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Prevalence of low serum zinc concentrations in Indian children and adolescents: findings from the Comprehensive National Nutrition Survey 2016–18

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ABSTRACT

Background: It is thought that there is a high risk of zinc deficiency in India, but there are no representative national estimates.

Objectives: We aimed to evaluate the national and state-level prevalence of low serum zinc concentrations (SZCs) in Indian children from the nationally representative Comprehensive National Nutrition Survey.

Methods: Prevalence of low SZC, adjusted for C-reactive protein, was estimated among preschool (1–4 y; $n = 7874$) and school-age children (5–9 y; $n = 10{,}430$) and adolescents (10–19 y; $n = 10{,}140$), using SZC cutoffs defined by the International Zinc Nutrition Consultative Group.

Results: Prevalence of low SZC was high among adolescents (31.1%; 95% CI: 29.8%, 32.4%), compared with school-age (15.8%; 95% CI: 15.3%, 16.3%) or preschool children (17.4%; 95% CI: 16.7%, 18.0%). However, stratification of prevalence by fasting status or using an alternative lower SZC cutoff independent of fasting status led to a reduction in prevalence by 3.7% or 7.8% in children <10 y, respectively. The prevalence of low SZC was higher among rural preschool children, those belonging to households with poor socioeconomic status, and those with severe stunting or underweight. Preschool children with diarrhea (22.6%; 95% CI: 20.8%, 24.4%), productive cough (22.7%; 95% CI: 18.5%, 27.5%), or malaria/dengue (38.5%; 95% CI: 29.4%, 48.2%) in the 2 wk preceding the survey had a higher prevalence of low SZC than those without morbidity (16.5%; 95% CI: 15.9%, 17.2%; 17.6%; 95% CI: 16.9%, 18.2%; and 17.5%; 95% CI: 16.8%, 18.1%, respectively).

Conclusions: The national prevalence of low SZC among preschool (17%) or school-age children (16%) was <20%, which is considered the cutoff indicating a problem of public health significance; but there were variations by state and socioeconomic status. In adolescents, however, the prevalence of low SZC was 31%, which warrants further investigation. The association of low SZC with diarrhea in preschool children necessitates better coverage of Zn administration in the management of diarrhea. *Am J Clin Nutr* 2021;114:638–648.

Keywords: zinc deficiency, serum zinc, stunting, diarrhea, children, adolescents, CNNS, India

Introduction

Zinc (Zn) is vital for normal growth and maintenance of general health. Chronic inadequate intake of Zn leads to Zn

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Supplemental Tables 1–5 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/ajcn/.

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Abbreviations used: BRINDA, Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia; CNNS, Comprehensive National Nutrition Survey; CRP, C-reactive protein; HAZ, height-for-age *z* score; IZiNCG, International Zinc Nutrition Consultative Group; LMIC, low- and middle-income country; LOD, limit of detection; NCT, national capital territory; SZC, serum zinc concentration; WASH, water, sanitation, and hygiene; WAZ, weight-for-age *z* score; WHZ, weight-for-height *z* score; ZD, zinc deficiency.

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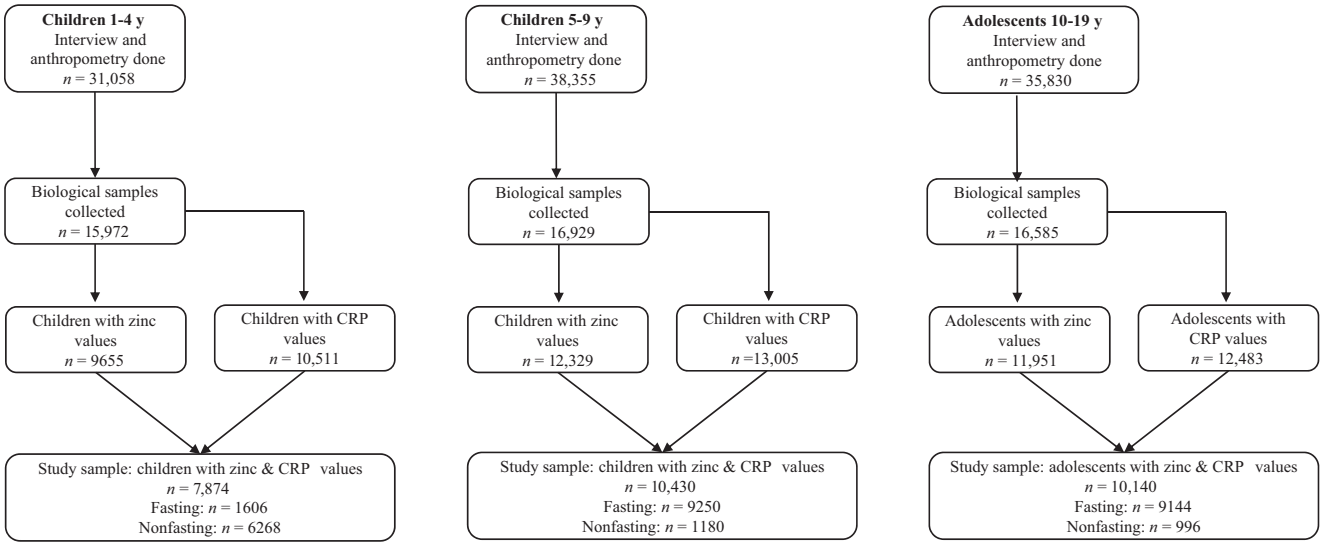

FIGURE 1 Study sample overview. The study sample included all participants with paired serum zinc concentration and CRP data. CRP, C-reactive protein.

deficiency (ZD), particularly in children owing to additional requirements of Zn for growth. ZD in children is believed to be one of the important causes of stunting and 4% of the worldwide morbidity and mortality among young children is attributed to ZD (1). Preventive Zn supplementation has been reported to reduce all-cause morbidity and mortality in children (2, 3), but its effect on linear growth remains uncertain (4, 5). Zn is a type-2 nutrient with no rapidly mobilizable stores in the body (6, 7). Dietary zinc depletion-repletion studies in humans show rapid responses in serum Zn concentration (SZC) and associated clinical symptoms (6, 7). Further, age-, gender-, and fasting status–based SZC cutoffs have been defined (8–11) for the evaluation of population Zn status. It has also been suggested that an elevated risk of ZD (8, 9) requiring public health action occurs in populations with high (>20%) prevalence of stunting in under-5 children, high (>20%) prevalence of low SZC, and inadequacy of dietary Zn (>25%).

The prevalence of stunting has declined in India over the past 3 decades, but it continues to be high (35%) among preschool children (12). In 2004, the International Zinc Nutrition Consultative Group (IZiNCG) categorized India as a high-risk country for ZD based on >25% dietary Zn inadequacy (9), in agreement with analyses of the FAO food balance sheets (13). Secular trends (from 1983 to 2012) have indicated that, in contrast to global patterns, dietary inadequacy of Zn in India increased by 7.5% over this period (14). Converging with these findings, scattered studies in Indian children and women have reported a high prevalence (25%–50%) of low SZC (15–17); however, no nationally representative SZC data were available until now. The recently concluded Indian Comprehensive National Nutrition Survey (CNNS) evaluated children and adolescents across Indian states for their anthropometry and serum micronutrient concentrations, including serum Zn (12). This provided an opportunity to quantify the prevalence of low SZC in India.

