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Dietary Iron Intake and Anemia Are Weakly Associated, Limiting Effective Iron Fortification Strategies in India

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ABSTRACT

Background: Anemia prevalence in India remains high despite preventive iron supplementation programs. Consequently, concurrent national policies of iron fortification of staple foods have been initiated.

Objectives: This study evaluated the relation between dietary iron intake and anemia (hemoglobin <12 g/dL) in women of reproductive age (WRA; 15–49 y) with respect to iron fortification in India.

Methods: Data from 2 national surveys were used. Data on hemoglobin in WRA were sourced from the National Family Health Survey-4, whereas dietary intakes were sourced from the National Sample Survey. Adjusted odds for anemia with increasing iron intake were estimated, along with the effect of modulating nutrients such as vitamins B-12 and C, from statistically matched household data from the 2 surveys. The risks of inadequate (less than the Estimated Average Requirement for WRA) and excess (more than the tolerable upper limit for WRA) intakes of iron were estimated by the probability approach.

Results: The relation between iron intake and the odds of anemia was weak (OR: 0.992; 95% CI: 0.991, 0.994); increasing iron intake by 10 mg/d reduced the odds of anemia by 8%. Phytate and vitamin B-12 and C intakes modified this relation by reducing the odds by 1.5% when vitamin B-12 and C intakes were set at 2 μg/d and 40 mg/d, respectively. The additional intake of 10 mg/d of fortified iron reduced the risk of dietary iron inadequacy from 24–94% to 9–39% across states, with no risk of excess iron intake. Approximately doubling this additional iron intake reduced the risk of inadequacy to 2–12%, but the risk of excess intake reached 22%.

Conclusions: Providing fortified iron alone may not result in substantial anemia reduction among WRA in India and could have variable benefits and risks across states. Geographically nuanced dietary strategies that include limited fortification and the intake of other beneficial nutrients should be carefully considered. *J Nutr* 2019;149:831–839.

Keywords: anemia, women of reproductive age, inadequate iron intake, tolerable upper limit, iron fortification, vitamin B-12, vitamin C, phytate

Introduction

An unacceptably high prevalence of anemia in women and children persists in India, despite several preventive programs over recent decades. The National Family Health Survey (NFHS) conducted in 1992–93 (1) and 2015–16 (2) reported a prevalence of 51.8% and 53.0%, respectively, in women of reproductive age (WRA), showing no decline in almost 2 decades. This suggests that the global nutrition target of a 50% reduction in anemia by 2025 is unlikely to be achieved in India (3), unless careful etiologic evaluations are made in a way that could inform prevention programs. Given that the Indian diet has a low iron density, along with evidence of low iron stores in scattered surveys (4), it might be logical to infer that most of the burden of anemia (~50%) is due to iron deficiency. Thus, preventive policies have been targeted towards alleviating dietary iron deficiency (5). However, the relation between iron intake and the odds of anemia is not known at a national level. This relation will be modulated by deficiencies of other micronutrients such as vitamin B-12, vitamin C, and folate (6, 7), and nonnutritional causes such as poverty, parasites, infections, hemoglobinopathies, and blood loss are also important (6).

Given the nonresponsiveness of the prevalence of anemia to supplementation programs such as the National Iron Plus Initiative (NIPI) (7), largely due to low compliance and improper implementation (2), there is now enthusiasm for the mandatory iron fortification of staple food items such as

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salt, wheat flour, and rice. Many Indian states are actively considering the fortification of salt and at least 1 cereal. The benefits from such a move should be balanced against the potential risks. Each of these fortified staples could add ∼10 mg Fe/d to the adult diet, which will be sustained over several years. In conjunction with the existing iron supplementation program (7), this presents a new risk of the iron intake exceeding the tolerable upper limit (TUL) (8). Exceeding the TUL is not trivial, as it has been shown that iron has many toxic effects, and unabsorbed iron affects the microbiome adversely (9–11). A recently released dashboard of nutrient intakes in India (12) shows that iron intakes are heterogeneous, with per-capita daily intakes varying from 21 mg/d in Rajasthan to 7 mg/d in Nagaland, suggesting that a more nuanced and precise public health nutrition approach may be required.

