Global Pediatric Health
Volume 8: 1–11

DOI: 10.1177/2333794X211048385
journals.sagepub.com/home/gph
SAGE

Is Vitamin A Supplementation Associated With Anemia in Children Under 5 Years of Age in Peru: Secondary Analysis of the "Demographic Health Survey" 2015-2018?

Isabella Ribaudo, MD[1], Camila B. Aramburú-Duclos, MD[1], and Dora Blitchtein, DrPH[1]

Abstract

Vitamin A deficiency (VAD) affects 12% of Peruvians under 5 years of age. Recent studies have shown an association with hematopoiesis and iron metabolism. In Peru, 3-quarters of a million children have anemia. We aimed to identify an association between Vitamin A supplementation (VAS) and anemia in children under 5 years of age. A cross-sectional secondary analytical study from the Peruvian Demographic Survey and Family Health (DHS) was conducted. The primary outcome, anemia, was measured through hemoglobin concentration and adjusted by altitude. The DHS interviewer ensured the participant's VAS in the last 6 months through a structural healthcare card. The association was statistically significant using crude regression but disappeared when adjusted per socioeconomic level and gender. VAS was not significantly associated with a lower prevalence of anemia. Further studies are required to help identify the association between VAS and anemia.

Keywords

Vitamin A supplementation, anemia, iron deficiency, hemoglobin, Peru

Received August 10, 2021. Accepted for publication September 6, 2021.

Introduction

Child undernutrition is currently a major public health challenge worldwide. According to the WHO,[1] "around 45% of deaths among children under 5 years of age are linked to undernutrition." A study published in 2018 estimates that more than 2 billion people are at risk of Vitamin A (VA), zinc, and iron deficiency worldwide.[2] Vitamin A deficiencies (VAD) and insufficiencies are widespread in developing countries and are gaining prevalence in industrialized nations.[3] According to a UNICEF report about children's health in Peru, VAD affects 12% of children under 5 years of age, with a higher incidence in those residing in the rainforest (17%).[4] VA plays an essential role in embryonic development, growth, vision, reproduction, and the immune system.[5] Recent studies have shown an association with hematopoiesis and iron metabolism, which may correlates with the development of anemia.

Iron deficiency is the most common cause of anemia in children. If not treated, this condition can lead to complications, such as physical and cognitive development delays in the pediatric population.[6] In Peru, iron deficiency anemia in children from 6 to 35 months has a prevalence greater than 60% in several departments; thus, overcoming anemia is a leading goal.[7] A large amount of the Health Ministry Budget in Peru is directed toward strategies to address anemia, including screening and treatment. Micronutrient powder use is associated with a significant reduction in the incidence of anemia.[8] The Peruvian government includes a dose

[1]Universidad Peruana de Ciencias Aplicadas, Lima, Perú

Corresponding Author:
Camila B. Aramburú-Duclos, Universidad Peruana de Ciencias Aplicadas, Av Alameda San Marcos 11, Chorrillos, Lima 15067, Perú.
Email: camilaaramburu@icloud.com

of 300 µg of VA in the micronutrient powder distributed nationwide.[15]

Regarding malnutrition and iron deficiency anemia, VAD is linked to impairing iron mobilization, and it is known to play a vital role in hematopoiesis. Firstly, a VA deficient diet is correlated with a decrease in erythropoietin expression, transferrin receptor saturation, and serum iron, as well as an increase in hepcidin expression.[9] Likewise, VAD has been associated with an increase in iron deposits, especially in the spleen, indicating ineffective erythropoiesis.[10] Secondly, VA is a fundamental element in hematopoiesis, as demonstrated by recent preclinical studies.[10] VA is partially transformed to retinoic acid to be translocated to the nucleus to bind to the retinoic acid nuclear receptors, RARs and RXRs. The receptors RARα and RARγ are expressed in bone marrow cells and hematopoietic progenitors, respectively; therefore, a deficiency causes a reduction in the human stem cell numbers. As supported in a significant number of animal model studies, VAD interferes with the function of the blood system and consequently contributes to the development of an iron deficiency anemia.[9]

Evidence in developed countries demonstrates a significant relationship between VA and anemia. In the cited studies, VAS increased mean hemoglobin by 0.7 g/dL and reduced the prevalence of anemia from 54% to 38% in children; nevertheless, it still needs to be assessed in developing countries like Peru.[11] A meta-analysis found that VA may reduce the risk of anemia, but its benefits in children under 6 years of age were inconclusive.[2] Currently, in Peru, there are limited articles that relate VAD and anemia. One of them mentions that its goal was "to evaluate the magnitude and determinants of VAD and nutritional anemia in children."[12] Still, it did not find a direct association between these variables. Another study evaluated zinc and VAS in the iron treatment for anemia. The investigation concluded that the addition of VA did not significantly improve the hematologic response; however, this investigation included zinc, and the study size was small.[13] The association of VAS and the prevalence of anemia in Peruvian children under 5 years old is unclear. This study aims to identify the association between VAS and anemia in children under 5 years of age.

