APJCN 2020: 29, Supplement 1: S1-S73 ISSN 0964-7058 DOI: 10.6133/apjcn

2020 **Volume 29 Supplement 1**

Asia Pacific

Journal of

Clinical Nutrition

Editor-in-Chief
Duo Li

Co-Editors
Dr Widjaja Lukito
Dr Safarina G Malik

HEC PRESS
(apjcn.cnsoc.org)

Chinese Nutrition Society • APCNS • IUNS

Supported by the Indonesian Danone Institute Foundation

Asia Pacific
Journal of
Clinical Nutrition

THE JOURNAL OF
THE ASIA PACIFIC CLINICAL NUTRITION SOCIETY
THE INTERNATIONAL UNION OF NUTRITIONAL SCIENCES
THE CHINESE NUTRITION SOCIETY

APJCN 2020: Volume 29 (Supplement 1): S1-S73 ISSN 0964-7058

EDITORIAL OFFICE
Chinese Nutrition Society
1405, Beijing Broadcasting Mansion NoA14, Jianguomen Outer Street, Chaoyang District 100022, Beijing, China
Tel: +86-10-83554781-810; Fax: +86-10-83554780; Email: apjcn@cnsoc.org, Website: apjcn.cnsoc.org

HEC PRESS
Technical Editor: Dr Yi-Chen Huang
Email: apjcn-apcns@umail.hinet.net

Asia Pacific Journal of Clinical Nutrition (APJCN) is a peer-reviewed journal to promote the education and training of clinical nutritionists in the region and to enhance the practice of human nutrition and related disciplines in their application to health and the prevention of disease. The journal publishes original research reports, short communications and reviews. All articles are peer-reviewed by two experts in the field of the submitted paper. For detailed instructions concerning the submission of manuscripts, please refer to the Instructions for Authors at the back of this issue or visit the journal web page, listed below.

The International Union of Nutritional Sciences (IUNS) is acknowledged as a non-financial co-sponsor of the Journal. http://www.iuns.org/

Abstracting and Indexing Services: The Journal is indexed by Australasian Medical Index (up to 2009), CAB Abstracts, Chemical Abstracts, Informit (Australia), ProQuest, PubMed, Science Citation Index, Scopus.

Business Correspondence and Advertisement Booking: All matters relating to publication fees, orders, subscriptions, back issues, offprints, and advertisement booking should be addressed via email to apjcn-apcns@umail.hinet.net.

Subscription Rates: The journal is published four times per year and the prices of hard copy per annum for 2020 are as follows:

Personal: US$200
Institution: US$460

The Journal is despatched to subscribers outside Australia by surface air-lifted delivery.

APJCN online

Disclaimer: The Publisher and the Editors cannot be held responsible for errors or any consequences arising from the use of information contained in this journal; the views and opinions expressed do not necessarily reflect those of the Publisher or the Editors, neither does the publication of advertisements constitute any endorsement by the Publisher, or the Editors of the products advertised.

Article Submission

Submission of articles and peer review are undertaken online using Scholar One.

Original Article

Intersectoral and eco-nutritional approaches to resolve persistent anemia in Indonesia

Widjaja Lukito MD, PhD[1,2], Mark L Wahlqvist MD, FRACP, FAFPHM[3,4,5,6]

[1]*Postgraduate Program in Physician Specialist-I in Clinical Nutrition/Department of Nutrition*
[2]*Human Nutrition Research Centre, Indonesian Medical Education and Research Institute (IMERI), Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia*
[3]*Institute of Population Health Sciences, National Health Research Institutes, Miaoli County, Taiwan*
[4]*School of Public Health, National Defense Medical Center, Taipei, Taiwan*
[5]*Department of Nutrition, China Medical University, Taichung, Taiwan*
[6]*Monash Asia Institute, Monash University, Melbourne, Australia*

Anemia in Indonesia has been of concerning persistence in all age groups for some 75 years since independence. The relationships between anemia and nutrition are complex being evident with compromised general health and nutrition. Increased micronutrient intakes, especially iron and folic acid, has alleviated the problem, but encouraged nutrient-specific micronutrient interventions as attractive policy directions as if anemia were a stand-alone disease irrespective of associated disorder. Concerted action to deal with the fundamental causality has been missing. Much of the pathogenetic pathway may be nutritional, but its multifactoriality is ultimately socioecological. Given the intransigence and progression of societal and ecosystem dysfunction, it can be expected that failure to recognize their causal importance will further entrench endemic anemia. This review deliberates the practical measures taken to recognize anemia by symptomatology, food and nutrition surveys, screening (fingerpick blood), nutrition assessment, and blood loss (menstrual and faecal). It identifies vulnerable groups including premenopausal and pregnant women, children and adolescents, unwell adults, and the dependent aged. Risk settings include food insecurity, infectious disease, non-communicable disease, inheritance and epigenetics, and socioeconomic disadvantage. Underlying socio-ecological problems are livelihood, food systems, cultural habits, belief systems, and social networks and activities. With this framework, policy directions could deal more comprehensively and effectively with the socioecological complexity which underpins and limits progress towards anemia eradication at a time of intense global food and health insecurity. It will require co-operative intersectoral and eco-nutritional approaches which take into account the need for universal, sustainable livelihoods. Recommendations have been made accordingly.

Key Words: econutrition, infectious diseases, non-communicable diseases, genetics, policy development

INTRODUCTION

Anemia is still prevalent worldwide, including in Indonesia.[1-5] It accounts for widespread morbidity which may be as non-descript and under-diagnosed as fatigue or as grave as intergenerational ill-health on account of compromised pregnancy.[6-8] Consecutive 5-year Indonesian Basic Health Research reports in 2008, 2013 and 2018 showed the persistent prevalence of anemia in various at-risk people. In 2008, the prevalence of anemia was 19.7%, 13.1%, and 9.8% in adult women, men, and children, consecutively.[9] In 2008, anemia data on pregnant women could not be considered due to the small sample size. In 2013, the prevalence of anemia were 29.7% and 26.5% in under-five boys and girls; and 22.7% and 37.1% in adult women and pregnant women.[10] In 2018, the prevalence of anemia were 27.2%, 20.3%, 38.5%, and 48.9% in adult women and men, under-five children, and pregnant women consecutively.[11] Anemia affects any at-risk population, under-five children, adolescents, reproductive-age women, pregnant women, and the aged. Although national data on anemia of the aged are not available, in a selected group of urban Indonesian elderly, Juguan et al reported that anemia was common, and the prevalence was ~25% and 32% in elderly men and women, respectively.[12] Clearly, anemia with its determinants and various health and non-health consequences, contribute to significant public health problems in Indonesia.

Corresponding Author: Dr Widjaja Lukito, Postgraduate Program in Physician Specialist I in Clinical Nutrition, Department of Nutrition, Faculty of Medicine, Universitas Indonesia, Salemba Raya 6, Jakarta 10430, Indonesia.
Tel: +6281381254730
Email: wlukito298@gmail.com
Manuscript received and initial review completed 23 December 2020. Revision accepted 26 December 2020.
doi: 10.6133/apjcn.202012_29(S1).01

The understanding of erythropoietic and iron physiology and the development of improved screening and diagnostic tools now enable more accurate typing for causality.[13] Pathogenetic biomarkers now include ferritin, transferrin saturation, hepcidin and erythropoietin,[14-16] along with inflammatory markers, enabling more distinction to be made between nutrient deficiency inflammatory anemias and other underlying disease such as chronic kidney disease and, in older people, the myelodysplastic syndrome.[13] The ready availability of a medical and nutritional history, a physical examination, finger prick blood for haematocrit, haemoglobin and microscopy for red cell morphology (and smears for malaria) still go a long way towards establishing the presumptive anemia type (refer to Table 2). However, in many developing countries, including Indonesia, it continues to be regarded principally as nutritional anemia, and is further presumed to be iron-deficiency anemia.[8,13,17-23] It is understandable given that WHO indicates that iron deficiency is the most common cause of anemia globally[24] and the Global Burden of Disease (GBD) reports now refer to inappropriate food intakes as risk factors or 'iron deficiency', rather than anemia, not being a disease, but a manifestation of various diseases.[25,26] Consequently, iron supplementation has been the policy priority to alleviate anemia. Decades of this type of program with increasing budget and different levels of compliance throughout the autonomous provinces and districts across archipelago of Indonesia has not demonstrated uniformly positive outcomes.[27] Fortification and the emerging biofortification of staple foods provide promising food-based approach, but await appropriate evaluation.[27]

With the escalating prevalence of non-communicable disease (NCD) and its underlying inflammatory mechanisms, the anemia of inflammation is of increasing relevance.[28-30] Individuals with long-term pharmacotherapy for NCDs, may also suffer from chronic occult blood loss contributing to the development of anemia.[3] Likewise, the major endemic public health problems of pulmonary tuberculosis (TB) and helminthiasis, contribute extensively to the incidence and prevalence of anemia.[3,30] In a tropical country like Indonesia, the benefits and risks of iron and folate tablet supplementation programs in areas endemic for malaria and TB cannot be overlooked.[30]

The genetics and epigenetics of anemia in Indonesia and the extent to which they contribute to anemia prevalence and its inadequate rectification by intervention programs are being clarified.[31] Anemia as found in Indonesia is complex in its underlying risk factors and ultimate causality, and in its related health and non-health consequences.

Indonesia is the largest economy in Southeast Asia region and the world's 10th largest economy in term of purchasing power. In term of population, Indonesia has a huge number of populations, which is about 250 million people in 2016. This makes Indonesia as the world's fourth most populous nation. Prior to the COVID-19 pandemic, it is predicted that by 2030, Indonesia will emerge as 7 largest economy in the world with $1.8 trillion market opportunity.[32] Therefore, alleviation of anemia is the cornerstone in materializing this prediction. It is timely to call for another review of anemia and recommend a better strategic approach in formulating the near future policies.

DEFINITIONS OF ANEMIA AND NUTRITIONAL ANEMIA

Anemia is arguably not a disease, but a manifestation of net erythropoiesis based on various underlying disorders or diseases. It is not generally defined but described by hematologic biomarkers, like low hemoglobin, low hematocrit concentrations, and low red blood cell counts, unable to meet the body's physiologic needs. In Indonesian communities, anemia is often regarded as a health complaint *'kurang darah'* (lack of blood) and *'pucat'* (pale). The World Health Organization uses hemoglobin concentration to define anemia and its severity (Table 1).[33]

Several approaches have been applied to classify anemia. In the hematologic literature, morphologic evaluation of red blood cells is used to classify anemia as presented in Table 2.[34,35] By using cytometric methods, it is nowadays possible to quantify the volume and size of red blood cells, and as a substitute for microscopic blood smear analyses, although the latter has its own value in diagnosing various blood disorders. Morphologic types of red blood cells indicate the potential causes of anemia.[5,34-36]

Nutritional anemia is that seen in association with nutritional deprivation or requiring conjoint nutritional management.[37] This may be evident with chronic energy deficiency (CED),[7] sub-optimal intakes and reduced bioavailabilities of haematinic nutrients (limited dietary di-

Table 1. Haemoglobin levels to diagnose anaemia at sea level (g/L)

Population	Non-anaemia†	Anaemia‡		
		Mild[a]	Moderate	Severe
Children 6-59 months of age	100 or higher	100-109	70-99	lower than 70
Children 5-11 years of age	115 or higher	110-114	80-109	lower than 80
Children 12-14 years of age	120 or higher	110-119	80-109	lower than 80
Non-pregnant women (15 years of age and above)	120 or higher	110-119	80-109	lower than 80
Pregnant women	110 or higher	100-109	70-99	lower than 70
Men (15 years of age and above)	130 or higher	110-129	80-109	lower than 80

References[33,36]
†Hemoglobin in grams per litre.
‡"Mild" is a misnomer: iron deficiency is already advanced by the time anemia is detected. The deficiency has consequences even when no anemia is clinically apparent.

Table 2. Morphologic assessment of anemia, and its potential risk factors and causes.

Morphology of anemia	MCV	Risk factors and causes
Microcytic	MCV <82fL	Iron deficiency Anemia of inflammation (chronic disease) Thalassemias Vitamin A deficiency
Normocytic	MCV=82–98fL	Anemia of inflammation (chronic disease) Renal disease Bone marrow failure (aplastic anemia, leukemia)
Macrocytic	MCV >98fL	Folate deficiency Vitamin B12 deficiency

MCV: mean corpuscular volme.
References[5,34,35].

versity and food intake quality, vitamins, elements, essential fatty acids, and other bioactive food components),[37] excessive nutrient loss by way of the gut (malabsorption, intestinal parasitosis, atrophic gastritis), reproductive tract (menstrual loss, lactation), integument or intravascular haemolysis (inherited or acquired including malaria),[31] with inflammatory diseases (including overfatness) and in association with a wide range of chronic diseases.[30] It is responsive, at least in part, to nutrition support if an oral, enteral or parenteral portal is available and losses can be met by intake or the underlying cause addressed. Non-nutritional anemia is where none of these situations apply.

UNDER RECOGNITION OF OTHER CAUSES AND RISK FACTORS OF ANEMIA AND MISCONCEPTION OF NUTRITIONAL ANEMIA

Many stakeholders have perceived nutritional anemia to be iron-deficiency anemia. Iron-deficiency anemia has been diagnosed without the assessment of iron status. This perception obtains because iron-deficiency anemia represents about half of nutritional anemia in developing countries including Indonesia, and because iron supplementation with acceptable recipient compliance has partly improved hemoglobin concentrations,[4,7,38] and, therefore, reduced morbidity and mortality related to IDA.[39-41] However, some reports indicate that anemia associated with iron deficiency is much less than 50% in reproductive age women, especially in developing countries, where the prevalence of anemia may be >40%, with a high burden of infection and inflammation.[2,29] Meta-analysis of anemia in pregnant Indonesian women, Lipoeto et al[7] have demonstrated that chronic energy deficiency, not iron deficiency, is the key determinant of anemia. Therefore, to reduce the burden of anemia in reproductive age Indonesian women by 50% in 2030 (as stipulated by the World Health Assembly and the Food and Agriculture Organization SDGs - Sustainable Developments Goals as Target 2.2),[42] it is timely to consider other underlying causes of anemia in Indonesia like infection burden, and implement targeted intervention strategies.

Indonesia has the second highest incidence of tuberculosis (TB) after India.[43] WHO acknowledges that TB is a communicable disease that is a major cause of ill health, one of the top 10 causes of death worldwide and the leading cause of death from a single infectious agent (ranking above HIV/AIDS).Nutritional factors are involved in susceptibility to it in Indonesia.[44] Without adequate treatment, chronic TB infection leads to malnutrition with further health consequences like anemia.[45-48] In a case-control study, Karyadi et al[49] reported that ~60% of active TB patients *vs* 20% of healthy controls were anemic.[50] Anemia in TB individuals is related to inflammation as evidenced by high ferritin concentrations in TB-associated anemia,[48,51] and adequate treatment of TB, not iron supplementation, to some extent, improve the hemoglobin status. Excess of iron due to iron supplementation to active TB sufferers potentially leads to exacerbation of TB and worsen the outcome of TB since M tuberculosis scavenges iron from the host-cell transferrin-iron acquisition pathway, which enhances its growth in the alveolar macrophages.[52,53]

Malaria is highly endemic in the eastern part of Indonesia, namely East Nusa Tenggara and Papua.[31,54] It is evident in many studies that in malaria-endemic malaria, anemia, so called malaria-associated anemia, is prevalent. The pathophysiology of anemia is described by Malik et al.[31] In the eastern part of Indonesia, malaria-associated anemia may worsen anemia related to malnutrition,[1,8,9] helminthiasis,[55] and inherited disorders related to red blood cells like hemoglobinopathies.[31]

In malaria endemic areas, anemia and iron/folate deficiency seem to protect individuals against malaria infection.[31,56-59] Despite the unknown definitive mechanisms for this phenomena, available data revealed that iron supplementation to young children living in an endemic area may increase the risk of malaria-related hospitalization and mortality.[60-63] Morbidity among breast-fed infants given iron supplementats is dependent on hemoglobin concentration being greater when Hb was ≥110 g/L.[64] Reticulocytosis stimulated by iron supplementation,[64] with a younger and larger RBC population increases their susceptibility to the malarial parasite and may lead to overwhelming parasitosis, especially in infants.[63,65]

In pregnant women, malaria-associated anemia is complex. It leads to adverse pregnancy outcomes like low-birth weight due to preterm delivery and intra-uterine growth retardation, most likely caused by placental malaria.[66-68] Iron deficiency may confer protection against malaria and all-cause mortality during early childhood, while needed for optimal neurodevelopment.[57] The management of anemia in malaria-endemic areas needs consideration of whether at-risk people have access to effective primary health care; and whether effective malaria case management is in place.[31,56,66] Malaria management and prevention arrangements must be in place prior to iron and folate supplementation. Interventions with biofortified grains and legumes, and bioavailability generated by food biodiversity, are safer and more preferable than iron and or folate supplementation. Since helminthiasis may co-exist with malaria and contribute to anaemia as well, its conjoint management is also required.[31,56,66,69]

THE NEED TO ADDRESS INTERSECTORAL AND ECO-NUTRITIONAL DESCRIPTION IN ANEMIA AND NUTRITIONAL ANEMIA

Perhaps one of the major weaknesses in many literatures on anemia and nutritional anemia of any forms, is the lack of eco-nutritional description. It has become apparent that human biology is strongly associated with its ecosystem, and, any disturbances, potentially lead to ecosystem health disorders.[71,72] As a megadiverse country, Indonesia is rich in plant foods and animal species, which support hematinic nutriture for its population. Therefore, it is fair to assume that iron- and vitamin B-rich foods are available in the daily life of Indonesian communities. In available publications of nutritional anemia, data on how background dietary patterns and consumption of iron- and vitamin B-rich foods are very limited. Consumption of varied food does not only mean consumption of iron-rich foods, but also means consumption of vitamin C-rich foods, given vitamin C enhances iron absorption. This may mean a reduction in phytate-rich foods consumption, as phytate inhibits iron absorption, but this is better managed by the inclusion of foods with phytase which retain inositol since phytate is a hexaphosphate. There is evidence that inositol is protective against metabolic disease, as in diabetic neuropathy.[72,73] This illustrates the advantage of consumption of biodiverse foods for better health outcomes.[74] (Table 3) Practical guidelines to obtain food variety scores should be developed, and the food variety check list as developed for Australians, could be developed for Indonesians.[71]

Socio-cultural factors affect food habits and dietary patterns. In many cultural contexts with patrilineal and matrilineal systems, marginal income generation, intra-household food distribution is discriminatory, with women and children getting less nutritious foods at mealtime.[75-79] In many Indonesian ethnic groups, food avoidance is traditionally practised, sometimes based on valid observation over generations; for example, pregnant mothers may not be allowed to consume fish as it is believed to cause helminth infestation. The increasingly wide use of smart phones may affect these traditions for better or worse, but provide opportunity for anemia mitigation.[80,81]

Table 3. Required food variety score to achieve dietary adequacy.

Total food variety score	Dietary adequacy
30 or more per week	Very good
25–29 per week	Good
20–24 per week	Fair
Less than 20 per week	Poor
Less than 10 per week	Very poor

The concept of dietary adequacy embraces that of essential nutrient adequacy, but also takes into account other food components and food properties.[71]

The inter-sectoral and eco-nutritional approaches enable us to deliberate practical measures taken to recognise anaemia by symptomatology, food and nutrition surveys, screening (fingerpick blood), nutrition assessment, blood loss recognition (menstrual and faecal). It identifies vulnerable groups including premenopausal and pregnant women, children and adolescents, unwell adults and the dependent aged. Risk settings include food insecurity, infectious disease, non-communicable disease, inheritance and epigenetics and socioeconomic disadvantage. Underlying socio-ecological problems are livelihood, food systems, cultural habits, belief systems, and social networks and activities (Figure 1).

ANEMIA AND THE COVID-19 PANDEMIC

Since the first two confirmed covid cases in early March 2020 in Indonesia, no decline in incidence has been in evidence before the calendar end of 2020. By mid-December 2020, there were more than 600,000 positive COVID-19 cases with the deaths approaching 20.000. The clinical syndromes of SARS-CoV-2 infection are many. The most common symptoms are fever (77%), dry cough (81%), expectoration (56%), headache (34%), myalgia or fatigue (52%), diarrhea (8%), and haemoptysis (3%). Three percent have shortness of breath on hospital admission. The median time from exposure to onset of illness is 4 days (ranges 3-5 days), and from onset of symptoms to first hospital admission is 2 (ranges 1-4) days. On hospital admission, ground-glass opacity (GGO) is the most common radiologic finding on chest computed tomography (CT) (56.4%). No radiographic or CT abnormality is found in 17.9% patients with nonsevere disease and in 2.9% of patients with severe disease. Lymphocytopenia is present in 83.2% of admissions, and of prognostic consequence for disease severity and mortality.

Anemia is an independent risk factor for adverse outcomes of community-acquired pneumonia, and this appears to apply with COVID-19 infection. Tao et al have reported that, among 222 COVID-19, patients, ~ 35% were anemic.[81] Of those who were anemic, 58% and 42% were classified as mild and moderate to severe anemia, respectively. In severe COVID-19 patients, hemoglobin concentrations is lower than those with mild COVID-19. With respect to anemia, serum iron deficiency is detected in COVID-19 patients and associated with severity and mortality. However, the relationships between iron deficiency and susceptibility to infection is moot . There is no evidence that iron supplementation in COVID-19 patients mitigates clinical progression of the disease.

The most evidence-based nutritional approach to COVID-19 and its complications, even where vaccination is available is to enhance innate immunity and to ensure the most optimal health and nutritional status compatible with physical (not social) isolation and compromised food systems.[83-85]

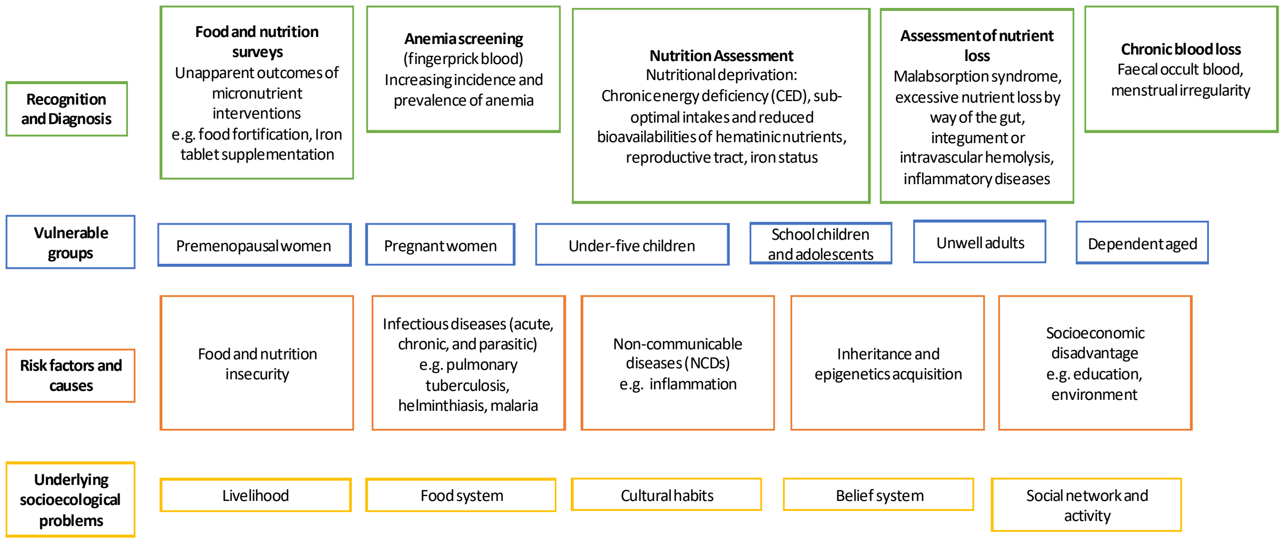


Figure 1. Conceptual framework for anemia in Indonesia.

RECOMMENDATIONS

1) Recognise that, currently, ***anemia in Indonesia remains endemic with an underlying societal and epigenetic persistence, and a co-existently high burden of TB, malaria, NCDs and other neglected diseases*** as barriers to its mitigation, which constitute an imprimatur for action.
2) Recognise that ***the endemicity of malaria and linkage with anemia is greatest in the eastern part of Indonesia***, where it is combined notably with inherited anaemias, a situation which might be more effectively addressed by socioculturally enhanced interventions and governance.
3) ***Empower local government*** which, since 2000, has had a consequential role in elevating the livelhoods of Indonesian people, to extend more effectively into the health and nutrition sectors. Intersectoral communication should be encouraged within and beyond the health and nutrition sectors.
4) Recognise that most health problems, including anemia, require a 'one package solution', albeit ecological and socio-cultural.
5) Mitigate underlying the ***root and multifactorial socio-ecological causes*** and risk factors for anemia in Indonesia.
6) Establish ***an independent national authority*** to integrate evidence-based strategies to reduce the burden of anemia in Indonesia.
7) Be ***action-orientated***, with vigilant monitoring and evaluation, and to support research in progress for better solutions. Action plans would take into account age and gender; women who are adolescent, of reproductive-age, pregnant and lactating would be specifically identified; the endemicity of infectious diseases like TB, malaria, and helminthiasis would be factored in. Biomarkers to allow the differential diagnosis of anemia would include serum ferritin to define not only iron-deficiency anemia, but also to provide an inflammatory marker together with C-reactive protein, and hepcidin, possibly in sub-samples of the target population.

The conceptual framework proposed in this review is intended to provide relevant stakeholder policy direction to deal more comprehensively and effectively with the socioecological complexity which underpins and limits progress towards anemia eradication at a time of intense global food and health insecurity. It will require co-operative intersectoral and eco-nutritional approaches which consider the need for sustainable livelihoods for all and require innovative financial arrangements, for which a consensus is evolving.[86]

ACKNOWLEDGEMENTS

On behalf of all authors of this special issue, Ms. Keisha M. Tuffahati is thanked for her assistance in editorial assistance and manuscript coordination.

AUTHOR DISCLOSURES

The authors declare no conflict of interest.

FUNDING DISCLOSURE

This special issue is supported by the Indonesian Danone Institute Foundation, an independent nonprofit organization that was established in 2007 and operates in accordance with the laws of the Republic of Indonesia.

REFERENCES

1. Kassebaum NJ, Jasrasaria R, Naghavi M, Wulf SK, Johns N, Lozano R et al. A systematic analysis of global anemia burden from 1990 to 2010. Blood. 2014;123:615-24. doi: 10.1182/blood-2013-06-508325.
2. Petry N, Olofin I, Hurrell RF, Boy E, Wirth JP, Moursi M, Donahue Angel M, Rohner F. The Proportion of anemia associated with iron deficiency in low, medium, and high human development index countries: A systematic analysis of national surveys. Nutrients. 2016;8:693. doi: 10.3390/nu8110693.
3. Nadiyah, 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(Suppl 1):S55-S73. doi: 10.6133/apjcn.202012_29(S1).06.
4. Juffrie M, Helmyati S, Hakimi M. Nutritional anemia in Indonesian children and adolescents: Diagnostic reliability for appropriate management. Asia Pac J Clin Nutr.

2020;29(Suppl 1):S18-S31. doi: 10.6133/apjcn.202012_29(S1).03.
5. 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.
6. Lim K, Beck KL, Von Hurst PR, Rutherfurd-Markwick KJ, Badenhorst CE. Iron deficiency and risk factors in pre-menopausal females living in Auckland, New Zealand. Asia Pac J Clin Nutr. 2020;29:638-47. doi: 10.6133/apjcn.202009_29(3).0024.
7. Lipoeto NI, Masrul, Nindrea RD. Nutritional contributors to maternal anemia in Indonesia: chronic energy deficiency and micronutrients. Asia Pac J Clin Nutr. 2020;29(Suppl 1):S9-S17. doi: 10.6133/apjcn.202012_29(S1).02.
8. Patterson AJ, Brown WJ, Powers JR, Roberts DC. Iron deficiency, general health and fatigue: results from the Australian Longitudinal Study on Women's Health. Qual Life Res. 2000;9:491-7. doi: 10.1023/a:1008978114650.
9. Indonesia MoH. Basic health research. Jakarta: Ministry of Health of Indonesia; 2008.
10. Indonesia MoH. Basic health research. Jakarta: Ministry of Health of Indonesia; 2013.
11. Indonesia MoH. Basic health research. Jakarta: Ministry of Health of Indonesia; 2018.
12. Andrade Juguan J, Lukito W, Schultink W. Thiamine deficiency is prevalent in a selected group of urban Indonesian elderly people. J Nutr. 1999;129:366-71. doi: 10.1093/jn/129.2.366.
13. Sangkhae V, Nemeth E. Regulation of the iron homeostatic hormone hepcidin. Adv Nutr. 2017;8:126-36. doi: 10.3945/an.116.013961.
14. Peyrin-Biroulet L, Williet N, Cacoub P. Guidelines on the diagnosis and treatment of iron deficiency across indications: a systematic review. Am J Clin Nutr. 2015;102:1585-94. doi: 10.3945/ajcn.114.103366.
15. Artunc F, Risler T. Serum erythropoietin concentrations and responses to anaemia in patients with or without chronic kidney disease. Nephrol Dial Transplant. 2007;22:2900-8. doi: 10.1093/ndt/gfm316.
16. Ferrucci L, Guralnik JM, Bandinelli S, Semba RD, Lauretani F, Corsi A, Ruggiero C, Ershler WB, Longo DL. Unexplained anaemia in older persons is characterised by low erythropoietin and low levels of pro-inflammatory markers. Br J Haematol. 2007;136:849-55. doi: 10.1111/j.1365-2141.2007.06502.x.
17. Dignass AU, Gasche C, Bettenworth D, Birgegård G, Danese S, Gisbert JP et al. European consensus on the diagnosis and management of iron deficiency and anaemia in inflammatory bowel diseases. J Crohns Colitis. 2015;9:211-22. doi: 10.1093/ecco-jcc/jju009.
18. Pasricha SR, Flecknoe-Brown SC, Allen KJ, Gibson PR, McMahon LP, Olynyk JK et al. Diagnosis and management of iron deficiency anaemia: a clinical update. Med J Aust. 2010;193:525-32.
19. Pettersson T, Kivivuori SM, Siimes MA. Is serum transferrin receptor useful for detecting iron-deficiency in anaemic patients with chronic inflammatory diseases? Br J Rheumatol. 1994;33:740-4. doi: 10.1093/rheumatology/33.8.740.
20. Rukuni R, Knight M, Murphy MF, Roberts D, Stanworth SJ. Screening for iron deficiency and iron deficiency anaemia in pregnancy: a structured review and gap analysis against UK national screening criteria. BMC Pregnancy Childbirth. 2015;15:269. doi: 10.1186/s12884-015-0679-9.
21. Pasricha SR. Should we screen for iron deficiency anaemia? A review of the evidence and recent recommendations. Pathology. 2012;44:139-47. doi: 10.1097/PAT.0b013e32834e8291.
22. Pasricha SR, Atkinson SH, Armitage AE, Khandwala S, Veenemans J, Cox SE et al. Expression of the iron hormone hepcidin distinguishes different types of anemia in African children. Sci Transl Med. 2014;6:235re3. doi: 10.1126/scitranslmed.3008249.
23. Tussing-Humphreys L, Pusatcioglu C, Nemeth E, Braunschweig C. Rethinking iron regulation and assessment in iron deficiency, anemia of chronic disease, and obesity: introducing hepcidin. J Acad Nutr Diet. 2012;112:391-400. doi: 10.1016/j.jada.2011.08.038.
24. Dignass A, Farrag K, Stein J. Limitations of serum ferritin in diagnosing iron deficiency in inflammatory conditions. Int J Chronic Dis. 2018;2018:9394060. doi: 10.1155/2018/93940 60.
25. GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet. 2020;396(10258):1204-22. doi: 10.1016/s0140-6736(20)30925-9.
26. Rastogi T, Mathers C. Global burden of iron deficiency anaemia in the year 2000. Geneva: WHO; 2002.
27. GBD 2019 Risk Factors Collaborators. Global burden of 87 risk factors in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet. 2020;396(10258):1223-49. doi: 10.1016/s0140-6736(20)30752-2.
28. Wiciński M, Liczner G, Cadelski K, Kołnierzak T, Nowaczewska M, Malinowski B. Anemia of chronic diseases: Wider diagnostics-better treatment? Nutrients. 2020;12:1784. doi: 10.3390/nu12061784.
29. Wirth JP, Woodruff BA, Engle-Stone R, Namaste SM, Temple VJ, Petry N et al. Predictors of anemia in women of reproductive age: Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia (BRINDA) project. Am J Clin Nutr. 2017;106:416s-27s. doi: 10.3945/ajcn.116.143073.
30. Bukhari A, Hamid F, Minhajat R, Sheryl N, Marsella CP. Non-nutritional and disease-related anemia in Indonesia: inflammation and helminthiasis. Asia Pac J Clin Nutr. 2020;29(Suppl 1):S41-S54. doi: 10.6133/apjcn.202012_29(S1).05.
31. Malik SG, Oktavianthi S, Asih PBS, Harahap A, Satyagraha AW, Syafruddin D. Nonnutritional anemia: malaria, thalassemia, and G6PD deficiency in Indonesia. Asia Pac J Clin Nutr. 2020;29(Suppl 1):S32-S40. doi: 10.6133/apjcn.202012_29(S1).04.
32. Oberman R, Dobbs R, Budiman A, Thompson F, Rossi M. The archipelago economy: unleashing Indonesia's potential. Shanghai: McKinsey Global Institute; 2012.
33. FAO, WHO. World Declaration and Plan of Action for Nutrition. International Conference on Nutrition. Rome: Food and Agriculture Organization of the United Nations; 1992.
34. Moreno Chulilla JA, Romero Colás MS, Gutiérrez Martín M. Classification of anemia for gastroenterologists. World J Gastroenterol. 2009;15:4627-37. doi: 10.3748/wjg.15.4627.
35. Ademola AS, Abiola OA. Morphologic evaluation of anemia. I Biol Med. 2016;8:1-7. doi: 10.4172/0974-8369.1000322.
36. WHO, UNICEF, UNU. Iron deficiency anaemia: assessment, prevention and control, a guide for programme managers. Geneva: World Health Organization; 2001.
37. Wahlqvist ML, Lee MS. Nutrition in health care practice. Journal of Medical Sciences. 2006;26:157-64.
38. Etheredge AJ, Premji Z, Gunaratna NS, Abioye AI, Aboud S, Duggan C et al. Iron supplementation in iron-replete and

nonanemic pregnant women in Tanzania: A randomized clinical trial. JAMA Pediatr. 2015;169:947-55. doi: 10.1001/jamapediatrics.2015.1480.
39. Bánhidy F, Ács N, Puhó EH, Czeizel AE. Iron deficiency anemia: pregnancy outcomes with or without iron supplementation. Nutrition. 2011;27:65-72. doi: 10.1016/j.nut.2009.12.005.
40. Lassi ZS, Salam RA, Haider BA, Bhutta ZA. Folic acid supplementation during pregnancy for maternal health and pregnancy outcomes. Cochrane Database Syst Rev. 2013;2013:Cd006896. doi: 10.1002/14651858.CD006896.pub2.
41. WHO. Guideline: daily iron and folic acid supplementation in pregnant women. Geneva: World Health Organization; 2012.
42. FAO. The state of food security and nutrition in the world: Building resilience for peace and food security. Rome: Food and Agriculture Organization of the United Nations; 2017 and 2019.
43. World Health Organization. Global tuberculosis report 2020. Geneva: World Health Organization; 2020.
44. Yani FF, Lipoeto NI, Supriyatno B, Darwin E, Basir D. Vitamin D status in under-five children with a history of close tuberculosis contact in Padang, West Sumatra. Asia Pac J Clin Nutr. 2017;26:S68-s72. doi: 10.6133/apjcn.062017.s2.
45. Schwenk A, Macallan DC. Tuberculosis, malnutrition and wasting. Curr Opin Clin Nutr Metab Care. 2000;3:285-91. doi: 10.1097/00075197-200007000-00008.
46. Ratledge C. Iron, mycobacteria and tuberculosis. Tuberculosis (Edinb). 2004;84:110-30. doi: 10.1016/j.tube.2003.08.012.
47. Isanaka S, Mugusi F, Urassa W, Willett WC, Bosch RJ, Villamor E, Spiegelman D, Duggan C, Fawzi WW. Iron deficiency and anemia predict mortality in patients with tuberculosis. J Nutr. 2012;142:350-7. doi: 10.3945/jn.111.144287.
48. Minchella PA, Donkor S, Owolabi O, Sutherland JS, McDermid JM. Complex anemia in tuberculosis: the need to consider causes and timing when designing interventions. Clin Infect Dis. 2015;60:764-72. doi: 10.1093/cid/ciu945.
49. Lee SW, Kang YA, Yoon YS, Um SW, Lee SM, Yoo CG et al. The prevalence and evolution of anemia associated with tuberculosis. J Korean Med Sci. 2006;21:1028-32. doi: 10.3346/jkms.2006.21.6.1028.
50. Karyadi E, Schultink W, Nelwan RH, Gross R, Amin Z, Dolmans WM, van der Meer JW, Hautvast JG, West CE. Poor micronutrient status of active pulmonary tuberculosis patients in Indonesia. J Nutr. 2000;130:2953-8. doi: 10.1093/jn/130.12.2953.
51. Gil-Santana L, Cruz LAB, Arriaga MB, Miranda PFC, Fukutani KF, Silveira-Mattos PS et al. Tuberculosis-associated anemia is linked to a distinct inflammatory profile that persists after initiation of antitubercular therapy. Sci Rep. 2019;9:1381. doi: 10.1038/s41598-018-37860-5.
52. Lounis N, Truffot-Pernot C, Grosset J, Gordeuk VR, Boelaert JR. Iron and Mycobacterium tuberculosis infection. J Clin Virol. 2001;20:123-6. doi: 10.1016/s1386-6532(00)00136-0.
53. Chao A, Sieminski PJ, Owens CP, Goulding CW. Iron acquisition in mycobacterium tuberculosis. Chem Rev. 2019;119:1193-220. doi: 10.1021/acs.chemrev.8b00285.
54. Lee J, Ryu JS. Current status of parasite infections in Indonesia: A literature review. Korean J Parasitol. 2019;57:329-39. doi: 10.3347/kjp.2019.57.4.329.
55. Nurdia DS, Sumarni S, Suyoko, Hakim M, Winkvist A. Impact of intestinal helminth infection on anemia and iron status during pregnancy: a community based study in Indonesia. Southeast Asian J Trop Med Public Health. 2001;32:14-22. doi:
56. English M, Snow RW. Iron and folic acid supplementation and malaria risk. Lancet. 2006;367(9505):90-1. doi: 10.1016/s0140-6736(06)67939-7.
57. Pasricha SR, Hayes E, Kalumba K, Biggs BA. Effect of daily iron supplementation on health in children aged 4-23 months: a systematic review and meta-analysis of randomised controlled trials. Lancet Glob Health. 2013;1:e77-e86. doi: 10.1016/s2214-109x(13)70046-9.
58. Cusick SE, John CC. Iron, inflammation, and malaria in the pregnant woman and her child: saving lives, saving brains. Am J Trop Med Hyg. 2016;95:739-40. doi: 10.4269/ajtmh.16-0533.
59. Sangaré L, van Eijk AM, Ter Kuile FO, Walson J, Stergachis A. The association between malaria and iron status or supplementation in pregnancy: a systematic review and meta-analysis. PLoS One. 2014;9:e87743. doi: 10.1371/journal.pone.0087743.
60. Rogerson SJ, Hviid L, Duffy PE, Leke RF, Taylor DW. Malaria in pregnancy: pathogenesis and immunity. Lancet Infect Dis. 2007;7:105-17. doi: 10.1016/s1473-3099(07)70022-1.
61. Adam I. Anemia, iron supplementation and susceptibility to Plasmodium falciparum malaria. EBioMedicine. 2016;14:13-4. doi: 10.1016/j.ebiom.2016.11.036.
62. Menendez C, Kahigwa E, Hirt R, Vounatsou P, Aponte JJ, Font F et al. Randomised placebo-controlled trial of iron supplementation and malaria chemoprophylaxis for prevention of severe anaemia and malaria in Tanzanian infants. Lancet. 1997;350(9081):844-50. doi: 10.1016/s0140-6736(97)04229-3.
63. Sazawal S, Black RE, Ramsan M, Chwaya HM, Stoltzfus RJ, Dutta A et al. Effects of routine prophylactic supplementation with iron and folic acid on admission to hospital and mortality in preschool children in a high malaria transmission setting: community-based, randomised, placebo-controlled trial. Lancet. 2006;367(9505):133-43. doi: 10.1016/s0140-6736(06)67962-2.
64. Dewey KG, Domellöf M, Cohen RJ, Landa Rivera L, Hernell O, Lönnerdal B. Iron supplementation affects growth and morbidity of breast-fed infants: results of a randomized trial in Sweden and Honduras. J Nutr. 2002;132:3249-55. doi: 10.1093/jn/132.11.3249.
65. Pasvol G, Weatherall DJ, Wilson RJ. The increased susceptibility of young red cells to invasion by the malarial parasite Plasmodium falciparum. Br J Haematol. 1980;45:285-95. doi: 10.1111/j.1365-2141.1980.tb07148.x.
66. Gies S, Roberts SA, Diallo S, Lompo OM, Tinto H, Brabin BJ. Risk of malaria in young children after periconceptional iron supplementation. Matern Child Nutr. 2020;2020:e13106. doi: 10.1111/mcn.13106.
67. Kabyemela ER, Fried M, Kurtis JD, Mutabingwa TK, Duffy PE. Decreased susceptibility to Plasmodium falciparum infection in pregnant women with iron deficiency. J Infect Dis. 2008;198:163-6. doi: 10.1086/589512.
68. Van Santen S, de Mast Q, Luty AJ, Wiegerinck ET, Van der Ven AJ, Swinkels DW. Iron homeostasis in mother and child during placental malaria infection. Am J Trop Med Hyg. 2011;84:148-51. doi: 10.4269/ajtmh.2011.10-0250.
69. Bhargava A. Iron status, malaria parasite loads and food policies: evidence from sub-Saharan Africa. Econ Hum Biol. 2013;11:108-12. doi: 10.1016/j.ehb.2012.02.004.
70. Wahlqvist ML. Ecosystem dependence of healthy localities, food and people. Ann Nutr Metab. 2016;69:75-8. doi: 10.1159/000449143

71. Wahlqvist ML. Ecosystem Health Disorders - changing perspectives in clinical medicine and nutrition. Asia Pac J Clin Nutr. 2014;23:1-15. doi: 10.6133/apjcn.2014.23.1.20.
72. Croze ML, Soulage CO. Potential role and therapeutic interests of myo-inositol in metabolic diseases. Biochimie. 2013;95:1811-27. doi: 10.1016/j.biochi.2013.05.011.
73. Dinicola S, Minini M, Unfer V, Verna R, Cucina A, Bizzarri M. Nutritional and acquired deficiencies in inositol bioavailability. Correlations with metabolic disorders. Int J Mol Sci. 2017;18:2187. doi: 10.3390/ijms18102187.
74. Wahlqvist ML, Specht RL. Food variety and biodiversity: Econutrition. Asia Pac J Clin Nutr. 1998;7:314-9.
75. Nurbani RA, Sulaksono BA, Sadaly HA. Eating in a time of food price volatility: Evidence from three villages in Indonesia (Year 3 findings from the Life in a Time of Food Price Volatility Study). United Kingdom: Institute of Development Studies and Oxfam International; 2015.
76. Bhanbhro S, Kamal T, Diyo RW, Lipoeto NI, Soltani H. Factors affecting maternal nutrition and health: A qualitative study in a matrilineal community in Indonesia. PLoS One. 2020;15:e0234545. doi: 10.1371/journal.pone.0234545.
77. Devine CM, Jastran M, Jabs J, Wethington E, Farell TJ, Bisogni CA. "A lot of sacrifices:" work-family spillover and the food choice coping strategies of low-wage employed parents. Soc Sci Med. 2006;63:2591-603. doi: 10.1016/j.socscimed.2006.06.029.
78. Mehta K, Booth S, Coveney J, Strazdins L. Feeding the Australian family: challenges for mothers, nutrition and equity. Health Promot Int. 2020;35:771-8. doi: 10.1093/heapro/daz061.
79. Kharisma V, Abe N. Food insecurity and associated socioeconomic factors: application of rasch and binary logistic models with household survey data in three megacities in Indonesia. Soc Indic Res. 2020;148:655-79.
80. Probandari A, Arcita A, Kothijah K, Pamungkasari EP. Barriers to utilization of postnatal care at village level in Klaten district, central Java Province, Indonesia. BMC Health Serv Res. 2017;17:541. doi: 10.1186/s12913-017-2490-y.
81. Widyawati W, Jans S, Utomo S, van Dillen J, Janssen AL. A qualitative study on barriers in the prevention of anaemia during pregnancy in public health centres: perceptions of Indonesian nurse-midwives. BMC Pregnancy Childbirth. 2015;15:47. doi: 10.1186/s12884-015-0478-3.
82. Tao Z, Xu J, Chen W, Yang Z, Xu X, Liu L et al. Anemia is associated with severe illness in COVID-19: A retrospective cohort study. J Med Virol. 2020. doi: 10.1002/jmv.26444.
83. Watanabe S, Wahlqvist ML. Covid-19 and dietary socioecology: Risk minimisation. Asia Pac J Clin Nutr. 2020;29:207-19. doi: 10.6133/apjcn.202007_29(2).0001.
84. Wahlqvist ML. Self-monitoring networks for personal and societal health: Dietary patterns, activities, blood pressure and Covid-19. Asia Pac J Clin Nutr. 2020;29:446-9. doi: 10.6133/apjcn.202009_29(3).0001.
85. Sigurdsson EL, Blondal AB, Jonsson JS, Tomasdottir MO, Hrafnkelsson H, Linnet K, Sigurdsson JA. How primary healthcare in Iceland swiftly changed its strategy in response to the COVID-19 pandemic. BMJ Open. 2020;10:e043151. doi: 10.1136/bmjopen-2020-043151.
86. Goddard AF, James MW, McIntyre AS, Scott BB. Guidelines for the management of iron deficiency anaemia. Gut. 2011;60:1309-16. doi: 10.1136/gut.2010.228874.

Review Article

Nutritional contributors to maternal anemia in Indonesia: Chronic energy deficiency and micronutrients

Nur Indrawaty Lipoeto MD, PhD[1], Masrul MD, PhD[1], Ricvan Dana Nindrea MPH, PhD[2]

[1]*Department of Nutrition, Faculty of Medicine, Universitas Andalas, Padang, Indonesia*
[2]*Department of Public Health and Community Medicine, Faculty of Medicine, Universitas Andalas, Padang, Indonesia*

Background and Objectives: Despite enduring efforts in Indonesia to eliminate anemia in pregnancy, it remains a major nutritional problem. Its nutritional contributors were reevaluated. **Methods:** A meta-analysis of reports on anemia during pregnancy in Indonesia from January 2001 to December 2019 in the PubMed and ProQuest databases was conducted. Pooled ORs were obtained in fixed- and random-effects models. Funnel plots and Egger's and Begg's tests were used to evaluate publication bias. Review Manager 5.3 and Stata version 14.2 were used for analysis. **Results:** A total of 2,474 articles were appraised. Systematic review and meta-analysis were performed on 10 studies including 4,077 participants. Chronic energy deficiency had the highest OR for the risk of anemia (3.81 [95% CI: 2.36–6.14]) followed by greater parity (OR=2.66 [95% CI: 1.20–5.89]), low education level (OR=2.56 [95% CI: 1.04–6.28]), and limited health knowledge (OR=1.70 [95% CI: 1.17–2.49]), whereas older age and inadequate iron supplementation were not apparently associated with maternal anemia ($p > 0.05$). **Conclusion:** Future policies and strategic action to reduce nutritional anemia during pregnancy in Indonesia should increase emphasis on local nutritional epidemiology to establish the pathogenesis of anemia and the validity of stand-alone single-nutrient interventions. Attention to chronic energy deficiency as a barrier to preventing anemia in pregnancy may be necessary to enable health workers and women at risk to be better informed in their efforts.

