RESEARCH ARTICLE

The magnitude and distribution of iron deficiency using serum/plasma ferritin among preschool children and non-pregnant women: a multi-country analysis

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The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention or the World Health Organization.

ABSTRACT

Background: In 2004, World Health Organization (WHO) recommended the use of serum ferritin as a primary indicator of iron deficiency. However, there was limited data on the magnitude and distribution of iron deficiency based on ferritin.

Objective: To describe the prevalence of iron deficiency as measured by serum/plasma ferritin in different regions of the world and its relationship with demographic and health indicators.

Methods: Data from the Biomarkers Reflecting Inflammation and Nutrition Determinants of Anemia and the WHO Vitamin and Mineral Nutrition Information System Micronutrients Database were used for this analysis. Unadjusted and inflammation-adjusted low ferritin prevalence were calculated for both databases. The prevalence of low ferritin among preschool children and non-pregnant women was examined according to its relationship with national gross domestic product (GDP), infant mortality rate (IMR), and anemia rate.

Results: In children, the median inflammation-adjusted prevalence of low ferritin was 35.3% (1^{st} and 3^{rd} quartiles: 17.5% and 48.1%). In non-pregnant women, the median inflammation-adjusted prevalence of low ferritin was 28.4% (1^{st} and 3^{rd} quartiles: 21.4% and 42.0%). For both children and women, the correlation between the prevalence of low ferritin and GDP, IMR, or anemia was consistently stronger using inflammation-adjusted prevalences than when using unadjusted prevalences.

Conclusions: The quartile values of low ferritin prevalence for children and non-pregnant women could be used to define the severity of ferritin as a public health problem.

Key words: Ferritin, iron deficiency, public health significance, children, women

1. Introduction

Ferritin and hemoglobin have been identified as the most efficient indicators of a population's response to iron interventions.[1] In 2004, the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC) recommended the use of serum ferritin as a primary indicator of a response to an intervention to control iron deficiency and in all programme evaluations.[2] However, there was limited data on the prevalence of iron deficiency as measured by serum/plasma ferritin in different regions of the world and the relationship with some demographic and health indicators. Also, most of the published prevalence of iron deficiency as measured by serum/plasma ferritin did not take inflammation into account. Further, there was no recommendation on how to measure the severity of iron deficiency as a public health problem. One approach that is often used in nutrition surveillance is the determination of prevalence ranges to assess the severity of a situation based on expert opinion. These classifications are very helpful for summarizing prevalence data and can be used for targeting purposes when establishing intervention priorities.[3]

In 1996, WHO defined the level of severity of vitamin A deficiency as a public health problem based on the prevalence of low serum retinol (< 0.70 µmol/L) in preschool children 6-71 months.[4] For mild, moderate, or severe public health problem of vitamin A deficiency the population level cutoffs are 2.0% - 9.9%, 10.0% - 19.9%, or ≥20.0%, respectively. In 2000, the WHO recommended cutoffs for defining the severity of the public health problem of anemia in a population.[5,6] For normal, mild, moderate, or severe public health problem of anemia the cutoffs are <4.9%, 5.0% - 19.9%, 20.0% - 39.9%, or ≥40.0%, respectively. However, there are no details on how theses cutoffs were determined.[4-6]

WHO is developing recommendations on the use and interpretation of serum/plasma ferritin concentrations for assessing iron status in populations following WHO processes for evidence-informed guideline development. The recommendations will address issues on how ferritin levels respond to public health interventions, laboratory methods for ferritin quantification, effects of infection and inflammation on ferritin concentrations, approaches for adjustments for inflammation and infection, and approaches to establish categories for determining the severity of iron deficiency, as measured by ferritin concentrations, as a public health problem.

The purpose of this analysis is to examine the magnitude and distribution of iron deficiency across countries as background for defining the severity of iron deficiency as a public health problem (measured by ferritin). National- or regional level data on iron deficiency for two target groups (pre-school aged children and women of reproductive age) were used for this analysis.

2. Method

2.1 Data sources

Two data sources were used for this analysis. The first data source is the database for Biomarkers Reflecting Inflammation and Nutrition Determinants of Anemia (BRINDA[7,8]) and the second data source is

the WHO Vitamin and Mineral Nutrition Information System (VMNIS) Micronutrients Database.[9]

The BRINDA database was developed collaboratively by the CDC, the Global Alliance for Improved Nutrition and the National Institute of Health (NIH) to better understand the determinants of anemia and the effects of inflammation and nutrition biomarkers. The BRINDA protocol was reviewed by the institutional review board (IRB) of NIH and deemed non-human subjects research, and also reviewed in accordance with CDC human research protection procedures and was determined as non-human subjects research. The methods for identifying datasets, inclusion and exclusion criteria, and data management for the BRINDA project have been described in detail elsewhere.[7] The surveys were nationally or regionally representative, and the data inclusion criteria were: 1) conducted after 2004; 2) including data on preschool-aged children and/or non-pregnant women of reproductive age; and 3) measured at least one marker of iron (ferritin or soluble transferrin receptor) or vitamin A status (retinol binding protein or retinol) and at least one marker of inflammation namely C-reactive protein (CRP) or/and α1-acid glycoprotein (AGP). Observations were included in this analysis only if they had measures of ferritin because the purpose of this analysis was to examine the unadjusted and adjusted (for inflammation) prevalence of low ferritin in countries (representative sample from national or subnational surveys).

The WHO VMNIS Micronutrients Database systematically retrieves and summarizes data on vitamin and mineral status of populations. Ferritin concentrations are recorded from surveys that are representative at the national or first administrative level in this database. These data will provide the national unadjusted prevalence of low ferritin.

We examined data on preschool-age children less than 5 years of age and non-pregnant women of childbearing age 15-49 years. We examined the relationship between the prevalence of low ferritin and some key social economic and health indicators for each country including gross domestic product (GDP), infant mortality rate (IMR), anemia, maternal mortality rate (MMR) (for women only), and stunting rate (for preschool age children only). Per capita GDP (at https://data.worldbank.org/indicator/NY.GDP.PCAP.CD), IMR (at https://data.worldbank.org/indicator/sp.dyn.imrt.in), MMR (at https://data.worldbank.org/indicator/sh.sta.mmrt), and stunting rate (at https://data.worldbank.org/indicator/sh.sta.stnt.zs) were based on data from the World Bank, and anemia estimates (at http://www.who.int/vmnis/anaemia/en/) were from the WHO global database. All GDP, IMR, MMR, and stunting data were obtained from either the same year of the survey for each country or within $\pm$1 year from the survey year.

