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EFFICACY AND SAFETY OF IRON FORTIFIED RICE IN INDIA

- A WHITE PAPER



**EFFICACY AND SAFETY OF IRON FORTIFIED RICE IN INDIA
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FOREWORD

India has made substantial progress in improving survival, health and nutrition. However, anemia still affects a significant portion of the population, with women and children being particularly vulnerable. Micronutrient deficiencies, including iron, vitamin B12, folate, and zinc, are major contributors to high levels of anemia. These deficiencies are primarily a result of unbalanced and poor diets, with low consumption of nutritious foods like fruit, vegetables, milk, pulses, and meat.

The Government of India has implemented the Anemia Mukht Bharat (AMB) initiative under the National Nutrition Mission, which aims to prevent and control anemia through six interventions targeting different age groups and institutions. These interventions include fortifying foods with iron and folic acid, providing iron and folic acid supplements to vulnerable populations, testing and treating anemia, behavior change communication, deworming, and addressing non-nutritional causes of anemia such as malaria and hemoglobinopathies.

I congratulate ICMR-National Institute of Nutrition for bringing out "Efficacy and Safety of Iron Fortified Rice in India - A White Paper." This paper summarizes evidence related to the strategy of rice fortification in India. It provides an overview of iron intake levels without and with consumption of fortified rice and salt utilizing data from nationally representative diet and nutrition surveys, and the risk of inadequacy or excessive intake using a probability based approach. The paper also summarizes empirical evidence of effectiveness of iron fortified rice in reducing anemia and iron deficiency, as well as evidence of potential adverse effects. Overall, the evidence synthesized in the paper is substantially in favour of benefits with little risk of adverse effects.

This white paper serves as a valuable resource for policymakers, public health professionals, researchers, and other individuals committed to addressing malnutrition and its adverse consequences.

Rajiv Bahl
(Rajiv Bahl)



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आज़ादी का
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MESSAGE

Anemia is a medical condition characterized by low hemoglobin resulting in an inadequate capacity of blood to transport oxygen to meet the body's physiological requirements. One significant cause of anemia is iron deficiency, which is one of the components of hemoglobin. Other nutritional causes include deficiencies of vitamin B12 and folic acid. Non-nutritional cause of infections may include chronic diseases (like chronic renal failures and chronic liver cell failure), advanced malignancy and chronic infections like tuberculosis.

Enhancing nutritional value of food through fortification may be a cost-efficient approach to enhance nutritional well-being of deficient populations. As a public health intervention, a sustained behavior change communication for consumption of fortified food must accompany these fortification efforts. We should also increase awareness about the deleterious health effects of anemia, the role of fortification and significance of diet diversity and appropriate cooking methods.

However, all universal measures concerning food fortification should be done for a limited period during which the effect of such fortification on health should be investigated by way of implementation research. If the fortification fails to show the desired results, the strategy should be re-looked at and re-evaluated.

It is with great pleasure that I introduce this comprehensive work on rice fortification in India. Rice has been traditionally a staple food for millions of people across the length and breadth of our country. This white paper provides a comprehensive insight into iron-fortified rice, which will hopefully benefit researchers as well as policymakers involved with Anemia-Mukt Bharat, a flagship programme of the Government aimed at controlling anemia in the Indian population.

Sudhansh Pant

(Sudhansh Pant)

Date : 31.10.2023

Place : New Delhi

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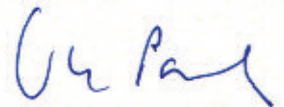
MESSAGE

Iron deficiency anemia negatively impacts health, wellbeing and socioeconomic status of millions of individuals. Prolonged insufficient intake of iron leads to depleted iron reserves and eventually results in iron deficiency anemia. While it can affect people of all ages, the most susceptible groups include children, women of reproductive age and pregnant women.

Food fortification is one of several complementary intervention approaches to address anaemia and micronutrient deficiencies. Universal salt iodization effectively addressed iodine deficiency disorders in India. A program for the fortification of rice with iron has been launched by the government, in addition to other policy interventions to promote nutritious foods, including the promotion of millets, crop varieties with higher nutrient content, and the establishment of nutri-gardens.

Rice fortification with iron involves adding Fortified Rice Kernels (FRK), containing FSSAI prescribed micronutrients such as iron, folic acid, and vitamin B12, to regular rice (custom milled rice) in a 1:100 ratio. Fortified rice closely resembles traditional rice in terms of aroma, taste, and texture. The fortification process takes place in rice mills during the milling of rice. Fortifying rice with vital nutrients represents an innovative approach that holds immense potential to combat malnutrition, particularly micronutrient deficiencies. By enhancing the nutritional content of rice, we can provide a sustainable and cost-effective solution to improve the health and well-being of millions of Indians, particularly women, children, and marginalized communities.

This white paper summarizes evidence on expected iron intake of Indian population, benefits of rice fortification and possible adverse effects. It presents a comprehensive overview of rice fortification, elucidating the scientific foundations, technological advancements, and regulatory considerations involved in this process. I believe the paper will be useful for policymakers, program managers and public health professionals, and other stakeholders committed to addressing malnutrition.


(Vinod Paul)



एक कदम स्वच्छता की ओर

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ABBREVIATIONS

AMB	- Anemia Mukh Bharat
CNNS	- Comprehensive National Nutrition Survey
EAR	- Estimated Average Requirements
FPP	- Ferric Pyrophosphate
FSSAI	- Food Safety & Standards Authority of India
GOI	- Government of India
ICDS	- Integrated Child Development Services
MDM	- Mid-Day Meal
MFPP	- Micronized Ferric Pyrophosphate
NNMB	- National Nutrition Monitoring Bureau
NPBI	- Non-protein bound Iron
NFHS	- National Family Health Survey
OWS	- Other Welfare Schemes
Na Fe EDTA	- Sodium iron ethylene diamine tetra acetate trihydrate
PM-POSHAN	- Pradhan Mantri Poshan Shakti Nirman
PUFA	- Poly Unsaturated Fatty Acids
RDA	- Recommended Dietary Allowances
RNI	- Recommended Nutrient Intakes
SBCC	- Social and Behaviour Change Communication
SCFA	- Short Chain Fatty Acids
SSNP	- Social Safety Net Programs
TPDS	- Total Public Distribution System
TUL	- Tolerable Upper Limit
WHO	- World Health Organization

EXECUTIVE SUMMARY

Anaemia is a major public health concern among all age groups in India. The nationwide data from the National Family Health Survey (NFHS-5) survey conducted in India, in 2019–21, showed prevalence of anaemia as 67%, 57% and 52% among children (aged 6–59 months), women in the reproductive age group and pregnant women respectively. Under the Anemia Mukht Bharat's (AMB) six-pronged strategy, the government launched fortified rice (with iron, folic acid and B12) through the social safety net programs such as PM-POSHAN, Integrated Child Development Services (ICDS), Targeted Public Distribution System (TPDS), and Other Welfare Schemes (OWS) as one of the strategies.

The Food Safety and Standards Authority of India (FSSAI) mandates the use of ferric pyrophosphate (FPP: 28–42.5mg/kg) or sodium iron ethylenediaminetetraacetate trihydrate (Na Fe EDTA 14–21.25 mg/kg) for fortification of rice with iron. Based on the level of rice intake from the NNMB data, the total iron intake from FFP fortified rice was estimated to be 0.9 mg/day among children aged 6–12 months, 5.9 mg/day among women of reproductive age, 6.0mg/day among pregnant women, and 6.2mg/day among adult men, with 35mg of ferric pyrophosphate (FPP) fortified in one kg rice. Alternatively, if Na Fe EDTA is used at 17.6mg per kg rice, the total estimated daily iron intake from fortified rice was estimated to be 0.5mg/day among children aged 6–12 months, 3.0mg/day among women of reproductive age, 3.0mg/day among pregnant women and 3.1mg/day among adult men. Fortification programs are designed to fill the gap between the actual intake and the requirement (Estimated Average Requirement-EAR) of the population. When comparing the estimated total iron intakes through FPP or Na Fe EDTA fortified rice, the iron intakes are around the EAR for all the age groups, except for men who may be taking 3mg iron higher than the RDA (ICMR-NIN, Nutrient Recommendations, 2020). However, the iron intakes are well below the Tolerable Upper Level (TUL) for all physiological age groups consuming fortified rice, and estimates show no risk of excess iron consumption through fortified rice in India.

By using the probability approach, the proportion of individuals with iron inadequacy without any fortification ranged from 34% to 80%. The lowest (34%) inadequacy level was found among sedentary adult males and highest (80%) was among 10–12 years and 16–17 years girls. Proportion of individuals with probability of inadequacy if rice alone is fortified ranged from 5% to 59%, and the highest probability of inadequacy was seen in 10–12 year-old girls (58%) followed by 16–17 year-old girls (59%). Proportion of individuals with probability of inadequacy if both rice and salt are fortified ranged from 0.2% to 29%. The highest probability of inadequacy was seen in 10–12 year-old girls with 29% followed by 23% in 16–17 year-old girls. However, with fortification of both rice and salt, using the intake distribution it was observed that 0.99% of boys aged 16–17; 2.4% of sedentary men and 3.8 % of moderate activity men are exposed to risk of excess iron intake (above TUL). The average total iron intake with iron fortified rice does not exceed 0.59 mg/kg/day. And, even with both fortified rice and fortified salt, the intake does not exceed 0.78mg/kg/day.

Studies have consistently shown improvement in haemoglobin status with supervised feeding, fortified foods or with iron supplements, but effectiveness studies are not available. A Cochrane review, on impact and safety of rice fortification, analysed some studies among children aged 5–18 year-old and non-pregnant, non-lactating women of 18–49 years, found a modest reduction in anaemia prevalence. As for safety issues, there are no studies with fortified rice intake, but soluble oral iron supplements with 1–2 mg iron/kg/day among children have shown increase in risk of diarrhoea, dysentery and malaria (in endemic areas). In addition, the form of iron used in fortified rice is different, from those that are commonly used in oral iron supplements, and therefore less likely to pose any risk. Similarly, there are no primary or secondary studies conducted on the association between fortified rice consumption and risk of diabetes mellitus or hypertension or haemoglobinopathies. Also, studies on dietary non-haem iron intake have not found any association of iron intake with type 2 diabetes, hypertension or haemoglobinopathies or increase the risk of the same.

Fortification of food is a cost-effective strategy to improve the nutrition status of populations. However, as a public health measure fortification effort requires to be dovetailed with regular monitoring of dietary intakes, impact evaluation, adverse effects in different segments of populations, risk of over consumption, development of biomarkers of excess intake and long-term health effects. Policy on Behavior Change Communication (BCC) on consequences of anemia, role of fortification, importance of dietary diversity and cooking procedures must be prioritized in the program. To inform policy decisions, an impact evaluation and adverse effect study along with cost-effectiveness analysis of fortified rice consumption is necessary.

SCOPE OF THE DOCUMENT

1. Scope of the document

This document provides a comprehensive analysis of the use of fortified rice in India with a focus on its efficacy and safety. It covers the prevalence of anemia in India, from two recent national surveys, and the various strategies adopted by the Government of India (GOI) to address the issue. The document describes the plan of the GOI to implement the usage of fortified rice through social safety net programs such as PM-POSHAN, Integrated Child Development Services (ICDS) scheme, Targeted Public Distribution System (TPDS), and Other Welfare Schemes (OWS).

The document also outlines the iron intake levels, the risk of inadequacy using the probability approach and expected risk of excess intake among Indian population through the consumption of fortified rice and salt using National Nutrition Monitoring Bureau (NNMB) data. The efficacy and safety of rice fortification are evaluated based on the latest update of the Cochrane review, other reviews that include randomized control trials from around the world.

In addition, the document examines the potential risks of excessive iron intake from fortified rice and its association with non-communicable diseases such as hypertension and type-2 diabetes. The feasibility of side effects associated with iron from fortified rice intake is analysed, and the impact of fortified rice on hemoglobinopathies is discussed.

Lastly, the document explores the role of social and behaviour change communication in promoting the uptake of fortified rice among the general population. Overall, this document provides a thorough assessment of the use of fortified rice in India, including its benefits and potential risks, and the strategies for its implementation.

1.1 Background and Introduction

Anemia and iron deficiency are major public health concerns caused by a long-term negative iron balance. Iron deficiency anemia, which is defined as low blood haemoglobin concentration, is the most severe stage of iron deficiency. Although the

terms ‘iron deficiency’ and ‘iron deficiency anemia’ are often used interchangeably, they are not the same condition(1).

Recent nationwide data on iron deficiency anemia in different age groups is available from the National Family Health Survey (NFHS-5) and the Comprehensive National Nutrition Survey (CNNS)(2,3). According to the NFHS-5 survey conducted in 2019–21, iron deficiency burden is highest among children aged 6–59 months (67.1%), women aged 15–19 years (59.1%), and non-pregnant women in the reproductive age group (57.2%). Men aged 15–19 years have a lower burden of 31.1%, while pregnant women have a burden of 52.2%. However, the NHFS survey has been criticized for potentially overestimating the anemia burden due to its use of capillary blood and estimation through Hemocue photometer (hb 201+)(2).

The CNNS, lead by the Ministry of Health and Family Welfare, used venous blood and estimated haemoglobin through the cyanmethaemoglobin method in children aged 1–19 years during 2016–2018. The prevalence of anemia in preschool children aged 1–4 years is 40.5%, while it is 23.5% in school children aged 5–9 years and 28.4% in adolescents. The prevalence of iron deficiency is 31.9% in preschool children (Serum Ferritin <12 mcg/lit), 17% in children aged 5–9 years (Serum Ferritin <15mcg/lit), and 21.5% in adolescents(4).

Paradoxically, the CNNS showed higher prevalence of anemia in rural and poorer children and adolescents and higher burden of iron deficiency in urban and richer participants. Haemoglobin synthesis needs many other nutrients apart from iron including good quality protein. The diets of poor children lack nutritious foods like fruits, vegetables, milk, eggs etc. Moreover, they have more infections due to unhygienic environment. Under these conditions, the utilization of iron for haemoglobin synthesis becomes less efficient resulting in anemia. States such as Madhya Pradesh, Bihar, Haryana, Jharkhand, U.P., West Bengal and Tripura have a high prevalence of anemia, especially in children under 5 years of age.

According to the World Health Organization (WHO), a prevalence of anemia $\geq 40\%$ is a serious public health problem, while a prevalence of 20–39.9% is a moderate public health problem. A prevalence of 5–19.9% is considered a mild public health problem, and less than 5% is not a public health problem(5).

1.2 Fortification strategy of Government of India

Anemia Mukht Bharat (AMB) was launched in March under the National Nutrition Mission in India (Figure 1). The AMB has a comprehensive approach to prevent and control anemia with six interventions, targeting six age groups, and six institutions(6). The interventions include iron and folic acid (IFA) supplements, behaviour change communication (BCC), test and treat anaemia, fortification with IFA, deworming and addressing non nutritional causes of anaemia such as malaria, fluorosis, hemoglobinopathies. One of the programs under intervention is the mandatory provision of iron and folic acid fortified foods in government-funded health programs(6). The implementation of fortified rice supply in India is planned in three phases with complete coverage by March 2024(7). The government is supplying fortified rice through social safety net programs like PM-POSHAN, ICDS, and Total PDS, targeting vulnerable and high-risk groups(7).