Key Words: anemia, pregnancy, risk factors, chronic energy deficiency, policies

INTRODUCTION

Anemia is a main cause of morbidity and mortality in pregnant women worldwide. Globally, 40% of pregnant women have anemia.[1] Studies have indicated that anemia is a serious health problem among pregnant women, with a prevalence of 66.2% in Sudan, 25.2% in Northwest Ethiopia, 90.5% in Pakistan, 84.5% in India, 40.4% in Southeastern Nigeria, and 22.0% in Uganda.[2–7] The Indonesia Basic Health Research 2018 survey reported that anemia occurred in 48.9% of pregnant women and was the most common among those aged 15–24 years.[8]

The mitigation of anemia during pregnancy in Indonesia and elsewhere may be limited by the widespread assumption that anemia is primarily caused by iron deficiency despite its likely multifactorial etiology; therefore, it is managed using a single-micronutrient approach with iron supplements, excluding other contributors. Risk factors might include age, a background dietary pattern with compromised nutrient bioavailability, chronic energy deficiency, parity, education level, iron supplementation, health knowledge, prenatal care, preconception and intercurrent health status and comorbidities such as menorrhagia, inflammatory and infectious diseases, and inherited hemolytic disorders such as glucose-6-phosphate dehydrogenase (G-6-PD) deficiency and hemoglobinopathies.[9-11] Anemia in pregnant women in Indonesia has unique risk factors that might differ from that in pregnant women in other countries.

Despite efforts to prevent maternal anemia through maternal and child health programs and iron tablet supplementation, its incidence remains high. Other unaddressed factors may play a role. A meta-analysis of available reports in Indonesia might increase understanding on the putative multifactoriality of anemia in pregnancy and inform policies and strategic actions for its mitigation.

MATERIALS AND METHODS

Study design and research sample

This meta-analysis complied with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Statement.[12] The samples in this study were

Corresponding Author: Dr Nur Indrawaty Lipoeto, Department of Nutrition, Faculty of Medicine, Universitas Andalas, Main Campus at Limau Manis, Gedung A 1st Floor, Pauh, Padang, 25166, West Sumatra, Indonesia.
Tel: +62751-31746
Email: indralipoeto@med.unand.ac.id/indra.liputo@gmail.com
Manuscript received and initial review completed 19 December 2020. Revision accepted 23 December 2020.
doi: 10.6133/apjcn.202012_29(S1).02

research articles published from January 2001 to December 2019 in the PubMed and ProQuest online databases. In each study, we identified risk factors for maternal anemia in Indonesia.

Operational definitions

Independent variables in this study were risk factors for maternal anemia, and the dependent variable was maternal anemia. Chronic energy deficiency was defined as a measured mid upper arm circumference of <23.5 cm.

Research procedure

First, data were collected from published research articles that identified the risk factors for maternal anemia in Indonesia in the PubMed and ProQuest online databases (Figure 1).

The following keywords were used to search titles and abstracts in the literature: ("risk factors" OR "determinant factors") AND ("anemia") AND ("Indonesia"). A total of 2,474 articles were identified by searching the titles, abstracts, and full text of articles.

Articles were excluded if (a) maternal anemia was not an outcome, (b) they were not cross-sectional studies, or (c) they included insufficient data for extraction.

Data collection technique

Data were collected in an online search. The collected data were limited to articles published in English and In-

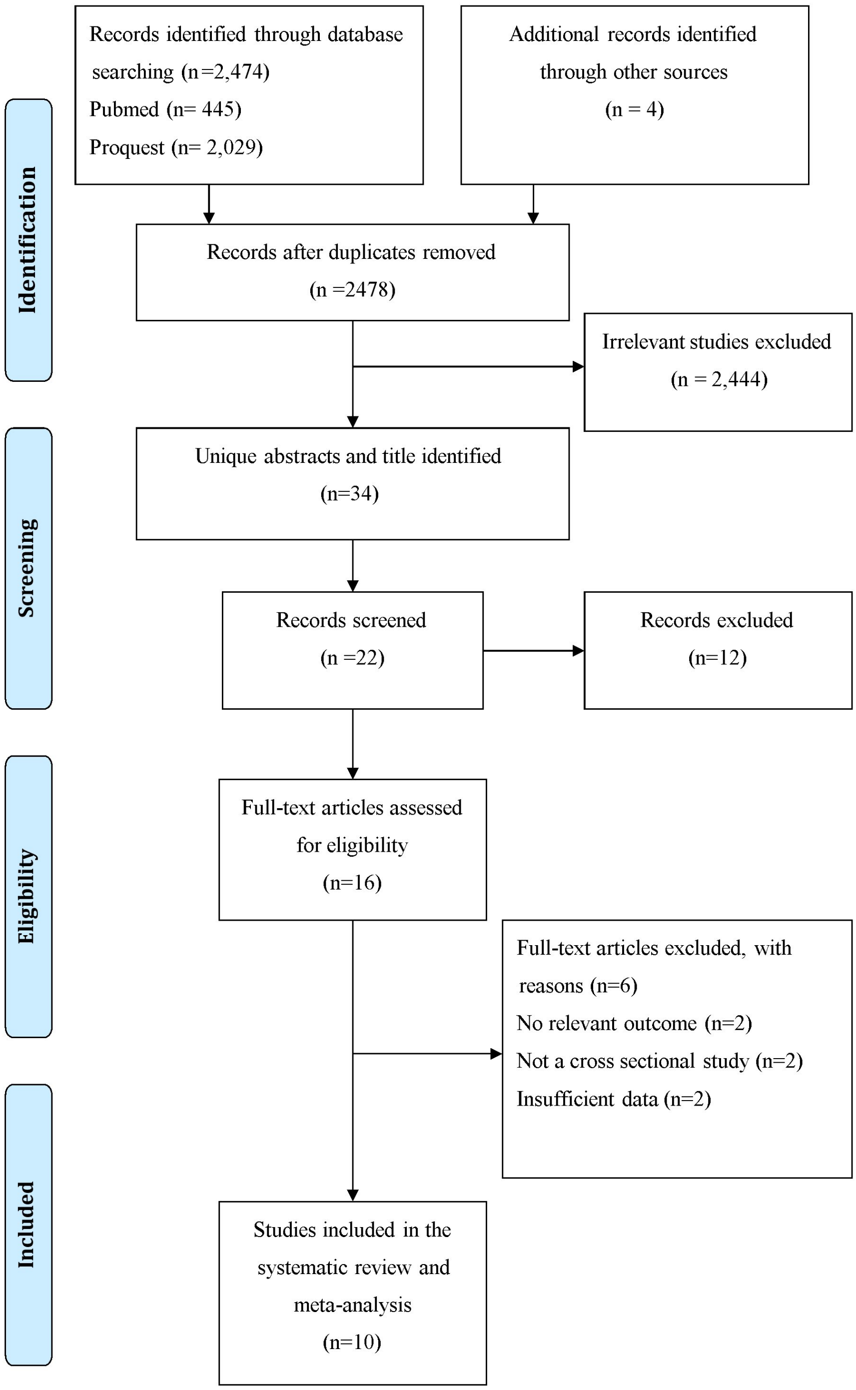


Figure 1. Publication selection protocol.

donesian that presented original research. The publication dates of articles were limited to January 2001–December 2019. Research participants were limited to humans only. Unique articles with conceivably significant titles were inspected, whereas insignificant articles were excluded. The full text of possibly significant unique articles was evaluated, after which nonessential articles were excluded. Inclusion criteria were research articles on risk factors for maternal anemia in Indonesia with a cross-sectional and observational analytical study design. Articles were excluded if (a) the inclusion criteria were non fulfilled, (b) their full text was unavailable, or (c) data provided in text were insufficient for extraction. The original author name, study location, study type, number of samples, and risk factors were also collected from the articles.

Information from all articles that fulfilled the inclusion criteria per a standardized protocol was carefully extracted by two investigators, and contradictions were settled by three different investigators. The Newcastle–Ottawa Quality Assessment Scale (NOS) was used to evaluate the quality of research articles. Articles were categorized as having poor (scores of 0–3), moderate (scores of 4–6), or high quality (scores of 7–9).[13]

Data analysis

Data analysis was conducted to obtain the pooled and combined ORs of collected articles. ORs with 95% CIs were utilized to pool results. These tests revealed articles with the minimum statistical power and small sample sizes that had significant heterogeneity (I^2 >50%). Articles with significant heterogeneity were assessed using a random-effects model, and those with homogeneity were assessed using a fixed-effects model. Review Manager 5.3 was used for data analysis. Publication bias was assessed using Egger's and Begg's tests and graphed on funnel plots. A two-tailed *p* value of <0.05 indicated significant publication bias. Stata version 14.2 was used to analyze publication bias.

RESULTS

Table 1 lists the results of the analysis of 10 studies including 4,077 pregnant Indonesian women evaluated for presumed maternal anemia and its potential risk factors. Covariates included older age, limited education, limited knowledge, inadequate iron supplementation, greater parity, and chronic energy deficiency.

As illustrated in Figure 2, chronic energy deficiency had the highest OR (OR=3.81 [95% CI 2.36–6.14]), followed by greater parity (OR=2.66 [95% CI 1.20–5.89]), limited education (OR=2.56 [95% CI 1.04–6.28]), and limited knowledge (OR=1.70 [95% CI 1.17–2.49]). Older age and inadequate iron supplementation were not associated with maternal anemia (p>0.05). Older age, limited education, inadequate iron supplementation, and greater parity exhibited heterogeneity in terms of the risk of maternal anemia ($p_{heterogeneity}$ <0.05; I^2 >50%), indicating variation in research on maternal anemia. Limited knowledge and chronic energy deficiency exhibited homogeneity in research on anemia ($p_{heterogeneity}$ >0.05; I^2 <50%); therefore, in population-level analyses, the results regarding these risk factors were consistent despite differences in time, place, and conditions.

Figure 3 indicates the heterogeneity of older age, limited education, inadequate iron supplementation, and greater parity in research on maternal anemia because the plot is asymmetrical about the vertical line. However, the funnel plots confirmed that limited knowledge and chronic energy deficiency were homogeneous in research on maternal anemia because the plot was symmetrical about the vertical line.

Figure 4 presents publication bias among studies on risk factors for iron-deficiency maternal anemia in Indonesia. These funnel plots were then tested using Egger's and Begg's tests (Table 2).

Table 2 indicates that Egger's and Begg's tests revealed no significant publication bias in included studies (p>0.05).

DISCUSSION

Among the prospective determinants of anemia during pregnancy in Indonesia, chronic energy deficiency had the highest OR, followed by greater parity, limited education, and limited knowledge. The Indonesian Ministry of Health has supported iron tablet distribution to pregnant mothers for generations. Baseline Health Research[24,25] reports have considered these efforts to be successful when more than 80% of mothers receive 90 iron tablets in the final trimester, but some studies have indicated that compliance with tablet consumption is low.[26,27]

Current situation of maternal nutritional anemia in Indonesia

The results of this study demonstrated the situation of iron-deficiency anemia in pregnant women in Indonesia. Systematic reviews and meta-analyses have revealed problems of low knowledge among pregnant women on maternal anemia in terms of its impact and prevention as well as chronic energy deficiency.

Limited knowledge among pregnant women on anemia prevention is evident in Indonesian Basic Health Research reports, which have demonstrated that approximately 40% of pregnant women receive information on pregnancy complications and 60% receive iron tablets usage services. Nevertheless, not all pregnant women who receive iron tablets consume them correctly, and more than 90% of pregnant women are not reached.[24,25] Moreover, iron deficiency may or may not be a cause of their anemia. Women are held accountable for managing and preventing maternal anemia even though its epidemiology and pathogenesis are inadequately understood and presumptive. The extent to which a woman's diet is sufficient, whether her iron bioavailability is questionable, and whether nutrient loss or comorbidities are present remain largely unknown, if not ignored. In reality, women in the reproductive age group and preconceptionally are ill prepared in nutritional health. They also have compromised intrapartum support services because of the narrow assessment of nutritional and nonnutritional risks.

Chronic energy deficiency in pregnant women may result from low awareness of the importance of dietary quantity and quality during pregnancy.[27] In the first trimester, pregnant women often experience nausea or vomiting with decreased food consumption, meaning that the needs of the mother and fetus are not met.[29,30] A study

Table 1. Systematic review of risk factors for maternal anemia in Indonesia

First author	Region	Study type	Patients characteristic	Sample size	Risk factors	Anemia parameter	Iron deficiency	NOS
Aji et al[13]	Padang	Cross sectional study	Women in early pregnancy	176	Socioeconomic, knowledge, Pre-pregnancy BMI status, Fe tablets consumption	Hb <11 g/dL	N/A	7
Seu et al[14]	Kupang, West Timor	Cross sectional study	Pregnant women who visited antenatal care in PHC Facilities	102	Underweight/ chronic energy deficiency	Hb <10.5 g/dL	Shine and Lal index (SLI) ≥1,530	7
Diana et al[15]	Madura	Cross sectional study	Anemic pregnant women	252	Dietary diversity	Hb <10 g/dL	N/A	7
Lestari et al[16]	North Sumatera	Cross sectional study	Not available	140	Knowledge, parity and chronic energy deficiency	Hb <11 g/dL	N/A	7
Ani et al[17]	Bali	Cross sectional study	Women with a year postpartum period	163	Parity, chronic energy deficiency	Hb <11 g/dL	N/A	7
Lisfi et al[18]	Padang	Cross sectional study	Mother's third trimester of pregnancy	44	Fe tablets consumption	Hb <11 g/dL	N/A	6
Mariza[19]	Lampung	Cross sectional study	Pregnant women who visited independent Midwifery	102	Level of education, social and economic	Hb <11 g/dL	N/A	7
Opitasari et al[20]	Two hospitals in Jakarta	Cross sectional study	Mother's third trimester of pregnancy	1,202	Parity, age	Hb <11 g/dL	N/A	7
Ristica et al[21]	Pekanbaru	Cross sectional study	Pregnant women	212	Level of education, knowledge, Fe tablets consumption, chronic energy deficiency, age	Hb <11 g/dL	N/A	7
Suega et al[22]	Bali	Cross sectional study	Not available	1,684	Educational background, Fe tablets consumption	Hb <11 g/dL	Ferritin serum <20 µg/L	7
Total				4,077				

NOS: Newcastle–Ottawa Quality Assessment Scale; articles were classified as having poor (scores of 0–3); moderate (scores of 4–6); and high quality (scores of 7–9).[12]

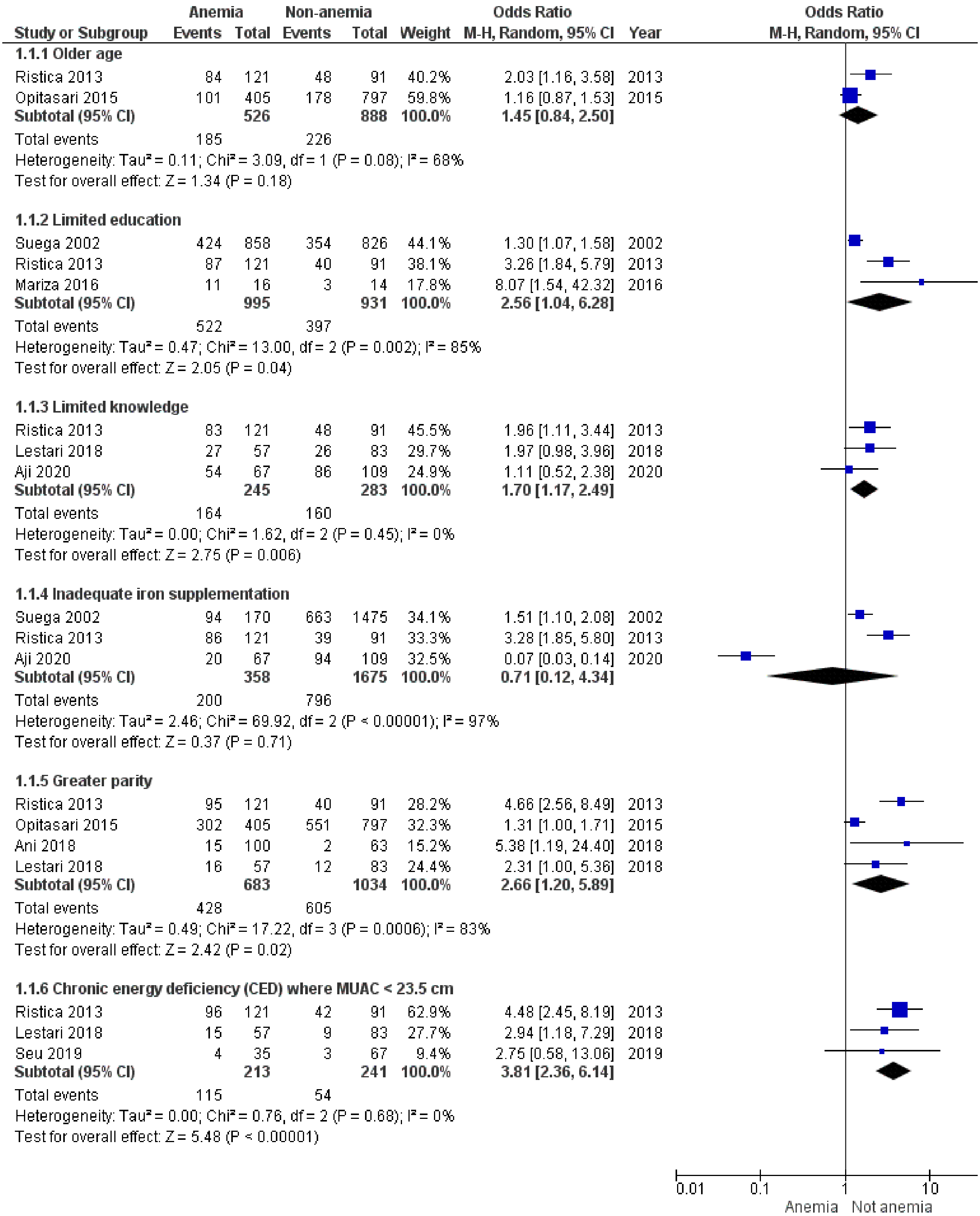


Figure 2. Meta-analysis of the likelihood of anemia in pregnancy by maternal and child clinical metrics.

conducted in West Sumatra, Indonesia,[30] reported the nutrient intake of 360 pregnant mothers, indicating that their energy intake reached only two-thirds of the RDA; their iron intake was approximately half of the RDA for Indonesian people. Although their protein intake exceeded the RDA, their intake of folic acid and fiber was more than a third of the RDA. The study also reported that the median food intake of pregnant women with chronic energy deficiency was lower than normal nutritional status for local dietary patterns. Pregnant women with normal nutritional status consumed more plant-based foods, meat, fish coconut milk, and dairy products.[31]

Chronic energy deficiency and anemia appear to be concurrent in pregnancy. A reduction in chronic energy deficiency may also reduce anemia. However, a study conducted in India[32] revealed no significant association of iron deficiency and energy intake with the risk of anemia and chronic energy deficiency. The study suggested that

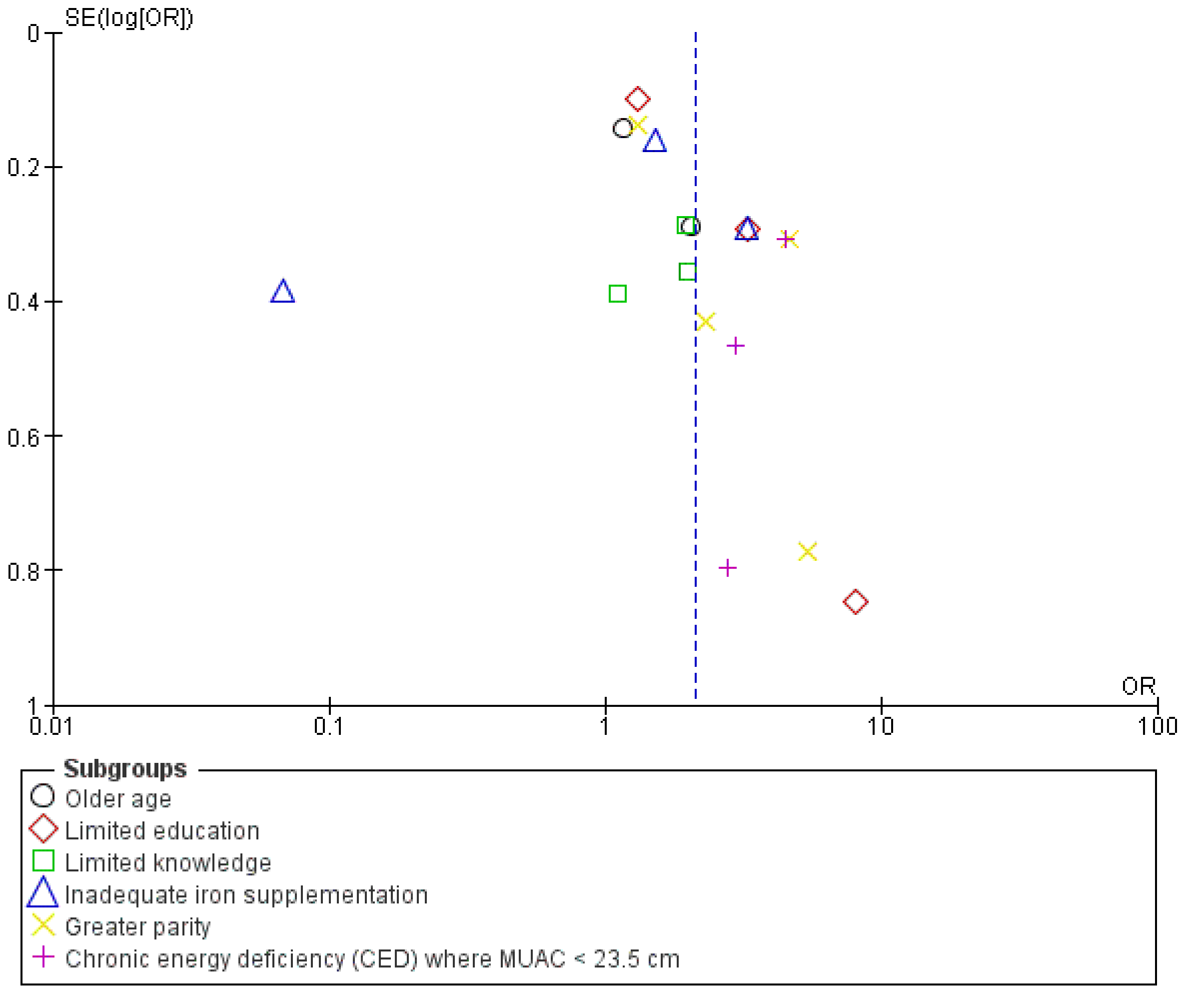


Figure 3. Funnel plots of risk factors for iron-deficiency anemia in pregnant women in Indonesia.

although diet optimization is obviously crucial for overall health, interventions that focus solely on diet may have limited efficacy in reducing the prevalence of anemia.

Prenatal care should be personalized to account for ethnicity, culture, education level, knowledge level on pregnancy, and diet. Educational efforts through increasing communication, information, and education can be used as a health promotion strategy in primary, secondary and tertiary education.[32] Information media widely used by health facilities in Indonesia tend to be conventional, namely involving counseling, brochures, and leaflets. The current rapid growth of the Internet and social media use presents an opportunity to disseminate information, increase literacy, and provide education.[33] As a result, educational content can become more engaging by utilizing interactive media; information can also be more widely shared and accessible than information shared using conventional methods.

Future policies and strategic actions

Many factors can affect the occurrence of maternal anemia, including chronic energy deficiency, iron deficiency in the diet, iron malabsorption, and the level of compliance with iron tablet consumption.[9,10] These factors are related to the knowledge of pregnant women regarding anemia and its effects and prevention methods. Knowledge is a factor that stimulates health behavior. If pregnant women understand the consequences of anemia and how to prevent it, they will exhibit favorable health behavior.[18,23] For example, the problem of nutritional anemia among pregnant women in Indonesia is related to chronic energy deficiency during pregnancy, which is caused by imbalanced nutrition of both macronutrients and micronutrients. Consequently, pregnant women are at risk of nutritional disorders. This condition occurs because pregnant women have insufficient knowledge on anemia.[14,17]

Lack of knowledge regarding anemia affects health behavior, especially during pregnancy. Consequently, pregnant women may have suboptimal health behavior to prevent anemia in pregnancy. Pregnant women who have little knowledge on anemia may not have a balanced diet of macronutrients, micronutrients, and foods containing iron because of their ignorance both before and during pregnancy.[16,21]

Knowledge regarding anemia can be increased through counseling based on the characteristics of target groups to ensure that informational materials can be accepted by all pregnant women even though their characteristics are different. For example, providing education to pregnant women with a low education level requires a different method from that used to counsel highly educated pregnant women.[34,35]

Policies that can be enacted by the government include campaigns, advocacy, education, and behavioral change communications for the prevention of anemia in pregnant

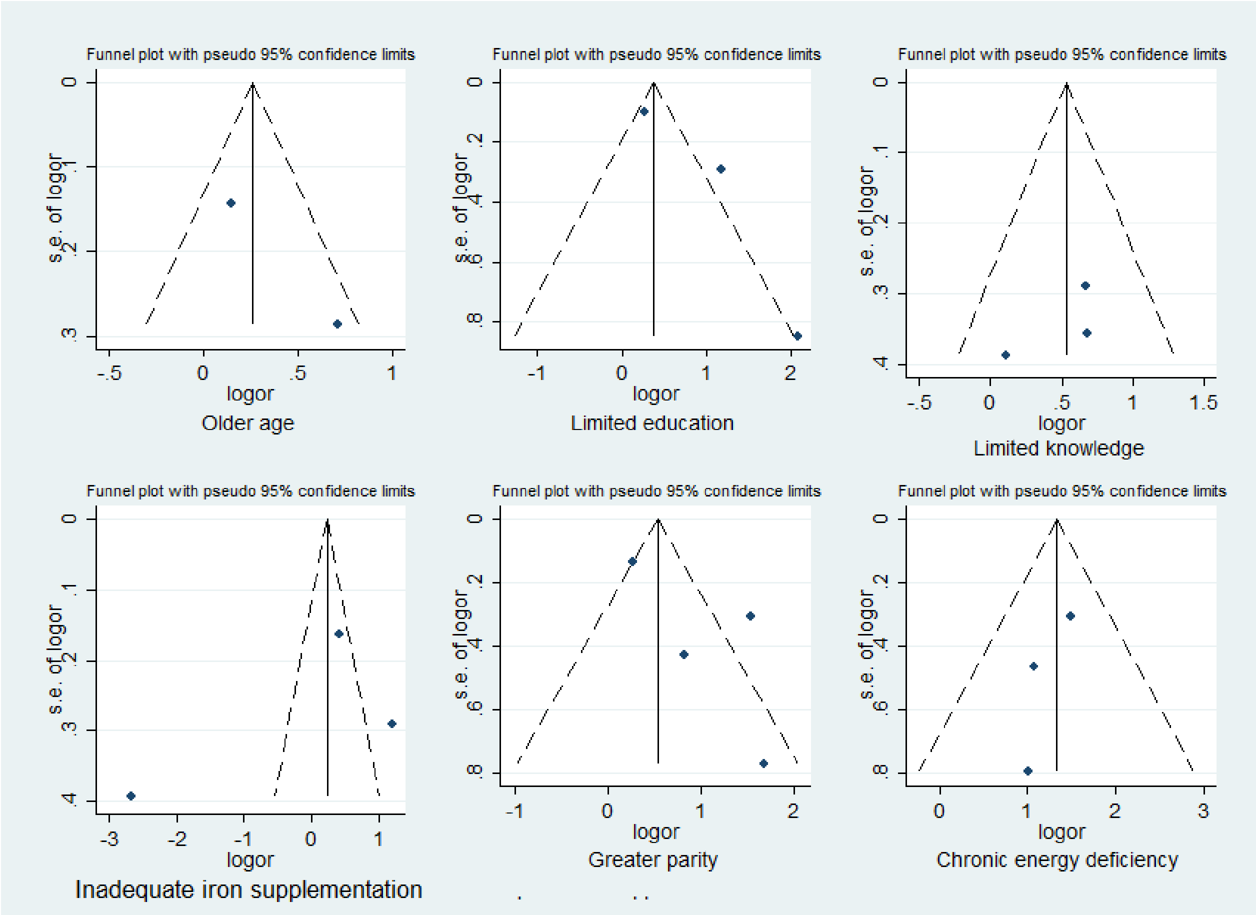


Figure 4. Publication bias for studies on the risk factors for iron-deficiency anemia in pregnant women in Indonesia

Table 2. Publication bias among studies based on Egger's and Begg's tests

Risk factors	Publication bias	
	Begg's test	Egger's test
Older age	0.317	0.310
Limited education	0.602	0.216
Limited knowledge	0.316	0.290
Inadequate iron supplementation	0.317	0.312
Greater parity	0.497	0.217
Chronic energy deficiency	0.602	0.358

p>0.05, no publication bias.

women by using innovative methods and various communication channels. These policies should be aimed at the systematic and innovative dissemination of iron anemia prevention information to pregnant women to increase awareness and community commitment. This policy strategy includes (a) involving the community, mothers, and first-level health service facilities in increasing awareness of iron-deficiency anemia prevention in pregnant women and the health benefits for both pregnant women and babies as well as pregnancy outcomes and (b) developing nutritional advocacy, communication, and mass mobilization by using clear and attractive messages tailored to specific age groups and enacting strategies that can be used by all stakeholders from the central level, namely that of the Ministry of Health of the Republic of Indonesia, to the community health level, namely first-level health facilities and independent midwives; support from organizations and all related parties can be disseminated through innovative communication channels, such as nonelectronic media and electronic social media.

Action programs to increase knowledge among pregnant women, namely in the form of campaigns, advertisements in various media, and collaboration with influential figures to promote prevention to the target audience and the wider community, can facilitate the prevention of maternal anemia. Radio and bus advertisements as well as leaflets, posters, and idol artists promoting anemia prevention in pregnant women improved anemia prevention in Ethiopia.[35] The use of posters, leaflets, and idol advertisements was effective in reducing the prevalence of maternal anemia in the Philippines.[37,38]

Apart from advertising, activities that empower communities are necessary to enable health cadres to recognize, prevent, and manage anemia in pregnant women, thereby increasing community-based social support. Through community involvement and empowerment efforts with health cadres, support for the prevention and management of maternal anemia can increase. Community empowerment activities to prevent maternal anemia include increasing the capacity of health cadres and pregnant women in first-level health facilities through efforts to increase knowledge.

Conclusion

In Indonesia, as expected, education level, health knowledge, parity, and iron supplementation (typically with folic acid) are associated with maternal anemia. The strong association of chronic energy deficiency with maternal anemia compared with any of the other factors indicate the need for more widespread of health and food system considerations. Future strategies should engage women in the reproductive age group by using programs that optimize general health and nutrition to ensure health at conception and uncompromised fetal development throughout pregnancy.

ACKNOWLEDGMENT

This study was supported by the Indonesian Danone Institute Foundation. We would like to thanks Prima Dasih for helping data collection.

AUTHOR DISCLOSURES

The authors declare no conflicts of interest.

REFERENCES

1. World Health Organization. Anaemia. 2020 [cited 2020/08/27]; Available from: https://www.who.int/health-topics/anaemia#tab=tab_1.
2. Adam I, Khamis AH, Elbashir MI. Prevalence and risk factors for anaemia in pregnant women of eastern Sudan. Trans R Soc Trop Med Hyg. 2005;99:739-43. doi: 10.1016/j.trstmh.2005.02.008
3. Asrie F. Prevalence of anemia and its associated factors among pregnant women receiving antenatal care at Aymiba Health Center, northwest Ethiopia. J Blood Med. 2017;8:35-40.
4. Baig-Ansari N, Badruddin SH, Karmaliani R, Harris H, Jehan I, Pasha O et al. Anemia prevalence and risk factors in pregnant women in an urban area of Pakistan. Food Nutr Bull. 2008;29:132-9.
5. Toteja GS, Singh P, Dhillon BS, Saxena BN, Ahmed FU, Singh RP et al. Prevalence of anemia among pregnant women and adolescent girls in 16 districts of India. Food Nutr Bull. 2006;27:311-5.
6. Dim CC, Onah HE. The prevalence of anemia among pregnant women at booking in Enugu, South Eastern Nigeria. Medscape Gen Med. 2007;9:11.
7. Namusoke F, Rasti N, Kironde F, Wahlgren M, Mirembe F. Malaria burden in pregnancy at Mulago National Referral Hospital in Kampala, Uganda. Malar Res Treat. 2010;2010:1-10.
8. Ministry of Health Republic of Indonesia. Jakarta: Indonesia Basic Health Research; 2018.
9. Balarajan Y, Ramakrishnan U, Özaltin E, Shankar AH, Subramanian SV. Anaemia in low-income and middle-income countries. Lancet. 2011;378(9809):2123-35.
10. Salhan S, Tripathi V, Singh R, Gaikwad HS. Evaluation of hematological parameters in partial exchange and packed cell transfusion in treatment of severe anemia in pregnancy. Anemia. 2012;2012:608658.
11. Lukito W, Wahlqvist ML. Intersectoral and eco-nutritional approaches to resolve persistent anemia in Indonesia. Asia Pac J Clin Nutr. 2020;29(Suppl 1):S1-S8. doi: 10.6133/apjcn.202012_29(S1).01.
12. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ. 2009;339:b2700.
13. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2009 [cited 2020/07/05]. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
14. Aji AS, Yusrawati Y, Malik SG, Lipoeto NI. Prevalence of anemia and factors associated with pregnant women in West Sumatra, Indonesia: Findings from VDPM Cohort Study. Indonesian Journal of Nutrition and Dietetics. 2020;7:1-12. (In Indonesian)
15. Seu MMV, Mose JC, Panigoro R, Sahiratmadja E. Anemia prevalence after iron supplementation among pregnant women in midwifes practice of primary health care facilities in Eastern Indonesia. Anemia. 2019;2019:1413906.
16. Diana R, Khomsan A, Anwar F, Christianti DF, Kusuma R, Rachmayanti RD. Dietary quantity and diversity among anemic pregnant women in Madura Island, Indonesia. J Nutr Metab. 2019;2019:2647230.
17. Lestari S, Fujiati II, Keumalasari D, Daulay M, Martina SJ, Syarifah S. The prevalence of anemia in pregnant women and its associated risk factors in North Sumatera, Indonesia. IOP Conference Series: Earth and Environmental Science. 2018;125:012195.
18. Ani LS, Utami NWA, Weta IW, Darmayani IGAS, Suwiyoga K. Anemia in preconception women in Sideman Sub District Karangasem Regency, Bali-Indonesia. Gineco eu. 2018;14:131-4.
19. Lisfi I, Serudji J, Kadri H. Relationship between iron tablet consumption and anemia among third trimester pregnant mothers of Air Dingin Public Health Centre in Padang. Jurnal Kesehatan Andalas. 2017;6:191-5. doi: 10.25077/jka.v6i1.669. (In Indonesian)
20. Mariza A. Relationship between level of education and socioeconomic status with anemia among pregnant mothers in Primary Health Care of Yohan Way Halim Bandar Lampung 2015. Jurnal Kesehatan Holistik. 2016;10:5-8. doi: 10.33024/hjk.v10i1.114. (In Indonesian)
21. Opitasari C, Andayasari L. Young mothers, parity and the risks of anemia in the third trimester of pregnancy. Health Science Journal of Indonesia. 2015;6:7-11. (In Indonesian)
22. Ristica OD. Risk factors related to anemia in pregnant women. Jurnal Kesehatan Komunitas. 2013;2:78-82. (In Indonesian)
23. Suega K, Dharmayuda TG, Sutarga IM, Bakta IM. Iron-deficiency anemia in pregnant women in Bali, Indonesia: a profile of risk factors and epidemiology. Southeast Asian J Trop Med Public Health. 2002;3:604-7.
24. Ministry of Health of Indonesia. Basic Health Research. Jakarta: Ministry of Health of Indonesia; 2013.
25. Ministry of Health of Indonesia. Basic Health Research. Jakarta: Ministry of Health of Indonesia; 2018.
26. Schultink W. Iron-supplementation programmes: Compliance of target groups and frequency of tablet intake. 1996. [cited 2020/11/15]; Available from: http://www.unu.edu/unupress/food/8F171e/8F171E06.htm.
27. Seck BC, Jackson RT. Determinants of compliance with iron supplementation among pregnant women in Senegal. Public Health Nutr. 2008;11:596-605.
28. Shaheen R, Lindholm L. Quality of life among pregnant women with chronic energy deficiency in rural Bangladesh. Health Policy. 2006;78:128-34.

29. Desyibelew HD, Dadi AF. Burden and determinants of malnutrition among pregnant women in Africa: A systematic review and meta-analysis. PLoS One. 2019;14:e0221712.
30. Alemayehu MS, Tesema EM. Dietary practice and associated factors among pregnant women in Gondar town north west, Ethiopia, 2014. Int J Nutr Food Sci. 2015;4:707-12.
31. Widyawati W, Jans S, Utomo S, van Dillen J, Janssen ALML. A qualitative study on barriers in the prevention of anaemia during pregnancy in public health centres: perceptions of Indonesian nurse-midwives. BMC Pregnancy Childbirth. 2015;15:47.
32. Subasinghe AK, Walker KZ, Evans RG, Srikanth V, Arabshahi S, Kartik K, Kalyanram K, Thrift AG. Association between Farming and Chronic Energy Deficiency in Rural South India. PLoS One. 2014;9:e87423.
33. Purnakarya I. Relationship of local-based dietary intake, patterns and quality with zinc status among Minangkabau pregnant women in West Sumatra, Indonesia. Thesis, Universitas Indonesia; 2017.
34. Souganidis ES, Sun K, de Pee S, Kraemer K, Rah JH, Moench-Pfanner R et al. Relationship of maternal knowledge of anemia with maternal and child anemia and health-related behaviors targeted at anemia among families in Indonesia. Matern Child Health J. 2012;16:1913-25.
35. Sunuwar DR, Sangroula RJ, Shakya NS, Yadav R, Chaudhary NK, Pradhan PMS. Effect of nutrition education on hemoglobin level in pregnant women: A quasi-experimental study. PLoS One. 2019;14:e0213982.
36. Shah S, Sharma G, Shris L, Shah SK, Sharma M, Sapkota NK. Knowledge on dietary patterns among pregnant women attending antenatal care check-up in Narayani hospital, Nepal. Int J Community Med Public Health. 2017;4:1466-72.
37. Karim AM, Betemariam W, Yalew S, Alemu H. Programmatic correlates of maternal healthcare seeking behaviors in Ethiopia. Ethiop J Health Dev. 2010;24:92-9.
38. Sanghvi TG, Harvey PWJ, Wainwright E. Maternal iron-folic acid supplementation programs: evidence of impact and implementation. Food Nutr Bull. 2010;31:S100-7.

Review Article

Nutritional anemia in Indonesia children and adolescents: Diagnostic reliability for appropriate management

Mohammad Juffrie MD, PhD[1,2,3], Siti Helmyati DCN, PhD[2,3,4], Mohammad Hakimi MD, PhD[3,5]

[1]*Department of Child Health, General Hospital Dr. Sardjito/Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia*
[2]*Center for Health and Human Nutrition, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia*
[3]*Doctorate Study Program, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia*
[4]*Department of Nutrition and Health, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia*
[5]*Department of Obstetrics and Gynecology, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia*

Background: Nutritional anemia in Indonesian children and adolescents is generally regarded and treated as iron-deficient anemia, as it is in individuals in other age groups. **Objectives:** Yet, it remains a public health threat without comprehensive management or a sustained solution. **Methods:** This review seeks to improve understanding of impediments to its resolution. Relevant studies reported in the past 5 years were identified in PubMed, Science Direct, Crossreff, Google Scholar, and Directory of Open Access Journals databases. **Results:** In all, 12 studies in several Indonesian cities provided the basis for the review. Most were conducted in schools, indicating the potential of these institutions as targets for intervention but pointing to serious deficiencies in identification of the problem across the archipelago and in remote and rural areas. No study has evaluated coexistent anemia and malnutrition, which likely would have revealed the multi-factoriality of nutritional anemia. Data regarding nutrition education, food-based innovation, and supplementation, which may alleviate anemia in children and adolescents, are available, although study lengths and sample sizes have limited interpretation and comparison. **Conclusions:** Broadly, three intervention approaches to nutritional anemia have been undertaken, namely food-based interventions, nutrient supplementation, and nutrition education. Some progress has been made with these approaches, presumably through increases in iron intake. More information is needed regarding the underlying causality and pathogenesis, suboptimal food patterns, and comorbidities, any of which might limit the effectiveness of programs designed to resolve childhood and adolescent anemia in Indonesia.

Key Words: multifactorial anemia, adolescent, children, Indonesia, nutritional interventions

INTRODUCTION

Nutrition-related anemia places a burden on the global public health sector, including the health care system in Indonesia.[1,2] It affects 1.62 billion people worldwide, mostly children, adolescents, and women.[3,4] In Indonesia, the Ministry of Health reported increasing prevalence of nutrition-related anemia among pregnant women, from 37% in 2013 to 48.9% in 2018. More than 80% of women aged 15–24 years are affected.[5] Children and adolescents face the same problem. In 2013, according to the Basic Health Research survey, more than 50% of Indonesian children and adolescents were anemic, consisting of 28% of children under 5 years and 26% of children aged 5–14 years.[6] A smaller study of 645 Indonesian elementary students revealed similar findings, with 27% of them being anemic. Aside from anemia, 20% had stunted growth, 14% had low weight for height, and 14% were overweight or obese.[7] Anemia often coexists with malnutrition.[8] Children with stunted growth have a 2.3-times higher risk of anemia than those without stunted growth.[9] Alzain[10] also mentioned that anemia and body height have a significant association.

Corresponding Author: Dr Mohammad Juffrie, Department of Child Health, General Hospital Dr. Sardjito/Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia.
Tel: +62274-545458
Email: arsipjuffrie@gmail.com
Manuscript received and initial review completed 19 December 2020. Revision accepted 23 December 2020.
doi: 10.6133/apjcn.202012_29(S1).03

Overcoming this problem is essential because anemia can have physical, cognitive, and emotional impacts. Pollitt[11] proposed that anemia can change cerebral function during infancy, affecting the ability to learn. Other studies have mentioned that anemia during childhood has long-lasting effects on neurodevelopment, including on the auditory and visual systems.[12,13] The condition is associated with other nutritional statuses. A study conducted in Vietnam determined that malnourished children, whether underweight or wasted or with stunted growth, were more likely to be anemic.[14] A study conducted in rural China indicated that improvement in anemia status increased the cognitive function of children.[15]

The WHO proposed iron and folic acid supplementation as a strategy to prevent anemia in adolescence.[16] In Indonesia, anemia management in pregnant and adolescent women is focused on iron supplementation, often independent of other approaches. These approaches might include understanding sociodemographic and lifestyle characteristics and managing community food systems, food pattern optimization, food fortification, nutrition education, probiotic administration, menstrual irregularities, comorbidities, and inter-current infections.[17-19]

This review gathers recent reports on the occurrence, prevention, and management of anemia among young Indonesians. The focus on children and adolescents reflects the greater prevalence of poor dietary practices in this age group, the risk of post-pubertal anemia in girls, and the propensity to infection.[16] Timely preventive strategies for anemia in early life have implications for future health. Pollitt[11] advocated conducting community-based trials to find effective ways of overcoming anemia. The present review seeks to identify current weaknesses and opportunities for governments, food and health systems, and community health workers attempting to reduce the burden of nutritional anemia among young Indonesians.

METHODS

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[20]

Inclusion and exclusion criteria

The authors determined the focus of the study by using the participant, intervention, comparison, outcome (PICO) approach summarized in Table 1

The eligibility criteria consisted of experimental studies carried out in Indonesia and related to the effects of nutritional interventions on anemia and malnutrition. Children and adolescents were regarded as the study population. The studies reviewed were limited to research conducted in Indonesia and published in English or Indonesian during 2015–2020. Articles that were not primary studies (such as reviews) or not published in a journal were excluded.

Table 1. PICO approach to study selection

Participants	Indonesian children or adolescent
Interventions	Nutrition intervention (nutrition education, food-based intervention, supplementation)
Comparisons	Indonesian children or adolescent who did not receive interventions
Outcomes	Hemoglobin level, knowledge, attitude

PICO: participants, interventions, comparisons, outcomes.

Search strategy

The articles were identified through a search on the following major electronic databases: PubMed, ScienceDirect, Crossref, Directory of Open Access Journals, and Google Scholar. Search terms used included "anemia AND (children OR adolescent OR infants) AND nutrition AND Indonesia AND intervention." The search strategy was adapted according to the database. Studies reported up until July 2020 were retrieved to be assessed for eligibility.

Study selection

The authors selected articles initially by reading titles and abstracts. Rayyan, a web application for systematic reviews (https://rayyan.qcri.org/), was used to review the articles. Subsequently, the authors independently read the full texts of the selected articles. Articles were included that met the eligibility criteria of this systematic review. Any disagreements that arose among the reviewers were resolved through discussion.

Data extraction and quality assessment

The following data were extracted for analysis: author name, year of publication, study location, sample size, type of nutrition intervention, data analysis method, and findings. The quality of the selected articles was assessed using the Cochrane risk of bias assessment tool.[21]

RESULTS

The study was conducted in two stages, initial research and article review. From the initial research, a total of 198 articles were obtained from various databases. During the initial review, 161 articles were excluded because they did not meet the inclusion criteria. Another was excluded during the full-text review due to a high score of potential bias. In the end, 12 studies were included; 6 were published in English and 6 were published in Indonesian (Figure 1).

All the research was conducted in Indonesia, namely in cities on Sumatra Island (3),[22-24] in Java (6),[25-30] in Madura (1),[31] in Kalimantan (1),[32] and on Sulawesi Island (1).[33] Six studies focused on anemia prevention in adolescents, and the others focused on anemia prevention in children. Specifically, three targeted children under 5 years of age. Of these studies, 75% were conducted at a school (either a primary or a junior or senior high school). This review offers perspectives on three anemia prevention approaches, namely food-based interventions, nutrition education, and supplementation. One food-based innovation made use of local foods such as *nagara* nut (*Vigna unguiculata* subsp. cylindrica) and *haruan* fish (*Channa striata*), which are rich in nutrition and easy to obtain.[32] Five studies tested the effects of a food-based intervention or supplementation combined with nutrition education.

