sleeping disorders, magnesium

	With insomnia/sleeping disorders	At risk of insomnia/sleeping disorders
Magnesium VS placebo/inactive control	Mah 2021	-
Magnesium + naturopathy co-intervention VS placebo/inactive control	Samara 2020 Zhan 2023	-

4.4.7.1. Magnesium versus placebo/inactive control for insomnia/sleeping disorders

Mah et al. (2021) (76) was the preferred review for examining magnesium alone in people with insomnia/sleeping disorders. There were concerns about risk of bias and robustness of findings, as the authors could not conduct sensitivity analyses due to the low number of studies. Similarly, due to low study numbers the authors could not assess possible publication bias with funnel plots. However, this was still the lowest risk of bias and most comprehensive review.

4.4.7.1. Magnesium + naturopathy co-intervention versus placebo/inactive control for insomnia/sleeping disorders

Three reviews reported on the efficacy of magnesium plus a naturopathy co-intervention for priority outcomes in sleep disorders. Samara et al. (2020) (75) was the preferred review, reporting results of a network meta-analysis (using results from one study (43 participants) examining older adults with primary insomnia). Zhan et al. (2023) (77) was the only review that reported on daytime functioning as an outcome, although the population was people with narcolepsy. The authors conducted a network meta-analysis based on data from one study (136 participants).

4.4.8. Summary of findings and evidence statements

Table 16. Magnesium compared to placebo/inactive control for insomnia/sleep disorders

Patient or population: Insomnia/sleep disorders Intervention: Magnesium Comparison: Placebo/inactive control								
NTWC Rating ^{g*}	Outcomes	Contributing review	Absolute Effects		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
			Comparison	Intervention				
9	Improvement in clinical levels of insomnia Population: Older adults (aged 55 or over) with insomnia Dose: 500mg elemental Magnesium daily Assessed with: ISI (score from 0 to 28; ≥15 = clinical insomnia; lower scores indicate better sleep quality) Follow-up: 8 weeks	Mah 2021	Mean (SD)change from baseline = -0.5 (1.71)‡	Mean (SD)change from baseline (SD) = -2.38 (2.24)‡	-	43 (1)	⊕○○○ VERY LOW ^a	The evidence is very uncertain about the effect of magnesium on improvement in clinical levels of insomnia for people with insomnia or sleep disorders.
8	Global improvement in sleep quality or quantity (subjective) Population: Older adults (aged 55 or over) with insomnia Dose: 320mg elemental Magnesium daily Assessed with: PSQI (scored from 0 to 21; ≥5 = poor sleeper) Follow-up: 8 weeks	Mah 2021	Mean (SD)change from baseline) = -4.1 (NR)†	Mean (SD) change from baseline = -3.4 (NR)†	-	96 (1)	⊕○○○ VERY LOW ^b	The evidence is very uncertain about the effect of magnesium on subjective global improvement in sleep quality or quantity for insomnia or sleep disorders.
8	Global improvement in sleep quality or quantity (objective)	-	-	-	-	-	-	No reviews found. The effect of magnesium on objective global improvement in sleep quality or quantity for insomnia or sleep disorders is unknown.
8	Improvement in individual sleep parameters							

Total sleep time				The mean change in the interventi on group was 16.06 min higher (95% CI: – 5.99 to 38.12)§		⊕○○○ VERY LOW ^c	The evidence is very uncertain about the effect of magnesium on total sleep time for insomnia or sleep disorders.
Population: Older adults (aged 55 or over) with insomnia Dose: 500-729mg elemental Magnesium daily Assessed with: Time from sleep onset to offset (min) Follow-up: 20 days to 8 weeks	Mah 2021	Mean at follow-up ranged from 326.2 to 456.0 min.		55 (2)			
Sleep onset latency				The mean change in the interventi on group was – 17.36 min lower (95% CI: – 27.27 to – 7.44)§		⊕○○○ VERY LOW ^d	The evidence is very uncertain about the effect of magnesium on sleep onset latency for insomnia or sleep disorders.
Population: Older adults (aged 55 or over) with insomnia Dose: 500-729mg elemental Magnesium daily Assessed with: Time from wakefulness to initiation of sleep (min), lower numbers indicate less night-time wakefulness and sleep initiation Follow-up: 20 days to 8 weeks	Mah 2021	Mean at follow-up ranged from 34.7 to 84.0 min.		55 (2)			
Sleep efficiency				-		⊕○○○ VERY LOW ^a	The evidence is very uncertain about the effect of magnesium on sleep efficiency for insomnia or sleep disorders.
Population: Older adults (aged 55 or over) with insomnia Dose: 500mg elemental Magnesium daily Assessed with: Sum of REM & non-REM sleep / total time in bed (h) Follow-up: 8 weeks	Mah 2021	Mean (SD)change from baseline = – 0.00 (0.05) hours ¶	Mean (SD) change from baseline = – 0.06 (0.01) hours ¶	43 (1)			
Early morning awakening				-		⊕○○○ VERY LOW ^e	The evidence is very uncertain about the effect of magnesium on early morning awakening for insomnia or sleep disorders.
Population: Older adults (aged 55 or over) with insomnia Dose: 500mg elemental Magnesium daily Assessed with: Premature termination of sleep (hours), lower numbers indicate less early morning awakenings and better sleep maintenance Follow-up: 8 weeks	Mah 2021	Mean (SD)change from baseline = 1.03 (0.02)^	Mean (SD)change from baseline = 1.01 (0.05)^	43 (1)			

8	Quality of life	-	-	-	-	-	-	No reviews found. The effect of magnesium on quality of life for insomnia or sleep disorders is unknown.
7	Daytime functioning	-	-	-	-	-	-	No reviews found. The effect of magnesium on daytime functioning for insomnia or sleep disorders is unknown.
7	Fatigue	-	-	-	-	-	-	No reviews found. The effect of magnesium on fatigue for insomnia or sleep disorders is unknown.

*Ratings 1-3 = of limited importance to decision making; 4-6 = important, but not critical, to decision making; 7-9 = critical for decision-making

‡MCID is 3.47 for ISI (defined as 30% reduction from baseline) (80).

†MCID is 3.0 for PSQI (79, 80).

§MCID is 40min for Total Sleep Time (TST) (higher is better), 30min for sleep-onset latency (SOL) (lower is better) (80).

¶MCID is 5% for sleep efficiency (80).

^Unable to find published MCID estimations for early morning awakening.

Abbreviations: CI=Confidence Interval, GAD=generalised anxiety disorder, HAM-A=Hamilton Anxiety Scale, ISI=Insomnia Severity Index, MD=Mean difference, REM=Rapid eye movement, PSQI=Pittsburgh Sleep Quality Index, NR=Not reported

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

- a. Methodological concerns in relevant primary study (downgrade one for risk of bias). Population in the included review was restricted to people ≥55 years old (downgraded one for indirectness). CIs not provided, naïve comparison across intervention and comparator would suggest a modest effect size from MCID, however, very small sample size raising concerns about optimal information size (downgraded one for imprecision). No inconsistency due to singular study (no change for inconsistency). Publication bias not assessed due to insufficient number of studies (no change for publication bias).
- b. High risk of bias from selective reporting in relevant primary study (downgraded one for risk of bias). Population in the included review was restricted to people ≥55 years old (downgraded one for indirectness). CIs not provided, naïve comparison across intervention and comparator would suggest an appreciable effect size from MCID, however, very small sample size raising concerns about optimal information size (downgraded one for imprecision). No inconsistency due to singular study (no change for inconsistency). Publication bias not assessed due to insufficient number of studies (no change for publication bias).
- c. Serious or concerning methodological limitations in contributing studies (downgraded one for risk of bias). Population in the included review was restricted to people ≥55 years old (downgraded one for indirectness). Wide CIs to where point estimate is uninterpretable; CIs appreciably crosses the threshold(s) of interest (40min for Total Sleep Time (TST) (higher is better)) (downgraded 3 for very serious imprecision). Publication bias not assessed due to insufficient number of studies (no change for publication bias).
- d. Serious or concerning methodological limitations in contributing studies (downgraded one for risk of bias). Population in the included review was restricted to people ≥55 years old (downgraded one for indirectness). CI boundaries suggest similar inferences about the magnitude of benefit based on MCID (30min for sleep-onset latency (SOL) (lower is better)), however, very small sample size raising concerns about optimal information size (downgraded one for imprecision). Publication bias not assessed due to insufficient number of studies (no change for publication bias).
- e. Methodological concerns in relevant primary study (downgrade one for risk of bias). Population in the included review was restricted to people ≥55 years old (downgraded one for indirectness). No MCID found, so threshold uninterpretable, CIs not provided, very small sample size raising concerns about optimal information size (downgraded two for serious imprecision). No inconsistency due to singular study (no change for inconsistency). Publication bias not assessed due to insufficient number of studies (no change for publication bias).

Table 17. Magnesium + naturopathy co-intervention compared to placebo/inactive control for insomnia/sleep disorders

Patient or population: Insomnia/sleep disorders Intervention: Magnesium + naturopathy co-intervention Comparison: Placebo/inactive control							
NTWC Rating*	Outcomes	Contributing review	Absolute effect	Relative effect (95% CI)^	Nº of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
9	Improvement in clinical levels of insomnia	-	-	-	-	-	No reviews found. The effect of magnesium + naturopathy co-intervention on improvement in clinical levels of insomnia for insomnia or sleep disorders is unknown.
8	Global improvement in sleep quality or quantity (subjective) Population: Older adults with insomnia (aged 65 or over) Dosage: 225mg Magnesium, plus 5mg of melatonin, 11.25mg zinc Assessed with: PSQI (scored from 0 to 21; ≥5 = poor sleeper) Follow-up: 8 weeks	Samara 2020	NR	SMD = -1.9 (-2.63, -1.17)^	NMA from 43 (1)	⊕○○○ VERY LOW _a	The evidence is very uncertain about the effect of magnesium + naturopathy co-intervention on global improvement in sleep quality or quantity (subjective) for insomnia or sleep disorders.
8	Global improvement in sleep quality or quantity (objective)	-	-	-	-	-	No reviews found. The effect of magnesium + naturopathy co-intervention on objective global improvement in sleep quality or quantity for insomnia or sleep disorders is unknown.
8	Improvement in individual sleep parameters Total sleep time Population: Older adults with insomnia (aged 65 or over) Dosage: 225mg Magnesium, plus 5mg of melatonin, 11.25mg zinc Assessed with: Total sleep time (minutes) Follow-up: 8 weeks	Samara 2020		WMD = 62.27 (28.80, 95.74)\$	NMA from 43 (1)	⊕○○○ VERY LOW _a	The evidence is very uncertain about the effect of magnesium + naturopathy co-intervention on total sleep time for insomnia or sleep disorders.
8	Quality of life Population: Older adults with insomnia (aged 65 or over)	Samara 2020		SMD = 0.61 (0.00, 1.22)^	NMA from 43 (1)	⊕○○○ VERY LOW _b	The evidence is very uncertain about the effect of magnesium + naturopathy co-intervention on quality of life for insomnia or sleep disorders.

Dosage: 225mg Magnesium, plus 5mg of melatonin, 11.25mg zinc Assessed with: NR Follow-up: 8 weeks						
Daytime functioning						
7	Population: Adults with narcolepsy Dosage: LXB (Magnesium, Calcium, Potassium, and Sodium; mgs NR) Assessed with: ESS Follow-up: NR	Zhan 2023	MD = -3.00 (-5.8, -0.12)‡	NMA from 136 (1)	⊕○○○ c VERY LOW	The evidence is very uncertain about the effect of magnesium + naturopathy co-intervention on daytime functioning for insomnia or sleep disorders.
7	Fatigue	-	-	-	-	No reviews found. The effect of magnesium + naturopathy co-intervention on fatigue for people with insomnia or sleep disorders is unknown.
<p>*Ratings 1-3 = of limited importance to decision making; 4-6 = important, but not critical, to decision making; 7-9 = critical for decision-making ^SMDs of 0.2, 0.5, and 0.8 are considered small, medium, and large, respectively (22). \$MCID is: 40min for Total Sleep Time (TST) (higher is better) ‡MCID is 2-point reduction for ESS.</p> <p>Abbreviations: Epworth Sleepiness Scale (ESS), CI=Confidence Interval, LXB=Lower-sodium oxybate, MD=Mean difference, NMA=Network meta-analysis, NR=Not reported, REM=Rapid eye movement, PSQI=Pittsburgh Sleep Quality Index, SMD=Standardised mean difference, WMD=Weighted mean difference</p> <p>GRADE Working Group grades of evidence High certainty: we are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.</p> <p>Explanations</p> <ol style="list-style-type: none"> Low risk of bias across all assessed domains for contributing study (no change for risk of bias). Population in the included review was restricted to people ≥65 years (downgraded one for indirectness). CI boundaries suggest different inferences based on MCID (absolute effect sizes NR, SMD = 0.2, total sleep time = 40 minutes) (downgraded two for serious imprecision). No inconsistency due to singular study (no change for inconsistency). Low risk of bias across all assessed domains for contributing study (no change for risk of bias). Population in the included review was restricted to people ≥65 years (downgraded one for indirectness). CI boundaries suggest different inferences based on MCID (SMD = 0.2) (downgraded two for serious imprecision). No inconsistency due to singular study (no change for inconsistency). Low risk of bias across all assessed domains for contributing study (no change for risk of bias). Population in the included review was restricted to narcolepsy; outcome measure was a proxy for daytime functioning (downgraded one for indirectness). CI boundaries suggest different inferences based on MCID (SMD = 0.2), with lower bound approaching the threshold for effect (ESS = 2 points) (downgraded two for serious imprecision). No inconsistency due to singular study (no change for inconsistency). 						

4.5. Depression (including post-natal), Omega-3 fatty acids

4.5.1. Description of condition

Depression (often referred to as major depressive disorder (MDD) or clinical depression), is an affective or mood disorder. These are a class of conditions that disrupt a person's mood to the point where it impairs function (81). Depression is characterised by a pervasive and persistent low mood, diminished interest or pleasure in activities, and multiple other symptoms that disrupt functioning (14). Worldwide, an estimated 5% (280 million people) of the adult population have depression, with prevalence increasing in recent years (82, 83). In addition, approximately 10% people who are pregnant or have just given birth experience depression, termed post-natal depression (82). Depression is commonly comorbid with other mental conditions, such as anxiety, as well as physical conditions such as cancer, cardiovascular disease, or neurological disorders (81, 84).

The symptoms of depression span across cognitive, emotional, behavioural, and physiological domains. Depressed individuals generally experience feelings of sadness and hopelessness, which can be accompanied by negative changes in appetite, weight, sleep (insomnia or hypersomnia), fatigue, and concentration (85). Depression can also lead to social withdrawal, diminished motivation, and impaired occupational or academic performance, and in severe cases, self-harm and suicide (85). In Australia, depressive disorders are one of the leading causes of burden of disease at all stages of life (86).

Depression is distinct from other affective disorders, such as bipolar disorder, and is diagnosed using the criteria defined in the Diagnostic and Statistical Manual of Mental Disorders (14). Diagnosis requires the presence of at least five specific symptoms over a two-week period that are a change from previous functioning (14). Assessment generally involves a clinical interview, medical history review, and may include standardised self-report measures.

4.5.2. Description of the intervention

Omega-3 fatty acids are a group of polyunsaturated fats essential for human health. There is evidence that Omega-3 fatty acids play crucial roles in various physiological processes, including brain function, inflammation, and cardiovascular health (87, 88). The main types of omega-3 fatty acids important for dietary considerations include eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and alpha-linolenic acid (89). Common dietary sources of omega-3 fatty acids include fatty fish (salmon, mackerel, herring, sardines, anchovies, tuna), nuts and seeds (walnuts, chia seeds, flaxseeds) and plant-based oils (flaxseed oil, soybean oil). The recommended dietary intake of omega-3 fatty acids varies depending on age, sex, and health status (19,89). Omega-3 supplements are available without prescription, often taken as fish oil, krill oil, cod liver oil, or vegetarian products that contain algae oil.

It is hypothesised that Omega-3 fatty acids play a crucial role in various bodily functions, that may help alleviate depression (90). Two types, DHA (docosahexaenoic acid) and EPA (eicosapentaenoic acid), can easily cross the brain cell membrane and interact with mood-related molecules inside the brain. It is thought that that individuals experiencing depression may have insufficient levels of EPA and DHA. In addition, Omega-3 fatty acids also have anti-inflammatory actions, which may contribute to their antidepressant effects. By reducing inflammation, they may help stabilize mood and alleviate depressive symptoms.

4.5.3. Prioritised outcomes

Seven priority outcomes were identified by NTCW as part of the Outcome Prioritisation Exercise. These are listed below by order of priority. Outcomes were rated by their importance to decision-making, with those rated 7-9 being critical for decision-making.

Table 18. List of prioritised outcomes – Depression (including post-natal), Omega-3 fatty acids (as assessed as part of the Outcome Prioritisation Exercise by NTCW).

#	Priority population	Priority intervention	Priority outcomes	
			NTWC Rating	Outcome domain
5	Depression (including post-natal)	Omega-3 fatty acids	9	Depression-related emotional functioning/mental health burden
			9	Improvement in clinical levels of depression (including post-natal depression)
			8	Specific depression dimensions (Anhedonia, Distress, Dysfunctional thoughts, Internalizing problems, Rumination, Self-esteem, Anger, Fatigue, Hopelessness, Irritability, Negative mood, Tension)
			8	Physiological symptoms of depression (respiration rate and capacity, heart rate, blood pressure, heart rhythm, vital signs, brain beta-nucleoside triphosphate levels, brain phosphodiester levels, brain phosphomonoester levels, serum norepinephrine levels, serum serotonin levels, frontal lobe phosphocreatine levels, body fat, metabolic measures, lactate levels, urinalysis results, lab panel results, weight, height, physical examination, temperature)
			8	Parent to infant bonding
			8	Quality of life
			7	Anxiety-related emotional functioning/mental health burden

Abbreviations: HRQoL=health-related quality of life

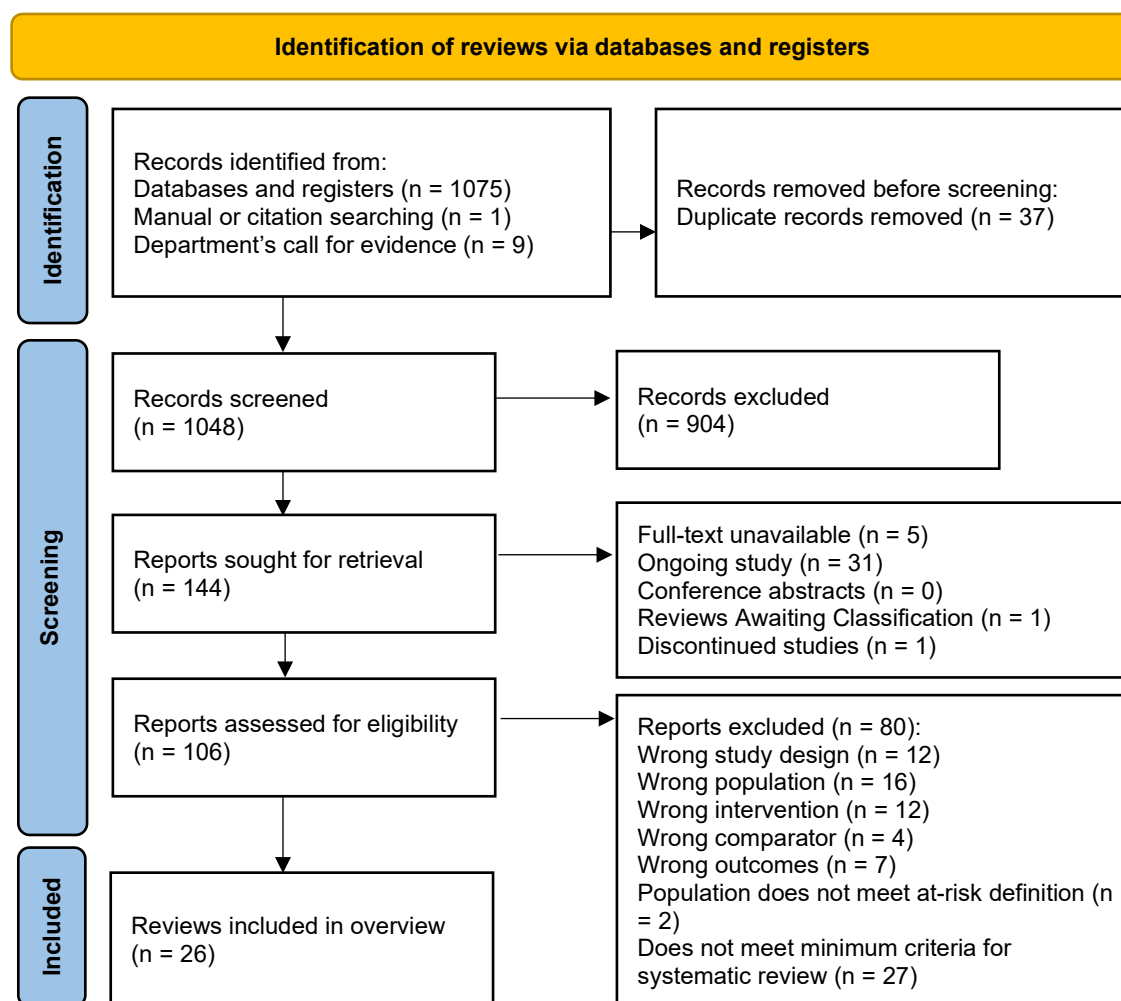
4.5.4. Search findings

In total, 1,048 reviews were screened following de-duplication. Nine reviews provided through the Department's call for evidence were relevant to this population-supplement pair; five were duplicates already identified in database searching and four were screened (see Appendix C2). After title and abstract screening, 144 reviews sought for retrieval for full-text screening:

- 5 reviews did not have full-text copies able to be retrieved (citation details recorded in Appendix C3)
- 31 reviews were ongoing (citation details recorded in Appendix C4)
- 1 review was published in languages other than English (citation details recorded in "Reviews awaiting classification" table in Appendix C3)
- 80 reviews did not meet inclusion criteria (citation details and reasons for exclusion recorded in Appendix C1)

Following assessment, 26 reviews met the inclusion criteria. A full PRISMA flowchart is presented below.

Figure 5. PRISMA flowchart – Depression (including post-natal), Omega-3 fatty acids



4.5.5. Description of included reviews

Twenty-six (26) reviews were identified as eligible for inclusion, conducted between 2006 and 2023. Most systematic reviews included only RCTs (three reviews also included observational studies).

Eleven (11) reviews aimed to assess the overview's research question directly, looking at the efficacy of omega-3 fatty acids for depression in adults (91-94), older adults (95, 96), and children (97); and for the prevention and treatment of perinatal depression (98-101). Other reviews examined interventions more generally (including nutritional supplements) for the treatment of depression and prevention of depression in other mood disorders, which included omega-3 fatty acids (21, 102-110). Some reviews also examined omega-3 fatty acids specifically across broader populations at risk of depression (and included depression-related outcomes) (111-114).

