Original Article

Mapping anemia prevalence across Indonesia

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Background and Objectives: Anemia is a major health problem worldwide, with complex etiologies and significantly affecting the quality of life and health outcomes. In Indonesia, anemia is a public health concern with a complex interplay between genetic, environmental, and infectious disease factors. The prevalence tends to increase in Indonesia from 2007 to 2018. This study aims to explore factors contributing to anemia in Indonesia. **Methods and Study Design:** We used archived data from various population studies collected between 1995 and 2023. A total of 5,486 subjects from 17 study populations in Indonesia were included in the analyses. **Results:** The proportions of anemic women are higher than anemic men (p<0.001), and the anemia prevalence in Indonesia is diverse in various populations. More than 50% of this study subjects were microcytic hypochromic anemia with 35% indicative of iron deficiency and 13% of thalassemia based on Mentzer Index and RDW index cut-off. Hb analysis showed that HbA2 and HbF proportions above normal were significantly higher in the anemic group (p<0.001). We also found beta thalassemia proportions were higher in the anemic group (p<0.001) indicating genetic disorders are prevalent in Indonesia. **Conclusions:** The anemia prevalence in Indonesia is high, and the etiology is very complex, with nutritional and non-nutritional factors. Therefore, anemia mitigation in the Indonesian population should consider nutritional and non-nutritional factors. Policy makers should consider intervention programs beyond nutrient-specific strategies such as genetic background of the individuals.

Key Words: anemia, nutritional, non-nutritional, iron deficiency, thalassemia

INTRODUCTION

Anemia is a major health problem worldwide, with complex etiologies and significantly affects the quality of life and health outcomes in affected populations, particularly in children and women.[1,2] The World Health Organization (WHO) reported that 40% of children under five, 30% of adult women, and 37% of pregnant women are suffering from anemia.[3] The prolonged effect of anemia leads to increased morbidity and mortality rates, poor birth outcomes, impaired neurological development in children, and decreased productivity in adults.[4–6]

In Indonesia, anemia is a public health concern and impacts various segments of the population. According to Indonesia's Basic Health Research reports from 2007 to 2018, and the National Health Survey Report in 2023, the prevalence of anemia has been notably high. From 2007 to 2018, the anemia prevalence showed an increase from 19.7% to 38.5% in children under five, from 19.7% to 27.2% in women (≥15 years), and from 13.1% to 20.3% in men (≥15 years). The latest report in 2023 showed the anemia prevalence was 23.8%, 18.0%, and 14.4% in children, adult women, and adult men, respectively.[7–10]

Anemia is described by hemoglobin (Hb) concentration and/or red blood cell (RBC) count below normal values.[11] Hb concentration is the common method for determining anemia, and WHO has published guidelines on hemoglobin cut-offs to define anemia.[12] The imbalance between RBC production (erythropoiesis) and RBC loss that can occur due to hemolysis and/or acute blood loss will lead to anemia. Commonly, anemia is divided into two categories: nutritional and non-nutritional. The causes of nutritional anemia include nutrient deficiencies through inadequate diets or inadequate absorption of nutrients.[13]

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Nutritional deficiencies are often seen as the main factor of anemia, although other factors also play a role, especially in regions with high infectious disease cases and genetic disorders.[14,15] Non-nutritional anemia can include excessive blood loss, genetic disorders like inherited red blood cell disorders, and anemia of inflammation (i.e., both are linked to infectious and noninfectious diseases).[16,17]

Indonesia is a country with complex interplay between genetic, environmental, and infectious disease factors. This study aims to explore and map the etiology of anemia, not only because of nutritional factors but also non-nutritional factors such as genetic disorders. Currently, national programs to overcome anemia only focus on nutritional factors, such as iron-folic acid supplementation for pregnant women and adolescent girls (12-18 years), education, and campaigns for a healthy and balanced diet.[18] This study may help develop more effective and comprehensive strategies to tackle anemia by expanding the focus with non-nutritional anemia as it is not a one-size-fits-all strategy for combating anemia in Indonesia.

METHODS

Study design and population

We used archived data from various population studies in Indonesia collected between 1995 and 2023 (Supplementary Table 1) generated by the Eijkman Institute for Molecular Biology (EIMB) and the Mochtar Riady Institute for Nanotechnology (MRIN). Samples from EIMB included two studies: firstly, population study on thalassemia consisting of 11 populations with 3989 subjects that conducted genetic testing for thalassemia and Southeast Asian Ovalocytosis (SAO), and secondly, study on G6PD deficiency consisting of 1 population with 610 subjects that screened for G6PD deficiency, thalassemia, and SAO. These samples that were genotyped for thalassemia, SAO, and G6PD deficiency were clinically healthy individuals from population genetics studies from regions in Indonesia that were either very remote or malaria endemic. Subjects were selected for thalassemia genetic screening based on the MCV value, red blood cell morphology using blood smear examination (microcytic hypochromic, present of target cells), and HbA2 and HbF levels using hemoglobin analysis by HPLC method, according to Dacie and Lewis Practical Haematology.[19] Subjects having low MCV value, microcytic hypochromic red blood cell morphology, the presence of target cells, and high (>3.5%) or low (<2.5%) levels of HbA2 were selected for alpha and/or beta thalassemia genetic testing. We are aware that subjects with normal MCV value, red blood cell morphology, and HbA2 levels, might still have thalassemia mutation(s), however, we decided to apply the selection criteria mentioned above for further thalassemia genetic screening. Subjects were selected for SAO genetic screening based on blood smear analyses. Those with SAO hallmarks (oval shaped erythrocytes, transbridged with two stomas) were further confirmed genotypically by PCR. These samples were phenotypically screened for G6PD deficiency using spectrophotometer-based assay and the deficient samples were then genotyped by PCR/RFLP or sanger sequencing. Samples from MRIN included 5 populations with a total of 981 subjects.

The total subjects for this study were 5,486 subjects from 17 populations. All studies performed complete blood count analyses including Hb, MCV, RDW, MCH, MCHC, RBC count, and hematocrit. For the blood count analyses, samples collected by EIMB were analyzed using the Sysmex pocH-100i Hematology Analyzer or Sysmex XN 1000 Hematology Analyzer, while those conducted at MRIN were analyzed at Prodia Laboratory using the Sysmex XN 2000 Hematology Analyzer. Hb variants (HbA2 and HbF) were detected using Bio-Rad VARIANT II Hemoglobin testing System. Subjects with incomplete information on either sex, age, or Hb concentration were excluded from the analysis. Anemia classification followed the WHO guidelines, categorized as anemic and non-anemic, based on age (Figure 1, Supplementary Table 2).[12] Ethical approvals for each of the study included in the analyses, were obtained from the Eijkman Institute Research Ethics Commission (EIREC No. 32, 2008; EIREC No. 52, 2012, EIREC No. 69, 2014, EIREC No. 90, 2015) and from the Mochtar Riady Institute for Nanotechnology Ethics Committee (No. 005/MRIN-EC/ECL/III/2022, No. 010/MRIN-EC/ECL/V/2023).