No study reported the effect of the intervention on the coexistence of anemia and undernutrition among the individuals involved. The study by Budiana et al[28] tested the

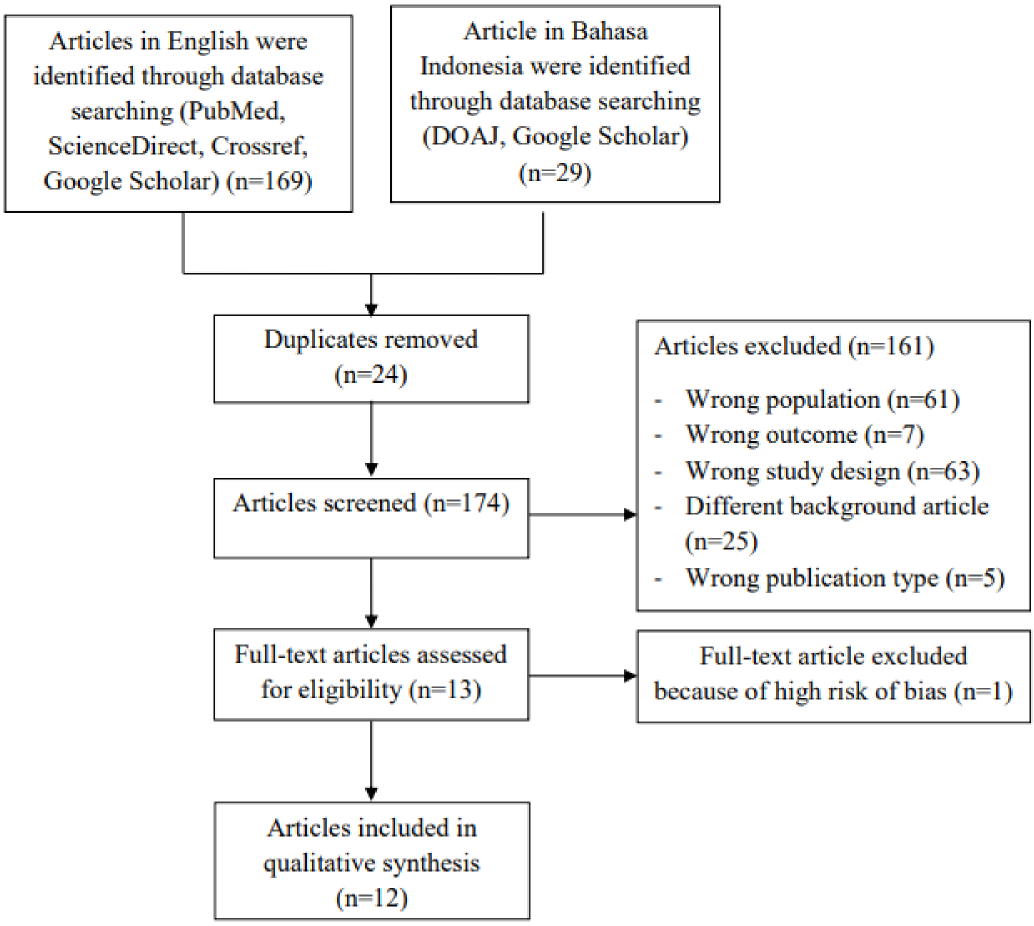


Figure 1. Information retrieval protocol.

effects of *Taburia* (a multimicronutrient powder) on hemoglobin (Hb) levels in anemic and wasted children aged under 5 years. However, the study did not report its effect on their nutritional status, only anemia. Another noteworthy study carried out by Sekiyama et al[26] investigated how a sustainable school lunch program can affect the nutritional status of children. Of the 68 participants, 32% had stunted growth, 3% were underweight, and 17% were overweight. During the program, the children received food with significant increases in protein, fat, calcium, and vitamin C, which improved the nutritional status of undernourished children. The complete results are provided in Table 2

DISCUSSION

Anemia is a major public health problem in Indonesia. The Basic Health Research report did not specify the type of anemia. Many researchers assume that the most common type is iron deficiency anemia (IDA), following the WHO, which mentioned that IDA is the most prevalent type of anemia worldwide.[22,23,34,35] This is in accordance with the research of Yip (1994) in Khusun et al,[36] who argued that the incidence of iron deficiency increases with the prevalence of anemia in a country. However, anemia has more than a single cause.

Anemia may be multifactorial, on account of diet, blood loss, chronic infection, micronutrient, or inherited red cell or Hb abnormalities. This is not to suggest that it necessarily has a complex causality and pathogenesis. Notably, the primary cause may well be related not to diet but instead to blood loss resulting from menstrual irregularities such as menorrhagia in women during the reproductive years, intestinal helminthiasis such as ascariasis or hookworm, or, in later life, large bowel tumours;[37,38] alternatively, it may result from malabsorption (as in cases of celiac disease). Nutritional measures are generally required, regardless of whether dietary characteristics are the primary factors.[39] The notion that most Indonesian cases of anemia are due to iron deficiency should be reevaluated; this may not be true for many cases of anemia. Understanding the distribution and prevalence of types of anemia is critical to designing targeted interventions.

Few published reports on anemia in Indonesia have provided direct evidence of iron deficiency or other causes. Few studies of anemia have reported iron deficiency, inflammation, or other biomarkers such as serum transferrin receptor (sTfR), serum ferritin, High-sensitivity C-reactive Protein (HS-CRP), IL-6, alpha 1-acid glycoprotein, or hepcidin. In chronic disease or infection, inflammation can occur, which results in increased use of iron as an essential component in the transport system.[40] Of the publications considered in this review, only three used ferritin as a biomarker of anemia. The remaining nine only reported on Hb levels and not red cell morphology or iron status. Thus, the type of anemia cannot be specified. Ferritin may be an indicator of iron deficiency and iron stores without any change in hematocrit or serum iron due to its role in inflammatory response.[30] Some 20% of Indonesian children aged 48–59 months have anemia

Table 2. Interventions for anemia prevention among young Indonesians by study design, locale, age, gender, diet, use of supplements, and outcomes

First author, year	City	Number of individuals		Intervention	Anemia biomarkers	Dietary information	Supplement
		Intervention	Control				
Zuraida et al, 2020a	Bandar Lampung	55 female adolescents (mean age 15 y)	47 female adolescents (mean age 15 y)	Nutrition education in the form of an "anemia free club" for 12 weeks	· Hemoglobin (Hb) levels were measured only preintervention. · 41 individuals from the intervention group and 43 the from control group had low Hb levels (10.1–11.9 g/dL).	· Dietary intake was measured twice (pre-post) using a food-frequency questionnaire. · Postintervention, the intakes of energy, iron, protein, and fat by subjects were significantly higher (p<0.05) than in the control.	This study did not include subjects who consumed any supplements.
Zuraida et al, 2020b	Bandar Lampung	55 female adolescents	47 female adolescents	Nutrition education in the form of an "anemia free club" for 12 weeks	· Hb levels were measured. · The control group had a higher percentage of individuals with low Hb levels (10.1–11.9 g/dL) than the intervention group (91.49% and 74.55%, respectively).	No information.	No information.
Muslihah et al, 2017	Madura	Two intervention groups, each with 56 infants (aged 6-59 months)	56 infants	· The lipid nutrient supplement paste—small quantity (SQ-LNS) group received 20 g of SQ-LNS per sachet per day for 6 months · The biscuit *Makanan Pendamping-Air Susu Ibu* (MP-ASI or complementary foods) group received three 30-g biscuits per day for 6 months	· Hb levels were measured three times (preintervention, mid-intervention, and postintervention). · The Hb levels in the SQ-LNS group were significantly higher than those in the control and biscuit groups (10.47±1.09 vs 9.98±0.97 vs 10.07±0.60 g/dL).	No information.	· The effects of supplement in the form of SQ-LNS were compared with fortified biscuit and control. · SQ-LNS contained energy (118 kcal), protein, essential fatty acids, 22 vitamins and minerals.
Sari et al, 2018	Banyumas	31 female students from SMA (senior high school) Negeri 2 Banyumas	39 female students from SMA Negeri 4 Banyumas	Six nutrition education meetings about anemia prevention (presentations, games, and lectures)	· Hb levels were measured. · Hb levels were significantly increased (from 12.17±1.29 to 12.68±1.22 g/dL) in the intervention group after treatment but not in the control group.	No information.	No information.

Table 2. Interventions for anemia prevention among young Indonesians by study design, locale, age, gender, diet, use of supplements, and outcomes (cont.)

First author, year	City	Number of individuals		Intervention	Anemia biomarkers	Dietary information	Supplement
		Intervention	Control				
Sekiyama et al, 2017	Bogor	68 elementary school students (boys and girls, mean age of 9 years)	–	· School lunch feeding intervention for 1 month (lunchbox contained rice, a vegetable dish, heme and nonheme protein dishes, and fruits) · The results were not categorized by gender	· Hb and hematocrit (Hct) levels were measured twice (preintervention and postintervention). · Hb (11.9±0.9 vs 11.2±0.9 g/dL) and Hct (34.0%±2.7% vs 31.7%±3.0%) levels were significantly increased after the intervention (p<0.05).	· Intakes of protein (41.7 vs 36.7 g), calcium (240 vs 205 mg), and vitamin C (64 vs 12.5 mg) were higher during the intervention compared with before the intervention (p<0.05). · The intake of fat (36.6 vs 47.3 g) was lower during the intervention (p<0.05).	No information about supplement consumption.
Syahwal and Dewi, 2018	Banjarbaru	Two intervention groups (P1 and P2), each consisting of 15 anemic female adolescents	15 anemic female adolescents	· P1 was given a snack bar made of *nagara* nut flour and *haruan* fish and 12 iron supplements · P2 was given a snack bar made of *nagara* nut flour and *haruan* fish · The control group was given 12 iron supplements · Foods and/or supplements were administered thrice a week for 1 month	· Hb levels were measured. · All individuals were cured of anemia after the intervention (Hb >12 g/dL). · The Hb levels of P1 were significantly higher than those of P2 and the control after the intervention (p<0.05). · Hb levels of P2 and the control were not significantly different postintervention.	No information.	No information.
Rusdi et al, 2018	Padang Panjang	17 anemic female adolescents (no information about age)	17 anemic female adolescents (no information about age)	The treatment group was given 100 g of guava processed into juice, once per day for a week	· Hb and ferritin levels were measured twice (preintervention and postintervention). · Significant increases in Hb and ferritin levels were observed postintervention in each group (p<0.001). · After the intervention, Hb levels in the intervention group were higher than those preintervention (12.48±0.67 vs 10.50±1.04 g/dL). · After intervention, the ferritin levels of the intervention (36.63±8.09 vs 57.40±14.09 µg/L) and control groups (33.63±6.15 vs 40.35±6.80 µg/L) were higher than those preintervention. ·	No information.	No information.

Table 2. Interventions for anemia prevention among young Indonesians by study design, locale, age, gender, diet, use of supplements, and outcomes (cont.)

First author, year	City	Number of individuals		Intervention	Anemia biomarkers	Dietary information	Supplement
		Intervention	Control				
Susanti et al, 2016	Tasikmalaya	P1: 59 and P2: 58 anemic female adolescents	58 anemic female adolescents	· P1: an iron supplement was given once a week and every day during menstruation · P2: an iron supplement was given once a week, accompanied by nutrition education · Control: an iron supplement was given once a week · The iron supplement consisted of 60 mg of elemental iron and 0.25 mg of folic acid · Nutrition education about anemia was provided through lectures, discussions, and pamphlets	· Hb levels were measured. · No significant differences in Hb levels after the intervention were observed between the three groups (ΔHb P1: 0.60; P2: 0.43; C: 0.52).	No information.	· Iron tablets (60 mg of elemental iron and 0.25 mg of folic acid). · The highest rate of compliance in taking supplements was observed for the P2 group (81.9%), and the lowest was observed for the P1 group (48.8%). · Iron supplementation in adolescents is better provided intermittently.
Budiana et al, 2016	Majalengka	33 anemic-wasting children aged 3–5 years	33 anemic-wasting children aged 3–5 years	· The treatment group was given *Taburia* (a sprinkle supplement) and nutrition counseling over a 2-month period · The control group received only nutrition counseling · The results did not differ by gender	· Hb levels were measured twice (postintervention and preintervention). · Hb levels were significantly increased postintervention in both the intervention (12.31 vs 11.14 g/dL) and control groups (11.8±0.53 vs 10.9±0.71 g/dL) (p<0.001). · The increase in Hb levels in the intervention group was significantly higher than that in the control group (1.55±0.98 vs 0.86±0.54 g/dL) (p<0.001).	· Dietary information was based on the percentage of adequacy of nutritional recommendations (no absolute number was reported). · Adequacy percentages of energy (94% vs 89%), protein (113% vs 106%), vitamin C (46% vs 40%), and Fe (74% vs 62%) were increased postintervention.	Supplementation in the form of *Taburia* (a sprinkle supplement) containing vitamin A, vitamin B complexes, vitamin D_3, vitamin E, vitamin K, vitamin C, folic acid, pantothenic acid, iron, iodine, zinc, and selenium.
Mulyantoro et al, 2015	Wonosobo	Three intervention groups (P1, P2, and P3), each consisting of 37 children aged 9–12 years	37 children aged 9–12 years	· P1 was given a supplement (840 µg iodine and 60 mg elemental iron) · P2 was given an iodine supplement (840 µg) · P3 was given an iron supplement (60 mg FeSO4) · The control was given a placebo · All supplements were given once a week for 13 weeks	· Ferritin levels in P1 (34.17 vs 51.19 µg/L) and P3 (36.85 vs 44.42 µg/L) were increased, whereas those in P2 were decreased (35.79 vs 33.52 µg/L). · The increase in ferritin levels in P1 and P2 (18.52 vs −2.63 µg/L) was significantly different (p<0.05).	No information.	Supplementation of iodine, iodine + iron, and iron was given to P1, P2, and P3.

Table 2. Interventions for anemia prevention among young Indonesians by study design, locale, age, gender, diet, use of supplements, and outcomes (cont.)

First author, year	City	Number of individuals		Intervention	Anemia biomarkers	Dietary information	Supplement
		Intervention	Control				
Kahayana et al, 2016	Semarang	P1: 30 children aged 10 months with normal nutritional status	30 children aged 10 months with normal nutritional status	· P1 was given 75 mg of vitamin C syrup during feeding time for 2 months · The control group was given a placebo	· Hb, serum iron, ferritin, total iron-binding capacity, and hepcidin levels were measured preintervention and postintervention. · Serum iron (45.70±17.4 vs 44.06±18.16 µg/dL) and ferritin (39.87±31.27 vs 36.43±25.33 µg/L) levels of the intervention group were significantly increased after the intervention (p<0.05). · No significant difference was noted for any biomarkers between the intervention and control groups either preintervention or postintervention.	Dietary information only compared the behavior of drinking formula milk, instant complementary food, and fruit consumption. No significant difference was observed between the two groups.	Supplementation in the form of vitamin C (75 mg) was compared with a placebo.
Manoppo et al, 2019	North Sulawesi	P1: 34 children aged 5–12 years with iron-deficient anemia	32 children aged 5–12 years with iron-deficient anemia	· P1 was given iron supplements with the addition of *L. reuteri* DSM 17938 · The control was given an iron supplement · The iron supplement was given in the form of 2 × 60 mg of elemental iron · *L. reuteri* DSM 17938 therapy was given as 3 × 108 CFU/day · The length of the intervention was 14 days	· Hb, hematocrit, and reticulocyte hemoglobin equivalent (Ret-He) levels were measured preintervention and postintervention. · Only Ret-He levels postintervention differed significantly between P1 (28.50 pg/L) and the control group (27.50 pg/L) (p<0.05).	No information.	Supplements in the form of 300 mg of sulfate ferrous (equivalent to 60 mg of elemental iron) were given.

Table 3. Classification of iron deficiency anemia

Stages	Hemoglobin	Ferritin (ng/mL)	sTfR (ng/L)	Transferrin (mg/dL)
Iron deficiency	Normal	<20	<5	360
Iron-deficient erythropoiesis	Normal	<12	>5	>380
Iron deficiency anemia	Lower	<12	>5	>380

sTfR: soluble transferrin receptor.
Adapted from Lianos and Jose with minor modification.[41]

according to their Hb levels, but only 12% have low ferritin.[41] Although Hb alone does not provide an indication of anemia causality, many Indonesian studies of anemia provide no further information.

Chronic iron deficiency is well-known as a common cause of anemia.[42-44] Naigamwalla et al[45] described three stages in IDA; iron deficiency, iron-deficient erythropoiesis, and finally IDA. Iron deficiency can occur for various reasons, one of which is the iron from dietary intake being too low for daily needs. Adolescent girls and women also lose iron due to blood loss during menstruation.[46] If an iron deficiency occurs latently, the body is not able to produce red blood cells properly. This causes the next stage, iron-deficient erythropoiesis, which is characterized by reduced heme synthesis and the formation of microcytic or hypochromic erythrocytes.[45] If this continues, it causes IDA. Lianos and Jose[42] described the characteristics of blood biomarkers according to the stages of anemia (Table 3).

As Table 3 indicates, further tests are required to confirm that cases are truly anemia due to iron deficiency. This is crucial because iron supplementation is currently central to anemia prevention and management programs. Clearly, where the prevalence of infection and inflammation is high, iron deficiency is not the only reason for anemia.[47] Often, it depends on contextual factors such as geographical location, the burden of infectious disease, and coexistence with other types of nutritional anemia; thus, further research is required.[44]

Infection is closely related to causality in anemia. Malaria, an example of an acute infection, causes anemia as a result of red blood cell damage due to parasites.[48] Another study conducted in Bandung, Indonesia, revealed that 63% of adult patients with pulmonary tuberculosis had anemia.[49] Research on 400 school-aged children in Vietnam reported a prevalence of hookworm infection of 92%; 25% of the infected were anemic (Hb <11.5 g/dL), and 2% had iron deficiency (TfR >8.5 mg/L). More than 30% exhibited elevated levels of C-reactive protein (≥8 mg/L) and 80% exhibited elevated levels of immunoglobulin E (>90 IU/mL).[50] This reinforces the notion that anemia occurring in areas with high infection rates might not be due to iron deficiency.

Iron status assessment among Indonesian people is commonly based on food intake and the types of food consumed.[51] This has several weaknesses resulting in inaccurate data because the assessment of food intake is based on estimation. The Indonesian Food Consumption Survey of 2018 revealed that the consumption of heme iron was lower than that of nonheme iron (32.2% vs 67.8%, respectively).[52] Fitri et al determined that the consumption of meats, fruits, and lentils in Indonesia has remained low.[53]

Policy directions addressing anemia among young populations

Indonesia has focused on anemia prevention through a program of iron-folate supplementation in the form of iron (60 mg $FeSO_4$) and folic acid (0.25 mg), otherwise known as iron tablets or *Tablet Tambah Darah* (TTD).[54] This program, intended for women of childbearing age, began in 1997.[55,56] In 2016, the Indonesian government adopted the iron supplement program launched by the WHO in 2011, where iron tablets are administered once a week at school.[55] The Indonesian Basic Health Research initiative in 2018 determined that 76.2% of adolescent girls received TTD, 80.9% of them at school and 19.1% elsewhere.[5] By region, Bali had the highest rate of iron supplementation (92.6%), and West Kalimantan had the lowest (9.6%).[57] In the *Taburia* program, the micronutrient sprinkle contains vitamin A, vitamin B_1, vitamin B_2, vitamin B_3, vitamin B_6, vitamin B_{12}, vitamin D_3, vitamin E, vitamin K, vitamin C, folic acid, pantothenic acid, iron, iodine, zinc, and selenium.[54] This program is aimed at improving the overall nutritional status of children under 5 years of age and has improved Hb counts in children.[28,58,59]

Iron supplementation is at the core of anemia prevention programs. An iron supplementation program targeting female adolescents and women of childbearing age should be evaluated briefly. The Indonesian Basic Health Research 2018 report noted that 76.2% of young women had received iron tablets in the previous 12 months. However, only 3.7% received iron tablets of ≥52 grains, and only 1.4% consumed them.[5] Many studies have been conducted in Indonesia to determine the effect of iron supplements in increasing Hb levels, but few have actually tested their effect on serum iron status. In this review, six studies tested the effects of iron or multimicronutrient supplements.[27-31,33]

As a country with large geographic and cultural variations, the nationally established youth iron supplementation program is likely inappropriate. Certain areas in Indonesia are particularly prone to infectious diseases. An example is malaria, which has a high prevalence in some areas of Papua.[60] A study by Schumann and Solomons[61] on a population of pregnant women with malaria discovered that iron supplementation actually increased the risk of infants being born with malaria. These results are consistent with research by Indrawanti[62] in Papua, Indonesia, which identified that infants had a nine-times greater risk of developing malaria if the mother was infected with malaria. Furthermore, at 3 months of age, infants had a three-times greater risk of experiencing nutritional problems, including underweight, wasting, or stunted growth. Other infectious diseases are also present in Indonesia, such as tuberculosis, worms, and HIV. Indonesia has a helminth infection prevalence rate of 45%–65%,[63] and data suggest that in 2017, Indonesia became one of the top three countries for number of cases of tuberculosis, with 8% of total cases in the world.[64] Furthermore, approximately 0.3% of the population aged 15 years or over are HIV-positive.[65]

Anemia prevention among children and adolescents

The results of the present review indicate that the prevention of anemia in children and adolescents in Indonesia has been based principally on three approaches: food-based interventions, nutrition education, and micronutrient supplementation, independently or in combination. Three of the articles examined nutrition education as a strategy for preventing anemia in adolescents,[22,23,25] and two others combined nutrition education with micronutrient supplementation.[28,66] No changes in the anemia indices of hemoglobin (Hb) or hematocrit (Hct) were evident when nutrition education interventions alone were applied. Micronutrient supplementation accompanied by nutrition education had a greater impact on Hb levels than did supplementation or education alone.[28] Previous studies have shown, however, that education changes knowledge and attitudes as well as consumption patterns.[22,23,67,68] Several countries have adopted multiple dietary approaches that combine nutrition education and sufficiently improve dietary quality to prevent anemia.[69,70] These have inevitably identified advantageous non-iron food and food pattern factors. Likewise, comprehensive educational interventions combined with food supplementation that benefits the child's general health and nutritional status is of hematological benefit.[71,72]

Evidently, anemia prevention strategies in Indonesia mostly target school-aged children,[21-27,29,30,32,66] with only three of the twelve reports being on children under 5 years old.[28,30,31] The target population predicates the type of intervention, and nutrition education, school feeding programs, and iron supplementation (TTD) are seen as more suitable and feasible for school-aged children who can be managed independently at school without reliance on their caregiver. Needless to say, opportunity costs and ethical considerations arise in not involving caregivers. With children aged under 5 years, parents and caregivers have an obligatory, vital role, and their goals are made more achievable by an aid such as *Taburia*, a micronutrient sprinkle that is mixed into food.[28,58,59] Locally sustainable school lunch interventions with traditional Sundanese meals for students improve the quality of children's food intake, their Hb and Hct levels, and their nutritional status.[26] Experiences in other countries confirm that school program–based approaches to anemia prevention in children have merit.[73-76]

Current approaches compromise anemia prevention

The efficacy of interventions to reduce anemia has both educational and therapeutic dimensions.[77] The possible pathways of the role of nutrition education in anemia prevention are preceded by improvements in nutrition knowledge.[23,25,70,78] Understanding the concept of anemia prevention leads to positive changes in behavior as well as iron status,[79] and providing education to caregivers may improve their feeding practices.[69,71] Caregivers with improved knowledge, skills, and self-efficacy are more likely to practice better hygiene in food preparation as well as ensure the proper composition of complementary diets.[80] However, whether an educational intervention can affect behavior depends on how knowledge is transferred by field technicians and their skills in conducting community activities.[81] Anemia prevention using an education approach has been implemented in some developing countries as an alternative strategy in cases of limited access to iron-rich food/heme iron sources.[82,83]

The consensus of the UNICEF, United Nations University (UNU), WHO, and Micronutrient Initiative (MI) is that if the prevalence of anemia among pregnant women is higher than 40%, then the administration of iron–folic acid supplements should also be provided to female adolescents.[16] The provision of iron supplements from adolescence is cost effective and enables an iron store to be accumulated before pregnancy.[84-86] However, although it is theoretically effective, a refusal to consume iron supplements persists in some countries.[16,87] Tolkien et al[88] proved that it this is due to the side effects of iron supplementation, such as black stool, constipation, nausea, and iron aftertaste.

Rusdi et al[24] and Kahayana et al[30] reported that the serum ferritin levels of individuals after an intervention were increased compared with individuals who received a placebo. In an intervention with guava juice,[24] serum ferritin increased from 36.63±8.09 μg/L to 57.40±14.09 μg/L; vitamin C supplementation[30] increased it from 36.43±25.33 μg/L to 39.87±31.27 μg/L (p<0.05). This is probably a reflection of the form of the vitamin C, either as a supplement or in guava juice, with the juice increasing iron absorption. An increase in serum ferritin means an increase in iron reserves. Iron derived from plant foods is classified as nonheme iron, which is more difficult to absorb (only 1%–10% uptake).[89] Nonheme iron is also generally associated with phytate, dietary fiber, and calcium, which inhibit absorption. If it is consumed together with a source of vitamin C, however, much more iron will be absorbed.[90-93] Vitamin C has many roles, including acting as an antioxidant, promoting immune function, and increasing the absorption of nonheme iron. Vitamin C plays a role in iron kinetics and red blood cell formation. The WHO[16] recommends giving weekly iron supplements if high compliance is observed. This preventive program has been proven to be cost effective, with fewer side effects, easier management, and greater efficacy than daily iron supplementation. In Indonesia, national monitoring of compliance with iron supplementation among adolescent girls is rarely reported. A small study by Susanti et al[27] involving 117 Indonesian female students determined that providing nutrition education is more effective than iron supplementation only. Titaley et al reported similar findings[94]; better knowledge can increase the compliance of pregnant women in consuming iron–folic acid supplements.

Iron supplements are rarely given to Indonesian children under 12 years old. In 1999, the UNICEF/WHO proposed that iron supplementation is necessary in children aged 6–18 months if the prevalence of anemia in children exceeds 40%.[95] However, the WHO also warned against iron supplementation in children who have an infectious disease because of the potential adverse effects.[96] Iannotti et al[97] explained that the administration of large amounts of iron can increase the number of pathogens and thus increase the risk of infection. A study of 478 Indonesian 4-month-old infants proved that iron supplementation effectively reduces the incidence of anemia but is inadequate for supporting their growth.[98] In the present review, the only study targeting Indonesian infants made use of food fortification to address anemia.[31]

In the past 5 years, 9 of the 12 studies on anemia prevention were carried out in schools. Schools are a potential environment for health promotion.[99] Moreover, a 12-year compulsory education program is in place; thus, children and adolescents spend most of their time in school.[100] In Indonesia, approximately 147,500 elementary schools, 37,000 junior secondary schools, and 25,300 senior secondary schools exist.[101] Despite their potential, collaboration between the education and health sectors is lacking. Research on school health promotion policies in the United States revealed that program implementation has been suboptimal due to the weakness of existing policies.[102]

Many health promotion programs for anemia prevention can be implemented in schools. In this review, three studies recommended nutrition education in schools for the prevention of anemia in adolescents.[22,23,25] One study recommended implementing a school lunch program,[26] two recommended a food-based approach,[24,32] and one recommended a supplementary intervention.[27]

The School Lunch Program proposed by Sekiyama et al[26] has not become a national program yet because of the wide variability of school characteristics in Indonesia. This is in contrast to several other countries, including Japan, which has had a national policy in place since 1954, governed by the School Lunch Act, to improve student health.[103] A study among 627 vulnerable households in Uganda reported substantial improvements in anemia status; the prevalence of anemia was significantly reduced in 25.7% of adolescent girls after they participated in a school feeding program.[104] Similar results were reported by Krämer et al[105] regarding the provision of iron-fortified salt in a school feeding program in India.

Anemia prevention studies in school settings had small sample sizes compared to Indonesia's total population of school-aged children. This makes generalizing the results difficult. The School Lunch Program carried out by Sekiyama et al,[26] although yielding good results, only involved 68 students. Not much research on anemia prevention in Indonesia has been conducted with large samples.

Anemia and sex

Both men and women can experience anemia. Various studies have shown that women, especially adolescent girls, have a higher risk of developing anemia due to menstruation.[16,27,37,42] Research by Susanti et al[27] on iron supplementation in adolescent girls revealed that taking a supplement once a week and every day during menstruation led to low adherence (48.8%) compared with the combination of once-weekly supplement consumption with nutrition education (81.9%).

In the reviewed studies, six included boys, either children or infants.[26,28-31,33] However, none stratified anemia based on gender. In research by Faiqah and Irmayani[106] on data for children under 5 years, reported by the 2013 Indonesian Basic Health Research, gender was significantly ($p<0.001$) associated with anemia. Of the 39,706 anemic children aged under 5 years, 57.9% were girls and 42% were boys. Another study of 712 Indonesian adolescents also discovered a significant relationship ($p<0.001$) between gender and incidence of anemia. Women and teenage boy account for up to 30% and 20% of anemia cases, reespectively.[107] No information regarding the types or causes of anemia has been provided. However, the results indicate that boys also experience anemia. Unfortunately, they have not been targeted for anemia prevention programs. Childhood and adolescence is a key phase for growth and development for both male and female individuals in which health status, including anemia, plays an essential role.[11,12,13,42] A need exists for programs such as anemia-related nutrition education and screening for boys as well as for girls.

Future directions

Anemia, like other public health problems, is multifactorial. The United States Agency for International Development[108] recommended an anemia prevention framework for children. This framework was based on the need to strengthen leadership, capacity, and policy in implementing various concordant programs in agriculture and health sectors. The authors suggested a need to identify the specific causes of anemia in smaller areas (such as cities/regions or provinces) and recommend preventive measures accordingly. Anemia in Indonesian children and adolescents may not be due to iron deficiency alone. Iron supplementation without understanding the exact underlying causes can lead to ineffective and inefficient programs.[109-111]

This review had several limitations. First, research only from the last 5 years was reviewed. Second, a meta-analysis was not feasible because of the low number of anemia intervention studies in Indonesia. Third, a major limitation is that the reports reflected the prevailing view among nutritionists and health policymakers that the causes of anemia are solely related to nutrition. This view does not take into account the likely multifactoriality of anemia and socioeconomic development. This entrenched approach has been fostered by an often commercial product–prescriptive approach with supplements rather than one in which food and health systems are informed and community-engaged. To say that anemia is strictly caused by iron deficiency, even if this is partly the case, blinds the intervener to the more complex causality and pathogenesis that may be involved and to the solutions actually required.

Conclusions

Despite the limitations identified in this review of studies on anemia among children and adolescents in Indonesian cities, progress has been made in these locations in terms of prevention and mitigation through food-based approaches, nutrition education, and nutrient supplementation (often unduly restricted to iron). These three types of intervention have ameliorated anemia among young people. Interventions across the Indonesian archipelago with attention to underlying causality and pathogenesis, socioculturally sensitive education, more optimal food patterns, and integrated embedment in local food and health systems would further alleviate the burdens of disorder and disease among young Indonesians.

ACKNOWLEDGMENT
The authors thank their research assistants, Rafly Abdurrasyid, Ridwan Bima Aria, Chatarina K Kayame, Maria Wigati, and Lintang Aryanti, for their help with data analysis and writing of the manuscript. This manuscript was edited by Wallace Academic Editing.

AUTHOR DISCLOSURES
The authors have no conflicts of interest to declare.

REFERENCES
1. Lukito W, Wahlqvist ML. Intersectoral and eco-nutritional approaches to resolve persistent anemia in Indonesia. Asia Pac J Clin Nutr. 2020;29(Suppl 1):S1-S8. doi: 10.6133/apjcn.202012_29(S1).01.
2. NEMO Study Group. Effect of a 12-mo micronutrient intervention on learning and memory in well-nourished and marginally nourished school-aged children: 2 parallel, randomized, placebo-controlled studies in Australia and Indonesia. Am J Clin Nutr. 2007;86:1082-93.
3. McLean E, Cogswell M, Egli I, Wojdyla D, de Benoist B. Worldwide prevalence of anaemia, WHO vitamin and mineral nutrition information system, 1993-2005. Public Health Nutr. 2009;12:444-54. doi: 10.1017/s1368980008002401.
4. Deng Q, Zhao T, Liu C, Kuang X, Zheng J, Wahlqvist ML, Li D. Dietary patterns and anemia morphology in young men and women in Shandong province, China. Asia Pac J Clin Nutr. 2020;29:513.
5. Indonesian Ministry of Health. Main results of Indonesian Basic Health Research 2018 [Internet]. 2018 [cited 2019/05/13]. Available from: http://www.depkes.go.id/resources/download/info-terkini/hasil-riskesdas-2018.pdf. (In Indonesian)
6. Indonesian Ministry of Health. Basic Health Research 2013 [Internet]. 2013 [cited 2019/05/13]. Available from: https://www.kemkes.go.id/resources/download/general/Hasil%20Riskesdas%202013.pdf. (In Indonesian)
7. Utama JL, Sembiring AC, Sine J. Breakfast behavior is related to nutritional status and anemia in elementary school children. J Gizi Indones (The Indones J Nutr). 2018;7:63-8. doi: 10.14710/jgi.7.1.63-68. (In Indonesian)
8. Lipoeto NI, Wattanapenpaiboon N, Malik A, Wahlqvist ML. Nutrition transition in west Sumatra, Indonesia. Asia Pac J Clin Nutr. 2004;13:312-6.
9. Al-Qaoud NM, Al-Shami E, Prakash P. Anemia and associated factors among Kuwaiti preschool children and their mothers. Alexandria J Med. 2015;51:161-6.
10. Alzain B. Anemia and nutritional status of pre-school children in North Gaza, Palestine. International Journal of Scientific and Technology Research. 2012;1:86-91.
11. Pollitt E. The developmental and probabilistic nature of the functional consequences of iron-deficiency anemia in children. J Nutr. 2001;131(2S-2):669S-675S.
12. Algarín C, Peirano P, Garrido M, Pizarro F, Lozoff B. Iron deficiency anemia in infancy: long-lasting effects on auditory and visual system functioning. Pediatr Res. 2003; 53:217-23.
13. Felt BT, Peirano P, Algarín C, Chamorro R, Sir T, Kaciroti N et al. Long-term neuroendocrine effects of iron-deficiency anemia in infancy. Pediatr Res. 2012;71:707-12.
14. Hoang NT, Orellana L, Le TD, Gibson RS, Worsley A, Sinclair AJ et al. Anaemia and its relation to demographic, socio-economic and anthropometric factors in rural primary school children in Hai Phong City, Vietnam. Nutrients. 2019; 11:1478.
15. Wang L, Li M, Dill S-E, Hu Y, Rozelle S. Dynamic anemia status from infancy to preschool-age: Evidence from rural China. Int J Environ Res Public Health. 2019;16:2761.
16. World Health Organization. Prevention of iron deficiency anaemia in adolescents [Internet]. World Health Organization; 2011. [cited 2020/08/10]; Available from: https://apps.who.int/iris/bitstream/handle/10665/205656/B4770.pdf?sequence=1&isAllowed=y.
17. Prieto-Patron A, Hutton ZV., Fattore G, Sabatier M, Detzel P. Reducing the burden of iron deficiency anemia in Cote D'Ivoire through fortification. J Health Popul Nutr. 2020;39: 1-15.
18. Osei A, Pandey P, Nielsen J, Pries A, Spiro D, Davis D et al. Combining home garden, poultry, and nutrition education program targeted to families with young children improved anemia among children and anemia and underweight among nonpregnant women in Nepal. Food Nutr Bull. 2017;38:49-64.
19. Vonderheid SC, Tussing-Humphreys L, Park C, Pauls H, Hemphill NO, LaBomascus B et al. A Systematic review and meta-analysis on the effects of probiotic species on iron absorption and iron status. Nutrients. 2019;11:2938.
20. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: Explanation and elaboration. PLoS Med. 2009;6:e1000100.
21. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343: d5928. doi: 10.1136/bmj.d5928.
22. Zuraida R, Lipoeto NI, Masrul M, Februhartanty J. The effect of anemia free club interventions to improve adolescent dietary intakes in Bandar Lampung city, Indonesia. Open Access Maced J Med Sci. 2020;8:145-9.
23. Zuraida R, Lipoeto NI, Masrul M, Februhartanty J. The effect of anemia free club interventions to improve knowledge and attitude of nutritional iron deficiency anemia prevention among adolescent schoolgirls in Bandar Lampung City, Indonesia. Open Access Maced J Med Sci. 2020;8:36-40.
24. Rusdi PHN, Oenzil F, Chundrayetti E. The effect of red guajava juice (Psidium guajava.L) on hemoglobin and ferritin serum levels for women with anemia. J Kesehat Andalas. 2018;7:74. (In Indonesian)
25. Sari HP, Subardjo YP, Zaki I. Nutrition Education, hemoglobin levels, and nutrition knowledge of adolescent girls in Banyumas District. Indones J Nutr Diet. 2018;6: 107-12.
26. Sekiyama M, Roosita K, Ohtsuka R. Locally sustainable school lunch intervention improves hemoglobin and hematocrit levels and body mass index among elementary schoolchildren in rural West Java, Indonesia. Nutrients. 2017;9:1-13.
27. Susanti Y, Briawan D, Martianto D. Weekly iron supplementation increases hemoglobin is as effective as the weekly and daily combination in young women. J Gizi Pangan. 2016;11:27-34. (In Indonesian)
28. Budiana TA, Kartasurya MI, Judiono J. Effect of sprinkle supplementation on hemoglobin levels of under-nutrition children aged 3-5 years in Lewimunding District,

Majalengka Regency. J Gizi Indones. 2016;5:34-41. (In Indonesian)
29. Mulyantoro DK, Nurcahyani YD, Ashar H. Dual supplementation on the levels of TSH, fT4, T3 and Ferritin in primary school children. Media Gizi Mikro Indonesia. 2015; 6:87-100. (In Indonesian)
30. Kahayana HP, Susanto JC, Tamam M. Iron status for healthy babies 8 - 10 months after giving vitamin C 75 mg at meals. Sari Pediatri. 2016;18:122. (In Indonesian)
31. Muslihah N, Khomsan A, Riyadi H, Briawan D. The comparison effect of small-quantity lipid-based nutrient supplements and biscuit on hemoglobin level of infants in Indonesia. Indones J Hum Nutr. 2017;4:97-107.
32. Syahwal S, Dewi Z. The provision of snack bars increases hemoglobin (Hb) levels in adolescent girls. AcTion Aceh Nutrition Journal. 2018;3:9. (In Indonesian)
33. Manoppo J, Tasiringan H, Wahani A, Umbih A, Mantik M. The role of Lactobacillus reuteri DSM 17938 for the absorption of iron preparations in children with iron deficiency anemia. Korean J Pediatr. 2019;62:173-8.
34. World Health Organization. The Global Prevalence in Anemia 2011 [Internet]. World Health Organization; 2011. [cited 2020/08/10]; Available from: https://apps.who.int/iris/bitstream/handle/10665/177094/9789241564960_eng.pdf;jsessionid=7D4DA6CDBD974E85C015CDE685E6950A?sequence=1.
35. Anggraini DD, Purnomo W, Trijanto B. Interaction of pregnant women with health workers and their effects on compliance of pregnant women consuming iron (Fe) tablets and anemia at the city health center in the southern region of Kediri City. Buletin Penelitian Sistem Kesehatan. 2018;21: 92-89. (In Indonesian)
36. Khusun H, Yip R, Schultink W, Dillon DH. World Health Organization hemoglobin cut-off points for the detection of anemia are valid for an Indonesian population. J Nutr. 1999;129:1669-74.
37. Goddard AF, James MW, McIntyre AS, Scott BB. Guidelines for the management of iron deficiency anaemia. Gut. 2011;60:1309-16.
38. Hughes RG, Sharp DS, Hughes MC, Akau'ola S, Heinsbroek P, Velayudhan R, Schulz D, Palmer K, Cavalli-Sforza T, Galea G. Environmental influences on helminthiasis and nutritional status among Pacific schoolchildren. Int J Environ Health Res. 2004;14:163-77
39. Wahlqvist ML, Lee M. Nutrition in health care practice. Journal of Medical Sciences. 2006;26:157.
40. Cappellini MD, Comin-Colet J, de Francisco A, Dignass A, Doehner W, Lam CS et al. Iron deficiency across chronic inflammatory conditions: International expert opinion on definition, diagnosis, and management. Am J Hematol. 2017; 92:1068-78.
41. Herawati AN, Palupi NS, Andarwulan N, Efriwati E. Contribution of iron and vitamin C intake on iron nutritional anemia status of Indonesian toddlers. Nutrition and food research. The Journal of Nutrition and Food Research. 2018; 4:65-76.
42. Llanos MJ. Significance of anaemia in the different stages of life/Significado de la anemia en las diferentes etapas de la vida. Enfermería Global. 2016;15:419-30.
43. Wieringa FT, Dahl M, Chamnan C, Poirot E, Kuong K, Sophonneary P et al. The high prevalence of anemia in Cambodian children and women cannot be satisfactorily explained by nutritional deficiencies or hemoglobin disorders. Nutrients. 2016;8:348.
44. Chaparro CM, Suchdev PS. Anemia epidemiology, pathophysiology, and etiology in low-and middle-income countries. Ann N Y Acad Sci. 2019;1450:15.
45. Naigamwalla DZ, Webb JA, Giger U. Iron deficiency anemia. Can Vet J. 2012;53:250-6.
46. Engle-Stone R, Aaron GJ, Huang J, Wirth JP, Namaste SM, Williams AM et al. Predictors of anemia in preschool children: Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia (BRINDA) project. Am J Clin Nutr. 2017;106:402S-15S.
47. Petry N, Olofin I, Hurrell RF, Boy E, Wirth JP, Moursi M, Donahue Angel M, Rohner F. The proportion of anemia associated with iron deficiency in low, medium, and high human development index countries: a systematic analysis of national surveys. Nutrients. 2016;8:693
48. Viana MB. Anemia and infection: a complex relationship. Revista brasileira de hematologia e hemoterapia. 2011;33: 90-2.
49. Adzani M, Dalimoenthe NZ, Wijaya I. Profile of anemia on lung tuberculosis at Dr. Hasan Sadikin General Hospital and Community Lung Health Center Bandung. Althea Medical Journal. 2016;3:137-40.
50. Le HT, Brouwer ID, Verhoef H, Nguyen KC, Kok FJ. Anemia and intestinal parasite infection in school children in rural Vietnam. Asia Pac J Clin Nutr. 2007;16:716-23.
51. Syahnuddin M, Gunawan G, Sumolang PP, Lobo LT. The Relationship between nutritional anemia and worms infection in young women in several senior high schools in Palu City. Media Penelitian dan Pengembangan Kesehatan. 2017;27:223-8. (In Indonesian)
52. Indonesian Food Security Agency. Directory of Development of Food Consumption 2019 [Internet]. Food Security Agency; 2019. [cited 2020/09/23] Available from: http://bkp.pertanian.go.id/storage/app/media/PPID%202019/PRINT%20DIREKTORI%20KONSUMSI%20PANGAN%202019.pdf. (In Indonesian)
53. Fitri YP, Briawan D, Tanziha I, Madanijah S. Adequacy level and bioavailability of iron intake in pregnant women in Tangerang City. Media Kesehatan Masyarakat Indonesia. 2016;12:185-91. (In Indonesian)
54. Sutrisna A, Vossenaar M, Izwardy D, Tumilowicz A. Sensory evaluation of foods with added micronutrient powder (MNP) "Taburia" to assess acceptability among children aged 6-24 months and their caregivers in indonesia. Nutrients. 2017;9:1-17.
55. Permatasari T, Briawan D, Madanijah S. The effectiveness of the iron supplementation program for young women in Bogor City. Media Kesehatan Masyarakat Indonesia. 2018;14:1. (In Indonesian)
56. Apriningsih A, Madanijah S, Dwiriani CM, Kolopaking R. The role of parents in improving the compliance of students in taking iron folate tablets in Depok City. Gizi Indonesia. 2019;42:71. (In Indonesian)
57. Indonesian Ministry of Health. Indonesia Health Profile 2018 [Internet]. 2018 [cited 2020/11/23]. Available from: https://pusdatin.kemkes.go.id/resources/download/pusdatin/profil-kesehatan-indonesia/PROFIL_KESEHATAN_ 2018_ 1.pdf. (In Indonesian)
58. Jahari AB, Prihatini S. Effect of "Taburia" intervention program on hemoglobin concentration among children under-five years of poor families in North Jakarta. Nutr Food Res. 2009;32:1-8. (In Bahasa Indonesia)
59. Kunayarti W, Julia M, Susilo J. Effect of taburia on anemia status and nutritional status of malnourished children under five. Jurnal Gizi Klinik Indonesia. 2014;11:38. (In Indonesian)
60. Kemenkes RI. InfoDATIN Malaria. Jakarta: Pusat Data dan Informasi Kementerian Kesehatan RI. 2016.

61. Schümann K, Solomons NW. Can iron supplementation be reconciled with benefits and risks in areas hyperendemic for malaria?. Food Nutr Bull. 2013;34:349-56.
62. Indrawanti R. Effects of maternal malaria on the susceptibility of malaria infection in infants during the first 1 year of life. Dissertation. Doctoral Program of Health and Medicine Science, Universitas Gadjah Mada; 2018. (In Indonesian)
63. Nuryanto N, Candra A. The relationship between worms and anemia and cognitive ability in elementary school children in Bandarharjo village, Semarang. Journal of Nutrition College. 2019;8:101-6. (In Indonesian)
64. World Health Organization. Global Tuberculosis Report 2019. Geneva: World Health Organization; 2019.
65. World Health Organization. National study of the HIV response in the health sector of the epublic of Indonesia. WHO report for Indonesia. Jakarta: World Health Organization. 2017. (In Indonesian)
66. Jack SJ, Ou K, Chea M, Chhin L, Devenish R, Dunbar M et al. Effect of micronutrient sprinkles on reducing anemia: a cluster-randomized effectiveness trial. Arch Pediatr Adolesc Med. 2012;166:842-50.
67. Sunuwar DR, Sangroula RK, Shakya NS, Yadav R, Chaudhary NK, Pradhan PM. Effect of nutrition education on hemoglobin level in pregnant women: A quasi-experimental study. PLoS One. 2019;14:e0213982.
68. Kulwa KB, Verstraeten R, Bouckaert KP, Mamiro PS, Kolsteren PW, Lachat C. Effectiveness of a nutrition education package in improving feeding practices, dietary adequacy and growth of infants and young children in rural Tanzania: Rationale, design and methods of a cluster randomised trial. BMC Public Health. 2014;14:1077.
69. Zhang Y, Wu Q, Wang W, van Velthoven MH, Chang S, Han H et al. Effectiveness of complementary food supplements and dietary counselling on anaemia and stunting in children aged 6-23 months in poor areas of Qinghai Province, China: A controlled interventional study. BMJ Open. 2016;6:e11234.
70. Alaofè H, Zee J, Dossa R, O'Brien HT. Education and improved iron intakes for treatment of mild iron-deficiency anemia in adolescent girls in southern Benin. Food Nutr Bull. 2009;30:24-36.
71. Inayati DA, Scherbaum V, Purwestri RC, Wirawan NN, Suryantan J, Hartono S et al. Improved nutrition knowledge and practice through intensive nutrition education: A study among caregivers of mildly wasted children on Nias Island, Indonesia. Food Nutr Bull. 2012;33:117-27.
72. Mannan T, Ahmed S, Akhtar E, Roy AK, Haq MA, Roy A et al. Maternal micronutrient supplementation and long term health impact in children in rural Bangladesh. PLoS One. 2016;11:e1061294.
73. García-Casal MN, Landaeta-Jiménez M, Puche R, Leets I, Carvajal Z, Patiño E et al. A program of nutritional education in schools reduced the prevalence of iron deficiency in students. Anemia. 2011;2011:284050. doi: 10.1155/2011/284050.
74. Kheirouri S, Alizadeh M. Process evaluation of a national school-based iron supplementation program for adolescent girls in Iran. BMC Public Health. 2014;14:959.
75. Angeles-Agdeppa I, Monville-Oro E, Gonsalves JF, Capanzana MV. Integrated school based nutrition programme improved the knowledge of mother and schoolchildren. Matern Child Nutr. 2019;15(Suppl 3): e12794.
76. Angeles-Agdeppa I, Magsadia C, Capanzana M. Multi-micronutrient fortified beverage delivered through the school-based system improved iron status and test scores of children. Eur J Nutr Food Saf. 2015;5:1049.
77. Balarajan Y, Ramakrishnan U, Özaltin E, Shankar AH, Subramanian SV. Anaemia in low-income and middle-income countries. Lancet. 2011;378(9809):2123-35.
78. Al-Delaimy AK, Al-Mekhlafi HM, Lim YAL, Nasr NA, Sady H, Atroosh WM et al. Developing and evaluating health education learning package (HELP) to control soil-transmitted helminth infections among Orang Asli children in Malaysia. Parasit Vectors. 2014;7:416.
79. Amani R, Soflaei M. Nutrition education alone improves dietary practices but not hematologic indices of adolescent girls in Iran. Food Nutr Bull. 2006;27:260-4.
80. Arikpo D, Edet ES, Chibuzor MT, Odey F, Cadwell DM. Educational interventions for improving primary caregiver complementary feeding practices for children aged 24 months and under. Cochrane Database Syst Rev. 2018;5: CD011768. doi: 10.1002/14651858.CD011768.pub2.
81. Fançony C, Soares Â, Lavinha J, Barros H, Brito M. Efficacy of nutrition and WASH/malaria educational community-based interventions in reducing anemia in preschool children from Bengo, Angola: study protocol of a randomized controlled trial. Int J Environ Res Public Health. 2019;16:466. doi: 10.3390/ijerph16030466.
82. Creed-Kanashiro HM, Uribe TG, Bartolini RM, Fukumoto MN, López TT, Zavaleta NM et al. Improving dietary intake to prevent anemia in adolescent girls through community kitchens in a periurban population of Lima, Peru. J Nutr. 2000;130:459-61.
83. Tseng M, Chakraborty H, Robinson DT, Mendez M, Kohlmeier L. Adjustment of iron intake for dietary enhancers and inhibitors in population studies: bioavailable iron in rural and urban residing Russian women and children. J Nutr. 1997;127:1456-68.
84. Mulugeta A, Tessema M, H/Sellasie K, Seid O, Kidane G, Kebede A. Examining means of reaching adolescent girls for iron supplementation in Tigray, Northern Ethiopia. Nutrients. 2015;7:9033-45.
85. Joshi M, Gumashta R. Weekly iron folate supplementation in adolescent girls--an effective nutritional measure for the management of iron deficiency anaemia. Glob J Health Sci. 2013;5:188-94.
86. Deshmukh PR, Garg BS, Bharambe MS. Effectiveness of weekly supplementation of iron to control anaemia among adolescent girls of Nashik, Maharashtra, India. J Heal Popul Nutr. 2008;26:74-8.
87. Khammarnia M, Amani Z, Hajmohammadi M, Ansari-Moghadam A, Eslahi M. A survey of iron supplementation consumption and its related factors in high school students in Southeast Iran, 2015. Malaysian J Med Sci. 2016;23:57-64.
88. Tolkien Z, Stecher L, Mander AP, Pereira DI. Ferrous sulfate supplementation causes significant gastrointestinal side-effects in adults: A systematic review and meta-analysis. PLoS ONE. 2015;10:e01178383. doi: 10.1371/journal.pone.0117383.
89. Beck KL, Conlon CA, Kruger R, Coad J. Dietary determinants of and possible solutions to iron deficiency for young women living in industrialized countries: a review. Nutrients. 2014;6:3747-76.
90. Astuti ND, Wirjatmadi B, Adriani M. The role of addition of vitamin C in iron supplementation on ferritin serum levels in anemia adolescent females. Health Notions. 2018;2:332-8.
91. Teucher B, Olivares M, Cori H. Enhancers of iron absorption: ascorbic acid and other organic acids. Int J Vitam Nutr Res. 2004;74:403-19.