Methods

The current study—cross-sectional—is a secondary analysis of the Peruvian Demographic Health Survey 2015-2018. The primary research is nationwide, divided by urban and rural areas of the coastal, highlands, and rainforest regions. It also covers the 43 districts of Lima from 2015 to 2018. The data was collected through home interviews following a previously validated questionnaire. The children undergo weight, height, and blood analysis during their evaluation by trained personnel.

The DHS-trained interviewers surveyed the mothers with standardized assessment tools and instruments. The primary sampling units were the villages in the rural areas and blocks in the urban areas. Furthermore, the secondary sampling units were the household.[14,15]

The participants of this study consisted of children between ages 6 and 59 months old of mothers between 15 and 49 years old. The inclusion criteria for our selected sample include the youngest child under 5 years of age, measurement of hemoglobin levels of the participant, and VAS registered in the documentation records. Furthermore, malnutrition (under 3 SD) for the selected participant's sample was an exclusion criterion.

The leading independent variable, VAS, was measured through a series of questions. The DHS personnel asked if they have received at least 2 doses of VA and verified the supplementation and date in the healthcare card. Then the trained interviewers asked if an additional dose of VA was administered to the participant in the last 6 months. This question is considered "Yes–1" or "No—0" for the present analysis. The number of children between 6 and 59 months who met the selection criteria of our study was 51 609 (Figure 1).

The dependent variable, iron deficiency anemia, was analyzed by measuring the hemoglobin concentration in children. DHS pollsters use a portable HemoCue analyzer by which the hemoglobin concentration is measured through a drop of capillary blood and then adjusted for altitude according to the WHO. If the value was less than 11 mg/dL, it is considered "Yes—1"; if not, it corresponds to "No—0" for the present analysis.

The Peruvian Ministry of Health provides 1 dose of VAS of 100 000 IU to children between 6 and 11 months, 29 days. Subsequently, 1 dose of 200 000 IU is administered twice a year until 59 months of age. Health care officials give VAS when children attend their vaccination control and then registered on their healthcare card. However, the vitamin levels of the children are not measured.[16]

The power calculated considering the design effect was more than 80%, was judged to be optimal since it still has a high power to identify the effect. The computation was using "OpenEpi 3.02." The calculation inputs were: 95% confidence level; 46.7% and 53.9% prevalence of anemia in supplemented and non-supplemented children. The relationship between exposed and

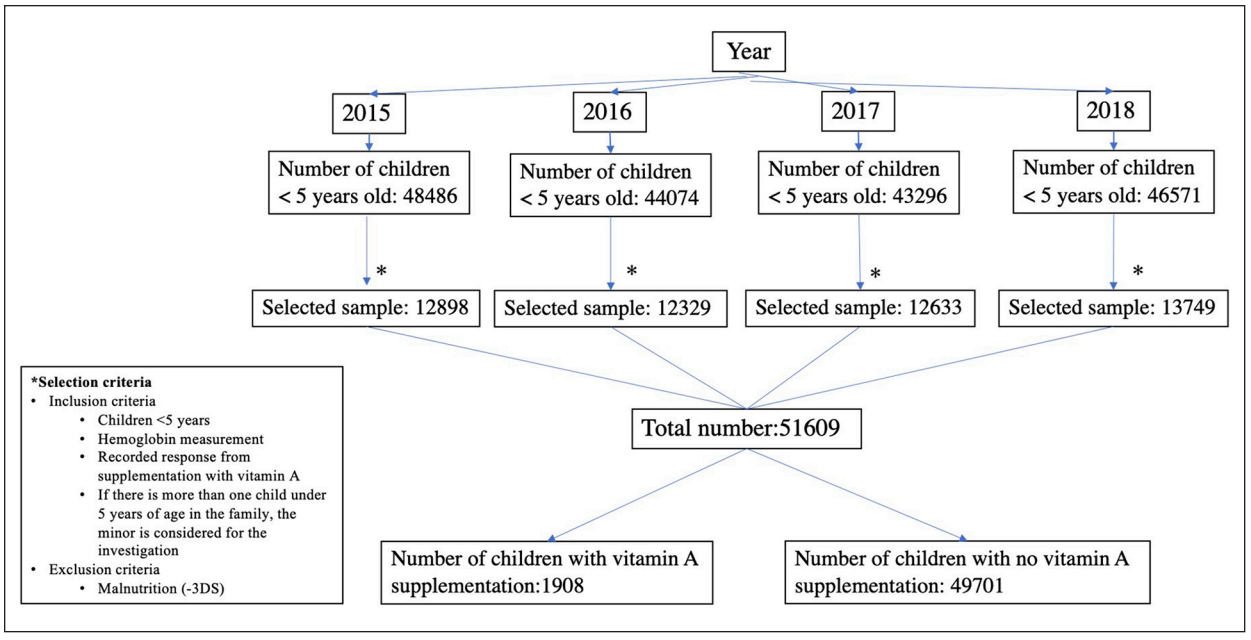

Figure 1. Flowchart of the selection of study participants. Peru ENDES 2015 to 2018.

non-exposed was 3954/32 214 = 0.12. This analysis is based on previous studies.[12,17]

This information was analyzed using the STATA 16 MP program. We considered the complex sampling of the survey in the analysis and implemented Optional svy commands in STATA. Strata based on rural-urban clusters of blocks, primary sampling units (PSU) comprise the homes, and the ponderable weights included the expansion factors. The association measure for the crude and adjusted model was the prevalence ratio with a confidence interval of 95%.