Food fortification is one of the measures to reduce the burden of micronutrient deficiencies and improve health of the population. CODEX defines fortification or enrichment as ‘the addition of one or more essential nutrients to a food for the purpose of preventing or correcting a demonstrated deficiency of nutrients in the population or specific population groups(8).’ Fortification is a temporary measure to control micronutrient deficiencies until more up-stream long term approaches such as diversification of diets are made available. Micronutrient fortification is the most cost-effective development intervention, as evidenced by reviews such as the Copenhagen Consensus(9,10). Currently, the government of India's strategy for food fortification with iron is targeted fortification, which aims to increase the intake of specific subgroups of the population, rather than universal fortification(5). In contrast, mass fortification, which adds one or more micronutrients to commonly consumed foods like cereals, milk, and

condiments, is usually mandated, and regulated by the government sector(5). Fortification programs are designed to fill the gap between the actual intake and the requirement (Estimated Average Requirement-EAR) of the population.

Several countries worldwide are fortifying rice with iron, either as mandatory or voluntary fortification, and details of fortification standards are described in Table 1.

Figure 1. Anemia Mukht Bharat Strategy

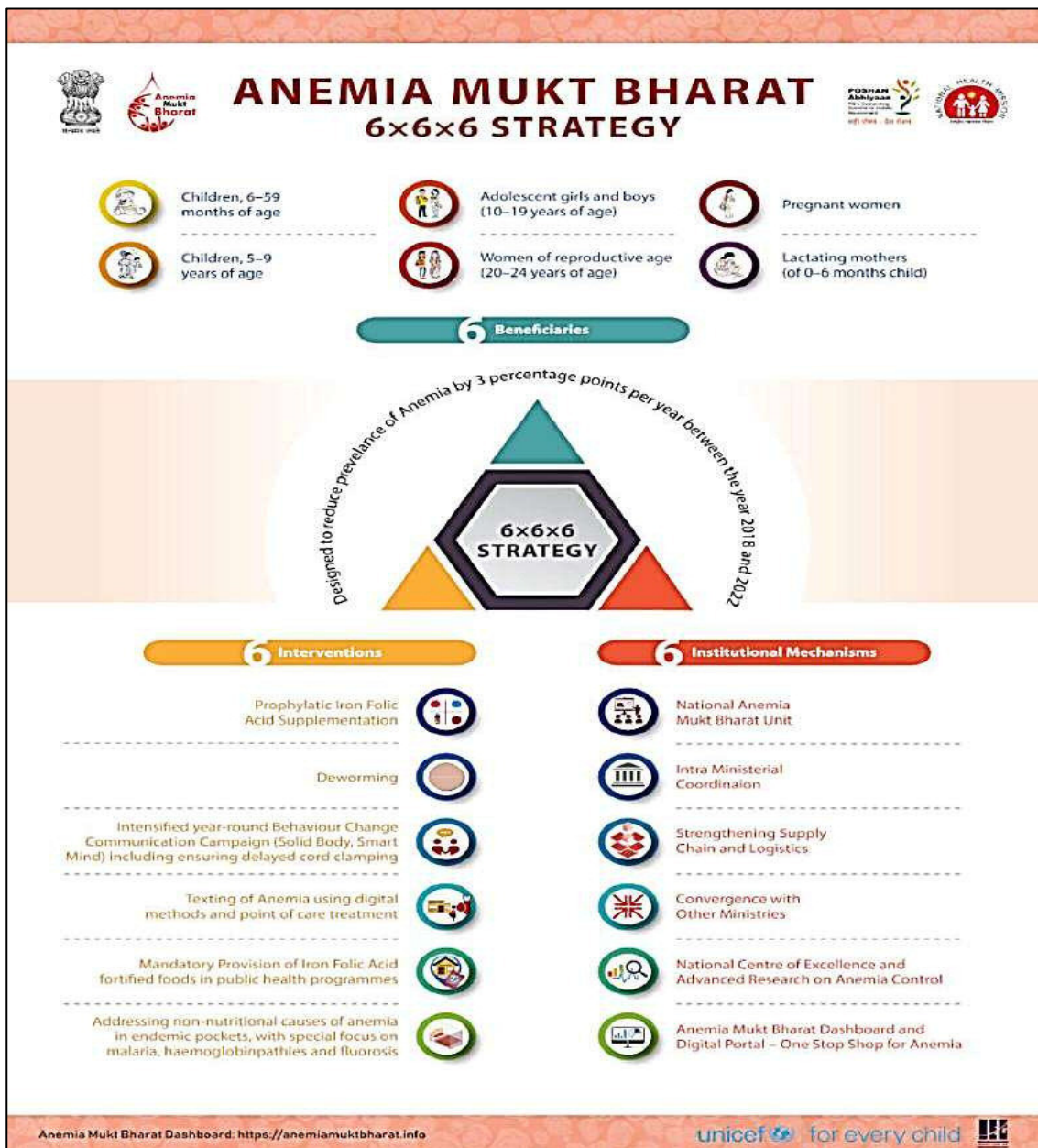


Table 1. List of countries with mandatory and voluntary fortification of Rice with Iron(9)

S. No	Country & year	Income status	Region	Legislation status	Nutrient level in standard (mg/kg)	Standard comment	
1	Nicaragua 2014	Lower middle income	Americas	Mandatory fortification	24	24mg/kg	
2	Panama 2009	High income			24	24mg/kg	
3	Papua New Guinea 2007	Lower middle income	Oceania		30	3mg/100g	
4	Peru 2018	Upper middle income	Americas		42	4.2mg/100g raw fortified rice	
5	Philippines 2000	Lower middle income	Asia		75	60–90mg/kg acceptable regulatory level raw rice	
6	Solomon Islands 2018		Oceania		60	Minimum level of 60mg/kg of iron	
7	United States of America 2017	High income	Americas		42.9	Each pound of the rice contains not less than 13mg and not more than 26mg of Iron (Fe)	
8	Bahrain 2012		Asia		Voluntary fortification	43	Minimum allowance ppm 29, Maximum allowance ppm 57
9	Bangladesh 2015	Lower middle income				60	5–7mg in 100 grams uncooked rice, target range at factory
10	Belize 2015	Upper middle income				19.5	Iron (Fe) Not less than 13mg and not more than 26mg; we assumed the units were/ kg
11	Canada 2021	High income		16		This nutrient is required if labeled ‘enriched’, at the following amount per 100g of pre-cooked rice: 1.6mg iron	
12	India 2018	Lower middle income	Asia	35.25		28–42.5mg/kg level required for Ferric pyrophosphate. Different levels required for Na Fe EDTA: 14–21.25mg/kg.	
13	Myanmar 2019			70		7mg per 100g uncooked rice; the factory target range is 6.00–8.00 mg per 100g uncooked rice	
14	Venezuela 1993	Upper middle income	Americas	150		15.0mg/100g	

2. Iron Intakes after rice fortification and comparison with EAR and RDA

2.1 Iron intakes among Indian population through fortified rice

The Food Safety and Standards Authority of India (FSSAI) mandates the use of ferric pyrophosphate (FPP: 28–42.5mg/kg) or sodium iron ethylenediaminetetraacetate trihydrate (Na Fe EDTA 14–21.25mg/kg) for fortification of rice with iron in India. Ferric pyrophosphate is added at a higher level to account for its lower bioavailability(17). National Nutrition Monitoring Bureau (NNMB) data provides rice and iron intake estimates for different age and physiological groups in the general population. These estimates enable us to determine the iron intakes through ferric pyrophosphate (Table 2) or Na Fe EDTA (Table 3) fortified rice consumption.

Table 2. Iron intakes with Rice fortification if Ferric Pyrophosphate is used for rice fortification based on the NNMB data

Age group	Rice consumption (g/Day)	Total iron intake from all foods in mg/day	Additional Iron intake through Fortified rice (mg/day) if FPP is used*	Total Iron intake with fortified rice (mg/day)	EAR (RDA) of Iron (mg/day) Requirement as per 2020	Iron deficit or excess (mg/day) (requirement (EAR) vs intake with fortified rice)	
Women (WRA)	168.2	13	5.9	18.9	15 (29)	3.9	
Pregnant women (0–6m)	172.7	13.23	6.0	19.3	21 (27)	-1.7	
Lactating women (0–6m)	185.6	14.35	6.5	20.8	16 (23)	4.8	
Men	177.8	15.19	6.2	21.4	11 (19)	10.4	
Infants 0–6m							
6–12m	27.1	2.16	0.9	3.1	4 (6)	1.1	
Children	1–3 y	63.5	4.88	2.2	7.1	6 (8)	1.1
	4–6 y	90.3	7.59	3.2	10.8	8 (11)	2.8
	7–9 y	115	9.02	4.0	13.0	10 (15)	3.0
Adolescents	10–12 y Boys	130.5	10.83	4.6	15.4	12 (16)	3.4
	10–12 y Girls	136.7	9.93	4.8	14.7	16 (28)	-1.3
	13–15 y Boys	163.4	12.82	5.7	18.5	15 (22)	3.5
	13–15 y Girls	147.4	11.2	5.2	16.4	17 (30)	-0.6
	16–18 y Boys	172.2	14.06	6.0	20.1	18 (26)	2.1
	16–18 y Girls	150.2	11.27	5.3	16.5	18 (32)	-1.5
*Ferric Pyrophosphate 35mg/kg is used for the above analysis							

If 35 mg of ferric pyrophosphate is used for fortifying one kg rice, the estimated additional daily iron intakes through rice consumption are 0.9mg/day among children aged 6–12 months, 5.9mg/day among women of reproductive age, 6.0mg/day among pregnant women, and 6.2mg/day among adult men (Table 2), according to the NNMB data.

If 17.6 mg of Na Fe EDTA is used for fortifying one kg rice, the estimated daily iron intakes through fortified rice consumption are 0.5mg/day among children aged 6–12 months, 3.1mg/day among adult men, 3.0mg/day among women of reproductive age, and 3.0mg/day among pregnant women (Table 3).

Table 3. Iron intakes with rice fortification if Na Fe EDTA is used for rice fortification based on the NNMB data

Age group	Rice consumption (g/Day)	Total iron intake from all foods in mg/day	Additional Iron intake through Fortified rice (mg/day) if Na Fe EDTA is used*	Total Iron intake with fortified rice (mg/day)	EAR (RDA) of Iron (mg/day) Requirement as per 2020	Iron deficit or excess (mg/day) (requirement (EAR) vs intake with fortified rice)	
Women (WRA)	168.2	13	3.0	16.0	15 (29)	1.0	
Pregnant women (0–6m)	172.7	13.23	3.0	16.3	21 (27)	-4.7	
Lactating women (0–6m)	185.6	14.35	3.3	17.6	16 (23)	1.6	
Men	177.8	15.19	3.1	18.3	11 (19)	7.3	
Infants 0–6m							
6–12m	27.1	2.16	0.5	2.6	4 (6)	0.6	
Children	1–3 y	63.5	4.88	1.1	6.0	6 (8)	0
	4–6 y	90.3	7.59	1.6	9.2	8 (11)	1.2
	7–9 y	115	9.02	2.0	11.0	10 (15)	1.0
Adolescents	10–12 y Boys	130.5	10.83	2.3	13.1	12 (16)	1.1
	10–12 y Girls	136.7	9.93	2.4	12.3	16 (28)	-3.7
	13–15 y Boys	163.4	12.82	2.9	15.7	15 (22)	0.7
	13–15 y Girls	147.4	11.2	2.6	13.8	17 (30)	-3.2
	16–18 y Boys	172.2	14.06	3.0	17.1	18 (26)	-0.9
	16–18 y Girls	150.2	11.27	2.6	13.9	18 (32)	-4.1
*Na Fe EDTA 17.6 mg per Kg is used for the above analysis							

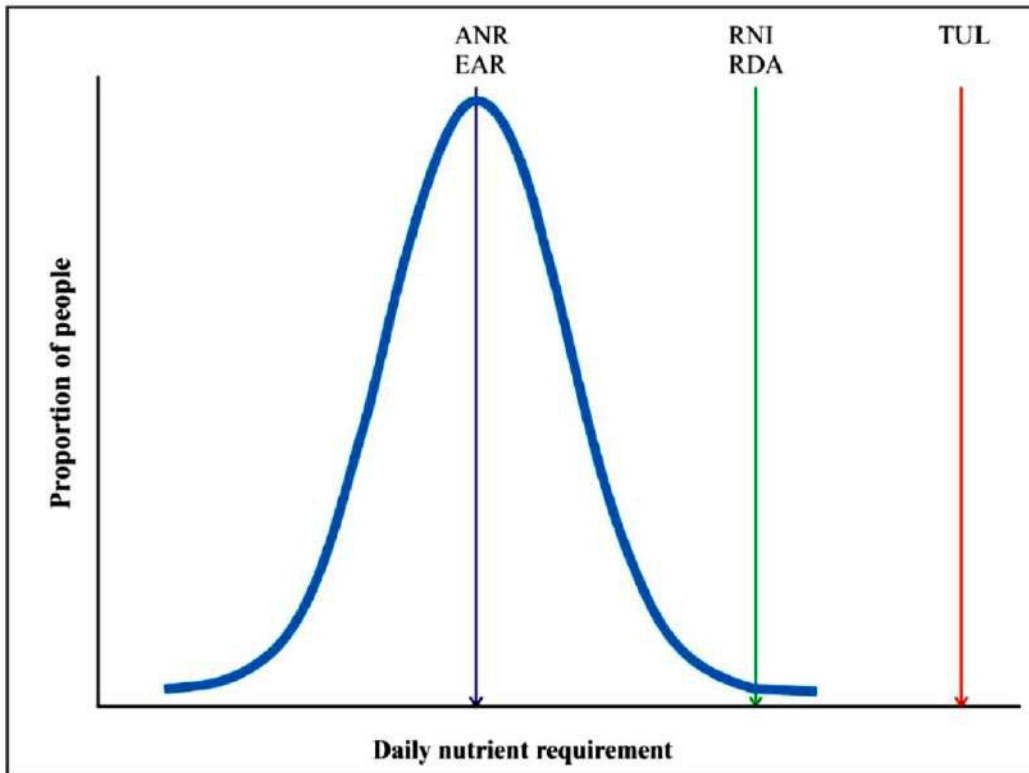
2.2 Total iron intake and risk of excess with iron fortified rice - Estimation by probability of inadequacy (PIA) approach

This section summarizes the iron intakes for various physiological age groups in India when rice is fortified with Ferric Pyrophosphate (FPP) or Na Fe EDTA and supplied through different social safety net programs. These intakes are compared to the EAR, RDA, and Tolerable Upper Limit (TUL) recommended by ICMR-National Institute of Nutrition, 2020 (18).

