Rapid growth is a dominant predictor of hepcidin suppression and declining ferritin in Gambian infants

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 doi:10.3324/haematol.2018.210146

Received: October 25, 2018.

Accepted: January 31, 2019.

Pre-published: February 7, 2019.

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Supplemental Information

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Running Title: Rapid growth and hepcidin suppression in infancy

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Supplemental Methods

Cohorts

We obtained biochemical, anthropometric and infection data at serial timepoints from two rural birth-cohort studies in The Gambia, West Africa:

- *VPM study*: The Vaccination and Paediatric Microbiome (VPM) study comprised 120 newborns including three sets of twins recruited sequentially at birth to avoid selection bias; biochemical data were available from plasma samples taken at birth (cord blood), and at 2, 5 and 12 months of age from N=114 infants. Weaning data were also collected from this cohort. This study was conducted between March 2013 and September 2015 in the Western Region of The Gambia. The majority of villagers belong to the Jola, Mandinka and Fula ethnic groups, and most are subsistence farmers growing maize, millet and groundnuts.
- *VA study*: A vitamin A supplementation randomised controlled trial conducted in the West Kiang Region between September 2001 and October 2004 (1); biochemical data were available from plasma samples taken at birth (cord blood), and at 2, 5, 9 and 12 months of age from N=193 infants. Ethnicity data was not available but the majority of individuals in this area are Mandinka. In this study, no significant effect of vitamin A intervention was found; consequently, we handled data from each intervention arm as one group in the analyses presented here.

Infants with prematurity (<37 weeks), congenital birth defects, or severe postpartum complications were excluded. Anthropometric data were obtained by trained fieldworkers. Data on breastfeeding practice (VPM only) and recent infections were obtained by questionnaire. None of the infants in either VPM or VA study were administered iron-containing formulations as part of the study and these were not programmatically administered in their respective locations at that time. However, we cannot exclude that participants took iron-containing supplements, breast-milk substitutes or fortified complementary diets during the study period. Characteristics of the cohorts are given in **Supplemental Table 1**.

Laboratory analysis

Full blood counts including hemoglobin (Hb) concentrations (VA only) were obtained using a Medonic CA620/530 automated analyser (Boule Medical AB). Ferritin, plasma iron, soluble transferrin receptor (sTfR), transferrin, alpha(1)-acid glycoprotein (AGP) and C-reactive protein (CRP) concentrations were measured in archived (-80ºC) plasma samples using a fully automated analyser (Cobas Integra 400plus, Roche). Hepcidin was measured using the Hepcidin-25 (human) EIA Kit (Bachem/Peninsula Laboratories), as previously described (2). Lower limits of detection (LODs) for hepcidin measurement were estimated for each study as the hepcidin value corresponding to 3 standard deviations below the mean hepcidin blank OD450 for the set of ELISAs that contributed to each study, adjusted for dilution factors (depending on study and dilution, this corresponded to LOD = 0.4, 0.5, 0.8 or 1.0 ng/mL). LODs

for other analytes were taken from the assay manuals for Cobas tests: 10 µg/L for ferritin; 1.0 mg/L for CRP; 0.9 µmol/L for plasma iron; and 0.1 g/L for AGP.

Definitions

Anthropometric Z-scores using the WHO child growth standards were generated using the STATA package *zscore06* (3). Wet season was defined as July-October. Weaning was classified as the first recorded occurrence of any type of feeding other than exclusive breastfeeding. A child was classified as positive for recent infection if occurrence of any of the following were recorded within the previous 4 weeks: ear infection, chest infection, meningitis/sepsis, or other symptoms associated with infection (including fever, diarrhea, vomiting), or if antibiotics were administered within the previous 2 weeks (VPM); or diarrhea, vomiting, fever, cough or clinic attendance (VA). As previously described (2), iron deficiency (ID) was defined as ferritin <12 µg/L or ferritin <30µg/L if CRP >5 mg/L; anemia was defined as Hb <11 g/dL. Inflammation was defined as CRP >5 mg/L. Iron deficiency anemia (IDA) was defined as anemia in the presence of ID.

Statistics

Handling of below Limit of Detection (LOD) data

Data returned as <LOD were randomly allocated values between 0 and LOD according to beta distributions consistent with the distribution of the data above the truncation resulting from the LOD.

Multiple Imputation

In datasets in which data are missing, population parameter estimates (e.g. means, variances, etc) are at risk of bias, depending on why data are missing: only when data are missing completely at random is there no risk of bias (4, 5). Furthermore, when original data are missing, a large proportion of participant observations may be excluded leading to a loss of precision and power. Multiple imputation is a widely used approach for overcoming this risk (4, 5). This approach generates multiple datasets in which, in cases where data are missing, plausible values are sampled from their predictive distribution based on the characteristics of all of the other observed variables included in the imputation model; analysis results from each of these multiple imputed datasets are then appropriately combined: this aims to represent the likely population structure of the dataset as a whole (i.e. as if there was no missing data in the whole dataset). Thus, the aim is not to obtain specific individual missing values themselves but to represent the observed data repeatedly (hence "multiple" imputation) with plausible values for missing data such that it can be analysed as a complete dataset with unbiased parameter estimates. The fact that *multiple* imputed datasets are generated highlights that the main aim is not to simulate individual missing datapoints.

Given the challenges of collecting infant samples in LMIC settings and limited available sample volumes, data were missing for certain individuals / timepoints / parameters in our cohorts (**Supplemental Table 2**). To address the potential bias that may arise when deriving parameter estimates in the presence of missing data (4, 5), we implemented multiple imputation by chained equations (MICE) (assuming data 'missing at random') to generate 100 independent datasets with missing data imputed after 300 iterations, using R software (6). Infant IDs were included in the imputation model as fixed effects to account for clustering. Imputed datasets were analysed and estimates were then pooled using Rubin's rules (7). Continuous variables were $\log_{10}$-transformed prior to multiple imputation. Imputation models included variables hepcidin, ferritin, plasma iron, sTfR, transferrin (VPM only), CRP, AGP, Hb (VA only), weight, head circumference, length, weaning status (VPM only), infection status, season, and month, and were stratified by sex and birthweight (using a cutoff of WHO Weight-for-age Z-score at birth of -0.5 (higher birthweight WAZ > -0.5; lower birthweight WAZ <= -0.5), which corresponds approximately to the median birthweight across the two cohorts combined); sex and birthweight were fully observed in both cohorts (no missing data). Convergence diagnostics of multiple imputation models were satisfactory; diagnostic results are available upon request. Derivative measures (weight-for-age z-scores, iron deficiency, anemia, iron deficiency anemia and inflammation status) were generated post-imputation. Subsequent analyses were performed on both imputed datasets and original pre-imputation datasets (i.e. with missing data); the latter are shown in Supplemental Information: Appendix.

Cross-sectional analyses

Pearson correlation coefficients for univariate associations of parameters with hepcidin and ferritin were estimated at ages 5 and 12 months. Multivariate models were then constructed, considering parameters that returned $p<0.2$ in univariate analysis; the following parameters expected to be highly co-linear with other parameters were omitted: transferrin (VPM only, co-linear with hepcidin and ferritin); AGP (correlated with CRP). Seemingly Unrelated Regression analysis(8), which enables simultaneous modelling of correlated outcomes, was used to investigate simultaneous effects on outcome variables hepcidin and ferritin. Besides being associated with smaller maternal iron endowment, lower birthweight can also be associated with compensatory increased growth rate during the first few months of life ("catch-up growth") (9, 10). We therefore used weight-for-age Z-score at birth as an instrumental variable in estimating the effect of weight gain on hepcidin and ferritin: this removes the effect of any association between birthweight and weight gain, enabling evaluation of the relationship between weight gain and hepcidin/ferritin irrespective of birthweight.

Longitudinal panel analyses

Utilising the longitudinal structure of the datasets, we fitted panel fixed effects models with Driscoll-Kraay standard errors (11) estimated using Stata command *xtscc* (st0128) (12, 13). Fixed effects models

enable investigation of how within-infant changes in time-variant explanatory variables over time predict changes in outcome variables - hepcidin and ferritin - addressing any confounding induced by time-invariant characteristics (e.g. sex, genotype, ethnicity), whether measured or unmeasured. Driscoll-Kraay standard errors are robust to heteroskedasticity, auto-correlation and cross-sectional dependence. Hepcidin and ferritin were analysed simultaneously as seemingly unrelated variables, as in Blackwell *et al* (12). To enable comparison of relative effect sizes, for each of the 100 imputed datasets, we standardised all variables for each infant for each variable using the formula $((value_{infant} - mean_{all\text{-}infants}) / standard\ deviation_{all\text{-}infants})$; we then pooled standardised imputed datasets and refitted fixed effects models as described above. Forest plots were then generated to visualise relative effect sizes.

Supplemental Tables

Supplemental Table 1: Baseline characteristics of the study populations

	VPM study		VA study	
Variables	Female	Male	Female	Male
Sex, n (%)	65 (57.0)	49 (43.0)	96 (49.7)	97 (50.3)
Ethnicity, n (%)				
Jola	45 (69.2)	32 (65.3)	N/A	N/A
Mandinka	14 (21.5)	12 (24.5)	N/A	N/A
Other	6 (9.2)	5 (10.2)	N/A	N/A
Birth weight, median (IQR)	3.1 (2.9-3.4)	3.2 (3.0-3.5)	2.93 (2.69-3.22)	3.05 (2.74-3.32)

Supplemental Table 2: Level of missing data and summary statistics of time-varying variables by time points for (A) VPM and (B) VA cohorts.