For the descriptive analysis, the categorical variables were evaluated using frequency and weighted percentages. For the bivariate analysis, the association between the sociodemographic variables and VAS exposure was described. For the categorical variables, the Pearson Chi^2 test was used. In the numerical variables in both exposure groups, the regression and the Wald test were used for this analysis.

Lastly, in the multivariable analysis, the association between VAS and anemia was identified by a GLM of the family Poisson and link log function, in a crude and adjusted version, to obtain prevalence ratios controlling any confusing variables epidemiological criteria.[17] We evaluated collinearity using variance inflation factors (VIF) to include the variables in the adjusted model. A correlation was identified between the participant's type of insurance and socioeconomic levels for which alternative models were developed.

Ethical Approval and Informed Consent

The present study has been approved by an ethics committee of a university in Peru given the following approval number: FSC-CEI/345-11-19.

Results

The number of children between 6 and 59 months who met the selection criteria of our study was 51 609 (Figure 1). About 3.5% received VAS and 36.8% had anemia. Furthermore, half of the children were male (50.6%) and most lived in the urban area of Peru (72.3%). Ultimately, it is essential to emphasize that 37% of the participants had anemia, and only 3% received VAS.

VAS was more frequent among those at the inferior quintile (6.8% vs 1% of superior quintile, $P < .001$); Most of the children with VAS belong to the highlands, in contrast with children who lived in the rainforest and coast (6.9% vs 3.9% vs 1.4% accordingly, $P < .001$). More than half (56.5%) of the children belonged to the public insurance SIS, only 4.6% received VAS. Of the 26.5% of children insured with EsSalud, only 1.5% received VAS from 2015 to 2018. Besides, 89.7% of the children were partially vaccinated, and 96.7% of them had not received VAS. Also, 78.2% did not received iron supplementation in the last 7 days, and compared to those who did, only 5% received VAS (Table 1).

Concerning the sociodemographic characteristics, we can see that 30% of the children evaluated have anemia

Table 1. Sociodemographic Characteristics of Children Between 6 and 59 Months According to Vitamin A Supplementation, Peru 2015 to 2018.

	Vitamin A supplementation in the last 6 months			
	Yes	No	Total	
	n = 1908	n = 49 701	n = 51 609	
	n (%)[a]	n (%)[a]	n (%)[a]	*P* value
Sociodemographic characteristics				
Socioeconomic level				
Inferior quintile	801 (6.82)	10 259 (93.18)	11 060 (23.29)	<.001
Second quintile	534 (3.42)	12 677 (96.58)	13 211 (22.69)	
Third quintile	300 (2.01)	11 108 (97.99)	11 408 (20.55)	
Fourth quintile	179 (1.56)	9033 (98.44)	9212 (18.32)	
Superior quintile	94 (1.04)	6624 (98.96)	6718 (15.15)	
Region				
Coast	451 (1.39)	24 125 (98.61)	24 576 (56.77)	<.001
Highlands	981 (6.94)	13 937 (93.06)	14 918 (24.88)	
Rainforest	476 (3.86)	11 639 (96.14)	12 115 (18.35)	
Place of residence				
Urban	999 (1.91)	37 892 (98.09)	38 891 (72.27)	<.001
Rural	909 (6.65)	11 809 (93.35)	12 718 (27.73)	
Sewage				
Public network	978 (2.26)	33 232 (97.74)	34 210 (65.04)	<.001
Other: latrine, river, etc	930 (5.02)	16 469 (94.98)	17 399 (34.96)	
Personal characteristics				
Gender				
Female	906 (3.09)	24 349 (96.91)	25 255 (49.36)	.189
Male	1002 (3.35)	25 352 (96.65)	26 354 (50.64)	
Age in months				
6 to 23 months	852 (3.61)	20 388 (96.39)	21 240 (41.65)	<.001
24 to 59 months	1056 (2.95)	29 313 (97.05)	30 369 (58.35)	
Type of insurance				
Private insurance	5 (0.21)	604 (99.79)	609 (1.73)	<.001
ENT	5 (1.08)	758 (98.92)	763 (2.22)	
FFAA	11 (2.20)	535 (97.80)	546 (1.08)	
EsSalud	293 (1.49)	13 973 (98.51)	14 266 (26.45)	
SIS	1474 (4.57)	28 058 (95.43)	29 532 (56.53)	
No insurance	120 (1.59)	5773 (98.41)	5893 (11.98)	
Deworming in the last 12 months				
Yes	814 (4.67)	15 388 (95.33)	16 202 (29.62)	<.001
No	1094 (2.61)	34 313 (97.39)	35 407 (70.38)	
Diarrhea in the last 2 weeks				
Yes	285 (3.55)	6748 (96.45)	7033 (13.27)	.183
No	1623 (3.17)	42 953 (96.83)	44 576 (86.73)	
Respiratory infections in the last 2 weeks				
Yes	302 (3.20)	7866 (96.80)	8168 (16.82)	.908
No	1606 (3.23)	41 835 (96.77)	43 441 (83.18)	
Current breastfeeding				
Yes	669 (3.67)	15 388 (96.33)	16 057 (31.59)	<.01
No	1239 (3.01)	34 313 (96.99)	35 552 (68.41)	

