The following .pdf file contains a poster displayed at the 2003 INACG Symposium: Integrating Programs to Move Iron Deficiency and Anemia Control Forward, Marrakech, Morocco, 6 February 2003.

The 2003 INACG Symposium was co-hosted by INACG and the Local Organizing Committee of the Moroccan Ministry of Health and representatives of the United Nations technical Agencies, the private sector, multilateral agencies, and nongovernmental organizations in Morocco.

Funding was provided from the Micronutrient Global Leadership project of the Office of Health, Infectious Disease and Nutrition Bureau for Global Health, U.S. Agency for International Development. The International Life Sciences Institute Research Foundation's Human Nutrition Institute serves as the INACG Secretariat.

This poster was provided to IDPAS by the authors. Requests for additional information or clarifications may be sent to the author(s) directly or through INACG or IDPAS.

Iron Status Alters Cognitive and Behavioral Functioning in Women During Reproductive Years

JL Beard[2], LE Murray-Kolb[2], E Perez[1], A Berg[1], M Tomlinson[1], J Irlam[1], W Isaacs[1], T Njengele[1], A Sive[1], M Hendricks[1]

[1]School of Child and Adolescent Health and Child Guidance Clinic, University of Cape Town, South Africa; [2]Dept. of Nutritional Sciences, The Pennsylvania State University, USA

Abstract:

Background: Strong evidence exists that young children are at significant risk for effects of iron deficiency on behavior and cognition. Recently we began to question whether or not iron deficient adults have cognitive or behavioral dysfunctions as a result of this nutrient deficiency and whether young mothers might have different mother-child interactions as a result. Aims: To determine the relationship between iron status and cognitive and behavioral variables in young women and mothers. In mothers, we also wanted to assess the impact of maternal iron deficiency on mother-infant interaction and infants' development. Methods: Two separate prospective intervention studies are reported: The first study was done with three groups of mothers (Cape Town, South Africa): a non-anaemic control group (C, n=31) and two anemic groups on placebo (A, n=30) and iron therapy (B, n=34). Mothers of full term infants were recruited at 6-weeks post-partum and followed up until their infants were 9-months old. Maternal iron, socio-economic status, intelligence, cognitive and emotional status; mother-infant interaction and infants' development were assessed at baseline and follow-up. In the second study of 4-months duration we enrolled 183 women between the ages of 18-35 assigned to iron supplements or placebo in either iron deficient anemic (IDA), iron deficient non-anemic (ID), or iron sufficient (CN) groups. We measured behavioral domains (anxiety, anger, and depression) and cognitive functioning at baseline and then again after 4 months. Results: Study 1: At follow-up, significant effects of iron status on depression scores, perceived stress, and Ravens Matrices persisted in placebo treated mothers while iron treatment resulted in "better" scores on these 3 measures of functioning. Mother-child interactions were also related to maternal iron status. Study 2: Iron status was significantly associated with memory, learning, and attention in women in the lowest quintile of plasma ferritin requiring more trials to learn, displaying poorer memory, and being less attentive than women in the higher quintiles. They also had more anger and anxiety than women in the higher quintiles. Conclusion: These studies demonstrate a significant relationship between iron status and cognitive functioning, depression, anxiety, and anger in adult women. In the USA and South Africa, women in vastly different social-economic, cultural, and social settings showed significant relationships between iron status and cognitive and behavioral variables. This robust finding is quite significant given the estimates of iron deficiency in the world's young women.

Introduction:

Iron deficiency is the most common single nutrient deficiency disease in the world with estimates of more than 50% of women of reproductive age and similar percentages of adolescents being affected (1, 2). Numerous intervention studies have been performed across the world with varying success and it is clear that in nearly all situations it is a preventable disease with preventable consequences. Although research on infants and young children has shown cognitive, behavioral and anthropometric effects of iron deficiency (3, 4, 5, 6), no research has focused on the effects of iron deficiency in adolescent or adult mothers. This research may be important because changes in their cognitive functioning and behavior could also impact on their children's functioning through impaired mother-child interaction.

