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Weekly Iron-Folic Acid Supplementation and Its Impact on children and adolescents iron status, Mental Health, and School Performance: A Systematic Review and Meta-Analysis in Sub-Saharan Africa.

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Weekly Iron-Folic Acid Supplementation and Its Impact on children and adolescents' iron status, Mental Health, and School Performance: A Systematic Review and Meta-Analysis in Sub-Saharan Africa.

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Abstract

Objective: This systematic review and meta-analysis aimed to comprehensively assess the impact of Weekly Iron-Folic Acid Supplementation (WIFAS) on the nutrition, health, and educational outcomes of children and adolescents in Sub-Saharan Africa.

Design: Systematic review and Meta-analysis was used.

Data Sources: Five databases, namely, MEDLINE, Scopus, Web of Science, Cochrane Library, and Google Scholar, were systematically searched for relevant articles up to August 23, 2023.

Eligibility Criteria: It was focused on randomized controlled trials involving children and adolescents in Sub-Saharan Africa, exploring the effects of iron supplementation on various outcomes, such as serum ferritin and hemoglobin levels, anemia, mental health, and school performance.

Data Extraction and Synthesis: The Joanna Briggs Institute Critical Appraisal tools were utilized for quality assessment, with two independent reviewers thoroughly evaluating each paper. **Results:** A systematic review of 17 articles revealed that WIFAS significantly increased serum ferritin levels in adolescent girls (Hedge's g = 0.53, 95% CI: 0.28, 0.78; heterogeneity I² = 41.21%, P < 0.001) and hemoglobin levels in school-age children (Hedge's g = 0.37, 95% CI: 0.01, 0.73; heterogeneity I² = 91.62%, P < 0.001). The analysis further demonstrated a substantial reduction in the risk of anemia by 20% (risk ratio = 0.8, 95% CI: 0.69, 0.93; heterogeneity I² = 28.12%, P < 0.001).

Conclusion: WIFAS proved effective in enhancing serum ferritin and hemoglobin concentrations and lowering the risk of anemia in school-age children and adolescents compared to placebo. Similarly, there are not enough studies to examine the effects of WIFAS on school performance. However, information regarding mental health problems, mortality, and potential side effects remains insufficient.

Strength and limitation

The review's strengths lie in its focus on iron status and school performance in Sub-Saharan Africa, despite challenges related to intervention design variations.

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Keywords: WIFAS, Anemia, Sub-Saharan Africa, School Performance, Adolescent

Introduction

Adolescence, marked by the transition to adulthood, is a critical phase characterized by significant growth, behavioral maturation, and sexual development. This represents the second growth spurt in life, particularly for girls who undergo unique experiences. Adolescents impose heightened nutritional demands, with a specific emphasis on the need for iron. This period lays the foundation for adult health and economic wellbeing. Adolescence witnesses the attainment of 20% final adult height and 50% adult weight, underscoring its pivotal role in shaping future health outcomes. Consequently, adolescent girls emerge as a physiologically significant group, warranting special attention to their nutritional requirements, given their role as potential future mothers ^{1,2}.

Anemia, a widespread global health concern, impacts approximately 1.6 billion individuals. According to the World Health Organization (WHO), approximately 50% of anemia cases are attributed to iron deficiency ³. This condition serves as a direct marker of undernutrition and insufficient iron intake, posing a significant public health challenge for adolescents ⁴. Iron deficiency anemia constitutes a significant portion, nearly half, of all anemia cases, particularly in Low- and Middle-Income Countries (LMICs) ^{3,5}. Iron deficiency anemia in adolescence has the potential to impede growth, hinder motor and brain development, and increase the risk of illness and mortality. Failure to promptly address anemia during this critical period may lead to persistent challenges later in life ⁶.

Adolescents are particularly prone to iron deficiency and anemia due to a range of factors, including rapid growth, insufficient dietary iron intake, reduced bioavailability of dietary iron, and heightened susceptibility to infectious diseases, parasitic infections, and menstrual blood loss ⁴. The combination of these factors contributes to an increased risk of iron deficiency anemia in adolescent girls, emphasizing the need for targeted interventions and education to address the specific challenges faced by this demographic group ⁷.

Anemia and iron deficiency anemia may have long-term consequences for individuals, limiting their educational achievements and subsequently impacting their economic potential^{2,7,8}. The evidence strongly supports the relationship between anemia and cognitive development. Both iron deficiency and iron deficiency anemia have been identified as contributors to cognitive deficits.

Understanding and addressing the relationship between anemia and cognitive development is vital for promoting optimal health and cognitive outcomes, especially in vulnerable populations such as children and adolescents ⁹⁻¹¹.

Iron plays a crucial role as an essential nutrient in the development and functioning of the brain. Its functions are diverse and contribute to various aspects of neural activity and neurotransmission. Some key roles of iron in the brain include ATP production, synthesis and packaging of neurotransmitters, and uptake and degradation of neurotransmitters ^{3,5}.

Indeed, adolescence and school-age children are recognized as a pivotal period for implementing interventions to address anemia and lay the foundation for future health, particularly in terms of childbearing ^(1,2). Implementing iron supplementation as an effective strategy to combat iron deficiency can have a substantial impact on reducing the prevalence of anemia, improving public health outcomes, and enhancing the well-being of affected populations, particularly in resource-constrained settings ^{12,13}.

The current body of evidence exhibits divergent findings on the multifaceted benefits of investing in this variability in results, which is largely attributed to methodological heterogeneity across studies. Furthermore, there is a notable scarcity of information regarding the efficacy of weekly folic acid supplementation concerning a broader spectrum of school performance and health outcomes including mental health ⁶. The limitations of the available data underscore the need for comprehensive and standardized research methodologies to elucidate the full range of effects associated with weekly iron-folic acid supplementation on diverse nutrition, education, and health parameters. Within the framework of this systematic review and meta-analysis, our primary objective was to evaluate the impact of weekly iron-folic acid supplementation on the iron status, mental health, and educational outcomes of children and adolescents in the Sub-Saharan African region.

Methods

Searching strategies

This systematic review and meta-analysis aimed to assess the impact of WIFAS on serum ferritin levels, school performance, and mental health status among children and adolescents. The review encompassed a comprehensive examination of various literature sources, including both published

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and unpublished research reports, to thoroughly investigate the effects of IFAS on serum ferritin levels, school performance, and mental health. Our search for published articles was confined to individuals aged 6-19 years and studies conducted exclusively in sub-Saharan Africa. We systematically searched international databases, including Scopus, Web of Science, PubMed (MEDLINE), Cochrane Library, and Google Scholar. (((Adolescen*[Title/Abstract] OR "Youth*"[Title/Abstract] OR "primary school"[Title/Abstract] OR "secondary school"[Title/Abstract] OR "teen*"[Title/Abstract] OR "School-age"[Title/Abstract] OR school[Title/Abstract] OR School*[Title/Abstract] OR pediatrics [Title/Abstract] OR pediatric*[Title/Abstract] OR paediatric*[Title/Abstract] OR peadiatric* [Title/Abstract] OR child[Title/Abstract] OR child*[Title/Abstract] OR children*[Title/Abstract] OR Pediatric[Mesh] OR Child[MeSH Terms] OR adolescent[MeSH Terms] OR "Schools"[Mesh]) AND (Iron[Title/Abstract] OR hematinics[Title/Abstract] OR ferrous[Title/Abstract] OR OR hematinic[Title/Abstract] OR haematinic[Title/Abstract] ferric[Title/Abstract] OR haematinics[Title/Abstract] OR "iron compounds"[Title/Abstract] OR "folic acid"[Title/Abstract] OR "Weekly Folic acid supplementation"[Title/Abstract] "Dietary Iron OR supplement*"[Title/Abstract] OR "Iron folic acid supplementation"[Title/Abstract] OR "iron folic acid tablet"[Title/Abstract] OR "Iron-folate supplement*"[Title/Abstract] OR "Iron-folate supplementation"[Title/Abstract] OR "Iron and folic acid supplementation"[Title/Abstract] OR "iron folic acid supplement*"[Title/Abstract] OR "Iron-folic acid"[Title/Abstract] OR Supplementation[Title/Abstract] OR Supplement[Title/Abstract] OR Supplement[Title/Abstract] OR IFAS[Title/Abstract] OR WIFAS[Title/Abstract] OR IFAS[Title/Abstract] OR "Iron and Folic-Acid Supplementation"[Title/Abstract] OR Iron[MeSH Terms] OR folic acid[MeSH Terms] OR Dietary supplements[MeSH Terms])) AND ("Randomized controlled trials" OR RCT OR RCTs OR "Clinical Trial" OR "Controlled Clinical Trial" OR "quasi-randomized trials") AND (Africa, south of the Sahara [MeSH Terms]))). The search terms were combined using Boolean operators 'AND'/'OR'. All published articles up to August 23, 2023, were incorporated into the systematic review.

Eligibility criteria

Inclusion criteria

Study area: Only studies conducted in Sub-Saharan Africa (South of the Sahara).Publication condition: articles published in peer-reviewed journals.Study design: all RCT and clinical trial studies

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Intervention: iron and/or folic acid supplementation

Language: Articles published in the English language.

Age: School-age children typically encompass a range of ages, including the adolescent group.

Notice: school-age children, including the age adolescent groups," suggests an inclusive consideration of children attending school, with a specific focus on the adolescent subset within this broader age range.

Exclusion criteria

Studies conducted related to iron fortification, and studies lacking specific outcome reporting were excluded from our analysis.

Outcome measurement

In this study, the main focus was on evaluating the impact of WIFAS on key health indicators, including serum ferritin levels, hemoglobin concentrations, anemia prevalence, mental health, and school performance. Measurement of outcomes involved assessing serum ferritin (in µg/L) and hemoglobin (in g/dl) through mean and standard deviation calculations. For anemia, the prevalence was examined as binary outcomes post-supplementation. Moreover, the study delved into the assessment of school performance by considering the average scores of subjects. Additionally, cognitive performance was thoroughly evaluated using a battery of cognitive tests specifically chosen, designed, or adapted for the age and cultural group under consideration. This battery included four subtests from the Kaufman Assessment Battery for children aged 3–18 years, second edition (KABC-II) ¹⁴, and the Hopkins Verbal Learning Test (HVLT) ¹⁵. The subtests chosen from the KABC-II encompassed the Atlantis (assessing working memory) and Atlantis Delayed (evaluating long-term memory and retrieval) tests from the learning scale, the Hand Movement test (measuring short-term memory) from the simultaneous processing scale, and the Triangles test (assessing visuospatial cognition) from the simultaneous processing scale ^{16–18}.

Data abstraction

The extraction of data was carried out independently by two authors (SK and BM) utilizing a standardized spreadsheet for data extraction. The format for data extraction encompassed details such as the primary author, year of publication, the geographical region where the study was conducted, sample size, frequency of supplementation, age, sex, dose of supplements, outcome measurement, duration of the intervention, and information related to the randomized controlled trials (mean, standard deviation, median, and interquartile range proportion).

Quality assessment

For the assessment of the methodological quality of the included studies, we employed the Joanna Briggs Institute (JBI) Critical Appraisal tools designed for use in systematic reviews of randomized controlled trials ¹⁹. This tool consists of thirteen questions addressing aspects such as selection bias, attrition bias, performance bias, and detection bias. Two independent reviewers (SK and BW) meticulously assessed each paper, engaging in discussions to resolve any discrepancies. In cases where disagreements persisted, a third reviewer (KH) was consulted to arbitrate and ensure consistency between the two independent reviewers. We have also contacted authors through email to get some outcome measurements that are mentioned by mean and median, as well as full texts. Each question in the Joanna Briggs Institute (JBI) Critical Appraisal tools was assigned a score: "Yes" received a score of 2, "No" was scored as 0, "Unclear" was denoted as 1, and "Not applicable" was recorded as NA. The overall quality of the studies was determined based on the cumulative score, classifying them as high quality if they scored 20 and above, good quality for scores between 13 and 19, and lower quality for scores below 13. The detailed results, including the breakdown of scores for each study, can be found in Table 1. Notably, nearly half of the studies (47%) achieved a high-quality score, while 11.7% were categorized as lower quality (Supplemental Table 1). The results of the database search were aggregated, and duplicate articles were eliminated using the online Rayyan Software (https://www.rayyan.ai/). This tool was also employed to download the full text of studies for further evaluation

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Statistical analysis

The extracted data were entered into the computer using an Excel sheet and imported to STATA 17 for analysis. Heterogeneity among reported was assessed by using the Higgins-I² with Cochran Q statistic at 25%, 50%, and 70% as low, moderate, and considerable heterogeneity respectively with p-values less than 0.05²⁰. Random effects meta-analysis model was used to estimate the pooled effect of WIFAS on serum ferritin level, hemoglobin, anemia, school performance, and mental health. A forest plot was also used to visualize the presence of heterogeneity subjectively. Possible differences between studies were explored by sub-group analyses and sensitivity analysis. Descriptive statistics (means and SD, median, IQR, 95%CI, and proportions) were used to summarize baseline information. The finding was presented using a forest plot with respective hedges and risk ratios and 95% confidence intervals. Evidence of publication bias was assessed using both Egger's and Begg's tests with a p-value of less than 0.05 as a cut-off point to declare the presence of publication bias ^{21,22}. The pooled hedges and risk ratios with 95% CI for each factor were used.

Registration and reporting

This study was registered with the International Prospective Register of Systematic Reviews (PROSPERO ID: <u>CRD42023397898</u>). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed during the systematic review process ²³.

Patient and public involvement

Due to the nature of our systematic review, it was regrettably impossible to include patients or the public in the planning, execution, or communication of our study.

Result

We identified a total of 2,026 articles (1,945 from Scopus, Web of Science, PubMed, Cochrane Library, and 81 from Google Scholar) through an extensive search across four electronic databases, supplemented by a manual search of references from key articles, previous reviews, and grey literature. After excluding 343 duplicates, a review of titles and abstracts against the review objectives and inclusion criteria led to the exclusion of 1,631 articles as irrelevant. Subsequently, the full texts of the remaining 52 studies were assessed, with 17 studies meeting the criteria for inclusion in the present systematic review and meta-analysis (Figure 1).

Study Characteristics

The current systematic review and meta-analysis were carried out in Sub-Saharan Africa. Among the included studies, six were conducted in Eastern Africa ^{24–29}, with one study in Ethiopia, three in Kenya, one in Tanzania, and one in Mozambique. Additionally, five studies were conducted in Western Africa ^{30–34}, with three in Mali, one in Burkina Faso, and one in Ghana. Moreover, five studies were carried out in Southern Africa^{35–39}, with two in Zambia and three in South Africa. Furthermore, a study was conducted in North-East Africa Sudan ⁴⁰.

Besides, concerning the frequency of supplementation, nine studies were included weekly ^{25,26,24,28,30,34,31,39,40}, one studies with twice weekly ²⁷, two studies with four times per week ^{35,37}, two studies with five times per week ^{33,32}, and three studies with daily ^{29,36} supplementation. Moreover, seven studies were included that primarily focused on adolescent girls, and the supplementation was conducted weekly ^{25,26,24,28,34,31,39}.

Regarding the supplement composition, ten studies were conducted on iron supplements in the form of ferrous sulfate or ferrous dextran which contains ranging from 50mg to 65mg elemental iron and/or folic acid in amounts ranging from 250µg to 2800µg ^{25–27,29–31,34,35,40}. Furthermore, seven studies used a factorial randomized control trial design ^{26,33,32,35,42,36,37}. Among these, one study employed ferrous dextran with 60mg elemental iron, 200% of the Recommended Dietary Allowance (RDA) for multivitamins, and an identical placebo³⁶. Additionally, two studies used ferrous sulfate (60mg elemental iron), 420mg DHA/80mg EPA, and a placebo ^{35,37}. Another study involved ferrous sulfate (120mg elemental iron) with vitamin A (8.3mg retinol), iron with vitamin A placebo, vitamin A with iron placebo, and a double placebo ^{35,37}. Moreover, two studies focused

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<text> on Praziquantel (40mg/kg) alone, Praziquantel with iron (60 mg elemental iron), Praziquantel with iron and multiple micronutrients, and Praziquantel with multiple micronutrients ^{33,32}. The supplementation period varied within the range of 2.2 months to 18 months. Seven studies were conducted in the form of folic acid supplemented with iron in the range of 0.1mg to 2.8 mg^{24,27,30,31,33,40,38} (Table 1).

s/	Author,	Setting	Sex and	Sample Size	Iron dose	Folic	Frequeries and	Outcome
n	(Year, Country),	and Study	Age	for		acid	duration of	measurement
	Reference	design		Intervention		dose	supple	
				Group (IG)			ine ies i	
				and Control			2024. relate	
				Group (CG)				
1	Beasly, et.al	School; RCT	Female,	IG= 50	400mg FS	-	Weekl g g or 4	Hgb, SF, CRP,
	(2000, Tanzania) ²⁴		12-18 years	CG= 57			monthe	Diarrhea, Malaria
			6				<u>s</u> e	and Wt. change
2	Yosef H, et.al	Community	Female,	IG= 92	60mg EI	0.4 mg	Weekl	Hgb, SF, and CRF
	(2021, Ethiopia) ²⁵	RCT	10-19 years	CG=112			month	
3	Andrew Hall, et.al	School	6-19 years	IG= 551	65mg EI	0.25	Weekl <u>y</u> for 2.2	Hgb, and Anemia
	(2001, Mali) ³⁰	CRCT		CG= 562		mg	month	status
4	Olsen, et.al	Community	4-15 years	IG= 108	60mg EI	-	Twice weekly	Hgb, and SF
	(2006, Kenya) ²⁷	RCT		CG= 92	•		for 12 month	
5	Lawless, et al	School; RCT	6-11 years	IG= 44	150 mg EI	-	Daily B 3.2	Hgb, and SF
	(1994, Kenya) ²⁹			CG= 42			montha	
6	Victor Mwanakasale	School; RCT	Male, 9-15	IG= 80	200mg FS	-	Weekly for 9	Hgb, and Anemia
	(2009, Zambia) ³⁹		years	CG= 87			month 💁 💆	status
6	Victor Mwanakasale	School; RCT	Female, 9-	IG= 73	200mg FS		Weekl ¥ . £ or 9	Hgb, and Anemia
	(2009, Zambia) ³⁹		15 years	CG= 84			month	status
7	Taylor (2002, South	School; RCT	6-15 years	IG= 101	65mg EI	100µg	Weekl g for 2.2	Hgb
	Africa) ³⁸			CG= 91			month	
8	Jeannine Baumgartner	School;	6-11 years	IG= 80	50mg EI	-	4*/week2or	Hgb, CRP, and
	(2012, South Africa)	FRCT		CG= 80			8.5 month	School
	37						Un	Performance
9	Leenstra, et.al	School; RCT	Female,	IG= 80	120mg EI	-	Weekly f or 5	Hgb, and SF
	(2009, Kenya) ²⁶		12-18 years	CG= 109			month 😫	
10	Jeannine Baumgartner	School; RCT	6-11 years	IG= 160	50mg EI	-	4*/week for	SF, TFR, ID
	(2013, South Africa)			CG= 161			8.5 mon∰i	
	35						Est	
.1							Creteil .	

BMJ Open Table 1: Descriptive summary of the studies included in the systematic review and meta-analysis among adolescents in Sub-Saharan Africa, 2023.

	BMJ Open dy copyrigh												
11	Mohamed Ag Ayoya, (2009, Mali) ³³	School; RCT	7-12 years	IG= 309 (3 groups)	60mg EI	-	5 days 2 week for 3 maggiths	Hgb, and SF					
12	Nchito (2003, Zambia) ³⁶	School; RCT	7-15 years	CG= 97 IG= 101 CG= 101	60mg EI	-	daily for 10 month 2	Hgb					
13	Mohamed Ag Ayoya, (2012, Mali) ³²	School; RCT	7-12 years	IG= 307 CG= 97	60mg EI		5 days where k for 3 mongths	School Performance, School Attenda					
14	Sabine G, et.al. (2018, Burkina Faso) ³⁴	Community	Female, 10-19 years		60mg EI	2.8mg	Weekly for 18 months	Hgb, SF, and anemia					
15	Lucas G, et.al, (2021, Ghana) ³¹	School, Pre- post longitudinal	Female, 10-19 years	1387 girls	60mg EI	0.4mg	Weeklar for 12 monthe	Anemia and Hg					
16	Peter H, et.al, (2005, Mozambique) ²⁸	School, Pre- post longitudinal study	Female, 10-18 years	991 girls	60mg EI	0.4mg	Weekly for 5/8 monthing, A	Anemia and Hg					
17	Maisoon NA Fageer,et.al, (2021, Sudan) ⁴⁰	School	School children	IG= 109 CG= 106	NM	NM	Weeklanning, and	Anemia and Sc Performance					

RCT: Randomized Control Trial; FRCT: Factorial Randomized Control Trial; IG: Intervention Group; CG: Control Grap; EI: Elemental Iron; FS: Ferrous Sulphate; CRP: Creative Reactive Protein; Hgb: Hemoglobin; SF: Serum Ferritin; Wt.: Weight; Ht: Height; IP: Intestinal parasitosis; BAZ: Body mass index for Z score; HAZ: Height for age Z score; ID: Iron Deficiency; TFR: Transferrin Receptor; SAC: School Age Children; 0, 2025 at Universite Paris Est Creteil . nologies. NM: Not Mentioned

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Effect of iron-folic acid supplementation (IFAS) on Serum Ferritin-Narrative synthesis

Nine studies assessed the impact of IFAS on serum ferritin ^{25,27,29,26,24,33–35,37} using various statistical measures, including mean, standard deviation, median, and interquartile range. Out of these, seven studies reported a significant improvement in the serum ferritin level of children with IFAS ^{25,29,26,24,33,35,37}. However, two studies, conducted by Sabine G. et al. (2018) ³⁴ and Olsen A. et al. (2006) ²⁷, did not find a significant effect between IFAS and serum ferritin.

Furthermore, three studies demonstrated that once-weekly IFAS led to a significantly greater increment in serum ferritin compared to the control group, with the favor of 9.1 μ g/l (P = 0.002), 39.1 μ g/l (P < 0.001), and 13.3 μ g/l with a p-value less than 0.0001, respectively ^{25,26,24}. Additionally, Ayoya G's study in 2009 administered IFAS for 12 weeks, resulting in an improvement in the median serum ferritin from 20.84 μ g/l (16.79–25.86) at the baseline to 93.33 μ g/l (82.43–105.66) at the endpoint, with a p-value less than 0.001 ³³. Similarly, Jeanine B, 2012 and 2013 studies showed that supplementing iron has a positive impact on median serum ferritin which increases by 33.3 μ g/l and 38.4 μ g/l compared to the control ^{35,37}.

Effect of weekly iron-folic acid supplementation (WIFAS) on Serum Ferritin-Meta analysis

Three studies were incorporated into the meta-analysis 25,26,24 , involving a total of 440 adolescent girls. Among them, 205 received weekly iron supplementation, while 235 were assigned to the placebo/non-intervention group. The analysis revealed a substantial impact of weekly iron supplementation on enhancing the serum ferritin levels of adolescent girls (Hedge's g 0.53, 95%CI: 0.28, 0.78; test for heterogeneity I² = 41.21%, P < 0.001). There is no publication bias with p value of 0.374 (Figure 2).

Effect of Iron Folic Acid Supplementation (IFAS) on serum Ferritin-Meta analysis

In this meta-analysis, five studies were included which encompassing a total of 653 school-age children including adolescents 25,29,26,24,33 . Within this group, 313 received iron supplementation, while 340 were part of the placebo/non-intervention group. The analysis indicated a significant effect of iron supplementation in improving the serum ferritin levels of the school-age children (Hedge's g 0.77, 95%CI: 0.33, 1.22; test for heterogeneity I² = 86.81%, P < 0.001) (Supplemental Figure 1).

Effect of IFAS on Serum ferritin- Subgroup Meta-analysis

The subgroup analysis revealed that both daily and weekly supplementation of iron had a significant effect on the serum ferritin levels of school-age children 25,29,26,24,33 . Additionally, the variability among the studies was within an acceptable range for the weekly supplementation compared to the daily regimen (Hedge's g 0.53, 95%CI: 0.28, 0.78; test for heterogeneity I² = 41.21%, P < 0.001) (Supplemental Figure 2).

Effect of IFAS on Hemoglobin-Narrative Synthesis

In this comprehensive review, 14 studies were incorporated to evaluate the impact of IFAS on hemoglobin levels. Out of these, five studies administered IFA every week ^(25,28,30,31,35), revealing a significant increase in hemoglobin concentration ranging from 0.12 g/dl to 4.8 g/dl. Moreover, four studies administered daily, four times weekly, and five times weekly also revealed a significant increase in hemoglobin concentration ranging from 0.3 g/dl to 1.12 g/dl ^{29,33,35,37}. However, four studies did not significant association between IFAS and hemoglobin concentration ^{27,24,34,39}.

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Effect of WIFAS on Hgb-Meta-analysis

In this meta-analysis, a total of five studies 25,26,24,30,39 involving 1949 school-age children, including adolescents, were included. Among them, 933 received weekly iron supplementation, while 1016 were part of the placebo/non-intervention group. The analysis demonstrated a significant effect of weekly iron supplementation in improving the hemoglobin levels of school-age children (Hedge's g 0.37, 95%CI: 0.01, 0.73; test for heterogeneity I² = 91.62%, P < 0.001). There is no influential study and publication bias (p-value of 0.924) (Figure 3).

Effect of WIFAS on Hgb-subgroup meta-analysis by Setting

The subgroup analysis revealed that both school 26,24,30,39 and community 25 setting supplementation of iron had a significant effect on the hemoglobin levels of school-age children. Additionally, the variability among the studies was within an acceptable range for both the school setting supplementation (Hedge's g 0.23, 95%CI: 0.12, 0.35; test for heterogeneity I² = 16.33%, P < 0.001) and the community setting (Hedge's g 1.28, 95%CI: 0.97, 1.58) (Supplemental Figure 3).

Effect of weekly iron-folic acid supplementation (WIFAS) on Anemia-Narrative synthesis

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In this systematic review, an analysis of seven studies was conducted to evaluate the impact of Iron and Folic Acid Supplementation (IFAS) on the prevalence of anemia. Out of these, three studies implemented IFAS every week $(^{28,32,36})$, demonstrating a noteworthy reduction in the prevalence of anemia, with percentages ranging from 0.35% to 8.2%. However, the findings from the remaining three studies did not show a significant association between WIFAS and the prevalence of anemia 28,34,39 . Despite our efforts to obtain the full-text article through email correspondence with the author, we were unable to secure it. Nonetheless, we relied on information from a conference proceeding abstract paper conducted in Sudan. According to this abstract, intermittent iron with folic acid supplementation demonstrated a significant 65.7% reduction in the likelihood of anemia (P = 0.002) in the experimental group when compared to the control group, which received folic acid alone. This highlights the potential impact of intermittent iron and folic acid supplementation in mitigating anemia ⁴⁰.

Effect of WIFAS on Anemia-Meta analysis

In this meta-analysis, four studies 26,30,34,39 were included, comprising a total of 2505 school-age children, including adolescent girls. Among them, 1233 received weekly iron supplementation in the treatment group, while 1272 were assigned to the placebo/non-intervention group. The analysis demonstrated a significant impact of weekly iron supplementation in reducing the risk of anemia by 20% (Risk ratio = 0.8, 95%CI: 0.69, 0.93; test for heterogeneity I² = 28.12%, P < 0.001). Moreover, there is no publication bias on the effect of WIFAS on Anemia with a p-value of 0.798 (Figure 4).

Effect of IFAS on School and cognitive Performance-Narrative synthesis

The study conducted in Mali 2012 ³² explored that iron-folic acid supplementation has a significant effect on school attendance increment (p = .049) and showed borderline significance on school grades (p = .08). Despite our efforts to secure the full-text article through email correspondence with the author, it remains unavailable. However, we relied on information from a conference proceeding abstract paper conducted in Sudan. According to this abstract, intermittent iron with folic acid supplementation did not show a significant association with school performance in the experimental group when compared to the control group, which received folic acid alone ⁴⁰. This lack of significance may be attributed to the complex nature of academic achievement, suggesting

that various factors contribute to school performance beyond the scope of iron and folic acid supplementation.

Regarding cognitive performance, the study conducted in South Africa ³⁷ revealed that iron supplementation increased the number of words recalled at HVLT recall 2 (intervention effect: 0.90; 95% CI: 0.18, 1.62). In anemic children, iron increased scores in the Atlantis Delayed test (1.51; 95% CI: 0.03, 2.99) and HVLT recall 2 (2.02; 95% CI: 0.55, 3.49).

Mental Health Problem- Narrative Synthesis

No trials were reported in this outcome in Sub-Sahara Africa.

Certainty of Evidence

To evaluate the certainty of evidence, we considered factors such as risk of bias, inconsistency, indirectness, imprecision, publication bias, and additional considerations like large effect, dose-response, and confounders. The assessment of risk of bias utilized the Cochrane⁴¹ risk of bias tool for 2019, encompassing criteria such as sequence generation, allocation concealment, blinding/masking of the intervention, intention-to-treat analysis, blinding/masking of outcome assessors, and freedom from other biases. Inconsistency was explored through the heterogeneity (I²) of the overall effect in the meta-analysis. Indirectness was scrutinized for external validity or generalizability (PICO), applicability, and any deviations from the research question. Imprecision was investigated through wide confidence intervals, including those indicating a null effect and high relative risk (RR > 0.75 or > 1.25). Additionally, we assessed publication and other biases. Based on our findings, we moderately recommend that weekly iron-folic acid supplementation (WIFAS) increases serum ferritin and hemoglobin levels while reducing both anemia and schistosomiasis (Supplemental Table 2).

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Discussion

The current study incorporated 17 randomized trials in a systematic review to assess the impact of weekly iron-folic acid supplementation (WIFAS) on various health indicators including serum ferritin, hemoglobin, anemia, mental, school, and cognitive performance. The trials were distributed across East Africa (six studies), Southern Africa (five studies), West Africa (five studies) and Northern Africa (One study).