The Estimated Average Requirement (EAR) is calculated based on balance studies or by factorial approach using absorption and losses studies data or enzyme activity studies. Thus, the EAR is adjusted for absorption. Adding two standard deviation to the EAR gives the Recommended Dietary Allowance (RDA), which is the daily intake of 97.5% of apparently healthy individuals in an age and sex-specific population group(18). The RDA is conceptually similar to the Recommended Nutrient Intake (RNI) but may have slightly different values for some micronutrients (Figure 2).

The probability of risk of inadequacy of nutrient intake was calculated as an average of individual risk against the age and gender specific requirement distribution. Since the NNMB data is a single day recall, it was not possible to derive the intra and inter-individual variation, therefore, a 10% variation in dietary intakes of iron was considered based on previous studies. The nutrient gap analysis was done by sequential and incremental addition of the nutrient to the actual intakes (mean and SD) using R-program. The iron inadequacy varied from 34 to 80% in the analyzed data; the lowest rate of iron inadequacy was among ≥ 18 year old male subjects, and high level of iron inadequacy was observed among adolescent girls and women (Table 4 & Fig 3). Also, inadequacy was relatively higher among >10 year old female children and women, compared to male subjects (Table 4).

Figure 2. Daily nutrient requirements in terms of EAR, RDA and TUL
(adopted from ICMR-NIN nutrient requirements for Indians, RDA & EAR, 2020)



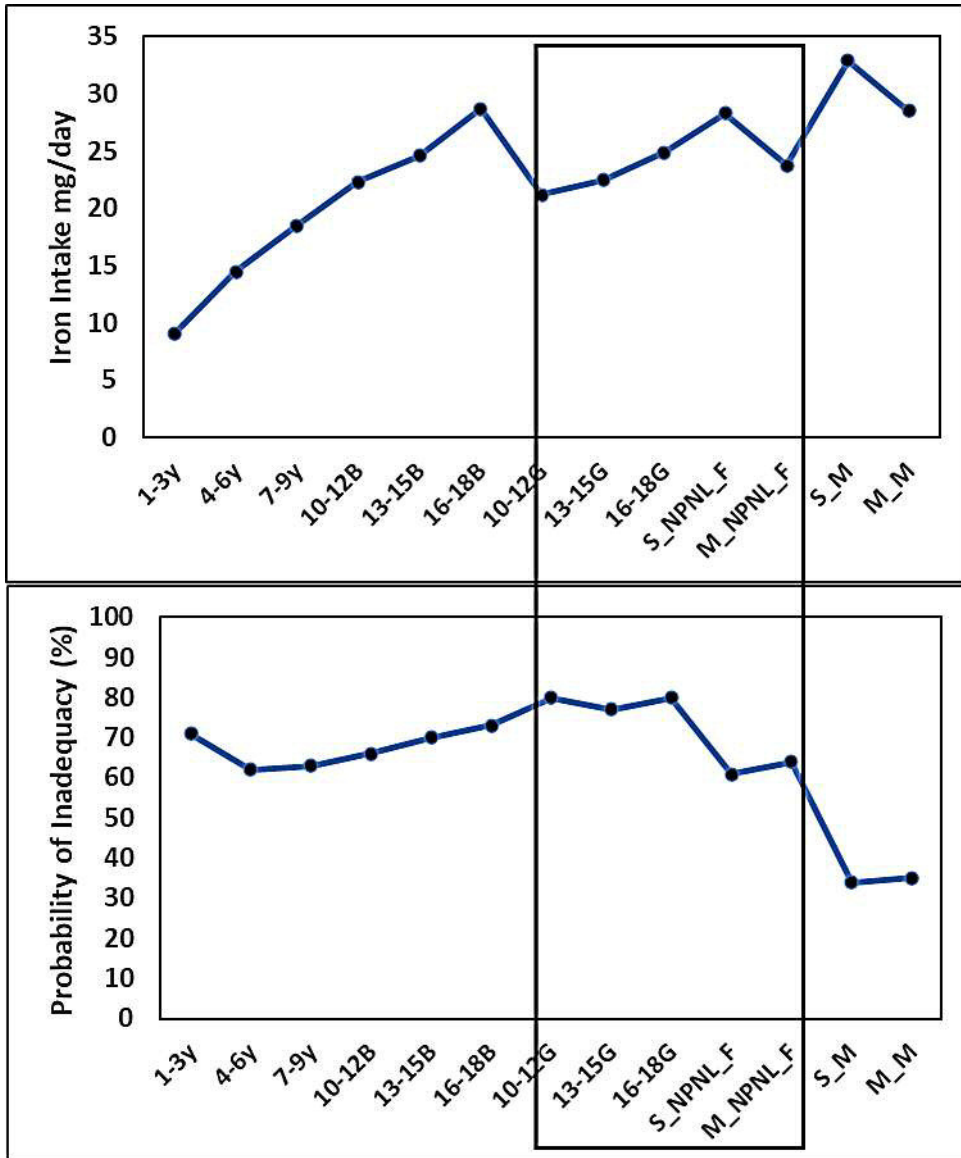
The proportion of individuals with iron inadequacy even with fortification of rice was significant; with probability of inadequacy ranging from 5% to 59%. The highest probability of inadequacy was seen in 16–17 year-old girls with 59% followed by 58% in 10–12 year-old girls. Proportion of Individuals with probability of inadequacy if both rice and salt are fortified ranged from 0.2% to 29%. The highest probability of inadequacy was seen in 10–12 year-old girls with 29% followed by 23% in 16–17 year-old girls. However, with consumption of both-fortified rice and salt, 1% of 16–17 year-old boys and 2.4% to 3.8% of men are likely to get excess iron intake (above TUL) (Table 4 & Fig 3). And, all age groups cross the level of TUL, except 1–3 year-old children, through regular intake of IFA through supplementation programs.

Table 4. Proportion of population with Probability of Inadequacy (PIA) and risk of excessive iron intakes beyond TUL with fortified cereals and salt

Physiological Group	Population with PIA without any fortification (%)	Population with PIA with fortified Rice (%)	Population with risk of over consumption of iron with fortified rice (%)	Salt Intake in gm	Population with PIA with both fortified Rice and Salt (%)	Population with Expected risk with both fortified Rice and salt (%)	TUL in mg
1-3 y	71	40	0	3	5	0	40
4-6 y	62	26	0	3	5	0	40
7-9 y	63	28	0.01	3	10	0.01	40
10-12 y Boys	66	28	0.04	6	2	0.13	40
10-12 y Girls	80	58	0.01	6	29	0.04	40
13-15 y Boys	70	34	0.06	6	7	0.1	45
13-15 y Girls	77	45	0.01	6	11	0.04	45
16-18 y Boys	73	41	0	8	7	0.99	45
16-18 y Girls	80	59	0	8	23	0.04	45
Male (Sedentary)	34	8	0.63	8	0.4	2.41	45
Male (Moderate)	35	5	0.89	8	0.2	3.76	45
Female (Sedentary)	61	35	0.13	8	10	0.6	45
Female (Moderate)	64	30	0.17	8	8	1.01	45

- The risk of probability of inadequacy (PIA) and excessive intakes beyond TUL were calculated based on EAR, RDA and TUL values of ICMR-Nutrient Requirements 2020.
- The proportion of Individuals with Iron inadequacy with fortification of all cereals and with double fortified salt was calculated by sequential and incremental addition of the nutrient to the actual intakes (mean and SD) (Table 4).
- The fortification level of 35mg iron/kg rice (FPP) and 1mg iron/g of salt were considered, as per FSSAI standards.
- The calculation is based on nutrient intake data of NNMB urban 2016.

Figure 3. Dietary iron intake and inadequacy by age groups
 (Adopted from NNMB Urban data 2016)



3. Limitations of the inadequacy analysis

1. Double Fortified Salt (DFS): The DFS is not a mandatory fortification in India like iodized salt. We have contacted 19 salt companies with whom NIN had MOU for transfer of DFS technology. Most of the companies have not renewed the MOU with NIN. Currently, only two states- Odisha and Himachal Pradesh are producing the NIN

DFS and are supplying through PDS. Using University of Toronto Technology, three companies are producing the DFS with fumarate, however the supply details are not shared. Nevertheless, assuming that DFS is consumed by every household we have calculated the adequacy level by probability approach (Table 4).

2. As for Take Home Rations (THR), we have analysed the data of THR from 30 states. Only few states like Madhya Pradesh (*Khichdi Premix*), Kerala (*Amrutham-Nutrimix*), Gujarat (*Bal Sakhti*) and Telangana (*Balamrutham*) are supplying iron fortified THRs. However, this has not been included in the adequacy calculation as the THR is not fortified in all states.
3. Prophylactic iron folic acid supplementation given through Anaemia Mukht Bharat programme are given weekly or biweekly in some age groups which cannot be considered for the daily iron intake estimations. Also, the compliance rates are extremely poor, which was found to be <20% in spite of best efforts in the STAR Trial. The NFHS-5 data also shows 29% compliance among pregnant women, which could be much lower among other groups.

4. Efficacy and safety of fortified rice

The Cochrane Review on Rice Fortification analysed seven RCTs with a total of 1634 participants, ranging from 5–18 year-old school children and 18–49 year-old non-pregnant, non-lactating women. The risk of anemia with unfortified rice was 388 per 1000, while fortified rice with iron alone or in combination with other micronutrients was 279 per 1000, resulting in an absolute reduction of 109 per 1000 and a relative risk of 0.72 (0.54–0.97). With TPDS coverage of 50% in urban regions and 75% in rural regions and considering that 36% of the population lives in urban areas and 64% lives in rural areas, fortified rice is estimated to have a minimum coverage of 66% in the country. We have extrapolated the cases averted by considering only the age groups which were included in the RCTs of the Cochrane review i.e Children in 5–19 years age group, WRA (20–49 yrs). As per census 2011 (Ref: Census of India 2011) the above-mentioned age groups will be 52.5% of the total population in India. Of this 52.5% population, 66% of individuals are beneficiaries of Public Distribution System (PDS). After extrapolating to

the above mentioned age groups, the fortified rice programme will be catering to 34.6% of the total population. Thus, we will be averting 5,26,22,545 ↓ (57,93,308–8,64,16,840) cases of anemia and 3,76,56,500 ↓ (1,78,62,699–5,40,70,872) cases of iron deficiency through iron fortified rice (Tables 5 & 6).

The Cochrane review also analysed eight RCTs with 1733 participants, including 4–18 year old school children and 18–49 year-old non-pregnant, non-lactating women. The risk of iron deficiency was reduced from 228 per 1000 with unfortified rice to 150 per 1000 with fortified rice, resulting in an absolute reduction of 78 per 1000 and a relative risk of 0.66 (0.51–0.84). This reduction in risk of iron deficiency in India could potentially benefit at least 7,17,32,697 people (Table 5).

Studies on haemoglobin concentration changes estimated in 11 RCTs, with a total of 2163 participants, comparing rice fortified with iron or iron with other micronutrients with unfortified rice showed some improvements. The mean haemoglobin concentration was 0.183g/dL higher in the intervention (fortified rice) group than the group with unfortified rice. The participants included 4–18 year-old school children and 18–49 year-old non-pregnant, non-lactating women (Tables 7 & 8). Furthermore, there was one RCT with 215 girls aged 14–18 years that found a 4.30 (nmol/L) higher mean serum or plasma folate (nmol/L) in the intervention group (fortified rice)(19). As regards to episodes of diarrhoea, one RCT with 258 participants showed no adverse effect(24); another RCT with 785 children aged 6–16 years assessed the risk of hookworm infection with rice fortified with multiple micronutrients. The risk with unfortified rice was 119 per 1000, while the risk with fortified rice was 211 per 1000, resulting in an increased risk of 92 per 1000 (RR 1.78, 95% CI 1.18–2.70) (Table 5).

Table 5. Summary of the Cochrane Review on rice fortification with iron or iron with other micronutrients

Outcome	Risk with unfortified rice	Risk with rice fortified with iron alone or in combination with other micronutrients	Absolute reduction	Relative effect (95% CI)	No. of participants (studies)	Population age group	Expected Impact in India*	Certainty of evidence
Anaemia	388 per 1000	279 per 1000	109 per 1000 (12-179)	RR 0.72 (0.54-0.97)	1634 (7 RCTs)	5–18-year-old school children, 18–49-year-old NPNL WRA	5,26,22,545 ↓ (57,93,308-8,64,16,840)	Low ¹
Iron deficiency	228 per 1000	150 per 1000	78 per 1000 (37-112)	RR 0.66 (0.51-0.84)	1733 (8 RCTs)	4–18-year-old school children, 18–49-year-old NPNL WRA	3,76,56,500 ↓ (1,78,62,699-5,40,70,872)	Low ²
Hemoglobin concentration (g/dL)	The mean hemoglobin concentration (g/dL) in the intervention groups was 0.183 g/dL higher (0.066 to 0.30 higher)				2163 (11 RCTs)	4–18-year-old school children, 18–49-year-old NPNL WRA		Low ³
Serum or plasma folate (nmol/L)	The mean serum or plasma folate (nmol/L) in the intervention group was 4.30 (nmol/L) higher (2.00 to 6.60 higher)				215 (1 RCT)	Girls aged 14-18 years (Avg age = 16.1y)		Low ⁴
Hook worm infection risk	119 per 1000	211 per 1000	Increase risk of 92 per 1000 (21-201)	RR 1.78 (1.18-2.70)	785 (1 RCT)	Children aged 6-16 years		Low ⁵
Diarrhoea	0 per 1000	0 per 1000		RR 3.52 (0.18-67.39)	258 (1 RCT)	Children aged 6-12 years with Hb>9g/dL and <11.5g/dL (6-11y) or <12g/dL (12y)		Very low ⁶

1; serious limitation in study design or execution (risk of bias), indirectness, Baseline characteristics not similar and method of randomization unclear in half of studies.

2; serious limitation in study design or execution (risk of bias), indirectness, as most of the studies except one were conducted among children.

3; serious limitations in study design or execution (risk of bias) and one for indirectness.

4; risk of bias being serious in the included study (Hardinsyah 2016), having selection bias, reporting bias and presence of other bias.

5; one for inconsistency and one for indirectness.

6; one for inconsistency, one for indirectness and one for imprecision.

*66% the population of India are covered with Fortified rice through TPDS, ICDS, PM POSHAN (pib.gov.in/beneficiaries of PDS).