4.5.6. Assessment of risk of bias of included systematic reviews

Risk of bias of the assessments of the included reviews, as appraised using the ROBIS tool, are presented below. Full assessments are reported in Appendix F.

Table 19. Summary of ROBIS assessments – Depression (including post-natal), Omega-3 fatty acids.

Review ID	ROBIS Domains	
-----------	---------------	--

	Domain 1: Study eligibility criteria	Domain 2: Identification and selection of studies	Domain 3: Data collection and study appraisal	Domain 4: Synthesis and findings	Overall risk of bias
Appleton 2015	Low	Low	Low	High	Low risk
Appleton 2016	Low	Low	Low	High	Low risk
Appleton 2021	Low	Low	Low	High	Low risk
Bae 2018	Low	Unclear	Low	Low	Low risk
Bai 2018	Low	Unclear	Low	Unclear	Unclear risk
Bai 2020	Low	Low	Low	Low	Low risk
Chowdhury 2020	Low	High	Unclear	Unclear	High risk
Farooq 2020	Low	Unclear	Low	Low	Low risk
Gabriel 2023	Low	High	High	Unclear	High risk
Liao 2019	Low	Unclear	Low	Low	Low risk
Miller 2013	Low	High	Low	High	Unclear risk
Mocking 2016	Low	Low	Low	Low	Low risk
Mocking 2020	Low	Low	Low	Low	Low risk
Morrell 2016	Low	Unclear	Low	High	Low risk
Newberry 2016	Low	Unclear	Low	Low	Low risk
Saccone 2016	Low	Low	Low	Unclear	Unclear risk
Sarris 2012	Low	Low	Low	Low	Low risk
Suradom 2021	Low	Low	Low	Low	Low risk
Troeung 2013	Low	Unclear	Low	Low	Low risk
Tsai 2023	Low	Unclear	Unclear	Low	Low risk
Tung 2023	Low	High	Low	Unclear	High risk
Viswanathan 2020	Low	High	Low	Unclear	High risk
Williams 2006	Low	High	Low	Unclear	High risk
Xu 2023	Low	Unclear	Low	Unclear	Unclear risk
Zhang 2019	Low	Low	Low	Unclear	Low risk
Zhang 2020	Low	Low	Low	Low	Low risk

4.5.7. Results

Evidence from the lowest risk of bias, relevant, and/or comprehensive review was chosen for each outcome. Preferred contributing reviews for each population and intervention combination are listed in the below table.

Table 20. Contributing reviews for each population and intervention/co-intervention combination – Depression (including post-natal), Omega-3 fatty acids.

	With depression (including post-natal)	At risk of depression (including post-natal)
Omega-3 fatty acids VS placebo/inactive control	Appleton 2021 Zhang 2019 Suradom 2021	Suradom 2021
Omega-3 fatty acids + naturopathy co- intervention VS placebo/inactive control	-	-

Appleton et al. (2021) conducted an updated Cochrane review of evidence for omega-3 fatty acids for treatment of depression in adults (115). Directly aligning with the overview's PICO and providing the most recent and comprehensive summary of data (meta-analysis of 33 studies, 1,848 participants), this was chosen as the preferred review. To supplement these findings, as

Appleton et al. (2021) was conducted for adults only, Zhang et al. (2019) (116) was also included (the most recent review examining the PICO of interest specific for children). Suradom et al. (2021) provided analysis of omega-3 fatty acids for depression-related outcomes in those with perinatal depression and those at risk of perinatal depression (99).

4.5.8. Summary of findings and evidence statements

Table 21. Omega-3 fatty acids compared to placebo for depression (including postnatal)

Patient or population: **Depression (including postnatal)**

Intervention: **Omega-3** fatty acids

Comparison: **Placebo**

NTWC Rating*	Outcomes	Contributing review	Absolute Effects		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
			Comparison	Intervention				
9	Depression-related emotional functioning/mental health burden							
	Depressive symptomology (continuous) Population: Adults Dose: Range of EPA, DHA or EPA/DHA combination supplements Assessed with: HDRS, MADRS, BDI, GDS (higher scores indicate greater symptomology) Follow up: 4-16 weeks	Appleton 2021	-	Mean HDRS score was equivalent to 2.5 (95% CI 1.0 – 4.0) lower in the intervention group	SMD = -0.40 (-0.64 to -0.16)^	1848 (33)	⊕○○○ VERY LOW ^a	The evidence is very uncertain about the effect of omega-3 fatty acids on depression-related emotional functioning/mental health burden for adults with depression.
	Depressive symptomology (continuous) Population: Children Dose: Omega-3 fatty acids, 1-3.4g daily Assessed with: CDRS, CDRS-R, CDI Follow up: 10-16 weeks	Zhang 2019	-	-	SMD = -0.12 (-0.53, 0.30)^	153 (4)	⊕○○○ VERY LOW ^b	The evidence is very uncertain about the effect of omega-3 fatty acids on depression-related emotional functioning/mental health burden for children with depression.
	Depressive symptomology (continuous) Condition: Perinatal depression Dose: Combination DHA + EPA (609-1638mg DHA, 414-2200mg EPA) Assessed with: EPDS, HAMD, CGI, MADRS, BDI, MINI Follow up: 6-12 weeks	Suradom 2021	-	-	SMD = -0.14 (-0.55 to 0.27)^	141 (4)	⊕○○○ VERY LOW ^c	The evidence is very uncertain about the effect of omega-3 fatty acids on depression-related emotional functioning/mental health burden for adults with perinatal depression.

Improvement in clinical levels of depression (including post-natal depression)								
9	Reemission (dichotomous, defined as an end point score within the “no/low” depression on corresponding scale)							Omega-3 fatty acids may result in little to no improvement in remission (as a dichotomous outcome) for people with depression.
	Population: Adults Dose: Range of EPA, DHA or EPA/DHA combination supplements Assessed with: HDRS, MADRS, BDI, GDS Follow up: 4-16 weeks	Appleton 2021	329 per 1000	27 more per 1000 (95%CI: 63 fewer to 128 more)	OR 1.13 (0.74 to 1.72)#	609 (8)	⊕⊕○○ LOW ^d	
	Response (dichotomous, defined as a 50% improvement in depression scale score)							
	Population: Adults Dose: Range of EPA, DHA or EPA/DHA combination supplements Assessed with: HDRS, MADRS, BDI, GDS Follow up: 4-16 weeks	Appleton 2021	445 per 1000#	45 more per 1000 (95% CI: 58 fewer to 144 more)	OR 1.20 (0.80 to 1.79)#	794 (17)	⊕⊕○○ LOW ^d	Omega-3 fatty acids may result in little to no improvement in remission (as a dichotomous outcome) for people with depression.
	Response (dichotomous, defined as ≥ 50% change from baseline on depression score or a score of ≤ 28 at the end-point of a trial on the CDRS-R)							
	Population: Children Dose: Omega-3, 1-3.4g daily Assessed with: CDRS, CDRS-R, CDI Follow up: 10-16 weeks	Zhang 2019	-	-	OR = 1.57 (0.26, 9.39)#	153 (4)	⊕○○○ VERY LOW ^b	The evidence is very uncertain about the effect of omega-3 fatty acids on response (as a dichotomous outcome) for children with depression.
8	Specific depression dimensions	-	-	-	-	-	-	No reviews found. The effect of omega-3 fatty acids on specific depression dimensions in depression is unknown.
8	Physiological symptoms of depression	-	-	-	-	-	-	No reviews found. The effect of omega-3 fatty acids on physiological symptoms of

								depression in depression is unknown.
8	Parent to infant bonding	-	-	-	-	-	-	No reviews found. The effect of omega-3 fatty acids on parent-to-infant bonding in depression is unknown.
8	Quality of life Dose: Range of EPA, DHA or EPA/DHA combination supplements Assessed with: CGI (7-point scale) GAF, SF-36, SF-36 (mental health summary scale), higher scores indicate poorer quality of life Follow up: 4-16 weeks	Appleton 2021	Mean CGI score was equivalent to 0.38 (95% CI 0.06 to 0.82) lower in the intervention group.§	SMD = -0.38 (-0.82 to 0.06)^	476 (12)	⊕○○○ VERY LOW ^e	The evidence is very uncertain about the effect of omega-3 fatty acids on quality of life for adults with depression.	
7	Anxiety-related emotional functioning/mental health burden	-	-	-	-	-	-	No reviews found. The effect of omega-3 fatty acids on anxiety-related emotional functioning/mental health burden in depression is unknown.

*Ratings 1-3 = of limited importance to decision making; 4-6 = important, but not critical, to decision making; 7-9 = critical for decision-making

[^]SMDs of 0.2, 0.5, and 0.8 are considered small, medium, and large, respectively (22)

[#]Source of baseline risk is the study population. There are no published MCID estimations for population level remission rates. A 20% relative risk difference (i.e., OR ≤ 0.8 or ≥ 1.2) was therefore considered as a minimal clinically important difference (MCID).

[§]MCID was 1 point for CGI (118).

Abbreviations: BDI=Beck Depression Inventory, CDI=Children's Depression Inventory, CDRS=Children's Depression Rating Scale, CGI=Clinician global impression, CI=Confidence interval, DHA=Docosahexaenoic acid, EPA=Eicosapentaenoic acid, GAP= Global Assessment of Functioning, GDS=Geriatric depression scale, HDRS=Hamilton Depression Rating Scale, MADRS=Montgomery-Asberg Depression Rating Scale, MINI=Mini-International Neuropsychiatric Interview, OR=Odds ratio, SF-36= RAND 36-Item Short Form Survey Instrument, SMD=Standardised mean difference

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

- Judgements of high risk of bias in all included studies, and different effects when comparing analyses across different risk of bias judgements (downgrade one for risk of bias). High I^2 values and statistically significant heterogeneity, point estimates indicated different directions of effect, inconsistency not explained by subgroup analysis (downgrade one for inconsistency). CI boundaries suggest different inferences (SMD = 0.2) (downgraded one for imprecision). Possible publication bias from visual inspection of funnel plot (downgrade one for publication bias).
- Risks of bias related to intervention blinding across included studies, which may impact results (downgrade one for risk of bias). Population included children only (downgrade one for indirectness). Low I^2 values and statistically non-significant heterogeneity, CIs mostly overlapping (no change for inconsistency). Wide CI to where point estimate is uninterpretable; CI appreciably crosses the threshold(s) of interest (SMD = 0.2; OR = 0.2) (downgraded 3 for very serious imprecision). Publication bias not assessed due to insufficient number of studies (no change for publication bias).

-
- c. Low risk of bias assessed across primary studies (no change for risk of bias). Population included perinatal depression only (downgrade one for indirectness). Low I^2 values and statistically non-significant heterogeneity, CIs mostly overlapping (no change for inconsistency). Wide CI to where point estimate is uninterpretable; CI appreciably crosses the threshold(s) of interest (SMD = 0.2) (downgraded 3 for very serious imprecision). Publication bias assessed by review authors, no evidence of bias supported by non-significant Egger's test (no change for publication bias).
 - d. High risk of bias of included primary studies (downgrade one for risk of bias). Low I^2 values and statistically non-significant heterogeneity, CIs mostly overlapping (no change for inconsistency). Absolute risk difference and OR CIs appreciably cross the threshold(s) for direction of effect (downgraded one for imprecision). Funnel plots not created for this analysis; only selected studies chosen, though no evidence of missing results (no change for publication bias).
 - e. Judgements of high risk of bias in all included studies (downgrade one for risk of bias). High I^2 values and statistically significant heterogeneity, point estimates lie on either side of direction of effect (downgrade one for inconsistency). CI boundaries suggest different inferences based on MCID (both CGI and SMD) with lower bound approaching the threshold for effect for CGI (= 1) and no effect for SMD (=0)). Possible publication bias from visual inspection of funnel plot (downgrade one for publication bias).
-

Table 22. Omega-3 fatty acids compared to placebo for people at risk of depression (including postnatal)

Patient or population: At risk of depression (including postnatal) Intervention: Omega-3 fatty acids Comparison: Placebo						
NTWC Rating*	Outcomes	Contributing review	Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
Depression-related emotional functioning/mental health burden						
Depressive symptomology (continuous)						
9	Population: Pregnant women without MDD Condition: Perinatal depression Dose: Range of combinations of DHA alone, or DHA + EPA Assessed with: BDI, EPDS, PDSS, CES-D, HAMD, MINI Follow up: 6-16 weeks	Suradom 2021	SMD = -0.03 (-0.20 to 0.13)^	779 (10 comparisons in 8 studies)	⊕⊕⊕○ MODERATE ^a	Omega-3 fatty acids probably results in little no difference in depression-related emotional functioning/ mental health burden for people at risk of perinatal depression.
9	Improvement in clinical levels of depression (including post-natal depression)	-	-	-	-	No reviews found. The effect of omega-3 fatty acids on improvement in clinical levels of depression for people at risk of depression is unknown.
8	Specific depression dimensions	-	-	-	-	No reviews found. The effect of omega-3 fatty acids on specific depression dimensions for people at risk of depression is unknown.
8	Physiological symptoms of depression	-	-	-	-	No reviews found. The effect of omega-3 fatty acids on physiological symptoms of depression for people at risk of depression is unknown.
8	Parent to infant bonding	-	-	-	-	No reviews found. The effect of omega-3 fatty acids on parent-to-infant bonding for people at risk of depression is unknown.
8	Quality of life	-	-	-	-	No reviews found. The effect of omega-3 fatty acids on parent-to-infant bonding for people at risk of depression is unknown.
7	Anxiety-related emotional functioning/mental health burden	-	-	-	-	No reviews found. The effect of omega-3 fatty acids on anxiety-related emotional functioning/mental health burden for people at risk of depression is unknown.

*Ratings 1-3 = of limited importance to decision making; 4-6 = important, but not critical, to decision making; 7-9 = critical for decision-making.

^aSMDs of 0.2, 0.5, and 0.8 are considered small, medium, and large, respectively (22)

Abbreviations: BDI=Beck Depression Inventory, CDI=Children's Depression Inventory, CDRS=Children's Depression Rating Scale, CGI=Clinician global impression, DHA=Docosahexaenoic acid, EPA=Eicosapentaenoic acid, GAP= Global Assessment of Functioning, GDS=Geriatric depression scale, HDRS=Hamilton Depression Rating Scale, MADRS=Montgomery-Asberg Depression Rating Scale, MINI=Mini-International Neuropsychiatric Interview, OR=Odds ratio, SF-36=Rand 36-Item Short Form Survey Instrument, SMD=Standardised mean difference

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

- a. Low risk of bias assessed across primary studies (no change for risk of bias). Population in the included review was restricted to pregnant women at risk of perinatal depression only (downgraded one for indirectness). Low risk of inconsistency, overlapping confidence intervals, low and non-significant I^2 and Chi^2 values (no change for inconsistency). Pooled effect confidence intervals within MCID (SMD = 0.2) (no change for imprecision). Publication bias assessed by review authors, no evidence of bias supported by non-significant Egger's test (no change for publication bias).
-

4.6. Dysmenorrhea, Cruciferous indoles (indole-3-carbinol, diindolylmethane)

4.6.1. Description of condition

Dysmenorrhea, also known as painful periods, is a common gynaecological condition characterised by severe and recurrent pain during menstruation. It affects a significant proportion of individuals who menstruate, with estimates suggesting a global prevalence of over 70% (119). In Australia, a recent cross-sectional study of women aged 13-25 years, over 92% of respondents reported experiencing dysmenorrhea (120).

The symptoms of dysmenorrhea can vary in intensity and duration, but typically include lower abdominal cramps, pelvic pain, back pain, nausea, vomiting, diarrhea, fatigue, and headaches (121). These symptoms can significantly impact daily life, leading to school or work absenteeism, decreased productivity, and impaired social functioning (121, 122).

Dysmenorrhea can be classified as either primary (no identifiable cause) or secondary (due to an underlying condition such as endometriosis, pelvic inflammatory disease, or uterine fibroids, accounting for approximately 10% of cases) (122). Diagnosis of dysmenorrhea relies on a detailed medical history, sometimes with physical pelvic examination.

4.6.2. Description of the intervention

Cruciferous indoles are a class of secondary metabolites found predominantly in cruciferous vegetables, a plant family that includes cabbage, broccoli, brussels sprouts, cauliflower, and kale. They are consumed primarily through the dietary intake of their parent vegetables. The most well-studied cruciferous indoles are indole-3-carbinol (I3C) and its biologically active dimer, diindolylmethane (123). Diindolylmethane is not naturally abundant in food sources but can be formed in the acidic environment of the stomach after I3C consumption or obtained through dietary supplements. Factors like cooking methods, processing, and even variations within the gut microbiome can influence the final indole compounds and their bioavailability (123).

Research on cruciferous indoles, particularly I3C and DIM, suggests potential biological activities relevant to health and disease prevention, though evidence is still in its infancy. Potential mechanisms under investigation include modulating estrogen metabolism, antioxidant effects, and influencing cell signalling pathways (124).

4.6.3. Prioritised outcomes

Seven priority outcomes were identified by NTCW as part of the Outcome Prioritisation Exercise. These are listed below by order of priority. Outcomes were rated by their importance to decision-making, with those rated 7-9 being critical for decision-making.

Table 23. List of prioritised outcomes – Dysmenorrhea, Cruciferous indoles (indole-3-carbinol, diindolylmethane) (as assessed as part of the Outcome Prioritisation Exercise by NTCW).

#	Priority population	Priority intervention	Priority outcomes	
			NTWC Rating	Outcome domain
6	Dysmenorrhea	Cruciferous Indoles (indole-3-	9	Abdominal pain burden
			9	Physiological symptoms of dysmenorrhoea

	carbinol, diindolylmethane)	9	Physical function burden from dysmenorrhoea (diahorrea, constipation, gastric upset, nausea)
		9	Global improvement of dysmenorrhoea
		8	Consumption of pain killers
		8	Quality of life
		7	Restriction of daily life activities

Abbreviations: BP=blood pressure; HRQoL=health-related quality of life

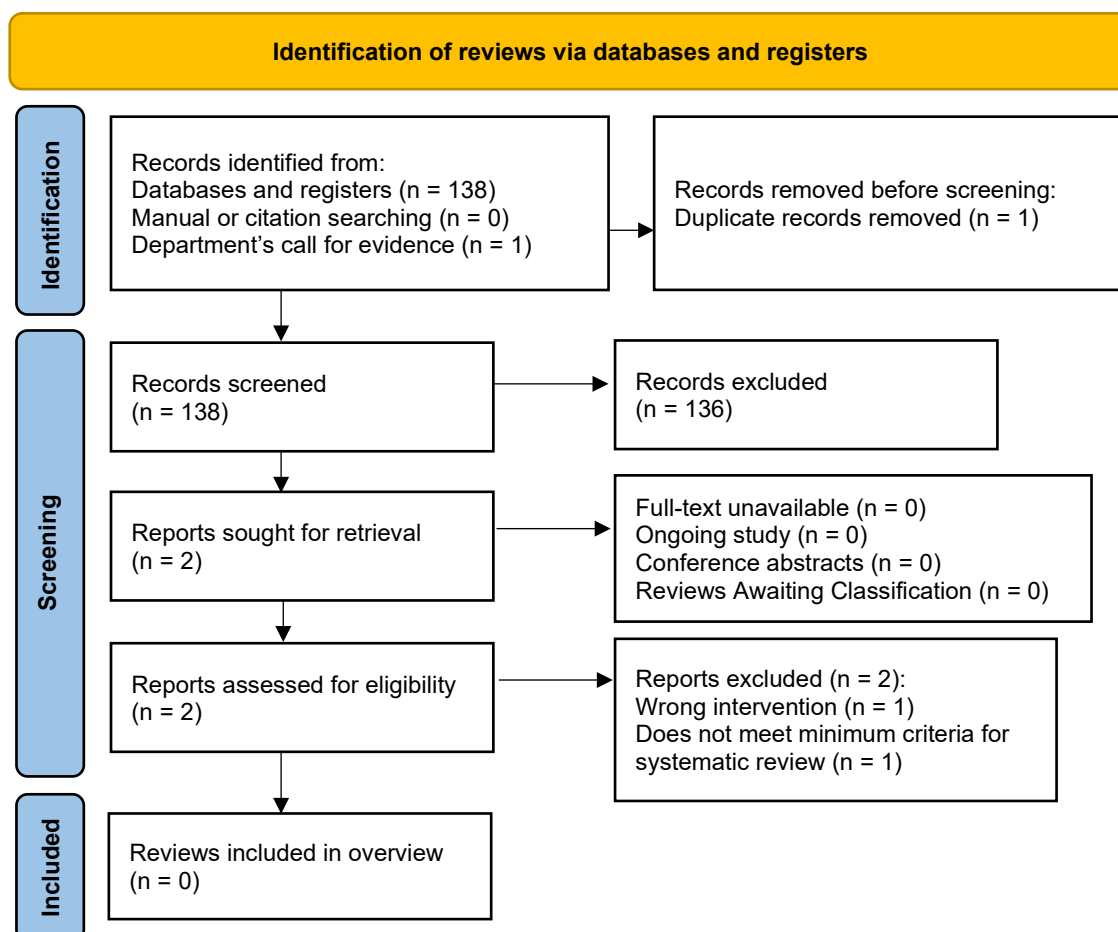
4.6.4. Search findings

In total, 138 reviews were screened following de-duplication. One additional review provided by the Department's call for evidence was relevant for this population-supplement pair and was screened (see Appendix C2). After title and abstract screening, 2 reviews were assessed for eligibility at full-text screening, where:

- 2 reviews did not meet inclusion criteria (citation details and reasons for exclusion recorded in Appendix C1)

Following assessment, no reviews met the inclusion criteria. A full PRISMA flowchart is presented below.

Figure 6. PRISMA flowchart – Dysmenorrhea, Cruciferous indoles (indole-3-carbinol, di-indolylmethane)



4.6.5. Description of included reviews

No reviews met inclusion criteria.

4.6.6. Assessment of risk of bias of included systematic reviews

No reviews met inclusion criteria.

4.6.1. Results

No reviews met inclusion criteria.

4.6.2. Summary of findings and evidence statements

The effect of cruciferous indoles on abdominal pain burden, physiological symptoms of dysmenorrhoea, physical function burden from dysmenorrhoea (diarrhoea, constipation, gastric upset, nausea), global improvement of dysmenorrhoea, consumption of pain killers, quality of life, restriction of daily life activities in people with dysmenorrhea is unknown.

4.7. Premenstrual syndrome (PMS), Cruciferous indoles (indole-3-carbinol, diindolylmethane)

4.7.1. Description of condition

Premenstrual Syndrome (PMS) is a complex condition encompassing a cluster of physical, emotional, and behavioural symptoms that occur cyclically in the luteal phase of the menstrual cycle and subsides with menstruation onset (125, 126). While many individuals experience mild premenstrual changes, PMS involves symptoms severe enough to significantly disrupt daily functioning and quality of life. A more severe form, premenstrual dysphoric disorder (PMDD), is characterised by additional mood-related symptoms with marked impairment (126). Globally, the prevalence of PMS requiring treatment is estimated at 30-40% of reproductive-aged individuals and PMDD affecting 3-8% (125).

