
| RESEARCH ARTICLE

Effectiveness and Safety of Dietary Interventions across ADHD Subgroups Defined by Baseline Nutrient Deficiency, Gastrointestinal Symptoms, and Medication Status: A Protocol for a Systematic Review

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| ABSTRACT

Background; Dietary interventions for attention-deficit/hyperactivity disorder (ADHD) have attracted increasing interest as potentially modifiable adjuncts to standard care. However, the evidence base remains fragmented, methodologically heterogeneous, and clinically difficult to interpret. Existing narrative evidence suggests that unhealthy dietary patterns may be associated with worse ADHD outcomes, whereas selected nutritional approaches, including supplementation and restrictive diets, may offer benefit in some patients. At the same time, restrictive approaches may carry meaningful harms, including nutritional deficiency and poor growth, and available evidence indicates that such interventions do not work uniformly across all patients. The literature therefore points toward a subgroup-sensitive, precision-oriented approach rather than broad claims of benefit for all individuals with ADHD. Yet no systematic review has specifically synthesized treatment effects according to baseline nutrient deficiency, gastrointestinal symptoms, and medication status. Objective; To systematically evaluate whether the effectiveness and safety of dietary interventions in children, adolescents, and adults with ADHD differ according to baseline nutrient deficiency, gastrointestinal symptom status, and medication status. Methods; This review will be conducted as a systematic review of intervention effectiveness with planned subgroup synthesis. Randomized controlled trials will form the core evidence base, and comparative nonrandomized studies of interventions will also be considered where they contribute clinically relevant evidence on effectiveness, subgroup response, or harms not adequately captured by randomized designs. Eligible interventions will include nutrient supplementation, restrictive or elimination diets, whole-diet interventions, and microbiome-targeted nutritional interventions. Primary outcomes will be change in core ADHD symptoms and functional impairment. Secondary outcomes will include executive function, emotional and behavioral symptoms, sleep outcomes, gastrointestinal symptoms, biomarkers relevant to nutrient status or inflammation, adverse events, nutritional deficiencies, growth outcomes, and treatment adherence or acceptability. Searches will be conducted in MEDLINE via PubMed, Embase via Elsevier, PsycINFO via EBSCOhost, Cochrane CENTRAL via the Cochrane Library, Web of Science Core Collection via Clarivate, and Scopus via Elsevier, supplemented by trial registries, backward and forward citation searching, reference list screening, and contact with corresponding authors when needed. Search reporting will follow PRISMA-S. Two reviewers will independently screen studies, assess full texts, conduct risk-of-bias appraisal, and oversee data extraction. RoB 2 will be used for randomized trials and ROBINS-I for comparative nonrandomized studies. Structured narrative synthesis will be the primary synthesis method, with random-effects meta-analysis undertaken only where clinical and methodological homogeneity permits. Certainty of evidence will be assessed using GRADE. Registration; The protocol will be registered prospectively in PROSPERO before full-text screening begins.

| KEYWORDS

ADHD; attention-deficit/hyperactivity disorder; dietary intervention; nutrition; elimination diet; vitamin D; omega-3; probiotic; gastrointestinal symptoms; medication status; subgroup analysis; nutrient deficiency.

| ARTICLE INFORMATION

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1. Introduction

1.1 Rationale

Attention-deficit/hyperactivity disorder is a common neurodevelopmental disorder characterized by developmentally inappropriate levels of inattention, hyperactivity, and impulsivity, often accompanied by difficulties in executive function, emotional regulation, and day-to-day functioning. Interest in dietary and nutritional interventions has expanded because

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standard treatment alone does not address all patient needs and because diet is, at least in principle, a modifiable exposure with potential therapeutic relevance. Existing narrative evidence suggests that unhealthy dietary patterns are positively associated with ADHD, while healthier dietary patterns may be inversely associated. Altered levels of nutrients such as vitamin D, iron, zinc, and polyunsaturated fatty acids have also been associated with aggravation and progression of ADHD symptoms.