Studies on the effects of iron deficiency in adolescent and young women are far less abundant than those in infants and pre-school age children. Groner showed that iron treatment improved psychomotor performance of adolescent mothers while placebo treatment did not (7). This study did not sample anemic young women hence affects of anemia coexisting with iron deficiency could not be evaluated. Ballin and colleagues (8) noted an improvement in 'affect' and in ability to concentrate in adolescents treated with iron. In a review of a large number of studies in India, Seshadri and Gopaldas, concluded that iron deficient anemic adolescents showed significant improvements in cognitive performance with iron therapy (9). Most recently, Bruner et al. (10) showed in a placebo controlled trial, that non-anemic iron depleted adolescents had an improvement in verbal learning and in memory following 8 weeks of oral iron intervention. Since the published data demonstrate that non-anemic iron deficient individuals are affected, it seems critical to define the relationship of the severity of the iron deficit to the severity of the functional outcome.

While iron deficiency was once presumed to exert most of its deleterious effects only if anemia were present, it is now clear that many organs and systems show morphologic, physiologic, and biochemical changes before there is any drop in hemoglobin concentration (11). Iron deficiency is associated with alterations in many metabolic processes that may impact on brain functioning; among them are mitochondria electron transport, neurotransmitter synthesis and degradation, protein synthesis, organogenesis, and others. While many studies have focused on the negative outcomes of iron deficiency during early childhood where active growth and development is associated with high requirements, it is important to consider that adolescents and young women still have a significant risk of iron deficiency.

Objectives:

Study 1

- To demonstrate that IDA is associated with decreased attention and less behavioral affect in mothers
- To demonstrate that this in turn affects the mother –child interaction*
- To demonstrate that the change in interaction affects the infant's development*
- To demonstrate that correction of iron status in mothers is associated with an improvement in their cognition and behavior
- To demonstrate that these changes have a favorable effect on their infant's development*

* Please see poster #Th27

Study 2

- To demonstrate that ID and IDA in young women will alter cognitive performance such that attentional, memory, and learning processes are affected
- To demonstrate that ID and IDA in young women will alter emotional behavior such that depression, anxiety, and anger are affected
- To demonstrate that an intervention that normalizes the iron status of the individuals will also normalize their cognitive and behavioral scores

Methods:

Study 1

This study was conducted in Khayelitsha, a periurban community located 40 km east of Cape Town. The monthly birth statistics of women who delivered in the area were reviewed. Based on the reported type of delivery, Apgar scores, birth weight and residence of the mothers we then contacted the mothers as potential subjects and requested that they be screened for inclusion into the study.

At 6 weeks postpartum, mothers came to the clinics for well baby visits at which time they were provided with the informed consent form and were screened using a Hemocue. All capillary sampling was done with standard protocols, by trained staff, and with the use of quality controls. If the Hb value was less than 12 g/dl and the woman consented to participate, a venous blood sample was drawn, a Ravens test and a socio-demographic questionnaire administered, and a home follow-up and follow-up clinic visit was scheduled. Once the hematological results were determined by the clinical laboratory and examined by the project hematologists, the mothers were allocated (randomly in the case of the anemic mothers) to their groups. Control mothers were matched for age, parity and level of maternal education to the mothers in the anemic intervention groups. Enrollment of control mothers was regulated to match the enrollment rate with anemic mothers so that there was always a constant proportion of anemic and non-anemic mothers being enrolled into the study. After all women were allocated to groups, there were 30 women in group A (anemic + placebo); 34 women in group B (anemic + $FeSO_4$); and 31 women in group C (non-anemic controls).

At 10-weeks postpartum, mothers returned to the community clinic site where they were tested for cognitive, behavior and emotional functioning. The mother's treatment intervention was started at this time with a detailed instruction on when to take the pills, how to safeguard them from others who might take them, and when to expect a visit from one of the field workers in her home. Mothers were followed up at 14 weeks, 20 weeks, 7.5 months and 9 months postpartum with home visits. At these visits compliance and side effects of the treatment were assessed and pills were dispensed. For a complete list of which tests were administered and at which time points, please see Table 1.