Diagnosing PMS relies on prospective charting emotional and physical symptoms associated with menstrual cycle (125). Symptoms vary between individuals and may include mood swings, irritability, depression, anxiety, bloating, breast tenderness, fatigue, food cravings, and cognitive difficulties (125). PMS can significantly impact an individual's physical and mental health, affecting social relationships, work or academic performance, and overall well-being. As the causes of PMS are unknown, treatment is targeted at relieving symptoms. Pharmacological and non-pharmacological treatment of PMS are used, including dietary supplementation (125).

4.7.2. Description of the intervention

Cruciferous indoles are a class of secondary metabolites found predominantly in cruciferous vegetables, a plant family that includes cabbage, broccoli, brussels sprouts, cauliflower, and kale. They are consumed primarily through the dietary intake of their parent vegetables. The most well-studied cruciferous indoles are indole-3-carbinol (I3C) and its biologically active dimer, diindolylmethane (123). Diindolylmethane is not naturally abundant in food sources but can be formed in the acidic environment of the stomach after I3C consumption or obtained through dietary supplements. Factors like cooking methods, processing, and even variations within the gut microbiome can influence the final indole compounds and their bioavailability (123).

Research on cruciferous indoles, particularly I3C and DIM, suggests potential biological activities relevant to health and disease prevention, though evidence is still in its infancy. Potential mechanisms under investigation include modulating estrogen metabolism, antioxidant effects, and influencing cell signalling pathways (124).

4.7.3. Prioritised outcomes

Seven priority outcomes were identified by NTWC as part of the Outcome Prioritisation Exercise. These are listed below by order of priority. Outcomes were rated by their importance to decision-making, with those rated 7-9 being critical for decision-making.

Table 24. List of prioritised outcomes – Premenstrual syndrome (PMS), Cruciferous indoles (indole-3-carbinol, di-indolylmethane) (as assessed as part of the Outcome Prioritisation Exercise by NTWC).

#	Priority population	Priority intervention	Priority outcomes	
			NTWC Rating	Outcome domain

7	Premenstrual syndrome (PMS)	Cruciferous Indoles (indole-3- carbinol, di-indolylmethane)	9	Global improvement in PMS or premenstrual/luteal phase symptoms
			8	Global pain burden
			8	Behavioural changes, mood swings or lability
			8	Physical function burden from PMS (bloating, appetite changes, food cravings, dizziness, vertigo, nausea, breast tenderness/soreness)
			8	Quality of life
			8	Change in severity of individual symptoms
			7	Cognitive function burden from PMS

Abbreviations: BP=blood pressure; HRQoL=health-related quality of life; NTWC=Natural Therapies Working Group

*1-3 = of limited importance to decision making; 4-6 = important, but not critical, to decision making; 7-9 = critical for decision-making

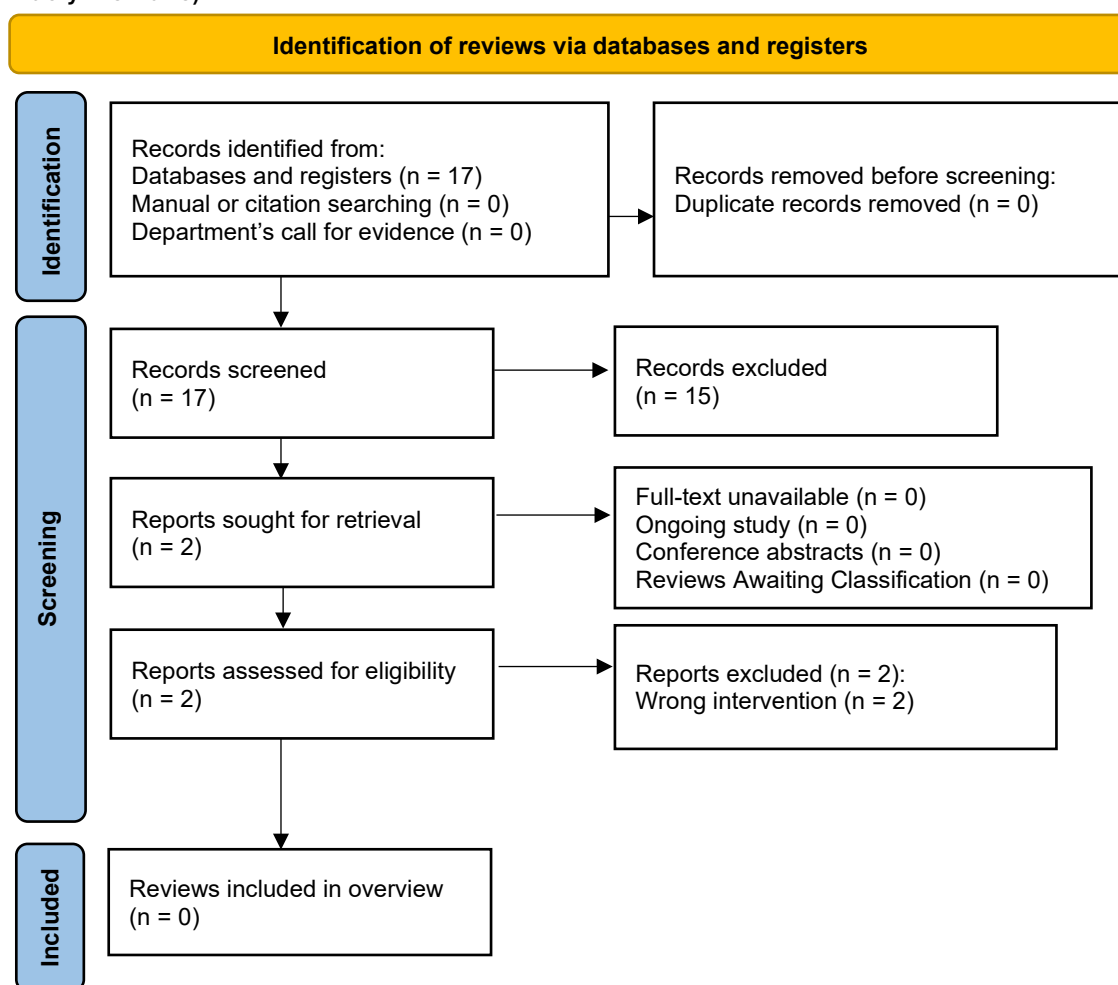
4.7.4. Search findings

In total, 17 unique reviews were found in searches and were screened. None of the reviews provided by the Department's call for evidence were relevant to this population-supplement pair. After title and abstract screening, 2 reviews were assessed for eligibility at full-text screening:

- 2 reviews did not meet inclusion criteria (citation details and reasons for exclusion recorded in Appendix C1)

Following assessment, no reviews met the inclusion criteria. A full PRISMA flowchart is presented below.

Figure 7. PRISMA flowchart – Premenstrual syndrome (PMS), Cruciferous indoles (indole-3-carbinol, di-indolylmethane)



4.7.5. Description of included reviews

No reviews met inclusion criteria.

4.7.6. Assessment of risk of bias of included systematic reviews

No reviews met inclusion criteria.

4.7.7. Results

No reviews met inclusion criteria.

4.7.8. Summary of findings and evidence statements

The effect of cruciferous indoles on global improvement in PMS or premenstrual/luteal phase symptoms, global pain burden, behavioural changes, mood swings or lability, physical function burden from PMS (bloating, appetite changes, food cravings, dizziness, vertigo, nausea, breast tenderness/soreness), quality of life, change in severity of individual symptoms or cognitive function burden from PMS in people with PMS is unknown.

4.8. Atopic disorders (including eczema, dermatitis, allergic rhinitis, allergies), Zinc

4.8.1. Description of condition

Atopic disorders are a group of conditions primarily characterised by a sensitivity to allergic reactions. This is typically a result of production of immunoglobulin E (IgE) antibodies in response to environmental allergens (127). The aetiology of atopic disorders is largely unknown, though evidence suggests the influence of genetic factors (128). Major subtypes of atopic disorders include atopic dermatitis, eczema, allergic rhinitis (hay fever), asthma, and food allergies. Symptoms vary depending on the specific subtype but commonly involve skin inflammation (eczema), nasal congestion and sneezing (allergic rhinitis), wheezing and shortness of breath (asthma), and a range of reactions to food allergens, including systemic anaphylaxis and hypotension (128). While incurable, their presentation can change over time.

Atopic disorders can significantly impact physical health, quality of life, and mental well-being. They are also correlated with other conditions, including psychological stress and depression (129, 130). Atopic disorders are diagnosed based on a comprehensive evaluation including clinical history, physical examination, and potentially diagnostic testing such as skin prick tests or allergen-specific IgE blood tests (128). Treatment of these conditions often consists of environmental control (to reduce exposure to allergens) and pharmacological interventions (128).

4.8.2. Description of the intervention

Zinc (Zn) is an essential trace mineral required by the human body in small amounts. Zinc plays crucial physiological roles, serving as a cofactor for numerous enzymes involved in diverse processes including DNA synthesis, immune function, wound healing, and growth and development (131, 132). Zinc is found in most tissues, but is particularly concentrated in bones, muscles, the prostate gland, and the eyes (132). The body cannot manufacture zinc, and so intake via diet or supplementation to maintain adequate levels is needed. Zinc is naturally found in various foods, including animal sources (oysters, red meat, poultry, and seafood), plant sources (legumes, nuts, seeds, and whole grains) and fortified foods (some breakfast cereals and other processed products). It is also available in dietary supplements, often in the forms of zinc gluconate, zinc sulphate, or zinc citrate and typically taken orally in capsule, tablet, or liquid form (131). The recommended dietary intake for zinc varies depending on age and sex, but generally ranges from 8-14 mg daily for adults (19). Zinc supplements often provide slightly higher doses than Recommended Dietary Intakes (RDI). This is generally safe, though excessive intake can lead to gastrointestinal issues and may interfere with the absorption of other minerals.

Zinc contributes to cellular respiration through carbonic anhydrase, supports immune functions, aids in protein synthesis, facilitates wound healing, participates in DNA synthesis, and plays a role in cell division (133). Activation of T lymphocytes, as well as the differentiation of helper lymphocytes (Th) into their various subgroups (Th1, Th2, Th17, regulatory T cells) depend on zinc homeostasis (134). Because zinc has many actions, zinc concentration could affect the pathogenesis of inflammatory and autoimmune diseases and increased intake could improve symptoms.

4.8.3. Prioritised outcomes

Five priority outcomes were identified by NTWC as part of the Outcome Prioritisation Exercise. These are listed below by order of priority. Outcomes were rated by their importance to decision-making, with those rated 7-9 being critical for decision-making.

Table 25. List of prioritised outcomes – atopic disorders (including eczema, dermatitis, allergic rhinitis, allergies), zinc (as assessed as part of the Outcome Prioritisation Exercise by NTWC).

#	Priority population	Priority intervention	Priority outcomes	
			NTWC Rating	Outcome domain
8	Atopic disorders (including eczema, dermatitis, allergic rhinitis, allergies (e.g. hay fever))	Zinc	9	Global severity of condition/improvement of symptoms
			8	Quality of life
			8	Long-term measure of control of disease
			7	Individual changes in symptoms (including degree of redness of skin, day-time itch, anterior rhinorrhoea (runny nose))
			6	Physical function/ disability (return to work/school)

Abbreviations: BP=blood pressure; HRQoL=health-related quality of life; NTWC=Natural Therapies Working Group

*1-3 = of limited importance to decision making; 4-6 = important, but not critical, to decision making; 7-9 = critical for decision-making

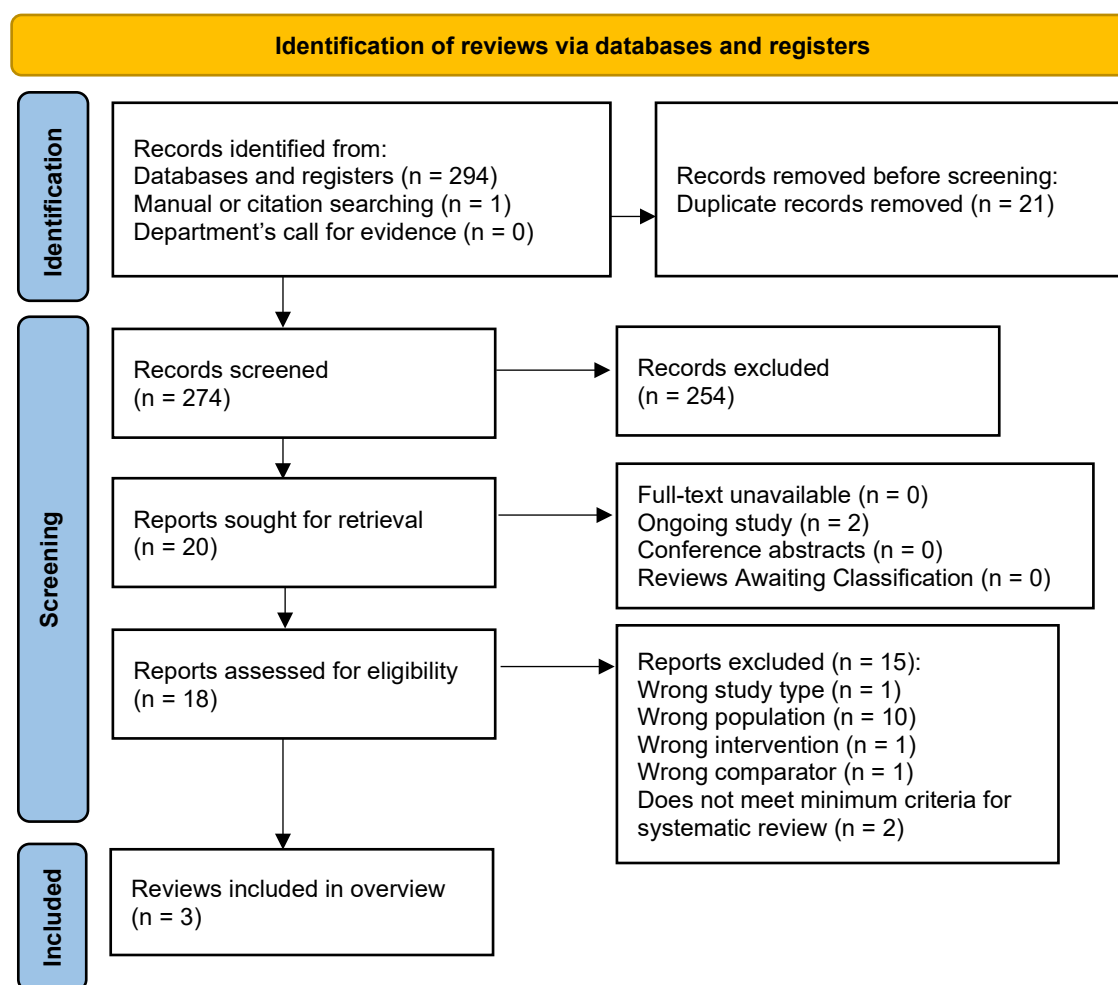
4.8.4. Search findings

In total, 274 reviews were screened following de-duplication. None of the reviews provided by the Department's call for evidence were relevant to this population-supplement pair. After title and abstract screening, 20 reviews were sought for retrieval for full-text screening:

- 2 reviews were ongoing (citation details recorded in Appendix C4)
- 15 reviews did not meet inclusion criteria (citation details and reasons for exclusion recorded in Appendix C1)

A final 3 reviews met the inclusion criteria. Characteristics of included reviews are presented in Appendix D. A full PRISMA flowchart is presented below.

Figure 8. PRISMA flowchart – atopic disorders, zinc.



4.8.5. Description of included reviews

Three reviews were identified as eligible for inclusion; review characteristics are reported in detail in Appendix D. The included reviews were conducted between 2012 and 2020.

All reviews examined atopic dermatitis as the condition of interest. Two reviews aimed to evaluate the evidence for zinc specifically in treatment of atopic dermatitis (135, 136); only one included a meta-analysis (135). The third eligible review was a Cochrane review aiming to evaluate a range of dietary supplements for treating established atopic eczema (dermatitis) (137).

4.8.6. Assessment of risk of bias of included systematic reviews

Risk of bias assessments of the included reviews, as appraised using the ROBIS tool, are presented below. Full assessments are reported in Appendix F.

Table 26. Summary of ROBIS assessments – atopic disorders, zinc

Review ID	ROBIS Domains				Overall risk of bias
	Domain 1: Study eligibility criteria	Domain 2: Identification and selection of studies	Domain 3: Data collection and study appraisal	Domain 4: Synthesis and findings	

Bath-Hextall 2012	Low	Low	Low	Unclear	Unclear risk
Dhaliwal 2020	Unclear	Unclear	Unclear	Unclear	Unclear risk
Gray 2019	Low	Low	Low	Unclear	Unclear risk

4.8.7. Results

The three identified reviews were all assessed to be at unclear risk of bias. The only review that presented effect sizes for all outcomes was Bath-Hextall et al. (2012) (137). Despite not being the most recent, there have been no changes to the literature (evidenced by all reviews including only the same single primary study), and therefore Bath-Hextall et al. (2012) was selected as the preferred review.

Table 27. Contributing reviews for each population and intervention/co-intervention combination – atopic disorders, zinc

	With atopic disorders	At risk of atopic disorders
Zinc VS placebo/inactive control	Bath-Hextall 2012	-
Zinc + naturopathy co-intervention VS placebo/inactive control	-	-

4.8.8. Summary of findings and evidence statements

Table 28. Zinc compared to placebo/inactive control for atopic disorders

Patient or population: Atopic disorders Intervention: Zinc Comparison: Placebo/inactive control								
NTWC Rating*	Outcomes	Contributing review	Absolute Effects			Nº of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
			Comparator Mean (SD)	Intervention Mean (SD)	Relative effect (95% CI)			
9	Global severity of condition/improvement of symptoms Condition: Atopic eczema (paediatric) Dosage: 61.8mg zinc sulphate							
	Combined disease severity score Assessed with: Affected surface area score multiplied by severity score	Bath-Hextall 2012				42 (1)	⊕○○○ VERY LOW ^a	The evidence is very uncertain about the effect of zinc on combined disease severity for atopic disorders (paediatric atopic eczema).
	Follow up: 4 weeks		37.8 (98.8)	41.8 (44.2)	MD = 4.00 (–43.07 to 51.07) [^]			
	Follow up: 8 weeks		39.3 (70.4)	48.7 (40.9)	MD = 9.40 (–25.87 to 44.67) [^]			
	Surface area of body affected by eczema Assessed with: Estimate based on percentage surface area of the body affected by eczema (scores across 14 separate body areas)	Bath-Hextall 2012				42 (1)	⊕○○○ VERY LOW ^a	The evidence is very uncertain about the effect of zinc on surface area of body affected by eczema for atopic disorders (paediatric atopic eczema).
	Follow up: 4 weeks		12.5 (19.6)	16.7 (14)	MD = 4.20 (–6.19 to 14.59) [^]			
	Follow up: 8 weeks		16 (17.5)	18.9 (11.2)	MD = 2.90 (–6.08 to 11.88) [^]			
8	Quality of life	-	-	-	-	-	-	No reviews found. The effect of zinc on improvement in quality

									of life for atopic disorders is unknown.
8	Long-term measure of control of disease	-	-	-	-	-	-		No reviews found. The effect of zinc on improvement in long-term control of disease for atopic disorders is unknown.
Individual changes in symptoms									
Condition: Atopic eczema (paediatric)									
Dosage: 61.8mg zinc sulphate									
7	Itch score							⊕○○○ VERY LOW a	The evidence is very uncertain about the effect of zinc on itch score for atopic disorders (paediatric atopic eczema).
	Assessed with: 1 to 10 scale, recorded by family	Bath-Hextall							
	Follow up: 4 weeks	2012	NR	NR	NR		42 (1)		
	Follow up: 8 weeks		3.4 (1.8)	4.6 (2.1)	MD = 1.20 (0.02 to 2.38)^				
	Erythema (redness)							⊕○○○ VERY LOW a	
Assessed with: Degree of erythema on an arbitrary scale from 1 to 5	Bath-Hextall								
Follow up: 4 weeks	2012	2.2 (1)	2.2 (0.7)	MD = 0.00 (-0.53 to 0.53)^		42 (1)			
Follow up: 8 weeks		1.9 (0.9)	2.4 (0.9)	MD = 0.50 (-0.04 to 1.04)^					
6	Physical function/ disability (return to work/school)	-	-	-	-	-	-		No reviews found. The effect of zinc on physical function/ disability (return to work/ school) for atopic disorders is unknown.
*Ratings 1-3 = of limited importance to decision making; 4-6 = important, but not critical, to decision making; 7-9 = critical for decision-making									
^There are no published MCID estimates for outcome measures used in this study.									
Abbreviations: CI=Confidence interval, MD=Mean difference, NR=Not reported									
GRADE Working Group grades of evidence									
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.									
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.									
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.									
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.									
Explanations									

a. Primary study assessed as having unclear risk of bias across most judgement documents (no change for risk of bias). Paediatric population only; atopic dermatitis only (no other atopic disorders) (downgrade one for indirectness). There are no published MCID estimations to assess precision, though the only included primary study had a very small sample size raising concerns about optimal information size (downgraded 2 for serious imprecision). No inconsistency due to singular study (no change for inconsistency). No evidence of publication bias, though noting that Smith, Kline, & French Laboratories supplied active and placebo capsules. The lead author was also supported by grants from Glaxo Group Research and Glaxo Laboratories (no change for publication bias).

4.9. Fatigue (general) (including CFS and ME), antioxidants (specifically CoQ10 and alpha-lipoic acid)

4.9.1. Description of condition

Fatigue is a complex and often debilitating condition characterised by persistent and extreme tiredness that is not alleviated by rest or sleep. It extends beyond normal feelings of tiredness and can significantly impact physical and mental functioning. Fatigue is a common outcome or symptom of many medical conditions (such as autoimmune disorders, cancer, and heart disease) but is also a primary condition. Chronic Fatigue Syndrome (CFS) and Myalgic Encephalomyelitis (ME) are fatigue-related conditions with a wide range of symptoms and clinical presentations. While the CFS and ME terms are often used interchangeably, there are key differences between the conditions (e.g. ME is a neuro-immune illness, and requires an infective agent as part of diagnostic criteria, where CFS does not) (138, 139).

Diagnosing fatigue often involves a multifaceted approach to identify potential underlying causes or primary fatigue-related conditions. There is no singular test for fatigue or to make a diagnosis of CFS or ME. Generally, fatigue is diagnosed thorough medical history, physical examination, and potentially laboratory tests or sleep studies. The primary symptom is overwhelming exhaustion, but may also include muscle weakness, cognitive difficulties, unrefreshing sleep, and post-exertional malaise (aggravation of symptoms after physical, mental or emotional effort).