However, the present literature is not mature enough to support broad clinical generalizations. The most directly relevant synthesis in this area is a narrative review rather than a formal systematic review, and its authors explicitly acknowledge that they did not conduct a detailed search strategy or an objective appraisal of study quality and result robustness. They further conclude that more robust scientific evidence is needed before dietary interventions can be confidently implemented as part of ADHD therapy. This is not a minor technical limitation. It means that the field lacks a decision-grade synthesis of who benefits, under which conditions, and at what potential cost.

The strongest conceptual gap concerns treatment effect modification. Existing evidence indicates that dietary interventions do not work for all patients and that a precision or personalized medicine approach should be considered, particularly given the phenotypic heterogeneity of ADHD. The same review explicitly calls for future studies to identify subgroups of individuals with ADHD who may benefit from such diets. From a clinical standpoint, this is the decisive issue. It is also inseparable from safety, because restrictive and elimination diets may lead to nutritional deficiencies and poor growth in children and should therefore be used with caution and rigorous monitoring.

This subgroup problem is reinforced by adjacent literature on the gut microbiome and neurodevelopmental disorders. The broader microbiome literature highlights serious inconsistency across studies, limited support for causal inference, and the need for future work incorporating longitudinal designs, dietary characteristics, physiological characteristics, metabolites, and more powerful microbial analytic tools. Although that literature is not specific to dietary intervention trials alone, it underscores the same point: heterogeneity is structural, not incidental, and clinically meaningful subgroup variables must be handled explicitly rather than treated as background noise.

A systematic review focused specifically on subgroup benefit and safety trade-offs is therefore needed. This protocol responds to that gap by asking whether dietary interventions in ADHD differ in effectiveness and harms according to baseline nutrient deficiency, gastrointestinal symptoms, and medication status. The protocol is structured in line with JBI expectations that review questions, objectives, and inclusion criteria should be explicitly aligned, and that protocol conduct should be transparent, reproducible, and prospectively specified.

1.2 Objectives

The primary objective is to systematically evaluate whether the effectiveness and safety of dietary interventions in people with ADHD differ according to baseline nutrient deficiency, gastrointestinal symptom status, and medication status.

The secondary objectives are:

1. To assess the effects of different classes of dietary interventions on core ADHD symptoms, functional impairment, sleep, physical and gastrointestinal symptoms, and adverse events.
2. To identify the ADHD subgroups most likely to derive clinically meaningful benefit from dietary interventions.
3. To evaluate harms associated with dietary interventions, particularly nutritional deficiency, growth-related harms, and poor tolerability in restrictive interventions.
4. To compare the strength and credibility of inference derived from randomized controlled trials and eligible comparative nonrandomized studies of interventions.

1.3 Review questions

The primary review question is:

Among children, adolescents, and adults with ADHD, which subgroups defined by baseline nutrient deficiency, gastrointestinal symptoms, and medication status derive the greatest benefit from dietary interventions compared with placebo, usual care, no intervention, medication alone, or alternative dietary interventions?

The secondary review questions are:

1. Do patients with ADHD and baseline nutrient deficiency show greater benefit from targeted supplementation than those without deficiency?
2. Do patients with gastrointestinal symptoms experience differential benefit from elimination diets, few-foods diets, or microbiome-targeted nutritional interventions?

3. Do medication-naive, currently medicated, medication-resistant, or off-medication patients show different patterns of response?
4. Do the harms and tolerability profiles of dietary interventions differ across these subgroups?

2. Methods

2.1 Protocol and registration

This review will be conducted using an a priori protocol. The protocol will be registered prospectively in PROSPERO before full-text screening begins. Any amendments to eligibility criteria, subgroup definitions, outcomes, or synthesis methods will be documented with the date of change, the rationale, and the anticipated implications for interpretation. These amendments will be reported in the final review. JBI guidance states that review protocols should specify whether a protocol exists, where it is available, and whether amendments occurred.

2.2 Review type

This study is designed as a systematic review of intervention effectiveness with planned subgroup synthesis. Randomized controlled trials will constitute the principal evidence base. Comparative nonrandomized studies of interventions will also be considered where they provide relevant evidence on effectiveness, subgroup response, or harms that randomized trials may not capture adequately. Contemporary AHRQ guidance recognizes that nonrandomized studies of interventions are valuable sources of information about both effectiveness and harms, not merely supplementary evidence to fill randomised evidence gaps. At the same time, their inclusion requires explicit attention to decisional relevance, internal validity, confounding, selection bias, and transparent reporting.

