Characterisation of the types of anaemia prevalent among children and adolescents aged 1–19 years in India: a population-based study

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Summary

Background Anaemia is a serious public health concern in India. However, national estimates for its prevalence are not available for the 5–14 years age group, nor are estimates available for the types of anaemia among children and adolescents (1–19 years). We aimed to assess the prevalence of anaemia among children and adolescents in India and to categorise types of anaemia on the basis of micronutrient deficiencies.

Methods We assessed the prevalence of anaemia among children (1–4 years and 5–9 years) and adolescents (10–19 years) using nationally representative data from the Comprehensive National Nutrition Survey. Anaemia was classified on the basis of age and sex-specific WHO cutoffs and serum ferritin, soluble transferrin receptor, folate, cyanocobalamin, and C-reactive protein concentrations as iron deficiency anaemia, folate or vitamin B12 deficiency anaemia, dimorphic anaemia (iron deficiency anaemia and folate or vitamin B12 deficiency anaemia), anaemia of other causes (anaemia not classified as iron deficiency anaemia and folate or vitamin B12 deficiency anaemia), and anaemia of inflammation.

Findings We included 26 765 children (11 624 aged 1–4 years and 15 141 aged 5–9 years) and 14 669 adolescents. In the weighted sample, anaemia prevalence was 40·5% (4553 of 11 233) among 1–4 year-olds, 23·4% (3439 of 14 664) among 5–9 year-olds, and 28·4% (4064 of 14 300) among adolescents. Among 2862 children aged 1–4 years, iron deficiency anaemia (1045 [36·5%]) was the most prevalent type, followed by anaemia of other causes (702 [24·5%]), folate or vitamin B12 deficiency anaemia (542 [18·9%]), dimorphic anaemia (387 [13·5%]), and anaemia of inflammation (186 [6·5%]). Among 2261 children aged 5–9 years, anaemia of other causes was the most common (986 [43·6%]), followed by folate or vitamin B12 deficiency anaemia (558 [24·6%]), iron deficiency anaemia (353 [15·6%]), dimorphic anaemia (242 [10·7%]), and anaemia of inflammation (122 [5·4%]). 861 (31·4%) of 2740 adolescents had anaemia of other causes, 703 (25·6%) had folate or vitamin B12 deficiency anaemia, 584 (21·3%) had iron deficiency anaemia, 498 (18·2%) and dimorphic anaemia, and 94 (3·4%) had anaemia of inflammation.

Interpretation Iron deficiency anaemia is the most common form of anaemia among younger children and anaemia of other causes among 5–9-year-old children and adolescents. Folate or vitamin B12 deficiency anaemia accounts for more than a third of anaemia prevalence. Anaemia prevention efforts should focus on strengthening the existing iron and folate supplementation programmes and prevention of folate or vitamin B12 deficiency anaemia.

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Introduction

Anaemia is a serious public health concern in India. National estimates show that 58% of children younger than 5 years and 29% of boys and 54% of girls aged 15–19 years are anaemic.[1] The Global Burden of Disease Study estimated the prevalence of anaemia in children under 5 years in India to be 59·7% in 2017.[2] Although national estimates for anaemia among children aged 5–9 years and adolescents aged 10–14 years are not available, smaller studies show that prevalence ranges from 41% to 69% among children aged 5–11 years and from 16% to 84·3% among adolescents aged 12–18 years.[3–5]

Erythrocytes contain haemoglobin, and a decrease in the production or increased loss of these cells can cause anaemia. These processes are broadly determined by nutrition, infectious disease, and genetics.[6,7] Iron deficiency is widely considered to be the main cause of anaemia, contributing to around 50% of anaemia cases.[6] However, other micronutrients, principally folate and vitamin B12, are equally necessary for erythropoiesis,[6,8] and the extent to which these deficiencies contribute to anaemia in India is not known. Small studies[5,9] done among children and adolescents in India indicate that folate deficiencies might be as high as 42–50% and vitamin B12 deficiencies 62–68%; however, a high prevalence of biochemical deficiencies might not necessarily translate into a comparable prevalence of anaemia.[10] Genetic

Research in context

Evidence before this study

Although estimates for anaemia prevalence are available from national surveys in India, they are based on haemoglobin testing using field-based HemoCue technology, and no data is available on the micronutrient deficiencies that contribute to anaemia. Before designing the Comprehensive National Nutrition Survey (CNNS), we reviewed recent large-scale surveys and found that national estimates for anaemia were available only for children younger than 5 years and adolescents aged 15–19 years from the 2015–16 National Family Health Survey 4 and state-level estimates for all age groups from the 2012–13 Annual Health Survey and District-Level Health and Facility Survey. The 2009 Coverage Evaluation Survey did not collect data on anaemia, while the 2012 National Nutrition Monitoring Bureau survey was done in some states and anaemia was assessed clinically. None of the surveys collected data on micronutrient deficiencies, and consequently no assessment of the different types of anaemia has been done. We also searched PubMed and Google Scholar between August and September, 2019, for literature on anaemia classification published between January, 2000, and December, 2019, using the search terms "anaemia", "ferritin", "folate", "vitamin B12", "soluble transferrin receptor", "C-reactive protein", "India", and "children and adolescents". Additionally, we searched for WHO technical reports on the diagnosis of anaemia, serum ferritin for the assessment of iron deficiency, and folate and vitamin B12 deficiencies. Smaller scale studies have assessed anaemia and associated micronutrient deficiencies in school children and adolescents and in rural communities in India. We did not find any report or paper providing national estimates on the types of anaemia or iron deficiency anaemia, which is the focus of the national anaemia prevention programme.

Added value of this study

The CNNS is the first national survey to undertake a detailed assessment of anaemia on the basis of haemoglobin testing using the gold-standard cyanmethemoglobin method and estimation of micronutrient deficiencies in a nationally representative sample of children and adolescents aged 1–19 years. Our results show that iron-deficiency anaemia is the most common form of anaemia among younger children (1–4 years), whereas anaemia of other causes was most common among 5–9-year-old children. Folate or vitamin B12 deficiency anaemia accounts for more than a third of anaemia in the three age groups, and 10–18% of children and adolescents with anaemia have both iron-deficiency anaemia and folate or vitamin B12 deficiency anaemia. Anaemia of inflammation was the least prevalent. We also report a higher prevalence of thalassaemia trait or haemoglobin E thalassaemia among participants with anaemia of other causes and folate or vitamin B12 deficiency anaemia than participants with iron-deficiency anaemia. None of these findings have been reported previously by any national population-based study in India.

