

Anemia Is Related to Iron Deficiency and Inflammation, But No to Global Overweight in Cuban Preschool Children

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Abstract: The main cause of anemia in the preschool population is dietary iron deficiency; however, there are other conditions that can lead to anemia such as diseases that produce chronic inflammation and obesity. The objective was to evaluate the prevalence of anemia and iron deficiency in children aged 6 to 59 months and the association with inflammation, global overweight and maternal educational level. A national sample of cross-sectional study design was carried out. Hemoglobin, ferritin, soluble transferrin receptors, leukocytes, C-reactive protein, and alpha-1 acid glycoprotein were assessed. Nutritional status was evaluated and level of mother education was collected by survey. A total of 1417 children were studied. Anemia prevalence was 22.5% and constitutes a moderate public health problem. Iron deficiency prevalence was 35.6% and erythropoietic dysfunction 13.3%; with elevated inflammation indicators 37.6% and leukocytosis 36.1%. Malnutrition occurred in 1.0% of the children, with a prevalence of overweight in 4.7% and obesity in 2.8%. Anemia was associated with iron storage deficiency OR=2.07 (1.45-2.97) and inflammation OR=2.01 (1.45-2.78). No associations were found between anemia OR=0.68 (95% CI= 0.35-1.32) and iron deficiency OR=0.96 (95% CI= 0.68-1.35) with global overweight. Global overweight does not explain the inflammation found OR=1.13 (95% CI= 0.54-2.37), neither by CRP OR=0.57 (0.24-1.37) or AGP OR=1.14 (0.54-2.42). Low education level of the mother was associated with anemia in the children (χ^2 trend= 4.327 p=0.037), but not with iron deficiency (χ^2 trend= 0.212 p=0.646). Anemia and iron deficiency in Cuban preschool children was a moderate public health problem associated with inflammation.

Keywords: Anemia, Iron Deficiency, Inflammation, Preschool Children, Overweight

1. Introduction

The main cause of anemia in the preschool population is

dietary iron deficiency, as well as hemoglobinopathies and hemolytic anemias. In 2019, the main attributable cause was dietary iron deficiency, mainly in the group aged 1 to 4 years [1]. However, there are other conditions that can lead to

anemia such as diseases that produce chronic inflammation, acute infections that often coexist with iron deficiency, and deficiency of other vitamins and minerals [2].

In developing countries, nutritional anemia due to iron deficiency affects more than 50% of children between 6 months and 5 years old and is considered one of the risk factors that lead to inadequate development and a serious public health problem [3]. Anemia is often a multifactorial pathophysiology condition with a high burden on health [4].

Iron deficiency and obesity commonly coexist, known as the double burden malnutrition, which can be found in the individual, in the family and in populations [5].

Maternal educational level is an important determinant of health. It has been suggested that women who lack education are at increased risk of anemia and their children are also more likely to develop it [6].

In Cuba, evaluations of the prevalence of anemia are carried out through a nutritional food surveillance system, but a national study for the evaluation of iron deficiency in the child population had not been carried out. Knowledge of the factors that may be influencing anemia and iron deficiency is necessary for the proposal of new actions. In addition, the evaluation of indicators of anemia and iron deficiency allows the monitoring of existing programs in the country.

The objective of this study was to evaluate the prevalence of anemia and iron deficiency in children aged 6 to 59 months and its association with inflammation, global overweight and maternal educational level.

2. Materials and Experiments

The universe consisted of children from 6 to 59 months. A sample size of 1,400 children was calculated assuming an overall anemia prevalence of 20% in the country in this age group, a predicted sample size reduction of 10% due to non respond, a confidence level of 95%, a relative precision of <3% and a design effect of 2%.

Cuba has 15 provinces and one Special Municipality. The sample was stratified by region: west, central, east (northeast and southeast) and the province of Havana, the latter considered a region in itself. Each region was represented by either one or two provinces. Two provinces were selected at random in the Western and Central regions: Mayabeque Province and the Isle of Youth Special Municipality, considered here as a province, in the West; and Sancti Spiritus and Cienfuegos Provinces in the Central Region. For the northeast and southeast regions, we randomly selected only one province per Region: Holguín Province for the northeast, and Santiago de Cuba province for the southeast. We randomly selected 30% of municipalities from each province, which included the municipal capital.