Statistical analysis

Statistical analyses were performed using R version 4.2.1 (www.r-project.org) with RStudio version 2023.12.1+402 (www.rstudio.com). Descriptive statistics were employed to describe the baseline characteristics of anemic and non-anemic groups. The continuous variables were presented as medians (interquartile range, IQR) and analyzed with Wilcoxon-Mann Whitney U test. The categorical variables were presented as percentages (%) and analyzed with Pearson's chi-squared test. We used Wilcoxon-Mann Whitney U test to compare the hemoglobin analysis between anemic and non-anemic group. For the proportions of red blood indices, hemoglobin analysis, and genetic risk factors between anemic and non-anemic group, we used Pearson's chi-squared test. Data analyses and graphical presentations were performed using "ggplot2", "ggpubr", "dplyr", "ggrepel", "data.table" packages in R.

RESULTS

Clinical characteristics of anemic and non-anemic subjects

We analyzed sex distribution, age, and various hematological parameters. In this study, there is a significant difference in anemia prevalence between women and men (p-value <0.001). The proportions of anemic women (15.9%) are higher than anemic men (9.0%). We found significant differences in the proportions of anemic and non-anemic groups among children (<15 years), women (≥15 years) and men (≥15 years). The highest proportions of anemic subjects are women (16.1%), followed by children (14.3%), and the lowest is men (8.3%). Further, we performed pairwise comparisons, and the significant results were observed between children vs. men and women vs. men. These significant results remained after adjustment with Bonferroni correction (Supplementary Table 3). All clinical hematological parameters showed

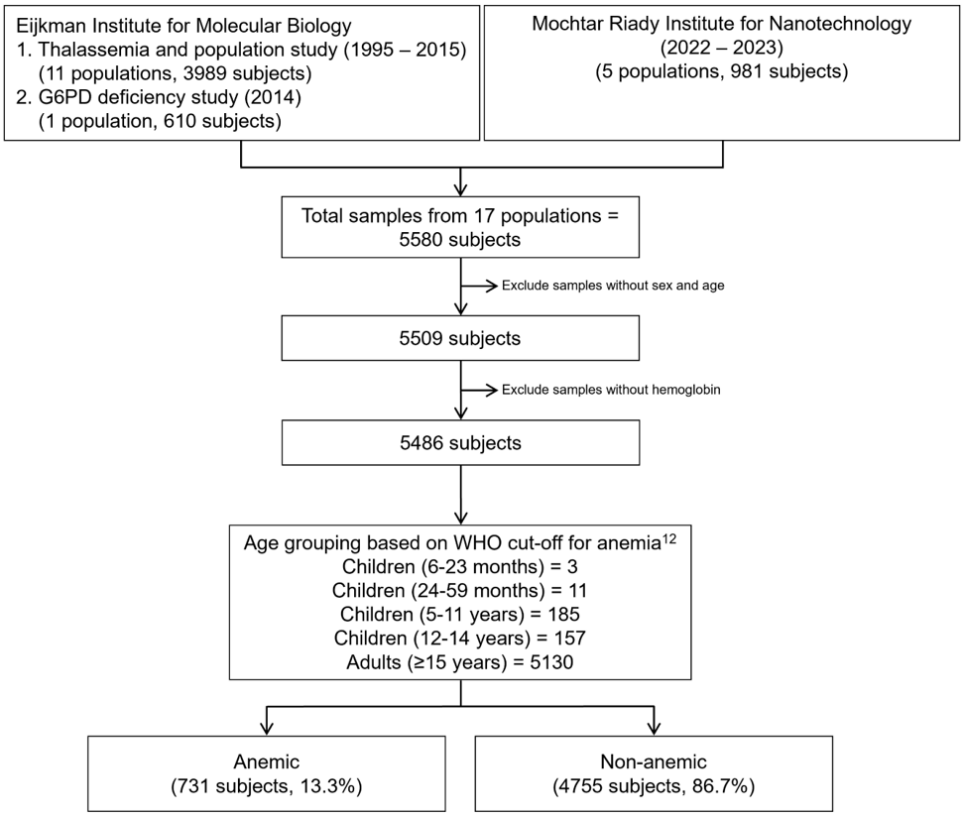

Figure 1. Flowchart of subject assessment.[12]

statistically significant differences between anemic and non-anemic groups, highlighting the distinct hematological profiles associated with anemia (Table 1).

Prevalence of anemia over the years across population from 1995 to 2023 in Indonesia

The result showed that anemia prevalence in Indonesia is diverse among various populations (Figure 2, Supplementary Figure 1). This study showed that Dieng has the lowest anemia prevalence (1%), while Sentani has the highest (49%) (Supplementary Table 4). In further analysis, we divided the region into West and East based on the Wallace line. We found that the anemic proportions in the Eastern region between 2006-2016 and 2017-2023 were higher than in the Western region (Supplementary Table 5).

Red blood cell analysis

The anemic group has a higher proportion of microcytic red cells (52.9%) and hypochromic red cells (55.6%) compared to non-anemic group. Meanwhile, macrocytic and hyperchromic red cells are rare in both groups (Figure 3). We also found that the Eastern region has a higher proportion of microcytic hypochromic compared to the Western region in the anemic group (Supplementary Table 6).

Hematological indices for differentiating iron deficiency anemia and thalassemia trait in the anemic group

We calculated the Mentzer index and RDW index according to the formula in Supplementary Table 7. The Mentzer Index has a cutoff of 13 or higher for iron deficiency anemia, while values below 13 indicates thalassemia, and the RDW index has a cutoff of 220 or higher for iron deficiency anemia, while values below 220 implies thalassemia. In this study, we found from the Mentzer index that 86.8% of subjects indicated iron deficiency anemia, whereas 13.2% suggested thalassemia. This result is also supported by RDW index that 85.5% of subjects might have iron deficiency anemia, and 14.5% might have thalassemia (Table 2). Further, we analyze the red blood cell type and hematological indices. We found the proportions of microcytic normocytic anemia were 35% indicating iron deficiency and 13% might have thalassemia in both indexes (Supplementary Table 8).

