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Effect of Iron and Zinc Supplementation on Cognitive Functions of Female Adolescents in Chennai, India

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Abstract. Objectives: Iron and zinc are micronutrients essential for brain function. Adolescent female population (college students) is expected to be deficient in iron and zinc due to inadequate dietary intake, socio-economic constraints and faulty food habits and lifestyle. It is well established that these deficiencies adversely affect cognitive performance. No systematic study has documented the cognitive effects of iron and zinc among this target population in India. Hence, this study was designed to test the efficacy of iron, zinc and combined iron and zinc supplementation on cognitive performance of female adolescents. **Methods:** A randomized, double-blind, placebo-controlled, intervention trial was conducted in Chennai, India among 4 groups of female adolescents who were aged 17 to 19 years. They were randomly assigned to any one of the four intervention groups and were given iron alone (Fe, 60 mg elemental iron), zinc alone (Zn, 30 mg elemental zinc), both iron and zinc (FeZn, 60 mg elemental iron and 30 mg elemental zinc) or placebo (PC) daily for 4 months. Hemoglobin, serum ferritin, serum zinc and 7 cognitive tests of mental speed, sustained attention, abstract reasoning, verbal and visual memory and verbal and visual recognition was assessed at baseline and after 4months of supplementation. **Results:** Post intervention, the groups supplemented with Fe and FeZn scored higher on the cognitive function of visual memory than the Zn alone and PC groups. Fe, Zn and FeZn were equally efficacious in improving the cognitive function of mental speed on accuracy levels. The Fe, Zn , and FeZn groups did not improve in other cognitive measures : sustained attention, abstract reasoning immediate and delayed recall of verbal material and verbal and visual recognition compared with the placebo group. **Conclusions:** Daily supplementation with iron, zinc and combined iron and zinc benefitted only certain cognitive functions among female adolescents in the college setting.

Keywords: Iron, Zinc, Cognition, Female adolescents

1. Introduction

It is well established that deficiencies of both iron and zinc are highly prevalent in developing and developed countries (1). An estimated 2 billion people are iron deficient (2) and an estimated 1.3 billion are at the risk of inadequate zinc intake (3). Deficiencies of iron and zinc often coexist (4, 5) because iron and zinc are most bioavailable from many of the same foods and their absorption is inhibited by many of the same dietary substances (6).

A large body of research findings suggests that deficiencies of iron and zinc can affect cognition. Most research on infants and young children are consistent with the beneficial effects of iron and zinc supplementation on cognitive functions (7-14). Less research has focused, however, on cognitive benefits of iron and zinc in female adolescents, particularly those in the college setting (15) ; thus the cognitive effects of iron and zinc on older adolescents are less clear. This is of particular interest since adolescent girls are a highly vulnerable group due to inadequate dietary intake of iron and zinc that fail to meet their high physiological requirements for growing body tissues, expanding red cell mass, and onset of menarche. In addition to these factors, certain non-dietary factors such as high menstrual losses, strenuous exercise,

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pregnancy, low socio-economic status and ethnicity may also increase their risk of both iron and zinc deficiencies (16). Therefore it is likely that cognitive deficits associated with low iron and zinc nutriture is possible among female adolescents and could be improved with iron and zinc repletion. Hence, the present study was undertaken to examine the relative effects of iron, zinc and combined iron and zinc supplementation on cognitive performance of female adolescents. The need to ascertain the cognitive effects of combined iron and zinc supplementation as a logical strategy was felt since deficiencies of iron and zinc may coexist in vulnerable populations. Given the widespread prevalence of iron and zinc deficiencies among female adolescents, a documented report on the cognitive effects of iron and zinc interventions would be relevant to the psychological functioning of a significant proportion of the world's population. This specific report will present data collected in female adolescents on the effect of iron and zinc on cognitive functions. A detailed report on the haematological response that resulted from this study will be published separately.

2. Methods

2.1. Subjects and Location

The study was conducted in Queen Mary's College, Chennai, run by the Government of Tamil Nadu. It is one of the oldest colleges catering to over 3000 students including 165 hostel residents belonging to low and middle income families. The subjects were adolescent girls, 17-19 y old, who met the following criteria: willing to participate in the study, healthy, residing in the hostel, had not taken multivitamin-mineral supplements and had not donated blood in the last 6months. Written informed consent was obtained from each of the subjects who were unaware of their entry into iron, zinc, iron and zinc and placebo groups. All procedures used in this study were reviewed and approved by the Doctoral Committee Board at the University of Madras, Chennai.