Two-stage cluster sampling was used, in which the health areas were the primary selection units within the municipality, and the family doctor's and nurse's offices were the secondary units. It was proposed to study 200 children in each selected province. The number of practices selected was the minimum necessary to reach the planned sample size

taking into account the number average number of children per offices in each municipality. All children seen in the selected offices were studied.

Inclusion criteria: The study included presumably healthy children, free of chronic disease (sickle cell anemia, diabetes, kidney disease, epilepsy, severe or moderate asthma, or any other disease requiring treatment or specialized medical care).

Based on these criteria, we enrolled 1417 children in the survey database. The chosen children were those with measurements of hemoglobin (Hb) to evaluate anemia, ferritin and soluble transferrin receptors (sTfR) to estimate iron deficiency; leukocytes, α -1 acid glycoprotein (AGP) and C-Reactive Protein (CRP) for inflammation.

The data formed the national survey of anemia and iron deficiency in Cuban preschool children, carried out by the National Institute of Hygiene, Epidemiology and Microbiology (INHEM acronym in Spanish) between the months of February and April during 2015-2018.

2.1. Procedures

Four mL of total blood were taken by antecubital puncture, 1 mL with 10% EDTA and 3 mL were extracted to obtain serum. Samples were centrifuged the same day as extraction, and blood serum was stored at -40°C for later analysis for ferritin, sTfR and inflammation indicators.

Hb and leukocytes were determined in an ABX Micros 60 Hematology Counter. Iron deficiency was measured through ferritin and sTfR concentration, and inflammation through serum high-sensitivity CRP and AGP. Ferritin and inflammation indicators were determined by the immunoturbidimetric method (CPM Scientifica Technologie Biomediche, Italy) on INLAB 240 equipment. Ferritin concentrations were adjusted for inflammation using the quantile regression method [7].

The sTfR was performed by ELISA method, Ramco Laboratories INC [8]. Adjustment of sTfR by inflammation was performed by the Correction Factor method, using the same methodology for the adjustment of ferritin [9].

These determinations were made in the INHEM Nutritional Anemia Laboratory.

Nutritional status was assessed by anthropometry in order to assess overweight and obesity. Body weight was measured, supine length was taken in infants, and standing height was obtained in those over 2 years, 12 months, and 29 days using standardized instruments. Triceps and subscapular skinfolds were measured to estimate body adiposity. The results for the evaluation of the children were grouped for their classification according to the Z scores of the WHO international standards.

In the analysis of the anthropometric results, the cases belonging to the "overweight" and "obese" groups were classified as "global overweight".

As an epidemiological variable, the educational level of the mother was analyzed.

2.2. Data Collection and Analysis

A database was created. The biochemical variables were described according to their distribution by percentiles

(Median, 25th Percentile and 75th Percentile). For the categorical variables, the total prevalence and the 95% confidence intervals (95% CI) were calculated, by age group and region. Prevalence calculations were made taking into account the sample design.

For the association analysis, the variables were categorized into two levels and the Odds Ratio (OR) with its 95% CI was used. In this case, for the estimates, the sample design was also taken into account.

The associations were stratified by region and by age group. Age group was defined as <2 years (6-23 months) and ≥ 2 years (24-59 months). To assess differences in these groups, Wald's χ^2 test was performed. A χ^2 trend analysis was performed for the mother's education level variable. The levels were defined as: None, Elementary and Junior High/Technical and Pre-university/University.

SPSS v20.0 statistical programs were used to prepare the database. The SAS 9.1 statistical package was used, which allows the complex sampling design of the sample to be taken into account for the estimation of the statistics and their standard errors, as well as the statistical tests used. The SPSS and SAS programs were used to evaluate the associations. In all cases, a significance level of $p < 0.05$ was considered.

Ethical aspects: The study was authorized by the Maternal-Child Division of the Ministry of Public Health, after reviewing the research's ethical aspects. All mothers gave informed consent to include their children in the study. It was conducted according to principles for conducting research in human subjects outlined by the Helsinki Declaration [15] and the protocol was approved by the research ethics committee assigned to this project.

Table 1 shows the study variables and cut-off points.

Table 1. Study variables in preschool children. Cuba 2015-2018.

