

Risk-Stratified Anemia Prevention among Adolescent Girls: Hemoglobin, Ferritin, and Supplement Adherence

Ruwiah^{1*}, Suhadi², Fithria³

^{1,3}Faculty of Public Health, Halu Oleo University, Kendari, Indonesia

²Department of Health Policy Administration, Faculty of Public Health, Halu Oleo University, Kendari, Indonesia

*Email Correspondence: ruwiah849@gmail.com

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ABSTRACT

Uniform school-based anemia programs may not adequately address differences in iron status, menstrual blood loss, diet, adherence barriers, and social support. This study evaluated a risk-stratified, multicomponent anemia prevention program among adolescent girls. In this parallel-group randomized controlled trial, 80 girls at SMP Negeri 6 Kendari City were classified as being at low, moderate, or high risk based on hemoglobin, ferritin, C-reactive protein, menstrual bleeding, dietary, adherence, nutritional, and social-support indicators, and were allocated 1:1 to the intervention or routine-services group. Intervention intensity increased according to risk level through education, reminders, counseling, supervised supplementation, support, and referral. Seventy-six participants completed the week-12 assessment, while all 80 were retained in the intention-to-treat analysis. Baseline anemia prevalence was 37.5% in each group. At week 12, adjusted hemoglobin was 0.40 g/dL higher in the intervention group (95% CI 0.12–0.68; Holm-adjusted $p=0.010$), and the adjusted ferritin geometric mean ratio was 1.28 (95% CI 1.08–1.52; Holm-adjusted $p=0.010$). Adherence of at least 80% was achieved by 82.5% of participants in the intervention group and 50.0% of controls (RR 1.65; 95% CI 1.17–2.32; $p=0.004$). Reductions in anemia (RR 0.50; $p=0.118$) and iron deficiency (RR 0.54; $p=0.130$) were not statistically significant. The program was associated with improved biomarkers and substantially higher adherence, but evidence of a reduction in anemia prevalence remained inconclusive. Multicenter trials with longer follow-up and economic evaluation are warranted.

INTRODUCTION

Anemia in adolescence reduces the blood's oxygen-carrying capacity and may contribute to fatigue, impaired physical performance, reduced concentration, and poorer educational participation. Adolescent girls are particularly vulnerable because pubertal growth increases iron requirements, while menstruation increases iron loss. Iron deficiency may precede anemia; therefore, hemoglobin should be interpreted alongside ferritin, and ferritin should be considered in conjunction with an inflammation marker such as C-reactive protein (CRP)¹⁻⁶.

The burden remains substantial. Global estimates indicate limited progress in anemia control among women and girls, while Indonesian surveillance and school-based studies continue to document inadequate iron-supplement coverage and a considerable burden of anemia^{1,7-10}. Program performance is influenced not only by supplement availability but also by gastrointestinal adverse effects, beliefs about benefits, teacher and family support, school distribution systems, and continuity

of monitoring¹¹⁻¹⁴. Poverty, household food insecurity, limited access to animal-source foods, and the cost of a diverse diet may further constrain responses to education and supplementation.

Universal weekly supplementation remains an essential population-level strategy, but risk is heterogeneous. Hemoglobin and ferritin reflect current anemia status and iron stores; heavy menstrual bleeding accelerates iron loss; dietary quality affects iron intake and absorption; and adherence determines the dose actually received. These domains interact with nutritional status and social support. The conceptual pathway used in this study was therefore as follows: biological, menstrual, dietary, behavioral, and social conditions shape baseline risk; risk classification determines intervention intensity; and greater support is expected to improve supplement adherence and dietary practices, which may, in turn, improve iron stores and hemoglobin levels.

Personalized and precision nutrition frameworks propose tailoring advice to measured characteristics rather than providing identical recommendations to all individuals^{15,16}. The present intervention did not constitute genomic or molecular precision medicine. Rather, it was a pragmatic, risk-stratified public health program in which established components were delivered at different intensities according to clinically and behaviorally relevant strata. This distinction avoids equating simple stratification with individualized biological precision while retaining the practical value of matching resources to need.