Study 2

This study was conducted in State College, a college community located in central Pennsylvania. Young women were recruited through advertisement in the local newspapers. Interested women called the lab and were given a detailed explanation of the study after which they were scheduled for screening. Screening involved filling out a health history questionnaire as well as undergoing a venous blood draw. Screening procedures were conducted by a nurse at the General Clinical Research Center (GCRC) on the University Park campus. The criteria for participating in the study included the following: female between 18 and 35 years of age, free from any chronic illness or serious health problems and with English as the primary language spoken in the home.

Eligible women (n=183) reported to the laboratory for testing within a week of screening and again after 4 months of intervention (n=143). Subjects first recorded their GPA, level of physical activity, mother and father's occupations, oral contraceptive use, and menstrual cycle information. Next, they completed paper/pencil tasks which included the Beck Depression Inventory (BDI) and the Spielberger State-Trait Anxiety and Anger Inventories followed by the Shipley Institute of Living Scale and the Digit Symbol Test. Lastly, the subjects completed tasks from the Detterman's Cognitive Abilities Test (CAT), a computerized battery administered by a video monitor with a touch screen. For this study, the women completed eight of the eleven available subtests: Tachistoscopic Threshold, Stimulus Discrimination, Reaction Time, Probed Recall, Sternberg Memory Search, Recognition Memory, Progressive Matrices, and Learning. The tasks correspond to levels of complexity as follows: Attention: Tachistoscopic Threshold, Symbol Digit, and Reaction Time; Memory: Probed Recall, Sternberg Search, and Recognition Memory; Learning: Learning and Progressive Matrices.

After baseline testing, each subject was given either a placebo or iron supplement (160 mg $FeSO_4$) and instructed to take one per day for the next 4 months. Weekly telephone calls were placed to each woman as a reminder to consume the pills and to report any missed doses. At the end of the study, any remaining pills were counted and recorded.

Women completed a 2-day food record both at the beginning and end of the study. Women were instructed to discontinue use of all vitamin/mineral supplements for the duration of the study.

CBCs were performed on whole blood using a Coulter Counter at the GCRC. Plasma iron, total iron binding capacity (TIBC), serum ferritin, and serum transferrin receptor were determined by standard methods.

Standard descriptive statistics (means, standard deviations) were determined by group (CN, ID, IDA). Data from each paper/pencil task as well as the computer tasks were sorted according to each iron status variable and then classified by quintile. ANOVAs were then run on the quintiles. All statistics were run using SAS 8 (SAS Institute, Cary, NC).

Table 1

Baby's age at visit	Maternal assessment
6 weeks	Hematology Socio-Demographic Intelligence[1]
10 weeks	Attention[2] Emotion[3] Mother-infant interaction[4]
14 weeks	Dietary Intake
20 weeks	Coping skills[5]
7.5 months	Control over their lives[6]
9 months	Hematology Socio-demographic Ravens[1] Attention[2] Emotion[3] Mother-infant interaction[4]

[1] Ravens progressive matrices
[2] Digit Symbol test
[3] Edinburgh Postnatal Depression Scale (EPDS), Spielberger State Trait Anxiety Inventory (STAI), Perceived Stress
[4] Videotape during 20 minutes of play
[5] Griffith's Developmental Test (gross motor, social, verbal, hand and eye coordination, performance and general quotient)
[6] Locus of Control

Results:

Study 1

- CN subjects had significantly different values from the IDA subjects for Hb, TfSat, and Ft concentrations at 10 weeks (Table 2).
- There were no significant differences at baseline for scores on the EPDS, STAI, Perceived Stress, or the Raven's Progressive Matrices. Digit Symbol scores of moms in group B were greater than moms in groups A and C at baseline (Table 3).
- Both groups of anemic mothers had an improvement in their Hb values at 9 months, although it was higher in group B. Transferrin saturation values increased in group B but remained significantly lower in both groups A and B compared to group C. Ferritin values increased in group B and were significantly different from group A at follow-up (Table 2).
- Group B moms had significantly lower scores on the EPDS, Perceived Stress, and Digit Symbol tasks at 9 months when compared to the moms in Groups A and C indicating that anemic moms who received iron had less depression and less stress than the control and anemic moms receiving placebo (Table 3).
- Scores on the Ravens task improved significantly in the group B moms and were no different from controls (group C) at 9 months indicating better cognitive performance by moms receiving supplements than moms receiving placebo (Table 3).
- Correlational analysis of the behavioral variables with iron status variables revealed that scores on the Raven's task were significantly correlated with Hb at 10 weeks as well as 9 months. At 9 months, they were also correlated with MCV and TfSat. Scores on the STAI, perceived stress, and EPDS were significantly correlated with Hb and MCV at 9 months. TfSat was also correlated with perceived stress scores at 9 months. Scores on the Digit Symbol were correlated with MCV at 9 months (Table 4).
- Dietary recalls performed at the 7.5 month visit revealed no significant differences in dietary intake patterns across groups so overall sample data are shown. The diets were generally inadequate in energy, iron, calcium, phosphorous, zinc, vitamins A, C, D, E, thiamin, riboflavin and nicotinate. They were adequate in protein, magnesium, folate, and B-12 (Table 5).