Implications of all the available evidence

Iron deficiency anaemia is the most common form of anaemia in children and adolescents, and anaemia prevention efforts should focus on strengthening the existing iron and folic acid supplementation programme implemented by The Ministry of Health and Family Welfare, Government of India. At the same time, folate and B12 deficiencies contribute substantially to anaemia prevalence, highlighting the need for the national programme to address these deficiencies. More research is needed to understand anaemia of other causes. The CNNS serves as a baseline for the future studies or surveys to evaluate the national nutrition and anaemia prevention programme.

haemoglobinopathies contribute to anaemia through defective haemoglobin formation and compensatory efforts at erythropoiesis, and consequently, iron, folate, and B12 deficiencies.[11,12] The average prevalence of β-thalassaemia trait in India is thought to be 3–4%.[13] Acute and chronic disease conditions such as infections, inflammatory disease, renal failure, and malignancy are also associated with anaemia owing to shortened survival and impaired production of erythrocytes.[14]

Anaemia diagnosis is based on low blood haemoglobin concentration according to age and sex-specific cutoffs.[15] Iron deficiency can be assessed from several indicators: microcytosis or hypochromia, low serum ferritin, increased total iron-binding capacity, and reduced transferrin saturation. In the absence of the gold-standard bone marrow staining for iron stores, serum ferritin measurement is the most specific test that correlates with total iron stores, and ferritin concentrations are typically reduced in iron-deficiency anaemia.[16] However, serum ferritin concentrations are elevated during acute and chronic inflammation, making it difficult to accurately diagnose iron deficiency in the presence of inflammation.[16,17] Studies have often excluded subjects with elevated C-reactive protein (CRP) concentrations from anaemia analyses.[18] Although soluble transferrin receptor (sTfR) is elevated in iron deficiency anaemia, it can only be an indicator of iron deficiency when iron stores are depleted.[19] Several studies[17,20,21] have shown that combining ferritin with sTfR or using sTfR-log-ferritin index increases the sensitivity and specificity in diagnosing iron deficiency anaemia and aids in differentiating it from anaemia of inflammation. CRP and α-1-acid glycoprotein are the two commonly used markers to detect underlying inflammation.[18] Anaemia of inflammation is typically a mild to moderate anaemia with adequate iron stores evidenced by normal ferritin concentrations and elevated inflammatory makers.[21] Folate and vitamin B12 deficiencies, however, are typically associated with mild to moderate macrocytic anaemia with normal ferritin

	Analyte	Laboratory method	Cutoffs used
Anaemia	Blood haemoglobin[15]	Cyanmethemoglobin method, Photometric estimation, Beckman Coulter, LH750, USA	1–4 years: <11 g/dL (mild: 10·0–10·9; moderate: 7·0–9·9; severe: <7·0); 5–11 years: <11·5 g/dL (mild: 11·0–11·4; moderate: 8·0–10·9; severe: <8·0); 12–14 years: <12 g/dL (mild: 11·0–11·9; moderate: 8·0–10·9; severe: <8·0); 15–19 years males: <13 g/dL (mild: 11·0–12·9; moderate: 8·0–10·9; severe: <8·0); 15–19 years females: <12 g/dL (mild: 11·0–11·9; moderate: 8·0–10·9; severe: <8·0)
Haemoglobinopathy	Variant haemoglobins[11]	High performance liquid chromatography, Bio-Rad CDM system, USA	Thalassaemia trait: haemoglobin A2 3·5–9·0%; haemoglobin E: haemoglobin A2 >9%; sickle cell: any haemoglobin S
Iron deficiency	Serum ferritin[19]	Two-site immunoassay using direct chemiluminescence, Siemens, Centaur, USA	1–4 years: <12 ng/mL; 5–19 years: <15 ng/mL
Iron deficiency	Serum transferrin receptor*	Particle enhanced immunonephelometry, Siemens, BN II, USA	≥1·76 mg/L
Folate deficiency	Erythrocyte folate[8]	Competitive immunoassay using direct chemiluminescence, Siemens, Centaur, USA	<151 ng/mL
Vitamin B12 deficiency	Serum cyanocobalamin[8]	Immunoassay using direct chemiluminescence, Siemens, Advia Centaur, USA	<203 pg/mL
Inflammation	Serum C-reactive protein[18]	Particle enhanced immunonephelometry, Siemens, BN II, USA	>5 mg/L

*Siemens N Latex sTfR Kit based cutoff >1·76 mg/L.

Table 1: **Laboratory methods and cutoffs used for the assessment of anaemia, haemoglobinopathy, iron deficiency, folate and vitamin B12 deficiencies, and inflammation**

concentrations. Patients can have overlapping anaemias with both iron deficiency and folate or vitamin B12 deficiency.[11] Thus, anaemia can be broadly classified into iron deficiency anaemia, folate or vitamin B12 deficiency anaemia, dimorphic anaemia (iron deficiency anaemia plus folate or vitamin B12 deficiency anaemia), anaemia of inflammation, and anaemia of other causes, in which ferritin, folate, and vitamin B12 concentrations are normal.

The Indian Ministry of Health and Family Welfare has implemented a national iron and folic acid (IFA) supplementation programme for children and adolescents in conjunction with the deworming programme that is delivered through community health workers and in government schools. For policy planning, the National Family Health Survey (NFHS) provides national estimates of anaemia prevalence among children 6–59 months of age and adolescents 15–19 years of age.[1] A review of other surveys done during the design of the first Comprehensive National Nutrition Survey (CNNS)[22] showed that national estimates for anaemia in the 5–14 year age group are not available, nor are estimates for micronutrient deficiencies or the types of anaemia among children and adolescents in India. In this study, we aimed to assess the prevalence of anaemia and categorise types of anaemia on the basis of micronutrient deficiencies among children and adolescents (1–19 years) using nationally representative data from the CNNS.

Methods

Study design and participants

The CNNS was done under the leadership of the Ministry of Health and Family Welfare in collaboration with UNICEF and the Population Council. The survey was designed to provide nationally representative and comprehensive nutritional profiling of pre-schoolers aged 0–4 years, school children aged 5–9 years, and adolescents aged 10–19 years on the basis of biological sample assessment and multiple anthropometric measures. The survey design and methods have been published elsewhere.[22] Briefly, the CNNS used a multistage, stratified, probability proportional to size cluster sampling design to select a nationally representative sample of households and individuals aged 0–19 years across all 29 states of India and the capital Delhi. Households with individuals aged 0–19 years were randomly selected from rural and urban primary sampling units; child or adolescent members were classified into three strata (0–4 years, 5–9 years, and 10–19 years), and only one child or adolescent was selected from each stratum per household. Children or adolescents who had a chronic illness, physical deformity, mental illness or cognitive disability, or ongoing current illness (fever and infection) were excluded.

Ethics approvals were obtained from the Ethics Committee of the Postgraduate Institute for Medical Education and Research in Chandigarh, India, and the Institutional Review Board of the Population Council, New York. Written, informed consent was obtained from caregivers of children aged 0–10 years. For adolescents aged 11–17 years, written informed consent was obtained from their caregivers and written informed assent obtained from the adolescents. Adolescents aged 18–19 years provided their own consent.