Hemoglobin analysis

The comparison of hemoglobin subtype between anemic and non-anemic individuals revealed that a higher percentage of the anemic group (22.4%) exceeded the HbA2 >3.5% cutoff compared to the non-anemic group (8.6%). Further, 16.3% of anemic subjects had HbF above the 1% cutoff. These findings indicated significant differences in hemoglobin subtypes between the anemic and non-anemic groups (Table 3).

Genetic risk factors for anemia

This study compiled data from various past studies. Some subjects were tested for red blood cell disorders (i.e., thalassemia, SAO, and G6PD deficiency). We found beta thalassemia to be significantly higher in the anemic group (17%). However, we did not find significant differences between the anemic and non-anemic groups for SAO and G6PD deficiency (Table 4), which is consistent with findings that SAO and G6PD deficiency are asymptomatic unless exposed to certain condition or drugs.

Table 1. Clinical characteristics of anemic and non-anemic subjects

Variables	All subjects N = 5486	Anemic N = 731	Non-anemic N = 4755	*p*-value
Sex				
Women	3469 (63.2%)	550 (15.9%)	2919 (84.1%)	<0.001*
Men	2017 (36.8%)	181 (9.0%)	1836 (91.0%)	
Age (N = 5486)	20.0 (17.0-32.0)	22.0 (18.0-41.0)	19.0 (17.0-30.0)	<0.001*
Children (<15 years)	356 (6.49%)	51 (14.3%)	305 (85.7%)	<0.001*
Women (≥15 years)	3270 (59.6%)	525 (16.1%)	2745 (83.9%)	
Men (≥15 years)	1860 (33.9%)	155 (8.3%)	1705 (91.7)	
Hb (g/dL) (N = 5486)	13.7 (12.7-14.9)	11.5 (10.7-11.8)	14.0 (13.1-15.1)	<0.001*
MCV (fl) (N = 5482)	84.3 (80.8-87.7)	79.0 (71.4-84.0)	85.0 (81.8-88.0)	<0.001*
RDW (%) (N = 5480)	13.9 (13.2-14.8)	15.0 (13.6-16.9)	13.8 (13.1-14.6)	<0.001*
MCH (pg) (N = 5480)	28.4 (26.6-29.7)	25.5 (22.4-27.9)	28.6 (27.1-29.8)	<0.001*
MCHC (g/dL) (N = 5480)	33.4 (32.4-34.5)	32.3 (31.1-33.4)	33.6 (32.6-34.6)	<0.001*
RBC count (millions/mm^3) (N = 5480)	4.9 (4.6-5.3)	4.4 (4.1-4.9)	5.0 (4.6-5.4)	<0.001*
Hematocrit (%) (N = 5480)	41.1 (38.2-44.4)	34.9 (32.9-36.9)	41.9 (39.3-44.9)	<0.001*

Hb: hemoglobin, MCV: mean corpuscular volume, RDW: red cell distribution width, MCH: mean corpuscular hemoglobin, MCHC: mean corpuscular hemoglobin concentration, RBC: red blood cell.
Normally distributed variables are summarized as mean (±standard deviation). Non-normally distributed variables are summarized as median (interquartile range).
The *p*-values were calculated using either Wilcoxon-Mann Whitney U test for continuous variables or Pearson's chi-squared test for categorical variables.
*Significant *p*-values are $p<0.050$.

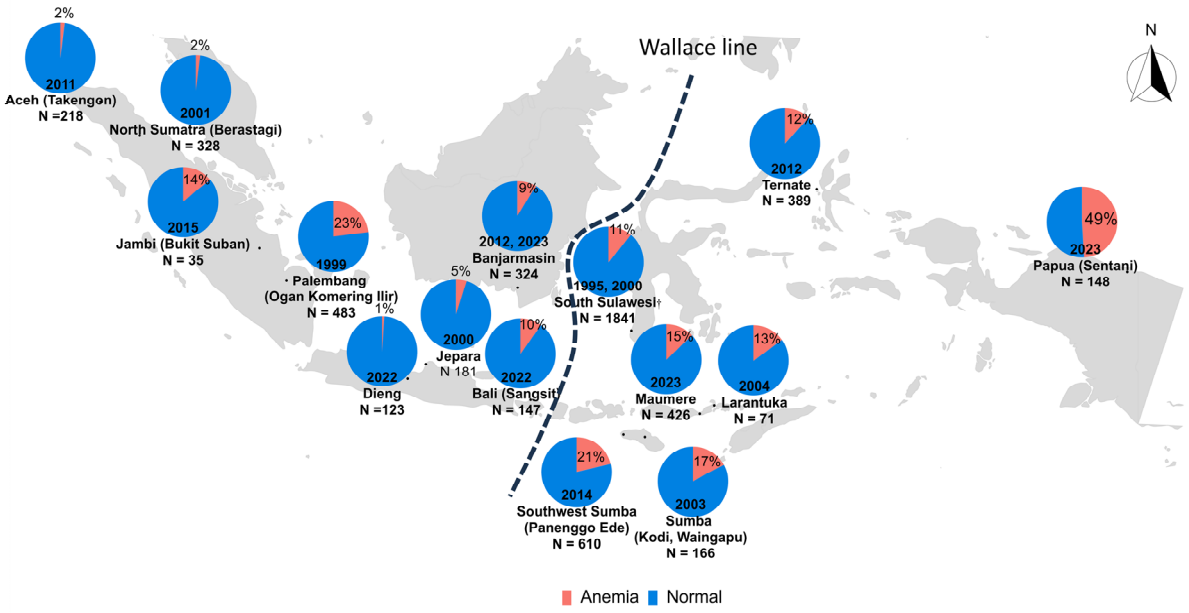

Figure 2. Anemia prevalence between year 1995 to 2023 of field sampling done by Eijkman Institute for Molecular Biology and Mochtar Riady Research Institute of Nanotechnology. †South Sulawesi includes Makassar, Toraja, Mandar, Kajang populations.