(continued)

Table 1. (continued)

	Vitamin A supplementation in the last 6 months			
	Yes	No	Total	
	n = 1908	n = 49 701	n = 51 609	
	n (%)[a]	n (%)[a]	n (%)[a]	*P* value
Nutritional status of the child				
Normal	1822 (3.37)	45 745 (96.63)	47 567 (91.87)	<.001
Overweight	71 (1.61)	3002 (98.39)	3073 (6.18)	
Obese	15 (1.39)	954 (98.61)	969 (1.97)	
Vaccination status—DHS				
Not vaccinated	6 (1.06)	476 (98.94)	482 (1.11)	<.05
Partially	1243 (3.26)	33 254 (96.74)	34 497 (69.48)	
Complete	177 (3.70)	4049 (96.30)	4226 (6.72)	
No answer	482 (3.06)	11 922 (96.93)	12 404 (23.68)	
Higher educational status of the mother				
Primary or prior	417 (4.02)	8550 (95.98)	8967 (18.39)	<.001
Secondary	233 (3.75)	5493 (96.25)	5726 (11.30)	
Higher non-university	390 (3.08)	10 588 (96.92)	10 978 (20.92)	
Higher university	146 (3.61)	3491 (96.39)	3637 (6.99)	
Degree	670 (2.61)	20 852 (97.39)	21 522 (40.78)	
No answer	52 (5.95)	727 (94.05)	779 (1.63)	
Supplementation and feeding characteristics				
Iron supplementation in the last 7 days				
Yes	644 (5.04)	10 989 (94.96)	11 633 (21.83)	<.001
No	1264 (2.71)	38 712 (97.29)	39 976 (78.17)	
Consumption of foods rich in iron in the last 24 hours				
Yes	1167 (3.47)	28 821 (96.53)	29 988 (58.34)	<.01
No	741 (2.87)	20 880 (97.13)	21 621 (41.66)	
Consumption of foods rich in vitamin A in the last 24 hours				
Yes	1235 (3.48)	30 266 (96.52)	31 501 (61.31)	<.001
No	673 (2.81)	19 435 (97.19)	20 108 (38.69)	

[a]Weighted percentage.
For all variables, Chi^2 was used.

on the Peruvian coast, compared to 47% and 45% in the highlands and jungle, respectively. 17.64% of children who use a latrine, river, etc, had moderate anemia in comparison with only 9% of those who had access to the public sewage network. Regarding personal characteristics, 23% of children between 6 and 23 months had moderate anemia compared to 4.7% of children between 24 and 59 months of age. As for VAS in the last 6 months, 42.2% of those supplemented presented mild to severe anemia, while 36.6% of the participants who were not supplemented had the same diagnosis (Table 2).

Regarding the unadjusted analysis of the variables associated with anemia (Table 3), the lower socioeconomic quintile is 2.22 times more likely to have anemia compared to the upper quintile (PRc 2.22, 95% CI 2.06-2.39, $P < .001$). Also, the participants living in the jungle are 57% more likely to have anemia than those living in the coast (PRc 1.57, 95% CI 1.49-1.64, $P < .001$). Children who lived in a household without public sewage network were 1.47 times more likely to have anemia than those who did (PRc 1.47, 95% CI 1.41-1.52, $P < .001$). Regarding gender, males were 9% more likely to have anemia than females (PRc 1.09, 95% CI 1.05-1.12, $P < .001$). Concerning insurance, children with privately insured parents had 37% less probability of anemia diagnosis than those not insured (PR 0.63, 95% CI 0.49-0.82, $P = .001$). Likewise, being certified by SIS indicates 1.27 times more probabilities of suffering from anemia compared to the uninsured (PR 1.27, 95% CI 1.20-1.35, $P < .001$).

In the unadjusted model, the association between VAS and anemia is illustrated. Those with VAS have a 15% higher prevalence of anemia than those not supplemented (PRc 1.15, 95% CI 1.06-1.24, $P < .001$). On the other hand, in the adjusted model 1, there was no association between VAS and anemia (PRa 0.95, 95% CI

Table 2. Sociodemographic characteristics of children between 6 and 59 months according to Anemia levels, Peru 2015-2018.