2.2. Study Design

This randomized, double-blind, placebo-controlled intervention study was carried out with 109 subjects assigned at random to one of the four following groups:1) Ferrous fumarate (184.6 mg equivalent to 60 mg elemental iron), 2) zinc sulphate(82.4 mg equivalent to 30 mg elemental zinc), 3) Ferrous fumarate (184.6 mg equivalent to 60 mg elemental iron) along with zinc sulphate (82.4 mg equivalent to 30 mg elemental zinc) and placebo (lactose, 200mg and dicalcium phosphate 190mg). This dosage was based on the beneficial effects in iron and zinc status and cognitive functions reported in earlier studies (17-19).The treatments were randomly assigned in a double-blind manner using lottery method to the four treatment groups in the form of coded capsules to be taken as one capsule per day in between meals for a period of four months (Figure-1) All the capsules were manufactured by Alved Pharma & Foods Pvt. Ltd., Chennai as per standard specifications. The capsules were packed in plastic containers, each containing 30 capsules and distributed at the beginning of each month. They were visited thrice a week to ensure intake of the capsules and were asked to fill out calendar forms every day covering a month to record their intake of the capsules and record side effects, if any. Compliance with supplementation was monitored on a monthly basis and the number of capsules remaining in each container was noted.

2.3. Measures

At entry, general socioeconomic information, weight and height were recorded. Three day food records were also collected. At base line and at the end of the intervention trial fasting venous blood samples were drawn from the subjects with the assistance of qualified medical /technical personnel for the assessment of haemoglobin, serum ferritin and serum zinc concentrations which was done using standard laboratory procedures .

The cognitive variables measured and the instruments used included the following : Mental speed-Digit Symbol Substitution Test(20), Sustained attention-Digit Vigilance test (21), Abstract reasoning- Standard Progressive Matrices(22), Immediate and delayed recall of verbal material, verbal recognition -Rey Auditory Verbal Learning Test(23), Immediate and delayed recall of visual material-Rey Complex Figure Test(24) and Recognition of visual material-PGI Memory Scale(25).After baseline testing, each subject was given the

assigned treatment and instructed to take 1 dose/d for the next 4 mo. After 16 wk the fasting venous blood was drawn and cognitive tests were repeated.