DISCUSSION

In our study, there is a higher proportion of anemia in women than in men. This gender discrepancy in anemia prevalence is more likely due to higher iron requirements in women during menstrual blood loss and pregnancy.[20,21] Our study is consistent with previous studies that have reported high anemia prevalence among women, particularly in the reproductive age.[22–24] In addition the anemia prevalence between children (<15 years) and adults (women and men) (≥15 years) is significantly different in this study, particularly between children vs. men and women vs. men. Some studies showed the persistence of a high prevalence of anemia in children under 5 years and adolescent, especially in low- and middle-income countries.[25–28] The high prevalence of anemia in children can be attributed to factors such as low socioeconomic status, nutritional deficiencies, poor sanitation, infections, hemoglobinopathies, and other chronic diseases.[28–31] This result showed that children and women are more vulnerable to anemia compared to men. To tackle anemia in these vulnerable groups, it requires targeted interventions. WHO and UNICEF recommend public health preventive strategies, such as nutrient supplementation, food fortification, educational programs, and the prevention and control of parasitic and protozoal infections.[32]

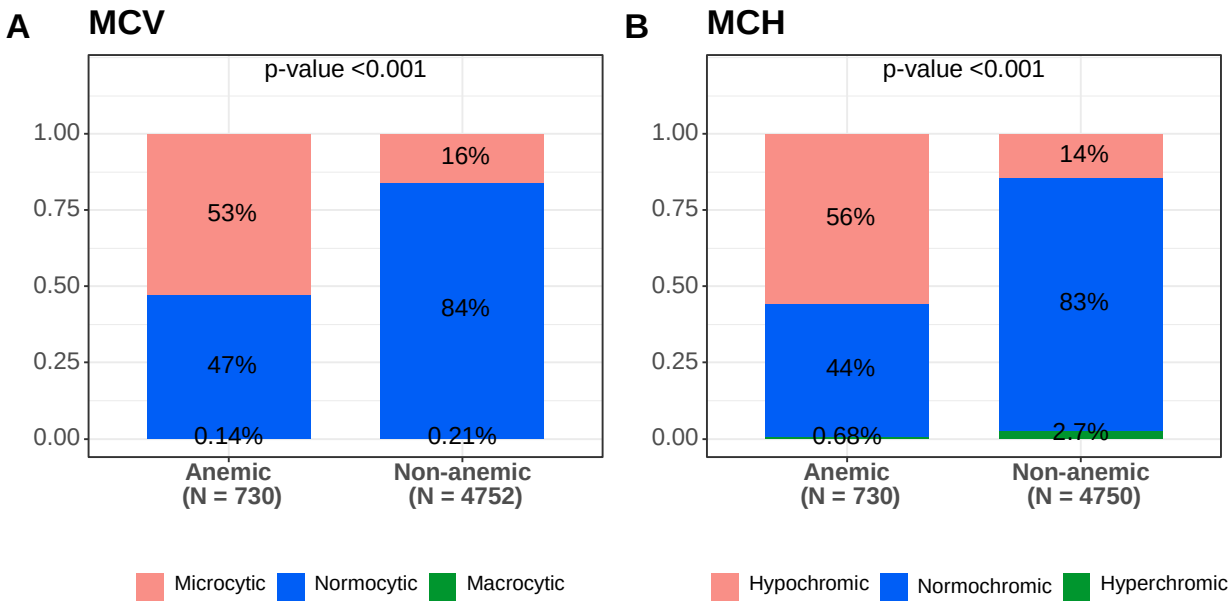

Figure 3. Red cell indices: (A) MCV; (B) MCH. MCV (N = 5482): Microcytic (<80 fl), Normocytic (80 - 100 fl), Macrocytic (>100 fl). MCH (N = 5480): Hypochromic (<26 pg), Normochromic (26 - 32 pg), Hyperchromic (>32 pg). The p-values were calculated using Pearson's chi-squared test. The significant *p*-values are $p<0.050$. MCV: mean corpuscular volume, MCH: mean corpuscular hemoglobin.

Table 2. Hematological indices for diagnosis of iron deficiency anemia and thalassemia trait

Variables	Anemic, N = 730
Mentzer Index	17.7 (14.7-20.5)
Iron deficiency ≥13	634 (86.8%)
Thalassemia <13	96 (13.2%)
RDW Index	263 (236-294)
Iron deficiency ≥220	624 (85.5%)
Thalassemia <220	106 (14.5%)

Mentzer Index and RDW Index were calculated using formula described in Supplementary Table 2.

Table 3. Hemoglobin analysis

Variables	Anemic	Non-anemic	*p*-value
HbA2 (%) (N = 4467)	2.80 (2.5-3.4)	2.80 (2.6-3.1)	0.890
Cut off			<0.001*
≤3.5%	433 (77.6%)	3573 (91.4%)	
>3.5%	125 (22.4%)	336 (8.6%)	
Total N (%)	558 (100%)	3909 (100%)	
HbF (%) (N = 4468)	0.30 (0.0-0.7)	0.3 (0.0-0.6)	<0.001*
Cut off			
<1%	467 (83.7%)	3570 (91.3%)	<0.001*
≥1%	91 (16.3%)	340 (8.70%)	
Total N (%)	558 (100%)	3910 (100%)	

HbA2: hemoglobin subunit alpha 2, HbF: fetal hemoglobin.
The *p*-values were calculated using either Wilcoxon-Mann Whitney U test for continuous variables or Pearson's chi-squared test for categorical variables.
*Significant *p*-values are $p<0.050$.

This study showed anemia prevalence in Indonesia from 1995 to 2023 varied by locations and populations. The result might be due to the complex interplay between environmental, socio-economic, and genetic factors. Indonesia is a vast and ethnically diverse country with over 17,000 islands and 730 ethnic groups, which contribute to the diversity of the Indonesian population.[33–35] This diversity led to various cultural practices, dietary habits, health beliefs, and genetic disorders, which could affect health outcomes like anemia. Chaparro and Suchdev stated that the causes of anemia vary by population, location, disease burden, and other factors (i.e., nutritional deficiencies, infections, chronic diseases, and genetic disorders).[13] This was in line with several studies in Indonesia that found the complex etiology of anemia, not only due to nutritional deficiency but also due to non-nutritional factors such as genetic factors, infection, and chronic diseases.[14,17,36] Notably, in the Eastern region of Indonesia, where malaria is still endemic and genetic factors like hemoglobinopathy and G6PD played a role as protective

Table 4. Genetic risk factors and anemia prevalence

Genetic factors	Subject tested (N)	Anemic N (%)†	Non-anemic N (%)†	*p*-value
Thalassemia traits	4517			<0.001*
Alpha thalassemia		40 (7.0)	244 (6.2)	
Alpha, Beta thalassemia		0 (0)	1 (0.03)	
Beta thalassemia		96 (17.0)	213 (5.4)	
Unknown/ No mutation		430 (76.0)	3493 (88.4)	
Total N (%)		566 (100)	3951 (100)	
SAO traits	1364			0.502
Positive		28 (12.7)	124 (10.8)	
Negative		193 (87.3)	1019 (89.2)	
Total N (%)		221 (100)	1143 (100)	
G6PD deficiency traits	610			1
Deficiency		8 (6.3)	33 (6.8)	
Normal		118 (93.7)	451 (93.2)	
Total N (%)		126 (100)	484 (100)	

†The percentage calculation: (N/N tested x 100).
The p-values were calculated using Pearson's chi-squared test.
*Significant *p*-values are $p<0.050$.