In the BRINDA database, we included 15 datasets from 13 countries in preschool children and 9 datasets from 8 countries in non-pregnant women. In the WHO VMNIS database, we included a total of 32 datasets from 28 countries in preschool children and

16 datasets from 13 countries in non-pregnant women.

2.2 Laboratory analysis

In the BRINDA database, venous or capillary blood was collected from each respondent and plasma or serum was stored at -20°C until analysis. Ferritin, sTfR, CRP and AGP concentrations were assessed using a sandwich enzyme-linked immunosorbent assay at the VitMin Lab (Willstaett, Germany[10]) in 8 out of 15 preschool children datasets and 4 out of 9 non-pregnant women datasets. Additional information on laboratory methods is further described in the methodologic overview in a supplement.[7,8] In the WHO VMNIS database, venous or capillary blood was collected from each respondent and the laboratory methods used to assess ferritin concentrations varied by country.[9]

Low ferritin for defining iron deficiency was defined as <12.0 µg/L for children and <15.0 µg/L for non-pregnant women.[2] Anemia was defined as Hb<11.0 g/dL for children and <12.0 g/dL for non-pregnant women.[2]

2.3 Statistical analysis

For the data from BRIDNA, we use previously published data from Namaste et al..[8] In that paper, linear models were first used to regress ferritin against acute-phase proteins (AGP and CRP). The resultant population regression coefficients for the acute-phase proteins were then extracted and used to correct ferritin for apparent inflammation effects of both AGP and CRP. Ferritin of participants with low levels of AGP and CRP (first decile) were not inflammation adjusted as their ferritin levels are thought not to be unduly influenced.

For the WHO VMNIS data, however, only unadjusted prevalence of low ferritin was available. To adjust the low ferritin prevalence of the WHO VMNIS data for inflammation, we used the average adjustments observed in the BRINDA dataset by region. To do so, we first converted the prevalence to a mean serum ferritin, assuming a log-normal distribution with a standard deviation as typically observed in BRINDA (average from BRINDA data). We then shifted the mean serum ferritin downward using the average of the ferritin adjustments observed from BRINDA in each WHO region. Finally, we converted the new mean serum ferritin back to a prevalence assuming a log-normal distribution and standard deviation as before.

We then examined the relationship between the adjusted prevalence of low ferritin and GDP, IMR, MMR (for women), anemia, and stunting rate (for preschool age children only) from all the available datasets from both BRINDA and VMNIS databases. We also examined the differences between the unadjusted and adjusted prevalence of low ferritin in both preschool children and non-pregnant women populations from the BRINDA database. Finally, for both BRINDA and VMNIS data, we also calculated the quartile values of the unadjusted and inflammation-adjusted low ferritin prevalence.

TABLE 1 Prevalence of low ferritin (<12.0 µg/L) in preschool children in relation with key social economic and health indicators, combined database for the Biomarkers Reflecting Inflammation and Nutrition Determinants of Anemia (BRINDA) and the WHO Vitamin and Mineral Nutrition Information System (VMNIS)

Region	Country	Year data collected	Data source	Age (mos)	Sample size	GDP per capita	IMR	Stunting	Anemia	% low ferritin	
						US$	per 1000 live births	(% < -2SD)	(% Hb<11.0 g/dL)	Unadjusted	Inflammation-adjusted*
Africa	Kenya	2007	BRINDA	6-35	896	721	68	41	65.5	38.9	73.3
	Gambia	1999	VMNIS	12-60	518	683	64.8	24.1	75.5	23	66.6
	Liberia	2011	BRINDA	6-35	1434	377	72	39	59.5	20.4	55.5
	Nigeria	2001	VMNIS	0-59	3091	350	109.5	39.7	75.8	19.4	61.2
	Kenya	2010	BRINDA	6-35	849	787	60	35	71.7	19.2	55.3
	Cameroon	2009	BRINDA	12-59	792	1103	87	33	54.3	14.9	34.7
	Cote d'Ivoire	2007	BRINDA	6-59	746	1103	87	39	71.2	11.7	40.7
	Nigeria	1993	VMNIS	6-71	1240	153	125.3	43.8	75.6	11.5	46.1
	Ghana	1998	VMNIS	6-59	152	416	68.7	31.3	83.5	10.5	43.7
	South Africa	1993-4	VMNIS	6-71	4454	3547	45.1	28.7	21.4	9.8	41.9
	South Africa	2012	VMNIS	0-59	511	7314	33.5	23.9	10.7	8.1	37.3
	Malawi	2009	VMNIS	6-59	980	345	55.4	48.8	55.2	6.8	33.4
	Botswana	1994	VMNIS	6-71	245	2757	43.3	35.1	38	6.1	31.1
Americas	Ecuador	1993	VMNIS	12-59	1230	1748	38.7	33	37.8	41.1	53.6
	Argentina	2004-5	VMNIS	6-23	7200	4785	16	8.2	34.1	35.3	46.6
	Nicaragua	2005	BRINDA	6-59	957	1159	26.3	18.8	20.2	33.2	48.1
	Nicaragua	2004	VMNIS	6-59	961	1076	27.4	18.8	22.4	33.1	43.9
	Canada	1970-2	VMNIS	12-59	87	4579	17.7	6.4	5.7	28.7	38.4
	Guatemala	2009	VMNIS	6-59	985	2697	29.3	48	47.7	26.3	35.3
	Costa Rica	1996	VMNIS	12-72	266	3321	12.9	9	26.3	24.4	32.9
	Mexico	2006	BRINDA	12-59	1590	8618	21	16	20.7	23.4	32.8
	Jamaica	1997-8	VMNIS	12-59	277	2949	21.4	8.6	48.2	16.2	21.8
	Mexico	2012	BRINDA	6-59	3864	9703	17	8.4	23.3	13.5	17.5
	Dominica	1996	VMNIS	12-59	157	3323	14.3	11	34.4	10.8	14.3
	Guyana	1996-7	VMNIS	12-59	140	965	41.6	14	48.2	10.6	14.1
	USA	2003-6	BRINDA	6-59	1138	43092	7	3	2.1	10.5	13.3
	Colombia	2012	BRINDA	12-59	3866	7748	19	14	13.2	10.1	13.3
	Saint Vincent and	1996-7	VMNIS	12-59	170	2605	19	-		8.8	11.6