A. VPM cohort

	VPM study (N=114)			
Variable	**Month 0**	**Month 2**	**Month 5**	**Month 12**
Hepcidin (ng/mL)				
Missing, n (%)	24 (21.1)	8 (7.2)	7 (6.14)	5 (4.4)
Median (Q1-Q3)	46.0 (31.3-55.1)	47.9 (34.8-63.3)	24.2 (11.4-39.7)	11.7 (2.7-33.2)
Ferritin (µg/L)				
Missing, n (%)	5 (4.4)	5 (4.4)	7 (6.1)	4 (3.5)
Median (Q1-Q3)	191.4 (133.1-266.3)	201.2 (138.8-331.5)	59.4 (28.3-87.8)	11.2 (3.5-27.3)
sTfR (mg/L)				
Missing, n (%)	5 (4.4)	4 (3.5)	7 (6.1)	4 (3.5)
Median (Q1-Q3)	6.2 (5.0-7.5)	3.1 (2.6-3.8)	5.9 (4.9-6.7)	7.1 (5.6-8.9)
Plasma iron (µmol/L)				
Missing, n (%)	5 (4.4)	4 (3.5)	7 (6.1)	4 (3.5)
Median (Q1-Q3)	16.0 (12.7-18.7)	8.7 (6.6-11.6)	1.5 (0.5-3.8)	1.0 (0.43-3.3)
Transferrin (g/L)				
Missing, n (%)	5 (4.4)	4 (3.5)	7 (6.1)	4 (3.5)
Median (Q1-Q3)	2.0 (1.8-2.2)	2.3 (2.0-2.5)	2.8 (2.5-3.2)	3.2 (2.7-3.6)
CRP (mg/L)				
Missing, n (%)	5 (4.4)	4 (3.5)	7 (6.1)	4 (3.5)
Median (Q1-Q3)	1.0 (0.3-1.3)	1.5 (1.3-2.2)	3.1 (2.0-6.2)	1.9 (0.9-4.0)
AGP (g/L)				
Missing, n (%)	5 (4.4)	4 (3.5)	7 (6.1)	6 (5.3)
Median (Q1-Q3)	0.2 (0.2-0.3)	0.7 (0.5-0.9)	1.2 (1.0-1.5)	1.3 (1.0-1.6)
Weight (Kg)				
Missing, n (%)	0 (0)	2 (1.8)	5 (4.4)	3 (2.6)
Median (Q1-Q3)	3.2 (3.0-3.4)	5.1 (4.6-5.5)	6.8 (6.2-7.3)	8.3 (7.5-8.9)
Head circumference (cm)				
Missing, n (%)	11 (9.7)	1 (0.9)	5 (4.4)	3 (2.6)
Median (Q1-Q3)	34.0 (33.0-35.0)	38.5 (38.0-39.3)	41.5 (40.5-42.1)	44.7 (43.5-45.5)
Length (cm)				
Missing, n (%)	11 (9.7)	1 (0.9)	5 (4.4)	3 (2.6)
Median (Q1-Q3)	48 (46-50)	57 (55-59)	64 (62-66)	72 (70-73)
Season at visit, n (%)				
Dry	69 (60.5)	42 (36.8)	56 (49.1)	90 (79.0)
Wet	45 (39.5)	72 (63.1)	58 (50.9)	24 (21.1)
Missing	0 (0)	0 (0)	0 (0)	0 (0)
Weaning, n (%)				
Yes	0 (0)	1 (0.9)	18 (15.8)	111 (97.4)
No	114 (100)	112 (93.3)	93 (77.5)	0 (0.0)
Missing	0 (0)	1 (0.9)	3 (2.6)	3 (2.6)
Infection, n (%)				
Yes	0 (0)	11 (9.7)	12 (10.5)	48 (42.1)
No	97 (85.1)	94 (82.4)	94 (82.4)	62 (54.4)
Missing	17 (14.9)	9 (7.9)	8 (7.0)	4 (3.5)

B. VA cohort

	VA study (N=193)				
Variable	**Month 0**	**Month 2**	**Month 5**	**Month 9**	**Month 12**
Hepcidin (ng/mL)					
Missing, n (%)	77 (39.9)	34 (17.6)	53 (27.5)	32 (16.6)	25 (13.0)
Median (Q1-Q3)	41.9 (26.3-56.6)	51.0 (32.6-82.1)	22.2 (9.3-46.6)	10.5 (2.5-32.3)	6.1 (2.3-17.5)
Ferritin (µg/L)					
Missing, n (%)	104 (53.9)	114 (59.1)	100 (51.8)	45 (23.3)	31 (16.1)
Median (Q1-Q3)	224.4 (142.1-303.3)	282.6 (148.9-381.9)	31.5 (13.8-59.5)	27.0 (12.8-47.0)	21.6 (9.5-35.3)
sTfR (mg/L)					
Missing, n (%)	118 (61.1)	146 (75.7)	138 (71.5)	46 (23.8)	52 (26.9)
Median (Q1-Q3)	5.6 (4.7-7.0)	3.7 (2.8-4.6)	6.4 (5.5-8.3)	7.4 (5.9-9.8)	7.2 (5.8-9.5)
Plasma iron (µmol/L)					
Missing, n (%)	126 (65.3)	158 (81.2)	163 (84.5)	63 (32.6)	94 (48.7)
Median (Q1-Q3)	18.8 (15.4-22.3)	8.0 (3.8-10.7)	2.3 (1.8-5.1)	4.2 (2.5-7.0)	3.2 (1.6-5.5)
CRP (mg/L)					
Missing, n (%)	10 (5.2)	38 (19.7)	23 (11.9)	29 (15.0)	60 (31.1)
Median (Q1-Q3)	0.5 (0.2-0.9)	0.9 (0.2-1.7)	1.4 (0.7-3.8)	3.1 (1.1-6.8)	2.5 (1.1-6.8)
AGP (g/L)					
Missing, n (%)	11 (5.7)	22 (11.4)	13 (6.7)	11 (5.7)	58 (30.1)
Median (Q1-Q3)	0.2 (0.1-0.2)	0.7 (0.5-0.9)	0.9 (0.8-1.2)	1.2 (0.9-1.5)	1.2 (0.9-1.5)
Hemoglobin (g/dL)					
Missing, n (%)	4 (2.1)	5 (2.6)	7 (3.6)	11 (5.7)	10 (5.2)
Median (Q1-Q3)	13.7 (12.4-14.6)	11.1 (10.3-12.0)	10.7 (10.1-11.5)	10.2 (9.4-10.8)	9.8 (8.9-10.5)
Weight (Kg)					
Missing, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Median (Q1-Q3)	3.0 (2.7-3.3)	4.8 (4.4-5.3)	6.7 (6.1-7.3)	7.6 (6.9-8.2)	8.0 (7.4-8.7)
Head circumference (cm)					
Missing, n (%)	0 (0)	1 (0.52)	0 (0)	0 (0)	0 (0)
Median (Q1-Q3)	34.5 (33.8-35.3)	38.3 (37.7-39.3)	41.6 (41.0-42.5)	43.6 (43.0-44.5)	44.5 (43.8-45.3)
Length (cm)					
Missing, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Median (Q1-Q3)	49.0 (47.8-50.4)	56.2 (55.0-57.7)	63.3 (61.9-64.9)	68.6 (66.8-70.2)	71.6 (70.0-73.5)
Season at visit, n (%)					
Dry	134 (69.4)	151 (78.2)	128 (66.3)	121 (62.7)	133 (68.9)
Wet	59 (30.6)	42 (21.8)	65 (33.7)	72 (37.3)	60 (31.1)
Missing	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Infection, n (%)					
Yes	0 (0)	147 (76.2)	159 (82.4)	172 (89.1)	148 (76.7)
No	193 (100)	46 (23.8)	34 (17.6)	21 (10.9)	45 (23.3)
Missing	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Supplemental Table 3: Prevalence of iron deficiency, inflammation, anemia and IDA by month of age