92. Péneau S, Dauchet L, Vergnaud AC, Estaquio C, Kesse-Guyot E, Bertrais S, Latino-Martel P, Hercberg S, Galan P. Relationship between iron status and dietary fruit and vegetables based on their vitamin C and fiber content. Am J Clin Nutr. 2008;87:1298-305.
93. Cook JD, Reddy MB. Effect of ascorbic acid intake on nonheme-iron absorption from a complete diet. Am J Clin Nutr. 2001;73:93-8
94. Titaley CR, Rahayu E, Damayanti R, Dachlia D, Sartika RT, Ismail A et al. Association between knowledge and compliance of taking iron/folic acid supplements during pregnancy. Asian J Pharm Clin Res. 2017;10:177-82.
95. UNICEF/WHO. Prevention and control of iron deficiency anaemia in women and children the commonwealth of independence states and the Baltic States WHO Regional Office for Europe. Geneva: UNICEF/WHO; 1999.
96. World Health Organization. Iron supplementation of young children in regions where malaria transmission is intense and infectious disease highly prevalent. Geneva: World Health Organization; 2010.
97. Iannotti LL, Tielsch JM, Black MM, Black RE. Iron supplementation in early childhood: health benefits and risks. Am J Clin Nutr. 2006;84:1261-76.
98. Dijkhuizen MA, Wieringa FT, West CE, Martuti S, Muhilal. Effects of iron and zinc supplementation In Bahasa Indonesia infants on micronutrient status and growth. J Nutr. 2001;131:2860-5.
99. Stewart-Brown S. What is the evidence on school health promotion in improving health or preventing disease and, specifically, what is the effectiveness of the health promoting schools approach? [Internet]. Copenhagen: WHO Regional Office for Europe; 2006.
100. Indonesian Ministry of Education and Culture. The management of national education in year 2014/2015 at a Glance [Internet]. Jakarta: Indonesian Ministry of Education and Culture; 2016.
101. Indonesian Ministry of Education and Culture. Indonesia education statistics in brief 2015/2016 [Internet]. Jakarta: Indonesian Ministry of Education and Culture; 2016.
102. Cox MJ, Ennett ST, Ringwalt CL, Hanley SM, Bowling JM. Strength and comprehensiveness of school wellness policies in Southeastern US school districts. J Sch Health. 2016;86: 631-7.
103. Tanaka N, Miyoshi M. School lunch program for health promotion among children in Japan. Asia Pac J Clin Nutr. 2012;21:155-8.
104. Adelman S, Gilligan DO, Konde-Lule J, Alderman H. School feeding reduces anemia prevalence in adolescent girls and other vulnerable household members in a cluster randomized controlled trial in Uganda. J Nutr. 2019;149: 659-66.
105. Krämer M, Kumar S, Vollmer S. Impact of delivering iron-fortified salt through a school feeding program on child health, education and cognition: evidence from a randomized controlled trial in rural India. Global Food Discussion Papers No. 116; 2018.
106. Faiqah S, Ristrini R, Irmayani I. Relationship between age, gender and birth weight with the incidence of anemia in toddlers in Indonesia Buletin Penelitian Sistem Kesehatan. 2018;21:281-9. (In Indonesian)
107. Permaesih D, Herman S. Factors affecting anemia in adolescents. Indonesian Bulletin of Health Research. 2005;33:20280. (In Indonesian)
108. USAID. Conceptual frameworks for anemia [Internet]. Washington, DC: USAID; 2013.
109. Bhan MK, Bhandari N, Bahl R. Management of the severely malnourished child: perspective from developing countries. BMJ. 2003;326:146-51.
110. World Health Organization. Guideline daily iron supplementation in infants and children. Geneva: World Health Organization; 2016.
111. Lönnerdal B. Excess iron intake as a factor in growth, infections, and development of infants and young children. Am J Clin Nutr. 2017;106:1681S-7S.

Original Article

Non-nutritional anemia: Malaria, thalassemia, G6PD deficiency and tuberculosis in Indonesia

Safarina G Malik DVM, MS, PhD[1], Sukma Oktavianthi BSc, MBiomed[1], Mark L Wahlqvist MD, FRACP, FAFPHM, FAIFST, FTSE[2,3,4], Puji Budi Setia Asih PhD[1], Alida Harahap MD, PhD[1], Ari W Satyagraha Dr.sc.hum[1], Din Syafruddin MD, PhD[1]

[1]*Eijkman Institute for Molecular Biology, Ministry of Research and Technology/National Agency for Research and Innovation, Jakarta, Indonesia*
[2]*Institute of Population Health Sciences, National Health Research Institutes, Miaoli County, Taiwan*
[3]*Fuli Institute of Food Science and Nutrition, Zhejiang University, Hangzhou, Zhejiang Province, China*
[4]*Monash Asia Institute, Monash University, Melbourne, Australia*

Anemia affects people worldwide and results in increased morbidity and mortality, particularly in children and reproductive-age women. Anemia is caused by an imbalance between red blood cell (RBC) loss and production (erythropoiesis), which can be caused by not only nutritional factors but also non-nutritional factors, such as inflammation and genetics. Understanding the complex and varied etiology of anemia is crucial for developing effective interventions and monitoring anemia control programs. This review focusses on two interrelated non-nutritional causes of anemia: malaria infection and RBC disorders (thalassemia and G6PD deficiency), as well as tuberculosis. According to the Haldane hypothesis, thalassemia occurs as a protective trait toward malaria infection, whereas G6PDd arises in malaria-endemic regions because of positive selection. Indonesia is a malaria-endemic region; thus, the frequency of thalassemia and G6PD deficiency is high, which contributes to a greater risk for non-nutritional anemia. As Indonesia is the second global contributor to the newly diagnosed tuberculosis, and active pulmonary tuberculosis patients are more anemic, tuberculosis is also contributes to the increasing risk of anemia. Therefore, to reduce anemia rates in Indonesia, authorities must consider non-nutritional causes that might influence the local incidence of anemia, and apply co-management of endemic infectious disease such as malaria and tuberculosis, and of genetic disease i.e. thalassemia and G6PDd.

Key Words: hemoglobin, malaria, thalassemia, G6PD, tuberculosis

INTRODUCTION

Anemia affects more than 1.93 billion people worldwide,[1,2] mostly children aged <5 years and women.[1,3] Anemia increases morbidity and mortality rate, particularly in children and reproductive-age women.[4,5] Anemia also contributes to poor birth outcomes,[4,6] impaired neurological development in children, and decreased work productivity in adults.[7]

Anemia is defined by a hemoglobin (Hb) concentration and/or red blood cell (RBC) count below the normal values and insufficient to fulfill an individual's physiological needs.[8] Typically, Hb concentration is the most common hematological assessment method and indicator for the diagnosis of anemia at the population level and in clinical practice. Anemia is caused by an imbalance between RBC loss and production (erythropoiesis). RBC loss may occur because of premature destruction (hemolysis) and/or acute blood loss. Reduced erythropoiesis can be caused by nutritional, inflammatory, and genetic factors. Anemia classification is commonly based on the biological mechanism, such as hemolytic anemia (inflammation), or RBC morphology (e.g., hereditary spherocytosis).[9] Understanding the complex and varied etiology of anemia, including the non-nutritional cause, is crucial for developing effective interventions and monitoring anemia control programs. In this review, two interrelated non-nutritional causes of anemia, namely malaria infection and RBC disorders (thalassemia and G6PD deficiency), are discussed. Malaria-endemic regions, such as Indonesia, have a high frequency of thalassemia and G6PD deficiency, which increases the risk for non-nutritional anemia. Discussion also include tuberculosis, which is associated with anemia, since Indonesia is the second global contributor to the increased cases of newly diagnosed tuberculosis. In Indonesia, patients with active pulmonary tuberculosis are more anemic with poor nutritional status. Thus, tuberculosis is also a contributing factor for the increasing risk of anemia.

Corresponding Author: Dr Safarina G Malik, Eijkman Institute for Molecular Biology, Ministry of Research and Technology/National Agency for Research and Innovation, Indonesia.
Tel: +62 213917131; Fax: +62 213147982
Email: ina@eijkman.go.id
Manuscript received and initial review completed 19 December 2020. Revision accepted 23 December 2020.
doi: 10.6133/apjcn.202012_29(S1).04

ANEMIA AND MALARIA

Malaria, a mosquito-borne disease caused by the parasite belonging to the genus *Plasmodium*, has become a major cause of anemia in tropical regions.[10] In 2018, an estimated 228 million cases of malaria were reported worldwide, compared with 231 million cases in 2017 and 251 million cases in 2010. In 2018, an estimated 405,000 people died of malaria globally, compared with 416,000 estimated deaths in 2017 and 585,000 in 2010.[11] Five *Plasmodium* species can infect humans: *Plasmodium falciparum*, *P. vivax*, *P. malariae*, *P. ovale*, and *P. knowlesi*.[12] Of these, *P. falciparum* is the more virulent and is responsible for approximately 1–3 million deaths per year, mainly in children and pregnant women.[13] *P. falciparum* infection may cause severe malaria syndrome, including severe anemia (defined as Hb concentration <5 g/dL).[10] By contrast, *P. vivax*, the commonest and most widespread species, is a largely nonlethal malarial species; however, it can also cause severe malaria syndrome because of relapse cases due to the flaring up of hypnozoites in the liver.[14]

The pathophysiology of anemia caused by malaria infection is complex and influenced by multiple factors.[15] During malaria infection, merozoite-stage parasites invade RBCs to undergo the asexual intraerythrocytic developmental cycle.[16] This results in a noticeable loss in RBCs due to parasite maturation and macrophage-mediated disruption of infected RBCs in the bone marrow.[17] However, the principal contributor to anemia severity is the accelerated disruption of uninfected RBCs, as observed in severe malaria cases caused by *P. falciparum*[18] and *P. vivax*.[19] Studies have revealed that, similar to infected RBCs, uninfected RBCs also exhibit reduced deformability,[18,20] which may impair microcirculatory flow[21] and trigger splenic retention and phagocytosis,[22] thereby contributing to malarial anemia. Moreover, studies have reported that increased apoptosis[23] and accelerated senescence[24] of uninfected RBCs, as well as the destruction of non-parasitized RBCs through opsonization and complement dysregulation,[25–27] greatly contribute to anemia caused by falciparum and vivax malaria. Furthermore, malarial anemia is compounded by defective development of RBCs in the bone marrow (dyserythropoiesis), which is mainly caused by the release of various immune mediators by both the host and parasite cells.[28]

In many developing countries burdened by malaria, the destruction of RBCs induced by the parasite at the end of the infection exacerbates pre-existing anemia; this typically due to malnutrition, helminthiasis, or inherited disorders related to RBCs, such as hemoglobinopathies.[29,30] The level of transmission also influences anemia severity.[31] In areas with high malaria transmission (e.g., sub-Saharan Africa), where most of the patients have developed immunity because of frequent exposure to malaria infection, anemia is predominantly observed in young children (aged <5 years).[14,32] As the children grow into adulthood, they develop immunity against the malaria infection, such that in adolescence nearly all malaria infections are asymptomatic.[31] By contrast, in regions with unstable and low transmission of malaria, in which protective immunity from malaria is not achieved, the age group that is most affected by malarial anemia tends to shift toward adolescents and young adults.[33]

Malaria is highly endemic in Eastern Indonesia, and most infections occur on the islands of Papua and East Nusa Tenggara,[34] as illustrated in Figure 1.[35] Annual

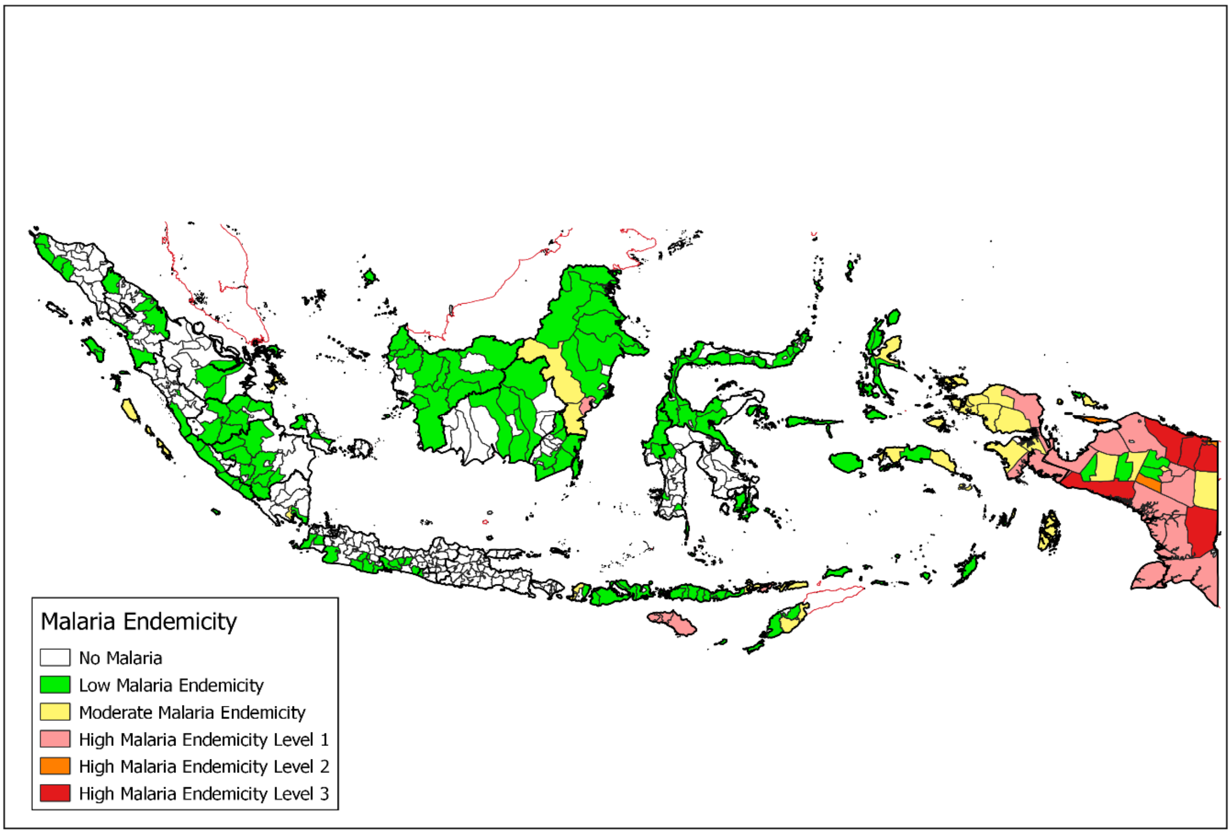


Figure 1. Malaria distribution in Indonesia. Source: World Malaria Report 2019.[11]

Table 1. Risk factors for anemia in women living in Sumba and Papua

Variable	Non-anemic (N=1481)	Anemic (N=2993)	Crude OR (95% CI)†	Adjusted OR (95% CI)‡
Malnourished, n (%)				
No	1094 (73.9)	2105 (70.3)	Reference	Reference
Yes	387 (26.1)	888 (29.7)	1.19 (1.04-1.37)***	1.36 (1.17-1.59)***
Malaria, n (%)				
No	1387 (93.7)	2731 (91.2)	Reference	Reference
Yes	94 (6.3)	262 (8.8)	1.42 (1.11-1.81)**	1.44 (1.13-1.84)**

MUAC: mid-upper arm circumference; OR: odds ratio; 95% CI: 95% confident interval.
Anemia criteria: hemoglobin <11 mg/dL for pregnant women or hemoglobin <12 mg/dL for nonpregnant women.[8] Malnourished: mid-upper-arm circumference <23 cm.[87]

†Unadjusted logistic regression. ‡Adjusted logistic regression after controlling for underweight, malnourished, and malaria status.

** $p<0.010$, *** $p<0.001$

parasite incidence in Indonesia was 0.84 in 2018 and 0.93 in 2019.[35] According to a related study conducted in Southern Papua, malaria infection due to *P. falciparum*, *P. vivax*, and *P. malariae* contributes to severe anemia risk, particularly in patients infected by mixed *Plasmodium* species, thus contributing to increased mortality risk.[15] Moreover, the burden of malaria-related anemia during pregnancy is overwhelming: almost 50% of pregnant mothers in Indonesia are anemic.[36] Malaria infection is a risk in approximately 6.3 million annual pregnancies in Indonesia.[37] Anemia is closely correlated with malaria infection, and in endemic regions, malaria is a major cause of anemia[31] as well as a large contributor to maternal anemia during pregnancy, resulting in poor birth outcomes.[38,39]

Asymptomatic microscopic parasitemia is associated with increased risk of anemia[40] and adverse birth outcomes, including premature delivery and low birth weight newborns.[41] In the Asia–Pacific region, 70% of pregnancies occur in malaria-endemic regions, of which 7% occur in Indonesia.[37] Malaria contributes to increased risk of anemia among women living in Sumba and Papua, independent of nutritional status (determined by body mass index and mid-upper arm circumference; Table 1).[42] Studies on the burden of malaria in West Sumba Regency, where malaria transmission is seasonal, revealed that anemia prevalence increased in younger children (aged <10 years) during the wet season.[43] Subsequent studies monitoring the efficacy of an antimalarial drug reported that the common clinical manifestation in the patients screened and involved in the studies was mild to severe anemia (Asih et al[44] and unpublished data, Eijkman Institute). Common concomitant genetic disorders that are also prevalent in Sumba include thalassemia, G6PD, and Southeast Asian ovalosytosis.[45,46]

The management of anemia in malaria endemic areas requires an intersectoral approach between nutritionists, hematologists, and infectious disease practitioners. This is because iron supplementation, rather than the provision of nutritious food as with biofortified grains and legumes, and bioavailability generated by food biodiversity, can exacerbate malaria, even to the point of overwhelming parasitosis.[47–51] This consideration applies to placental malaria in particular where even periconceptional iron is a risk factor.[52,53]

ANEMIA AND THALASSEMIA

Haldane (1949)[54] proposed that the high frequency of thalassemia in Mediterranean populations might be due to natural selection that resulted in increased prevalence of protective traits toward malaria infection; this is known as the Haldane hypothesis or malaria hypothesis. As a result of this survival advantage against malaria, inherited RBC disorders such as thalassemias are the most common diseases attributable to single defective genes. Considering its selective pressure in the human genome, malaria is regarded as an evolutionary force of some genetic diseases that mainly present as abnormal Hbs and RBC enzyme deficiencies.[55]

The thalassemias—characterized by decreased Hb production—are the most common inherited hemoglobin disorders and also the most common human monogenic diseases.[56] The two main types of thalassemia are α and β thalassemia, referring to the affected globin chains.[57,58] On the basis of globin chain expression, thalassemia can be classified as α^+ and α^0 or β^+ and β^0.[59] Although these disorders are most common in tropical and subtropical regions, they are now encountered in most countries because of global population migration and marriage between ethnic groups. Of all globin disorders, α thalassemia is the most widely distributed and occurs at high frequencies throughout tropical and subtropical regions; in these areas, carrier frequency can reach up to 80%–90% in the population.[60,61] For β thalassemia, the carrier frequency is approximately 1.5% of the global population (80–90 million people), with approximately 60,000 individuals with clinical manifestations born annually.[62]

Thalassemias are a heterogeneous group of anemias that result from defective synthesis of the globin chains of adult hemoglobin. In Southeast Asia, α-thalassemia, β-thalassemia, hemoglobin E (HbE), and hemoglobin Constant Spring (HbCS) are prevalent. HbE and HbCS are hemoglobin variants that cause a decrease in hemoglobin production. HbE mutation alternates the mRNA splicing, whereas HbCS mutation produces unstable mRNA due to a stop codon shift that causes longer but unstable mRNA, resulting in the reduction of the α-globin chain. The gene frequencies of α^0-thalassemia in Indonesia range from 1.5% to 11.8% and that of α^+-thalassemia from 3.2% to 38.6% (unpublished data, Eijkman Institute).[63] The gene frequencies of β-thalassemia in Indonesia vary from 0.5% to 17.45% for the HbE mutation and 0.5% to 5.4% for the other β-thalassemia mutations (unpublished data, Eijkman Institute).

α-Thalassemia

α-Thalassemia is an autosomal recessive hereditary RBC disorder due to mutations in the α-globin genes, causing a decrease in or absence of α-globin chain production; it is characterized by microcytic hypochromic anemia. The clinical phenotype of α-thalassemia varies from almost asymptomatic to lethal hemolytic anemia. α-thalassemia is a condition related to a deficit in the production of α-globin chains, which form a tetrameric molecule together with β- or γ- globin chains of the hemoglobin molecule. Healthy individuals have four α-globin genes: two sets of two tandemly encoded (in *cis)* genes, located on chromosome 16 in band 16p13.3.[60]

The α-globin chains are subunits for both fetal (α2Γ2) and adult (α2β2) hemoglobin; therefore, homozygous α-thalassemia can cause anemia in fetuses and adults.[58] The most frequent mutation of α-thalassemia is deletion of one (α^+-thalassemia) or both (α^0-thalassemia) of the α-globin genes. The severity of clinical and hematological phenotypes (degree of microcytic hypochromic anemia) is closely correlated with the reduction of α-globin chain synthesis in each mutated α gene.[64]

β-Thalassemia

The other autosomal recessive hereditary RBC disorder is β-thalassemia, which is caused by mutations in the β-globin gene. β-thalassemia is characterized by the reduction in or absence of β-globin chain synthesis, resulting in reduced Hb, decreased RBC production, and anemia. On the basis of the clinical manifestations, β-thalassemia is classified as thalassemia major, thalassemia intermedia, and thalassemia minor.[59,62]

The beta globin gene maps in the short arm of chromosome 11 at position 15.4. Approximately 200 β-globin gene mutations have been reported.[65] β-globin gene mutations result in a reduction or absence of β-globin chains production, with variable phenotypes ranging from severe anemia to clinically asymptomatic. The clinical severity of β-thalassemia is associated with the imbalance between the α-globin and non–α-globin chains.

Even though thalassemia is closely associated with anemia, some of the hematologic features of the RBCs could appear normal in the thalassemia trait, as observed in our population studies in several ethnic groups in Indonesia (Table 2). The prevalence of anemia (according to Hb concentration) in the population of Banjarmasin and Ternate was 11.4% (67/587; cutoff is <12 g/dL for women individuals and <13 g/dL for men individuals; according to the World Health Organization criteria[8]). We applied trait thalassemia screening according to the complete blood count, Hb analysis, and blood smear of these 67 individuals with anemia; we noted that only approximately 82% exhibited an indication of thalassemia (microcytic hypochromic). If molecule detection were also included, the confirmed thalassemia cases would be even lower. However, those with nonconfirmed thalassemia with microcytic hypochromic anemia could still harbor

Table 2. Clinical characteristics of individuals with and without anemia in the Banjarmasin and Ternate population

Population	Variable	Non-anemic	Anemic	*p*
Banjarmasin		(N=179)	(N=19)	
	Age [years, median (IQR)]	20.0 (19.0-21.0)	19.0 (19.0-20.0)	0.175
	Sex [n (%)]			
	Male	74 (41.7)	1 (5.3)	0.002
	Female	105 (58.3)	18 (94.7)	
	Hb [mg/dL, median (IQR]	14.1 (13.3-15.2)	10.8 (10.6-11.7)	<0.001
	MCV [fL, median (IQR)]	84.7 (82.3-87.5)	80.0 (71.4-82.7)	<0.001
	MCH [pg, median (IQR)]	28.3 (27.4-29.2)	24.4 (21.4-26.1)	<0.001
	MCHC [g/dL, median (IQR)]	33.2 (32.5-33.8)	31.2 (30.6-32.2)	<0.001
	RDW [n (%)]	13.4 (13.0-13.9)	15.7 (14.7-17.0)	<0.001
	HbA2 [n (%)]	2.8 (2.7-2.9)	2.6 (2.5-2.9)	0.021
	HbF [n (%)]	0.3 (0-0.5)	0.0 (0.0-0.4)	0.281
	HbE [n (%)]	2 (1.0)	0 (0.0)	1.000
Ternate		(N=341)	(N=48)	
	Age [years, median (IQR)]	20.0 (17.0-21.0)	19.5 (18.8-20.0)	0.185
	Sex [n (%)]			
	Male	146 (42.8)	1 (2.1)	<0.001
	Female	195 (57.2)	47 (97.9)	
	Hb [mg/dL, median (IQR]	14.0 (13.1-15.6)	11.2 (9.6-11.6)	<0.001
	MCV [fL, median (IQR)]	82.9 (80.4-85.2)	74.6 (66.6-79.2)	<0.001
	MCH [pg, median (IQR)]	28.2 (26.9-29.3)	23.4 (19.9-25.4)	<0.001
	MCHC [g/dL, median (IQR)]	33.8 (32.9-34.9)	31.4 (29.5-32.4)	<0.001
	RDW [n (%)]	13.6 (13.1-14.3)	15.7 (14.8-19.2)	<0.001
	HbA2 [n (%)]	2.8 (2.6-2.9)	2.5 (2.3-2.7)	<0.001
	HbF [n (%)]	0.3 (0.2-1.0)	0.2 (0.0-0.9)	0.036
	HbE [n (%)]	4 (1.2)	2 (4.2)	0.162

Hb: hemoglobin; MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; RDW: red cell distribution width; HbA2: hemoglobin subunit alpha 2; HbF: fetal hemoglobin; HbE: hemoglobin E.
World Health Organization anemia criteria were employed: hemoglobin <12 mg/dL for women or hemoglobin <13 mg/dL for men.[8]
The *p* values were calculated using either the Wilcoxon–Mann Whitney U test for continuous variables or Fisher's exact test for categorical variables. Significant *p* values are in bold (p<0.05). Unpublished data, Eijkman Institute.

thalassemia traits because a comprehensive molecular screening has not yet been conducted; in this case, screening was only performed for the most common mutations. Microcytic hypochromic anemia could result from not only thalassemia but also iron deficiency because thalassemia can coexist with iron deficiency. However, in cases where thalassemia is not confirmed, the microcytic hypochromic anemia is most likely due to iron deficiency. Hence, nutritional anemia could coexist with RBC disorders, such as thalassemia.

We included hemoglobin analysis when screening for thalassemia, either in patients at our genetic clinic or as part of our population studies. We observed that RBC morphology (microcytic hypochromic) was similar between thalassemia and iron deficiency anemia and noted that this similarity could obscure the real cause of the underlying anemia because both abnormalities are commonly noted in the Indonesian population. Therefore, iron status must be examined to confirm the cause of the anemia, which is crucial to determining prevention, therapy, and management strategies. However, government guidelines do not include iron status examination for determining the cause of anemia. The current policy is to provide iron supplementation for every person with anemia. Thus, we propose complete blood count and iron status screening in the Indonesian population in cases where iron supplementation does not improve iron content.

ANEMIA AND GLUCOSE-6-PHOSPHATE DEHYDROGENASE DEFICIENCY

Another genetic disorder associated with the selective pressure of malaria is glucose-6-phosphate dehydrogenase deficiency (G6PDd), which has been reported to confer resistance to malarial infection.[66–68] Population genetic analyses of the G6PD locus have supported the association between G6PD and malaria; these studies have revealed that the frequency of G6PD gene mutations have increased recently in certain geographic regions where malaria is endemic, as a result of positive selection.[69,70]

The G6PD gene is located on chromosome X and maps to Xq28, making the disorder X-linked; consequently, men can only be hemizygous G6PD normal or hemizygous G6PD deficient. Women can either be homozygous G6PD normal, homozygous G6PD deficient, or heterozygous because women have two *G6PD* alleles. Similar to most X-linked genes, G6PD is affected by the random X-chromosome inactivation phenomenon, and somatic cells in G6PD heterozygous women are a mosaic of G6PD-normal and G6PD-deficient RBCs.[71–73]

G6PDd is a common RBC enzyme disorder worldwide, affecting approximately 400 million people. The clinical manifestations of G6PDd are broad, ranging from asymptomatic to acute hemolytic anemia, renal failure, and death. These manifestations result from mutations in the G6PD gene that cause instability in the produced enzyme. Approximately 400 biochemical variants are known, but only 186 mutations have been genotyped.[74] These mutations are region- or ethnic-specific. In Indonesia, G6PDd is most prevalent in malaria-endemic areas, such as south Lampung, central and south Kalimantan, and most of eastern Indonesia, such as Sumba and Papua. Certain variants, such as Vanua-Lava, Viangchan, Coimbra Shunde, are found predominantly in eastern Indonesia.[75,76]

Most individuals with G6PDd do not exhibit any symptoms unless exposed to exogenous agents that trigger oxidative stress resulting in acute hemolytic anemia. In affected individuals, a defect in the G6PD enzyme causes RBCs to break down prematurely in response to oxidative medication, infections, or fava beans, leading to hemolytic anemia that may be severe and life-threatening.[77] We noted no difference in G6PD enzyme activity between those with and without anemia in normal conditions (i.e., not exposed to oxidative agents), whereas older age and being a woman increased the risk for acute hemolytic anemia (Table 3).

TUBERCULOSIS

Anemia is also found in association with tuberculosis. In Taiwan's nationwide population-based study covering 12 years of data, iron deficiency anemia was associated with a 99% increased incidence of tuberculosis compared with the matched group, which supports the hypothesis that individuals with micronutrient deficiency, including iron deficiency, are more susceptible to infections.[78] Data from study conducted in Indonesia showed that patients with active pulmonary tuberculosis are more anemic with

Table 3. Predictors of anemia in those with and without G6PD deficiency

Variable	Non-anemic	Anemic	Crude		Adjusted	
	(N=424)	(N=182)	OR (95% CI)	*p*	OR (95% CI)	*p*
Age (years)	15.0 (10.0-32.0)	30.0 (16.3-40.0)	1.03 (1.01-1.04)	<0.001	1.03 (1.02-1.05)	<0.001
Weight (kg)	39.0 (23.0-48.0)	40.0 (34.3-45.0)	1.01 (1.00-1.03)	0.045	1.00 (0.98-1.02)	0.947
Sex						
Female	210 (49.5)	139 (76.4)	Reference		Reference	
Male	214 (50.5)	43 (23.6)	0.3 (0.21-0.45)	<0.001	0.27 (0.17-0.41)	<0.001
G6PD activity						
Non-deficient	399 (94.1)	170 (93.4)	Reference		Reference	
Deficient	25 (5.9)	12 (6.6)	1.13 (0.55-2.29)	0.743	1.31 (0.59-2.90)	0.502
Malaria						
Negative	415 (97.9)	176 (96.7)	Reference		Reference	
Positive	9 (2.1)	6 (3.3)	1.57 (0.55-4.48)	0.398	2.68 (0.87-8.26)	0.085

G6PD: glucose-6-phosphate dehydrogenase; OR: odds ratio; 95% CI: 95% confident interval.
World Health Organization anemia criteria were employed: age <5 years, Hb <11 mg/dL; age 5–11 years, Hb <11.5 mg/dL; age 12–14 years, Hb <12 mg/dL; age >15 years, Hb <12 mg/dL for female individuals or Hb <13 mg/dL for male individuals.[8]
Data were extracted from Satyagraha et al.[75]

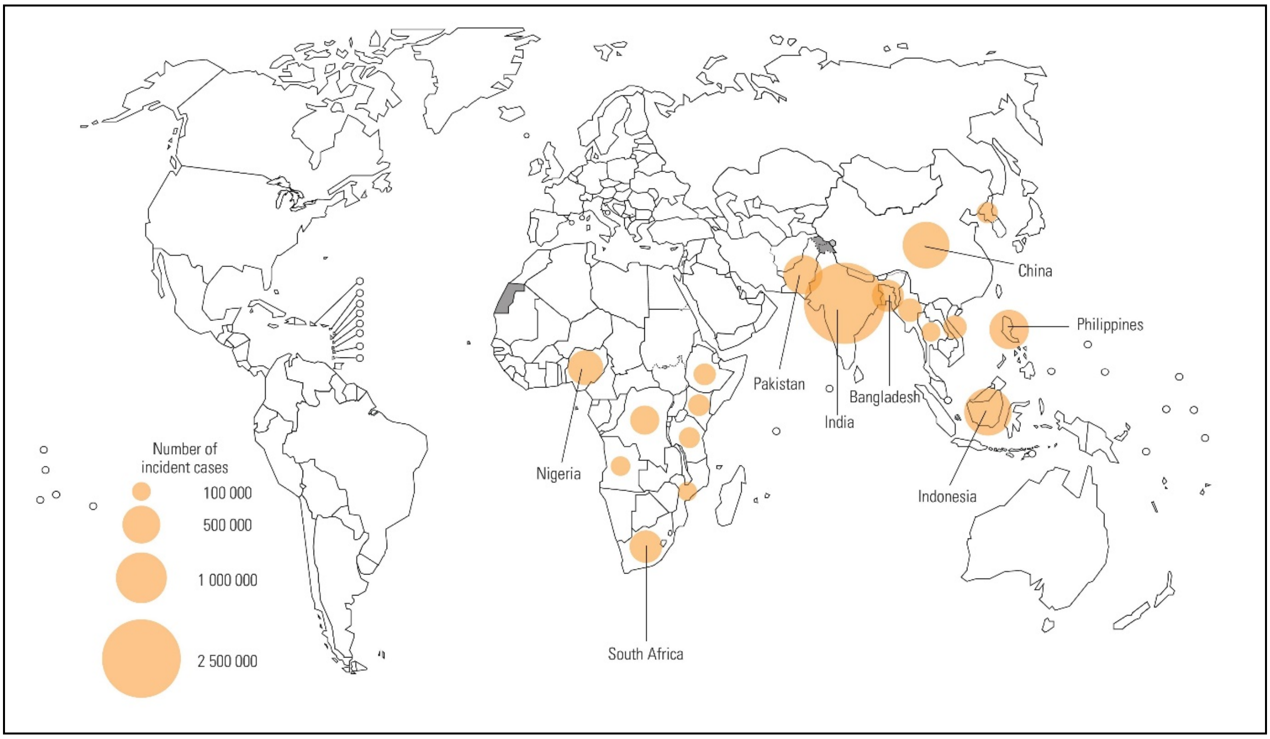


Figure 2. Countries that had at least 100 000 incident cases of TB in 2019. Source: Global Tuberculosis Report 2020.[80]

poor nutritional status as compared to healthy subjects.[79] Indonesia is ranked second (8.5%) as the biggest contributors to the global increase of newly diagnosed tuberculosis, after India (26%) (Figure 2).[80] Nevertheless, similar with malaria, iron supplementation may exacerbate tuberculosis, since the tuberculosis causative pathogen, *Mycobacterium tuberculosis*, requires iron for essential metabolic pathways. Therefore, in tuberculous areas, iron supplementation approaches to the problem should be avoided without co-management of tuberculosis and monitoring for iron biomarkers, since the management of dietary iron is most likely influential in supporting the outcome of this disease.[81–86]

CONCLUSION: THE ROLE OF MALARIA, THALASSEMIA, G6PD DEFICIENCY AND TUBERCULOSIS IN ANEMIA IN INDONESIA

The prevalence of anemia is high in Indonesia.[36] The health authorities tend to highlight iron deficiency and/or malnutrition as the cause of anemia. Indonesia is an archipelago country with numerous islands, ethnic groups, cultures, languages, as well as tropical and genetic diseases including malaria, thalassemia, and G6PD deficiency. Multiple malaria infections can cause severe anemia in children or adults living in malaria-endemic areas. Genetic factors that have arisen from malaria pressure in these areas can also cause anemia. Thus, anemia does not occur solely due to malnutrition and iron deficiency but can be due to other internal or external factors, which may play a role in modulating the incidence of anemia in Indonesia. Whenever iron supplementation does not improve anemia status, particularly microcytic hypochromic anemia, practitioners should consider other causes. In our population studies, the prevalence of both thalassemia trait and iron deficiency was high, both of which contribute to the high prevalence of anemia. Therefore, in the management of anemia in the Indonesian population, conducting complete blood count screening, Hb analysis, and iron status examination is necessary, because anemia could be due to either chronic infection (e.g., malaria, tuberculosis) or genetic disorders (e.g., thalassemia and G6PDd). Anemia, particularly in children, may cause irreversible neurological damage that may affect the quality and global competitiveness of future human resources. Anemia in adults limit the quality of people's work and their productivity. Thus, to eliminate anemia in Indonesia, the authorities should employ a comprehensive and multidisciplinary approach in collaboration with research and government institutions. Anemia elimination in Indonesia requires a knowledge of local pathogens, as well as nutritional factors, especially since iron supplementation may otherwise worsen infectious disease such outcomes as in malaria and tuberculosis.

ACKNOWLEDGEMENTS

The authors are grateful to the Scientific Members of the Indonesian Danone Institute Foundation for their input during the development of this review. We are grateful to Ms. Keisha M. Tuffahati for her assistance in editing the manuscript. This manuscript was edited by Wallace Academic Editing.

AUTHOR DISCLOSURES

The authors declare no conflict of interest.

REFERENCES

1. Kassebaum NJ, GBD 2013 Anemia Collaborators. The global burden of anemia. Hematol Oncol Clin North Am. 2016;30:247-308. doi: 10.1016/j.hoc.2015.11.002.
2. Lukito W, Wahlqvist ML. Intersectoral and eco-nutritional approaches to resolve persistent anemia in Indonesia. Asia

Pac J Clin Nutr. 2020;29(Suppl 1):S1-S8. doi: 10.6133/apjcn.202012_29(S1).01.
3. 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.
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. Balarajan Y, Ramakrishnan U, Ozaltin E, Shankar AH, Subramanian SV. Anaemia in low-income and middle-income countries. Lancet Lond Engl. 2011;378:2123-35. doi: 10.1016/S0140-6736(10)62304-5.
6. 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. doi: 10.1136/bmj.f3443.
7. Krebs NF, Lozoff B, Georgieff MK. Neurodevelopment: The impact of nutrition and inflammation during infancy in low-resource settings. Pediatrics. 2017;139:S50-8. doi: 10.1542/peds.2016-2828G.
8. World Health Organization. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity [Internet]. World Health Organization; 2011. [2020/10/04]; Available from: https://apps.who.int/iris/handle/10665/85839.
9. 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.
10. Haldar K, Mohandas N. Malaria, erythrocytic infection, and anemia. ASH Educ Program Book. 2009;2009:87-93. doi: 10.1182/asheducation-2009.1.87.
11. World Health Organization. World Malaria Report 2019. Geneva: World Health Organization; 2019.
12. White NJ. Plasmodium knowlesi: the fifth human malaria parasite. Clin Infect Dis Off Publ Infect Dis Soc Am. 2008; 46:172-3. doi: 10.1086/524889.
13. Snow RW, Guerra CA, Noor AM, Myint HY, Hay SI. The global distribution of clinical episodes of Plasmodium falciparum malaria. Nature. 2005;434:214-7. doi: 10.1038/nature03342.
14. Kenangalem E, Karyana M, Burdarm L, Yeung S, Simpson JA, Tjitra E et al. Plasmodium vivax infection: a major determinant of severe anaemia in infancy. Malar J. 2016;15: 321. doi: 10.1186/s12936-016-1373-8.
15. Douglas NM, Lampah DA, Kenangalem E, Simpson JA, Poespoprodjo JR, Sugiarto P et al. Major burden of severe anemia from non-falciparum malaria species in Southern Papua: a hospital-based surveillance study. PLoS Med. 2013; 10:e1001575. doi: 10.1371/journal.pmed.1001575.
16. Tuteja R. Malaria − an overview. FEBS J. 2007;274:4670-9. doi: 10.1111/j.1742-4658.2007.05997.x.
17. Phillips RE, Pasvol G. Anaemia of Plasmodium falciparum malaria. Baillières Clin Haematol. 1992;5:315-30. doi: 10.1016/S0950-3536(11)80022-3.
18. Looareesuwan S, Davis TM, Pukrittayakamee S, Supanaranond W, Desakorn V, Silamut K et al. Erythrocyte survival in severe falciparum malaria. Acta Trop. 1991;48: 263-70. doi: 10.1016/0001-706x(91)90014-b.
19. Collins WE, Jeffery GM, Roberts JM. A retrospective examination of anemia during infection of humans with Plasmodium vivax. Am J Trop Med Hyg. 2003;68:410-2. doi: 10.4269/ajtmh.2003.68.410.
20. Suwanarusk R, Cooke BM, Dondorp AM, Silamut K, Sattabongkot J, White NJ et al. The deformability of red blood cells parasitized by Plasmodium falciparum and P. vivax. J Infect Dis. 2004;189:190-4. doi: 10.1086/380468.
21. Dondorp AM, Pongponratn E, White NJ. Reduced microcirculatory flow in severe falciparum malaria: pathophysiology and electron-microscopic pathology. Acta Trop. 2004;89:309-17. doi: 10.1016/j.actatropica.2003.10.004.
22. Safeukui I, Correas JM, Brousse V, Hirt D, Deplaine G, Mule S et al. Retention of Plasmodium falciparum ring-infected erythrocytes in the slow, open microcirculation of the human spleen. Blood. 2008;112:2520-8. doi: 10.1182/blood-2008-03-146779.
23. Totino PRR, Magalhães AD, Silva LA, Banic DM, Daniel-Ribeiro CT, de Ferreira-da-Cruz M. Apoptosis of non-parasitized red blood cells in malaria: a putative mechanism involved in the pathogenesis of anaemia. Malar J. 2010;9: 350. doi: 10.1186/1475-2875-9-350.
24. Omodeo-Salè F, Motti A, Basilico N, Parapini S, Olliaro P, Taramelli D. Accelerated senescence of human erythrocytes cultured with Plasmodium falciparum. Blood. 2003;102: 705-11. doi: 10.1182/blood-2002-08-2437.
25. Awah NW, Troye-Blomberg M, Berzins K, Gysin J. Mechanisms of malarial anaemia: potential involvement of the Plasmodium falciparum low molecular weight rhoptry-associated proteins. Acta Trop. 2009;112:295-302. doi: 10.1016/j.actatropica.2009.08.017.
26. Brattig NW, Kowalsky K, Liu X, Burchard GD, Kamena F, Seeberger PH. Plasmodium falciparum glycosylphosphatidylinositol toxin interacts with the membrane of non-parasitized red blood cells: a putative mechanism contributing to malaria anemia. Microbes Infect. 2008;10:885-91. doi: 10.1016/j.micinf.2008.05.002.
27. Oyong DA, Kenangalem E, Poespoprodjo JR, Beeson JG, Anstey NM, Price RN et al. Loss of complement regulatory proteins on uninfected erythrocytes in vivax and falciparum malaria anemia. JCI Insight. 2018;3:e124854. doi: 10.1172/jci.insight.124854.
28. Pathak VA, Ghosh K. Erythropoiesis in malaria infections and factors modifying the erythropoietic response. Anemia. 2016;2016:9310905. doi: 10.1155/2016/9310905.
29. Calis JCJ, Phiri KS, Faragher EB, Brabin BJ, Bates I, Cuevas LE et al. Severe anemia in Malawian children. N Engl J Med. 2008;358:888-99. doi: 10.1056/NEJMoa072727.
30. Weatherall DJ. Genetic variation and susceptibility to infection: the red cell and malaria. Br J Haematol. 2008;141: 276-86. doi: 10.1111/j.1365-2141.2008.07085.x.
31. White NJ. Anaemia and malaria. Malar J. 2018;17:371. doi: 10.1186/s12936-018-2509-9.
32. Sumbele IUN, Sama SO, Kimbi HK, Taiwe GS. Malaria, moderate to severe anaemia, and malarial anaemia in children at presentation to hospital in the mount cameroon area: A cross-sectional study. Anemia. 2016;2016:1-12. doi: 10.1155/2016/5725634.
33. Lopez-Perez M, Álvarez Á, Gutierrez JB, Moreno A, Herrera S, Arévalo-Herrera M. Malaria-related anemia in patients from unstable transmission areas in Colombia. Am J Trop Med Hyg. 2015;92:294-301. doi: 10.4269/ajtmh.14-0345.
34. Elyazar IR, Hay SI, Baird JK. Malaria distribution, prevalence, drug resistance and control in Indonesia. Adv Parasitol. 2011;74:41. doi: 10.1016/B978-0-12-385897-9.00002-1.
35. Ministry of Health Republic of Indonesia. Current situation development of malaria control programs in Indonesia.

