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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 I^2 = 41.21%, P < 0.001) and hemoglobin levels in school-age children (Hedge's g = 0.37, 95% CI: 0.01, 0.73; heterogeneity I^2 = 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 I^2 = 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

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 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 "Weekly Iron Folic acid supplementation"[Title/Abstract] OR "Dietary 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'. 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

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 sequential 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 Table1). 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

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-I^2 with Cochran Q statistic at 25%, 50%, and 70% as low, moderate, and considerable heterogeneity respectively with p-values less than 0.05 [20]. 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: CRD42023397898). 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 placebo[36]. 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

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).

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

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

11	Mohamed Ag Ayoya, (2009, Mali) [33]	School; RCT	7-12 years	IG= 309 (3 groups) CG= 97	60mg EI	-	5 days/week for 3 months	Hgb, and SF
12	Nchito (2003, Zambia) [36]	School; RCT	7-15 years	IG= 101 CG= 101	60mg EI	-	daily for 10 months	Hgb
13	Mohamed Ag Ayoya, (2012, Mali) [32]	School; RCT	7-12 years	IG= 307 CG= 97	60mg EI		5 days/week for 3 months	School Performance, School Attendance
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	Weekly for 12 months	Anemia and Hgb
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 months	Anemia and Hgb
17	Maisoon NA Fageer,et.al, (2021, Sudan) [40]	School	School children	IG= 109 CG= 106	NM	NM	Weekly	Anemia and School Performance

RCT: Randomized Control Trial; FRCT: Factorial Randomized Control Trial; IG: Intervention Group; CG: Control Group; 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; NM: Not Mentioned

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 µg/l (P = 0.002), 39.1 µg/l (P < 0.001), and 13.3 µg/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 µg/l (16.79–25.86) at the baseline to 93.33 µg/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 µg/l and 38.4 µg/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 I^2 = 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 I^2 = 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 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 [29,33,35,37]. However, four studies did not significant association between IFAS and hemoglobin concentration [27,24,34,39].

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 I^2 = 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 I^2 = 16.33%, P < 0.001) and the community setting (Hedge's g 1.28, 95%CI: 0.97, 1.58) (Supplemnetal 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 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 I^2 = 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 Cochrane[41] 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 (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 both anemia and schistosomiasis (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 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.

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.

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Figures

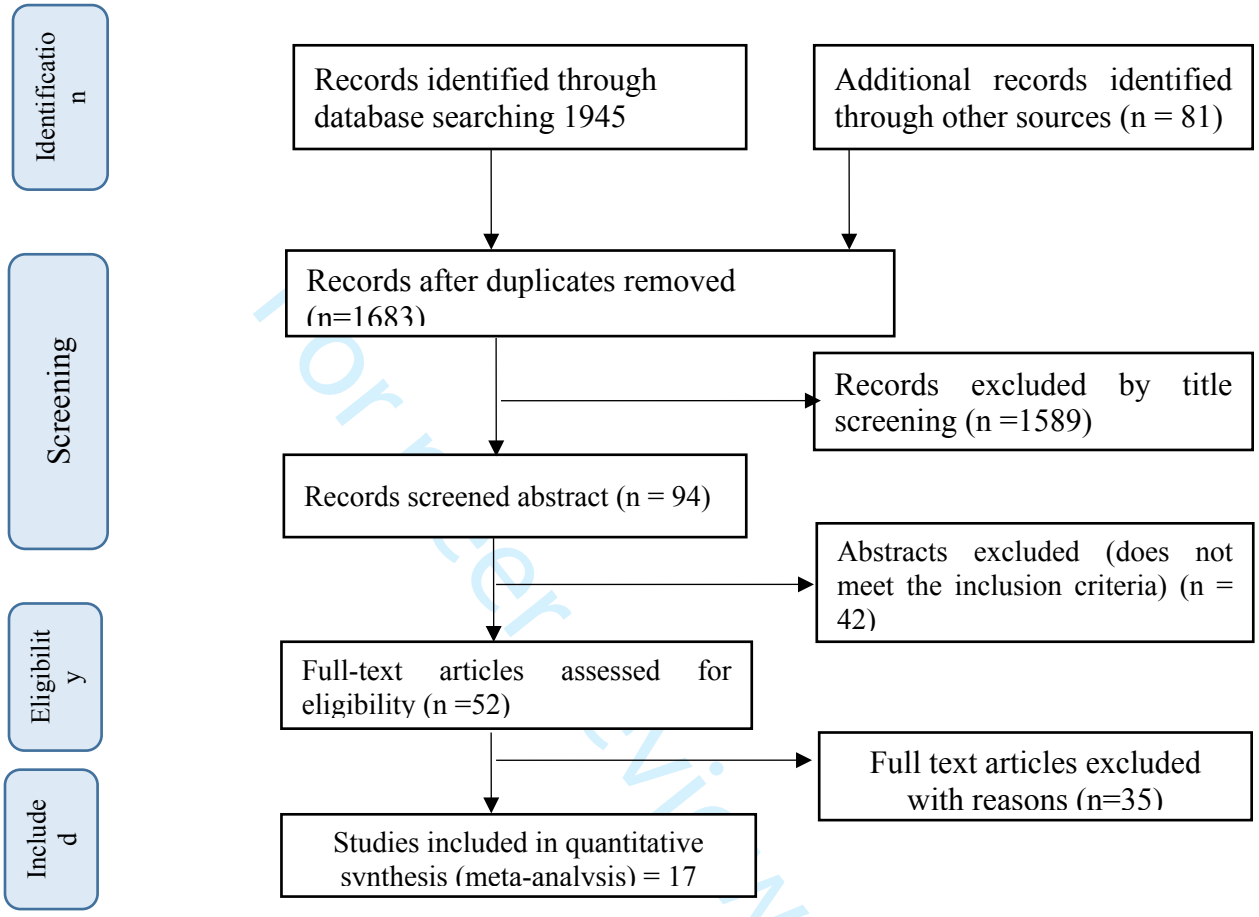


Figure 1. PRISMA flow diagram illustrating the study selection process of iron and folic acid supplementation effect on iron status, mental health and school performance articles.