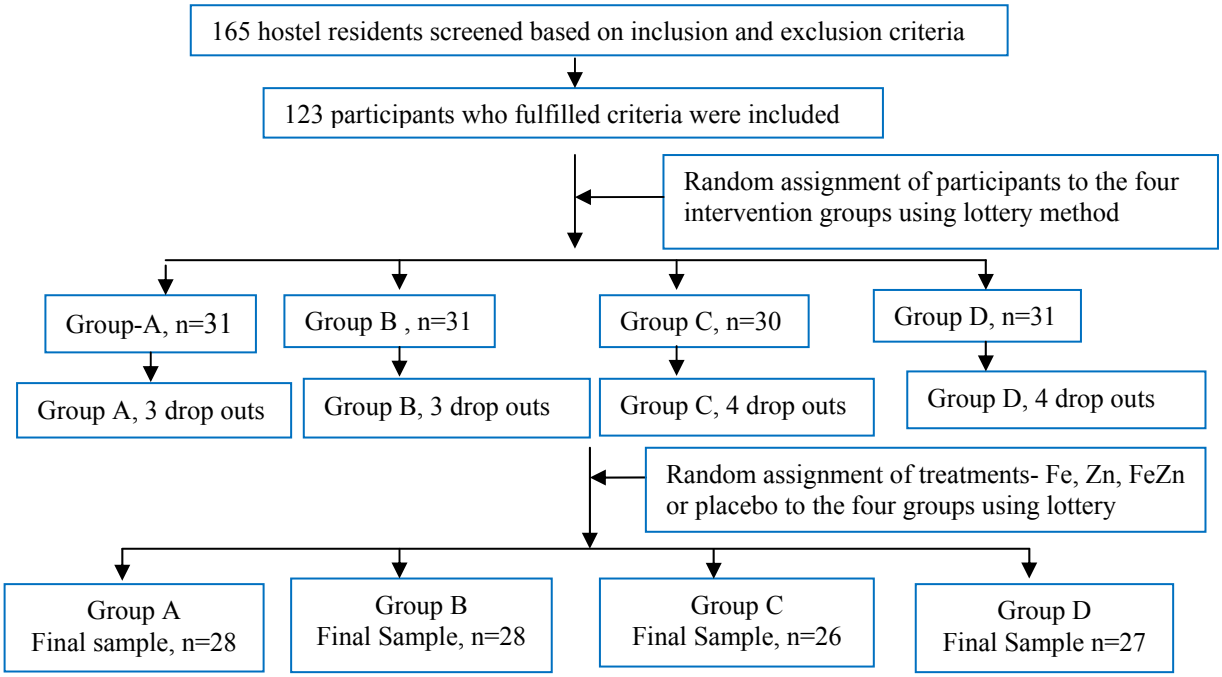

Fig. 1: Trial Profile. Allotment of participants and treatments to the four intervention groups

2.4. Statistical Analyses

The data obtained in the study were subjected to descriptive analysis using mean and standard deviation. After testing the data for normality and homogeneity of variance, inter-group comparison on the effect of iron, zinc, and combined iron and zinc and placebo on certain cognitive and haematological variables was done using ANCOVA. When the F-test result was significant, post hoc comparisons were performed with Bonferroni adjustment for multiple comparisons in a general linear model for ANCOVA. All analyses were adjusted for baseline performance on a given test. All statistical analyses were performed using SPSS version-10 .

3. Results

The 109 participants included in the study were between 17and 19 years of age, the mean age being 18.44. Most of them were “intellectually average” based on Ravens Progressive Matrices test scores. Based on the inclusion and exclusion criteria, the final sample consisted of 123 students who were selected out of 165 students by following the convenience sampling technique. Only 109 students completed the study. The subjects who dropped out of the study reported that they discontinued because they experienced side effects such as headache, hair fall, increased menstrual blood flow, giddiness and increased appetite. Fear of blood collection and sudden illness were the other reasons reported by the drop-outs. The compliance rate in all the four treatment groups was almost similar and ranged from 83%-86%.

Analysis of the nutrient intake of the participants showed that the intake of energy, protein, carotene, riboflavin, thiamine, niacin, folic acid, ascorbic acid calcium, iron and zinc of the participants was below the Recommended Dietary Allowances (26) for Indian female adolescents. Based on Body Mass Index, 63 out of 109 (57%) participants were of normal weight, 41 out of 109 (38%) were underweight, 5 out of 109 (5%) were overweight while none of them were obese.

Haemoglobin, serum ferritin, serum zinc and cognitive variables were assessed at baseline and after 4 months of supplementation. At baseline 86 out of the 109 participants (79%) were iron deficient (serum ferritin levels <12 µg/L). Zinc deficiency (serum zinc concentrations <70µg/L) coexisted with iron deficiency in 30 out of the 86 participants (35%) with almost even number of cases in all four groups .After four months of supplementation, multiple comparisons of the four treatment groups showed that the mean haemoglobin concentrations improved, though not significantly in the Fe and FeZn groups when compared

to the PC group. Significant improvement in the mean serum ferritin concentrations was observed in the groups supplemented with Fe alone (P<0.01) and FeZn (P<0.05) when compared to the PC group. The Zn group had significantly higher mean serum zinc concentrations (P<0.01) than the Fe, FeZn and PC groups.

Regarding cognitive functions, multiple comparisons of the four treatment groups showed that the groups supplemented with Fe and FeZn scored higher on the cognitive function of visual memory than the Zn and PC groups. Fe, Zn and FeZn were equally efficacious in improving the cognitive functions of mental speed on accuracy levels. Fe, Zn and FeZn supplementation produced modest improvement, though not significantly in other cognitive measures: sustained attention, abstract reasoning, immediate and delayed recall of verbal material and verbal and visual recognition compared with the PC group. These results support a beneficial effect of iron, zinc and both iron and zinc only on certain cognitive functions among female adolescents in the college setting (Table1 and Table 2).