We report the prevalence of low SZC in India, stratified by state, age, gender, and other sociodemographic variables, and evaluated its association with anthropometric and socioeconomic indexes and recent history of morbidity in preschool children.

Methods

Study design and sampling

CNNS, a cross-sectional survey in 29 states and the national capital territory (NCT) of Delhi, was conducted under the aegis of the Ministry of Health and Family Welfare, Government of India in collaboration with UNICEF, India and the Population Council. The prevalence of undernutrition and micronutrient status were estimated in a nationally representative sample of Indian children and adolescents (12). The survey design and sampling methodology have been published elsewhere (12). Briefly, a multistage, population proportional to size cluster sampling was done to enroll preschool (1–4 y) and school-age (5–9 y) children, and adolescents (10–19 y), to adequately represent the national, state, male–female, and urban–rural population. For biological sampling, 50% of all the children who completed their anthropometry were selected by systematic random sampling. Children/adolescents with physical deformity, cognitive disabilities, chronic illness, acute febrile/infectious illness, acute injury, ongoing fever, and pregnancy were excluded.

Ethical approvals

The Population Council's International Review Board (New York, USA) and the ethics committee of the Post Graduate Institute of Medical Education and Research (Chandigarh, India) gave ethical approval (12). Written consent from a parent/caregiver for children <10 y old, consent of a parent/caregiver as well as assent from adolescents 11–17 y old, and written consent of adolescents >17 y old were obtained after due description of study details in local languages.

Data collection

Household socioeconomic and demographic characteristics and information on history of morbidity in the preceding 2 wk, and anthropometric data of 1 child/adolescent per age group, were collected from each household. The Wealth Index, based on possession of common household items and facilities, was

TABLE 1 Characteristics of the study population[1]

	1–4 y, % (95% CI)	5–9 y, % (95% CI)	10–19 y, % (95% CI)
Age, y	2.8 (2.8, 2.9)	7.0 (7.0, 7.1)	14.3 (14.2, 14.4)
Sex			
Male	52.3 (49.6, 55.0)	51.2 (49.0, 53.4)	48.4 (46.4, 50.5)
Female	47.7 (45.0, 50.4)	48.8 (46.6, 51.0)	51.6 (49.5, 53.6)
Residence			
Urban	25.5 (22.0, 29.3)	23.9 (20.7, 27.4)	25.0 (21.7, 28.7)
Rural	74.5 (70.7, 78.0)	76.1 (72.6, 79.3)	75.0 (71.3, 78.3)
Caste			
Scheduled castes	24.1 (21.6, 26.9)	24.6 (22.2, 27.2)	24.4 (21.9, 27.0)
Scheduled tribes	11.4 (9.3, 14.0)	11.2 (9.2, 13.4)	8.7 (7.3, 10.4)
Other backward castes	43.7 (40.7, 46.7)	41.0 (38.2, 43.8)	41.9 (38.9, 44.9)
Others	20.8 (18.5, 23.3)	23.2 (20.8, 25.8)	25.1 (22.5, 27.8)
Wealth Index			
Poorest	16.5 (14.0, 19.2)	16.7 (14.7, 18.9)	17.7 (15.4, 20.4)
Poor	19.5 (17.1, 22.2)	20.8 (18.9, 22.8)	20.1 (18.2, 22.1)
Middle	21.5 (19.2, 23.9)	22.0 (20.3, 23.8)	20.8 (19.1, 22.5)
Rich	21.5 (19.4, 23.8)	21.7 (19.8, 23.7)	21.2 (19.5, 23.1)
Richest	21.1 (18.8, 23.6)	18.8 (17.0, 20.7)	20.2 (17.9, 22.6)
Mother's education			
Primary	35.3 (32.4, 38.4)	47.9 (45.1, 50.6)	57.2 (54.7, 59.7)
Secondary	42.8 (40.2, 45.4)	40.2 (37.9, 42.6)	35.2 (33.1, 37.5)
Higher secondary	11.9 (10.1, 14.1)	6.5 (5.7, 7.4)	5.0 (3.9, 6.3)
Graduation and above	9.9 (8.6, 11.4)	5.4 (4.7, 6.2)	2.6 (2.1, 3.1)
Father's occupation			
Professional	7.8 (6.7, 9.0)	9.2 (8.0, 10.5)	10.0 (8.4, 11.9)
Sales and services	28.2 (25.6, 31.0)	24.2 (22.2, 26.4)	25.6 (23.8, 27.5)
Manual, agriculture	50.8 (47.6, 53.9)	53.2 (50.6, 55.8)	50.8 (48.2, 53.3)
Others	13.2 (11.2, 15.6)	13.4 (11.6, 15.4)	13.6 (11.8, 15.5)
Child currently in school			
Yes	—	92.2 (91.0, 93.3)	81.3 (79.3, 83.2)
No	—	7.8 (6.7, 9.0)	18.7 (16.8, 20.7)
Stunting (HAZ < -2 SD)			
Not present (≥ -2 SD)	64.7 (62.2, 67.2)	79.4 (77.5, 81.2)	73.7 (71.4, 75.9)
Moderate (-3 SD to -2.1 SD)	23.1 (21.1, 25.3)	15.9 (14.5, 17.3)	20.6 (18.7, 22.6)
Severe (< -3 SD)	12.2 (10.6, 14.0)	4.7 (3.9, 5.7)	5.7 (4.9, 6.6)
Underweight (WAZ < -2 SD)			
Not present (≥ -2 SD)	65.1 (62.3, 67.8)	—	—
Moderate (-3 SD to -2.1 SD)	26.3 (23.8, 29.1)	—	—
Severe (< -3 SD)	8.6 (7.2, 10.2)	—	—
Wasting (WHZ < -2 SD, 1–4 y) or thinness (BMI-for-age z score < -2 SD, 5–19 y)			
Not present (≥ -2 SD)	84.9 (83.0, 86.5)	76.3 (74.6, 77.9)	75.9 (73.9, 77.8)
Moderate (-3 SD to -2.1 SD)	11.6 (10.2, 13.2)	18.5 (17.0, 20.1)	17.8 (16.2, 19.6)
Severe (< -3 SD)	3.5 (2.7, 4.6)	5.2 (4.4, 6.2)	6.3 (5.4, 7.3)
Drinking water source			
Piped and improved	85.6 (82.7, 88.1)	85.4 (82.9, 87.6)	87.1 (85.2, 88.7)
Nonpiped and improved	9.4 (7.2, 12.1)	8.9 (7.0, 11.2)	8.1 (6.8, 9.6)
Unimproved	5.0 (3.9, 6.6)	5.7 (4.6, 7.0)	4.8 (3.8, 6.0)
Handwashing			
Basic	50.8 (47.6, 53.9)	47.0 (44.1, 49.9)	48.3 (45.5, 51.2)
Limited	34.3 (31.5, 37.3)	38.4 (35.5, 41.4)	35.4 (32.9, 38.0)
No facility	14.9 (12.5, 17.6)	14.6 (12.6, 16.9)	16.3 (14.1, 18.8)
Sanitation			
Improved and not shared	44.8 (41.3, 48.4)	40.9 (38.2, 43.6)	48.0 (45.1, 50.8)
Improved and shared	11.6 (10.2, 13.2)	12.5 (11.0, 14.2)	8.8 (7.8, 9.9)
Unimproved	43.6 (39.6, 47.7)	46.6 (43.2, 50.0)	43.2 (40.2, 46.4)
Diarrhea in the last 2 wk			
Yes	15.1 (13.2, 17.3)	8.9 (7.7, 10.3)	—
No	84.9 (82.7, 86.8)	91.1 (89.7, 92.3)	—
Productive cough in the last 2 wk			
Yes	7.2 (5.9, 8.7)	6.6 (5.5, 8.0)	7.0 (6.0, 8.1)
No	92.8 (91.3, 94.1)	93.4 (92.0, 94.5)	93.0 (91.9, 94.0)