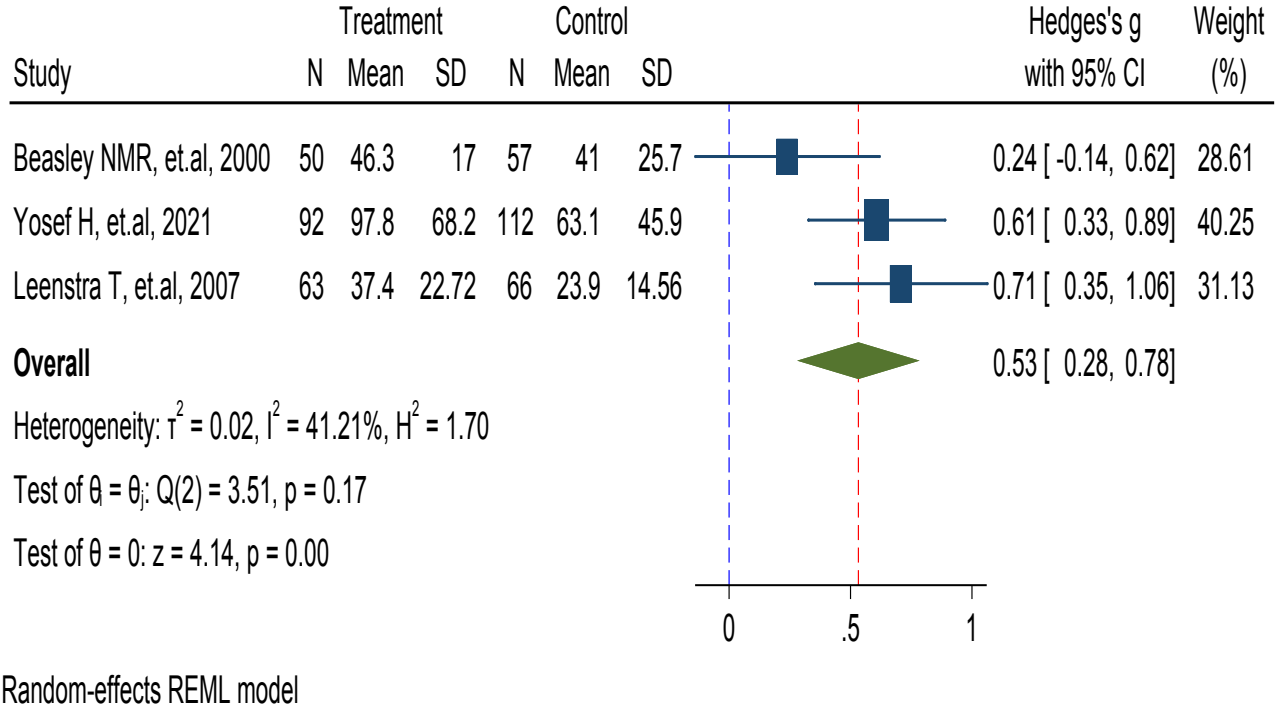


Figure 2: Meta-analysis of the effect of once-weekly IFAS on serum ferritin

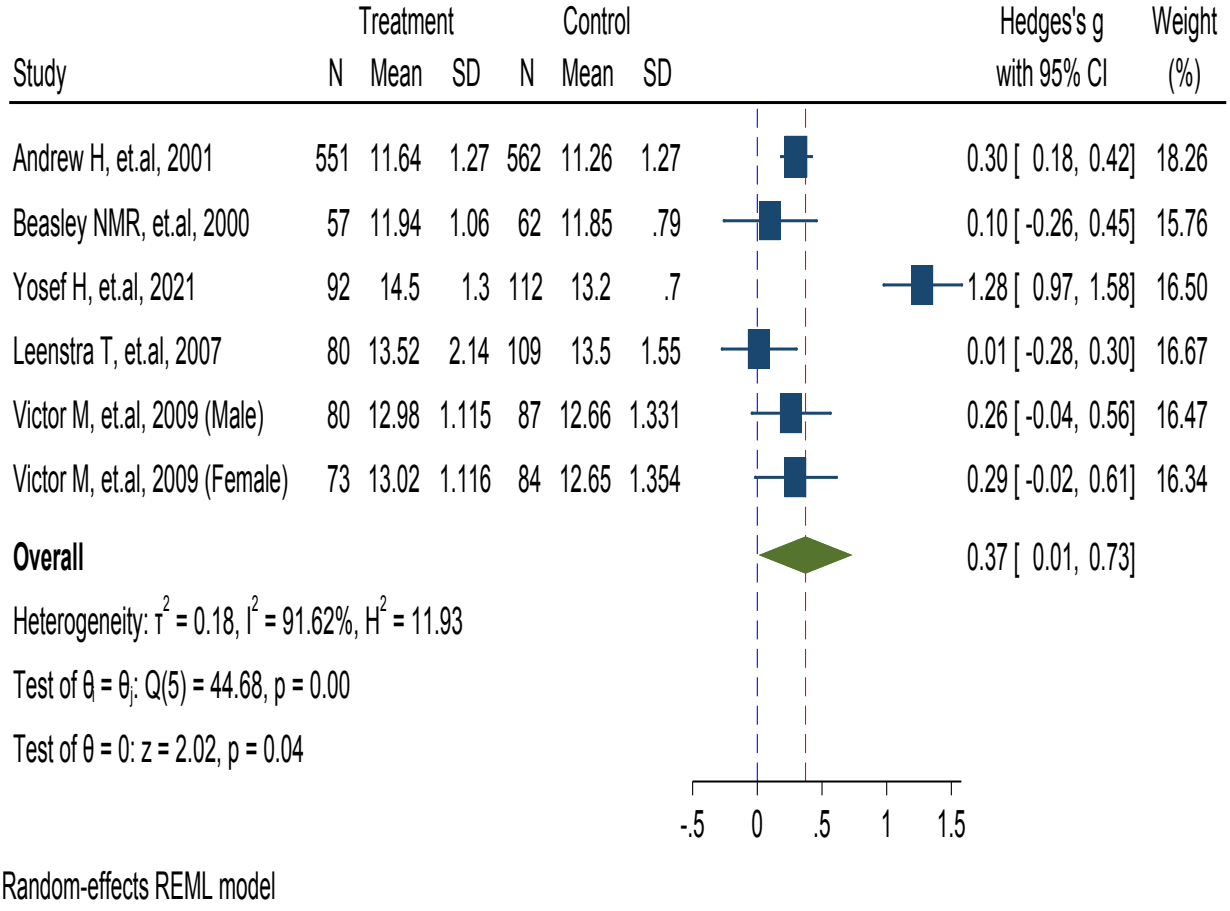


Figure 3: Meta-analysis of the effect of once-weekly IFAS on Hemoglobin

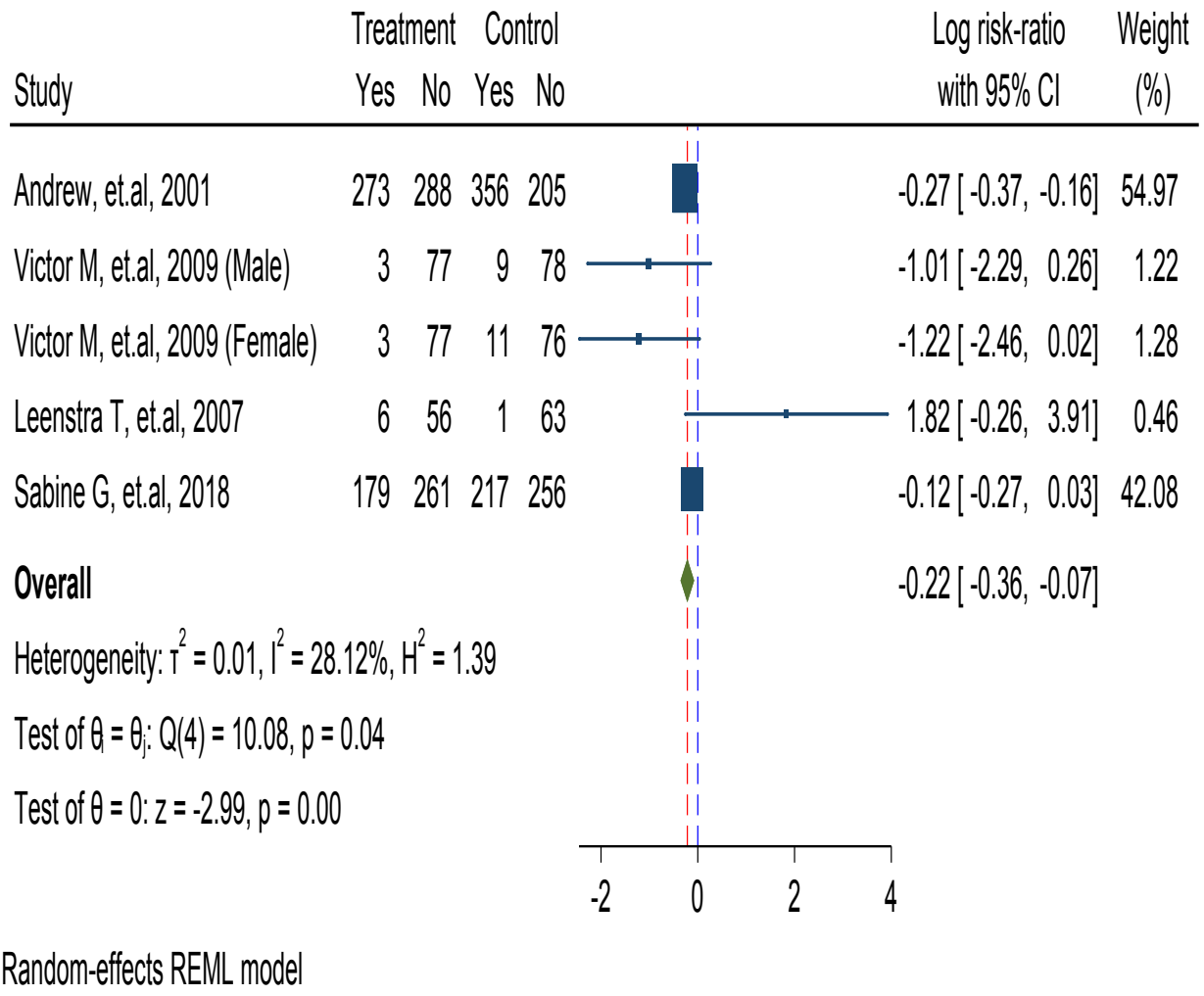
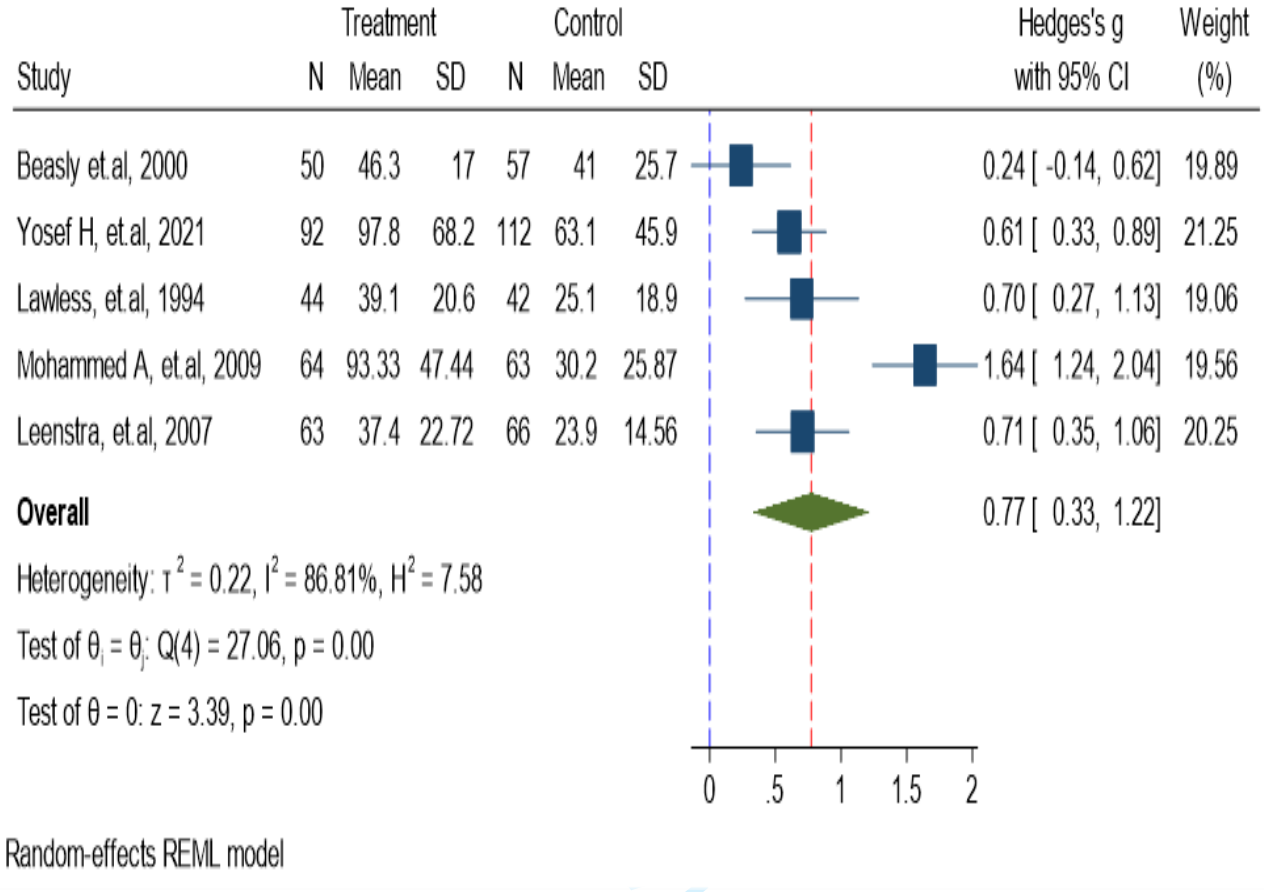
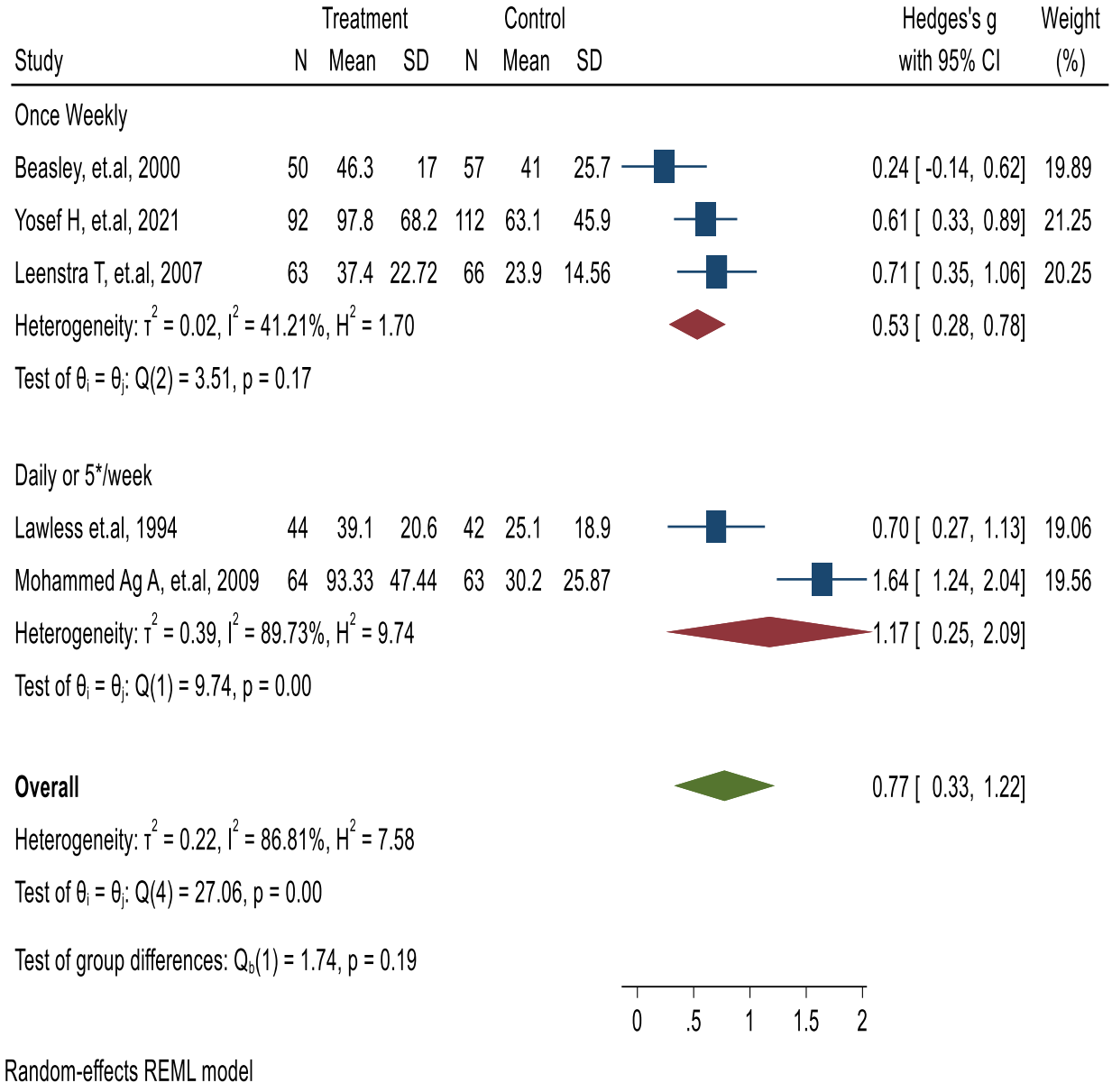


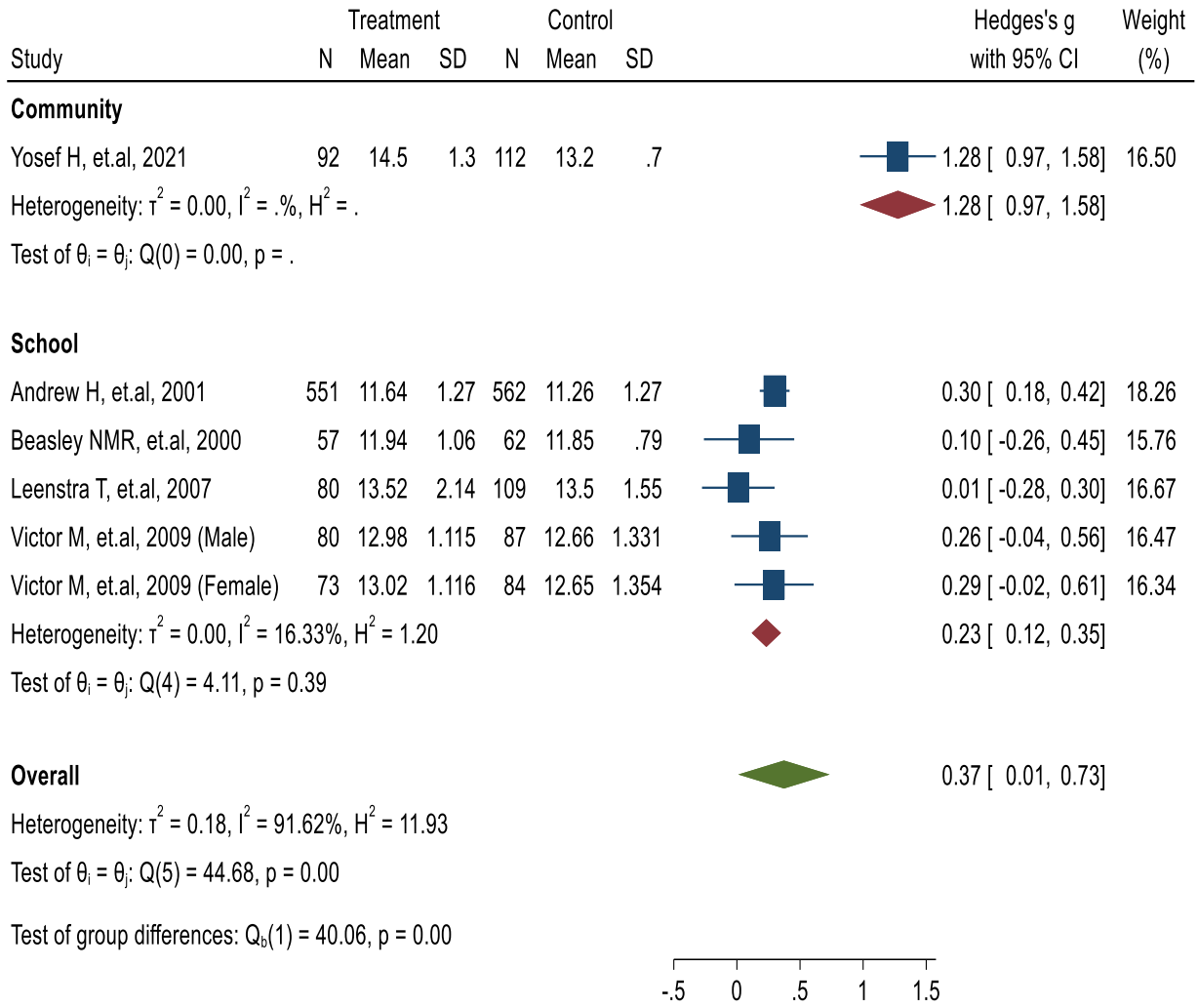
Figure 4: Meta-analysis of the effect of once-weekly IFAS on Anemia



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



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



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

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

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?	same way for 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		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		2	2	2	16
4.	Olsen, et.al (2006, Kenya)	2	2	2	2	2	2	2	2	2		1	2	2	24
5.	Lawless, et al (1994, Kenya)	2	2	2	2	2	1	2	2	2		1	2	2	22
6.	Victor Mwanakasale (2009, Zambia)	1	1	2	1	1	1	1	1	0		1	2	2	8
7.	Nchito (2009, Zambia)	2	2	2	2	2	2	2	2	1	2	1	2	2	22
8.	J. Baumgartner (2012, South Africa)	2	2	2	2	2	2	2	2	2	2	2	2	2	26

9.	Leenstra, et.al (2007, Kenya)	2	2	2	2	2	2	2	2	1	1	2	2	22
10.	J. Baumgartner (2013, South Africa)	2	2	2	2	2	2	2	2	2	2	2	2	26
11.	Mohamed Ag Ayoya, (2009, Mali)	2	0	2	0	0	1	2	1	0	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	2	2	2	14
14.	Sabine G, et.al. (2018, Burkina Faso)	2	2	2	0	2	2	2	2	2	2	2	2	24
15.	Lucas G, et.al, (2021, Ghana)	0	NA	NA	0	NA	NA	2	2	2	2	2	2	14
16.	Peter H, et.al, (2005, Mozambique)	1	1	2	0	0	1	2	2	2	2	2	2	16
17.	Maisoon NA Fageer,et.al, (2021, Sudan)	2	2	1	2	2	2	2	2	1	1	2	2	18

Supplemental Table 2: The assessment of the certainty of evidence of included studies in Meta-analysis

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 RR)	Certainty of evidence
Serum Ferritin (Once-Weekly)	3	440	RCT	Serious	Low	No	No	No	No	H=0.53 (0.28, 0.78)	Moderate
Serum Ferritin (More than once weekly)	5	653	RCT	Serious	Low	No	No	No	Concern	H=0.77 (0.33, 1.22)	Low
Hemoglobin (Once weekly)	5	1949	RCT	Serious	Low	No	No	No	No	H=0.37 (0.01, 0.73)	Moderate
Anemia (Once-weekly)	4	2505	RCT	Low	Low	No	concern	No	No	RR=0.8 (0.69, 0.93)	Moderate

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	
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.	
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	
	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.	
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 many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	
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.	
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	
	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.	
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	

PRISMA 2020 Checklist

Section and Topic	Item #	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 number of studies included in the review, ideally using a flow diagram.	
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	
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 effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate 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.	
	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 assessed.	
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 INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	
	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 extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	

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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 $I^2 = 41.21\%$, $P < 0.001$) and hemoglobin levels in school-age children (Hedge's g = 0.37, 95% CI: 0.01, 0.73; heterogeneity $I^2 = 91.62\%$, $P < 0.001$). 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 $I^2 = 28.12\%$, $P < 0.001$).