The meta-analysis revealed the positive effects of WIFAS on serum ferritin and hemoglobin levels. Additionally, the WIFAS demonstrated a reduction in anemia consistent with findings from a study reviewed by De-Regil LM, et.al. This suggests that intermittent iron supplementation is effective in improving hemoglobin concentrations and reducing the risk of anemia or iron deficiency in children under 12 years of age, although it is less effective than daily supplementation in preventing or controlling anemia ⁶. The findings of Ana C Fernández-Gaxiola 1 and Luz Maria De-Regil about Intermittent iron supplementation for reducing anemia and its associated impairments in adolescent and adult menstruating women supported our findings ⁶.

The findings of our study align with the World Health Organization (WHO) recommendations, supporting the guideline that advocates for the intermittent use of iron and folic acid supplements as a public health measure. This recommendation aims to reduce anemia and enhance iron status among menstruating women, emphasizing the global significance of evidence-informed strategies in addressing nutritional deficiencies ⁴². Furthermore, our findings are consistent with the recommendation advocating for weekly iron-folic acid supplementation (WIFS) over daily supplements. This approach serves as a preventive and sustainable long-term strategy for improving iron status and reducing the prevalence of anemia. The rationale behind this approach is rooted in the understanding that daily oral iron administration can surpass an individual's safe capacity to assimilate iron effectively—covering absorption, utilization, and metabolism. The positive outcomes observed with WIFS align with the "mucosal block" hypothesis. According to this hypothesis, administering iron every week allows sufficient time for the shedding of cells loaded with iron from a previous dose. This shedding process contributes to increased iron absorption, reinforcing the efficacy of the WIFS approach ^{43,44}.

UNICEF's latest nutrition strategy, released in 2021, incorporates WIFAS as an intervention in the result area focusing on 'middle childhood and adolescents' ⁴⁵. Nutrition guidance specific to this target group has also been issued by UNICEF ⁴⁶. In regions where the prevalence of anemia among

menstruating adult women and adolescent girls falls within the range of 20-39.9%, the guidance recommends weekly supplementation of 60 mg of elemental iron and 2800 µg of folic acid for three months, followed by three months of no supplementation, and then restarting the supplementation. It further suggests that, if feasible, intermittent supplementation should continue throughout the school calendar year in these settings.

The systematic review indicates that IFAS has a positive impact on school attendance and cognitive performance. This aligns with assessments from the WHO and Copenhagen Consensus Challenge, which estimate a high benefit-to-cost ratio for iron interventions. The ratio is based on resource savings, enhancements in cognitive development and schooling, and increased physical productivity, reaching as high as 200:1. Emphasizing the prevention of iron deficiency anemia (IDA) in adolescents is strategically crucial, considering potential gains in physical capacity, cognitive ability, and, for adolescent girls, improved pregnancy outcomes and intergenerational benefits ^{47,48}.

Strength and limitations of the study

The strength of this study lies their quality in the incorporation of five databases to search for articles. Additionally, we investigated the impact of once-weekly iron-folic acid supplementation on serum ferritin, hemoglobin, anemia, and academic performance. However, our study is subject to inherent limitations related to the effects of intermittent iron and folic acid supplementation on serum ferritin, hemoglobin, anemia, cognitive and school performance, which broadens the scope of the study. The analysis faces challenges owing to the use of various tools to assess specific domains, complicating comparisons between intervention outcomes. Substantial differences in intervention design, including dose, form of iron supplements, and frequency and duration of supplementation, add complexity. Establishing an optimal dose, frequency, or duration for improved or reduced outcomes for school performance remains elusive. There is no trial regarding the effect of IFAS on mental health. Additionally, the potential influence of other micronutrients remains unclear in some studies. With two studies featuring low-quality studies, and the researchers acknowledge the possibility of missing relevant studies.

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Conclusion

Weekly iron folic acid supplementation proves effective in enhancing serum ferritin, hemoglobin concentrations and lowering the risk of anemia or iron deficiency in adolescents compared to a

placebo or no intervention. Moreover, iron supplementation demonstrates positive effects on verbal and nonverbal learning and memory, especially in children with anemia. Similarly, there are no good enough studies to examine the effect of WIFAS and school performance. Despite these benefits, information on mental health problems, mortality, and potential side effects remains insufficient.

Author Contributions

The authors' responsibilities were as follows: SK, BW, KHA: Designed and supervised the study, ensured the quality of the data, and made a substantial contribution to the local implementation of the study and SK, KHA, BW, BM assisted in the analysis and interpretation of the data. All authors critically reviewed the manuscript. SK, the corresponding author did the analysis & drafted the manuscript and had the responsibility to submit the manuscript for publication.

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Competing interests: The authors declare that they have no competing interests.

Patient and public involvement: Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Consent for publication: Not applicable

Ethics approval: Not applicable

Provenance and peer review: Not commissioned; externally peer reviewed.

Data availability statement: All data relevant to the study are included in the article or uploaded as supplementary information.

Refe	rences
1.	UNICEF, WHO, and C. Iron & Folic Acid (IFA) Supplementation for Adolescent Girls and Women. Participants Manual for Health Workers. (2017).
2.	Leroy, J. L., Ruel, M., Habicht, JP. & Frongillo, E. A. Linear Growth Deficit Continues to Accumulate beyond the First 1000 Days in Low- and Middle-Income Countries: Global Evidence from 51 National Surveys. <i>J. Nutr.</i> 144 , 1460–1466 (2014).
3.	Safiri, S. <i>et al.</i> Burden of anemia and its underlying causes in 204 countries and territories 1990–2019: results from the Global Burden of Disease Study 2019. <i>J. Hematol. Oncol.</i> 14 185 (2021).
4.	Toteja, G. S. <i>et al.</i> Prevalence of Anemia among Pregnant Women and Adolescent Girls in 16 Districts of India. <i>Food Nutr. Bull.</i> 27 , 311–315 (2006).
5.	Camaschella, C. Iron-Deficiency Anemia. N. Engl. J. Med. 372, 1832–1843 (2015).
6.	Sylvetsky, A. C., Jefferds, M. E. D., De-Regil, L. M. & Dowswell, T. Intermittent iron supplementation for improving nutrition and developmental outcomes in children. in <i>Cochrane Database of Systematic Reviews</i> (ed. De-Regil, L. M.) (John Wiley & Sons, Ltd, 2011). doi:10.1002/14651858.CD009085.
7.	WHO. Anaemia Policy Brief, WHO, Geneva, Switzerland. (2019).
8.	Gelli, A. <i>et al.</i> Evaluation of alternative school feeding models on nutrition, education, agriculture and other social outcomes in Ghana: rationale, randomised design and baseline data. <i>Trials</i> 17 , 37 (2016).
9.	Lam, L. F. & Lawlis, T. R. Feeding the brain – The effects of micronutrient interventions on cognitive performance among school-aged children: A systematic review of randomized controlled trials. <i>Clin. Nutr.</i> 36 , 1007–1014 (2017).
10.	Jáuregui-Lobera, I. Iron deficiency and cognitive functions. <i>Neuropsychiatr. Dis. Treat.</i> 2087 (2014) doi:10.2147/NDT.S72491.
11.	Samson, K. L. I., Fischer, J. A. J. & Roche, M. L. Iron Status, Anemia, and Iron Interventions and Their Associations with Cognitive and Academic Performance in Adolescents: A Systematic Review. <i>Nutrients</i> 14 , 224 (2022).
12.	Low, M., Farrell, A., Biggs, BA. & Pasricha, SR. Effects of daily iron supplementation in primary-school–aged children: systematic review and meta-analysis of randomized controlled trials. <i>Can. Med. Assoc. J.</i> 185 , E791–E802 (2013).
13.	Chen, Z. <i>et al.</i> Effect of Oral Iron Supplementation on Cognitive Function among Children and Adolescents in Low- and Middle-Income Countries: A Systematic Review and Meta-Analysis. <i>Nutrients</i> 14 , 5332 (2022).
14.	Kaufman AS, Lichtenberger EO, Fletscher-Janzen E, K. L. Essentials of KABC-II Assessment. (2005).
15.	Brandt, J. The Hopkins Verbal Learning Test development of a new memory test with six equivalent forms. <i>Clin Neuropsychol</i> 5 , 125–42 (1991).
20	
	For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

16. Ogunlade, A. O. et al. Point-of-use micronutrient fortification: lessons learned in implementing a preschool-based pilot trial in South Africa. Int. J. Food Sci. Nutr. 62, 1–16 (2011).Muthavya, S. *et al.* Effect of fortification with multiple micronutrients and n-3 fatty acids 17. on growth and cognitive performance in Indian schoolchildren: the CHAMPION (Children's Health and Mental Performance Influenced by Optimal Nutrition) Study. Am. J. Clin. Nutr. 89, 1766–1775 (2009). 18. Dalton, A. et al. A randomised control trial in schoolchildren showed improvement in cognitive function after consuming a bread spread, containing fish flour from a marine source. Prostaglandins, Leukot. Essent. Fat. Acids 80, 143–149 (2009). 19. JBI. Joanna Briggs Institute (JBI) Critical Appraisal tools for use in JBI Systematic Reviews Checklist for Randomized Controlled Trials. (2017). 20. Rücker G, Schwarzer G, Carpenter JR, S. M. Undue reliance on I2 in assessing heterogeneity may mislead. BMC Med Res Methodol 8, 79 (2008). 21. Begg CB, M. M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1088–101 (1994). Egger M, Smith GD, Schneider M, M. C. Bias in meta-analysis detected by a simple, 22. graphical test. BMJ 315, 629-34 (1997). 23. Moher D, Liberati A, Tetzlaff J, A. D. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 151, 264-9 w264 (2009). 24. Beasley, N. M. R. et al. The impact of weekly iron supplementation on the iron status and growth of adolescent girls in Tanzania. Trop. Med. Int. Heal. 5, 794-799 (2000). Handiso, Y. H., Belachew, T., Abuye, C., Workicho, A. & Baye, K. A community-based 25. randomized controlled trial providing weekly iron-folic acid supplementation increased serum- ferritin, -folate and hemoglobin concentration of adolescent girls in southern Ethiopia. Sci. Rep. 11, 9646 (2021). 26. Leenstra, T. et al. The effect of weekly iron and vitamin A supplementation on hemoglobin levels and iron status in adolescent schoolgirls in western Kenya. Eur. J. Clin. Nutr. 63, 173-182 (2009). Olsen, A., Nawiri, J., Magnussen, P., Krarup, H. & Friis, H. Failure of twice-weekly iron 27. supplementation to increase blood haemoglobin and serum ferritin concentrations: results of a randomized controlled trial. Ann. Trop. Med. Parasitol. 100, 251–263 (2006). 28. Horjus, P., Aguavo, V. M., Roley, J. A., Pene, M. C. & Meershoek, S. P. School-Based Iron and Folic Acid Supplementation for Adolescent Girls: Findings from Manica Province, Mozambique. Food Nutr. Bull. 26, 281–286 (2005). 29. Lawless, J. W., Latham, M. C., Stephenson, L. S., Kinoti, S. N. & Pertet, A. M. Iron Supplementation Improves Appetite and Growth in Anemic Kenyan Primary School Children. J. Nutr. 124, 645–654 (1994). 21

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3 4 5 6	30.	Hall, A. <i>et al.</i> A randomised trial in Mali of the effectiveness of weekly iron supplements given by teachers on the haemoglobin concentrations of schoolchildren. <i>Public Health Nutr.</i> 5 , 413–418 (2002).
7 8 9 10	31.	Gosdin, L. <i>et al.</i> A School-Based Weekly Iron and Folic Acid Supplementation Program Effectively Reduces Anemia in a Prospective Cohort of Ghanaian Adolescent Girls. <i>J. Nutr.</i> 151 , 1646–1655 (2021).
11 12 13 14 15	32.	Ayoya, M. A., Spiekermann-Brouwer, G. M., Traoré, A. K. & Garza, C. Effect on School Attendance and Performance of Iron and Multiple Micronutrients as Adjunct to Drug Treatment of Schistosoma-Infected Anemic Schoolchildren. <i>Food Nutr. Bull.</i> 33 , 235–241 (2012).
16 17 18 19	33.	Ayoya, M. A. <i>et al.</i> Multiple Micronutrients Including Iron Are Not More Effective Than Iron Alone for Improving Hemoglobin and Iron Status of Malian School Children ,. <i>J. Nutr.</i> 139 , 1972–1979 (2009).
20 21 22 23 24	34.	Gies, S. <i>et al.</i> Effects of Weekly Iron and Folic Acid Supplements on Malaria Risk in Nulliparous Women in Burkina Faso: A Periconceptional, Double-Blind, Randomized Controlled Noninferiority Trial. <i>J. Infect. Dis.</i> 218 , 1099–1109 (2018).
24 25 26 27 28	35.	Baumgartner, J. <i>et al.</i> Overweight impairs efficacy of iron supplementation in iron- deficient South African children: a randomized controlled intervention. <i>Int. J. Obes.</i> 37 , 24–30 (2013).
29 30 31 32	36.	Nchito, M., Wenzel Geissler, P., Mubila, L., Friis, H. & Olsen, A. Effects of iron and multimicronutrient supplementation on geophagy: a two-by-two factorial study among Zambian schoolchildren in Lusaka. <i>Trans. R. Soc. Trop. Med. Hyg.</i> 98 , 218–227 (2004).
33 34 35 36	37.	Baumgartner, J. <i>et al.</i> Effects of iron and n-3 fatty acid supplementation, alone and in combination, on cognition in school children: a randomized, double-blind, placebo-controlled intervention in South Africa. <i>Am. J. Clin. Nutr.</i> 96 , 1327–1338 (2012).
37 38 39 40 41	38.	Taylor, M., Jinabhai, C. C., Couper, I., Kleinschmidt, I. & Jogessar, V. B. The effect of different anthelmintic treatment regimens combined with iron supplementation on the nutritional status of schoolchildren in KwaZulu-Natal, South Africa: a randomized controlled trial. <i>Trans. R. Soc. Trop. Med. Hyg.</i> 95 , 211–216 (2001).
42 43 44 45	39.	Mwanakasale, V., Siziya, S., Mwansa, J., Koukounari, A. & Fenwick, A. Impact of iron supplementation on schistosomiasis control in Zambian school children in a highly endemic area. <i>Malawi Med. J.</i> 21 , (2009).
46 47 48 49 50 51 52	40.	Nagmeldin Abbas Fageer, M., Hussein, M. D., N Abbas Fagiri, M. & Osman, M. 1239 Randomized controlled trial on the effect of weekly iron/folic acid supplementation on anemia and school performance among school children in rural Sudan. in <i>Abstracts</i> A288.1-A288 (BMJ Publishing Group Ltd and Royal College of Paediatrics and Child Health, 2021). doi:10.1136/archdischild-2021-rcpch.501.
53	41.	Cochrane. RoB 2: A revised Cochrane risk-of-bias tool for randomized trials. (2019).
54 55 56 57	42.	WHO. Guideline: Intermittent Iron and Folic Acid Supplementation in Menstruating Women. Guideline: Intermittent Iron and Folic Acid Supplementation in Menstruating
57 58	22	
59 60		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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Women (2011).

- 43. Wright, A. J. A. & Southon, S. The effectiveness of various iron-supplementation regimens in improving the Fe status of anaemic rats. *Br. J. Nutr.* **63**, 579–585 (1990).
- 44. FE, V. Global consultation on Weekly Iron-Folic Acid Supplementation for preventing Anaemia in women of Reproductive Age Group. (2007).
- 45. UNICEF, U. N. C. F. Nutrition, for every child. UNICEF Nutrition Strategy 2020- 2030. (2020).
- 46. United Nations Children's Fund, U. Programming Guidance: Nutrition in Middle Childhood and Adolescence. (2021).
- 47. Hoddinott, J., Rosegrant, M. & Torero, M. HUNGER AND MALNUTRITION: Copenhagen Consensus Challenge. (2012).
- 48. WHO. Preventing Iron deficiency Anemia in Adolescents: Role of WIFAS: World Health Organization, Regional Office for South-East Asia, Indraprastha Estate, Mahatma Gandhi Marg, New Delhi-110 002. (2011).

Figures

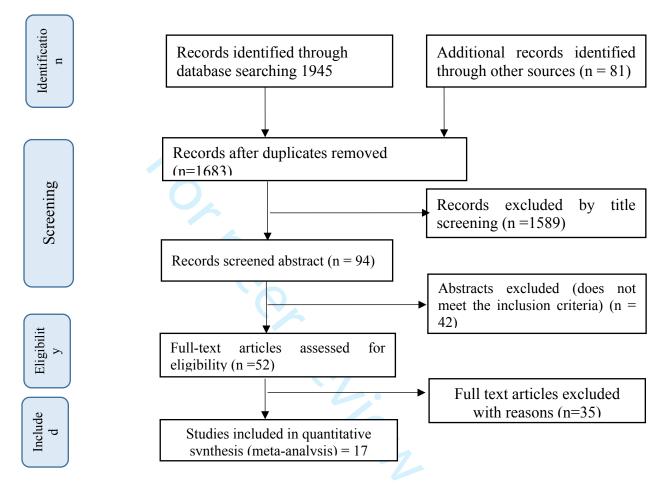
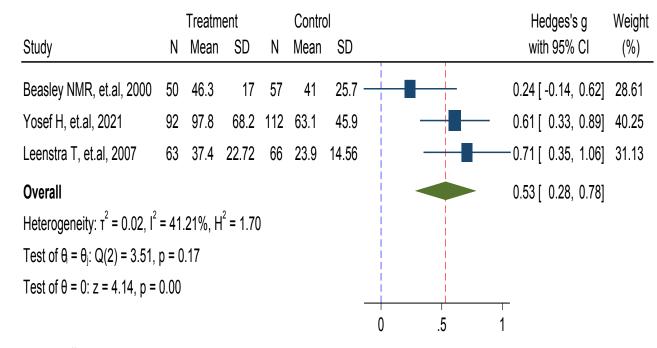


Figure 1. PRISMA flow diagram illustrating the study selection process of iron and folic acid supplementation effect on iron status, mental health and school performance articles.

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Random-effects REML model

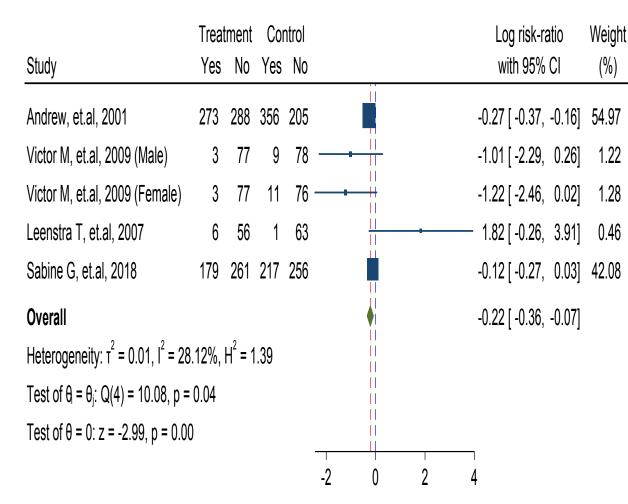
Figure 2: Meta-analysis of the effect of once-weekly IFAS on serum ferritin

		Treatm	ent		Contro	ol			Hedges's g	We
Study	N	Mean	SD	N	Mean	SD			with 95% Cl	(
Andrew H, et.al, 2001	551	11.64	1.27	562	11.26	1.27		ŀ	0.30 [0.18, 0.42]	18
Beasley NMR, et.al, 2000	57	11.94	1.06	62	11.85	.79			0.10 [-0.26, 0.45]	15
Yosef H, et.al, 2021	92	14.5	1.3	112	13.2	.7			 -1.28 [0.97, 1.58]	16
Leenstra T, et.al, 2007	80	13.52	2.14	109	13.5	1.55			0.01 [-0.28, 0.30]	16
Victor M, et.al, 2009 (Male)	80	12.98	1.115	87	12.66	1.331			0.26 [-0.04, 0.56]	16
Victor M, et.al, 2009 (Female)	73	13.02	1.116	84	12.65	1.354			0.29 [-0.02, 0.61]	16
Overall									0.37 [0.01, 0.73]	
Heterogeneity: $\tau^2 = 0.18$, $I^2 = 91$.62%,	$H^2 = 1^2$	1.93				i I			
Test of $\theta_i = \theta_j$: Q(5) = 44.68, p =	0.00							 		
Test of θ = 0: z = 2.02, p = 0.04										

Random-effects REML model

Figure 3: Meta-analysis of the effect of once-weekly IFAS on Hemoglobin

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Random-effects REML model

Figure 4: Meta-analysis of the effect of once-weekly IFAS on Anemia

		Treatm	ent		Contro	ol				Hedges	's g	Weight
Study	Ν	Mean	SD	Ν	Mean	SD				with 959	6 CI	(%)
Beasly et.al, 2000	50	46.3	17	57	41	25.7				0.24 [-0.14	4, 0.62]	19.89
Yosef H, et.al, 2021	92	97.8	68.2	112	63.1	45.9	-	i T		0.61 [0.33	8, 0.89]	21.25
Lawless, et.al, 1994	44	39.1	20.6	42	25.1	18.9	_	-		0.70 [0.27	7, 1.13]	19.06
Mohammed A, et.al, 2009	64	93.33	47.44	63	30.2	25.87				— 1.64 [1.24	l, 2.04]	19.56
Leenstra, et.al, 2007	63	37.4	22.72	66	23.9	14.56	_	-		0.71 [0.3	5, 1.06]	20.25
Overall										0.77 [0.33	8, 1.22]	
Heterogeneity: $\tau^2 = 0.22$, I^2	² = 86.	81%, H	² = 7.58									
Test of $\theta_i = \theta_j$: Q(4) = 27.06	6, p =	0.00										
Test of θ = 0: z = 3.39, p =	0.00											
							0.5	1	1.5	2		
Random-effects REML mode)											

Supplemental Figure 1: Meta-analysis of the effect of IFAS on serum ferritin

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		Treatm	ent		Contro	ol		Hedges's g	Weight
Study	Ν	Mean	SD	N	Mean	SD		with 95% CI	(%)
Once Weekly									
Beasley, et.al, 2000	50	46.3	17	57	41	25.7		0.24 [-0.14, 0.62]	19.89
Yosef H, et.al, 2021	92	97.8	68.2	112	63.1	45.9		0.61 [0.33, 0.89]	21.25
Leenstra T, et.al, 2007	63	37.4	22.72	66	23.9	14.56		0.71 [0.35, 1.06]	20.25
Heterogeneity: $\tau^2 = 0.02$, $I^2 = 4$	1.219	%, H ² = ⁻	1.70				•	0.53 [0.28, 0.78]	
Test of $\theta_i = \theta_j$: Q(2) = 3.51, p =	0.17								
Daily or 5*/week									
Lawless et.al, 1994	44	39.1	20.6	42	25.1	18.9		0.70 [0.27, 1.13]	19.06
Mohammed Ag A, et.al, 2009	64	93.33	47.44	63	30.2	25.87		- 1.64 [1.24, 2.04]	19.56
Heterogeneity: $\tau^2 = 0.39$, $I^2 = 8$	9.73%	%, H ² = 9	9.74					-1.17 [0.25, 2.09]	
Test of $\theta_i = \theta_j$: Q(1) = 9.74, p =	0.00								
Overall								0.77 [0.33, 1.22]	
Heterogeneity: $\tau^2 = 0.22$, $I^2 = 8$	6.81%	%, H ² = ⁻	7.58						
Test of $\theta_i = \theta_j$: Q(4) = 27.06, p	= 0.0	0							
Test of group differences: $Q_b(1)$) = 1.	74, p =	0.19						
							0 .5 1 1.5	⊤ 2	

Random-effects REML model

Supplemental Figure 2: Sub-group Meta-analysis of the effect of IFAS on serum ferritin

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		Treatmo	ent		Contro	ol		Hedges's g	Weigł
Study	Ν	Mean	SD	Ν	Mean	SD		with 95% CI	(%)
Community									
Yosef H, et.al, 2021	92	14.5	1.3	112	13.2	.7	-	- 1.28 [0.97, 1.58]	16.50
Heterogeneity: $\tau^2 = 0.00$, $I^2 = .9$	ώ, Η ² =							1.28 [0.97, 1.58]	
Test of $\theta_i = \theta_j$: Q(0) = 0.00, p =									
School									
Andrew H, et.al, 2001	551	11.64	1.27	562	11.26	1.27	-	0.30 [0.18, 0.42]	18.2
Beasley NMR, et.al, 2000	57	11.94	1.06	62	11.85	.79		0.10 [-0.26, 0.45]	15.7
Leenstra T, et.al, 2007	80	13.52	2.14	109	13.5	1.55		0.01 [-0.28, 0.30]	16.6
Victor M, et.al, 2009 (Male)	80	12.98	1.115	87	12.66	1.331		0.26 [-0.04, 0.56]	16.4
Victor M, et.al, 2009 (Female)	73	13.02	1.116	84	12.65	1.354		0.29 [-0.02, 0.61]	16.3
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 16$	5.33%	, H ² = 1.	20				•	0.23 [0.12, 0.35]	
Test of $\theta_i = \theta_j$: Q(4) = 4.11, p =	0.39								
Overall								0.37 [0.01, 0.73]	
Heterogeneity: $\tau^2 = 0.18$, $I^2 = 9^{-1}$	1.62%	, H ² = 11	1.93						
Test of $\theta_i = \theta_j$: Q(5) = 44.68, p =	0.00								
Test of group differences: Q _b (1)	= 40.	06, p =	0.00						
						٦ 5	5 0 .5 1	1.5	
Random-effects REML model									

Supplemental Figure 3: Sub-group Meta-analysis of the effect of once-weekly IFAS on Hemoglobin

	nental Table 1: The Joanna 1				B№	IJ Open					36/bmjopen-202 ted by copyrigt			Ρ	age 32
	nental Table 1: The Joanna l									byed to as	ΞΞ	qualit	y of ir	cluded	
S/No	Studies	Was there true randomization	Was allocation to treatment groups concealed?	Were treatment groups similar at the baseline?	Were participants blind to treatment assignment?	Were those delivering treatment blind to treatment assignment?	Were outcomes assessors blind to treatment assignment?	Are groups identically other than intervention?	Was follow-up complete and if not, were differences b/n groups	Were participants analyzed in the groups to which they were randomized?	sdnoid for uses related to text and data mining Al training, and similar technologies. المزبودة te 33 مەنباتلىنا بايمەتە2024. Sowenioaded from http://bmjopen.bmj.com/ on June 10, 2025 at Universite 33 مەنباتلىنا بايمەتە 10, 2025 at Universite	Were outcomes measured reliably?	Was appropriate statistical analysis used?	Was the trial design appropriate, and any deviations from the standard RCT	Total Yes
1.	Beasly, et.al (2000, Tanzania)	2	0	2	0	0	1	0	2	0	om http:// ta mining	1	0	2	10
2.	Yosef H, et.al (2021, Ethiopia)	2	1	2	0	0	1	2	2	2	bmjopen. A traini	2	2	2	18
3.	Andrew Hall, et.al (2001, Mali)	2	0	2	1	1	1	2	2	0	.bmj.com ng, and s	2	2	2	16
4.	Olsen, et.al (2006, Kenya)	2	2	2	2	2	2	2	2	2	imilar	1	2	2	24
5.	Lawless, et al (1994, Kenya)	2	2	2	2	2	1	2	2	2	une 10 techn	1	2	2	22
6.	Victor Mwanakasale (2009, Zambia)	1	1	2	1	1	1	1	1	0	, 2025 at ologies.	1	2	2	8
7.	Nchito (2009, Zambia)	2	2	2	2	2	2	2	2	1	Unive	1	2	2	22
8.	J. Baumgartner (2012, South Africa)	2	2	2	2	2	2	2	2	2	rsite Paris	2	2	2	26

					BN	1J Open					136/bmjopen-2024-084033 on 11 June 2024. Downloaded from <u>http://bmjopen.bmj.com/</u> on June 10, 2025 at Universite Paris Est Creteil . Including for uses related to text and data mining. Al training, and similar technologies.				
9.	Leenstra, et.al (2007, Kenya)	2	2	2	2	2	2	2	2	1	-2024-08403 /righ <u>t, incluc</u>	1	2	2	22
10	J. Baumgartner (2013, South Africa)	2	2	2	2	2	2	2	2	2	3 on 11 Ju ling for us	2	2	2	26
11	. Mohamed Ag Ayoya, (2009, Mali)	2	0	2	0	0	1	2	1	0	une 2024. Ses relater	2	2	2	14
12	Nchito, (2003, Zambia)	2	2	2	2	2	2	2	2	1	d to te	1	2	2	22
13	. Mohamed Ag Ayoya, (2012, Mali)	2	0	2	0	0	1	2	1	0	Noaded fro	2	2	2	14
14	. Sabine G, et.al. (2018, Burkina Faso)	2	2	2	0	2	2	2	2	2	om http:// ta mining	2	2	2	24
15	. Lucas G, et.al, (2021, Ghana)	0	NA	NA	0	NA	NA	2	2	2	omjopen.t Al trainir	2	2	2	14
16	. Peter H, et.al, (2005, Mozambique)	1	1	2	0	0	1	2	2	2	omi.com/ 1g, and si	2	2	2	16
17	Maisoon NA Fageer,et.al, (2021, Sudan)	2	2	1	2	2	2	2	2	1	on June 1 milar tech	1	2	2	18

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Supplemental Table 2:	The assessment of t	the certainty of	f evidence of include	d studies in Meta-analysis
11		2		5

										ing	
Outcomes	Number of studies	Number of participants	Study design	Risk of Bias	Inconsistency (Heterogeneity	Indirectness	Imprecision	Publication bias (Eggers test with P-	Other considerations (Large effect, dose-response,	Effect size on population spen to built of PEOPEOE dum, qt uo g RR)	Certainty of evidence
Serum Ferritin (Once-Weekly)	3	440	RCT	Seriou s	Low	No	No	No	No	H=0053 (0.28, 0.78)	Moderate
Serum Ferritin (More than once weekly)	5	653	RCT	Seriou s	Low	No	No	No	Concern	H H H H H H H H H H H H H H H H H H H	Low
Hemoglobin (Once weekly)	5	1949	RCT	Seriou s	Low	No	No	No	No	H=2037 (0.01, 0.73)	Moderate
Anemia (Once- weekly)	4	2505	RCT	Low	Low	No	conc ern	No	No	RI .8 (0.69, 0.93)	Moderate
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		F	or peer r	eview only	- http://b	mjopen.l	omj.com/	/site/about/g	uidelines.xhtml	÷	

PRISMA 2020 Checklist

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PRIS	SMA 2	BMJ Open ded by copyrig 2020 Checklist	
3 Section and Topic	ltem #	Checklist item	Location where item is reported
6 TITLE			
7 Title	1	Identify the report as a systematic review.	
8 ABSTRACT			
9 Abstract	2	See the PRISMA 2020 for Abstracts checklist.	
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	
1 Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	
14 METHODS	1		
15 Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	
16 Information 17 sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted benefity studies. Specify date when each source was last searched or consulted.	/ the
18 Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	
19 Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each r and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	ecord
2 Data collection 22 process 23	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each reports whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of antomation tools used in process.	the
24 25 24	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each success of the sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	ו
20 27 28	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe ar assumptions made about any missing or unclear information.	Ŋ
29 Study risk of bias	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how not study and whether they worked independently, and if applicable, details of automation tools used in the process.	each
3 Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presenta	
32 Synthesis 33 methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study in exertion characteristics a comparing against the planned groups for each synthesis (item #5)).	and
34 35	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	
36	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	
37 38 20	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	
39 40	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	
41	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	
42 Reporting bias 43 assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases)	
44 Certainty 45 assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome. For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	
46 47		·	I



PRISMA 2020 Checklist

		BMJ Open de by	Page 3	36 of
PRIS	SMA 2	BMJ Open 2020 Checklist		
Section and Topic	ltem #	Checklist item	Locatio where i is repor	tem
RESULTS		dir -		
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the review, ideally using a flow diagram.	er of studies included in	
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were by	эd.	
Study characteristics	17	Cite each included study and present its characteristics.		
Risk of bias in studies	18	Present assessments of risk of bias for each included study.		
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an efective (e.g. confidence/credible interval), ideally using structured tables or plots.	mate and its precision	
Results of	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.		
syntheses	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate a confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the summary estimates and the summary estimates analysis was done, present for each the summary estimates and the		
	20c	Present results of all investigations of possible causes of heterogeneity among study results.		
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.		
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis asses		
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.		
DISCUSSION				
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.		
	23b	Discuss any limitations of the evidence included in the review.		
	23c	Discuss any limitations of the review processes used.		
	23d	Discuss implications of the results for practice, policy, and future research.		
OTHER INFORMA	TION			
Registration and	24a	Provide registration information for the review, including register name and registration number, or state that the rai www.	as not registered.	
protocol	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.		
	24c	Describe and explain any amendments to information provided at registration or in the protocol.		
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.		
Competing interests	26	Declare any competing interests of review authors.		
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data studies; data used for all analyses; analytic code; any other materials used in the review.	racted from included	
From: Page MJ, Mo 10.1136/bmj.n71	cKenzie	JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting system For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml For more information, visit: <u>http://www.prisma-statement.org/</u>	stematic reviews. BMJ 2021;372:n71.	do

Weekly Iron-Folic Acid Supplementation and Its Impact on children and adolescents iron status, Mental Health, and School Performance: A Systematic Review and Meta-Analysis in Sub-Saharan Africa.