Table1: Multiple comparisons among the treatment groups on adjusted posttest scores on cognitive measures- mental speed, sustained attention, abstract reasoning

	Baseline	Posttest	Adjusted posttest [8]
Mental Speed (Time component)			
Iron supplemented (Fe)	211.82±47.48[7]	175.89±50.30	175.00±7.82 [1c,4c,6c]
Zinc supplemented Zn)	205.18±50.87	175.25±47.16	175.99±7.82 [2c,5c]
Iron and zinc supplemented (FeZn)	214.69±56.76	173.96±39.67	172.36±8.12 [3c]
Placebo controlled(PC)	201.30±57.47	183.07±32.94	184.77±7.98
Mental speed (error component)			
Iron supplemented	4.04±6.21	0.14±0.45	0.08±0.17 [1a,4c,6c]
Zinc supplemented	1.29±3.20	0.00±0.00	0.02±0.16 [2a,5c]
Iron and zinc supplemented	1.23±3.23	0.01±0.27	0.10±0.17 [3a]
Placebo controlled	1.63±2.96	0.89±1.65	0.90±0.17
Sustained attention (time component)			
Iron supplemented	423.18±90.27	373.43±76.19	382.00±13.23 [1c,4c,6c]
Zinc supplemented	447.32±90.17	368.75±63.24	367.79±13.13 [2c,5c]
Iron and zinc supplemented	466.15±102.26	350.42±92.13	342.03±13.72 [3c]
Placebo controlled	444.44±73.03	391.07±77.54	391.25±13.37
Sustained attention (error component)			
Iron supplemented	6.96±7.10	3.25±3.85	3.19±0.86 [1c,4c,6c]
Zinc supplemented	6.96±7.41	2.86±2.85	2.80±0.86 [2c,5c]
Iron and zinc supplemented	6.85±5.67	5.12±5.38	2.80±0.86 [3c]
Placebo controlled	6.26±6.42	5.59±6.59	5.72±0.88
Abstract reasoning			
Iron supplemented	37.82±10.84	42.14±10.43	42.52±1.45 1c,4c,6c
Zinc supplemented	38.68±10.44	40.64±11.97	40.46±1.45 [2c,5c]
Iron and zinc supplemented	39.62±10.15	43.77±8.73	42.97±1.51 [3c]
Placebo Controlled	37.56±11.02	41.07±9.77	41.62±1.48

Iron supplemented: n=28, 60mg elemental iron; zinc supplemented: n=28, 30mg elemental zinc,
Iron and zinc supplemented : n=26,60mg elemental iron+ 30 mg elemental zinc, placebo,n=27.Values in the row with different superscript letters and numbers show differences between groups in adjusted posttest scores
[1] Fe vs PC, [2] Zn vs PC, [3] FeZn vs PC, [4] Fe vs FeZn, [5] Zn vs Fe Zn, [6] Fe vs Zn;
[7] Mean ±SE, [8] Adjusted for baseline performance on a given test
[a] Significant differences between groups ,P< 0.01 level , [b] Significant differences between groups ,P< 0.05 level
[c] No Significant differences between groups

4. Discussion

This double-blind randomized placebo- controlled intervention trial examined the effect of iron (Fe), zinc (Zn) and combined iron and zinc (FeZn) on cognitive functions in female adolescents. The decrease in the number of errors in the test for mental speed committed by all the groups supplemented with Fe, Zn and FeZn compared to the PC group reflects the beneficial effect of these two micronutrients either as single supplements or in the combined form in improving accuracy levels of the participants. The lack of discernible difference in the error score among the three groups indicates that Fe, Zn and FeZn are equally effective in improving accuracy levels. Further, the lack of significant improvement in the time component of the test for mental speed in the Fe and Zn supplemented group compared to the PC group could be due to

the fact that the participants under study may have paid more attention to the accuracy component of the test rather than the speed component of the same test. Perhaps the use of cognitive tests that exclusively measure speed might have yielded definitive results on the potential role of Fe and Zn supplements on the cognitive function of mental speed.