There is no representative Indian national survey that simultaneously collected data on anemia, sociodemographic status, and dietary nutrient intake, restricting the ability to evolve a thoughtful and effective public health nutrition strategy for anemia. This study therefore triangulated data from 2 different Indian national surveys on anemia and diet, conducted within 4 y of each other, to evaluate the association of iron intake and other etiologic factors with the risk of anemia in WRA at a national and state level in India. It also evaluated the benefits and risks of staple food–based iron fortification, as well the interaction of other nutrients with the iron-anemia risk relation.

Methods

Two Indian national-level survey data sets were considered for this study. Anemia in nonpregnant WRA (age range 15–49 y) and their sociodemographic factors were obtained from the NFHS-4, 2015–2016 (2), whereas data on household nutrient and food consumption were obtained from the 68th round survey (2011–2012) of the National Sample Survey Office (NSSO) (13).

NFHS-4

The NFHS-4 collected data on household and individual sociodemographic characteristics, and blood biochemistry including hemoglobin from 699,686 nonpregnant WRA residing in 601,509 households, across 640 districts covering 29 states and 6 union territories of India (2). A stratified 2-stage sampling with the 2011 census as the base sampling frame was used. Hemoglobin was measured from capillary blood samples and anemia was based on hemoglobin <12.0 g/dL, after adjustment for cigarette smoking and altitude >1000 m (14, 15).

NSSO-68

The 9th quinquennial Household Consumer Expenditure survey of the 68th round of the NSSO covered all regions of India (29 states and 6 union territories, across 7469 villages and 5268 urban blocks), apart from a few interior villages. The total number of households surveyed was 59,683 in rural India and 41,968 in urban India. Households were selected by multistage stratified sampling. Monthly per-capita consumer expenditure as well as the household food purchase of 223 food items was collected through this survey, for a recall period of 30 d. The quantities of food purchased by a household were converted to nutrients of interest through the use of the Indian food composition table (16, 17). Food items that were listed by number or cost were converted to food weights. Per-capita nutrient intake was calculated as the total household nutrient purchased/household size. These iron intakes were validated against intakes of rural WRA based on household diet recalls, from 10 states in the National Nutrition Monitoring Bureau (NNMB) rural survey (18), which was conducted during the same period. Average iron intake (mg/d, per consumer unit, and for rural WRA) from both surveys correlated strongly ($r = 0.81$, $P < 0.001$) and the average difference in iron intake was 0.33 ± 2.2 mg/d between surveys.

Statistical matching of NFHS-4 and NSSO-68

The NFHS-4 household level data were triangulated with NSSO data for the same district of a state. The donor data set for triangulation was the food and nutrient intake data from NSSO-68, whereas the NFHS-4 household survey data was the recipient. A set of matching variables ("family size," "religion," "locality (rural/urban)," "socioeconomic status"), which were common in both surveys, were considered to triangulate 2 data sets by the "nearest-neighbour hot deck" method (19). The predictability of the household-level food intake by the matching variables was used to validate the matching technique and was validated by a k-fold (k = 10) cross-validation technique where the generalizability of the regression models of different foods consumed on the matching variables were compared. The k-fold cross-validation indirectly provides uncertainty estimates of the triangulation process through Pearson's correlation coefficients between observed and predicted food intakes.