2.3 Eligibility criteria

2.3.1 Participants

Eligible studies will include children, adolescents, or adults with a diagnosis of ADHD established using DSM criteria, ICD criteria, a validated clinical assessment process, or a clinician diagnosis described sufficiently to permit appraisal of diagnostic credibility.

Studies will be excluded if they:

- involve mixed populations in which ADHD-specific data cannot be separated from other neurodevelopmental conditions such as autism spectrum disorder;
- do not clearly define ADHD diagnosis;
- are non-human, in vitro, or preclinical.

2.3.2 Interventions

Eligible interventions will be dietary or nutritional interventions intended to modify ADHD symptoms or related outcomes. These will include:

- nutrient supplementation, such as vitamin D, zinc, iron, magnesium, omega-3/polyunsaturated fatty acids, or multivitamin formulations;
- restrictive or elimination diets, including few-foods and oligoantigenic diets;
- whole-diet interventions, such as Mediterranean-style or other structured healthy eating approaches;
- microbiome-targeted nutritional interventions, including probiotics, prebiotics, synbiotics, and postbiotics where their use is appropriately nutritional or dietary in character.

Interventions will be excluded if they are:

- purely psychological;
- purely pharmacological without a nutritional component;
- observational studies of dietary patterns without an intervention component.

2.3.3 Comparators

Eligible comparators will include placebo, usual care, no intervention, active comparators, medication alone, or alternative dietary or nutritional interventions.

2.3.4 Outcomes

Primary outcomes:

1. Change in core ADHD symptoms.

2. Change in functional impairment.

Secondary outcomes:

- executive function;
- emotional and behavioral symptoms;
- sleep outcomes;
- gastrointestinal symptoms or physical complaints;
- biomarkers relevant to nutrient status or inflammation;
- adverse events;
- nutritional deficiencies;
- growth outcomes;
- treatment adherence and acceptability.

2.3.5 Study designs

The primary evidence base will include:

- randomized controlled trials;
- cluster randomized controlled trials;
- nonrandomized controlled trials;
- prospective comparative cohort studies;
- retrospective comparative cohort studies;
- controlled before-after studies;
- interrupted time series, where the design permits interpretation of intervention effects.

Single-group studies will not be included in the main synthesis of comparative effectiveness. However, they may be considered in a limited safety synthesis if they contribute important evidence on harms, nutritional deficiency, growth effects, or tolerability. This distinction is justified because AHRQ guidance emphasizes that inclusion of nonrandomized evidence should reflect the decisional question and the likely contribution of that evidence to understanding both effectiveness and harms.

2.3.6 Context

Studies conducted in clinical, community, school, or household settings will be eligible.

2.4 Operational definitions of subgroups

2.4.1 Baseline nutrient deficiency

Nutrient deficiency will be classified hierarchically as:

1. biochemical deficiency defined using study-reported laboratory thresholds;
2. clinical deficiency or insufficiency where laboratory cut-offs are unavailable;
3. low nutrient intake, recorded as a separate category and not merged with biochemical deficiency.

This distinction is essential because the source literature identifies altered levels of nutrients such as vitamin D, iron, zinc, and polyunsaturated fatty acids as potentially relevant to ADHD progression, but low intake and biochemical deficiency are not equivalent constructs.

2.4.2 Gastrointestinal symptoms

Gastrointestinal subgroup classification will distinguish:

- any gastrointestinal symptoms;
- functional gastrointestinal symptoms;
- specific symptoms such as constipation, diarrhea, abdominal pain, and bloating;
- formal gastrointestinal diagnoses where reported.

2.4.3 Medication status

Medication status will be categorized, at minimum, as:

- medication-naive;
- currently medicated;
- stimulant-treated;

- non-stimulant-treated;
- off medication or washout;
- medication-resistant.