Table 2: Multiple comparisons among the treatment groups on adjusted posttest scores on cognitive measures- verbal memory and recognition, visual memory and recognition

	Baseline	Posttest	Adjusted posttest[8]
Verbal memory (immediate recall)			
Iron supplemented	11.82±2.92[7]	13.61±2.35	13.41±0.41 [1c,4c,6c]
Zinc supplemented	11.18±2.37	12.68±2.44	12.70±0.41 [2c,5c]
Iron and zinc supplemented	10.85±2.81	13.35±1.94	13.48±0.43 [3c]
Placebo Controlled	11.11±3.71	12.30±2.77	12.34±0.42
Verbal memory (delayed recall)			
Iron supplemented	12.25±2.78	13.43±2.15	13.32±0.38 [1c,4c,6c]
Zinc supplemented	11.46±2.62	12.54±2.73	12.72±0.38 [2c,5c]
Iron and zinc supplemented	11.65±2.67	13.35±1.77	13.38±0.39 [3c]
Placebo Controlled	11.85±3.05	12.63±2.15	12.61±0.38
Verbal recognition			
Iron	14.04±1.71	14.86±0.59	14.82±0.15 [1c,4c,6c]
Zinc	13.71±1.63	14.64±1.06	14.64±0.15 [2c,5c]
Iron and zinc supplemented	13.62±2.17	14.73±0.67	14.74±0.16 [6c]
Placebo Controlled	13.59±1.78	14.59±0.89	14.61±0.15
Visual memory (immediate recall)			
Iron supplemented	30.00±4.13	34.00±1.36	34.16±0.44 [1a 4c 6c]
Zinc supplemented	31.82±3.91	32.93±2.55	32.59±0.44 [2c 5c]
Iron and zinc supplemented	29.92±3.93	32.58±3.21	32.76±0.45 [1b]
Placebo Controlled	30.63±3.40	31.82±2.66	31.80±0.44
Visual memory (Delayed recall)			
Iron supplemented	30.29±4.20	33.50±1.73	33.64±0.46 [1b 4c 6c]
Zinc supplemented	31.14±4.13	32.71±2.65	32.68±0.45 [2c 5c]
Iron and zinc supplemented	30.73±3.87	32.73±3.12	32.78±0.47 [3b]
Placebo Controlled	31.74±3.08	31.11±2.41	30.96±0.47
Visual recognition			
Iron supplemented	9.14±1.04	9.79±0.57	9.82±0.08 [1c,4c,6c]
Zinc supplemented	9.50±0.79	9.86±0.36	9.83±0.08 [2c,5c]
Iron and zinc supplemented	9.46±0.71	9.77±0.59	9.74±0.08 [6c]
Placebo Controlled	9.30±0.95	9.96±0.19	9.17±0.08

Iron supplemented :n=28, 60mg elemental iron; zinc supplemented: n=28, 30mg elemental zinc,
Iron and zinc supplemented ;n=26,60mgelemental iron+ 30 mg elemental zinc, placebo,n=27
Iron and zinc supplemented ;n=26,60mgelemental iron+ 30 mg elemental zinc, placebo=27
Values in the row with different superscript letters and numbers show differences between groups in adjusted posttest scores
[1] Fe vs PC, [2] Zn vs PC, [3] FeZn vs PC, [4] Fe vs FeZn, [5] Zn vs Fe Zn, [6] Fe vs Zn;
[7] Mean ±SE, [8] Adjusted for baseline performance on a given test
[a] Significant differences between groups ,P< 0.01 level , [b] Significant differences between groups ,P< 0.05 level ,
[c] No Significant differences between groups

The present study also intended to see the effect of Fe and Zn supplements in improving sustained attention, a higher order cognitive function. Supplementation with Fe and Zn did not improve the cognitive function of sustained attention which was measured using the Digit Vigilance Test in terms of the time taken to complete the test as well as the number of errors committed in this test. This finding is inconsistent with the findings of Murray-Kolb and Beard (8) and Groner *et al*., (27) who reported improvement in attention with iron supplementation among young women and adolescents respectively. Similarly, the lack of significant improvement in sustained attention with zinc supplements is in contrast with the findings of Penland *et al***.** (12) who reported improvement in attention tasks in the group supplemented with zinc.