traits toward malaria infection, the region is still underdeveloped compared to its western counterpart.[37–39]

The analysis of red blood cell indices between anemic and non-anemic subjects in our study revealed significant differences. The anemic group showed a higher proportion of microcytic and hypochromic red cells compared to the non-anemic group, especially in the Eastern region. Microcytic anemia is the type of anemia whose RBC is smaller than normal, while hypochromic anemia has less Hb and thus red blood cell looks paler.[40] These conditions are usually caused by iron deficiency, chronic diseases, thalassemia, and defects in the synthesis of the heme group (sideroblastic anemia).[41,42] In this study, more than 50% of the subjects have microcytic and hypochromic anemia, which most probably might be due to iron deficiency. A review in 2021 reported that 8 studies out of 13 studies showed that anemia in Indonesian adolescents was associated with iron deficiency.[43] Further, we used the Mentzer index and RDW index to differentiate between iron deficiency anemia and thalassemia trait in the anemic group. Some studies used these alternative indexes to differentiate iron deficiency anemia and thalassemia due to limited resources, and these indexes have good sensitivity and specificity results.[44–46] Both indexes showed similar result, most microcytic hypochromic anemia cases were iron deficiency anemia, however, there were also subjects with thalassemia traits, demonstrating the importance of distinguishing iron deficiency anemia and thalassemia trait as the common causes of anemia. Additionally, considering that the Eastern region has high rate of malaria infection, and the contribution of genetic factors, if iron supplementation does not improve anemia status, especially in microcytic hypochromic anemia, practitioners should consider thalassemia factors. Moreover, microcytic hypochromic anemia also could result from thalassemia coexist with iron deficiency.[47] Most of the normocytic and normochromic anemia occurs as a result of infections, chronic diseases, or non-nutritional anemia.[48] These non-nutritional anemia prevalence increases with infection conditions such as malaria, TBC, HIV, and helminthiasis, as well as with chronic diseases such as diabetes, cardiovascular diseases, metabolic syndrome, and chronic kidney diseases.[14,17]

Other non-nutritional anemia contributing factors were genetic factors and thus, we further analyzed the hemoglobin subtypes. This study showed that the anemic group has a higher proportion of elevated HbA2 and HbF levels than the non-anemic group. Elevated HbA2 and HbF levels were found in beta thalassemia carriers.[49,50] These might be an indication of the presence of beta thalassemia carriers or other hemoglobinopathies among anemic subjects. Beta thalassemia is characterized by the reduction in or absence of beta globin chain synthesis, resulting in reduced Hb, decreased RBC production, leading to anemia.[51] This showed that hemoglobin subtype analysis is relevant in diagnosing and understanding the etiology of anemia. Our study was from various past studies, some subjects were from thalassemia and G6PD studies and were tested for thalassemia, SAO, and G6PD.[52] We found that beta thalassemia was significantly higher in the anemic group. We found no significant differences were observed between the anemic and non-anemic groups for SAO and G6PD deficiency. However, the genetic mutation on SAO and G6PD altering the stability of the RBC could contribute to hemolytic anemia when exposed to certain conditions.[53–55] Thalassemia, SAO, and G6PD prevalences were increased in certain geographic regions where malaria is endemic, as a result of positive selection.[56–58] Thus, the results in this study highlight the importance of addressing not only nutritional factors but also non-nutritional factors to mitigate anemia elimination in Indonesia. Although iron deficiency is the main cause of anemia incidence in Indonesia, it is not sufficient to only focus on nutritional intervention since the main national program is iron-folic supplementation to decrease the prevalence of anemia.[36] Policy makers should consider other etiological factors when designing a comprehensive intervention program to overcome anemia.

Region-specific disparities were evident in this study, especially for intervention programs. Sentani in Jayapura, Papua, had the highest anemia prevalence in this study. The poverty rate in Jayapura was 11.45% higher than

national poverty rate in 2023 which was 9.36%[59] and there was a high incidence of malaria infection.[60] Anemia interventions in this region should address not only nutritional factor but non-nutritional factors such as malaria infection. The programs should include malaria prophylaxis and genetic screening since genetic factors like hemoglobinopathy and G6PD play a role as protective traits toward malaria infection. The second highest prevalence was in rural area in Palembang (Ogan Komering Ilir). According to Badan Pusat Statistik (Central Agency of Statistics) the poverty rate in this region reached 15.98 % in 2010 decreased to 13.15% in 2023 this number was higher than the national poverty rate 13.33% (2010) and 9.36% (2023).[59,61] This region had a low socio-economic status, thus the intervention might focus in nutritional aspects, such as iron supplementation and education.

For more than three decades, Indonesia has implemented an iron supplementation program. Since 2016, Indonesia's Ministry of Health updated its national program for anemia prevention and control in adolescent girls and women of reproductive age and release the new specifications for iron folic acid (IFA) tablet in accordance with the WHO recommendations.[62] Food fortification has been recognized as a cost-effective strategy for micronutrient malnutrition; thus, Indonesia launched the Wheat Flour Food Fortification Program in 2002. This program mandated that wheat flour should be fortified with iron, zinc, folic acid, and vitamins B1 and B2.[63] Nevertheless, these intervention programs face challenges such as inadequate supply of IFA tablet, lack of follow-up, facilities and infrastructure were insufficient for IFA tablet distribution, and dietary preferences different across regions of Indonesia.[36] In 2017, the Ministry of Health introduced Regulation No. 15 on helminthiasis control.[64] Helminth infections can cause anemia especially for children. However, deworming programs are hindered by lack of compliance, and inconsistency of application of deworming programs.[64] Further, cultural practices complicated anemia management. Indonesia has several customs and beliefs that are circulating in society regarding food taboos. Food taboos during pregnancy often restrict the intake of iron-rich foods like meat, fish and green vegetable, leading to higher anemia risks.[65–69] These taboos exist to protect the health of mothers and their babies but may also increase the risk of deficiency of iron in pregnant women. Misinformation on modern drugs also contribute to the reluctance to take iron supplement, due to some beliefs that taking iron supplements will make the baby bigger and more difficult to deliver.[67] Addressing these customs and beliefs is crucial to effectively reduce anemia in Indonesia.

Compared to neighboring countries, the prevalence of anemia in Indonesia among women of reproductive age (31%) exceeds Thailand (24%) and Vietnam (21%) but almost closely with Malaysia (32%).[70] Malaysia has integrated health programs and public health campaigns to mitigate anemia elimination.[71] Thailand implements several programs such as, iron supplementation and food fortification programs, dietary improvement and complementary public health measures.[72] Vietnam develops strategy implemented in National Nutrition Strategy in 2022 to minimize inequities or barriers to access to care.[73] Meanwhile, Indonesia's efforts for anemia mitigation require strengthened supplementation supply, infrastructure, and multifactorial approaches to address its unique etiological landscape.