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Weekly Iron-Folic Acid Supplementation and Its Impact on children and adolescents' Iron Status, Mental Health, and School Performance: A Systematic Review and Meta-Analysis in Sub-Saharan Africa.

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Abstract

Objective: This systematic review and meta-analysis aimed to comprehensively assess the impact of Weekly Iron-Folic Acid Supplementation (WIFAS) on the nutrition, health, and educational outcomes of children and adolescents in Sub-Saharan Africa.

Design: Systematic review and Meta-analysis was used.

Data Sources: Five databases, namely, MEDLINE, Scopus, Web of Science, Cochrane Library, and Google Scholar, were systematically searched for relevant articles up to August 23, 2023.

Eligibility Criteria: It was focused on randomized controlled trials involving children and adolescents in Sub-Saharan Africa, exploring the effects of iron supplementation on various outcomes, such as serum ferritin and hemoglobin levels, anemia, mental health, and school performance.

Data Extraction and Synthesis: The Joanna Briggs Institute Critical Appraisal tools were utilized for quality assessment, with two independent reviewers thoroughly evaluating each paper. Using the Cochrane risk of bias tool, we evaluated certainty of evidence such as risk of bias, inconsistency, indirectness, imprecision, and publication bias.

Results: A systematic review of 17 articles revealed that WIFAS significantly increased serum ferritin levels in adolescent girls (Hedge's g = 0.53, 95% CI: 0.28, 0.78; heterogeneity I² = 41.21%, P < 0.001) and hemoglobin levels in school-age children (Hedge's g = 0.37, 95% CI: 0.01, 0.73; heterogeneity I² = 91.62%, P < 0.001). The analysis further demonstrated a substantial reduction in the risk of anemia by 20% (risk ratio = 0.8, 95% CI: 0.69, 0.93; heterogeneity I² = 28.12%, P < 0.001).

Conclusion: WIFAS proved effective in enhancing serum ferritin and hemoglobin concentrations and lowering the risk of anemia in school-age children and adolescents compared to placebo. Similarly, there are not enough studies to examine the effects of WIFAS on school performance. However, information regarding mental health problems, mortality, and potential side effects remains insufficient.

Strength and limitation

- Hedge's g addresses the issue of overestimation of the effect size in small samples.

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- Certainity of evidence for serum ferritin, hemoglobin and anemia are moderate.
- Incorporation of five databases to search for articles.
- Diverse intervention designs, spanning dose, and iron supplement form contributes to complexity
- Substantial differences in intervention design, including dose, form of iron supplements, and frequency and duration of supplementation, add complexity.

Prospero Registration: CRD42023397898

Keywords: WIFAS, Anemia, Sub-Saharan Africa, School Performance, Adolescent

Introduction

Adolescents are a subset of children whose age ranges from 10-19 years ¹. This age group makes up the greatest proportion of the population (23%) in Sub-Saharan Africa, which is about twice that of the industrialized countries ². Adolescence, marked by the transition to adulthood, is a critical phase characterized by significant growth, behavioral maturation, and sexual development. This represents the second growth spurt in life, particularly for girls who undergo unique experiences including menstruation, emotional changes, nutritional requirements, and identity formation. Adolescents require heightened nutritional demands, with a specific emphasis on the need for iron. This period lays the foundation for adult health and economic wellbeing. Adolescents attain 20% final adult height and 50% adult weight, underscoring its pivotal role in shaping future health outcomes. Consequently, adolescent girls emerge as a physiologically significant group, warranting special attention to their nutritional requirements, given their role as potential future mothers ^{3,4}.

Anemia, a widespread global health concern, impacts approximately 1.6 billion individuals. According to the World Health Organization (WHO), approximately 50% of anemia cases are attributed to iron deficiency ⁵ and Moreover, the prevalence of anemia in Sub-Saharan Africa surpass to 39% ⁶. This condition serves as a direct marker of undernutrition and insufficient iron intake, posing a significant public health challenge for adolescents ⁷. Iron deficiency anemia in adolescence has the potential to impede growth, hinder motor and brain development, and increase the risk of illness and mortality. Failure to promptly address anemia during this critical period may lead to persistent challenges later in life ⁸.

Adolescents are particularly prone to iron deficiency and anemia due to a range of factors, including rapid growth, insufficient dietary iron intake, reduced bioavailability of dietary iron, and heightened susceptibility to infectious diseases, parasitic infections, and menstrual blood loss ⁷. The combination of these factors contributes to an increased risk of iron deficiency anemia in adolescent girls, emphasizing the need for targeted interventions and education to address the specific challenges faced by this demographic group ⁹.

Anemia and iron deficiency anemia may have long-term consequences for individuals, limiting their educational achievements and subsequently impacting their economic potential^{4,9,10}. The evidence strongly supports the relationship between anemia and cognitive development. Both iron deficiency and iron deficiency anemia have been identified as contributors to cognitive deficits. Understanding and addressing the relationship between anemia and cognitive development is vital for promoting optimal health and cognitive outcomes, especially in vulnerable populations such as children and adolescents ⁹⁻¹¹.

Iron plays a crucial role as an essential nutrient in the development and functioning of the brain. Its functions are diverse and contribute to various aspects of neural activity and neurotransmission. Some key roles of iron in the brain include ATP production, synthesis and packaging of neurotransmitters, and uptake and degradation of neurotransmitters ^{5,12}.

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Indeed, adolescence and school-age children are recognized as a pivotal period for implementing interventions to address anemia and lay the foundation for future health, particularly in terms of childbearing ^(1,2). Implementing iron supplementation as an effective strategy to combat iron deficiency can have a substantial impact on reducing the prevalence of anemia, improving public health outcomes, and enhancing the well-being of affected populations, particularly in resource-constrained settings ^{13–15}.

Although daily IFAS studies including systematic review and meta-analysis revealed that it improves iron status and reduces anemia but there is a notable scarcity of information regarding the effectiveness of weekly IFAS concerning a broader spectrum of school performance and health outcomes including mental health ⁸. The limitations of the available data underscore the need for comprehensive and standardized research methodologies to elucidate the full range of effects associated with WIFAS on diverse nutrition, education, and health parameters. Within the framework of this systematic review and meta-analysis, we aimed to assess the impact of WIFAS

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on serum ferritin levels, school performance, and mental health status among children and adolescents in the Sub-Saharan African region.

Methods

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Searching strategies

The review encompassed a comprehensive examination of various literature sources through an extensive search across four electronic databases, supplemented by a manual search of references from key articles, previous reviews, and grey literature, to thoroughly investigate the effects of IFAS on serum ferritin levels, school performance, and mental health. Our search for published articles was confined to individuals aged 6-19 years and studies conducted exclusively in sub-Saharan Africa. We systematically searched international databases, including Scopus, Web of PubMed (MEDLINE), Cochrane Science, Library, and Google Scholar. (((Adolescen*[Title/Abstract] OR "Youth*"[Title/Abstract] OR "primary school"[Title/Abstract] OR "teen*"[Title/Abstract] OR "secondary school"[Title/Abstract] OR "Schoolage"[Title/Abstract] OR school[Title/Abstract] OR School*[Title/Abstract] OR pediatrics [Title/Abstract] OR pediatric*[Title/Abstract] OR paediatric*[Title/Abstract] OR pediatric* [Title/Abstract] OR child[Title/Abstract] OR child*[Title/Abstract] OR children*[Title/Abstract] OR Pediatric[Mesh] OR Child[MeSH Terms] OR adolescent[MeSH Terms] OR "Schools"[Mesh]) AND (Iron[Title/Abstract] OR hematinics[Title/Abstract] OR ferrous[Title/Abstract] OR ferric[Title/Abstract] OR hematinic[Title/Abstract] OR haematinic[Title/Abstract] OR haematinics[Title/Abstract] OR "iron compounds"[Title/Abstract] OR "folic acid"[Title/Abstract] OR "Dietary "Weekly Iron Folic acid supplementation"[Title/Abstract] OR supplement*"[Title/Abstract] OR "Iron folic acid supplementation"[Title/Abstract] OR "iron folic acid tablet"[Title/Abstract] OR "Iron-folate supplement*"[Title/Abstract] OR "Iron-folate supplementation"[Title/Abstract] OR "Iron and folic acid supplementation"[Title/Abstract] OR "iron folic acid supplement*"[Title/Abstract] OR "Iron-folic acid"[Title/Abstract] OR Supplementation[Title/Abstract] OR Supplement[Title/Abstract] OR Supplement[Title/Abstract] OR IFAS[Title/Abstract] OR WIFAS[Title/Abstract] OR IFA[Title/Abstract] OR "Iron and Folic-Acid Supplementation"[Title/Abstract] OR Iron[MeSH Terms] OR folic acid[MeSH Terms] OR Dietary supplements [MeSH Terms])) AND ("Randomized controlled trials" OR RCT OR RCTs OR "Clinical Trial" OR "Controlled Clinical Trial" OR "quasi-randomized trials") AND (Africa, south of the Sahara [MeSH Terms]))). The search terms were combined using Boolean operators 'AND'/'OR'.

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All published articles up to August 23, 2023, were incorporated into the systematic review. The results of the database search were aggregated, and duplicate articles were eliminated using the online Rayyan Software (<u>https://www.rayyan.ai/</u>). This tool was also employed to download the full text of studies for further evaluation

Eligibility criteria

Inclusion criteria

Study area: Only studies conducted in Sub-Saharan Africa (South of the Sahara).

Publication condition: articles published in peer-reviewed journals.

Study design: all RCT and clinical trial studies

Intervention: Iron and/or folic acid supplementation

Language: Articles published in the English language.

Age: School-age children typically encompass a range of ages, including the adolescent group. In this study, individuals aged between 4 and 19 years, and both primary and secondary school children were included.

Exclusion criteria

Studies conducted related to iron fortification, and studies lacking specific outcome reporting were excluded from our analysis.

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Outcome measurement

In this study, the main focus was on evaluating the impact of WIFAS on key health indicators, including serum ferritin levels, hemoglobin concentrations, anemia prevalence, mental health, and school performance. Measurement of outcomes involved assessing serum ferritin (in µg/L) and hemoglobin (in g/dl) through mean and standard deviation calculations. For anemia, the prevalence was examined as binary outcomes post-supplementation. Moreover, the study delved into the assessment of school performance by considering the average scores of subjects, school grades and school attendance increment. Additionally, cognitive performance was thoroughly evaluated using a battery of cognitive tests specifically chosen, designed, or adapted for the age and cultural group under consideration. This battery included four subtests from the Kaufman Assessment Battery for children aged 3–18 years, second edition (KABC-II) ¹⁶, and the Hopkins Verbal Learning Test (HVLT) ¹⁷. The subtests chosen from the KABC-II encompassed the Atlantis (assessing working memory) and Atlantis Delayed (evaluating long-term memory and retrieval)

tests from the learning scale, the Hand Movement test (measuring short-term memory) from the sequential processing scale, and the Triangles test (assessing visuospatial cognition) from the simultaneous processing scale ^{18–20}.

Data extraction

The extraction of data was carried out independently by two authors (SK and BM) utilizing a standardized spreadsheet for data extraction. The format for data extraction encompassed details such as the primary author, year of publication, the geographical region where the study was conducted, sample size, frequency of supplementation, age, sex, dose of supplements, outcome measurement, duration of the intervention, and information related to the randomized controlled trials (mean, standard deviation, median, and interquartile range proportion).

Quality assessment

For the assessment of the methodological quality of the included studies, we employed the Joanna Briggs Institute (JBI) Critical Appraisal tools designed for use in systematic reviews of randomized controlled trials ²¹. This tool consists of thirteen questions addressing aspects such as selection bias, attrition bias, performance bias, and detection bias. Two independent reviewers (SK and BW) meticulously assessed each paper, engaging in discussions to resolve any discrepancies. In cases where disagreements persisted, a third reviewer (KH) was consulted to arbitrate and ensure consistency between the two independent reviewers. We have also contacted authors through email to get some outcome measurements that are mentioned by mean and median, as well as full texts. Each question in the Joanna Briggs Institute (JBI) Critical Appraisal tools was assigned a score: "Yes" received a score of 2, "No" was scored as 0, "Unclear" was denoted as 1, and "Not applicable" was recorded as NA. The overall quality of the studies was determined based on the cumulative score, classifying them as high quality if they scored 20 and above, good quality for scores between 13 and 19, and lower quality for scores below 13. The detailed results, including the breakdown of scores for each study, can be found in Table 1. Notably, nearly half of the studies (47%) achieved a high-quality score, while 11.7% were categorized as lower quality (Supplemental Table1).

Statistical analysis

The extracted data were entered into the computer using an Excel sheet and imported to STATA 17 for analysis. Heterogeneity among reported was assessed by using the Higgins-I² with Cochran Q statistic at 25%, 50%, and 70% as low, moderate, and considerable heterogeneity respectively with p-values less than 0.05²². Random effects meta-analysis model was used to estimate the pooled effect of WIFAS on serum ferritin level, hemoglobin, anemia, school performance, and mental health. A forest plot was also used to visualize the presence of heterogeneity subjectively. Possible differences between studies were explored by sub-group analyses and sensitivity analysis. Descriptive statistics (means and SD, median, IQR, 95%CI, and proportions) were used to summarize baseline information. The finding was presented using a forest plot with respective hedges and risk ratios and 95% confidence intervals. Evidence of publication bias was assessed using both Egger's and Begg's tests with a p-value of less than 0.05 as a cut-off point to declare the presence of publication bias ^{23,24}. The pooled hedges and risk ratios with 95% CI for each factor were used.

Registration and reporting

This study was registered with the International Prospective Register of Systematic Reviews (PROSPERO ID: <u>CRD42023397898</u>). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed during the systematic review process ²⁵.

Patient and public involvement

None

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Result

We identified a total of 2,026 articles of which 1,945 from Scopus, Web of Science, PubMed, Cochrane Library, and 81 from Google Scholar. After excluding 343 duplicates, a review of titles and abstracts against the review objectives and inclusion criteria led to the exclusion of 1,631 articles as irrelevant. Subsequently, the full texts of the remaining 52 studies were assessed, with 17 studies meeting the criteria for inclusion in the present systematic review and meta-analysis (Figure 1).

Study Characteristics

The current systematic review and meta-analysis were carried out in Sub-Saharan Africa. Among the included studies, six were conducted in Eastern Africa ^{26–31}, with one study in Ethiopia, three in Kenya, one in Tanzania, and one in Mozambique. Additionally, five studies were conducted in Western Africa ^{32–36}, with three in Mali, one in Burkina Faso, and one in Ghana. Moreover, five studies were carried out in Southern Africa^{37–41}, with two in Zambia and three in South Africa. Furthermore, a study was conducted in North-East Africa Sudan ⁴².

Besides, concerning the frequency of supplementation, nine studies were included weekly ^{26–28,30,32,33,36,41,42}, one studies with twice weekly ²⁹, two studies with four times per week ^{37,39}, two studies with five times per week ^{34,35}, and three studies with daily ^{31,38} supplementation. Moreover, seven studies were included that primarily focused on adolescent girls, and the supplementation was conducted weekly ^{26–28,30,33,36,41}.

Regarding the supplement composition, ten studies were conducted on iron supplements in the form of ferrous sulfate or ferrous dextran which contains ranging from 50mg to 65mg elemental iron and/or folic acid in amounts ranging from 250μ g to 2800μ g $^{25-27,29-31,34,35,40}$. Only three studies were conducted in community based. The supplementation period varied within the range of 2.2 months to 18 months. Seven studies were conducted in the form of folic acid supplemented with iron in the range of 0.1mg to 2.8 mg^{26,29,32,33,5,40,42} (Table 1).

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Table 1: Descriptive summary of the stud	dies included in the systematic review and meta-analysis amor	ng adolescents in Sub-Saharan Africa, 2023.

Author,	Setting	Sex and	Sample	Interventi	Comparator	Frequen	La Sugation	Outcome
(Year, Country),	and Study	Age	Size for	on arm	arm	cy of	05 1.	measurement
Reference	design	(Years)	Intervention	(Iron		supplem	sgippleme	
			Group (IG)	and/or		ent	nase	
			and Control	folic acid			rela	
			Group (CG)	dose)			n 11 ppleme Ser upting 2024. D na related	
Beasly, et.al	School;	Female,	IG= 50	400mg FS	Vitamin_B12	Weekly	ed downloade@fromAttighths 40 text and defrom ths and data wing y	Hgb, SF, CRP,
(2000, Tanzania) ²⁶	RCT	12-18	CG= 57				/nlo	Diarrhea, Malaria
							bade t an	and Wt. change
Yosef H, et.al	Communi	Female,	IG= 92	60mg	No	Weekly	3 months	Hgb, SF, and CRF
(2021, Ethiopia) 27	ty RCT	10-19	CG= 112	EI+0.4mg			rom	
Andrew Hall, et.al	School	6-19 years	IG= 551	65mg	No	Weekly	21.2	Hgb, and Anemia
(2001, Mali) ³²	CRCT		CG= 562	EI+0.25m			ngonths	status
				g			g, A	
Olsen, et.al	Communi	4-15	IG= 108	60mg EI	Placebo	Twice	ig, Altrapotenths ming, Buttanting,	Hgb, and SF
(2006, Kenya) ²⁹	ty	years	CG= 92			weekly	manths	
	RCT						ng,	
Lawless, et al	School;	6-11 years	IG= 44	150 mg	Placebo	Daily	322 months	Hgb, and SF
(1994, Kenya) ³¹	RCT		CG= 42	EI			months	
Victor Mwanakasale	School;	Male, 9-	IG= 80	200mg FS	Vitamin-C	Weekly	9 months	Hgb, and Anemia
(2009, Zambia) ⁴¹	RCT	15 years	CG= 87				Jun ar to	status
Victor Mwanakasale	School;	Female,	IG= 73	200mg FS	Vitamin-C	Weekly	95muonths	Hgb, and Anemia
(2009, Zambia) ⁴¹	RCT	9-15 years	CG= 84				0, 2 nol	status
Taylor (2002, South	School;	6-15 years	IG= 101	65mg	Anti-	Weekly	001	Hgb
Africa) ⁴⁰	RCT		CG= 91	EI+100µg	helmenthic		9700 onths 9700 o	
Jeannine	School;	6-11 years	IG= 80	50mg EI	n-3 fatty acid	4*/week	8.5 5	Hgb, CRP, and
Baumgartner	FRCT	-	CG= 80	_	supplements		mognths	School
(2012, South Africa)							site	Performance
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0							Cre	
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Leenstra, et.al (2009, Kenya) ²⁸	School; RCT	Female, 12-18 years	IG= 80 CG= 109	120mg EI	Vitamin-A	Weekly	9244033 914 Ancluding 917 Ancludin	Hgb, and SF			
Jeannine Baumgartner (2013, South Africa) 37	School; RCT	6-11 years	IG= 160 CG= 161	50mg EI	Mebendazole	4*/week	no oon months ses re 20	SF, TFR, ID			
Mohamed Ag Ayoya, (2009, Mali) ³⁵	School; RCT	7-12 years	IG= 309 (3 groups) CG= 97	60mg EI	MMS	5 days/we ek	3 Down	Hgb, and SF			
Nchito (2003, Zambia) ³⁸	School; RCT	7-15 years	IG= 101 CG= 101	60mg EI	MMS	daily	1 and a second s	Hgb			
Mohamed Ag Ayoya, (2012, Mali) ³⁴	School; RCT	7-12 years	IG= 307 CG= 97	60mg EI	praziquantel	5 days/we ek	3 3 3 3 3 3 3 3 3 3 3 4 5 6 1 1 1 1 1 1 1 1 1 1 1 1 1	School Performance, School Attendance			
Sabine G, et.al. (2018, Burkina Faso) ³⁶	Communi ty	Female, 10-19 years	913 girls	60mg EI+2.8mg	2.8mg folic acid	Weekly	ng and the air	Hgb, SF, and anemia			
Lucas G, et.al, (2021, Ghana) ³³	School, Pre-post longitudin al	Female, 10-19 years	1387 girls	60mg EI+0.4mg	No comparator	Weekly	nonths gonths similar	Anemia and Hgb			
Peter H, et.al, (2005, Mozambique) ³⁰	School, Pre-post longitudin al study	Female, 10-18 years	991 girls	60mg EI+0.4mg	-	Weekly	10, 2022 40, 10, 2024 40, 10, 2024 40, 10, 10, 10, 10, 10, 10, 10, 10, 10, 1	Anemia and Hgb			
Maisoon NA Fageer,et.al, (2021, Sudan) ⁴²	Communi ty RCT	School children	IG= 109 CG= 106	EI	Folic acid	Weekly	4 Sing Contract Contr	Anemia and School Performance			

RCT: Randomized Control Trial; FRCT: Factorial Randomized Control Trial; IG: Intervention Group; CG: Control Group; EI: Elemental Iron; Factorial Randomized Control Trial; CRP: Creative Reactive Protein; Hgb: Hemoglobin; SF: Serum Ferritin; Wt.: Weight; Ht: Height; IP: Intestinal parasitosis; BAZ: Body mass index for a score; HAZ: Height for age Z score; ID: Iron Deficiency; TFR: Transferrin Receptor; SAC: School Age Children; NM: Not Mentioned, MMS: Multiple Micronutrient supplements 11 For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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measures, including mean, standard deviation, median, and interquartile range. Out of these, seven studies reported a significant improvement in the serum ferritin level of children with IFAS ^{26–28,31,35,37,39}. However, two studies, conducted by Sabine G. et al. (2018) ³⁶ and Olsen A. et al. (2006) ²⁹, did not find a significant effect between IFAS and serum ferritin.

Furthermore, three studies demonstrated that once-weekly IFAS led to a significantly greater increment in serum ferritin compared to the control group, with the favor of 9.1 μ g/l (P = 0.002), 39.1 μ g/l (P < 0.001), and 13.3 μ g/l with a p-value less than 0.0001, respectively ^{26–28}. Additionally, Ayoya G's study in 2009 administered IFAS for 12 weeks, resulting in an improvement in the median serum ferritin from 20.84 μ g/l (16.79–25.86) at the baseline to 93.33 μ g/l (82.43–105.66) at the endpoint, with a p-value less than 0.001 ³⁵. Similarly, Jeanine B, 2012 and 2013 studies showed that supplementing iron has a positive impact on median serum ferritin which increases by 33.3 μ g/l and 38.4 μ g/l compared to the control ^{37,39}.

Effect of weekly iron-folic acid supplementation (WIFAS) on Serum Ferritin-Meta analysis

Three studies were incorporated into the meta-analysis $^{26-28}$, involving a total of 440 adolescent girls. Among them, 205 received weekly iron supplementation, while 235 were assigned to the placebo/non-intervention group. The analysis revealed a positive impact of weekly iron supplementation on enhancing the serum ferritin levels of adolescent girls (Hedge's g 0.53, 95%CI: 0.28, 0.78; test for heterogeneity I² = 41.21%, P < 0.001). There is no publication bias with p value of 0.374 (Figure 2).

Effect of Iron Folic Acid Supplementation (IFAS) on serum Ferritin-Meta analysis

In this meta-analysis, five studies were included which encompassing a total of 653 school-age children including adolescents $^{26-28,31,35}$. Within this group, 313 received iron supplementation, while 340 were part of the placebo/non-intervention group. The analysis indicated a significant effect of iron supplementation in improving the serum ferritin levels of the school-age children (Hedge's g 0.77, 95%CI: 0.33, 1.22; test for heterogeneity I² = 86.81%, P < 0.001) (Supplemental Figure 1).

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Effect of IFAS on Serum ferritin- Subgroup Meta-analysis

The subgroup analysis revealed that both daily and weekly supplementation of iron had a significant effect on the serum ferritin levels of school-age children ^{26–28,31,35}. Additionally, the variability among the studies was within an acceptable range for the weekly supplementation compared to the daily regimen (Hedge's g 0.53, 95%CI: 0.28, 0.78; test for heterogeneity $I^2 = 41.21\%$, P < 0.001) (Supplemental Figure 2).

Effect of IFAS on Hemoglobin-Narrative Synthesis

In this comprehensive review, 14 studies were incorporated to evaluate the impact of IFAS on hemoglobin levels. Out of these, five studies administered IFA every week ^(25,28,30,31,35), revealing a significant increase in hemoglobin concentration ranging from 0.12 g/dl to 4.8 g/dl. Moreover, four studies administered daily, four times weekly, and five times weekly also revealed a significant increase in hemoglobin concentration ranging from 0.3 g/dl to 1.12 g/dl ^{31,35,37,39}. However, four studies did not significant association between IFAS and hemoglobin concentration ^{26,29,36,41}.

Effect of WIFAS on Hgb-Meta-analysis

In this meta-analysis, a total of five studies $^{26-28,32,41}$ involving 1949 school-age children, including adolescents, were included. Among them, 933 received weekly iron supplementation, while 1016 were part of the placebo/non-intervention group. The analysis demonstrated a significant effect of weekly iron supplementation in improving the hemoglobin levels of school-age children (Hedge's g 0.37, 95%CI: 0.01, 0.73; test for heterogeneity I² = 91.62%, P < 0.001). There is no influential study and publication bias (p-value of 0.924) (Figure 3).

Effect of WIFAS on Hgb-subgroup meta-analysis by Setting

The subgroup analysis revealed that both school 26,28,32,41 and community 27 setting supplementation of iron had a significant effect on the hemoglobin levels of school-age children. Additionally, the variability among the studies was within an acceptable range for both the school setting supplementation (Hedge's g 0.23, 95%CI: 0.12, 0.35; test for heterogeneity I² = 16.33%, P < 0.001) and the community setting (Hedge's g 1.28, 95%CI: 0.97, 1.58) (Supplemental Figure 3).

Effect of weekly iron-folic acid supplementation (WIFAS) on Anemia-Narrative synthesis

In this systematic review, an analysis of seven studies was conducted to evaluate the impact of Iron and Folic Acid Supplementation (IFAS) on the prevalence of anemia. Out of these, three studies implemented IFAS every week $(^{28,32,36})$, demonstrating significant reduction in the prevalence of anemia, with percentages ranging from 0.35% to 8.2%. However, the findings from the remaining three studies did not show a significant association between WIFAS and the prevalence of anemia 30,36,41 . Despite our efforts to obtain the full-text article through email correspondence with the author, we were unable to secure it. Nonetheless, we relied on information from a conference proceeding abstract paper conducted in Sudan. According to this abstract, intermittent iron with folic acid supplementation demonstrated a significant (65.7%) reduction in the likelihood of anemia (P = 0.002) in the experimental group when compared to the control group, which received folic acid alone ⁴².