(*Continued*)

TABLE 1 (*Continued*)

	1–4 y, % (95% CI)	5–9 y, % (95% CI)	10–19 y, % (95% CI)
Rapid breathing/grunting/wheezing in the last 2 wk			
Yes	7.1 (5.6, 8.9)	—	—
No	92.9 (91.1, 94.4)	—	—
Pneumonia in the last 2 wk			
Yes	4.4 (3.1, 6.1)	—	—
No	95.6 (93.9, 96.9)	—	—
Fever in the last 2 wk			
Yes	31.2 (28.1, 34.5)	22.1 (20.1, 24.2)	—
No	68.8 (65.5, 71.9)	77.9 (75.8, 79.9)	—
Malaria/dengue in the last 2 wk			
Yes	1.2 (0.6, 2.3)	1.1 (0.7, 1.7)	1.2 (0.7, 2.0)
No	98.8 (97.7, 99.4)	98.9 (98.3, 99.3)	98.8 (98.0, 99.3)

[1]Participants with serum zinc and C-reactive protein values from the Comprehensive National Nutrition Survey, 2016–18. 1–4 y, $n = 7874$; 5–9 y, $n = 10{,}430$; 10–19 y, $n = 10{,}140$. Except for age [mean (95% CI)], all values are percentages (95% CIs). All analyses were weighted. HAZ, height-for-age z score; WAZ, weight-for-age z score; WHZ, weight-for-height z score.

computed as described in the National Family Health Survey-4 (18). Access to facilities like drinking water, handwashing, and sanitation was categorized based on the WHO/UNICEF Joint Monitoring Program guidelines (19). Age-sex standardized height-for-age (HAZ), weight-for-height (WHZ), weight-for-age (WAZ), and BMI-for-age z scores were calculated using the WHO Growth Reference Standards (20, 21).

Blood collection, serum Zn, and C-reactive protein estimation

The day before sample collection, parents and children were instructed to ensure overnight fasting (8–10 h). Venous blood samples with binary (yes/no) information on fasting status and time of sample collection were obtained by trained phlebotomists, and a 4-mL aliquot of blood was collected in trace element–free tubes (Red top with yellow ring, Greiner Bio One, India) for the measurement of SZC. The blood samples were transported in cool bags (3L-12H-08P, PronGo) to the nearest collection center, where the serum was separated and divided into aliquots within 6 h of sample collection, and stored frozen at −20°C until analysis. Biochemical analysis was carried out by a commercial laboratory (SRL Labs). Serum Zn was estimated by atomic absorption spectrometry with D2 correction (Perkin Elmer, Analyst 600), against Zn standards (MERK); the CV of the method was 6.7%. C-reactive protein (CRP) was measured using immunonephelometry, with 2 different kit-based methods of varying sensitivity as described below in the Statistical analyses section. In addition, rigorous quality control procedures were implemented using standard internal and external quality assurance procedures (12).

Definition of low SZC cutoffs

Age-, sex-, and fasting state–specific SZC cutoffs, set by the IZiNCG or Biomarkers of Nutrition for Development groups, were used to define low SZC (8, 9). The cutoff of SZC <65 μg/dL was considered to define low SZC in children <10 y of age, irrespective of fasting status. The prevalence of low SZC in children <10 y old was also assessed with a lower cutoff of 59 μg/dL (22), independently of fasting status. For children ≥10 y, low SZC was defined by a value <70 μg/dL (morning fasting sample) or <66 μg/dL (morning nonfasting) in girls, and <74 μg/dL (morning fasting) or <70 μg/dL (morning nonfasting) in boys.

Statistical analyses

Statistical analyses were conducted using SPSS version 23 (SPSS Inc.) and R version 4.0.2 (R Core Team, 2020). Relevant survey weights were used wherever survey estimates are reported. The demographic characteristics of the study sample were compared in terms of proportion against the same from the total CNNS survey to rule out possible selection bias due to nested sampling. Pearson's product-moment correlation coefficients and regression coefficients were derived to assess the strength of association between serum Zn and any relevant measured variable such as CRP. The distribution of serum Zn was compared by nonparametric density plots across high (>5 mg/L) compared with low CRP (≤5 mg/L), and fasting compared with nonfasting participants.

The prevalence of low SZC was adjusted for the serum CRP concentration by the probability method of correction for inflammation (23), which is a modification of the Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia (BRINDA) correction approach (24, 25). The CRP measurements in the CNNS were performed with 2 different kit-based methods of varying resolution (12, 23), where 1 high-resolution method had a limit of detection (LOD) for CRP of 0.2 mg/L, whereas the equivalent value for the other method was 3 mg/L. The majority of the measurements were made by the latter method. Using the original BRINDA correction approach could lead to overestimation of the prevalence of low SZC owing to the left-censored CRP data (truncated at the LOD) arising from the less sensitive method. Therefore, we used a recently reported probability method of correction for inflammation that accounts for censored data (23).