Variable	Category
Biochemistry variable	
Anemia [10]	
Yes	Hb <110 g/L
No	Hb \geq 110 g/L
Anemia severity [10]	Severe: Hb <70 g/L
	Moderate: 70–99 g/L
	Mild: 100–109 g/L
Anemia as a Public Health Problem [11]	Severe: $\geq 40\%$ of the population
	Moderate: 20–39.9%
	Mild: 5–19.9%
	No Health Problem: <5%
Iron storage deficiency [11]	
Iron storage deficiency:	Ferritin <12 μ g/L
No Iron storage deficiency:	Ferritin \geq 12 μ g/L
Iron storage deficiency as a Public Health Problem [11]	High: $\geq 40\%$ of the population
	Moderate: 20–39.9%
	Mild: 5–19.9%
	No Health Problem: <5%
Soluble Transferrin Receptor (sTfR)*	
Iron erythropoietic dysfunction	>8,3 μ g/mL
No Iron erythropoietic dysfunction	\leq 8,3 μ g/mL
Leukocytes [12]	
Leukocytosis	> 10,000/mm ³
Normal	\leq 10,000/mm ³
Inflammation [11]	C-Reactive Protein (hs): >5 mg/L
Nutritional variables	α -1 acid glycoprotein: >1g/L
	Zscore
Nutritional status [13, 14]	<-2SD Wasting
	-2DS-+2DS Normal
	>+2DS Overweight
	>+3DS Obesity
Adiposity [13, 14]	Tricipital and Subscapular Skinfolts
	<-2SDLow Adiposity
	-2DS-+2DS Normal
	>+2DS High Adiposity
	>+3DS Very High Adiposity
Epidemiology variable	
	None
	Elementary
Mother Instruction	Junior High School
	Technical
	Pre-university
	University

* kit references values.

3. Results

A total 1370 children with of Hb and Leukocytes were included, 1375 with indicators of iron deficiency and inflammation and 1363 with sTfR. The cause of the missing

data does not represent a risk of bias, because it responds to random causes.

The descriptive biochemical results studied in children are shown in Table 2.

Table 2. Biochemistry indicators in 6 to 59 month preschool children. Cuba 2015-2018.

Indicator	P25	P50	P75	Min	Max
Hb (g/L) n=1370	111	117	124	71	145
Ferritin (µg/L) n=1375	7,98	18,08	35,90	0,54	236,45
Soluble Transferrin Receptors (sTfR) (µg/mL) n=1365	4,84	5,90	7,15	2,87	27,96
Leukocytes N=1370 n/mm ³	7,5	9,0	11,1	2,9	22,6
CRP (mg/L) n=1375	0,65	0,98	1,97	0,10	137,44
AGP (g/L) n=1375	0,74	0,90	1,10	0,04	2,76

The Hb percentiles indicate that more than 75% of the population studied has adequate values for their age, although the 25th percentile (P25) is very close to the Hb cut-off point for anemia.

Of the indicators of iron deficiency, more than 25% of the children had values indicative of iron storage (ferritin) deficiency and more than 75% of the children had adequate values of sTfR.

More than 25% of the children had leukocytosis, an indicator of some type of unreported infection. Median CRP

values were below the recommended cutoff point for acute inflammation, and more than 75% of children had no inflammation. However, more than 25% of the children had elevated AGP values (chronic inflammation).

The prevalence of anemia in Cuba in preschool children was 22.5%, classified as a Moderate Public Health problem (Table 3). Mild anemia was the most founding with 81.1% and Moderate 18.9%; Severe anemia was not finding. No differences were found in anemia by sex (male 22.5%, female 22.4%).

Table 3. Anemia, iron deficiency and inflammation prevalence in preschool children by group of age. Cuba 2015-2018.

Indicators	% (CI95%) 6-23 months (<2 years)	% (CI95%) 24 a 59 months (≥2 years)	% (CI95%) Total
Anemia	41,2 (35,9-46,5)	11,6 (7,8-15,3)	22,5 (18,1-26,9)
Iron storage deficiency (Ferritin <12µg/L)	41,5 (32,1-51,0)	31,8 (26,4-37,3)	35,5 (29,4-41,6)
Iron erythropoietic dysfunction (sTfR>8,3 µg/mL)	21,3 (10,3-32,2)	8,6 (3,6-13,5)	13,3 (5,6-21,0)
Leukocytosis (> 10,000/mm ³)	46,6 (39,8-53,4)	30,1 (24,2-35,9)	36,1 (33,5-38,7)
CRP>5mg/L	13,8 (10,6-17,0)	11,5 (8,6-14,3)	13,3 (10,0-14,7)
AGP>1g/L	40,6 (33,4-47,7)	32,3 (26,8-37,9)	35,4 (29,8-41,0)
Inflammation (high CRP o AGP)	42,4 (36,4-48,4)	34,7 (29,5-39,8)	37,6 (32,5-42,6)

In infants, anemia was found in 57.0% (95% CI = 47.4%-66.6%), which is why it was considered a Severe Public Health problem. The prevalence of anemia in <2 years (41.2%) was also considered a Severe Public Health problem, and was approximately 3.5 time higher than ≥2 years.