Effect of WIFAS on Anemia-Meta analysis

In this meta-analysis, four studies 28,32,36,41 were included, comprising a total of 2505 school-age children, including adolescent girls. Among them, 1233 received weekly iron supplementation in the treatment group, while 1272 were assigned to the placebo/non-intervention group. The analysis demonstrated a significant impact of weekly iron supplementation in reducing the risk of anemia by 20% (Risk ratio = 0.8, 95%CI: 0.69, 0.93; test for heterogeneity I² = 28.12%, P < 0.001). Moreover, there is no publication bias on the effect of WIFAS on Anemia with a p-value of 0.798 (Figure 4).

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Effect of IFAS on School and cognitive Performance-Narrative synthesis

The study conducted in Mali 2012 ³⁴ explored that iron-folic acid supplementation has a significant effect on school attendance increment (p = .049) and showed borderline significance on school grades (p = .08). Despite our efforts to secure the full-text article through email correspondence with the author, it remains unavailable. However, we relied on information from a conference proceeding abstract paper conducted in Sudan. According to this abstract, intermittent iron with folic acid supplementation did not show a significant association with school performance in the experimental group when compared to the control group, which received folic acid alone ^{42,43}.

Regarding cognitive performance, the study conducted in South Africa ³⁹ revealed that iron supplementation increased the number of words recalled at HVLT recall 2 (intervention effect:

0.90; 95% CI: 0.18, 1.62). In anemic children, iron increased scores in the Atlantis Delayed test (1.51; 95% CI: 0.03, 2.99) and HVLT recall 2 (2.02; 95% CI: 0.55, 3.49).

Mental Health Problem- Narrative Synthesis

No trials were reported in this outcome in Sub-Sahara Africa.

Certainty of Evidence

To evaluate the certainty of evidence, we considered factors such as risk of bias, inconsistency, indirectness, imprecision, publication bias, and additional considerations like large effect, doseresponse, and confounders. The assessment of risk of bias utilized the Cochrane risk of bias tool for 2019, encompassing criteria such as sequence generation, allocation concealment, blinding/masking of the intervention, intention-to-treat analysis, blinding/masking of outcome assessors, and freedom from other biases ⁴⁴. Inconsistency was explored through the heterogeneity (I^2) of the overall effect in the meta-analysis. Indirectness was scrutinized for external validity or generalizability (PICO), applicability, and any deviations from the research question. Imprecision was investigated through wide confidence intervals, including those indicating a null effect and high relative risk (RR > 0.75 or > 1.25). Additionally, we assessed publication and other biases. Based on our findings, we moderately recommend that weekly iron-folic acid supplementation (WIFAS) increases serum ferritin and hemoglobin levels while reducing anemia. (Supplemental Table 2).

Discussion

The current study incorporated 17 randomized trials in a systematic review to assess the impact of weekly iron-folic acid supplementation (WIFAS) on various health indicators including serum ferritin, hemoglobin, anemia, mental, school, and cognitive performance. The trials were distributed across East Africa (six studies), Southern Africa (five studies), West Africa (five studies) and Northern Africa (One study).

The current meta-analysis revealed the positive effects of WIFAS on serum ferritin and hemoglobin levels. Additionally, the WIFAS demonstrated a reduction in anemia. These findings are consistent with findings from a study done by De-Regil LM, et.al. This suggests that intermittent iron supplementation is effective in improving hemoglobin concentrations and reducing the risk of anemia or iron deficiency in children under 12 years of age ⁸. The findings of Ana C Fernández-Gaxiola 1 and Luz Maria De-Regil about Intermittent iron supplementation for reducing anemia and its associated impairments in adolescent and adult menstruating women supported our findings ⁸.

The findings of our study align with the World Health Organization (WHO) recommendations, supporting the guideline that advocates for the intermittent use of iron and folic acid supplements as a public health measure. This recommendation aims to reduce anemia and enhance iron status among menstruating women, emphasizing the global significance of evidence-informed strategies in addressing nutritional deficiencies ⁴⁵. Furthermore, our findings are consistent with the recommendation advocating for weekly iron-folic acid supplementation (WIFS). This approach serves as a preventive and sustainable long-term strategy for improving iron status and reducing the prevalence of anemia. The positive outcomes observed with WIFS align with the "mucosal block" hypothesis. According to this hypothesis, administering iron every week allows sufficient time for the shedding of cells loaded with iron from a previous dose. This shedding process contributes to increased iron absorption, reinforcing the efficacy of the WIFS approach ^{46,47}.

UNICEF's latest nutrition strategy, released in 2021, incorporates WIFAS as an intervention in the result area focusing on 'middle childhood and adolescents' ⁴⁸. Nutrition guidance specific to this target group has also been issued by UNICEF ⁴⁹. In regions where the prevalence of anemia among menstruating adult women and adolescent girls falls within the range of 20–39.9%, the guidance recommends weekly supplementation of 60 mg of elemental iron and 2800 µg of folic acid for three months, followed by three months of no supplementation, and then restarting the

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supplementation. It further suggests that, if feasible, intermittent supplementation should continue throughout the school calendar year in these settings.

A subgroup analysis was conducted to examine the distribution modalities of iron folic acid supplementation programs, distinguishing between school-based and community-based approaches. The results revealed that only one study focused on community-based distribution, demonstrating a positive impact on hemoglobin levels. Whereas, five studies centered on school-based modalities and indicated a favorable effect on hemoglobin levels. These findings prompt a discussion on comparing the feasibility of implementing iron folic acid supplementation programs in schools versus communities, considering factors such as accessibility for adolescent groups and cost-effectiveness. More than 90% adolescents are found in schools and cost effective at school ⁵⁰. Hence, distributing WIFAS at school modalities are beneficial compare to community.

The systematic review indicates that IFAS has a positive impact on school attendance and cognitive performance. This aligns with assessments from the WHO and Copenhagen Consensus Challenge, which estimate a high benefit-to-cost ratio for iron interventions. The ratio is based on resource savings, enhancements in cognitive development and schooling, and increased physical productivity, reaching as high as 200:1. Emphasizing the prevention of iron deficiency anemia (IDA) in adolescents is strategically crucial, considering potential gains in physical capacity, cognitive ability, and, for adolescent girls, improved pregnancy outcomes and intergenerational benefits ^{51,52}. However, regarding mental health trials were not reported in this outcome in Sub-Sahara Africa.

Given the positive impact of weekly iron folic acid supplementation on improving iron status and reducing anemia, it is crucial for policymakers to prioritize the implementation of such programs in public health initiatives. Ensuring access to affordable and high-quality supplements, as well as promoting awareness about the importance of iron folic acid supplementation, can significantly contribute to reducing the burden of anemia and improving overall health outcomes.

Strength and limitations of the study

The strength of this study lies their quality in the incorporation of five databases to search for articles. Additionally, we investigated the impact of once-weekly iron-folic acid supplementation on serum ferritin, hemoglobin, anemia, and academic performance. However, our study is subject to inherent limitations related to the effects of intermittent iron and folic acid supplementation on

serum ferritin, hemoglobin, anemia, cognitive and school performance, which broadens the scope of the study. The analysis faces challenges owing to the use of various tools to assess specific domains, complicating comparisons between intervention outcomes. Substantial differences in intervention design, including dose, form of iron supplements, and frequency and duration of supplementation, add complexity. Establishing an optimal dose, frequency, or duration for improved or reduced outcomes for school performance remains elusive. There is no trial regarding the effect of IFAS on mental health. Additionally, the potential influence of other micronutrients remains unclear in some studies. With two studies featuring low-quality studies, and the researchers acknowledge the possibility of missing relevant studies.

Conclusion

Weekly iron folic acid supplementation proves effective in enhancing serum ferritin, hemoglobin concentrations and lowering the risk of anemia or iron deficiency in adolescents compared to a placebo or no intervention. Moreover, iron supplementation demonstrates positive effects on verbal and nonverbal learning and memory, especially in children with anemia. Similarly, there are no good enough studies to examine the effect of WIFAS and school performance. Despite these benefits, information on mental health problems, mortality, and potential side effects remains insufficient.

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Based on the findings supporting the effectiveness of weekly iron folic acid supplementation, current recommendations include integrating this intervention into existing school health programs. Health and education authorities should consider incorporating routine screening for anemia and providing supplementation to at-risk populations, such as young children. Additionally, healthcare providers and teachers should be trained to counsel patients on the benefits of iron folic acid supplementation and monitor their adherence to the regimen. Continuous monitoring and evaluation of these programs are essential to assess their impact and make necessary adjustments to optimize outcomes.

Author Contributions

The authors' responsibilities were as follows: SK, BW, KHA: Designed and supervised the study, ensured the quality of the data, and made a substantial contribution to the local implementation of the study and SK, KHA, BW, BM assisted in the analysis and interpretation of the data. All authors

critically reviewed the manuscript. SK, the corresponding author did the analysis & drafted the manuscript and had the responsibility to submit the manuscript for publication.

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Competing interests: The authors declare that they have no competing interests.

Patient and public involvement: Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Consent for publication: Not applicable

Ethics approval: Not applicable

Provenance and peer review: Not commissioned; externally peer reviewed.

Data availability statement: All data relevant to the study are included in the article or uploaded as supplementary information.

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2 3	D	
4	Refe	erences
5 6	1.	WHO. Adolescent health.
7 8 9	2.	UNFPA. The state of the world population 2014. The power of 1.8 billion; adolescents, youth and the transformation of the future.
10 11 12 13	3.	UNICEF, WHO, and C. Iron & Folic Acid (IFA) Supplementation for Adolescent Girls and Women. Participants Manual for Health Workers. (2017).
14 15 16 17	4.	Leroy, J. L., Ruel, M., Habicht, JP. & Frongillo, E. A. Linear Growth Deficit Continues to Accumulate beyond the First 1000 Days in Low- and Middle-Income Countries: Global Evidence from 51 National Surveys. <i>J. Nutr.</i> 144 , 1460–1466 (2014).
18 19 20 21 22	5.	Safiri, S. <i>et al.</i> Burden of anemia and its underlying causes in 204 countries and territories, 1990–2019: results from the Global Burden of Disease Study 2019. <i>J. Hematol. Oncol.</i> 14 , 185 (2021).
22 23 24 25	6.	World-Bank. Prevalence of anemia among reproductive age (% of women ages 15–49). (2021).
26 27 28	7.	Toteja, G. S. <i>et al.</i> Prevalence of Anemia among Pregnant Women and Adolescent Girls in 16 Districts of India. <i>Food Nutr. Bull.</i> 27 , 311–315 (2006).
29 30 31 32 33 34	8.	Sylvetsky, A. C., Jefferds, M. E. D., De-Regil, L. M. & Dowswell, T. Intermittent iron supplementation for improving nutrition and developmental outcomes in children. in <i>Cochrane Database of Systematic Reviews</i> (ed. De-Regil, L. M.) (John Wiley & Sons, Ltd, 2011). doi:10.1002/14651858.CD009085.
35 36	9.	WHO. Anaemia Policy Brief, WHO, Geneva, Switzerland. (2019).
37 38 39 40	10.	Gelli, A. <i>et al.</i> Evaluation of alternative school feeding models on nutrition, education, agriculture and other social outcomes in Ghana: rationale, randomised design and baseline data. <i>Trials</i> 17 , 37 (2016).
41 42 43 44 45	11.	Lam, L. F. & Lawlis, T. R. Feeding the brain – The effects of micronutrient interventions on cognitive performance among school-aged children: A systematic review of randomized controlled trials. <i>Clin. Nutr.</i> 36 , 1007–1014 (2017).
46 47 48	12.	Jáuregui-Lobera, I. Iron deficiency and cognitive functions. <i>Neuropsychiatr. Dis. Treat.</i> 2087 (2014) doi:10.2147/NDT.S72491.
49 50 51 52 53	13.	Samson, K. L. I., Fischer, J. A. J. & Roche, M. L. Iron Status, Anemia, and Iron Interventions and Their Associations with Cognitive and Academic Performance in Adolescents: A Systematic Review. <i>Nutrients</i> 14, 224 (2022).
54 55 56	14.	Camaschella, C. Iron-Deficiency Anemia. N. Engl. J. Med. 372, 1832–1843 (2015).
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15. Low, M., Farrell, A., Biggs, B.-A. & Pasricha, S.-R. Effects of daily iron supplementation in primary-school-aged children: systematic review and meta-analysis of randomized controlled trials. Can. Med. Assoc. J. 185, E791-E802 (2013). 16. Kaufman AS, Lichtenberger EO, Fletscher-Janzen E, K. L. Essentials of KABC-II Assessment. (2005). 17 Brandt, J. The Hopkins Verbal Learning Test development of a new memory test with six equivalent forms. Clin Neuropsychol 5, 125-42 (1991). Ogunlade, A. O. et al. Point-of-use micronutrient fortification: lessons learned in 18. implementing a preschool-based pilot trial in South Africa. Int. J. Food Sci. Nutr. 62, 1-16 (2011).19. Muthayya, S. et al. Effect of fortification with multiple micronutrients and n-3 fatty acids on growth and cognitive performance in Indian schoolchildren: the CHAMPION (Children's Health and Mental Performance Influenced by Optimal Nutrition) Study. Am. J. Clin. Nutr. 89, 1766–1775 (2009). 20. Dalton, A. et al. A randomised control trial in schoolchildren showed improvement in cognitive function after consuming a bread spread, containing fish flour from a marine source. Prostaglandins, Leukot. Essent. Fat. Acids 80, 143–149 (2009). 21. JBI. Joanna Briggs Institute (JBI) Critical Appraisal tools for use in JBI Systematic Reviews Checklist for Randomized Controlled Trials. (2017). 22. Rücker G, Schwarzer G, Carpenter JR, S. M. Undue reliance on I2 in assessing heterogeneity may mislead. BMC Med Res Methodol 8, 79 (2008). 23. Begg CB, M. M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1088–101 (1994). Egger M, Smith GD, Schneider M, M. C. Bias in meta-analysis detected by a simple, 24. graphical test. BMJ 315, 629–34 (1997). 25. Moher D, Liberati A, Tetzlaff J, A. D. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 151, 264-9 w264 (2009). 26. Beasley, N. M. R. et al. The impact of weekly iron supplementation on the iron status and growth of adolescent girls in Tanzania. Trop. Med. Int. Heal. 5, 794-799 (2000). 27. Handiso, Y. H., Belachew, T., Abuye, C., Workicho, A. & Baye, K. A community-based randomized controlled trial providing weekly iron-folic acid supplementation increased serum- ferritin, -folate and hemoglobin concentration of adolescent girls in southern Ethiopia. Sci. Rep. 11, 9646 (2021). 28. Leenstra, T. et al. The effect of weekly iron and vitamin A supplementation on hemoglobin levels and iron status in adolescent schoolgirls in western Kenya. Eur. J. Clin. 21 For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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2 3 4		Nutr. 63, 173–182 (2009).
5 6 7 8	29.	Olsen, A., Nawiri, J., Magnussen, P., Krarup, H. & Friis, H. Failure of twice-weekly iron supplementation to increase blood haemoglobin and serum ferritin concentrations: results of a randomized controlled trial. <i>Ann. Trop. Med. Parasitol.</i> 100 , 251–263 (2006).
9 10 11 12 13	30.	Horjus, P., Aguayo, V. M., Roley, J. A., Pene, M. C. & Meershoek, S. P. School-Based Iron and Folic Acid Supplementation for Adolescent Girls: Findings from Manica Province, Mozambique. <i>Food Nutr. Bull.</i> 26 , 281–286 (2005).
14 15 16 17	31.	Lawless, J. W., Latham, M. C., Stephenson, L. S., Kinoti, S. N. & Pertet, A. M. Iron Supplementation Improves Appetite and Growth in Anemic Kenyan Primary School Children. J. Nutr. 124 , 645–654 (1994).
18 19 20 21 22	32.	Hall, A. <i>et al.</i> A randomised trial in Mali of the effectiveness of weekly iron supplements given by teachers on the haemoglobin concentrations of schoolchildren. <i>Public Health Nutr.</i> 5 , 413–418 (2002).
22 23 24 25 26	33.	Gosdin, L. <i>et al.</i> A School-Based Weekly Iron and Folic Acid Supplementation Program Effectively Reduces Anemia in a Prospective Cohort of Ghanaian Adolescent Girls. <i>J. Nutr.</i> 151 , 1646–1655 (2021).
27 28 29 30 31 32	34.	Ayoya, M. A., Spiekermann-Brouwer, G. M., Traoré, A. K. & Garza, C. Effect on School Attendance and Performance of Iron and Multiple Micronutrients as Adjunct to Drug Treatment of Schistosoma-Infected Anemic Schoolchildren. <i>Food Nutr. Bull.</i> 33 , 235–241 (2012).
33 34 35 36	35.	Ayoya, M. A. <i>et al.</i> Multiple Micronutrients Including Iron Are Not More Effective Than Iron Alone for Improving Hemoglobin and Iron Status of Malian School Children ,. <i>J.</i> <i>Nutr.</i> 139 , 1972–1979 (2009).
37 38 39 40 41	36.	Gies, S. <i>et al.</i> Effects of Weekly Iron and Folic Acid Supplements on Malaria Risk in Nulliparous Women in Burkina Faso: A Periconceptional, Double-Blind, Randomized Controlled Noninferiority Trial. <i>J. Infect. Dis.</i> 218 , 1099–1109 (2018).
41 42 43 44 45	37.	Baumgartner, J. <i>et al.</i> Overweight impairs efficacy of iron supplementation in iron- deficient South African children: a randomized controlled intervention. <i>Int. J. Obes.</i> 37 , 24–30 (2013).
46 47 48 49	38.	Nchito, M., Wenzel Geissler, P., Mubila, L., Friis, H. & Olsen, A. Effects of iron and multimicronutrient supplementation on geophagy: a two-by-two factorial study among Zambian schoolchildren in Lusaka. <i>Trans. R. Soc. Trop. Med. Hyg.</i> 98 , 218–227 (2004).
50 51 52 53 54	39.	Baumgartner, J. <i>et al.</i> Effects of iron and n-3 fatty acid supplementation, alone and in combination, on cognition in school children: a randomized, double-blind, placebo-controlled intervention in South Africa. <i>Am. J. Clin. Nutr.</i> 96 , 1327–1338 (2012).
55 56 57	40.	Taylor, M., Jinabhai, C. C., Couper, I., Kleinschmidt, I. & Jogessar, V. B. The effect of
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different anthelmintic treatment regimens combined with iron supplementation on the nutritional status of schoolchildren in KwaZulu-Natal, South Africa: a randomized controlled trial. *Trans. R. Soc. Trop. Med. Hyg.* **95**, 211–216 (2001).

- 41. Mwanakasale, V., Siziya, S., Mwansa, J., Koukounari, A. & Fenwick, A. Impact of iron supplementation on schistosomiasis control in Zambian school children in a highly endemic area. *Malawi Med. J.* **21**, (2009).
- 42. Nagmeldin Abbas Fageer, M., Hussein, M. D., N Abbas Fagiri, M. & Osman, M. 1239 Randomized controlled trial on the effect of weekly iron/folic acid supplementation on anemia and school performance among school children in rural Sudan. in *Abstracts* A288.1-A288 (BMJ Publishing Group Ltd and Royal College of Paediatrics and Child Health, 2021). doi:10.1136/archdischild-2021-rcpch.501.
- 43. Olsen, A., Nawiri, J. & Friis, H. The impact of iron supplementation on reinfection with intestinal helminths and Schistosoma mansoni in western Kenya. *Trans. R. Soc. Trop. Med. Hyg.* **94**, 493–499 (2000).
- 44. Cochrane. RoB 2: A revised Cochrane risk-of-bias tool for randomized trials. (2019).
- 45. WHO. Guideline: Intermittent Iron and Folic Acid Supplementation in Menstruating Women. Guideline: Intermittent Iron and Folic Acid Supplementation in Menstruating Women (2011).
- 46. Wright, A. J. A. & Southon, S. The effectiveness of various iron-supplementation regimens in improving the Fe status of anaemic rats. *Br. J. Nutr.* **63**, 579–585 (1990).
- 47. FE, V. Global consultation on Weekly Iron-Folic Acid Supplementation for preventing Anaemia in women of Reproductive Age Group. (2007).
- 48. UNICEF, U. N. C. F. Nutrition, for every child. UNICEF Nutrition Strategy 2020- 2030. (2020).
- 49. United Nations Children's Fund, U. Programming Guidance: Nutrition in Middle Childhood and Adolescence. (2021).
- 50. WHO. Making every school a health promoting school: Adolescent and Young Adult Health. (2023).
- 51. WHO. Preventing Iron deficiency Anemia in Adolescents: Role of WIFAS: World Health Organization, Regional Office for South-East Asia, Indraprastha Estate, Mahatma Gandhi Marg, New Delhi-110 002. (2011).
- 52. Hoddinott, J., Rosegrant, M. & Torero, M. HUNGER AND MALNUTRITION: Copenhagen Consensus Challenge. (2012).

Figure Legend:

nd: Figure 1. PRISMA flow diagram illustrating the study selection process of iron and folic acid supplementation effect on iron status, mental health and school performance articles.

Figure 2: Meta-analysis of the effect of once-weekly IFAS on serum ferritin

Figure 3: Meta-analysis of the effect of once-weekly IFAS on Hemoglobin

Figure 4:Meta-analysis of the effect of once-weekly IFAS on anemia

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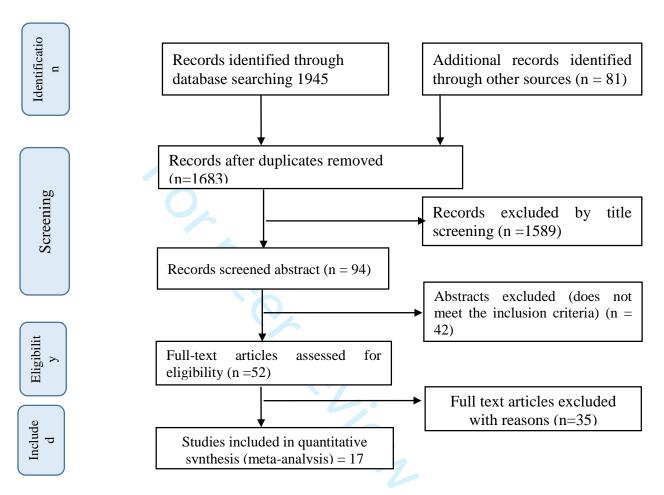


Figure 1. PRISMA flow diagram illustrating the study selection process of iron and folic acid supplementation effect on iron status, mental health and school performance articles.

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		Treatm	ent		Contro	ol		Hedges's g	Wei
Study	Ν	Mean	SD	N	Mean	SD		with 95% CI	(%
Beasley NMR, et.al, 2000	50	46.3	17	57	41	25.7		0.24 [-0.14, 0.62]	28.0
Yosef H, et.al, 2021	92	97.8	68.2	112	63.1	45.9		0.61 [0.33, 0.89]	40.
Leenstra T, et.al, 2007	63	37.4	22.72	66	23.9	14.56		0.71 [0.35, 1.06]	31.
Overall								0.53 [0.28, 0.78]	
Heterogeneity: $\tau^2 = 0.02$, I^2	= 41	.21%, H	l ² = 1.7()					
Test of $\theta_i = \theta_j$: Q(2) = 3.51,	p = 0).17							
Test of θ = 0: z = 4.14, p =	0.00								
							0.5	1	

Random-effects REML model

Figure 2: Meta-analysis of the effect of once-weekly IFAS on serum ferritin

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		Treatme	ent		Contro	bl			Hedges's g	Weight
Study	N	Mean	SD	N	Mean	SD			with 95% CI	(%)
Andrew H, et.al, 2001	551	11.64	1.27	562	11.26	1.27			0.30 [0.18, 0.42]	18.26
Beasley NMR, et.al, 2000	57	11.94	1.06	62	11.85	.79			0.10 [-0.26, 0.45]	15.76
Yosef H, et.al, 2021	92	14.5	1.3	112	13.2	.7			- 1.28 [0.97, 1.58]	16.50
Leenstra T, et.al, 2007	80	13.52	2.14	109	13.5	1.55			0.01 [-0.28, 0.30]	16.67
Victor M, et.al, 2009 (Male)	80	12.98	1.115	87	12.66	1.331			0.26 [-0.04, 0.56]	16.47
Victor M, et.al, 2009 (Female)	73	13.02	1.116	84	12.65	1.354		-	0.29 [-0.02, 0.61]	16.34
Overall									0.37 [0.01, 0.73]	
Heterogeneity: $\tau^2 = 0.18$, $I^2 = 91$.62%,	$H^2 = 11$.93							
Test of $\theta_i = \theta_j$: Q(5) = 44.68, p =	0.00									
Test of θ = 0: z = 2.02, p = 0.04										
						-	5 0 .5	1 1.	- 5	

Random-effects REML model

Figure 3: Meta-analysis of the effect of once-weekly IFAS on Hemoglobin

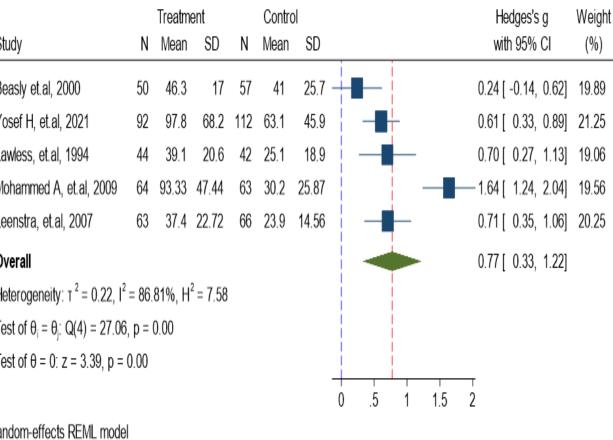
	Treat	tment	Со	ntrol				Log risk-ratio	Weig
Study	Yes	No	Yes	No				with 95% CI	(%)
Andrew, et.al, 2001	273	288	356	205				-0.27 [-0.37, -0.16]	54.9
Victor M, et.al, 2009 (Male)	3	77	9	78				-1.01 [-2.29, 0.26]	1.2
Victor M, et.al, 2009 (Female)	3	77	11	76		 ++ 		-1.22 [-2.46, 0.02]	1.2
Leenstra T, et.al, 2007	6	56	1	63				— 1.82 [-0.26, 3.91]	0.4
Sabine G, et.al, 2018	179	261	217	256				-0.12 [-0.27, 0.03]	42.0
Overall						•		-0.22 [-0.36, -0.07]	
Heterogeneity: $\tau^2 = 0.01$, $I^2 = 28$	8.12%,	$H^{2} = 1$	1.39						
Test of $\theta_i = \theta_j$: Q(4) = 10.08, p =	0.04								
Test of θ = 0: z = -2.99, p = 0.00)								
					-2	0	2	4	

Random-effects REML model

Figure 4: Meta-analysis of the effect of once-weekly IFAS on Anemia

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Supplemental figure 1: Meta-analysis of the effect of IFAS on serum ferritin

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		Treatm	ent		Contro	ol		Hedges's g	Weigł
Study	Ν	Mean	SD	N	Mean	SD		with 95% CI	(%)
Once Weekly									
Beasley, et.al, 2000	50	46.3	17	57	41	25.7		0.24 [-0.14, 0.62]	19.89
Yosef H, et.al, 2021	92	97.8	68.2	112	63.1	45.9	-	0.61 [0.33, 0.89]	21.25
Leenstra T, et.al, 2007	63	37.4	22.72	66	23.9	14.56	-	0.71 [0.35, 1.06]	20.25
Heterogeneity: $r^2 = 0.02$, $I^2 = 41$.21%	%, H ² = 1	.70				•	0.53 [0.28, 0.78]	
Test of $\theta_i = \theta_j$: Q(2) = 3.51, p = 0).17								
Daily or 5*/week									
Lawless et.al, 1994	44	39.1	20.6	42	25.1	18.9	-	0.70 [0.27, 1.13]	19.06
Mohammed Ag A, et.al, 2009	64	93.33	47.44	63	30.2	25.87		— 1.64 [1.24, 2.04]	19.56
Heterogeneity: $\tau^2 = 0.39$, $I^2 = 89$).73%	%, H ² = 9	9.74					-1.17 [0.25, 2.09]	
Test of $\theta_i = \theta_j$: Q(1) = 9.74, p = 0	0.00								
Overall								0.77 [0.33, 1.22]	
Heterogeneity: $\tau^2 = 0.22$, $I^2 = 86$	6.81%	6, H ² = 7	7.58						
Test of $\theta_i = \theta_j$: Q(4) = 27.06, p =	0.00)							
Test of group differences: $Q_b(1)$	= 1.	74, p = ().19					-	
Random-effects REML model							0.511.5	2	

Supplemental figure-2: Sub-group Meta-analysis of the effect of IFAS on serum ferritin

		Treatmo	ent		Contro	ol			Hedges's g	Weight
Study	Ν	Mean	SD	Ν	Mean	SD			with 95% CI	(%)
Community										
Yosef H, et.al, 2021	92	14.5	1.3	112	13.2	.7			— 1.28 [0.97, 1.58]	16.50
Heterogeneity: $\tau^2 = 0.00$, $I^2 = .\%$	$H^2 =$								► 1.28 [0.97, 1.58]	
Test of $\theta_i = \theta_j$: Q(0) = 0.00, p = .										
School										
Andrew H, et.al, 2001	551	11.64	1.27	562	11.26	1.27	-		0.30 [0.18, 0.42]	18.26
Beasley NMR, et.al, 2000	57	11.94	1.06	62	11.85	.79			0.10 [-0.26, 0.45]	15.76
Leenstra T, et.al, 2007	80	13.52	2.14	109	13.5	1.55			0.01 [-0.28, 0.30]	16.67
Victor M, et.al, 2009 (Male)	80	12.98	1.115	87	12.66	1.331		_	0.26 [-0.04, 0.56]	16.47
Victor M, et.al, 2009 (Female)	73	13.02	1.116	84	12.65	1.354		_	0.29 [-0.02, 0.61]	16.34
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 16$	5.33%,	$H^2 = 1.$	20				•		0.23 [0.12, 0.35]	
Test of $\theta_i = \theta_j$: Q(4) = 4.11, p = 0).39									
Overall									0.37 [0.01, 0.73]	
Heterogeneity: $\tau^2 = 0.18$, $I^2 = 91$.62%,	$H^2 = 11$	1.93							
Test of $\theta_i = \theta_j$: Q(5) = 44.68, p =	0.00									
Test of group differences: Q _b (1)	= 40.	06, p =	0.00							
							5 0 .	5 1	1.5	
Random-effects REML model										

