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Systemic Review

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Iron Supplementation in the Prevention and Treatment of Iron Deficiency Anemia in Children Under Five: A Systematic Review

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ABSTRACT

Iron deficiency anemia (IDA) is a public health issue in children under 5 years of age, mostly in low and middle-income countries. Iron supplements are given for preventing or treating iron deficiency. **Objectives:** To systematically evaluate the effectiveness, safety considerations, and implementation characteristics of iron supplementation strategies used for the prevention and treatment of iron deficiency anemia among children under five years of age. **Methods:** An electronic literature search was performed in PubMed, Scopus, and Cochrane Library for any studies written in English and published between 2019 and 2024. Primary human research of any type assessing iron supplementation in children aged 0-59 months was encompassed. This excluded systematic reviews, meta-analyses, case reports, and animal studies. The study selection was in accordance with PRISMA 2020. The synthesis of the data was conducted narratively, and the risk of bias was assessed using the RoB-2 and Joanna Briggs Institute tools. **Results:** A total of 15 studies reported significant improvements in hemoglobin levels and iron status after iron supplementation, using either oral ferrous preparations or iron-containing micronutrient powders. Prevention measures reduced the rate of anemia, and treatment supplementation successfully corrected known IDA. High anemia burden, inconsistent adherence to supplementation, and dietary iron deficit were observed in observational studies. **Conclusions:** Iron supplementation remains an effective approach for preventing and treating iron deficiency anemia in children. Optimizing program delivery, adherence, and safety monitoring is essential to maximize benefits, particularly in resource-limited settings.

INTRODUCTION

Iron deficiency anemia is among the most widespread nutritional illnesses that impacts children below the age of five years all over the world, and has been a leading cause of childhood morbidity and poor development [1]. The young children are especially susceptible because of the rapid growth, higher iron demands, and lack of bioavailable iron in the food. The situation is further worsened in the low- and middle-income nations by food insecurity, frequent infections, and insufficient health services [2, 3]. Iron supplementation is commonly used in early childhood to address low iron stores and reduce the risk of anemia. Widespread strategies are oral iron preparations, as well as the iron-containing multi-micronutrient powders administered via community and healthcare settings [4]. Although their earlier-evidence has demonstrated their hematologic benefits, adherence, safety in high-infection settings, and inconsistent program effectiveness have raised concerns necessitating a new assessment [5]. Over

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the past few years, several clinical trials and community-based interventions, as well as observational studies, have been published, which represent a further development in terms of supplementation approaches and implementation settings[6, 7].

Results, however, are mixed, and evidence that is specific to children below the age of five has not continuously been synthesized without statistical pooling.The systematic review aimed to systematically evaluate the effectiveness, safety considerations, and implementation characteristics of iron supplementation strategies used for the prevention and treatment of iron deficiency anemia among children under five years of age.

METHODS

The systematic review was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines 2020 [8]. The search strategy, screening, and data extraction were pre-determined by a structured protocol. The purpose of the review was to single out the research that assessed iron supplementation as a measure to prevent and treat iron deficiency anemia in children below the age of five years. Studies were located by searching major biomedical databases, namely 'PubMed, Scopus, and the Cochrane Library', which located the appropriate studies released no earlier than January 2019 and no later than December 2024. The search was narrowed down to the English language and human subjects. The combinations of the terms were used as keywords and Medical Subject Headings (MeSH). "Iron supplementation", "iron deficiency anemia", "micronutrient powder", "ferrous sulfate", "anemia prevention", "children under five", and related synonyms. An example search syntax for PubMed was: ("iron supplementation" OR "micronutrient powder" OR "ferrous sulfate") AND ("iron deficiency anemia" OR "anemia") AND ("child" OR "children" OR "infant" OR "under five"). All search results were exported into EndNote for deduplication. Eligibility of studies was determined using predefined inclusion criteria. Population: Children aged under five years (0–59 months). Intervention: Iron supplementation in any form (e.g., oral iron preparations, micronutrient powders with iron). Outcomes: Studies reporting at least one relevant hematological outcome (e.g., hemoglobin, ferritin, anemia prevalence). Types of studies: Original human studies employing experimental or observational designs, including randomized and non-randomized approaches, were considered. Time frame: Published between 2019 and 2024, in English. Exclusion Criteria: Systematic reviews, meta-analyses, case reports, case series, editorials, and animal or in-vitro studies. Studies not reporting anemia or iron-related outcomes. Studies where the under-five subgroup data could not be extracted separately. All records found were put into EndNote, and duplication was eliminated. Title and abstract screening were conducted by two reviewers against the eligibility criteria. All the potentially relevant articles were retrieved and evaluated to determine eligibility. Where discrepancies arose, these discrepancies were fixed by discussion or referring to a third reviewer. The PRISMA 2020 flow chart was made to record the selection procedure. PRISMA 2020 flow diagram illustrating the identification, screening, eligibility assessment, and inclusion of studies for the systematic review focusing on the use of iron supplements to improve iron status and anemia-related outcomes in children younger than five years. A total of 716 records were identified through database searches, and 15 studies met the inclusion criteria and were included in the qualitative synthesis(Figure 1).