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.

- 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].

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

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 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 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 "Weekly Iron Folic acid supplementation"[Title/Abstract] OR "Dietary 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'.

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 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-I^2 with Cochran Q statistic at 25%, 50%, and 70% as low, moderate, and considerable heterogeneity respectively with p-values less than 0.05 [22]. 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: CRD42023397898). 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 250µg to 2800µg [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).

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

Author, (Year, Country), Reference	Setting and Study design	Sex and Age (Years)	Sample Size for Intervention Group (IG) and Control Group (CG)	Intervention arm (Iron and/or folic acid dose)	Comparator arm	Frequency of supplement	Duration of supplements	Outcome measurement
Beasly, et.al (2000, Tanzania) [26]	School; RCT	Female, 12-18	IG= 50 CG= 57	400mg FS	Vitamin_B12	Weekly	4.5 months	Hgb, SF, CRP, Diarrhea, Malaria, and Wt. change
Yosef H, et.al (2021, Ethiopia) [27]	Community RCT	Female, 10-19	IG= 92 CG= 112	60mg EI+0.4mg	No	Weekly	4 months	Hgb, SF, and CRP
Andrew Hall, et.al (2001, Mali) [32]	School CRCT	6-19 years	IG= 551 CG= 562	65mg EI+0.25mg	No	Weekly	12 months	Hgb, and Anemia status
Olsen, et.al (2006, Kenya) [29]	Community RCT	4-15 years	IG= 108 CG= 92	60mg EI	Placebo	Twice weekly	12 months	Hgb, and SF
Lawless, et al (1994, Kenya) [31]	School; RCT	6-11 years	IG= 44 CG= 42	150 mg EI	Placebo	Daily	3 months	Hgb, and SF
Victor Mwanakasale (2009, Zambia) [41]	School; RCT	Male, 9-15 years	IG= 80 CG= 87	200mg FS	Vitamin-C	Weekly	9 months	Hgb, and Anemia status
Victor Mwanakasale (2009, Zambia) [41]	School; RCT	Female, 9-15 years	IG= 73 CG= 84	200mg FS	Vitamin-C	Weekly	9 months	Hgb, and Anemia status
Taylor (2002, South Africa) [40]	School; RCT	6-15 years	IG= 101 CG= 91	65mg EI+100µg	Anti-helmenthic	Weekly	6 months	Hgb
Jeannine Baumgartner (2012, South Africa) [39]	School; FRCT	6-11 years	IG= 80 CG= 80	50mg EI	n-3 fatty acid supplements	4*/week	8.5 months	Hgb, CRP, and School Performance

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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	4 months	Hgb, and SF
Jeannine Baumgartner (2013, South Africa) [37]	School; RCT	6-11 years	IG= 160 CG= 161	50mg EI	Mebendazole	4*/week	8 months	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/week	3 months	Hgb, and SF
Nchito (2003, Zambia) [38]	School; RCT	7-15 years	IG= 101 CG= 101	60mg EI	MMS	daily	12 months	Hgb
Mohamed Ag Ayoya, (2012, Mali) [34]	School; RCT	7-12 years	IG= 307 CG= 97	60mg EI	praziquantel	5 days/week	3 months	School Performance, School Attendance
Sabine G, et.al. (2018, Burkina Faso) [36]	Community	Female, 10-19 years	913 girls	60mg EI+2.8mg	2.8mg folic acid	Weekly	12 months	Hgb, SF, and anemia
Lucas G, et.al, (2021, Ghana) [33]	School, Pre-post longitudinal	Female, 10-19 years	1387 girls	60mg EI+0.4mg	No comparator	Weekly	12 months	Anemia and Hgb
Peter H, et.al, (2005, Mozambique) [30]	School, Pre-post longitudinal study	Female, 10-18 years	991 girls	60mg EI+0.4mg	-	Weekly	3 months	Anemia and Hgb
Maisoon NA Fageer,et.al, (2021, Sudan) [42]	Community RCT	School children	IG= 109 CG= 106	EI	Folic acid	Weekly	4 months	Anemia and School Performance

RCT: Randomized Control Trial; FRCT: Factorial Randomized Control Trial; IG: Intervention Group; CG: Control Group; 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 age Z score; HAZ: Height for age Z score; ID: Iron Deficiency; TFR: Transferrin Receptor; SAC: School Age Children; NM: Not Mentioned, MMS: Multiple Micronutrient supplements

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 µg/l (P = 0.002), 39.1 µg/l (P < 0.001), and 13.3 µg/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 µg/l (16.79–25.86) at the baseline to 93.33 µg/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 µg/l and 38.4 µg/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 I^2 = 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 I^2 = 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 [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 I^2 = 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 I^2 = 16.33%, P < 0.001) and the community setting (Hedge's g 1.28, 95%CI: 0.97, 1.58) (Supplemnetal 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 I^2 = 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 [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, 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 (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

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.

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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Figure Legend:

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

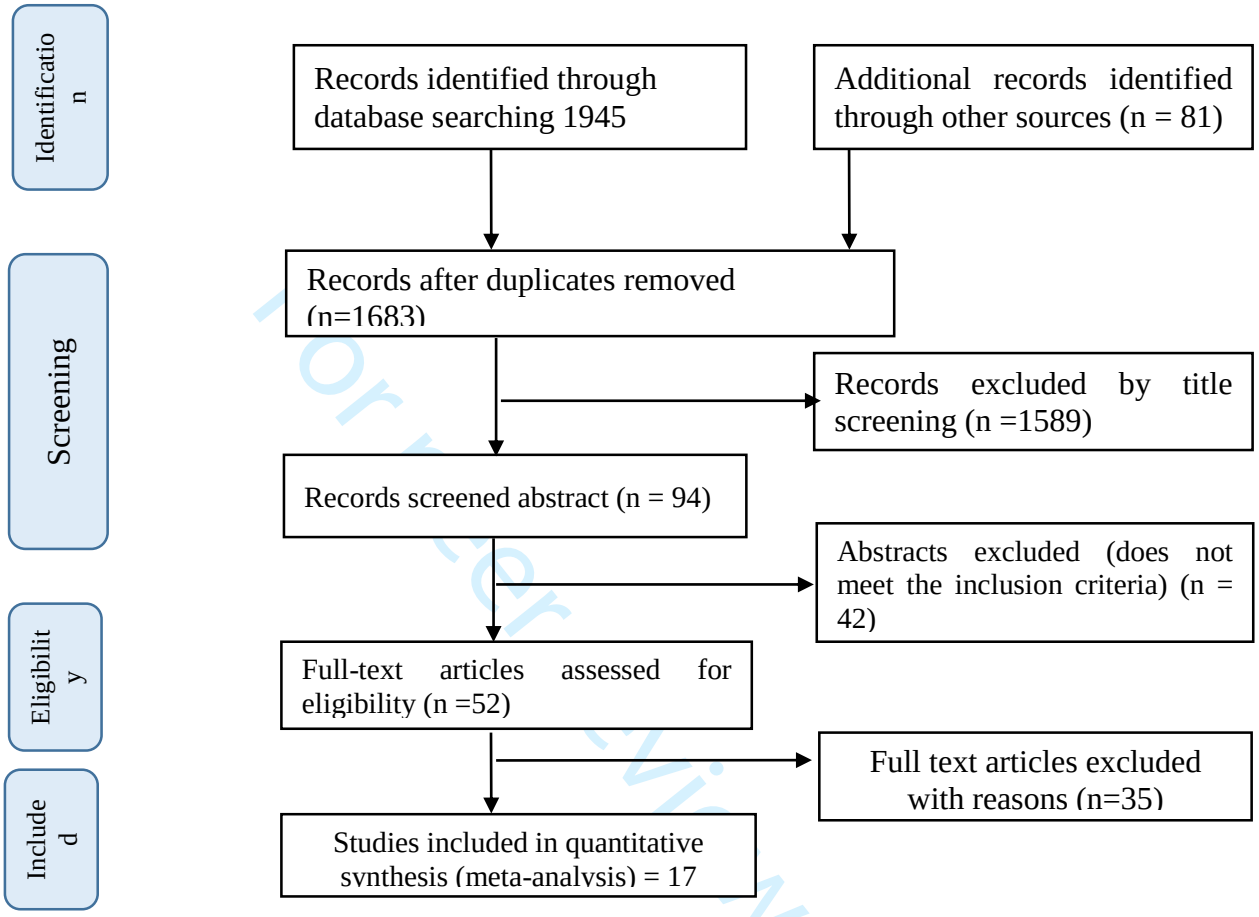


Figure 1. PRISMA flow diagram illustrating the study selection process of iron and folic acid supplementation effect on iron status, mental health and school performance articles.