Iron storage deficiency was found in a third of the children studied and less than a fifth of the population had erythropoietic dysfunction.

Iron storage deficiency explained 48.6% of cases of anemia, while in children without anemia 31.3% had iron storage deficiency.

No differences were found by age groups in the deficiency of iron stores. However, higher prevalence of erythropoietic dysfunction were observed in the group <2 years.

Just over a third of the children had elevated indicators of inflammation (37.6%) and leukocytosis (36.1%), a sign of the presence of some infection (viral or bacterial), with higher prevalence in children <2 years.

The analysis by region of anemia as a public health problem allowed the classification of the Western Region as Mild, unlike the Eastern, Central and Havana Regions, which are considered Moderate.

Children <2 years presented higher prevalence of anemia

in the Eastern and Central regions, compared to the Western and Havana (Figure 1).

Table 4 shows the prevalence of anemia, iron deficiency and inflammation by region.

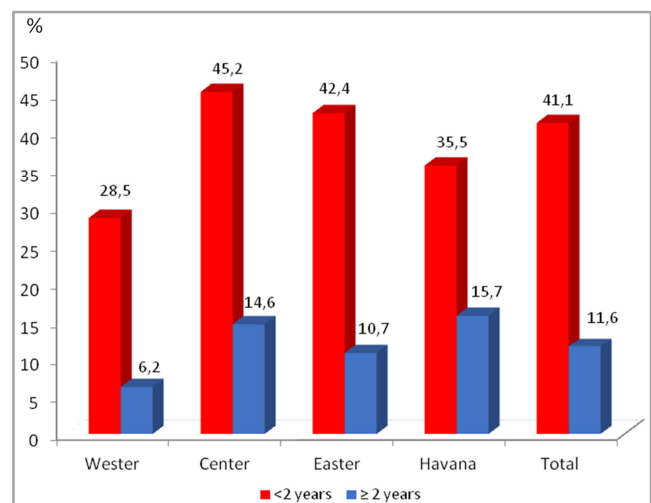


Figure 1. Anemia prevalence by region and group of age. Cuba 2015-2018.

Table 4. Anemia, Iron deficiency and Inflammation prevalence by region of preschool children 6 to 59 months. Cuba 2015-2018.

Indicator	West Region % (CI95%)	Central Region % (CI95%)	East Region (CI95%)	Havana % (CI95%)	Total % (CI95%)
Anemia	14,1 (9,6-18,6)	24,9 (13,6-36,2)	22,7 (18,3-27,2)	24,4 (20,3-28,5)	22,5 (18,2-26,8)
Iron storage deficiency (Ferritin <12µg/L)	17,2 (9,3-29,7)	38,2 (25,7-52,4)	37,4 (31,2-43,9)	38,3 (25,8-52,6)	35,6 (29,7-41,9)
Iron erythropoietic dysfunction (sTfR>8,3µg/mL)	6,7 (4,2-9,3)	8,6 (5,5-11,7)	17,1 (4,9-29,4)	12,1 (8,1-16,2)	13,3 (5,7-20,9)
Leukocytosis (>10,000/mm ³)	29,4 (23,2-36,4)	33,1 (28,8-37,9)	39,3 (35,6-43,2)	31,3 (22,5-41,7)	36,1 (33,5-38,7)
CRP (>5mg/L)	9,4 (3,4-15,4)	14,2 (6,0-22,3)	11,9 (9,6-14,2)	13,2 (7,4-18,9)	12,3 (9,8-14,7)
AGP (>1g/L)	14,0 (7,6-20,3)	38,7 (31,2-46,2)	35,8 (26,5-45,2)	53,6 (41,8-65,4)	35,4 (29,8-41,0)
Inflammation (high CRP o AGP)	20,4 (9,7-31,1)	38,6 (32,1-45,1)	38,4 (31,3-45,6)	53,4 (43,5-63,3)	37,5 (32,5-42,5)

Leukocytosis was higher in the Eastern Region and less than a third of the children in the rest of the regions.