Previous studies have shown that digital education, reminders, supervision, and social support can improve anemia-related knowledge and adherence to iron supplementation¹¹⁻¹⁴. However, many interventions evaluate hemoglobin or self-reported adherence alone, deliver a uniform intervention, or do not combine biomarkers with menstrual, dietary, behavioral, and social information. The innovation of the present study was the integration of hemoglobin, ferritin, CRP, menstrual bleeding, dietary indicators, supplement adherence, adverse effects, nutritional status, and social support into a single school-based classification process that determined intervention intensity.

This study aimed to evaluate whether a 12-week, risk-stratified, multicomponent anemia prevention program produced greater improvements in hemoglobin, ferritin, and iron-supplement adherence than routine school services. Hemoglobin was the outcome used for sample-size determination; ferritin and adherence were key additional outcomes evaluated with multiplicity control. We hypothesized that participants receiving the risk-stratified program would have higher week-12 hemoglobin and ferritin concentrations and better adherence than controls.

METHODS

Study Design

This study used a parallel group randomized controlled design with baseline and post-intervention measurements. Participants were allocated in a 1:1 ratio to the Risk-Stratified

Multicomponent Anemia Prevention Program or routine anemia prevention services after baseline assessment and risk classification. Laboratory personnel and outcome assessors were blinded to group allocation. The intervention lasted 12 weeks, with assessments at baseline and week 12. Reporting was guided by the CONSORT 2025 statement¹⁷.

Study Setting and Period

The study was conducted at SMP Negeri 6 Kendari City, Southeast Sulawesi, Indonesia, from March to June 2026. The period covered preparation, recruitment, baseline assessment, the 12-week intervention, endline assessment, and data processing. Blood collection was performed by trained laboratory personnel in a room meeting privacy, safety, and infection-prevention requirements.

Population and Sample

The target population comprised junior high school-aged girls in Kendari City, and the accessible population comprised all female students enrolled at SMP Negeri 6 Kendari City during the study period. Eligible participants were 12–15 years old, enrolled as active students, willing to complete the study procedures, and able to provide assent with written parental or guardian consent. Exclusion criteria included a diagnosed chronic disease or hematological disorder, current therapeutic treatment for anemia, allergy or contraindication to iron supplementation, acute infection at baseline, or an intention to transfer schools during follow-up. Students with severe anemia or a condition requiring immediate clinical care were excluded from randomization and referred to a healthcare facility².

The sample size was calculated to detect a between-group difference of 0.50 g/dL in hemoglobin change, assuming a standard deviation of 1.00 g/dL, a two-sided alpha of 0.05, 80% power, and equal allocation. The calculation yielded 64 participants. After allowing 20% attrition, the target was 80 participants, with 40 per group. The calculation was powered for hemoglobin and not separately for ferritin, adherence, anemia, or iron-deficiency prevalence; these outcomes were therefore interpreted with confidence intervals and multiplicity-adjusted p values.

Sampling and Group Allocation

Potential participants were selected using proportionate stratified random sampling by grade to ensure proportional representation of grades VII, VIII, and IX. Eligible students underwent baseline assessment of hemoglobin, ferritin, CRP, nutritional status, menstrual characteristics, dietary intake, previous iron supplement adherence, adverse effects, and social support.

Participants were classified into three prespecified risk levels. Low risk required normal hemoglobin and ferritin, no heavy menstrual bleeding, and no major behavioral risk factor. Moderate risk comprised depleted iron stores without anemia or at least two of the following: low dietary diversity, dietary iron intake below the recommended level, infrequent consumption of iron-rich foods, previous supplement adherence below 80%, supplement-related adverse effects, or low social

support. High risk was assigned when hemoglobin was <12.0 g/dL, ferritin was <15.0 $\mu\text{g/L}$, or heavy menstrual bleeding was present. Ferritin was interpreted with CRP because inflammation may elevate ferritin independently of iron status^{2,4}. The algorithm was developed pragmatically from guideline thresholds and measured determinants; it was not a previously validated prediction model.