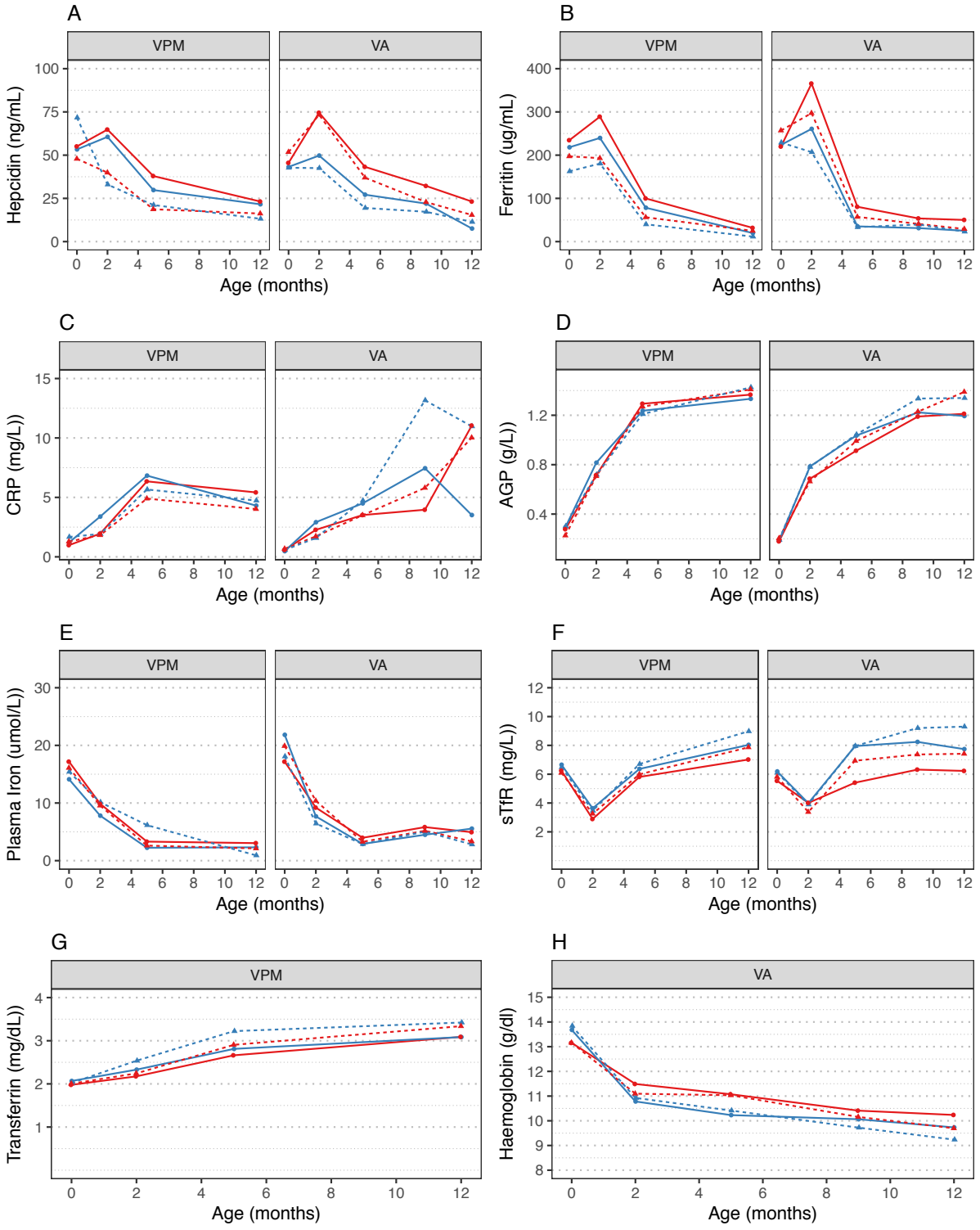
	VPM study		VA study	
	Female (n=65)	Male (n=49)	Female (n=96)	Male (n=97)
Iron deficient, % (95% CI)				
Month 5	9.1 (1.4 – 16.7)	30.6 (17.5 – 43.7)	24.2 (13.0 – 35.3)	41.8 (29.2 – 54.4)
Month 9	-	-	23.2 (13.9 – 32.4)	49.5 (38.6 – 60.4)
Month 12	67.7 (56.2 – 79.2)	77.8 (65.6 – 90.0)	36.4 (25.6 – 47.3)	45.3 (34.5 – 56.1)
Inflamed, % (95% CI)				
Month 2	5.6 (-0.4 – 11.7)	12.2 (2.9 – 21.6)	9.7 (2.4 – 17.0)	10.6 (3.8 – 17.4)
Month 5	39.2 (26.6 – 51.8)	30.6 (17.5 – 43.7)	16.7 (8.5 – 24.9)	25.7 (16.4 – 35.0)
Month 9	-	-	33.9 (23.5 – 44.3)	33.7 (23.6 – 43.7)
Month 12	20.0 (10.2 – 29.8)	26.6 (13.6 – 39.6)	42.4 (30.3 – 54.5)	33.4 (22.1 – 44.8)
Anemic, % (95% CI)				
Month 2	-	-	34.8 (25.1 – 44.6)	54.9 (44.8 – 65.0)
Month 5	-	-	43.8 (33.8 – 53.7)	70.3 (60.7 – 79.9)
Month 9	-	-	75.1 (66.3 – 84.0)	82.7 (74.7 – 90.7)
Month 12	-	-	86.5 (79.5 – 93.5)	93.1 (87.8 – 98.4)
IDA, % (95% CI)				
Month 5	-	-	15.3 (7.1 – 23.5)	31.6 (20.8 – 42.6)
Month 9	-	-	17.1 (8.7 – 25.4)	43.0 (32.3 – 53.6)
Month 12	-	-	32.1 (21.6 – 42.6)	43.0 (32.3 – 53.7)
Recent infection, % (95% CI)				
Month 2	6.6 (-0.1 – 13.3)	21.0 (8.6 – 33.5)	69.8 (60.5 – 79.0)	82.5 (74.9 – 90.1)
Month 5	16.1 (6.5 – 25.7)	13.2 (3.3 – 23.1)	82.3 (74.6 – 90.0)	82.5 (74.9 – 90.1)
Month 9	-	-	91.7 (86.1 – 97.2)	86.6 (79.8 – 93.4)
Month 12	46.4 (34.0 – 58.8)	40.9 (26.7 – 55.2)	79.2 (71.0 – 87.3)	74.2 (65.5 – 83.0)

Supplemental Table 4: 95% Confidence Interval estimates for the data presented in Figure 1. Data are stratified by sex and birthweight group (based on < or > WHO weight-for-age z-score (WAZ) -0.5); ll95 = lower limit of 95% confidence interval; ul95 = upper limit of 95% confidence interval. *(Please see end of Supplemental Information for Table.)*

Supplemental Information: Appendix

Equivalent analyses based on pre-imputation datasets.

Appendix Figure 1:



Appendix Figure 1: (Equivalent to Figure 1) Changes in hepcidin and iron/inflammatory biomarkers across the first year of life in Gambian infants. Plots summarize changes in (A) hepcidin, (B) ferritin, (C) C-reactive protein (CRP), (D) alpha(1)-acid Glycoprotein (AGP), (E) Plasma iron, (F) soluble transferrin receptor (sTfR), (G) transferrin (VPM only) and (H) hemoglobin (VA cohort) occurring across the first year of life in two cohorts of Gambian infants, VPM (left panels) and VA (right panels). Plots depict mean for cross-sectional data at each timepoint, stratifying by sex (male = blue; female = red) and birthweight group (WHO weight-for-age z-score -0.5: above = solid line, or below = dashed line), based on the pre-imputation datasets. 95% Confidence Intervals are available in Supplemental File "Figure1_CIs.xlsx".

Appendix Table 1 (Equivalent to Table 1): Cross-sectional univariate associations between hepcidin, ferritin, and explanatory variables in infants at 5 months of age: equivalent analysis based on original pre-imputation datasets.

MONTH 5 Sensitivity (pre-imputation data)		VPM study		VA study	
	Statistic	Hepcidin	Ferritin	Hepcidin	Ferritin
Ferritin	r	0.642		0.368	
	p	<0.001		<0.001	
	N	107		88	
Transferrin	r	-0.654	-0.617	ND	ND
	p	<0.001	<0.001	ND	ND
	N	107	107	ND	ND
Plasma iron	r	-0.124	-0.089	0.101	0.275
	p	0.203	0.36	0.603	0.141
	N	107	107	29	30
sTfR	r	-0.534	-0.332	-0.436	-0.538
	p	<0.001	0.001	0.001	<0.001
	N	107	107	54	55
Hb	r	ND	ND	0.045	0.169
	p	ND	ND	0.597	0.109
	N	ND	ND	134	91
CRP	r	0.32	0.243	0.153	-0.207
	p	0.001	0.018	0.078	0.052
	N	107	107	134	89
AGP	r	0.271	0.228	0.173	-0.05
	p	0.005	0.018	0.044	0.641
	N	107	107	136	90
Infection reported in previous 4 weeks	r	0.149	0.106	-0.021	-0.149
	p	0.137	0.289	0.805	0.155
	N	102	102	140	93
Sample taken in wet season (Jul-Oct)	r	0.221	0.026	0.074	-0.311
	p	0.022	0.79	0.385	0.002
	N	107	107	140	93
Sex	r	-0.134	-0.271	-0.251	-0.227
	p	0.169	0.005	0.003	0.029
	N	107	107	140	93
Weight-for-Age Z score at birth	r	0.388	0.201	0.247	0.105
	p	<0.001	0.038	0.003	0.317
	N	107	107	140	93
Weight	r	-0.161	-0.273	-0.275	0.194
	p	0.1	0.005	0.001	0.063
	N	105	105	140	93

Length	r	-0.033	-0.018	-0.196	-0.143
	p	0.735	0.856	0.02	0.171
	N	105	105	140	93
Head Circumference	r	0.121	0.022	-0.169	-0.197
	p	0.217	0.82	0.046	0.059
	N	105	105	140	93
Weight gain between 0-5 months	r	-0.455	-0.391	-0.441	-0.237
	p	<0.001	<0.001	<0.001	0.022
	N	105	105	140	93
Length gain between 0-5 months	r	-0.269	-0.171	-0.235	-0.097
	p	0.008	0.097	0.005	0.357
	N	95	95	140	93
Head Circ. gain between 0-5 months	r	-0.187	-0.201	0.289	-0.131
	p	0.069	0.051	0.001	0.212
	N	95	95	140	93

Footnote: Data based on pre-imputation datasets (i.e. with missing data). Infection was coded as "no infection=0" and "occurrence of infection=1'; Season was coded as "dry season (November-June)=0" and "wet season (July-October)=1"; Sex was coded as "female=0" and "male=1"; Head Circ. = Head Circumference. "r" = Pearson correlation coefficient; "p" = p-value; "N" = number of observations.