Study 2

- CN subjects had significantly different values from the ID and IDA subjects for every hematology variable measured at baseline. ID subjects differed from IDA subjects with respect to TfR, Hb, and Hct at baseline (Table 6).
- Two of the tasks assessing memory (PR, ST) showed an association with iron status variables (Figure 1, Table 7a) while one of the memory tasks (RC) did not (Table 7a).
- Two out of the 4 attention tasks (TT, RT) showed an association with iron status variables (Figure 2, Table 7b).
- The learning tasks (LR, PM) showed an association with iron status variables (Figure 3, Table 7c).
- For the emotional variables measured, depression (BDI) showed no association with iron. However, iron had an effect on the scores of both the STAI and STAS (Figure 4, Table 7d).

Table 2: Maternal hematological and iron status variables at 10 weeks and 9 months

Group	Hb (g/dL)		MCV (fL)		TfSat (%)		Ft (ng/mL)	
	10 wks	9 months	10 wks	9 months	10 wks	9 months	10 wks	9 months
A	10.9±0.7[a]	12.0±0.8[a*]	84.4±6.7[a]	86.1±5.6[a]	8.9±4.2[a]	12.9±7.0[a]	11.9±5.1[a]	17.1±13.9[a]
B	10.8±0.9[a]	12.9±0.8[a*]	87.0±7.6[a]	89.3±4.1[a]	8.4±4.3[a]	21.3±8.5[b*]	10.6±6.6[a]	33.8±19.8[b*]
C	13.6±0.5[b]	13.4±0.9[b]	90.7±12.4[a]	91.7±4.4[a]	27.4±10.4[b]	28.6±11.6c	56.0±28[b]	48.4±33.6[b]

*Significantly different from baseline
Differing superscripts within a column represent significantly different values (p<0.05)

Table 3: Scores on cognitive and behavioral variables at 10 weeks and 9 months

Group	EPDS		STAI		Perceived Stress		Ravens		Digit Symbol	
	10 wks	9 months	10 wks	9 months	10 wks	9 months	10 wks	9 months	10 wks	9 months
A	2.4+0.4[a]	2.9±0.5[a]	27.9+1.0[a]	27.6±0.1[a]	12.4±0.7[a]	17.2±1.1[a*]	16.6±0.6[a]	16.7±1[a]	7.0±0.2[a]	6.3±0.5[a]
B	2.5±0.3[a]	2.1±0.3[b]	27.5±1.0[a]	27.9±0.1[a]	16.5±1.0[a]	15.7±1.2[b]	15.8±0.6[a]	20.4±1[b*]	9.9±0.2[b]	6.1±0.3[b*]
C	3.1±0.4[a]	3.3±0.5[a]	27.2±0.9[a]	28.6±0.2[a]	15.3±0.8[a]	19.1±1[a*]	18.1±0.7[a]	20.3±1[b*]	6.5±0.2[a]	6.8±0.6[c]

*Significantly different from baseline
Differing superscripts within a column represent significantly different values (p<0.05)

Table 4: Simple Pearson product moment correlations of behavioral variables with iron status variables at 10 weeks and 9 months