	the Grenadines										
	Antigua and Barbuda	1996-7	VMNIS	12-59	83	7703	17	-	49.4	5.7	7.3
Eastern Mediterranean	Pakistan	2001	VMNIS	6-59	5611	492	86.2	41.5	63.1	56.3	65.9
	Pakistan	2011	BRINDA	6-59	7221	1214	71	43	43	46.9	51.3
	Iran	2001	VMNIS	12-23	8493	1727	27.1	12.4	37.6	32.8	39.0
	Jordan	2002	VMNIS	12-59	1066	1902	22.1	12	20.1	26.1	30.8
	Lebanon	1997-8	VMNIS	12-72	307	5093	19.9	17.2	24.8	25.4	29.9
	Iraq	2011	VMNIS	12-59	2087	6019	29.4	27.5	21.6	14.4	16.3
	Jordan	2010	VMNIS	12-59	940	4371	17.5	8.3	17	13.7	15.4
Europe	The former Yugoslav Republic of Macedonia	1999	VMNIS	6-59	1048	1806	15	8	25.8	13.7	12.8
	Georgia	2009	BRINDA	12-59	2142	2441	29	11	23	0.3	0.3
South-East Asia	Bhutan	1985	VMNIS	12-59	135	367	113	60.9	58	38	57.9
	Maldives	2007	VMNIS	6-60	1268	5003	15.3	20.3	26.3	25.6	42.1
	Bangladesh	2010	BRINDA	6-11	1493	664	44	47	83.5	8.0	16.1
Western Pacific	Mongolia	1999	VMNIS	6-24	156	445	52	30.1	48.5	41	59.4
	Mongolia	2001	VMNIS	6-59	374	524	46.7	29.8	31.6	34	51.1
	Philippines	2011	BRINDA	6-23	1691	2358	23	34	42.8	26.2	35.2
	Mongolia	2004	VMNIS	6-59	386	798	39.2	23.5	21.4	22.3	35.5
	Laos	2006	BRINDA	6-59	482	586	58	50	40.7	16.6	27.0
	Viet Nam	2010	VMNIS	6-75	568	1334	20.6	23.3	9.1	12.9	21.4

GDP: gross domestic product; IMR: infant mortality rate; Hb: hemoglobin; Stunting: <-2 SD length/height-for-age z-score

* For BRINDA databases, adjusted prevalence was calculated from the adjusted ferritin values using the approach developed in the BRINDA project [8, 9] and the prevalence were first published elsewhere [9]. For VMNIS databases, adjusted prevalence was calculated by converting the unadjusted prevalence to a log-mean of ferritin and shifting it downward using the average adjustment in the BRINDA datasets of the respective region.