Directorate General of Disease Control and Environmental Health; 2020. (In Indonesian)
36. 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)
37. Dellicour S, Tatem AJ, Guerra CA, Snow RW, ter Kuile FO. Quantifying the number of pregnancies at risk of malaria in 2007: a demographic study. PLoS Med. 2010;7:e1000221. doi: 10.1371/journal.pmed.1000221.
38. Desai M, ter Kuile FO, Nosten F, McGready R, Asamoa K, Brabin B, et al. Epidemiology and burden of malaria in pregnancy. Lancet Infect Dis. 2007;7:93-104. doi: 10.1016/S1473-3099(07)70021-X.
39. Rogerson SJ, Desai M, Mayor A, Sicuri E, Taylor SM, van Eijk AM. Burden, pathology, and costs of malaria in pregnancy: new developments for an old problem. Lancet Infect Dis. 2018;18:e107-18. doi: 10.1016/S1473-3099(18)30066-5.
40. Pava Z, Burdam FH, Handayuni I, Trianty L, Utami RAS, Tirta YK et al. Submicroscopic and asymptomatic Plasmodium parasitaemia associated with significant risk of anaemia in Papua, Indonesia. PLoS One. 2016;11: e0165340. doi: 10.1371/journal.pone.0165340.
41. Cottrell G, Moussiliou A, Luty AJF, Cot M, Fievet N, Massougbodji A et al. Submicroscopic Plasmodium falciparum infections are associated with maternal anemia, premature births, and low birth weight. Clin Infect Dis. 2015;60:1481-8. doi: 10.1093/cid/civ122.
42. Ahmed R, Poespoprodjo JR, Syafruddin D, Khairallah C, Pace C, Lukito T et al. Efficacy and safety of intermittent preventive treatment and intermittent screening and treatment versus single screening and treatment with dihydroartemisinin-piperaquine for the control of malaria in pregnancy in Indonesia: a cluster-randomised, open-label, superiority trial. Lancet Infect Dis. 2019;19:973-87. doi: 10.1016/S1473-3099(19)30156-2.
43. Syafruddin D, Krisin, Asih P, Sekartuti, Dewi RM, Coutrier F et al. Seasonal prevalence of malaria in West Sumba district, Indonesia. Malar J. 2009;8:8. doi: 10.1186/1475-2875-8-8.
44. Asih PBS, Dewi RM, Tuti S, Sadikin M, Sumarto W, Sinaga B et al. Efficacy of artemisinin-based combination therapy for treatment of persons with uncomplicated Plasmodium falciparum malaria in West Sumba District, East Nusa Tenggara Province, Indonesia, and genotypic profiles of the parasite. Am J Trop Med Hyg. 2009;80:914-8. doi: 10.4269/ajtmh.2009.80.914.
45. Syafruddin D, Asih PBS, Coutrier FN, Trianty L, Noviyanti R, Luase Y et al. Malaria in Wanokaka and Loli sub-districts, West Sumba District, East Nusa Tenggara Province, Indonesia. Am J Trop Med Hyg. 2006;74:733-7.
46. Kimura M, Soemantri A, Ishida T. Malaria species and Southeast Asian ovalocytosis defined by a 27-bp deletion in the erythrocyte band 3 gene. Southeast Asian J Trop Med Public Health. 2002;33:4-6.
47. Gwamaka M, Kurtis JD, Sorensen BE, Holte S, Morrison R, Mutabingwa TK et al. Iron deficiency protects against severe Plasmodium falciparum malaria and death in young children. Clin Infect Dis. 2012;54:1137-44. doi: 10.1093/cid/cis010.
48. Menendez C, Kahigwa E, Hirt R, Vounatsou P, Aponte JJ, Font F et al. Randomised placebo-controlled trial of iron supplementation and malaria chemoprophylaxis for prevention of severe anaemia and malaria in Tanzanian infants. Lancet. 1997;350(9081):844-50. doi: 10.1016/S0140-6736(97)04229-3.
49. Sazawal S, Black RE, Ramsan M, Chwaya HM, Stoltzfus RJ, Dutta A et al. Effects of routine prophylactic supplementation with iron and folic acid on admission to hospital and mortality in preschool children in a high malaria transmission setting: community-based, randomised, placebo-controlled trial. Lancet. 2006;367(9505):133-43. doi: 10.1016/S0140-6736(06)67962-2.
50. Etheredge AJ, Premji Z, Gunaratna NS, Abioye AI, Aboud S, Duggan C et al. Iron supplementation in iron-replete and nonanemic pregnant women in Tanzania: A randomized clinical trial. JAMA Pediatr. 2015;169:947-55. doi: 10.1001/jamapediatrics.2015.1480.
51. Kabyemela ER, Muehlenbachs A, Fried M, Kurtis JD, Mutabingwa TK, Duffy PE. Maternal peripheral blood level of IL-10 as a marker for inflammatory placental malaria. Malar J. 2008;7:26. doi: 10.1186/1475-2875-7-26.
52. Van Santen S, de Mast Q, Luty AJF, Wiegerinck ET, Van der Ven AJAM, Swinkels DW. Iron homeostasis in mother and child during placental malaria infection. Am J Trop Med Hyg. 2011;84:148-51. doi: 10.4269/ajtmh.2011.10-0250.
53. Gies S, Roberts SA, Diallo S, Lompo OM, Tinto H, Brabin BJ. Risk of malaria in young children after periconceptional iron supplementation. Matern Child Nutr. 2020;2020: e13106. doi: 10.1111/mcn.13106.
54. Lederberg JJBS. Haldane (1949) on infectious disease and evolution. Genetics. 1999;153:1-3.
55. Weatherall DJ. Thalassaemia and malaria, revisited. Ann Trop Med Parasitol. 1997;91:885-90. doi: 10.1080/00034983.1997.11813215.
56. Taher AT, Weatherall DJ, Cappellini MD. Thalassaemia. Lancet. 2018;391(10116):155-67. doi: 10.1016/S0140-6736(17)31822-6.
57. Weatherall DJ, Clegg JB. Thalassemia--a global public health problem. Nat Med. 1996;2:847-9. doi: 10.1038/nm0896-847.
58. Weatherall DJ. The thalassaemias. BMJ. 1997;314:1675-8. doi: 10.1136/bmj.314.7095.1675.
59. Cao A, Galanello R. Beta-thalassemia. Genet Med. 2010;12: 61-76. doi: 10.1097/GIM.0b013e3181cd68ed.
60. Harteveld CL, Higgs DR. Alpha-thalassaemia. Orphanet J Rare Dis. 2010;5:13. doi: 10.1186/1750-1172-5-13.
61. Piel FB, Weatherall DJ. The α-thalassemias. N Engl J Med. 2014;371:1908-16.
62. Galanello R, Origa R. Beta-thalassemia. Orphanet J Rare Dis. 2010;5:11. doi: 10.1186/1750-1172-5-11.
63. Setianingsih I, Harahap A, Nainggolan IM. Alpha thalassaemia in Indonesia: phenotypes and molecular defects. Adv Exp Med Biol. 2003;531:47-56. doi: 10.1007/978-1-4615-0059-9_4.
64. Gibbons R, Higgs DR, Olivieri NF, Wood WG. The α thalassaemias and their interactions with structural haemoglobin variants. In Weatherall DJ, Clegg JB, editors. London: Wiley; 2008. pp.484-525. doi: 10.1002/9780470696705.ch11.
65. Giardine B, van Baal S, Kaimakis P, Riemer C, Miller W, Samara M et al. HbVar database of human hemoglobin variants and thalassemia mutations: 2007 update. Hum Mutat. 2007;28:206. doi: 10.1002/humu.9479.
66. Luzzatto L, Usanga FA, Reddy S. Glucose-6-phosphate dehydrogenase deficient red cells: resistance to infection by malarial parasites. Science. 1969;164:839-42. doi: 10.1182/blood.2019000944.
67. Cappadoro M, Giribaldi G, O'Brien E, Turrini F, Mannu F, Ulliers D et al. Early phagocytosis of glucose-6-phosphate dehydrogenase (G6PD)-deficient erythrocytes parasitized by Plasmodium falciparum may explain malaria protection in

G6PD deficiency. Blood. 1998;92:2527-34. doi: 10.1182/blood.V92.7.2527.
68. Hedrick PW. Population genetics of malaria resistance in humans. Heredity. 2011;107:283-304. doi: 10.1038/hdy.2011.16.
69. 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.
70. 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
71. Wang J, Xiao Q-Z, Chen Y-M, Yi S, Liu D, Liu Y-H, et al. DNA hypermethylation and X chromosome inactivation are major determinants of phenotypic variation in women heterozygous for G6PD mutations. Blood Cells Mol Dis. 2014;53:241-5. doi: 10.1016/j.bcmd.2014.06.001.
72. Moreira de Mello JC, de Araújo ÉS, Stabellini R, Fraga AM, de Souza JE, Sumita DR et al. Random X inactivation and extensive mosaicism in human placenta revealed by analysis of allele-specific gene expression along the X chromosome. PLoS One. 2010;5:e10947. doi: 10.1371/journal.pone.0010947.
73. Mathai CK, Ohno S, Beutler E. Sex-linkage of the glucose-6-phosphate dehydrogenase gene in Equidae. Nature. 1966;210:115-6. doi: 10.1038/210115a0.
74. Minucci A, Moradkhani K, Hwang MJ, Zuppi C, Giardina B, Capoluongo E. Glucose-6-phosphate dehydrogenase (G6PD) mutations database: review of the “old” and update of the new mutations. Blood Cells Mol Dis. 2012;48:154-65. doi: 10.1016/j.bcmd.2012.01.001.
75. 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:e0004457. doi: 10.1371/journal.pntd.0004457.
76. Sulistyaningrum N, Arlinda D, Hutagalung J, Sunarno S, Oktoberia IS, Handayani S et al. Prevalence of glucose 6-phosphate dehydrogenase variants in malaria-endemic areas of south central Timor, eastern Indonesia. Am J Trop Med Hyg. 2020;103:760-6. doi: 10.4269/ajtmh.19-0780.
77. Luzzatto L, Ally M, Notaro R. Glucose-6-phosphate dehydrogenase deficiency. Blood. 2020;136:1225-40. doi: 10.1182/blood.2019000944.
78. Chu K-A, Hsu C-H, Lin M-C, Chu Y-H, Hung Y-M, Wei JC-C. Association of iron deficiency anemia with tuberculosis in Taiwan: A nationwide population-based study. PLoS One. 2019;14:e0221908. doi: 10.1371/journal.pone.0221908.
79. Karyadi E, Schultink W, Nelwan RH, Gross R, Amin Z, Dolmans WM et al. Poor micronutrient status of active pulmonary tuberculosis patients in Indonesia. J Nutr. 2000;130:2953-8. doi: 10.1093/jn/130.12.2953.
80. World Health Organization. Global tuberculosis report 2020. Geneva, Switzerland: WHO; 2020.
81. Lounis N, Truffot-Pernot C, Grosset J, Gordeuk VR, Boelaert JR. Iron and Mycobacterium tuberculosis infection. J Clin Virol. 2001;20:123-6. doi: 10.1016/s1386-6532(00)00136-0.
82. Boelaert JR, Vandecasteele SJ, Appelberg R, Gordeuk VR. The effect of the host’s iron status on tuberculosis. J Infect Dis. 2007;195:1745-53. doi: 10.1086/518040.
83. Ratledge C. Iron, mycobacteria and tuberculosis. Tuberc Edinb Scotl. 2004;84:110-30. doi: 10.1016/j.tube.2003.08.012.
84. Isanaka S, Mugusi F, Urassa W, Willett WC, Bosch RJ, Villamor E et al. Iron deficiency and anemia predict mortality in patients with tuberculosis. J Nutr. 2012;142:350-7. doi: 10.3945/jn.111.144287.
85. Minchella PA, Donkor S, Owolabi O, Sutherland JS, McDermid JM. Complex anemia in tuberculosis: the need to consider causes and timing when designing interventions. Clin Infect Dis. 2015;60:764-72. doi: 10.1093/cid/ciu945.
86. Rodriguez GM. Control of iron metabolism in Mycobacterium tuberculosis. Trends Microbiol. 2006;14:320-7. doi: 10.1016/j.tim.2006.05.006.
87. Kumar P, Sareen N, Agrawal S, Kathuria N, Yadav S, Sethi V. Screening maternal acute malnutrition using adult mid-upper arm circumference in resource-poor settings. Indian J Community Med. 2018;43:132-4. doi: 10.4103/ijcm.IJCM_248_17.

Review Article

Non-nutritional and disease-related anemia in Indonesia: A systematic review

Agussalim Bukhari MD, MMed, PhD[1], Firdaus Hamid MD, PhD[2], Rahmawati Minhajat MD, PhD[3,4], Nathania Sheryl Sutisna MD[1], Caroline Prisilia Marsella MD[1]

[1]*Department of Nutrition, Faculty of Medicine, Universitas Hasanuddin, Makassar, Indonesia*
[2]*Department of Microbiology, Faculty of Medicine, Universitas Hasanuddin, Makassar, Indonesia*
[3]*Division of Hematology and Oncology, Department of Internal Medicine, Faculty of Medicine, Universitas Hasanuddin, Makassar, Indonesia*
[4]*Department of Histology, Faculty of Medicine, Universitas Hasanuddin, Makassar, Indonesia*

Non-nutritional anemia, the second most common type of anemia worldwide after nutritional anemia, includes the anemia of inflammation (AI) and that due to helminthiasis. In this review, we examine the contribution that non-nutritional anemia makes to incidence in Indonesia. Anemia due to helminthiasis is a common problem in Indonesia and contributes to prevalence, particularly in children under 5 years. We conducted a systematic literature review based on Google Scholar and Pubmed for non-nutritional anemia. We supplemented this with hemoglobin and chronic disease data in Makassar where prevalence and type of anemia were available. To effectively reduce anemia prevalence in Indonesia, interventions should address both nutritional and non-nutritional contributing factors, including infection and genetic predisposition.

Key Words: anemia of inflammation, helminthiasis, non-nutritional anemia, chronic disease, iatrogenic anemia

BACKGROUND

Anemia is a major public health problem in Indonesia.[1-3] Despite the various efforts of the Indonesian government, such as providing iron and folic acid supplements to pregnant women and food fortification, anemia prevalence has remained high.[4] Anemia typically presents as a symptom of a disease caused by various factors, including that that are nutritional and non-nutritional.[5] The primary causes of nutritional anemia include low nutrient intake but may also be nutritionally responsive and secondary.[6] The secondary causes include impaired absorption, blood transport, metabolism, and storage of nutrients. Because genetic factors underlie the secondary causes, their pathomechanisms are increasingly being delineated through nutrigenomics. For instance, gene polymorphisms affect nutrient metabolism, causing variations in the nutritional requirements for erythrocyte formation. Therefore, to prevent anemia, individuals with such gene variants are required to consume certain nutrients at levels higher than the recommended daily allowance.

Anemia of inflammation (AI) and iron deficiency (ID) anemia (IDA), the two most common forms of anemia worldwide, often coexist in developing countries where the prevalence of malnutrition and infectious disease is typically high.[7] AI is a frequently reported anemia in hospitalized patients and those with ***chronic, metabolic, or infectious disease***. AI prevalence typically increases along with that of its associated diseases including diabetes mellitus (DM), CVD, cancer, tuberculosis (TB), malaria[8] and HIV infection in Indonesia. Obesity, the metabolic syndrome, type 2 DM (T2DM) and CVD are also associated with anemia. In addition, Anemia is also a key feature of ***chronic kidney disease (CKD)***, itself a serious complication of T2DM and hypertension.

Helminthiasis is endemic disease in Indonesia (particularly in <5-year-old children), and contributes to anemia. Therefore, for comprehensive anemia management, the health authorities, systems and workers must identify and mitigate the underlying non-nutritional factors. Intersectoral and eco-nutritional approaches are needed to resolve persistent anemia in Indonesia.[1]

This systematic review discusses AI pathomechanisms and prevalence in Indonesia and globally. Several Indonesian studies, not only of anemia in infectious, chronic, and metabolic disease, but also in helminthiasis are considered. The genetic variations contributory to nutrient absorption, transport, metabolism, and storage and to erythropoiesis are considered.

Corresponding Author: Dr Agussalim Bukhari, Faculty of Medicine, Universitas Hasanuddin, Jl. Perintis Kemerdekaan Km. 10 Tamalanrea, Makassar 90245, Indonesia.
Tel: +62411591236
Email: agussalim.bukhari@med.unhas.ac.id
Manuscript received and initial review completed 19 December 2020. Revision accepted 24 December 2020.
doi: 10.6133/apjcn.202012_29(S1).05

METHODS

We searched the PubMed databases as well as Google Scholar and Google search engines for relevant literature using the following keywords: "anemia," "hemoglobin," "inflammation," "kidney," "obesity," "chronic disease," "heart failure," "helminthiasis," "tuberculosis," "HIV," and "Indonesia." Original articles published in both international and Indonesian journals, unpublished theses, and registry data were selected. In total, 39 Indonesian studies from Indonesian journals (35 studies) and university theses (4 studies) were finally included. Internationally published articles on AI in Indonesia were scant. The studies were typically cross-sectional or descriptive, with some o only reporting the proportions or mean hemoglobin levels without describing anemia type. Anemia in helminthiasis data were mostly observational, conducted in Indonesia and published variously in international and Indonesian journals. The definitions of anemia varied with different cutoff points for hemoglobin.

We also obtained data for Makassar from patients of the Clinical Nutrition Department, Universitas Hasanuddin affiliated to the Dr. Wahidin Sudirohusodo Hospital, in Makassar, Indonesia from July 2019 to September 2020.

INFLAMMATION

AI most commonly presents as a mild-to-moderate ***normocytic normochromic anemia,*** which is caused by systemic inflammation that inhibits erythrocyte formation and survival. In AI, hemoglobin rarely drops below 8 g/dL. In contrast to IDA, which is characterized by low serum iron and ferritin, AI exhibits low serum iron but normal or high serum ferritin levels. This phenomenon may be due to the iron redistribution in AI shifting from the location of utilization to that of storage, particularly in the hepatic and splenic mononuclear phagocyte system.[9]

AI is commonly found in patients with chronic systemic inflammatory conditions including both infectious and noninfectious diseases. Thus, AI is typically associated with chronic systemic inflammatory diseases including TB, malaria HIV, acquired immunodeficiency syndrome (AIDS), immune-mediated diseases (e.g., systemic lupus erythematosus), cancerous and hematological malignancies, obesity, T2DM, anemia in elderly persons, anemia in critical illness, congestive heart failure, CKD, and chronic pulmonary diseases.[10]

Tropical infectious diseases, which are typically acute (e.g., typhoid fever), are highly prevalent infectious diseases in Indonesia. The prevalence of other acute infectious diseases, such as diphtheria, pertussis, and morbilli, is extremely low due to successful vaccination by the Indonesian government. However, the prevalence of chronic infectious diseases such as TB and chronic hepatitis remains high, both in children and adults. In Indonesia, the highest prevalence of infectious diseases is seem with upper respiratory tract infection, diarrhea, and pneumonia (4.4%–9.3%, 6.8%–8%, and 2%–4%, respectively), followed by filariasis, pulmonary TB, hepatitis, and malaria (0.8%, 0.42%, 0.39%, and 0.37%, respectively (Indonesian Basic Health Research Data, 2018).[4]

Pathophysiology

Inflammation that occurs in both infectious and noninfectious diseases can lead to increased levels of cytokines, particularly tumor necrosis factor (TNF)-α, interferon (IFN)-γ, interleukin (IL)-1, and IL-6. IFN-γ elicits leucocyte proliferation, thus activating macrophages to phagocytose erythrocytes and shortening the erythrocyte life; TNF-α inhibits erythroid precursor proliferation; and IL-6 promotes liver hepcidin synthesis.[11,12] Moreover, proinflammatory cytokines suppress erythropoietin production; this natural mechanism reduces iron availability in the blood to inhibit the survival and reproduction of microorganisms that use iron. Although this adaptative mechanism is beneficial in mitigating acute infections, its chronic continuation in chronic infections can lead to AI and disrupt metabolism.[11]

In plasma, iron binds to transferrin, which carries it to the bone marrow for hemoglobin synthesis. Hepcidin is an iron-regulating hormone that binds to ferroportin to block the iron transfer from duodenal enterocyte cells, macrophages, and liver cells to blood plasma. Under normal conditions, hepcidin synthesis is regulated by the number of iron stores and serum iron levels. However, in low-grade chronic inflammatory conditions such as those in obesity and anemia, increased hepcidin levels have been reported worldwide, including in Indonesia.[13] Hepcidin also worsens impaired renal function and is associated with inflammation.[14]

AI is typically normocytic and normochromic, which means that AI exhibits normal erythrocyte size and normal hemoglobin content (Table 1). In some cases, particularly those of chronic inflammation, AI may be microcytic (small erythrocyte size) and hypochromic (low hemoglobin content).[7]

CHRONIC AND METABOLIC DISEASE

Noncommunicable diseases (NCDs) or chronic diseases result from a combination of factors including those that are genetic, behavioral, and environmental. In Indonesia, hypertension and T2DM incidence is 84 and 20 per 1000 population, respectively.[4] The prevalence of anemia in some chronic diseases among the patients from our department is illustrated in Figure 1.

The prevalence of obesity, a major risk factor for metabolic syndrome, has also increased considerably in Indonesia (Table 2A). In adults, central obesity prevalence

Table 1. Differences in IDA and AI biomarkers

Biomarker	Iron deficiency anemia (IDA)	Anemia of inflammation (AI)
Mean corpuscular volume	Low	Normal
Mean hemoglobin volume	Low	Normal
Reticulocyte hemoglobin content	Low	Normal
Serum transferrin	High	Low
Serum transferrin receptor	High	Normal
Serum ferritin	Low	High
Serum hepcidin	Low	High

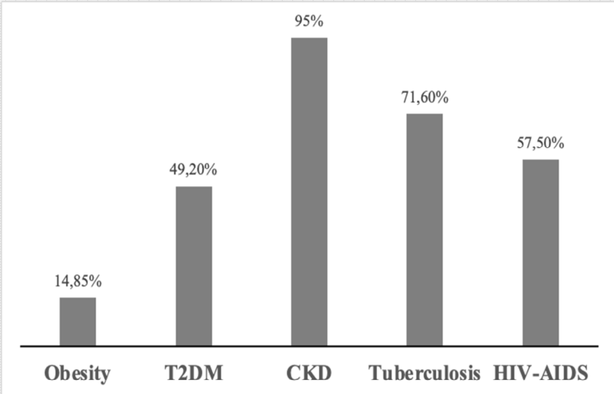


Figure 1. AI prevalance in patients at Dr. Wahidin Sudirohusodo Hospital, Makassar, Indonesia.

has reached 31%—exceeding the global obesity and overweight prevalence (13% and 39%, respectively).[15] This means that 1 in 3 Indonesian adults has central obesity and thus has an increased metabolic syndrome risk compared with general population.[4]

Corresponding to the increasing national prevalence of obesity reported in Indonesian Basic Health Research (Riskesdas) 2018,[4] Herningtyas et al also found a high metabolic syndrome prevalence (21.7%) among 8573 individuals from 20 provinces and of 27 ethnicities in Indonesia—with the most common metabolic syndrome components being a low HDL concentration and hypertension.[16]

The obesity–ID association has been discussed previously.[17,18] Obesity induces inflammation, thereby increasing the cytokine and hepcidin levels and thus promoting the sequestration of iron in the mononuclear phagocytes system, particularly in the liver and spleen, and reducing iron absorption in the gut.[13]

In four extracted studies including obese individuals,[19-22] the average anemia incidence was 14.85% (range: 6.9%–30%), but not all studies mentioned the anemia type (Table 2B): Wijayanti et al[19] found 12% (4.3% men and 23.8% women) of the included 50 obese individuals to have anemia, but they neither detailed the type of anemia observed nor included nonobese controls in their study. Although obesity is associated with ID, anemia prevalence was lower in obese individuals than in their normal-weight counterparts.[20,21,23] In some conditions, micronutrient deficiency, such as vitamin B-12 or folate deficiency, inflammation, sickle cell disease, bone marrow disorders, thalassemia, and other hemolysis types, might contribute to total anemia.[23,24]

In a Taiwanese study, Huang et al[25] reported BMI to be positively associated with hemoglobin levels, meaning that the BMI the lower is, the higher is the risk of anemia. Moreover, BMI is correlated positively with serum ferritin levels but inversely with serum iron levels. Hence, the BMI–IDA association can be defined to be similar to the definition of IDA.

Moreover, in two Indonesian studies, the anemia prevalence was higher in nonobese individuals than in obese

Table 2A. Obesity by BMI for age groups in Indonesia[1]

No	Age group	Prevalence (%)	CI 95%
1	Children 5–12 years old†	9.2	9.0–9.5
2	Adolescent 13–15 years old†	4.8	4.6–5.1
3	Adolescent 16–18 years old†	4	3.8–4.3
4	Adult >18 years old	21.8	21.7–22.0
5	Adult with Central Obesity	31	30.8–31.2

†Body mass index for age obesity Z score was used.

Table 2B. Anemia in obesity in Indonesia

No	Author	Population	Study design	Anemia prevalence (%)
1	Wijayanti et al., 2018[19]	50 obesity patients. No nonobesity controls	Cross-sectional study	12%
2	Heryati et al., 2014[20]	38 elementary school students with overweight and obesity and 62 students with normal nutritional status	Cross-sectional study	10.5% of obese students 21% in normal nutritional status students
3	Sukarno, Marunduh, Pangemanan, 2016[21]	29 subjects with BMI >25 kg/m^2 31 subjects with BMI <25 kg/m^2	Cross-sectional study	6.9% in obese subjects 15.78% in BMI <18.5 8.33% in BMI 18.5–24.9
4	Nisa, Nissa, Probosari, 2019[22]	30 obesity and 30 non-obesity (based on BMI over age) patients age 15–18 years old	Cross-sectional study	30% in obese subjects and 30% in nonobese subjects

Table 3. Anemia in T2DM in Indonesia

No	Author	Population	Study design	Anemia prevalence (%)
1	Wijaya et al., 2015[26]	46 patients with T2DM with mildly to severely impaired renal GFR (Data from the medical records)	Cross-sectional study	80.4% total anemia, 26.1%, 39.1, 15.2% in mildly, moderately, and severely impaired GFR, respectively
2	Wijaya et al., 2014[27]	192 T2DM patients in RSUP Sanglah Hospital, Bali (Data from the medical record)	Cross-sectional study	Total anemia 41.67%, mild anemia 76.25%, moderate anemia 21.25%, severe anemia 2.5%
3	Balela, Arifin, Noor, 2014[28]	78 T2DM patients	Cross-sectional study	57% in patients with T2DM <5 years 86% in patients with T2DM ≥5 years

GRF: glomerular filtration rate; T2DM: type 2 diabetes mellitus.

individuals: Heryati et al[20] found that among elementary students (aged 10–12 years), anemia was present in 21% of those with normal nutritional status and in only 10.5% of those overweight and obese. Among adults, Sukarno et al. found that nonobese participants with a BMI of <18.5 and 18.5–24.9 kg/m^2 had an anemia prevalence of 15.78% and 8.33%, respectively, whereas obese participants with a BMI of >25 kg/m^2 had an anemia prevalence of only 6.9%.[21] However, none of these studies performed any serum iron assessments. Hence, future studies investigating the iron status–obesity association in Indonesia are warranted.

Type 2 diabetes mellitus

In the Indonesian Basic Health Research in 2018, T2DM prevalence in individuals aged >15 years was 2%[4] based on diagnoses made by a physician—higher than the 2019 global T2DM prevalence (estimated to be 9.3% [i.e., 463 million persons]).[29]

Moreover, the prevalence of AI in T2DM was high in Indonesia: 27.9% and 33.4% in well-controlled and poorly controlled T2DM, respectively.[30] This trend accords with that found by another study: 50 (34%) of 146 patients with T2DM had anemia.[31]

Both obesity and T2DM are associated with low-grade chronic inflammation.[32] In addition, hyperglycemia in T2DM can lead to increased free radical production and worsened inflammation.[33] Hyperglycemia is directly associated with the development of inflammation, as shown by increased levels of proinflammatory cytokines such as IL-6, TNF-α, and nuclear factor κB.[31] Increased IL-6 concentration can lead to a reduction in the sensitivity of the erythrocyte progenitor to erythropoietin and induce apoptosis in immature erythrocytes, in turn reducing the hemoglobin concentration.[34,35]

Studies on anemia in T2DM in Indonesia have generally focused on patients who have experienced complications in the kidney such that the cause of anemia is a combination of inflammation and impaired erythropoietin production.[26-28] The anemia incidence can increase up to 80% with increases in disease duration and kidney disorder severity.[26,28] Based on the Indonesian studies (Table 3), the average prevalence of anemia in T2DM is 49.2%.

In the data on anemia in T2DM obtained from our department patients (Table 4), the prevalence of anemia in T2DM was 79.6%—higher than the prevalence indicated by the national data. The reason for this phenomenon may be the following: as a referral hospital, our hospital receives patients with high-severity T2DM. According to our data, of 93 patients with T2DM, 74 (62.8%) patients had anemia. Of these, 58 (78.3%) had normocytic normochromic anemia, 8 (10.8%) had microcytic hypochromic anemia, 7 (9.5%) had microcytic normochromic anemia, and 1 (1.4%) had macrocytic hypochromic anemia. Our study were was in line with the 2019 study of Saraswati et al[30] in Indonesia: even when the HbA1c levels indicated severe T2DM, the mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration were normal; moreover, the mean hemoglobin concentration was 13.5 (range: 8.3–17.7) g/dL.

Normocytic normochromic anemia is a common type of anemia in chronic diseases due to the erythrocyte lifecycle being shortened to 80 days in these diseases; moreover, the circulating erythrocyte removal process is related to inflammatory processes.[31]

Chronic kidney disease

Anemia in CKD was initially considered to be associated with impaired erythropoietin production, and thus, it was not considered to be AI. However, recently, inflammation was found to be involved in anemia in CKD. Inflammation increases hepcidin synthesis, promotes erythrophagocytosis, suppresses erythropoiesis in the bone marrow, and reduces erythropoietin production in the kidney. According to the 11th Report of the Indonesian Renal Registry, 78% of patients with CKD had hemoglobin concentrations <10 g/dL.[39] Patients with CKD have the highest rate of anemia, among other chronic metabolic diseases, particularly at the advanced CKD stage, reaching up to 95% (Table 5).[36-40] Minhajat et al[38] found that 95.38% of patients with CKD had anemia, most (88.56%) of whom were at CKD stage 5. Normocytic normochromic anemia was the predominant (66.13%) type of anemia in CKD, consistent with a characteristic of AI. However, microcytic hypochromic anemia was noted only in 13.71% of the patients.

Cardiovascular disease

According to the 2018 Indonesian Basic Health Research (Riskesdas),[4] CVD prevalence in Indonesia is 15 per 1000 population. In their 2018 Indonesian study, Dzakiyah et al[41] found the prevalence of anemia in chronic heart failure to be 37.5%, with most (78.1%) of the participants having NYHA Functional Class III heart failure. The

Table 4. Prevalence of anemia in various diseases in patients at Dr. Wahidin Sudirohusodo Hospital, Makassar, Indonesia

Disease	n	Mean hemoglobin (g/dL)	Prevalence of anemia (%)	Type of anemia
Malignancy	92	8.1	88	70.4% Normocytic normochromic 12.4% Microcytic hypochromic 3.7% Normocytic hypochromic 1.2% Macrocytic hypochromic 12.3% Microcytic normochromic
Tuberculosis	28	11.1	67.8	57.9% Normocytic normochromic 10.5% Microcytic hypochromic 21% Normocytic hypochromic 5.2% Macrocytic hypochromic 5.2% Microcytic normochromic
HIV	58	10.4	89.6	80.7% Normocytic normochromic 9.6% Microcytic hypochromic 1.9% Normocytic hypochromic 3.8% Macrocytic hypochromic 3.8% Microcytic normochromic
Cardiovascular disease	105	11.7	62	67.9% Normocytic normochromic 29.3% Microcytic hypochromic 3% Normocytic hypochromic
T2DM	93	11.1	79.6	78.4% Normocytic normochromic 10.8% Microcytic hypochromic 9.4% Microcytic normochromic 1.3% Macrocytic hypochromic

T2DM: type 2 diabetes mellitus.

prevalence of anemia in heart failure regardless of the ejection fraction is up to 30% in outpatients and up to 50% in hospitalized patients. Anemia is associated with mortality in heart failure, with a crude mortality risk of up to 1.96. Moreover, in heart failure, anemia might be caused by several neurohormonal activations, which increase inflammatory cytokine levels, resulting in functional ID. Moreover, heart failure can cause renal dysfunction and thus eventually affect erythrocyte production. Loss of appetite in heart failure is also a common finding that leads to absolute ID. Finally, fluid retention can cause hemodilution, which in turn results in reduced hemoglobin concentrations.[42,43]

In our collected patient data, the prevalence of anemia in CVD (including heart failure and myocardial infarction) was 62% (Table 4). Of the 105 patients admitted to the cardiovascular ward, 65 (62%) patients had anemia, of whom 44 (67.7%) had normocytic normochromic anemia, 19 (29.2%) had microcytic hypochromic anemia, and 2 (3%) had normocytic hypochromic anemia. Therefore, in CVD, the predominant type of anemia was normocytic and normochromic—consistent with the characteristics of AI.

Because ID prevalence potentially contributes to ane-

Table 5. Anemia in CKD in Indonesia

No	Author	Population	Study design	Prevalence
1	Adiatma DC et al., 2014[36]	35 CKD patients with hemodialysis. stage 1-4 CKD 29%, stage 5 CKD 71%	Cross-sectional study	Total anemia: 86%, anemia of chronic disease 80%, IDA 10%, hemolytic anemia 3.3%, posthemorrhagic anemia 6.7%
2	Aisara S, Azmi S, Yanni M. 2018[37]	104 CKD patients with HD	Observational-descriptive study	Hb <7: 6.7% Hb 7-10: 68.3% Hb >10: 25%
3	Minhajat, 2016[38]	130 CKD patients stage 3b (2 pts), stage 4 (8 pts) stage 5 (120 pts), 43% with HD in RSUP dr. Wahidin Sudirohusodo Makassar	Cross-sectional study	Total anemia: 95.38% (88.56% in stage 5) Normocytic normochrom: 66.13% Microcytic hypochromic: 13.71%
4	PERNEFRI. 11th Report of Indonesian Renal Registry, 2018[39]	87,710 chronic kidney disease patients	Registry	Hb <10: 78% Hb >10: 22%
5	Suega K, Bakta M, Dharmayudha TG et al. 2005[40]	26 CKD-dialytic patients 26 CKD-predialysis patients	Cross-sectional study	96.2% in dialytic group 30.8% in the predialysis group

CKD: Chronic Kidney Disease; IDA: Iron Deficiency Anemia; HD: Hemodialysis; RSUP: Rumah Sakit Umum Pusat (Central General Hospital); PERNEFRI: Perhimpunan Nefrologi Indonesia (Indonesian Nephrology Association); Hb: Hemoglobin.

mia in heart failure, further relevant studies are recommended.

CANCER

In cancer, anemia can occur independently due to chemotherapy, typically as a consequence of chronic inflammation, and its features can resemble those of anemia in chronic inflammatory diseases. In most cases, anemia in cancer is normochromic and normocytic, with normal-to-low serum iron levels, low total iron-binding capacity,[44] and possibly, normal-to-high serum ferritin levels.

In an Indonesian study,[45] 50% of the four hematology and lymphoma malignancy cases had anemia; moreover, 47.8% of patients with solid cancer had anemia, and the factor that significantly influenced the hemoglobin concentration was radiotherapy dose: when the dose was <60 and >60 Gy, anemia prevalence was 29.4% and 57.6%, respectively. However, in 2002, Harrison et al[46] found that 41% of patients with cancer has anemia before radiotherapy initiation, and this number increased as radiotherapy progressed. Moreover, anemia prevalence was the highest in patients with uterine or cervical cancer both before and after radiotherapy (75% and 79%, respectively), and patients with head and neck cancer had the lowest mean hemoglobin concentrations during radiotherapy (1.8 g/dL).

According to our data on department patients with malignancies such as colon cancer, head and neck cancer, and ovarian cancer, the prevalence of anemia in cancer was 88% (Table 4). Of 92 patients with malignancy, 81 (88.1%) had anemia, of whom 57 (70.4%) had normocytic normochromic anemia, 10 (12.3%) had microcytic hypochromic anemia, 3 (3.7%) had normocytic hypochromic anemia, 10 (12.3%) had microcytic normochromic anemia, and 1 (1.2%) had macrocytic hypochromic anemia. Thus, our data indicated that the most common type of anemia in cancer was normocytic and normochromic—the typical AI.

TUBERCULOSIS

The highest TB burden in the world is in India, followed by China and Indonesia.[47] Indonesia has a pulmonary TB prevalence of 0.4%.[4] As a disease involving chronic inflammation, the incidence of anemia in TB is high. Pulmonary TB can be characterized by several inflammatory markers, such as C-reactive protein (CRP) and other cytokines (i.e. IFN-γ, IL-6 and TNF-α). Hence, in patients with pulmonary TB, anemia may be caused by AI, blood loss, hemoptysis, malnutrition, and pyridoxin deficiency (a side effect of isoniazid).[48]

Of all studies found in our literature search, most (n=13) were discussed anemia in patients with pulmonary TB (Table 6). The average prevalence of anemia in pulmonary TB was 50%–70%, including that of normocytic normochromic and microcytic hypochromic anemia being 5.8%–54.8% and 47%–81.48%, respectively (Table 6).[48-60] In Indonesia, in addition to inflammation, a combination of many factors such as low protein and micronutrient intake can contribute to anemia.

In one study,[61] the use of antimicrobial agents in patients with anemia in pulmonary TB completely alleviated the anemia in nearly one-third of the patients after 1 month of treatment and in approximately half of the patients after 2 months of treatment.

In the extracted Indonesian studies, the average prevalence of anemia in TB was 71.6%. In our department patients with pulmonary TB, anemia prevalence was 67.9%. Of 28 patients with pulmonary TB, 19 (67.9%) had anemia, of whom 11 (39.2%) had normocytic normochromic anemia, 4 (14.2%) had normocytic hypochromic anemia, 2 (7.2%) had microcytic hypochromic anemia, 1 (3.6%) had macrocytic hypochromic anemia, and 1 (3.6%) had microcytic normochromic anemia. In 2019, Mukherjee et al[63] also found normocytic normochromic anemia to be the predominant type of anemia in pulmonary TB, with a prevalence of 56.9%.

HIV/AIDS

In 2018, Indonesia had 640 000 individuals living with HIV, and it had an HIV infection prevalence of 0.17% among all age groups and of 0.4% among adults.[62] In 2017, the number of new HIV cases was 1.94 million globally. Although the number of new cases has decreased recently, the increased use of antiretroviral therapy has increased patient survival and in turn increased HIV prevalence (with 35.8 million individuals living with HIV).[63]

Being an infectious disease, HIV/AIDS also leads to AI in many patients (prevalence reaching 76%; Table 7).[64-67] In the Indonesian studies, the average prevalence of anemia in HIV/AIDS was 57.5%. In our department patients (Table 4), the prevalence of anemia in HIV/AIDS was 89.6% (the relatively high prevalence might be due to the generally high disease severity among our referral hospital's patients). Of all 58 patients with HIV/AIDS, 52 (80%) had anemia, of whom 42 (80.7%) had normocytic normochromic anemia, 5 (9.6%) had microcytic hypochromic anemia, 2 (3.8%) had macrocytic hypochromic anemia, 2 (3.8%) had microcytic normochromic anemia, and 1 (1.9%) had normocytic hypochromic anemia. Consistent with other worldwide reports, we also found normocytic normochromic anemia to be the predominant type of AI.

PREGNANCY

Anemia in pregnancy is common worldwide, particularly in developing countries.[5] In Indonesia, the prevalence of anemia in pregnancy (at age >15 years) was 45.1% in 1997; it then increased to 46.5% in 2000, decreased to 37.5% in 2008,[68] and finally, increased again to 48.9% in 2018.[4] The etiology of anemia in pregnancy is multifactorial. However, in general, ID is assumed to be the major cause[69,70] because anemia diagnosis is generally based on hemoglobin measurement alone. Other possible etiologies of anemia include erythrocyte disorders (e.g., thalassemia), malaria, inflammatory diseases, hookworm infestation, and other micronutrient deficiencies, which may be significant factors depending on the geographic setting and population type.[70]

More detailed laboratory examinations are required to distinguish the underlying etiologies. In their study on 399 women in the first trimester of pregnancy, Siridamrongvattana et al[71] found an unexpectedly low prevalence of anemia (19.3%), ID (20.1%), and IDA (6%); of the 77

Table 6. Anemia in pulmonary TB in Indonesia

No	Author	Population	Study design	Anemia prevalence
1	Kalma et al., 2019[49]	21 samples, including seven patients with treatment of 2 months, seven patients with treatment of 4 months, and seven patients with treatment of 6 months at Maccini Sawah Public Health Centre Makassar	Cross-sectional study	Normal hemoglobin level (42.86%) and anemia (57.14%).
2	Sundari et al., 2017[54]	74 pulmonary TB-infected patients: 61% men, 39% women; ages ranged from 18 to 63 (32.6 + 12.2) years; 24 (32%) with the Beijing strain, and 50 (68%) with non-Beijing strain infections.	Cross-sectional study	Hemoglobin level ranged from 8.6 to 14.8 (11.8) g/dL and 8.1 to 16.5 (12.0) g/dL for the Beijing strain and non-Beijing strain, respectively, with more anemia found in Beijing strain patients (71%) than non-Beijing strain (62%) patients.
3	Adzani, Dalimoenthe, Wijaya, 2016[48]	49 pulmonary TB patients	Cross-sectional study	Total: 63.26% of patients with anemia. In men: mild anemia 57.14%, moderate anemia 42.86%; in women: mild anemia 58.82%, moderate anemia 41.18%. In men: 42.86% normochromic normocytic, 42.86% hypochromic microcytic, 7.14% normochromic microcytic, and 7.14% hypochromic normocytic; in women: 5.88% normochromic normocytic, 47.06% hypochromic microcytic, 17.65% normochromic microcytic, 29.41% hypochromic normocytic.
4	Sadewo et al., 2014[55]	692 pulmonary TB patients in West Borneo (2010–2012)	Cross-sectional study	76.4% anemia -59.1% mild anemia -54.8% normocytic normochromic anemia
5	Lasut et al., 2014[56]	67 patients with pulmonary TB at Prof. Dr. R. D. Kandou Manado General Hospital (January 2014–December 2014)	Cross-sectional study	Among 67 patients, 45 patients had hemoglobin levels below the normal value or anemia (65.67%)
6	Fauziah et al., 2013[57]	30 patients with pulmonary TB, 15 men and 15 women (Haji Abdul Halim Hasan Public Health Centre Binjai)	Cross-sectional study	Hemoglobin level before treatment: men: 15.4±0.68, women: 12.94±0.33. After 3 months of treatment, men: 11.88±0.52, women: 10.42±0.44.
7	Fathan et al., 2013[58]	61 pulmonary TB patients in West Nusa Tenggara Barat Province Hospital	Case–control study	Total anemia: 78.7%; normocytic normochromic: 19.52%; microcytic hypochromic: 81.48%
8	Lokollo et al. 2010[59]	22 pulmonary TB patients aged 1–14 years in Kariadi Hospital Semarang	Case–control study	40.9% with anemia
9	Purnasari et al., 2011[60]	30 pulmonary TB child patients at Community Pulmonary Health Center (BKPM) Semarang in Jun–Jul 2011. Patients aged 1–11 years	Cross-sectional study	43.3% of pulmonary TB pediatric patients were anemic. Anemia of chronic disease was found at 61.5%, and iron deficiency anemia at 38.5%.
10	Pramono & Meida, 2003[50]	66 pulmonary TB patients; 43 men, 23 women, PKU Muhammadyah Hospital, Yogyakarta	Cross-sectional study, retrospective from medical records (2000)	65.15% anemia: 100% men, 0% women
11	Karyadi, 2000[51]	41 active TB patients (25 men, 16 women) in Cipto Mangunkusumo Hospital and 41 healthy participant (25 men, 16 women)	Case–control study	58.5% TB patients had anemia; 21.9% healthy controls had anemia. TB patients had mean hemoglobin concentrations 13% lower than healthy controls and 11% lower median hematocrit.
12	Karyadi, 2002[52]	110 TB patients before antituberculosis treatment	Double-blind, placebo-controlled trial	57% TT patients before antituberculosis treatment

TB: Tuberculosis; BKPM: Balai Kesehatan Paru Masyarakat (Community Pulmonary Health Center).

Table 7. Anemia in HIV/AIDS in Indonesia

No	Author	Population	Study design	Anemia prevalence
1	Wisaksana et al., 2011[66]	611 HIV/AIDS patients – ART naïve	Cross-sectional study	Total anemia: 49.6% of 611 ART-naïve patients. Mild anemia: 62%, mod–severe anemia: 38% 67.36% with a high ferritin level
2	Yolanda, 2016[67]	201 HIV/AIDS patients who underwent voluntary counseling and testing	Cross-sectional	76% anemia 5.5% pancytopenia
3	Massang, Edward, Purwanto, 2018[68]	68 HIV/AIDS patients, 34 with Antiretroviral agents and 34 without Antiretroviral agent; nutritional anemia was excluded	Cross-Sectional	Total Median Hb: 11.7 g/dL Median Hb in ARV group: 10.60 Median Hb in non-ARV group 12.63
4	Defiaroza, 2018[69]	10 HIV/AIDS patients	Descriptive	Mean: 13 gr%, SD: 2.26 gr%

ART: Antiretroviral Therapy; ARV: Antiretroviral.

women with anemia, 24 (31.2%) had ID, 20 (26.0%) had thalassemia-related genes, and 33 (42.9%) had unknown underlying factors.

Pregnant women have been reported to have systemic low-grade inflammation,[72] which is correlated with AI.[9] However, Finkelstein et al reported a relatively low prevalence of inflammation (CRP >5 mg/L: 17%; ambulatory glucose >1.0 g/L: 11%) and AI (hemoglobin <11.0 g/dL and serum ferritin >15.0 µg/L plus CRP>5 mg/L or ambulatory glucose >1.0 g/L: 2%) in pregnant women.[73] Nevertheless, AI risk in pregnant women with chronic infectious or metabolic diseases may still be high.[9]

In 2018, Judistiani et al[74] found that 7.5% (201) of pregnant women had anemia, with 24.9% of them noted to have hyperferritinemia. Moreover, proinflammatory cytokine levels increased in women with late pregnancy.