Supplemental figure 3: Sub-group Meta-analysis of the effect of once-weekly IFAS on Hemoglobin

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	Supplemental Table 1: The Joanna Briggs Institute (JBI) Quality Assessment tool was employed to assess the quality of included	L
	Randomized Controlled Trials (RCTs) in this systematic review and meta-analysis, 2023.	
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S/No	Studies	mization	treatment	groups similar	blind to L?	g treatment signment?	ssors blind ent?	ally other	b/n groups	analyzed in h they were	i səsn loj b i t əuti mitiheic art groups?	measured	statistical	design deviations CT	
		Was there true randomization	Was allocation to groups concealed?	Were treatment grou at the baseline?	Were participants b treatment assignment?	Were those delivering treatment blind to treatment assignment?	Were outcomes assessors to treatment assignment?	Are groups identically than intervention?	Was follow-up complete and if not, were differences b/n groups	Were participants analyzed in the groups to which they were randomized?	રડે કે	Were outcomes reliably?	Was appropriate analysis used?	Was the trial design appropriate, and any deviations from the standard RCT	Total Yes
1.	Beasly, et.al (2000, Tanzania)	2	0	2	0	0	1	0	2	0	rom http://	1	0	2	10
2.	Yosef H, et.al (2021, Ethiopia)	2	1	2	0	0	1	2	2	2	/bmjopen. Al traini	2	2	2	18
3.	Andrew Hall, et.al (2001, Mali)	2	0	2	1	1	1	2	2	0	hmj.com	2	2	2	16
4.	Olsen, et.al (2006, Kenya)	2	2	2	2	2	2	2	2	2	imilar	1	2	2	24
5.	Lawless, et al (1994, Kenya)	2	2	2	2	2	1	2	2	2	une 10 techn	1	2	2	22
6.	Victor Mwanakasale (2009, Zambia)	1	1	2	1	1	1	1	1	0	, 2025 at ologies.	1	2	2	8
7.	Nchito (2009, Zambia)	2	2	2	2	2	2	2	2	1	Upive	1	2	2	22
8.	J. Baumgartner (2012, South Africa)	2	2	2	2	2	2	2	2	2	rsite Pari	2	2	2	26

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	Leenstra, et.al (2007, Kenya)	2	2	2	2	2	2	2	2	1	2024-08403: igh <u>t, includ</u>	1	2	2	22
10.	J. Baumgartner (2013, South Africa)	2	2	2	2	2	2	2	2	2	3 on 11 Ju ing for us	2	2	2	20
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Supplemental Table 2: The assessmen	t of the certainty of evidence	of included studies in Meta-analysis
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Outcomes	Number of studies	Number of participants	Study design	Risk of Bias	Inconsistency (Heterogeneity	Indirectness	Imprecision	Publication bias (Eggers test with P-	Other considerations (Large effect, dose-response,	Effect size to patelat sean to b websees authy qu uo RR)	Certainty of evidence
Serum Ferritin (Once-Weekly)	3	440	RCT	Seriou s	Low	No	No	No	No	H=20253 (0.28, 0.78)	Moderate
Serum Ferritin (More than once weekly)	5	653	RCT	Seriou s	Low	No	No	No	Concern	H=20577 (0.33, 1.22)	Low
Hemoglobin (Once weekly)	5	1949	RCT	Seriou s	Low	No	No	No	No	H=20237 (0.01, 0.73)	Moderate
Anemia (Once- weekly)	4	2505	RCT	Low	Low	No	conc ern	No	No	RR 20.8 (0.69, 0.93)	Moderate
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PRISMA 2020 Checklist

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	SMA 2	BMJ Open d by copyrig 2020 Checklist	
Section and Topic	ltem #	Checklist item	Location where item is reported
TITLE		<u>e</u> .33	
7 Title	1	Identify the report as a systematic review.	1
ABSTRACT			2
9 Abstract	2	See the PRISMA 2020 for Abstracts checklist.	
	ſ		3-5
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	4 & 5
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	4 & 5
4 METHODS			
5 Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	6
6 Information	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted benefity studies. Specify the date when each source was last searched or consulted.	5&6
8 Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	5&6
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	7
2 2 2 2 2 2 2 2 2 2 3 2 3 2 3 2 3 2 3 2	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each reports whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of action tools used in the process.	7
24 Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	7
20 27	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	7
Study risk of bias	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how reading reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	15
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	8
2 Synthesis 3 methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study in the planned groups for each synthesis (item #5)).	10
34 35 36	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	8
36	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	9
37 38	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was pere-reader med, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	8
រឲ្ ហ	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analys , meta-regression).	8
.1	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	NA
2 Reporting bias 3 assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biase	15
14 Certainty 15 assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome. For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	15

PRISMA 2020 Checklist

age 37 of 36	BMJ Open dia					
PRIS	SMA 2	2020 Checklist				
Section and Topic	ltem #	Checklist item	Location where iten is reported			
RESULTS						
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	9			
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were by guded.	9			
Study characteristics	17	Cite each included study and present its characteristics.	10			
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	10			
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an efective estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	9			
Results of	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	12-15			
syntheses	20b Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary existing ate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.					
)	20c	Present results of all investigations of possible causes of heterogeneity among study results.	12-15			
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	NA			
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	15			
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	15			
DISCUSSION						
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	16			
}	23b	Discuss any limitations of the evidence included in the review.	17			
	23c	Discuss any limitations of the review processes used.	17			
)	23d	Discuss implications of the results for practice, policy, and future research.	17			
OTHER INFORMA	ΓΙΟΝ					
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the range was not registered.	8			
F -	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	8			
Support	24c	Describe and explain any amendments to information provided at registration or in the protocol.	8			
, Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	19			
Competing interests	26	Declare any competing interests of review authors.	19			
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	19			

44 From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 45 10.1136/bmj.n71 .

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Weekly Iron-Folic Acid Supplementation and Its Impact on children and adolescents iron status, Mental Health, and School Performance: A Systematic Review and Meta-Analysis in Sub-Saharan Africa.

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Weekly Iron-Folic Acid Supplementation and Its Impact on children and adolescents' Iron Status, Mental Health, and School Performance: A Systematic Review and Meta-Analysis in Sub-Saharan Africa.

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Abstract

Objective: This systematic review and meta-analysis aimed to comprehensively assess the impact of Weekly Iron-Folic Acid Supplementation (WIFAS) on the nutrition, health, and educational outcomes of children and adolescents in Sub-Saharan Africa.

Design: Systematic review and Meta-analysis was used.

Data Sources: Five databases, namely, MEDLINE, Scopus, Web of Science, Cochrane Library, and Google Scholar, were systematically searched for relevant articles up to August 23, 2023.

Eligibility Criteria: It was focused on randomized controlled trials involving children and adolescents in Sub-Saharan Africa, exploring the effects of iron supplementation on various outcomes, such as serum ferritin and hemoglobin levels, anemia, mental health, and school performance.

Data Extraction and Synthesis: The Joanna Briggs Institute Critical Appraisal tools were utilized for quality assessment, with two independent reviewers thoroughly evaluating each paper. Using the Cochrane risk of bias tool, we evaluated certainty of evidence such as risk of bias, inconsistency, indirectness, imprecision, and publication bias.

Results: A systematic review of 17 articles revealed that WIFAS significantly increased serum ferritin levels in adolescent girls (Hedge's g = 0.53, 95% CI: 0.28, 0.78; heterogeneity I² = 41.21%, P < 0.001) and hemoglobin levels in school-age children (Hedge's g = 0.37, 95% CI: 0.01, 0.73; heterogeneity I² = 91.62%, P < 0.001). The analysis further demonstrated a substantial reduction in the risk of anemia by 20% (risk ratio = 0.8, 95% CI: 0.69, 0.93; heterogeneity I² = 28.12%, P < 0.001).

Conclusion: WIFAS proved effective in enhancing serum ferritin and hemoglobin concentrations and lowering the risk of anemia in school-age children and adolescents compared to placebo. Similarly, there are not enough studies to examine the effects of WIFAS on school performance. However, information regarding mental health problems, mortality, and potential side effects remains insufficient.

Strength and limitation

- Hedge's g addresses the issue of overestimation of the effect size in small samples.

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- Certainity of evidence for serum ferritin, hemoglobin and anemia are moderate.
- Incorporation of five databases to search for articles.
- Diverse intervention designs, spanning dose, and iron supplement form contributes to complexity
- Substantial differences in intervention design, including dose, form of iron supplements, and frequency and duration of supplementation, add complexity.

Prospero Registration: CRD42023397898

Keywords: WIFAS, Anemia, Sub-Saharan Africa, School Performance, Adolescent

Introduction

Adolescents are a subset of children whose age ranges from 10-19 years ¹. This age group makes up the greatest proportion of the population (23%) in Sub-Saharan Africa, which is about twice that of the industrialized countries ². Adolescence, marked by the transition to adulthood, is a critical phase characterized by significant growth, behavioral maturation, and sexual development. This represents the second growth spurt in life, particularly for girls who undergo unique experiences including menstruation, emotional changes, nutritional requirements, and identity formation. Adolescents require heightened nutritional demands, with a specific emphasis on the need for iron. This period lays the foundation for adult health and economic wellbeing. Adolescents attain 20% final adult height and 50% adult weight, underscoring its pivotal role in shaping future health outcomes^{3,4}.

Anemia, a widespread global health concern, impacts approximately 1.6 billion individuals. According to the World Health Organization (WHO), approximately 50% of anemia cases are attributed to iron deficiency ⁵ and Moreover, the prevalence of anemia in Sub-Saharan Africa surpass to 39% ⁶. This condition serves as a direct marker of undernutrition and insufficient iron intake, posing a significant public health challenge for adolescents ⁷. Iron deficiency anemia in adolescence has the potential to impede growth, hinder motor and brain development, and increase the risk of illness and mortality. Failure to promptly address anemia during this critical period may lead to persistent challenges later in life ⁸.

Adolescents are particularly prone to iron deficiency and anemia due to a range of factors, including rapid growth, insufficient dietary iron intake, reduced bioavailability of dietary iron, and

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heightened susceptibility to infectious diseases, parasitic infections, and menstrual blood loss ⁷. The combination of these factors contributes to an increased risk of iron deficiency anemia in adolescent girls, emphasizing the need for targeted interventions and education to address the specific challenges faced by this demographic group ⁹.

Anemia and iron deficiency anemia may have long-term consequences for individuals, limiting their educational achievements and subsequently impacting their economic potential^{4,9,10}. The evidence strongly supports the relationship between anemia and cognitive development. Both iron deficiency and iron deficiency anemia have been identified as contributors to cognitive deficits. Understanding and addressing the relationship between anemia and cognitive development is vital for promoting optimal health and cognitive outcomes, especially in vulnerable populations such as children and adolescents 9-11.

Iron plays a crucial role as an essential nutrient in the development and functioning of the brain. Its functions are diverse and contribute to various aspects of neural activity and neurotransmission. Some key roles of iron in the brain include ATP production, synthesis and packaging of neurotransmitters, and uptake and degradation of neurotransmitters ^{5,12}.

Indeed, adolescence and school-age children are recognized as a pivotal period for implementing interventions to address anemia and lay the foundation for future health, particularly in terms of childbearing ^(1,2). Implementing iron supplementation as an effective strategy to combat iron deficiency can have a substantial impact on reducing the prevalence of anemia, improving public health outcomes, and enhancing the well-being of affected populations, particularly in resourceconstrained settings ^{13–15}.

Following robust literature review, there is a notable scarcity of information regarding the effectiveness of once weekly IFAS concerning a broader spectrum of school performance and health outcomes including mental health⁸. The limitations of the available data underscore the need for comprehensive and standardized research methodologies to elucidate the full range of effects associated with WIFAS on diverse nutrition, education, and health parameters. Within the framework of this systematic review and meta-analysis, we aimed to assess the impact of once WIFAS on serum ferritin levels, school performance, and mental health status among children and adolescents in the Sub-Saharan African region.

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Methods

Searching strategies

The review encompassed a comprehensive examination of various literature sources through an extensive search across four electronic databases, supplemented by a manual search of references from key articles, previous reviews, and grey literature, to thoroughly investigate the effects of IFAS on serum ferritin levels, school performance, and mental health. Our search for published articles was confined to individuals aged 6-19 years and studies conducted exclusively in sub-Saharan Africa. We systematically searched international databases, including Scopus, Web of Science, PubMed (MEDLINE), Cochrane Library, and Google Scholar. The search terms were combined using Boolean operators 'AND'/'OR'. All published articles up to August 23, 2023, were incorporated into the systematic review. The results of the database search were aggregated, and duplicate articles were eliminated using the online Rayyan Software (https://www.rayyan.ai/). This tool was also employed to download the full text of studies for further evaluation

Eligibility criteria

Inclusion criteria

Study area: Only studies conducted in Sub-Saharan Africa (South of the Sahara).

Publication condition: articles published in peer-reviewed journals.

Study design: all RCT and clinical trial studies

Intervention: Iron and/or folic acid supplementation

Language: Articles published in the English language.

Age: School-age children typically encompass a range of ages, including the adolescent group.

In this study, individuals aged between 4 and 19 years, and both primary and secondary school children were included.

Exclusion criteria

Studies conducted related to iron fortification, and studies lacking specific outcome reporting were excluded from our analysis.

Outcome measurement

In this study, the main focus was on evaluating the impact of WIFAS on key health indicators, including serum ferritin levels, hemoglobin concentrations, anemia prevalence, mental health, and school performance. Measurement of outcomes involved assessing serum ferritin (in μ g/L) and

hemoglobin (in g/dl) through mean and standard deviation calculations. For anemia, the prevalence was examined as binary outcomes post-supplementation. Moreover, the study delved into the assessment of school performance by considering the average scores of subjects, school grades and school attendance increment. Additionally, cognitive performance was thoroughly evaluated using a battery of cognitive tests specifically chosen, designed, or adapted for the age and cultural group under consideration. This battery included four subtests from the Kaufman Assessment Battery for children aged 3–18 years, second edition (KABC-II) ¹⁶, and the Hopkins Verbal Learning Test (HVLT) ¹⁷. The subtests chosen from the KABC-II encompassed the Atlantis (assessing working memory) and Atlantis Delayed (evaluating long-term memory and retrieval) tests from the learning scale, the Hand Movement test (measuring short-term memory) from the sequential processing scale, and the Triangles test (assessing visuospatial cognition) from the simultaneous processing scale ^{18–20}.

Data extraction

The extraction of data was carried out independently by two authors (SK and BM) utilizing a standardized spreadsheet for data extraction. The format for data extraction encompassed details such as the primary author, year of publication, the geographical region where the study was conducted, sample size, frequency of supplementation, age, sex, dose of supplements, outcome measurement, duration of the intervention, and information related to the randomized controlled trials (mean, standard deviation, median, and interquartile range proportion).

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Quality assessment

For the assessment of the methodological quality of the included studies, we employed the Joanna Briggs Institute (JBI) Critical Appraisal tools designed for use in systematic reviews of randomized controlled trials ²¹. This tool consists of thirteen questions addressing aspects such as selection bias, attrition bias, performance bias, and detection bias. Two independent reviewers (SK and BW) meticulously assessed each paper, engaging in discussions to resolve any discrepancies. In cases where disagreements persisted, a third reviewer (KH) was consulted to arbitrate and ensure consistency between the two independent reviewers. We have also contacted authors through email to get some outcome measurements that are mentioned by mean and median, as well as full texts. Each question in the Joanna Briggs Institute (JBI) Critical Appraisal tools was assigned a score: "Yes" received a score of 2, "No" was scored as 0, "Unclear" was denoted as 1, and "Not

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applicable" was recorded as NA. The overall quality of the studies was determined based on the cumulative score, classifying them as high quality if they scored 20 and above, good quality for scores between 13 and 19, and lower quality for scores below 13. The detailed results, including the breakdown of scores for each study, can be found in Table 1. Notably, nearly half of the studies (47%) achieved a high-quality score, while 11.7% were categorized as lower quality (Supplemental Table1).

Statistical analysis

The extracted data were entered into the computer using an Excel sheet and imported to STATA 17 for analysis. Heterogeneity among reported was assessed by using the Higgins-I² with Cochran Q statistic at 25%, 50%, and 70% as low, moderate, and considerable heterogeneity respectively with p-values less than 0.05²². Random effects meta-analysis model was used to estimate the pooled effect of WIFAS on serum ferritin level, hemoglobin, anemia, school performance, and mental health. A forest plot was also used to visualize the presence of heterogeneity subjectively. Possible differences between studies were explored by sub-group analyses and sensitivity analysis. Descriptive statistics (means and SD, median, IQR, 95%CI, and proportions) were used to summarize baseline information. The finding was presented using a forest plot with respective hedges and risk ratios and 95% confidence intervals. Evidence of publication bias was assessed using both Egger's and Begg's tests with a p-value of less than 0.05 as a cut-off point to declare the presence of publication bias ^{23,24}. The pooled hedges and risk ratios with 95% CI for each factor were used.

Registration and reporting

This study was registered with the International Prospective Register of Systematic Reviews (PROSPERO ID: <u>CRD42023397898</u>). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed during the systematic review process ²⁵.

Patient and public involvement

None

Result

We identified a total of 2,026 articles of which 1,945 from Scopus, Web of Science, PubMed, Cochrane Library, and 81 from Google Scholar. After excluding 343 duplicates, a review of titles and abstracts against the review objectives and inclusion criteria led to the exclusion of 1,631 articles as irrelevant. Subsequently, the full texts of the remaining 52 studies were assessed, with 17 studies meeting the criteria for inclusion in the present systematic review and meta-analysis (Figure 1).

Study Characteristics

The current systematic review and meta-analysis were carried out in Sub-Saharan Africa. Among the included studies, six were conducted in Eastern Africa ^{26–31}, with one study in Ethiopia, three in Kenya, one in Tanzania, and one in Mozambique. Additionally, five studies were conducted in Western Africa ^{32–36}, with three in Mali, one in Burkina Faso, and one in Ghana. Moreover, five studies were carried out in Southern Africa^{37–41}, with two in Zambia and three in South Africa. Furthermore, a study was conducted in North-East Africa Sudan ⁴².

Besides, concerning the frequency of supplementation, nine studies were included weekly ^{26–} ^{28,30,32,33,36,41,42}, one studies with twice weekly ²⁹, two studies with four times per week ^{37,39}, two studies with five times per week ^{34,35}, and three studies with daily ^{31,38} supplementation. Moreover, seven studies were included that primarily focused on adolescent girls, and the supplementation was conducted weekly ^{26–28,30,33,36,41}.

Regarding the supplement composition, ten studies were conducted on iron supplements in the form of ferrous sulfate or ferrous dextran which contains ranging from 50mg to 65mg elemental iron and/or folic acid in amounts ranging from $250\mu g$ to $2800\mu g^{25-27,29-31,34,35,40}$. Only three studies were conducted in community based. The supplementation period varied within the range of 2.2 months to 18 months. Seven studies were conducted in the form of folic acid supplemented with iron in the range of 0.1mg to 2.8 mg^{26,29,32,33,35,40,42} (Table 1).

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 Table 1: Descriptive summary of the studies included in the systematic review and meta-analysis among adolescents and the systematic review and meta-analysis among adolescents are specific to the systematic review and meta-analysis among adolescents are specific to the systematic review and meta-analysis among adolescents are specific to the systematic review and meta-analysis among adolescents are specific to the systematic review and meta-analysis among adolescents are specific to the systematic review and meta-analysis among adolescents are specific to the systematic review and meta-analysis among adolescents are specific to the systematic review and meta-analysis among adolescents are specific to the systematic review and meta-analysis among adolescents are specific to the systematic review and meta-analysis among adolescents are specific to the systematic review and meta-analysis among adolescents are specific to the systematic review and meta-analysis among adolescents are specific to the systemat

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Author,	Setting	Sex and	Sample	Interventi	Comparator	Frequen	La sation	Outcome
(Year, Country),	and Study	Age	Size for	on arm	arm	cy of	्रवे न	measurement
Reference	design	(Years)	Intervention	(Iron		supplem	sgippleme	
			Group (IG)	and/or		ent	nitist	
			and Control	folic acid			elat	
			Group (CG)	dose)			2024. D related	
Beasly, et.al	School;	Female,	IG= 50	400mg FS	Vitamin_B12	Weekly	4	Hgb, SF, CRP,
(2000, Tanzania) ²⁶	RCT	12-18	CG= 57				nlo text	Diarrhea, Malaria
							tan	and Wt. change
Yosef H, et.al	Communi	Female,	IG= 92	60mg	No	Weekly	3 months	Hgb, SF, and CR
(2021, Ethiopia) ²⁷	ty RCT	10-19	CG= 112	EI+0.4mg			ron	
Andrew Hall, et.al	School	6-19 years	IG= 551	65mg	No	Weekly	40 mg on this text and the formation of the second	Hgb, and Anemia
(2001, Mali) ³²	CRCT		CG= 562	EI+0.25m			months	status
				g			g, A	
Olsen, et.al	Communi	4-15	IG= 108	60mg EI	Placebo	Twice	₩ <u></u>	Hgb, and SF
(2006, Kenya) ²⁹	ty	years	CG= 92			weekly	machths	
	RCT							
Lawless, et al	School;	6-11 years	IG= 44	150 mg	Placebo	Daily	322 months	Hgb, and SF
(1994, Kenya) ³¹	RCT		CG= 42	EI			months	
Victor Mwanakasale	School;	Male, 9-	IG= 80	200mg FS	Vitamin-C	Weekly	9 E mSonths	Hgb, and Anemi
(2009, Zambia) 41	RCT	15 years	CG= 87				Simonths	status
Victor Mwanakasale	School;	Female,	IG= 73	200mg FS	Vitamin-C	Weekly	95months	Hgb, and Anemia
(2009, Zambia) ⁴¹	RCT	9-15 years	CG= 84				10, 2025	status
Taylor (2002, South	School;	6-15 years	IG= 101	65mg	Anti-	Weekly	69.02 91.22	Hgb
Africa) ⁴⁰	RCT		CG= 91	EI+100µg	helmenthic		nionenths	
Jeannine	School;	6-11 years	IG= 80	50mg EI	n-3 fatty acid	4*/week	8.5 5	Hgb, CRP, and
Baumgartner	FRCT		CG= 80		supplements		months	School
(2012, South Africa)					11		<u>s</u>	Performance
39							Pa	
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			E	BMJ Open			136/bmjopen-2024-000000000000000000000000000000000	
Leenstra, et.al (2009, Kenya) ²⁸	School; RCT	Female, 12-18 years	IG= 80 CG= 109	120mg EI	Vitamin-A	Weekly	9024490nths ghty-includii	Hgb, and SF
Jeannine Baumgartner (2013, South Africa) ³⁷	School; RCT	6-11 years	IG= 160 CG= 161	50mg EI	Mebendazole	4*/week	on 15ths ng on 15ths nuses re	SF, TFR, ID
Mohamed Ag Ayoya, (2009, Mali) ³⁵	School; RCT	7-12 years	IG= 309 (3 groups) CG= 97	60mg EI	MMS	5 days/we ek	3 and the second	Hgb, and SF
Nchito (2003, Zambia) ³⁸	School; RCT	7-15 years	IG= 101 CG= 101	60mg EI	MMS	daily	1 and a the second	Hgb
Mohamed Ag Ayoya, (2012, Mali) ³⁴	School; RCT	7-12 years	IG= 307 CG= 97	60mg EI	praziquantel	5 days/we ek	3 3 3 3 3 3 3 3 3 3 3 3 3 3	School Performance, School Attendanc
Sabine G, et.al. (2018, Burkina Faso) ³⁶	Communi ty	Female, 10-19 years	913 girls	60mg EI+2.8mg	2.8mg folic acid	Weekly	neonths	Hgb, SF, and anemia
Lucas G, et.al, (2021, Ghana) ³³	School, Pre-post longitudin al	Female, 10-19 years	1387 girls	60mg EI+0.4mg	No comparator	Weekly	narain and similar for the similar for the for th	Anemia and Hgb
Peter H, et.al, (2005, Mozambique) ³⁰	School, Pre-post longitudin al study	Female, 10-18 years	991 girls	60mg EI+0.4mg	-	Weekly	And	Anemia and Hgb
Maisoon NA Fageer,et.al, (2021, Sudan) ⁴²	Communi ty RCT	School children	IG= 109 CG= 106	EI	Folic acid	Weekly	4 ginat Unive	Anemia and School Performance

S RCT: Randomized Control Trial; FRCT: Factorial Randomized Control Trial; IG: Intervention Group; CG: Control Group; EI: Elemental Iron; F8: Ferrous Sulphate; CRP: Creative Reactive Protein; Hgb: Hemoglobin; SF: Serum Ferritin; Wt.: Weight; Ht: Height; IP: Intestinal parasitosis; BAZ: Body mass index for g score; HAZ: Height for age Z score; ID: Iron Deficiency; TFR: Transferrin Receptor; SAC: School Age Children; NM: Not Mentioned, MMS: Multiple Micronutrient supplements 10 For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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Effect of iron-folic acid supplementation (IFAS) on Serum Ferritin-Narrative synthesis

Nine studies assessed the impact of IFAS on serum ferritin ^{26–29,31,35–37,39} using various statistical measures, including mean, standard deviation, median, and interquartile range. Out of these, seven studies reported a significant improvement in the serum ferritin level of children with IFAS ^{26–28,31,35,37,39}. However, two studies, conducted by Sabine G. et al. (2018) ³⁶ and Olsen A. et al. (2006) ²⁹, did not find a significant effect between IFAS and serum ferritin.

Furthermore, three studies demonstrated that once-weekly IFAS led to a significantly greater increment in serum ferritin compared to the control group, with the favor of 9.1 μ g/l, 39.1 μ g/l, and 13.3 μ g/l with a p-value less than , respectively ^{26–28}. Additionally, Ayoya G's study in 2009 administered IFAS for 12 weeks, resulting in an improvement in the median serum ferritin from 20.84 μ g/l (16.79–25.86) at the baseline to 93.33 μ g/l (82.43–105.66) at the endpoint³⁵. Similarly, Jeanine B, 2012 and 2013 studies showed that supplementing iron has a positive impact on median serum ferritin which increases by 33.3 μ g/l and 38.4 μ g/l compared to the control ^{37,39}.

Effect of weekly iron-folic acid supplementation (WIFAS) on Serum Ferritin-Meta analysis

Three studies were incorporated into the meta-analysis $^{26-28}$, involving a total of 440 adolescent girls. Among them, 205 received weekly iron supplementation, while 235 were assigned to the placebo/non-intervention group. The analysis revealed a positive impact of weekly iron supplementation on enhancing the serum ferritin levels of adolescent girls (Hedge's g 0.53, 95%CI: 0.28, 0.78; test for heterogeneity I² = 41.21%). There is no publication bias with p value of 0.374 (Figure 2).

Effect of Iron Folic Acid Supplementation (IFAS) on serum Ferritin-Meta analysis

In this meta-analysis, five studies were included which encompassing a total of 653 school-age children including adolescents $^{26-28,31,35}$. Within this group, 313 received iron supplementation, while 340 were part of the placebo/non-intervention group. The analysis indicated a significant effect of iron supplementation in improving the serum ferritin levels of the school-age children (Hedge's g 0.77, 95%CI: 0.33, 1.22; test for heterogeneity I² = 86.81%) (Supplemental Figure 1).

Effect of IFAS on Serum ferritin- Subgroup Meta-analysis

The subgroup analysis revealed that both daily and weekly supplementation of iron had a significant effect on the serum ferritin levels of school-age children ^{26–28,31,35}. Additionally, the

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variability among the studies was within an acceptable range for the weekly supplementation compared to the daily regimen (Hedge's g 0.53, 95%CI: 0.28, 0.78; test for heterogeneity $I^2 = 41.21\%$) (Supplemental Figure 2).

Effect of IFAS on Hemoglobin-Narrative Synthesis

In this comprehensive review, 14 studies were incorporated to evaluate the impact of IFAS on hemoglobin levels. Out of these, five studies administered IFA every week ^(25,28,30,31,35), revealing a significant increase in hemoglobin concentration ranging from 0.12 g/dl to 4.8 g/dl. Moreover, four studies administered daily, four times weekly, and five times weekly also revealed a significant increase in hemoglobin concentration ranging from 0.3 g/dl to 1.12 g/dl ^{31,35,37,39}. However, four studies did not significant association between IFAS and hemoglobin concentration ^{26,29,36,41}.

Effect of WIFAS on Hgb-Meta-analysis

In this meta-analysis, a total of five studies $^{26-28,32,41}$ involving 1949 school-age children, including adolescents, were included. Among them, 933 received weekly iron supplementation, while 1016 were part of the placebo/non-intervention group. The analysis demonstrated a significant effect of weekly iron supplementation in improving the hemoglobin levels of school-age children (Hedge's g 0.37, 95%CI: 0.01, 0.73; test for heterogeneity I² = 91.62%). There is no influential study and publication bias (p-value of 0.924) (Figure 3).

Effect of WIFAS on Hgb-subgroup meta-analysis by Setting

The subgroup analysis revealed that both school 26,28,32,41 and community 27 setting supplementation of iron had a significant effect on the hemoglobin levels of school-age children. Additionally, the variability among the studies was within an acceptable range for both the school setting supplementation (Hedge's g 0.23, 95%CI: 0.12, 0.35; test for heterogeneity I² = 16.33%) and the community setting (Hedge's g 1.28, 95%CI: 0.97, 1.58) (Supplemental Figure 3).