Computer-generated block randomization with varying block sizes was stratified by grade and baseline risk category. The allocation sequence was generated by a researcher who was not involved in recruitment. Allocation was concealed in sequentially numbered, opaque, sealed envelopes until baseline procedures had been completed.

Intervention

The intervention group received a 12-week risk-stratified multicomponent anemia prevention program while all participants continued weekly iron supplementation through the national program [18]. Intervention contacts were documented weekly. Low-risk participants received digital education and one reminder per week. Moderate-risk participants received the same education, two reminders per week, adherence monitoring, individualized dietary counseling, and peer support. High-risk participants received the low and moderate-risk components plus supervised weekly supplementation, individual counseling by a health professional, adverse-effect monitoring, parent and teacher involvement, and referral according to clinical findings.

Low-risk participants received digital education on anemia, iron-rich foods, vitamin C, inhibitors of iron absorption, menstrual health, and appropriate supplement use, together with one weekly reminder. Moderate-risk participants received the same education, two reminders per week, adherence monitoring, individualized dietary counseling, and peer support. High-risk participants received more intensive reminders, individual counseling by a health professional, adverse-effect monitoring, parent and teacher involvement, supervised supplementation, and consultation or referral according to clinical findings.

Content was delivered through mobile-accessible materials, brief school discussions, monitoring cards, and direct support. Education addressed anemia, iron-rich foods, vitamin C, inhibitors of iron absorption, menstrual health, and appropriate supplement use. Participants reporting discomfort received guidance on administration timing and avoiding tea or coffee near supplementation. Facilitators used a common delivery checklist and recorded completed contacts, missed contacts, counseling, supervision, and referrals. Because all components were delivered as a package, the study could not estimate the independent contribution of any component.

The control group received routine services consisting of weekly iron supplement distribution and general education delivered by the school or primary healthcare center. After endline data collection, control participants were given access to the digital educational materials.

Outcomes and Variables

The co-primary outcomes were changes in hemoglobin concentration, ferritin concentration, and iron supplement adherence from baseline to week 12. Hemoglobin was expressed in g/dL and ferritin in µg/L. Adherence was calculated as the number of tablets consumed divided by the number scheduled, multiplied by 100. Participants consuming at least 80% of scheduled doses were classified as adherent.

Secondary outcomes reported in this manuscript were anemia, iron deficiency, supplement-related adverse effects, and tablet discontinuation due to adverse effects. The independent variable was treatment allocation. Covariates defined a priori were age, grade, menarche and menstrual bleeding status, BMI-for-age z score, baseline hemoglobin and ferritin, CRP, dietary iron intake, and social support. Dietary diversity, fatigue, and school absence were measured for program monitoring but were not included as inferential outcomes because complete prespecified analytic outputs were unavailable.

Study Instruments

Hemoglobin was measured in venous blood using a calibrated automated hematology analyzer. Serum ferritin was measured by chemiluminescent immunoassay and CRP by immunoturbidimetry in a laboratory implementing internal quality control. Coded specimens were analyzed by personnel blinded to allocation. Measurement and interpretation followed WHO recommendations^{2,4}. The archived manuscript did not retain the analyzer model, reagent lot, or within- and between-run assay coefficients; this reporting limitation is acknowledged and should be resolved from the laboratory log before final submission.

Body weight was measured to the nearest 0.1 kg with a digital scale and height to the nearest 0.1 cm with a stadiometer. BMI-for-age z scores were calculated using the WHO 2007 reference¹⁹. Menstrual blood loss was assessed with a pictorial blood-assessment method and questions on duration, pad changes, leakage, and clots²⁰. Two interviewer-administered 24-hour recalls, covering one school day and one non-school day, were supported by household portion-size aids. A food-frequency questionnaire assessed iron-rich foods and inhibitors of iron absorption²¹. Reported foods were converted to grams and matched to the Indonesian food-composition database; mixed dishes were decomposed using standardized household recipes.