Fatigue can profoundly disrupt daily functioning, occupational performance and overall quality of life. As there is no cure for CFS or ME, treatment is directed at symptom relief. For those experiencing fatigue as an adverse outcome resultant from other conditions, treating the primary condition may help in reducing fatigue and associated symptoms.

4.9.2. Description of the intervention

Oxidative stress is associated with cellular damage and an increased risk of chronic diseases like cardiovascular disease, cancer, and neurodegenerative disorders. Antioxidants are substances which can prevent or delay oxidations of cell components, thereby reducing oxidative stress (140). Antioxidants help reduce inflammation by modulating cytokines and other immune responses. By maintaining cellular health, antioxidants may indirectly alleviate fatigue and enhance overall well-being (141). Coenzyme Q10 (CoQ10) and alpha-lipoic acid (ALA) are two antioxidant molecules which are commonly taken to increase and support antioxidant levels in the body (140). CoQ10, also called ubiquinone, is present in all human cells and is found in various foods like organ meats, oily fish, and whole grains (142). ALA is an antioxidant made in small amounts by the human body and found in foods like red meat and certain vegetables (e.g. potatoes, beets, spinach and broccoli) (143). Both CoQ10 and ALA are available as dietary supplement in capsules, tablets, and liquid forms.

4.9.3. Prioritised outcomes

Five priority outcomes were identified by NTWC as part of the Outcome Prioritisation Exercise. These are listed below by order of priority. Outcomes were rated by their importance to decision-making, with those rated 7-9 being critical for decision-making.

Table 29. List of prioritised outcomes – fatigue (general) (including CFS and ME), antioxidants (specifically CoQ10 and ALA) (as assessed as part of the Outcome Prioritisation Exercise by NTWC).

#	Priority population	Priority intervention	Priority outcomes	
			NTWC Rating	Outcome domain
9	Fatigue (general) (including myalgic encephalomyelitis (ME) and Chronic Fatigue Syndrome (CFS))	Antioxidants (specifically: CoQ10 and alpha-lipoic acid)	9	Global improvement in fatigue severity/burden
			8	Clinical recovery or improvement (dichotomous)
			8	Self-perceived change in overall health
			8	Physical function burden from fatigue
			8	HRQoL
			7	Cognitive function burden from fatigue
			7	Sleep quality/quantity

Abbreviations: BP=blood pressure; HRQoL=health-related quality of life; NTWC=Natural Therapies Working Group

*1-3 = of limited importance to decision making; 4-6 = important, but not critical, to decision making; 7-9 = critical for decision-making

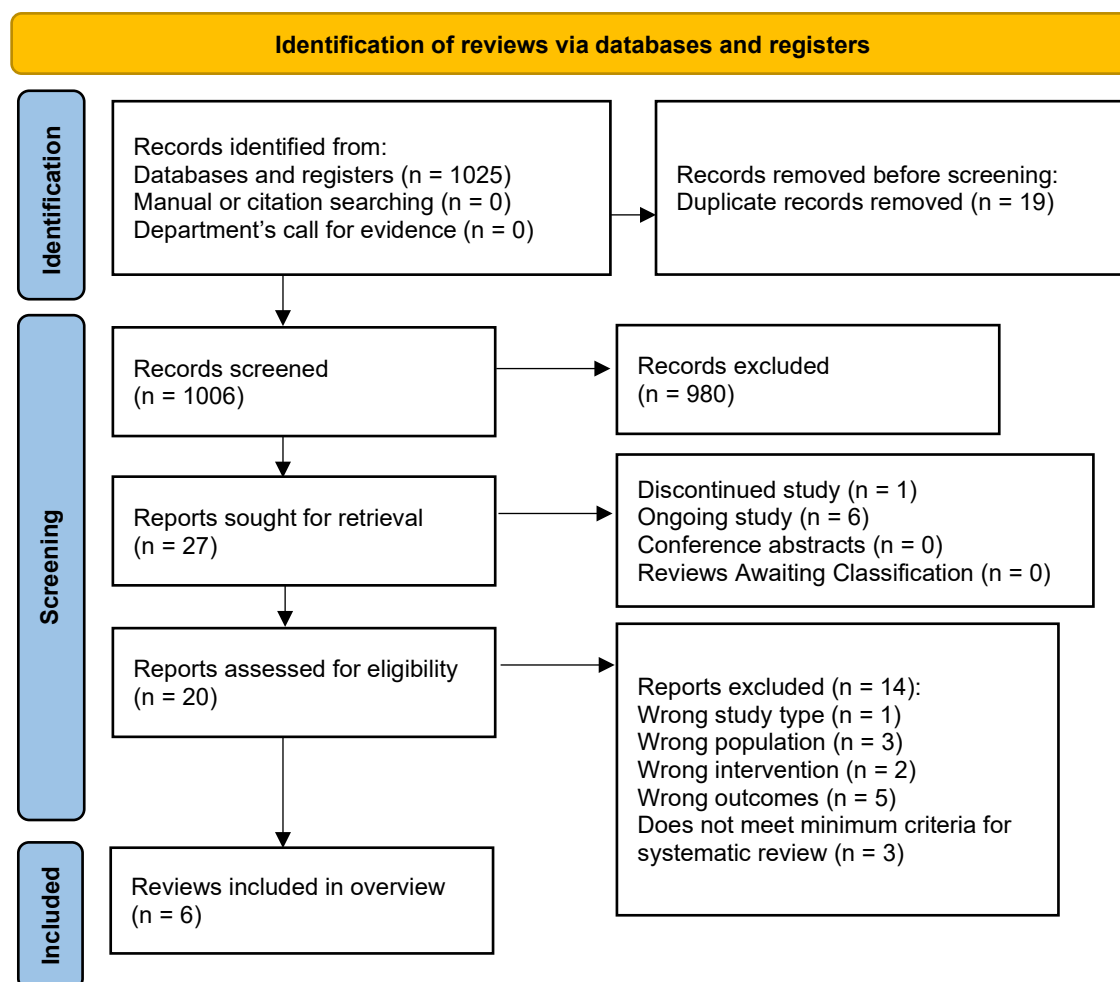
4.9.4. Search findings

In total, 1,006 reviews were identified in the searches after de-duplication and underwent screening. None of the reviews provided by the Department's call for evidence were relevant to this population-supplement pair. After title and abstract screening, 27 reviews were sought for retrieval for full-text screening:

- 6 reviews were ongoing (citation details recorded in Appendix C4)
- 1 review was discontinued
- 14 reviews did not meet inclusion criteria (citation details and reasons for exclusion recorded in Appendix C1)

A final 6 reviews met the inclusion criteria. Characteristics of included reviews are presented in Appendix D. A full PRISMA flowchart is presented below.

Figure 9. PRISMA flowchart – fatigue (general) (including CFS and ME), antioxidants (specifically CoQ10 and alpha-lipoic acid).



4.9.5. Description of included reviews

Six reviews were identified as eligible for inclusion; review characteristics are reported in detail in Appendix D. The included reviews were conducted between 2017 and 2022; only one included a meta-analysis.

Two reviews aimed to examine the effects of antioxidants (specifically CoQ10) on fatigue (144, 145). Four reviews aimed to examine the impact of dietary supplements on symptoms (including fatigue) associated with specific conditions (CFS/ME, multiple sclerosis, breast cancer) (146-149). Three of the 6 reviews only included RCTs (144, 147, 148)

4.9.6. Assessment of risk of bias of included systematic reviews

Risk of bias assessments of the included reviews, as appraised using the ROBIS tool, are presented below. Full assessments are reported in Appendix F.

Table 30. Summary of ROBIS assessments – fatigue (general) (including CFS and ME), antioxidants (specifically CoQ10 and ALA)

Review ID	ROBIS Domains	
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	Domain 1: Study eligibility criteria	Domain 2: Identification and selection of studies	Domain 3: Data collection and study appraisal	Domain 4: Synthesis and findings	Overall risk of bias
Campagnolo 2017	Low	Unclear	Unclear	Unclear	Unclear risk
Kim 2020	Low	Unclear	Unclear	Unclear	Unclear risk
Marx 2019	Low	Low	Unclear	Unclear	Unclear risk
Mehrabani 2019	Low	Unclear	Low	Unclear	Unclear risk
Pereira 2018	Low	Low	Low	Unclear	Low risk
Tsai 2022	Low	Low	Low	Low	Low risk

4.9.7. Results

Preferred contributing reviews are listed in the table below. All six included reviews reported on global improvement in fatigue severity/burden as an outcome, although mostly for specific conditions (e.g. multiple sclerosis or breast cancer), and therefore most analyses only included one primary study. Tsai et al. (2022) (144) included both healthy people and people with a range of fatigue-associated diseases, and so was assessed as the most comprehensive and also the most recent with low risk of bias. Tsai et al. (2022) reported results of a subgroup meta-analysis of 10 RCTs (899 participants) spanning various conditions (CFS, end-stage heart failure, fibromyalgia, breast cancer, end-stage renal disease, poliomyelitis, multiple sclerosis and obesity).

Marx 2019 was the only review that reported results for HRQoL, including results from one primary study of participants with secondary progressive MS conducted over 2 years (147).

No reviews reported results for the following outcomes: clinical recovery or improvement (dichotomous), self-perceived change in overall health, physical function burden from fatigue, cognitive function burden from fatigue, or sleep quality/quantity.

Table 31. Contributing reviews for each population and intervention/co-intervention combination – fatigue (general) (including CFS and ME), antioxidants (specifically CoQ10 and ALA)

	With fatigue (general) (including CFS and ME)	At risk of fatigue (general) (including CFS and ME)
Antioxidants (specifically CoQ10 and ALA) VS placebo/inactive control	Tsai 2022 Marx 2019	-
Antioxidants (specifically CoQ10 and ALA) + naturopathy co-intervention VS placebo/inactive control	-	-

4.9.8. Summary of findings and evidence statements

Table 32. Antioxidants (specifically CoQ10 and ALA) compared to placebo/inactive control for fatigue (general) (including CFS and ME).

Patient or population: **Fatigue (general) (including CFS and ME)**
Intervention: **Antioxidants (specifically CoQ10 and ALA)**
Comparison: **Placebo/inactive control**

NTWC Rating*	Outcomes	Contributing review	Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
Global improvement in fatigue severity/burden						
9	Conditions: CFS, end-stage heart failure, obesity, fibromyalgia, breast cancer, end-stage renal disease, poliomyelitis, multiple sclerosis Dose: CoQ10 60-500mg/day Assessed with: Minnesota Living with Heart Failure Questionnaire fatigue score (0-5), Fatigue Severity Scale (9-63), Fibromyalgia Impact Questionnaire fatigue score (0-10), Profile of Mood States fatigue subscale (0-4), Fatigue Impact Scale (0-160), Fatigue Scale (0-32), Multidimensional Assessment of Fatigue (1-50), Functional Assessment of Chronic Illness Therapy (0-44) Follow up: 4 to 24 weeks	Tsai 2022	SMD = -0.433 (-0.732 to -0.133)^	899 (10)	⊕⊕⊕○ MODERATE ^a	Antioxidants probably result in a global improvement in fatigue severity/burden for fatigue.
9	Clinical recovery or improvement (dichotomous)	-	-	-	-	No reviews found. The effect of antioxidants on improvement in clinical recovery or improvement (dichotomous) in fatigue is unknown.
9	Self-perceived change in overall health	-	-	-	-	No reviews found. The effect of antioxidants on self-perceived change in overall health in fatigue is unknown.
8	Physical function burden from fatigue	-	-	-	-	No reviews found. The effect of antioxidants on physical function burden from fatigue in fatigue is unknown.

8	HRQoL Conditions: Secondary progressive multiple sclerosis Dose: ALA 1200 mg per day Assessed with: SF-36 Follow up: 2 years	Marx 2019	Fatigue was decreased in participants receiving the intervention compared to placebo.	54 (1)	⊕○○○ VERY LOW ^b	The evidence is very uncertain about the effect of antioxidants on HRQoL for fatigue.
			Effect sizes NR#8			
8	Cognitive function burden from fatigue	-	-	-	-	No reviews found. The effect of antioxidants on cognitive function burden from fatigue in fatigue is unknown.
8	Sleep quality/quantity	-	-	-	-	No reviews found. The effect of antioxidants on sleep quality/quantity in fatigue is unknown.
<p>*Ratings 1-3 = of limited importance to decision making; 4-6 = important, but not critical, to decision making; 7-9 = critical for decision-making</p> <p>^Hedges' g values of 0.2, 0.5, and 0.8 were considered small, moderate, and large effect sizes, respectively (22).</p> <p>#Absolute risk differences or relative effect sizes not reported. Unable to make judgements about MCID.</p> <p>§Results were incorrectly reported in text (wrong primary study and results were referenced under the intervention).</p> <p>Abbreviations: ALA= alpha-lipoic acid, CoQ10= Coenzyme Q10, CFS=Chronic fatigue syndrome; CI=Confidence interval, MD=Mean difference, NR=Not reported, SF-36= RAND 36-Item Short Form Survey Instrument, ME= Myalgic Encephalomyelitis, HRQoL=health-related quality of life</p> <p>GRADE Working Group grades of evidence</p> <p>High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.</p> <p>Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.</p> <p>Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.</p> <p>Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.</p> <p>Explanations</p> <p>a. Generally low risk of bias in included studies, some unclear risks of bias primarily related to allocation concealment. On balance, this should not impact findings (no change for risk of bias). Point estimates consistently favoured the intervention with overlapping CIs; no statistical measures of heterogeneity provided (no change for inconsistency). CI boundaries suggest different inferences about the magnitude of benefit based on MCID (SMD = 0.2), however lower boundary still falls about the MCID threshold (where Hedges' g = 0.2) (no change for imprecision). Possible publication bias supported by visual inspection of funnel plot (downgraded one for publication bias).</p> <p>b. Risk of bias in included primary study (downgraded one for risk of bias). Population in the included review was restricted to people with secondary progressive multiple sclerosis only (downgraded one for indirectness). No effect estimates provided to assess precision; results only presented in terms of statistical significance. Additionally, very small sample size raising concerns about optimal information size (downgraded 3 for imprecision). No inconsistency due to singular study (no change for inconsistency). Publication bias not assessed likely due to insufficient number of studies (no change for publication bias).</p>						

4.10. Headache and migraine, magnesium

4.10.1. Description of condition

Headaches are a common neurological complaint, consisting of pressure, tension or pain in the head or face. Primary headache disorders are characterised by recurrent headaches not due to an underlying medical condition. Categorisations of headache disorders include migraines, tension-type headaches, cluster headaches and medication overuse headaches. With varying estimates, a recent review estimated the global prevalence of active headache disorders to be nearly one in two people, with migraines affecting around 1 in 7 people (150). While migraines share common features with other primary headache disorders like tension-type headaches, they generally present with a distinct clinical profile. Migraine attacks typically involve throbbing or pulsating head pain, often unilateral, worsened by activity, and accompanied by nausea, vomiting, and sensitivity to light and sound.

Both migraines and other types of headache disorders can significantly impact daily functioning, affecting work, school, and social life. Comorbidities are common with headache disorders (particularly migraines) and include psychiatric conditions, sleep disorders, and other chronic pain conditions (151).

Criteria established by the International Headache Society (IHS) guide classification and diagnosis of headache disorders (152). Treatment involves a range of options, primarily related to pain relief (either over the counter or prescription medications). For migraines, rest in a quiet, dark room is also usually prescribed due to light and sound sensitivities. Preventive medications are also available via prescription, and complementary or alternative therapies are also common (such as acupuncture or massage therapy).

4.10.2. Description of the intervention

Magnesium (often abbreviated as its chemical symbol: Mg) is a naturally occurring mineral in the human body. It is an essential mineral playing numerous crucial roles in the human body, including enzymatic reactions, energy production, muscle function, and bone health (16, 17). Recent evidence suggests that magnesium levels in the body may be associated with some health conditions, including Diabetes Mellitus (Type II), cardiovascular disease, osteoporosis, and migraines (17).

It is thought that Magnesium may have multifaceted actions, including preventing cortical Spreading Depression (CSD), regulating neurotransmitters, and relaxing muscles. Cortical spreading depression (CSD) is a wave of abnormal brain signalling associated with migraines, particularly the visual and sensory changes seen in aura, as above Mg can play a role in lowering abnormally/supraphysiological levels of cortisol and may reduce CSD. Proper neurotransmitter balance may contribute to reducing the frequency and severity of migraines and Mg helps regulate neurotransmitters (such as serotonin and dopamine) in the brain hence possibly alleviating the symptoms of headache (18). In addition, Mg may act to relax muscles, potentially shortening the duration of a migraine attack and promoting a calmer state (153).

The recommended dietary intake for magnesium varies depending on age and sex, typically ranging from 310-420 mg daily for adults (19). While it is a typical component of most diets, and is abundant in foods such as leafy vegetables, nuts, legumes, and grains, supplementation is available. Magnesium supplements come in several forms with varying bioavailability (absorption rates), including magnesium oxide, citrate, glycinate, or lactate (17).

Oral magnesium supplements are readily available without prescription and are sometimes sold in tandem with one or multiple other nutritional supplements. Magnesium supplements are generally safe for most people when taken at appropriate doses⁴; though some medications may interact with magnesium (including antibiotics, diuretics and bisphosphonates) (17). Excess magnesium is usually excreted by the kidneys as urine, though very high amounts of magnesium from dietary supplements can result in diarrhea, nausea and abdominal cramping (17).

4.10.3. Prioritised outcomes

Seven priority outcomes were identified by NTWC as part of the Outcome Prioritisation Exercise. These are listed below by order of priority. Outcomes were rated by their importance to decision-making, with those rated 7-9 being critical for decision-making.

Table 33. List of prioritised outcomes – Headache and migraine, magnesium (as assessed as part of the Outcome Prioritisation Exercise by NTWC).

#	Priority population	Priority intervention	Priority outcomes	
			NTWC Rating	Outcome domain
10	Headache and migraine	Magnesium	9	Global improvement in headache/migraine
			8	Headache pain intensity
			8	Headache pain frequency
			8	Headache/migraine-associated symptoms (nausea and vomiting, photophobia and phonophobia, visual aura)
			8	QoL
			7	Cognitive function burden
			7	Medication use

Abbreviations: BP=blood pressure; HRQoL=health-related quality of life; NTWC=Natural Therapies Working Group

*1-3 = of limited importance to decision making; 4-6 = important, but not critical, to decision making; 7-9 = critical for decision-making

4.10.4. Search findings

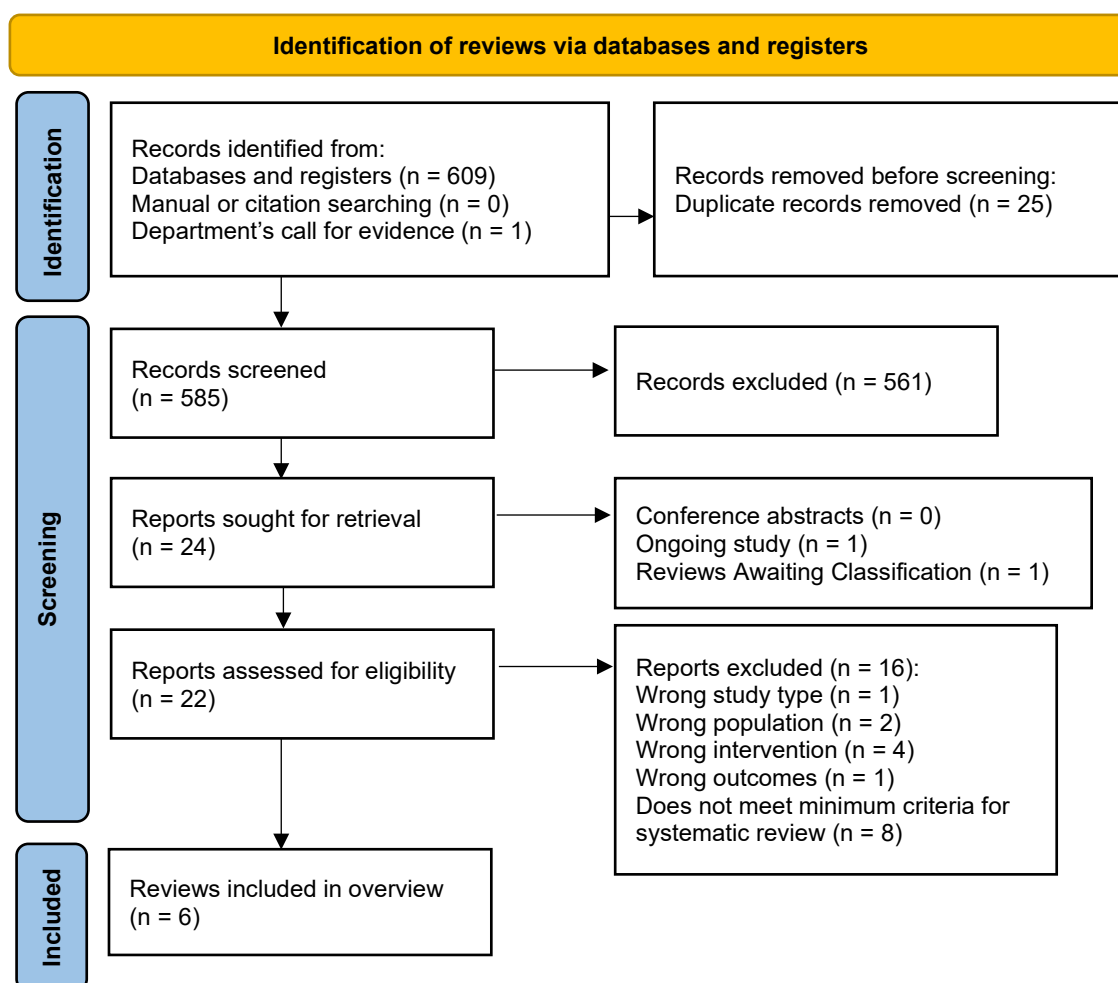
In total, 585 reviews were screened following de-duplication. One review provided by the Department's call for evidence was relevant to this population-supplement pair, which was already identified in database searching and excluded as a duplicate (see Appendix C2). After title and abstract screening, 24 reviews were sought for retrieval for full-text screening:

- 1 review was ongoing (citation details recorded in Appendix C4)
- 1 review was published in languages other than English (citation details recorded in "Reviews awaiting classification" table in Appendix C3)
- 16 reviews did not meet inclusion criteria (citation details and reasons for exclusion recorded in Appendix C1)

⁴ The TGA has recently updated warning labels for supplements containing B6 due to over 30 reports of peripheral neuropathy (symptoms of which include tingling, burning and numbness). The TGA notes "In many cases, people reported they were not aware they had consumed vitamin B6, as the product they were taking was a magnesium supplement." See [Why TGA made these labelling and use changes | Health supplements containing vitamin B6 can cause peripheral neuropathy | Therapeutic Goods Administration \(TGA\)](#)

A final 6 reviews met the inclusion criteria. Characteristics of included reviews are presented in Appendix D. A full PRISMA flowchart is presented below.