3. Results

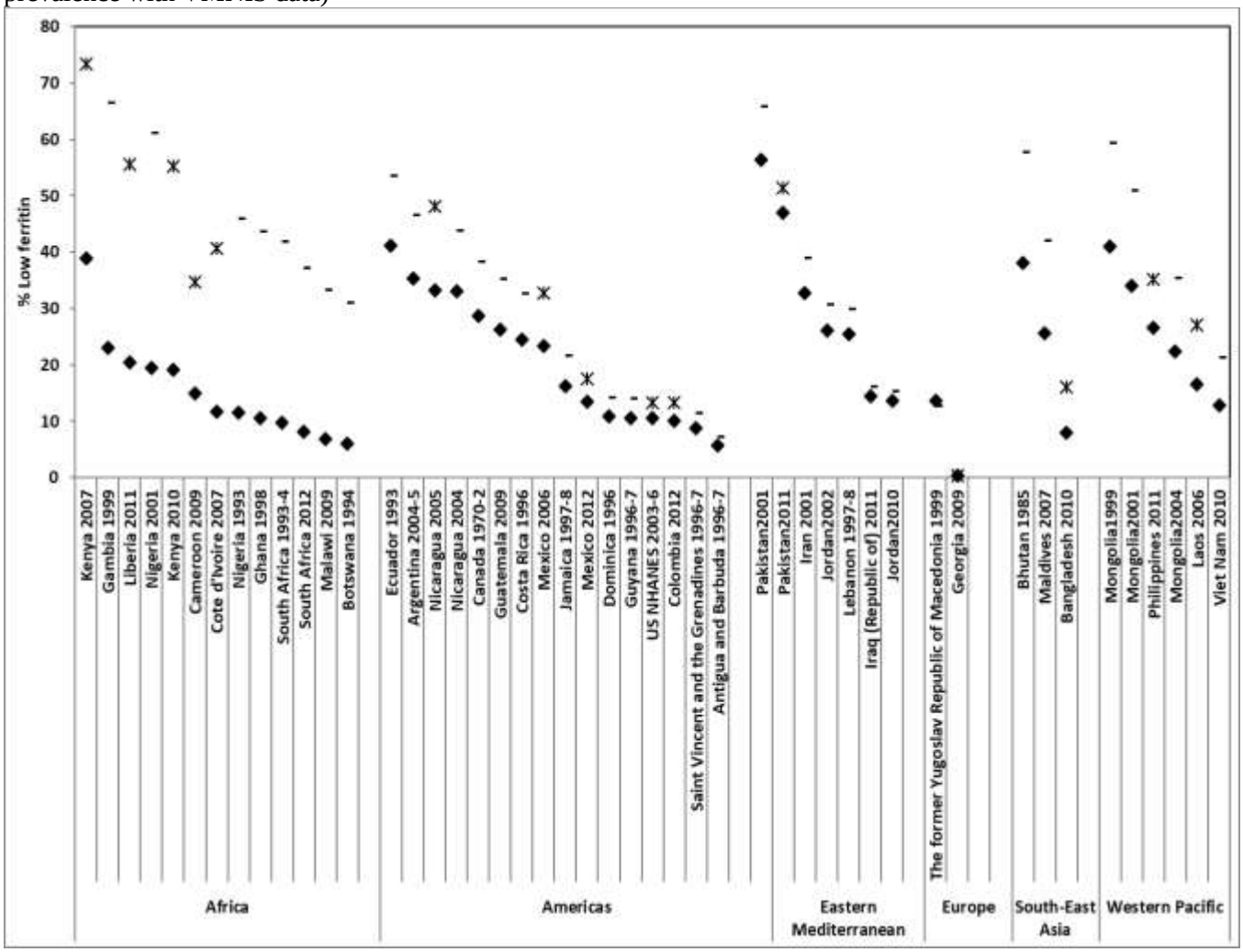
3.1 Preschool children

The BRINDA and VMNIS databases for preschool children are listed in Table 1. There were totally 47 datasets from 38 countries (13 datasets from 10 countries in Africa; 16 datasets from 14 countries in the Americas; 7 datasets from 5 countries in Eastern Mediterranean; 2 datasets from 2 countries in Europe; 3 datasets from 3 countries in South-East Asia; and 6 datasets from 4 countries in the Western Pacific). All the data were from national or sub-national surveys collected from 1970 to 2012. The majority of the datasets were for 6-59 month olds or 12-59 month olds, but four datasets excluded children above 24 months of age and one dataset (Bangladesh) only included children 6-11 months of age.

The unadjusted prevalence of low ferritin ranged from 0.3% in Georgia to 56.3% in Pakistan (Table 1). The median unadjusted prevalence of low ferritin was 19.2% with 1st and 3rd quartiles were 10.6% and 28.7%, respectively (Table 3). There were no clear regional patterns, with wide variability across countries within each region (Figure 1). However, after inflammation-adjusted, the adjusted prevalence of low ferritin was higher (except Georgia, ranged from 0.3% in Georgia to 73.3% in Kenya 2007) than that of the unadjusted prevalence across countries, particularly among African countries (Table 1 and Figure 1). The median inflammation-adjusted prevalence of low ferritin was 35.3% with 1st and 3rd quartiles were 17.5% and 48.1%, respectively (Table 3).

FIGURE 1 The prevalence of low ferritin in preschool children. Comparison of unadjusted and inflammation-adjusted prevalence of low ferritin by regions from data of the Biomarkers Reflecting

Inflammation and Nutrition Determinants of Anemia (BRINDA) and the WHO Vitamin and Mineral Nutrition Information System (VMNIS) (Diamond marker for unadjusted prevalence; star marker for inflammation-adjusted prevalence with BRINDA data; and dash marker for inflammation-adjusted prevalence with VMNIS data)

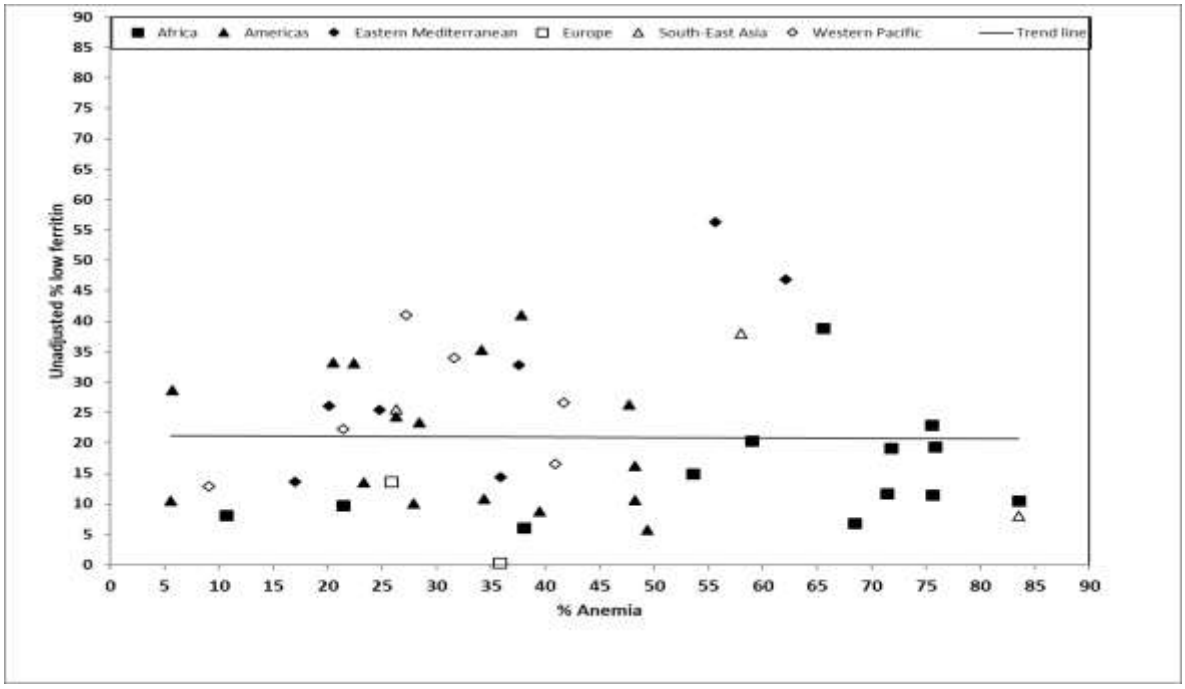


The Pearson correlation coefficients between the unadjusted prevalence of low ferritin and GDP, IMR, anemia, or stunting were consistently lower than those with the inflammation-adjusted prevalence of low ferritin, no matter which database was used (Table 4). There was a negative correlation between GDP and the prevalence of low ferritin but positive correlations between IMR, anemia or stunting and the prevalence of low ferritin. When BRINDA and VMNIS data were combined, all the correlations were significant after adjusting for inflammation (Table 4).