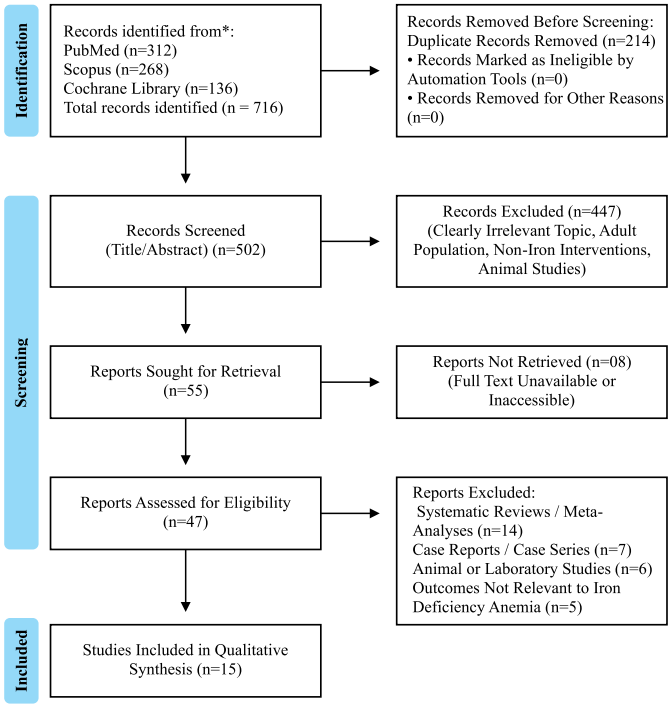

Figure 1: Process of Study Selection

Each of the included studies provided the following data on the standardized data extraction form: author(s), publication date, country or setting of the study and its design, population characteristics, type and duration of iron intervention, comparator, and key outcomes (e.g., changes in hemoglobin, anemia prevalence). In case of observational studies, exposure and key findings concerning iron supplementation or other determinants associated with the same were extracted. The methodological quality of randomized controlled trials was evaluated by the Cochrane Risk of Bias tool version 2 (RoB-2) [9, 10]. To conduct non-randomized intervention and quasi-experimental studies, the Joanna Briggs Institute (JBI) critical appraisal checklist was employed [11]. The JBI

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analytical cross-sectional checklist was used to evaluate Cross-sectional studies. Two reviewers independently assessed risk of bias, and a consensus was reached by discussing. Since the study designs, interventions, and outcomes were heterogeneous, a narrative synthesis was used. The grouping of studies was based on the type of intervention and study design. Results were described descriptively without meta-analysis. Observational studies were provided individually as contextual evidence and implementation evidence.

RESULTS

The evidence on iron supplementation in children under 5 years between 2019 and 2024 comes from South Asia, Africa, the Middle East, and the Americas. Most intervention studies were randomized controlled trials, and cross-sectional designs provided evidence related to the context of interventions and implementation. Most interventions were with micronutrient powders or oral ferrous sulfate used preventively and/or therapeutically. The various studies differed in duration, delivery platforms, and baseline anemia status that were clinically heterogeneous in accordance with real-world settings relevant to public health (Table 1).