This study has several limitations, we did not perform laboratory tests for iron deficiency and only a limited samples were analyzed for specific genetic disorders (thalassemia, SAO and G6PD deficiency). Additionally, we did not perform statistical analysis to determine sample size, as this study used data from previous studies with pre-existing blood count analyses. The population used in this study may not fully represent the entire state of the vast Indonesia. Nevertheless, this study included 9 populations from the Western and 8 populations from the Eastern regions in Indonesia. These populations were representative of the big islands of Indonesian archipelago, such as Sumatra (4 populations), Borneo (2 populations), Java-Bali (3 populations), Sulawesi (2 populations), Maluku (1 population), Nusa Tenggara Islands (4 populations), and Papua (1 population). A larger sample size and diverse demographic characteristics would provide a more comprehensive understanding of the underlying causes of anemia and inform targeted intervention strategies. Future research should include more representative sample of the Indonesian population, comprehensive tests for iron deficiency and genetic disorders across all samples.

Conclusion

The anemia prevalence in Indonesia is quite high, and the etiology is very complex, with not only nutritional factors but also non-nutritional factors. Therefore, the mitigation of anemia in the Indonesian population should not solely depend on Hb concentration analysis but also requires conducting complete blood count screening, Hb analysis, iron status, or genetic screening especially in areas that are known to have high RBC disorder prevalence prioritizing in women and children. Interventions should address both nutritional and non-nutritional factors, including infections and genetic factors. Authorities must consider non-nutritional factors and should make programs beyond nutrient-specific strategies and consider the complex interplay of personal behavior, sociocultural factors, dietary and health patterns, local community, and genetic diversity.[36]

SUPPLEMENTARY MATERIALS

All supplementary tables and figures are available upon request from the editorial office.

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CONFLICT OF INTEREST AND FUNDING DISCLOSURE

The authors declare no conflict of interest.

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REFERENCES

1. Kassebaum NJ. The Global Burden of Anemia. Hematol Oncol Clin North Am 2016;30:247–308; doi: 10.1016/j.hoc.2015.11.002.
2. Stevens GA, Finucane MM, De-Regil LM, Paciorek CJ, Flaxman SR, Branca F, et al. Global, regional, and national trends in haemoglobin concentration and prevalence of total and severe anaemia in children and pregnant and non-pregnant women for 1995-2011: a systematic analysis of population-representative data. Lancet Glob Health 2013;1:e16-25; doi: 10.1016/S2214-109X(13)70001-9.
3. World Health Organization. Anaemia. [cited 2024/9/17]. Available from: https://www.who.int/health-topics/anaemia
4. Scott SP, Chen-Edinboro LP, Caulfield LE, Murray-Kolb LE. The impact of anemia on child mortality: an updated review. Nutrients 2014;6:5915–32; doi: 10.3390/nu6125915.
5. Haider BA, Olofin I, Wang M, Spiegelman D, Ezzati M, Fawzi WW, et al. Anaemia, prenatal iron use, and risk of adverse pregnancy outcomes: systematic review and meta-analysis. BMJ 2013;346:f3443.
6. Krebs NF, Lozoff B, Georgieff MK. Neurodevelopment: The Impact of Nutrition and Inflammation During Infancy in Low-Resource Settings. Pediatrics 2017;139:S50–S8; doi: 10.1542/peds.2016-2828G.
7. National Institute of Health Research and Development, Indonesian Ministry of Health. Basic Health Research (Riskesdas) 2007. Jakarta: Ministry of Health Republic of Indonesia; 2007. (In Indonesian)
8. National Institute of Health Research and Development, Indonesian Ministry of Health. Basic Health Research (Riskesdas) 2013. Jakarta: Ministry of Health Republic of Indonesia; 2013. (In Indonesian)
9. National Institute of Health Research and Development, Indonesian Ministry of Health. Basic Health Research (Riskesdas) 2018. Jakarta: Ministry of Health Republic of Indonesia; 2018. (In Indonesian)
10. Survei Kesehatan Indonesia (SKI) 2023. Badan Kebijakan Pembangunan Kesehatan | BKPK Kemenkes. [cited 2024/9/17]. Available from: https://www.badankebijakan.kemkes.go.id/hasil-ski-2023/
11. World Health Organization. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. 2011 [cited 2024/10/2]. Available from: https://www.who.int/publications/i/item/WHO-NMH-NHD-MNM-11.1
12. World Health Organization. Guideline on haemoglobin cutoffs to define anaemia in individuals and populations. 2024 [cited 2024/9/17]. Available from: https://www.who.int/publications/i/item/9789240088542
13. Chaparro CM, Suchdev PS. Anemia epidemiology, pathophysiology, and etiology in low- and middle-income countries. Ann N Y Acad Sci 2019;1450:15–31; doi: 10.1111/nyas.14092.
14. Malik SG, Oktavianthi S, Wahlqvist ML, Asih PBS, Harahap A, Satyagraha AW, et al. Non-nutritional anemia: Malaria, thalassemia, G6PD deficiency and tuberculosis in Indonesia. Asia Pac J Clin Nutr 2020;29:S32–S40; doi: 10.6133/apjcn.202012_29(S1).04.
15. Lukito W, Wahlqvist ML. Intersectoral and eco-nutritional approaches to resolve persistent anemia in Indonesia. Asia Pac J Clin Nutr 2020;29:S1–S8; doi: 10.6133/apjcn.202012_29(S1).01.
16. Weiss G, Ganz T, Goodnough LT. Anemia of inflammation. Blood 2019;133:40–50; doi: 10.1182/blood-2018-06-856500.
17. Bukhari A, Hamid F, Minhajat R, et al. Non-nutritional and disease-related anemia in Indone-sia: A systematic review. Asia Pac J Clin Nutr 2020;29:S41–S54; doi: 10.6133/apjcn.202012_29(S1).05.
18. Kementerian Kesehatan Republik Indonesia. Saat Remaja Menderita Anemia, Ibu Hamil Berisiko Lahirkan Anak Stunting. 2021 [cited 2024/10/2]. Available from: https://kemkes.go.id/id/rilis-kesehatan/saat-remaja-menderita-anemia-ibu-hamil-berisiko-lahirkan-anak-stunting
19. Lewis SM, Bain BJ. Dacie and Lewis Practical Haematology. 10th ed. Churchill Livingstone: Philadelphia, PA; 2006.
20. Camaschella C. Iron-Deficiency Anemia. N Engl J Med 2015;372:1832–43; doi: 10.1056/NEJMra1401038.
21. Harvey LJ, Armah CN, Dainty JR, Foxall RJ, Lewis DJ, Langford NJ, et al. Impact of menstrual blood loss and diet on iron deficiency among women in the UK. Br J Nutr 2005;94:557–64; doi: 10.1079/BJN20051493.
22. Ali SA, Razzaq S, Aziz S, Allana A, Ali AA, Naeem S, et al. Role of iron in the reduction of anemia among women of reproductive age in low-middle income countries: insights from systematic review and meta-analysis. BMC Womens Health 2023;23:184; doi: 10.1186/s12905-023-02291-6.
23. Alem AZ, Efendi F, McKenna L, Felipe-Dimog EB, Chilot D, Tonapa SI, et al. Prevalence and factors associated with anemia in women of reproductive age across low- and middle-income countries based on national data. Sci Rep 2023;13:20335; doi: 10.1038/s41598-023-46739-z.
24. Owais A, Merritt C, Lee C, et al. Anemia among Women of Reproductive Age: An Overview of Global Burden, Trends, Determinants, and Drivers of Progress in Low- and Middle-Income Countries. Nutrients 2021;13:2745; doi: 10.3390/nu13082745.
25. Sun J, Wu H, Zhao M, Magnussen CG, Xi B. Prevalence and changes of anemia among young children and women in 47 low- and middle-income countries, 2000-2018. eClinicalMedicine 2021;41; doi: 10.1016/j.eclinm.2021.101136.
26. Anonymous. Prevalence, years lived with disability, and trends in anaemia burden by severity and cause, 1990–2021: findings from the Global Burden of Disease Study 2021. Lancet Haematol 2023;10:e713–e34; doi: 10.1016/S2352-3026(23)00160-6.
27. Kurpad AV, Sachdev HS. Childhood and Adolescent Anemia Burden in India: The Way Forward. Indian Pediatr 2022;59:837–40; doi: 10.1007/s13312-022-2639-6.
28. Kundu S, Alam SS, Mia MAT, Hossan T, Hider P, Khalil MdI, et al. Prevalence of Anemia among Children and Adolescents of Bangladesh: A Systematic Review and Meta-Analysis. Int J Environ Res Public Health 2023;20:1786; doi: 10.3390/ijerph20031786.
29. Dutta M, Bhise M, Prashad L, Chaurasia H, Debnath P. Prevalence and risk factors of anemia among children 6–59 months in India: A multilevel analysis. Clin Epidemiol Glob Health 2020;8:868–78; doi: 10.1016/j.cegh.2020.02.015.
30. Gallagher PG. Anemia in the pediatric patient. Blood 2022;140:571–93; doi: 10.1182/blood.2020006479.
31. Balarajan Y, Ramakrishnan U, Özaltin E, Shankar AH, Subramanian SV. Anaemia in low-income and middle-