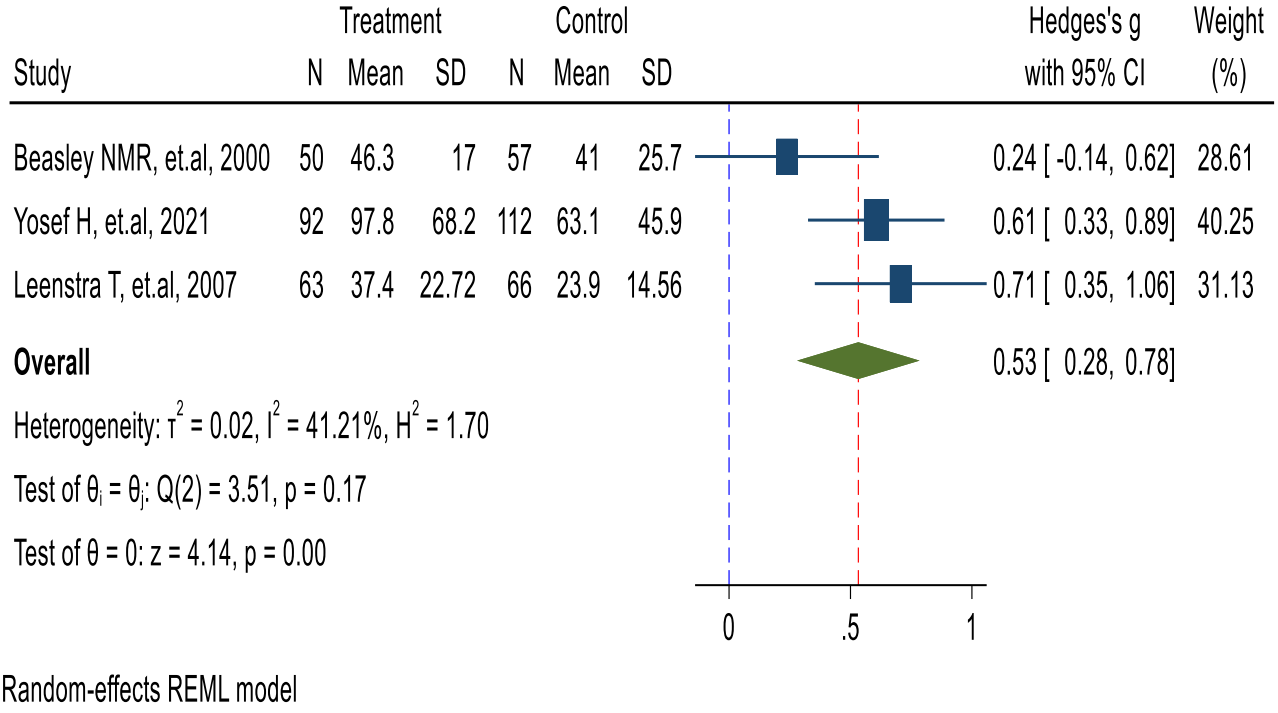


Figure 2: Meta-analysis of the effect of once-weekly IFAS on serum ferritin

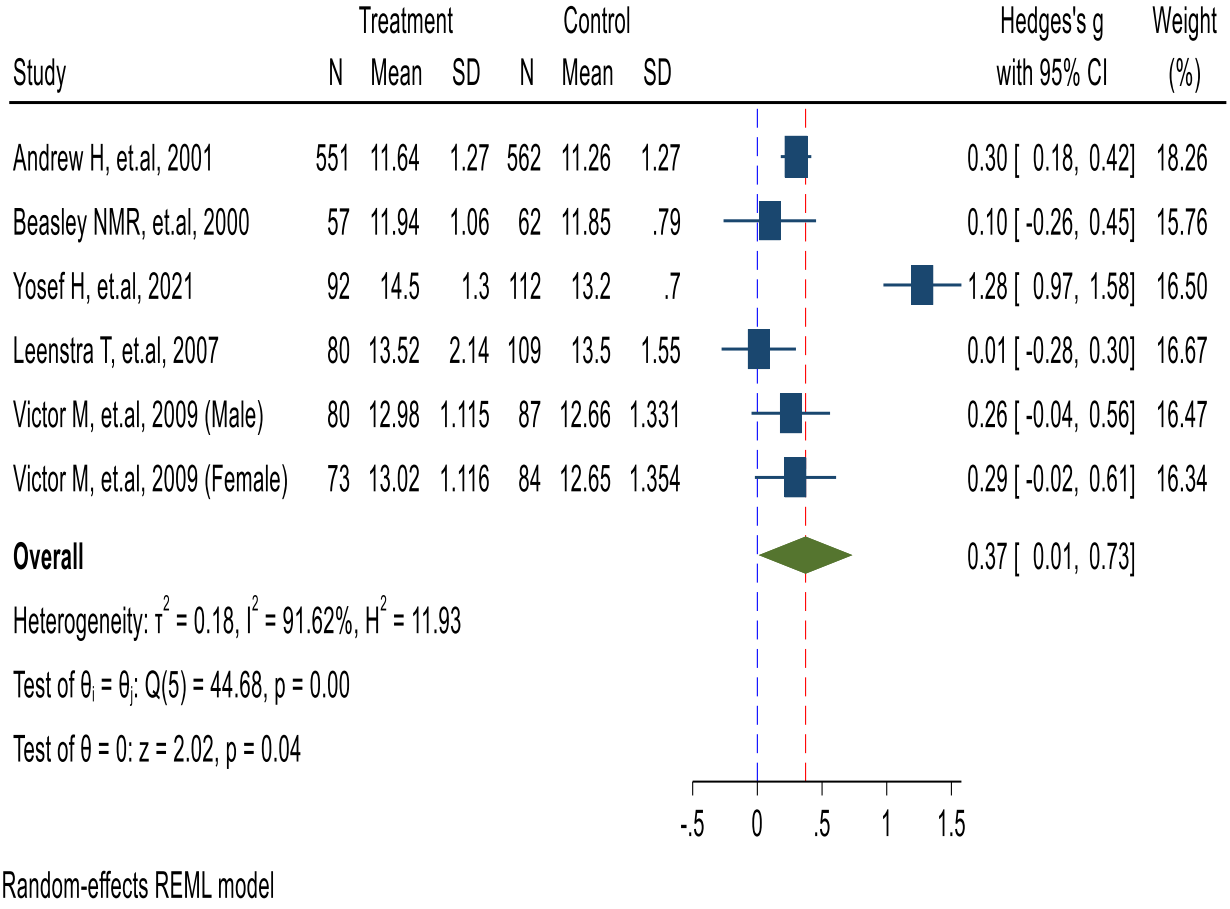


Figure 3: Meta-analysis of the effect of once-weekly IFAS on Hemoglobin

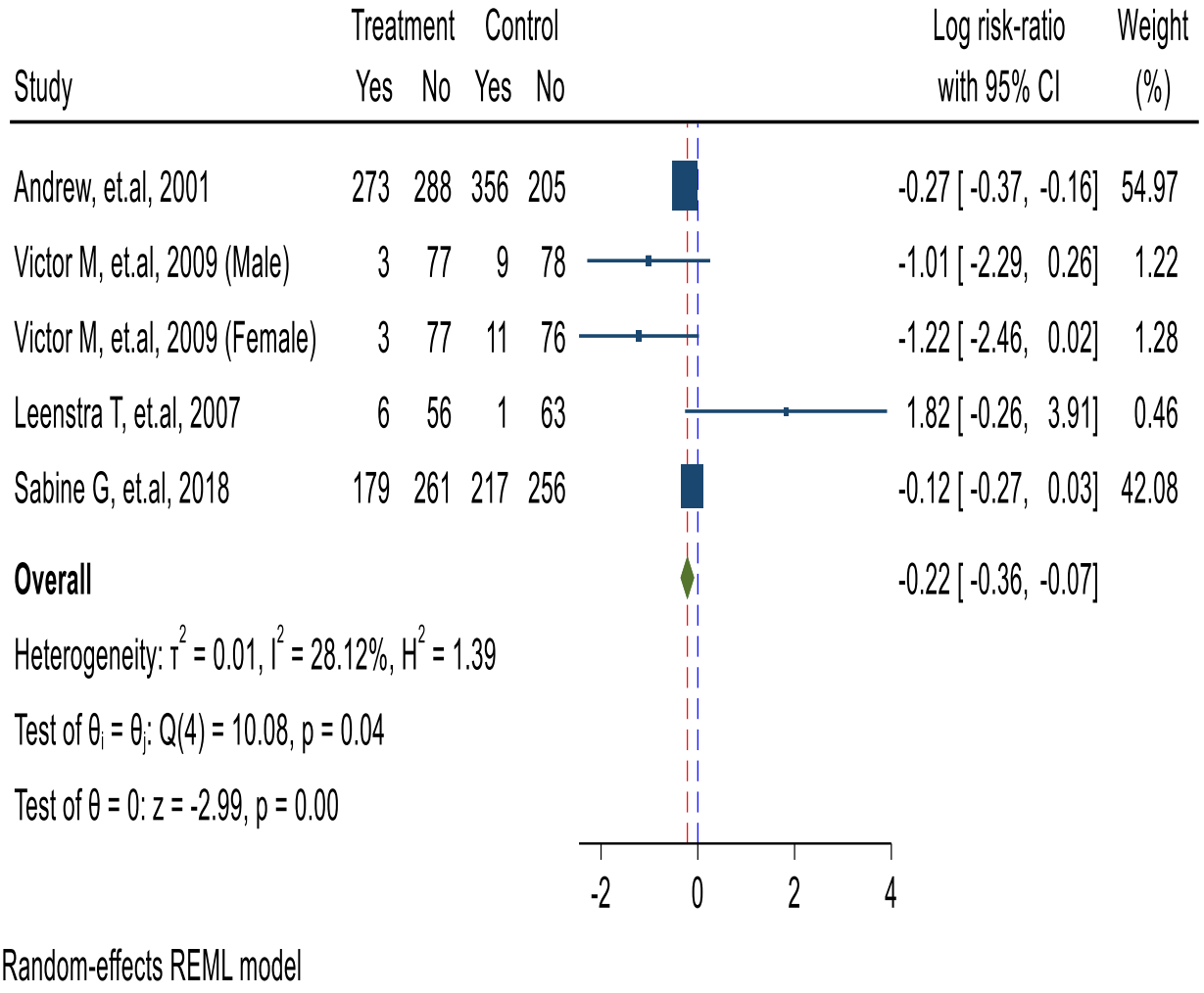
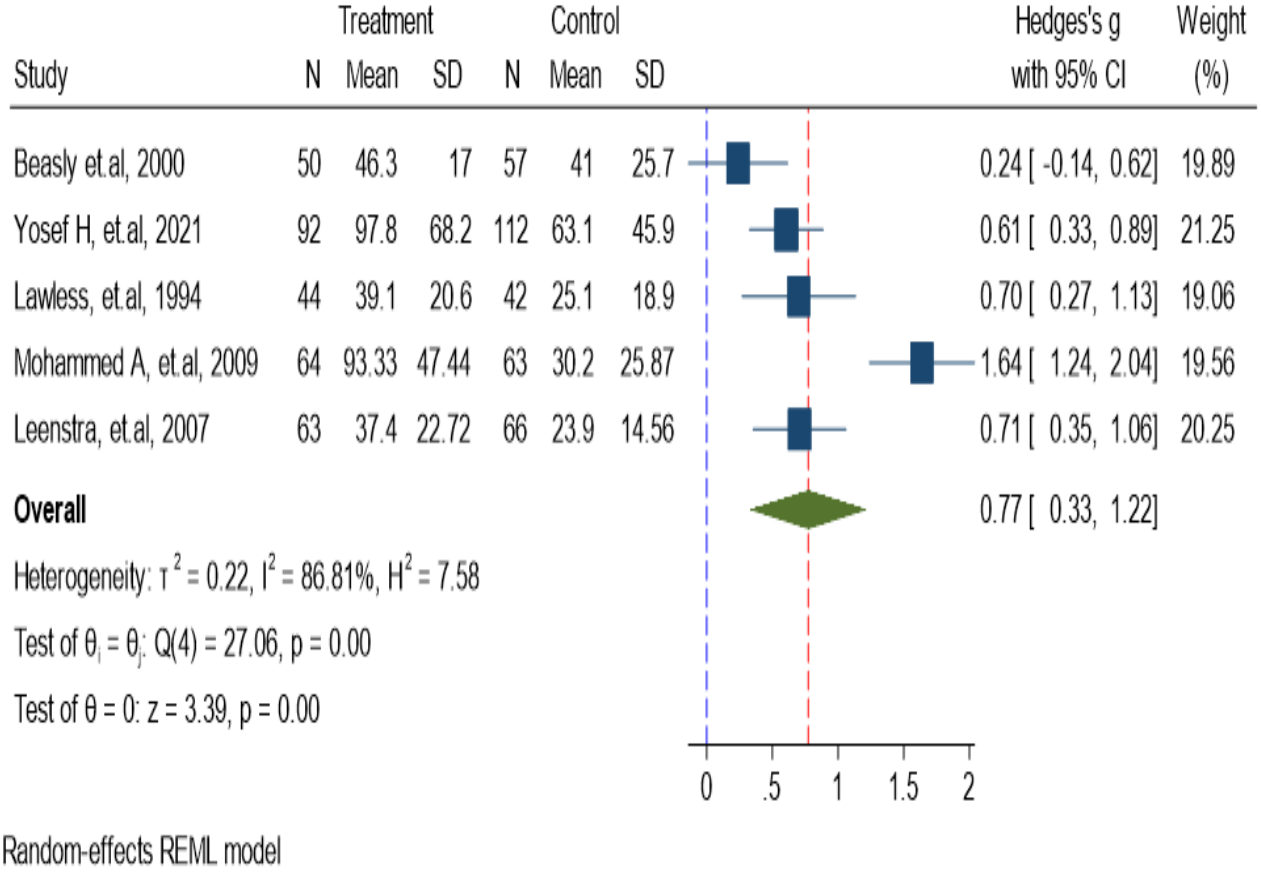
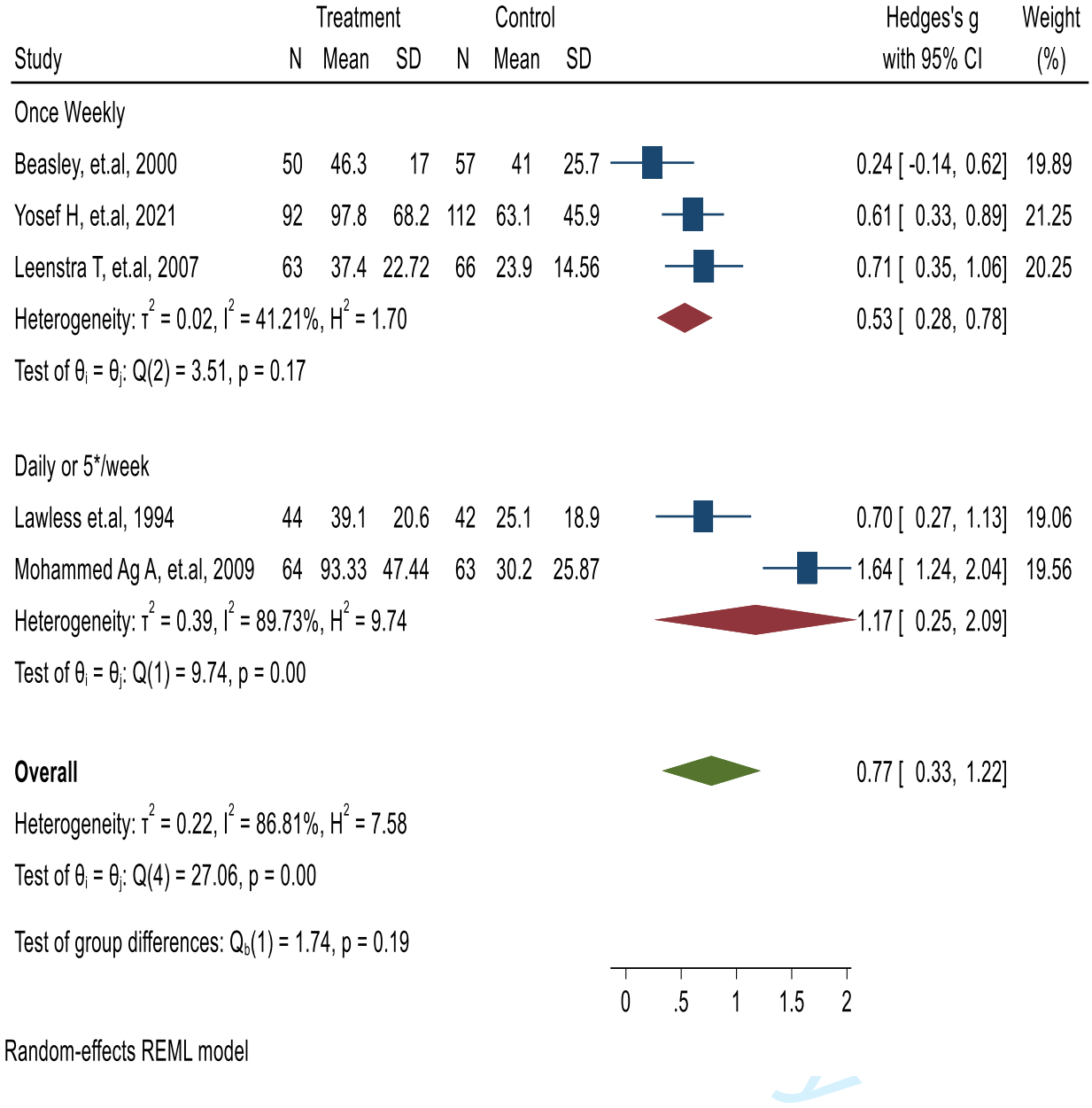


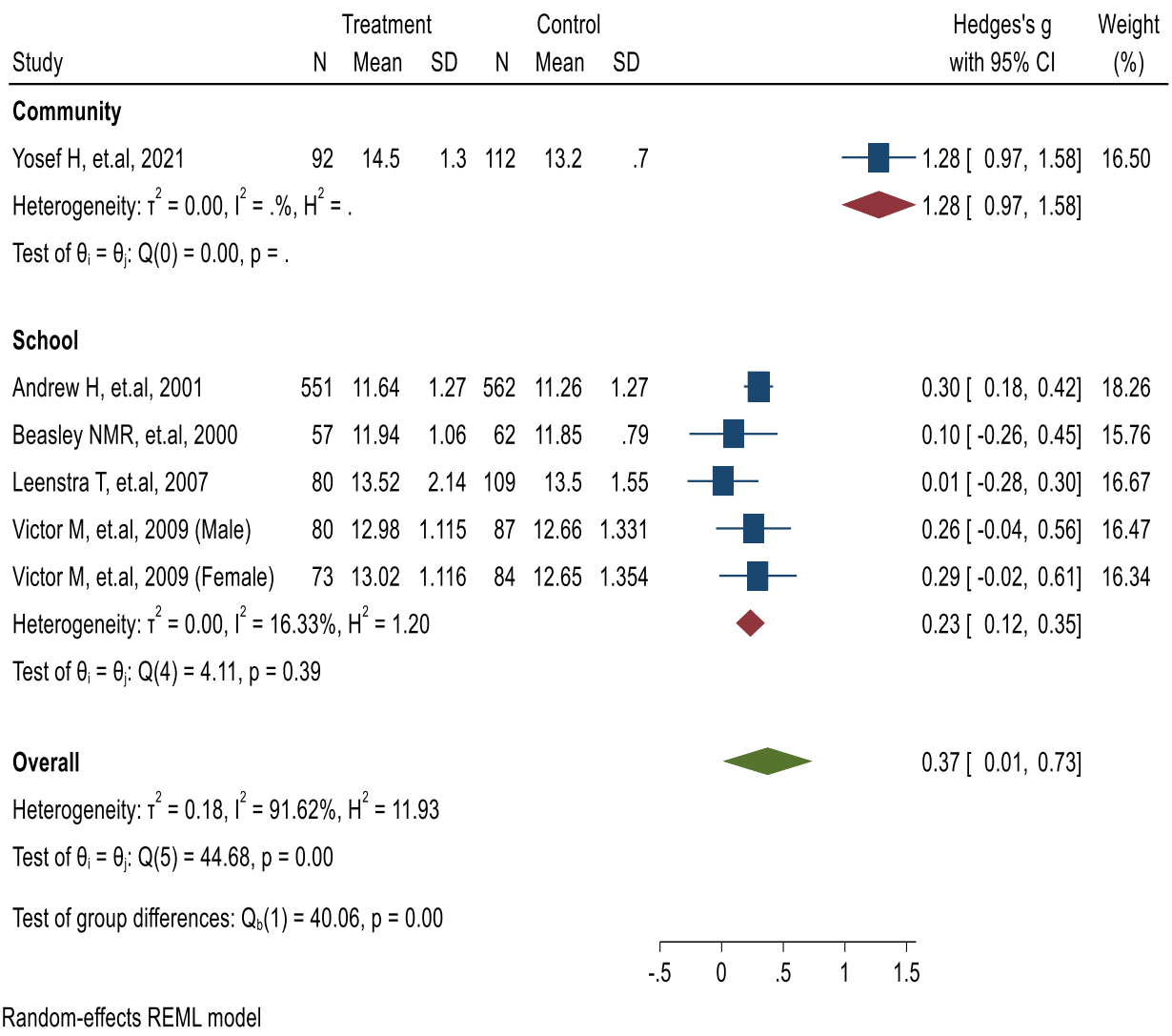
Figure 4: Meta-analysis of the effect of once-weekly IFAS on Anemia