Table 6. Individual studies of fortified rice usage and its impact on Anemia(10)

Study name	Study Population	Type of fortification	Duration of intervention	Intervention (Anemia/N)	Control (Anemia/N)	Effect size (Relative Risk, 95% CI)
Angeles-Agdeppa 2008	Children aged 6-9 years with Hb \geq 7 and <12 g/dL	Ferrous Sulphate and Micronized Ferric Pyrophosphate (FeP80)	6 months	40/112	37/59	RR 0.57 [0.41-0.78]
Hotz 2008	NPWL women with Hb>10.5 and <13.5	Micronized Ferric Pyrophosphate (20mg iron daily through fortified rice)	6 months	3/75	9/70	RR 0.31 [0.09-1.1]
Radhika 2011	Children aged 5-11 years	Micronized Ferric Pyrophosphate (MDM consisting of 125 g rice (dry weight) containing 19 mg Fe)	8 months	10/63	9/65	RR 1.15 [0.5-2.63] At the end of 8 months: FR: 38.1 to 15.9, UFR: 40 to 13.8
Hardinsyah 2016	Girls aged 14-18 years (Avg age = 16.1y)	Iron (na), zinc, thiamine, folic acid, vitamin B12, niacin, and vitamin A to fulfil 75% RDA) (150g fortified rice per day)	15 weeks	20/108	49/107	RR 0.4 [0.26-0.63] At the end of 15 weeks: Intervention: 50 to 18.5, Control: 18.7 to 45.7
Parker 2015 (C)	Children aged 7-11 years with Hb \geq 7.0 and <12.0 Cluster RCT	Iron (17.8mg), Zinc, Thiamine, FA (150g fortified rice for 5 days a week for 7 months)	7 months	84/152	77/146	RR 1.05 [0.85-1.29]
Perignon 2016 (C)	Children aged 6-16 years	Iron, Zinc, FA, Vit A, B1, B3, B12, B6	6 months	60/339	22/106	RR 0.85 [0.55-1.32]
Thankachan 2012	Children aged 6-12 years with Hb>9g/dL and <11.5g/dL (6-11y) or <12g/dL (12y)	40–50% recommended nutrient intake (RNI) for vitamin A, thiamine, niacin, vitamin B-6, vitamin B-12, folate, iron (Micronized Ferric Pyrophosphate), and zinc (High iron (12.5mg/100g of rice), Low iron (6.25mg/ 100g))	6 months	71/156	41/76	RR 1.05 [0.85-1.29] At the end of 6 months: HI: 59 to 53, LI: 61 to 39, C: 62 to 54

Table 7. Individual studies of fortified rice usage and its impact on hemoglobin

Study name	Study population	Type of fortification	Intervention (n)	Control (n)	Duration of intervention and the effect Size (Hb in g/dL)
Angeles-Agdeppa 2008	Children aged 6–9 years with Hb \geq 7 and <12 g/dL	Ferrous Sulphate and Micronized Ferric Pyrophosphate (FeP80)	i. 55; FeSo4 ii. 57; FeP80	59; UFR	At the end of 6 months: FeSO4: 11.19 \pm 0.61 to 12.1 \pm 0.85, FeP80: 11.31 \pm 0.48 to 12.23 \pm 0.73, Control: 11.35 \pm 0.44 to 11.65 \pm 0.82
Hardinsyah 2016	Girls aged 14–18 years (Avg age = 16.1y)	Iron (na), zinc, thiamin, folic acid, vitamin B12, niacin, and vitamin A to fulfil 75% RDA)	108; 150g fortified rice per day	107; UFR	At the end of 15 weeks: Intervention: 12.03 \pm 1.19 to 12.46 \pm 0.99, Control: 12.45 \pm 1.04 to 12.08 \pm 1.20
Hotz 2008	NPNL women with Hb>10.5 and <13.5	Micronized Ferric Pyrophosphate	75; 20mg iron daily through fortified rice	70; UFR	At the end of 6 months: Intervention: 13.1 (12.9–13.4) to 14.2 (13.9–14.4), Control: 13.0 (12.8–13.3) to 13.8 (13.5 - 14.1) p=0.069
Moretti 2006b	6–13y old iron deplete children	Micronized ferric pyrophosphate	80; Fortified rice meals (10mg/g)	90; UFR	At the end of 7 months: FR: 12.1 \pm 1.2 to 11.9 \pm 0.9, UFR: 12.1 \pm 1.3 to 11.6 \pm 1.1
Perignon 2016 (C)	Children aged 6–16 years	Iron, Zinc, FA, Vit A, B1, B3, B12, B6	URO: 445, URN: 464, Nutririce: 454	425; Placebo	At the end of 6 months: Pl:12.36 to 12.26, URO:12.43 to 12.41, URN: 12.36 to 12.30, Nutririce: 12.41 to 12.35; Non-Significant differences
Pinkaew 2013	4–12 y-old children	Extruded rice with 10 mg Fe, 9 mg Zn, and 1050 mg VA/g extruded rice (140 g cooked rice per school meal per child)	101; Triple Fortification	102; UFR	At the end of 5 months: TFR: 12.7 (8-14.1) to 12.5 (10.2-14.7), UFR: 12.6 (9.9-15.2) to 12.4 (10.3-14.9); non-significant difference

Radhika 2011	Children aged 5–11 years	Micronized Ferric Pyrophosphate	63; MDM consisting of 125 g rice (dry weight) containing 19 mg Fe	65; UFR	At the end of 8 months: FR: 11.5±1.09 to 12.5± 1.05, UFR: 11.4±1.00 to 12.5±1.01 [Not significant]
Thankachan 2012	Children aged 6–12 years with Hb>9g/dL and <11.5g/dL (6- 11y) or <12g/dL (12y)	40–50% recommended nutrient intake (RNI) for vitamin A, thiamine, niacin, vit B6, vit B12, folate, iron (Micronized Ferric Pyrophosphate), and zinc	i.76; High iron (12.5mg/100g of rice) ii.80; Low iron (6.25mg/100g)	76; UFR	At the end of 6 months: HI: 11.2±0.61 to 11.4±0.87, LI: 11.1±0.72 to 11.5±0.99, C: 11.2±0.63 to 11.3±0.77; (p<0.05)
Hussain 2014	Iron and vitamin A depleted 5-8y old school children	Micronized Ferric Pyrophosphate (4 mgFe/100g), retinyl palmitate 600IU/g, and beta-carotene 2000IU/g	35 in each group; Gp1: Iron fortified meals, Gp2 : Beta- carotene fortified meals, Gp3: Retinyl palmitate fortified meals, Gp4: Iron + retinyl palmitate fortified meals, Gp5: Iron + beta- carotene fortified meals	37; UFR	At the end of 6 months: Gp1: 10.5±0.17 to 12.3±0.15, Gp2: 10.4±0.26 to 12.1±0.17, Gp3: 9.9±0.21 to 11.6±0.31, Gp4: 10.0±0.21 to 11.9±0.30, Gp5: 10.2±0.15 to 12.0±0.21, C: 10.4±0.10 to 10.6±0.21
Parker 2015 (C)	Children aged 7–11 years with Hb >=7.0 and <12.0	Iron (17.8mg), Zinc, Thiamine, FA	547; 150g fortified rice for 5 days a week for 7 months	524; UFR	At the end of 7 months: Intervention: 10.6 (1.1) to 11.7 (1.5), Control: 10.9 (0.9) to 11.8 (1.6): Not Significant
Losso 2017	Seventeen women with iron deficiency (low iron and/or low ferritin) anemia	Iron-fortified rice (18 mg/100g as FeSO4)	9; 100 g/d of fortified rice rice (two cooked 0.75 cup servings)	6; 100 g/d of UFR (two cooked 0.75 cup servings)	Baseline Hb 10.6 ± 1.6 g At the end of 2 weeks: Subjects in the iron fortified group (+0.52) had a statistically significant increase compared to placebo (-0.30) in Hb (0.82 g, p=0.0035)

Table 8. Individual studies of fortified rice usage and its impact on iron deficiency

Study name	Study population	Type of fortification	Duration of intervention	Intervention (n/N)	Control (n/N)	Effect size RR, 95% CI
Angeles-Agdeppa 2008	Children aged 6–9 years with Hb>=7 and <12 g/dL	Ferrous Sulphate and Micronized Ferric Pyrophosphate (FeP80)	6 months	1/112	0/59	1.59 [0.07-38.51]
Hardinsyah 2016	Girls aged 14–18 years (Avg age = 16.1y)	Iron (na), zinc, thiamin, folic acid, vitamin B12, niacin, and vitamin A to fulfil 75% RDA)	15 weeks	27/108	34/107	0.79 [0.51,1.21]
Hotz 2008	NPNL women with Hb>10.5 and <13.5	Micronized Ferric Pyrophosphate	6 months	17/75	19/70	0.84[0.47,1.47]
Moretti 2006b	6–13 y-old iron deplete children	Micronized ferric pyrophosphate	7 months	23/92	45/92	0.51 [0.34, 0.77]
Perignon 2016 (C)	Children aged 6–16 years	Iron, Zinc, FA, Vit A, B1, B3, B12, B6	6 months	37/366	14/119	0.86 [0.48, 1.53]
Pinkaew 2013	4–12 y-old children	Extruded rice with 10 mg Fe, 9 mg Zn, and 1050 mg VA/g extruded rice (140 g cooked rice per school lunch meal per child)	5 months	2/91	8/84	0.23 [0.05, 1.06]
Radhika 2011	Children aged 5–11 years	Micronized Ferric Pyrophosphate	8 months	9/63	24/65	0.39 [0.2, 0.77]
Thankachan 2012	Children aged 6–12 years with Hb>9g/dL and <11.5g/dL (6-11y) or <12g/dL (12y)	40–50% recommended nutrient intake (RNI) for vitamin A, thiamine, niacin, vitamin B-6, vitamin B-12, folate, iron (Micronized Ferric Pyrophosphate), and zinc	6 months	16/154	9/76	0.88 [0.41, 1.89]

5. Dosage of oral iron supplements and its safety

This section examines various clinical trials to analyse the relationship between the dose of supplemental iron used and its adverse effects on outcomes such as mortality, hospitalization, diarrhoea, respiratory tract infections, inflammation, and dysbiosis. There are no studies that have looked at safety of fortified rice consumption across different age groups, hence we have summarised some studies that dealt with oral iron supplements and safety. Fortification programs aim to prevent nutrient deficiencies, while supplementation is used to treat nutrient deficiencies. Iron is unique among nutrients in that it has a narrow range of adequacy, making it challenging to fortify foods with it without risk of adverse effects. Two possible mechanisms are explained behind the adverse effects of excess iron: firstly, excessive non-protein bound iron (NPBI) can lead to the production of reactive oxygen species and inflammation. Secondly, gut microbial dysbiosis can occur due to unabsorbed iron. Since, the absorption rate of oral iron rarely exceeds 30%, the unabsorbed iron can impact the microbial balance in the distal gut. However, these findings from supplemental studies may not be directly applicable to fortified rice consumption. Nevertheless, we have attempted to compare the safety level. To determine the safe dose of iron when fortifying rice, the dose associated with adverse effects is compared with the total daily intake of iron.

5.1 Oral iron supplements and malaria

The Pemba Clinical Trial conducted in Tanzania in 2006 was a key study that raised concerns about iron supplementation (Annexure Table 1)(26). The trial used a dose of approximately 1mg/kg/day of iron for 18 months, and supplementation was stopped due to an increase in mortality and morbidity in the intervention group. Further analysis showed that adverse effects were more common in iron-replete children than in those who were iron deficient(26). Another study conducted in Ghana in 2013 by Zlotkin et al., also reported an increased risk of hospitalization in the iron intervention group. This study used a microencapsulated form of ferrous fumarate at a dose of 1–2 mg/kg/day for five months. However, a concurrent study in Nepal, which is non-endemic for malaria and

was conducted by the same researchers who conducted the Pemba Trial, did not observe any adverse effects of iron supplementation(27). Therefore, it is recommended that in malaria endemic areas, iron deficiency must be corrected after prevention and treatment of malaria(28). Three Cochrane reviews conducted after the Pemba Trial found no evidence of increased adverse effects of iron in malaria-endemic regions if malaria control and treatment programs were implemented(29–31).

5.2 Oral iron supplements and diarrhoea, dysentery, and respiratory infections

Well-designed randomized controlled trials by Jaeggi et al., (2014) in Kenya and Soofi et al., (2013) in Pakistan reported an increase in diarrhoea and dysentery upon iron supplementation(34,35) (Annexure Table 2). These studies used ferrous fumarate at a dose of 2mg/kg/day and found that children under the age of two were more predisposed to gastrointestinal adverse effects. Mitra et al., (1997) from Bangladesh observed an increased risk of diarrhoea, especially in infants, when supplemented with ferrous gluconate at 2–3mg/kg/day(33). However, older children did not have an increased risk for diarrhoea or respiratory illness. Soofi et al., (2013) also reported a negative effect of zinc when supplemented along with iron (35) (Annexure Table 2). The co-administration of zinc with iron increased the incidence rate of bloody diarrhoea and proportion of days with watery diarrhoea, which may be due to competition between zinc and iron for the surface transporter on the luminal epithelium of the gut. A systematic review by Neuberger et al., (2016) also reported an increased risk of diarrhoea in studies that supplemented with zinc and iron(29) (Annexure Table 3). However, iron supplementation without zinc did not increase the risk of diarrhoea in children, as evidenced by a systematic analysis of several studies (Annexure Table 4). Analysis by Neuberger et al., (2016) did not show an increased risk for respiratory infections on iron supplementation (29) (Annexure Table 5). Similarly, Gera et al., (2012) did not find any conclusive evidence for the risk of RTIs and diarrhoea in their systematic review(36). A dose of 1mg/kg/day of soluble iron, when not administered with zinc, is likely to be optimal for

supplementation programs. However, depending on host and environmental factors, this dose may be associated with diarrhoea/dysentery in children less than two years of age.

Gastrointestinal side effects (diarrhoea, constipation and abdominal pain) are observed in adult women on iron supplementation (Annexure Table 6). A dose of more than 60 mg/day of elemental iron is associated with an increase in GI side effects.

5.3 Oral iron supplements and gut inflammation and dysbiosis

Excess unabsorbed iron in the colon can potentially impact the microbiome. A study conducted in Kenya by Jaeggi et al., (2014) found that a daily dose of 1 mg/kg of iron as ferrous fumarate increased faecal calprotectin and Enterobacteriaceae, indicating potential dysbiosis(34) (Annexure Table 7). However, an Ivory Coast study that used ~1mg/kg/day of electrolytic iron for six months in school children did not report any increase in gastrointestinal side effects but did find an increase in faecal calprotectin and enterobacteria, as well as a decrease in lactobacilli. Additionally, the baseline levels of enterobacteria were already high in the population studied and supplementation did not improve iron stores(37). In South African children with a low enteropathogen burden, iron supplementation (2mg/kg/day as FeSO₄) did not significantly affect the dominant bacterial groups in the gut, faecal SCFA concentration, or gut inflammation(38). Thus, the efficacy and side effects of iron supplementation are related to baseline levels of enteropathogens in the host.

Both iron deficiency and excess can lead to dysbiosis and inflammation. Iron supplementation (30–60mg) during pregnancy has been shown to decrease diarrhea and puerperal infection (Annexure Table 8). Furthermore, iron supplementation (60mg as FeSO₄) during pregnancy has been shown to decrease serum levels of hs-CRP in an Indian study by Rajendran et al(39). In an Australian study by Nitert et al., low-dose iron supplementation was found to increase the faecal levels of butyrate-producing bacteria(40). Additionally, supplementation with vitamin E along with iron has been shown to minimize the adverse effects of freely available colonic iron on the microbiome(41). Concurrent administration of prebiotic galacto-oligosaccharide (GOS)

has also been found to decrease adverse effects and reduce the required supplementation dose(42). In a study conducted in Kenyan children, the supplementation of 5 mg of iron along with GOS was as effective as 12.5mg in reducing anemia(43). Finally, n-3 PUFA supplementation along with iron has also been shown to reduce adverse effects and increase iron stores effectively(44, 45).