Procedures

Blood samples were collected from children and adolescents 1–19 years of age (infants younger than 12 months were excluded). Trained phlebotomists collected 8 mL of blood from children aged 1–4 years

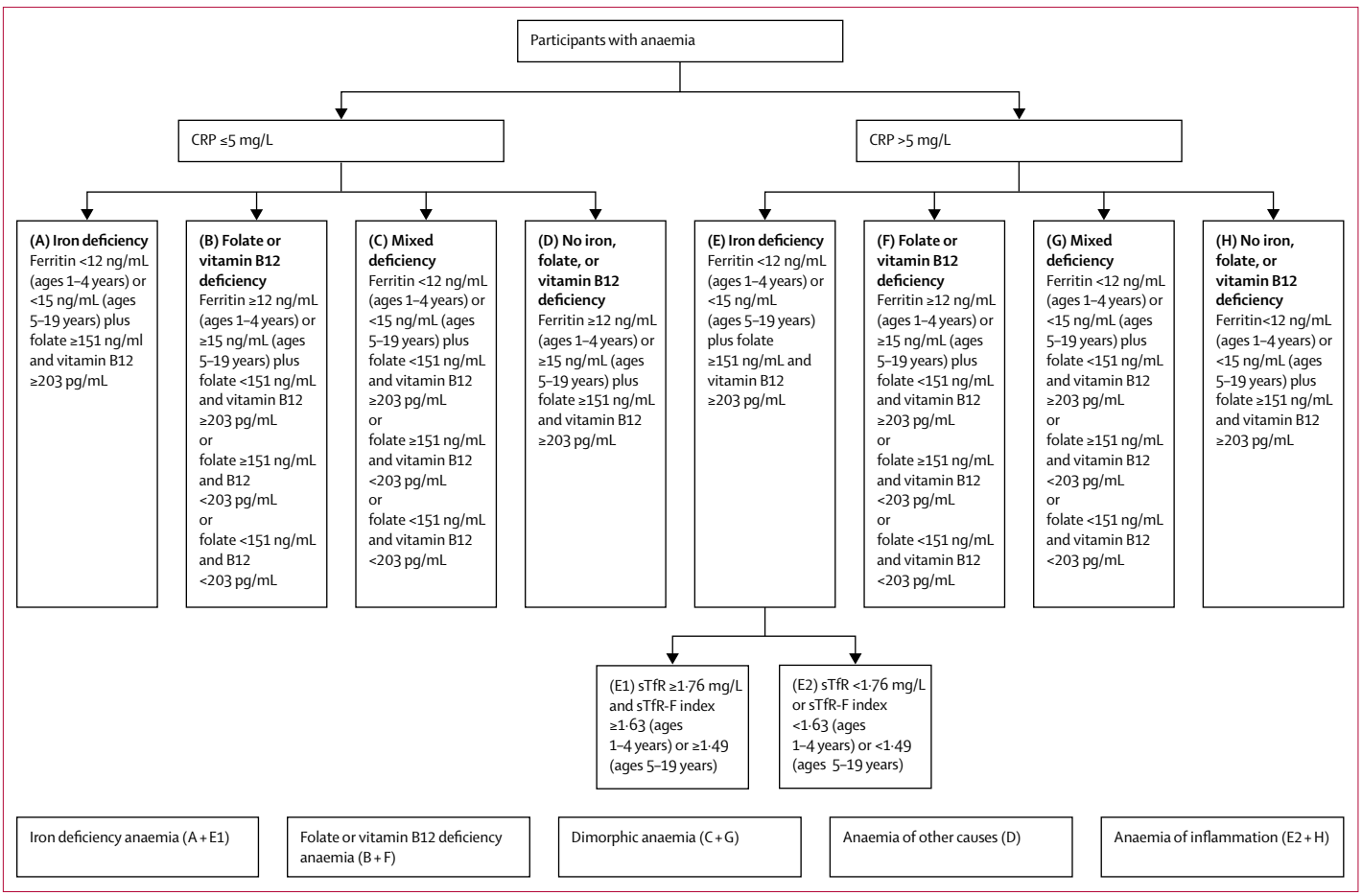

Figure 1: **Classification of anaemia**
CRP=C-reactive protein. sTfR=serum transferrin receptor.

and 10 mL from those aged 5–19 years for assessing micronutrient concentrations and biomarkers for non-communicable diseases for the survey (details available in the CNNS report).[22] All testing was done at three branches of an accredited private reference laboratory in Mumbai, Gurugram, and Kolkata. Rigorous quality control and monitoring procedures were implemented for sample collection, transportation, and testing using standard internal quality control procedures, and externally through the US Centers for Disease Control and Prevention quality assurance programme—5% of all samples were tested at the All India Institute of Medical Sciences, Delhi, and the National Institutes of Nutrition, Hyderabad.[22]

In this study, we analysed the following anaemia-related parameters: haemoglobin, haemoglobin variants, ferritin, sTfR, folate, vitamin B12, and CRP (marker of inflammation). Haemoglobin concentrations were adjusted for altitude in survey enumeration areas higher than 1000 m. Anaemia was based on age–gender-specific criteria per WHO guidelines (table 1).[15] WHO cutoffs were also used to define ferritin, folate, and vitamin B12 deficiencies.[8,19] Because an international reference standard is not available for sTfR, we used the kit-based cutoff of more than 1·76 mg/L to define high sTfR (table 1).[23] The sTfR-ferritin index was calculated using the following equation: sTfR/log-ferritin(base-10 log); the calculated index value was 1·63 for children aged 1–4 years and 1·49 for children and adolescents aged 5–19 years. Participants with CRP of more than 5 mg/L were considered to have inflammation.[18,24]

All anaemia cases based on WHO cutoffs were selected as the primary sample (figure 1).[15] Of these cases, participants with values for ferritin, folate, vitamin B12, and CRP were included in the analytical sample. Because the presence of concurrent inflammation prevents the accurate assessment of iron deficiency, and in the absence of a standardised correction factor,[17,18,23] we first divided participants with anaemia into those with no underlying inflammation (CRP ≤5 mg/L) and those with inflammation (CRP >5 mg/L). Within these two categories we further classified anaemias into four broad categories: iron deficiency anaemia, folate or vitamin B12 deficiency anaemia, dimorphic anaemia (ie, iron deficiency anaemia

plus folate or vitamin B12 deficiency anaemia), and anaemia of other causes (figure 1). To validate iron deficiency status we examined sTfR concentrations and sTfR–ferritin indices in participants with iron deficiency anaemia or dimorphic anaemia; participants with sTfR of at least 1·76 mg/L and elevated sTfR–ferritin index were considered to have iron deficiency anaemia. Among participants with inflammation and iron deficiency, we identified participants with sTfR of at least 1·76 mg/L and elevated sTfR-ferritin index and classified them as pure iron deficiency anaemia or iron-deficiency anaemia within dimorphic anaemia. Participants with folate or vitamin B12 deficiency were classified as such irrespective of CRP concentrations. Participants with anaemia of inflammation comprised those with inflammation who had anaemia that could not be classified as iron deficiency anaemia or folate or vitamin B12 deficiency anaemia with sTfR of less than 1·76 mg/L, low sTfR–ferritin index, or both. Thus, all anaemia cases were classified into one of the following five categories of anaemia: iron deficiency anaemia, folate or vitamin B12 deficiency anaemia, dimorphic anaemia, anaemia of other causes, and anaemia of inflammation.