This categorization is clinically relevant because existing ADHD diet literature suggests that restrictive diets may be especially pertinent in children who are resistant to medication or too young to start pharmacotherapy.

2.4.4 Information sources

The following databases and platforms will be searched:

- MEDLINE via PubMed;
- Embase via Elsevier;
- PsycINFO via EBSCOhost;
- Cochrane CENTRAL via the Cochrane Library;
- Web of Science Core Collection via Clarivate;
- Scopus via Elsevier.

The following study registries will also be searched:

- ClinicalTrials.gov;
- World Health Organization International Clinical Trials Registry Platform;
- EU Clinical Trials Register, where relevant.

Other sources will include:

- backward citation searching;
- forward citation searching;
- reference lists of included studies and relevant reviews;
- contact with corresponding authors for missing subgroup or outcome data;
- dissertations and theses databases, where feasible;
- conference proceedings, where feasible.

PRISMA-S requires explicit reporting of each individual database searched, the platform used, any study registries searched, citation searching methods, contact with authors, and other search methods. JBI also recommends backward and forward citation searching as supplementary strategies for complex review questions.

2.4.5 Search strategy

The search strategy will combine controlled vocabulary terms and free-text keywords. The main concept blocks will address:

1. ADHD;
2. dietary interventions;
3. subgroup effects or effect modifiers;
4. nutrient deficiency, gastrointestinal symptoms, and medication status.

Full search strategies for all databases, registers, and other formal sources will be reported verbatim in an appendix, together with limits, filters, and field tags, in accordance with PRISMA-S. No date limits will be applied unless justified during search piloting. No language restrictions will be applied where feasible. If restrictions or validated filters are used, they will be reported and justified. The date of the last search for each source will be documented. Search strategies will be peer reviewed by an information specialist or librarian where feasible. PRISMA-S explicitly requires full search strategies, documentation of limits and filters, search dates, and search peer review where undertaken.

The search will be updated before final analysis if a substantial interval has elapsed. JBI states that reviews should not be submitted with searches older than 12 months and notes that 6 months is ideal, particularly for evolving topics.

2.6 Study records

2.6.1 Data management

References will be managed using EndNote or Zotero, and screening and data extraction will be managed using Covidence or Rayyan. Software and versions will be reported in the final review.

2.6.2 Deduplication

Duplicate records will first be removed using software-assisted deduplication. Potential duplicates excluded automatically will be manually reviewed before permanent removal. Duplicates identified later during screening or extraction will be documented separately. The number of records identified from each source and the deduplication process will be reported transparently. PRISMA-S explicitly requires reporting of deduplication processes and software.

2.6.3 Selection process

Two reviewers will independently screen titles and abstracts against the eligibility criteria. Full texts of potentially relevant articles will then be assessed independently by the same two reviewers. Disagreements will be resolved by discussion and, where necessary, by consultation with a third reviewer. Reasons for exclusion at the full-text stage will be recorded. The selection process will be presented using a PRISMA flow diagram. JBI expects protocols to specify eligibility criteria and selection procedures clearly.

2.6.4 Data collection process

A piloted data extraction form will be developed and refined before full extraction begins. One reviewer will perform initial extraction and a second reviewer will verify all extracted data, or two reviewers will extract independently during a calibration phase until sufficient agreement is achieved.

2.6.5 Data items

The following variables will be extracted:

- study identification details;
- study design;
- country and setting;
- participant characteristics;
- ADHD diagnostic criteria and method;
- intervention and comparator details;
- duration of follow-up;
- subgroup definitions;
- outcome definitions and instruments;
- overall and subgroup-specific results;
- interaction tests, if reported;
- adverse events;
- nutritional harms;
- funding sources and conflicts of interest;
- numerical data required for effect size calculation.

Additional subgroup-credibility fields will include:

- whether subgroup analyses were prespecified or post hoc;
- whether confounding adjustment was undertaken;
- which confounders were adjusted for;
- whether medication stability was defined and maintained;
- whether dietary co-interventions or background dietary changes were monitored.

This added detail is necessary because the ADHD dietary literature identifies residual confounding, unmeasured lifestyle factors, measurement error in food frequency questionnaires, and short or methodologically weak intervention studies as major threats to interpretation.