Table 1: Characteristics of Included Studies (2019–2024)

References	Country	Design	Population (Under-5)	Intervention (Iron Strategy)	Comparator	Key Outcomes Reported
[12]	Arusha District Tanzania	Trial (frequency comparison)	Children 6–59 months	Micronutrient powder (iron-containing) with different dosing frequencies	Alternate frequency arms	Anemia/iron status indicators
[13]	Gaza Strip Clinics (UNRWA)	RCT (parallel)	Healthy infants 6 months (followed by 12 months)	MNP Iron-containing MNP administered thrice weekly with standard supplementation	National supplement alone	Growth + anemia/ iron indicators
[14]	NR	Open-label therapeutic trial	Young children with mild to moderate IDA (young age group)	Ferrous sulfate oral solution	No parallel comparator (single-arm)	Hb response, safety, acceptability
[15]	Rural Bangladesh	Individually randomized, placebo-controlled trial	Infants/young children (under-2 at start)	Iron syrup OR iron-containing MNPs (3 months)	Placebo control	Anemia prevalence, iron status, safety outcomes
[16]	US	RCT	Infants/young children (includes 6–23 months)	MNP point-of-use fortification	Placebo	Anemia + iron deficiency outcomes
[5]	Brazil	Randomized clinical trial	Children 6–48 months	MNP fortification	Comparator arm (as per trial design)	Iron deficiency/ iron markers; anemia outcomes
[17]	Pakistan (Community-Based)	Non-randomized community trial	Children 6–23 months	Lipid-based supplementary food with micronutrients (iron-containing)	Control group	Hb, micronutrient status, growth indicators
[18]	Pakistan (Community Setting)	Community intervention study	Children 24–59 months	MNP supplementation (1 year)	Control/ comparison group	Hb/anemia + micronutrient status + growth
[19]	Bangladesh (Sub-Study Within Trial)	Randomized trial sub-study	Young children (trial infants; under-5)	Iron syrup vs iron-containing MNP	Placebo	Neurocognitive/ brain activity + trial outcomes
[20]	Rural Bangladesh	RCT (microbiome analysis within trial)	Infants (under-2 at start)	Iron and iron-containing MNPs (3 months)	Placebo	Gut microbiome safety signals + follow-up
[21]	Multi-Site (I.E., Kampala and Fort Portal, Uganda)	Masked randomized placebo trial	Infants between 6 and 23 months of age and ≥24 months (includes under-5)	Ferrous sulfate tablets (dose by age band)	Placebo	Safety/efficacy outcomes (anemia/ iron indicators)
[22]	Pakistan (Multan)	RCT	Children with IDA (age NR in abstract snippet)	Ferrous sulfate + vitamin C vs ferrous sulfate alone	Active comparator	Hb/iron response as per trial outcomes
[23]	Ethiopia (Survey-Based)	Cross-sectional	Infants 6–23 months	Exposure: received MNP	Not applicable	Prevalence + predictors of MNP use
[24]	Ethiopia (Hospital-Based)	Cross-sectional	Children 6–59 months	Exposure includes supplementation variables (as reported)	Not applicable	Anemia prevalence + associated factors

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[25]	Ethiopia	Cross-sectional (secondary analysis)	Children 6–59 months	Exposure: iron-related feeding/ supplement variables	Not applicable	Iron-related consumption patterns

Intervention trials showed that children under-five who received micronutrient powders or oral ferrous sulphate had improved hemoglobin and iron status and decreased risk of iron deficiency. The use of micronutrient powders and oral ferrous sulfate was effective in the prevention of anemia, while treatment improved hemoglobin recovery of children with developed iron deficiency anemia. Some research shows positive knock-on effects on growth and neurodevelopment. The evaluation of safety and specific effects of various formulations has been highly inconsistent. The direction of effect for some results in some trials differed, but overall, the direction of effect for iron either with micronutrient powders or oral was markedly favourable (Table 2).