Adherence was triangulated from supervised school-administration records, participant monitoring cards, and returned-tablet counts. The social-support questionnaire covered family, teacher, and peer support, underwent translation, expert content review, and pilot testing in a comparable school, and was used as a risk-classification measure rather than a primary outcome. The archived report documented acceptable internal consistency but did not retain the exact coefficient; no unverified coefficient is reported.

Study Procedures

The research team coordinated with the school, local primary healthcare center, parents, and students. After consent and assent were obtained, eligibility screening and baseline assessments were completed. Baseline data included participant characteristics, anthropometry, blood biomarkers, menstrual history, dietary intake, supplement use and adverse effects, and social support.

Participants were assigned a risk category and then randomized to intervention or control. Trained facilitators delivered and monitored the program weekly for 12 weeks using standardized materials and checklists. Adverse events, concomitant medication use, absences, and health changes were documented. At week 12, assessments were repeated using the same procedures and equipment. Participants with clinically important findings received counseling and referral. Quantitative fidelity summaries were not retained in the archived analytic output and are treated as a reporting limitation.

Bias Control

Selection bias was reduced through uniform eligibility criteria, probability sampling, random allocation, and allocation concealment. Laboratory personnel and endline biomarker assessors were blinded, whereas participants and facilitators could not be blinded to the behavioral program. Standardized instruments, trained collectors, operating procedures, calibrated equipment, and coded specimens reduced measurement bias. Intervention and control activities were scheduled separately, although information exchange among students in the same school could not be excluded.

Bias from self-reported adherence was reduced by triangulating supervised administration records, returned-tablet counts, and monitoring cards. Dietary data were collected on different days with household portion-size aids. Intervention fidelity was assessed using facilitator checklists. Protocol deviations and losses to follow-up were documented.

Ethical Considerations

Ethical approval was obtained from the Health Research Ethics Committee of the Health Workforce Education and Training Association–Health Scientific Progress (approval no. 038/PROMISE/KEPK/III/2026), together with permission from the education authority, school, and relevant institutions. Parents or guardians provided written informed consent, and participants provided written assent. Participant identities were replaced with codes, and data were stored on password-protected devices. Participation was voluntary, and participants could withdraw without academic or healthcare consequences. Students with clinically important abnormalities were referred for appropriate care.

Statistical Analysis

Analyses followed the intention-to-treat principle. Categorical variables were summarized as frequencies and percentages; continuous variables as means and standard deviations or medians

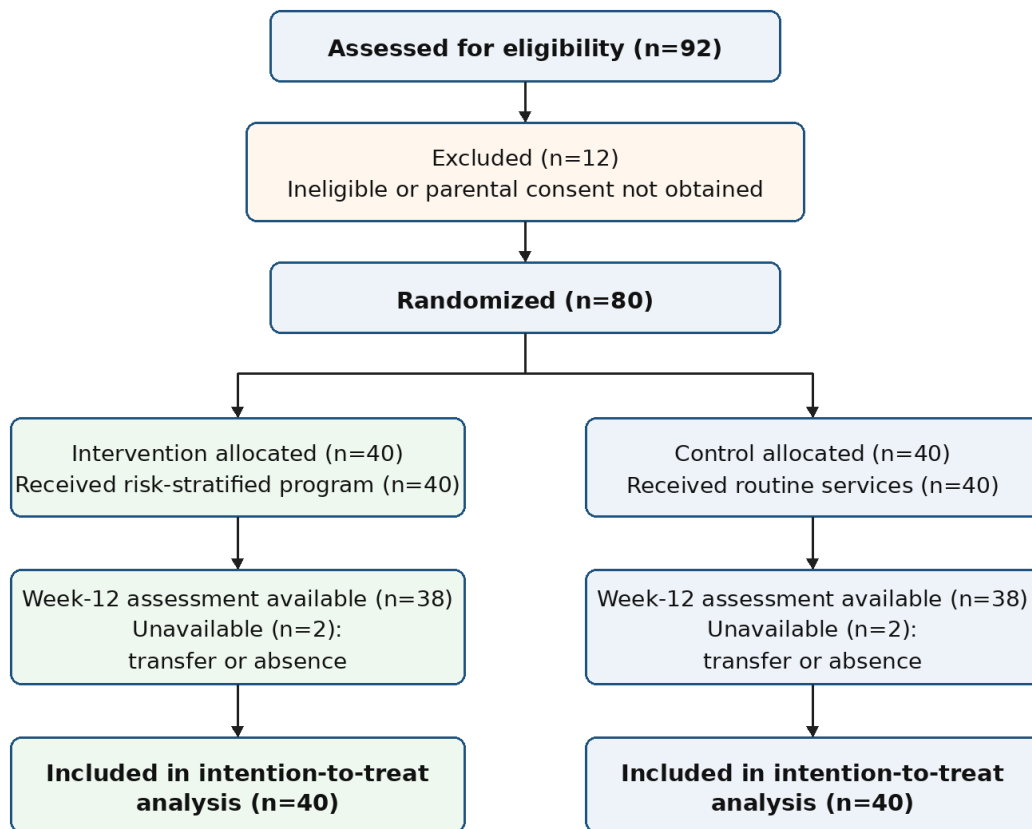
and interquartile ranges. Distributional assumptions were assessed with the Shapiro–Wilk test and graphical inspection. Standardized mean differences (SMDs) described baseline balance. Four participants (5.0%) lacked week-12 measurements. The archived analysis retained all randomized participants in the intention-to-treat output, but the imputation specification was not preserved; therefore, no imputation-specific sensitivity claim is made.