Figure 10. PRISMA flowchart – Headache and migraine, magnesium



4.10.5. Description of included reviews

Six reviews were identified as eligible for inclusion (154-159); review characteristics are reported in detail in Appendix D. The included reviews were conducted between 2008 and 2020. All reviews only included RCTs; three included meta-analyses (157-159).

Two reviews specifically aimed to examine the impact of magnesium on migraine (154, 157); and another summarised the impact of magnesium on chronic pain more generally (including results presented separately for migraine) (156). Three reviews aimed to summarise the evidence for vitamins and minerals (159), drugs (155) and existing therapies (158) for migraine; (specifically menstruation-related migraine in one review) (158).

4.10.6. Assessment of risk of bias of included systematic reviews

Risk of bias of the systematic reviews, as assessed using the ROBIS tool, is presented below. Full assessments are reported in Appendix F.

Table 34. Summary of ROBIS assessments – Headache and migraine, magnesium

Review ID	ROBIS Domains	
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	Domain 1: Study eligibility criteria	Domain 2: Identification and selection of studies	Domain 3: Data collection and study appraisal	Domain 4: Synthesis and findings	Overall risk of bias
Chiu 2016	Low	Unclear	Low	Low	Low risk
Okoli 2019	Low	Low	Low	High	High risk
Park 2020	Low	Unclear	Low	Unclear	Unclear risk
Pringsheim 2008	Low	Unclear	Low	High	High risk
Pringsheim 2012	Low	Unclear	Low	High	High risk
vonLuckner 2018	Low	Unclear	Low	Unclear	Low risk

4.10.7. Results

Preferred contributing reviews are listed in the population-intervention matrix in Table 35. Okoli et al. (2019) (159) was one of the most recent reviews and included the largest meta-analysis. Chiu (2016) had the lowest risk of bias with a similar sized meta-analysis to Okoli 2019, however results for magnesium alone versus with a co-intervention and with active versus inactive controls could not be separated. Despite being assessed as having a high risk of bias related to unexplained heterogeneity and non-assessment of publication bias in findings, Okoli et al. (2019) was therefore chosen as the preferred review, and these limitations were noted in GRADE assessments.

No reviews reported the effect of magnesium on improvement in headache/migraine-associated symptoms (nausea and vomiting, photophobia and phonophobia, visual aura), QoL, cognitive function burden or medication use for people with IBS.

Table 35. Preferred reviews for each population and intervention/co-intervention combination – headache and migraine, magnesium.

	With headache and migraine	At risk of headache and migraine
Magnesium VS placebo/inactive control	Okoli 2019	-
Magnesium + naturopathy co-intervention VS placebo/inactive control	-	-

4.10.8. Summary of findings and evidence statements

Table 36. Magnesium compared to placebo/inactive control for headache and migraine.

Patient or population: Headache and migraine Intervention: Magnesium Comparison: Placebo/inactive control						
NTWC Rating*	Outcomes	Contributing review	Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
Global improvement in headache/migraine						
Population: Average-risk individuals (no history of head trauma or neurological disease) with a history of migraines						
9	Migraine duration Dose: 600mg per day Assessed with: Hours Follow up: 12 weeks	Okoli 2019	MD = -0.21 (-0.70 to 0.28)^	81 (1)	⊕○○○ VERY LOW ^a	The evidence is very uncertain about the effect of magnesium on migraine duration for headache and migraine.
	Days with migraine Dose: 500-600mg per day Follow up: 12 weeks	Okoli 2019	MD = -3.00 (-5.02 to -0.98) §	226 (3)	⊕⊕○○ LOW ^b	Magnesium may reduce the number of days with migraine for headache and migraine.
8	Headache pain intensity Conditions: Average-risk individuals (no history of head trauma or neurological disease) with a history of migraines Dosage: 500-600mg magnesium per day Assessed with: VAS, 3-point scales, NR	Okoli 2019	RoM = -0.17 (-0.36 to 0.02)#+	226 (3)	⊕○○○ VERY LOW ^c	The evidence is very uncertain about the effect of magnesium on headache pain intensity for headache and migraine.
8	Headache pain frequency Conditions: Average-risk individuals (no history of head trauma or neurological disease) with a history of migraines Dosage: 500-600mg per day Assessed with: Migraine frequency per month (number of migraine attacks)	Okoli 2019	MD = -2.57 (-4.21 to -0.94) ^	266 (4)	⊕⊕○○ LOW ^d	Magnesium may reduce headache pain frequency for headache and migraine.
8	Headache/migraine-associated symptoms (nausea and vomiting, photophobia and phonophobia, visual aura)	-	-	-	-	No reviews found. The effect of magnesium on Headache/migraine-associated symptoms (nausea and vomiting, photophobia and phonophobia, visual aura) for headache and migraine is unknown.

8	QoL	-	-	-	-	No reviews found. The effect of magnesium on QoL for headache and migraine is unknown.
7	Cognitive function burden	-	-	-	-	No reviews found. The effect of magnesium on cognitive function burden for headache and migraine is unknown.
7	Medication use	-	-	-	-	No reviews found. The effect of magnesium on medication use for headache and migraine is unknown.

*Ratings 1-3 = of limited importance to decision making; 4-6 = important, but not critical, to decision making; 7-9 = critical for decision-making.

^Unable to find published MCID estimations for migraine duration, or number of migraine attacks per month.

\$MCID for days with headache/migraine has been reported as 1 day (160).

#This result is log RoM. The log scale was not mentioned in the review, though it is probably the case that it was used given the negative value. The log measure as reported in the review is presented given that the inverse would require reanalysis.

+A 20% ratio of means difference (i.e. RoM ≤ 0.8 or ≥ 1.2) was considered as a minimal clinically important difference (MCID).

Abbreviations: CI=Confidence interval, MD=Mean difference, NR=Not reported, VAS=Visual analogue scale, RoM=ratio of means

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

- a. High risk of bias for multiple domains assessed for primary study (downgraded one for risk of bias). Unable to assess precision as unable to find MCID for migraine duration (hours), the only included primary study had a very small sample size raising concerns about optimal information size (downgrade 2 for serious imprecision). No inconsistency due to singular study (no change for inconsistency). Unable to assess publication bias as funnel plots and Egger's test results not presented (though described in methods) (no change for publication bias).
- b. High risk of bias for multiple domains assessed for primary studies (downgraded one for risk of bias). Point estimates all favoured the intervention, though confidence intervals had little overlap; lower bound of confidence interval would still be on threshold of clinically meaningful effect (where days with migraine = 1). However, small aggregate sample size which raises concerns about optimal information size. On balance, imprecision is a concern (downgrade one for imprecision). Inconsistency supported by high I^2 values and statistically significant heterogeneity, however, point estimates all favoured the intervention and no confidence intervals crossed the direction of effect threshold (no change for inconsistency). Unable to assess publication bias as funnel plots and Egger's test results not presented (though described in methods) (no change for publication bias).
- c. High risk of bias for multiple domains assessed for primary studies (downgraded one for risk of bias). Using MCID for RoM of 0.2, CI boundaries have an appreciable difference in interpretation of effect (downgrade 2 for serious imprecision). Low inconsistency supported by low I^2 values and non-statistically significant heterogeneity, point estimates favoured the intervention for most studies (no change for inconsistency). Unable to assess publication bias as funnel plots and Egger's test results not presented (though described in methods) (no change for publication bias).
- d. High risk of bias for multiple domains assessed for primary studies (downgraded one for risk of bias). Unable to find MCID for migraine frequency, though confidence intervals did not cross the direction of effect threshold (downgrade one for imprecision). Inconsistency supported by high I^2 values and statistically significant heterogeneity, however, point estimates all favoured the intervention and no confidence intervals crossed the direction of effect threshold (no change for inconsistency). Unable to assess publication bias as funnel plots and Egger's test results not presented (though described in methods) (no change for publication bias).

4.11. Arthritis/osteoarthritis, magnesium

4.11.1. Description of condition

Arthritis is a broad term encompassing over 100 distinct conditions characterised by joint pain, inflammation, and stiffness (161). These conditions can affect people of all ages, affecting mobility, daily activities, and overall quality of life. Age, obesity, injury and genetic aspects are all risk factors for arthritis (161). A recent large-scale longitudinal survey in the USA estimated that arthritis, in its various forms, affects over 25% of people, with the most common form being osteoarthritis (162). In Australia, recent prevalence estimates are slightly lower, at 14.5% of the population (163).

Osteoarthritis is assumed to be a result from wear and tear on joints over time, whereas other forms of arthritis can be a result of injury or autoimmune disease. Osteoarthritis involves the breakdown of cartilage leading to structural changes within the joint, and commonly affects weight-bearing joints like the knees, hips, and spine (though can occur in any joint in the body) (164, 165). Besides the direct physical impact, arthritis can significantly affect mental well-being and contribute to a greater risk of comorbidities. Osteoarthritis is associated with an increased risk of cardiovascular disease, obesity, mood disorders, and other chronic conditions (166, 167).

Diagnosing specific types of arthritis involves a combination of clinical history, physical examination, imaging (e.g. X-rays or MRI) and sometimes laboratory tests (Hunter et al., 2021). Typical symptoms of arthritis include joint pain, stiffness (particularly after inactivity), swelling, limited range of motion, and sometimes redness and warmth around the affected joint.

4.11.2. Description of the intervention

Magnesium (often abbreviated as its chemical symbol: Mg) is a naturally occurring mineral in the human body. It is an essential mineral playing numerous crucial roles in the human body, including enzymatic reactions, energy production, muscle function, and bone health (16, 17). Recent evidence suggests that magnesium levels in the body may be associated with some health conditions, including Diabetes Mellitus (Type II), cardiovascular disease, osteoporosis, and migraines (17).

The recommended dietary intake for magnesium varies depending on age and sex, typically ranging from 310-420 mg daily for adults (19). While it is a typical component of most diets, and is abundant in foods such as leafy vegetables, nuts, legumes, and grains, supplementation is available. Magnesium supplements come in several forms with varying bioavailability (absorption rates), including magnesium oxide, citrate, glycinate, or lactate (17).

Magnesium may play a multifaceted role in treatment of arthritis, including: protective role in cartilage, inflammation reduction, and potential cartilage-sparing effects (168). Adequate magnesium levels help prevent cartilage degradation. Magnesium also prevents cytokine storms, which are inflammatory immune responses where the body attacks its own cells, including cartilage. Magnesium sulphate (MgSO_4) has been used in anaesthesia to reduce postoperative opioid needs and has demonstrated reduced joint pain, inflammation, and cartilage cell death, slowing disease progression using a rat model (169). Intra-articular MgCl_2 (magnesium chloride) prevents joint damage progression as it decreases expression of matrix metalloproteinase and interleukin-6 genes in synovium and cartilage, suggesting anti-inflammatory and cartilage-sparing effects (170).

Oral magnesium supplements are readily available without prescription and are sometimes sold in tandem with one or multiple other nutritional supplements. Magnesium supplements are generally safe for most people when taken at appropriate doses⁵; though some medications may interact with magnesium (including antibiotics, diuretics and bisphosphonates) (17). Excess magnesium is usually excreted by the kidneys as urine, though very high amounts of magnesium from dietary supplements can result in diarrhea, nausea and abdominal cramping (17).

4.11.3. Prioritised outcomes

Seven priority outcomes were identified by NTWC as part of the Outcome Prioritisation Exercise. These are listed below by order of priority. Outcomes were rated by their importance to decision-making, with those rated 7-9 being critical for decision-making.

Table 37. List of prioritised outcomes – arthritis/osteoarthritis, magnesium (as assessed as part of the Outcome Prioritisation Exercise by NTWC).

#	Priority population	Priority intervention	Priority outcomes	
			NTWC Rating	Outcome domain
11	Arthritis/ Osteoarthritis	Magnesium	9	Pain
			9	Physical function
			8	Pain interference/work-related limitations
			8	Patient's global assessment of condition
			8	Clinician's global assessment of condition
			8	Quality of life
			7	Arthritis self-efficacy

Abbreviations: BP=blood pressure; HRQoL=health-related quality of life; NTWC=Natural Therapies Working Group

*1-3 = of limited importance to decision making; 4-6 = important, but not critical, to decision making; 7-9 = critical for decision-making

4.11.4. Search findings

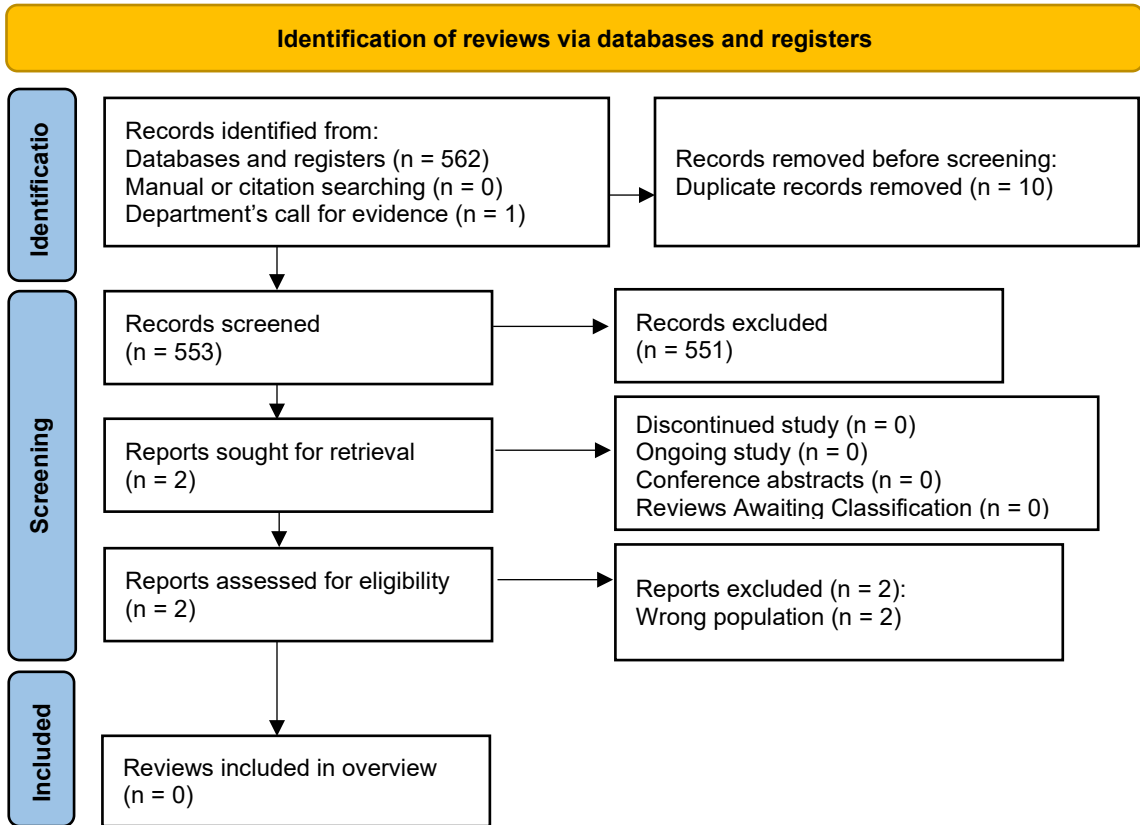
In total, 553 reviews were screened following de-duplication. One review provided by the Department's call for evidence was relevant to this population-supplement pair, which was already identified in database searching and excluded as a duplicate (see Appendix C2). After title and abstract screening, 2 reviews were assessed for eligibility at full-text screening, where:

- 2 reviews did not meet inclusion criteria (citation details and reasons for exclusion recorded in Appendix C1)

Following assessment, no reviews met the inclusion criteria. A full PRISMA flowchart is presented below.

⁵ The TGA has recently updated warning labels for supplements containing B6 due to over 30 reports of peripheral neuropathy (symptoms of which include tingling, burning and numbness). The TGA notes "In many cases, people reported they were not aware they had consumed vitamin B6, as the product they were taking was a magnesium supplement." See [Why TGA made these labelling and use changes | Health supplements containing vitamin B6 can cause peripheral neuropathy | Therapeutic Goods Administration \(TGA\)](#)

Figure 11. PRISMA flowchart – Arthritis/Osteoarthritis, Magnesium.



4.11.5. Description of included reviews

No reviews met inclusion criteria.

4.11.6. Assessment of risk of bias of included systematic reviews

No reviews met inclusion criteria.

4.11.1. Results

No reviews met inclusion criteria.

4.11.2. Summary of findings and evidence statements

The effect of magnesium on pain, physical function, pain interference/work-related limitations, patient's global assessment of condition, clinician's global assessment of condition, quality of life, arthritis self-efficacy in people with arthritis/osteoarthritis is unknown.

4.12. Hypertension, Omega-3 fatty acids

4.12.1. Description of condition

Hypertension is a chronic condition characterised by persistently elevated blood pressure readings that put undue stress on the cardiovascular system, impacting an estimated 3 million people in Australia (171). Often called the "silent killer," hypertension frequently presents without overt symptoms until significant damage has occurred (172). Over time, uncontrolled hypertension causes damage to blood vessels, accelerating atherosclerosis and putting individuals at heightened risk for heart disease, stroke, kidney failure, cognitive decline, and vision problems (172). Prevalence increases with age, and other risk factors include family history, obesity, sedentary lifestyle, high salt intake, and excessive alcohol consumption (171).

In Australia, hypertension is diagnosed based on published guidelines (173). Treatment approaches generally prioritise lifestyle modifications, including regular physical activity, a heart-healthy diet (low in salt, high in fruits and vegetables), weight management, and smoking cessation. Pharmacological therapy is also used in certain instances, with choice of medication dependent on individual patient factors, including indications, age, comorbidities, and potential side effects (173).

Blood pressure includes systolic pressure (when the heart pushes blood out) and diastolic pressure (when the heart rests between beats). It is measured by millimetres of mercury (mmHg). Generally, blood pressure is considered normal when systolic levels are less than 120mmHg and diastolic levels are less than 80mmHg. Hypertension is considered when systolic levels are greater than 140mmHg or diastolic levels are greater than 90mmHg.

4.12.2. Description of the intervention

Omega-3 fatty acids are a group of polyunsaturated fats essential for human health. There is evidence that Omega-3 fatty acids play crucial roles in various physiological processes, including brain function, inflammation, and cardiovascular health (87, 88). Main types of omega-3 fatty acids important for dietary considerations include eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and alpha-linolenic acid (89). Common dietary sources of omega-3 fatty acids include fatty fish (salmon, mackerel, herring, sardines, anchovies, tuna), nuts and seeds (walnuts, chia seeds, flaxseeds) and plant-based oils (flaxseed oil, soybean oil). The recommended dietary intake of omega-3 fatty acids varies depending on age, sex, and health status (19,89). Omega-3 supplements are available without prescription, often taken as fish oil, krill oil, cod liver oil, or vegetarian products that contain algae oil.

Omega-3 fatty acids may offer effects in managing hypertension through vascular tone regulation, anti-inflammatory properties, endothelial function enhancement, and enhanced nitric oxide (NO) production (174). It is thought that these effects primarily occur through the regulation of vascular tone as omega-3 fatty acids may influence endothelium-dependent (improve endothelial function) and independent mechanisms, contributing to blood pressure control (175). By reducing inflammation, omega 3 fatty acids may indirectly impact blood vessel function and blood pressure. Nitric oxide is a vasodilator, relaxing blood vessels and promoting healthy blood pressure levels, Mg may enhance nitric oxide bioavailability.

4.12.3. Prioritised outcomes

Five priority outcomes were identified by NTWC as part of the Outcome Prioritisation Exercise. These are listed below by order of priority. Outcomes were rated by their importance to decision-making, with those rated 7-9 being critical for decision-making.

Table 38. List of prioritised outcomes – hypertension, omega-3 fatty acids (as assessed as part of the Outcome Prioritisation Exercise by NTWC).

#	Priority population	Priority intervention	Priority outcomes	
			NTWC Rating	Outcome domain
12	Hypertension	Omega-3 fatty acids	9	Blood pressure (systolic, diastolic)
			8	Quality of life
			8	Cardiovascular events (fatal or non-fatal myocardial infarction, excluding heart failure and if possible angina)
			8	Cerebrovascular events (fatal or non-fatal strokes, excluding transient ischaemic attacks if possible)
			7	Death from cardiovascular

Abbreviations: BP=blood pressure; HRQoL=health-related quality of life; NTWC=Natural Therapies Working Group

*1-3 = of limited importance to decision making; 4-6 = important, but not critical, to decision making; 7-9 = critical for decision-making

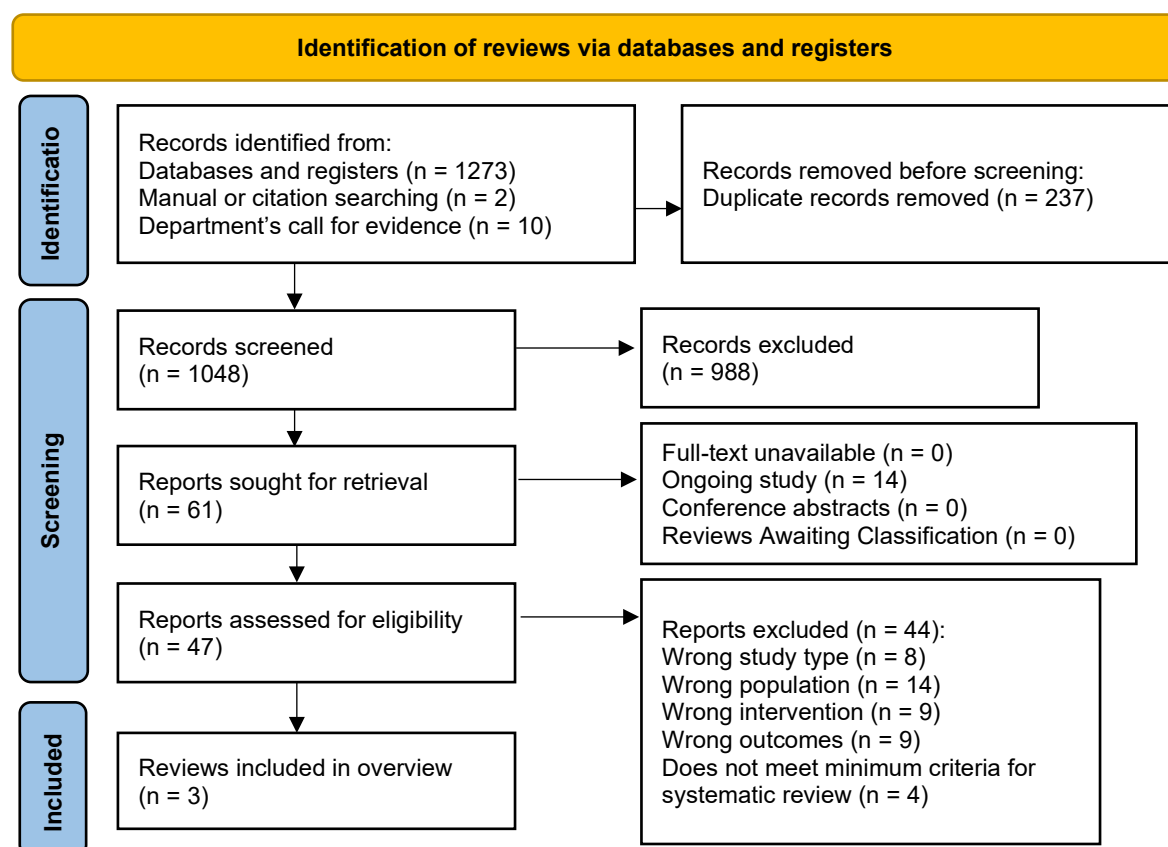
4.12.4. Search findings

In total, 1,047 reviews were screened following de-duplication. Ten reviews were provided by the Department's call for evidence were relevant to the population-supplement pair; five were duplicates already identified in database searching and five were screened (see Appendix C2). After title and abstract screening, 61 reviews were assessed for eligibility at full-text screening, where:

- 14 reviews were ongoing (citation details recorded in Appendix C4)
- 44 reviews did not meet inclusion criteria (citation details and reasons for exclusion recorded in Appendix C1)

A final 3 reviews met the inclusion criteria. Characteristics of included reviews are presented in Appendix D. A full PRISMA flowchart is presented below.