The iron deposit deficit was similar in the Central, Eastern and Havana regions and lower in the Western Region. However, erythropoietic dysfunction was higher in the Eastern and Havana regions, and less in the Western and Central regions.

Acute inflammation was higher in the Central Region and Havana; it was found that more than half of the children in Havana had inflammation, mainly by AGP. The Western Region had low values of both acute and chronic inflammation.

The prevalence of Chronic malnutrition (stunted) was low, since it was found in 5.6% (95% CI= 3.5-7.8) of children, so it does not represent a health problem in the child population in Cuba.

Current malnutrition (wasting) was present in 1.0% (95% CI= 0.0-2.1). A prevalence of overweight of 4.7% (95% CI= 3.8-5.7) and obesity of 2.8% (95% CI= 0.8-4.8) was found, global overweight was low (7.5%). Triceps skinfold values were high in 4% (95% CI= 2.4-5.5) and very high in 1.7% (95% CI= 0.4-3.0). The adiposity assessed by subscapular skinfold was slightly higher but did not reach 10% of the children studied (high adiposity 7.2% (95% CI= 5.3-9.1) and very high adiposity 2.1% (95% CI=0.5-3.7)).

The results of mother's instruction levels (n=1,402) the highest percentages were pre-university graduates (42.3%), followed by university graduates (25.8%), junior high school (18.5%) and technical graduates (11.8%). Only one mother presented with no completed any school grade (0.2%) and 1.4% with elementary school. There was a significant difference in the level of education of the mother according to the region ($\chi^2=64$ p<0.001).

Anemia was associated with a deficit in iron stores OR=2.07 (95% CI= 1.45-2.97), more important in ≥ 2 years OR=2.63 (95% CI= 1.28-2.97), compared to <2 years OR=1.57 (95% CI= 1.13-5.38). The association of erythropoietic deficiency with anemia resulted in OR=2.93 (95% CI= 1.97-4.37), mostly in ≥ 2 years OR=3.49 (95% CI 1.79-6.80), than in <2 years OR=1.70 (95% CI= 0.97-2.98).

Inflammation was also a factor that was associated with anemia OR=2.01 (95%CI=1.45-2.78), similar between age groups: <2 years OR=1.82 (95%CI=1.07-3.10) and ≥ 2 years OR=1.96 (95% CI= 1.08-3.55), with no significant differences in relation to the CRP or AGP inflammation

indicator independently.

No associations were found to explain anemia with weight gain OR=0.68 (95% CI= 0.35-1.32), nor with high levels of adiposity, which resulted in low percentages (data not shown). No association was found to explain iron deficiency due to global overweight OR=0.96 (95% CI= 0.68-1.35).

Global overweight does not explain the inflammation found OR=1.13 (95% CI= 0.54-2.37), neither by CRP OR=0.57 (95% CI= 0.24-1.37) or AGP OR=1.14 (95% CI= 0.54-2.42).

The level mother's instruction was a factor to consider, since it was found that anemia in children decreases with higher education of the mother (χ^2 trend= 4.327 p=0.037), but not iron storage deficiency (χ^2 trend= 0.212 p=0.646).

4. Discussion

The prevalence of anemia does not differ from that was founded in the national study carried out from 2010-2013 in 4,162 children (21.6%) [16].

In the current results, there are differences in the prevalence between the regions, compared to those of the previous study, with a slight decrease in the Eastern Region in 2011 (26.0%) [17], where the largest interventions have been carried out, and in the Western (20.2%), with worse results in the Central (12.1%) [18].

Rodríguez-Suárez [19], in a report carried out in 2016, show 34.1% prevalence of anemia in the age group 6-23 months in the eastern provinces and Pinar del Rio, considered the most vulnerable in the country, and with the most critical situation in the children from 6 to 11 months old (41.4%), lower values than report in our study, but equally high.

According to these results, progress in reducing the prevalence of anemia in preschool children has been slow, where greater efforts must be made in interventions.

Erythropoietic dysfunction evaluation confirms compromised hemoglobin synthesis due to iron deficiency. The strongest associations of anemia with tissue iron depletion were in children ≥ 2 years old. It is likely there are other factors that may be influencing the development of anemia in children <2 years old that have not been explored.

Iglesias Vázquez et al [20], carried out a systematic review and meta-analysis that included 61 studies from 21 countries in Latin America and the Caribbean. They found 32.9% of anemia in preschool children, with no difference between sex,

and anemia is a public health problem in the Latin Caribbean.