However, the authors did not report any inflammatory markers and reported a positive correlation between ferritin status and anemia only in the first trimester. In addition, they reported that pregnant women with low cholecalciferol levels tended to have anemia, particularly in the third trimester (relative risk: 2.96; 95% CI: 0.36–24.53). Nevertheless, vitamin D deficiency is associated with inflammatory status, and supplementation can alleviate the inflammatory status in some diseases.[75]

HELMINTHIASIS

Infection by soil-transmitted helminths (STH; i.e., helminthiasis), including *Necator americanus* (hookworm), *Ascaris lumbricoides*, and *Trichuris trichiura*, represents a major community health concern in regions worldwide.[76] The pathological process underlying the host response for helminthiasis may lead to inflammatory conditions.[77] In helminthiasis, altered intestinal iron uptake and iron metabolism and intestinal bleeding can lead to ID.[78,79] Moreover, the destruction of the intestinal mucosa impedes the absorption of nutrients, including micronutrients such as iron, negatively affecting the host's nutritional status and immune system.[80]

Globally, a main cause of IDA is infection by parasites such as hookworms, whipworms, and roundworms, which results in intestinal bleeding in the stool.[81] Hookworm infection leads to anemia by inducing chronic intestinal blood loss: infection by *Ancylostoma duodenale* and *N. americanus* can cause blood loss of 0.15–0.2 mL per day. These hookworms release anticlotting factors such as coagulase to prevent blood clots and ensure continuous blood flow.[82]

Disruption of iron absorption can also be due to damage to the intestinal integrity caused by the inflammatory process. Helminthic infection can increase inflammation: in a host, the existence of helminths is detected by the epithelial or immune cells in response to worm products; these cells then release cytokines (e.g., IL-25) from the enterocytes, promote Th2 cell proliferation, and upregulate effector mechanisms (e.g., evocation of eosinophils by IL-5), all to destroy the parasite. However, the helminths manipulate the host immune system by releasing molecules to facilitate the formation of a leaky epithelial barrier.[83] In general, this damage to intestinal integrity can reduce intestinal iron uptake and induce anemia: in children with such parasitic infections, malnutrition may occur due to a lack of essential nutrients, resulting in nutritional anemia.[84]

Prevalence of anemia due to helminthiasis in Indonesia

Approximately 42% of global STH infections occur in Southeast Asia. Of children with STH infections in Southeast Asia, 64% are from India, 15% from Indonesia, and 13% from Bangladesh. In Indonesia, 17 million preschool-age children and 42 million school-age children have an STH infection.[85] STH infection is thus one of Indonesia's leading public health issues, with a high prevalence in the range of 45%–65%. In Indonesia, the highest STH infection prevalence is 80%, mainly in areas with poor sanitation.[86] In a cross-sectional survey in Semarang, Central Java, STH infection prevalence was approximately 34% in 6466 individuals aged 2–93 years.[87] Pegelow et al[88] reported that soil-transmitted nematode infection was predominant in 8–10-year-old children in the rural area of Sukaraja, West Java: based on the testing of 348 stool samples, *T. trichiura* infection was the most prevalent (76%), followed by *A. lumbricoides* (44%) and hookworm (9%) infections. Among 365 blood samples, anemia prevalence was 13%. Moreover, the prevalence of low nutritional status was 51% in general. Table 8 lists the prevalence of anemia in helminthiasis in Indonesia from several studies.[88-98]

In several districts of North Sumatra, helminthiasis prevalence differed considerably between suburban and rural areas. A report from Medan, North Sumatra, reported a high STH infection prevalence in school-age chil-

Table 8. Anemia in Helminthiasis in Indonesia

No	Population/Location	Lab examination	Prevalence (%)					
			Any†	HK	AL	TT	SS	Anemia
1	60 students from five grade 3 and 4 elementary schools in North Pontianak, West Kalimantan[91]	Kato–Katz thick smear Blood tests	16.7					55
2	140 stools of school-age children, Makassar Sulsel[93]	Katokatz method	33.6		24.3	27.9		
3	A total of 331 individuals, aged 1 month to 44 years, Mimika Papua[94]	A single stool sample, using Real Time-Polymerase Chain Reaction for SS		17.2	23.9	18.4	32	
4	132 students, aged 8–12 years, Medan and Deli Serdang Sumut[89]	Direct examination and Kato–Katz method Cobas e601 in the hematology laboratory	7.6					11.4 (serum iron)
5	3 to 70 years Controls: n=244; intervention: n=283 Two villages, Central Java, Indonesia[95]	Microscopically, according to the Willis-Mollay flotation technique	STH: 21.7% in controls and 25.8% in the interventional group					
6	629 children aged 1–59 months from 800 households Mimika Papua[92]	Katokatz method Hb by electronc coulter counter (HB <10 gr/dL = anemia)	37.9 (105/269)	13	27.9	20.8		24.5 (122/497)
7	99 children (3–13 years old) in two villages (intervention and control) south of Semarang City[96]	Microscopic method	20					
8	418 boys and girls aged 0 to 12 years at recruitment[97]	Katokatz method Hb		-	30.6	23.4		22.4
9	8 to 10-year-old students from 10 schools located in the rural district of Sukaraja, West Java, Indonesia[88]	348 stools 365 blood samples		9	44	76		13
10	Two elementary schools in Makassar, the capital city of South Sulawesi[98]	340 stools from individuals of high socioeconomic status 271 stools from individuals of low socioeconomic status Katokatz method	22.4 vs 90.4		5.9 vs 76.8	19.1 vs 87.1		
11	1982 people assigned to albendazole treatment and 2022 to a placebo Ende, East Nusa Tenggara[90]	Polymerase Chain Reaction for HW and AL, microscopic for TT	Baseline Placebo vs Albendazole Any helm 87.2 (571/655) vs 87.7 (533/609) HK 74.5 (509/683) vs 77.3 (486/629) AL 34.9 (238/683) vs 33.2 (209/629) TT 27.1 (258/953) vs 27.8 (237/852)					

†Any: any helminthiasis. HK: hookworm; AL: *Ascaris lumbricoides*; TT: *Trichuris trichiura*; SS: *Strongyloides stercoralis.*

dren (40.3%).[89] Nasution et al[99] reported that STH infection prevalence was 76.8% in Singkuang (56 children) and 87.2% in Sikapas (242 children) primary schools: the prevalence of *A. lumbricoides* infection was 58.9% in Singkuang and 69.8% in Sikapas, that of *T. trichiura* infection was 57.1% in Singkuang and 78.1% in Sikapas, and that of hookworm infection was 1.8% in Singkuang and 19.4% in Sikapas. A consecutive fecal analysis of 132 8–12-year-old students during May–October 2016 in Public Primary School 060925 Amplas, Medan, and 101747 Hamparan Perak, Deli Serdang, indicated that the prevalence of helminthiasis was 7.6%, with that of low serum iron levels being 11.4%.[89]

In North Pontianak, West Kalimantan, helminthiasis was noted in 16.7% of 60 elementary school students, with an anemia prevalence of 55%.[91] In Mimika, Papua, helminthiasis was present in 105 (43%) of 269 children. Anemia (defined as hemoglobin <10 g/dL) was noted in 122 (24.5%) of 497 included children and was associated with hookworm carriage (OR: 2.6, p=0.026) and *Plasmodium*–helminth coinfection (OR: 4.0, 95% CI: 1.4–11.3, p=0.008).[92]

A cohort study[100] on 442 pregnant women in Purworejo District, Central Java, reported that the anemia prevalence was the highest in the second trimester (approximately 37.1%). Moreover, low iron stores were noted in approximately 49.5% women in the third trimester. Most of the included pregnant women (69.7%) were infected with at least one species of intestinal helminths; *T. trichiura* was the most common, followed by hookworm and *A. lumbricoides*.

OTHER CAUSES OF NON-NUTRITIONAL ANAEMIA

Genetic factors

Genetic disorders can also lead to non-nutritional anemia. Iron absorption may be impaired due to genetic abnormalities in the metal divalent transporter-1 gene (*MDT1*). Mutations in *MDT1* have been noted in patients with microcytic anemia, low serum ferritin levels, and liver iron overload.[101] After the iron is absorbed, it is carried by transferrin (TF) in the blood to the liver storage areas, spleen, red bone marrow, and tissues with demand for iron.[102,103] Genetic abnormalities in the TF gene can cause atransferrinemia and IDA.[104] Moreover, iron carried by TF enters the tissue after being captured by the TF receptor (TFR). Thus, genetic abnormalities in the TFR gene can also cause anemia.

Hepcidin, a regulator of iron levels in the body, inhibits iron absorption by binding to MDT-1. Hepcidin can also attach to ferroportin and block the release of iron from the macrophages to be carried to the site of erythrocyte synthesis. *TMPRSS6* encodes the enzyme maptriptase-2, which controls hepcidin levels and thus plays a role in the development of anemia. The G allele of rs4820268 is associated with low serum iron levels.[104]

Vitamin B-12 deficiency has been linked to many complications, including increased macrocytic anemia risk. In total, 16 studies have identified single-nucleotide polymorphisms (SNPs) that exhibit significant associations with vitamin B-12 concentrations; of these SNPs, 59 are vitamin B-12-related gene polymorphisms, which are thus associated with vitamin B-12 status. However, most of the genes that could explain variations in vitamin B-12 concentrations have been identified in Caucasian populations.[105]

Megaloblastic anemia involves disturbed DNA synthesis, which results in morphologic and functional changes in erythrocytes, leukocytes, platelets, and their precursors in the blood and bone marrow. This type of anemia is characterized by the presence of large, immature, abnormal erythrocyte progenitors in the bone marrow, and 95% of megaloblastic anemia cases are attributable to folic acid or vitamin B-12 deficiency.[106]

Methylenetetrahydrofolate reductase (MTHFR) and methionine synthase reductase (MTRR) are two important folate-metabolizing enzymes involved in the remethylation of homocysteine into methionine as well as in the synthesis of DNA.[107] The common polymorphisms in *MTHFR* (C677T and A1298C) and *MTRR* (A66G) result in reduced in vivo MTHFR and MTRR activity and thus in folate metabolism impairment. Zhang et al[108] found that *MTHFR* (C677T) is strongly correlated with megaloblastic anemia and might participate in its pathogenesis.

The risk of low iron status has been assessed based on a combination of rs3811647 in the TF gene, rs7385804 in the TRF gene, and rs4820268 in *TMPRSS6*; that of low folate status was assessed using the two common *MTHFR* polymorphisms, C677T and A1298C;[108] and that of low vitamin B-12 status was evaluated using rs1801131, rs2298585, rs41281112, and rs3760776. Citrate lyase beta-like (*CLYBL*) encodes a human mitochondrial enzyme. The risk allele A of rs41281112 terminates the translation of *CLYBL*, resulting in the disruption of protein–metal ion binding and leading to vitamin B-12 malabsorption. The rs2298585 in *MS4A3* might disrupt intestinal and gastric epithelial cells rejuvenation as well as vitamin B-12 absorption.

Gastric pathogens reduce vitamin B-12 absorption in the gut. *FUT6* encodes fucosyl-transferase 6, which is involved in forming Lewis-associated antigens, which inhibit the adherence of gastric pathogens to the gastric mucosa. A study showed that rs3760775 in *FUT6* was associated with elevated vitamin B-12 levels.[105]

Iatrogenic anemia

Drugs can induce anemia via several pathways: immunohemolytic anemia, nonimmune hemolytic anemia, methemoglobinemia, megaloblastic anemia, sideroblastic anemia, aplastic anemia, and pure red cell aplasia. Immuno-hemolytic anemia due to the destruction caused by the reaction between antibodies and antigens in the erythrocyte membrane (e.g., penicillins and cephalosporins). Non-immune hemolytic anemia is hemolytic anemia that is typically caused by side effects of drugs such as primaquine and nitrofurantoin; in these cases, glucose-6-phosphate dehydrogenase deficiency is common. Methemoglobinemia, which is anemia due to excessive methemoglobin production, can be induced by several drugs that oxidize hemoglobin (e.g., phenazopyridine, dapsone, primaquine, local anesthetics, isobutyl nitrite). Acquired megaloblastic anemia can be caused by vitamin B-12 with or without folic acid deficiencies induced by drugs such as trimethoprim, pyrimethamine, sulfasalazine, phenytoin, and antiretrovirals. Drugs such as isoniazid, chloramphenicol, and linezolid can cause sideroblastic anemia by interfering with heme biosynthesis. Aplastic anemia—the failure to produce blood cells (hemoglobin, leukocyte, and platelet)—can be induced by chloramphenicol, sulfonamide, trimethoprim/sulfamethoxazole, and other drugs that can suppress bone marrow function. Pure red cell aplasia can be caused by azathioprine and other immunosuppressants, linezolid, isoniazid, rifampin, IFN-α, chloroquine, allopurinol, and other drugs.[109]

Iatrogenic anemia or hospital-acquired anemia occurs after blood loss due to medical procedures such as surgery, hemodilution due to excessive intravenous fluid administration, and phlebotomy. Surgery can cause blood loss in >20% cases, particularly in high-risk surgical procedures. Phlebotomy also contributes to hospital-acquired anemia.[110,111] Thavendiranathan et al[112] showed that every milliliter of blood drawn can reduce hemoglobin by 0.07 ± 0.011 g/L.

CONCLUSIONS

Despite the many governmental measures, anemia remains a major public health problem in Indonesia. A possible reason for the failure of anemia intervention to reduce anemia prevalence is that the causes underlying anemia are not only nutritional but also non-nutritional. AI, the most common type of non-nutritional anemia, is associated with chronic infectious diseases and NCDs. IDA can also coexist in patients with chronic AI. Anemia in helminthiasis is another type of non-nutritional anemia. For comprehensive and successful mitigation of anemia prevalence in Indonesia, the causes of nutritional and non-nutritional anemia, including genetic and iatrogenic factors must be acknowledged and addressed.

AUTHOR DISCLOSURES

The authors declare no conflict of interest.

REFERENCES

1. Lukito W, Wahlqvist M. Intersectoral and eco-nutritional approaches to resolve persistent anemia in Indonesia. Asia Pac J Clin Nutr. 2020;29(Suppl 1):S1-S8. doi: 10.6133/apjcn.202012_29(S1).01.

2. Juffrie M, Helmyati S, Hakimi M. Nutritional anemia in Indonesian children and adolescents: diagnostic realibility for appropiate management. Asia Pac J Clin Nutr. 2020; 29(Suppl 1):S18-S31. doi: 10.6133/apjcn.202012_29(S1). 03.
3. Nadiyah, Dewanti L, Mulyani E, 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(Suppl 1):S55-S73. doi: 10.6133/apjcn.202012_ 29(S1).03.
4. Kementrian Kesehatan Republik Indonesia. Main result of Indonesian basic health research. Jakarta; Kementrian Kesehatan Republik Indonesia; 2018. (In Indonesian?)
5. Lipoeto N, Masrul, Nindrea R. Nutritional contributors to maternal anemia in Indonesia: chronic energy deficiency and micronutrients. Asia Pac J Clin Nutr. 2020;29(Suppl 1:S9-S17. doi: 10.6133/apjcn.202012_ 29(S1).02.
6. Wahlqvist ML, Lee MS. Nutrition in health care practice. Journal of Medical Sciences. 2006;26:157-64.
7. Nemeth E, Ganz T. Anemia of inflammation. Hematol Oncol Clin North Am. 2014;28:671-81.
8. Malik S, Oktavianthi S, Wahlqvist M. Non-nutritional anemia: Malaria, thalassemia, G6PD deficiency and tuberculosis in Indonesia. Asia Pac J Clin Nutr. 2020; 29(Suppl 1):S32-S40. doi: 10.6133/apjcn.202012_29(S1). 04.
9. Nairz M, Theurl I, Wolf D, Weiss G. Iron Deficiency or Anemia of Inflammation? Differential diagnosis and mechanisms of anemia of inflammation. Wiener Medizinische Wochenschrift. 2016;166:411-23.
10. Weiss G, Goodnough LT. Anemia of chronic disease. N Engl J Med. 2005;352:1011-23.
11. Ganz T. Anemia of inflammation. N Engl J Med. 2019;381: 1148-57.
12. Madu AJ, Ughasoro MD. Anaemia of chronic disease: An in-depth review. Med Princ Pract. 2017;26:1-9.
13. Aigner E, Feldman A, Datz C. Obesity as an emerging risk factor for iron deficiency. Nutrients. 2014;6:3587-600.
14. Ganz T, Nemeth E. Iron balance and the tole of hepcidin in chronic kidney disease Tomas. Semin Nephrol. 2016;36:87-93.
15. WHO, World Health Organization. Obesity and overweight [Internet]. WHO. 2020 [cited 2020/06/20]. Available from: https://www.who.int/en/news-room/fact-sheets/detail/obesity-and-overweight.
16. Herningtyas EH, Ng TS. Prevalence and distribution of metabolic syndrome and its components among provinces and ethnic groups in Indonesia. BMC Public Health. 2019;19:377.
17. Cheng HL, Bryant C, Cook R, O'Connor H, Rooney K, Steinbeck K. The relationship between obesity and hypoferraemia in adults: A systematic review. Obes Rev. 2012;13:150-61.
18. Del Giudice EM, Santoro N, Amato A, Brienza C, Calabrò P, Wiegerinck ET et al. Hepcidin in obese children as a potential mediator of the association between obesity and iron deficiency. J Clin Endocrinol Metab. 2009;94:5102-7.
19. Wijayanti E, Retnoningrum D, Hendrianintyas M. Relationship between inflammatory marker with hemoglobin in obesity in Faculty of Medicine, Universitas Diponegoro Mei - September 2018. Intisari Sains Medis. 2019;10:242–6. (In Indonesian)
20. Heryati L, Setiawan B. Obesity, anemia, and school grade in elementary school in Bogor. Jurnal Gizi dan Pangan. 2014; 9:159-66 (In Indonesian)
21. Sukarno KJ, Marunduh SR, Pangemanan DHC. Relationship between body mass index with hemoglobin concentration in adolescent in Bolangitang District, Bolaang Regency, North Mongondow. Jurnal Kedokteran Klinis [Internet]. 2016;1:29-35. (In Indonesian)
22. Nisa AK, Nissa C, Probosari E. Difference of nutritional intake and hemoglobin concentration in obese and non-obese female adolescent. Journal of Nutrition College. 2019; 8:21. (In Indonesian)
23. Zheng H, Long W, Tan W, Yang C, Cao M, Zhu Y. Anaemia, iron deficiency, iron-deficiency anaemia and their associations with obesity among schoolchildren in Guangzhou, China. Public Health Nutr. 2020;23:1693-702.
24. Wang M. Iron deficiency and other types of anemia in infants and children. Am Fam Physician. 2016;93:270-8.
25. Huang YF, Tok TS, Lu CL, Ko HC, Chen MY, Chen SCC. Relationship between being overweight and iron deficiency in adolescents. Pediatr Neonatol. 2015;56:386-92. doi: 10. 1016/j.pedneo.2015.02.003.
26. Wijaya CA, Kusnadi Y, Zen NF. Correlation between hemoglobin and renal dysfunction in type 2 diabetes mellitus in Mohammad Hoesin General Hospital, Palembang. Majalah Kedokteran Sriwijaya. 2015;47:39-44. (In Indonesian)
27. Wijaya IGANR, Mulyantari NK, Yasa IWPS. Prevalence of anemia in diabetes melitus type 2 in Sanglah Denpasar Hospital 2014. E-Jurnal Med Udayana. 2018;7:1-8. (In Indonesian)
28. Balela N, Arifin M, Noor M. Anemia in less than 5 years compared to more than 5 Years duration of type 2 diabetes mellitus patients. Berk Kedokt J Kedokt dan Kesehat. 2014;10.
29. Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9th edition. Diabetes Res Clin Pract. 2019;157: 107843.
30. AlDallal SM, Jena N. Prevalence of anemia in type 2 diabetic patients. J Hematol. 2018;7:57-61.
31. Barbieri J, Fontela PC, Winkelmann ER, Zimmermann CEP, Sandri YP, Mallet EKV et al. Anemia in patients with type 2 diabetes mellitus. Anemia. 2015;2015:354737.
32. van Greevenbroek MMJ, Schalkwijk CG, Stehouwer CDA. Obesity-associated low-grade inflammation in type 2 diabetes mellitus: Causes and consequences. Neth J Med. 2013;71:174-87.
33. Giacco F, Brownlee M. Oxidative stress and diabetic complications. Circ Res. 2010;107:1058-70.
34. Fava S, Azzopardi J, Ellard S, Hattersley AT. ACE gene polymorphism as a prognostic indicator in patients with type 2 diabetes and established renal disease. Diabetes Care. 2001;24:2115-20.
35. Angelousi A, Larger E. Anaemia, a common but often unrecognized risk in diabetic patients: A review. Diabetes Metab. 2015;41:18-27.
36. Adiatma D, Tobing M. Prevalence and type of anemia in chronic kidney disease in regular hemodialysis: A study in Dr. Kariadi General Hospital Semarang. Jurnal Kedokteran Diponegoro. 2014;3:137839. (In Indonesian)
37. Aisara S, Azmi S, Yanni M. Clinical picture of chronic kidney disease in hemodialysis therapy in Dr. M. Djamil General Hospital, Padang. J Kesehat Andalas. 2018;7:42.
38. Minhajat. Profile of anemia in chronic kidney disease Patient in dr. Wahidin Sudirohusodo Hospital in 2015-2016. Universitas Hasanuddin; 2016. (In Indonesian)
39. Indonesian Renal Registry [Internet] PERNEFRI. 11th Indonesian Renal Registry 2018;2018 [Cited 2020/10/01]. Available from: https://www.indonesianrenalregistry.org/

data/IRR2018.pdf. (In Indonesian)
40. Suega K, Bakta M, Dharmayudha TG, Lukman JS, Suwitra K. Profile of anemia in chronic renal failure patients: comparison between predialyzed and dialyzed patients at the Division of Nephrology, Department of Internal Medicine, Sanglah Hospital, Denpasar, Bali, Indonesia. Acta Medica Indonesiana. 2005;37:190-4.
41. Dzakiyah A, Anggriyani N, Wijayahadi N. Relationship between quality of life in chronic heart failure patients. Jurnal Kedokteran Diponegoro. 2018;7:962-76. (In Indonesian)
42. Anand IS, Gupta P. Anemia and iron deficiency in heart failure. Circulation 2018;138:80-98. doi: 10.1161/CIRCULATIONAHA.118.030099.
43. Groenveld HF, Januzzi JL, Damman K, van Wijngaarden J, Hillege HL, van Veldhuisen DJ et al. Anemia and mortality in heart failure patients. A systematic review and meta-analysis. J Am Coll Cardiol. 2008;52:818-27.
44. Rodgers GM, Gilreath JA. The role of intravenous Iron in the treatment of anemia associated with cancer and chemotherapy. Acta Haematol. 2019;142:13-20.
45. Hidayati AO, Arifah S. Prevalence of anemia in cancer patient with radiotherapy and/or chemotherapy. Jurnal Kesehatan. 2020;11:29-36. (In Indonesian)
46. Harrison LB, Shasha D, Homel P. Prevalence of anemia in cancer patients undergoing radiotherapy: Prognostic significance and treatment. Oncology. 2002;63(Suppl 2):11-8.
47. WHO. Tuberculosis. 2020 [cited 2020/09/30]; Available from: https://www.who.int/news-room/fact-sheets/detail/tuberculosis.
48. Adzani M, Dalimoenthe NZ, Wijaya I. Profile of anemia on lung tuberculosis at Dr Hasan Sadikin General Hospital and Community Lung Health Center Bandung. Althea Medical Journal. 2016;3:137-40.
49. Kalma, Rafika, Bachtiar AR. Platelet and hemoglobin concentration in tuberculosis patients With anti-tuberculosis medication. Jurnal Media Analis Kesehatan. 2019;10:143-51. (In Indonesian)
50. Pramono A, Meida NS. Anemia in lung tuberculosis. Mutiara Medika. 2003;3:10-4. (In Indonesian)
51. Karyadi E, Schultink W, Nelwan RHH, Gross R, Amin Z, Dolmans WMV et al. Poor micronutrient status of active pulmonary tuberculosis patients in Indonesia. J Nutr. 2000; 130:2953-8.
52. Karyadi E, West C, Schultink W, Nelwan RHH, Gross R, Amin Z et al. A double-blind, placebo-controlled study of vitamin A and zinc supplementation in persons with tuberculosis in Indonesia: Effects on clinical response and nutritional status. Am J Clin Nutr. 2002;75:720-7.
53. Aryanti AD. Prevalence of anemia in chronic obstructive pulmonary disease in public central lung clinic in Surakarta. Universitas Muhammadiyah Surakarta; 2014.
54. Sundari R, Parwati I, Mose JC, Setiabudiawan B. The differences of haematology profile in patients with lung tuberculosis infected by mycobacterium tuberculosis Beijing Strain vs non-Beijing strain. Majalah Kedokteran Bandung. 2017;49:35-41. (In Indonesian)
55. Sadewo S. Status of anemia in lung tuberculosis patient in pulmonology clinic in West Borneo 2010-2012. Universitas Tanjungpura; 2014. (In Indonesian)
56. Lasut NM, Rotty LW, Polii EB. Clinical profile of hemoglobin and thrombocytopenia in tuberculosis patients in RSUP Dr. R. D. Kandou Manadou Manado January 2014 - December 2014. Jurnal E-Clinic. 2016;4:1-6. (In Indonesian)
57. Fauziah I, Siahaan G. Hemoglobin concentration in lung tuberculosis patients in anti tuberculosis treatment in Haji Abdul Halim Hasan Medical Center, Binjai. BioLink (Jurnal Biologi Lingkungan, Ind Kesehatan). 2014;1:13-7. (In Indonesian)
58. Fathan PB, Buanayuda GW, Putri NA. Hematologic examination in pulmonary tuberculosis patient admitted in General Hospital West Nusa Tenggara Barat Province in 2011 - 2012. Jurnal Kedokteran. 2013;2:27-35.
59. Lokollo DN, Wastoro D, Suromo L. Difference of serum ferritin in pediatric patients with or without lung tuberculosis. Sari Pediatr. 2010;11:335-40. (In Indonesian)
60. Purnasari G. Anemia in pediatric lung tuberculosis patients in varied nutritional status and intake. Universitas Diponegoro; 2011. (In Indonesian)
61. Gil-Santana L, Cruz LAB, Arriaga MB, Miranda PFC, Fukutani KF, Silveira-Mattos PS et al. Tuberculosis-associated anemia is linked to a distinct inflammatory profile that persists after initiation of antitubercular therapy. Sci Rep. 2019;9:1381.
62. UNAIDS. HIV Estimates with uncertainty bounds 1990-2019 [Internet]. 2020. [cited 2020/10/01]; Available from: https://www.unaids.org/en/resources/documents/2020/HIV_estimates_with_uncertainty_bounds_1990-present.
63. Frank TD, Carter A, Jahagirdar D, Biehl MH, Douwes-Schultz D, Larson SL et al. Global, regional, and national incidence, prevalence, and mortality of HIV, 1980-2017, and forecasts to 2030, for 195 countries and territories: A systematic analysis for the Global Burden of Diseases, Injuries, and Risk Factors Study 2017. Lancet HIV. 2019;6:e831-59.
64. Wisaksana R, Sumantri R, Indrati A, Zwitser A, Jusuf H, de Mast Q et al. Anemia and iron homeostasis in a cohort of HIV-infected patients in Indonesia. BMC Infect Dis. 2011; 11:213.
65. Yolanda AR. Relationship between hemoglobin concentration, leukocyte and thrombocyte count with CD4 level in pre-antiretrovirus HIV/AIDS patients. Universitas Udayana; 2016. (In Indonesian)
66. Massang B, Edward K, Purwanto A. Relationship between CD4 count with hemoglobin concentration in HIV patients]. Media Medika Muda. 2018;3:1-4. (In Indonesia)
67. Defiaroza. Analysis of hemoglobin of HIV/AIDS patient in Yayasan Lantera Minangkabau Padang, 2017. Jurnal Penelitian dan Kajian Ilmiah Menara Ilmu: 2018;XII:79-88.
68. Barkley JS, Kendrick KL, Codling K, Muslimatun S, Pachón H. Anaemia prevalence over time in Indonesia: Estimates from the 1997, 2000, and 2008 Indonesia Family Life Surveys. Asia Pac J Clin Nutr. 2015;24:452-5.
69. World Health Organization (WHO). Worldwide prevalence of anaemia 1993–2005. WHO Global Database on Anaemia. Geneva: WHO; 2005. pp. 51.
70. Pasricha SR. Anaemia in pregnancy - not just iron deficiency. Acta Haematol. 2013;130:279-80.
71. Siridamrongvattana S, Van Hoa N, Sanchaisuriya K, Dung N, Hoa PTT, Sanchaisuriya P et al. Burden of anemia in relation to thalassemia and iron deficiency among vietnamese pregnant women. Acta Haematol. 2013;130: 281-7.
72. Fink NR, Chawes B, Bønnelykke K, Thorsen J, Stokholm J, Rasmussen MA et al. Levels of systemic low-grade inflammation in pregnant mothers and their offspring are correlated. Sci Rep. 2019;9:3043.
73. Finkelstein JL, Kurpad AV, Thomas T, Srinivasan K, Duggan C. Maternal anemia of inflammation and adverse pregnancy and neonatal outcomes in India. FASEB J. 2016;30:668.3.
74. Judistiani RTD, Gumilang L, Nirmala SA, Irianti S,

Wirhana D, Permana I et al. Association of colecalciferol, ferritin, and anemia among pregnant women: Result from cohort study on vitamin D status and its impact during pregnancy and childhood in Indonesia. Anemia. 2018;2018: 2047981.
75. Cannell JJ, Grant WB, Holick MF. Vitamin D and inflammation. Dermatoendocrinol. 2014;6:e983401.
76. Bethony J, Brooker S, Albonico M, Geiger SM, Loukas A, Diemert D, et al. Soil-transmitted helminth infections: ascariasis, trichuriasis, and hookworm. Lancet. 2006; 367(9521):1521-32.
77. Yazdanbakhsh M, Maizels R. Immune regulation by helminth parasites: Cellular and molecular mechanisms. Nat Rev Immunol. 2003;3:733-44. doi: 10.1038/nri1183.
78. Adebara OV, Ernest SK, Ojuawo IA. Association between intestinal helminthiasis and serum ferritin levels among school children. Open J Pediatr. 2011;1:12-6.
79. Olsen A, Magnussen P, Ouma JH, Andreassen J, Friis H. The contribution of hookworm and other parasitic infections to haemoglobin and iron status among children and adults in western Kenya. Trans R Soc Trop Med Hyg. 1998;92:643-9.
80. Galvao FC. Anemia in patients with intestinal parasitic infection. Rev Ibero-Latinoam Parasitol. 2011;70:206-11.
81. Mohammed Mujib AS, Mohammad Mahmud AS, Halder M, Monirul Hasan CM. Study of hematological parameters in children suffering from iron deficiency anaemia in chattagram maa-o-shishu general hospital, Chittagong, Bangladesh. Anemia. 2014;2014:503981.
82. Hotez PJ, Molyneux DH. Tropical anemia: One of Africa's great killers and a rationale for linking malaria and neglected tropical disease control to achieve a common goal. PLoS Negl Trop Dis. 2008;2:e270.
83. McKay DM, Shute A, Lopes F. Helminths and intestinal barrier function. Tissue Barriers. 2017;5:e1283385.
84. Feleke BE. Nutritional status and intestinal parasite in school age children: A comparative cross-sectional study. Int J Pediatr. 2016;2016:1962128.
85. World Health Organization. Eliminating soil transmitted helminthiasies as a public health problem in children. France: WHO Press; 2012.
86. Keiser J, Utzinger J. The drugs we have and the drugs we need against major helminth infections. In: Advances in Parasitology. Bassel: Elsevier, 2010. p. 197-230.
87. Kurscheid J, Bendrups D, Susilo J, Williams C, Amaral S, Laksono B et al. Shadow puppets and neglected diseases: Evaluating a health promotion performance in rural Indonesia. Int J Environ Res Public Health. 2018;15:2050.
88. Pegelow K, Gross R, Pietrzik K, Lukito W, Richards AL, Fryauff DJ. Parasitological and nutritional situation of school children in the Sukaraja district, West Java, Indonesia. Southeast Asian J Trop Med Public Health. 1997; 28:173-90.
89. Arrasyid NK, Sinambela MN, Tala ZZ, Darlan DM, Warli SM. Correlation between soil-transmitted helminths infection and serum iron level among primary school children in Medan. Open Access Maced J Med Sci. 2017; 5:117-20.
90. Wiria AE, Hamid F, Wammes LJ, Kaisar MMM, May L, Prasetyani MA et al. The effect of three-monthly albendazole treatment on malarial parasitemia and allergy: A household-based cluster-randomized, double-blind, placebo-controlled trial. PLoS One. 2013;8:e57899.
91. Puspita WL, Khayan K, Hariyadi D, Anwar T, Wardoyo S, Ihsan BM. Health education to reduce helminthiasis: Deficits in diets in children and achievement of students of elementary schools at Pontianak, West Kalimantan. J Parasitol Res. 2020;2020:4846102.
92. Burdam FH, Hakimi M, Thio F, Kenangalem E, Indrawanti R, Noviyanti R et al. Asymptomatic vivax and falciparum parasitaemia with helminth co-infection: Major risk factors for anaemia in early life. PLoS One. 2016;11:e0160917.
93. Amaruddin AI, Hamid F, Koopman JPR, Muhammad M, Brienen EAT, van Lieshout L et al. The bacterial gut microbiota of schoolchildren from high and low socioeconomic status: A study in an urban area of makassar, indonesia. Microorganisms. 2020;8:961.
94. Kridaningsih TN, Sukmana DJ, Mufidah H, Diptyanusa A, Kusumasari RA, Burdam FH et al. Epidemiology and risk factors of Strongyloides stercoralis infection in Papua, Indonesia: a molecular diagnostic study. Acta Trop. 2020;209:105575.
95. Gray DJ, Kurscheid JM, Park MJ, Laksono B, Wang D, Clements ACA et al. Impact of the "balatrine" intervention on soil-transmitted helminth infections in central Java, Indonesia: A pilot study. Trop Med Infect Dis. 2019;4:141.
96. Park MJ, Laksono B, Clements A, Sadler R, Stewart D. Worm-free children: an integrated approach to reduction of soil-transmitted helminth infections in Central Java. Rev Environ Health. 2016;31:111-3.
97. Sekiyama M, Roosita K, Ohtsuka R. Developmental stage-dependent influence of environmental factors on growth of rural Sundanese children in West Java, Indonesia. Am J Phys Anthropol. 2015;157:94-106.
98. Hamid F, Wahyuni S, van Leeuwen A, van Ree R, Yazdanbakhsh M, Sartono E. Allergic disorders and socio-economic status: A study of schoolchildren in an urban area of Makassar, Indonesia. Clin Exp Allergy. 2015;45:1226-36.
99. Nasution RKA, Nasution BB, Lubis M, Lubis IND. Prevalence and knowledge of soil-transmitted helminth infections in Mandailing Natal, North Sumatera, Indonesia. Open Access Maced J Med Sci. 2019;7:3443-6.
100. Nurdiati DS, Sumarni S, Suyoko, Hakimi M, Winkvist A. Impact of intestinal helminth infection on anemia and iron status during pregnancy: A community based study in Indonesia. Southeast Asian J Trop Med Public Health. 2001;32:14-22.
101. Lolascon A, De Falco L, Beaumont C. Molecular basis of inherited microcytic anemia due to defects in iron acquisitionor heme synthesis. Haematologica. 2009;94:395-408.
102. Abbaspour N, Hurrell R, Kelishadi R. Review on iron and its importance for human health. J Res Med Sci. 2014;19: 164-74.
103. Mackenzie EL, Iwasaki K, Tsuji Y. Intracellular iron transport and storage: From molecular mechanisms to health implications. Antioxidants Redox Signal. 2008;10:997-1030.
104. Blanco-Rojo R, Baeza-Richer C, Lápez-Parra AM, Pérez-Granados AM, Brichs A, Bertoncini S et al. Four variants in transferrin and HFE genes as potential markers of iron deficiency anaemia risk: An association study in menstruating women. Nutr Metab. 2011;8:69.
105. Surendran S, Adaikalakoteswari A, Saravanan P, Shatwaan IA, Lovegrove JA, Vimaleswaran KS. An update on vitamin B12-related gene polymorphisms and B12 status. Genes Nutr. 2018;13:2.
106. Aslinia F, Mazza JJ, Yale SH. Megaloblastic anemia and other causes of macrocytosis. Clin Med Res. 2006;4:236-41.
107. Unnikrishnan V, Dutta TK, Badhe BA, Bobby Z, Panigrahi AK. Clinico-aetiologic profile of macrocytic anemias with special reference to megaloblastic anemia. Indian J Hematol Blood Transfus. 2008;24:155-65.
108. Zhang J, Wang S. MTHFR (C677T, A1298C) and MTRR (A66G) polymorphisms associated with the risk of megaloblastic anemia in China. Reaearch Square. 2019. doi:

10.21203/rs.2.14459/v1. (In preprint)
109. Mintzer DM, Billet SN, Chmielewski L. Drug-induced hematologic syndromes. Adv Hematol. 2009;2009.
110. Chandrashekar S. Hospital-Acquired anemia: A hazard of hospitalization. Glob J Transfus Med. 2018;3:83.
111. Koch CG, Li L, Sun Z, Hixson ED, Tang A, Phillips SC et al. Hospital-acquired anemia: Prevalence, outcomes, and healthcare implications. J Hosp Med. 2013;8:506-12.
112. Thavendiranathan P, Bagai A, Ebidia A, Detsky AS, Choudhry NK. Do blood tests cause anemia in hospitalized patients? The effect of diagnostic phlebotomy on hemoglobin and hematocrit levels. J Gen Intern Med. 2005; 20:520-4.

Review Article

Nutritional anemia: Limitations and consequences of Indonesian intervention policy restricted to iron and folic acid

Nadiyah MSc, CSRS, Lintang Purwara Dewanti MSc, Erry Yudhya Mulyani PhD, Idrus Jus'at PhD

Department of Nutrition, Faculty of Health Sciences, University of Esa Unggul, Jakarta, Indonesia

Background and Objective: Currently, anemia is a severe public health issue in Indonesia. The aim of this review was to examine policy measures and program implementation to reduce anemia attributed to iron deficiency in Indonesia. **Methods and Study Design**: A literature search was conducted using Google Search, Sciencedirect.com, and PubMed to retrieve relevant studies in the last three decades. Qualitative data were also obtained from service providers. The search yielded 141 articles, of which 32 were excluded, and further screening was conducted based on the type and scale of the intervention program. **Results**: In the iron–folic acid (IFA) supplementation programs studied, antenatal care and health personnel capacity information were limited. Implementation often did not correspond to standard operating procedures. Analysis, follow-up, and feedback on IFA tablet programs were lacking. Moreover, the IFA tablet supply was inadequate, facilities and infrastructure were insufficient, and counseling guidance, relevant material, and information media were lacking. In the national fortification program, wheat flour was used as a vehicle for anemia prevention. However, evidence from the Total Diet Study indicated that wheat noodles have limited value across the Indonesian archipelago. **Conclusion**: Programs to reduce the likelihood of anemia will be more successful if they are less dependent on nutrient-specific strategies and focus more on the pathogenetic complexity arising from personal behavior, sociocultural factors, dietary and health patterns, local community, and ecology. Partnerships between the community and government reflected in evidence-based policy will always be of value, but continued research is required to examine the factors contributing to the successful outcomes of such programs.

Key Words: iron deficiency anemia, Indonesia, program policy, supplementation, fortification

INTRODUCTION

In patients with anemia, the number and size of red blood cells or the hemoglobin concentration is below the established cut-off value, consequently impairing blood's oxygen-transporting capacity.[1-4] Anemia is an indicator of both poor nutrition and poor health.[5] Anemia, especially that due to iron deficiency (IDA), is the most common micronutrient deficiency, especially among children under 5 years and women of reproductive age.[6,7] It leads to a higher risk of infections as well as impaired cognitive function and physical work capacity. Moreover, maternal anemia is associated with intrauterine growth restrictions.[6] If treated early, anemia due to acute blood loss has a favorable prognosis. Iron supplementation is a relatively inexpensive intervention for treating and preventing anemia related to iron deficiency.[6,8,9]

According to the 2018 Global Nutrition Report, globally, the incidence of anemia has increased slightly to 32.8%.[10] In 2016, Indonesia had the highest anemia prevalence (42%) among pregnant women compared with that in neighboring countries such as Malaysia (37%), Singapore (32%), Brunei Darussalam (27%), Vietnam (37%), the Philippines (30%), and Thailand (40%).[11]

Anemia is considered a public health concern when the national anemia prevalence among women of reproductive age (15–49 years) is ≥20%. Public health concern related to anemia is categorized as mild, moderate, and severe when the prevalence is 5%–19%, 20%–39%, and >40%, respectively.[12] On the basis of the 2018 Basic Health Research project, the anemia prevalence among pregnant women in Indonesia increased from 37.1% in 2013 to 48.9% in 2018, and currently, it is a severe public health issue.[13]

In 2012, the World Health Assembly Resolution endorsed the implementation of a comprehensive plan for maternal, infant (younger than 1 year), and young-child nutrition;[14] a 50% reduction of anemia in reproductive-age women was specified as one of six global nutrition targets for 2025.[15] There has been an increase in the number and breadth of national nutrition policies and nutrition

Corresponding Author: Dr Idrus Jus'at, Department of Nutrition, Faculty of Health Sciences, University of Esa Unggul, Jakarta, Indonesia.
Tel: +62 811-904-435
Email: idrus.jusat@esaunggul.ac.id
Manuscript received and accepted 19 December 2020.
doi: 10.6133/apjcn.202012_29(S1).06

targets, and their financing and implementation are outstanding challenges. More countries are prioritizing nutrition by establishing national nutrition policies and action plans: 164 countries have such plans, 61% of which are multisectoral.[10] Public health strategies for anemia prevention and control include improvements to dietary diversity; food fortification with iron, folic acid, and other micronutrients; distribution of iron-containing supplements; and control of infections and malaria.[5]

For more than three decades, Indonesia has implemented an iron intervention program. Since the 2000s, iron has been added to wheat flour as mandatory fortification. This food-based approach has been promoted. However, currently, anemia is a severe public health and nutrition issue. This paper aims to review policy measures and program implementation to reduce anemia attributed to iron deficiency in Indonesia.

IRON DEFICIENCY ANEMIA IN INDONESIA

Anemia was listed as a public health burden worldwide in 2011; the World Health Organization (WHO) reported that the prevalence of anemia is the highest in children (42.6%) and the lowest in nonpregnant women (29.0%).[16] Anemia is currently among the most common and intractable nutritional problems globally. It is a global public health problem affecting both developing and developed countries, with major consequences for human health and social and economic development. WHO estimates the number of anemic people worldwide to be 2 billion in which 50% of all anemia cases attributable to iron deficiency. Iron deficiency anemia occurs at all stages of life but is more prevalent in pregnant women and young children. Adolescents, particularly girls, are vulnerable to iron deficiency. The 2002 World Health Report identified iron deficiency as one of the 10 most severe risks in countries with high infant and adult mortality.[17] A previous study also reported that addressing iron deficiency anemia is one of the most cost-effective public health interventions.[18]

The 2013 Basic Health Research in Indonesia showed that the prevalence of anemia in children aged 1–4, 5–14, and 15–24 years was 28.1%, 26.4%, and 18.4%, respectively.[19] The prevalence of anemia increased compared with that in the previous survey conducted in 2007, which was 27.7%, 9.4%, and 6.9% in children aged 1–4, 5–14, and 15–24 years, respectively.[20] In particular, the prevalence of anemia in school-age children and adolescents almost tripled. The Basic Health Research project also showed that the anemia prevalence was higher in the suburbs than in urban areas.[19]

Compared with anemia prevalence estimates in 1997, anemia prevalence estimates were lower in 2008 for all groups, with the greatest decline occurring in children aged 5 to 11 years (25.4%). The highest prevalence of anemia was observed in children aged 0–5 years, those aged 12–15 years, and nonpregnant and pregnant women in 2000. However, a chi-squared trend analysis revealed that the anemia prevalence declined significantly in all groups over the survey years (p=0.005 for pregnant women, p<0.0001 for all other groups). From this first-ever trend analysis of anemia in different populations in Indonesia, we concluded that the prevalence of anemia has decreased from 1997 to 2008 in all age and sex groups studied. Despite this progress, anemia remains a moderate public health problem in children aged <12 years and >15 years and in nonpregnant and pregnant women.[21]

In 1996, Muhilal reported that the prevalence of anemia among pregnant women in various parts of Indonesia ranged between 38.0% and 71.5%, and the average prevalence for the general population of Indonesia was approximately 63.5% (Table 1).

Unexpectedly, Java, the most developed part of Indonesia, was among the areas with the highest anemia prevalence of 57.8%–71.5%. Irian Jaya, one of the less developed areas, had the lowest prevalence (38%).[22] Moreover, the 1992 Household Health Survey showed that 63.5% of pregnant women and 55% of children under five had iron deficiency anemia. Similarly, the 1995 Household Health Survey showed that 50% of pregnant women had anemia. Pregnant women are the most at-risk population, and the prevalence of anemia (defined as hemoglobin <11 g/L) among this population is approximately 60% in Indonesia.[23] Among reproductive-age women, the prevalence of anemia in Indonesia is 30%–40%.[24]

In 1996, the prevalence of anemia in preschool children in various parts of Indonesia ranged between 35.8% and 60.6%, and the average prevalence at the national level was 55.5%. Similar to the situation for pregnant women, the lowest prevalence in preschool children was observed in Irian Jaya (35.8%). In Central Java, the prevalence in school children (44.9%) was the lowest, whereas the prevalence in pregnant women (62.5%) was the highest.[22] Nationally, the prevalence of anemia in children under 5 years was 28.1% and in children aged 5–14 years it was 26.4%.[19] Thus, with a cut off of anemia prevalence ≥40%, anemia has become a severe public health problem in Indonesia.

CURRENT POLICY AND IMPLEMENTATION

Iron Supplementation

Research on gardeners in Indonesia showed that the ad-

Table 1. Anemia prevalence in children, women, and men measured during the second, third, and fourth waves of the Indonesia Family Life Surveys (IFLS)

Group	Year	Anemia (%)
Children 0–4 y	1997/8	46.0
	2000	54.6
	2007/8	31.4
Children 5–11 y	1997/8	46.0
	2000	36.4
	2007/8	20.6
Children 12–15 y	1997/8	27.5
	2000	28.2
	2007/8	15.8
Women >15 y (nonpregnant)	1997/8	36.0
	2000	38.8
	2007/8	26.6
Women >15 y (pregnant)	1997/8	45.1
	2000	46.5
	2007/8	37.3
Men >15 y	1997/8	29.0
	2000	22.8
	2007/8	15.4

Source: Barkley, 2015 [21]

ministration of 100 mg iron for 60 days resulted in a significant improvement in hematological status, performance, work output, and morbidity among anemic workers.[25] This result endorses the WHO recommendation of an iron supplementation program for pregnant mothers.

Supplementation with daily oral iron and folic acid is recommended by WHO as a part of antenatal care to reduce the risks of low birth weight, maternal anemia, and iron deficiency (strong recommendation). Management of major nutrition deficiency in Indonesia, including nutritional anemia, is an important part of the effort to reduce infant and toddler mortality. Hence, since 1985 several activities related to Family Nutrition Improvement Efforts (*Upaya Perbaikan Gizi Keluarga-UPGK),* such as toddler weight measurement, mother and child nutrition counseling, vitamin A supplementation, iron tablets, and oral rehydration salt administration, were conducted in *Posyandu* (Integrated Healthcare Center) as an integrated service. In the first 3 years of REPELITA (Five-Year Development Plan) IV, more than 2 million pregnant mothers had received iron tablets: 150,000 individuals in 1984/85; 660,000 individuals in 1985/86; and more than a million individuals in 1986/87.[26]

Jus'at demonstrated that the iron folic acid supplementation program (iron–folic acid [IFA] tablets) implemented in collaboration with the Religious Office (*Kantor Urusan Agama-KUA*), accompanied by the provision of education (KIE) on the importance of IFA tablets and their early consumption prior to pregnancy, reduced anemia prevalence from 23.8% to 14.0% during the program.[27] The research findings caused the release of PERMENKES RI (The Minister of Health of Republic of Indonesia Regulation) Number 97 of 2014 on Health Services Prior to Pregnancy, which aims to eradicate anemia problems.

The Regulation of Minister of Health Number 97 of 2014 on Health Service During Pregnancy states that every pregnant mother should receive a minimum of 90 IFA tablets during pregnancy from the first contact and must also be provided counseling and education on the benefits, side effects, storing instruction, and methods of consuming IFA tablets. Moreover, PERMENKES RI Number 88 of 2014 on Iron Folic Acid Tablets Standard for Reproductive Women and Pregnant Mothers and PERMENKES RI Number 51 of 2016 on Standard Nutritional Supplementation Product were established.

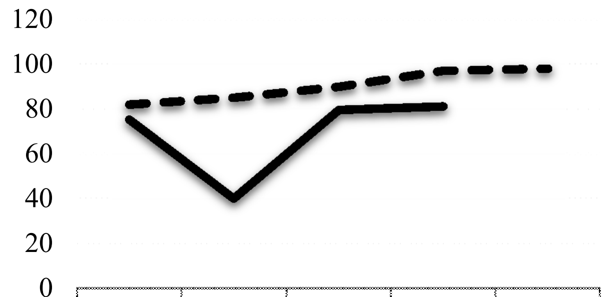
The Ministry of Health (MoH) through PERMENKES RI Number 88 of 2014 released the new technical specification for IFA tablets, which was valid from 2016. This new technical specification regulates the composition, dosage, and packaging of IFA tablets with the aim of increasing the effectiveness of IFA tablet administration. Each IFA tablet consists of ferrous fumarate iron equal to 60 mg elemental iron and 0.400 mg folic acid. The dosage specification is in accordance with the WHO recommendation.[28]

PERMENKES RI Number 51 of 2016 on Standard Nutritional Supplementation Products mentioned that for iron and folic acid tablets, iron is added in the form of a ferrous fumarate compound to increase the effectiveness of IFA tablet administration. However, Toto Sudargo, Dewanti, and Vista Ari Rahmawati showed that Fe-fumarate IFA tablets had reduced compliance among pregnant mothers in Yogyakarta, whereas commercial IFA tablets had higher compliance rates because of their preferable flavor, smaller tablet size, and fewer side effects.[29] Fitriana evaluated IFA tablet program adherence in female adolescents in East Sempaja, Palu, in which Kimia Farma IFA tablets were replaced with Hemafort Pharos; female adolescents preferred Hemafort Pharos IFA tablets.[30] Both types of IFA tablets are Fe-fumarate, but Hemafort Pharos tablets contain multinutrients, whereas Kimia Farma IFA tablets contain only iron and folic acid. IFA tablets with multinutrients tend to be more favored and could have higher compliance (in terms of IFA tablet consumption) than IFA tablets, which contain only folic acid and iron (regardless of whether it is Fe-Fumarate or not).