Figure 12. PRISMA flowchart – hypertension, omega-3 fatty acids.



4.12.5. Description of included reviews

Three reviews were identified as eligible for inclusion; review characteristics are reported in detail in Appendix D. The included reviews were conducted between 1989 and 2019 and contained meta-analyses.

One review matched the overview's PICO, seeking to investigate the impact of omega-3 fatty acids on preventing and treating hypertension (176). Two reviews aimed to assess the effects of omega-3 fatty acids on specific outcomes including blood pressure and presented results for those with or at risk of hypertension (177, 178).

4.12.6. Assessment of risk of bias of included systematic reviews

Risk of bias of the systematic reviews, as assessed using the ROBIS tool, is presented below. Full assessments are reported in Appendix F.

Table 39. Summary of ROBIS assessments – hypertension, omega-3 fatty acids

Review ID	ROBIS Domains				Overall risk of bias
	Domain 1: Study eligibility criteria	Domain 2: Identification and selection of studies	Domain 3: Data collection and study appraisal	Domain 4: Synthesis and findings	
Campbell 2013	Low	Unclear	Low	Low	Low risk
Guo 2019	Low	Unclear	Low	Low	Low risk
Radack 1989	Low	Unclear	Unclear	Low	Unclear risk

4.12.7. Results

Preferred contributing reviews are listed in the population-intervention matrix in Table 40. Campbell et al. (2013) (176) was the only review specifically examining the impacts of omega-3 fatty acids for people with hypertension. Compared to Radack et al. (1989) (177), it was also more recent, including 8 trials (versus 1 trial in Radack et al., 1989). While Guo et al., 2019 was more recent, results were only provided for EPA and DHA separately. In addition, the standard definition of hypertension (using SBP and DBP cut-offs) was not used.

Importantly, some studies included in Campbell et al. (2013) had populations with exposure to antihypertensive treatments. In two studies participants were newly diagnosed and not taking any anti-hypertensive medication; in three studies, any treatment was stopped prior to study commencement. In the remaining 3 studies, there was anti-hypertensive treatment that was not changed (although the details were only specified in 1 study). While this may confound any direct efficacy results of a nutritional supplement, this was considered likely to happen in the context of nutritional supplementation in naturopathic practice for hypertension given there are efficacious pharmacological treatment options. The certainty of evidence has been downgraded accordingly. An updated systematic review and meta-analysis examining the impact of omega-3 fatty acids on hypertensive patients specifically is needed.

Table 40. Contributing reviews for each population and intervention/co-intervention combination – hypertension, omega-3 fatty acids.

	With hypertension	At risk of hypertension
Omega-3 fatty acids VS placebo/inactive control	Campbell 2013	-
Omega-3 fatty acids + naturopathy co-intervention VS placebo/inactive control	-	-

4.12.8. Summary of findings and evidence statements

Table 41. Omega-3 fatty acids compared to placebo/inactive control for people with hypertension

Patient or population: Hypertension Intervention: Omega-3 fatty acids Comparison: Placebo/inactive control						
NTWC Rating*	Outcomes	Contributing review	Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
Blood pressure (systolic, diastolic)						
Dose: Fish-oil (EPA + DHA, capsule form, up to 13.33g/day; 8 to 24 weeks) Follow up: 8-24 weeks						
9	Systolic blood pressure (mm Hg)	Campbell 2013	MD = -2.56 (-0.58 to -4.53)#	475 (8)	⊕⊕○○ LOW ^a	Omega-3 fatty acids may result in a slight improvement in systolic blood pressure for people with hypertension.
	Diastolic blood pressure (mm Hg)		MD = -1.47 (-0.41 to -2.53)#	475 (8)	⊕⊕○○ LOW ^a	Omega-3 fatty acids may result in little to no improvement in diastolic blood pressure for people with hypertension.
8	Quality of life	-	-	-	-	No reviews found. The effect of omega-3 fatty acids on quality of life for hypertension is unknown.
8	Cardiovascular events (fatal or non-fatal myocardial infarction, excluding heart failure and if possible angina)	-	-	-	-	No reviews found. The effect of omega-3 fatty acids on cardiovascular events for hypertension is unknown.
8	Cerebrovascular events (fatal or non-fatal strokes, excluding transient ischaemic attacks if possible)	-	-	-	-	No reviews found. The effect of omega-3 fatty acids on cerebrovascular events for hypertension is unknown.
7	Death from cardiovascular	-	-	-	-	No reviews found. The effect of omega-3 fatty acids on death from cardiovascular for hypertension is unknown.
*Ratings 1-3 = of limited importance to decision making; 4-6 = important, but not critical, to decision making; 7-9 = critical for decision-making #MCID for SBP and DBP = 2mmHg (179).						
Abbreviations: CI=Confidence interval, MD=Mean difference, NR=Not reported, EPA= eicosapentaenoic acid, DHA=docosahexaenoic acid						
GRADE Working Group grades of evidence High certainty: we are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.						

Explanations

- a. Moderate risk of bias assessed for 6/8 included primary studies; there are concerns that fish oil has a strong taste and therefore study arm concealment may be compromised. On balance, key risk of bias concerns would be unlikely to impact results (no change for risk of bias). Some populations were receiving hypertensive treatment which may impact the applicability of results (downgrade one for indirectness). CI boundaries suggest different inferences based on MCID (SBP, DBP = 2mmHg) (downgraded one for imprecision). Low inconsistency supported by low I^2 values and non-statistically significant heterogeneity, point estimates favoured the intervention for the majority (no change for inconsistency). Publication bias unlikely from visual inspection of funnel plot (no change for publication bias).
-

4.13. Fibromyalgia, magnesium

4.13.1. Description of condition

Fibromyalgia is a chronic condition primarily characterized by widespread pain, fatigue, sleep disturbances, and cognitive difficulties ("fibro fog") (180, 181). It is a complex and often debilitating syndrome of multifactorial origin, with a significant impact on quality of life and functional abilities. The underlying mechanisms of fibromyalgia are not fully understood, but research suggests a dysregulation in pain processing within the central nervous system (182).

Globally, fibromyalgia is estimated to affect approximately 3-5% of the population, with a higher prevalence among women (183). No specific diagnostic test exists, and fibromyalgia is diagnosed based on clinical criteria that include chronic musculoskeletal pain and tenderness, as well as fatigue, sleep problems, cognitive disturbance (183). A careful evaluation is needed to rule out other medical conditions that might cause similar presentations, and fibromyalgia is often missed as a diagnosis when it coexists with another chronic illness, particularly when it occurs with another condition causing similar symptoms such as arthritis, endocrine disorders, depression or sleep apnoea (183).

Beyond chronic pain, fatigue, sleep difficulties, and cognitive problems, individuals with fibromyalgia may also experience a range of associated symptoms, including headaches, gastrointestinal issues, anxiety, and depression (180, 183). Fibromyalgia can also significantly hinder daily activities, employment, and social relationships, leading to a diminished quality of life. As a complex condition, fibromyalgia requires an integrated approach to management, and often includes both pharmacological and non-pharmacological interventions (183).

4.13.2. Description of the intervention

Magnesium (often abbreviated as its chemical symbol: Mg) is a naturally occurring mineral in the human body. It is a typical component of most diets, and is abundant in foods such as leafy vegetables, nuts, legumes, and grains (17). Magnesium is an essential mineral playing numerous crucial roles in the human body, including enzymatic reactions, energy production, muscle function, and bone health (16, 17).

Magnesium supplements come in several forms with varying bioavailability (absorption rate). Common forms include magnesium oxide, citrate, glycinate, or lactate (17). The recommended dietary intake (RDI) for magnesium varies depending on age and sex, typically ranging from 310-420 mg daily for adults (19). Recent evidence suggests that magnesium levels in the body may be associated with some health conditions, including Diabetes Mellitus (Type II), cardiovascular disease, osteoporosis, and migraines (17).

Magnesium may play a role in preventing central sensitization, reducing muscle pain, and Substance P and Pain Intensity Correlation. It is thought that fibromyalgia involves central sensitization, where the brain amplifies pain signals. Magnesium blocks N-methyl-D-aspartate (NMDA) receptors (184), which may prevent central sensitization and reduce pain perception. Magnesium deficiency is associated with muscle pain, fatigue, sleep disturbances, and anxiety, which are all common symptoms in fibromyalgia (185). Increased levels of substance P, a neurotransmitter linked to pain perception, are correlated with magnesium deficiency and pain intensity in fibromyalgia (185).

Oral magnesium supplements are readily available without prescription and are often marketed in tandem with one or multiple other nutritional supplements. Magnesium supplements are generally safe for most people when taken at appropriate doses⁶; though some medications may interact with magnesium (including antibiotics, diuretics and bisphosphonates). Excess magnesium is usually excreted by the kidneys as urine, though very high amounts of magnesium from dietary supplements can result in diarrhea, nausea and abdominal cramping (17).

4.13.3. Prioritised outcomes

Seven priority outcomes were identified by NTWC as part of the Outcome Prioritisation Exercise. These are listed below by order of priority. Outcomes were rated by their importance to decision-making, with those rated 7-9 being critical for decision-making.

Table 42. List of prioritised outcomes – fibromyalgia, magnesium (as assessed as part of the Outcome Prioritisation Exercise by NTWC).

#	Priority population	Priority intervention	Priority outcomes	
			NTWC Rating	Outcome domain
13	Fibromyalgia	Magnesium	9	Pain
			9	Function/Disability
			9	Global assessment of condition
			8	HRQoL
			7	Tenderness
			7	Cognitive function burden from fibromyalgia
			7	Stiffness

Abbreviations: BP=blood pressure; HRQoL=health-related quality of life; NTWC=Natural Therapies Working Group

*1-3 = of limited importance to decision making; 4-6 = important, but not critical, to decision making; 7-9 = critical for decision-making

4.13.4. Search findings

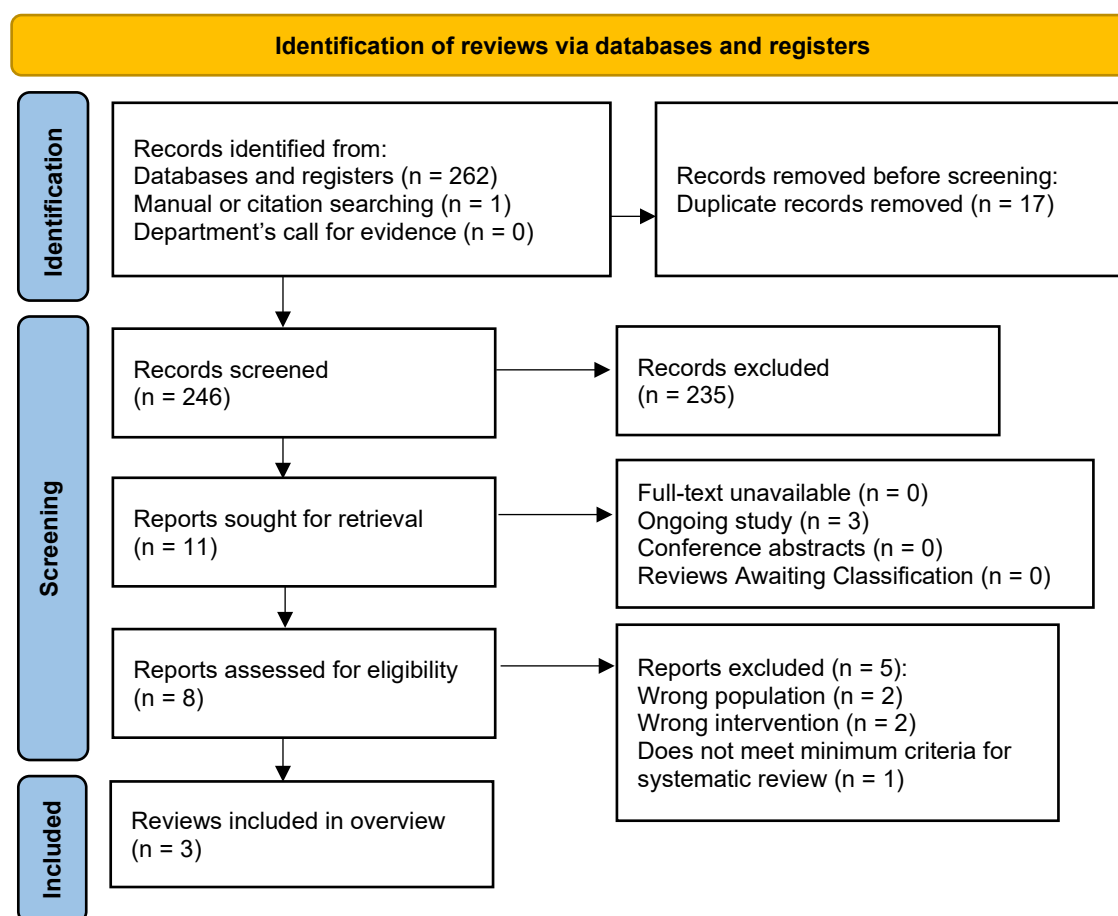
In total, 246 reviews were screened following de-duplication. None of the reviews provided by the Department's call for evidence were relevant for this population-supplement pair. After title and abstract screening, 11 reviews were sought for retrieval for full-text screening:

- 3 reviews were ongoing (citation details recorded in Appendix C4)
- 5 reviews did not meet inclusion criteria (citation details and reasons for exclusion recorded in Appendix C1)

A final 3 reviews met the inclusion criteria. Characteristics of included reviews are presented in Appendix D. A full PRISMA flowchart is presented below.

⁶ The TGA has recently updated warning labels for supplements containing B6 due to over 30 reports of peripheral neuropathy (symptoms of which include tingling, burning and numbness). The TGA notes "In many cases, people reported they were not aware they had consumed vitamin B6, as the product they were taking was a magnesium supplement." See [Why TGA made these labelling and use changes | Health supplements containing vitamin B6 can cause peripheral neuropathy | Therapeutic Goods Administration \(TGA\)](#)

Figure 13. PRISMA flowchart – fibromyalgia, magnesium.



4.13.5. Description of included reviews

Three reviews were identified as eligible for inclusion; review characteristics are reported in detail in Appendix D. Two systematic reviews were conducted in 2003 and 2010, each evaluating complementary and alternative medicine therapies for fibromyalgia (186), and fibromyalgia and CFS/ME (187). Both included RCTs and NSRIs. A Cochrane review was conducted in 2018 examining combination pharmacotherapies for the treatment of fibromyalgia, including only RCTs (188).

4.13.6. Assessment of risk of bias of included systematic reviews

Risk of bias of the assessments of the included reviews, as appraised using the ROBIS tool, are presented below. Full assessments are reported in Appendix F.

Table 43. Summary of ROBIS assessments – fibromyalgia, magnesium

Review ID	ROBIS Domains				Overall risk of bias
	Domain 1: Study eligibility criteria	Domain 2: Identification and selection of studies	Domain 3: Data collection and study appraisal	Domain 4: Synthesis and findings	

Holdcraft 2003	Low	Unclear	High	Unclear	High risk
Porter 2010	Low	Unclear	High	Unclear	High risk
Thorpe 2018	Low	Low	Low	Unclear	Low risk

4.13.7. Results

Preferred contributing reviews are listed in the population-intervention matrix in Table 44. The only review assessed as having a low risk of bias was Thorpe 2018 - a Cochrane review (188) – it was also the most recent and thus was the preferred contributing review. One small primary study (24 participants) evaluated the effects of a combination of magnesium and malic acid supplements in people with fibromyalgia (188).

Table 44. Contributing reviews for each population and intervention/co-intervention combination – fibromyalgia, magnesium.

	With fibromyalgia	At risk of fibromyalgia
Magnesium VS placebo/sham/inactive control	-	-
Magnesium + naturopathy co-intervention VS placebo/sham/inactive control	Thorpe 2018	-

4.13.8. Summary of findings and evidence statements

Table 45. Magnesium + naturopathy cointervention compared to placebo for people with fibromyalgia

Patient or population: Fibromyalgia Intervention: Magnesium + naturopathy cointervention Comparison: Placebo/inactive control						
NTWC Rating*	Outcomes	Contributing review	Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
Pain						
9	Dose: 150 mg Magnesium hydroxide + 600 mg malic acid, twice per day for 4 weeks Assessed with: VAS Follow up: 4, 6 10 and 12 weeks	Thorpe 2018	Effect sizes NR#	20 (1)	⊕○○○ VERY LOW ^a	The evidence is very uncertain about the effect of magnesium + naturopathy cointervention on pain in people with fibromyalgia.
Function/Disability						
9	Dose: 150 mg Magnesium hydroxide + 600 mg malic acid, twice per day for 4 weeks Assessed with: Health Assessment Questionnaire Follow up: 4, 6 10 and 12 weeks	Thorpe 2018	Effect sizes NR#	20 (1)	⊕○○○ VERY LOW ^a	The evidence is very uncertain about the effect of magnesium + naturopathy cointervention on function/disability in people with fibromyalgia.
9	Global assessment of condition	-	-	-	-	No reviews found. The effect of magnesium + naturopathy cointervention on global assessment of condition for people with fibromyalgia is unknown.
8	HRQoL	-	-	-	-	No reviews found. The effect of magnesium + naturopathy cointervention on HRQoL for people with fibromyalgia is unknown.
Tenderness						
7	Intervention: 150 mg Magnesium hydroxide + 600 mg malic acid, twice per day for 4 weeks Assessed with: Tender point index (sum of tenderness severity at 18 tender points); tender point average (mean tenderness at 18 tender points measured by dolorimeter) Follow up: 4, 6 10 and 12 weeks	Thorpe 2018	Effect sizes NR#	20 (1)	⊕○○○ VERY LOW ^a	The evidence is very uncertain about the effect of magnesium + naturopathy cointervention on tenderness in people with fibromyalgia.
7	Cognitive function burden from fibromyalgia	-	-	-	-	No reviews found. The effect of magnesium + naturopathy cointervention on cognitive function burden from fibromyalgia for people with fibromyalgia is unknown.

7	Stiffness	-	-	-	-	No reviews found. The effect of magnesium + naturopathy cointervention on stiffness for people with fibromyalgia is unknown.
<p>*Ratings 1-3 = of limited importance to decision making; 4-6 = important, but not critical, to decision making; 7-9 = critical for decision-making #Absolute risk differences or relative effect sizes not reported. Unable to make judgements about MCID or direction of effect.</p> <p>Abbreviations: CI=Confidence interval, MD=Mean difference, NR=Not reported, VAS=Visual Analogue Scale, HRQoL=health related quality of life</p> <p>GRADE Working Group grades of evidence High certainty: we are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.</p>						
<p>Explanations</p> <p>a. High risk of bias in primary study from incomplete outcome data and sample sizes not consistent with reported attrition (downgraded one for risk of bias). No effect estimates provided to assess precision. Additionally, very small sample size raising concerns about optimal information size (downgraded 3 for very serious imprecision). No inconsistency due to singular study (no change for inconsistency). Publication bias not assessed likely due to insufficient number of studies (no change for publication bias).</p>						

4.14. Recurrent infection/s (including urinary tract infections, cystitis, respiratory tract infection, otitis media in children), zinc

4.14.1. Description of condition

Recurrent infections refer to a pattern of experiencing multiple infections of a similar type within a specific timeframe. Common types of recurrent infections include recurrent respiratory infections (189), recurrent skin infections (e.g. erysipelas, cellulitis, impetigo) (190) and recurrent urinary tract infections (UTIs) (191). While anyone can experience occasional infections, recurrent infections can be chronic and debilitating, significantly impacting quality of life, leading to missed school or work, social limitations, and potential long-term health consequences if the underlying cause remains unaddressed. Symptoms of recurrent infections depend on the infection site and type. General symptoms accompanying infections often include fever, fatigue, inflammation, and pain.

Diagnosing the root cause of recurrent infections involves a thorough history, physical examination, and potentially laboratory tests like blood counts, immune function testing, and genetic analysis. This helps rule out underlying conditions like immunodeficiencies, anatomical abnormalities, or chronic diseases. First line of treatment for most infections is antibiotics, though infections that are recurrent often require prevention. Prevention and treatment options that are used in current practice, with varying evidence, include behavioural changes and naturopathy-based interventions such as dietary supplementation (e.g. cranberry products, probiotics) and Chinese herbal medicines (192).

Many infections are at risk of recurrence (depending on their definition). To keep scope manageable, articles were only included if they were focused on prevention and treatment of relapse, reinfection, or recurrence of an infection (and not on initial infection that may reoccur). This had to be clearly specified in the review of interest.

4.14.2. Description of the intervention

Zinc (Zn) is an essential trace mineral required by the human body in small amounts. Zinc plays crucial physiological roles, serving as a cofactor for numerous enzymes involved in diverse processes including DNA synthesis, immune function, wound healing, and growth and development (131, 132). Zinc is found in most tissues, but is particularly concentrated in bones, muscles, the prostate gland, and the eyes (132). The body cannot manufacture zinc, and so intake via diet or supplementation to maintain adequate levels is needed. Zinc is naturally found in various foods, including animal sources (oysters, red meat, poultry, and seafood), plant sources (legumes, nuts, seeds, and whole grains) and fortified foods (some breakfast cereals and other processed products). It is also available in dietary supplements, often in the forms of zinc gluconate, zinc sulfate, or zinc citrate and typically taken orally in capsule, tablet, or liquid form (131). The recommended dietary intake for zinc varies depending on age and sex, but generally ranges from 8-14 mg daily for adults (19). Zinc supplements often provide slightly higher doses than RDI. This is generally safe, though excessive intake can lead to gastrointestinal issues and may interfere with the absorption of other minerals.