Table 2: Summary of Main Findings from Intervention Trials (2019–2024)

References	Prevention or Treatment Focus	Main Outcomes Assessed	Direction of Effect (As Reported)	Descriptive Summary of Findings
[12]	Prevention	Hemoglobin, iron status	Improved	Different dosing frequencies of iron-containing MNPs were associated with improvements in hemoglobin and iron status indicators among children aged 6–59 months.
[13]	Prevention	Growth, anemia, and iron indicators	Improved	Long-term MNP supplementation alongside routine care resulted in reduced anemia risk and improved iron indicators, with additional positive effects on growth.
[14]	Treatment (IDA)	Hemoglobin response, safety	Improved	Ferrous sulfate oral solution led to clinically meaningful hemoglobin improvement and was generally well tolerated in young children with mild to moderate IDA.
[15]	Prevention / Early-Life Risk	Anemia prevalence, iron status, safety	Mixed	Iron syrup and iron-containing MNPs improved anemia and iron status, while also highlighting formulation-specific safety considerations in high-infection settings.
[16]	Prevention	Anemia, iron deficiency	Improved	Point-of-use MNP fortification reduced anemia and iron deficiency and was associated with improved expressive language development.
[5]	Prevention/Treatment	Iron deficiency markers, anemia	Improved	MNP fortification demonstrated beneficial effects on iron deficiency and anemia outcomes in Brazilian children under five.
[17]	Prevention	Hemoglobin, micronutrients, and growth	Improved	Iron-containing supplementary food improved hemoglobin levels and plasma micronutrient concentrations, with concurrent improvements in growth indicators.
[18]	Prevention (Long-Term)	Hemoglobin, micronutrients, and growth	Improved	One-year MNP supplementation was associated with sustained improvements in hemoglobin, micronutrient status, and growth among children aged 24–59 months.
[19]	Prevention (Substudy)	Neurocognitive markers, iron exposure	Physiologic change	Iron syrup and iron-containing MNPs altered resting brain activity patterns, suggesting potential neurodevelopmental relevance alongside hematologic effects.
[21]	Treatment	Safety and efficacy (Hb/iron)	Improved	Daily ferrous sulfate supplementation for three months improved anemia indicators under controlled safety monitoring in a vulnerable pediatric population.
[22]	Treatment (IDA)	Hemoglobin, iron response	No added benefit	The addition of vitamin C to ferrous sulfate did not demonstrate a clear advantage over ferrous sulfate monotherapy in improving hematologic outcomes.

Observational studies do not provide effect estimates, but important contextual information. The high prevalence of anemia in children under-five is reinforced by widespread variation in the use of micronutrient powder and consumption of iron-rich foods. Consistent predictors of use were socioeconomic position, maternal education, and access to health services. Moreover, they did not allow us to infer causality, but this study highlights significant implementation challenges that can affect the iron supplementation (Table 3).

Table 3: Findings from Observational Studies (Contextual and Implementation Evidence)

References	Study Focus	Population	Key Outcomes	Main Findings
[23]	MNP Program Coverage	Infants 6–23 months	Prevalence, predictors	MNP consumption varied widely, with maternal education, health-service contact, and household factors influencing uptake.

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[24]	Anemia Burden and Correlates	Children 6–59 months	Anemia prevalence	High anemia prevalence was observed, with nutritional and health-related factors, including supplementation variables, associated with anemia status.
[25]	Dietary Iron Exposure	Children 6–59 months	Iron-rich food intake	Consumption of iron-rich foods was suboptimal and socially patterned, highlighting dietary gaps that may limit the effectiveness of supplementation programs.

A review of the risk-of-bias for RCTs indicates that overall, 8 of 10 RCTs had a low risk of bias. Moreover, we demonstrated that the domains concerned with outcome measures and completeness of data were at low risk. The assessment of the RCTs and evaluations showed high and moderate risk for the other two domain areas. Nonetheless, the other ROBINS-I evaluated the non-randomized studies and the community-based intervention studies. The lack of allocation concealment and potential made their moderate to high risk of bias (Table 4).