Stevens et al [21] performed a national, regional, and global estimate of the severity of anemia in children aged 6-59 months old. They reported a prevalence of 40% (95%CI=36-44%), with a decrease in Severe and Moderate anemia. The decline in anemia per decade was mostly in the Latin American and Caribbean region, but that prevalence was even higher than we founded in this study.

Wirth et al [22] carried out a study in Somalia in 1456 children aged 6-59 months old where they explored, in addition to anemia and iron deficiency, vitamin A deficiency. They obtained anemia figures of 43.4% and iron deficiency 47.2% but anemia was attributed to iron deficiency in 36% and vitamin A deficiency in only 6%.

In the 2010-2013 national study, plasma retinol concentrations were evaluated in a sample of 2,205 children, finding that vitamin A classifies as Mild Health Problem at the national level (8.5%). Retinol concentrations correlated significantly with Hb concentrations, but only subclinical vitamin A deficiency was associated with anemia in the Eastern provinces [18].

No studies have been found in Cuba where folate concentrations in preschool children were estimated. There are only dietary studies indicating intake deficiency [19, 23].

Grefeuille et al [24] evaluated the concentrations of Zn and Hb in preschool children from nationally representative studies from different countries (n=18658) and found a prevalence of Zn deficiency between 9.2-78.4%. The prevalence of Zn deficiency was greater than 20% in most countries. Zn concentration had a positive association with Hb in about half of the countries, regardless of iron status, and significantly related to anemia in most, so they conclude that strategies to combat Zn deficiency can help to reduce the prevalence of anemia. No publications have been reported in Cuba on the nutritional status of zinc in children.

Inflammation was a factor to consider in the development of anemia and iron deficiency, since the prevalence of leukocytosis and subclinical indicators CRP and AGP were high. Anemia was associated with subclinical inflammation, regardless of iron status impairment, and should be kept in mind when explaining the pathophysiology of anemia in this age group.

Anemia of Inflammation is the second leading cause after iron deficiency [25]. Pathophysiological mechanisms have been proposed in the adult population and those with chronic diseases that include: restriction of iron availability for erythropoiesis, hepcidin-mediated decrease in erythropoietin production, a decrease in the production of erythrocytes and a decrease in the half-life of erythrocytes due to increased erythrophagocytosis of hepatic and splenic macrophages. Anemia of inflammation is usually Mild to Moderate [26]. No studies have been found that explain the inflammation associated with anemia in preschool children.

The results of the nutritional status in the child population reflect the priority attention of this group by the state and the Maternal-Child Program, since the percentage of acute and chronic malnourished was very low, confirming that

malnutrition is not a population health problem in Cuba [27].

A low prevalence of overweight and obesity was found in preschool children, and global overweight was not associated with inflammation, anemia, or iron deficiency in the children, unlike what has been reported by other studies in developing and developed countries.

Delaney et al [28] found that higher adiposity is associated with higher systemic inflammation in Montreal preschool children. Nappo et al [29] found that high levels of CRP were associated with high BMI and overweight/obesity in a population of European children.

Wirth et al [30] found that the prevalence of anemia does not differ substantially by wasting, overweight, or stunted children. Kamruzzaman [31], in a study in Bangladesh, using nationally representative data, found no association between BMI in children and anemia.

The education of the mother turned out to be an important factor in the prevalence of anemia in the child, since the higher the level of education of the mother, the less prevalence of anemia the child presents.

Wirth et al (30) found no significant differences between the education of the mother and anemia in the child, although there was a tendency to decrease the prevalence of anemia with increasing education of the mother. However, Castro Bedriñana et al [32] in Jauja-Peru observed a high prevalence of childhood anemia, inversely associated with maternal education.

The inclusion of the level of education of the mother provides information to keep in mind in nutritional education programs on this subject.

Limitations: The first limitation is the design of the study (cross-sectional study) so it was impossible to examine the temporality of the indicators with other factors. The second limitation is that other important nutritional causes of anemia in the vulnerable population, such as folic acid and zinc deficiency, could not be studied.

It is recommended to design further research to explore other nutritional factors as folate and zinc serum deficiency, as well as household wealth status and the number of siblings could be related to anemia in this group of age.

5. Conclusion

Anemia and iron deficiency in Cuban preschool children are classified as Moderate Public Health problems associated with inflammation, a condition not explored in this vulnerable group in Cuba. No association of overweight and obesity with anemia or iron deficiency was found. The low educational level of the mother was significantly associated with anemia in the children.

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