Endline hemoglobin was analyzed using analysis of covariance with treatment group and baseline hemoglobin as predictors and relevant prespecified covariates. Ferritin was log-transformed because of right skew; the corresponding model included baseline log-ferritin and CRP, and results were back-transformed as geometric mean ratios. Week-12 adherence percentage was analyzed with adjusted linear regression and reported as a mean difference in percentage points. Model assumptions were examined before interpretation.

Adherence of at least 80% was achieved by 82.5% of intervention participants and 50.0% of controls (RR 1.65; 95% CI 1.17–2.32; $p=0.004$). Anemia was less frequent in the intervention group at week 12 (15.0% vs 30.0%), but the difference was not statistically significant (RR 0.50; 95% CI 0.21–1.19; $p=0.118$). Iron deficiency was also lower (17.5% vs 32.5%) without statistical significance (RR 0.54; 95% CI 0.24–1.20; $p=0.130$). Mild adverse effects were similar, and no serious adverse event occurred (Table 3). Risk-stratum-specific effects were not estimated because the study was not powered for interaction testing.

RESULTS

Ninety-two students were assessed for eligibility; 12 were excluded because they did not meet the eligibility criteria or parental consent was not obtained. Eighty participants completed the baseline assessment and were randomized equally between the two groups. At week 12, 76 participants completed the assessment (38 per group); two participants in each group were unavailable because of school transfer or absence. Thus, four participants had missing week-12 measurements, while the archived intention-to-treat analysis retained all 80 randomized participants (Figure 1).



Participant flow through the trial

Figure 1. Flow of participants through the randomized trial

Table 1. Baseline characteristics of participants by study group

Characteristic	Intervention (n=40)	Control (n=40)	SMD
Age, years, mean $\pm$ SD	13.4 $\pm$ 0.9	13.5 $\pm$ 0.8	-0.12
Grade VII, n (%)	14 (35.0)	13 (32.5)	0.05
Grade VIII, n (%)	14 (35.0)	14 (35.0)	0.00
Grade IX, n (%)	12 (30.0)	13 (32.5)	-0.05
Post-menarche, n (%)	35 (87.5)	36 (90.0)	-0.08
Heavy menstrual bleeding, n (%)	8 (20.0)	9 (22.5)	-0.06
BMI-for-age z score, mean $\pm$ SD	-0.12 $\pm$ 1.04	-0.08 $\pm$ 1.01	-0.04
Hemoglobin, g/dL, mean $\pm$ SD	11.96 $\pm$ 0.79	11.99 $\pm$ 0.82	-0.04
Ferritin, μ g/L, median (IQR)	17.2 (10.8–25.6)	17.8 (11.1–26.0)	—
CRP, mg/L, median (IQR)	0.8 (0.4–1.7)	0.9 (0.4–1.8)	—
Anemia, n (%)	15 (37.5)	15 (37.5)	0.00
Iron deficiency, n (%)	17 (42.5)	16 (40.0)	0.05