According to the 2018 Basic Health Research project, the proportion of female adolescents receiving IFA tablets was as low as 22.9%, whereas the proportion was 48.5% in the Performance Report of the Directorate of Community Nutrition of the MoH. This discrepancy is caused by the data collection methods. The percentage of girls who receive IFA tablets (TTD) was determined as the percentage of girls aged 12–18 years in junior high/high school or equivalent who receive regular iron tablets every week. Each teenage girl is expected to receive 52 iron tablets for 1 year.[31] On the basis of the survey results, the main reasons why female adolescents did not consume IFA tablets were the bad taste and smell of IFA tablets and because they believed that it was unnecessary to consume the tablets.[13]

The 2018 Basic Health Research project revealed that the percentage of pregnant women who received IFA tablets was 73.2%, which is slightly lower than the percentage of pregnant women who received IFA tablets in the 2018 Performance Report of the Directorate of Community Nutrition, MoH (81.2%). A positive trend was found for the percentage of pregnant women who received 90 IFA tablets during pregnancy from 2015 to 2018, even though it was still below the target (Figure 1). Moreover, the level of compliance of pregnant women in consuming ≥90 iron tablets during pregnancy only reached 38.1%.[13,32] Generally, the main reasons for noncompliance with IFA consumption by pregnant women were dislike, boredom, forgetfulness, feeling nauseous, and/or vomiting due to pregnancy.[13]

Tablet consumption was defined as the taking of IFA tablets containing iron and folic acid, both from the program and independently, by adolescent girls or pregnant women. This definition does not accurately describe the government's capacity to cover the requirements of IFA tablets in the supplementation program. On the basis of information related to the realization of iron supplement availability from the Directorate of Public Medicines and Health Supplies, the Directorate General of Pharmacy and Health Equipment, MoH, the iron supplement supply in 2017 was only 75% due to budget efficiency measures. Starting from 2019 to 2020, each region in Indonesia outside the stunting locus (priority area of stunting) was required to procure IFA tablets using Health Special Allocation Funds (DAK). IFA tablets for regions in the stunting locus were procured using the central budget. For 2021, the procurement of all iron supplements (in regions both in the stunting locus and outside the stunting locus) will be conducted by the center.



	2015	2016	2017	2018	2019
Target	82	85	90	97	98
old OD realization	75.4	40.2	79.6	81.2	
revised OD realization				97	

Figure 1. Percentage of pregnant women who received 90 IFA tablets during pregnancy (2015–2018). Source: Directorate of Community Nutrition of the MoH, 2018.[32]

Table 2 provides a summary of IFA tablet supplementation program evaluation in various areas in Indonesia. In general, the quality of antenatal care was low; the capacity of health personnel was low; IFA tablet program implementation did not correspond to the SOP; analyses, follow-up, and feedback were lacking in IFA tablet program reports; facilities and infrastructure were insufficient; counseling guidance was lacking; and counseling material, information media, and IFA tablet supply were insufficient.

On the basis of the Directorate of Community Nutrition's 2018 Budget Realization Report, the available budget for procuring IFA tablets for pregnant women was Rp 6,283,713,000, and Rp 5,810,354,524 of this amount has been spent (amounting to 92.47% of the total budget).[32] According to the results of an inspection, the Audit Board of the Republic of Indonesia (BPK-RI) concluded that the MoH of the Republic of Indonesia was not effective in managing funds for goods in 2018. Rp 6.13 billion of state money was wasteful spending; IFA tablets remained undistributed throughout 2018 until the expiration date in 2019. The MoH has not conducted adequate planning for delivering goods to local governments. The calculation for planning the need of goods was not carried out with the adequate basic variables for the central and regional governments. The variables used in the calculation at the provincial health office differ between the program implementing division and the pharmaceutical installation division. This has resulted in an inconsistency in the planning calculations for IFA tablet (TTD) procurement by provincial health offices; these calculations are used in the joint preparation of the drug given nationally. An examination of the dropping realization due to this inappropriate planning showed that a proportion of vitamin A tablets and IFA tablets for pregnant women and teenage girls was not used by the expiration date, resulting in a loss of IDR 6.13 billion.[33]

Supplementation is generally effective on a small scale. However, when it is implemented on a larger or national scale, its effectiveness is influenced by four aspects: appropriate planning for procurement and distribution, preparation of health service providers and communication with mothers, quality control and effective product traceability, and intensive monitoring and supervision.[34] WHO guidance for iron and folic acid supplementation has already emphasized the following:

"The implementation of a behavior change communication strategy to communicate the benefits of the intervention and management of side effects is vital to improving the acceptability of and adherence to recommended supplementation schemes".[6]

Iron fortification

For reducing anemia, the fortification program is considered cheaper and more effective than the supplementation program. WHO recommends iron fortification in various compound categories, including water-soluble, poorly water-soluble but soluble in dilute acid, water-insoluble, and poorly soluble in dilute acid, and encapsulated forms. The selection of the iron fortificant depends on the type of food vehicle targeted for fortification because it influences the effectiveness of iron fortification in terms of iron availability.[35] The iron compounds recommended by WHO to fortify cereals are ferrous sulfate, ferrous fumarate, ferric pyrophosphate, and electrolytic iron.[36]

In 1993, the New Order Government established the State Ministry of Food Affair and initiated a policy on food fortification and strengthened it in REPELITA III in one of the chapters of Food Law of 1996 Article 27. Chapter III on Food Quality and Nutrition in Article 27 of the Law states the following: "In terms of deficiency or decrease in society's nutritional status, the government can set requirements for improvement and enrichment of certain circulated food nutrient." The term nutrient enrichment means fortification. In response to the effectuation of this food law, the MoH issued a ministerial decree dated

Table 2. Evaluation studies of the iron supplementation program for adolescent girls and pregnant women in various regions of Indonesia

No	Authors (year)	Title	Location	Method	Result	Suggestion
1	Siekmans et al. (2018)[79]	Barriers and enablers of IFA supplementation for pregnant women	Afghanistan, Bangladesh, Indonesia, Ethiopia, Kenya, Nigeria, Senegal	Formative research was conducted using mixed qualitative and quantitative methods. Indonesia: FGD: PW or PPW (n=6 groups), influential persons (n=6 groups); IDI: PW or PPW (n=24), key influencers (n=24), village health workers—midwives or nurses (n=6), facility health workers (n=12), TBA (n=8), cadres or CHWs (n=8), community leaders (n=12), district and provincial level (n=18)	Opportunity: All pregnant mothers and health care workers understand the description of anemia symptoms. Hindrance: - Pregnant mothers do not think that they are at risk. - The low access and quality of ANC services reduce the scope of and compliance with IFA tablet consumption: a. Inadequacy of IFA tablet provision b. Insufficiency of counseling to encourage compliance with IFA tablet consumption	- Community-based delivery and counseling of IFA and referral to ANC - Improve ANC access and quality - Renewed investment in training for service providers - Ensure effective behavioral changes
2	Natalia et al. (2017)[80]	The scope of ANC and Fe tablets, their relationship with anemia prevalence in East Java	21 Regencies/ Cities in East Java	Quantitative study using secondary data from a regency/city on anemia prevalence in pregnant mothers with Hb level of <11 g/dL registered in the Nutrition and Family Health Section of East Java Province Health Services. Data analysis was through Pearson correlation.	- There was no correlation between ANC coverage and Fe tablets and anemia prevalence (p>0.05). - The coverage of Fe tablet administration to pregnant mothers through ANC services did not describe high or low anemia prevalence in pregnant mothers.	
3	Toto Sudargo, Dewanti, Vista Ari Rahmawati (2020)[29]	Comparing the efficiency between commercial and governmental iron-folic acid (IFA) supplement among pregnant women in Yogyakarta and Sleman	Yogyakarta City and Sleman Regency within the Yogyakarta Province	Using the mixed-method approach, the study evaluated and compared the efficiency between commercial IFA and IFA provided free by the government to pregnant women across all community health centers (Puskesmas). Hemoglobin was measured using a rapid test kit to determine anemia status. An interview was conducted to qualitatively evaluate participants' perception toward both types of supplementation.	- Yogyakarta had the highest prevalence of anemia (35.49%), whereas the prevalence was 8.90% in Sleman. - Yogyakarta City has preferably been using commercial IFA, replacing supplements provided by the government, since 2006, whereas in Sleman Regency, a similar change was noted between 2015 and 2018. However, in 2019, modified IFA was introduced in Sleman with Fe-Fumarate as the iron compound, replacing Fe-Sulfate. This has caused a decrease in compliance, leading to a return to the use of commercial IFA. - In Yogyakarta City, total coverage (100%) was achieved with commercial IFA in Puskesmas Danurejan 2, whereas the lowest coverage (66.9%) was found in Puskesmas Mantrijeron. In Sleman Regency, the highest and lowest coverage was 99.14% (Puskesmas Depok 2) and 77.68% (Puskesmas Pakem), respectively. - The use of commercial IFA has resulted in higher compliance as it has a more preferable taste and flavor, smaller size, and fewer side effects.	The use of commercial IFA in the government supplementation program to improve compliance and acceptance among pregnant women.

PPW: postpartum women; PW: pregnant women; CHW: community health worker; FGD: focus group discussion; IDI: in-depth interview; IFA: iron–folic acid; TBA: traditional birth attendant; ANC: antenatal care; IDA: iron deficiency anemia; IFE: internal factor evaluation; EFE: external factor evaluation; SWOT: strengths, weaknesses, opportunities, and threats; AHP: analytical hierarchy process; SOP: standard operating procedure; Hb: Hemoglobin.

Table 2. Evaluation studies of the iron supplementation program for adolescent girls and pregnant women in various regions of Indonesia (cont.)

No	Authors (year)	Title	Location	Method	Result	Suggestion
4	Rahmiati et al. (2018)[81]	Qualitative study about factors and strategy improvement of iron supplementation on pregnant woman in Tasikmalaya District	Tasikmalaya Regency	Cross sectional study and in-depth interview with the head of the IDA tablet program stakeholder. IFE and EFE analyses were used to reveal the situation of IDA supplementation. A SWOT analysis was used to provide an alternative strategy, and the AHP was used to determine the priority of strategies.	- An IFE score of 2.14 demonstrates that internally, the program did not optimize the strengths and did not improve the weaknesses. - EFE score of 2.10 indicates that the program did not optimize opportunities and did not improved the weakness.	- The alternative strategy involved the improvement of commitment, roles, and partnerships among stakeholders; the improvement of the action program; the improvement of facilities and infrastructure; and the improvement of health worker capacity.
5	Permatasari et al. (2018)[82]	The effectiveness of an iron supplementation program among adolescent girls in Bogor City	Bogor City, West Java Province	Quasi-experiment, pre–post intervention, effectiveness study. This study was performed parallel to the Prevention and Management Program of IDA on Junior High School and High School Adolescent Girls that was conducted by the Health Service of Bogor City (by administering iron supplement tablets; 60 mg of elemental iron and 0.25 mg of folic acid) for 16 weeks, with weekly supplementation and 10 tablets during the menstrual period. Tablets that must be consumed were 52 in total.	- The anemia prevalence among adolescent girls decreased after the intervention. The most influential factor for the increase in the Hb level in this study was the initial status of Hb. - The IDA Prevention Program was considered as ineffective, though there was a decrease in prevalence. The level of IFA tablet consumption compliance was still low.	- The IFA tablet administration program should be conducted by ensuring that participants consume the tablets together on the appointed day to increase compliance and place their compliance card on the shelf in their classroom. - The popularization of IFA tablet consumption for parents should be conducted so that students can obtain support and parents can understand the importance of consuming IFA tablets and provide food that is rich in iron, particularly animal-derived food, which is rarely consumed by participants (meat, chicken, liver, and fish).

PPW: postpartum women; PW: pregnant women; CHW: community health worker; FGD: focus group discussion; IDI: in-depth interview; IFA: iron–folic acid; TBA: traditional birth attendant; ANC: antenatal care; IDA: iron deficiency anemia; IFE: internal factor evaluation; EFE: external factor evaluation; SWOT: strengths, weaknesses, opportunities, and threats; AHP: analytical hierarchy process; SOP: standard operating procedure; Hb: Hemoglobin.

Table 2. Evaluation studies of the iron supplementation program for adolescent girls and pregnant women in various regions of Indonesia(cont.)

No	Authors (year)	Title	Location	Method	Result	Suggestion
6	Briawan et al. (2009)[83]	The determinant of success iron supplementation program for school students	Bekasi	The intended success of the program is determined based on a change in anemia status and increase in hemoglobin level. The brand of the capsules provided for the IDA Prevention Program by Bekasi Health Service was Diabion. The analyzed variables were capsule consumption compliance, health status, and initial status of anemia, age, nutritional status, and hand-washing habits as well as animal food consumption frequency.	- Overall, anemia prevalence was reduced, but a difference was noted between the change pattern of anemia prevalence of high school girls, which was increasing, and that of junior high school girls, which was also increasing. - The average compliance level of capsule consumption was 84.9% (good) presumably due to the absence of side effects - A relationship was found between initial anemia status, menstruation status, hand-washing habit, animal food consumption frequency, and increase in hemoglobin level. - The determinants of the iron supplementation program (the anemia status change and the increase in the hemoglobin level) were hand-washing habits and initial status of anemia.	The frequency of students' consumption of animal food was very low; this should be of concern to parents.
7	Dahlia et al. (2013)[84]	The evaluation of iron tablet administration program for pregnant mothers at Binamu Community Health Center, Binamu Subdistrict, Jeneponto Regency	The area of Binamu Community Health Center, Binamu Subdistrict, Jeneponto Regency.	This was a descriptive survey study describing the IFA tablet program implementation for pregnant mothers in terms of input, process, and output through interviews and observations.	- The availability of IFA tablets was not sufficient. - No technical guidance was available. - In the planning process (Health Office Work Unit Budget Plan), planning for IFA tablet accessibility based on the target/beneficiary was not conducted.	
8	Tuju et al. (2013)[85]	The analysis of IFA administration program implementation by midwife in community health center in the area of South Minahasa Regency Community Health Center	17 subdistricts of South Minahasa Regency	The type of research was observational descriptive analytic and cross-sectional.	- The variable affecting the implementation of the IFA tablet program was bureaucracy - The implementation of the IFA tablet program did not follow the existing SOP.	- Provision of education for midwives regarding the benefits in complying with the SOP of IFA tablet administration. - Give incentives to midwives who must implement the program in accordance with standards that fulfill coverage requirements.

PPW: postpartum women; PW: pregnant women; CHW: community health worker; FGD: focus group discussion; IDI: in-depth interview; IFA: iron–folic acid; TBA: traditional birth attendant; ANC: antenatal care; IDA: iron deficiency anemia; IFE: internal factor evaluation; EFE: external factor evaluation; SWOT: strengths, weaknesses, opportunities, and threats; AHP: analytical hierarchy process; SOP: standard operating procedure; Hb: Hemoglobin.

Table 2. Evaluation studies of the iron supplementation program for adolescent girls and pregnant women in various regions of Indonesia (cont.)

No	Authors (year)	Title	Location	Method	Result	Suggestion
9	Secapramana (2015)[86]	Fe tablet administration at Klari Subdistrict Community Health Center, Karawang Regency, West Java.	Klari Subdistrict Community Health Center, Karawang Regency, West Java	An evaluation was conducted by comparing the coverage of the Fe tablet administration program for pregnant mothers in Klari Subdistrict Community Health Center, Karawang Regency, West Java, from January to December 2015 using the standard system approach.	- The need for Fe tablets in Klari Community Health Center, Kawarang Regency, was 277,200 Fe tablets. The provision of Fe tablets was conducted by the government and a private party. - Leaflets and posters for education were absent. - Transportation was available, but there were some areas that could be reached by car. - The majority of the population in Klari subdistrict, Karawang Regency, have low education, and many pregnant mothers had not checked their pregnancy status regularly, and some of them were purposely not taking the Fe tablet or not consuming them. - In the planning of the program, no written data were available. - Planning for the designated service for Fe distribution does not exist. - No recording or reporting was performed.	NA
10	Maitri et al. (2017)[87]	The Evaluation of iron folic acid (IDA) tablet administration as the preventive and curative effort for anemia among pregnant women at Kraton Community Health Center in Yogyakarta City.	Kraton Community Health Center in Yogyakarta City	Data were obtained from secondary data and an in-depth interview with the chief of the Community Health Center, KIA staff, nutrition staff, pharmaceutical personnel, the cadre of pregnant mothers' companions, and pregnant mothers; also, interviews were conducted using questionnaire to determine the knowledge level of pregnant mothers.	- The level of IFA tablet consumption compliance was good. Education related to IFA tablets from midwives was good, and there were high levels of knowledge, self-motivation, and family support, with an absence of side effects from consuming IFA tablets. The high prevalence of anemia in pregnant women in 2016 (33%), was caused by the following: - The lack of IFA tablet distribution. - The consumption of various IFA tablets from the market with an IFA content that did not meet the standard - IFA tablet administration was not performed from the beginning of the pregnancy. - The consumption pattern of pregnant mothers was not appropriate.	NA
11	Fitriana and Dwi Pramardika (2019)[30]	Evaluation of iron folic acid tablet program for female adolescents	Bengkuring Community Health Center, East Sempaja, Palu	Evaluation research using the qualitative research method in the form of in-depth interviews followed by content analysis. The quantitative method was performed to examine Hb level.	- As many as 3 of 10 female adolescents in the Integrated Service Unit Community Health Center of Bengkuring had anemia. - The replacement of IFA tablet Kimia Farma (2018) with Hemafort Pharos (2019) increased compliance among female adolescents in the IFA tablet program. - Facilities and infrastructure were lacking in the anemia and IFA tablet program. - There was a discrepancy in distribution, which was performed once a month at Bengkuring Community Health Center. - Monitoring of IFA tablet consumption compliance and hemoglobin levels in female adolescents was not performed.	NA

PPW: postpartum women; PW: pregnant women; CHW: community health worker; FGD: focus group discussion; IDI: in-depth interview; IFA: iron–folic acid; TBA: traditional birth attendant; ANC: antenatal care; IDA: iron deficiency anemia; IFE: internal factor evaluation; EFE: external factor evaluation; SWOT: strengths, weaknesses, opportunities, and threats; AHP: analytical hierarchy process; SOP: standard operating procedure; Hb: Hemoglobin.

Table 2. Evaluation studies of the iron supplementation program for adolescent girls and pregnant women in various regions of Indonesia (cont.)

No	Authors (year)	Title	Location	Method	Result	Sugges-tion
11	Fitriana and Dwi Pramardika (2019)[30]	Evaluation of iron folic acid tablet program for female adolescents	Bengkuring Community Health Center, East Sempaja, Palu	Evaluation research using the qualitative research method in the form of IDI followed by content analysis. The quantitative method was performed to examine Hb level.	- The data on IFA tablet program were not recorded in the report book by the school. - No analysis or follow-up was conducted, and feedback was not available in the IFA tablet program report from schools, community health centers, or Samarinda Health Services. - There was an inconsistency between the aim and objective of the IFA tablet program of the community health center.	NA
12	Triana Mutmainah et al. (2014)[88]	Analysis of the differences between the implementation of and iron tablet supplementation program for pregnant mothers by the nutrition officer of a high-coverage community health center and by the nutrition officer of a low-coverage community health center in Kendal Regency Area.		Qualitative design presented in a descriptive, exploratory manner with the type of case study through IDI and observations.	- A specific bureaucratic structure does not exist - No SOP was available. - The coverage was still much lower than the minimum service standard. - The implementer was not aware that IFA tablet supplementation is important. - The delivery of information and education to pregnant mothers was not considered as an important part of the program because the program had been running for a long time. - The specific promotional material and information media for the IFA tablet supplementation program for pregnant mothers were not available. - All of the community health centers do not have counseling guidance and implementation instructions for the IFA tablet supplementation program.	NA

PPW: postpartum women; PW: pregnant women; CHW: community health worker; FGD: focus group discussion; IDI: in-depth interview; IFA: iron–folic acid; TBA: traditional birth attendant; ANC: antenatal care; IDA: iron deficiency anemia; IFE: internal factor evaluation; EFE: external factor evaluation; SWOT: strengths, weaknesses, opportunities, and threats; AHP: analytical hierarchy process; SOP: standard operating procedure; Hb: Hemoglobin.

Table 3. Average levels of nutrients to be added to fortified wheat flour based on extraction, fortificant compound, and estimated per capita flour availability

Nutrient	Flour extraction rate	Compound	Level of nutrient to be added in parts per million (ppm) by estimated average per capita wheat flour availability (g/day)†			
			<75‡	75–149	150–300	>300
Iron	Low	NaFeEDTA	40	40	20	15
		Ferrous sulfate	60	60	30	20
		Ferrous fumarate	60	60	30	20
		Electrolytic iron	NR§	NR§	60	40
	High	NaFeEDTA	40	40	20	15
Folic acid	Low or high	Folic acid	5	2.6	1.3	1
Vitamin B-12	Low or high	Cyanocobalamin	0.04	0.02	0.01	0.008
Vitamin A	Low or high	Vitamin A palmitate	5.9	3	1.5	1
Zinc¶	Low	Zinc oxide	95	55	40	30
	High	Zinc oxide	100	100	80	70

†These estimated levels account for only wheat flour as the main fortification vehicle in a public health program. If other mass-fortification programs with other food vehicles are implemented effectively, these suggested fortification levels may need to be adjusted downwards as required.
‡Estimated per capita consumption of <75 g/day does not allow for the addition of a sufficient level of fortificant to cover the micronutrient needs of women of childbearing age. Fortification of additional food vehicles and other interventions should be considered.
§NR: Not recommended because very high levels of electrolytic iron could negatively affect the sensory properties of fortified flour.
¶For these zinc fortification levels, 5-mg zinc intake and no additional phytate intake from other dietary sources are assumed.
Source: WHO, 2009.[40]

June 16th, 1996 regarding Wheat Flour Fortification.

The State Ministry of Food Affair formed the cross-sector Fortification Commission with active support from UNICEF. A national-level discussion, namely National Workshop on Food and Nutrition (Widyakarya Nasional Pangan dan Gizi) VI, was held in 1998. Since then, various experiments on wheat flour fortification started, and the implementation of wheat flour fortification began in 1998 in a wheat flour factory in Jakarta. Finally, on January 14, 1999, the wheat flour fortification program was officially launched by the government.

Two years later, wheat flour fortification with iron, zinc, folic acid, vitamin B-1, and B-2 became mandatory after the release of Decree of the Minister of Industry Trade number 153 in 2001 (Indonesian National Standard; Standar Nasional Indonesia [SNI]) for wheat flour. In February 2008, the mandatory wheat flour fortification program by SNI was once withdrawn by the government because wheat flour fortification was thought to be one of the causes of a dramatic increase in staple food prices, including the price of wheat flour. After several interministerial consultations, SNI wheat flour fortification was re-implemented in 2009. Twenty-six rules have been established for the food fortification policy in Indonesia. There are 10 general rules and 16 specific rules for mandatory fortification, among which 10 are specific fortification rules for wheat flour.[37]

The requirements for fortificant addition to wheat flour products as food vehicles in SNI 3751-2009 are described in the Decree of the Minister of Health, Republic of Indonesia No. 1452/Menkes/SK/X/2003. It is mentioned that produced, imported, or circulated wheat flour in Indonesia should be fortified to contain iron at a minimum of 50 mg/kg, zinc at a minimum of 30 mg/kg, vitamin B-1 (thiamine) at a minimum of 2.5 mg/kg, vitamin B-2 (riboflavin) at a minimum of 4 mg/kg, and folic acid at a minimum of 2 mg/kg.

From January to December 2011, the Laboratory of Balai Besar Industri Agro (Center for Agro-based Industry) analyzed 583 samples of wheat flour from various wheat flour companies considering that the period from January to December 2011 was the transition period for the application of mandatory SNI 3751-2009 in accordance with the Regulation of the Minister of Industry of Republic of Indonesia Number 35/M-IND/PER/3/2011, which was valid from March 22, 2012. According to the test results of 583 samples, the majority (95.85%) of samples complied with the requirements of SNI 3751-2009, whereas the remaining 4.15% did not fulfill the requirements of SNI 3751-2009. It can be assumed that in 2011, wheat flour products as food commodities that were circulated and marketed in Indonesia already met the SNI requirements according to the applied regulation.[38]

The National Standardization Agency of Indonesia requires fortification with iron of a minimum concentration of 50 ppm without any iron compound specified.[39] For iron fortification, manufacturers in Indonesia use elemental iron because it costs less and causes few, if any, sensory changes.

In 2004, a Center for Disease Control and Prevention (CDC) expert group in Cuernavaca, Mexico, made global recommendations for the type and level of different iron compounds (Table 3) to be added to wheat flour.[40] WHO recommended the same iron compounds but suggested that each country should estimate the level of fortification that would provide the required iron lacking in the traditional diet.[35]

Because elemental iron powders are organoleptically inert, they are widely used for wheat flour fortification. In 2002, a SUSTAIN task force evaluated the usefulness of the different elemental iron powders commonly employed in wheat flour fortification.[41] On the basis of in vitro, rat, and human studies, the task force recommended that electrolytic iron should be the only elemental iron powder used and that its amount added should be twice the iron level of ferrous sulfate, as its absorption capacity is approximately half of that of iron. They also recommended that carbon monoxide–reduced iron should not be used because of unacceptably low absorption. Furthermore, they indicated that more studies of carbonyl- and hydrogen-reduced iron powders are required before a recommendation can be made. It was subsequently found that another form of reduced iron (i.e., atomized iron powder) is widely used for wheat flour fortification because of its low cost. However, because of its low solubility in dilute acid under standardized conditions and its low absorption in rat hemoglobin repletion studies and human iron tolerance tests, atomized, reduced iron powder is not recommended for wheat flour fortification.[42]

The analysis results of the 2014 Indonesian Total Diet Study showed that among cereal groups, rice was the most consumed product by the majority of the Indonesian population (97.7%), with a consumption of 201.3 g per capita per day, followed by wheat and its products consumed by approximately 30.2% of the population (51.6 g per capita per day). A similar consumption pattern for cereal groups was found based on age, with rice consumption and its products as the highest consumed product followed by wheat and its products. The 51.6-g consumption of wheat and its products comprised wheat flour (9.4 g), wheat flour products (9.6 g), and noodles (32.6 g). Noodles were the third most consumed (by 23.4% of the population) cereal food commodity, with an average consumption of 32.6 g per capita per day.[43]

We compiled a list of wheat flour-based food products. Table 4 provides the estimates of iron content (mg) in wheat flour and its derivative products. Given that the average consumption of wheat flour and its derivative products in Indonesia is only 51.6 g per person per day and the estimated iron content is 8.8 mg (in 100 g per serving), the additional iron obtained from average wheat flour consumption is estimated to be 4.5 mg per capita per day. For noodles, as one of the most common wheat products consumed, the estimated iron content is as high as 5.5 mg per instant noodle serving (Table 4); thus, the iron content acquired from noodles is approximately 2.6 mg iron per capita per day.

The average amount of additional iron from fortified wheat flour is 4.5 mg per capita per day. The lowest dose of electrolytic iron with a significant impact on iron status is 10 mg. However, in a trial, electrolytic iron was shown to be less efficacious than ferrous sulfate in reducing iron deficiency, and no reduction was demonstrated in the percentage of participants with anemia.[44] Moreover, iron deficiency anemia remained in 60% of children in China after a 6-month trial using more than twice this 10-mg dose.[45] Because of the uncertainty regarding the lowest effective dose of electrolytic iron, the recommendation from the Cuernavaca Workshop should not be changed; this groups recommends that electrolytic iron twice the concentration of ferrous sulfate should be added.[35]

However, the wheat consumption range in Indonesia is below 75 g/day; as per the WHO recommendation (2009), electrolytic iron is not recommended when the average consumption of wheat flour is below 75 g/day because high levels of electrolytic iron could negatively affect the sensory properties of fortified flour.

The iron compounds that are recommended when wheat consumption is below 75 g/day are Na Fe-EDTA, ferrous sulfate, and ferrous fumarate. The results of experimental studies in animal and human models demonstrated that regardless of how beneficial the iron fortificant may be, its intake in combination with enhancers and inhibitors determines the final effect.[36] All the fortified condiments have been used in cereal-based diets high in phytic acid; therefore, Na Fe-EDTA is more preferable than ferrous sulfate and ferrous fumarate, and the enhanced iron absorption through EDTA in the presence of phytate is expected to reduce the variability in iron status responses caused by differences in overall meal bioavailability.[42]

Fe fortification using Fe-sulfate, Fe-fumarate, and Na Fe-EDTA in wheat flour does not significantly affect the sensory properties of breads and baozi. Na Fe-EDTA slightly affects the texture (slightly harder) of cookies. For noodles and macaroni, Fe-sulfate and Na-Fe-EDTA affect the color of products (darker color). Fe-fumarate is recommended for the iron fortification of wheat flour, with the lowest effect on the sensory properties of wheat products.[39]

The national wheat flour fortification program appears to use fortification levels that are too low in relation to the wheat flour consumption pattern, or the coverage of the program is limited. No study has investigated the effectiveness of iron compounds used in fortification in Indonesia, except for the Family Life Survey analysis series on anemia by Kendrick et al.[46] Kendrick et al concluded that wheat flour fortification has not significantly reduced the anemia prevalence among reproductive-age women in Indonesia.[47] Therefore, it seems unlikely that a meaningful reduction in the national prevalence of iron deficiency would be achieved through wheat flour fortification unless current practices are changed. The nine countries that can expect a positive impact from wheat flour fortification programs use ferrous sulfate: Argentina, Chile, Egypt, Iran, Jordan, Lebanon, Syria, Turkmenistan, and Uruguay. They could provide an average of 5.4–9.6 mg of additional iron per day through fortified flour, with optimal coverage.[42]

Quality monitoring for the wheat flour fortification program is lacking; quality monitoring is crucial because there are still reports of falsified fortification labels and the existence of low-quality, unfortified wheat flour in market circulation. Some local governments do not realize the importance of fortification; thus, the regional regulations that have been issued are ineffective.

Regarding the fortification of wheat flour, the government must immediately conduct an effectiveness test to determine its impact on reducing the prevalence of anemia. The replacement of supplementation with fortification results in savings in the state budget because the fortification program is cheaper and more effective than supplementation.

An effective and continuous food fortification program could enhance the nutrition status of vulnerable groups when the fortified food is consumed regularly, and the micronutrient substances added to the food vehicle are based on the daily average food intake per capita. The adequately fortified food must be consumed consistently by the majority of the population (approximately >80%).

Table 4. Iron content in flour and its products on the market

No.	Category	Brand Name	RDA† (%)	Iron content‡ (mg)
1	Flour	Bogasari Kunci Biru (Untuk Kue Kering, Cake, dan Biskuit)	40	8.8
2	Flour	Bogasari Segitiga Biru (Untuk Aneka Makanan)	50	11
4	Flour	Bogasari Cakra Kembar (Untuk Roti & Mie)	60	13.2
5	Flour	MILA Serbaguna	25	5.5
6	Flour	Golden Eagle	25	5.5
7	Flour	Hana Emas	60	13.2
8	Instant noodles	Indomie Rasa Soto Mie	25	5.5
9	Instant noodles	Indomie Goreng Rasa Rendang	20	4.4
10	Instant noodles	Indomie Mie Goreng Jumbo	35	7.7
11	Instant noodles	Indomie Rasa Ayam Bawang	15	3.3
12	Instant noodles	Indomie Mie Goreng	25	5.5
13	Instant noodles	Indomie Mie Goreng Iga Penyet	15	3.3
14	Instant noodles	Indomie Mie Goreng Sambal Rica-Rica	35	7.7
15	Instant noodles	Indomie Mie Goreng Pedas	45	9.9
16	Instant noodles	Indomie Mie Keriting Goreng Spesial	15	3.3
17	Instant noodles	Indomie Mie Keriting Rasa Ayam Panggang	20	4.4
18	Instant noodles	Indomie Mi Goreng Aceh	20	4.4
19	Instant noodles	Indomie Mi Goreng Rasa Ayam Geprek	30	6.6
20	Instant noodles	Indomie Rasa Seblak Hot Jeletot	30	6.6
21	Instant noodles	Mie Sedaap Rasa Ayam Spesial	10	2.2
22	Instant noodles	Mie Sedaap Rasa White Curry	15	3.3
23	Instant noodles	Mie Sedaap Rasa Kari Ayam	10	2.2
24	Instant noodles	Mie Sedaap Rasa Ayam Bawang	10	2.2
25	Instant noodles	Mie Sedaap Rasa Baso Spesial	10	2.2
26	Instant noodles	Mie Sedaap Rasa Soto	25	5.5
27	Instant noodles	Mie Sedaap Rasa Kari Spesial	10	2.2
28	Instant noodles	Mie Sedaap Goreng Ayam Krispi	10	2.2
29	Instant noodles	Mie Sedaap Mi Goreng	10	2.2
30	Instant noodles	Mie Sedaap Korean Spicy Chicken	10	2.2
31	Instant noodles	Mie Sedaap Cup Rasa Baso Spesial	10	2.2
32	Instant noodles	Mie Sedaap Cup Rasa Ayam Bawang Telur	10	2.2
33	Instant noodles	Mie Sedaap Cup Rasa Soto	10	2.2
34	Instant noodles	Mie Sedaap Cup Mi Goreng	10	2.2
35	White bread	Sari Roti Double Soft	10	2.2
36	White bread	Sari Roti Tawar Kupas	20	4.4
37	Biscuit	Lucky Stick Strawberry	10	2.2
38	Biscuit	Hello Panda Rasa Susu	6	1.32
39	Biscuit	Hello Panda Cookies & Cream	8	1.76
40	Biscuit	Biskuat Original	4	0.88
41	Biscuit	Belvita Breakfast Rasa Pisang & Sereal	20	4.4

†BPOM (National Agency of Drug and Food Control) RDA label reference: 2150 calories with 22 mg iron.
‡Estimated value
Weight per service for the flour category is generally 100 g and for instant noodles it is 70 g.
Source: Market survey compilation by author, 2020.

Therefore, the latest data on the target of food consumption to be fortified are crucial for determining the national standard.

Iron fortification of rice should be considered, which is a food commodity widely (97.7%) consumed by the Indonesian population, with an average consumption as high as 201.3 g per capita per day, which is much higher than the consumption level of wheat flour and its products. In a previous study, biofortified high-iron rice provided benefits for iron-deficient populations by increasing iron stores; this food also maintained the iron stores in populations without deficiency. From this feeding trial, it can be concluded that biofortified rice has the potential to improve the diets of the low-income population in developing countries.[48]

In the 1940s, the Philippines government started to fortify rice with thiamin, niacin, and iron and succeeded in decreasing the beriberi incidence, which, at that time, was a severe health problem caused by a lack of thiamine. In 1952, the Philippines government established laws on rice fortification that required all rice mills and wholesalers to fortify the rice milled and sold.

In the last decade, significant developments have been made in low-cost rice fortification technology, which have contributed to the reduction of micronutrient deficiency. The technology can affordably generate fortified rice having the same shape, smell, and taste as unfortified rice.

According to WFP (2018), nine studies have shown that fortifying rice with iron (alone or in combined with other micronutrients) can increase iron status (evidence of moderate certainty), other studies have shown small effect on iron status. One study demonstrated that fortified rice can increase the hookworm infection risk (evidence with low certainty).[8]

In Indonesia, to overcome the problem of anemia, a pilot project of fortification with iron and other substances in *Raskin* (rice for low-income individuals) was conducted in

2011. The feasibility of rice fortification was also examined in terms of cost and its impact on iron deficiency anemia (IDA). The fortification project was executed in 80 villages in Karawang and 15 villages in Bekasi using 14000 tons of *Raskin*. The monthly production amount of 1167 tons of *Raskin* was fortified for 3 years (2010–2012), costing US$2,220,440, with a possible time extension until 2013. The existing technology was assumed to be able to produce premix (artificial rice with a high iron content) with an identical shape and color as actual rice. At that time, no funding was available to conduct a premix trial and other necessary tests; thus, the cheapest premix was imported from India. The best and the most expensive premix was from the Philippines.[49]

In 2014, *BULOG* (Indonesian Bureau of Logistics) was involved in the development of the Rice Fortification for Poor Families pilot project in collaboration with the government and the Asian Development Bank using the Japan Fund for Poverty Reduction. The Indonesian Bureau of Logistics was actively involved, particularly in fortified *Raskin* production and distribution. The Southeast Asian Food and Agricultural Science and Technology Center of Bogor Agricultural University/IPB University conducted a fortified rice acceptance trial; the results showed that fortified rice was well accepted by the consumer because the fortification did not alter the color, taste, and smell of the rice. Moreover, 100 g of *Raskin* in 2014 comprised iron (8 mg), folic acid (20 µg), vitamin B-1 (0.64 mg), vitamin B-12 (1.0 µg), niacin (6 mg), and zinc (3 mg).

In 2015, a rice fortification program was conducted by the private producer AMARTA with the aim of fulfilling society's daily nutritional requirements. The nutritional components in 100 g of rice were folic acid (125 mcg), vitamin A (200 mcg), vitamin B-1 (thiamine; 0.4 mg), vitamin B-2 (riboflavin; 0.5 mg), vitamin B-3 (niacin; 6 mg), vitamin B-6 (pyridoxine; 0.6 mg), vitamin B-12 (cobalamin; 2 mcg), vitamin D (cholecalciferol; 1.5 mcg), vitamin E (tocopherol; 3 mg), vitamin K; 25 mcg), iron (5 mg), magnesium (30 mg), calcium (100 mg), iodine (50 mcg), zinc (5 mg). The rice cost was approximately Rp 20,000 per kg, and the rice was available in 5-, 10-, and 25-kg packs.[50]

In 2019, *BULOG* introduced rice containing vitamins (fortified) under the brand Fortivit, which does not require rinsing. The rice was enriched with vitamins and minerals. Specifically, 100 g of rice contained 195 µg of vitamin A, 0.65 mg of vitamin B-1 (thiamine), 9.1 mg of vitamin B-3 (niacin), 0.78 mg of vitamin B-6, 169 µg of vitamin B-9 (folic acid), 4 mg of iron (Fe), and 6 mg of zinc (Zn). This rice was developed in collaboration with the Kernel fortificant provider company, and it would be sold for IDR 20,000 per kg under the premium category and IDR 12,000 under the medium category.[51]

The consumption of micronutrient powder containing iron has some potential side effects in babies and children. In a recent study of children in Kenya, the administration of micronutrient powder containing iron (12.5 mg iron as ferrous fumarate) caused the development of intestinal inflammation (the increase of fecal calprotectin concentration) and an increase in the number of enteropathogens (including *Shigella*, *Escherichia coli*, and *Clostridium*) compared with micronutrient powder without iron.[52,53]

The adverse effects of micronutrient iron on intestinal microbiota can be reduced through the addition of prebiotic galacto-oligosaccharides to micronutrient powder, although further studies are required to confirm this. Thus, compared with iron interventions such as oral iron supplementation or fortification with micronutrient powder containing iron, rice fortification is preferred, as it is associated with a lower risk of infectious diseases in individuals with high or adequate iron intake. The daily iron dosage from the consumption of iron fortificant in the amount of rice is commonly lower and limited per person. In addition, iron fortificant is added to the food matrix thus reduces the potency of transferrin-bound iron accumulation in blood.

Therefore, the success of rice fortification interventions depends on the population and context as well as the prevalence of anemia. This is because iron deficiency can have other causes. The potential damage of fortified rice is low considering the low daily iron dosage and the limit on how much rice an individual can consume. More studies should be conducted to examine the possible biological and clinical adverse effects of iron-fortified rice from excess iron intake.

A study found that the fortification of cooking oil may be an alternative method of increasing vitamin A intake in mothers and children, especially in rural communities.[54] Mean oil consumption ranges from 2.4 mL/capita per day for infants aged 6–11 months to 31.5 mL/capita per day for lactating mothers. Moreover, the Recommended Nutrient Intake (daily) of vitamin A from fortified oil ranged from 26% in children aged 12–23 months to 35%–40% in older children and nonlactating women.[55] The increased intake of vitamin A is also attributed to the consumption of various foods that improve serum retinol in preschool children.[56]

Food-based approach

The International Conference on Nutrition was convened in 1992 for the development of food-based dietary guidelines (FBDGs) to promote appropriate diets and healthy lifestyles. In total, 159 heads of state committed to a plan of action on nutrition.[57] The popularization of nutrition messages started in the 1950s when a highly regarded nutrition expert in Indonesia, Prof. Poerwo Soedarmo MD, developed the slogan "Four Healthy Five Perfect" (locally known as Empat Sehat Lima Sempurna [ESLS] to educate people about the importance of nutrition. The message is a modification of the United States slogan "Basic seven and basic four."[58,59] This slogan is presented in a circlular form, with staple (carbohydrate source), side dish (protein and fat sources), vegetables, and fruits (vitamin and mineral sources) on the outside and milk in the middle. In the subsequent 25 years, ESLS became preferred in nutrition education and is widely known, especially among school-age children. It is well-known by the public even today.[60]

ESLS, which unintentionally provided a higher value for milk, produced a problematic situation for the governments of developing nations because of the unavailability of milk locally and its high price.[61] The government of Indonesia introduced the Guide to a Balanced Diet in 1993 (locally known as Pedoman Umum Gizi Seimbang [PUGS]). This was a result of the commitment of countries to the International Conference on Nutrition in 1992. In

1995, the guide was launched by the MoH and formally incorporated in the nutrition policy and program of REPELITA VI (1994–1998).[62] The guidelines were developed based on the results of research by the Nutrition Center for Research and Development, MoH. The guide has 13 messages: (1) food biodiversity, (2) eat food with sufficient energy, (3) consume complex carbohydrates for energy, (4) energy from fat and oil should only provide 25% of total energy, (5) use only iodized salt, (6) eat iron-rich foods, (7) exclusively give breast milk to infants 0–4 months (now 0–6 months), (8) eat breakfast daily, (9) drink sufficient clean and safe water, (10) do physical activity and exercise regularly, (11) avoid alcoholic drinks, (12) eat clean and safe food, and (13) always read food labels.[61]

The illustrative representation (as a cone) of the guidelines is a pyramid with three layers: (1) bottom layer: energy sources, (2) middle layer: fruit and vegetables, (3) top layer: foods that are sources of animal and plant protein. In 2002, the cone was altered to four layers, with energy source foods, vegetables and fruit, animal and plant protein, and sugar and salt from the bottom to top layers separately. Additionally, the following revisions were made: (1) separation between animal and plant proteins, in which milk is incorporated into the animal protein group, (2) addition of sugar and salt, (3) insertion of the recommended amount for consumption (servings), (4) fats and oils were excluded in the guide, and (5) message no. 7 was revised to "provide only breast milk for the baby until 4 months old, after which breast milk should be supplemented with complementary foods." In the next 8 years, no attempt was to modify the guidelines or popularize healthy eating and physical well-being.[63]

For children younger than 5 years, in addition to iron intake, the intake of zinc and calcium was consistently found to be limited in young children's diets, especially during the complementary feeding period.[64,65] However, the current FBDG messages do not specifically address the need to increase the density of these nutrients or to incorporate foods fortified with these nutrients. The anemia prevalence over the last 10 years has indicated that balanced nutrition has not yet been applied by the majority of individuals. Research on iron-rich food in Indonesia is lacking. An analysis of iron-rich food intake has been conducted by evaluating the consumption of animal protein source food, which is recognized as a good source of highly available iron.

Effect of optimal nutrition promotion and education on anemia status

The protein intake of the Indonesian population is still dominated by plant foods. For the prevention of anemia, protein and iron from animal foods are much more effective. Animal protein has high available iron, partly through the hem iron content of animals, and iron content is mostly unaffected by interactions with other food components.[36] The Deputy for Food and Agriculture of the Coordinating Ministry for Economic Affairs revealed that the consumption of animal protein in the country is only 8%, which is far below that in Malaysia (28%), the Philippines (21%), and Thailand (20%).[66]

On the basis of the Total Diet Study,[43] the meat most consumed by the population of Indonesia is poultry, with a consumption rate of 21.5% for all ages, followed by processed beef and buffalo, which are consumed by approximately 8.1% of the population. The 19–55 and 5–12 year age groups have the highest consumption of chicken (22.5%) and processed beef (13.8%), respectively.

Based on data from the Central Bureau of Statistics of Indonesia, the average daily per capita protein consumption decreased slightly from 47.25% in early 2011 to 45.21% in 2012 and continued to decline until it increased again at the end of 2015 (45.32%), reaching the highest at the end of 2016 (48.56%) and then stabilizing at 47.8% at the end of 2018.[67] This same pattern was identified for the consumption of processed foods.

The Executive Summary of Indonesian Population Expenditure and Consumption[67] revealed that the lower protein consumption may be the result of the low income level of the Indonesian population. Another problem is the quality of protein consumed because quality protein sources, such as livestock products, are expensive compared with vegetable protein sources.

In September 2018, the average daily protein consumption of every Indonesian citizen was 64.64 g, which is sufficient (in terms of quantity) based on the protein adequacy rate (2018 Indonesian protein adequacy rate is 57 g/capita/day). However, the largest contributor to protein consumption is grains (19.51 g), which makes up approximately 30% of total protein consumption. Consumption of protein in the form of fish, meat, egg, and milk is 16.67 g, or approximately one-quarter of total protein consumption. This amount is still less than the consumption of protein from whole grains. This finding in is in line with the conclusions of Harper, who researched the proportion of food ingredients commonly consumed in Indonesia and in other Asian countries.[68] According to Harper, most residents consume protein derived from plants. He also suggested increasing the consumption of animal protein if the income level of the population increases.[69]

According to Sediaoetama, the recommendation for animal protein consumption in the daily diet is 30% of total protein consumption.[70] Even if the quantity of protein consumed is sufficient in the Indonesian diet, its composition is still dominated by vegetable protein, whereas the proportion of animal protein consumed is still below the recommended level.