It is hypothesised that zinc's immune-boosting, anti-inflammatory (193), and antiviral properties contribute to its role in preventing recurrent infections (194). Zinc is essential for the proper functioning of immune cells, including T cells, B cells, and natural killer (NK) cells. It enhances

immune responses, helping the body fight off infections more effectively. Zinc also possesses anti-inflammatory properties by inhibiting NF-κB signalling. This modulation of inflammatory pathways may limit the severity of infections, including recurrent ones. In addition, Zinc has been shown to have an antiviral effect by inhibiting virus-host cell interactions and viral replication. This effect may reduce vulnerability to infectious diseases. As above, Zinc supplementation is thought to decrease oxidative stress biomarkers, maintaining cellular health, thereby zinc indirectly supports immune function and reduces infection risk.

4.14.3. Prioritised outcomes

Six priority outcomes were identified by NTWC as part of the Outcome Prioritisation Exercise. These are listed below by order of priority. Outcomes were rated by their importance to decision-making, with those rated 7-9 being critical for decision-making.

Table 46. List of prioritised outcomes – recurrent infections, zinc (as assessed as part of the Outcome Prioritisation Exercise by NTWC).

#	Priority population	Priority intervention	Priority outcomes	
			NTWC Rating	Outcome domain
14	Recurrent infection/s (including urinary tract infections, cystitis, respiratory tract infection, otitis media in children, etc.)	Zinc	9	Overall control of disease (recurrence)
			9	Overall severity of symptoms
			8	Time (days) from initiation of treatment to resolution of symptoms
			8	HRQoL
			7	Use of acute and prophylactic antibiotics for conditions where antibiotics are indicated
			7	Duration of hospital stay

Abbreviations: BP=blood pressure; HRQoL=health-related quality of life; NTWC=Natural Therapies Working Group

*1-3 = of limited importance to decision making; 4-6 = important, but not critical, to decision making; 7-9 = critical for decision-making

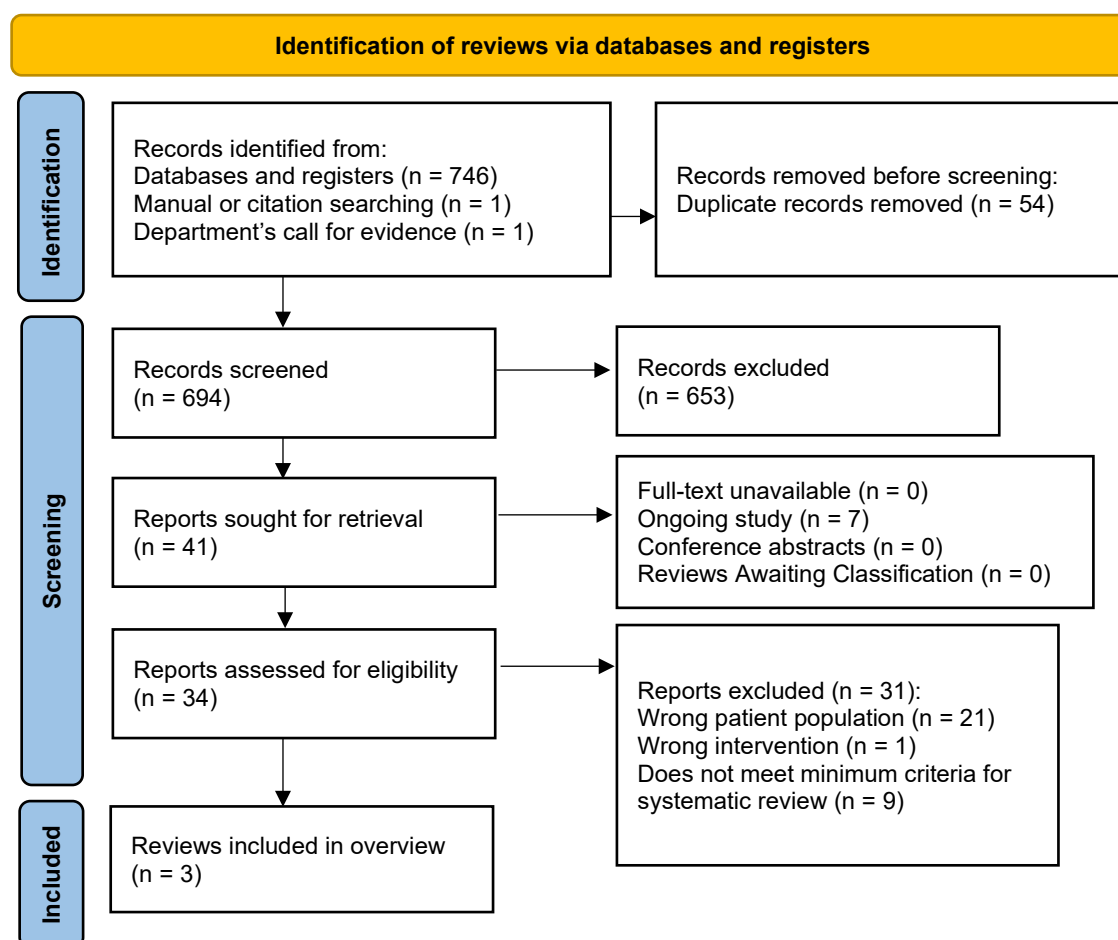
4.14.4. Search findings

In total, 694 reviews were screened following de-duplication. One review provided by the Department's call for evidence was relevant to this population-supplement pair, which was already identified in database searching and excluded as a duplicate (see Appendix C2). After title and abstract screening, 41 reviews were sought for retrieval for full-text screening:

- 7 reviews were ongoing (citation details recorded in Appendix C4)
- 31 reviews did not meet inclusion criteria (citation details and reasons for exclusion recorded in Appendix C1)

A final 3 reviews met the inclusion criteria. Characteristics of included reviews are presented in Appendix D. A full PRISMA flowchart is presented below.

Figure 14. PRISMA flowchart – recurrent infections, zinc.



4.14.5. Description of included reviews

Three reviews were identified as eligible for inclusion. Two reviews were Cochrane reviews including only RCTs (195, 196), and one was a systematic review including controlled trials (197). Reviews were conducted in 2014, 2016 and 2020. A detailed summary of characteristics of the included reviews are reported in Appendix D.

Each review examined a recurrent infection in children. One Cochrane review aimed specifically to review zinc supplementation for prevention of otitis media. Two reviews summarised preventative and therapeutic interventions more broadly (including zinc supplementation) for URTI in children with Down's Syndrome (197) and pulmonary infection in children with cystic fibrosis (195).

4.14.6. Assessment of risk of bias of included reviews

Risk of bias of the systematic reviews, as assessed using the ROBIS tool, is presented below. Full assessments are reported in Appendix F.

Table 47. Summary of ROBIS assessments – recurrent infections, zinc

Review ID	ROBIS Domains	
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	Domain 1: Study eligibility criteria	Domain 2: Identification and selection of studies	Domain 3: Data collection and study appraisal	Domain 4: Synthesis and findings	Overall risk of bias
Gulani 2014	Low	Low	Low	Unclear	Low risk
Hurley 2020	Low	Low	Low	Unclear	Low risk
Manikam 2016	Low	Low	Low	Unclear	Unclear risk

4.14.7. Results

Preferred contributing reviews are listed in the population-intervention matrix in Table 48. As each review reported on a different type of infection (otitis media, URTI, pulmonary infection), results from all reviews which correspond to relevant outcomes have been presented.

Table 48. Contributing reviews for types of populations and interventions examined in each review – recurrent infections, zinc

	With recurrent infections	At risk of recurrent infections
Zinc VS placebo/sham/inactive control	Gulani 2014 Hurley 2020 Manikam 2016	-
Zinc + naturopathy co-intervention VS placebo/sham/inactive control	-	-

4.14.8. Summary of findings and evidence statements

Table 49. Zinc compared to placebo for recurrent infection/s

Patient or population: Recurrent infection/s Intervention: Zinc Comparison: Placebo						
NTWC Rating*	Outcomes	Contributing review	Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
9	Overall control of disease (recurrence)					
	Number of participants with at least one episode of definite infection during follow-up					
	Condition: Otitis media Population: Children aged 6 to 30 months Dose: Zinc gluconate syrup taken daily for 4 months (contained 10 mg elemental zinc for infants and 20 mg for older children); 12.5 mg zinc sulphate, in tablet form, daily (except Sundays) Follow-up: 6 months	Gulani 2014	Risk ratio = 1.05 (0.82, 1.36)#	3191 (2)	⊕⊕○○ LOW ^a	Zinc may not reduce the number of children with at least one episode of definite infection during follow-up for children with recurrent infection (otitis media).
	Number of episodes of definite acute otitis media per participant per year of follow-up					
	Condition: Otitis media Population: Children aged 2 to 12 months Dose: Zinc acetate 70 mg once weekly for 12 months Follow-up: 6 months	Gulani 2014	Rate ratio = 0.69 (95% CI: 0.61 to 0.79)^	1621 (1)	⊕⊕⊕○ MODERATE ^b	Zinc probably results in a reduction in the number of episodes of definite infection per person per year for children with recurrent infection (otitis media).
9	Number of people with URTI					
	Condition: URTI Population: Children with Down's syndrome aged 1 to 19 years Dose: Zinc sulfate supplements 25mg/d for 1–9 year and 50 mg/d for older children Follow-up: 6 months	Manikam 2016	Effect sizes NR.	64 (1)	⊕○○○ VERY LOW ^c	The evidence is very uncertain about the effect of zinc on the number of children with Down's syndrome who have recurrent URTI.
9	Overall severity of symptoms					
	Per cent (%) predicted forced expiratory volume in one second (FEV1)					
	Condition: Pulmonary infection Population: Children with cystic fibrosis	Hurley 2020	Study 1: MD = -5.46 (-19.44, 8.52)§	62 (2)	⊕○○○ VERY LOW ^d	The evidence is very uncertain about the effect of zinc on per cent (%) predicted forced expiratory volume in one

	Dose: 30mg zinc per day Follow-up: 24 months		Study 2: Median (IQR) predicted FEV1 % = 8.97% (-18.23%, 0.33%) lower than baseline in the zinc group; 9.55% (-9.59%, 12.88%) higher in the placebo group§			second (FEV1) in children with cystic fibrosis and recurrent pulmonary infection.
	Per cent (%) predicted forced vital capacity (FVC) Condition: Pulmonary infection Population: Children with cystic fibrosis Dose: 30mg zinc per day Follow-up: 24 months	Hurley 2020	MD = -1.75 (-13.09, 9.59)†	25 (1)	⊕○○○ VERY LOW ^e	The evidence is very uncertain about the effect of zinc on per cent (%) predicted forced vital capacity (FVC) in children with cystic fibrosis and recurrent pulmonary infection.
8	Time (days) from initiation of treatment to resolution of symptoms	-	-	-	-	No reviews found. The effect of zinc on time (days) from initiation of treatment to resolution of symptoms in recurrent infections is unknown.
8	HRQoL	-	-	-	-	No reviews found. The effect of zinc on HRQoL in recurrent infections is unknown.
Use of acute and prophylactic antibiotics for conditions where antibiotics are indicated						
	Number of participants requiring intravenous antibiotics Condition: Pulmonary infection Population: Children with cystic fibrosis Dose: 30mg Zinc once daily Follow-up: 24 months	Hurley 2020	179 per 1000 more in the zinc group ^o RR = 1.85 (0.65 to 5.26) ^o	37 (1)	⊕○○○ VERY LOW ^f	The evidence is very uncertain about the effect of zinc on the number of people requiring intravenous antibiotics in children with cystic fibrosis and recurrent pulmonary infection.
7	Antibiotic use Condition: Pulmonary infection Population: Children with cystic fibrosis Dose: 30mg Zinc once daily Follow-up: 24 months Measure: Number of days on intravenous or oral antibiotics; number of antibiotics needed	Hurley 2020	Study 1: Fewer oral antibiotics needed by participants in the zinc group: MD = -17.74 (-26.98, -8.50); need for IV antibiotics: MD = 0.52 (-3.07, 4.11). Study 2: Effect size NR	62 (2)	⊕○○○ VERY LOW ^d	The evidence is very uncertain about the effect of zinc on antibiotic in children with cystic fibrosis and recurrent pulmonary infection.
	Antibiotic use Condition: URTI Population: Children with Down's syndrome	Manikam 2016	Effect sizes NR	64 (1)	⊕○○○ VERY LOW ^c	The evidence is very uncertain about the effect of zinc on the number of children with Down's

Evidence Evaluation for the Clinical Effectiveness of Selected Nutritional Supplements Prescribed in Naturopathy: Overview of Systematic Reviews

4.15. Diabetes (Type II) (including metabolic syndrome), Antioxidants (specifically CoQ10 and ALA)

4.15.1. Description of condition

Diabetes Mellitus (Type 2; T2DM) is a chronic metabolic disorder characterised by persistent hyperglycaemia (elevated blood sugar). It arises from insulin resistance (diminished response to insulin) and progressive pancreatic beta-cell dysfunction, leading to insufficient insulin production (200). In its early stages, T2DM may present with subtle or no symptoms, however common symptoms can include increased thirst, frequent urination, fatigue, blurred vision, slow-healing wounds, and recurrent infections (200). Diagnosis of T2DM relies on established diagnostic criteria that typically involve blood tests measuring glucose levels (200).

Type 2 diabetes affects almost 4.6% of the Australian population, with higher rates in specific populations (e.g. Aboriginal and Torres Strait Islander peoples) and in areas of higher remoteness (201). In the previous two decades, the incidence of Type 2 diabetes in Australia increased almost 3-fold between, to over 1.2 million people (201). Risk factors for Type 2 diabetes include age, sex, and family history, as well as biomedical factors (such as high blood pressure or obesity), and behavioural risk factors (such as smoking status, diet or physical activity) (201). Unmanaged diabetes can lead to serious long-term complications, including cardiovascular disease, kidney failure, blindness, nerve damage, and lower limb amputations (202), which can place a significant burden on individuals and healthcare systems.

4.15.2. Description of the intervention

Oxidative stress is associated with cellular damage and an increased risk of chronic diseases like cardiovascular disease, cancer, and neurodegenerative disorders. Antioxidants are substances which can prevent or delay oxidations of cell components, thereby reducing oxidative stress (140). Coenzyme Q10 (CoQ10) and alpha-lipoic acid (ALA) are two antioxidant molecules which are commonly taken to increase and support antioxidant levels in the body (140). CoQ10, also called ubiquinone, is present in all human cells and is found in various foods like organ meats, oily fish, and whole grains (142). ALA is an antioxidant made in small amounts by the human body and found in foods like red meat and certain vegetables (e.g. potatoes, beets, spinach and broccoli) (143). Both CoQ10 and ALA are available as dietary supplement in capsules, tablets, and even liquid forms.

Antioxidants may play a role in managing type 2 diabetes through mechanisms of reducing oxidative stress, improving insulin sensitivity, protecting beta cells and their anti-inflammatory effects. In diabetes, oxidative stress occurs due to an imbalance between free radicals and antioxidants, the antioxidants could work through neutralizing free radicals, preventing cellular damage and reducing the risk of diabetes-related complications. Oxidative stress can also harm Beta cells in the pancreas (which produce insulin) so antioxidants may help protect beta cells. Some antioxidants, such as alpha-lipoic acid are thought to enhance insulin sensitivity (203). Improved insulin sensitivity helps regulate blood sugar levels and prevents hyperglycaemia. Chronic inflammation contributes to insulin resistance and diabetes. Antioxidants may reduce inflammation, promoting better glucose control.

4.15.3. Prioritised outcomes

Seven priority outcomes were identified by NTWC as part of the Outcome Prioritisation Exercise. These are listed below by order of priority. Outcomes were rated by their importance to decision-making, with those rated 7-9 being critical for decision-making.

Table 50. List of prioritised outcomes – Diabetes (Type II) (including metabolic syndrome), antioxidants (specifically CoQ10 and ALA) (as assessed as part of the Outcome Prioritisation Exercise by NTWC).

#	Priority population	Priority intervention	Priority outcomes	
			NTWC Rating	Outcome domain
15	Diabetes (Type II) (including metabolic syndrome)	Antioxidants (specifically: CoQ10 and alpha-lipoic acid)	8	Glycaemic control <ul style="list-style-type: none"> • HbA1c • Fasting glucose • Fasting insulin • Homeostatic model assessment of insulin resistance • 2 hour post-prandial blood sugar • Hyperglycemia (frequency) • Hypoglycemia (frequency)
			8	Blood pressure <ul style="list-style-type: none"> • Systolic • Diastolic
			8	Oxidative stress <ul style="list-style-type: none"> • Malonaldehyde • Total antioxidant status/capacity • Free oxygen radical test • Reactive oxygen metabolites • Biological antioxidant potential • Lipo-peroxidation products • Catalase • Glutathione peroxidase
			8	Diabetes related symptoms
			8	Overall diabetes related complications
			8	HRQoL
			8	Incidence of type 2 diabetes mellitus (relevant for at-risk populations)

Abbreviations: BP=blood pressure; HRQoL=health-related quality of life; NTWC=Natural Therapies Working Group

*1-3 = of limited importance to decision making; 4-6 = important, but not critical, to decision making; 7-9 = critical for decision-making

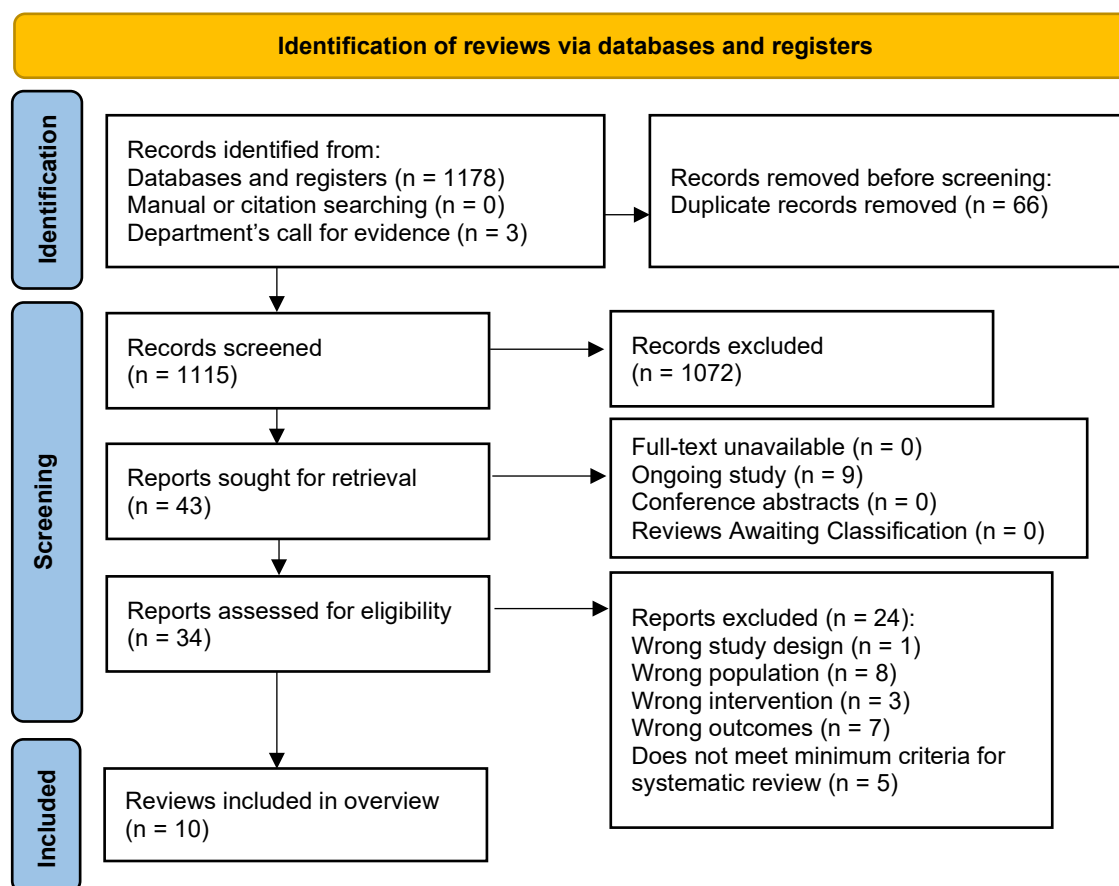
4.15.4. Search findings

In total, 1,115 reviews were screened following de-duplication. Three reviews provided through the Department's call for evidence were relevant to this population-supplement pair; two were duplicates already identified in database searching and one was screened (see Appendix C2). After title and abstract screening, 43 reviews were sought for retrieval for full-text screening:

- 9 reviews were ongoing (citation details recorded in Appendix C4)
- 24 reviews did not meet inclusion criteria (citation details and reasons for exclusion recorded in Appendix C1)

A final 10 reviews met the inclusion criteria. Characteristics of included reviews are presented in Appendix D. A full PRISMA flowchart is presented below.

Figure 15. PRISMA flowchart – Diabetes (Type II) (including metabolic syndrome), antioxidants (specifically CoQ10 and ALA).



4.15.5. Description of included reviews

Ten reviews were identified as eligible for inclusion; review characteristics are reported in detail in Appendix D. The included reviews were conducted between 2018 and 2023. The only study design included across all reviews was RCTs, and most reviews included a meta-analysis.

One review examined the impact of antioxidant supplementation in obese individuals (42), considered as a population at risk of T2DM (204). Six reviews examined one antioxidant – Coenzyme Q10 (205-207) or ALA (208-210) – specifically for patients with T2DM (or diabetes/inflammatory and metabolic factors generally, where T2DM results could be independently determined). Four reviews included multiple dietary supplements for diabetes, which included antioxidants (211-214).

4.15.6. Assessment of risk of bias of included systematic reviews

Risk of bias of the systematic reviews, as assessed using the ROBIS tool, is presented below. Full assessments are reported in Appendix F.

Table 51. Summary of ROBIS assessments – Diabetes (Type II) (including metabolic syndrome), antioxidants (specifically CoQ10 and ALA)

Review ID	ROBIS Domains	
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	Domain 1: Study eligibility criteria	Domain 2: Identification and selection of studies	Domain 3: Data collection and study appraisal	Domain 4: Synthesis and findings	Overall risk of bias
Araújo 2022	Low	Low	Low	Low	Low risk
Dludla 2020	Low	Low	Low	Low	Low risk
Dludla 2023	Low	Unclear	Unclear	Unclear	Unclear risk
Huang 2018	Low	Unclear	Low	Low	Low risk
Huo 2022	Low	Low	Low	Low	Low risk
Jibril 2022	Low	Unclear	Low	Low	Low risk
Kim 2022	Low	Low	Low	Low	Low risk
Rahimlou 2019	Low	Low	Unclear	Low	Low risk
Wang 2022	Low	Unclear	Unclear	Low	Unclear risk
Zhang 2018	Low	Low	Low	High	High risk

4.15.7. Results

Preferred contributing reviews are listed in the population-intervention matrix in Table 52. Evidence from the most relevant, recent and/or comprehensive review was chosen for each outcome. Jibril et al. (2022) was selected as the preferred review (equally most recent and lowest risk of bias, and most comprehensive conducting a dose-response meta-analysis) and reported outcomes for fasting blood glucose (FBG), Hb1AC and blood pressures. Dludla et al. (2020) and Kim et al. (2022) were the preferred reviews to report on fasting blood insulin and HOMA-IR, respectively (205).