Low risk, n (%)	13 (32.5)	14 (35.0)	-0.05
Moderate risk, n (%)	17 (42.5)	16 (40.0)	0.05
High risk, n (%)	10 (25.0)	10 (25.0)	0.00

Baseline anemia prevalence was 37.5% in both groups. Most absolute SMDs were below 0.10, indicating little observed imbalance; age showed a small imbalance (SMD=-0.12). Ferritin and CRP SMDs were not calculated because only medians and interquartile ranges were available. The distribution of low-, moderate-, and high-risk categories was similar between groups (Table 1).

Table 2. Changes in hemoglobin, ferritin, and iron supplement adherence

Outcome	Group	Baseline	Week 12	Adjusted effect (95% CI)	p value	Holm-adjusted p
Hemoglobin, g/dL, mean $\pm$ SD	Intervention	11.96 $\pm$ 0.79	12.58 $\pm$ 0.72	Mean difference 0.40 g/dL (0.12–0.68)	0.006	0.010
	Control	11.99 $\pm$ 0.82	12.16 $\pm$ 0.78			
Ferritin, μ g/L, median (IQR)	Intervention	17.2 (10.8–25.6)	24.8 (17.0–34.2)	Geometric mean ratio 1.28 (1.08–1.52)	0.005	0.010
	Control	17.8 (11.1–26.0)	19.1 (12.7–28.0)			
Adherence, %, mean $\pm$ SD	Intervention	—	88.1 $\pm$ 11.3	Mean difference 17.5 percentage points (10.7–24.3)	<0.001	0.003
	Control	—	70.2 $\pm$ 18.6			

At week 12, mean hemoglobin was 12.58 g/dL in the intervention group and 12.16 g/dL in controls. Adjusted endline hemoglobin was 0.40 g/dL higher in the intervention group (95% CI 0.12–0.68; Holm-adjusted p=0.010). Median ferritin was 24.8 versus 19.1 μ g/L; after log transformation and adjustment for baseline ferritin and CRP, the geometric mean ratio was 1.28 (95% CI 1.08–1.52; Holm-adjusted p=0.010). Mean adherence was 88.1% versus 70.2%, corresponding to an adjusted difference of 17.5 percentage points (95% CI 10.7–24.3; Holm-adjusted p=0.003) (Table 2).

Table 3. Categorical adherence and secondary outcomes at week 12

Outcome	Intervention (n=40)	Control (n=40)	Effect estimate (95% CI)	p value
Adherence ≥80%, n (%)	33 (82.5)	20 (50.0)	RR 1.65 (1.17–2.32)	0.004
Anemia, n (%)	6 (15.0)	12 (30.0)	RR 0.50 (0.21–1.19)	0.118
Iron deficiency, n (%)	7 (17.5)	13 (32.5)	RR 0.54 (0.24–1.20)	0.130
Mild adverse effects, n (%)	9 (22.5)	8 (20.0)	RR 1.13 (0.49–2.58)	0.785
Discontinued tablets because of adverse effects, n (%)	1 (2.5)	3 (7.5)	RR 0.33 (0.04–3.05)	0.339

Adherence of at least 80% was achieved by 82.5% of intervention participants and 50.0% of controls (RR 1.65; 95% CI 1.17–2.32; $p=0.004$). Anemia was less frequent in the intervention group at week 12 (15.0% vs 30.0%), but the difference was not statistically significant (RR 0.50; 95% CI 0.21–1.19; $p=0.118$). Iron deficiency was also lower (17.5% vs 32.5%) without statistical significance (RR 0.54; 95% CI 0.24–1.20; $p=0.130$). Mild adverse effects were similar, and no serious adverse event occurred (Table 3). Risk-stratum-specific effects were not estimated because the study was not powered for interaction testing.