The prevalence of low SZC along with 95% CIs was estimated at the national and state levels. Stratified prevalence was estimated to understand the urban–rural, age and sex,

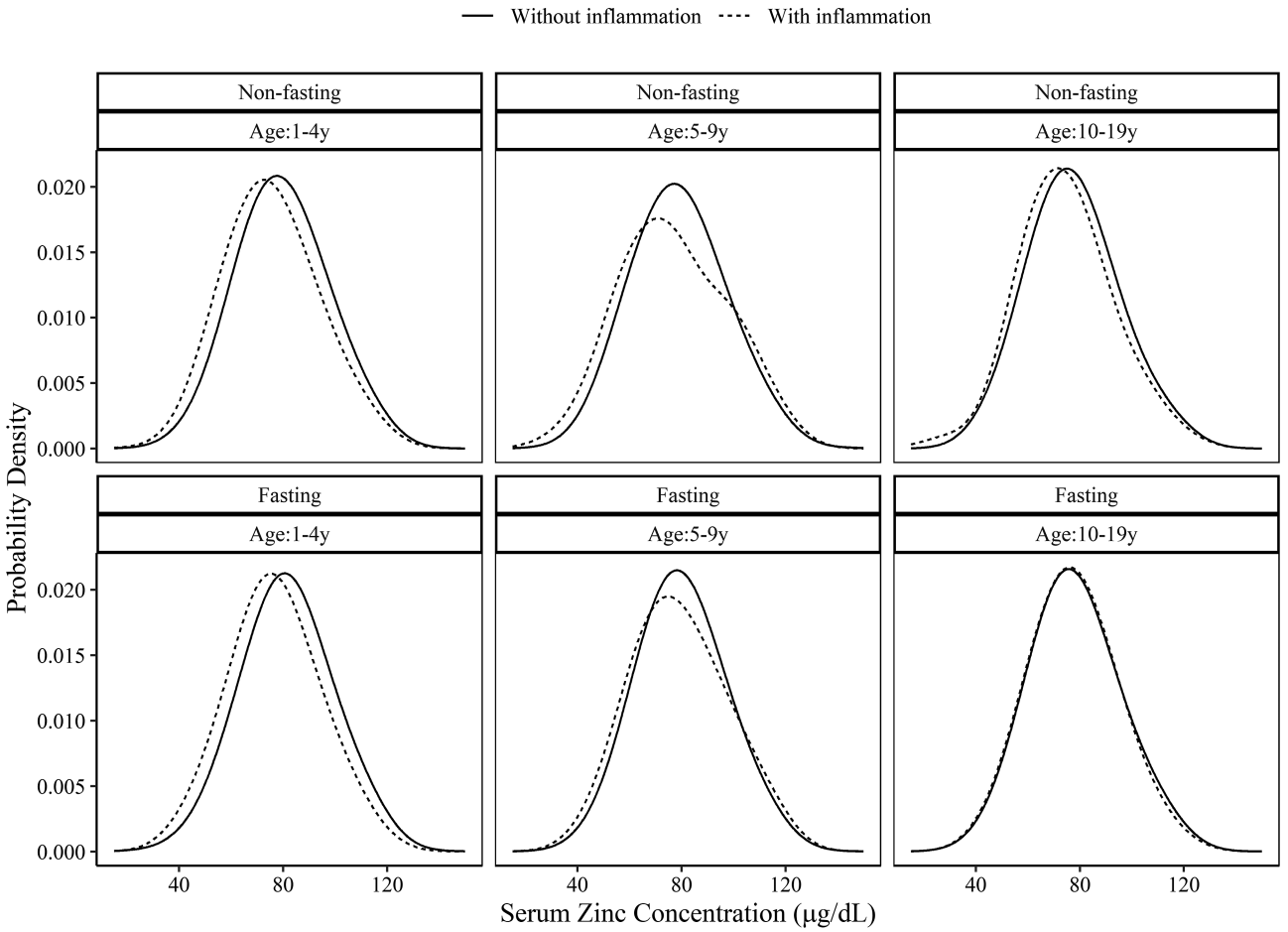

FIGURE 2 Distribution of SZCs without (solid line) and with (dotted line) inflammation (C-reactive protein >5 mg/L) in nonfasting (upper panel) and fasting (bottom panel) children, across different age groups. Distributions are presented using nonparametric density plots. The sample sizes of various groups were as follows. Nonfasting groups: 1–4 y, $n = 6268$ (with inflammation, $n = 558$; without inflammation, $n = 5710$); 5–9 y, $n = 1180$ (with inflammation, $n = 62$; without inflammation, $n = 1118$); and 10–19 y, $n = 996$ (with inflammation, $n = 48$; without inflammation, $n = 948$). Fasting groups: 1–4 y, $n = 1606$ (with inflammation, $n = 143$; without inflammation, $n = 1463$); 5–9 y, $n = 9250$ (with inflammation, $n = 501$; without inflammation, $n = 8749$); and 10–19 y, $n = 9144$ (with inflammation, $n = 447$; without inflammation, $n = 8697$). SZC, serum zinc concentration.

sociodemographic, and water, sanitation, and hygiene (WASH) differentials. The age- and sex-specific mean values of SZC and prevalence of low SZC were graphically compared by nonparametric smoothed curves. Prevalence of low SZC, as well as risk ratios of low SZC, were estimated in relation to undernutrition categories of HAZ, WHZ, and WAZ, and recent history (2 wk prior) of diarrhea, fever, pneumonia, symptoms like productive cough, rapid breathing/wheezing/grunting, and malaria/dengue with and without adjusting for mother's schooling, Wealth Index, area of residence (urban or rural), WASH, and fasting status. The 95% CI of the risk ratio was derived by estimating the SE of the ratio of 2 prevalence estimates.

TABLE 2 Effect of inflammation on prevalence of low SZC[1]

	Low SZC, % (95% CI)		
	1–4 y	5–9 y	10–19 y
Low SZC prevalence without inflammation correction[2]	19.6 (17.3, 22.1)	17.4 (15.8, 19.1)	32.7 (30.4, 35.1)
Low SZC prevalence after exclusion of cases with CRP >5 mg/L[3]	18.6 (16.2, 21.3)	17.0 (15.5, 18.7)	32.8 (30.5, 35.3)
Low SZC prevalence after BRINDA (modified) correction for inflammation[2]	17.4 (16.7, 18.0)	15.8 (15.3, 16.3)	31.1 (29.8, 32.4)

[1]Prevalence estimates of low SZC are based on International Zinc Nutrition Consultative Group cutoffs. BRINDA, Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia; CRP, C-reactive protein; SZC, serum zinc concentration.

[2]All participants with paired SZC and CRP values: 1–4 y, $n = 7874$; 5–9 y, $n = 10{,}430$; 10–19 y, $n = 10{,}140$.

[3]Participants with SZC value and CRP ≤5 mg/L: 1–4 y, $n = 7173$; 5–9 y, $n = 9867$; 10–19 y, $n = 9645$.

Results

Sample size and general characteristics of the study population

A total of 105,243 children and adolescents (preschool: $n = 31,058$; school-age: $n = 38,355$; and adolescents: $n = 35,830$) were interviewed and anthropometric data collected, of which paired data on serum Zn and CRP measurements were available for 28,444 children and adolescents (preschool: $n = 7874$; school-age: $n = 10,430$; and adolescents: $n = 10,140$) (**Figure 1**). Of these, information on the time of sample collection was available only for 2008 (preschool) and 2218 (school-age) children and 2343 adolescents, and samples collected in the afternoon were ≤1% across all age groups. The sociodemographic characteristics were similar among participants from whom anthropometric data were collected (total sample) and the study sample (with paired serum Zn and CRP), except that the proportion of 3- to 4-y-old children included in the study was higher than for 1- to 2-y-olds (61% compared with 39%) (**Supplemental Table 1**). **Table 1** shows the age-specific general characteristics of the study population. Among preschool children, 35% were stunted, 15% were wasted, 35% were underweight, and ∼15% had diarrhea in the 2 wk before the survey.