5.4 Safety of iron used in rice fortification

Ferric Pyrophosphate is a type of iron used in rice fortification. Unlike other soluble forms of iron like Ferrous Sulphate, Ferric Pyrophosphate is insoluble. However, its bioavailability is enhanced through micronization, which increases the surface area of the fortificant. Another recommended fortificant is Sodium iron ethylenediaminetetraacetate trihydrate (Na Fe EDTA), which is a soluble form of iron that increases bioavailability in the presence of phytates and polyphenols.

The use of EDTA in food is limited and approved by the FAO/WHO. Although the approved limit of iron from Na Fe EDTA is 0.2mg Fe/kg/day, the recommended dose for fortified rice (14–21.25mg/kg) is well within the approved limits for the dietary intake of various age groups (Table 10).

The adverse effects of iron supplementation based on studies using soluble iron compounds like FeSO₄ and Fe Na EDTA cannot be extrapolated to micronized ferric pyrophosphate, an insoluble form. Studies have shown that micronized FPP fortified with rice or salt (20mg/day) has not caused an increase in serum CRP levels in India and Africa.

Although Na Fe EDTA is more expensive and used at a lower concentration, the daily intake of soluble Na Fe EDTA at the recommended low level is unlikely to cause any side effects. With rice fortification using MFPP or Na Fe EDTA, the total intake of iron is less than 1mg/kg/day in all age groups and, therefore, unlikely to cause adverse effects (Table 10).

Table 10. Total iron intake in mg/kg body weight per day on consumption of rice fortified with Ferric Pyrophosphate or Na Fe EDTA and fortified salt (FPP 35mg/kg rice and Na FeEDTA 17.6 mg/kg rice)

Age group	Body weight (kg)	Rice consumption (g/Day)	Total iron intake if FPP is used* (mg/kg/day)	Total iron intake if Na Fe EDTA is used# (mg/kg/day)	Total iron intake if fortified salt is used with FPP rice (mg/kg/day)	
Women (WRA)	55	168.2	0.34	0.29	0.49	
Pregnant women (0–6m)	65	172.7	0.30	0.25	0.42	
Lactating women (0–6)	55	185.6	0.38	0.32	0.52	
Men	65	177.8	0.33	0.28	0.45	
Infants 0–6m	5.8					
6–12m	8.5	27.1	0.36	0.31	-	
Children	1–3 y	12.9	63.5	0.55	0.47	0.78
	4–6 y	18.3	90.3	0.59	0.50	0.75
	7–9 y	25.3	115	0.51	0.43	0.63
Adolescents	10–12 y Boys	34.9	130.5	0.44	0.38	0.61
	10–12 y Girls	36.4	136.7	0.40	0.34	0.57
	13–15 y Boys	50.5	163.4	0.37	0.31	0.49
	13–15 y Girls	49.6	147.4	0.33	0.28	0.49
	16–18 y Boys	64.4	172.2	0.31	0.27	0.44
	16–18 y Girls	55.7	150.2	0.30	0.25	0.44

Summary of Evidence

- The form of Iron used in rice fortification in India is insoluble micronized Ferric pyrophosphate. Adverse effects are seen with soluble forms of iron like FeSO₄ or Ferric Fumarate at high dose (more than 1mg/kg body weight per day). Therefore, studies on the adverse effects of soluble iron compounds cannot be applied to iron-fortified rice with FPP.

- The total iron intake through fortified rice is less than 0.59mg/kg/day for any age group. Even if fortified salt is consumed, the highest daily iron intake for any age group is 0.78mg/kg/day which is less than 1mg/kg/day.
- The dose (28-42.5mg/kg rice) and form of iron (FPP) used for rice fortification in India is less likely to cause any adverse effects.

6. Consumption of oral iron and the risk of Non-Communicable Diseases (NCDs): Diabetes Mellitus (DM) and Hypertension

6.1 Diabetes Mellitus

There is currently no Cochrane review available on the relationship between iron intake (whether through diet, fortification, or supplementation) and non-communicable diseases (NCDs) such as diabetes or hypertension. However, for the purpose of this white paper, we have examined the evidence from four systematic reviews that explore the association between dietary iron intake and type 2 diabetes mellitus (T2DM)(51–54). We excluded systematic reviews on type 1 DM and gestational diabetes mellitus since they do not address diabetes mellitus as an NCD outcome.

The most recent systematic review by Shahinfar et al., (2022) is an improvement on previous reviews since it addresses many limitations, including a predominantly western population, short follow-up durations, and a lack of dose-response relations(63). It includes 11 prospective cohort studies with over 320,000 participants and 28,837 incident cases of T2DM from different geographic areas, with a mean follow-up period of 9.7 years. Most studies have adjusted for various factors, including age, gender, BMI, hypertension, and lifestyle habits. However, the main limitation of this review is that since the studies are observational, and with a long follow-up period, the causality of the risk factors being investigated can be affected by unmeasured or residual confounding factors.

The review assessed the risk of T2DM associated with four dietary iron intake forms: total dietary iron intake, dietary haem iron intake, dietary non-haem iron intake, and dietary supplemental iron. The findings show that dietary total iron, non-haem iron, or supplemental iron intakes are not significantly associated with T2DM. A 5mg/day increment in non-haem iron intake was not associated with the risk of T2DM, and a 5 mg/day increment in total iron intake was not related to the risk of T2DM. However, there was a non-significant inverse association, with the risk decreasing from total iron intake of 5–20mg/ day, with flattening of the curve at higher intake (Annexure Table 9 &10).

On the other hand, a higher haem iron intake was significantly associated with a greater risk of T2DM, with individuals with the highest level of haem iron intake having a 20% higher risk than those with the lowest level. The association was significant independent of family history of T2D and intake of saturated fats and dietary fibre. A 1mg/day increment in haem iron intake was related to a 16% higher risk of T2DM (Annexure Table 9 & Table 10). The main dietary source of haem iron is red and processed meat. Previous meta-analyses of cohort studies have also shown a positive association between haem iron intake and the risk of T2DM(64-66).

The underlying mechanisms of the positive association of dietary haem iron consumption and T2DM appear to be complex and varied, with various hypotheses being proposed. These include high bioavailability of iron from the haem form, excessive load of iron stores due to the absence of iron excretion, oxidative stress, DNA damage, and disrupting the integrity of the cell membrane, thus interfering with glucose uptake of muscle cells and adipocytes and decreasing the action of insulin, long-term hyperinsulinemia, elevated iron deposition, and the hazardous effects of reactive oxygen species on β -cells, all contributing to β -cells destruction and T2DM.

Summary of Evidence

A systematic review based on long term cohort studies on dietary iron intake (as a proxy for fortified iron) shows a positive association between haem iron intake and diabetes mellitus but no association between non-haem iron intake and type 2 diabetes mellitus. As rice fortification in India uses non-haem form of iron (FPP), type 2 diabetes mellitus is not a cause of concern (67,68).

6.2 Hypertension

One prospective cohort study from China (69) provides evidence on the association between iron intake and new onset hypertension, while no Cochrane or systematic reviews are available. However, other studies have found inconsistent results on the association between dietary iron intake and BP levels, and they were predominantly cross-sectional studies(70–72).

The study on Chinese adults found a U-shaped association between dietary total iron intake (including non-heme iron) and new-onset hypertension, with the lowest risk observed at quintile 2–3(69). However, the association between dietary heme iron intake and new-onset hypertension followed an L-shape. Participants with quintiles 2–5 of dietary heme iron intake had a significantly lower risk of new-onset hypertension compared to those in quintile 1 (Annexure Table 11). These findings suggest that the association between dietary iron and the risk of hypertension is nonlinear, following a U-shape for total or nonheme iron intake, and an L-shape for heme iron intake. If confirmed, these findings highlight the importance of maintaining appropriate levels of dietary iron for primary prevention of hypertension.

Adjustments for important covariates, including physical activity levels and the intakes of vitamins A, B2, niacin, C, sodium, potassium, calcium, copper, zinc, magnesium, and selenium, the intake of red meats, grains, fruits, and vegetables, or self-reported diabetes, stroke, and myocardial infarction did not substantially alter the association between dietary iron and new-onset hypertension.

The mechanism underlying this association is not certain, but low iron intake is thought to deplete iron storage and contribute to iron deficiency, which may have adverse effects on enzymatic reactions(73,74). Iron deficiency is also thought to activate chronic inflammation and produce reactive oxygen species(75,76), leading to endothelial dysfunction, which is the initial phase in the development of hypertension(77). Therefore, moderate iron intake may be significantly associated with a reduced risk of hypertension. However, when total or nonheme iron intake exceeds a certain level, the risk of hypertension may increase. Higher iron intake may catalyse the generation of reactive oxygen species, lipid peroxidation, and LDL-oxidation, which damage cellular macromolecules, promote endothelial injury, and atherosclerotic plaque formation(78,79). Further studies are needed to confirm these mechanisms.

Summary of Evidence

Primary or secondary studies have not examined the association between iron intake through fortified rice and hypertension. A single prospective study on dietary iron intake and new onset hypertension among Chinese adults shows an association between haem iron intake and new onset hypertension. From the available evidence, it cannot be concluded that the consumption of iron fortified rice increases the risk of hypertension.

7. Fortified rice intake and Hemoglobinopathies

Hemoglobinopathies

Hemoglobinopathies are genetic disorders that result from structural changes in haemoglobin, which cause red blood cells to be improperly formed and prevent them from effectively carrying oxygen to the body's tissues. In India, hemoglobinopathies like sickle cell haemoglobin, beta-thalassemia, and haemoglobin E-related disorders are major contributors to genetic morbidity and mortality (80).

The most affected states and communities are (80)

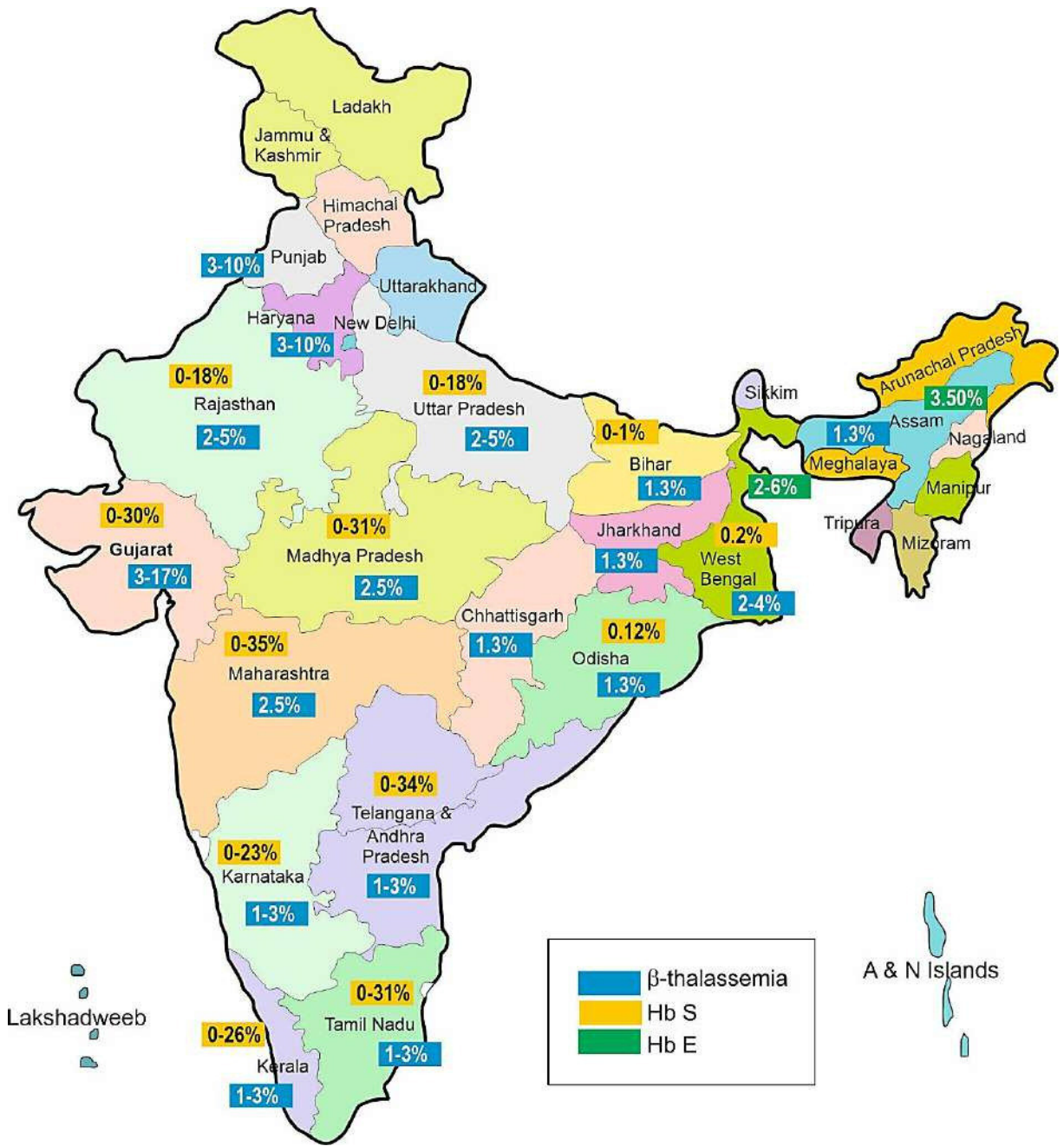
1. Sickle Cell Anemia (SCD)-Tribal populations (ST communities) in all Indian states.

2. Thalassemia (beta type is most common) - Sindhis, Punjabis, Gujaratis, Bengalis, Mahars, Kolis, Saraswats, Lohanas, and Gaurs are the most affected populations.
3. Hb-E-North eastern India.

Prevalence/ Burden of Hemoglobinopathies in India (80)

1. Sickle Cell Anemia (SCD)-The national prevalence ranges from 1 to 35%. However, there are almost 7.5 crores carriers of the sickle cell trait in India.
2. Thalassemia (beta type is most common) - The national prevalence ranges from 1 to 10%. There are 65,000 beta-thalassemia patients with an annual increase of 10,000 patients. However, there are almost 3 crores carriers of beta-thalassemia in India.
3. Hb-E - The prevalence ranges from 5% in the Bengali population to 3–50% in a few pockets of Assam. However, other parts of India have not reported this trait.

Figure 4. Reported prevalence of hemoglobinopathies in India(80)



Iron Metabolism in Hemoglobinopathies

There are three types of presentations in any type of hemoglobinopathy. The first is the carrier state, where individuals are apparently normal. The second type is where individuals have mild symptoms with impairment of iron metabolism (absorption, utilization, and storage). The third and most severe type of presentation is where symptoms of iron impairment are worse, and regular blood transfusion is required(81,82).