Appendix Table 2 (Equivalent to Table 2): Cross-sectional univariate associations between hepcidin, ferritin, and explanatory variables in infants at 12 months of age: equivalent analysis based on original pre-imputation datasets.

MONTH 12 Sensitivity (pre-imputation data)		VPM study		VA study	
	Statistic	**Hepcidin**	**Ferritin**	**Hepcidin**	**Ferritin**
Ferritin	r	0.47		0.548	
	p	0		0	
	N	109		155	
Transferrin	r	-0.504	-0.445	ND	ND
	p	0	0	ND	ND
	N	109	110	ND	ND
Plasma iron	r	0.085	0.061	0.075	0.187
	p	0.0377	0.527	0.468	0.064
	N	109	110	96	99
sTfR	r	-0.435	-0.221	-0.508	-0.502
	p	0	0.02	0	0
	N	109	110	134	138
Hb	r	ND	ND	0.185	0.211
	p	ND	ND	0.019	0.008
	N	ND	ND	161	156
CRP	r	0.298	0.198	0.385	0.356
	p	0.002	0.039	0	0
	N	109	110	119	116
AGP	r	0.323	0.258	0.327	0.426
	p	0.001	0.007	0	0
	N	107	108	120	116

Infection reported in previous 4 weeks	r	0.23	0.155	0.078	0.015
	p	0.017	0.109	0.313	0.848
	N	107	108	168	162
Sample taken in wet season (Jul-Oct)	r	0.19	0.048	0.251	0.207
	p	0.048	0.617	0.001	0.008
	N	109	110	168	162
Sex	r	-0.109	-0.172	-0.366	-0.237
	p	0.259	0.072	0	0.002
	N	109	110	168	162
Weight-for-Age Z score at birth	r	0.294	0.058	0.121	0.164
	p	0.002	0.541	0.119	0.037
	N	109	110	168	162
Weight	r	-0.071	-0.086	-0.249	-0.195
	p	0.469	0.375	0.001	0.013
	N	108	109	168	162
Length	r	-0.157	-0.225	0.245	-0.198
	p	0.106	0.0185	0.001	0.012
	N	108	109	168	162
Head Circumference	r	-0.04	-0.027	-0.132	-0.153
	p	0.682	0.78	0.088	0.052
	N	108	109	168	162
Weight gain between 0-12 months	r	-0.308	-0.11	-0.301	-0.305
	p	0.001	0.256	0	0
	N	108	109	168	162
Weight gain between 0-5 months	r	-0.388	-0.204	-0.258	-0.297
	p	0	0.037	0.001	0
	N	104	105	168	162
Weight gain between 5-12 months	r	0.102	0.133	-0.101	-0.031
	p	0.305	0.176	0.192	0.693
	N	104	100	168	162
Length gain between 0-12 months	r	-0.287	-0.169	-0.233	-0.265
	p	0.004	0.093	0.002	0.001
	N	99	100	168	162
Length gain between 0-5 months	r	-0.0244	-0.13	-0.224	-0.269
	p	0.017	0.203	0.004	0.001
	N	96	97	168	162
Length gain between 5-12 months	r	-0.086	-0.086	-0.046	-0.034
	p	0.383	0.381	0.559	0.668
	N	104	105	168	162
Head Circ. gain between 0-12 months	r	-0.374	-0.15	-0.107	-0.201
	p	0	0.137	0.167	0.011
	N	99	100	168	162
Head Circ. gain between 0-5 months	r	-0.199	-0.197	-0.123	-0.201
	p	0.052	0.053	0.113	0.01
	N	96	97	168	162
Head Circ. gain between 5-12 months	r	-0.158	0.075	0.007	-0.03
	p	0.108	0.449	0.933	0.0704
	N	104	105	168	162

Footnote: Data based on pre-imputation datasets (i.e. with missing data). Infection was coded as "no infection=0" and "occurrence of infection=1'; Season was coded as "dry season (November-June)=0" and "wet season (July-October)=1"; Sex was coded as "female=0" and "male=1"; Head Circ. = Head Circumference. "r" = Pearson correlation coefficient; "p" = p-value; "N" = number of observations.

Appendix Table 3 (Equivalent to Table 3): Cross-sectional multivariate associations between hepcidin, ferritin, and explanatory variables in infants at 5 months of age: equivalent analysis based on original pre-imputation datasets.

A. VPM – 5 months (data available for all model parameters from N=102 infants)

Overall p-value: *Hepcidin, p<0.0001 ; Ferritin, p<0.0001*; R-square: *Hepcidin = 0.39; Ferritin = 0.26.*

Variable (outcomes in **BOLD**)	Coefficient	95% CI	p-value
HEPCIDIN			
Plasma iron, µmol/L	-0.133	-0.242 – -0.024	0.017
sTfR, mg/L	-0.667	-1.470 – 0.135	0.103
CRP, mg/L	0.321	0.070 – 0.572	0.012
Infection in last 4 weeks	0.173	-0.063 – 0.410	0.151
Sex	-0.121	-0.292 – 0.050	0.165
Weight change (0-5 months), kg	-4.971	-7.548 – -2.394	<0.001
Season	0.256	0.105 – 0.407	0.001
FERRITIN			
sTfR, mg/L	-1.120	-2.118 – -0.122	0.028
CRP, mg/L	0.342	0.037 – 0.646	0.028
Sex	-0.241	-0.449 – -0.032	0.024
Weight change (0-5 months), kg	-1.985	-5.059 – 1.090	0.206

B. VA – 5 months (data available for all model parameters from N=28 infants)

Overall p-value: *Hepcidin, p=0.042 ; Ferritin, p=0.017*; R-square: *Hepcidin = 0.06; Ferritin = 0.21.*

Variable (outcomes in **BOLD**)	Coefficient	95% CI	p-value
HEPCIDIN			
sTfR, mg/L	-1.227	-3.225 – 0.772	0.229
CRP, mg/L	0.177	-0.147 – 0.501	0.284
Infection in last 4 weeks	0.131	-0.502 – 0.763	0.685
Weight change (0-5 months), kg	-8.130	-16.710 – 0.451	0.063
FERRITIN			
Plasma iron, µmol/L	0.159	-0.136 – 0.455	0.291
sTfR, mg/L	-1.838	-3.799 – 0.122	0.066
CRP, mg/L	0.142	-0.127 – 0.412	0.300
Hb, g/dL	-0.096	-5.605 – 5.413	0.973
Sex	-0.209	-0.558 – 0.140	0.241
Weight change (0-5 months), kg	2.131	-5.274 – 9.537	0.573

Footnote: The outcome variables hepcidin and ferritin were handled using Seemingly Unrelated Regressions, with WHO birth weight-for-age Z-score used as an instrument for weight change. Only variables with p<0.2 in univariate regressions were included in multivariable models, omitting correlated indices as described in Methods. Analysis based on pre-imputation datasets that included missing data; the number of observations with complete data available for the model is indicated above each table. Infection was coded as "no infection=0" and "occurrence of infection=1' as described in Supplementary Methods – note that definitions varied due to study design between VPM and VA cohorts; Season was coded as "dry season (November-June)=0" and "wet season (July-October)=1; "Sex was coded as "female=0" and "male=1".

Appendix Table 4 (Equivalent to Table 4): Cross-sectional multivariate associations between hepcidin, ferritin, and explanatory variables in infants at 12 months of age: equivalent analysis based on original pre-imputation datasets.