income countries. The Lancet 2011;378:2123–35; doi: 10.1016/S0140-6736(10)62304-5.
32. Baltussen R, Knai C, Sharan M. Iron fortification and iron supplementation are cost-effective interventions to reduce iron deficiency in four subregions of the world. J Nutr 2004;134:2678–84; doi: 10.1093/jn/134.10.2678.
33. MP L. Ethnologue: Languages of the World. 2014.
34. Karafet TM, Hallmark B, Cox MP, Sudoyo H, Downey S, Lansing JS, et al. Major east-west division underlies Y chromosome stratification across Indonesia. Mol Biol Evol 2010;27:1833–44; doi: 10.1093/molbev/msq063.
35. Tumonggor MK, Karafet TM, Hallmark B, Lansing JS, Sudoyo H, Hammer MF, et al. The Indonesian archipelago: an ancient genetic highway linking Asia and the Pacific. J Hum Genet 2013;58:165–73; doi: 10.1038/jhg.2012.154.
36. Nadiyah null, Dewanti LP, Mulyani EY, Jus'at I. Nutritional anemia: Limitations and consequences of Indonesian intervention policy restricted to iron and folic acid. Asia Pac J Clin Nutr 2020;29:S55–S73; doi: 10.6133/apjcn.202012_29(S1).06.
37. Elyazar IRF, Hay SI, Baird JK. Malaria Distribution, Prevalence, Drug Resistance and Control in Indonesia. Adv Parasitol 2011;74:41–175; doi: 10.1016/B978-0-12-385897-9.00002-1.
38. Lederberg J. J. B. S. Haldane (1949) on infectious disease and evolution. Genetics 1999;153:1–3.
39. Hedrick PW. Population genetics of malaria resistance in humans. Heredity 2011;107:283–304; doi: 10.1038/hdy.2011.16.
40. Chaudhry HS, Kasarla MR. Microcytic Hypochromic Anemia. In: StatPearls StatPearls Publishing: Treasure Island (FL); 2024.
41. Massey AC. Microcytic anemia: Differential Diagnosis and Management of Iron Deficiency Anemia. Med Clin North Am 1992;76:549–66; doi: 10.1016/S0025-7125(16)30339-X.
42. DeLoughery TG. Microcytic Anemia. N Engl J Med 2014;371:1324–31; doi: 10.1056/NEJMra1215361.
43. van Zutphen KG, Kraemer K, Melse-Boonstra A. Knowledge Gaps in Understanding the Etiology of Anemia in Indonesian Adolescents. Food Nutr Bull 2021;42:S39–S58; doi: 10.1177/0379572120979241.
44. Mentzer WC. Differentiation of iron deficiency from thalassaemia trait. Lancet Lond Engl 1973;1:882; doi: 10.1016/s0140-6736(73)91446-3.
45. Tabassum S, Khakwani M, Fayyaz A, Taj N. Role of Mentzer index for differentiating iron deficiency anemia and beta thalassemia trait in pregnant women. Pak J Med Sci 2022;38:878–82; doi: 10.12669/pjms.38.4.4635.
46. Tp S, A S, Jp A, et al. Role of Mentzer Index for Differential Diagnosis of Iron Deficiency Anaemia and Beta Thalassemia Trait. J Nepal Health Res Counc 2023;21; doi: 10.33314/jnhrc.v21i1.4479.
47. Verma S, Gupta R, Kudesia M, Mathur A, Krishan G, Singh S. Coexisting Iron Deficiency Anemia and Beta Thalassemia Trait: Effect of Iron Therapy on Red Cell Parameters and Hemoglobin Subtypes. ISRN Hematol 2014;2014:293216; doi: 10.1155/2014/293216.
48. Yilmaz G, Shaikh H. Normochromic Normocytic Anemia. In: StatPearls StatPearls Publishing: Treasure Island (FL); 2024.
49. Perseu L, Satta S, Moi P, Demartis FR, Manunza L, Sollaino MC, et al. KLF1 gene mutations cause borderline HbA(2). Blood 2011;118:4454–8; doi: 10.1182/blood-2011-04-345736.
50. Topfer SK, Feng R, Huang P, Ly LC, Martyn GE, Blobel GA, et al. Disrupting the adult globin promoter alleviates promoter competition and reactivates fetal globin gene expression. Blood 2022;139:2107–18; doi: 10.1182/blood.2021014205.
51. Galanello R, Origa R. Beta-thalassemia. Orphanet J Rare Dis 2010;5:11; doi: 10.1186/1750-1172-5-11.
52. Satyagraha AW, Sadhewa A, Elvira R, Elyazar I, Feriandika D, Antonjaya U, et al. Assessment of Point-of-Care Diagnostics for G6PD Deficiency in Malaria Endemic Rural Eastern Indonesia. PLoS Negl Trop Dis 2016;10(2):e0004457; doi: 10.1371/journal.pntd.0004457.
53. Lavinya AA, Razali RA, Razak MA, Mohamed R, Moses EJ, Soundararajan M, et al. Homozygous Southeast Asian ovalocytosis in five live-born neonates. Haematologica 2021;106:1758–61; doi: 10.3324/haematol.2020.268581.
54. Yamsri S, Kawon W, Duereh A, Fucharoen G, Fucharoen S. Southeast Asian Ovalocytosis and Hemoglobinopathies in Newborns: Prevalence, Molecular, and Hematologic Analyses. J Pediatr Hematol Oncol 2021;43:e341–e5; doi: 10.1097/MPH.0000000000001920.
55. Orman B, Çetinkaya S, Öner N, Akçaboy M, Fettah A, Güleray Lafcı N, et al. Hemolytic Anemia due to Glucose 6 Phosphate Dehydrogenase Deficiency Triggered by Type 1 Diabetes Mellitus. J Clin Res Pediatr Endocrinol 2023;15:417–20; doi: 10.4274/jcrpe.galenos.2022.2021-11-10.
56. Tishkoff SA, Varkonyi R, Cahinhinan N, Abbes S, Argyropoulos G, Destro-Bisol G, et al. Haplotype Diversity and Linkage Disequilibrium at Human G6PD: Recent Origin of Alleles That Confer Malarial Resistance. Science 2001;293:455–62; doi: 10.1126/science.1061573.
57. Saunders MA, Slatkin M, Garner C, Hammer MF, Nachman MW. The Extent of Linkage Disequilibrium Caused by Selection on G6PD in Humans. Genetics 2005;171:1219–29; doi: 10.1534/genetics.105.048140.
58. Flint J, Harding RM, Boyce AJ, Clegg JB. The population genetics of the haemoglobinopathies. Baillieres Clin Haematol 1998;11:1–51; doi: 10.1016/s0950-3536(98)80069-3.
59. Indonesia BPS. Statistik Indonesia 2023. [cited 2025/3/5]. Available from: https://www.bps.go.id/id/publication/2023/02/28/18018f9896f09f03580a614b/statistik-indonesia-2023.html
60. World Health Organization. World Malaria Report 2019. World Health Organization: Geneva; 2019.
61. Ilir BPSKOK. Kabupaten Ogan Komering Ilir Dalam Angka 2018. [cited 2025/3/4]. Available from: https://okikab.bps.go.id/id/publication/2018/08/16/e92c73890db87748e2affc74/kabupaten-ogan-komering-ilir-dalam-angka-2018.html
62. Roche ML, Bury L, Yusadiredja IN, Asri EK, Purwanti TS, Kusyuniati S, et al. Adolescent girls' nutrition and prevention of anaemia: a school based multisectoral collaboration in Indonesia. 2018; doi: 10.1136/bmj.k4541.
63. Bagriansky J, Ahsan S, Syarifudin A, Dey S, Walters D. Implementing a revised standard for wheat flour fortification in Indonesia: A Benefit-Cost Analysis. Nutr Int 2023.
64. Adrizain R, Setiabudi D, Faridah L, Fauziah N, Setiabudiawan B. Challenges for national deworming policy in Indonesia: experience from Bandung district West Java province. J Public Health 2022;30:1613–8; doi: 10.1007/s10389-020-01461-2.
65. Diana R, Rachmayanti RD, Anwar F, Khomsan A, Christianti DF, Kusuma R. Food taboos and suggestions among Madurese pregnant women: a qualitative study. J Ethn Foods 2018;5:246–53; doi: 10.1016/j.jef.2018.10.006.