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



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



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

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

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?	same way for 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		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		2	2	2	16
4.	Olsen, et.al (2006, Kenya)	2	2	2	2	2	2	2	2	2		1	2	2	24
5.	Lawless, et al (1994, Kenya)	2	2	2	2	2	1	2	2	2		1	2	2	22
6.	Victor Mwanakasale (2009, Zambia)	1	1	2	1	1	1	1	1	0		1	2	2	8
7.	Nchito (2009, Zambia)	2	2	2	2	2	2	2	2	1	2	1	2	2	22
8.	J. Baumgartner (2012, South Africa)	2	2	2	2	2	2	2	2	2	2	2	2	2	26

9.	Leenstra, et.al (2007, Kenya)	2	2	2	2	2	2	2	2	1	1	2	2	22
10.	J. Baumgartner (2013, South Africa)	2	2	2	2	2	2	2	2	2	2	2	2	26
11.	Mohamed Ag Ayoya, (2009, Mali)	2	0	2	0	0	1	2	1	0	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	2	2	2	14
14.	Sabine G, et.al. (2018, Burkina Faso)	2	2	2	0	2	2	2	2	2	2	2	2	24
15.	Lucas G, et.al, (2021, Ghana)	0	NA	NA	0	NA	NA	2	2	2	2	2	2	14
16.	Peter H, et.al, (2005, Mozambique)	1	1	2	0	0	1	2	2	2	2	2	2	16
17.	Maisoon NA Fageer,et.al, (2021, Sudan)	2	2	1	2	2	2	2	2	1	1	2	2	18

Supplemental Table 2: The assessment of the certainty of evidence of included studies in Meta-analysis

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 RR)	Certainty of evidence
Serum Ferritin (Once-Weekly)	3	440	RCT	Serious	Low	No	No	No	No	H=0.53 (0.28, 0.78)	Moderate
Serum Ferritin (More than once weekly)	5	653	RCT	Serious	Low	No	No	No	Concern	H=0.77 (0.33, 1.22)	Low
Hemoglobin (Once weekly)	5	1949	RCT	Serious	Low	No	No	No	No	H=0.37 (0.01, 0.73)	Moderate
Anemia (Once-weekly)	4	2505	RCT	Low	Low	No	concern	No	No	RR=0.8 (0.69, 0.93)	Moderate

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			2
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	
INTRODUCTION			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
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	6
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	5 & 6
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
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	7
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in 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
	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 assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many 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
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	10
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	8
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	9
	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.	8
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	8
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	NA
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	15
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	15

PRISMA 2020 Checklist

Section and Topic	Item #	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 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 excluded.	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 effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	9
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	12-15
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	12-15
	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 INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	8
	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

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: 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 $I^2 = 41.21\%$, $P < 0.001$) and hemoglobin levels in school-age children (Hedge's g = 0.37, 95% CI: 0.01, 0.73; heterogeneity $I^2 = 91.62\%$, $P < 0.001$). 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 $I^2 = 28.12\%$, $P < 0.001$).

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.

- 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

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 resource-constrained 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 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 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 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 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-I^2 with Cochran Q statistic at 25%, 50%, and 70% as low, moderate, and considerable heterogeneity respectively with p-values less than 0.05 [22]. 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: CRD42023397898). 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 250µg to 2800µg [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).

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

Author, (Year, Country), Reference	Setting and Study design	Sex and Age (Years)	Sample Size for Intervention Group (IG) and Control Group (CG)	Intervention arm (Iron and/or folic acid dose)	Comparator arm	Frequency of supplement	Duration of supplements	Outcome measurement
Beasly, et.al (2000, Tanzania) [26]	School; RCT	Female, 12-18	IG= 50 CG= 57	400mg FS	Vitamin_B12	Weekly	4.5 months	Hgb, SF, CRP, Diarrhea, Malaria, and Wt. change
Yosef H, et.al (2021, Ethiopia) [27]	Community RCT	Female, 10-19	IG= 92 CG= 112	60mg EI+0.4mg	No	Weekly	4 months	Hgb, SF, and CRP
Andrew Hall, et.al (2001, Mali) [32]	School CRCT	6-19 years	IG= 551 CG= 562	65mg EI+0.25mg	No	Weekly	12 months	Hgb, and Anemia status
Olsen, et.al (2006, Kenya) [29]	Community RCT	4-15 years	IG= 108 CG= 92	60mg EI	Placebo	Twice weekly	12 months	Hgb, and SF
Lawless, et al (1994, Kenya) [31]	School; RCT	6-11 years	IG= 44 CG= 42	150 mg EI	Placebo	Daily	3 months	Hgb, and SF
Victor Mwanakasale (2009, Zambia) [41]	School; RCT	Male, 9-15 years	IG= 80 CG= 87	200mg FS	Vitamin-C	Weekly	9 months	Hgb, and Anemia status
Victor Mwanakasale (2009, Zambia) [41]	School; RCT	Female, 9-15 years	IG= 73 CG= 84	200mg FS	Vitamin-C	Weekly	9 months	Hgb, and Anemia status
Taylor (2002, South Africa) [40]	School; RCT	6-15 years	IG= 101 CG= 91	65mg EI+100µg	Anti-helmenthic	Weekly	6 months	Hgb
Jeannine Baumgartner (2012, South Africa) [39]	School; FRCT	6-11 years	IG= 80 CG= 80	50mg EI	n-3 fatty acid supplements	4*/week	8.5 months	Hgb, CRP, and School Performance

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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	4 months	Hgb, and SF
Jeannine Baumgartner (2013, South Africa) [37]	School; RCT	6-11 years	IG= 160 CG= 161	50mg EI	Mebendazole	4*/week	8 months	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/week	3 months	Hgb, and SF
Nchito (2003, Zambia) [38]	School; RCT	7-15 years	IG= 101 CG= 101	60mg EI	MMS	daily	12 months	Hgb
Mohamed Ag Ayoya, (2012, Mali) [34]	School; RCT	7-12 years	IG= 307 CG= 97	60mg EI	praziquantel	5 days/week	3 months	School Performance, School Attendance
Sabine G, et.al. (2018, Burkina Faso) [36]	Community	Female, 10-19 years	913 girls	60mg EI+2.8mg	2.8mg folic acid	Weekly	12 months	Hgb, SF, and anemia
Lucas G, et.al, (2021, Ghana) [33]	School, Pre-post longitudinal	Female, 10-19 years	1387 girls	60mg EI+0.4mg	No comparator	Weekly	12 months	Anemia and Hgb
Peter H, et.al, (2005, Mozambique) [30]	School, Pre-post longitudinal study	Female, 10-18 years	991 girls	60mg EI+0.4mg	-	Weekly	3 months	Anemia and Hgb
Maisoon NA Fageer,et.al, (2021, Sudan) [42]	Community RCT	School children	IG= 109 CG= 106	EI	Folic acid	Weekly	4 months	Anemia and School Performance

RCT: Randomized Control Trial; FRCT: Factorial Randomized Control Trial; IG: Intervention Group; CG: Control Group; 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 age Z score; HAZ: Height for age Z score; ID: Iron Deficiency; TFR: Transferrin Receptor; SAC: School Age Children; NM: Not Mentioned, MMS: Multiple Micronutrient supplements

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 µg/l , 39.1 µg/l , and 13.3 µg/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 µg/l (16.79–25.86) at the baseline to 93.33 µg/l (82.43–105.66) at the endpoint[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 µg/l and 38.4 µg/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 I^2 = 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 I^2 = 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

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 I^2 = 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 I^2 = 16.33%) and the community setting (Hedge's g 1.28, 95%CI: 0.97, 1.58) (Supplemnetal 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 I^2 = 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 (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 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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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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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

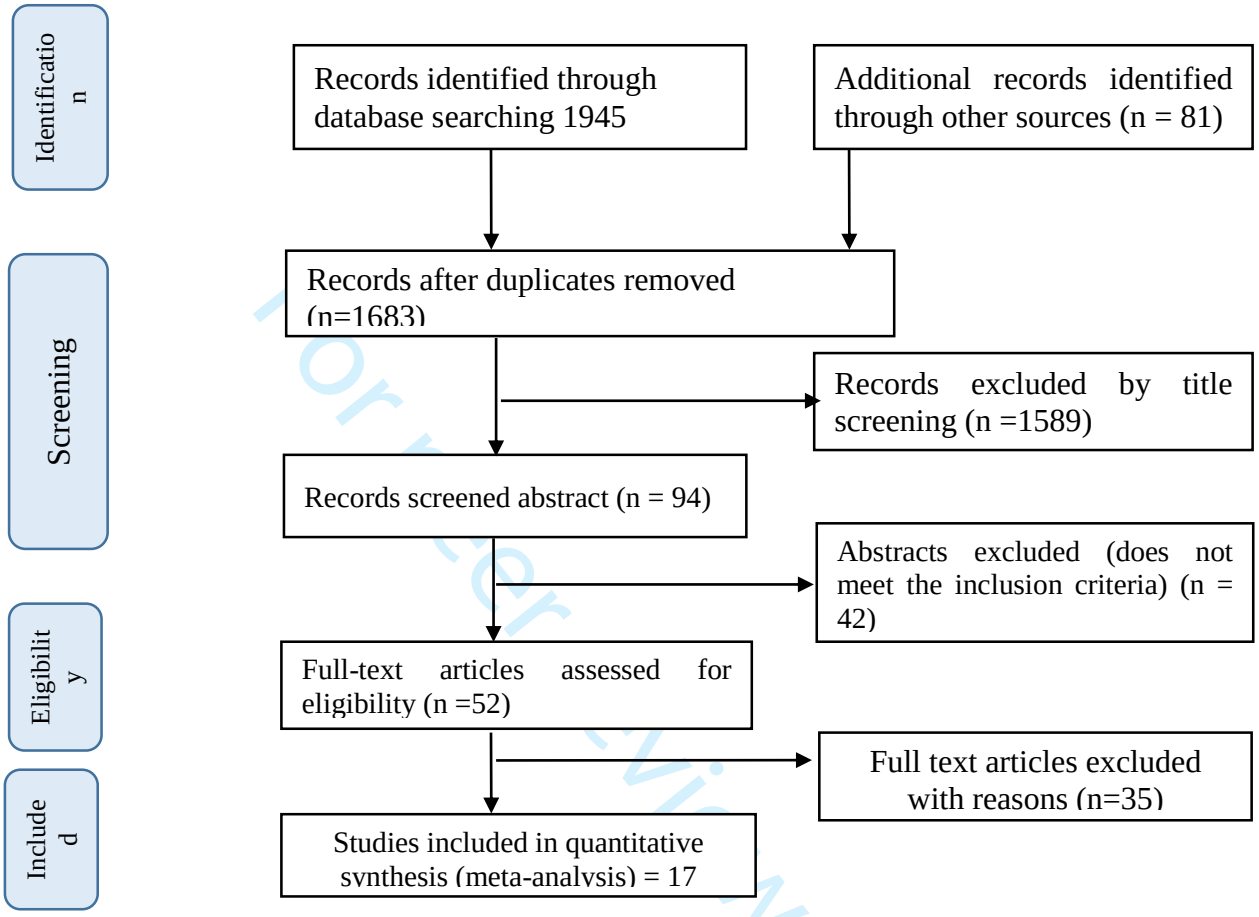


Figure 1. PRISMA flow diagram illustrating the study selection process of iron and folic acid supplementation effect on iron status, mental health and school performance articles.