A. VPM – 12 months (data available for all model parameters from N=107 infants)

Overall p-value: *Hepcidin, p<0.0001 ; Ferritin, p=0.002*; R-square: *Hepcidin = 0.41; Ferritin = 0.13.*

Variable (outcomes in **BOLD**)	Coefficient	95% CI	p-value
HEPCIDIN			
sTfR, mg/L	-1.590	-2.322 – -0.858	<0.001
CRP, mg/L	0.233	0.128 – 0.337	<0.001
Infection in last 4 weeks	0.146	-0.059 – 0.352	0.163
Weight change (0-12 months), kg	-3.143	-5.498 – -0.787	0.009
Season	0.345	0.123 – 0.566	0.002
FERRITIN			
sTfR, mg/L	-1.288	-2.318 – -0.257	0.014
CRP, mg/L	0.167	0.001 – 0.334	0.049
Infection in last 4 weeks	0.238	-0.076 – 0.551	0.138
Sex	-0.240	-0.532 – 0.053	0.108

B. VA – 12 months (data available for all model parameters from N=91 infants)

Overall p-value: *Hepcidin, p<0.0001 ; Ferritin, p<0.0001*; R-square: *Hepcidin = 0.44; Ferritin = 0.24.*

Variable (outcomes in **BOLD**)	Coefficient	95% CI	p-value
HEPCIDIN			
sTfR, mg/L	-1.617	-2.672 – -0.562	0.003
CRP, mg/L	0.267	0.116 – 0.419	0.001
Hb, g/dL	-0.144	-3.798 – 3.509	0.938
Sex	-0.268	-0.512 – -0.024	0.031
Weight change (0-12 months), kg	-1.737	-6.286 – 2.811	0.454
Season	0.374	0.115 – 0.634	0.005
FERRITIN			
sTfR, mg/L	-1.153	-2.215 – -0.091	0.033
CRP, mg/L	0.214	0.061 – 0.367	0.006
Hb, g/dL	1.677	-2.001 – 5.355	0.371
Sex	-0.070	-0.315 – 0.176	0.579
Weight change (0-12 months), kg	0.458	-4.121 – 5.036	0.845
Season	0.274	0.013 – 0.535	0.040

Footnote: The outcome variables hepcidin and ferritin were handled using Seemingly Unrelated Regressions, with WHO birth weight-for-age Z-score used as an instrument for weight change. Only variables with p<0.2 in univariate regressions were included in multivariable models, omitting correlated indices as described in Methods. Analysis based on pre-imputation datasets that included missing data; the number of observations with complete data available for the model is indicated above each table. Infection was coded as "no infection=0" and "occurrence of infection=1' as described in Supplementary Methods – note that definitions varied due to study design between VPM and VA cohorts; Season was coded as "dry season (November-June)=0" and "wet season (July-October)=1; "Sex was coded as "female=0" and "male=1".

Appendix Table 5 (Equivalent to Table 5): The relative influence of time-variant factors on changes in hepcidin and iron biomarkers ferritin and transferrin over time during the first year of life in Gambian infants: Fixed effect models – equivalent analysis based on pre-imputation datasets – VPM cohort

Unstandardised: Overall p-value, p<0.0001; Within R-squared: 0.636

Standardised: Overall p-value, p<0.0001, Within R-squared = 0.610

Variable (outcomes in **BOLD**)	Coefficient (un-standardised)	95% CI (un-standardised)	**Coefficient (standardized)**	**95% CI (standardized)**	p-value
HEPCIDIN					
Season	0.115	0.036 – 0.194	**0.102**	**0.032 – 0.172**	0.005
Infection in last 4 weeks	0.219	0.191 – 0.246	**0.147**	**0.128 – 0.165**	0.001
Weaning	-0.079	-0.142 – -0.016	**-0.064**	**-0.115 – -0.013**	0.015
Plasma iron, µmol/L	-0.073	-0.118 – -0.029	**-0.010**	**-0.160 – -0.039**	0.001
sTfR, mg/L	-0.963	-1.080 – -0.846	**-0.330**	**-0.370 – -0.290**	<0.001
CRP, mg/L	0.102	0.051 – 0.153	**0.139**	**0.069 – 0.209**	<0.001
Weight, kg	-1.256	-1.420 – -1.092	**-0.380**	**-0.429 – -0.330**	<0.001
- lower birthweight females	*-0.600*	*-0.900 – -0.300*	***-0.181***	***-0.272 – -0.091***	*<0.001*
- lower birthweight males	*-1.072*	*-1.360 – -0.783*	***-0.324***	***-0.411 – -0.237***	*<0.001*
- higher birthweight males	*-0.319*	*-0.438 – -0.201*	***-0.096***	***-0.132 – -0.061***	*<0.001*
FERRITIN					
Season	0.103	0.044 – 0.162	**0.065**	**0.028 – 0.102**	0.001
Infection in last 4 weeks	0.076	0.028 – 0.124	**0.036**	**0.013 – 0.059**	0.002
Weaning	-0.436	-0.562 – -0.310	**-0.252**	**-0.324 – -0.179**	<0.001
Plasma iron, µmol/L	-0.053	-0.095 – -0.011	**-0.051**	**-0.093 – -0.010**	0.014
sTfR, mg/L	-1.120	-1.392 – -1.001	**-0.292**	**-0.339 – -0.244**	<0.001
CRP, mg/L	0.071	0.033 – 0.108	**0.069**	**0.032 – 0.105**	<0.001
Weight, kg	-1.793	-2.126 – -1.459	**-0.386**	**-0.458 – -0.314**	<0.001
- lower birthweight females	*-0.217*	*-0.537 – -0.103*	***-0.047***	***-0.116 – 0.022***	*0.182*
- lower birthweight males	*-0.625*	*-0.801 – -0.450*	***-0.135***	***-0.172 – -0.097***	*<0.001*
- higher birthweight males	*-0.868*	*-1.445 – -0.291*	***-0.187***	***-0.311 – -0.063***	*0.003*

Footnote: Data represent the analysis of pre-imputation. Unstandardized coefficients indicate the effect of a unit change over time of an explanatory variable on changes over time within a child in the outcome variables hepcidin and ferritin, which were handled using seemingly unrelated regression to account for strong correlations between outcome variables. Standardized coefficients indicate the effect of a change of one standard deviation of an explanatory variable over time on standard deviation of outcome variables over time within a child. Infection was coded as "no infection=0" and "occurrence of infection=1'; Season was coded as "dry season (November-June)=0" and "wet season (July-October)=1"; Sex was coded as "female=0" and "male=1". Interactions of weight change with birthweight group (above or below WHO weight-for-age z-score of -0.5) and sex were modelled with coefficients/p-values representing differences for weight change relative to higher birthweight females as reference group.

Appendix Table 6 (Equivalent to Table 6): The relative influence of time-variant factors on changes in hepcidin and iron biomarkers ferritin and transferrin over time during the first year of life in Gambian infants: Fixed effect models – equivalent analysis based on pre-imputation datasets – VA cohort

Unstandardised: Overall p-value, p<0.0001; Within R-squared = 0.612

Standardised: Overall p-value, p<0.0001, Within R-squared = 0.612

Variable (outcomes in **BOLD**)	Coeff.	95% CI	**Coefficient (standardized)**	**95% CI (standardized)**	**p-value**
HEPCIDIN					
Season	-0.060	-0.204 – 0.084	**-0.038**	**-0.128 – 0.053**	**0.415**
Infection in last 4 weeks	0.187	0.016 – 0.357	**0.121**	**0.010 – 0.231**	**0.032**
Plasma iron, µmol/L	-0.142	-0.270 – -0.014	**-0.106**	**-0.201 – -0.011**	**0.030**
sTfR, mg/L	-1.219	-1.498 – -0.939	**-0.280**	**-0.345 – -0.216**	**<0.001**
CRP, mg/L	0.156	0.073 – 0.240	**0.184**	**0.086 – 0.282**	**<0.001**
Hb, g/dL	1.082	-0.496 – 2.660	**0.113**	**-0.052 – 0.277**	**0.178**
Weight, kg	-1.959	-2.295 – -1.622	**-0.447**	**-0.524 – -0.370**	**<0.001**
- lower birthweight females	*-0.145*	*-0.358 – 0.067*	***-0.033***	***-0.082 – 0.015***	***0.179***
- lower birthweight males	*-0.230*	*-0.433 – -0.026*	***-0.052***	***-0.099 – -0.006***	***0.027***
- higher birthweight males	*-0.564*	*-1.018 – -0.111*	***-0.129***	***-0.232 – -0.025***	***0.015***
FERRITIN					
Season	-0.012	-0.091 – 0.066	**-0.008**	**-0.058 – 0.042**	**0.758**
Infection in last 4 weeks	0.212	0.108 – 0.316	**0.139**	**0.071 – 0.208**	**<0.001**
Plasma iron, µmol/L	0.050	0.013 – 0.086	**0.038**	**0.010 – 0.066**	**0.008**
sTfR, mg/L	-1.396	-1.741 – -1.051	**-0.327**	**-0.408 – -0.246**	**<0.001**
CRP, mg/L	0.051	0.002 – 0.101	**0.061**	**0.002 – 0.121**	**0.042**
Hb, g/dL	1.063	-0.068 – 2.195	**0.113**	**-0.007 – 0.233**	**0.065**
Weight, kg	-2.901	-3.557 – -2.245	**-0.674**	**-0.826 – -0.521**	**<0.001**
- lower birthweight females	*1.142*	*0.654 – 1.630*	***0.265***	***0.152 – 0.378***	***<0.001***
- lower birthweight males	*1.233*	*0.600 -1.866*	***0.286***	***0.139 – 0.433***	***<0.001***
- higher birthweight males	*0.529*	*-0.015 – 1.073*	***0.123***	***-0.004 – 0.249***	***0.057***

Footnote: Data represent the analysis of pre-imputation. Unstandardized coefficients indicate the effect of a unit change over time of an explanatory variable on changes over time within a child in the outcome variables hepcidin and ferritin, which were handled using seemingly unrelated regression to account for strong correlations between outcome variables. Standardized coefficients indicate the effect of a change of one standard deviation of an explanatory variable over time on standard deviation of outcome variables over time within a child. Infection was coded as "no infection=0" and "occurrence of infection=1'; Season was coded as "dry season (November-June)=0" and "wet season (July-October)=1"; Sex was coded as "female=0" and "male=1". Interactions of weight change with birthweight group (above or below WHO weight-for-age z-score of -0.5) and sex were modelled with coefficients/p-values representing differences for weight change relative to higher birthweight females as reference group.