FIGURE 2 The relationship between the prevalence of anemia and the prevalence of low ferritin in preschool children from combined BRINDA and the WHO Vitamin and Mineral Nutrition Information

System (VMNIS) databases. Panel A, unadjusted prevalence with regression trend line; Panel B, inflammation-adjusted prevalence with regression trend line

A



B

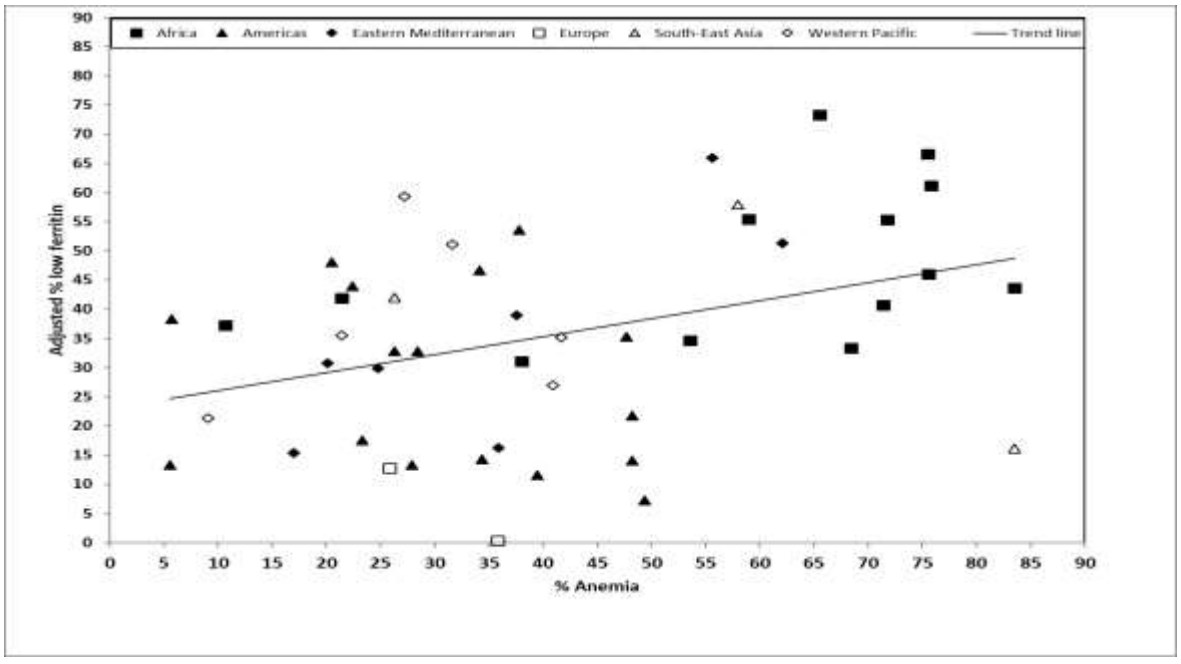


FIGURE 3 The prevalence of low ferritin in non-pregnant women. Comparison of unadjusted and inflammation-adjusted prevalence of low ferritin by regions from data of the Biomarkers Reflecting Inflammation and Nutrition Determinants of Anemia (BRINDA) and the WHO Vitamin and Mineral

Nutrition Information System (VMNIS) (Diamond marker for unadjusted prevalence; star marker for inflammation-adjusted prevalence with BRINDA data; and dash marker for inflammation-adjusted prevalence with VMNIS data)