Relation of inflammation with serum Zn and prevalence of low SZC

The prevalence of inflammation (>5 mg/L CRP) was 9% in preschool and 5% each in school-age children and adolescents. The SZC had a significant negative correlation with CRP among preschool (r: −0.13, $P < 0.0001$) and school-age children (r: −0.04, $P = 0.01$), but not in adolescents (r: −0.03, $P = 0.13$), when data on paired serum Zn and CRP (where test results were recorded without left censoring) were analyzed. Similarly, the distribution of SZC among children with inflammation was shifted to the left compared with normal children independently of fasting status (except in fasted adolescents), implying a negative association of inflammation with SZC (**Figure 2**). Exclusion of high-CRP samples (by 0%–1%) or inflammation adjustment by the modified BRINDA correction method (by 1.6%–2.2%) reduced the prevalence of low SZC among the 3 age groups, the greatest decrease being in under-5 children (**Table 2**). Therefore, all the prevalence estimates were adjusted for inflammation using the modified BRINDA method.

Serum Zn concentration by age and gender

The SZCs were normally distributed in all age groups (Figure 2). Between the age groups, the mean SZCs (μg/dL) remained similar among preschoolers (79.7; 95% CI: 79.3, 80.0) and adolescents (79.3; 95% CI: 78.7, 79.8) but were significantly higher in school-age children (80.8; 95% CI: 80.5, 81.2) (**Table 3**). The SZCs were significantly lower in girls than in boys within the same age group in preschoolers (79.0; 95% CI: 78.4, 79.5 compared with 80.3; 95% CI: 79.8, 80.8) and adolescents (78.4; 95% CI: 77.8, 78.9 compared with 80.2; 95% CI: 79.6, 80.6), but not in school-age children. The SZCs tended to increase between 1 and 7 y of age, higher in girls than boys, followed by decline until the age of 15 y in both boys and girls (**Figure 3**A).

TABLE 3 SZCs and prevalence of low SZCs in Indian children and adolescents[1]

	1–4 y			5–9 y			10–19 y		
	Mean SZC, μg/dL	Low SZC with IZiNCG cutoffs, %	Low SZC with SZC cutoff at 59 μg/dL, %	Mean SZC, μg/dL	Low SZC with IZiNCG cutoffs, %	Low SZC with SZC cutoff at 59 μg/dL, %	Mean SZC, μg/dL	Low SZC with IZiNCG cutoffs, %
Boys	80.3[a] (79.8, 80.8)	16.3[a] (15.5, 17.2)	8.6[a] (8.1, 9.1)	80.9[a] (80.5, 81.4)	15.7[a] (15.0, 16.3)	8.3[a] (7.8, 8.7)	80.2[a] (79.6, 80.6)	33.7[a] (32.4, 35.0)
Girls	79.0[b] (78.4, 79.5)	18.5[b] (17.6, 19.5)	10.0[b] (9.4, 10.6)	80.7[a] (80.3, 81.2)	16.0a (15.3, 16.7)	8.5[a] (8.0, 8.9)	78.4[b] (77.8, 78.9)	28.4[b] (27.2, 29.6)
Total	79.7[c] (79.3, 80.0)	17.4[e] (16.7, 18.0)	9.3 (8.9, 9.7)	80.8[d] (80.5, 81.2)	15.8[f] (15.3, 16.3)	8.4 (8.0, 8.7)	79.3[c] (78.7, 79.8)	31.1[g] (29.8, 32.4)

[1] Values in parentheses are 95% CIs. 1–4 y, $n = 7874$ (boys, $n = 4238$; girls, $n = 3636$); 5–9 y, $n = 10,430$ (boys, $n = 5601$; girls, $n = 4829$); and 10–19 y, $n = 10,140$ (boys, $n = 5115$; girls, $n = 5025$). Mean SZC and prevalence of low SZC (%) were corrected for inflammation (C-reactive protein) using the modified Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia correction method. Low SZC prevalence was calculated with IZiNCG cutoffs for all age groups and also with a lower cutoff of 59 μg/dL for age groups 1–4 y and 5–9 y. IZiNCG, International Zinc Nutrition Consultative Group; SZC, serum zinc concentration.

[a,b] Different letters in the same column indicate group estimates with nonoverlapping CIs among boys and girls.

[c–g] Different letters in a row indicate groups which have nonoverlapping CIs for SZC[(c,d)] and prevalence of low SZC[(e,f,g)].