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Supplemental Table 4: 95% Confidence Interval estimates for the data presented in Figure 1. Data are stratified by sex and birthweight group (based on < or > WHO weight-for-age z-score (WAZ) -0.5); ll95 = lower limit of 95% confidence interval; ul95 = upper limit of 95% confidence interval.

Cohort	Group	Month	Marker	Unit	Mean	ll95	ul95
VPM	Females, birth-WAZ<-0.5	0	Hepcidin	ng/mL	36.89	24.03	56.63
VPM	Females, birth-WAZ>-0.5	0	Hepcidin	ng/mL	39.54	30.45	51.33
VPM	Males, birth-WAZ<-0.5	0	Hepcidin	ng/mL	46.58	21.61	100.37
VPM	Males, birth-WAZ>-0.5	0	Hepcidin	ng/mL	42.67	29.14	62.48
VPM	Females, birth-WAZ<-0.5	2	Hepcidin	ng/mL	35.01	26.75	45.82
VPM	Females, birth-WAZ>-0.5	2	Hepcidin	ng/mL	56.74	44.84	71.79
VPM	Males, birth-WAZ<-0.5	2	Hepcidin	ng/mL	23.14	13.27	40.35
VPM	Males, birth-WAZ>-0.5	2	Hepcidin	ng/mL	50.55	40.40	63.25
VPM	Females, birth-WAZ<-0.5	5	Hepcidin	ng/mL	13.22	8.91	19.61
VPM	Females, birth-WAZ>-0.5	5	Hepcidin	ng/mL	28.41	20.24	39.88
VPM	Males, birth-WAZ<-0.5	5	Hepcidin	ng/mL	9.79	4.35	22.04
VPM	Males, birth-WAZ>-0.5	5	Hepcidin	ng/mL	19.61	12.96	29.67
VPM	Females, birth-WAZ<-0.5	12	Hepcidin	ng/mL	7.09	4.10	12.26
VPM	Females, birth-WAZ>-0.5	12	Hepcidin	ng/mL	12.75	8.39	19.38
VPM	Males, birth-WAZ<-0.5	12	Hepcidin	ng/mL	3.76	1.40	10.07
VPM	Males, birth-WAZ>-0.5	12	Hepcidin	ng/mL	11.01	6.69	18.12
VPM	Females, birth-WAZ<-0.5	0	Ferritin	µg/L	157.02	109.45	225.25
VPM	Females, birth-WAZ>-0.5	0	Ferritin	µg/L	205.07	172.97	243.13
VPM	Males, birth-WAZ<-0.5	0	Ferritin	µg/L	144.35	116.53	178.81
VPM	Males, birth-WAZ>-0.5	0	Ferritin	µg/L	205.48	152.07	277.66
VPM	Females, birth-WAZ<-0.5	2	Ferritin	µg/L	174.83	137.02	223.07
VPM	Females, birth-WAZ>-0.5	2	Ferritin	µg/L	247.67	196.95	311.45
VPM	Males, birth-WAZ<-0.5	2	Ferritin	µg/L	151.80	113.16	203.62
VPM	Males, birth-WAZ>-0.5	2	Ferritin	µg/L	199.11	158.89	249.51
VPM	Females, birth-WAZ<-0.5	5	Ferritin	µg/L	49.41	34.23	71.33
VPM	Females, birth-WAZ>-0.5	5	Ferritin	µg/L	76.63	56.59	103.76
VPM	Males, birth-WAZ<-0.5	5	Ferritin	µg/L	21.68	11.45	41.03
VPM	Males, birth-WAZ>-0.5	5	Ferritin	µg/L	35.72	17.51	72.86
VPM	Females, birth-WAZ<-0.5	12	Ferritin	µg/L	7.22	3.46	15.06
VPM	Females, birth-WAZ>-0.5	12	Ferritin	µg/L	14.19	8.44	23.88
VPM	Males, birth-WAZ<-0.5	12	Ferritin	µg/L	4.46	1.80	11.03
VPM	Males, birth-WAZ>-0.5	12	Ferritin	µg/L	6.10	2.59	14.36
VPM	Females, birth-WAZ<-0.5	0	Iron	µmol/L	14.51	9.83	21.40
VPM	Females, birth-WAZ>-0.5	0	Iron	µmol/L	16.11	14.14	18.37
VPM	Males, birth-WAZ<-0.5	0	Iron	µmol/L	13.22	9.68	18.04
VPM	Males, birth-WAZ>-0.5	0	Iron	µmol/L	13.80	10.34	18.42
VPM	Females, birth-WAZ<-0.5	2	Iron	µmol/L	8.28	6.31	10.87
VPM	Females, birth-WAZ>-0.5	2	Iron	µmol/L	9.32	7.38	11.76
VPM	Males, birth-WAZ<-0.5	2	Iron	µmol/L	9.46	7.92	11.29
VPM	Males, birth-WAZ>-0.5	2	Iron	µmol/L	6.47	5.02	8.35
VPM	Females, birth-WAZ<-0.5	5	Iron	µmol/L	0.98	0.44	2.17
VPM	Females, birth-WAZ>-0.5	5	Iron	µmol/L	1.60	0.97	2.66
VPM	Males, birth-WAZ<-0.5	5	Iron	µmol/L	0.57	0.20	1.61
VPM	Males, birth-WAZ>-0.5	5	Iron	µmol/L	1.25	0.79	1.98
VPM	Females, birth-WAZ<-0.5	12	Iron	µmol/L	0.81	0.41	1.61

VPM	Females, birth-WAZ>-0.5	12	Iron	µmol/L	1.44	0.91	2.28
VPM	Males, birth-WAZ<-0.5	12	Iron	µmol/L	0.83	0.44	1.55
VPM	Males, birth-WAZ>-0.5	12	Iron	µmol/L	0.71	0.29	1.77
VPM	Females, birth-WAZ<-0.5	0	sTfR	mg/L	6.15	5.47	6.92
VPM	Females, birth-WAZ>-0.5	0	sTfR	mg/L	5.89	5.28	6.57
VPM	Males, birth-WAZ<-0.5	0	sTfR	mg/L	6.25	5.50	7.10
VPM	Males, birth-WAZ>-0.5	0	sTfR	mg/L	6.31	5.63	7.07
VPM	Females, birth-WAZ<-0.5	2	sTfR	mg/L	3.17	2.84	3.54
VPM	Females, birth-WAZ>-0.5	2	sTfR	mg/L	2.78	2.54	3.05
VPM	Males, birth-WAZ<-0.5	2	sTfR	mg/L	3.35	2.96	3.79
VPM	Males, birth-WAZ>-0.5	2	sTfR	mg/L	3.49	3.14	3.87
VPM	Females, birth-WAZ<-0.5	5	sTfR	mg/L	5.86	5.35	6.41
VPM	Females, birth-WAZ>-0.5	5	sTfR	mg/L	5.56	5.01	6.17
VPM	Males, birth-WAZ<-0.5	5	sTfR	mg/L	6.54	5.89	7.26
VPM	Males, birth-WAZ>-0.5	5	sTfR	mg/L	5.96	5.26	6.76
VPM	Females, birth-WAZ<-0.5	12	sTfR	mg/L	7.55	6.71	8.48
VPM	Females, birth-WAZ>-0.5	12	sTfR	mg/L	6.59	5.93	7.33
VPM	Males, birth-WAZ<-0.5	12	sTfR	mg/L	8.31	6.99	9.88
VPM	Males, birth-WAZ>-0.5	12	sTfR	mg/L	7.32	6.35	8.45
VPM	Females, birth-WAZ<-0.5	0	CRP	mg/L	0.57	0.29	1.12
VPM	Females, birth-WAZ>-0.5	0	CRP	mg/L	0.36	0.18	0.74
VPM	Males, birth-WAZ<-0.5	0	CRP	mg/L	0.53	0.15	1.90
VPM	Males, birth-WAZ>-0.5	0	CRP	mg/L	0.67	0.39	1.16
VPM	Females, birth-WAZ<-0.5	2	CRP	mg/L	1.25	0.70	2.23
VPM	Females, birth-WAZ>-0.5	2	CRP	mg/L	1.31	0.84	2.05
VPM	Males, birth-WAZ<-0.5	2	CRP	mg/L	1.72	1.40	2.11
VPM	Males, birth-WAZ>-0.5	2	CRP	mg/L	1.94	1.33	2.83
VPM	Females, birth-WAZ<-0.5	5	CRP	mg/L	3.38	2.12	5.39
VPM	Females, birth-WAZ>-0.5	5	CRP	mg/L	4.49	2.86	7.05
VPM	Males, birth-WAZ<-0.5	5	CRP	mg/L	3.82	2.61	5.59
VPM	Males, birth-WAZ>-0.5	5	CRP	mg/L	4.00	2.91	5.49
VPM	Females, birth-WAZ<-0.5	12	CRP	mg/L	1.33	0.68	2.62
VPM	Females, birth-WAZ>-0.5	12	CRP	mg/L	1.54	0.83	2.86
VPM	Males, birth-WAZ<-0.5	12	CRP	mg/L	1.19	0.27	5.32
VPM	Males, birth-WAZ>-0.5	12	CRP	mg/L	1.65	0.74	3.70
VPM	Females, birth-WAZ<-0.5	0	AGP	g/L	0.21	0.18	0.25
VPM	Females, birth-WAZ>-0.5	0	AGP	g/L	0.26	0.23	0.29
VPM	Males, birth-WAZ<-0.5	0	AGP	g/L	0.26	0.21	0.33
VPM	Males, birth-WAZ>-0.5	0	AGP	g/L	0.26	0.21	0.31
VPM	Females, birth-WAZ<-0.5	2	AGP	g/L	0.66	0.57	0.77
VPM	Females, birth-WAZ>-0.5	2	AGP	g/L	0.67	0.60	0.75
VPM	Males, birth-WAZ<-0.5	2	AGP	g/L	0.66	0.55	0.81
VPM	Males, birth-WAZ>-0.5	2	AGP	g/L	0.75	0.64	0.88
VPM	Females, birth-WAZ<-0.5	5	AGP	g/L	1.21	1.05	1.39
VPM	Females, birth-WAZ>-0.5	5	AGP	g/L	1.21	1.07	1.38
VPM	Males, birth-WAZ<-0.5	5	AGP	g/L	1.13	0.95	1.36
VPM	Males, birth-WAZ>-0.5	5	AGP	g/L	1.19	1.07	1.31
VPM	Females, birth-WAZ<-0.5	12	AGP	g/L	1.36	1.23	1.51
VPM	Females, birth-WAZ>-0.5	12	AGP	g/L	1.26	1.12	1.42
VPM	Males, birth-WAZ<-0.5	12	AGP	g/L	1.30	1.01	1.67
VPM	Males, birth-WAZ>-0.5	12	AGP	g/L	1.26	1.11	1.43