Examination of the cause of anaemia was beyond the scope of this study. However, we assessed the prevalence of two haemoglobinopathies that are prevalent and associated with anaemia in India: thalassaemia trait or haemoglobin E thalassaemia (haemoglobin A2 >3·5%) and sickle cell β-thalassaemia (any haemoglobin S), for each of the five categories of anaemia.[12,13]

Statistical analysis

In the statistical analysis, sampling weights were used to account for differences in probabilities of selection across states and non-response rates. The weighting method has been published elsewhere.[22] All analyses were done in weighted samples. Univariate analysis was used to present the sample size in different age groups. Bivariate analyses were done to assess the prevalence of various micronutrient deficiencies based on CRP values (CRP ≤5 mg/L and CRP >5 mg/L) and the prevalence of haemoglobinopathies by type of anaemia. The prevalence of different types of anaemia was estimated with 95% CIs for three age groups: 1–4 years, 5–9 years, and 10–19 years. χ^2 tests were used to determine sex differences in anaemia classification. Stata version 16.0 was used for all analyses.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Feb 24, 2016, and Oct 26, 2018, 22 817 preschool children (aged 1–4 years), 22 577 school-aged children (aged 5–9 years), and 22 113 adolescents (aged 10–19 years) were approached for blood sample collection (figure 2). Blood samples were collected from 15 972 (70%) preschool children, 16 929 (75%) school-aged children, and 16 585 (75%) adolescents; of these, 11 624 (72·8%), 15 141 (89·4%), and 14 669 (88·4%) samples were tested for anaemia in the three age groups, respectively. 3912 preschool children, 3047 school-aged children, and 3687 adolescents were anaemic and formed the study sample for this analysis (figure 2).[15] The weighted analytical sample included only participants with results for ferritin, folate, vitamin B12, sTfR, and CRP (2862 1–4 preschool children [1552 boys and 1310 girls], 2261 school-aged children [1086 boys and 1175 girls], and 2740 adolescents [828 boys and 1912 girls]). Participants in whom blood samples were collected and those assessed for anaemia did not significantly differ (appendix p 1) and

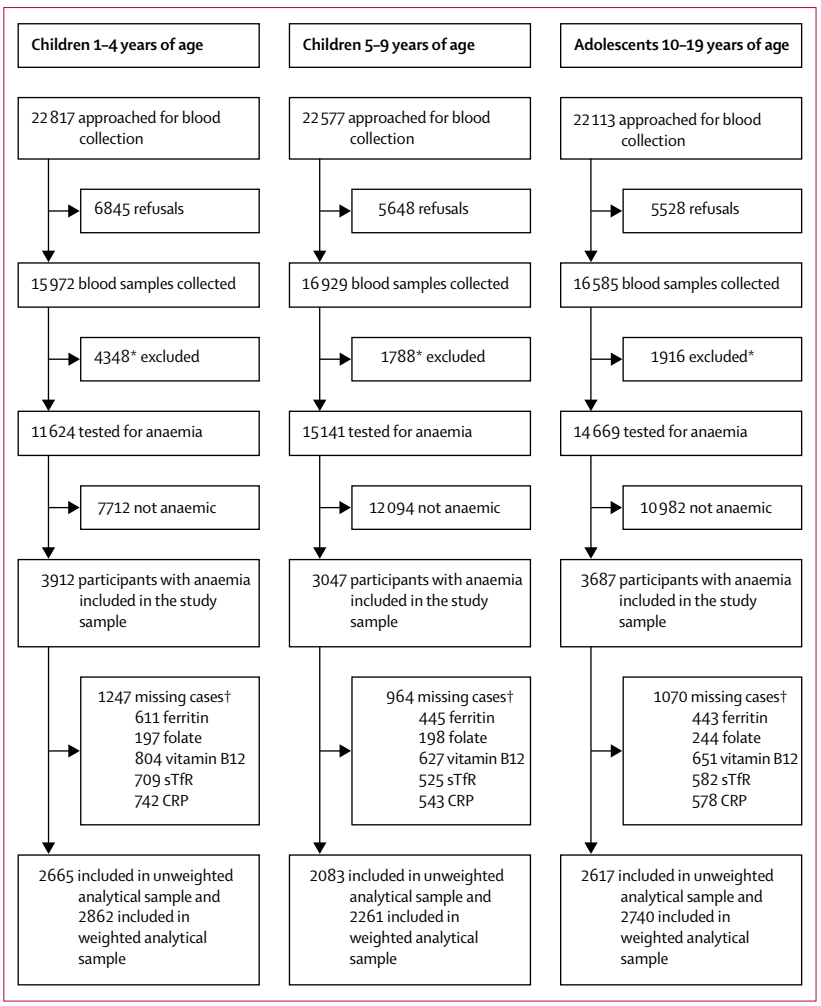

Figure 2: **Study profile**
The analytical sample included all participants with the required variables: CRP, ferritin, folate, sTfR, folate and vitamin B12. CRP=C-reactive protein. QNS=quantity not sufficient. sTfR=soluble transferrin receptor. *Blood samples were excluded if the quantity was insufficient or if the sample was spoilt (haemolysed). †Not mutually exclusive.

See Online for appendix

	1–4 years of age (weighted N=11 233*)	5–9 years of age (weighted N=14 664†)	10–19 years of age (weighted N=14 300‡)
Anaemia	4553/11233 (40·5%, 38·6–42·6)	3439/14664 (23·4%, 21·8–25·2)	4064/14300 (28·4%, 26·8–30·0)
Micronutrient deficiencies among anaemic participants			
Ferritin deficiency§	1359/2511 (54·1%, 49·6–58·6)	578/2064 (28%, 24·4–31·9)	1065/2589 (41·2%, 37·3–45·1)
Folate deficiency	513/2862 (17·9%, 14·7–21·7)	476/2261 (21·1%, 17·6–25·0)	710/2740 (25·9%, 22·5–29·6)
Vitamin B12 deficiency	505/2862 (17·6%, 13·2–23·2)	395/2261 (17·5%, 12·6–23·7)	756/2740 (27·6%, 23·6–31·9)

Data are n/N (%, 95% CI). *Corresponding unweighted Ns is 11 624. †Corresponding unweighted Ns is 15 141. ‡Corresponding unweighted Ns is 14 669. §Ferritin deficiency reported only among those with C-reactive protein <5 mg/L.

Table 2: **Prevalence of anaemia and micronutrient deficiencies, by age group**

neither did the study sample and the analytical sample in age, sex, place of residence (rural or urban), religion, or wealth quintiles (appendix p 2).

In the weighted sample, the prevalence of anaemia was 40·5% (95% CI 38·6–42·6) in children aged 1–4 years, 23·4% (21·8–25·2) in children aged 5–9 years, and 28·4% (26·8–30·0) in adolescents aged 10–19 years (table 2). 2511 (87·7%) of 2862 preschool children, 2064 (91·3%) of 2261 of school-aged children, and 2589 (95%) of 2740 adolescents had no evidence of underlying inflammation (CRP ≤5 mg/L; table 3). In this group, iron deficiency anaemia was found in 990 (39·4%) pre-schoolers, 337 (16·3%) school-aged children, and 574 (22·2%) adolescents; all three groups had low ferritin concentrations with moderate anaemia (mean haemoglobin 9·3–10·4 g/dL).[15] Folate or vitamin B12 deficiency occurred in 450 (17·9%) pre-schoolers, 500 (24·2%) school-aged children, and 663 (25·6%) of adolescents; all three groups had moderate anaemia (mean haemoglobin 10·3–10·9 g/dL) with high ferritin concentrations. Dimorphic anaemia occurred in 369 (14·7%) pre-schoolers, 241 (11·7%) school-aged children, and 491 (19·0%) adolescents. Participants had moderate anaemia and advanced iron deficiency, and the majority had elevated sTfR and sTfR–ferritin index. Anaemia of other causes occurred in 702 (30·0%) pre-schoolers, 986 (47·8%) school-aged children, and 861 (33·3%) adolescents; anaemia was mild among pre-schoolers and adolescents and moderate in school-aged children, with normal ferritin concentrations.