66. Trisyani M, Kyung K, Widiasih R. Food and Activities Taboos among Sundanese Pregnant Women. J Keperawatan Padjadjaran 2019;7; doi: 10.24198/jkp.v7i1.993.
67. Ashriady A, Mariana D, Tiyas AH, Supriadi RF. Aspek Sosial Budaya dalam Perawatan Kehamilan pada Masyarakat Pesisir Kabupaten Mamuju. J Kesehat Terpadu Integr Health J 2022;13:53–65; doi: 10.32695/jkt.v13i1.249.
68. Suyitno, Suwarni L, Asmarawanti, Sadli M, Sera A. Exploring tabooed food among Dayaknese of Ngaju Women in Central Kalimantan Province, Indonesia. Public Health Indones 2023;9:123–32; doi: 10.36685/phi.v9i3.715.
69. K DH, Suriyani A. Cultural Aspects (Food Taboos) and Management of Anaemia in Pregnancy: A Systematic Review. J Humanit Soc Stud 2023;1:1336–41.
70. World Bank Open Data. Prevalence of anemia among women of reproductive age (% of women ages 15-49). World Bank Open Data. [cited 2025/3/3]. Available from: https://data.worldbank.org
71. Rahman RA, Idris IB, Isa ZM, Rahman RA. The effectiveness of a theory-based intervention program for pregnant women with anemia: A randomized control trial. PLOS ONE 2022;17:e0278192; doi: 10.1371/journal.pone.0278192.
72. Winichagoon P. Prevention and Control of Anemia: Thailand Experiences. J Nutr 2002;132:862S-6S; doi: 10.1093/jn/132.4.862S.
73. Nguyen TT, Huynh NL, Huynh PN, Zambrano P, Withers M, Cashin J, et al. Bridging the evidence-to-action gap: enhancing alignment of national nutrition strategies in Cambodia, Laos, and Vietnam with global and regional recommendations. Front Nutr 2023;10:1277804; doi: 10.3389/fnut.2023.1277804.