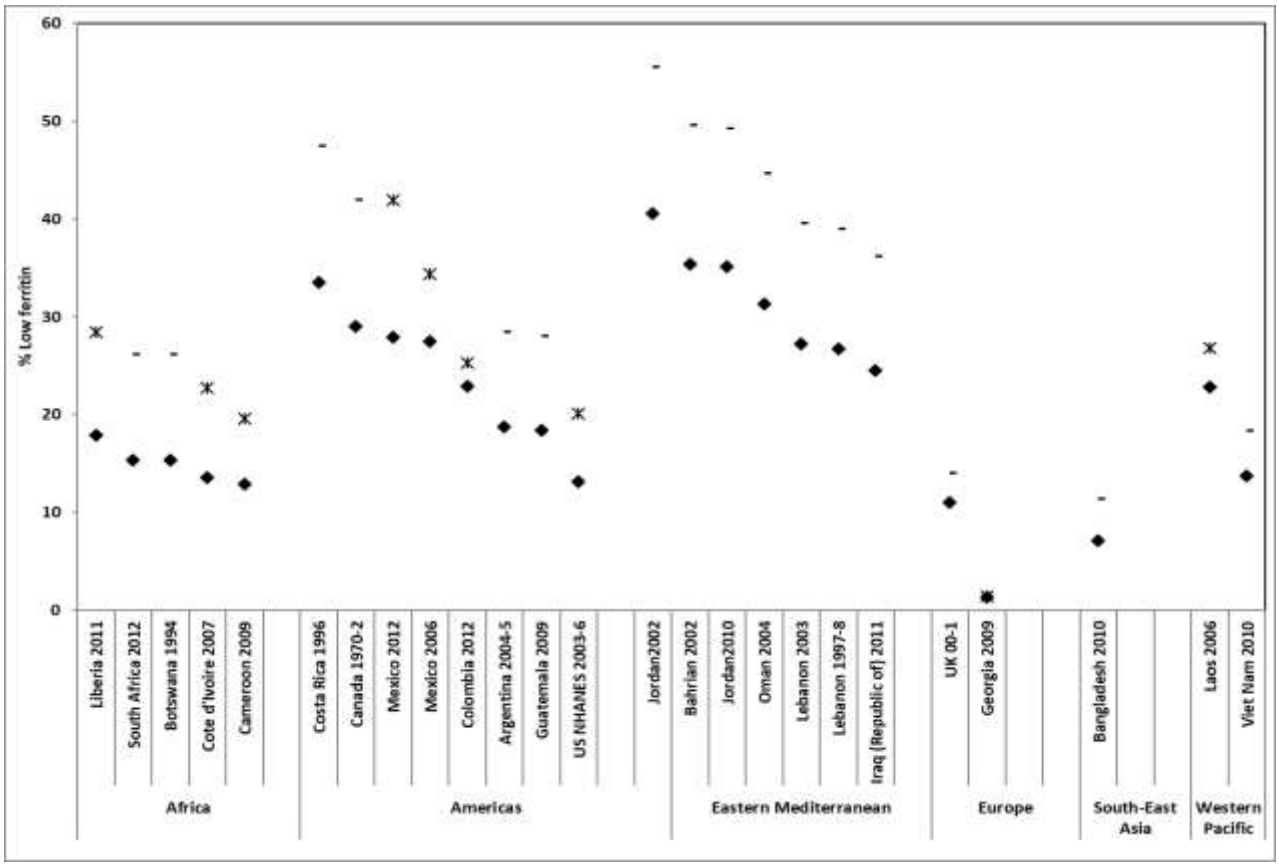


Figure 2 shows the relationship between the prevalence of anemia and the prevalence of low ferritin in preschool children from combined BRINDA and VMNIS databases. Panel A shows the unadjusted prevalence of low ferritin and panel B shows the inflammation-adjusted prevalence. After adjustment for inflammation, countries with higher prevalence of low ferritin tended to have a higher prevalence of anemia (panel B).

TABLE 2 Prevalence of low ferritin (<15.0 µg/L) in non-pregnant women in relation with key social economic and health indicators, combined database for the Biomarkers Reflecting Inflammation and Nutrition Determinants of Anemia (BRINDA) and the WHO Vitamin and Mineral Nutrition Information System (VMNIS)

Regions	Country	Year data collected	Data source	Age (ys)	Sample size	GDP	IMR	MMR	Anemia	Low ferritin (% <15 ug/L)	
						US$	per 1000	per 10000	(% Hb<12.0	Unadjusted	Inflammation -adjusted*

							live births	0 live births	g/dL)		
Africa	Liberia	2011	BRINDA	15-49	1942	377	72	640	33.4	17.9	28.4
	South Africa	2012	VMNIS	16-35	1223	7314	33.5	140	23.1	15.3	26.2
	Botswana	1994	VMNIS	15-49	262	2757	43.3	370	32.7	15.3	26.2
	Cote d'Ivoire	2007	BRINDA	15-49	834	1103	87	750	50.1	13.6	22.7
	Cameroon	2009	BRINDA	15-49	760	1103	87	690	35.7	12.9	19.6
Americas	Costa Rica	1996	VMNIS	15-44	820	3321	12.9	710	18.6	33.5	47.5
	Canada	1970-2	VMNIS	20-39	100	4579	17.7	-	6	29	42.0
	Mexico	2012	BRINDA	15-49	3612	9703	17	45	11.6	27.9	41.9
	Mexico	2006	BRINDA	15-49	3036	8618	21	50	14	27.5	34.4
	Colombia	2012	BRINDA	15-49	9087	7748	19	83	7.6	22.9	25.3
	Argentina	2004-5	VMNIS	10-49	5322	4785	16	70	18.7	18.7	28.5
	Guatemala	2009	VMNIS	15-49	1418	2697	29.3	140	21.4	18.4	28.1
	USA	2003-6	BRINDA	15-49	3184	43092	7	17	6.4	13.1	20.1
Eastern Mediterranean	Jordan	2002	VMNIS	15-49	1122	1902	22.1	65	32.2	40.6	55.6
	Bahrain	2002	VMNIS	14-49	384	13149	10.2	27	51.3	35.4	49.7
	Jordan	2010	VMNIS	15-49	2035	4371	17.5	53	30.6	35.1	49.3
	Oman	2004	VMNIS	15-49	341	10014	15	22	38.8	31.3	44.8
	Lebanon	2003	VMNIS	15-49	470	5442	14.2	26	16	27.2	39.7
	Lebanon	1997-8	VMNIS	15-49	559	5093	19.9	47	23.1	26.7	39.0
	Iraq	2011	VMNIS	15-49	1206	6019	29.4	73	19.9	24.5	36.2
Europe	UK	2000-1	VMNIS	19-64	670	25362	5.6	11	8	11	14.0
	Georgia	2009	BRINDA	15-49	1688	2441	29	48	24.3	1.3	1.4
South-East Asia	Bangladesh	2010	VMNIS	15-49	882	664	44	170	26	7.1	11.5
Western Pacific	Laos	2006	BRINDA	15-49	816	586	58	410	36	22.8	26.8
	Viet Nam	2010	VMNIS	15-49	1529	1334	20.6	51	11.6	13.7	18.4

GDP: gross domestic product; IMR: infant mortality rate; MMR: maternal mortality rate; Hb: hemoglobin

* For BRINDA databases, adjusted prevalence was calculated from the adjusted ferritin values using the approach developed in the BRINDA project [8, 9] and the prevalence were first published elsewhere [9]. For VMNIS databases, adjusted prevalence was calculated by converting the unadjusted prevalence to a log-mean of ferritin and shifting it downward using the average adjustment in the BRINDA datasets of the respective region.

Table 3 Quartile values calculated from the prevalence of low ferritin (unadjusted or inflammation-adjusted), database for the Biomarkers Reflecting Inflammation and Nutrition Determinants of Anemia (BRINDA) and the WHO Vitamin and Mineral Nutrition Information System (VMNIS)

	Quartile 1	Quartile 2	Quartile 3
Children (n=47)			
Unadjusted	10.6	19.2	28.7
Inflammation-adjusted	17.5	35.3	48.1
Non-pregnant women (n=25)			
Unadjusted	13.7	22.8	28.5
Inflammation-adjusted	21.4	28.4	42.0

Table 4 Pearson correlation coefficients (p values in parentheses) between the prevalence of low ferritin (unadjusted or inflammation-adjusted) and key social economic and health indicators, database for the Biomarkers Reflecting Inflammation and Nutrition Determinants of Anemia (BRINDA) and the WHO Vitamin and Mineral Nutrition Information System (VMNIS)