The present finding could possibly be attributed to the difference in the nature of the instrument that was used for measuring sustained attention compared to the computerized tests used in the earlier studies. It may be noted that the Digit Vigilance test which was used in the present study demands high level of mental

effort and attention over a longer period i.e. 10-15 minutes and also requires coordination of the mind, concentration and visual acuity for a long period since the participants are required to scan 50 rows of digits that are closely packed on a sheet with each row comprising 30 digits and cancel the target digits 6 and 9 among other distracter digits. In addition to the above mentioned factors, it is quite likely that mental fatigue, eye strain, boredom, lack of motivation could have also influenced the outcomes of the test (28)

Assessment of the cognitive function of immediate and delayed recall of visual material revealed that the Fe and combined Fe Zn groups showed significant improvement in the immediate and delayed recall of visual material compared to the PC group, whereas, no improvement was seen in the Zn group. The favorable improvement in visual memory in the Fe group confirms the results of previous studies that demonstrated the beneficial effect of iron on the cognitive function of visual memory (19,29). Perhaps the marked increase in serum ferritin concentrations in the Fe and FeZn groups may have mediated improvement in the cognitive function of visual memory. Based on these findings it appears that the cognitive function of visual memory is influenced more by iron status than zinc status.

On assessing the effect of supplementation on other cognitive functions such as abstract reasoning, immediate and delayed recall of verbal material and verbal as well as visual recognition, no significant improvement was observed in the groups supplemented with Fe and Zn compared to the PC group. The lack of significant improvement in the cognitive functions of delayed recall and recognition of verbal material in the Fe group is consistent with the finding of Bruner *et al.*(30) who also reported the same. Similarly, the lack of improvement in verbal memory in the Zn group is in accordance with the findings of Darnell and Sandstead (19) who also reported no significant improvement in verbal learning and memory among women who were supplemented with zinc. However, the present findings failed to support the findings in earlier studies that demonstrated significant improvement in the cognitive function of immediate recall of verbal material and abstract reasoning with iron supplementation (15,19,30-31). Also, the results observed in the Zn group, failed to support the findings of other researchers who demonstrated significant improvement in reasoning ability and recognition of visual and verbal material among those who were treated with zinc (18,32-33).There are several possible explanations for these negative findings :

Firstly, the iron status of most of the participants in all four treatment groups was poor before supplementation as evidenced by their low serum ferritin concentrations (serum ferritin concentrations <12µg/L). Similarly, low zinc status (serum zinc concentrations <70µg/L) was also observed among many of them. It is quite possible that lowered iron and zinc status observed among the participants before supplementation may have exerted a cumulative effect over time on cognitive functioning which may not have facilitated a distinct and significant improvement in all cognitive domains with supplementation over a period of four months.

Secondly, the period of supplementation (4 months) in the present study may not have been adequate enough to facilitate favorable increments in brain iron and zinc pools for substantial enhancement in all the cognitive functions that were assessed. Further, the lack of significant improvement in cognitive functions in this study could be attributed to the possibility of other coexisting micronutrient deficiencies such folate, riboflavin, vitamin C and vitamin B-12 in the population studied. This inference is supported by the findings of Goodwin *et al*.,(34) who found significant correlation between biochemical indices of vitamin status and cognitive functioning. They reported significant correlation between folate, riboflavin, vitamin C and vitamin B-12 status and memory capacity. The levels of riboflavin and folate were also found to be positively related to the ability to think abstractly. Besides, other double- blind placebo-controlled studies reported, that multivitamin and mineral supplementation are associated with better moods, memory, attention and scores of intelligence (35-37). In fact, a few researchers also demonstrated that the benefits of iron and zinc supplements on cognitive functions are further amplified with the addition of other limiting micronutrients (18,32,38).These observation suggest that it is quite possible that the inclusion of a multiple micronutrient supplement along with iron and zinc could have yielded more favorable results among the adolescent population in the present study.

5. Conclusions

Daily supplementation with iron, zinc and combined iron and zinc were efficacious in improving the cognitive function of mental speed on accuracy levels. Iron and combined iron and zinc were both efficacious in improving the cognitive function of visual memory. This study suggests that supplementation with 60 mg elemental iron, 30 mg elemental zinc and both 60 mg elemental iron and 30 mg elemental zinc combined for a period of four months improves certain cognitive functions among female adolescents. Additional studies should be conducted to examine the recommendation of giving iron and zinc along with other limiting micronutrients for better expression of cognitive potential in vulnerable populations.

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