Wang et al. (2022) conducted a meta-analysis examining the use of antioxidants for obese individuals (BMI ≥ 30 kg/m²) (42), considered a population at risk of T2DM.

Table 52. Contributing reviews for types of populations and interventions examined in each review – Diabetes (Type II) (including metabolic syndrome), antioxidants (specifically CoQ10 and ALA)

	With T2DM	At risk of T2DM
Antioxidants VS placebo/sham/inactive control	Jibril 2022 Kim 2022 Dludla 2020	Wang 2022
Antioxidants VS placebo/sham/inactive control	-	-

4.15.8. Summary of findings and evidence statements

Table 53. Antioxidants compared to placebo/inactive control for people with T2DM

Patient or population: T2DM Intervention: Antioxidants Comparison: Placebo/inactive control						
NTWC Rating*	Outcomes	Contributing review	Relative effect (95% CI)^	Nº of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
Glycaemic control						
8	Fasting blood insulin Dose: CoQ10 100-200mg daily for 8 to 12 weeks Follow-up: 8 to 12 weeks	Dludla 2020	SMD = 0.19 (-0.30 to 0.68)^	308 (5)	⊕○○○ VERY LOW ^a	The evidence is very uncertain about the effect of antioxidants on fasting blood insulin in T2DM.
	Fasting blood glucose Dose: ALA 200-1200mg daily for 8 to 26 weeks Follow-up: 8 to 26 weeks	Jibril 2022	MD = -6.08 mg/dL (-9.74 to -2.42)#	620 (9)	⊕⊕⊕○ MODERATE ^b	Antioxidants probably result in little to no difference in fasting blood glucose in T2DM.
	Hb1AC Dose: ALA 570-800mg daily for 12 to 52 weeks Follow-up: 4 to 52 weeks	Jibril 2022	MD = -0.17% (-0.30 to -0.05)#	782 (11)	⊕⊕⊕○ MODERATE ^c	Antioxidants probably result in little to no difference in Hb1AC levels in T2DM.
	HOMA-IR Dose: CoQ10 100-200mg daily for 8 to 24 weeks Follow-up: 8 to 24 weeks	Kim 2022	MD = -0.83; (-2.12 to 0.47)#	228 (4)	⊕○○○ VERY LOW ^d	The evidence is very uncertain about the effect of antioxidants on HOMA-IR in T2DM.
Blood pressure						
8	Systolic blood pressure Dose: ALA 570-800mg daily for 4 to 52 weeks Follow-up: 4 to 52 weeks	Jibril 2022	MD = -1.71 mmHg; (-5.48 to 2.07)§	388 (5)	⊕○○○ VERY LOW ^e	The evidence is very uncertain about the effect of antioxidants on systolic blood pressure in T2DM.
	Diastolic blood pressure Dose: ALA 570-800mg daily for 4 to 52 weeks Follow-up: 4 to 52 weeks	Jibril 2022	MD = 1.03 mmHg; (0.05 to 2.02)§	388 (5)	⊕⊕⊕○ MODERATE ^f	Antioxidants probably result in little to no difference in diastolic blood pressure in T2DM.
8	Oxidative stress	-	-	-	-	No reviews found. The effect of antioxidants on oxidative stress in T2DM is unknown.

8	Diabetes related symptoms	-	-	-	-	No reviews found. The effect of antioxidants on diabetes related symptoms in T2DM is unknown.
8	Overall diabetes related complications	-	-	-	-	No reviews found. The effect of antioxidants on overall diabetes-related complications in T2DM is unknown.
8	HRQoL	-	-	-	-	No reviews found. The effect of antioxidants on HRQoL in T2DM is unknown.

*Ratings 1-3 = of limited importance to decision making; 4-6 = important, but not critical, to decision making; 7-9 = critical for decision-making

^SMDs of 0.2, 0.5, and 0.8 are considered small, medium, and large, respectively.

MCID for fasting blood glucose = 29 mg/dL (1.60mmol/L) (MCID for Hb1AC = 0.5%; MCID for HOMA-IR reported as 0.05 (209, 215).

\$MCID for SBP and DBP = 2mmHg (179).

Abbreviations: ALA=alpha-lipoic acid, CoQ10=Coenzyme Q10, CI=Confidence interval, MD=Mean difference, NR=Not reported, T2DM=Type II Diabetes Mellitus; Homeostatic Model Assessment for Insulin Resistance=HOMA-ir; Hb1AC=Hemoglobin A1C

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

- No serious risk of bias concerns (no change for risk of bias). CI boundaries suggest very different inferences based on MCID (SMD = 0.2), CI appreciably crosses the threshold(s) of effect (downgraded 2 for serious imprecision). Inconsistency supported by high I^2 values and statistically significant heterogeneity, point estimates varied in direction of effect, limited overlap of CIs (downgrade one for inconsistency). Publication bias unlikely, supported by visual inspection of funnel plot (no change for publication bias).
- No serious risk of bias concerns (no change for risk of bias). Inconsistency supported by high I^2 values and statistically significant heterogeneity, however, while point estimates sometimes crossed direction of effect threshold, on balance, they were similar and confidence intervals overlapped (no change for inconsistency). CI boundaries fall within MCID (FBG = 29 mg/dL) (no change for imprecision). Suspected publication bias based on inspection of funnel plot and Egger's test (downgrade one).
- No serious risk of bias concerns (no change for risk of bias). Inconsistency supported by high I^2 values and statistically significant heterogeneity; point estimates varied and lay on different sides of the direction of effect threshold (downgrade one for inconsistency). CI boundaries fall within MCID (Hb1AC = 0.5%) (no change for imprecision). Publication bias unlikely supported by non-significant Egger test and visual inspection of funnel plot (no change for publication bias).
- Risks of bias in included primary studies (most RCTs did not report randomization methods and allocation concealment) (downgrade one for risk of bias). Inconsistency supported by high I^2 values and statistically significant heterogeneity, however, while point estimates varied greatly and sometimes crossed direction of effect threshold, point estimates favoured the intervention for the majority (no change for inconsistency). Small sample size, CI boundaries suggest very different inferences based on MCID (HOMA-IR = 0.05) (downgraded 2 for serious imprecision). Publication bias unlikely supported by non-significant Egger test and visual inspection of funnel plot (no change for publication bias).
- No serious risk of bias concerns (no change for risk of bias). Inconsistency supported by high I^2 values and statistically significant heterogeneity, point estimates varied in direction of effect, limited overlap of CIs (downgrade one for inconsistency). Small sample size, CI boundaries suggest very different inferences based on MCID (SBP = 2mmHg) (downgraded 2 for serious imprecision). Suspected publication bias based on inspection of funnel plot (downgrade one for publication bias).
- Risks of bias concerns in most included primary studies as assessed by review authors (downgrade one for risk of bias). Low inconsistency supported by low I^2 values and non-statistically significant heterogeneity, point estimates generally favoured the intervention (no change for inconsistency). Pooled effect confidence intervals were within MCID (DBP = 2mmHg) (no change for imprecision). Publication bias unlikely supported by non-significant Egger test and visual inspection of funnel plot (no change for publication bias).

Table 54. Antioxidants compared to placebo/inactive control for people at risk of T2DM

Patient or population: **At risk of T2DM**

Intervention: **Antioxidants**

Comparison: **Placebo/inactive control**

NTWC Rating*	Outcomes	Contributing review	Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
8	Glycaemic control Condition: Obesity (BMI ≥30 kg/m ²) Dosage: Range of antioxidants and dosage amounts Follow up: 30 days to 6 months					
	Fasting blood glucose	Wang 2022	SMD = -4.92 (-6.87 to -2.98)^	315 (6)	⊕⊕⊕○ MODERATE ^a	Antioxidants probably result in a large improvement in fasting blood glucose levels in people at risk of T2DM.
	HOMA-IR	Wang 2022	MD = -0.45 (-0.61 to -0.30)#	395 (8)	⊕⊕⊕○ MODERATE ^b	Antioxidants probably result in a large improvement in HOMA-ir in people at risk of T2DM.
8	Blood pressure	-	-	-	-	No reviews found. The effect of antioxidants on blood pressure in people at risk of T2DM is unknown.
8	Oxidative stress	-	-	-	-	No reviews found. The effect of antioxidants on oxidative stress in people at risk of T2DM is unknown.
8	Diabetes related symptoms	-	-	-	-	No reviews found. The effect of antioxidants on diabetes related symptoms in people at risk of T2DM is unknown.
8	Overall diabetes related complications	-	-	-	-	No reviews found. The effect of antioxidants on overall diabetes-related complications in people at risk of T2DM is unknown.
8	HRQoL	-	-	-	-	No reviews found. The effect of antioxidants on HRQoL in people at risk of T2DM is unknown.
8	Incidence of T2DM	-	-	-	-	No reviews found. The effect of antioxidants on incidence of T2DM in people at risk of T2DM is unknown.

*Ratings 1-3 = of limited importance to decision making; 4-6 = important, but not critical, to decision making; 7-9 = critical for decision-making

^aSMDs of 0.2, 0.5, and 0.8 are considered small, medium, and large, respectively.

#MCID for HOMA-IR reported as 0.05 (209, 215).

Abbreviations: BMI=Body mass index, CVD=cardiovascular disease, T2DM=Type II Diabetes Mellitus, CoQ10= Coenzyme Q10, CI=Confidence interval, MD=Mean difference, NR=Not reported, HRQoL=health-related quality of life; Homeostatic Model Assessment for Insulin Resistance=HOMA-ir

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Some concerns about risk of bias primarily related to allocation concealment, however unlikely to impact FBG as this is an objective measure (no change for risk of bias). Low inconsistency supported by low I^2 values and non-statistically significant heterogeneity, point estimates generally favoured the intervention with overlapping CIs (no change for inconsistency). Small sample size, CIs are wider than MCID, though lower bound would still indicate clinically important difference (downgrade one for imprecision). Publication bias unlikely supported by non-significant Egger test and visual inspection of funnel plot (no change for publication bias).

b. Some concerns about risk of bias primarily related to allocation concealment, however unlikely to impact HOMA-IR as this is an objective measure (no change for risk of bias). Low inconsistency supported by low I^2 values and non-statistically significant heterogeneity, point estimates generally favoured the intervention with overlapping CIs (no change for inconsistency). Small sample size, CIs are wider than MCID, though lower bound would still indicate clinically important difference (downgrade one for imprecision). Publication bias unlikely supported by non-significant Egger test and visual inspection of funnel plot (no change for publication bias).

5. Discussion

This overview was designed to summarise the evidence relating to nutritional supplementation in the context of naturopathy in preventing and/or treating injury, disease, medical conditions or pre-clinical conditions. The target populations, interventions, and conditions of interest were determined as those which are most commonly seen by naturopaths in Australia. This overview is a companion review to the systematic review of primary studies on the effects of whole system, multi-modal or single modal interventions delivered in the context of naturopathic practice, for preventing and treating health conditions. However, for this overview, the intervention (supplement) was not required to be delivered by a naturopath for the review to be included for analysis in this report. As per the protocol, the review did not compare different forms of the intervention (e.g. different strains of probiotic) or different ways of administering. When considering the effectiveness of naturopathy, the companion review on western herbal medicine should also be considered.

5.1. Summary of main results

The objective was to provide an overview of systematic review evidence for 15 priority population-supplement pairs.

In total, 480 systematic reviews were sought for full text assessment, of which 97 were included in this overview. Results from 26 reviews contribute to the findings, chosen as the most relevant, comprehensive and with the lowest risk of bias for a population, intervention, and priority outcome. In total, 437 citations were provided through the Department's public call for evidence or by other key stakeholders. Following screening and assessment, one review met inclusion criteria and was included (96). For most population-supplement pairs, results were not available for many prioritised outcomes, and therefore are unknown.

An overview of the key findings and appraisal of the certainty of evidence for each outcome where evidence was identified is presented below. Where the GRADE assessment was "very low", we have not provided key results given the uncertainty of evidence.

There was **moderate certainty** evidence that nutritional supplements probably **improve** some key health outcomes for people with and at-risk of four conditions:

- Probiotics probably increases the number of people with global symptom improvement of 10%-50% when assessed as a dichotomous outcome for people with irritable bowel syndrome (IBS) although probiotics **may have little to no effect** on global IBS symptoms or response on average (continuous scale).
- Antioxidants (specifically CoQ10 and ALA) probably reduce global fatigue severity/burden in people with fatigue (including myalgic encephalomyelitis and Chronic Fatigue Syndrome).
- Zinc **probably reduces** recurrent infections when measured by the number of episodes of definite infection per child per year in children with otitis media (although when recurrence is measured by the number of children with at least one episode of infection during follow-up, zinc may have little to no effect on recurrent infections in children with otitis media).
- Antioxidants (specifically CoQ10 and ALA) probably improves fasting blood glucose and HOMA-IR (glycaemic control) in people at risk of Type II Diabetes Mellitus due to obesity.

There was **low certainty** evidence that nutritional supplements may **improve** some key health outcomes for people with and at-risk of four conditions:

- Magnesium + a naturopathy co-intervention may improve anxiety-related emotional functioning/mental health burden in people with anxiety.
- Probiotics may improve stool consistency and health-related quality of life, and slightly improve abdominal pain and stool frequency in people with IBS.
- Magnesium may reduce headache pain frequency and the number of days with migraine in people with headache and migraine.
- Omega-3 fatty acids may slightly improve systolic blood pressure in people with hypertension.

There was **moderate certainty** evidence that nutritional supplements probably result in **little to no difference** for some key health outcomes for people with and at-risk of two conditions:

- Omega-3 fatty acids probably has little to no effect on depression-related emotional functioning/mental health burden in people at-risk of perinatal depression.
- Antioxidants (specifically CoQ10 and ALA) probably have little to no effect on fasting blood glucose and Hb1AC levels (glycaemic control), or diastolic blood pressure in people with Type II Diabetes.

There was **low certainty** evidence that nutritional supplements probably result in **little to no difference** for some key health outcomes for people with and at-risk of four conditions:

- Omega-3 fatty acids may have little to no effect on the number of people with response (50% improvement) or remission (no or low depression) in people with depression.
- Omega-3 fatty acids may have little to no effect on diastolic blood pressure in people with hypertension.

The overview found only very low certainty evidence for the following pairings: magnesium for insomnia/sleeping disorders, zinc for atopic disorders, magnesium for fibromyalgia, and for some priority outcomes within the conditions listed above.

No relevant reviews were identified for: magnesium for stress (perceived, occupational), cruciferous indoles for dysmenorrhea, cruciferous indoles for premenstrual syndrome (PMS), and magnesium for arthritis/osteoarthritis.

5.2. Overall completeness and applicability of evidence

There were very few reviews identified which directly matched the PICO's under consideration. Definitions of conditions varied across reviews, particularly for conditions like fatigue where there is no agreed upon definition outside of clinical diagnoses of CFS or ME. In addition, it is important to note that some priority populations were a broad class of conditions, although the identified reviews may only examine one or two subclasses (e.g. for atopic disorders, only reviews related to atopic dermatitis were identified). Although this was taken into consideration within GRADE assessments, it still limits overall applicability of many of the results to the research question.

This overview only included results from reviews published in English. We do not believe non-inclusion of other language reviews will impact findings, as there were only four identified (Table F2) and these were superseded in each case by more recent reviews for the priority population-supplement pair (though we were unable to assess whether the non-English reviews were at lower risk of bias or were more comprehensive). However, databases in languages other than

English were not searched, and therefore there is potential for language bias impacting overall completeness.

For some of the priority population-conditions, the most recent reviews were 10 years old or older, which means that primary studies published after reviews were published are not considered in the evidence. No checks were completed to assess if evidence was still current, due to the overall volume of work for the overview and the additional work required to conduct systematic checks (effectively a new systematic review). Consideration of more recent primary studies was intended, but due to the volume of literature, was not completed (listed as a deviation from the protocol in Appendix G). As this overview only summarised the results of included reviews without reanalysis data from primary studies would not have been incorporated into findings.

5.3. Certainty of the evidence

Certainty of the evidence was undertaken using GRADE for each outcome. There was no evidence that was assessed as high certainty. There was moderate and low certainty evidence for certain outcomes in certain population-supplement pairs. Most outcomes had very low certainty evidence, where confidence in the present results was so limited that interpretation was not provided. Overall, the ability to draw conclusions about the efficacy of nutritional supplements in the naturopathic context is limited by the paucity and quality of evidence.

Preferred reviews were selected based on risk of bias, comprehensiveness and recency. Reviews which did not conduct risk of bias assessment of primary studies were excluded, which may have resulted in inclusion and assessment of better quality evidence. Risk of bias of primary studies was not reappraised.

GRADE assessments of the evidence were often downgraded based on risk of bias of included primary studies. The risk or bias or quality of primary studies within reviews was primarily assessed using the Cochrane Risk of Bias tool or the Jadad scale.

Downgrading for publication bias only occurred if the preferred review included an assessment of publication bias. Downgrading for inconsistency was rare.

As noted in the previous section, there was often mismatch between the PICO of the preferred reviews and the objectives, and therefore evidence was often downgraded for indirectness.

The certainty of evidence was generally downgraded for issues with imprecision related to sample size and wide confidence intervals that were compatible with both important benefit and little or no difference.

5.4. Potential biases in the overview process

There are several potential biases in the overview process, although steps were taken to reduce bias. This overview was completed in line with a pre-determined protocol; differences between intended methods and completed methods are outlined in Appendix G. None of the overview authors have conflicts of interest; none of the overview authors were involved in any of the included reviews or primary studies.

As this overview summarised the available data from preferred reviews, we relied on accurate reporting of information in each of the reviews. Risk of bias assessments of primary studies were not independently completed by overview authors due to volume. Thus, across included reviews,

different risk of bias assessment measures and procedures, as well as review author subjectivity, may introduce bias to the overview.

Interpretation of results was completed independently by overview authors. Subjectivity of authors is a limitation of the overview process, particularly in regard to choosing preferred reviews as there was not rigid criteria for selection (per protocol). Rationales for selection of reviews, interpretation of results and GRADE judgements (downgrading the certainty of evidence) are provided for transparency.

Many of the identified reviews were ongoing with published data not available, and therefore unable to be included in the overview. There is also potential that search or eligibility limitations for practicality reasons (such as language restrictions and not searching grey literature) may mean that information has been missed.

5.5. Agreements and disagreements with other studies or reviews

This review is a companion review to Naturopathy review A (PROSPERO: CRD42021266381), which considers the evidence on whole-system naturopathy. The review of whole-system naturopathy considered conditions for which eligible studies were available. The included populations/conditions were cancer, type 2 diabetes, polycystic ovarian syndrome, overweight and obesity, anxiety, multiple sclerosis, cardiovascular disease, allergic rhinitis, low back pain, rotator cuff tendinitis, menopausal symptoms, and cardiovascular disease risk. The results of that review indicate that naturopathy may improve some conditions and outcomes and not others. However, for most of the populations considered there was very low certainty, so an interpretation was not made, and none of the conditions for which there was low certainty had comparable conditions assessed in the current overview. Thus, it is not possible to assess consistency of results across the companion reviews. It was considered likely that the available evidence for whole-system naturopathic treatment was limited due to it being a system of health care and not an individual treatment. The purpose of the current overview on nutritional supplements was therefore to provide a companion review for conditions for which Australians commonly see naturopaths, and the “tools of the trade” (supplements) which naturopaths commonly use for those conditions. A second companion review on “tools or the trade” examines western herbal medicines.

5.6. Limitations

5.6.1. At the review and primary study level

There were some limitations in the included systematic reviews and their respective primary studies which contributed to the findings of this overview. These are discussed above in Section 5.3. However, by reporting results from the most relevant and comprehensive reviews with the lowest risk of bias, many potential limitations were minimised. Many reviews did not attempt (or did not report attempts) to minimise error in screening, extraction, and risk of bias appraisal; where this could not be dealt with in choice of review, it was considered in GRADE assessments. Some reviews only searched English databases or included English studies, although this was taken into consideration during ROBIS assessments.

In addition, some of contributing reviews were dated, which may mean more recent primary studies which could influence results were not considered. Many ongoing reviews were identified which had not yet been published and data were not available. These may provide more updated

findings once published. For many of population-supplement pairs, only a few studies exist (of varying quality, and usually with small sample sizes), so evidence was sparse.

5.6.2. At the overview level

This overview was limited to assessment of the evidence for certain conditions and groups of people to inform the Australian Government about health policy decisions for private health insurance rebates. This overview was not designed to assess all the reasons that people use supplements within naturopathic practice, or the reasons naturopaths prescribe supplements and was not intended to inform individual choices about using supplements.

Interpretations of effect size were conducted with reference to minimal clinically important differences (MCID) of outcomes sourced from the literature. However, the overview authors do not have clinical expertise in the specific population/conditions of interest. Given there are multiple methods of determining MCIDs, clinical experts may consider different values more appropriate.

In some cases, the most relevant and comprehensive review did not report sufficient results required for a Summary of Findings table, or key information was missing. Sometimes this was due to issues at the primary study level, which would not have been addressed with re-analysis, though sometimes this was at the review level, where re-analysis during the overview may have been beneficial. This reflects a limitation of the chosen overview procedures.

The outcomes assessed were limited to those prioritised by NTWC. For many population-intervention pairs, evidence was only available for a few of the outcomes.

It was out of scope to consider safety or cost-effectiveness in this review; therefore no information is included about these.

Both probiotics and antioxidants have many different chemical formulas/strains, but as per the protocol these comparisons were out of scope for the current review. Future work evaluating the most efficacious combinations of ingredients for key outcomes in specific conditions is encouraged.

6. Authors' conclusions

This report was commissioned by the Australian Government as part of the Natural Therapies Review, with findings intended to inform decisions relating to whether private health insurance cover should be reinstated to naturopathy. As such, specific recommendations are not provided.

The evidence provided moderate certainty that some nutritional supplements can improve some key health outcomes in specific conditions, specifically, probiotics for irritable bowel syndrome (IBS); antioxidants (specifically CoQ10 and alpha-lipoic acid) for fatigue (general) (including myalgic encephalomyelitis and Chronic Fatigue Syndrome) and antioxidants for people at risk of Type II Diabetes. There is limited evidence that other nutritional supplements for certain conditions that are frequently used in the naturopathic context in Australia may be effective.

This review is a companion review to Naturopathy review A (PROSPERO: CRD42021266381), which considers the evidence on the overall effectiveness of naturopathy. In considering the evidence on the overall effectiveness of naturopathy, the current overview should be considered in context with Naturopathy A and the second companion review, an overview of systematic

reviews that assesses the clinical effectiveness of western herbal medicines for certain conditions and populations (PROSPERO CRD42021243337).

7. Author contributions and declaration of interests

All authors report no known conflicts of interest.

MD, KM and CG developed the protocols and performed the searches of the databases. KM and CG carried out the article screening and MD was involved in the discussion for final decision making. KM and CG carried out the article assessment and data extraction. All authors were involved in evidence synthesis and final report writing.

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