	BRINDA		VMNIS		BRINDA + VMNIS	
	Unadjusted	inflammation-adjusted	Unadjusted	inflammation-adjusted	Unadjusted	inflammation-adjusted
Children	n=15	n=15	n=32	n=32	n=47	n=47
GDP	-0.26 (0.36)	-0.41 (0.13)	-0.30 (0.10)	-0.48 (0.01)	-0.22 (0.14)	-0.35 (0.02)
IMR	0.25 (0.37)	0.59 (0.02)	0.17 (0.36)	0.64 (0.00)	0.18 (0.22)	0.61 (0.00)
Anemia	0.15 (0.59)	0.47 (0.08)	-0.07 (0.69)	0.34 (0.06)	-0.01 (0.93)	0.37 (0.01)
Stunting	0.35 (0.20)	0.54 (0.04)	0.13 (0.51)	0.52 (0.00)	0.18 (0.22)	0.51 (0.001)
Non-pregnant women	n=9	n=9	n=16	n=16	n=25	n=25
GDP	-0.03 (0.94)	0.01 (0.99)	-0.09 (0.73)	-0.14 (0.61)	-0.08 (0.69)	-0.10 (0.65)
IMR	-0.24 (0.53)	-0.12 (0.75)	-0.49 (0.06)	-0.42 (0.11)	-0.39 (0.05)	-0.35 (0.09)
MMR	-0.18 (0.64)	-0.04 (0.92)	0.03 (0.91)	0.07 (0.81)	-0.16 (0.47)	-0.11 (0.62)
Anemia	-0.33 (0.39)	-0.22 (0.58)	0.42 (0.10)	0.45 (0.08)	0.12 (0.56)	0.17 (0.41)

GDP: gross domestic product; IMR: infant mortality rate; MMR: maternal mortality rate

2.2 Non-pregnant women

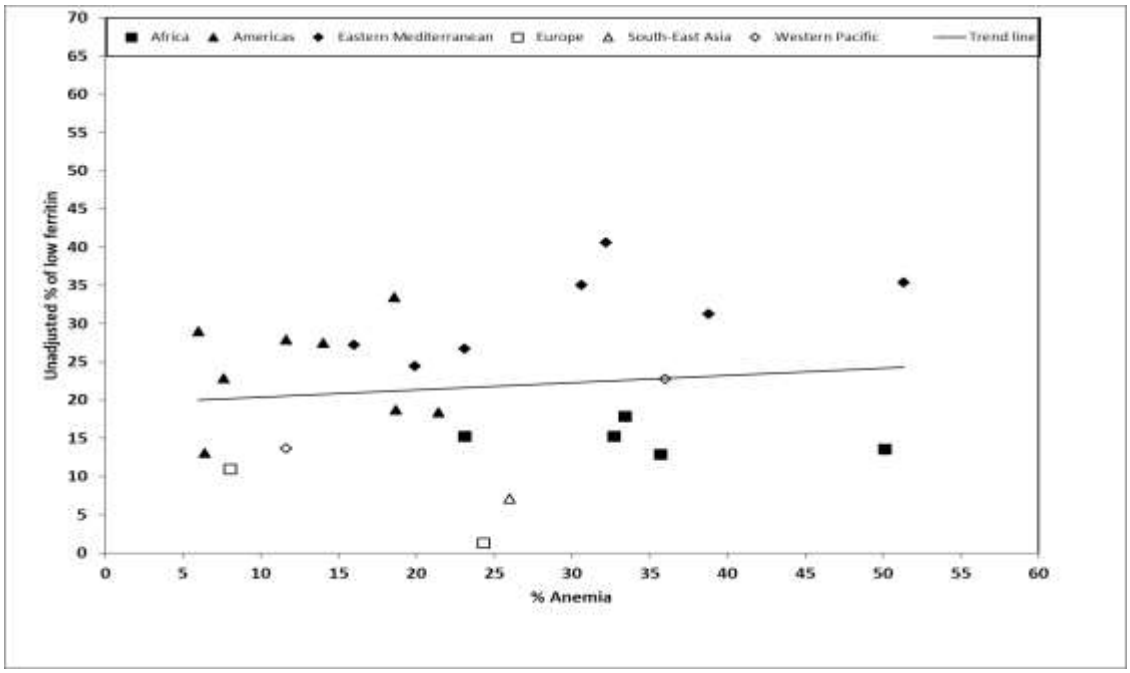
The BRINDA and VMNIS databases for non-pregnant women are shown in Table 2. There were totally 25 datasets from 22 countries (5 datasets from 5 countries in Africa; 8 datasets from 7 countries in the Americas; 7 datasets from 5 countries in Eastern Mediterranean; 2 datasets from 2 countries in Europe; 1 dataset in South-East Asia; and 2 datasets from 2 countries in the Western Pacific). All the data were from national or sub-national surveys collected from 1970 to 2012. The majority of datasets included women 15-49 years of age (Table 2).

The unadjusted prevalence of low ferritin ranged from 1.3% in Georgia to 40.6% in Jordan (Table 2). The median unadjusted prevalence of low ferritin was 22.8% with 1st and 3rd quartiles were 17.5% and 48.1%,