	Hb		MCV		TfSat	
	10 weeks	9 months	10 weeks	9 months	10 weeks	9 months
STAI	ns	r =0.6 p<0.001	ns	r =0.5 p<0.001	ns	ns
Perceived Stress	ns	r =0.4 p=0.001	ns	r =0.3 p=0.005	ns	r =0.3 p=0.004
Digit Symbol	ns	ns	ns	r =0.3 p=0.019	ns	ns
EPDS	ns	r =-0.3 p=0.004	ns	r =-0.3 p=0.008	ns	ns
Ravens	r=0.2 p=0.03	r=0.6 p<0.001	ns	r =0.4 p<0.001	ns	ns r =0.2 p=0.050

Table 5: Nutrient Intake as a Percentage of the South African RDAs

	Mean	Std	Median	Min	Max
ENERGY	65.01	28.5	61.99	14.58	195.37
PROTEIN	105.17	51.7	101.28	13.73	285.84
CALCIUM	31.52	30.01	23.39	2.07	198.43
IRON	54.05	39.11	46.77	7.27	304.26
MAGNESIUM	94.03	49.19	90.04	19.66	295.43
PHOSPHOROUS	77.21	44.37	67.15	10.9	330.27
ZINC	56.28	28.23	53.04	7.61	181.81
VITAMIN A	78.46	107.6	24.08	0	435.18
THIAMIN	73.34	38.02	68.14	17.23	239.27
RIBOFLAVIN	46.6	37.64	35.31	6.46	217.35
NICOTINIC ACID	61.43	34.56	55.47	7.3	170.27
VITAMIN B6	48.5	24.92	46.97	11.14	123.35
FOLIC ACID	133.73	102.68	108.28	13.25	508.42
VITAMIN B12	101.2	281.98	25	0	2367
VITAMIN C	34.42	43.21	21.42	0	239.83
VITAMIN D	25.38	44.56	5	0	165.15
VITAMIN E	75.19	68.02	58.12	2.81	287.75

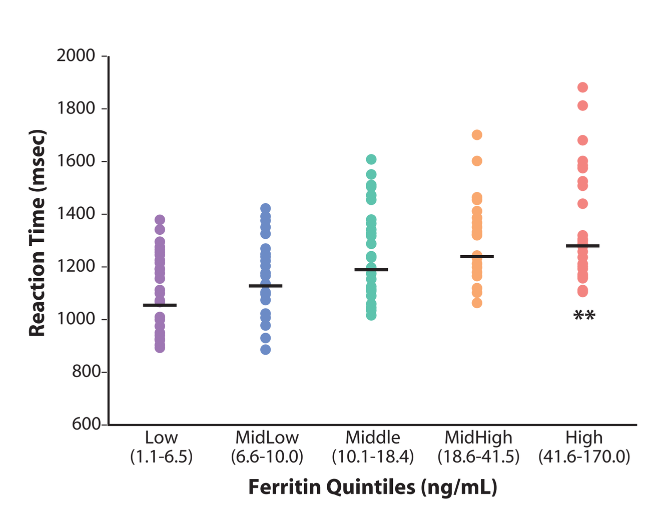
Table 6: Hematological parameters of young women at baseline

	Iron (μg/dL)	TIBC (μg/dL)	TfSat (%)	Ft (ng/mL)	TfR (μg/mL)	Hb (g/dL)	Hct (%)
CN (n=55)	121.3 ± 41.5[a]	387.9 ± 68.1[a]	32 ± 11[a]	49.8 ± 30.1[a]	4.0 ± 1.5[a]	13.8 ± 0.9[a]	42 ± 3[a]
ID (n=90)	101.0 ± 46.1[b]	460.7 ± 144.9[b]	23 ± 11[b]	11.3 ± 8.2[b]	5.6 ± 2.2[b]	13.3 ± 0.8[b]	40 ± 3[b]
IDA (n=38)	86.1 ± 53.1[b]	474.5 ± 105.0[b]	18 ± 11[b]	14.4 ± 15.9[b]	7.9 ± 4[c]	11.3 ± 0.5[c]	35 ± 2[c]

Differing superscripts within a column represent significantly different values (p ≤ 0.05)