Effect of Iron fortified rice on Haemoglobinopathies

According to available literature, iron-fortified rice may be beneficial for individuals with mild forms of hemoglobinopathies with iron deficiency and those in carrier states(81,82). However, caution must be exercised for those with severe forms of hemoglobinopathies, where lifelong blood transfusion is required(81,82). According to the Thalassemia International Federation guidelines, transfusion dependent patients should focus on chelation and less on iron content from food.

Summary of Evidence

Iron overload and adverse effects in sickle cell anemia and thalassemia patients is due to repeated blood transfusion and not due to rice fortification. Evidence shows that there is no harm in carriers and in mild forms of hemoglobinopathies; and dietary iron is in fact beneficial. However, people with severe hemoglobinopathies are under close supervision; and the primary focus of people on transfusion dependant hemoglobinopathies should be on chelation rather than iron content from food.

8. Fortified rice intake and behaviour change communication

8.1 Role of social and behaviour change communication on fortified rice intake

Any concerns from the public could be addressed through effective Social and Behaviour Change Communication (SBCC) programs tailored to specific populations and cultural practices. A study conducted in 2006 in Bengaluru(83) found that rice grains fortified with Micronized Ferric Pyrophosphate (MFPP) were indistinguishable from unfortified

rice in both cooked and uncooked forms. Similarly, a feeding trial(66) conducted in Hyderabad in 2011 found that the sensory qualities of cooked fortified rice and unfortified rice were similar, with an overall acceptability of 86% and 97%, respectively. However, SBCC can help to encourage choosing, identifying, and consuming fortified rice and address any concerns regarding taste or acceptability.

In China(85), the National Nutrition Improvement Program of China used social marketing strategies based on the six Ps (Product, Price, Place, Promotion, Policy, and Partnership) to improve women's knowledge and attitudes about Iron-Fortified Soy Sauce (FeSS). Similarly, an intervention program in Tanzania(86) encouraged vitamin A fortified oil through community events and mobilization activities, resulting in significantly higher knowledge and consumption of fortified oil in the intervention districts compared to the control districts after nine months.

While rice fortification can be a midterm strategy for controlling iron deficiency, a long-term approach is to improve dietary diversity, which can also prevent other micronutrient deficiencies. SBCC can be used to improve dietary diversity, as demonstrated by the Alive and Thrive initiative in Bangladesh(87) and a pilot-scale randomized trial among women in Ghana(88), both of which showed improved diet diversity and consumption of animal-sourced foods through counselling, community mobilization, and mass media campaigns.

An amalgamation of fortification strategies and effective BCC strategies are thus a prudent requirement for the success of any fortification intervention. SBCC should be designed to include the importance of iron deficiency anemia and role of fortification, importance of dietary diversity and cooking procedures.

9. CONCLUSIONS

9. Conclusions

The goal of food fortification is to ensure that 95% of the population in each life-stage group consumes the Estimated Average Requirement (EAR) of the nutrient of concern. Accurate intake data, including nutrient and vehicle, are critical for determining the appropriate level of nutrients to be added, the vehicle to be used, and the population to be targeted. Public health efforts to fortify food require regular monitoring of dietary intakes, impact evaluation, adverse effects in different population segments, risk of overconsumption, development of biomarkers for excess intakes, and long-term health effects.

- There is a high level of iron inadequacy in Indian diet.
- Iron inadequacy may persist among adolescent girls despite rice fortification.
- Fortified rice consumption will result in a modest decrease in anaemia.
- The total iron intake through fortified rice is less than 0.59mg/kg body weight/day for any age group, hence it is unlikely to cause any adverse effect.
- The form of iron used for rice fortification is insoluble micronized ferric pyrophosphate. Adverse effects are observed when employing soluble iron forms such as FeSO₄ or ferric fumarate at high doses (exceeding 1mg/kg body weight per day). Consequently, studies investigating the adverse effects of high doses of soluble iron compounds cannot be extrapolated to fortified rice containing the insoluble form of iron.
- There is no evidence that dietary non-haem form of iron increases the risk of type 2 diabetes mellitus or hypertension.
- There is no evidence for adverse outcomes related to iron fortified foods among people with haemoglobinopathies. Iron overload and adverse effects in sickle cell anemia and thalassemia patients is due to repeated blood transfusion and not due to rice fortification. The primary focus of people on transfusion dependent haemoglobinopathies should be on chelation rather than iron content from food.
- The dose (28–42.5mg/kg rice) and form of iron (FPP) used for rice fortification in India should not be a cause of concern for any adverse effects.

10. REFERENCES

References

1. Nutritional anaemias: tools for effective prevention and control [Internet]. [cited 2023 Jan 18]. Available from: <https://www.who.int/publications-detail-redirect/9789241513067>
2. IIPS. National Family Health Survey-5 India Fact sheet [Internet]. 2019 [cited 2022 Jul 22]. Available from: http://rchiips.org/nfhs/NFHS-5_FCTS/India.pdf
3. Comprehensive National Nutrition Survey (CNNS). CNNS National Report 2016–18 [Internet]. New Delhi: Ministry of Health and Family Welfare (MoHFW), Government of India, UNICEF and Population Council; 2019; [cited 2021 Nov 11]. Available from: <https://nhm.gov.in/WriteReadData/l892s/1405796031571201348.pdf>
4. NFHS-5 CAB Manual_Eng.pdf [Internet]. [cited 2023 Jan 18]. Available from: http://rchiips.org/NFHS/NFHS5/manuals/NFHS-5%20CAB%20Manual_Eng.pdf
5. Guidelines on food fortification with micronutrients [Internet]. [cited 2023 Jan 18]. Available from: <https://www.who.int/publications-detail-redirect/9241594012>
6. 6 Interventions of the Anemia Mukht Bharat Programme [Internet]. Anemia Mukht Bharat Dashboard. [cited 2023 Feb 7]. Available from: <https://anemiamukhtbharat.info/home/interventions/>
7. Scaling up of fortification of rice (phase i to phase iii) [Internet]. [cited 2023 Jan 2]. Available from: https://dfpd.gov.in/scaling_up_of_fortification_of_rice_new.htm
8. FAO. Codex standard for rice. Internet: [ww.fao.org/input/download/standards/61/CXS_198e.pdf](http://www.fao.org/input/download/standards/61/CXS_198e.pdf) (accessed 22 August 2018).
9. Horton S. The economics of food fortification. *J Nutr.* 2006 Apr;136(4):1068–71.
10. Baltussen R, Knai C, Sharan M. Iron fortification and iron supplementation are cost-effective interventions to reduce iron deficiency in four subregions of the world. *J Nutr.* 2004 Oct;134(10):2678–84.
11. Viteri FE, Gonzalez H. Adverse outcomes of poor micronutrient status in childhood and adolescence. *Nutr Rev.* 2002 May;60(5 Pt 2):S77-83.
12. Semba RD. The historical evolution of thought regarding multiple micronutrient nutrition. *J Nutr.* 2012 Jan;142(1):143S-56S.
13. Victora CG, Adair L, Fall C, Hallal PC, Martorell R, Richter L, et al. Maternal and child undernutrition: consequences for adult health and human capital. *Lancet* [Internet]. 2008 Jan 26 [cited 2023 Jan 7];371(9609):340–57. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2258311/>

14. Boy E, Mannar V, Pandav C, de Benoist B, Viteri F, Fontaine O, et al. Achievements, challenges, and promising new approaches in vitamin and mineral deficiency control. *Nutr Rev*. 2009 May;67 Suppl 1:S24-30.
15. Spohrer R, Larson M, Maurin C, Lailou A, Capanzana M, Garrett GS. The growing importance of staple foods and condiments used as ingredients in the food industry and implications for large-scale food fortification programs in Southeast Asia. *Food Nutr Bull*. 2013 Jun;34(2 Suppl):S50-61.
16. Map: Number of Food Vehicles – Global Fortification Data Exchange | GFDx [Internet]. [cited 2023 Feb 13]. Available from: <https://fortificationdata.org/map-number-of-food-vehicles/>
17. Operational guidelines on pilot scheme for fortification of rice and its distribution under pds.pdf [Internet]. [cited 2023 Jan 2]. Available from: <https://dfpd.gov.in/1sGbO2W68mUlunCgKmpnLF5WHm/pdf/operational%20guidelines%20on%20pilot%20scheme%20for%20fortification%20of%20rice%20and%20its%20distribution%20under%20pds.pdf>
18. RDA Full Book_27-10-2021_03_33PM.pdf [Internet]. Google Docs. [cited 2023 Jan 18]. Available from: https://drive.google.com/file/d/1og-NaMrwdsL73WZFRMDBIRzE9xZJkNDs/view?usp=embed_facebook
19. Peña-Rosas JP, Mithra P, Unnikrishnan B, Kumar N, De-Regil LM, Nair NS, et al. Fortification of rice with vitamins and minerals for addressing micronutrient malnutrition. *Cochrane Database Syst Rev* [Internet]. 2019 Oct 25 [cited 2022 Aug 11];2019(10):CD009902. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6814158/>
20. Beneficiaries of PDS [Internet]. [cited 2023 Jan 18]. Available from: <https://pib.gov.in/newsite/PrintRelease.aspx?relid=92902>
21. India: population by region [Internet]. Statista. [cited 2023 Feb 7]. Available from: <https://www.statista.com/statistics/1012239/india-population-by-region/>
22. Rural population (% of total population) - India | Data [Internet]. [cited 2023 Feb 7]. Available from: <https://data.worldbank.org/indicator/SP.RUR.TOTL.ZS?locations=IN>
23. Clinical-impact-study-of-micronutrients-fortified-rice-in-Indonesia.pdf [Internet]. [cited 2023 Jan 9]. Available from: https://snrd-asia.org/download/better_rice_initiative_asia_bria/clinical-impact-study-of-micronutrients-fortified-rice-in-Indonesia.pdf
24. Thankachan P, Rah JH, Thomas T, Selvam S, Amalrajan V, Srinivasan K, et al. Multiple micronutrient-fortified rice affects physical performance and plasma vitamin B-12 and homocysteine concentrations of Indian school children. *J Nutr*. 2012 May;142(5):846–52.
25. Georgieff MK, Krebs NF, Cusick SE. The Benefits and Risks of Iron Supplementation in Pregnancy and Childhood. *Annu Rev Nutr*. 2019;39(1):121–46.

26. 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 Lond Engl*. 2006 Jan 14;367(9505):133–43.
27. Tielsch JM, Khattry SK, Stoltzfus RJ, Katz J, LeClerq SC, Adhikari R, et al. Effect of daily zinc supplementation on child mortality in southern Nepal: a community-based, cluster randomised, placebo-controlled trial. *Lancet*. 2007 Oct 6;370(9594):1230–9.
28. Zlotkin S, Newton S, Aimone AM, Azindow I, Amenga-Etego S, Tchum K, et al. Effect of iron fortification on malaria incidence in infants and young children in Ghana: a randomized trial. *JAMA*. 2013 Sep 4;310(9):938–47.
29. Neuberger A, Okebe J, Yahav D, Paul M. Oral iron supplements for children in malaria-endemic areas. *Cochrane Database Syst Rev*. 2016 Feb 27;2016(2):CD006589.
30. Ojukwu JU, Okebe JU, Yahav D, Paul M. Oral iron supplementation for preventing or treating anaemia among children in malaria-endemic areas. *Cochrane Database Syst Rev* [Internet]. 2009 [cited 2023 Feb 15];(3). Available from: <https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD006589.pub2/full>
31. Okebe JU, Yahav D, Shbita R, Paul M. Oral iron supplements for children in malaria-endemic areas. *Cochrane Database Syst Rev* [Internet]. 2011 [cited 2023 Feb 15];(10). Available from: <https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD006589.pub3/abstract>
32. Jaramillo EG, Mupere E, Opoka RO, Hodges JS, Lund TC, Georgieff MK, et al. Delaying the start of iron until 28 days after antimalarial treatment is associated with lower incidence of subsequent illness in children with malaria and iron deficiency. *PloS One*. 2017;12(8):e0183977.
33. Mitra AK, Akramuzzaman SM, Fuchs GJ, Rahman MM, Mahalanabis D. Long-term oral supplementation with iron is not harmful for young children in a poor community of Bangladesh. *J Nutr*. 1997 Aug;127(8):1451–5.
34. Jaeggi T, Kortman GAM, Moretti D, Chassard C, Holding P, Dostal A, et al. Iron fortification adversely affects the gut microbiome, increases pathogen abundance and induces intestinal inflammation in Kenyan infants. *Gut*. 2015 May;64(5):731–42.
35. Soofi S, Cousens S, Iqbal SP, Akhund T, Khan J, Ahmed I, et al. Effect of provision of daily zinc and iron with several micronutrients on growth and morbidity among young children in Pakistan: a cluster-randomised trial. *Lancet Lond Engl*. 2013 Jul 6;382(9886):29–40.
36. Gera T, Sachdev HS, Boy E. Effect of iron-fortified foods on hematologic and biological outcomes: systematic review of randomized controlled trials. *Am J Clin Nutr*. 2012 Aug;96(2):309–24.

37. Zimmermann MB, Chassard C, Rohner F, N'goran EK, Nindjin C, Dostal A, et al. The effects of iron fortification on the gut microbiota in African children: a randomized controlled trial in Cote d'Ivoire. *Am J Clin Nutr.* 2010 Dec;92(6):1406–15.
38. Dostal A, Baumgartner J, Riesen N, Chassard C, Smuts CM, Zimmermann MB, et al. Effects of iron supplementation on dominant bacterial groups in the gut, faecal SCFA and gut inflammation: a randomised, placebo-controlled intervention trial in South African children. *Br J Nutr.* 2014 Aug 28;112(4):547–56.
39. Rajendran S, Bobby Z, Habeebullah S, Elizabeth Jacob S. Differences in the response to iron supplementation on oxidative stress, inflammation, and hematological parameters in nonanemic and anemic pregnant women. *J Matern-Fetal Neonatal Med Off J Eur Assoc Perinat Med Fed Asia Ocean Perinat Soc Int Soc Perinat Obstet.* 2022 Feb;35(3):465–71.
40. Dekker Nitert M, Gomez-Arango LF, Barrett HL, McIntyre HD, Anderson GJ, Frazer DM, et al. Iron supplementation has minor effects on gut microbiota composition in overweight and obese women in early pregnancy. *Br J Nutr.* 2018 Aug;120(3):283–9.
41. Tang M, Frank DN, Sherlock L, Ir D, Robertson CE, Krebs NF. Effect of Vitamin E With Therapeutic Iron Supplementation on Iron Repletion and Gut Microbiome in US Iron Deficient Infants and Toddlers. *J Pediatr Gastroenterol Nutr.* 2016 Sep;63(3):379–85.
42. Paganini D, Uyoga MA, Cercamondi CI, Moretti D, Mwasi E, Schwab C, et al. Consumption of galacto-oligosaccharides increases iron absorption from a micronutrient powder containing ferrous fumarate and sodium iron EDTA: a stable-isotope study in Kenyan infants. *Am J Clin Nutr.* 2017 Oct 1;106(4):1020–31.
43. Paganini D, Zimmermann MB. The effects of iron fortification and supplementation on the gut microbiome and diarrhea in infants and children: a review. *Am J Clin Nutr.* 2017 Dec;106(Suppl 6):1688S-1693S.
44. Malan L, Baumgartner J, Calder PC, Zimmermann MB, Smuts CM. n-3 Long-chain PUFAs reduce respiratory morbidity caused by iron supplementation in iron-deficient South African schoolchildren: a randomized, double-blind, placebo-controlled intervention. *Am J Clin Nutr.* 2015 Mar 1;101(3):668–79.
45. Baumgartner J, Smuts CM, Malan L, Kvalsvig J, van Stuijvenberg ME, Hurrell RF, et al. Effects of iron and n-3 fatty acid supplementation, alone and in combination, on cognition in school children: a randomized, double-blind, placebo-controlled intervention in South Africa. *Am J Clin Nutr.* 2012 Dec 1;96(6):1327–38.
46. Moretti D, Zimmermann MB, Muthayya S, Thankachan P, Lee TC, Kurpad AV, et al. Extruded rice fortified with micronized ground ferric pyrophosphate reduces iron deficiency in Indian schoolchildren: a double-blind randomized controlled trial. *Am J Clin Nutr.* 2006 Oct; 84 (4): 822-9.