DISCUSSION

The risk-stratified multicomponent program was associated with higher week-12 hemoglobin, ferritin, and iron-supplement adherence than routine services. The largest behavioral difference was adherence: 82.5% of intervention participants reached the 80% threshold compared with 50.0% of controls. Biomarker improvements were statistically significant, but reductions in anemia and iron-deficiency prevalence were not. The findings therefore support short-term improvement in treatment exposure and continuous iron-status measures, not definitive prevention of anemia.

The adjusted hemoglobin difference of 0.40 g/dL was smaller than the pooled increases reported in some iron-supplementation reviews but directionally consistent with school and community interventions that combined supplementation, education, or monitoring^{22–25}. Direct quantitative comparisons require caution because intervention duration, baseline anemia, supplement dose, adherence ascertainment, and comparators differed. The present control group also received weekly supplementation, so the estimated contrast represents the added value of risk-adapted support rather than supplementation versus no supplementation.

The ferritin geometric mean ratio of 1.28 indicates better iron-store replenishment after accounting for baseline ferritin and CRP. Improved adherence is a plausible mechanism because received iron dose directly affects the substrate available for erythropoiesis and storage. Counseling on iron-rich foods, vitamin C, and absorption inhibitors may also have contributed, while management

of gastrointestinal effects could reduce tablet discontinuation. Because education, reminders, supervision, counseling, and family or teacher support were bundled, their independent effects cannot be separated.

Risk stratification was intended to allocate support according to need, not to claim molecular precision. This approach is compatible with stratified nutrition frameworks that use phenotype and behavior to tailor advice, while recognizing that individual interventions cannot replace population measures or address structural food insecurity^{15,16}. The trial did not estimate risk-stratum interactions; consequently, it cannot determine whether low, moderate, or high-risk participants benefited most. Validation of the classification algorithm and adequately powered subgroup analyses are required.

The non-significant anemia and iron-deficiency outcomes are clinically important. The study was powered for mean hemoglobin rather than categorical disease status, and 12 weeks may be insufficient for participants with heavy menstrual bleeding, low iron intake, or markedly depleted stores to cross diagnostic thresholds. A change in a continuous biomarker can occur without a statistically detectable shift in prevalence, particularly in a small trial. Longer follow-up is needed to determine whether biomarker gains translate into sustained reductions in anemia, fatigue, absence, and other functional outcomes.

Implementation would require reliable supplement supply, trained school and healthcare personnel, laboratory or point-of-care assessment, protected data systems, referral pathways, and time for counseling and monitoring. These requirements may limit scalability and could widen inequities if resource-poor schools cannot deliver the same intensity. Indonesian multisectoral experience suggests that school, health-service, family, and community coordination is central to sustainable weekly supplementation²⁵. Cost, feasibility, and equity should therefore be assessed before broader adoption.

Strengths included randomized allocation, concealment, blinded biomarker assessment, use of hemoglobin, ferritin, and CRP, and intention-to-treat reporting. Limitations were recruitment from one school, short follow-up, absence of prospective trial registration, inability to blind participants and facilitators, possible contamination, reliance partly on behavioral adherence records, lack of validated external risk prediction, incomplete archived assay and imputation documentation, absence of quantitative fidelity summaries, and insufficient power for anemia, iron-deficiency, and risk-stratum effects. The study also did not evaluate cost-effectiveness or persistence after intervention withdrawal.

CONCLUSION

A 12-week risk-stratified multicomponent anemia prevention program was associated with higher hemoglobin and ferritin concentrations and substantially better iron-supplement adherence

than routine services among girls at one junior high school. Adherence showed the clearest practical benefit. Anemia and iron-deficiency prevalence were lower but not significantly different, so the study does not establish sustained anemia prevention. The program should be considered preliminary and requires multicenter validation, longer follow-up, risk-stratum analysis, and assessment of feasibility, cost, and equity before routine scale-up.

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