Inflammation (CRP >5 mg/L) was found in 351 (12·3%) of 2862 preschool children, 197 (8·7%) of 2261 school-aged children, and 151 (5·5%) of 2589 adolescents with anaemia (table 3). 58 (16·6%) pre-schoolers, 16 (8·2%) school-aged children, and 11 (7·4%) adolescents had iron deficiency; of these participants, 55 (94·8%) pre-schoolers, 16 (100%) school-aged children, and 10 (90·9%) adolescents had sTfR of 1·76 mg/L or more and elevated sTfR–ferritin index and were classified as having iron deficiency anaemia. The three pre-schoolers and one adolescent with sTfR of less than 1·76 mg/L and low sTfR–ferritin index were classified as anaemia of inflammation. Folate or vitamin B12 deficiency was found in 92 (26·2%) pre-schoolers, 58 (29·6%) school-aged children, and 40 (26·4%) adolescents. Mixed folate or vitamin B12 deficiencies were found in 18 (5·2%) pre-schoolers, one school-aged child, and seven (4·4%) adolescents, with all having evidence of iron deficiency anaemia; these participants were classified as dimorphic anaemia. The remaining participants—183 (51·9%) pre-schoolers, 122 (61·9%) school-age children, and 93 (61·6%) of adolescents—had anaemia of other causes with underlying inflammation and were classified as having anaemia of inflammation.

Among children aged 1–4 years, iron deficiency anaemia was the most common, followed by anaemia of other causes and folate or vitamin B12 deficiency anaemia (table 4). The proportion of participants with iron deficiency anaemia and with folate or vitamin B12 deficiency anaemia increased to 50·0% (1432 of 2862) for iron-deficiency anaemia and 32·4% (929 of 2862) for folate or vitamin B12 deficiency anaemia when individuals with dimorphic anaemia were included in the two categories. Among 5–9-year-old children, anaemia of other causes was the most common, followed by folate or vitamin B12 deficiency anaemia and iron deficiency anaemia. As with younger children, the proportion with iron deficiency anaemia (595 [26·3%] of 2261) and folate or vitamin B12 deficiency anaemia (800 [35·4%] of 2261) increased when dimorphic anaemia cases were added to the two categories. Among adolescents, anaemia of other causes was most common followed by folate or vitamin B12 deficiency anaemia and iron deficiency anaemia; similarly, the proportion of participants with iron deficiency (1082 [39·4%] of 2740) and folate or vitamin B12 deficiency anaemia (1201 [43·8%] of 2740) increased when adolescents with dimorphic anaemia were included. Anaemia of inflammation had the lowest prevalence in all three age groups.

Sex differences were most apparent in adolescents. Female adolescents had a higher prevalence of iron deficiency anaemia than their male counterparts (26·8% *vs* 8·6%, p<0·0001; figure 3). For anaemia of other causes, female adolescents (27·9% *vs* 39·5%; p<0·0001) had markedly lower prevalence than male adolescents. The prevalence of folate or vitamin B12 deficiency anaemia was also lower among female adolescents

	No inflammation (CRP ≤5 mg/l)			Inflammation present (CRP >5 mg/l)		
	n/N (%, 95% CI)	Mean haemoglobin, g/dL (95% CI)	Mean ferritin, ng/mL (95% CI)	n/N (%, 95% CI)	Mean haemoglobin, g/dL (95% CI)	Mean ferritin, ng/mL (95% CI)
Children 1–4 years of age						
Iron deficiency anaemia	990/2511 (39·4%, 35·5–43·5)	9·3 (9·2–9·5)	6·2 (5·8–6·5)	58/351 (16·6%, 10·9–24·5)	9·1 (8·6–9·7)	7·6 (6·7–8·6)
sTfR ≥1·76 and sTfR-log ferritin index ≥1·63	956/990 (96·6%, 94·9–97·8)	9·3 (9·2–9·5)	6·2 (5·8–6·5)	55/58 (93·7%, 79·1–98·3)	9·1 (8·5–9·7)	7·5 (6·5–8·5)
sTfR <1·76 or sTfR-log ferritin index <1·63	34/990 (3·4%, 2·2–5·1)	8·9 (8·3–9·5)	5·5 (3·3–7·2)	3/58 (6·4%, 1·7–20·9)	9·9 (6·8–13·0)	9·1 (1·1–18·9)
Folate or vitamin B12 deficiency	450/2511 (17·9%, 13·5–23·4)	10·3 (10·2–10·4)	40·8 (32·0–49·5)	92/351 (26·2%, 16·8–38·3)	10·0 (9·8–10·3)	54·3 (24·7–83·9)
Dimorphic anaemia (iron and folate or vitamin B12 deficiency)	369/2511 (14·7%, 11·6–18·4)	9·5 (9·3–9·6)	6·3 (5·8–6·8)	18/351 (5·2%, 2·0–12·9)	8·5 (6·7–10·4)	7·3 (4·6–9·9)
sTfR ≥1·76 and sTfR-log ferritin index ≥1·63	361/369 (97·7%, 94·7–98·9)	9·4 (9·3–9·6)	6·3 (5·8–6·7)	18/18 (100·0%, NA)	8·5 (6·7–10·4)	7·3 (4·6–9·9)
sTfR <1·76 or sTfR-log ferritin index <1·63	9/369 (2·3%, 1·0–5·3)	9·9 (9·2–10·7)	8·4 (4·8–12·0)	0	NA	NA
Anaemia of other causes	702/2511 (30·0%, 23·5–32·8)	10·1 (10·0–10·2)	32·2 (27·9–36·4)	183/351 (51·9%, 40·7–63·1)	9·8 (9·6–10·1)	49·9 (37·5–62·2)
Children 5–9 years of age						
Iron deficiency anaemia	337/2064 (16·3%, 13·6–19·4)	9·9 (9·7–10·2)	8·4 (7·8–9·1)	16/197 (8·2%, 3·4–18·7)	10·5 (9·7–11·4)	9·3 (5·5–13·1)
sTfR ≥1·76 and sTfR-log ferritin index ≥1·49	325/337 (96·4%, 93·4–98·0)	10·0 (9·7–10·2)	8·3 (7·7–8·9)	16/16 (100·0%, NA)	10·6 (9·7–11·5)	9·5 (5·5–13·4)
sTfR <1·76 or sTfR-log ferritin index <1·49	12/337 (3·6%, 1·9–6·7)	10·7 (10·0–11·4)	10·9 (9·2–12·5)	0	NA	NA
Folate or vitamin B12 deficiency	500/2064 (24·2%, 19·2–30·1)	10·9 (10·8–11·0)	41·8 (36·1–47·4)	58/197 (29·6%, 17·9–44·8)	10·8 (10·6–11·0)	63·9 (40·5–87·3)
Dimorphic anaemia (iron and folate or vitamin B12 deficiency)	241/2064 (11·7%, 9·2–14·6)	10·4 (10·1–10·6)	8·1 (7·5–8·7)	1/197 (0·4%, 0·0–1·5)	11·1 (10·9–11·2)	13·1(10·4–15·9)
sTfR ≥1·76 and sTfR-log ferritin index ≥1·49	210/241 (87·1%, 79·1–92·4)	10·3 (10·0–10·6)	8·0 (7·4–8·5)	1/1 (100·0%, NA)	11·1 (10·9–11·2)	13·2 (10·4–15·9)
sTfR <1·76 or sTfR-log ferritin index <1·49	31/241 (12·9%, 7·6–20·9)	10·9 (10·4–11·3)	8·8 (6·2–11·3)	0	NA	NA
Anaemia of other causes	986/2064 (47·8%, 42·2–53·4)	10·8 (10·8–10·9)	51·9 (44·7–59·2)	122/197 (61·9%, 47·2–74·6)	10·5 (10·3–10·8)	91·6 (67·8–97·2)
Adolescents 10–19 years of age						
Iron deficiency anaemia	574/2589 (22·2%, 18·9–25·7)	10·4 (10·2–10·6)	8·4 (7·7–9·1)	11/151 (7·4%, 3·0–16·8)	9·9 (9·1–10·8)	11·5 (9·3–13·6)
sTfR ≥1·76 and sTfR-log ferritin index ≥1·49	524/574 (91·3%, 85·9–94·7)	10·3 (10·1–10·5)	8·3 (7·6–9·0)	10/11 (91·0%, 60·6–98·6)	10·2 (9·3–11·0)	11·6 (9·4–13·9)
sTfR <1·76 or sTfR-log ferritin index <1·49	50/574 (8·7%, 5·3–14·0)	10·9 (10·3–11·6)	9·6 (7·0–12·2)	1/11 (9·0%, 1·4–39·4)	7·7 (2·4–12·9)	9·6 (3·2–22·3)
Folate or vitamin B12 deficiency	663/2589 (25·6%, 21·7–29·9)	10·3 (10·1–10·5)	47·6 (40·5–54·8)	40/151 (26·5, 16·1–40·3)	11·2 (10·6–11·7)	71·2 (48·8–93·6)
Dimorphic anaemia (iron and folate or vitamin B12 deficiency)	491/2589 (19·0%, 16·3–21·9)	10·5 (10·3–10·7)	7·6 (7·2–8·0)	7/151 (4·4%, 1·6–11·4)	9·6 (8·7–10·4)	5·9 (2·8–9·1)
sTfR ≥1·76 and sTfR-log ferritin index ≥1·49	437/491 (88·8, 84·3–92·2)	10·4 (10·2–10·6)	7·3 (6·9–7·7)	7/7 (100·0%, NA)	9·6 (8·7–10·4)	5·9 (2·8–9·1)
sTfR <1·76 or sTfR-log ferritin index <1·49	55/491 (11·2%, 7·8–15·7)	11·2 (10·8–11·6)	9·8 (8·6–10·9)	0	NA	NA
Anaemia of other causes	861/2589 (33·3%, 28·8–38·1)	11·3 (11·3–11·4)	46·7 (40·9–52·5)	93/151 (61·6%, 47·9–73·9)	11·1 (10·7–11·5)	71·6 (43·7–99·5)