In terms of each group of animal protein, the maximum protein consumption is from fish compared with meat, eggs, and milk. On average, each Indonesian resident consumes 8.78 g of protein a day from fish. Protein consumption from meat is 4.46 g, half of the protein consumption from fish. Moreover, protein consumption from eggs and milk is only 3.43 g per capita a day.[67]

In the first quintile, protein consumption from eggs and milk (20.32%) is higher than that from meat (17.48%; Figure 2). This indicates that eggs and milk are more popular and affordable for low-income individuals. However, milk and eggs are not good sources of iron. Iron in egg yolk is poorly absorbed because of the presence of phosvitin.[71]

The emphasis on protein for evaluating nutritional quality has become counter-productive, as food product development is encouraged on this basis alone, without regard to the wider spectrum of food characteristics necessary for

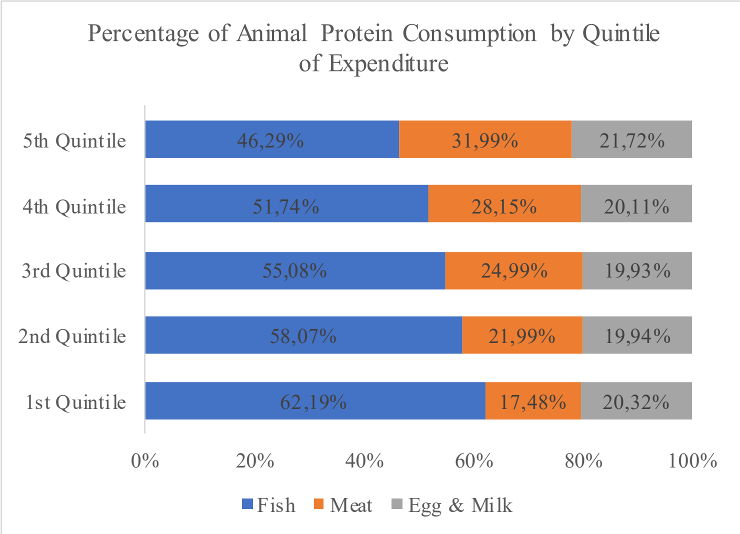


Figure 2. Proportion of animal protein consumption by quintile of expenditure. Source: BPS, 2018.[67]

optimal nutrition. Food intake biodiversity is a preferable measure of dietary quality and a basis of the prevention of nutritional anemia. It is now recommended by FAO as an index of food security[72,73] and in health outcome evaluation[74] and costs.[75,76]

Food production, supply, and distribution

The supply, availability, and distribution of animal protein sources is still uneven in all regions of Indonesia. The livestock sector in each region should be increased through local wisdom. According to the National Socioeconomic Survey, the consumption of animal protein at the provincial level varies between 11 and 27 g per capita a day.[77] The province with the highest average consumption of animal protein is the Riau Islands (27.12 g). More than 50% of the total consumption of animal protein in the Riau Islands is from fish (52.75%). By contrast, East Nusa Tenggara has the lowest protein consumption, which is 11.11 g per capita a day or less than half the protein consumption of the Riau Islands.

In general, in all provinces, the consumption of protein from fish is greater than that from meat, egg, and milk, except in the province of DI Yogyakarta. The consumption of protein from meat in Yogyakarta is 5.70 g per capita a day, the consumption of protein from eggs and milk is 3.89 g, and that from fish is 3.58 g. In addition, in terms of the proportion of the total animal protein consumption of each province, DI Yogyakarta has the highest proportion of protein consumption from meat (43.27%).[77]

CONCLUSION

Small-scale iron supplementation interventions are occasionally effective; however, regarding iron supplementation interventions on a larger scale, many regions in Indonesia had inadequate IFA tablet supply and ineffective implementation. Fortification should provide budgetary savings, but this concept may be ill-conceived or misplaced. Indonesian manufacturers add electrolytic iron to wheat flour, but wheat consumption is below the required 75 g/day in Indonesia, negating its effectiveness. The average amount of additional iron in fortified wheat flour is below the lowest dose of electrolytic iron necessary for a significant impact on iron status. WHO recommends that electrolytic iron should not be used when the average wheat flour consumption is below 75 g/day. Iron fortification of rice, a staple more widely consumed by Indonesians (rather than wheat flour), is a preferable alternative.

A feasibility study on iron-fortified cooking oil is recommended since its consumption level is relatively stable across life stages. The mean oil consumption ranges from 2.4 mL/capita per day for infants aged 6–11 months to 31.5 mL/capita per day for lactating mothers. However, no evaluation of its benefit and risk has been conducted, so the widespread use in this industry, where unintended consequences such as increased consumption of energy-dense fried foods would be encouraged, among other risks and costs.[78]

Although iron and folic acid supplementation has been implemented since the 1980s, iron fortification has been mandatory for two decades as a national intervention in Indonesia, and dietary modification has been promoted by the government. On the basis of the anemia prevalence among pregnant women, anemia is still a severe public health problem. Poor-quality diets, lack of food biodiversity, and compromised optimal nutrition and nutrient bioavailability, with adverse consequences for food security and health including nutritional anemia, are causes of iron deficiency and have an effect on its complex pathogenesis. Vulnerable life stages, such as the reproductive life span of women, childhood, and later life, and adverse socioeconomic circumstances are associated with the high prevalence of nutritional anemia, including that attributed to iron deficiency. Programs to reduce the likelihood of anemia in these settings will be more successful if they are less dependent on nutrient-specific strategies and focus more on the pathogenetic complexity arising from personal behavior, sociocultural factors, dietary and health patterns, local community, and ecology. Partnerships between the community and government reflected in evidence-based policy will always be of value, but continued research is required to examine the factors contributing to the successful outcomes of such programs.

ACKNOWLEDGMENT
We express our gratitude to the Danone Institute Indonesia (DII) for its research grant in 2020, which fully supported the writing of this manuscript. We also thank the officers of the Directorate of Community Nutrition Ministry of Health of the Republic of Indonesia, Community Health Centers, and National Institute of Health Research and Development for their assistance with the data collection.

AUTHOR DISCLOSURES
The authors have no conflicts of interest to declare. The study reported in this publication was supported by Danone Institute International (DII).

REFERENCES
1. Saxena R, Sharma G, Gulati N. Iron-deficiency anemia and chronic kidney disease: An overview. World J Anemia. 2018; 2:85-9. doi: 10.5005/jp-journals-10065-0030
2. Warner M, Kamran M. Anemia, iron deficiency. 2020 Jan. StatPearls. Treasure Island (FL), editor. StatPearls Publishing; 2020. [2020/09/15]; Available from: https://www.ncbi.nlm.nih.gov/books/NBK448065/.
3. Miller JL. Iron deficiency anemia: A common and curable disease. Cold Spring Harb Perspect Med. 2013;3:a011866. doi: 10.1101/cshperspect.a011866.
4. Lukito W, Wahlqvist M. Intersectoral and eco-nutritional approaches to resolve persistent anemia in Indonesia. Asia Pac J Clin Nutr. 2020;29(Suppl 1):S1-S8. doi: 10.6133/apjcn.202012_29(S1).01.
5. WHO. Global nutrition targets 2025: anaemia policy brief (WHO/NMH/NHD/14.4). Geneva; WHO; 2014 [cited 2020/04/16]; Available from: https://www.who.int/nutrition/publications/globaltargets2025_policybrief_anaemia/en/
6. Shekar M, Kakietek J, Dayton Eberwein J, Walters D. An investment framework for nutrition: Reaching the global targets for stunting, anemia, breastfeeding, and wasting. Washington, DC: World Bank; 2017. p. 6. doi: 10.1596/978-1-4648-1010-7_ch5 PMid:27744533.
7. Akhtar S, Ahmed A, Ahmad A, Ali Z, Riaz M, Ismail T. Iron status of the Pakistani population-current issues and strategies. Asia Pac J Clin Nutr. 2013;22:340-7. doi: 10.6133/apjcn.2013. 22.3.17.
8. World Food Programme. Scalling up rice fortification in West Africa. Switzerland: Sight and Life; 2018 [cited 2020/11/25]; Available from: https://sightandlife.org/wp-content/uploads/2018/12/SALWFP_RFSuppl18_en_web.pdf
9. 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.
10. Hawkes C. 2018 Global Nutrition Report. Shining a light to spur action on nutrition. Bristol, UK: Development Initiatives; 2018 [cited 2020/07/15]; Available from: https://www.who.int/nutrition/globalnutritionreport/2018_Global_Nutrition_Report.pdf?ua=1
11. World Bank. Prevalence of anemia among pregnant women. World Health Organization, Global Health Observatory Data Repository/World Health Statistics; 2020 [cited 2020/09/03]; Available from: https://data.worldbank.org/indicator/SH.PRG.ANEM.
12. World Bank. Repositioning nutrition as central to development a strategy for large-scale action. Washington: World Bank; 2006. p. 210 [cited 2020/04/18]; Available from: https://openknowledge.worldbank.org/handle/10986/ 7409
13. Ministry of Health of the Republic of Indonesia. Main results of 2018 basic health research. Jakarta: Ministry of Health of the Republic of Indonesia; 2018 [cited 2020/06/05]; Available from: https://kesmas.kemkes.go.id/assets/upload/dir_519d41d8cd98f00/files/Hasil-riskesdas-2018_1274.pdf
14. WHO. Sixty-fifth world health assembly. Geneva: WHO; 2020. p. 11–3 [cited 2020/09/03]; Available from: https://www.who.int/nutrition/topics/WHA65.6_resolution_en.pdf.
15. WHO. World Health Organization Global targets 2025 to improve maternal, infant and young child nutrition. Geneva: WHO; 2020. [cited 2020/09/03]; Available from: www.who.int/nutrition/topics/nutrition_%0Aglobaltargets2025/en/.
16. WHO. The global prevalence of anaemia in 2011. Geneva: WHO; 2015 [cited 2020/05/20]; Available from: https://www.who.int/nutrition/publications/micronutrients/global_prevalence_anaemia_2011/en/
17. WHO. World Health Report 2002 - Reducing risks, promoting healthy life. World Heal Rep. 2002;232.
18. WHO. Assessment, prevention and control. A guide for programme managers. Iron deficiency anaemia. Geneva: WHO; 2001 [cited 2020/09/10]; Available from: https://www.who.int/nutrition/publications/en/ida_assessment_prevention_control.pdf
19. Ministry of Health of the Republic of Indonesia. 2013 Basic health research. Jakarta: National Institute of Health Research and Development; 2013. [cited 2020/11/17]; Available from: https://www.litbang. kemkes.go.id/laporan-riset-kesehatan-dasar-riskesdas/
20. Ministry of Health of the Republic of Indonesia. 2007 Basic health research. Jakarta: National Institute of Health Research and Development; 2008 [cited 2020/11/15]; Available from: https://www.litbang.kemkes.go.id/laporan-riset-kesehatan-dasar-riskesdas/
21. Barkley J, Kendrick KL, Codling K, Muslimatun S, Pachón H. Anaemia prevalence over time in Indonesia: estimates from the 1997, 2000, and 2008 Indonesia Family Life Surveys. Asia Pac J Clin Nutr. 2015;24:452-5. doi: 10.6133/apjcn.2015.24.3.22
22. Muhilal, Sumarno I, Komari. Review of surveys and supplementation studies of anaemia in Indonesia. Food Nutr Bull. 1996;17:1-4. doi: 10.1177/156482659601700102.
23. Schultink W, Dillon D. Supplementation strategies to alleviate iron deficiency: Experiences from Indonesia. Nutr Res. 1998;18:1943-52. doi: 10.1016/S0271-5317(98)00164-X.
24. Helen Keller International [Indonesia]. Iron deficiency anemia in Indonesia. Report of the Policy Workshop. Jakarta: Helen Keller International Indonesia; 1997. p.1-16
25. Basta SS, Soekirman, Karyadi D, Scrimshaw NS. Iron deficiency anemia and the productivity of adult males in Indonesia. Am J Clin Nutr. 1979;32:916-25. doi: 10.1093/ajcn/32.4.916 PMid:107787.
26. National Development Planning Agency. Five Year Development Plan IV. Jakarta: National Development Planning Agency; 1988 [cited 2020/10/15]; Available from: https://www.bappenas.go.id/id/data-dan-informasi-utama/dokumen-perencanaan-dan-pelaksanaan/dokumen-rencana-pembangunan-lima-tahun-repelita/
27. Jus'at, I, Achadi EL, Galloway R, Dyanto A, Zazri A, Supratikto G et al. Reaching young Indonesian women through marriage registries: An innovative approach for anemia control. J Nutr. 2000;130:456S-8S. doi: 10.1093/jn/130.2.456S.
28. WHO. Guideline : Daily iron and folic acid supplementation in pregnant women. Geneva: WHO; 2012 [cited 2020/08/15]; Available from: https://apps.who.int/iris/bitstream/handle/10665/77770/9789241501996_eng.pdf

29. Sudargo T, Dewanti D, Rahmawati VA. Comparing the efficiency between commercial and governmental iron-folic acid (IFA) supplement among pregnant women in Yogyakarta and Sleman. Researchers and Experts Discussion on Multiple Micronutrient Supplementations (MMS) for Pregnant Women as A Measure for Stunting Prevention. Jakarta, 13th January 2020. [cited 2020/04/15]; Available from: https://www.researchgate.net/profile/Mamik_Sri_Sumarmi/publication/343376882_PROCEEDINGRESEARCHERS_AND_EXPERTS_DISCUSSION_ON_MULTIPLE_MICRONUTRIENT_SUPPLEMENTATIONS_MMS_FOR_PREGNANT_WOMEN_AS_A_MEASURE_FOR_STUNTING_PREVENTION/links/5f25fba1299bf134049a3b4e
30. Fitriana F, Dwi Pramardika D. Evaluation of the IFA Tablet Program in Adolescent Girls. Indonesian Journal of Health Promotion. 2019;2:200-7. doi: 10.31934/mppki.v2i3.807.
31. Directorate of Community Nutrition. Guidelines for the iron deficiency anemia prevention program in adolescent girls and women at reproductive age. Jakarta: Ministry of Health of the Republic of Indonesia 2016. p.97.
32. Directorate of Community Nutrition. 2018 Performance accountability report. Jakarta: Ministry of Health of the Republic of Indonesia; 2019 [cited 2020/07/07]; Available from: https:// kesmas.kemkes.go.id/assets/upload/dir_60248a365b4ce1e /files/SAKIP-GIZI-2018_1559.pdf.
33. Financial Audit Agency Republic of Indonesia. Summary of 2019 semester audit results. Jakarta: The Audit Agency; 2020 [cited 2020/08/25]; Available from: https://www.bpk.go.id/ihps
34. Ministry of Health of the Republic of Indonesia. Program guidelines for procurement and monitoring the quality of IFA tablets for pregnant women in community-based. Jakarta: Ministry of Health of the Republic of Indonesia and Millenium Challenge Account - Indonesia; 2015 [cited 2020/08/19]. Available from: https://www.academia.edu/28222067/Pedoman_Program_Pemberian_dan_Pemantauan_Mutu_Tablet_Tambah_Darah_Untuk_Ibu_Hamil_Millennium_Challenge_Account_Indonesia
35. WHO & FAO. Guidelines on food fortification with micronutrients. Geneva: World Health Organization; 2006 [cited 2020/07/15]; Available from: https://www.who.int/nutrition/publications/guide_food_fortification_micronutrients.pdf
36. Blanco-Rojo R, Vaquero MP. Iron bioavailability from food fortification to precision nutrition. A review. Innovative Food Science and Emerging Technologies. 2019;51:126-38. doi: 10.1016/j.ifset.2018.04.015.
37. Gustian A El. Development of food fortification programs and identification of fortified foods. Bogor: Bogor Agricultural University: 2013 [cited 2020/04/17]; Available from: https://repository.ipb.ac.id/handle/123456789/63945
38. Hartanto ES. Review of Indonesian national standard application of wheat product as a food ingredient. Jurnal Standardisasi [Journal of Standardization]. 2012;14:164-72. doi: 10.31153/js.v14i2.97.
39. Adawiyah DR, Muhandri T, Subarna S, Sugiyono1 S. The effect of iron fortification using Fe-sulfate, Fe-fumarate and Na Fe EDTA on the sensory quality of wheat flour. Jurnal Mutu Pangan Indonesia [Journal of Food Quality]. 2019;6:54-62. doi: 10.29244/jmpi.2019.6.54.
40. WHO, FAO, UNICEF, GAIN, MI, FFI. Recommendations on wheat and maize flour fortification. Meeting Report: Interim Consensus Statement. Geneva: WHO; 2009 [cited 2020/04/12]; Available from: http://www.who.int/nutrition/publications/micronutrients/wheat_maize_fort.pdf
41. Hurrell R, Bothwell T, Cook JD, Dary O, Davidsson L, Fairweather-Tait S et al. The usefulness of elemental iron for cereal flour fortification: a SUSTAIN Task Force report. Sharing United States Technology to Aid in the Improvement of Nutrition. Nutr Rev. 2002;60:391-406. doi: 10.1301/002966402320964061.
42. Hurrell R, Ranum P, De Pee S, Biebinger R, Hulthen L, Johnson Q et al. Revised recommendations for iron fortification of wheat flour and an evaluation of the expected impact of Current national wheat flour fortification programs. Food Nutr Bull. 2010;31(Suppl):S7-21. doi: 10.1177/15648265100311S102.
43. Siswanto et al. 2014 Total Diet Study: Indonesian Individual Food Consumption Survey. Jakarta: National Institute of Research and Development: 2014. [2020/06/14]; Available from: https://labmandat.litbang.kemkes.go.id/images/download/laporan/RIKHUS/2012/Laporan_SDT2014.pdf.
44. Zimmermann MB, Winichagoon P, Gowachirapant S, Hess SY, Harrington M, Chavasit V et al. Comparison of the efficacy of wheat-based snacks fortified with ferrous sulfate, electrolytic iron, or hydrogen-reduced elemental iron: Randomized, double-blind, controlled trial in Thai women. Am J Clin Nutr. 2005;82:1276-82. doi: 10.1093/ajcn/82.6.1276.
45. Sun J, Huang J, Li W, Wang L, Wang A, Huo J et al. Effects of wheat flour fortified with different iron fortificants on iron status and anemia prevalence in iron deficient anemic students in Northern China. Asia Pac J Clin Nutr. 2007;16: 116-21. doi : 10.6133/APJCN.2007.16.1.15
46. Kendrick K, Codling K, Pachon H. The contribution of wheat flour fortification to reducing anemia in Indonesia. Eur J Nutr Food Soc. 2015;5:446-7. doi: 10.9734/EJNFS/2015/20904.
47. Soekirman, Jus'at I. Food fortification in Indonesia. Malays J Nutr. 2017;23:1-7.
48. Haas JD, Beard JL, Murray-Kolb LE, Del Mundo AM, Felix A, Gregorio GB. Community and international nutrition iron-biofortified rice improves the iron stores of nonanemic Filipino women. J Nutr. 2005;135:2823-30. doi: 10.1093/jn/135.12.2823 PMid:16317127.
49. National Development Planning Agency. 2011-2015 National action plan for food and nutrition. Jakarta: National Development Planning Agency: 2011 [cited 2020/07/10]; Available from: https://www.bappenas.go.id/files/4613/5228/2360/ran-pg-2011-2015.pdf.
50. Food Safety Competent Authority. Amarta, the fortified rice. Food Safety Agency. 2020. [cited 2020/07/31]; Available from: http://keamananpangan.bkp.pertanian.go.id/.
51. Alika R. BULOG (National Logistical Supply Organization) sells vitamin enrichment rice which no need to be washed. Katadata.co.id, September 20,2019 [cited 2020/08/27]; Available from: https://katadata.co.id/ agustiyanti/berita/5e9a4e6d09ae8/bulog-jual-beras-bervitamin-tanpa-perlu-dicuci.
52. Ramsay LC, Charles CV. Review of iron supplementation and fortification. INTECH. 2015;175-95. doi: 10.5772/58987.
53. Mwangi M, Phiri K, Abkari A, Gbané M, Bourdet-Sicard R, Braesco V et al. Iron for Africa—Report of an Expert Workshop. Nutrients. 2017;9:576. doi: 10.3390/nu9060576.
54. Sandjaja S, Jus'at I, Jahari A, Tilden R, Ernawati F, Soekarjo D et al. Fortifying cooking oil with vitamin A in two rural districts of Indonesia: Impact on vitamin A status of mothers and children. Eur J Nutr Food Saf. 2015;5:802-3. doi: 10.9734/EJNFS/2015/21099.
55. Sandjaja, Jusat I, Jahari AB, Ifrad, Htet MK, Tilden RL et al. Vitamin A-fortified cooking oil reduces Vitamin A deficiency in infants, young children and women: Results from a programme evaluation in Indonesia. Public Health Nutr.

2015;18:2511-22. doi: 10.1017/S136898001400322X.
56. Mulyani EY, Kuswari M, Sudikno, Sandjaja, Ernawati F. Limitations in vitamin A supplementation to optimise serum retinol in preschool children from two central Java districts. Asia Pac J Clin Nutr. 2016;25(Suppl 1):S305. doi: 10.6133/apjcn.122016.s8
57. WHO & FAO. Preparation and use of food-based dietary guidelines: Report of a joint FAO/WHO consultation. Nicosia, Cyprus: WHO; 1998 [cited 2020/05/23]; Available from: https://www.who.int/nutrition/publications/nutrientrequirements/WHO_TRS_880/en/.
58. Soedarmo P. Gizi dan Saya (Nutrition and Me). Jakarta: Balai Penerbit FKUI; 1995. p. 35
59. Soekirman. Nutrition science and its application. Jakarta: Directorate General of Higher Education, Ministry of Education and Culture of the Republic of Indonesia; 2000. p. 150.
60. Achadi E, Pujonarti SA, Sudiarti T, Rahmawati, Kusharisupeni, Mardatillah et al. Primary schools are the entrance to improve knowledge, attitudes and behavior of balanced nutrition in the community. Jurnal Kesehatan Masyarakat Indonesia [Indonesian Journal of Public Health]. 2010;5:42-7. doi: 10.21109/ KESMAS.V5I1.161.
61. Soekirman. Taking the Indonesian nutrition history to leap into betterment of the future generation: Development of the Indonesian Nutrition Guidelines. Asia Pac J Clin Nutr. 2011;20:447-51. doi: 10.6133/APJCN.2011.20.3.14.
62. National Development Planning Agency. Five year development Plan VI. National Development Planning Agency; 1994 [cited 2020/06/24]; Available from: https://www.bappenas.go.id/id/data-dan-informasi-utama/dokumen-perencanaan-dan-pelaksanaan/dokumen-rencana-pembangunan-lima-tahun-repelita/.
63. Soekirman. "Neglected" Nutrition in National Development in Indonesia (1999-2008). In Paper presentated at the ACN Meeting in Hanoi, Vietnam; 2005.
64. Fahmida U, Rospita L. Report compilation of studies related to food consumption, physical exercise, healthy lifestyle, and nutritional status conducted in Indonesia between 2000-2010: Age group children under the age of five. Jakarta; 2010 [cited 2020/07/13]; Available from: http://www.danonenutrindo.org/pdf/Fahmida.pdf.
65. Santika O, Fahmida U, Ferguson EL. Development of food-based complementary feeding recommendations for 9- to 11-month-old peri-urban indonesian infants using linear programming. J Nutr. 2009;139:135-41. doi: 10.3945/jn.108.092270.
66. Prasetyo A. Indonesia's animal protein consumption is still low. Media of Indonesia. July 4, 2018 [cited 2020/08/4]. Available from: https://mediaindonesia.com/read/detail/170087-konsumsi-protein-hewani-indonesia-masih-rendah.
67. Central Bureau of Statistics. Average daily per capita protein and calorie consumption in the 1990 - 2018. 2018 [cited 2020/08/20]; Available from: https://www.bps.go.id/statictable/2018/01/11/1986/rata-rata-harian-konsumsi-protein-per-kapita-dan-konsumsi-kalori-per-kapita-tahun-1990---2018.html.
68. Harper JL, Brady JD, Driskel JA. Food, nutrition, and agriculture. Jakarta: UI Press; 1985. p. 154
69. Setiawan N. Development of animal protein consumption in Indonesia: Analysis of the results of the National Socio-Economic Survey. Jurnal Ilmu Ternak [Journal of Animal Science]. 2006;6:1:68-74. doi: 10.24198/jit.v6i1.2270.
70. Sediaoetama, Djaelani A. Nutrition science for students and professionals. Jakarta: Dian Rakyat; 2000. p. 56
71. Mahan LK, Escott-Stump S, Raymond JL. Krause's food and the nutrition care process 14th edition. St. Louis, Missouri: Elsevier; 2013 p. 636.
72. Ruel MT. Is dietary diversity an indicator of food security or dietary quality? A review of measurement issues and research needs. Food Nutr Bull. 2003;24:231-2. doi: 10.1177/156482650302400217.
73. Hoddinott J, Yohannes Y. Dietary diversity as a food security indicator; food consumption and nutrition division discussion paper. Int Food Policy Res Inst. 2002;24:163-80. doi: 10.22004/AG.ECON.16474.
74. Lee MS, Huang YC, Su HH, Lee MZ, Wahlqvist ML. A simple food quality index predicts mortality in Elderly Taiwanese. J Nutr Heal Aging. 2011;15:815-21. doi: 10.1007/s12603-011-0081-x.
75. Lo YT, Chang YH, Lee MS, Wahlqvist ML. Dietary diversity and food expenditure as indicators of food security in older Taiwanese. Appetite. 2012;58:180-7. doi: 10.1016/j.appet.2011.09.023.
76. Lo YT, Chang YH, Wahlqvist ML, Huang HB, Lee MS. Spending on vegetable and fruit consumption could reduce all-cause mortality among older adults. Nutr J. 2012;11:1-9. doi: 10.1186/1475-2891-11-113.
77. Central Bureau of Statistics. Socio-Economic Monitoring Survey. Central Bureau of Statistics: 2017 [cited 2020/03/17]; Available from: https://www.bps.go.id/publication/download.html.
78. Wahlqvist ML. Benefit risk and cost ratios in sustainable food and health policy: Changing and challenging trajectories. Asia Pac J Clin Nutr. 2020;29:1-8. doi: 10.6133/apjcn.202003_29(1).0001.
79. Siekmans K, Roche M, Kung'u JK, Desrochers RE, De-Regil LM. Barriers and enablers for iron folic acid (IFA) supplementation in pregnant women. Matern Child Nutr. 2018;5(Suppl):1-13. doi: 10.1111/mcn.12532.
80. Natalia S, Sumarmi S, Nadhiroh SR. Antenatal and Fe tablet coverage and its relationship with anemia prevalence in East Java. Media Gizi Indonesia [Indonesian Nutrition Media]. 2016;11:70-6. doi: 10.20473/ mgi.v11i1.70-76.
81. Rahmiati BF, Briawan D, Madanijah S. Qualitative study of improvement factor and strategy of supplementation program in Tasikmalaya regency. Media Gizi Mikro Indonesia [Indonesian Micronutrients Media]. 2018;9:113-22. doi: 10.22435/mgmi.v9i2.619.
82. Permatasari T, Briawan D, Madanijah S. The effectiveness of the iron supplementation program for adolescent girl in Bogor City. Media Kesehatan Masyarakat Indonesia [Indonesian Public Health Media]. 2018;14:1-8. doi: 10.30597/mkmi.v14i1.3705.
83. Briawan D, Adriyani A, Pusporini P. Determinants of supplementation program success on female students. Jurnal Gizi Klinik Indonesia [Indonesian Journal of Clinical Nutrition]. 2009;6:78-83. doi: 10.22146/ijcn.17715.
84. Dahlia S, Sirajuddin S, Citrakesumasari. A Report of evaluation of the IFA tablet program for pregnant women in the Binamu Community Health Center, Binamu District, Jeneponto Regency. Makassar: Postgraduate Program of Hasanuddin University; 2013 [cited 2020/04/18]; Available from: http://pasca.unhas.ac.id/jurnal/files/d85bd49a48de2af3e4f15020ee7c7b34.pdf.
85. Tuju SO, Nugraheni SA, Wulan LRK. Analysis on the implementation of iron supplementation program by midwives at primary healthcare center in South Minahasa. Jurnal Manajemen Kesehatan Indonesia [Indonesian Journal of Health Management]. 2013;1:153-8. doi: 10.14710/jmki.1.3.2013.%25p.
86. Secapramana ED. A Report of evaluation of the IFA tablet program for pregnant women at the public health center, Klari

District, Karawang Regency, January - December 2015. Jakarta: Faculty of Medicine, Kristen Krida Wacana University; 2015 [cited 2020/07/05]; Available from: https://fdokumen.com/document/artikel-evaluasi-program-pemberian-tablet-fe-pada-ibu-hamil.html

87. Maitri AK, Shanti KM, Rosselo J, Destriani, Friday LC, Novriana R. Evaluation of the IFA tablet program as an effort to prevent and cure anemia among pregnant women at the Kraton Public Health Center. Berita Kedokteran Masyarakat [Public Medicine News]. Gadjah Mada University. 2017;33:11-7. doi: 10.22146/bkm.37448

88. Triana Mutmainah V, Achadi Nugraheni S, Suparwati A. Analysis of the difference between iron supplementation program and primary healthcare center in Kendal. Jurnal Manajemen Kesehatan Indonesia [Indonesian Journal of Health Management]. 2014;2:140-9. doi: 10.14710/jmki.2.2.2014.%25p.

Instructions for Authors

(Revised October 2020)

AIMS AND SCOPE

The aims of the *Asia Pacific Journal of Clinical Nutrition* (*APJCN*) are to publish high quality clinical nutrition relevant research findings which can build the capacity of clinical nutritionists in the region and enhance the practice of human nutrition and related disciplines for health promotion and disease prevention. *APJCN* will publish original research reports, reviews, short communications and case reports. News, book reviews and other items will also be included. The acceptance criteria for all papers are the quality and originality of the research and its significance to our readership. Except where otherwise stated, manuscripts are peer-reviewed by at least two anonymous reviewers and the Editor. The Editorial Board reserves the right to refuse any material for publication and advises that authors should retain copies of submitted manuscripts and correspondence as material cannot be returned. Final acceptance or rejection rests with the Editorial Board.

Short Communications about special group or regional diets, nutrition and health

It is the APJCN policy and approach to descriptive studies, which record and monitor special group, local or regional food habits, nutritional status and their health relevance, to provide a short communication option. Studies which may be considered would be well-designed and conducted, with a representative and adequate sample to allow for generalisability to the purported groups studied. Such publications need to satisfy the following criteria: (1) Brevity, with no more than 3 tables or figures to succinctly present foods, nutrients and health (not longer than 3 pages of the Journal including references) (2) Novel and not simply repetitive of what others have done, although documentation of adverse or favourable trends is encouraged (3) Problem-solving in approach. These papers will be published as an identifiable section of an issue "Short Communications about Asia Pacific Food Patterns and their Health Relevance".

SUBMISSION OF MANUSCRIPTS

All articles submitted to the journal must comply with these instructions. Failure to do so will result in return of the manuscript and possible delay in publication. Manuscripts should be written so that they are intelligible to the professional reader who is not a specialist in the particular field. Where contributions are judged as acceptable for publication on the basis of scientific content, the Editor or the Publisher reserve the right to modify typescripts to eliminate ambiguity and repetition and improve communication between author and reader. If extensive alterations are required, the manuscript will be returned to the author for revision. Authors are advised to have their manuscripts reviewed by a scientific colleague who is fluent in English so that the manuscripts will conform to English usage and grammar.

Attribution of Authorship

The editors and readership need reassurance that the scholarship required of a scientific paper in APJCN has been duly executed and recognized by the stated authorship.

Authors should have regard to the following steps and contributions ordinarily required to develop, execute and report a scientific project (specify in the **Title page**):

- Conception and design
- Doing the field, experimental, clinical, data collection or compilation work, provided there is also a scholarly input during the process
- Data analysis and interpretation
- Preparation of draft manuscript, doing revisions or providing critique
- Overall and/or sectional scientific management

If the contributions are of a more technical or secretarial nature than intellectual or scholarly, they can be acknowledged as a final footnote to the paper in the usual way. However, this note should be brief and represent significant input without which the work would not have materialized.

APJCN acknowledges only one corresponding author. The corresponding author assumes contractual responsibility for all arrangements between the Journal and the authors while all authors remain collectively responsible for the scientific integrity of the paper.

Covering letter

Papers are accepted for publication in the journal on the understanding that the content has not been published or submitted for publication elsewhere; a statement indicating the paper's originality should be included. This must be part of the covering letter. Authors must also state that the protocol for the research project has been approved by a suitably constituted Ethics Committee of the institution within which the work was undertaken and that it conforms to the provisions of the Declaration of Helsinki in 1995 (as revised in Edinburgh 2000). All investigations on human subjects must include a statement that the subject gave informed consent and patient anonymity should be preserved. Any experiments involving animals must be demonstrated to be ethically acceptable and where relevant conform to National Guidelines for animal usage in research. Details of at least 4 potential referees.

Submission

The manuscript and other required documents including a completed Copyright Assignment Form and a list of four potential referees (see below) should be uploaded through the APJCN web-site: **apjcn.cnsoc.org**

Professor Duo Li
Editor-in-Chief
Asia Pacific Journal of Clinical Nutrition

Once the manuscript has reached our Editor, normally the corresponding author will be informed by email within a week. When the review process (between 1 and 4 months) is completed, we will send by email a note of acceptance or non-acceptance for publication of the manuscript.

Copyright

Papers accepted for publication become copyright of HEC Press and authors are asked to provide a transfer of copyright form, which can be downloaded from the Journal's website. In signing the transfer of copyright, it is assumed that authors have obtained permission to use any copyrighted or previously published material. All authors must read and agree to the conditions outlined in the Copyright Assignment Form, and must sign the Form or agree that the corresponding author can sign on their behalf. Articles cannot be processed until a signed Copyright Assignment Form has been received. This should be emailed to HEC Press at apjcn-apcns@umail.hinet.net

Potential referees

Authors are required to provide at least 4 potential referees, with affiliations and addresses, including email addresses. At least two of the referees should work or reside in a country other than that of the authors, and none should come from any of the authors' own institutions. We do not necessarily use your recommended referees. The onus is on all authors of a submission to ensure that selected referees are not in a conflict of interest likely to result in an un-objective peer review report.

Proof of scientific English standard

To ensure the quality of the manuscript, manuscripts should be professionally edited for scientific English. Certificate for manuscripts that underwent professional editing services should be provided prior to submission to APJCN. A discount service of Wallace editing (http://www.editing.tw/en/en) is available for those who are submitting their manuscripts to APJCN.

PREPARATION OF THE MANUSCRIPT

Format your manuscript for ISO A4 (212 _ 297 mm) with margins of 2.5 cm; use double-spacing and Times New Roman 12-point font size throughout by computer software WORD. **The abstract and text pages should have line numbers in the left margin**. All pages should be numbered consecutively in the top right-hand corner, beginning with the title page. Indent new paragraphs. Turn the hyphenation option off, including only those hyphens that are essential to the meaning.

Style

Manuscripts should follow the style of the Vancouver agreement detailed in the 'Uniform Requirements for Manuscripts Submitted to Biomedical Journals', as presented in JAMA 1997;277:927–34 (www.acponline.org/ journals/anals/01jan97/unifreqr.htm). *APJCN* uses US/ UK spelling and authors should therefore follow the latest edition of the Merriam–Webster's Collegiate Dictionary/Concise Oxford Dictionary. Please indicate your preference and use one or the other exclusively. If you do not specify, by default UK spelling will be used. A Guide for Medical and Scientific Editors and Authors (Royal Society of Medicine Press, London). Abbreviations should be used sparingly and only where they ease the reader's task by reducing repetition of long, technical terms. Initially use the word in full, followed by the abbreviation in parentheses. Thereafter use the abbreviation. At the first mention of a chemical substance, give the generic name only. Trade names should not be used. Drugs should be referred to by their generic names, rather than brand names.

For vitamins, notation use is B-2, B-2, B-3, B-6 and B-12 not B_1, B_2, B_3, B_6 and B_{12}. "Fetal" is more etymologically correct than "Foetal".

Note style for probability: $p<0.01$, with a lower case letter *p*. Avoid reporting an excessive number of digits beyond the decimal for estimates. They may alternatively be reported as less than some specified value (eg, $p<0.05$ or $p<0.001$).

Parts of the manuscript

Present your manuscript in the following order: (1) title page, (2) abstract and keywords, (3) text, (4) acknowledgements, (5) conflict of interest and funding disclosure, (6) references, (7) figure legends, (8) tables (each table complete with title and footnotes) and (9) figures. Footnotes to the text are not allowed and any such material should be incorporated into the text as parenthetical matter. Save and submit the above materials in **one** single Word file only.

Please do not use "level" when "concentration" is intended; or "life style" when "personal behaviour" is meant. Prefer "men" and "women" to "male" and "female".

Title page

The title page should contain (1) the title of the paper, which should be short, informative and contain the major key words, (2) a short running title (less than 50 characters, including spaces), (3) the full name (given name, middle initial, if any, and family name in that order) of each author along with principal qualification, email address and **individual contribution** (4) the addresses of the institutions at which the work was carried out together with (5) the full postal and email, and alternate email (to ensure email contact at all times) address, plus facsimile and telephone numbers, of the author to whom correspondence about the manuscript, proofs and requests for offprint should be sent.

Note: Names and principal qualification of authors should be presented as follow:
John Doe PhD[1], Mary Jane MSc[2]

Abstract and key words

The abstract should be structured with Background and Objectives, Methods and Study Design, Results, and Conclusions in 250 words or less. The abstract should not contain abbreviations or references. Five key words should be supplied below the abstract.

Graphical abstract

Authors are encouraged to submit a Graphical Abstract in addition to the convention written Abstract as it provides readers with a general understanding of the study and helps capture readership. Graphical abstracts should be concise and submitted as a figure included in the manuscript. Similar to any figures submitted to APJCN, the graphical abstract should be high resolution (300 dpi or higher).

Text

Authors should use subheadings to divide the sections of their manuscript:
INTRODUCTION, MATERIALS AND METHODS, RESULTS, DISCUSSION, ACKNOWLEDGMENTS, REFERENCES.
Numerical results and *p* values should be presented in text, tables and figures with no more than **3 significant figures**, unless there are exceptional circumstances.
Examples would be:
52.37 kg which should be 52.4 kg
p=0.15234 which should be p=0.152
Authors can make a case that their methodology requires further exception to these guidelines.

Methods

All manuscripts should provide the **clinical trial registration number** (if applicable). **Ethical approval number** should also be stated in the manuscript along with a statement in regards to the informed consent of participants in all trials.

Acknowledgements

Technical assistance and advice may be acknowledged in this section.

Conflict of Interest and Funding Disclosure

Authors should declare any financial support or relationships that may pose a conflict of interest. The source of financial grants and other funding should be acknowledged, including a frank declaration of the authors' industrial links and affiliations.

References

APJCN uses the Vancouver system for referencing. In the text, references should be cited using superscript Arabic numerals, after comma or full stop, in the order in which they appear, eg 'There is increasing recognition of antecedents of chronic disease like diabetes and cardiovascular disease in early life.[1,2] If cited only in tables or figure legends, number them according to the first identification of the table or figure in the text. In the reference list, the references should be numbered and listed in order of appearance in the text. Cite the names of all authors. When an article has more than ten authors, only the names of the first six authors should be given followed by 'et al'. The issue number should be omitted if there is continuous pagination throughout a volume. Names of journals should be abbreviated in the style used in Index Medicus (ftp://ftp.nlm.nih.gov/online/journals/archive/ljiweb.pdf). Reference to unpublished data and personal communications should appear in the text only. Please consult http://www.nlm.nih.gov/bsd/uniform_requirements.html for detail. If you use EndNote to manage bibliography, you can download the APJCN citation style from our website (apjcn.cnsoc.org) and locate the copy under your EndNote/styles. Some examples are listed as follows:

Journal article

1. Zarrin R, Ibiebele TI, Marks GC. Development and validity assessment of a diet quality index for Australians. Asia Pac J Clin Nutr. 2013;22:177-87. doi: 10.6133/apjcn.2013.22.2.15.
2. Weiss R, Dziura J, Burgert TS, Tamborlane WV, Taksali SE, Yeckel CW et al. Obesity and the metabolic syndrome in children and adolescents. N Engl J Med. 2004;350:2362-74. doi: 10.1056/Nejmoa031049.

Book

3. Fildes VA. Breasts, bottles, and babies. A history of infant feeding. Edinburgh: Edinburgh University Press; 1986.

Chapter in a Book

4. Willett W. The use of biomarkers in nutritional epidemiology. In: Kok F, Veer P, editors. Biomarkers of dietary exposure. London: Smith-Gordon; 1991. pp. 9-14.

Internet linkage

5. Mahowald ML. Overview of the evaluation and management of gout and hyperuricemia. Rheumatology & Musculoskeletal Medicine for Primary Care, Gout. 2004/10/8 [cited 2005/5/12]; Available from: http://www.rheumatology.org/publications/primarycare/number4/hrh0021498.asp
6. Talukder A, Haselow NJ, Osei AK, Villate E, Reario D, Kroeun H et al. Homestead food production model contributes to improved household food security and nutrition status of young children and women in poor populations. Lessons learned from scaling-up programs in Asia (Bangladesh, Cambodia, Nepal and Philippines). 2000/2/17 [cited 2012/8/6]; Available from: http://factsreports.revues.org/404.

Tables

Tables should be self-contained and complement, but not duplicate, information contained in the text. Each table must be formatted by using the table feature in WORD and presented as a separate file with a comprehensive but concise heading. Tables should be numbered consecutively in Arabic numerals in the sequence in which they are mentioned in the text. Use a single top rule, a single rule below the headings, and a single bottom rule. Do not use rules within the table body. Column headings should be clearly delineated, with straddle rules over pertinent columns to indicate subcategories. Column headings should be brief, with units of measurement in parentheses; all abbreviations should be defined in footnotes. Footnote symbols: †, ‡, §, ¶, ††, should be used (in that order) and *, **, *** should be reserved for ***p*** values. The table and its legend/ footnotes should be understandable without reference to the text. All lettering/ numbers used in tables should be font style 'Times New Roman' and font size 8.5 or 9.

Figures

All illustrations (line drawings, bar charts and photographs) are classified as figures. Figures should be cited in consecutive order in the text. Figures should be sized to fit within the column (85 mm), intermediate (114 mm) or the full text width (177 mm). Line figures or bar chart figures should be drawn in a computer graphics package (e.g. EXCEL, Sigma Plot, SPSS etc.). All lettering used in figures should be font style 'Times New Roman' and font size 9.

Important: All figures must be electronically inserted at the end of the manuscript. Photographs should be supplied as 300 dpi or more, black and white photographic prints and must be unmounted. Individual photographs forming a composite figure should be of equal contrast, to facilitate printing, and should be accurately squared. Photographs need to be cropped sufficiently to prevent any subject being recognized, or an eye bar used; otherwise, written permission to publish must be obtained. Colour photographs should be submitted digitally with the pixel characteristics of good quality, for on-line publication. Where hard copy colour is required, a charge of AU$1,100/US$660 for the first three colour figures and AU$550/US$330 for each extra colour figure thereafter will be charged to the author.

Figure legends: Legends should be self-explanatory and typed on a separate sheet. The legend should incorporate definitions of any symbols used and all abbreviations and units of measurement should be explained so that the figure and its legend is understandable without reference to the text. (Provide a letter stating copyright authorisation if figures have been reproduced from another source.)

Abbreviations

The following abbreviations are accepted without definition by APJCN

ANCOVA (analysis of covariance)
ANOVA (analysis of variance)
BMI (body mass index)
BMR (basal metabolic rate)
CHD (coronary heart disease)
CI (confidence interval)
CVD (cardiovascular disease)
df (degrees of freedom)
DHA (docosahexaenoic acid)
DNA (deoxyribonucleic acid)
DRIs (dietary reference intakes)
EDTA (ethylenediamine tetra-acetic acid)
ELISA (enzyme-linked immunosorbent assay)
EPA (eicosapentaenoic acid)
FAO (Food and Agriculture Organization) (except when used as an author)
FFQ (food-frequency questionnaire)
GC (gas chromatography)
Hb (haemoglobin)
HDL (high-density lipoprotein)
HIV (human immunodeficiency virus)
HPLC (high-performance liquid chromatography)
IHD (ischaemic heart disease)
LDL (low-density lipoprotein)
MRI (magnetic resonance imaging)
MUFA (monounsaturated fatty acids)
NS (not significant)
OR (odds ratio)
PCR (polymerase chain reaction)
PUFA (polyunsaturated fatty acids)
RDA (recommended dietary allowance)
RER (respiratory exchange ratio)
RIA (radioimmunoassay)
RMR (resting metabolic rate)
RNA, mRNA etc. ribonucleic acid, messenger RNA etc.
SFA (saturated fatty acids)
SNP (single nucleotide polymorphism)
UN (United Nations) (except when used as an author)
UNICEF (United Nations International Children's Emergency Fund)

UV (ultra violet)
VLDL (very-low-density lipoprotein)
WHO (World Health Organization) (except when used as an author)

UPLOADING MANUSCRIPTS

Authors should upload their manuscripts and all required documents to apjcn.cnsoc.org. The entire article (including tables and figures) should be supplied. The following instructions should be adhered to:

- *It is essential that the final, revised version of the accepted manuscript is identical.*
- *Do not use the carriage return (enter) at the end of lines within a paragraph.*
- *Specify any special characters used to represent non-keyboard characters.*
- *Take care not to use l (ell) for 1 (one) or O (capital o) for 0 (zero).*
- *Use a tab, not spaces, to separate data points in tables.*
- *If you use a table editor function, ensure that each data point is contained within a unique cell, i.e. do not use returns within cells.*
- *Digital figures must be supplied as high-resolution output (>300 dpi).*

PROOFS, OFFPRINTS AND CHARGES FOR PAPERS

(Please see **PAYMENT FORM** for payment options).

Publication fee

For papers submitted from January 1st 2020, the publication fee will be US$850 (+GST if from Australia), payable on acceptance.

Proofs

Proofs will be sent via email as a WORD file formatted in *APJCN* style with 'tracking' activated so that all changes made to the manuscript by the author are clearly visible. Please also highlight all changes in yellow to ensure all edits are picked up. The edited proofs must be emailed *within 5 days of receipt*. Alterations to the text and figures (other than the essential correction of errors) are unacceptable at proof stage and authors may be charged for excessive alterations. Authors should therefore supply an email address to which proofs can be emailed. If absent, authors should arrange for a colleague to access their email, retrieve the emailed manuscript and check and return them to the publisher on their behalf.

Offprints

Free offprints are not provided to authors
Charges: 50 offprints - US$180 for 1-5 pages, US$265 for >5 pages; 100 offprints - US$230, 1-5 pages, US$320 for >5 pages

***APJCN* online**

All papers are available free-of-charge; Journal abstracts and full papers are available on-line free-of-charge via the website (apjcn.cnsoc.org).

APJCN PAYMENT FORM 2021

Asia Pacific Journal of Clinical Nutrition
Editor-in-Chief: Prof Duo Li; **Editor Emeritus:** Prof Mark L Wahlqvist
Co-Editors: Prof Jonathan Hodgson, Prof Geok-Lin Khor, Prof Anura V Kurpad, Prof Oran Kwon, Prof Meei-Shyuan Lee, Prof Safarina G Malik, Prof Andrew J Sinclair, Prof Shaw Watanabe, Prof Yuexin Yang
Print ISSN: 0964-7058; **Online ISSN:** 1440-6047; **Frequency:** Quarterly (plus supplements)

HEC PRESS

ABN: 24 120 774 923
apjcn-apcns@umail.hinet.net

Free on-line access: abstracts and full papers www.apjcn.org

SUBSCRIPTIONS: Please tick the boxes below corresponding to the type of subscription, whether you wish to

	Personal price	*Institution*
HARD COPY	☐ US$200	☐ US$460

Subscriptions are for current calendar year only – back issues will be supplied for current calendar year for late subscriptions

REPRINTS: Manuscripts 1-5 pages	☐ 50 copies US$180	☐ 100 copies US$230
Manuscripts >5 pages	☐ 50 copies US$265	☐ 100 copies US$320

Reprint details: vol………..issue……….pages……………title…..……………………………………..……………………….

SINGLE ISSUES: Year ………………Volume…………………Issue…………………………............ ☐ 1 copy US$45

SINGLE PAPERS (pdf file): Year ………………Volume…………………Issue……………………… ☐ 1 copy US$15

PUBLICATION FEE

The publication fee is **US$850** (+GST if from Australia), payable on acceptance.

*List first 2 authors on accepted paper*____

*Title of paper*____

PAY BY

☐ **Direct Debit to HEC Press account:**

Bank of Melbourne Ltd, Level 2/ 525 Collins Street, Melbourne, VIC 3000, Australia
BSB: 333-055 Account number: 552023032 swift code SGBLAU2S (same as St George bank)

Date paid__________ **Where paid**__________ **Name of bank**__________ **Country**__________

☐ **I wish to pay by credit card (the invoice will be sent by Paypal):**

Total US$ _________

INFORMATION REQUIRE FOR A RECEIPT

Name...

Address...

....**Postcode**.......................................

Email........ ....

Return this form to: HEC Press
Administrative Officer, Email: apjcn-apcns@umail.hinet.net

Asia Pacific Journal of Clinical Nutrition. Volume 29, Supplement 1, 2020

Contents:

Review Articles

HEC PRESS