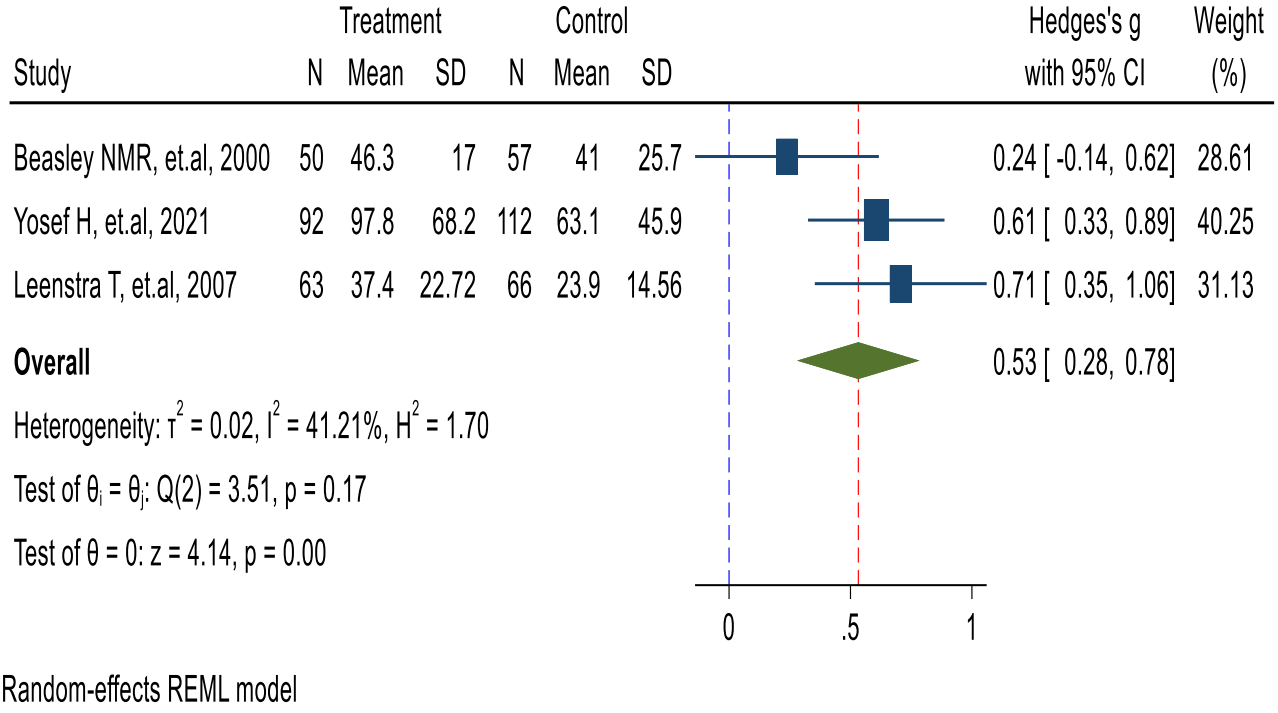


Figure 2: Meta-analysis of the effect of once-weekly IFAS on serum ferritin

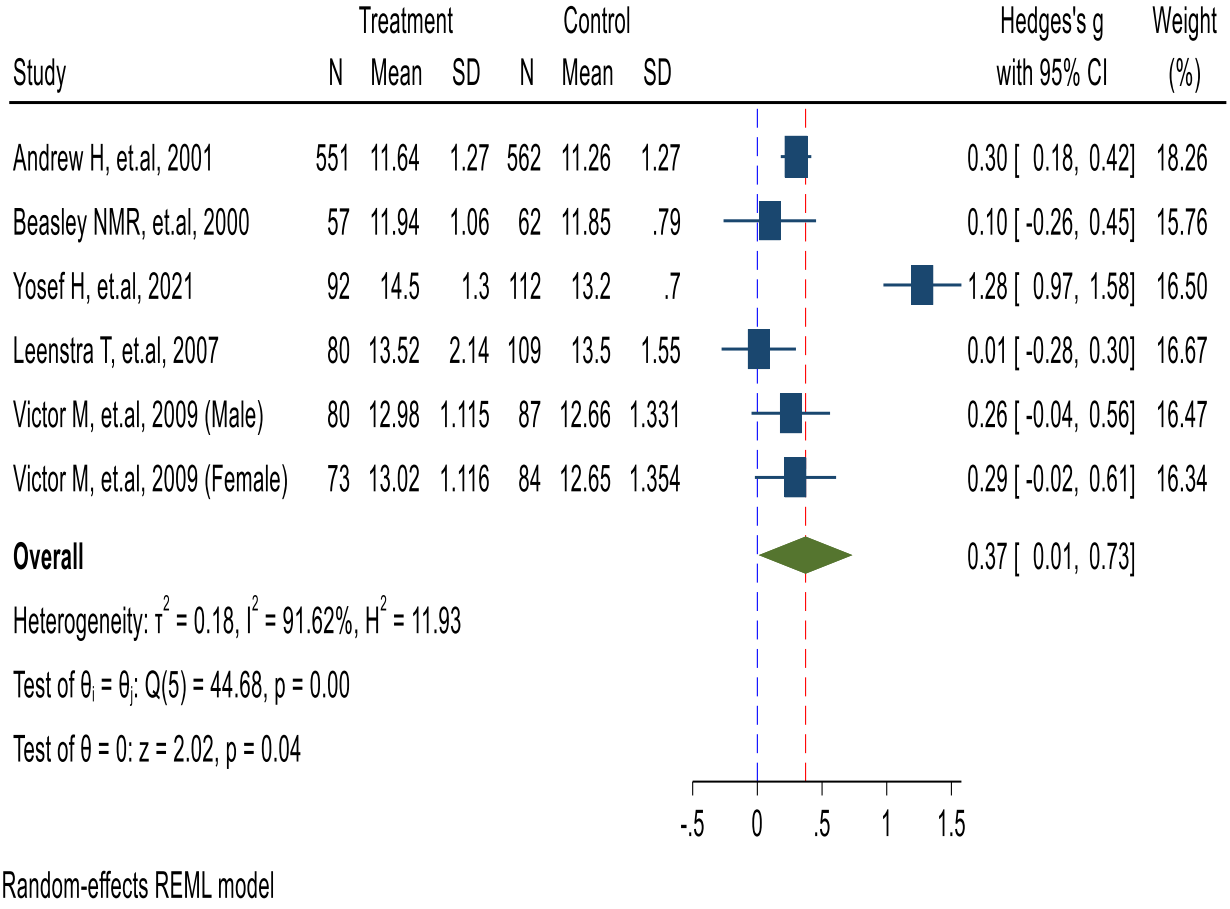


Figure 3: Meta-analysis of the effect of once-weekly IFAS on Hemoglobin

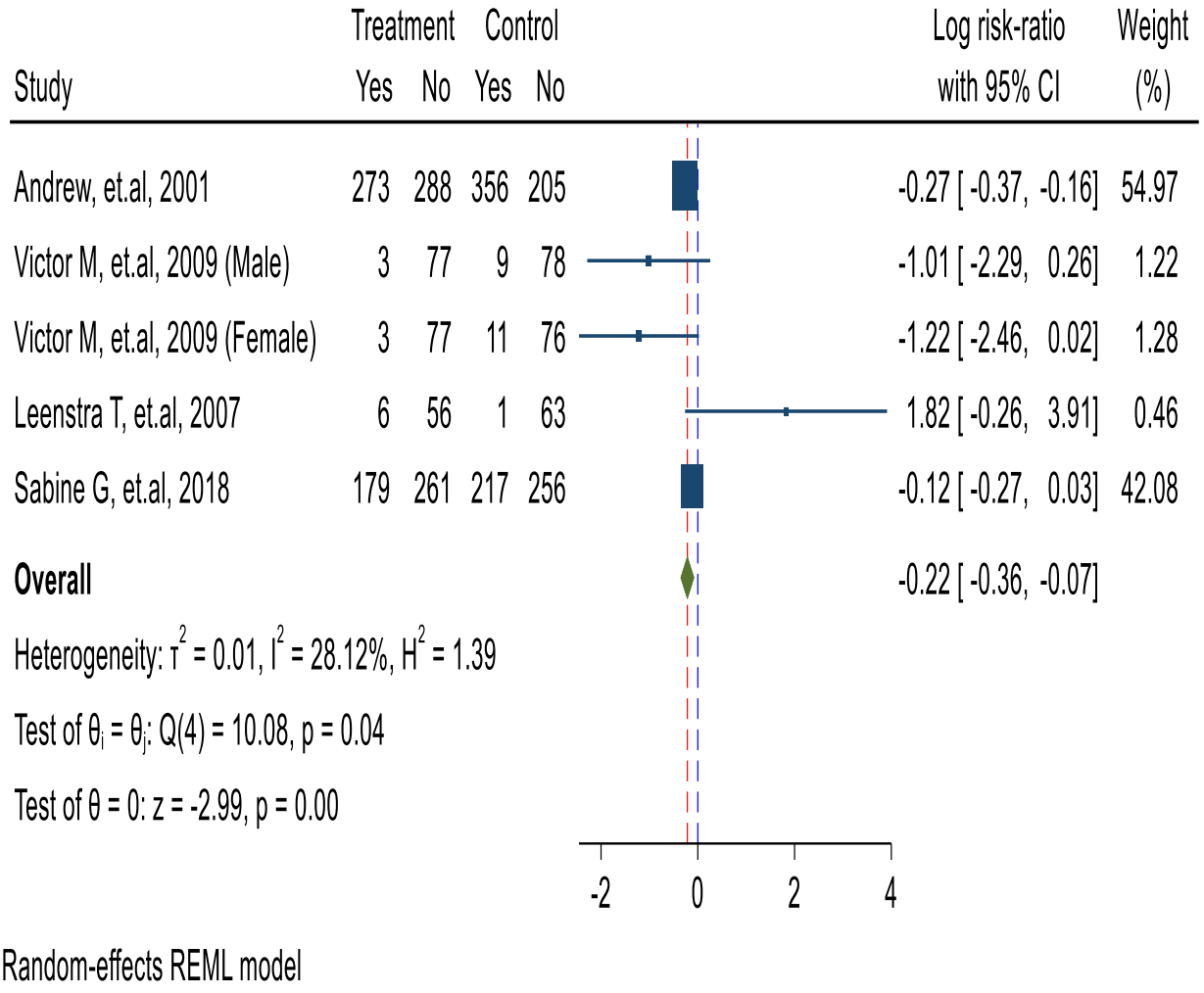
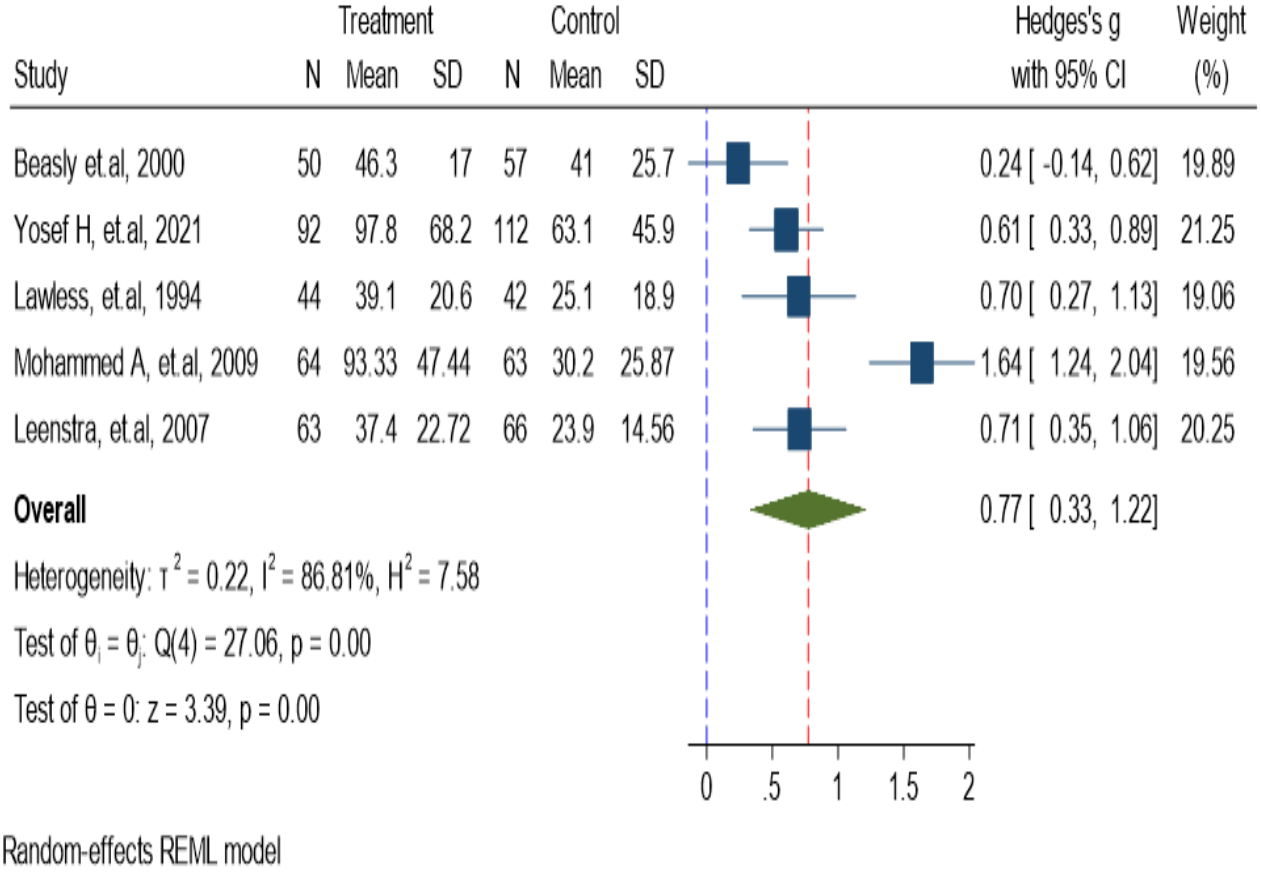
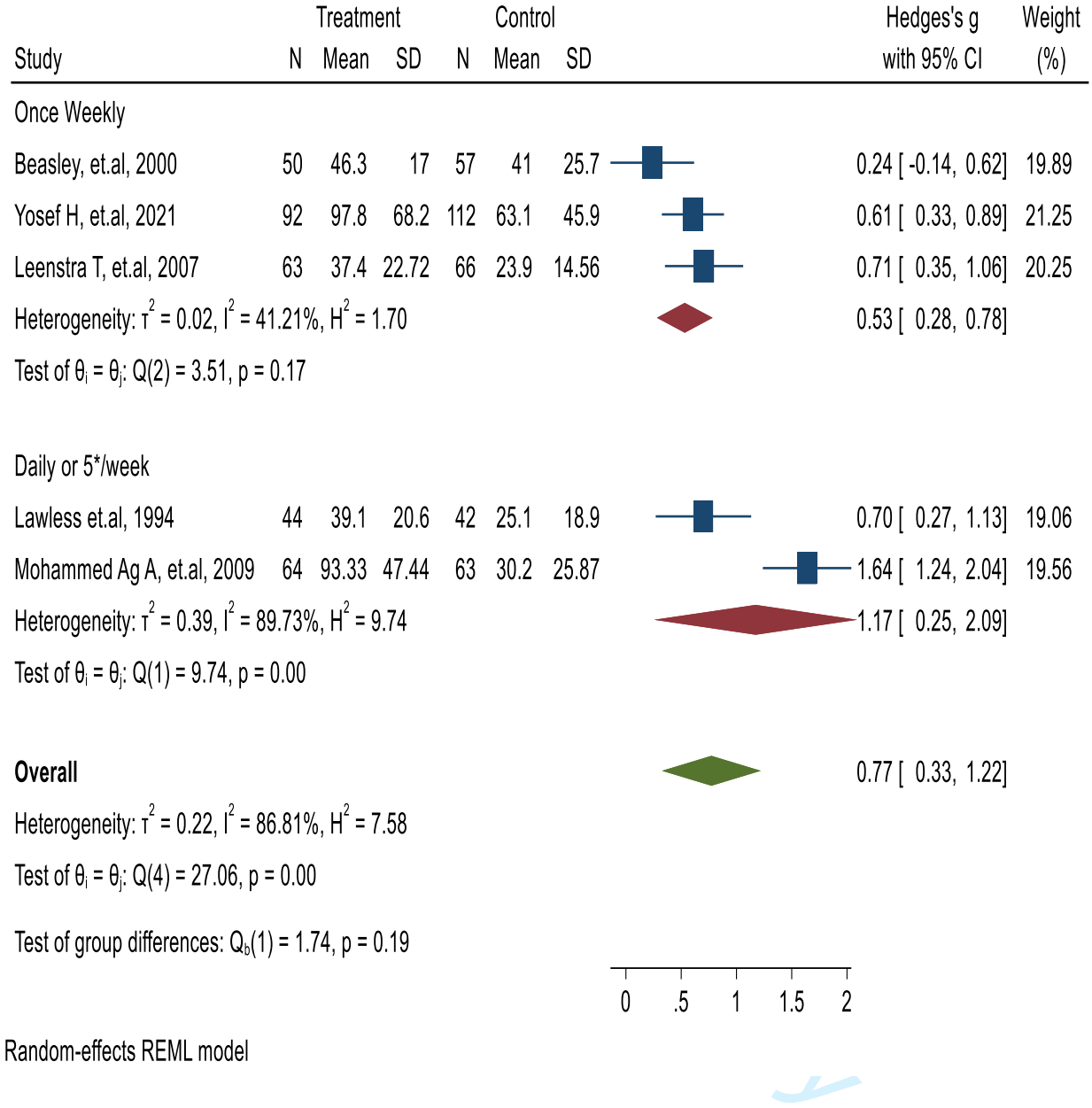