Table 4: Risk of Bias Assessment of Intervention Trials (RoB-2 / JBI) F

References	Study Design	Assessment Framework	Allocation Process	Adherence to Assigned Intervention	Completeness of Outcome Data	Outcome Assessment	Reporting Transparency	Overall Methodological Concern
[12]	Frequency-Based Intervention Study	JBI Critical Appraisal Tool for Quasi- Experimental Studies	Minor Concerns	Minimal Concern	Minimal Concern	Minimal Concern	Minor Concerns	Moderate Concern
[13]	Randomized Intervention Study	Cochrane Risk Assessment Framework (RoB-2)	Minimal Concern	Minimal Concern	Minimal Concern	Minimal Concern	Minimal Concern	Minimal Concern
[14]	Non-Masked Intervention Study	JBI Critical Appraisal Tool for Quasi-Experimental Studies	Major Concerns	Minor Concerns	Minimal Concern	Minimal Concern	Minor Concerns	Major Concern
[15]	Randomized Intervention with Placebo Comparator	Cochrane Risk Assessment Framework (RoB-2)	Minimal Concern	Minimal Concern	Minimal Concern	Minimal Concern	Minimal Concern	Minimal Concern
[16]	Randomized Intervention Study	Cochrane Risk Assessment Framework (RoB-2)	Minimal Concern	Minimal Concern	Minor Concerns	Minimal Concern	Minimal Concern	Minimal Concern
[5]	Randomized Intervention Study	Cochrane Risk Assessment Framework (RoB-2)	Minimal Concern	Minimal Concern	Minimal Concern	Minimal Concern	Minor Concerns	Minimal Concern
[17]	Non-Randomized Intervention Study	JBI Critical Appraisal Tool for Quasi-Experimental Studies	Major Concerns	Minor Concerns	Minor Concerns	Minimal Concern	Minor Concerns	Moderate to High Concern
[18]	Community-Based Intervention Study	JBI Critical Appraisal Tool for Quasi-Experimental Studies	Major Concerns	Minor Concerns	Minor Concerns	Minimal Concern	Minor Concerns	Moderate to High Concern
[19]	Nested Analysis within a Randomized Study	Cochrane Risk Assessment Framework (RoB-2)	Minimal Concern	Minimal Concern	Minimal Concern	Minimal Concern	Minor Concerns	Minimal Concern
[20]	Randomized Intervention Study	Cochrane Risk Assessment Framework (RoB-2)	Minimal Concern	Minimal Concern	Minimal Concern	Minimal Concern	Minimal Concern	Minimal Concern
[21]	Masked Randomized Intervention	Cochrane Risk Assessment Framework (RoB-2)	Minimal Concern	Minimal Concern	Minimal Concern	Minimal Concern	Minimal Concern	Minimal Concern
[22]	Randomized Intervention Study	Cochrane Risk Assessment Framework (RoB-2)	Minor Concerns	Minimal Concern	Minimal Concern	Minimal Concern	Minor Concerns	Moderate Concern

Every study that was observed showed an underlying moderate risk of bias, which is mainly due to selection bias and residual confounding. Hospital-based research had an increased risk because of poor generalizability, whereas national survey research had strong sampling designs. Statistical analysis and measurement areas were usually satisfactory in studies. Such results confirm the applicability of observational evidence to contextual interpretation and not causal patterns (Table 5).

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Table 5: Methodological Appraisal of Observational Studies

References	Study Design	Appraisal Framework	Participant Selection	Exposure and Outcome Assessment	Control of Confounding	Analytical Approach	Overall Methodological Concern
[23]	Cross-Sectional Survey	JBI Analytical Appraisal Checklist	Minor Concerns	Minimal Concern	Moderate Concern	Minimal Concern	Moderate Concern
[24]	Hospital-Based Cross-Sectional Study	JBI Analytical Appraisal Checklist	Major Concerns	Minimal Concern	Moderate Concern	Minimal Concern	Moderate to Great Concern
[25]	National Survey Secondary Analysis	JBI Analytical Appraisal Checklist	Minor Concerns	Minimal Concern	Moderate Concern	Minimal Concern	Moderate Concern

The methodological quality of observational studies was evaluated using the Joanna Briggs Institute analytical appraisal framework. Assessment focused on participant selection procedures, accuracy of exposure and outcome measurement, handling of potential confounding factors, and adequacy of analytical methods. Terminology was adapted to reflect levels of methodological concern rather than categorical bias labels.