Figure 1: Memory tasks

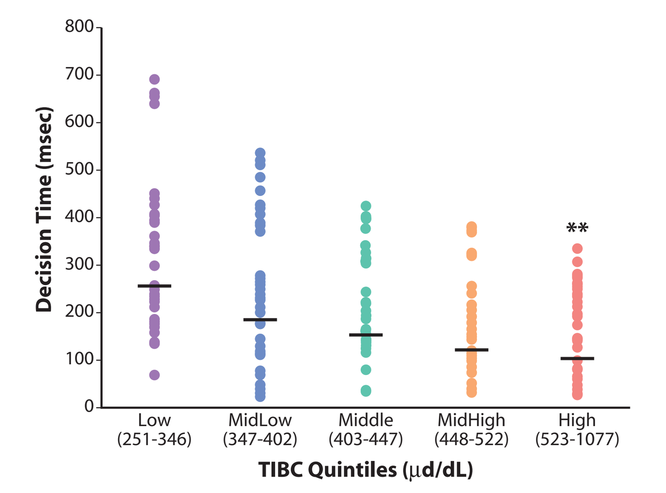
1A: Reaction time on the Probed Recall Task for young women at baseline arranged by ferritin levels



** Significantly different from low group (p ≤ 0.07)

Figure 2: Attention tasks

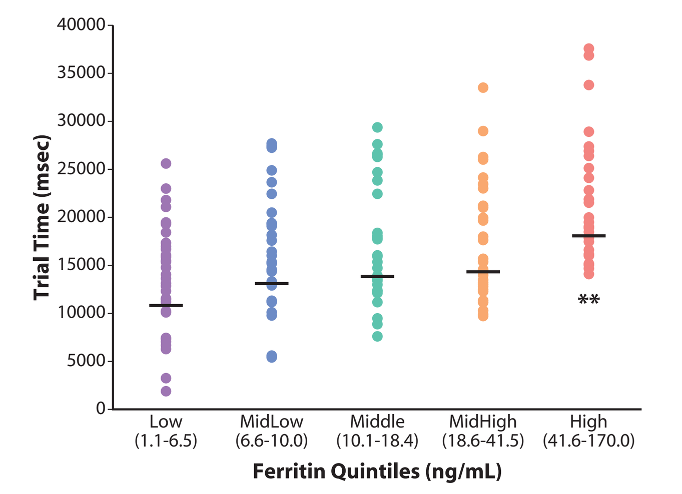
Decision time on the Tachistoscopic Threshold Test for young women at baseline arranged by TIBC levels



** Significantly different from low group (p ≤ 0.05)

Figure 3: Learning tasks

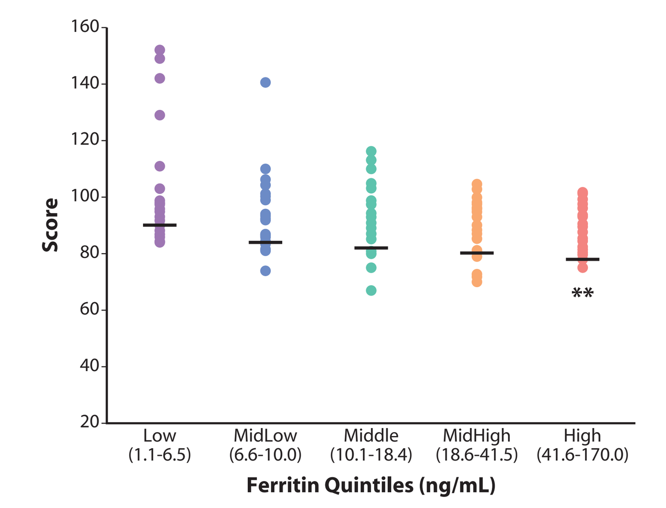
Trial time on the Progressive Matrices Task for young women at baseline arranged by ferritin levels



** Significantly different from low group (p ≤ 0.05)

Figure 4: Emotional variables

Score on the State-Trait Anxiety Inventory for young women at baseline arranged by ferritin levels



** Significantly different from low group (p ≤ 0.05)

Table 7: Significant associations between iron status parameters and cognitive/emotional variables for young women at baseline testing