Effect of weekly iron-folic acid supplementation (WIFAS) on Anemia-Narrative synthesis

In this systematic review, an analysis of seven studies was conducted to evaluate the impact of Iron and Folic Acid Supplementation (IFAS) on the prevalence of anemia. Out of these, three studies implemented IFAS every week ^(28,32,36), demonstrating significant reduction in the prevalence of anemia, with percentages ranging from 0.35% to 8.2%. However, the findings from the remaining three studies did not show a significant association between WIFAS and the

prevalence of anemia ^{30,36,41}. Despite our efforts to obtain the full-text article through email correspondence with the author, we were unable to secure it. Nonetheless, we relied on information from a conference proceeding abstract paper conducted in Sudan. According to this abstract, intermittent iron with folic acid supplementation demonstrated a significant (65.7%) reduction in the likelihood of anemia in the experimental group when compared to the control group, which received folic acid alone ⁴².

Effect of WIFAS on Anemia-Meta analysis

In this meta-analysis, four studies 28,32,36,41 were included, comprising a total of 2505 school-age children, including adolescent girls. Among them, 1233 received weekly iron supplementation in the treatment group, while 1272 were assigned to the placebo/non-intervention group. The analysis demonstrated a significant impact of weekly iron supplementation in reducing the risk of anemia by 20% (Risk ratio = 0.8, 95%CI: 0.69, 0.93; test for heterogeneity I² = 28.12%). Moreover, there is no publication bias on the effect of WIFAS on Anemia with a p-value of 0.798 (Figure 4).

Effect of IFAS on School and cognitive Performance-Narrative synthesis

The study conducted in Mali 2012 ³⁴ explored that iron-folic acid supplementation has a significant effect on school attendance increment and showed borderline significance on school grades. Despite our efforts to secure the full-text article through email correspondence with the author, it remains unavailable. However, we relied on information from a conference proceeding abstract paper conducted in Sudan. According to this abstract, intermittent iron with folic acid supplementation did not show a significant association with school performance in the experimental group when compared to the control group, which received folic acid alone ^{42,43}.

Regarding cognitive performance, the study conducted in South Africa ³⁹ revealed that iron supplementation increased the number of words recalled at HVLT recall 2 (intervention effect: 0.90; 95% CI: 0.18, 1.62). In anemic children, iron increased scores in the Atlantis Delayed test (1.51; 95% CI: 0.03, 2.99) and HVLT recall 2 (2.02; 95% CI: 0.55, 3.49).

Mental Health Problem- Narrative Synthesis

No trials were reported in this outcome in Sub-Sahara Africa.

Certainty of Evidence

To evaluate the certainty of evidence, we considered factors such as risk of bias, inconsistency, indirectness, imprecision, publication bias, and additional considerations like large effect, dose-

response, and confounders. The assessment of risk of bias utilized the Cochrane risk of bias tool for 2019, encompassing criteria such as sequence generation, allocation concealment, blinding/masking of the intervention, intention-to-treat analysis, blinding/masking of outcome assessors, and freedom from other biases ⁴⁴. Inconsistency was explored through the heterogeneity (I²) of the overall effect in the meta-analysis. Indirectness was scrutinized for external validity or generalizability (PICO), applicability, and any deviations from the research question. Imprecision was investigated through wide confidence intervals, including those indicating a null effect and high relative risk (RR > 0.75 or > 1.25). Additionally, we assessed publication and other biases. Based on our findings, we moderately recommend that weekly iron-folic acid supplementation (WIFAS) increases serum ferritin and hemoglobin levels while reducing anemia. (Supplemental Table 2).

Discussion

The current study incorporated 17 randomized trials in a systematic review to assess the impact of weekly iron-folic acid supplementation (WIFAS) on various health indicators including serum ferritin, hemoglobin, anemia, mental, school, and cognitive performance. The trials were distributed across East Africa (six studies), Southern Africa (five studies), West Africa (five studies) and Northern Africa (One study).

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The current meta-analysis revealed the positive effects of WIFAS on serum ferritin and hemoglobin levels. Additionally, the WIFAS demonstrated a reduction in anemia. These findings are consistent with findings from a study done by De-Regil LM, et.al. This suggests that intermittent iron supplementation is effective in improving hemoglobin concentrations and reducing the risk of anemia or iron deficiency in children under 12 years of age ⁸. The findings of Ana C Fernández-Gaxiola 1 and Luz Maria De-Regil about Intermittent iron supplementation for reducing anemia and its associated impairments in adolescent and adult menstruating women supported our findings ⁸.

The findings of our study align with the World Health Organization (WHO) recommendations, supporting the guideline that advocates for the intermittent use of iron and folic acid supplements as a public health measure. This recommendation aims to reduce anemia and enhance iron status among menstruating women, emphasizing the global significance of evidence-informed strategies in addressing nutritional deficiencies ⁴⁵. Furthermore, our findings are consistent with the recommendation advocating for weekly iron-folic acid supplementation (WIFS). This approach

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serves as a preventive and sustainable long-term strategy for improving iron status and reducing the prevalence of anemia. The positive outcomes observed with WIFS align with the "mucosal block" hypothesis. According to this hypothesis, administering iron every week allows sufficient time for the shedding of cells loaded with iron from a previous dose. This shedding process contributes to increased iron absorption, reinforcing the efficacy of the WIFS approach ^{46,47}.

UNICEF's latest nutrition strategy, released in 2021, incorporates WIFAS as an intervention in the result area focusing on 'middle childhood and adolescents' ⁴⁸. Nutrition guidance specific to this target group has also been issued by UNICEF ⁴⁹. In regions where the prevalence of anemia among menstruating adult women and adolescent girls falls within the range of 20–39.9%, the guidance recommends weekly supplementation of 60 mg of elemental iron and 2800 μ g of folic acid for three months, followed by three months of no supplementation, and then restarting the supplementation. It further suggests that, if feasible, intermittent supplementation should continue throughout the school calendar year in these settings.

A subgroup analysis was conducted to examine the distribution modalities of iron folic acid supplementation programs, distinguishing between school-based and community-based approaches. The results revealed that only one study focused on community-based distribution, demonstrating a positive impact on hemoglobin levels. Whereas, five studies centered on school-based modalities and indicated a favorable effect on hemoglobin levels. These findings prompt a discussion on comparing the feasibility of implementing iron folic acid supplementation programs in schools versus communities, considering factors such as accessibility for adolescent groups and cost-effectiveness. More than 90% adolescents are now found in schools and cost effective at school setting ⁵⁰. Hence, distributing WIFAS at school modalities are beneficial compare to community.

The systematic review indicates that IFAS has a positive impact on school attendance and cognitive performance. This aligns with assessments from the WHO and Copenhagen Consensus Challenge, which estimate a high benefit-to-cost ratio for iron interventions. The ratio is based on resource savings, enhancements in cognitive development and schooling, and increased physical productivity, reaching as high as 200:1. Emphasizing the prevention of iron deficiency anemia (IDA) in adolescents is strategically crucial, considering potential gains in physical capacity, cognitive ability, and, for adolescent girls, improved pregnancy outcomes and intergenerational

benefits ^{51,52}. However, regarding mental health trials were not reported in this outcome in Sub-Sahara Africa.

Given the positive impact of weekly iron folic acid supplementation on improving iron status and reducing anemia, it is crucial for policymakers to prioritize the implementation of such programs in public health initiatives. Ensuring access to affordable and high-quality supplements, as well as promoting awareness about the importance of iron folic acid supplementation, can significantly contribute to reducing the burden of anemia and improving overall health outcomes.

Strength and limitations of the study

The strength of this study lies their quality in the incorporation of five databases to search for articles. Additionally, we investigated the impact of once-weekly iron-folic acid supplementation on serum ferritin, hemoglobin, anemia, and academic performance. However, our study is subject to inherent limitations related to the effects of intermittent iron and folic acid supplementation on serum ferritin, hemoglobin, anemia, cognitive and school performance, which broadens the scope of the study. The analysis faces challenges owing to the use of various tools to assess specific domains, complicating comparisons between intervention outcomes. Substantial differences in intervention design, including dose, form of iron supplements, and frequency and duration of supplementation, add complexity. Establishing an optimal dose, frequency, or duration for improved or reduced outcomes for school performance remains elusive. There is no trial regarding the effect of IFAS on mental health. Additionally, the potential influence of other micronutrients remains unclear in some studies. With two studies featuring low-quality studies, and the researchers acknowledge the possibility of missing relevant studies.

Conclusion

Weekly iron folic acid supplementation proves effective in enhancing serum ferritin, hemoglobin concentrations and lowering the risk of anemia or iron deficiency in adolescents compared to a placebo or no intervention. Moreover, iron supplementation demonstrates positive effects on verbal and nonverbal learning and memory, especially in children with anemia. Similarly, there are no good enough studies to examine the effect of WIFAS and school performance. Despite these benefits, information on mental health problems, mortality, and potential side effects remains insufficient.

Based on the findings supporting the effectiveness of weekly iron folic acid supplementation, current recommendations include integrating this intervention into existing school health programs. Health and education authorities should consider incorporating routine screening for anemia and providing supplementation to at-risk populations, such as young children. Additionally, healthcare providers and teachers should be trained to counsel patients on the benefits of iron folic acid supplementation and monitor their adherence to the regimen. Continuous monitoring and evaluation of these programs are essential to assess their impact and make necessary adjustments to optimize outcomes.

Author Contributions

The authors' responsibilities were as follows: SK, BW, KHA: Designed and supervised the study, ensured the quality of the data, and made a substantial contribution to the local implementation of the study and SK, KHA, BW, BM assisted in the analysis and interpretation of the data. All authors critically reviewed the manuscript. SK, the corresponding author did the analysis & drafted the manuscript and had the responsibility to submit the manuscript for publication.

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Patient and public involvement: Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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References

WHO. Adolescent health.

youth and the transformation of the future.

and Women. Participants Manual for Health Workers. (2017).

in 16 Districts of India. Food Nutr. Bull. 27, 311-315 (2006).

WHO. Anaemia Policy Brief, WHO, Geneva, Switzerland. (2019).

randomized controlled trials. Clin. Nutr. 36, 1007-1014 (2017).

Adolescents: A Systematic Review. Nutrients 14, 224 (2022).

Ltd, 2011). doi:10.1002/14651858.CD009085.

data. Trials 17, 37 (2016).

2087 (2014) doi:10.2147/NDT.S72491.

Evidence from 51 National Surveys. J. Nutr. 144, 1460–1466 (2014).

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185 (2021).

(2021).

UNFPA. The state of the world population 2014. The power of 1.8 billion; adolescents,

UNICEF, WHO, and C. Iron & Folic Acid (IFA) Supplementation for Adolescent Girls

Leroy, J. L., Ruel, M., Habicht, J.-P. & Frongillo, E. A. Linear Growth Deficit Continues

to Accumulate beyond the First 1000 Days in Low- and Middle-Income Countries: Global

Safiri, S. *et al.* Burden of anemia and its underlying causes in 204 countries and territories, 1990–2019: results from the Global Burden of Disease Study 2019. *J. Hematol. Oncol.* 14,

World-Bank. Prevalence of anemia among reproductive age (% of women ages 15–49).

Toteja, G. S. et al. Prevalence of Anemia among Pregnant Women and Adolescent Girls

Sylvetsky, A. C., Jefferds, M. E. D., De-Regil, L. M. & Dowswell, T. Intermittent iron

Gelli, A. et al. Evaluation of alternative school feeding models on nutrition, education,

agriculture and other social outcomes in Ghana: rationale, randomised design and baseline

Lam, L. F. & Lawlis, T. R. Feeding the brain – The effects of micronutrient interventions

Jáuregui-Lobera, I. Iron deficiency and cognitive functions. Neuropsychiatr. Dis. Treat.

on cognitive performance among school-aged children: A systematic review of

Samson, K. L. I., Fischer, J. A. J. & Roche, M. L. Iron Status, Anemia, and Iron

Interventions and Their Associations with Cognitive and Academic Performance in

Camaschella, C. Iron-Deficiency Anemia. N. Engl. J. Med. 372, 1832–1843 (2015).

supplementation for improving nutrition and developmental outcomes in children. in *Cochrane Database of Systematic Reviews* (ed. De-Regil, L. M.) (John Wiley & Sons,

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37 38

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40 41 42

43

44 45

46

47 48

49

50

51 52

53 54

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56 57 58

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60

15. Low, M., Farrell, A., Biggs, B.-A. & Pasricha, S.-R. Effects of daily iron supplementation in primary-school-aged children: systematic review and meta-analysis of randomized controlled trials. Can. Med. Assoc. J. 185, E791-E802 (2013). 16. Kaufman AS, Lichtenberger EO, Fletscher-Janzen E, K. L. Essentials of KABC-II Assessment. (2005). 17 Brandt, J. The Hopkins Verbal Learning Test development of a new memory test with six equivalent forms. Clin Neuropsychol 5, 125-42 (1991). Ogunlade, A. O. et al. Point-of-use micronutrient fortification: lessons learned in 18. implementing a preschool-based pilot trial in South Africa. Int. J. Food Sci. Nutr. 62, 1-16 (2011).19. Muthayya, S. et al. Effect of fortification with multiple micronutrients and n-3 fatty acids on growth and cognitive performance in Indian schoolchildren: the CHAMPION (Children's Health and Mental Performance Influenced by Optimal Nutrition) Study. Am. J. Clin. Nutr. 89, 1766–1775 (2009). 20. Dalton, A. et al. A randomised control trial in schoolchildren showed improvement in cognitive function after consuming a bread spread, containing fish flour from a marine source. Prostaglandins, Leukot. Essent. Fat. Acids 80, 143–149 (2009). 21. JBI. Joanna Briggs Institute (JBI) Critical Appraisal tools for use in JBI Systematic Reviews Checklist for Randomized Controlled Trials. (2017). 22. Rücker G, Schwarzer G, Carpenter JR, S. M. Undue reliance on I2 in assessing heterogeneity may mislead. BMC Med Res Methodol 8, 79 (2008). 23. Begg CB, M. M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1088–101 (1994). Egger M, Smith GD, Schneider M, M. C. Bias in meta-analysis detected by a simple, 24. graphical test. BMJ 315, 629-34 (1997). 25. Moher D, Liberati A, Tetzlaff J, A. D. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 151, 264-9 w264 (2009). 26. Beasley, N. M. R. et al. The impact of weekly iron supplementation on the iron status and growth of adolescent girls in Tanzania. Trop. Med. Int. Heal. 5, 794-799 (2000). 27. Handiso, Y. H., Belachew, T., Abuye, C., Workicho, A. & Baye, K. A community-based randomized controlled trial providing weekly iron-folic acid supplementation increased serum- ferritin, -folate and hemoglobin concentration of adolescent girls in southern Ethiopia. Sci. Rep. 11, 9646 (2021). 28. Leenstra, T. et al. The effect of weekly iron and vitamin A supplementation on hemoglobin levels and iron status in adolescent schoolgirls in western Kenya. Eur. J. Clin. 19 For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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Nutr.	63,	173-	-182	(2009).	

- 29. Olsen, A., Nawiri, J., Magnussen, P., Krarup, H. & Friis, H. Failure of twice-weekly iron supplementation to increase blood haemoglobin and serum ferritin concentrations: results of a randomized controlled trial. *Ann. Trop. Med. Parasitol.* **100**, 251–263 (2006).
- Horjus, P., Aguayo, V. M., Roley, J. A., Pene, M. C. & Meershoek, S. P. School-Based Iron and Folic Acid Supplementation for Adolescent Girls: Findings from Manica Province, Mozambique. *Food Nutr. Bull.* 26, 281–286 (2005).
- 31. Lawless, J. W., Latham, M. C., Stephenson, L. S., Kinoti, S. N. & Pertet, A. M. Iron Supplementation Improves Appetite and Growth in Anemic Kenyan Primary School Children. J. Nutr. **124**, 645–654 (1994).
- 32. Hall, A. *et al.* A randomised trial in Mali of the effectiveness of weekly iron supplements given by teachers on the haemoglobin concentrations of schoolchildren. *Public Health Nutr.* **5**, 413–418 (2002).
- 33. Gosdin, L. *et al.* A School-Based Weekly Iron and Folic Acid Supplementation Program Effectively Reduces Anemia in a Prospective Cohort of Ghanaian Adolescent Girls. *J. Nutr.* **151**, 1646–1655 (2021).
- 34. Ayoya, M. A., Spiekermann-Brouwer, G. M., Traoré, A. K. & Garza, C. Effect on School Attendance and Performance of Iron and Multiple Micronutrients as Adjunct to Drug Treatment of Schistosoma-Infected Anemic Schoolchildren. *Food Nutr. Bull.* **33**, 235–241 (2012).
- 35. Ayoya, M. A. *et al.* Multiple Micronutrients Including Iron Are Not More Effective Than Iron Alone for Improving Hemoglobin and Iron Status of Malian School Children ,. *J. Nutr.* **139**, 1972–1979 (2009).
- 36. Gies, S. *et al.* Effects of Weekly Iron and Folic Acid Supplements on Malaria Risk in Nulliparous Women in Burkina Faso: A Periconceptional, Double-Blind, Randomized Controlled Noninferiority Trial. *J. Infect. Dis.* **218**, 1099–1109 (2018).
- Baumgartner, J. *et al.* Overweight impairs efficacy of iron supplementation in irondeficient South African children: a randomized controlled intervention. *Int. J. Obes.* 37, 24–30 (2013).
- 38. Nchito, M., Wenzel Geissler, P., Mubila, L., Friis, H. & Olsen, A. Effects of iron and multimicronutrient supplementation on geophagy: a two-by-two factorial study among Zambian schoolchildren in Lusaka. *Trans. R. Soc. Trop. Med. Hyg.* **98**, 218–227 (2004).
- 39. Baumgartner, J. *et al.* Effects of iron and n-3 fatty acid supplementation, alone and in combination, on cognition in school children: a randomized, double-blind, placebo-controlled intervention in South Africa. *Am. J. Clin. Nutr.* **96**, 1327–1338 (2012).
- 40. Taylor, M., Jinabhai, C. C., Couper, I., Kleinschmidt, I. & Jogessar, V. B. The effect of

different anthelmintic treatment regimens combined with iron supplementation on the nutritional status of schoolchildren in KwaZulu-Natal, South Africa: a randomized controlled trial. *Trans. R. Soc. Trop. Med. Hyg.* **95**, 211–216 (2001).

- 41. Mwanakasale, V., Siziya, S., Mwansa, J., Koukounari, A. & Fenwick, A. Impact of iron supplementation on schistosomiasis control in Zambian school children in a highly endemic area. *Malawi Med. J.* **21**, (2009).
- 42. Nagmeldin Abbas Fageer, M., Hussein, M. D., N Abbas Fagiri, M. & Osman, M. 1239 Randomized controlled trial on the effect of weekly iron/folic acid supplementation on anemia and school performance among school children in rural Sudan. in *Abstracts* A288.1-A288 (BMJ Publishing Group Ltd and Royal College of Paediatrics and Child Health, 2021). doi:10.1136/archdischild-2021-rcpch.501.
- 43. Olsen, A., Nawiri, J. & Friis, H. The impact of iron supplementation on reinfection with intestinal helminths and Schistosoma mansoni in western Kenya. *Trans. R. Soc. Trop. Med. Hyg.* **94**, 493–499 (2000).
- 44. Cochrane. RoB 2: A revised Cochrane risk-of-bias tool for randomized trials. (2019).
- 45. WHO. Guideline: Intermittent Iron and Folic Acid Supplementation in Menstruating Women. Guideline: Intermittent Iron and Folic Acid Supplementation in Menstruating Women (2011).
- 46. Wright, A. J. A. & Southon, S. The effectiveness of various iron-supplementation regimens in improving the Fe status of anaemic rats. *Br. J. Nutr.* **63**, 579–585 (1990).
- 47. FE, V. Global consultation on Weekly Iron-Folic Acid Supplementation for preventing Anaemia in women of Reproductive Age Group. (2007).
- 48. UNICEF, U. N. C. F. Nutrition, for every child. UNICEF Nutrition Strategy 2020- 2030. (2020).
- 49. United Nations Children's Fund, U. Programming Guidance: Nutrition in Middle Childhood and Adolescence. (2021).
- 50. WHO. Making every school a health promoting school: Adolescent and Young Adult Health. (2023).
- 51. WHO. Preventing Iron deficiency Anemia in Adolescents: Role of WIFAS: World Health Organization, Regional Office for South-East Asia, Indraprastha Estate, Mahatma Gandhi Marg, New Delhi-110 002. (2011).
- 52. Hoddinott, J., Rosegrant, M. & Torero, M. HUNGER AND MALNUTRITION: Copenhagen Consensus Challenge. (2012).

Figure Legends

Figure 1- PRISMA flow diagram illustrating the study selection process of iron and folic acid supplementation effect on iron status, mental health and school performance articles.

- Figure 2- Meta-analysis of the effect of once-weekly IFAS on serum ferritin
- Figure 3- Meta-analysis of the effect of once-weekly IFAS on Hemoglobin
- Figure 4- Meta-analysis of the effect of once-weekly IFAS on Anemia

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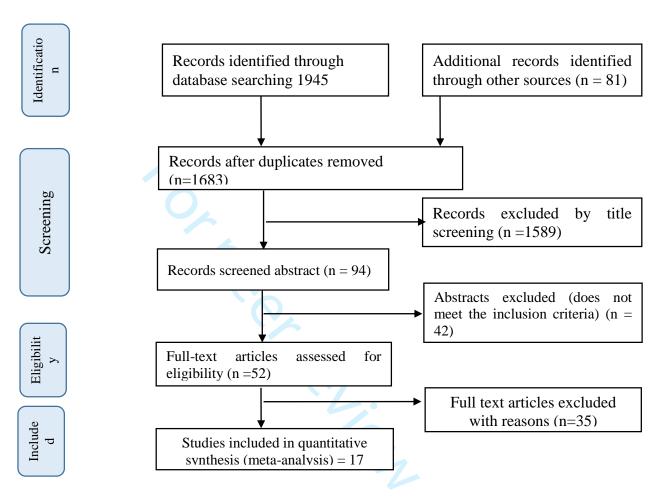


Figure 1. PRISMA flow diagram illustrating the study selection process of iron and folic acid supplementation effect on iron status, mental health and school performance articles.

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	Treatment				Contro	bl		Hedges's g	Weight
Study	Ν	Mean	SD	N	Mean	SD		with 95% CI	(%)
Beasley NMR, et.al, 2000	50	46.3	17	57	41	25.7		0.24 [-0.14, 0.62]	28.6
Yosef H, et.al, 2021	92	97.8	68.2	112	63.1	45.9	╡─┤╋─	— 0.61 [0.33, 0.89]	40.2
Leenstra T, et.al, 2007	63	37.4	22.72	66	23.9	14.56		0.71 [0.35, 1.06]	31.1
Overall								0.53 [0.28, 0.78]	
Heterogeneity: $\tau^2 = 0.02$, I^2	= 41	.21%, H	l ² = 1.7()					
Test of $\theta_i = \theta_j$: Q(2) = 3.51,	p = 0	.17							
Test of θ = 0: z = 4.14, p =	0.00								
							0.5	1	

Random-effects REML model

Figure 2: Meta-analysis of the effect of once-weekly IFAS on serum ferritin

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		Treatme	ent		Contro	bl			Hedges's g	Weight
Study	N	Mean	SD	N	Mean	SD			with 95% CI	(%)
Andrew H, et.al, 2001	551	11.64	1.27	562	11.26	1.27			0.30 [0.18, 0.42]	18.26
Beasley NMR, et.al, 2000	57	11.94	1.06	62	11.85	.79			0.10 [-0.26, 0.45]	15.76
Yosef H, et.al, 2021	92	14.5	1.3	112	13.2	.7			- 1.28 [0.97, 1.58]	16.50
Leenstra T, et.al, 2007	80	13.52	2.14	109	13.5	1.55			0.01 [-0.28, 0.30]	16.67
Victor M, et.al, 2009 (Male)	80	12.98	1.115	87	12.66	1.331			0.26 [-0.04, 0.56]	16.47
Victor M, et.al, 2009 (Female)	73	13.02	1.116	84	12.65	1.354		-	0.29 [-0.02, 0.61]	16.34
Overall									0.37 [0.01, 0.73]	
Heterogeneity: $\tau^2 = 0.18$, $I^2 = 91$.62%,	$H^2 = 11$.93							
Test of $\theta_i = \theta_j$: Q(5) = 44.68, p =	0.00									
Test of θ = 0: z = 2.02, p = 0.04										
						-	5 0 .5	1 1.	- 5	

Random-effects REML model

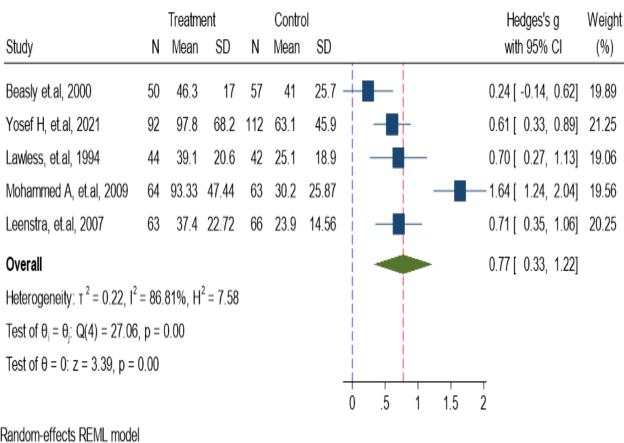
Figure 3: Meta-analysis of the effect of once-weekly IFAS on Hemoglobin

Ctudu		tment		ntrol				Log risk-ratio	Wei
Study	Yes	No	res	No				with 95% CI	(%
Andrew, et.al, 2001	273	288	356	205				-0.27 [-0.37, -0.16]	54.9
Victor M, et.al, 2009 (Male)	3	77	9	78				-1.01 [-2.29, 0.26]	1.2
Victor M, et.al, 2009 (Female)	3	77	11	76	-+	 ++ 		-1.22 [-2.46, 0.02]	1.:
Leenstra T, et.al, 2007	6	56	1	63		<u> </u> 		— 1.82 [-0.26, 3.91]	0.4
Sabine G, et.al, 2018	179	261	217	256				-0.12 [-0.27, 0.03]	42.
Overall						•		-0.22 [-0.36, -0.07]	
Heterogeneity: $r^2 = 0.01$, $l^2 = 28$	8.12%,	$H^{2} = 1$.39						
Test of $\theta_i = \theta_j$: Q(4) = 10.08, p =	0.04					II II			
Test of θ = 0: z = -2.99, p = 0.00)								
					-2	0	2	4	

Random-effects REML model

Figure 4: Meta-analysis of the effect of once-weekly IFAS on Anemia

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Supplemental figure 1: Meta-analysis of the effect of IFAS on serum ferritin

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		Treatm	ent		Contro	bl		Hedges's g	Weight
Study	N	Mean	SD	N	Mean	SD		with 95% CI	(%)
Once Weekly									
Beasley, et.al, 2000	50	46.3	17	57	41	25.7		0.24 [-0.14, 0.62]	19.89
Yosef H, et.al, 2021	92	97.8	68.2	112	63.1	45.9	-	0.61 [0.33, 0.89]	21.25
Leenstra T, et.al, 2007	63	37.4	22.72	66	23.9	14.56		0.71 [0.35, 1.06]	20.25
Heterogeneity: $\tau^2 = 0.02$, $I^2 = 4$	1.21%	%, H ² = 1	.70				•	0.53 [0.28, 0.78]	
Test of $\theta_i = \theta_j$: Q(2) = 3.51, p =	0.17								
Daily or 5*/week									
Lawless et.al, 1994	44	39.1	20.6	42	25.1	18.9		0.70 [0.27, 1.13]	19.06
Mohammed Ag A, et.al, 2009	64	93.33	47.44	63	30.2	25.87		— 1.64 [1.24, 2.04]	19.56
Heterogeneity: $\tau^2 = 0.39$, $I^2 = 89$	9.73%	%, H ² = 9	9.74					-1.17 [0.25, 2.09]	
Test of $\theta_i = \theta_j$: Q(1) = 9.74, p =	0.00								
Overall								0.77 [0.33, 1.22]	
Heterogeneity: $\tau^2 = 0.22$, $I^2 = 8$	6.81%	6, H ² = 7	7.58						
Test of $\theta_i = \theta_j$: Q(4) = 27.06, p =	= 0.00)							
Test of group differences: $Q_b(1$) = 1.	74, p = ().19					-	
							0 .5 1 1.5	2	
Random-effects REML model									

Supplemental figure-2: Sub-group Meta-analysis of the effect of IFAS on serum ferritin

		Treatme	ent		Contro	ol					Hedges's g	Weight
Study	Ν	Mean	SD	Ν	Mean	SD					with 95% CI	(%)
Community												
Yosef H, et.al, 2021	92	14.5	1.3	112	13.2	.7					— 1.28 [0.97, 1.58] 16.50
Heterogeneity: $\tau^2 = 0.00$, $I^2 = .\%$, H ² =										► 1.28 [0.97, 1.58]
Test of $\theta_i = \theta_j$: Q(0) = 0.00, p = .												
School												
Andrew H, et.al, 2001	551	11.64	1.27	562	11.26	1.27		-	ŀ		0.30 [0.18, 0.42] 18.26
Beasley NMR, et.al, 2000	57	11.94	1.06	62	11.85	.79	-		_		0.10 [-0.26, 0.45] 15.76
Leenstra T, et.al, 2007	80	13.52	2.14	109	13.5	1.55	_	-			0.01 [-0.28, 0.30] 16.67
Victor M, et.al, 2009 (Male)	80	12.98	1.115	87	12.66	1.331			-		0.26 [-0.04, 0.56] 16.47
Victor M, et.al, 2009 (Female)	73	13.02	1.116	84	12.65	1.354			-		0.29 [-0.02, 0.61] 16.34
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 16$.33%,	$H^2 = 1.$	20					•	•		0.23 [0.12, 0.35]
Test of $\theta_i = \theta_j$: Q(4) = 4.11, p = 0).39											
Overall											0.37[0.01, 0.73]
Heterogeneity: $\tau^2 = 0.18$, $I^2 = 91$.62%,	H ² = 11	.93									
Test of $\theta_i = \theta_j$: Q(5) = 44.68, p =	0.00											
Test of group differences: $Q_b(1)$	= 40.	06, p = (0.00									
							5	0	.5	1 1	.5	
Random-effects REML model												

Supplemental figure 3: Sub-group Meta-analysis of the effect of once-weekly IFAS on Hemoglobin

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34	BMJ Open BMJ Open	
	y copen	
	Supplemental Table 1: The Joanna Briggs Institute (JBI) Quality Assessment tool was employed to as the quality of included	
	Randomized Controlled Trials (RCTs) in this systematic review and meta-analysis, 2023.	