DISCUSSION

This systematic review states that iron supplementation is an effective intervention for iron deficiency anemia (IDA) in children under age 5, in line with the existing evidence on hematologic benefits. Prophylactic use of micronutrient powders (MNPs) containing iron and operative use of oral preparations of iron remained consistently beneficial in enhancing hemoglobin and iron status in a variety of environments. The results are in line with the larger clinical evidence, such as large syntheses of the effects of iron supplementation in children's populations [4, 26]. Iron supplementation is not only beneficial at raising hemoglobin but also helps to lower the general prevalence of anemia in high-burden areas, which can be concluded from the systematic evidence [27]. Most of the previous systematic reviews and meta-analyses integrate various outcomes of trials, but one can point out that the similarity of benefit can be observed even when the schedules of interventions differ [28, 29]. MNPs' preventive supplementation was successful in diverse demographic backgrounds, yet programmatic receipt and compliance are important issues of practical effectiveness. The recent meta-analyses have associated a low dietary diversity and micronutrient sources with increased odds of anemia among young children, which highlights the necessity of implementing combined nutrition interventions in addition to supplementation [30]. Oral iron is still a first-line form of treatment, therapeutically. New formulations, including liposomal iron, have the potential to be better tolerated and can have a beneficial effect on developmental outcomes, so that areas of further clinical research are possible [31]. Similarly, there is also evidence of alternate-day supplementation as a measure to enhance iron absorption and possibly lower the side effects, which would fine-tune dosing strategies in young children [32]. Although the hematologic effects remain consistent, the results are not always positive. There is some evidence that low-dose iron supplementation in healthy, low-risk infants does not significantly prevent anemia or improve development [33].

These results indicate that the strategy of supplementation should be specific to the risk population profiles, and not applied universally in low-impact situations. This subtlety is significant when making policy recommendations in an environment where anemia prevalence in the baseline differs. Safety is also one of the issues to consider, as it is a high burden in terms of infectious diseases in places where iron may affect gut bacteria or have endemic interactions with other infections. Literature indicates the possible measurable microbiome responses to iron supplementation, which should be monitored in program roll-outs [34]. It has been observed that anemia is very prevalent in most under-five populations, and predominantly where the intake of iron through the diet and dietary diversity is low [35]. These results support the need to consider iron supplementation with comprehensive approaches to nutrition in general and dietary enhancement and maternal education, in particular. Community-based supplementation models are promising in the context of Pakistan, but need a stricter assessment to accommodate confounding. The implementation research is required to learn how to integrate the iron supplementation with the regular child-health services most successfully, and also to control the dietary determinants and infection prevention.

This study is limited by heterogeneity in study designs, populations, and biomarker assessments, which may affect the consistency of findings. Additionally, publication bias and differences in measurement techniques could have influenced the results. Further studies are needed on standardized outcome measures, longer follow-up of developmental outcomes, and the relative effectiveness of newer iron preparations. Also, program evaluation research involving a combination of supplementation with diet and health system strengthening can give an insight into the sustainable control of anemia.

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CONCLUSIONS

This systematic review indicates that iron supplementation remains an effective strategy for both the prevention and treatment of iron deficiency anemia in children under five years of age. Evidence from recent trials demonstrates consistent improvements in hemoglobin and iron status with the use of oral iron preparations and iron-containing micronutrient powders. Preventive interventions appear beneficial at the community level, while therapeutic supplementation effectively corrects established anemia when adherence is ensured. However, variability in program implementation, safety monitoring, and baseline nutritional status influences observed outcomes. Observational evidence highlights persistent anemia burden and suboptimal dietary iron intake, underscoring the need for integrated nutrition approaches. Future research should prioritize context-specific implementation studies and standardized outcome reporting to inform sustainable child health policies, particularly in low-resource settings such as Pakistan.

Authors' Contribution

Conceptualization: UB
Methodology: UB, HT, FH
Formal analysis: UB
Writing and Drafting: TT, UB, FTZ, HT, FH, MI
Review and Editing: TT, UB, FTZ, HT, FH, MI

All authors approved the final manuscript and take responsibility for the integrity of the work.

Conflicts of Interest

All the authors declare no conflict of interest.

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