47. Radhika MS, Nair KM, Kumar RH, Rao MV, Ravinder P, Reddy CG, et al. Micronized ferric pyrophosphate supplied through extruded rice kernels improves body iron stores in children: a double-blind, randomized, placebo-controlled midday meal feeding trial in Indian schoolchildren. *Am J Clin Nutr.* 2011 Nov;94(5):1202–10.
48. Andersson M, Thankachan P, Muthayya S, Goud RB, Kurpad AV, Hurrell RF, et al. Dual fortification of salt with iodine and iron: a randomized, double-blind, controlled trial of micronized ferric pyrophosphate and encapsulated ferrous fumarate in southern India. *Am J Clin Nutr.* 2008 Nov;88(5):1378-87.
49. Zimmermann MB, Wegmueller R, Zeder C, Chaouki N, Rohner F, Saïssi M, et al. Dual fortification of salt with iodine and micronized ferric pyrophosphate: a randomized, double-blind, controlled trial. *Am J Clin Nutr.* 2004 Oct;80(4):952–9.
50. Wegmüller R, Camara F, Zimmermann MB, Adou P, Hurrell RF. Salt dual-fortified with iodine and micronized ground ferric pyrophosphate affects iron status but not hemoglobin in children in Cote d’Ivoire. *J Nutr.* 2006 Jul;136(7):1814–20.
51. Shahinfar H, Jayedi A, Shab-Bidar S. Dietary iron intake and the risk of type 2 diabetes: a systematic review and dose-response meta-analysis of prospective cohort studies. *Eur J Nutr.* 2022 Aug;61(5):2279–96.
52. Kunutsor SK, Apekey TA, Walley J, Kain K. Ferritin levels and risk of type 2 diabetes mellitus: an updated systematic review and meta-analysis of prospective evidence. *Diabetes Metab Res Rev.* 2013 May;29(4):308–18.
53. Bao W, Rong Y, Rong S, Liu L. Dietary iron intake, body iron stores, and the risk of type 2 diabetes: a systematic review and meta-analysis. *BMC Med.* 2012 Oct 10;10:119.
54. Zhao Z, Li S, Liu G, Yan F, Ma X, Huang Z, et al. Body iron stores and heme-iron intake in relation to risk of type 2 diabetes: a systematic review and meta-analysis. *PloS One.* 2012;7(7):e41641.
55. Sogaard KL, Ellervik C, Svensson J, Thorsen SU. The Role of Iron in Type 1 Diabetes Etiology: A Systematic Review of New Evidence on a Long-Standing Mystery. *Rev Diabet Stud RDS.* 2017;14(2–3):269–78.
56. Yang K, Yang Y, Pan B, Fu S, Cheng J, Liu J. Relationship between iron metabolism and gestational diabetes mellitus: A systemic review and meta analysis. *Asia Pac J Clin Nutr.* 2022;31(2):242–54.
57. Miranda VIA, Pizzol T da SD, Jesus PR de, Silveira MPT, Bertoldi AD. Iron Salts, High Levels of Hemoglobin and Ferritin in Pregnancy, and Development of Gestational Diabetes: A Systematic Review. *Rev Bras Ginecol E Obstet Rev Fed Bras Soc Ginecol E Obstet.* 2022 Nov;44(11):1059–69.

58. Meka S, Geddamuri BG, Varghese B, Nath B, Vishwakarma G, Adela R. Circulatory hepcidin levels association with gestational diabetes mellitus: a meta-analysis of observational studies. *Int J Pharm Pract.* 2022 Jun 25;30(3):195–203.
59. D’Arcy E, Rayner J, Hodge A, Ross LJ, Schoenaker DAJM. The Role of Diet in the Prevention of Diabetes among Women with Prior Gestational Diabetes: A Systematic Review of Intervention and Observational Studies. *J Acad Nutr Diet.* 2020 Jan;120(1):69-85.e7.
60. Fernández-Cao JC, Aranda N, Ribot B, Tous M, Arija V. Elevated iron status and risk of gestational diabetes mellitus: A systematic review and meta-analysis. *Matern Child Nutr.* 2017 Oct;13(4):e12400.
61. Zhao L, Lian J, Tian J, Shen Y, Ping Z, Fang X, et al. Dietary intake of heme iron and body iron status are associated with the risk of gestational diabetes mellitus: a systematic review and meta-analysis. *Asia Pac J Clin Nutr.* 2017;26(6):1092–106.
62. Khambalia AZ, Aimone A, Nagubandi P, Roberts CL, McElduff A, Morris JM, et al. High maternal iron status, dietary iron intake and iron supplement use in pregnancy and risk of gestational diabetes mellitus: a prospective study and systematic review. *Diabet Med J Br Diabet Assoc.* 2016 Sep;33(9):1211–21.
63. Jiang R, Ma J, Ascherio A, Stampfer MJ, Willett WC, Hu FB. Dietary iron intake and blood donations in relation to risk of type 2 diabetes in men: a prospective cohort study. *Am J Clin Nutr.* 2004 Jan 1;79(1):70–5.
64. Andrews NC. Disorders of Iron Metabolism. *N Engl J Med.* 1999 Dec 23;341(26):1986–95.
65. Cooksey RC, Jouihan HA, Ajioka RS, Hazel MW, Jones DL, Kushner JP, et al. Oxidative Stress, β -Cell Apoptosis, and Decreased Insulin Secretory Capacity in Mouse Models of Hemochromatosis. *Endocrinology.* 2004 Nov 1;145(11):5305–12.
66. Radhika MS, Nair KM, Kumar RH, Rao MV, Ravinder P, Reddy CG, et al. Micronized ferric pyrophosphate supplied through extruded rice kernels improves body iron stores in children: a double-blind, randomized, placebo-controlled midday meal feeding trial in Indian schoolchildren. *Am J Clin Nutr.* 2011 Nov;94(5):1202–10.
67. Draft Operational Guidelines on Quality Control for Fortified Rice Kernels (FRK) and Fortified Rice (FR). Government of India Ministry of Consumer Affairs, Food & Public Distribution Department of Food & Public Distribution (Quality Control Cell);
68. Zhang Z, Liu C, Liu M, Zhou C, Li Q, He P, et al. Dietary Iron Intake and New-Onset Hypertension: A Nationwide Cohort Study from China. *J Nutr Health Aging.* 2022;26(11):1016–24.

69. Tzoulaki I, Brown IJ, Chan Q, Van Horn L, Ueshima H, Zhao L, et al. Relation of iron and red meat intake to blood pressure: cross sectional epidemiological study. *BMJ*. 2008 Jul 15;337:a258.
70. Galan P, Vergnaud AC, Tzoulaki I, Buyck JF, Blacher J, Czernichow S, et al. Low Total and Nonheme Iron Intakes Are Associated with a Greater Risk of Hypertension. *J Nutr*. 2010 Jan 1;140(1):75–80.
71. Esfandiar Z, Hosseini-Esfahani F, Mirmiran P, Habibi-Moeini AS, Azizi F. Red meat and dietary iron intakes are associated with some components of metabolic syndrome: Tehran Lipid and Glucose Study. *J Transl Med*. 2019 Sep 18;17:313.
72. Waldvogel-Abramowski S, Waeber G, Gassner C, Buser A, Frey BM, Favrat B, et al. Physiology of Iron Metabolism. *Transfus Med Hemotherapy*. 2014 Jun;41(3):213–21.
73. Oliveira F, Rocha S, Fernandes R. Iron Metabolism: From Health to Disease. *J Clin Lab Anal*. 2014 Jan 29;28(3):210–8.
74. von Haehling S, Ebner N, Evertz R, Ponikowski P, Anker SD. Iron Deficiency in Heart Failure: An Overview. *JACC Heart Fail*. 2019 Jan;7(1):36–46.
75. Ames BN, Atamna H, Killilea DW. Mineral and vitamin deficiencies can accelerate the mitochondrial decay of aging. *Mol Aspects Med*. 2005;26(4–5):363–78.
76. Chen B, Lu Y, Chen Y, Cheng J. The role of Nrf2 in oxidative stress-induced endothelial injuries. *J Endocrinol*. 2015 Jun;225(3):R83-99.
77. Rajapurkar MM, Shah SV, Lele SS, Hegde UN, Lensing SY, Gohel K, et al. Association of catalytic iron with cardiovascular disease. *Am J Cardiol*. 2012 Feb 1;109(3):438–42.
78. Spasojevic-Kalimanovska V, Bogavac-Stanojevic N, Kalimanovska-Ostic D, Memon L, Spasic S, Kotur-Stevuljevic J, et al. Factor analysis of risk variables associated with iron status in patients with coronary artery disease. *Clin Biochem*. 2014 May;47(7–8):564–9.
79. Sullivan JL. Iron in arterial plaque: modifiable risk factor for atherosclerosis. *Biochim Biophys Acta*. 2009 Jul;1790(7):718–23.
80. Guidelines_on_Hemoglobinopathies_in India.pdf [Internet]. [cited 2023 Feb 14]. Available from: https://nhm.gov.in/images/pdf/programmes/RBSK/Resource_Documents/Guidelines_on_Hemoglobinopathies_in%20India.pdf
81. Zimmermann MB, Fucharoen S, Winichagoon P, Sirankapracha P, Zeder C, Gowachirapant S, et al. Iron metabolism in heterozygotes for hemoglobin E (HbE), α -thalassemia 1, or β -thalassemia and in compound heterozygotes for HbE/ β -thalassemia. *Am J Clin Nutr*. 2008 Oct 1; 88 (4): 1026–31.
82. Mariani R, Trombini P, Pozzi M, Piperno A. Iron Metabolism in Thalassemia and Sickle Cell Disease. *Mediterr J Hematol Infect Dis*. 2009 Oct 27;1(1):e2009006.

83. Moretti D, Zimmermann MB, Muthayya S, Thankachan P, Lee TC, Kurpad AV, et al. Extruded rice fortified with micronized ground ferric pyrophosphate reduces iron deficiency in Indian schoolchildren: a double-blind randomized controlled trial. *Am J Clin Nutr* [Internet]. 2006 Oct 1 [cited 2023 Feb 3];84(4):822–9. Available from: <https://academic.oup.com/ajcn/article/84/4/822/4633059>
84. Radhika MS, Nair KM, Kumar RH, Rao MV, Ravinder P, Reddy CG, et al. Micronized ferric pyrophosphate supplied through extruded rice kernels improves body iron stores in children: a double-blind, randomized, placebo-controlled midday meal feeding trial in Indian schoolchildren. *Am J Clin Nutr* [Internet]. 2011 Nov 1 [cited 2023 Feb 3];94(5):1202–10. Available from: <https://academic.oup.com/ajcn/article/94/5/1202/4597832>
85. Sun X, Guo Y, Wang S, Sun J. Social marketing improved the consumption of iron-fortified soy sauce among women in China. *J Nutr Educ Behav*. 2007;39(6):302–10.
86. Wu DCN, Corbett K, Horton S, Saleh N, Mosha TC. Effectiveness of social marketing in improving knowledge, attitudes and practice of consumption of vitamin A-fortified oil in Tanzania. *Public Health Nutr* [Internet]. 2019 Mar [cited 2023 Feb 3];22(3):466–75. Available from: https://www.cambridge.org/core/product/identifier/S1368980018003373/type/journal_article
87. Warren AM, Frongillo EA, Nguyen PH, Menon P. Nutrition Intervention Using Behavioral Change Communication without Additional Material Inputs Increased Expenditures on Key Food Groups in Bangladesh. *J Nutr* [Internet]. 2020 May [cited 2023 Feb 3];150(5):1284–90. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0022316622021794>
88. Ludwig-Borycz EF, Wilson ML, Colecraft EK, Jones AD. A behavior change communication intervention, but not livelihood interventions, improves diet diversity and animal-source food consumption among Ghanaian women. *Food Nutr Res* [Internet]. 2022 Jul 27 [cited 2023 Feb 3];66. Available from: <https://foodandnutritionresearch.net/index.php/fnr/article/view/7570>
89. Food Safety and Standards (Fortification of Foods) Amendment Regulations, 2020 [Internet]. Available from: https://fssai.gov.in/upload/uploadfiles/files/Compendium_Food_Fortification_Regulations_03_03_2022.pdf

ANNEXURES

ANNEXURES

Table 1. Adverse effects of oral iron: Children mortality and hospitalization in malaria endemic regions

Study	Participants /groups	Intervention	Duration	Results
Sasawal 2006, Pemba trial, RCT with 3 arms	Children 1–35 months; Tanzania, Gp1: Fe+FA (4037), Gp2: Fe+FA+Zn (4085) Gp3: Placebo (4073)	1-11 months Iron 6.25mg/d; 12-35 months 12.5mg/d as ferrous sulfate (~1mg/kg/d)	18 months	Iron suppl. groups (Gp1+Gp2) vs Placebo a) Adverse events RR 1.12 (1.02–1.23; p= 0.02) b) Mortality RR 1.15 (0.93–1.41; p=0.19) c) Hospital admission RR 1.11 (1.01–1.23; p=0.03) Gp1 (Fe without Zn) vs Placebo Hospital admission RR 1.08 (0.97–1.21; p = 0.16) Gp2 (Fe with Zn) vs Placebo Hospital admission RR 1.14 (1.03–1.28; p = 0.02)
Pemba sub-study	Gp1: Fe+FA (412), Gp2: Fe+FA+Zn (429) Gp3: Placebo (380)			Adverse effect in a) Iron deficient vs placebo – RR 0.62 (0.41–0.93; p = 0.02) b) Iron sufficient vs placebo RR 1.63 (0.72–3.66; p = 0.24)
Zlotkin 2013, RCT with 2 arms	Children 6 to 35 months, (Hb>7g/dl), Ghana Gp1: Iron+Zn+VitA+VitC (942) Gp2: No iron (962)	12.5 mg/d iron as micro encapsulated ferrous fumarate. (1-2mg/kg/d)	5 months	Iron group vs No iron group Hospital admission RR, 1.23 (1.02-1.49). (Malaria, Diarrhoea, RTI and others)
Jaramillo 2017, RCT with 2 arms (33)	Children 6–59 months Uganda with malaria and anaemia Gp1: Immediate Iron (45) Gp2: Delayed Iron (43)	2mg/kg/d as liquid ferrous sulfate	28 days concurrent/delayed	immediate vs delayed iron IRR all-cause sick-child visits to the clinic = 1.76 (1.05–3.03, p = 0.033)