		Anemia								
		No Anemia		Mild		Moderate		Severe		
		n = 32170		n = 12593		n = 6679		n = 167		*p* value
Sociodemographic Characteristics		n	%[a]	n	%[a]	n	%[a]	n	%[a]	
Socioeconomic Level	Inferior Quintile	5618	50.63	3242	29.40	2143	19.44	57	0.52	<0.001
	Second Quintile	7482	57.56	3621	27.17	2062	14.98	46	0.29	
	Third Quintile	7371	65.64	2684	23.22	1306	10.84	47	0.30	
	Fourth Quintil	6542	71.43	1863	20.20	792	8.23	15	0.13	
	Superior Quintile	5157	77.79	1183	17.02	376	5.16	2	0.02	
Region	Coast	17076	69.99	5244	21.23	2222	8.66	34	0.10	<0.001
	Highlands	8201	55.26	3986	26.51	2629	17.57	102	0.65	
	Rainforrest	6893	53.02	3363	29.53	1828	17.19	31	0.25	
Plac of Residence	Urban	25469	67.32	8946	22.30	4375	10.20	101	0.18	<0.001
	Rural	6701	52.52	3647	28.67	2304	18.30	66	0.49	
Sewage	Public Network	9328	68.38	4950	21.76	3045	9.64	76	0.19	<0.001
	Other: latrine, river, etc	22842	53.59	7643	28.35	3634	17.64	91	0.40	
Personal Characteristics										
Gender	Female	16201	64.75	6023	23.58	2980	11.51	51	0.15	<0.001
	Male	15969	61.72	6570	24.54	3699	13.35	116	0.38	
Age in months	6 to 23 months	9314	45.17	6725	31.07	5063	23.22	138	0.55	<0.001
	24 to 59 months	22856	76.09	5868	19.07	1616	4.77	29	0.08	
Type of Insurance	Private Insurance	479	78.87	106	18.39	23	2.72	1	0.02	<0.001
	ENT	614	81.12	111	14.55	38	4.32	0	0.00	
	FFAA	380	71.14	126	20.78	40	8.08	0	0.00	
	EsSalud	9885	71.07	3029	20.39	1320	8.36	32	0.15	
	SIS	16887	57.49	7925	26.80	4607	15.36	113	0.35	
	No Insurance	3925	66.58	1296	22.15	651	10.97	21	0.31	
Deworming in the last 12 months	Yes	11717	72.99	3405	20.86	1070	6.10	10	0.52	<0.001
	No	20435	59.10	9188	25.41	5609	15.12	157	0.36	
Diarrhea in the last 2 weeks	Yes	3623	50.98	2029	29.02	1339	19.38	42	0.61	<0.001
	No	28547	65.08	10564	23.31	5340	11.39	125	0.22	
Respiratory infecctions in the last 2 weeks	Yes	4764	59.12	2137	25.96	1231	14.55	36	0.36	<0.001
	No	27406	64.04	10456	23.68	5448	12.02	131	0.25	
Current Breastfeeding	Yes	6365	40.84	5236	32.06	4329	26.44	127	0.65	<0.001
	No	25805	73.54	7357	20.37	2350	5.98	40	0.10	

(continued)

Table 2. (continued)

		Anemia								
		No Anemia		Mild		Moderate		Severe		
		n = 32170		n = 12593		n = 6679		n = 167		*p* value
Nutritional status of the child	Normal	29277	62.32	11858	24.68	6276	12.71	156	0.27	<0.001
	Overweight	2137	71.54	599	18.32	328	9.92	9	0.22	
	Obese	756	78.62	136	13.26	75	7.97	2	0.14	
Vaccination status - DHS	Not vaccinated	226	42.79	129	28.66	122	27.13	5	1.41	<0.042
	Partially	21619	64.21	8480	23.91	4293	11.62	105	0.26	
	Complete	3042	72.51	846	19.57	332	7.8	6	0.13	
	No answer	7283	58.66	3138	25.56	1932	15.47	51	0.31	
Higher educational status of the mother	Primary or prior	5268	59.66	2386	25.94	1267	14.00	46	0.40	<0.001
	Secondary	3557	62.93	1345	23.74	806	13.03	18	0.29	
	Higher Non-university	7096	65.92	2530	22.26	1320	11.54	32	0.28	
	Higher University	2076	57.76	983	26.52	570	15.58	8	0.14	
	Degree	13763	64.94	5118	23.52	2583	11.30	58	0.24	
	No answer	410	50.64	231	31.38	133	17.63	5	0.35	
Supplementation and Feeding Characteristics										
Iron Supplementation in the last 7 days	Yes	6039	52.97	3367	28.61	2180	18.03	47	0.38	<0.001
	No	26131	66.07	9226	22.79	4499	10.89	120	0.24	
Consumption of foods rich in iron in the last 24 hours	Yes	16018	54.87	8552	27.78	5280	16.98	138	0.36	<0.001
	No	16152	74.90	4041	18.86	1399	6.08	29	0.13	
Supplementation of Vitamin A in the last 6 months	Yes	1087	57.82	519	26.87	285	14.30	17	1.01	<0.001
	No	31083	63.39	12074	23.97	6394	12.38	150	0.25	
Consumption of foods rich in Vitamin A in the last 24 hours	Yes	16687	54.33	9017	28.03	5649	17.25	148	0.38	<0.001
	No	15483	77.29	3576	17.78	1030	4.84	19	0.09	

[a] Weighted percentage
For all variables, Chi2 was used

Table 3. Unadjusted and Adjusted Analysis Between Vitamin A Supplementation and Anemia in Children Between 6 and 59 Months, Peru 2015 to 2018.