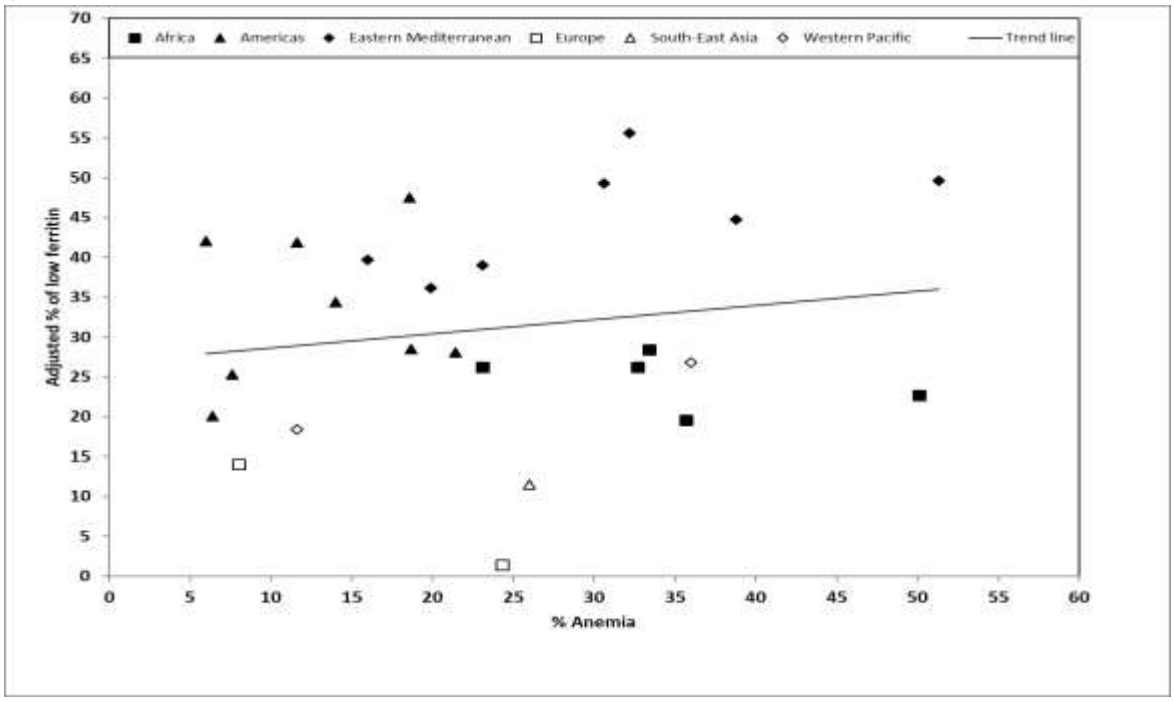
respectively (Table 3). As with the data on pre-school children, there were no clear regional patterns (Figure 3). The variability within each region was somewhat smaller than that for pre-school children. Inflammation-adjusted prevalence of low ferritin was higher (ranged from 1.4% in Georgia to 55.6% in Jordan) than that of the unadjusted prevalence across countries, particularly among countries in Americas and Eastern Mediterranean (Table 2 and Figure 3). However, the differences between unadjusted and inflammation-adjusted prevalence of low ferritin in non-pregnant women were smaller compared to children. The median inflammation-adjusted prevalence of low ferritin was 28.4% with 1st and 3rd quartiles were 21.4% and 42.0%, respectively (Table 3).

FIGURE 4 The relationship between the prevalence of anemia and the prevalence of low ferritin in non-pregnant women from combined BRINDA and the WHO Vitamin and Mineral Nutrition Information System (VMNIS) databases. Panel A, unadjusted prevalence with regression trend line; Panel B, inflammation-adjusted prevalence with regression trend line

A



B



The Pearson correlation coefficients in women between the prevalence of low ferritin and GDP, IMR, MMR, or anemia were not statistically significant and much lower than those among preschool children (Table 4).

Figure 4 shows the relationship between the prevalence of anemia and the prevalence of low ferritin in non-pregnant women from combined BRINDA and VMNIS databases. Panel A shows the unadjusted prevalence of low ferritin and panel B shows the inflammation-adjusted prevalence of low ferritin. In general, inflammation adjustment did not dramatically change the prevalence of low ferritin as it did in children. African women did not have the highest prevalence of low ferritin. Instead, women from the Eastern Mediterranean had the highest prevalence of low ferritin before and after the adjustment.

3. **Discussion**

In this paper, we described how the prevalence of iron deficiency defined by low ferritin varies by country and region. We found that there were no clear regional patterns, with wide variability across countries within each region for both preschool children and non-pregnant women of reproductive age. After inflammation adjustment, Africa region had the highest prevalence of low ferritin in children, but Americas and Eastern Mediterranean region had the highest prevalence in women. Quartile values of low ferritin prevalence were also calculated for both children and non-pregnant women to describe the magnitude and distribution of iron deficiency measured by ferritin. The median inflammation-adjusted prevalence of low ferritin was 35.3% in children and 28.4% in non-pregnant women. Correlations between the prevalence of low ferritin and socio-

economic or health characteristics of the country were weaker and not statistically significant in non-pregnant women. Correlations were stronger and statistically significant if inflammation-adjusted prevalence of low ferritin was used in children. This information will serve to inform guidelines on the use of serum ferritin to assess iron deficiency in populations and to describe magnitude of iron deficiency using serum/plasma ferritin.

Iron deficiency remains an important public health problem worldwide primarily among women, infants and children, and approximately affect 1.62 billion people worldwide.[11,12] Iron deficiency with or without anemia has important consequences for human health and child development.[2] For example, iron deficiency in infancy is associated with impaired mental and psychomotor development; anemic women and their infants are at greater risk of dying during the perinatal period, etc..[2]

Ferritin is recommended by WHO as the primary measure of iron status,[2] but interpretability is challenging in settings with high-levels of infection and inflammation. In populations with high levels of inflammation, ferritin concentrations not only reflect nutritional iron but are also impacted by the acute phase response such as infection and inflammation.[13] Several approaches have been applied before to account for inflammation and infections, such as malaria, to increase the sensitivity of detecting depleted iron stores at the population-level,[14-16] but the recent BRINDA study[7,8] concluded that the current best approach is to the use of internal regression correction to estimate the prevalence of depleted iron stores in regions with inflammation and malaria.[8] Our data show that the correlations (between key social economic and health indicators and the prevalence of low ferritin at the country level) became much stronger after adjusting for inflammation in children.

The main strength of this paper is that we were able to obtain most available ferritin survey data from both BEINDA and VMNIS database and presented both unadjusted and inflammation-adjusted prevalence of low ferritin and described the magnitude and distribution by region. However, the inflammation-adjusted prevalence estimates from VMNIS were based on statistical approach and did not adjusted from inflammation biomarkers directly.

The data we presented in this paper should only be used as a reference for overviewing the magnitude and distribution across countries of iron deficiency using low ferritin based on current available data. The quartile values of low ferritin prevalence calculated from the data for children and non-pregnant women could be used to define the severity of ferritin as a public health problem. In fact, quartile values have been used by WHO before in childhood anthropometry for defining public health significance for stunting, wasting and overweight.[17] When more data available, this analysis could be repeated and further examine if any cutoffs needed to define iron deficiency as a public health problem.

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