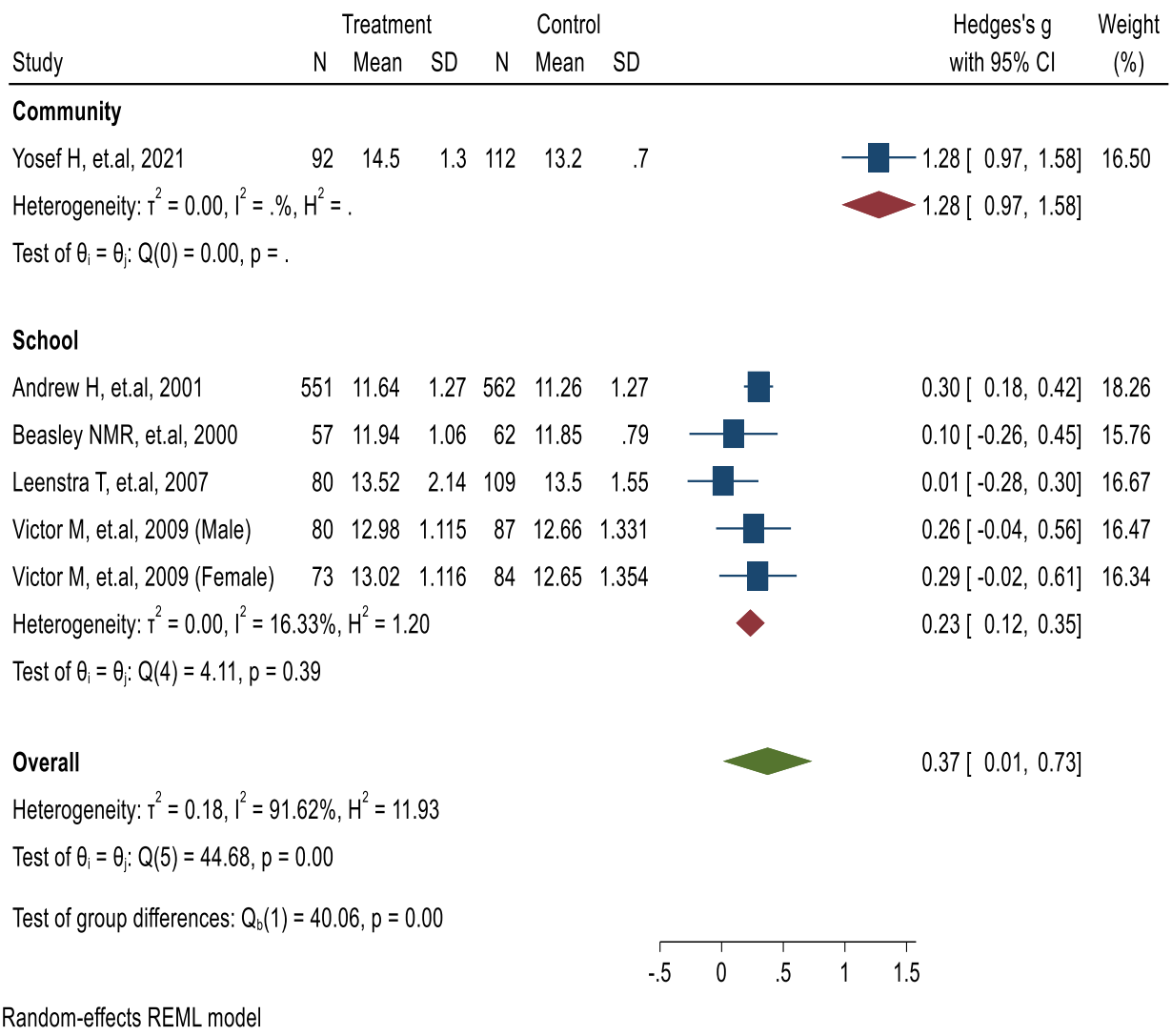
Figure 4: Meta-analysis of the effect of once-weekly IFAS on Anemia



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



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



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

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

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?	same way for 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		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		2	2	2	16
4.	Olsen, et.al (2006, Kenya)	2	2	2	2	2	2	2	2	2		1	2	2	24
5.	Lawless, et al (1994, Kenya)	2	2	2	2	2	1	2	2	2		1	2	2	22
6.	Victor Mwanakasale (2009, Zambia)	1	1	2	1	1	1	1	1	0		1	2	2	8
7.	Nchito (2009, Zambia)	2	2	2	2	2	2	2	2	1	2	1	2	2	22
8.	J. Baumgartner (2012, South Africa)	2	2	2	2	2	2	2	2	2	2	2	2	2	26

9.	Leenstra, et.al (2007, Kenya)	2	2	2	2	2	2	2	2	1	1	2	2	22
10.	J. Baumgartner (2013, South Africa)	2	2	2	2	2	2	2	2	2	2	2	2	26
11.	Mohamed Ag Ayoya, (2009, Mali)	2	0	2	0	0	1	2	1	0	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	2	2	2	14
14.	Sabine G, et.al. (2018, Burkina Faso)	2	2	2	0	2	2	2	2	2	2	2	2	24
15.	Lucas G, et.al, (2021, Ghana)	0	NA	NA	0	NA	NA	2	2	2	2	2	2	14
16.	Peter H, et.al, (2005, Mozambique)	1	1	2	0	0	1	2	2	2	2	2	2	16
17.	Maisoon NA Fageer,et.al, (2021, Sudan)	2	2	1	2	2	2	2	2	1	1	2	2	18

Supplemental Table 2: The assessment of the certainty of evidence of included studies in Meta-analysis

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 RR)	Certainty of evidence
Serum Ferritin (Once-Weekly)	3	440	RCT	Serious	Low	No	No	No	No	H=0.53 (0.28, 0.78)	Moderate
Serum Ferritin (More than once weekly)	5	653	RCT	Serious	Low	No	No	No	Concern	H=0.77 (0.33, 1.22)	Low
Hemoglobin (Once weekly)	5	1949	RCT	Serious	Low	No	No	No	No	H=0.37 (0.01, 0.73)	Moderate
Anemia (Once-weekly)	4	2505	RCT	Low	Low	No	concern	No	No	RR=0.8 (0.69, 0.93)	Moderate

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			2
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	
INTRODUCTION			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
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	6
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	5 & 6
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
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	7
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in 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
	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 assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many 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
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	10
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	8
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	9
	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.	8
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	8
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	NA
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	15
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	15

PRISMA 2020 Checklist

Section and Topic	Item #	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 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 excluded.	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 effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	9
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	12-15
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	12-15
	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 INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	8
	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

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: 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 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 $I^2 = 41.21\%$, $P < 0.001$) and hemoglobin levels in school-age children (Hedge's g = 0.37, 95% CI: 0.01, 0.73; heterogeneity $I^2 = 91.62\%$, $P < 0.001$). 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 $I^2 = 28.12\%$, $P < 0.001$).

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.

- 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].

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

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 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) [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-I^2 with Cochran Q statistic at 25%, 50%, and 70% as low, moderate, and considerable heterogeneity respectively with p-values less than 0.05 [21]. 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: CRD42023397898). 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

Result

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 iron[25], 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).

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

Author, (Year, Country), Reference	Setting and Study design	Sex and Age (Years)	Sample Size for Intervention Group (IG) and Control Group (CG)	Intervention arm (Iron and/or folic acid dose)	Comparator arm	Frequency of supplement	Duration of supplements	Outcome measurement
Beasly, et.al (2000, Tanzania) [27]	School; RCT	Female, 12-18	IG= 50 CG= 57	400mg FS	Vitamin_B12	Weekly	4 months	Hgb, SF, CRP, Diarrhea, Malaria, and Wt. change
Yosef H, et.al (2021, Ethiopia) [26]	Community RCT	Female, 10-19	IG= 92 CG= 112	60mg EI+0.4mg	No	Weekly	4 months	Hgb, SF, and CRP
Andrew Hall, et.al (2001, Mali) [30]	School CRCT	6-19 years	IG= 551 CG= 562	65mg EI+0.25mg	No	Weekly	9 months	Hgb, and Anemia status
Victor Mwanakasale (2009, Zambia) [33]	School; RCT	Male, 9-15 years	IG= 80 CG= 87	200mg FS	Vitamin-C	Weekly	9 months	Hgb, and Anemia status
Victor Mwanakasale (2009, Zambia) [33]	School; RCT	Female, 9-15 years	IG= 73 CG= 84	200mg FS	Vitamin-C	Weekly	9 months	Hgb, and Anemia status
Taylor (2002, South Africa) [32]	School; RCT	6-15 years	IG= 101 CG= 91	65mg EI+100µg	Anti-helminthic	Weekly	4 months	Hgb
Leenstra, et.al (2009, Kenya) [25]	School; RCT	Female, 12-18 years	IG= 80 CG= 109	120mg EI	Vitamin-A	Weekly	4 months	Hgb, and SF
Sabine G, et.al. (2018, Burkina Faso) [29]	Community	Female, 10-19 years	913 girls	60mg EI+2.8mg	2.8mg folic acid	Weekly	12 months	Hgb, SF, and anemia
Lucas G, et.al, (2021, Ghana) [31]	School, Pre-post longitudinal	Female, 10-19 years	1387 girls	60mg EI+0.4mg	No comparator	Weekly	12 months	Anemia and Hgb

Peter H, et.al, (2005, Mozambique) [28]	School, Pre-post longitudinal study	Female, 10-18 years	991 girls	60mg EI+0.4mg	-	Weekly	3, 6 months	Anemia and Hgb
Maisoon NA Fageer,et.al, (2021, Sudan) [34]	Community RCT	School children	IG= 109 CG= 106	EI	Folic acid	Weekly	4 months	Anemia and School Performance

RCT: Randomized Control Trial; FRCT: Factorial Randomized Control Trial; IG: Intervention Group; CG: Control Group; 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 age Z score; HAZ: Height for age Z score; ID: Iron Deficiency; TFR: Transferrin Receptor; SAC: School Age Children; NM: Not Mentioned, MMS: Multiple Micronutrient supplements

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 I^2 = 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 I^2 = 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 [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 $I^2 = 16.33\%$) 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 $I^2 = 28.12\%$). 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 alone[34].

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 (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 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 settings[41]. Hence, distributing WIFAS at school modalities is beneficial compared to the 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 [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.

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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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

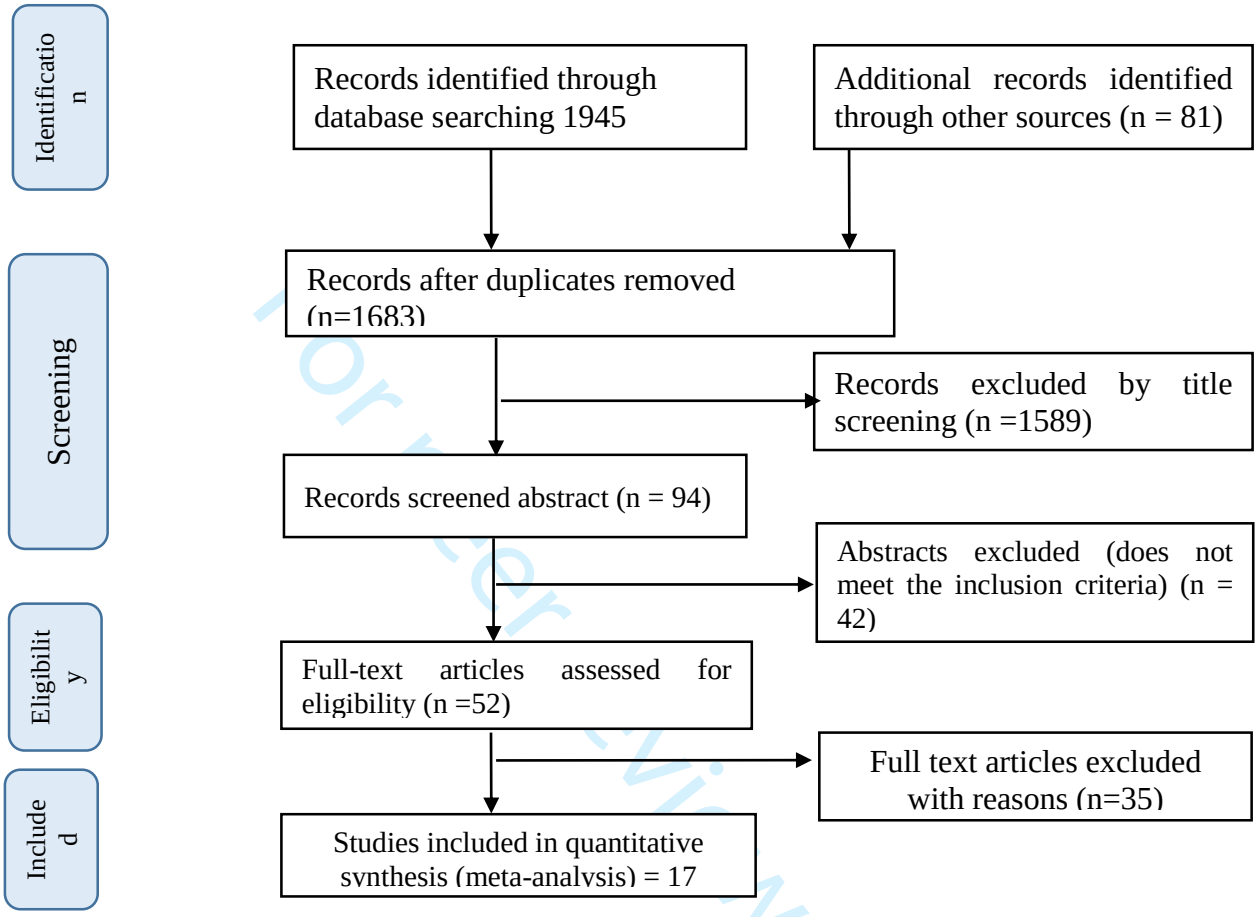


Figure 1. PRISMA flow diagram illustrating the study selection process of iron and folic acid supplementation effect on iron status, mental health and school performance articles.