S/No	Studies	Was there true randomization	o treatment	groups similar	t blind to nt?	ng treatment ssignment?	sessors blind ment?	identically other ion?	nplete and if ss b/n groups	analyzed in h they were	əl səsn loj b i Beland muthec nent groups?	measured	statistical	al design y deviations RCT	
			Was allocation to groups concealed?	Were treatment groat the baseline?	Were participants b treatment assignment?	Were those delivering treatment blind to treatment assignment?	Were outcomes assessors blind to treatment assignment?	Are groups ident than intervention?	Was follow-up complete and if not, were differences b/n groups	Were participants analyzed in the groups to which they were randomized?	sdnorg treated to text and data mining. Al training, and similar technologies. ما الماريجة الم	Were outcomes reliably?	Was appropriate analysis used?	Was the trial design appropriate, and any deviations from the standard RCT	Total Yes
1.	Beasly, et.al (2000, Tanzania)	2	0	2	0	0	1	0	2	0	from http://	1	0	2	10
2.	Yosef H, et.al (2021, Ethiopia)	2	1	2	0	0	1	2	2	2	bmjopen 4 Al traini	2	2	2	18
3.	Andrew Hall, et.al (2001, Mali)	2	0	2	1	1	1	2	2	0	ng, and s	2	2	2	16
4.	Olsen, et.al (2006, Kenya)	2	2	2	2	2	2	2	2	2	imilar	1	2	2	24
5.	Lawless, et al (1994, Kenya)	2	2	2	2	2	1	2	2	2	une 10 techn	1	2	2	22
6.	Victor Mwanakasale (2009, Zambia)	1	1	2	1	1	1	1	1	0	, 2025 at l plogies.	1	2	2	8
7.	Nchito (2009, Zambia)	2	2	2	2	2	2	2	2	1	Unive 2ive	1	2	2	22
8.	J. Baumgartner (2012, South Africa)	2	2	2	2	2	2	2	2	2	rsite Pari	2	2	2	26

Page	32	of	34
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					BM	1J Open					136/bmjopen-2024-084033 on 11 June 2024. Downloaded from <u>http://bmjopen.bmj.com/</u> on June 10, 2025 at Universite Paris Est Creteil . cted by copyrigh <u>t, including for uses related to text and data mining. At training, and similar techn</u> ologies.				Pag
	Leenstra, et.al (2007 Kenya)	, 2	2	2	2	2	2	2	2	1	2024-08403; igh <u>t, includ</u>	1	2	2	2
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	Mohamed Ag Ayoya (2009, Mali)	, 2	0	2	0	0	1	2	1	0	ine 2024. I ses relatec	2	2	2	1
12. 1	Nchito, (2003, Zambia)	2	2	2	2	2	2	2	2	1	L Down	1	2	2	2
	Mohamed Ag Ayoya (2012, Mali)	, 2	0	2	0	0	1	2	1	0	loaded fro <u>xt and dat</u>	2	2	2	1
	Sabine G, et.al. (2018 Burkina Faso)	, 2	2	2	0	2	2	2	2	2	m http://b a mining.	2	2	2	2
	Lucas G, et.al, (2021 Ghana)	, 0	NA	NA	0	NA	NA	2	2	2	miopen.b Al trainin	2	2	2	1
	Peter H, et.al, (2005 Mozambique)	, 1	1	2	0	0	1	2	2	2	mi.com/ o g, and sir	2	2	2	1
	Maisoon NA Fageer,et.al (2021, Sudan)	, 2	2	1	2	2	2	2	2	1	n June 1 nilar tech	1	2	2	1

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Outcomes	Number of studies	Number of participants	Study design	Risk of Bias	Inconsistency (Heterogeneity	Indirectness	Imprecision	Publication bias (Eggers test with P-	Other considerations (Large effect, dose-response,	Effect size Effect size (RR) RR) BRD)	Certainty of evidence
Serum Ferritin (Once-Weekly)	3	440	RCT	Seriou s	Low	No	No	No	No	H= 0253 (0.28, 0.78)	Moderate
Serum Ferritin (More than once weekly)	5	653	RCT	Seriou s	Low	No	No	No	Concern	H=100 mining	Low
Hemoglobin (Once weekly)	5	1949	RCT	Seriou s	Low	No	No	No	No	H=20237 (0.01, 0.73)	Moderate
Anemia (Once- weekly)	4	2505	RCT	Low	Low	No	conc ern	No	No	RI 0.8 (0.69, 0.93)	Moderate

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PRISMA 2020 Checklist

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1	PRIS	SMA 2	BMJ Open Ed by Contract of the second	n jopen-20	
4	Section and Topic	ltem #	Checklist item	24-0840	Location where item is reported
5	TITLE			33	
7	Title	1	Identify the report as a systematic review.		1
8	ABSTRACT				2
9	Abstract	2	See the PRISMA 2020 for Abstracts checklist.		
10	INTRODUCTION			N N	3-5
	Rationale	3	Describe the rationale for the review in the context of existing knowledge.	024	4 & 5
13	Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.		4 & 5
14	METHODS			Š	
15	Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	<u>م</u>	6
	Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted at the when each source was last searched or consulted.		5&6
18	Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.		5&6
19 20	Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many review and each report retrieved, whether they worked independently, and if applicable, details of automation tools used provided independently.	ewers screened each record	7
22 23	Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of process.		7
24 25	Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results		7
20 27 28		10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funder assumptions made about any missing or unclear information.	sources). Describe any	7
<u> </u>	Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how reastudy and whether they worked independently, and if applicable, details of automation tools used in the process.	Ty reviewers assessed each	15
31	Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presenta	of results.	8
	Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study in comparing against the planned groups for each synthesis (item #5)).		10
34 35		13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing sun	gry statistics, or data	8
36		13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	live	9
37 38		13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was perf model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	armed, describe the	8
39 40		13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysi	, meta-regression).	8
40 41		13f		m	NA
42	Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases	stor	15
	Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome. For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml		15

PRISMA 2020 Checklist

Page 35 of 34		BMJ Open Grad B	
PRIS	SMA 2	BMJ Open 2020 Checklist	
Section and Topic	ltem #	Checklist item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the member of studies included in the review, ideally using a flow diagram.	9
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were by guded.	9
Study characteristics	17	Cite each included study and present its characteristics.	10
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	10
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an efectivate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	9
Results of	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	12-15
syntheses	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary e diagate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	12-15
P D	20c	Present results of all investigations of possible causes of heterogeneity among study results.	12-15
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	NA
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	15
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	15
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	16
8	23b	Discuss any limitations of the evidence included in the review.	17
)	23c	Discuss any limitations of the review processes used.	17
	23d	Discuss implications of the results for practice, policy, and future research.	17
OTHER INFORMA	TION		
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the ray was not registered.	8
ŀ.	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	8
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	8
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	19
Competing interests	26	Declare any competing interests of review authors.	19
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	19
3 4 <i>From:</i> Page MJ, Mo 5 10.1136/bmj.n71	cKenzie	JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 202 For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml For more information, visit: <u>http://www.prisma-statement.org/</u>	21;372:n71. do

Weekly Iron-Folic Acid Supplementation and Its Impact on children and adolescents iron status, Mental Health, and School Performance: A Systematic Review and Meta-Analysis in Sub-Saharan Africa.

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Primary Subject Heading :	Epidemiology
Secondary Subject Heading:	Ethics
Keywords:	Adolescent, Anaemia < HAEMATOLOGY, Public health < INFECTIOUS DISEASES, MENTAL HEALTH, NUTRITION & DIETETICS, PAEDIATRICS





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Weekly Iron-Folic Acid Supplementation and its impact on children and adolescents Iron Status, Mental Health, and School Performance: A Systematic Review and Meta-Analysis in Sub-Saharan Africa.

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Abstract

Objective: This systematic review and meta-analysis aimed to comprehensively assess the impact of Weekly Iron-Folic Acid Supplementation (WIFAS) on the nutrition, health, and educational outcomes of children and adolescents in Sub-Saharan Africa.

Design: Systematic review and Meta-analysis were used.

Data Sources: Five databases, namely, MEDLINE, Scopus, Web of Science, Cochrane Library, and Google Scholar, were systematically searched for relevant articles up to August 23, 2023.

Eligibility Criteria: It was focused on randomized controlled trials involving children and adolescents in Sub-Saharan Africa, exploring the effects of iron supplementation on various outcomes, such as serum ferritin and hemoglobin levels, anemia, mental health, and school performance.

Data Extraction and Synthesis: The Joanna Briggs Institute Critical Appraisal tools were utilized for quality assessment, with two independent reviewers thoroughly evaluating each paper. Using the Cochrane risk of bias tool, we evaluated the certainty of evidence such as the risk of bias, inconsistency, indirectness, imprecision, and publication bias.

Results: A systematic review of 10 articles revealed that WIFAS significantly increased serum ferritin levels in adolescent girls (Hedge's g = 0.53, 95% CI: 0.28, 0.78; heterogeneity I² = 41.21%, P < 0.001) and hemoglobin levels in school-age children (Hedge's g = 0.37, 95% CI: 0.01, 0.73; heterogeneity I² = 91.62%, P < 0.001). The analysis further demonstrated a substantial reduction in the risk of anemia by 20% (risk ratio = 0.8, 95% CI: 0.69, 0.93; heterogeneity I² = 28.12%, P < 0.001).

Conclusion: WIFAS proved effective in enhancing serum ferritin and hemoglobin concentrations and lowering the risk of anemia in school-age children and adolescents compared to placebo. Similarly, there are not enough studies to examine the effects of WIFAS on school performance. However, information regarding mental health problems, mortality, and potential side effects remains insufficient.

Strength and limitation

- Hedge's g addresses the issue of overestimation of the effect size in small samples.

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- Certainity of evidence for serum ferritin, hemoglobin, and anemia is moderate.
- Incorporation of five databases to search for articles.
- Diverse intervention designs, spanning dose, and iron supplement form contributes to complexity
- Substantial differences in intervention design, including dose, form of iron supplements, and frequency and duration of supplementation, add complexity.

Prospero Registration: CRD42023397898

Keywords: WIFAS, Anemia, Sub-Saharan Africa, School Performance, Adolescent

Introduction

Adolescents are a subset of children whose age ranges from 10-19 years ¹. This age group makes up the greatest proportion of the population (23%) in Sub-Saharan Africa, which is about twice that of the industrialized countries ². Adolescence, marked by the transition to adulthood, is a critical phase characterized by significant growth, behavioral maturation, and sexual development. This represents the second growth spurt in life, particularly for girls who undergo unique experiences including menstruation, emotional changes, nutritional requirements, and identity formation. Adolescents require heightened nutritional demands, with a specific emphasis on the need for iron. This period lays the foundation for adult health and economic well-being. Adolescents attain 20% final adult height and 50% adult weight, underscoring its pivotal role in shaping future health outcomes^{3,4}.

Anemia, a widespread global health concern, impacts approximately 1.6 billion individuals. According to the World Health Organization (WHO), approximately 50% of anemia cases are attributed to iron deficiency ⁵ Moreover, the prevalence of anemia in Sub-Saharan Africa surpasses 39% ⁶. This condition serves as a direct marker of undernutrition and insufficient iron intake, posing a significant public health challenge for adolescents ⁷. Iron plays a crucial role as an essential nutrient in the development and functioning of the brain. Its functions are diverse and contribute to various aspects of neural activity and neurotransmission. Some key roles of iron in the brain include ATP production, synthesis and packaging of neurotransmitters, and uptake and degradation of neurotransmitters ^{5,8}.

Iron deficiency anemia in adolescence has the potential to impede growth, hinder motor and brain development, and increase the risk of illness and mortality. Failure to promptly address anemia during this critical period may lead to persistent challenges later in life ⁹ including limiting their educational achievements and subsequently impacting their economic potential^{4,10,11}.

Adolescents are particularly prone to iron deficiency and anemia due to a range of factors, including rapid growth, insufficient dietary iron intake, reduced bioavailability of dietary iron, and heightened susceptibility to infectious diseases, parasitic infections, and menstrual blood loss ⁷. The combination of these factors contributes to an increased risk of iron deficiency anemia in adolescent girls, emphasizing the need for targeted interventions and education to address the specific challenges faced by this demographic group ¹⁰.

Indeed, adolescence and school-age children are recognized as a pivotal period for implementing interventions to address anemia and lay the foundation for future health, particularly in terms of childbearing ^(1,2). Implementing iron supplementation as an effective strategy to combat iron deficiency can have a substantial impact on reducing the prevalence of anemia, improving public health outcomes, and enhancing the well-being of affected populations, particularly in resource-constrained settings ^{12–14}.

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Following the robust literature review, there is a notable scarcity of information regarding the effectiveness of once-weekly IFAS concerning a broader spectrum of school performance and health outcomes including mental health ⁹. The limitations of the available data underscore the need for comprehensive and standardized research methodologies to elucidate the full range of effects associated with WIFAS on diverse nutrition, education, and health parameters. Within the framework of this systematic review and meta-analysis, we aimed to assess the impact of once WIFAS on serum ferritin levels, school performance, and mental health status among children and adolescents in the Sub-Saharan African region.

Methods

Searching strategies

The review encompassed a comprehensive examination of various literature sources through an extensive search across four electronic databases, supplemented by a manual search of references from key articles, previous reviews, and grey literature, to thoroughly investigate the effects of

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WIFAS on serum ferritin levels, school performance, and mental health. Our search for published articles was confined to individuals aged 6-19 years and studies conducted exclusively in sub-Saharan Africa. We systematically searched international databases, including Scopus, Web of Science, PubMed (MEDLINE), Cochrane Library, and Google Scholar. The search terms were combined using Boolean operators 'AND'/'OR' (Supplementary material 1). All published articles up to August 23, 2023, were incorporated into the systematic review. The results of the database search were aggregated, and duplicate articles were eliminated using the online Rayyan Software (https://www.rayyan.ai/). This tool was also employed to download the full text of studies for further evaluation

Eligibility criteria

Inclusion criteria

Study area: Only studies conducted in Sub-Saharan Africa (South of the Sahara).

Publication condition: articles published in peer-reviewed journals.

Study design: all RCT and clinical trial studies

Intervention: Weekly Iron and/or folic acid supplementation

Language: Articles published in the English language.

Age: School-age children typically encompass a range of ages, including the adolescent group. In this study, individuals aged between 4 and 19 years, and both primary and secondary school

children were included.

Exclusion criteria

Studies conducted related to iron fortification, and studies lacking specific outcome reporting were excluded from our analysis.

Outcome measurement

In this study, the main focus was on evaluating the impact of WIFAS on key health indicators, including serum ferritin levels, hemoglobin concentrations, anemia prevalence, mental health, and school performance. Measurement of outcomes involved assessing serum ferritin (in μ g/L) and hemoglobin (in g/dl) through mean and standard deviation calculations. For anemia, the prevalence was examined as binary outcomes post-supplementation. Moreover, the study delved into the assessment of school performance by considering the average scores of subjects, school grades, and school attendance increment. Additionally, cognitive performance was thoroughly evaluated

using a battery of cognitive tests specifically chosen, designed, or adapted for the age and cultural group under consideration. This battery included four subtests from the Kaufman Assessment Battery for children aged 3–18 years, second edition (KABC-II) ¹⁵, and the Hopkins Verbal Learning Test (HVLT) ¹⁶. The subtests chosen from the KABC-II encompassed the Atlantis (assessing working memory) and Atlantis Delayed (evaluating long-term memory and retrieval) tests from the learning scale, the Hand Movement test (measuring short-term memory) from the sequential processing scale, and the Triangles test (assessing visuospatial cognition) from the simultaneous processing scale ^{17–19}.

Data extraction

The extraction of data was carried out independently by two authors (SK and BM) utilizing a standardized spreadsheet for data extraction. The format for data extraction encompassed details such as the primary author, year of publication, the geographical region where the study was conducted, sample size, frequency of supplementation, age, sex, dose of supplements, outcome measurement, duration of the intervention, and information related to the randomized controlled trials (mean, standard deviation, median, and interquartile range proportion).

Quality assessment

For the assessment of the methodological quality of the included studies, we employed the Joanna Briggs Institute (JBI) Critical Appraisal tools designed for use in systematic reviews of randomized controlled trials ²⁰. This tool consists of thirteen questions addressing aspects such as selection bias, attrition bias, performance bias, and detection bias. Two independent reviewers (SK and BW) meticulously assessed each paper, engaging in discussions to resolve any discrepancies. In cases where disagreements persisted, a third reviewer (KH) was consulted to arbitrate and ensure consistency between the two independent reviewers. We have also contacted authors through email to get some outcome measurements that are mentioned by mean and median, as well as full texts. Each question in the Joanna Briggs Institute (JBI) Critical Appraisal tools was assigned a score: "Yes" received a score of 2, "No" was scored as 0, "Unclear" was denoted as 1, and "Not applicable" was recorded as NA. The overall quality of the studies was determined based on the cumulative score, classifying them as high quality if they scored 20 and above, good quality for scores between 13 and 19, and lower quality for scores below 13. The detailed results, including the breakdown of scores for each study, can be found in Table 1. Notably, nearly half of the studies

(47%) achieved a high-quality score, while 11.7% were categorized as lower quality (Supplemental Table 1).

Statistical analysis

The extracted data were entered into the computer using an Excel sheet and imported to STATA 17 for analysis. Heterogeneity among reported was assessed by using the Higgins-I² with Cochran Q statistic at 25%, 50%, and 70% as low, moderate, and considerable heterogeneity respectively with p-values less than 0.05²¹. A random effects meta-analysis model was used to estimate the pooled effect of WIFAS on serum ferritin level, hemoglobin, anemia, school performance, and mental health. A forest plot was also used to visualize the presence of heterogeneity subjectively. Possible differences between studies were explored by sub-group analyses and sensitivity analysis. Descriptive statistics (means and SD, median, IQR, 95%CI, and proportions) were used to summarize baseline information. The finding was presented using a forest plot with respective hedges and risk ratios and 95% confidence intervals. Evidence of publication bias was assessed using both Egger's and Begg's tests with a p-value of less than 0.05 as a cut-off point to declare the presence of publication bias ^{22,23}. The pooled hedges and risk ratios with 95% CI for each factor were used.

Registration and reporting

This study was registered with the International Prospective Register of Systematic Reviews (PROSPERO ID: <u>CRD42023397898</u>). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed during the systematic review process ²⁴.

Patient and public involvement

None

We identified a total of 2,026 articles of which 1,945 were from Scopus, Web of Science, PubMed, Cochrane Library, and 81 from Google Scholar. After excluding 343 duplicates, a review of titles and abstracts against the review objectives and inclusion criteria led to the exclusion of 1,631 articles as irrelevant. Subsequently, the full texts of the remaining 52 studies were assessed, with 10 studies meeting the criteria for inclusion in the present systematic review and meta-analysis (Figure 1).

Study Characteristics

The current systematic review and meta-analysis were carried out in Sub-Saharan Africa. Among the included studies, four were conducted in Eastern Africa^{25–28}, with one study in Ethiopia, one in Kenya, one in Tanzania, and one in Mozambique. Additionally, three studies were conducted in Western Africa^{29–31}, with one in Mali, one in Burkina Faso, and one in Ghana. Moreover, two studies were carried out in Southern Africa^{32,33}, with one in Zambia and one in South Africa. Furthermore, a study was conducted in North-East Africa Sudan ³⁴.

Besides, concerning the frequency of supplementation, all of the studies were included on a weekly basis ^{25–34}, and seven studies were included that primarily focused on adolescent girls ^{25–29,31,34}

Regarding the supplement composition, four studies were conducted on 60mg of elemental iron and folic acid in amounts ranging from 0.4mg to 2.8mg ^{26,28,29,31}. Two studies were conducted in the form of 65mg elemental iron and folic acid amounts ranging from 0.1mg to 0.25mg ^{30,32}. Moreover, two studies were conducted in the form of ferrous sulphate^{27,33}, one study in the form of 120mg elemental iron²⁵, and one study did not know the dosage ³⁴. Only three studies were conducted in community-based27,30,35. The supplementation period varied within the range of 2.2 months to 18 months (Table 1).

BMJ Open Table 1: Descriptive summary of the studies included in the systematic review and meta-analysis among adolescents meta-babaran Africa, 2023.

	1						<u> </u>	
Author,	Setting	Sex and	Sample	Interventi	Comparator	Frequen	La Signation	Outcome
(Year, Country),	and Study	Age	Size for	on arm	arm	cy of	og <u>1</u>	measurement
Reference	design	(Years)	Intervention	(Iron		supplem	sgippleme	
			Group (IG)	and/or		ent	näsa	
			and Control	folic acid			202 rela	
			Group (CG)	dose)			of 11 ppleme of uppleme marchated	
Beasly, et.al	School;	Female,	IG= 50	400mg FS	Vitamin B12	Weekly	455meonths	Hgb, SF, CRP,
(2000, Tanzania) ²⁷	RCT	12-18	CG= 57		_		vnlo	Diarrhea, Malaria
							tar	and Wt. change
Yosef H, et.al	Communi	Female,	IG= 92	60mg	No	Weekly	text and defficiently	Hgb, SF, and CR
(2021, Ethiopia) ²⁶	ty RCT	10-19	CG= 112	EI+0.4mg			ron	
Andrew Hall, et.al	School	6-19 years	IG= 551	65mg	No	Weekly	ata a ningaths	Hgb, and Anemia
(2001, Mali) ³⁰	CRCT		CG= 562	EI+0.25m			months	status
				g			g, jon	
Victor Mwanakasale	School;	Male, 9-	IG= 80	200mg FS	Vitamin-C	Weekly	9 months	Hgb, and Anemi
(2009, Zambia) 33	RCT	15 years	CG= 87				aini	status
Victor Mwanakasale	School;	Female,	IG= 73	200mg FS	Vitamin-C	Weekly	E nonths	Hgb, and Anemia
(2009, Zambia) 33	RCT	9-15 years	CG= 84		1		an	status
Taylor (2002, South	School;	6-15 years	IG= 101	65mg	Anti-	Weekly	j.conn. and si	Hgb
Africa) ³²	RCT		CG= 91	EI+100µg	helminthic	-	neomeths	-
Leenstra, et.al	School;	Female,	IG= 80	120mg EI	Vitamin-A	Weekly	a finonths	Hgb, and SF
(2009, Kenya) ²⁵	RCT	12-18	CG= 109				ech	
· · · · ·		years					nol 0, 2	
Sabine G, et.al.	Communi	Female,	913 girls	60mg	2.8mg folic	Weekly	Junionths artechnology	Hgb, SF, and
(2018, Burkina Faso)	ty	10-19	C C	EI+2.8mg	acid		1 months	anemia
29		years					Un	
Lucas G, et.al, (2021,	School,	Female,	1387 girls	60mg	No	Weekly	12ér mogaths	Anemia and Hgb
Ghana) ³¹	Pre-post	10-19		EI+0.4mg	comparator		mount	
,	longitudin	years			1			
	al	5					Paris	
						·	Est	
							Est Creteil .	
							ite	

11 of 31					BMJ Open			136/bmjopen cted by copy	
	Peter H, et.al, (2005, Mozambique) ²⁸	School, Pre-post longitudin al study	Female, 10-18 years	991 girls	60mg EI+0.4mg	-	Weekly	6/bmjopen-2024-08-033 on 1100 by copyright 208-033 on 1100 funding for us	Anemia and Hgb
	Maisoon NA Fageer,et.al, (2021, Sudan) ³⁴	Communi ty RCT	School children	IG= 109 CG= 106	EI	Folic acid	Weekly	4 months ses relation	Anemia and School Performance
	Creative Reactive Protein; Hgb score; ID: Iron Deficiency; TFF	: Hemoglobin; SF	: Serum Ferritin, eptor; SAC: Sch	; wt.: weight; Ht:	NM: Not Mention	-	: Body mass inde	ex rescore; H score;	IAZ: Height for age Z

Effect of WIFAS on Serum Ferritin-Narrative Synthesis

Four studies assessed the impact of WIFAS on serum ferritin $^{26-29}$ using various statistical measures, including mean, standard deviation, median, and interquartile range. Out of these, three studies reported a significant improvement in the serum ferritin level of children with IFAS^{25–27}. However, a study conducted by Sabine G. et al. (2018) ²⁹ did not find a significant effect between IFAS and serum ferritin. Furthermore, three studies demonstrated that once-weekly IFAS led to a significantly greater increment in serum ferritin compared to the control group, with the favor of 9.1 µg/l, 39.1 µg/l, and 13.3 µg/l respectively^{25–27}.

Effect of WIFAS on Serum Ferritin-Meta Analysis

Three studies were incorporated into the meta-analysis $^{25-27}$, involving a total of 440 adolescent girls. Among them, 205 received weekly iron supplementation, while 235 were assigned to the placebo/non-intervention group. The analysis revealed a positive impact of weekly iron supplementation on enhancing the serum ferritin levels of adolescent girls (Hedge's g 0.53, 95%CI: 0.28, 0.78; test for heterogeneity I² = 41.21%). There is no publication bias with p value of 0.374 (Figure 2).

Effect of WIFAS on Hemoglobin-Narrative Synthesis

In this comprehensive review, 10 studies were incorporated to evaluate the impact of WIFAS on hemoglobin levels. Out of these, five studies administered IFA every week ^(25,28,30,31,35), revealing a significant increase in hemoglobin concentration ranging from 0.12 g/dl to 4.8 g/dl. However, three studies did not significant association between WIFAS and hemoglobin concentration^{27,29,33}.

Effect of WIFAS on Hgb-Meta-analysis

In this meta-analysis, a total of five studies $^{25-27,30,33}$ involving 1949 school-age children, including adolescents, were included. Among them, 933 received weekly iron supplementation, while 1016 were part of the placebo/non-intervention group. The analysis demonstrated a significant effect of weekly iron supplementation in improving the hemoglobin levels of school-age children (Hedge's g 0.37, 95%CI: 0.01, 0.73; test for heterogeneity I² = 91.62%). There is no influential study and publication bias (p-value of 0.924) (Figure 3).

Effect of WIFAS on Hgb-subgroup meta-analysis by Setting

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The subgroup analysis revealed that both school 25,27,30,33 and community 26 setting supplementation of iron had a significant effect on the hemoglobin levels of school-age children. Additionally, the variability among the studies was within an acceptable range for both the school setting supplementation (Hedge's g 0.23, 95%CI: 0.12, 0.35; test for heterogeneity I² = 16.33%) and the community setting (Hedge's g 1.28, 95%CI: 0.97, 1.58) (Supplemental Figure 1).

Effect of WIFAS on Anemia-Narrative Synthesis

In this systematic review, an analysis of seven studies was conducted to evaluate the impact of Iron and Folic Acid Supplementation (IFAS) on the prevalence of anemia. Out of these, three studies implemented IFAS every week ^(28,32,36), demonstrating a significant reduction in the prevalence of anemia, with percentages ranging from 0.35% to 8.2%. However, the findings from the remaining three studies did not show a significant association between WIFAS and the prevalence of anemia ^{28,29,33}. Despite our efforts to obtain the full-text article through email correspondence with the author, we were unable to secure it. Nonetheless, we relied on information from a conference proceeding abstract paper conducted in Sudan. According to this abstract, intermittent iron with folic acid supplementation demonstrated a significant (65.7%) reduction in the likelihood of anemia in the experimental group when compared to the control group, which received folic acid alone ³⁴.

Effect of WIFAS on Anemia-Meta analysis

In this meta-analysis, four studies 25,29,30,33 were included, comprising a total of 2505 school-age children, including adolescent girls. Among them, 1233 received weekly iron supplementation in the treatment group, while 1272 were assigned to the placebo/non-intervention group. The analysis demonstrated a significant impact of weekly iron supplementation in reducing the risk of anemia by 20% (Risk ratio = 0.8, 95%CI: 0.69, 0.93; test for heterogeneity I² = 28.12%). Moreover, there is no publication bias on the effect of WIFAS on Anemia with a p-value of 0.798 (Figure 4).

Effect of WIFAS on School and cognitive Performance-Narrative synthesis

In this systematic review and meta-analysis, we couldn't get enough studies regarding the effect of WIFAS on school and cognitive performance.. Despite our efforts to secure the full-text article through email correspondence with the author, it remains unavailable. However, we relied on information from a conference proceeding abstract paper conducted in Sudan. According to this abstract, intermittent iron with folic acid supplementation did not show a significant association with school performance in the experimental group when compared to the control group, which received folic acid alone³⁴.

Effect of WIFAS on Mental Health Problem- Narrative Synthesis

No trials were reported in this outcome in Sub-Sahara Africa.

Certainty of Evidence

To evaluate the certainty of evidence, we considered factors such as risk of bias, inconsistency, indirectness, imprecision, publication bias, and additional considerations like large effect, dose-response, and confounders. The assessment of risk of bias utilized the Cochrane risk of bias tool for 2019, encompassing criteria such as sequence generation, allocation concealment, blinding/masking of the intervention, intention-to-treat analysis, blinding/masking of outcome assessors, and freedom from other biases ³⁵. Inconsistency was explored through the heterogeneity (I²) of the overall effect in the meta-analysis. Indirectness was scrutinized for external validity or generalizability (PICO), applicability, and any deviations from the research question. Imprecision was investigated through wide confidence intervals, including those indicating a null effect and high relative risk (RR > 0.75 or > 1.25). Additionally, we assessed publication and other biases. Based on our findings, we moderately recommend that WIFAS increases serum ferritin and hemoglobin levels while reducing anemia. (Supplemental Table 2).