VPM	Females, birth-WAZ<-0.5	0	Tf	g/L	1.95	1.80	2.11
VPM	Females, birth-WAZ>-0.5	0	Tf	g/L	1.95	1.86	2.05
VPM	Males, birth-WAZ<-0.5	0	Tf	g/L	1.98	1.80	2.18
VPM	Males, birth-WAZ>-0.5	0	Tf	g/L	2.03	1.89	2.17
VPM	Females, birth-WAZ<-0.5	2	Tf	g/L	2.23	2.13	2.34
VPM	Females, birth-WAZ>-0.5	2	Tf	g/L	2.17	2.05	2.28
VPM	Males, birth-WAZ<-0.5	2	Tf	g/L	2.50	2.32	2.70
VPM	Males, birth-WAZ>-0.5	2	Tf	g/L	2.29	2.12	2.46
VPM	Females, birth-WAZ<-0.5	5	Tf	g/L	2.88	2.73	3.04
VPM	Females, birth-WAZ>-0.5	5	Tf	g/L	2.62	2.46	2.78
VPM	Males, birth-WAZ<-0.5	5	Tf	g/L	3.18	2.95	3.43
VPM	Males, birth-WAZ>-0.5	5	Tf	g/L	2.75	2.55	2.97
VPM	Females, birth-WAZ<-0.5	12	Tf	g/L	3.29	3.08	3.52
VPM	Females, birth-WAZ>-0.5	12	Tf	g/L	3.04	2.87	3.22
VPM	Males, birth-WAZ<-0.5	12	Tf	g/L	3.34	3.09	3.61
VPM	Males, birth-WAZ>-0.5	12	Tf	g/L	3.03	2.82	3.26

Cohort	**Group**	**Month**	**Marker**	**Unit**	**Mean**	**ll95**	**ul95**
VA	Females, birth-WAZ<-0.5	0	Hepcidin	ng/µL	40.30	24.09	67.41
VA	Females, birth-WAZ>-0.5	0	Hepcidin	ng/µL	31.04	20.14	47.84
VA	Males, birth-WAZ<-0.5	0	Hepcidin	ng/µL	28.76	17.23	47.99
VA	Males, birth-WAZ>-0.5	0	Hepcidin	ng/µL	41.94	26.74	65.78
VA	Females, birth-WAZ<-0.5	2	Hepcidin	ng/µL	51.58	32.36	82.23
VA	Females, birth-WAZ>-0.5	2	Hepcidin	ng/µL	60.93	40.82	90.96
VA	Males, birth-WAZ<-0.5	2	Hepcidin	ng/µL	31.45	22.83	43.31
VA	Males, birth-WAZ>-0.5	2	Hepcidin	ng/µL	39.90	26.91	59.15
VA	Females, birth-WAZ<-0.5	5	Hepcidin	ng/µL	18.68	11.66	29.93
VA	Females, birth-WAZ>-0.5	5	Hepcidin	ng/µL	31.93	20.92	48.73
VA	Males, birth-WAZ<-0.5	5	Hepcidin	ng/µL	13.77	8.93	21.22
VA	Males, birth-WAZ>-0.5	5	Hepcidin	ng/µL	26.39	16.54	42.10
VA	Females, birth-WAZ<-0.5	9	Hepcidin	ng/µL	8.15	4.90	13.54
VA	Females, birth-WAZ>-0.5	9	Hepcidin	ng/µL	18.79	12.24	28.85
VA	Males, birth-WAZ<-0.5	9	Hepcidin	ng/µL	2.92	1.46	5.84
VA	Males, birth-WAZ>-0.5	9	Hepcidin	ng/µL	6.34	3.38	11.91
VA	Females, birth-WAZ<-0.5	12	Hepcidin	ng/µL	9.17	6.18	13.62
VA	Females, birth-WAZ>-0.5	12	Hepcidin	ng/µL	12.79	7.63	21.46
VA	Males, birth-WAZ<-0.5	12	Hepcidin	ng/µL	2.95	1.81	4.81
VA	Males, birth-WAZ>-0.5	12	Hepcidin	ng/µL	4.43	3.00	6.56
VA	Females, birth-WAZ<-0.5	0	Ferritin	µg/L	173.26	108.59	276.44
VA	Females, birth-WAZ>-0.5	0	Ferritin	µg/L	176.33	98.52	315.60
VA	Males, birth-WAZ<-0.5	0	Ferritin	µg/L	178.45	95.07	334.95
VA	Males, birth-WAZ>-0.5	0	Ferritin	µg/L	169.97	80.59	358.45
VA	Females, birth-WAZ<-0.5	2	Ferritin	µg/L	252.31	157.69	403.72
VA	Females, birth-WAZ>-0.5	2	Ferritin	µg/L	385.18	200.63	739.51
VA	Males, birth-WAZ<-0.5	2	Ferritin	µg/L	144.62	80.58	259.58
VA	Males, birth-WAZ>-0.5	2	Ferritin	µg/L	296.16	164.15	534.33
VA	Females, birth-WAZ<-0.5	5	Ferritin	µg/L	28.95	18.89	44.36
VA	Females, birth-WAZ>-0.5	5	Ferritin	µg/L	34.37	18.69	63.22
VA	Males, birth-WAZ<-0.5	5	Ferritin	µg/L	16.06	8.35	30.87
VA	Males, birth-WAZ>-0.5	5	Ferritin	µg/L	22.38	10.40	48.18
VA	Females, birth-WAZ<-0.5	9	Ferritin	µg/L	26.55	18.96	37.16