NA=not applicable. sTfR=soluble transferrin receptor.

Table 3: **Prevalence of types of anaemia, mean haemoglobin, and mean ferritin among children and adolescents by inflammation status in India, 2016–18**

(22·2% *vs* 33·5%; p<0·0001). There were no significant sex differences for anaemia of inflammation.

Among participants with folate or vitamin B12 deficiency anaemia (folate or vitamin B12 deficiency anaemia alone and dimorphic anaemia), combined folate and vitamin B12 deficiency was most common in all three age groups. Although the prevalence of stand-alone folate and vitamin B12 deficiency was lower among 1–4 year-old children and adolescents, a third of 5–8-year-old children had stand-alone folate and vitamin B12 deficiency (figure 4). Overall, among anaemic participants, 248 (8·7%) of 2862 1–4-year-old children, 278 (12·3%) of 2261 5–9-year-old children, and 323 (11·8%) of 2740 adolescents had stand-alone vitamin B12 deficiency.

The prevalence of thalassaemia trait or haemoglobin E thalassaemia (haemoglobinA2 >3·5%) was greater than sickle cell β-thalassaemia in all age groups (table 5). Thalassaemia trait or haemoglobin E thalassaemia prevalence ranged from 2·8% to 4·8% among participants

	1–4 years of age (N=2862)	5–9 years of age (N=2261)	10–19 years of age (N=2740)
Iron deficiency anaemia	1045 (36·5%, 32·8–40·3)	353 (15·6%, 13·0–18·6)	584 (21·3%, 18·3–24·7)
Folate or vitamin B12 deficiency anaemia	543 (18·9%, 14·8–23·9)	558 (24·6%, 19·6–30·6)	703 (25·6%, 21·9–29·8)
Dimorphic anaemia	387 (13·5%, 10·8–16·9)	242 (10·7%, 8·4–13·4)	498 (18·2%, 15·7–20·9)
Anaemia of other causes	702 (24·5%, 23·5–32·8)	986 (43·6%, 42·2–53·4)	861 (31·4%, 28·9–38·1)
Anaemia of inflammation	186 (6·5%, 4·9–8·8)	122 (5·4%, 3·8–7·5)	94 (3·4%, 2·3–4·5)

Data are n (%, 95% CI).

Table 4: **Prevalence of types of anaemia among children and adolescents in India, 2016–18**

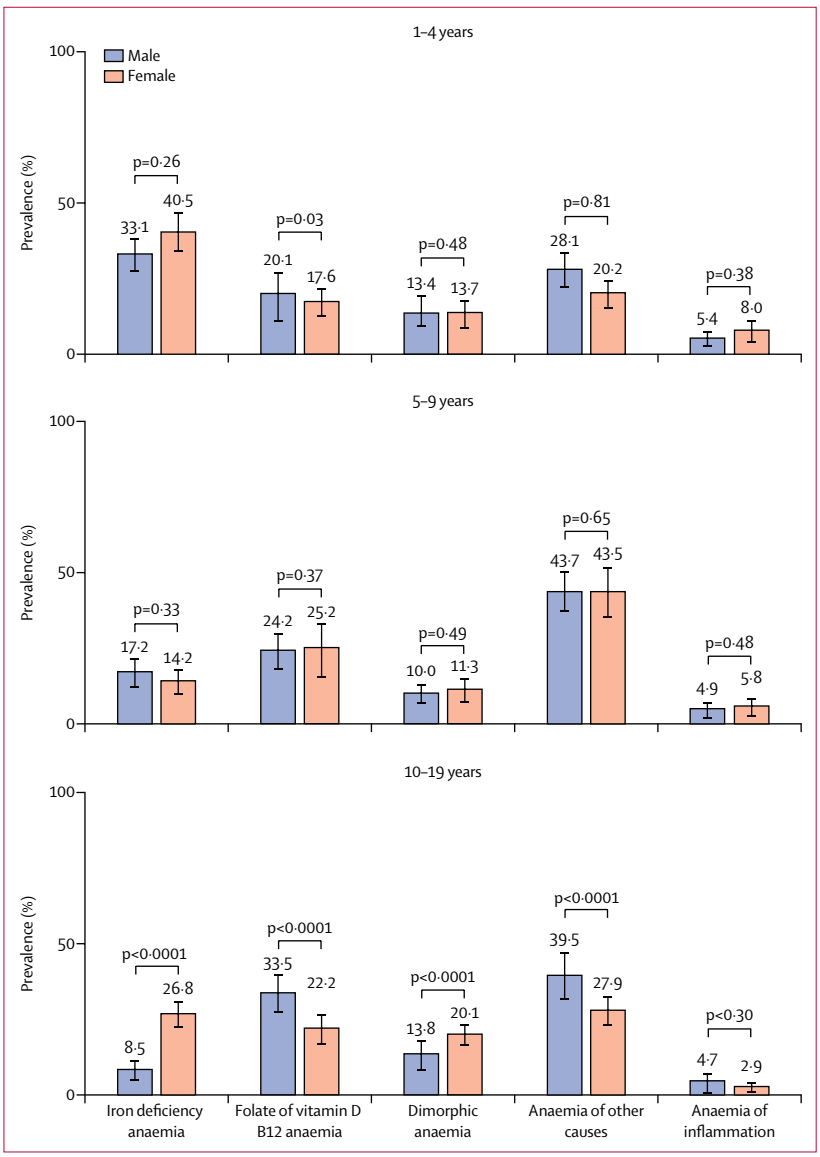

Figure 3: **Prevalence of anaemia by sex among children and adolescents in India, 2016–18**
Error bars represent 95% CIs.

with iron deficiency anaemia and from 0·8% to 4·3% among participants with dimorphic anaemia; the prevalence was higher in those with folate or vitamin B12 deficiency anaemia (5·5–10·7%) and highest among those with anaemia of other causes (8·2–12·8%). Sickle cell β-thalassaemia was less prevalent, ranging from 0·6% to 4·3%. There were no cases of thalassaemia major (homozygous).