7A: Memory Tasks

	Probed Recall		Sternberg Search			Recognition Memory			
	RT	TT	DT	MT	TT	RT	DT	MT	TT
Iron (μg/dL)		X		X					
TIBC (μg/dL)	X	X			X	X	X		
TfSat (%)	X	X		X				~	
Ft (ng/mL)	~	X			~				
TfR (μg/mL)		X		X	X	~			X
Hb (g/dL)				X					
Hct (%)				~					

7B: Attention Tasks

	Tachistoscopic Threshold			Reaction Time			Stimulus Discrimination			Digit Symbol
	DT	MT	TT	DT	MT	TT	DT	MT	TT	Score
Iron (μg/dL)					~					
TIBC (μg/dL)	X									
TfSat (%)		~								
Ft (ng/mL)					X					
TfR (μg/mL)	X	~			X					
Hb (g/dL)										
Hct (%)										

7C: Learning Tasks

	Learning		Progressive Matrices	
	RT	TT	RT	TT
Iron (μg/dL)				
TIBC (μg/dL)				
TfSat (%)				
Ft (ng/mL)			~	X
TfR (μg/mL)				X
Hb (g/dL)				
Hct (%)				

7D: Emotional Variables

	BDI	STAI	STAS
	Score	Score	Score
Iron (μg/dL)		X	
TIBC (μg/dL)		X	X
TfSat (%)		~	~
Ft (ng/mL)		X	X
TfR (μg/mL)			
Hb (g/dL)			
Hct (%)		X	X

RT=Reaction Time
TT=Trial Time
DT=Decision Time
MT=Movement Time
X = significant at 0.05 level
~ = significant at 0.07 level

Conclusions:

- Iron status is related to performance on attentional, memory, and learning tasks in young women with iron stores (Ft levels) having a stronger affect on these variables than moderate anemia (Hb level)
- Iron status is also related to behavioral "affect" in young women such that women with lower iron stores (Ft) have increased anxiety, depression, and anger levels
- Women in vastly different social-economic, cultural, and social settings show significant relationships between iron status and cognitive and behavioral variables. This robust finding is quite significant given the estimates of iron deficiency in the world's young women.

Implication:

The results of this data imply that cognitive and emotional variables are altered in young women as a result of iron deficiency even in the absence of anemia. These data are in agreement with those published by Bruner et al. (10) who showed that iron had an impact on verbal learning and memory in iron deficient non-anemic adolescent females.

References:

1. World Health Organization. The prevalence of anemia in Women: A tabulation of available information (2nd ed.). WHO/MCH/MSM/92.2, 1992.
2. International Center for Research on Women Report, prepared by K Kurtz and C Johnson-Welch, USAID publication, 1994.
3. Lozoff B, Jimenez E, Wolf AW. Long-term developmental outcome of infants with iron deficiency. N Engl J Med 1991;325:687–694.
4. Walter T, de Andraca I, Chadud P, Perales CG. Iron deficiency anemia: adverse effects on infant psychomotor development. Pediatrics 1989; 84:7–17.
5. Pollit E. Behavioural effects of iron deficiency in childhood. Am J Clin Nutr 1989; 50 (suppl): 666–667.
6. Aukett MA, Parks YA, Scott PH, Wharton BA. Treatment with iron increases weight gain and psychomotor development. Arch Dis Child 1986; 61,849–857.
7. Groner JA, Holtzman NA, Charney E, et al. A randomized trial of oral iron on tests of short-term memory and attention span in young pregnant women. J Adolesc Health Care 7:44–48, 1986.
8. Ballin A, Berar M, Rubinstein U, et al. Iron state in the female adolescent. Am J Dis Childhood 146:803–805, 1992.
9. Seshadri S, Gopaldas T. Impact of iron supplementation on cognitive functions in preschool and school aged children: the Indian experience. Am J Clin Nutr 50:675–686, 1989.
10. Bruner AB, Joffe A, Duggan AK, Casella F, Brandt J.† Randomized study of cognitive effects of iron supplementation in non-anemic iron-deficient adolescent girls.† Lancet 348:992–996, 1996.
11. Dallman PR. Manifestations of iron deficiency. Seminars in Hematology 19:19–30, 1982.