VA	Females, birth-WAZ>-0.5	9	Ferritin	µg/L	31.08	19.37	49.88
VA	Males, birth-WAZ<-0.5	9	Ferritin	µg/L	11.20	6.18	20.31
VA	Males, birth-WAZ>-0.5	9	Ferritin	µg/L	18.79	11.27	31.31
VA	Females, birth-WAZ<-0.5	12	Ferritin	µg/L	19.27	13.30	27.92
VA	Females, birth-WAZ>-0.5	12	Ferritin	µg/L	32.51	21.65	48.80
VA	Males, birth-WAZ<-0.5	12	Ferritin	µg/L	11.29	7.31	17.45
VA	Males, birth-WAZ>-0.5	12	Ferritin	µg/L	15.86	9.10	27.63
VA	Females, birth-WAZ<-0.5	0	Iron	µmol/L	23.63	12.79	43.63
VA	Females, birth-WAZ>-0.5	0	Iron	µmol/L	21.59	10.03	46.51
VA	Males, birth-WAZ<-0.5	0	Iron	µmol/L	23.09	11.48	46.47
VA	Males, birth-WAZ>-0.5	0	Iron	µmol/L	22.59	6.64	76.83
VA	Females, birth-WAZ<-0.5	2	Iron	µmol/L	3.25	1.29	8.19
VA	Females, birth-WAZ>-0.5	2	Iron	µmol/L	6.93	1.77	27.19
VA	Males, birth-WAZ<-0.5	2	Iron	µmol/L	4.60	1.96	10.80
VA	Males, birth-WAZ>-0.5	2	Iron	µmol/L	5.90	1.61	21.65
VA	Females, birth-WAZ<-0.5	5	Iron	µmol/L	2.48	1.30	4.75
VA	Females, birth-WAZ>-0.5	5	Iron	µmol/L	2.99	0.85	10.56
VA	Males, birth-WAZ<-0.5	5	Iron	µmol/L	1.76	0.70	4.46
VA	Males, birth-WAZ>-0.5	5	Iron	µmol/L	0.69	0.09	5.40
VA	Females, birth-WAZ<-0.5	9	Iron	µmol/L	3.57	2.38	5.37
VA	Females, birth-WAZ>-0.5	9	Iron	µmol/L	5.03	3.35	7.56
VA	Males, birth-WAZ<-0.5	9	Iron	µmol/L	3.51	2.17	5.68
VA	Males, birth-WAZ>-0.5	9	Iron	µmol/L	4.25	1.81	9.98
VA	Females, birth-WAZ<-0.5	12	Iron	µmol/L	2.20	1.41	3.42
VA	Females, birth-WAZ>-0.5	12	Iron	µmol/L	3.95	2.35	6.64
VA	Males, birth-WAZ<-0.5	12	Iron	µmol/L	2.02	1.20	3.40
VA	Males, birth-WAZ>-0.5	12	Iron	µmol/L	4.10	1.55	10.87
VA	Females, birth-WAZ<-0.5	0	sTfR	mg/L	5.31	4.43	6.38
VA	Females, birth-WAZ>-0.5	0	sTfR	mg/L	5.28	4.46	6.26
VA	Males, birth-WAZ<-0.5	0	sTfR	mg/L	5.47	4.88	6.14
VA	Males, birth-WAZ>-0.5	0	sTfR	mg/L	5.40	4.45	6.56
VA	Females, birth-WAZ<-0.5	2	sTfR	mg/L	3.85	3.09	4.80
VA	Females, birth-WAZ>-0.5	2	sTfR	mg/L	3.62	2.84	4.63
VA	Males, birth-WAZ<-0.5	2	sTfR	mg/L	3.67	3.22	4.19
VA	Males, birth-WAZ>-0.5	2	sTfR	mg/L	3.54	2.82	4.45
VA	Females, birth-WAZ<-0.5	5	sTfR	mg/L	6.44	5.39	7.68
VA	Females, birth-WAZ>-0.5	5	sTfR	mg/L	5.64	4.54	7.00
VA	Males, birth-WAZ<-0.5	5	sTfR	mg/L	7.85	6.87	8.96
VA	Males, birth-WAZ>-0.5	5	sTfR	mg/L	6.68	5.43	8.22
VA	Females, birth-WAZ<-0.5	9	sTfR	mg/L	7.21	6.43	8.08
VA	Females, birth-WAZ>-0.5	9	sTfR	mg/L	6.14	5.53	6.81
VA	Males, birth-WAZ<-0.5	9	sTfR	mg/L	8.73	7.89	9.66
VA	Males, birth-WAZ>-0.5	9	sTfR	mg/L	7.31	6.36	8.42
VA	Females, birth-WAZ<-0.5	12	sTfR	mg/L	6.78	5.96	7.70
VA	Females, birth-WAZ>-0.5	12	sTfR	mg/L	5.92	5.23	6.71
VA	Males, birth-WAZ<-0.5	12	sTfR	mg/L	9.08	8.28	9.95
VA	Males, birth-WAZ>-0.5	12	sTfR	mg/L	7.20	6.20	8.36
VA	Females, birth-WAZ<-0.5	0	CRP	mg/L	0.42	0.27	0.65
VA	Females, birth-WAZ>-0.5	0	CRP	mg/L	0.32	0.20	0.51
VA	Males, birth-WAZ<-0.5	0	CRP	mg/L	0.36	0.26	0.51
VA	Males, birth-WAZ>-0.5	0	CRP	mg/L	0.17	0.08	0.36

VA	Females, birth-WAZ<-0.5	2	CRP	mg/L	0.76	0.43	1.36
VA	Females, birth-WAZ>-0.5	2	CRP	mg/L	0.63	0.32	1.25
VA	Males, birth-WAZ<-0.5	2	CRP	mg/L	0.29	0.14	0.60
VA	Males, birth-WAZ>-0.5	2	CRP	mg/L	0.64	0.30	1.40
VA	Females, birth-WAZ<-0.5	5	CRP	mg/L	1.38	0.85	2.25
VA	Females, birth-WAZ>-0.5	5	CRP	mg/L	1.24	0.67	2.31
VA	Males, birth-WAZ<-0.5	5	CRP	mg/L	1.74	1.08	2.82
VA	Males, birth-WAZ>-0.5	5	CRP	mg/L	1.58	0.75	3.32
VA	Females, birth-WAZ<-0.5	9	CRP	mg/L	2.39	1.41	4.06
VA	Females, birth-WAZ>-0.5	9	CRP	mg/L	2.45	1.51	3.98
VA	Males, birth-WAZ<-0.5	9	CRP	mg/L	2.37	1.38	4.09
VA	Males, birth-WAZ>-0.5	9	CRP	mg/L	2.02	0.78	5.22
VA	Females, birth-WAZ<-0.5	12	CRP	mg/L	4.68	2.84	7.71
VA	Females, birth-WAZ>-0.5	12	CRP	mg/L	3.01	1.37	6.64
VA	Males, birth-WAZ<-0.5	12	CRP	mg/L	2.32	1.22	4.39
VA	Males, birth-WAZ>-0.5	12	CRP	mg/L	2.66	1.03	6.84
VA	Females, birth-WAZ<-0.5	0	AGP	g/L	0.15	0.10	0.21
VA	Females, birth-WAZ>-0.5	0	AGP	g/L	0.16	0.15	0.19
VA	Males, birth-WAZ<-0.5	0	AGP	g/L	0.17	0.14	0.19
VA	Males, birth-WAZ>-0.5	0	AGP	g/L	0.13	0.08	0.20
VA	Females, birth-WAZ<-0.5	2	AGP	g/L	0.63	0.54	0.73
VA	Females, birth-WAZ>-0.5	2	AGP	g/L	0.64	0.56	0.73
VA	Males, birth-WAZ<-0.5	2	AGP	g/L	0.74	0.66	0.83
VA	Males, birth-WAZ>-0.5	2	AGP	g/L	0.55	0.35	0.87
VA	Females, birth-WAZ<-0.5	5	AGP	g/L	0.92	0.80	1.05
VA	Females, birth-WAZ>-0.5	5	AGP	g/L	0.85	0.75	0.96
VA	Males, birth-WAZ<-0.5	5	AGP	g/L	0.99	0.89	1.09
VA	Males, birth-WAZ>-0.5	5	AGP	g/L	1.04	0.86	1.25
VA	Females, birth-WAZ<-0.5	9	AGP	g/L	1.18	1.05	1.33
VA	Females, birth-WAZ>-0.5	9	AGP	g/L	1.11	0.99	1.25
VA	Males, birth-WAZ<-0.5	9	AGP	g/L	1.26	1.15	1.39
VA	Males, birth-WAZ>-0.5	9	AGP	g/L	1.17	0.94	1.45
VA	Females, birth-WAZ<-0.5	12	AGP	g/L	1.35	1.10	1.65
VA	Females, birth-WAZ>-0.5	12	AGP	g/L	1.11	0.94	1.32
VA	Males, birth-WAZ<-0.5	12	AGP	g/L	1.17	1.01	1.36
VA	Males, birth-WAZ>-0.5	12	AGP	g/L	1.14	0.78	1.66
VA	Females, birth-WAZ<-0.5	0	Hb	g/dL	12.84	12.04	13.68
VA	Females, birth-WAZ>-0.5	0	Hb	g/dL	13.05	12.47	13.65
VA	Males, birth-WAZ<-0.5	0	Hb	g/dL	13.71	13.18	14.27
VA	Males, birth-WAZ>-0.5	0	Hb	g/dL	13.39	12.49	14.35
VA	Females, birth-WAZ<-0.5	2	Hb	g/dL	10.91	10.35	11.49
VA	Females, birth-WAZ>-0.5	2	Hb	g/dL	11.46	11.15	11.79
VA	Males, birth-WAZ<-0.5	2	Hb	g/dL	10.87	10.58	11.18
VA	Males, birth-WAZ>-0.5	2	Hb	g/dL	10.67	10.24	11.12
VA	Females, birth-WAZ<-0.5	5	Hb	g/dL	11.00	10.76	11.24
VA	Females, birth-WAZ>-0.5	5	Hb	g/dL	11.03	10.71	11.35
VA	Males, birth-WAZ<-0.5	5	Hb	g/dL	10.40	10.17	10.64
VA	Males, birth-WAZ>-0.5	5	Hb	g/dL	10.12	9.53	10.74
VA	Females, birth-WAZ<-0.5	9	Hb	g/dL	10.11	9.82	10.41
VA	Females, birth-WAZ>-0.5	9	Hb	g/dL	10.37	10.09	10.65
VA	Males, birth-WAZ<-0.5	9	Hb	g/dL	9.70	9.38	10.04

VA	Males, birth-WAZ>-0.5	9	Hb	g/dL	10.07	9.71	10.45
VA	Females, birth-WAZ<-0.5	12	Hb	g/dL	9.65	9.36	9.95
VA	Females, birth-WAZ>-0.5	12	Hb	g/dL	10.16	9.86	10.48
VA	Males, birth-WAZ<-0.5	12	Hb	g/dL	9.19	8.91	9.49
VA	Males, birth-WAZ>-0.5	12	Hb	g/dL	9.68	9.31	10.05