Discussion

This is the first study to characterise the types of anaemia present among children and adolescents in India, using a nationally representative sample. Iron deficiency anaemia was the most common type among children aged 1–4 years, with a lower prevalence seen in school-aged children aged 5–9 years and adolescents aged 10–19 years. The prevalence of iron deficiency anaemia increased substantially in our study when cases of iron deficiency anaemia in the dimorphic category were included. These results are consistent with the widely hypothesised view that iron deficiency accounts for almost half of anaemias among children, adolescents, and women of reproductive age.[6] Among adolescents, iron deficiency anaemia and dimorphic anaemia were significantly more prevalent among females than males, which could be due to the onset of menstruation.[6] Folate or vitamin B12 deficiency anaemia accounted for a quarter of the anaemias among school-aged children and adolescents and almost 20% among 1–4 year-olds. As with iron deficiency anaemia, the prevalence of folate or vitamin B12 deficiency anaemia increased sharply when dimorphic anaemia cases were considered. Among those with folate or vitamin B12 deficiency anaemia, combined folate–vitamin B12 deficiency was most common in all three age groups.

Anaemia of other causes was the most common type of anaemia among 5–9 year-olds and constituted a third of the anaemias among adolescents. Although we did not examine the causes of anaemia, we did find a higher prevalence of thalassaemia trait or haemoglobin E thalassaemia among participants with anaemia of other causes and those with folate or vitamin B12 deficiency anaemia compared with those with iron deficiency anaemia. Overall, the prevalence of haemoglobin trait or haemoglobin E thalassaemia was significantly greater than sickle cell β-thalassaemia in our sample of anaemic children and adolescents; this is consistent with findings from a laboratory study of 65 779 cases,[25] and a six-city study reporting the overall prevalence of β-thalassaemia trait to be around 2·78% among 17–26-year-old Indians.[13]

In our study, anaemia of inflammation (CRP >5 mg/L) was the least common form of anaemia in all age groups. This finding was unexpected, because underlying inflammation is widely thought to be common among children in India.[26] The low levels of inflammation in our study could be because the CNNS was done among healthy individuals; children and adolescents with any current illness, chronic disease, or physical deformity were excluded from participation, thus excluding other contributors to anaemia—eg, malaria, liver or kidney disease, and malignancy.

Large national surveys in India (eg, NFHS-4 and the 2012–13 District Level Health and Facility Survey 4) have provided estimates of anaemia on the basis of field-measured haemoglobin levels. Because such surveys do not collect data on micronutrient status, they are unable to distinguish between the different types of anaemia present in the population. Although some smaller and local studies[5,27] have reported rates of anaemia and related deficiencies (ferritin, folate, and vitamin B12), they have not categorised the prevailing types of anaemia. Several studies have used sTfR and sTfR-ferritin index to distinguish iron deficiency anaemia from anaemia of inflammation.[17,20,28] We were able to confirm iron deficiency anaemia in 91–97% of cases classified as iron deficiency anaemia, and correctly identify iron deficiency anaemia among participants with elevated CRP concentrations. Three 1–4-year-old children and one adolescent with low ferritin concentrations were classified as anaemia of inflammation based on low sTfR and sTfR-ferritin index; with ferritin concentrations well below the cutoff, these individuals were considered to have iron deficiency in anaemia of inflammation. sTfR is a non-invasive alternative to bone-marrow iron estimation for the identification of iron deficiency anaemia that can be included in field surveys.

India has attempted to address child malnutrition, including anaemia, through various policy initiatives such as the Integrated Child Development Scheme launched in 1975, the National Nutrition Policy of 1993,[29] the Mid-Day Meal Scheme for school-going children launched in 1995,[30] and the Weekly Iron and Folic acid Supplementation programme launched in 2012,[31] with some success. The Global Burden of Disease study reports a 1·8% reduction in the annualised prevalence of anaemia between 2010 and 2017 among children younger than 5 years.[2] Despite this reduction, the prevalence remains high. The National Nutrition Mission (Poshan Abhiyaan) was launched in 2018 to give momentum to these efforts through intersectoral convergence between the different programmes for better service delivery, with increased focus on dietary diversity and food fortification, and through addressing non-nutritional causes of anaemia in endemic pockets, with a special focus on malaria, haemoglobinopathies, and fluorosis, under the Anaemia Mukt Bharat strategy. Poshan Abhiyaan has set a target of reducing anaemia by 3% per year, along with reductions in stunting and underweight by 2% per year. The focus of India's national programme has been on iron deficiency anaemia, with weekly IFA supplementation provided to children and adolescents through school-based distribution, and to children younger than 5 years, and out-of-school children and adolescent girls, through anganwadi centres in the community, delivered in conjunction with biannual mass deworming in the community and schools (National Deworming Days) under the Anaemia Mukt Bharat strategy.[32] However, poor compliance owing to side effects remains a barrier.[33] Our findings show that iron deficiency anaemia remains a concern, contributing about half the anaemias among pre-schoolers and a quarter of the anaemias in school-aged children and adolescents, with a significantly higher prevalence among adolescent girls. The existing IFA supplementation programme needs strengthening with additional focus on compliance and service delivery. Although twice weekly, directly observed, IFA supplementation for children younger than 5 years delivered by Accredited Social Health Activist (ASHA) workers should serve to improve compliance, the programme should also include community education and awareness for mothers and caregivers that emphasises the need for dietary diversity and knowledge of micronutrient food sources and food combinations to enhance iron absorption. The CNNS data show that 21% of children younger than 2 years were fed an adequately diverse diet and 9% received iron-rich foods.[22] Furthermore, adolescent girls need targeted focus in the IFA supplementation programme, with an emphasis on dietary diversity and regular monitoring of their anaemia status, including ferritin concentrations. Folate or vitamin B12 deficiency anaemia contributes to more than a third of anaemia cases; IFA supplementation only addresses folate deficiency and individuals with stand-alone vitamin B12

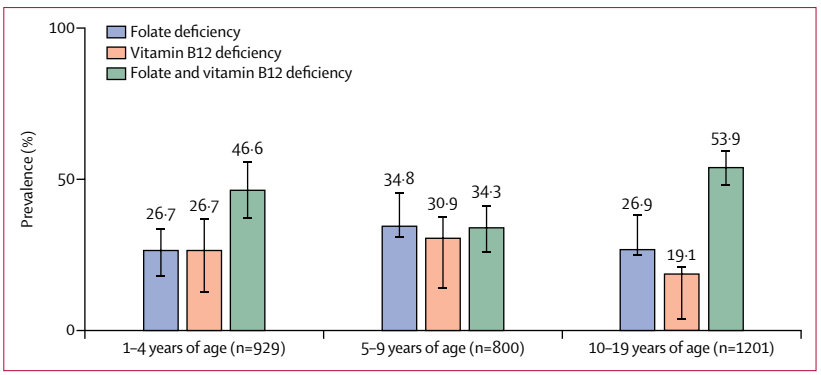

Figure 4: **Prevalence of folate and vitamin B12 deficiencies among children and adolescents with folate or vitamin B12 deficiency anaemia in India, 2016–18**
Error bars represent 95% CIs.