2.7 Outcomes and prioritization

Primary outcomes will be analyzed as the main basis for subgroup inference. Secondary outcomes will be used to refine understanding of response profiles, harms, and mechanism-relevant correlates, but will not override the primary clinical outcomes.

2.8 Risk of bias in individual studies

Randomized controlled trials will be assessed using RoB 2. Comparative nonrandomized studies will be assessed using ROBINS-I. If single-group harms studies are included, they will be appraised using an appropriate design-specific tool and interpreted cautiously outside the main comparative synthesis.

Particular attention will be paid to:

- subgroup ascertainment credibility;
- selective reporting of subgroup findings;
- adequacy of baseline subgroup measurement;
- confounding by indication;
- imbalance in co-interventions;
- medication-related confounding;
- adherence-related bias.

3. Data synthesis

3.1 Criteria for quantitative synthesis

The primary synthesis will be a structured narrative synthesis organized first by subgroup domain and then by intervention class.

Subgroup domains:

1. baseline nutrient deficiency;
2. gastrointestinal symptoms;
3. medication status.

Intervention classes:

- supplementation;
- elimination or restrictive diets;
- microbiome-targeted nutritional interventions;
- whole-diet interventions.

Meta-analysis will be conducted only where there is sufficient clinical and methodological homogeneity in:

- participant characteristics;
- intervention class;
- comparator;
- outcome definition and measurement;
- subgroup definition;
- follow-up timing.

3.2 Summary measures

Where pooling is appropriate, random-effects meta-analysis will be used by default. Standardized mean differences will be used for continuous outcomes measured on different scales. Risk ratios or odds ratios will be used for binary outcomes such as responder status or adverse events.

3.3 Additional analyses

Randomized and comparative nonrandomized studies will be synthesized separately unless there is a clear methodological and clinical justification for combining them. Statistical heterogeneity will be assessed using I^2 and τ^2 . Where sufficient studies are available, subgroup analysis or meta-regression will be used to explore heterogeneity.

Planned sensitivity analyses will include:

- randomized controlled trials only;
- low-risk-of-bias studies only;
- studies using biochemical ascertainment of nutrient deficiency only;
- studies with clearly reported medication stability only;

- exclusion of studies at serious risk of confounding.

3.4 Meta-biases

Where protocols, trial registrations, or registry records are available, they will be compared with published reports to assess selective outcome reporting or missing subgroup results. If enough studies are pooled quantitatively, small-study effects and publication bias will be explored using appropriate graphical and statistical methods.

3.4 Confidence in cumulative evidence

Certainty of evidence will be assessed using GRADE for primary and major secondary outcomes. JBI endorses use of GRADE regardless of whether the synthesis is quantitative or narrative. Subgroup-specific conclusions will be graded cautiously, particularly where evidence derives from post hoc analyses, sparse data, serious inconsistency, or substantial indirectness.

4. Discussion

This protocol addresses a central weakness in the ADHD nutrition literature: the tendency to discuss dietary interventions as though they exert uniform effects across a clinically heterogeneous population. The current evidence does not support that assumption. Existing narrative review evidence explicitly states that dietary interventions do not work for all patients and that future studies should identify which subgroups benefit. The same body of work also warns that restrictive interventions may lead to nutritional deficiency and poor growth, underscoring the need to place safety at the centre of the evidence synthesis rather than at its margins.

The review also addresses a second methodological problem: overreliance on broad average effects in a field characterized by structural heterogeneity. Observational dietary studies cannot establish causality, residual confounding remains likely even after statistical adjustment, lifestyle factors such as physical activity, screen time, and sleep may distort observed associations, and many intervention studies have serious limitations, including short duration, lack of randomization, inadequate placebo control, and limited prospective monitoring. A review that ignores these weaknesses will inevitably overstate what the field knows.

The strength of the present protocol lies in its explicit focus on subgroup benefit and safety trade-offs, its alignment with PRISMA-S and JBI expectations for reproducibility and reporting, and its principled inclusion of comparative nonrandomized evidence where such evidence is decisively relevant to harms or real-world subgroup response. The main limitation is that subgroup definitions may vary markedly across studies and many subgroup findings may be exploratory rather than prespecified. As a result, the final review may yield stronger conclusions about where uncertainty lies than about definitive clinical recommendations. That is not a weakness of the review. It is an honest reflection of the field.