Discussion

The current study incorporated 17 randomized trials in a systematic review to assess the impact of weekly iron-folic acid supplementation (WIFAS) on various health indicators including serum ferritin, hemoglobin, anemia, mental, school, and cognitive performance. The trials were distributed across East Africa (four studies), Southern Africa (two studies), West Africa (three studies) and Northern Africa (One study).

The current meta-analysis revealed the positive effects of WIFAS on serum ferritin and hemoglobin levels. Additionally, the WIFAS demonstrated a reduction in anemia. These findings are consistent with findings from a study done by De-Regil LM, et.al. This suggests that intermittent iron supplementation is effective in improving hemoglobin concentrations and reducing the risk of anemia or iron deficiency in children under 12 years of age ⁹. The findings of Ana C Fernández-Gaxiola 1 and Luz Maria De-Regil about Intermittent iron supplementation for reducing anemia and its associated impairments in adolescent and adult menstruating women supported our findings ⁹.

The findings of our study align with the World Health Organization (WHO) recommendations, supporting the guideline that advocates for the intermittent use of iron and folic acid supplements as a public health measure. This recommendation aims to reduce anemia and enhance iron status among menstruating women, emphasizing the global significance of evidence-informed strategies in addressing nutritional deficiencies ³⁶. Furthermore, our findings are consistent with the recommendation advocating for WIFS. This approach serves as a preventive and sustainable long-term strategy for improving iron status and reducing the prevalence of anemia. The positive outcomes observed with WIFS align with the "mucosal block" hypothesis. According to this hypothesis, administering iron every week allows sufficient time for the shedding of cells loaded with iron from a previous dose. This shedding process contributes to increased iron absorption, reinforcing the efficacy of the WIFS approach ^{37,38}.

UNICEF's latest nutrition strategy, released in 2021, incorporates WIFAS as an intervention in the result area focusing on 'middle childhood and adolescents' ³⁹. Nutrition guidance specific to this target group has also been issued by UNICEF ⁴⁰. In regions where the prevalence of anemia among menstruating adult women and adolescent girls falls within the range of 20–39.9%, the guidance recommends weekly supplementation of 60 mg of elemental iron and 2800 µg of folic acid for three months, followed by three months of no supplementation, and then restarting the supplementation. It further suggests that, if feasible, intermittent supplementation should continue throughout the school calendar year in these settings.

A subgroup analysis was conducted to examine the distribution modalities of iron-folic acid supplementation programs, distinguishing between school-based and community-based approaches. The results revealed that only one study focused on community-based distribution, demonstrating a positive impact on hemoglobin levels. Whereas, five studies centered on school-based modalities and indicated a favorable effect on hemoglobin levels. These findings prompt a discussion on comparing the feasibility of implementing iron-folic acid supplementation programs in schools versus communities, considering factors such as accessibility for adolescent groups and cost-effectiveness. More than 90% of adolescents are now found in schools and cost effective in school settings⁴¹. Hence, distributing WIFAS at school modalities is beneficial compared to the community.

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The systematic review indicates that IFAS has a positive impact on school attendance and cognitive performance. This aligns with assessments from the WHO and Copenhagen Consensus Challenge, which estimate a high benefit-to-cost ratio for iron interventions. The ratio is based on resource savings, enhancements in cognitive development and schooling, and increased physical productivity, reaching as high as 200:1. Emphasizing the prevention of iron deficiency anemia (IDA) in adolescents is strategically crucial, considering potential gains in physical capacity, cognitive ability, and, for adolescent girls, improved pregnancy outcomes and intergenerational benefits ^{42,43}. However, mental health trials were not reported in this outcome in Sub-Sahara Africa.

Given the positive impact of WIFAS on improving iron status and reducing anemia, policymakers must prioritize the implementation of such programs in public health initiatives. Ensuring access to affordable and high-quality supplements, as well as promoting awareness about the importance of iron folic acid supplementation, can significantly contribute to reducing the burden of anemia and improving overall health outcomes.

Strengths and limitations of the study

The strength of this study lies in the quality of the incorporation of five databases to search for articles. Additionally, we investigated the impact of once-weekly iron-folic acid supplementation on serum ferritin, hemoglobin, anemia, and academic performance. However, our study is subject to inherent limitations related to the effects of intermittent iron and folic acid supplementation on serum ferritin, hemoglobin, anemia, cognitive, and school performance, which broadens the scope of the study. The analysis faces challenges owing to the use of various tools and instruments including outcome measurement of mean, median, interquartile range, and standard deviation, particularly for serum ferritin and hemoglobin complicating comparisons between intervention outcomes. Substantial differences in intervention design, including dose, form of iron supplements, and frequency and duration of supplementation, add complexity. Establishing an optimal dose, frequency, or duration for improved or reduced outcomes for school performance remains elusive. There is no trial regarding the effect of WIFAS on mental health. Additionally, the potential influence of other micronutrients remains unclear in some studies. With two studies featuring low-quality studies, the researchers acknowledge the possibility of missing relevant studies.

Conclusion

WIFAS proves effective in enhancing serum ferritin, hemoglobin concentrations and lowering the risk of anemia or iron deficiency in adolescents compared to a placebo or no intervention. Moreover, iron supplementation demonstrates positive effects on verbal and nonverbal learning and memory, especially in children with anemia. Similarly, there are no good enough studies to examine the effect of WIFAS and school performance. Despite these benefits, information on mental health problems, mortality, and potential side effects remains insufficient.

Based on the findings supporting the effectiveness of weekly iron-folic acid supplementation, current recommendations include integrating this intervention into existing school health programs. Health and education authorities should consider incorporating routine screening for anemia and providing supplementation to at-risk populations, such as young children. Additionally, healthcare providers and teachers should be trained to counsel patients on the benefits of iron-folic acid supplementation and monitor their adherence to the regimen. Continuous monitoring and evaluation of these programs are essential to assess their impact and make necessary adjustments to optimize outcomes.

Author Contributions

The authors' responsibilities were as follows: SK, BW, KHA: Designed and supervised the study, ensured the quality of the data, and made a substantial contribution to the local implementation of the study and SK, KHA, BW, BM assisted in the analysis and interpretation of the data. All authors critically reviewed the manuscript. SK, the corresponding author did the analysis & drafted the manuscript and had the responsibility to submit the manuscript for publication.

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Competing interests: The authors declare that they have no competing interests.

Patient and public involvement: Patients and/or the public were not involved in the design, conduct, reporting, or dissemination plans of this research.

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Ethics approval: Not applicable

Provenance and peer review: Not commissioned; externally peer reviewed.

Data availability statement: All data relevant to the study are included in the article or uploaded as supplementary information.

References

- 1. WHO. Adolescent health.
- 2. UNFPA. The state of the world population 2014. The power of 1.8 billion; adolescents, youth and the transformation of the future.
- 3. UNICEF, WHO, and C. Iron & Folic Acid (IFA) Supplementation for Adolescent Girls and Women. Participants Manual for Health Workers. (2017).
- 4. Leroy, J. L., Ruel, M., Habicht, J.-P. & Frongillo, E. A. Linear Growth Deficit Continues to Accumulate beyond the First 1000 Days in Low- and Middle-Income Countries: Global Evidence from 51 National Surveys. *J. Nutr.* **144**, 1460–1466 (2014).
- 5. Safiri, S. *et al.* Burden of anemia and its underlying causes in 204 countries and territories, 1990–2019: results from the Global Burden of Disease Study 2019. *J. Hematol. Oncol.* **14**, 185 (2021).
- 6. World-Bank. Prevalence of anemia among reproductive age (% of women ages 15–49). (2021).
- 7. Toteja, G. S. *et al.* Prevalence of Anemia among Pregnant Women and Adolescent Girls in 16 Districts of India. *Food Nutr. Bull.* **27**, 311–315 (2006).
- 8. Jáuregui-Lobera, I. Iron deficiency and cognitive functions. *Neuropsychiatr. Dis. Treat.* 2087 (2014) doi:10.2147/NDT.S72491.
- 9. Sylvetsky, A. C., Jefferds, M. E. D., De-Regil, L. M. & Dowswell, T. Intermittent iron supplementation for improving nutrition and developmental outcomes in children. in *Cochrane Database of Systematic Reviews* (ed. De-Regil, L. M.) (John Wiley & Sons, Ltd, 2011). doi:10.1002/14651858.CD009085.
- 10. WHO. Anaemia Policy Brief, WHO, Geneva, Switzerland. (2019).
- 11. Gelli, A. *et al.* Evaluation of alternative school feeding models on nutrition, education, agriculture and other social outcomes in Ghana: rationale, randomised design and baseline

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	data. Trials 17, 37 (2016).
12.	Camaschella, C. Iron-Deficiency Anemia. N. Engl. J. Med. 372, 1832-1843 (2015).
13.	Low, M., Farrell, A., Biggs, BA. & Pasricha, SR. Effects of daily iron supplementation in primary-school–aged children: systematic review and meta-analysis of randomized controlled trials. <i>Can. Med. Assoc. J.</i> 185 , E791–E802 (2013).
14.	Samson, K. L. I., Fischer, J. A. J. & Roche, M. L. Iron Status, Anemia, and Iron Interventions and Their Associations with Cognitive and Academic Performance in Adolescents: A Systematic Review. <i>Nutrients</i> 14, 224 (2022).
15.	Kaufman AS, Lichtenberger EO, Fletscher-Janzen E, K. L. Essentials of KABC-II Assessment. (2005).
16.	Brandt, J. The Hopkins Verbal Learning Test development of a new memory test with six equivalent forms. <i>Clin Neuropsychol</i> 5 , 125–42 (1991).
17.	Ogunlade, A. O. <i>et al.</i> Point-of-use micronutrient fortification: lessons learned in implementing a preschool-based pilot trial in South Africa. <i>Int. J. Food Sci. Nutr.</i> 62 , 1–16 (2011).
18.	Muthayya, S. <i>et al.</i> Effect of fortification with multiple micronutrients and n–3 fatty acids on growth and cognitive performance in Indian schoolchildren: the CHAMPION (Children's Health and Mental Performance Influenced by Optimal Nutrition) Study. <i>Am. J. Clin. Nutr.</i> 89 , 1766–1775 (2009).
19.	Dalton, A. <i>et al.</i> A randomised control trial in schoolchildren showed improvement in cognitive function after consuming a bread spread, containing fish flour from a marine source. <i>Prostaglandins, Leukot. Essent. Fat. Acids</i> 80 , 143–149 (2009).
20.	JBI. Joanna Briggs Institute (JBI) Critical Appraisal tools for use in JBI Systematic Reviews Checklist for Randomized Controlled Trials. (2017).
21.	Rücker G, Schwarzer G, Carpenter JR, S. M. Undue reliance on I2 in assessing heterogeneity may mislead. <i>BMC Med Res Methodol</i> 8 , 79 (2008).
22.	Begg CB, M. M. Operating characteristics of a rank correlation test for publication bias. <i>Biometrics</i> 1088–101 (1994).
23.	Egger M, Smith GD, Schneider M, M. C. Bias in meta-analysis detected by a simple, graphical test. <i>BMJ</i> 315 , 629–34 (1997).
24.	Moher D, Liberati A, Tetzlaff J, A. D. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. <i>Ann Intern Med</i> 151 , 264–9 w264 (2009).
25.	Leenstra, T. <i>et al.</i> The effect of weekly iron and vitamin A supplementation on hemoglobin levels and iron status in adolescent schoolgirls in western Kenya. <i>Eur. J. Clin.</i>
18	
	For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Nutr. 63, 173–182 (2009).

- 26. Handiso, Y. H., Belachew, T., Abuye, C., Workicho, A. & Baye, K. A community-based randomized controlled trial providing weekly iron-folic acid supplementation increased serum- ferritin, -folate and hemoglobin concentration of adolescent girls in southern Ethiopia. *Sci. Rep.* **11**, 9646 (2021).
- 27. Beasley, N. M. R. *et al.* The impact of weekly iron supplementation on the iron status and growth of adolescent girls in Tanzania. *Trop. Med. Int. Heal.* **5**, 794–799 (2000).
- 28. Horjus, P., Aguayo, V. M., Roley, J. A., Pene, M. C. & Meershoek, S. P. School-Based Iron and Folic Acid Supplementation for Adolescent Girls: Findings from Manica Province, Mozambique. *Food Nutr. Bull.* **26**, 281–286 (2005).
- 29. Gies, S. *et al.* Effects of Weekly Iron and Folic Acid Supplements on Malaria Risk in Nulliparous Women in Burkina Faso: A Periconceptional, Double-Blind, Randomized Controlled Noninferiority Trial. *J. Infect. Dis.* **218**, 1099–1109 (2018).
- Hall, A. *et al.* A randomised trial in Mali of the effectiveness of weekly iron supplements given by teachers on the haemoglobin concentrations of schoolchildren. *Public Health Nutr.* 5, 413–418 (2002).
- 31. Gosdin, L. *et al.* A School-Based Weekly Iron and Folic Acid Supplementation Program Effectively Reduces Anemia in a Prospective Cohort of Ghanaian Adolescent Girls. *J. Nutr.* **151**, 1646–1655 (2021).
- 32. Taylor, M., Jinabhai, C. C., Couper, I., Kleinschmidt, I. & Jogessar, V. B. The effect of different anthelmintic treatment regimens combined with iron supplementation on the nutritional status of schoolchildren in KwaZulu-Natal, South Africa: a randomized controlled trial. *Trans. R. Soc. Trop. Med. Hyg.* **95**, 211–216 (2001).
- 33. Mwanakasale, V., Siziya, S., Mwansa, J., Koukounari, A. & Fenwick, A. Impact of iron supplementation on schistosomiasis control in Zambian school children in a highly endemic area. *Malawi Med. J.* **21**, (2009).
- 34. Nagmeldin Abbas Fageer, M., Hussein, M. D., N Abbas Fagiri, M. & Osman, M. 1239 Randomized controlled trial on the effect of weekly iron/folic acid supplementation on anemia and school performance among school children in rural Sudan. in *Abstracts* A288.1-A288 (BMJ Publishing Group Ltd and Royal College of Paediatrics and Child Health, 2021). doi:10.1136/archdischild-2021-rcpch.501.
- 35. Cochrane. RoB 2: A revised Cochrane risk-of-bias tool for randomized trials. (2019).
- 36. WHO. Guideline: Intermittent Iron and Folic Acid Supplementation in Menstruating Women. Guideline: Intermittent Iron and Folic Acid Supplementation in Menstruating Women (2011).
- 37. Wright, A. J. A. & Southon, S. The effectiveness of various iron-supplementation

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	regimens in improving the Fe status of anaemic rats. Br. J. Nutr. 63, 579-585 (1990).
38.	FE, V. Global consultation on Weekly Iron-Folic Acid Supplementation for preventing Anaemia in women of Reproductive Age Group. (2007).
39.	UNICEF, U. N. C. F. Nutrition, for every child. UNICEF Nutrition Strategy 2020- 2030. (2020).
40.	United Nations Children's Fund, U. Programming Guidance: Nutrition in Middle Childhood and Adolescence. (2021).
41.	WHO. Making every school a health promoting school: Adolescent and Young Adult Health. (2023).
42.	WHO. Preventing Iron deficiency Anemia in Adolescents: Role of WIFAS: World Health Organization, Regional Office for South-East Asia, Indraprastha Estate, Mahatma Gandhi Marg, New Delhi-110 002. (2011).
43.	Hoddinott, J., Rosegrant, M. & Torero, M. HUNGER AND MALNUTRITION: Copenhagen Consensus Challenge. (2012).
Figu	re Legends
	e 1- PRISMA flow diagram illustrating the study selection process of iron and folic acid ementation effect on iron status, mental health and school performance articles.
Figur	e 2- Meta-analysis of the effect of once-weekly IFAS on serum ferritin
Figur	e 3- Meta-analysis of the effect of once-weekly IFAS on Hemoglobin
Figur	e 4- Meta-analysis of the effect of once-weekly IFAS on Anemia

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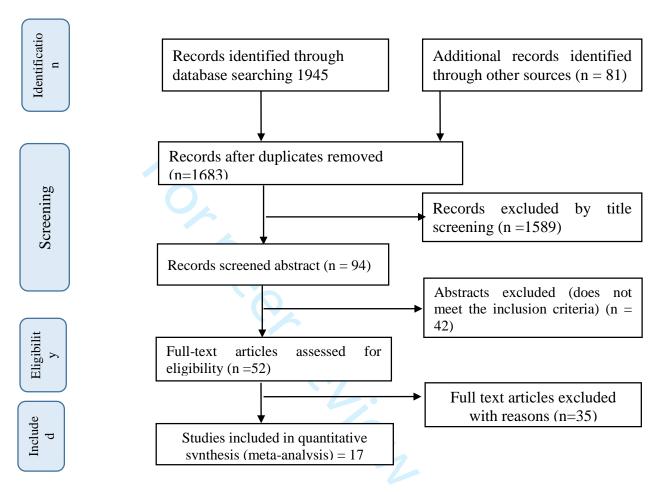


Figure 1. PRISMA flow diagram illustrating the study selection process of iron and folic acid supplementation effect on iron status, mental health and school performance articles.

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		Treatm	ent		Contro	bl		Hedges's g	Weig
Study	Ν	Mean	SD	N	Mean	SD		with 95% CI	(%
Beasley NMR, et.al, 2000	50	46.3	17	57	41	25.7		0.24 [-0.14, 0.62]	28.6
Yosef H, et.al, 2021	92	97.8	68.2	112	63.1	45.9		- 0.61 [0.33, 0.89]	40.2
Leenstra T, et.al, 2007	63	37.4	22.72	66	23.9	14.56		0.71 [0.35, 1.06]	31.1
Overall								0.53 [0.28, 0.78]	
Heterogeneity: $\tau^2 = 0.02$, I^2	= 41	.21%, H	l ² = 1.7()					
Test of $\theta_i = \theta_j$: Q(2) = 3.51,	p = 0	.17							
Test of θ = 0: z = 4.14, p =	0.00								
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Random-effects REML model

Figure 2: Meta-analysis of the effect of once-weekly IFAS on serum ferritin

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		Treatmo	ent		Contro	ol					Hedges's g	Weight
Study	N	Mean	SD	N	Mean	SD					with 95% CI	(%)
Andrew H, et.al, 2001	551	11.64	1.27	562	11.26	1.27					0.30 [0.18, 0.42]	18.26
Beasley NMR, et.al, 2000	57	11.94	1.06	62	11.85	.79			l T		0.10 [-0.26, 0.45]	15.76
Yosef H, et.al, 2021	92	14.5	1.3	112	13.2	.7			 		— 1.28 [0.97, 1.58]	16.50
Leenstra T, et.al, 2007	80	13.52	2.14	109	13.5	1.55	_	-	 		0.01 [-0.28, 0.30]	16.67
Victor M, et.al, 2009 (Male)	80	12.98	1.115	87	12.66	1.331		÷			0.26 [-0.04, 0.56]	16.47
Victor M, et.al, 2009 (Female)	73	13.02	1.116	84	12.65	1.354		-	-		0.29 [-0.02, 0.61]	16.34
Overall											0.37 [0.01, 0.73]	
Heterogeneity: $\tau^2 = 0.18$, $I^2 = 91$.62%,	H ² = 11	1.93					i I	 			
Test of $\theta_i = \theta_j$: Q(5) = 44.68, p =	0.00								 			
Test of θ = 0: z = 2.02, p = 0.04									 			
						-	Г Б	0	.5	1 1	⊤ .5	

Random-effects REML model

Figure 3: Meta-analysis of the effect of once-weekly IFAS on Hemoglobin

	Treat	tment	Со	ntrol				Log risk-ratio	Weig
Study	Yes	No	Yes	No				with 95% Cl	(%)
Andrew, et.al, 2001	273	288	356	205				-0.27 [-0.37, -0.16]	54.9
Victor M, et.al, 2009 (Male)	3	77	9	78				-1.01 [-2.29, 0.26]	1.2
Victor M, et.al, 2009 (Female)	3	77	11	76		 -+		-1.22 [-2.46, 0.02]	1.28
Leenstra T, et.al, 2007	6	56	1	63				— 1.82 [-0.26, 3.91]	0.40
Sabine G, et.al, 2018	179	261	217	256				-0.12 [-0.27, 0.03]	42.08
Overall						•		-0.22 [-0.36, -0.07]	
Heterogeneity: $\tau^2 = 0.01$, $I^2 = 28$	5.12%,	$H^{2} = 1$.39						
Test of $\theta_i = \theta_j$: Q(4) = 10.08, p =	0.04								
Test of θ = 0: z = -2.99, p = 0.00)								
					-2	0	2	4	

Random-effects REML model

Figure 4: Meta-analysis of the effect of once-weekly IFAS on Anemia

	nental Table 1: The Joanna B				BN	IJ Open					cted by copyri			Ρ	age 26
upplen landom	nental Table 1: The Joanna B nized Controlled Trials (RCTs)	riggs) in th	Institu is syste	ite (JB ematic	I) Quali review a	ty Asse	essment a-analys	tool wa sis, 2023	s emplo	byed to as	ghtencludi	qualit	y of ir	ncluded	
S/No	Studies	Was there true randomization	Was allocation to treatment groups concealed?	Were treatment groups similar at the baseline?	Were participants blind to treatment assignment?	Were those delivering treatment blind to treatment assignment?	Were outcomes assessors blind to treatment assignment?	Are groups identically other than intervention?	Was follow-up complete and if not, were differences b/n groups	Were participants analyzed in the groups to which they were randomized?	treatment groups?	Were outcomes measured reliably?	Was appropriate statistical analysis used?	Was the trial design appropriate, and any deviations from the standard RCT	Total Yes
1.	Beasly, et.al (2000, Tanzania)	2	0	2	0	0	1	0	2	0	om http:// ta mining	1	0	2	10
2.	Yosef H, et.al (2021, Ethiopia)	2	1	2	0	0	1	2	2	2		2	2	2	18
3.	Andrew Hall, et.al (2001, Mali)	2	0	2	1	1	1	2	2	0	mjopen.hmj.com/ on Ju Al training, and similar t	2	2	2	16
4.	Olsen, et.al (2006, Kenya)	2	2	2	2	2	2	2	2	2	on Ju imilar	1	2	2	24
5.	Lawless, et al (1994, Kenya)	2	2	2	2	2	1	2	2	2	ine 10 techn	1	2	2	22
6.	Victor Mwanakasale (2009, Zambia)	1	1	2	1	1	1	1	1	0	ne 10, 2025 at Upiversite technologies.	1	2	2	8
7.	Nchito (2009, Zambia)	2	2	2	2	2	2	2	2	1	Unive	1	2	2	22
8.	J. Baumgartner (2012, South Africa)	2	2	2	2	2	2	2	2	2	rsite Paris	2	2	2	26

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	9.	Leenstra, et.al (2007, Kenya)	2	2	2	2	2	2	2	2	1	136/bmjopen-2024-084033 on 11 June 2024. Downloaded from http://bi cted by copyrigh <u>t. Including for uses related to text and data mining.</u>	1	2	2	22
	10	J. Baumgartner (2013, South Africa)	2	2	2	2	2	2	2	2	2)33 on 11 J uding for u	2	2	2	26
	11.	Mohamed Ag Ayoya, (2009, Mali)	2	0	2	0	0	1	2	1	0	une 2024. ses relatec	2	2	2	14
	12	Nchito, (2003, Zambia)	2	2	2	2	2	2	2	2	1		1	2	2	22
	13.	Mohamed Ag Ayoya, (2012, Mali)	2	0	2	0	0	1	2	1	0	loaded fro <u>xt and dat</u>	2	2	2	14
	14.	Sabine G, et.al. (2018, Burkina Faso)	2	2	2	0	2	2	2	2	2	m http://b a mining.	2	2	2	24
	15.	Lucas G, et.al, (2021, Ghana)	0	NA	NA	0	NA	NA	2	2	2	miopen.k Al trainin	2	2	2	14
	16.	Peter H, et.al, (2005, Mozambique)	1	1	2	0	0	1	2	2	2	mi.com/ o ig. and sir	2	2	2	16
	17.	Maisoon NA Fageer,et.al, (2021, Sudan)	2	2	1	2	2	2	2	2	1	on June 1 nilar tech	1	2	2	18
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Outcomes	Number of studies	Number of participants	Study design	Risk of Bias	Inconsistency (Heterogeneity	Indirectness	Imprecision	Publication bias (Eggers test with P-	Other considerations (Large effect, dose-response,	Effect size ot patelas sesn to bui to the sest authy out up to RR) RR)	Certainty of evidence
Serum Ferritin (Once-Weekly)	3	440	RCT	Seriou s	Low	No	No	No	No	H=\$0\$53 (0.28, 0.78)	Moderate
Serum Ferritin (More than once weekly)	5	653	RCT	Seriou s	Low	No	No	No	Concern	H=10577 (0.33, 1.22)	Low
Hemoglobin (Once weekly)	5	1949	RCT	Seriou s	Low	No	No	No	No	H=1937 (0.01, 0.73)	Moderate
Anemia (Once- weekly)	4	2505	RCT	Low	Low	No	conc ern	No	No	RI 0.8 (0.69, 0.93)	Moderate
									74	n.b.0.8 (0.69, 0.93) n.b.0.8 (0.69, 0.93) and similar technologies.	
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		Treatm	ent		Contro	ol		Hedges's g	Weigl
Study	Ν	Mean	SD	Ν	Mean	SD		with 95% CI	(%)
Community									
Yosef H, et.al, 2021	92	14.5	1.3	112	13.2	.7		1.28 [0.97, 1.58]	16.5
Heterogeneity: $\tau^2 = 0.00$, $I^2 = .00$	%, H ² =	:.						1.28 [0.97, 1.58]	
Test of $\theta_i = \theta_j$: Q(0) = 0.00, p =	•								
School									
Andrew H, et.al, 2001	551	11.64	1.27	562	11.26	1.27	-	0.30 [0.18, 0.42]	18.2
Beasley NMR, et.al, 2000	57	11.94	1.06	62	11.85	.79		0.10 [-0.26, 0.45]	15.7
Leenstra T, et.al, 2007	80	13.52	2.14	109	13.5	1.55		0.01 [-0.28, 0.30]	16.6
Victor M, et.al, 2009 (Male)	80	12.98	1.115	87	12.66	1.331		0.26 [-0.04, 0.56]	16.4
Victor M, et.al, 2009 (Female)	73	13.02	1.116	84	12.65	1.354		0.29 [-0.02, 0.61]	16.3
Heterogeneity: $\tau^{2} = 0.00$, $I^{2} = 1$	6.33%	, H ² = 1.	.20				•	0.23 [0.12, 0.35]	
Test of $\theta_i = \theta_j$: Q(4) = 4.11, p =	0.39								
Overall								0.37 [0.01, 0.73]	
Heterogeneity: $\tau^2 = 0.18$, $I^2 = 9$	1.62%	, H ² = 1′	1.93						
Test of $\theta_i = \theta_j$: Q(5) = 44.68, p	= 0.00								
Test of group differences: Qb(1) = 40.	06, p =	0.00						
						ר ל	5 0 .5 1	1.5	
Random-effects REML model									

Supplemental Figure 1: Sub-group Meta-analysis of the effect of once-weekly IFAS on Hemoglobin

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1	PRIS	SMA 2	2020 Checklist	136/bmjopen-20)	
4	Section and Topic	ltem #	Checklist item	24-0840	Location where item is reported
5 6 1	TITLE			<u>.</u>	
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9 /	Abstract	2	See the PRISMA 2020 for Abstracts checklist.	lun	
	NTRODUCTION				3-5
	Rationale	3		2024.	4 & 5
	Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.		4 & 5
14	METHODS				
15 E	Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	xt pa	6
	nformation sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted date when each source was last searched or consulted.	entify studies. Specify the	5&6
18 g	Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	om	5&6
19 g 20	Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many r and each report retrieved, whether they worked independently, and if applicable, details of automation tools used		7
	Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each rep independently, any processes for obtaining or confirming data from study investigators, and if applicable, details o process.	whether they worked	7
24 25	Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which rest		7
20 27 29		10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, fund assumptions made about any missing or unclear information.	sources). Describe any	7
~ /	Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how r study and whether they worked independently, and if applicable, details of automation tools used in the process.	any reviewers assessed each	15
31 E	Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation	of results.	8
	Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study int comparing against the planned groups for each synthesis (item #5)).	Arcention characteristics and	10
34 35		13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing sum conversions.		8
36		13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	live	9
37 38 20		13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was p model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used		8
39 40		13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analy	/se, meta-regression).	8
40		13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	n	NA
	Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting bias	ି କେନ୍ଦ୍ର ଜୁ	15
	Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome. For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	6 	15

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PRISMA 2020 Checklist

Checklist item For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect. For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies. For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies. Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary effect. For each synthesis, of possible causes of heterogeneity. If comparing groups, describe the direction of the effect.	Location where item is reported 9 9 10 10 10 9 12-15 12-15 12-15
the review, ideally using a flow diagram. 9 1 Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were Excluded. Cite each included study and present its characteristics. For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots. For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies. Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary effect. For each the summary effect. Present results of all investigations of possible causes of heterogeneity among study results. For each the summary effect.	9 9 10 10 9 9 12-15 12-15
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	NA
Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	15
Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	15
Provide a general interpretation of the results in the context of other evidence.	16
Discuss any limitations of the evidence included in the review.	17
Discuss any limitations of the review processes used.	17
Discuss implications of the results for practice, policy, and future research.	17
Provide registration information for the review, including register name and registration number, or state that the raise was not registered.	8
Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	8
Describe and explain any amendments to information provided at registration or in the protocol.	8
Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	19
Declare any competing interests of review authors.	19
Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	19
	Discuss implications of the results for practice, policy, and future research.