For the **Integrated Child Development Scheme** see https://icds-wcd.nic.in/

For **Poshan Abhiyaan** see https://icds-wcd.nic.in/nnm/home.htm

	1–4 years of age			5–9 years of age			10–19 years of age		
	N	Thalassaemia trait or haemoglobin E thalassaemia	Haemoglobin S	N	Thalassaemia trait or haemoglobin E thalassaemia	Haemoglobin S	N	Thalassaemia trait or haemoglobin E thalassaemia	Haemoglobin S
Iron deficiency anaemia	1026	29 (2·8%, 1·3–5·9)	13 (1·3%, 0·6–3·0)	349	16 (4·8%, 2·2–9·5)	9 (2·8%, 8·9–8·4)	578	28 (4·8%, 2·6–8·6)	4 (0·6%, 0·2–2·0)
Folate or vitamin B12 deficiency anaemia	515	28 (5·5%, 3·0–9·9)	4 (0·8%, 0·3–1·6)	531	51 (9·5%, 5·6–15·5)	15 (2·9%, 1·5–5·3)	683	73 (10·7%, 7·2–15·7)	13 (1·9%, 0·9–4·0)
Dimorphic anaemia	375	4 (0·8%, 0·2–3·7)	9 (2·3%, 0·7–6·8)	238	9 (4·1%, 2·1–7·8)	9 (3·7%, 1·8–7·6)	487	21 (4·3%, 2·6–6·9)	14 (2·8%, 1·4–5·7)
Anaemia of other causes	671	66 (9·9%, 6·7–14·5)	15 (2·3%, 1·3–3·9)	942	120 (12·8%, 8·9–18·5)	8 (0·8%, 0·4–1·4)	830	67 (8·2%, 5·4–12·1)	8 (0·9%, 0·4–1·8)
Anaemia of inflammation	174	7 (4·3%, 1·8–9·7)	3 (1·5%, 0·4–5·5)	121	7 (5·9%, 2·2–14·4)	1 (0·8%, 0·2–3·3)	90	6 (7·1%, 2·7–17·1)	4 (4·3%, 0·9–17·8)
Total	2761	135 (4·9%, 3·6–6·5)	44 (1·6%, 1·1–2·4)	2181	203 (9·3%, 7·2–12·1)	42 (1·9%, 1·3–2·9)	2668	195 (7·3%, 5·8–9·2)	43 (1·6%, 1·0–2·4)

Data are n (%, 95% CI) unless otherwise specified. Thalassaemia trait or haemoglobin E thalassaemia was defined as haemoglobin A2 >3·5%. Sickle cell β-thalassaemia was defined as any haemoglobin S.

Table 5: **Prevalence of thalassaemia among children and adolescents with anaemia in India, 2016–18**

deficiency derive no benefit from it. CNNS data shows that around 55% of Indian children and adolescents have vegetarian diets that are generally considered to be deficient in vitamin B12.[22] Furthermore, the CNNS data show that folate (1–4 years 23·3%, 5–9 years 28·2%, and 10–19 years 36·7%) and vitamin B12 deficiencies (1–4 years 13·8%, 5–9 years 17·2%, and 10–19 years 30·9%) were prevalent among children and adolescents irrespective of their anaemia status. The national programme needs to consider strategies to alleviate these deficiencies. The prevalence of anaemia of other causes has implications for the national programme, because individuals with this form of anaemia have adequate ferritin concentrations and might not require or benefit from iron supplementation, and for those with thalassaemia trait, iron supplements could contribute to iron overload.[34] More research is needed to understand anaemia of other causes among school-aged children and adolescents. Screening for haemoglobinopathies should be a part of childhood anaemia evaluation, particularly in high prevalence regions.[26] Future research could consider the benefits, safety, and cost-effectiveness of vitamin B12 supplementation.

Low participation, especially among 1–4-year-old children, is a limitation of this study. Despite extensive community preparedness activities, parents of young children were reluctant to allow 8–10 mL blood draws; however, refusals occurred randomly across primary sampling units, which is unlikely to affect the classification of anaemias. Furthermore, there were missing test results in all three age groups, mainly because a large number of serum tests were done in the serum tube, with issues of insufficient blood sample, especially from younger children. Because samples were drawn from fasting children and adolescents who were dehydrated, especially in warmer temperatures, the required blood volume was not always obtained. However, sociodemographic variables (age, sex, place of residence [rural or urban], religion, and wealth index) did not differ between the study sample and analytical sample, and we are confident the analytical sample is representative of the study sample. Another limitation is that we did not have blood counts with cytometric classification of erythrocytes, which could have strengthened the classification of anaemia, understanding of anaemia of other causes, and diagnosis of haemoglobinopathies. Inflammation can also be assessed by measuring α-1-acid glycoprotein, which was not done in our study. However, evidence suggests that CRP explains serum ferritin's variance better than other markers of inflammation, including α-1-acid glycoprotein,[35] and other studies[17,20] have used CRP as the marker of inflammation. Furthermore, CRP might be more suitable for monitoring acute inflammation, because it increases within 24–48 h and falls sharply once clinical symptoms disappear, whereas α-1-acid glycoprotein slowly increases over 4–5 days and reflects the later stages of inflammation.[36] Notwithstanding, the inclusion of a second measure of inflammation (eg, α-1-acid glycoprotein) would have strengthened the analysis of anaemia of inflammation in our study.

In conclusion, this study has filled an information gap in India by providing nationally representative estimates for micronutrient deficiency anaemias, anaemia of inflammation, and anaemia of other causes among children and adolescents 1–19 years of age. Although iron deficiency anaemia was the most common form of anaemia among younger children and anaemia of other causes among 5–9-year-old children, folate and vitamin B12 deficiencies contributed to a high percentage of anaemia in all age groups. Anaemia prevention efforts in India, and strengthening of the existing IFA supplementation program, should also focus on the prevention of folate or B12 deficiency anaemia and haemoglobinopathy screening in high prevalence regions.

Contributors

AS, SR, and RS conceptualised the manuscript. HPSS and PKA designed the survey, RajA computed sample weights, and NK did data quality control. AP conducted all statistical analyses. AS, RajA, SR, and RS guided the analysis and interpreted the results. HPSS, KMN, LR, and RanA served as technical experts on micronutrient deficiencies. SD and AK provided input on policy implications. AS wrote the manuscript. KMN, RJ, RanA, and RajA reviewed the manuscript.

Declaration of interests

We declare no competing interests.

Data sharing

The Ministry of Health and Family Welfare, Government of India, owns the CNNS data. Data used in this paper will be made available on the Ministry of Health and Family Welfare's portal for open access. Before publication on the portal, data are available on request from PKA (pkagrawal@unicef.org).

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