4.1 Amendments

Any protocol amendment occurring after registration will be documented with the date, rationale, and implications for the review. The PROSPERO record will be updated where appropriate, and all amendments will be reported in the final publication.

4.2 Timeline and current review stage

At the time of registration, the review question, eligibility criteria, and preliminary search strategy will be finalized, and full-text screening will not yet have commenced.

Indicative timeline:

- Month 1: finalize protocol and register;
- Month 2: run searches and deduplicate records;
- Months 3-4: title/abstract and full-text screening;
- Month 5: data extraction and risk-of-bias appraisal;
- Month 6: synthesis and GRADE assessment;
- Month 7: manuscript drafting.

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Conflicts of Interest: The authors declare no conflict of interest.

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Appendix 1. Draft PubMed search strategy

Database: MEDLINE via PubMed

Platform: PubMed

Draft date: [insert date of final search]

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(
"Attention Deficit Disorder with Hyperactivity"[Mesh]
OR ADHD[tiab]
OR "attention deficit hyperactivity disorder"[tiab]
OR "attention-deficit/hyperactivity disorder"[tiab]
OR "attention deficit disorder"[tiab]
)
AND
(
"Diet"[Mesh]
OR "Diet Therapy"[Mesh]
OR "Nutritional Physiological Phenomena"[Mesh]
OR "Nutritional Status"[Mesh]
OR "Dietary Supplements"[Mesh]
OR "Probiotics"[Mesh]
OR diet*[tiab]
OR nutrition*[tiab]
OR supplement*[tiab]
OR "dietary intervention*"[tiab]
OR "diet therapy"[tiab]
OR "vitamin D"[tiab]
OR zinc[tiab]
OR iron[tiab]
OR magnesium[tiab]
OR "omega-3"[tiab]
OR PUFA[tiab]
OR PUFAs[tiab]
OR "polyunsaturated fatty acid*"[tiab]
OR probiotic*[tiab]
OR prebiotic*[tiab]
OR synbiotic*[tiab]
OR postbiotic*[tiab]
OR "few-foods diet"[tiab]
OR "few foods diet"[tiab]
OR "elimination diet"[tiab]
OR "oligoantigenic diet"[tiab]
OR Mediterranean[tiab]
OR "Mediterranean diet"[tiab]
OR "healthy diet"[tiab]
OR "diet pattern*"[tiab]
)
AND
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(
  subgroup*[tiab]
  OR stratif*[tiab]
  OR "effect modifier"*[tiab]
  OR responder*[tiab]
  OR predict*[tiab]
  OR interaction*[tiab]
  OR heterogeneity[tiab]
)
AND
(
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  OR insufficien*[tiab]
  OR ferritin[tiab]
  OR "nutrient status"[tiab]
  OR gastrointestinal[tiab]
  OR "GI symptom"*[tiab]
  OR constipation[tiab]
  OR diarrhea[tiab]
  OR diarrhoea[tiab]
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  OR bloating[tiab]
  OR medication[tiab]
  OR medicated[tiab]
  OR "medication-naive"[tiab]
  OR "drug-naive"[tiab]
  OR stimulant*[tiab]
  OR methylphenidate[tiab]
  OR atomoxetine[tiab]
  OR "off medication"[tiab]
  OR washout[tiab]
  OR "treatment resistant"[tiab]
  OR "medication resistant"[tiab]
)

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Notes for final execution:

1. The PubMed strategy should be peer reviewed before final use if an information specialist is available. PRISMA-S recommends reporting any search peer review process.
2. The final manuscript should report the exact strategy as run, the date last searched, any limits or filters applied, and the total records retrieved from PubMed.
3. Equivalent controlled vocabulary and syntax will be adapted for Embase, PsycINFO, CENTRAL, Web of Science, and Scopus. JBI recommends combining controlled vocabulary with keywords and presenting full search strategies for reproducibility.