	PR[b] unadjusted		PR[b] Adjusted Model 1		PR[b] Adjusted Model 2	
	PRc[c] (95% IC, [LI-LS])	*P* value	PRa[d] (95% IC, [LI-LS]	*P* value	PRa[d] (95% IC, [LI-LS]	*P* value
Vitamin A supplementation in the last 6 months						
No	Ref.		Ref.		Ref.	
Yes	1.15 (1.06-1.24)	<.001	0.95 (0.87-1.04)	.234	0.97 (0.88-1.05)	.415
Sociodemographic characteristics						
Socioeconomic level						
Top quintile	Ref.		Ref.			
Inferior quintile	2.22 (2.06-2.39)	<.001	1.83 (1.68-2.00)	<.001		
Second quintile	1.91 (1.77-2.05)	<.001	1.74 (1.60-1.89)	<.001		
Third quintile	1.55 (1.44-1.67)	<.001	1.51 (1.39-1.65)	<.001		
Fourth quintile	1.29 (1.19-1.40)	<.001	1.28 (1.17-1.40)	<.001		
Region						
Coast	Ref.		Ref.		Ref.	
Highlands	1.49 (1.43-1.56)	<.001	1.29 (1.22-1.36)	<.001	1.43 (1.36-1.51)	<.001
Rainforest	1.57 (1.49-1.64)	<.001	1.21 (1.15-1.28)	<.001	1.37 (1.29-1.44)	<.001
Place of residence						
Urban	Ref.					
Rural	1.45 (1.40-1.51)	<.001				
Sewage						
Public network	Ref.					
Other: latrine, river, etc	1.47 (1.41-1.52)	<.001				
Personal characteristics						
Gender						
Female	Ref.		Ref.		Ref.	
Male	1.09 (1.05-1.12)	<.001	1.11 (1.07-1.15)	<.001	1.11 (1.07-1.15)	<.001
Age in months	0.97 (0.96-0.97)	<.001	0.96 (0.96-0.97)	<.001	0.96 (0.96-0.97)	<.001
Type of insurance						
No insurance	Ref.				Ref.	
SIS	1.27 (1.20-1.35)	<.001			1.13 (1.06-1.22)	<.001
Essalud	0.87 (0.81-0.93)	<.001			0.91 (0.85-0.99)	.021
FFAA	0.86 (0.72-1.04)	.123			0.94 (0.76-1.16)	.558
ENT	0.57 (0.46-0.70)	<.001			0.60 (0.48-0.77)	<.001
Private insurance	0.63 (0.49-0.82)	.001			0.70 (0.54-0.91)	.008
Deworming in the last 12 months						
No	Ref.		Ref.		Ref.	
Yes	0.66 (0.64-0.69)	<.001	0.88 (0.84-0.92)	<.001	0.89 (0.84-0.93)	<.001
Diarrhea in the last 2 weeks						
No	Ref.		Ref.		Ref.	
Yes	1.40 (1.35-1.46)	<.001	1.10 (1.05-1.15)	<.001	1.11 (1.06-1.16)	<.001
Respiratory infections in the last 2 weeks						
No	Ref.		Ref.		Ref.	
Yes	1.14 (1.09-1.19)	<.001	1.06 (1.01-1.11)	.020	1.07 (1.02-1.12)	.004
Nutritional status of the child						
Overweight	Ref.		Ref.		Ref.	
Normal	1.32 (1.22-1.43)	<.001	1.12 (1.03-1.22)	.007	1.15 (1.05-1.25)	.002
Obese	0.75 (0.63-0.90)	.002	0.85 (0.69-1.05)	.122	0.84 (0.68-1.04)	.103
Vaccination status—DHS						
Complete	Ref.		Ref.		Ref.	
Partially	1.35 (1.25-1.46)	<.001	0.86 (0.79-0.93)	<.001	0.87 (0.80-0.94)	.001
Not vaccinated	2.45 (2.10-2.86)	<.001	1.10 (0.96-1.26)	.184	1.21 (1.05-1.39)	.007

(continued)

Table 3. (continued)

	PR[b] unadjusted		PR[b] Adjusted Model 1		PR[b] Adjusted Model 2	
	PRc[c] (95% IC, [LI-LS])	*P* value	PRa[d] (95% IC, [LI-LS]	*P* value	PRa[d] (95% IC, [LI-LS]	*P* value
Supplementation and feeding characteristics						
Iron supplementation in the last 7 days						
No	Ref.					
Yes	1.39 (1.34-1.43)	<.001				
Consumption of foods rich in iron in the last 24 hours						
No	Ref.					
Yes	1.80 (1.73-1.87)	<.001				
Consumption of foods rich in vitamin A in the last 24 hours						
No	Ref.					
Yes	2.01 (1.93-2.10)	<.001				

[b]PR: Prevalence ratio (c = crude, a = adjusted), 95 CI%: 95% confidence level.
[c]Crude generalized linear model of the logarithmic Poisson link log family. The results are presented as prevalence ratios (PRc).
[d]Adjusted generalized linear model of the logarithmic Poissong link log family. The results are presented as prevalence ratios (PRd). For the entire analysis, complex sampling (svy) was considered.