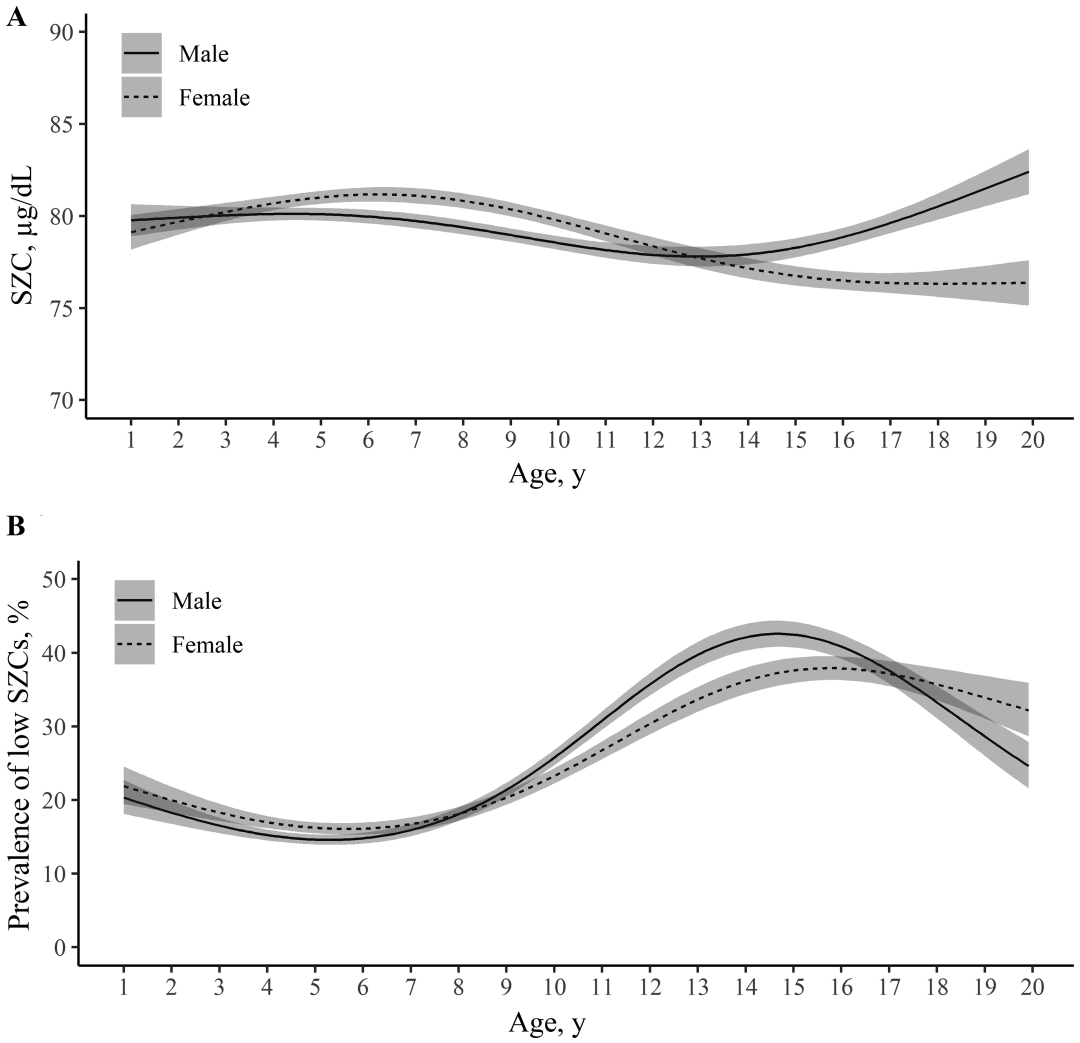

FIGURE 3 SZCs (A) and prevalence of low SZCs (B) as a function of age and gender. Male, $n = 14{,}954$ and female, $n = 13{,}490$. Nonparametric smoothed curves with 95% confidence bands. SZCs and prevalence of low SZCs are corrected for inflammation using the modified Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia method; and low SZC (%) estimates are based on International Zinc Nutrition Consultative Group cutoffs. The line indicates the mean, and the shaded area the 95% confidence bands. SZC, serum zinc concentration.

However, beyond this age, the SZC steadily increased in boys but reached a plateau in girls.

Prevalence of low SZC among Indian children and adolescents

The overall prevalence of low SZC adjusted for inflammation (in all age groups) and fasting status (in adolescents) was highest in adolescents (31.1%; 95% CI: 29.8%, 32.4%), followed by preschool (17.4%; 95% CI: 16.7%, 18.0%) and school-age (15.8%; 95% CI: 15.3%, 16.3%) children (Table 3). The low SZC prevalence was higher in preschool girls than boys (18.5%; 95% CI: 17.6%, 19.5%; compared with 16.3%; 95% CI: 15.5%, 17.2%). However, adolescent boys (33.7%; 95% CI: 32.4%, 35.0%) had 5% higher prevalence of low SZC than girls (28.4%; 95% CI: 27.2%, 29.6%). As expected, concurrent to changes in SZCs we also observed inverse changes in the prevalence of low SZCs (Figure 3B). When stratified by fasting status, the differences in nonfasted compared with fasted low SZC prevalence in children among the 3 age groups were 3.8% (preschool), 3.6% (school-age), and 2.5% (adolescents) (**Supplemental Table 2**). The prevalence of low SZCs among preschool and school-age children was 9.3% (95% CI: 8.9%, 9.7%) and 8.4% (95% CI: 8.0%, 8.7%), respectively when the alternative SZC cutoff of 59 µg/dL was used (Table 3). Almost all the samples (99%) in the present study were collected in the forenoon, and thus the time of sample collection was not adjusted in assessing the prevalence of low SZCs.

Prevalence of low SZCs in Indian states

Figure 4 shows the inflammation- (all age groups) and fasting status–adjusted (in adolescents) prevalence of low SZCs across different states in India. The IZiNCG recommends that >20% prevalence of low SZCs in a population or in a subgroup be treated as a public health problem (8, 9). The prevalence of low

SZCs remained >20% in 10 (preschool: Assam, Chhattisgarh, Goa, Gujarat, Himachal Pradesh, Jharkhand, Manipur, Punjab, Sikkim, Uttar Pradesh), 8 (school-age: Assam, Gujarat, Himachal Pradesh, Manipur, Meghalaya, Delhi, Punjab, and Tripura), and 26 (adolescents: all states except Kerala, Madhya Pradesh, Mizoram, and Nagaland) states across the 3 age groups. However, when low SZC was assessed using the lower SZC cutoff of 59 μg/dL, only 1 state in preschool (Himachal Pradesh) and 1 state in school-age children (Manipur) had a low SZC prevalence >20% (**Supplemental Table 3**).

Prevalence of low SZC by sociodemographic and WASH characteristics

The prevalence of low SZCs (adjusted for inflammation) was higher in preschool children belonging to rural areas, with lower maternal education, lower Wealth Index, and suboptimal drinking water sources and handwashing facilities, but there were no such differences in higher age groups (**Supplemental Table 4**).

Association of undernutrition and morbidity with low SZCs among preschool children

Severely stunted children had a significantly higher prevalence of low SZCs (19.2%; 95% CI: 17.4%, 21.1%) than nonstunted children (16.3%; 95% CI: 15.6%, 17.0%). Similarly, children who were underweight had a significantly higher prevalence of low SZCs (moderate: 18.6%; 95% CI: 17.3%, 19.8% and severe: 21.1%; 95% CI: 18.9%, 23.5%) than those with normal weight (16.3%; 95% CI: 15.6%, 17.0%); however, both SZCs and prevalence of low SZCs remained similar in wasted compared with normal children (**Table 4**). Children with diarrhea (22.6%; 95% CI: 20.8%, 24.4%), productive cough (22.7%; 95% CI: 18.5%, 27.5%), and malaria/dengue (38.5%; 95% CI: 29.4%, 48.2%) in the 2 wk preceding the survey had a significantly higher prevalence of low SZCs than their counterparts without these morbidities (16.5%; 95% CI: 15.9%, 17.2%; 17.6%; 95% CI: 16.9%, 18.2%; and 17.5%; 95% CI: 16.8%, 18.1%, respectively). However, when adjusted for confounders (mother's schooling, Wealth Index, residence, source of drinking water, handwashing facilities, fasting status, and sanitation), the risk of low SZCs was not higher in children who were undernourished or had a recent history of morbidity (Table 4).

Discussion

This study, to our knowledge for the first time, provides a representative national and state-level prevalence of low SZCs in Indian children and adolescents. The prevalence of low SZCs, adjusted for inflammation, was high among adolescents (31.1%), with ∼50% lower prevalence in preschool (17.4%) and school-age (15.8%) children. In addition, the prevalence of low SZCs was higher in rural preschool children, or those with lower Wealth Index, lower maternal education, and poor WASH indicators. Further, the prevalence of low SZCs was higher in children with severe stunting, underweight, or with a recent history of morbidity (diarrhea, productive cough, malaria, or dengue).