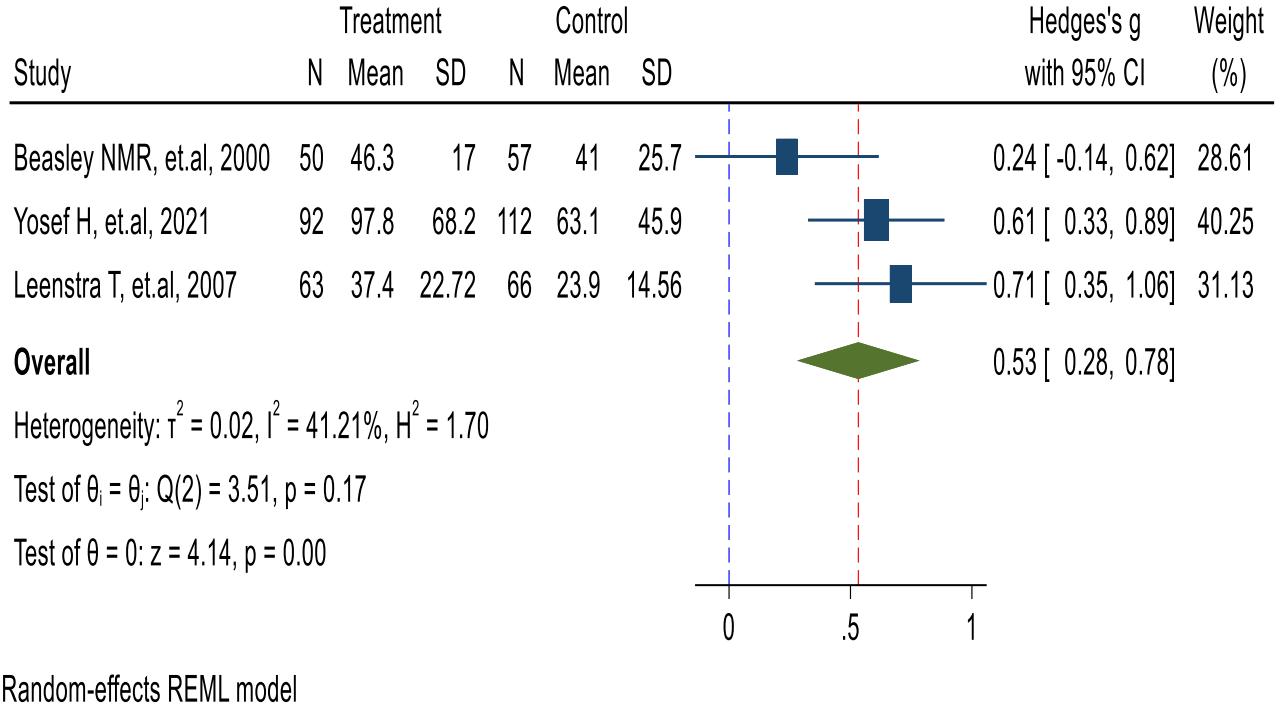


Figure 2: Meta-analysis of the effect of once-weekly IFAS on serum ferritin

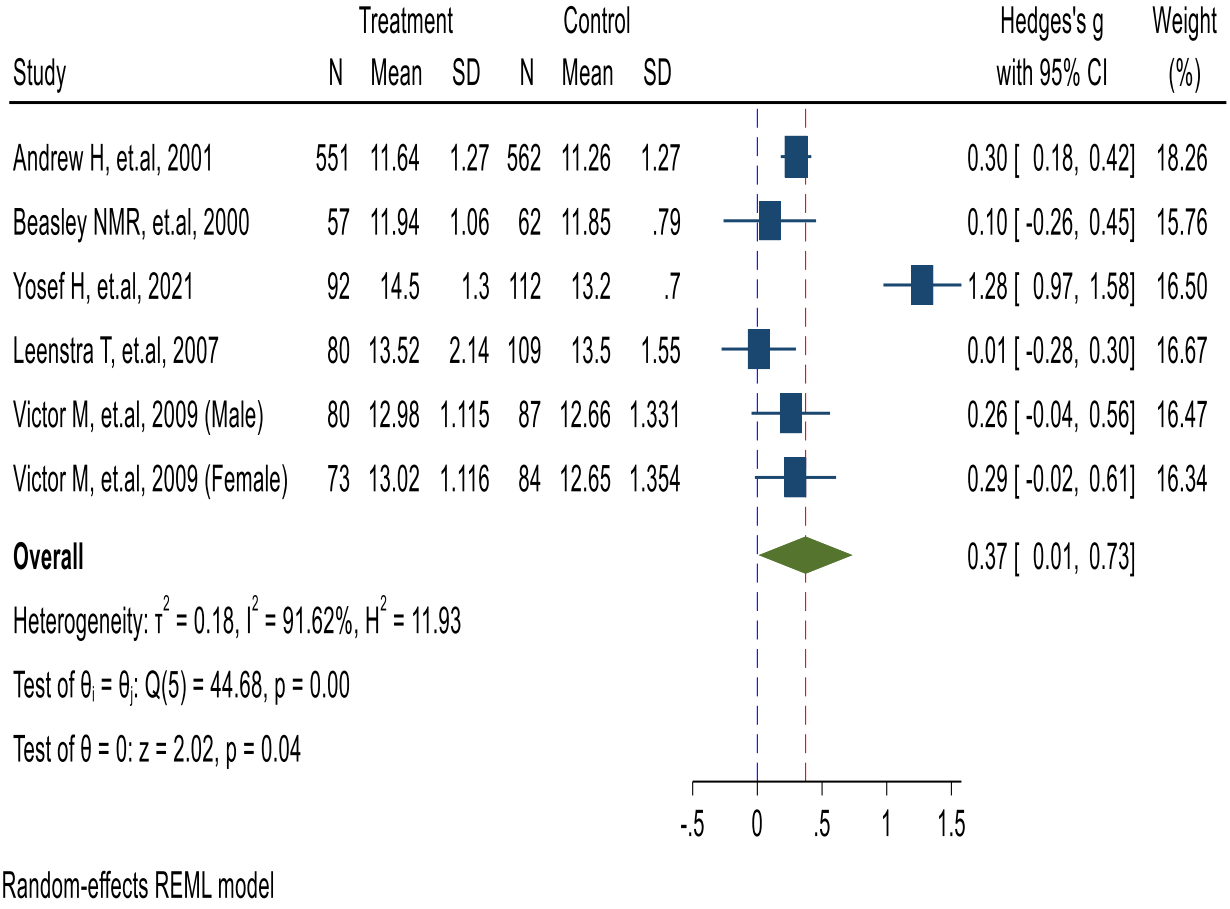


Figure 3: Meta-analysis of the effect of once-weekly IFAS on Hemoglobin

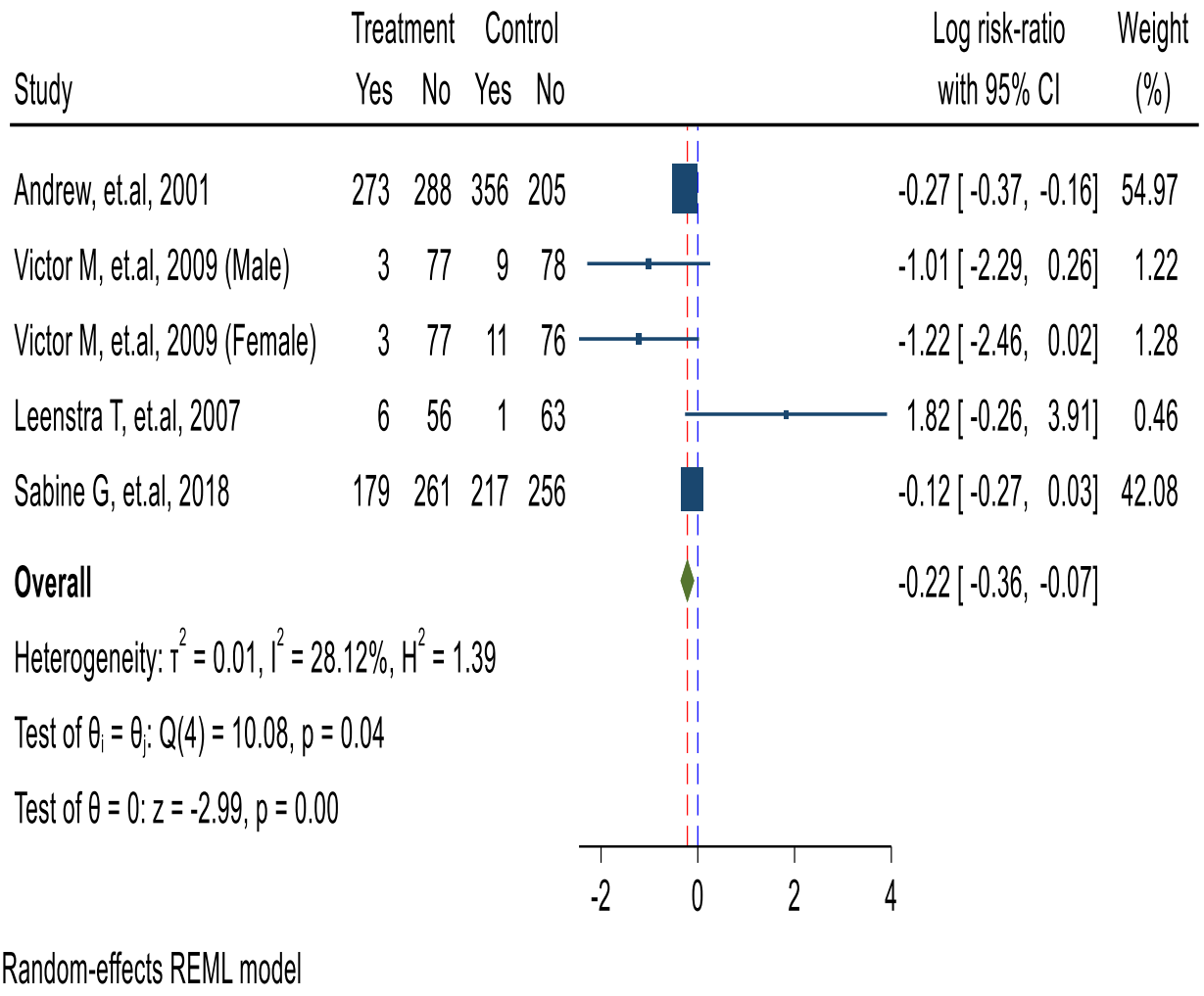


Figure 4: Meta-analysis of the effect of once-weekly IFAS on Anemia

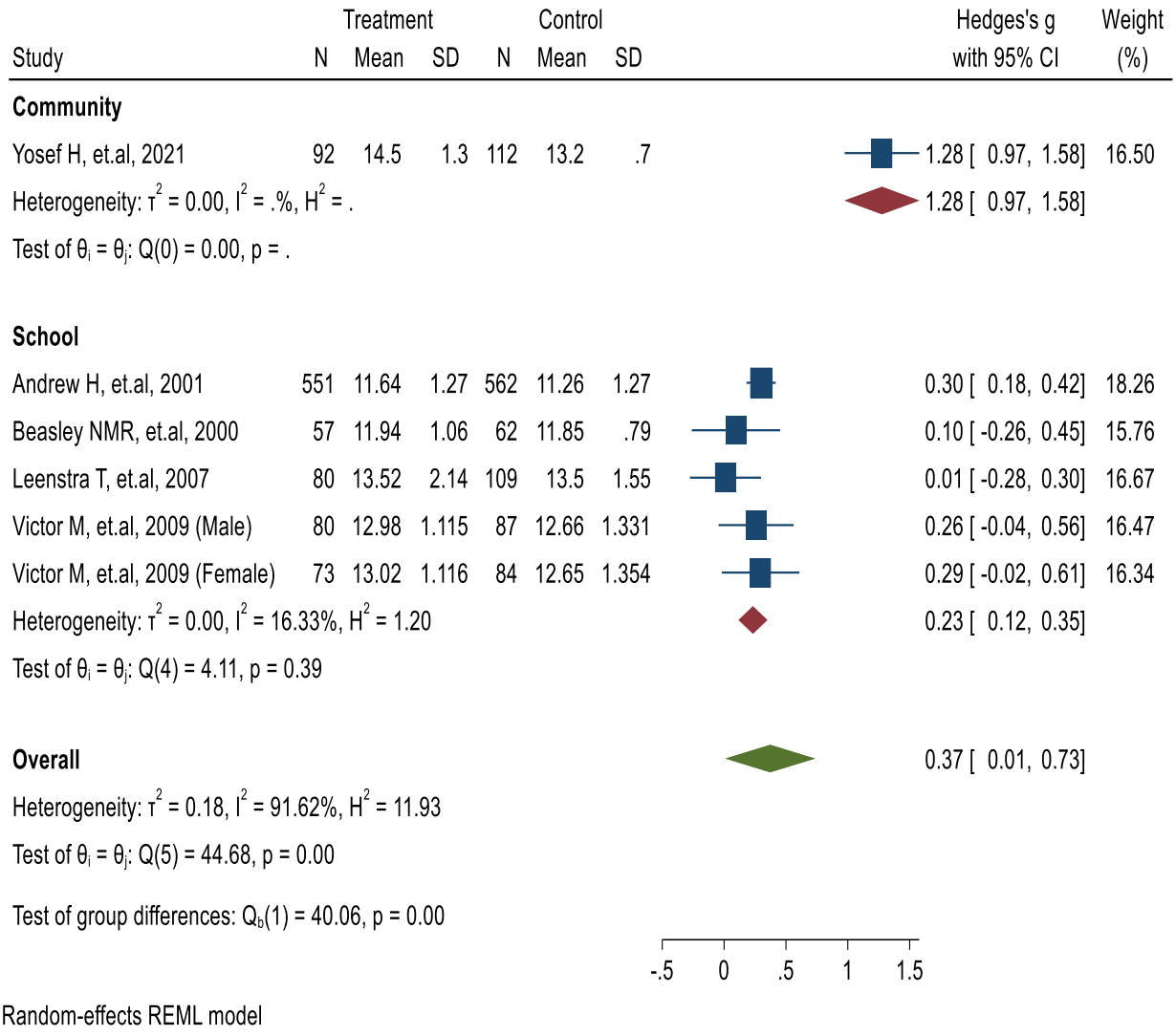
Supplemental Table 1: The Joanna Briggs Institute (JBI) Quality Assessment tool was employed to assess the quality of included Randomized Controlled Trials (RCTs) in this systematic review and meta-analysis, 2023.

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?	same way for 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		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		2	2	2	16
4.	Olsen, et.al (2006, Kenya)	2	2	2	2	2	2	2	2	2		1	2	2	24
5.	Lawless, et al (1994, Kenya)	2	2	2	2	2	1	2	2	2		1	2	2	22
6.	Victor Mwanakasale (2009, Zambia)	1	1	2	1	1	1	1	1	0		1	2	2	8
7.	Nchito (2009, Zambia)	2	2	2	2	2	2	2	2	1	2	1	2	2	22
8.	J. Baumgartner (2012, South Africa)	2	2	2	2	2	2	2	2	2	2	2	2	2	26

9.	Leenstra, et.al (2007, Kenya)	2	2	2	2	2	2	2	2	1	1	2	2	22
10.	J. Baumgartner (2013, South Africa)	2	2	2	2	2	2	2	2	2	2	2	2	26
11.	Mohamed Ag Ayoya, (2009, Mali)	2	0	2	0	0	1	2	1	0	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	2	2	2	14
14.	Sabine G, et.al. (2018, Burkina Faso)	2	2	2	0	2	2	2	2	2	2	2	2	24
15.	Lucas G, et.al, (2021, Ghana)	0	NA	NA	0	NA	NA	2	2	2	2	2	2	14
16.	Peter H, et.al, (2005, Mozambique)	1	1	2	0	0	1	2	2	2	2	2	2	16
17.	Maisoon NA Fageer,et.al, (2021, Sudan)	2	2	1	2	2	2	2	2	1	1	2	2	18

Supplemental Table 2: The assessment of the certainty of evidence of included studies in Meta-analysis

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 RR)	Certainty of evidence
Serum Ferritin (Once-Weekly)	3	440	RCT	Serious	Low	No	No	No	No	H=0.53 (0.28, 0.78)	Moderate
Serum Ferritin (More than once weekly)	5	653	RCT	Serious	Low	No	No	No	Concern	H=0.77 (0.33, 1.22)	Low
Hemoglobin (Once weekly)	5	1949	RCT	Serious	Low	No	No	No	No	H=0.37 (0.01, 0.73)	Moderate
Anemia (Once-weekly)	4	2505	RCT	Low	Low	No	concern	No	No	RR=0.8 (0.69, 0.93)	Moderate



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

Search term

(((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 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 "Weekly Iron Folic acid supplementation"[Title/Abstract] OR "Dietary 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]))).

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			2
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	
INTRODUCTION			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
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	6
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	5 & 6
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
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	7
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in 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
	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 assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many 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
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	10
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	8
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	9
	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.	8
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	8
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	NA
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	15
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	15

PRISMA 2020 Checklist

Section and Topic	Item #	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 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 excluded.	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 effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	9
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	12-15
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	12-15
	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 INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	8
	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

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: 10.1136/bmj.n71