0.87-1.04, $P = .284$) when adjusted by the socioeconomic level, gender of the child, region, deworming in the last 12 months, diarrhea in the past 2 weeks, respiratory infections during the previous 2 weeks, child's nutritional status and child's immunization status. This association was not significant. Likewise, in the adjusted model 2, modified by region, gender, type of insurance, deworming in the last 12 months, diarrhea in the past 2 weeks, respiratory infections in the past 2 weeks, nutritional status of the child and vaccination status, VAS continues without a significant association (PRa 0.97, 95% CI 0.88-1.05, $P = .415$). Children with SIS insurance were 1.13 times more likely to have anemia in comparison with those who were not insured (PRa 1.13, 95% CI 1.06-1.22, $P < .001$) when adjusted for VAS, region, gender, deworming in the last 12 months, diarrhea in the previous 2 weeks, respiratory infections in the last 2 weeks, child's nutritional status, and immunization status. Also, children ensured by private entities were 30% less likely to suffer from anemia than the uninsured (PRa 0.70, 95% CI 0.54-0.91, $P = .008$), being a protective factor when adjusted by VAS, region, gender, deworming in the last 12 months, diarrhea in the previous 2 weeks, respiratory infections in the past 2 weeks, child's nutritional status and vaccination status (Table 3).

Discussion

The results of this study show no significant association between VAS and anemia (PRa 0.95, 95% CI 0.87-1.04, $P = .284$). Despite this, there was a 5% reduction of anemia in supplemented children. Similarly, another Peruvian study found a non-significant association between iron deficiency anemia in children who received VAS.[13] These results differ from an investigation in Ethiopian children 6 to 59 months of age where VAS was associated with a 9% reduction in the risk of anemia (RR = 0.91 (95% CI: 0.86-0.96).[17] Likewise, another study in 5 to 13-year-old children from local primary schools in the Rif Mountains of northern Morocco concluded that VA treatment increased mean hemoglobin by 0.7 g/dL and reduced the prevalence of anemia from 54% to 38%.[11] Still, VA was administered only to children with a low VA status, contrary to our research and the Ethiopian investigation where VA levels were unknown.

According to the guides established by the Health Ministry of Peru,[15] the government should supplement all children between 6 and 59 months with VA. We found that the health officials supplemented only 3.2% of the referred population with VA, a very low coverage rate. This result can explain the insignificant association between VAS and anemia found in this study. A study based on Peru mentioned that from 2013 onward, VA capsules were bought by the Ministry of Health directly to supplement the infant population. Still, data showed low coverage of VAS (6.5% for 2015) explained by acquisition and supply drawbacks.[18] An Ethiopian investigation that related a single dose of VAS with anemia using mean difference also had a small supplemented population (2397 children); however, they did found that children who received VA had 1.50 g/L (95% CI: 0.30-2.70) higher mean difference ($P = .014$) in favor of the supplemented group.[17]

The Peruvian Ministry of Health indicates 1 dose of VAS of 100 000 IU to children between 6 and 11 months

and 29 days. Subsequently, 1 dose of 200 000 IU is administered twice a year until 59 months.[15] In a Moroccan study, the VAS was 200 000 IU; nevertheless, the supplementation was exclusive to participants with VAD.[11] The Ethiopian children received a declared dose of 30 or 60 mg (1200 or 2400 UI) of VA, a smaller quantity; however, in our study, the supplementation was administered without knowledge of the VA status.[17] As the results show, the Moroccan research had a more considerable decrease in the prevalence of anemia than the Ethiopian investigation, yet both studies are contrary to our findings. More research is needed to discern if the relationship between VAS and anemia depends on previous VAD status and the optimal VAS dose.

Regarding the VAS among sociodemographic factors, our study found no significant difference in supplementation according to age, but the VAS coverage is higher in urban areas compared to rural areas. A study conducted in sub-Saharan Africa revealed that the coverage of VAS appeared to vary across categories of children's age and socioeconomic status; children aged 6 to 11 months were less likely to have received VAS (48.6%) than older children (57.9%). The coverage in urban areas (63.9%) was significantly higher than that of rural areas (53.9%).[19] This information supports the concern that the VAS in the Peruvian pediatric population might not be optimized and focused correctly and thus restraining the possible investigated benefits in this study.

Regarding the study's limitations, VA levels were not measured in blood; we only know if they were supplemented or not. Likewise, there was no registration of how many children receive VA and iron from other sources. There may be sub-registers; children supplemented with VA without a Healthcare card, without registration, or with cards incorrectly registered that are not being considered. As a cross-sectional study, it is impossible to know how VA and Hb levels change with the supplementation. Moreover, zinc levels were not measured, and they are known to be related to VA levels in the blood. Additionally, the number and administration sources of VAS were poorly registered in the healthcare card. While iron supplementation was considered in the study, those supplemented with micronutrients that include a dose of 300 µg of VA were not specified.[15] Even though iron deficiency anemia is the most prevalent, it is important to keep in mind that there are other causes of anemia and in the primary study these other causes were not evaluated.

The present study can encourage others to continue exploring the association between anemia and VAS, yet selecting a larger supplemented population, comparing different VA doses, and comparing its effectiveness in those with and without VAD and anemia. Furthermore, the results identified in this investigation can guide the Peruvian government to optimize VAS approaches.