Table 2. Adverse effects of oral iron: Diarrhoea/Dysentery

Study	Participants/groups	Intervention	Duration	Results
Jaeggi 2014, 2 RCTs with 2 arms each	Children 6 months, Kenya, RCT1 Gp1: MNP NaFeEDTA (25) Gp2: No iron (25) RCT2 Gp1: MNP ferfumarate (25) Gp2: No iron (25)	Home-fortified maize porridge with MNP (2mg/kg/d) a) 2.5mg/d Fe as NaFeEDTA b) 12.5 mg/d Fe as ferrous fumarate	4 months	27.3% of infants in +12.5 mgFeMNP required treatment for diarrhoea versus 8.3% in -12.5 mgFeMNP (p=0.092);
Soofi 2013, RCT with 3 arms	Children 6 months. Pakistan. Gp1: control (671), Gp2: MNP without Zn (646) Gp3: MNP with Zn (659)	Iron 12.5 mg/d as microencapsulated ferrous fumarate (2mg/kg/d)	For 18 months; outcome at 24 months	Between 6-18 months Proportion of days with diarrhoea Fe MNP – OR 1.15 (1.00-1.33) Fe+Zn MNP – OR 1.31 (1.13-1.51) Bloody diarrhoea IRR Fe MNP- IRR 1.63 (1.12–2.39) Fe+Zn MNP- IRR 1.88 (1.29– 2.74)
Mitra 1997, RCT with 2 arms (34)	Children 2-48 months, Bangladesh, Iron + MVit(172) Gp2: Mvit (177)	Iron as Ferrous gluconate 15mg/d (1-3mg/kg/d)	15 months	49% greater episodes of dysentery in a subset of the study children < 12 months old on supplementation (p = 0.03). No difference in older children with respect to diarrhoea, dysentery, and ARI.

Table 3. Systematic review: Iron and evidence for increased risk of Diarrhoea (studies with and without zinc)

Studies without ZINC		Iron (n)	Control (n)	Iron form/dose	Risk Ratio, 95% CI
Richard	6mth-15 yrs	1060	1073	0.75mg/kg/d 7mth FeSO4	0.99 [0.81,1.2]
Zlotkin	20 ± 8 mth	4835	4955	1mg/kg/d 5mth Fe-Fum	1.13 [0.85,1.5]
Adam	6-84 mth	1215	1146	3mg/kg/d 12wks FeSO4	1.03 [0.73,1.45]
Berger 2006	6 ± 1 mth	1200	1182	1.5mg/kg/d 6mth FeSO4	0.89 [0.6,1.32]
Berger 2000	6-36 mth	252	237	2-3mg/kg/d 3mth Febetain	0.56 [0.28,1.15]
Lawless	6-11 yrs	154	147	1.5mg/kg/d 14wks FeSO4	0.84 [0.3,2.3]
Dossa	3-30 mth	52	58	7.5mg/kg/d 6wks Fe-Fum	1.34 [0.41,4.39]
Subtotal	42.67%	8768	8798		0.99 [0.87,1.13]
Studies with ZINC		Iron (n)	Control (n)	Iron form/dose	Risk Ratio, 95% CI
Richard	0.5-15 yrs.	1071	1087	0.75mg, Zn 20mg/d 7mth	1.36 [1.19,1.57]
Fahmida	5 ± 1 mth	930	954	2mg/kg/d FeSO4 Zn 10mg 6mth	1.18 [0.93,1.51]
Berger 2006	6 ± 1 mth	1134	1170	1.5mg/kg/d 6mth FeSO4	0.99 [0.67,1.46]
Subtotal	57.33%	3135	3211		1.29 [1.15,1.44]
Total	100%	11903	12009		1.15 [1.06,1.26]

Table 4. Systematic review: Iron and no evidence for increased risk of diarrhoea

Study	Age	Iron Epi/ch-yr	Control Epi/ch-yr	Iron form/dose	Risk Ratio, 95% CI
Irigoyen	6 mth	20/114	13/53	3-6 mg/kg/d 3mth FeSO4	0.72 [0.34,1.56]
Idjradinata	12-18 mth	19/8	21/7.6	3 mg/kg/d 4mth FeSO4	0.87 [0.44,1.69]
Rosando	1.5-3 yrs	122/109	102/110	2 mg/kg/d 12mth FeSO4	1.2 [0.92,1.59]
Mitra	2-48 mth	670/127	695/139	1-3 mg/kg/d 15mth Fe Gluconate	1.05 [0.95,1.17]
Rice	3-56 mth	388/268	376/267	0.5-2 mg/kg/d 12mthFeSO4	1.03 [0.89,1.19]
Lawless	6-11 yrs	7/11	8/10.5	1.4 mg/kg/d 3mth FeSO4	0.84 [0.26,2.63]
Atukorala	5-10 yrs	31/43	7/17	1 mg/kg/d 2mth FeSO4	1.72 [0.74,4.63]
Tielsch, 2006	1-36 mth	1327/341	1355/352	1 mg/kg/d until 36mth FeSO4	1.01 [0.94,1.09]
Soofi, 2013	6 mth	5813/3709	5607/3460	2 mg/kg/d 18 mth Fe Fumarate	1.05 [0.94,1.17]
Total		2584/1022	2577/957		0.97 [0.93,1.0]

Table 5. Systematic review: Iron and risk of RTIs

Study	Age	Iron (n)	Control (n)	Iron form/dose	Risk Ratio, 95% CI
Berger 2006	6 ± 1 mth	1200	1182	1.5mg/kg/d 6mth FeSO4	1.05 [0.81,1.37]
Berger 2006	6 ± 1 mth	1134	1170	1.5mg/kg/d 6mth FeSO4	1.05 [0.8,1.38]
Richard2006	6mth-15 yrs	1060	1073	0.75mg/kg/d 7mth FeSO4	0.8 [0.52,1.23]
Richard2006	6mth-15 yrs	1071	1087	0.75mg/kg/d 7mth FeSO4	0.83 [0.52,1.33]
Esan 2013	6 -59 mth	315	312	3mg/kg/d 3mth	1.07 [0.5,2.27]
Zlotkin 2013	20 ± 8 mth	4835	4955	1mg/kg/d 5mth Fe-Fumarate	1.21 [0.54,2.7]
Berger 2000	6-36 mth	252	237	2-3mg/kg/d 3mth Febetaine	0.75 [0.3,1.91]
Fahmida 2007	5 ± 1 mth	930	954	2mg/kg/d FeSO4 Zn 10mg 6mth	1.54 [0.26,9.21]
Total		10797	10970		0.99 [0.85,1.15]

Table 6. Systematic review: Adverse effects of iron in Non-Pregnant Women

Adverse effect	No. of trials	No. of participants	Measure of difference
Non-Pregnant Women 19–49 years			
Gastrointestinal side effect	5	521	RR 1.99 [1.26 to 3.12]
Gastrointestinal side effect dose			
31–60 mg	2	293	RR 1.23 [0.84,1.81]
61–100 mg	1	145	RR 3.00 [1.45,6.20]
>100 mg	2	83	RR 2.42 [1.45,4.05]
Loose stools/diarrhoea	6	604	RR 2.13 [1.10,4.11]
Hard stools/constipation	8	1036	RR 2.07 [1.35,3.17]
Abdominal pain	7	1190	RR 1.55 [0.99,2.41]
Nausea	8	1214	RR 1.19 [0.78,1.82]

Table 7. Adverse effects of Iron: Gut inflammation and dysbiosis

Study	Participants /groups	Intervention	Duration	Results
Jaeggi 2014, 2 RCTs with 2 arms each	Children 6 months, Kenya, RCT1 Gp1: MNP NaFeEDTA (25) Gp2: No iron (25) RCT2 Gp1: MNP ferfumarate (25) Gp2: No iron (25)	Home-fortified maize porridge with MNP a) 2.5mg/d Fe as NaFeEDTA b) 12.5 mg/d Fe as ferrous fumarate	4 months	+FeMNPs increased faecal calprotectin (p=0.002) +FeMNPs increased enterobacteria, particularly Escherichia/Shigella (p=0.048), the enterobacteria/bifidobacteria ratio (p=0.020), and Clostridium (p=0.030). c) 27.3% in +12.5 mgFeMNP required treatment for diarrhoea versus 8.3% in -12.5 mgFeMNP (p=0.092);
Zimmermann 2010, RCT with 2 arms	Children 6-14 years. Ivory Coast Gp1: Fe fortified biscuits(70) Gp2: nonfortifiedbiscuits(69)	20mg Fe as electrolytic iron (insoluble but bioavailable iron)	6 months 4d/wk	a significant increase in the number of enterobacteria (P < 0.005) and a decrease in lactobacilli (P < 0.0001) increase in the mean faecal calprotectin concentration (P < 0.01) No significant difference in gastrointestinal illness Anemic African children carry an unfavorable ratio of fecal enterobacteria to bifidobacteria and lactobacilli, which is increased by iron fortification.
Dostal 2014, RCT with 2 arms	Children 6-11 years. South Africa Gp1: Fe deficient (22) Gp2: Placebo (27) Gp3: Fe sufficient (24) (microbiome comparison)	50 mg Fe as FeSO4	9 months 4d/wk	African children with a low enteropathogen burden, Fe status and dietary Fe supplementation did not significantly affect the dominant bacterial groups in the gut, faecal SCFA concentration or gut inflammation.

Table 8. Systematic review: Beneficial effects of iron in Pregnant Women

Adverse effect	No. of trials	No. of participants	Measure of difference
Pregnant Women 15–49 years (Daily supplements containing iron 30-60 mg versus same supplements without iron)			
Any adverse effect	11	2423	RR 1.29 [0.83,2.02]
Diarrhoea	3	1088	RR 0.55 [0.32, 0.93]
Puerperal infection	4	4374	RR 0.68 [0.50, 0.92]
Any adverse effect vs Dose of Iron			
≤ 30 mg	6	1533	RR 1 [0.86,1.16]
30-59 mg	2	225	RR 2 [0.66,6.02]
≥ 60 mg	5	665	RR 4.42 [0.61,30.67]
Any adverse effect Intermittent vs Daily dose	11	1777	RR 0.56 [0.37,0.84]

Table 9. Dietary iron intake and risk of diabetes mellitus
(Systematic review: Shahinfar, Jayedi, and Shab-Bidar 2022)

Risk factor (Highest vs. lowest category)	Outcome	Number if cohorts sample (n) incident cases	Relative effect (95% CI)	Certainty of evidence
Dietary total iron intake	Type 2 Diabetes	7 Cohorts n=197,672; Cases=19,175	RR 1.09 (0.92, 1.28)	GRADE = very low (downgrades for imprecision and inconsistency)
Dietary heme iron intake	Type 2 Diabetes	11 Cohorts n=323,788; Cases=28,837	RR 1.2 (1.07, 1.35)	GRADE=moderate
Dietary non-heme iron intake	Type 2 Diabetes	6 Cohorts n=135,893 Cases=8,978	RR 0.96 (0.81, 1.15)	GRADE=very low
Supplemental iron	Type 2 Diabetes	2 cohorts n=120,729 Cases=6520	RR 1.03 (0.86, 1.23)	GRADE=very low

Table 10. Dietary Iron Intake and Risk of Diabetes Mellitus
Systematic Review: Shahinfar, Jayedi, and Shab-Bidar 2022)(15)

Risk factor (dose response)	Outcome	Number if cohorts sample (n) incident cases	Relative effect (95% CI)	Certainty of evidence
5 mg/day increment in total iron intake	Type 2 Diabetes	7 Cohorts n=197,672; Cases=19,175	RR 0.99 (0.97, 1.02)	GRADE=very low (downgrades for imprecision and inconsistency)
1 mg/day increment in heme iron intake	Type 2 Diabetes	11 Cohorts n=323,788; Cases=28,837	RR 1.16 (1.03, 1.30)	GRADE = moderate
5 mg/day increment in non-heme iron intake	Type 2 Diabetes	6 Cohorts n=135,893 Cases=8,978	RR 0.92 (0.82, 1.03)	GRADE = very low
5 mg/day increment in supplemental iron intake	Type 2 Diabetes	2 cohorts n=120,729 Cases=6520	RR 1.02 (0.96, 1.09)	GRADE = very low

Table 11. Association between dietary iron intake and the risk of new-onset Hypertension (Zhang et al. 2022) (21)

Iron intake, mg/day	N	Events* (rate)	Adjusted model [†]	
			HR (95% CI)	P value
Total iron				
Quintile				
Q1 (<18.2)	2449	864(48.7)	Ref	
Q2 (18.2-<20.2)	2449	768(37.9)	0.80(0.72,0.88)	<0.001
Q3 (20.2-<22.1)	2449	797(38.9)	0.80(0.71,0.89)	<0.001
Q4 (22.1-<25.0)	2449	888(44.2)	0.89(0.80,0.99)	0.036
Q5 (≥25.0)	2449	987(58.0)	1.08(0.96,1.21)	0.189
Categories				
Q1 (<18.2)	2449	864(48.7)	1.26(1.15,1.38)	<0.001
Q2-3 (18.2-22.1)	4898	1565(38.4)	Ref	
Q4-5 (≥22.1)	4898	1875(50.5)	1.21(1.13,1.31)	<0.001
Heme iron				
Categories				
Q1 (<0.25)	2448	1213(63.0)	Ref	
Q2-5 (≥0.25)	9797	3091(40.5)	0.71(0.65,0.78)	<0.001
Non-heme iron				
Categories				
Q1 (<17.4)	2448	843(47.9)	1.33(1.21,1.46)	<0.001
Q2-3 (17.4-21.3)	4899	1531(37.9)	Ref	
Q4-5 (≥21.3)	4898	1930(51.4)	1.24(1.15,1.34)	<0.001

*Incident rate is presented per 1000 person-years of follow-up.

† Adjusted for age, sex, body mass index, smoking, systolic blood pressure, diastolic blood pressure, education, urban or rural residence, region, occupations at baseline, as well as cumulative intake levels of carbohydrate, protein, fat, red meats, grains, fruits and vegetables, and sodium to potassium intake ratio during the follow-up. Mutual adjustment was performed for dietary heme and nonheme iron.