Inflammation is a major confounder in assessing micronutrient status using blood biomarker estimates (24, 25). In a recent analysis of 10 country data sets of preschool children, SZC showed a significant negative correlation (r_s −0.12 to −0.23,

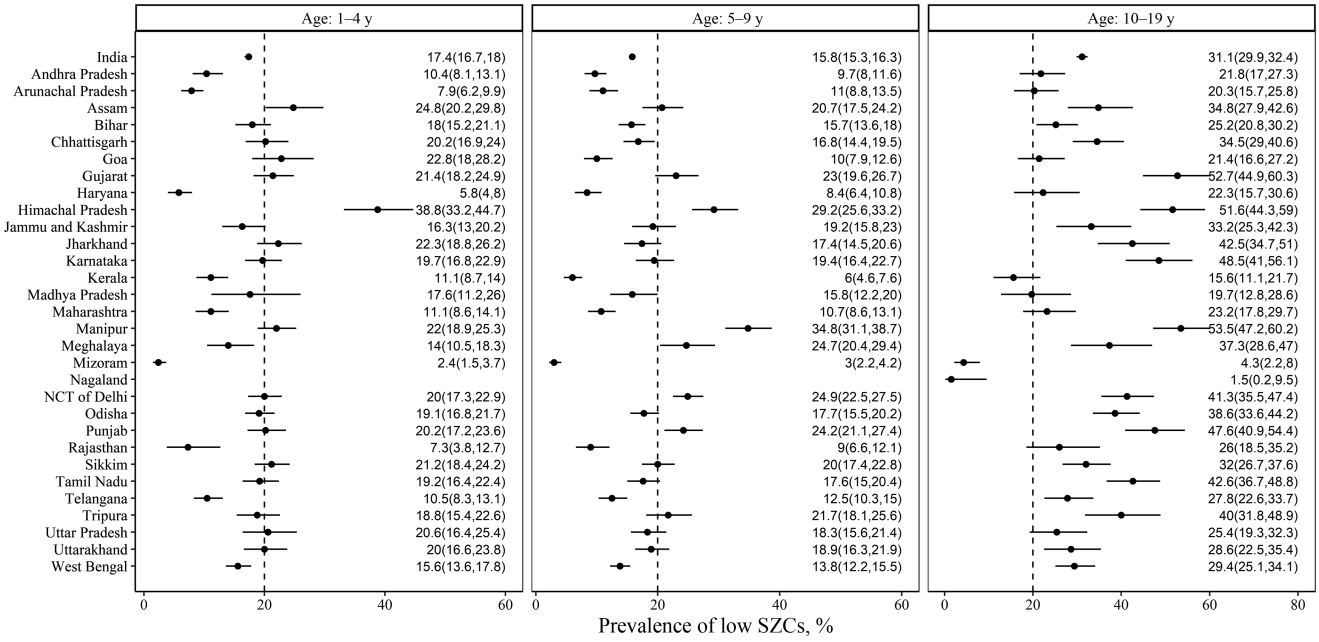

FIGURE 4 The inflammation- (modified Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia correction method) and fasting status–adjusted (only among children 10–19 y old) prevalence of low SZCs among Indian states. The prevalence estimates of low SZCs are based on International Zinc Nutrition Consultative Group cutoffs. **Supplemental Table 5** gives the state-specific sample sizes. The dot indicates the mean, and the bars the 95% CI. The dotted vertical lines intersecting at 20% prevalence were provided to highlight public health significance. The prevalence estimate for 1- to 9-y-old children for Nagaland could not be calculated owing to a small sample. SZC, serum zinc concentration.

TABLE 4 Undernutrition, morbidity, and the risk of low SZC prevalence in children aged 1–4 y[1]

Undernutrition/morbidity groups	Mean SZC, μg/dL	Low SZC, %	Unadjusted RR	Adjusted RR[2]
Stunting (HAZ < −2 SD)				
No stunting (HAZ ≥ −2 SD)*	80.2[a] (79.8, 80.7)	16.3[a] (15.6, 17.0)		
Moderate (HAZ −3 SD to −2.1 SD)	79.3[a,b] (78.6, 80.1)	17.8[a,b] (16.5, 19.1)	1.09 (1.00, 1.19)	1.02 (0.63, 1.42)
Severe (HAZ < −3 SD)	78.5[b] (77.4, 79.6)	19.2[b] (17.4, 21.1)	1.18 (1.05, 1.31)	1.37 (0.82, 1.91)
Wasting (WHZ < −2 SD)				
Not present (WHZ ≥ −2 SD)*	79.7 (79.2, 80.1)	17.4 (16.7, 18.1)		
Moderate (WHZ −3 SD to −2.1 SD)	80.5 (79.4, 81.6)	16.2 (14.5, 17.9)	0.93 (0.83, 1.04)	0.91 (0.54, 1.27)
Severe (WHZ < −3 SD)	80.5 (78.5, 82.4)	16.1 (13.2, 19.4)	0.93 (0.73, 1.12)	0.81 (0.42, 1.21)
Underweight (WAZ < −2 SD)				
Not present (WAZ ≥ −2 SD)*	80.3[a] (79.8, 80.8)	16.3[a] (15.6, 17.0)		
Moderate (WAZ −3 SD to −2.1 SD)	78.9[b] (78.2, 79.7)	18.6[b] (17.3, 19.8)	1.14 (1.05, 1.23)	1.14 (0.72, 1.57)
Severe (WAZ < −3 SD)	77.5[b] (76.2, 78.8)	21.1[b] (18.9, 23.5)	1.29 (1.14, 1.45)	1.29 (0.77, 1.81)
History of diarrhea in the 2 wk before the survey				
Yes	76.7[a] (75.8, 77.7)	22.6[a] (20.8, 24.4)	1.37 (1.25, 1.49)	1.25 (0.80, 1.70)
No*	80.2[b] (79.8, 80.6)	16.5[b] (15.9, 17.2)		
History of productive cough in the 2 wk before the survey				
Yes	76.8[a] (74.4, 79.2)	22.7[a] (18.5, 27.5)	1.29 (1.01, 1.57)	1.01 (0.48, 1.54)
No*	79.7[b] (79.3, 80.1)	17.6[b] (16.9, 18.2)		
Rapid breathing/grunting/wheezing in the 2 wk before the survey				
Yes	79.0 (77.6, 80.3)	18.5 (16.3, 21.0)	1.07 (0.92, 1.22)	0.99 (0.59, 1.39)
No*	79.7 (79.3, 80.1)	17.3 (16.7, 17.9)		
History of pneumonia in the 2 wk before the survey				
Yes	77.9 (76.1, 79.6)	20.5 (17.5, 23.8)	1.19 (0.99, 1.39)	1.15 (0.66, 1.65)
No*	79.7 (79.3, 80.1)	17.2 (16.6, 17.9)		
History of fever in the 2 wk before the survey				
Yes	79.7 (79.0, 80.4)	17.3 (16.2, 18.4)	0.99 (0.92, 1.07)	0.99 (0.65, 1.33)
No*	79.6 (79.2, 80.1)	17.4 (16.7, 18.2)		
History of malaria/dengue fever in the 2 wk before the survey				
Yes	69.6[a] (65.7, 73.5)	38.5[a] (29.4, 48.2)	2.20 (1.64, 2.76)	0.52 (0.001, 1.58)
No*	79.7[b] (79.3, 80.1)	17.5[b] (16.8, 18.1)		

[1] $n = 7874$. Values in parentheses are 95% CIs. Mean SZC and prevalence of low SZC (%) are adjusted for inflammation using the modified Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia correction method. The prevalence of low SZC was calculated with International Zinc Nutrition Consultative Group (IZiNCG) SZC cutoffs. *Reference category. RR, risk ratio; SZC, serum zinc concentration.