VAS was not significantly associated with a lower prevalence of anemia in children under 5 years of age in Peru, 2015-2018. The association was statistically significant using crude regression but disappeared when adjusted per socioeconomic level and gender. This can be explained by the uneven distribution of VA among socioeconomic levels and by the higher prevalence of anemia in males. Future studies may consider conducting a longitudinal study instead of cross-sectional so that VA and hemoglobin levels can be measured and evaluated over time. Further studies are required to help identify the association between VAS and anemia. For future investigations, we recommend measuring VA levels in the blood and relating them to hemoglobin levels.

Author Contributions

IR and CA contributed with the main idea. IR, CA, and DB, contributed equally with the design, analysis, interpretation, critical revision, and final approval of the manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iDs

Camila B. Aramburú-Duclos https://orcid.org/0000-0001-8260-7647
Dora Blitchtein https://orcid.org/0000-0002-9986-7442

References

1. World Health Organization. Malnutrition. WHO. 2016. Accessed September 4, 2019. https://www.who.int/news-room/fact-sheets/detail/malnutrition
2. Campos Ponce M, Polman K, Roos N, Wieringa FT, Berger J, Doak CM. What approaches are most effective at addressing micronutrient deficiency in children 0-5 Years? A review of systematic reviews. *Matern Child Health J*. 2019;23:4-17.
3. Penkert RR, Rowe HM, Surman SL, Sealy RE, Rosch J, Hurwitz JL. Influences of vitamin A on vaccine immunogenicity and efficacy. *Front Immunol*. 2019;10:1576.
4. UNICEF., (Peru) IN de E e I. Estado de la niñez en el Perú. UNICEF; 2011.
5. Zhang X, Yang K, Chen L, et al. Vitamin A deficiency in critically ill children with sepsis. *Crit Care*. 2019;23:267. doi:10.1186/s13054-019-2548-9

6. Mayo Clinic. Iron deficiency anemia. Rochester: Mayo Clinic. 2016. Accessed September 4, 2019. https://www.mayoclinic.org/diseases-conditions/iron-deficiency-anemia/symptoms-causes/syc-20355034
7. Alcázar L. Impacto Económico de la Anemia en el Perú. GRADE. 2012. Accessed September 4, 2019. http://www.grade.org.pe/upload/publicaciones/archivo/download/pubs/LIBROGRADE_ANEMIA.pdf
8. Suchdev PS, Ruth LJ, Woodruff BA, et al. Selling sprinkles micronutrient powder reduces anemia, iron deficiency, and vitamin A deficiency in young children in western Kenya: a cluster-randomized controlled trial. *Am J Clin Nutr*. 2012;95(5):1223-1230.
9. Cañete A, Cano E, Muñoz-Chápuli R, Carmona R. Role of vitamin A/retinoic acid in regulation of embryonic and adult hematopoiesis. *Nutrients*. 2017;9(2):159.
10. Arruda SF, Siqueira EM, de Valência FF. Vitamin a deficiency increases hepcidin expression and oxidative stress in rat. *Nutrition*. 2009;25(4):472-478.
11. Zimmermann MB, Biebinger R, Rohner F, et al. Vitamin A supplementation in children with poor vitamin a and iron status increases erythropoietin and hemoglobin concentrations without changing total body iron. *Am J Clin Nutr*. 2006;84(3):580-586.
12. Pajuelo J, Miranda M, Zamora R. Prevalence of vitamin A deficiency and anemia in children under five years of age in Peru. *Rev Peru Med Exp Salud Publica*. 2015;32(2):245-251.
13. Alarcon K, Kolsteren PW, Prada AM, et al. Effects of separate delivery of zinc or zinc and vitamin a on hemoglobin response, growth, and diarrhea in young Peruvian children receiving iron therapy for anemia. *Am J Clin Nutr*. 2004;80:1276-1282.
14. INEI. PERÚ Instituto Nacional de Estadística e Informática. Accessed January 12, 2021. http://iinei.inei.gob.pe/microdatos/
15. ENDES. Encuesta Demgráfica y de Salud Familiar, Ficha Técnica 2017. Accessed January 12, 2021. http://iinei.inei.gob.pe/iinei/srienaho/Descarga/FichaTecnica/605-Ficha.pdf
16. Dirección General de Salud M de Salud del P. RM N° 706-2014-MINSA. Directiva sanitaria que establece la suplementación con multimicronutrientes y hierro para la prevención de anemia en niñas y niños menores de 36 meses. 2014. Accessed October 28, 2020. http://bvs.minsa.gob.pe/local/MINSA/3933.pdf
17. Gebremedhin S. Effect of a single high dose vitamin A supplementation on the hemoglobin status of children aged 6Ł59Łmonths: propensity score matched retrospective cohort study based on the data of Ethiopian Demographic and Health Survey 2011. 2014. Accessed September 11, 2019. http://www.biomedcentral.com/1471-2431/14/79
18. Huicho L, Tavera M, Huayanay-Espinoza CA, et al. Drivers of the progress achieved by Peru in reducing childhood diarrhea mortality: a country case study. *J Glob Health*. 2019;9(2):020805.
19. Berde AS, Bester P, Kruger IM. Coverage and factors associated with vitamin A supplementation among children aged 6-59 months in twenty-three sub-Saharan African countries. *Public Health Nutr*. 2019;22(10):1770-1776.