[2] RRs adjusted for mother's schooling, Wealth Index, residence, source of drinking water, handwashing, fasting status, and sanitation.

[a,b] Different letters in the same column indicate group estimates with nonoverlapping CIs in each category.

$P < 0.05$) with CRP in 5 country data sets (25), and it was suggested that correction for underlying inflammation should be performed when assessing the prevalence of low SZCs. In the present study, SZC negatively correlated with CRP in children <10 y old, but not in adolescents. In addition to inflammation, the SZCs are also influenced by fasting status and diurnal rhythms. Therefore, keeping operational feasibility in mind, SZC cutoffs were stratified by fasting status and time of sampling (forenoon compared with afternoon) (8, 9). Based on these, the overall prevalence of low SZCs was higher in adolescents than in children <10 y of age, and low SZC prevalence was higher in nonfasted than in fasted children (preschool: 18.5% compared with 14.7%; school-age: 18.9% compared with 15.3%). However, the IZiNCG suggested specific SZC cutoffs only for nonfasted children <10 y of age (65 μg/dL), and this value is close to the lower SZC in fasted Canadian children 1–5 y old (9, 26). In children <10 y of age, the prevalence of low SZC was 3.6 times higher in nonfasted than in fasted children, implying that an adjustment for fasting status is required in this age group. A study in healthy Australian children suggested a lower SZC cutoff (2.5th percentile) of 59 and 52 μg/dL for children 9–23 and 24–35 mo of age, respectively, without considering the fasting status or time of sample collection (9, 22). Therefore, we also assessed the prevalence of low SZC using the 59 μg/dL cutoff and this showed a dramatically reduced low SZC prevalence (preschool: 17.4% compared with 9.3%; school-age: 15.8% compared with 8.4%).

The mean SZC was higher in boys than in girls, except in school-age children, consistent with previous findings (9, 27). The SZC has been reported to increase with age between 3 and 30 y in males ($P < 0.02$), but not in females ($P = 0.45$) (27). However, in the present study, although the mean SZC was higher in boys than in girls (except in school-age children), the SZC among boys remained similar across age groups. To probe this further, we assessed the mean SZC and prevalence of low SZC in relation to age and sex. The mean SZC showed a specific pattern of increase until the age of 7–8 y, higher in girls, followed by a decline until the age of 14 y in both boys and girls, after which SZC increased in boys but reached a plateau in girls. The higher SZC in boys >15 y could be due to their higher pubertal lean mass gain than girls (28). Nevertheless, the hyperbolic trend in both SZC and prevalence of low SZC as a function of age, between 1 and 15 y in either sex, implies a broader physiological or nutritional significance. It is possible that the decline in SZC at 14–15 y of age could be a consequence of higher Zn requirements due to peak growth velocity at this

age, and thus this age group is an ideal target group for a more systematic assessment of Zn status. Alternatively, the higher prevalence of low SZC in adolescents could also be due to higher SZC cutoffs derived from the SZC distribution in a reference population (8, 9), rather than clinical or functional outcomes. Clearly, more data on SZC are required, specifically in well-nourished populations from low- and middle-income countries (LMICs).

Overall 10 (preschool), 8 (school-age), and 26 (adolescents) states out of 30 had a higher prevalence of low SZC (>20%) among different age groups, the highest being in adolescents. Further, when the alternative SZC cutoff (59 μg/dL) was used (22), only 1 state in each of the preschool and school-age groups had a prevalence of low SZC that was >20%. In contrast, previous studies in Indian children, adolescents, and women reported a prevalence of low SZC that was close to 50% (15, 16, 29). A recent study in 12- to 24-mo-old children from New Delhi slums reported a low SZC prevalence of 25% (17). The higher prevalence of low SZC in these studies could be a reflection of their including poorer participants at high risk of diarrheal/infectious morbidity. Interestingly, 4 states from northern India (Himachal Pradesh, Gujarat, Punjab, NCT of Delhi) and 3 states from north-eastern India (Assam, Manipur, Sikkim) showed >20% prevalence of low SZC across all the age groups. Although there could be multiple environmental and dietary etiological factors for this, it is worth noting that the majority of these states have alluvial soils with intense cereal cultivation and low soil Zn content (30).

Two important health benefits attributed to Zn are its impact on linear growth and in reducing infectious morbidity in children (1–3, 31). The higher prevalence of low SZC in preschool children with a recent history of morbidity was expected, owing to higher losses or redistribution of body Zn pools (6, 32). Equally, the higher prevalence of low SZC among stunted and underweight children converges with the postulated effect of Zn on linear growth and weight gain (1, 31); however, this could also be due to confounders such as Wealth Index, WASH, and maternal education.

The observed prevalence of low SZC (<20%) among children <10 y of age implies that low SZC is not a public health problem in this age group but it is of concern in adolescents (>20%). Indeed, the higher prevalence of low SZCs among children belonging to rural households with poor socioeconomic indicators suggests a need for holistic societal strategies. Short-term targeted supplementation or fortification approaches are also useful, but evidence on the efficacy of Zn-fortified foods in improving SZC, or even improving growth and lowering morbidity in LMIC settings, including India, is equivocal (33, 34). Prevention and optimal management of common infectious morbidities would also be an important strategy for improving Zn status. In light of higher prevalence of low SZCs among children with recent diarrhea, Zn should be distributed for the management of diarrhea as recommended by the WHO/UNICEF. Indeed, Zn is distributed under the National Rural Health Mission for this purpose, but very low coverage has been documented (35), and a greater impetus should be given to optimal coverage of this program.

The strengths of the present study are the large sample size of the CNNS, with national representation, along with well-defined and quality-controlled laboratory assays. A limitation is the lack of detailed reporting of quality assurance data for the serum Zn and CRP assays. In addition, the SZC was adjusted only with CRP, but not α1-acid glycoprotein, which is a more robust marker of long-term inflammation.

In conclusion, this study fills a critical information gap on the prevalence of low SZCs among Indian children and adolescents. A systematic assessment of Zn status in adolescents now emerges as a research priority.

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Data availability

The Ministry of Health and Family Welfare (MoHFW), Government of India, owns the CNNS data. Data used in this article will be made available on the MoHFW's portal for open access. Before publication on the portal, data described in the article, code book, and analytical code will be made available upon reasonable request to the corresponding author.

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