Statistical analysis

The survey-weighted district-level prevalence of anemia among WRA was estimated from NFHS-4, and average per-capita dietary iron intake was estimated from NSSO-68. State variations in the prevalence of anemia and per-capita iron intake at the district level were examined with the use of 2 separate choropleth maps. Additionally, the intake of bioavailable iron was calculated from an algorithm for predicting bioavailable iron intake (20, 21), although this has not been validated in India. To estimate the effect of daily dietary iron intake on odds of anemia, a logistic regression model adjusted for other potential risk factors [wealth index, source of drinking water, toilet facility, year of education, BMI, family size, place of residence (rural/urban), and religion] was fitted. The confounders and effect modifiers were selected based on a thorough literature review and their availability in NFHS-4 survey data. To account for state-level unobserved confounding, beyond what was captured by NFHS-4, dummies for each state were also included as the risk factor in the regression model. The OR and 95% CI of anemia for every milligram increase in daily per-capita iron intake is reported. The dose-response curve was generated by allowing iron intake to be nonlinear through the use of a penalized smoothing spline technique (**Supplemental methods**; SPE-1). Further variation in effect size across all states and union territories was captured by estimating the state-level regression coefficient through the use of a dummy interaction model (Supplemental Methods; SPE-2).

A similar analysis was conducted by stratification for other risk factors such as wealth index, type of toilet use, source of drinking water, and BMI. Further, interaction effects of vitamin C intake from fruits alone (because vitamin C is lost when cooking vegetables, and assuming fruits are consumed without cooking), vitamin B-12, folate, and phytate with dietary iron intake on anemia were examined by introducing an additional interaction term in SPE-2. To avoid extreme value effects in the statistical methods, the households with the lower 2.5th and

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Supplemental Methods, Supplemental Figures 1–6, and Supplemental Table 1 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/jn/.

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Abbreviations used: EAR, Estimated Average Requirement; NIPI, National Iron Plus Initiative; NFHS, National Family Health Survey; NNMB, National Nutrition Monitoring Bureau; NSSO, National Sample Survey Office; TUL, tolerable upper limit; WRA, women of reproductive age.

upper 97.5th percentiles of dietary intake were excluded from the analysis.

Existing iron fortification and supplementation programs in India

A weekly prophylactic supplementation of iron (60 mg elemental iron) and folic acid (500 μg) is provided for WRA through the National Iron Plus Initiative (NIPI) (7). Additionally, the fortification of staple foods with iron has also been proposed. Thus, iron fortification is regulated as follows: salt (850–1100 ppm), wheat flour (20 mg/kg for NaFeEDTA), refined wheat flour or rice (20 mg/kg for NaFeEDTA and 60 mg/kg for ferrous fumarate/ferrous lactate/ferric pyrophosphate), effectively providing for an additional intake of ∼10 mg Fe/d from each of these staples (22).

Calculation of risk of inadequate intakes and the effect of iron fortification and supplementation

The risk of inadequate iron intake was calculated for the population of WRA in each state through the use of the probability approach (23), considering that the distribution of iron requirement for WRA is non-Gaussian. The requirement distribution was assumed to be log normally distributed with the mean representing the Estimated Average Requirement (EAR) and 10% CV at log scale. The usual intake distribution was estimated for each state by the maximum likelihood method. The details of the computation are provided in Supplemental Methods SPE-3 and SPE-4.

Further, assuming heterogeneity in the distribution of iron intakes across states, a simulation-based analysis was carried out to evaluate the range of iron intake, through staple food fortification, that would result in total intakes that would diminish the risk of iron deficiency, but not exceed the TUL. The risk curve of an inadequate intake of iron with varying amounts of iron fortification starting from zero was compared against the risk curve of the same intake exceeding the TUL, for each state. If δ is the amount of fortified iron, the estimated distribution of the usual intake can calculated by the method of moments as $Z = X + \delta;\ X \sim g(x)$ is the probability distribution of usual intake. If $\delta \in [0,\ TUL]$, then the risk of inadequate intake at each δ can be estimated. Similarly, the risk of excess intake was derived at each δ by $P_\delta(Z > TUL)$. The EAR for iron was taken as 15 mg/d, as defined for WRA with an iron bioavailability of 8% (4, 24), whereas the TUL was taken as 45 mg/d (8).

The data were analyzed by R statistical software version 3.5.0 (R Core Team, 2018). Statistical matching was executed by the "StatMatch" package (19) developed under the R computational environment.

Results

Data triangulation

The process followed for triangulation of household-level data between NFHS-4 and the NSSO-68 is illustrated in **Supplemental Figure 1**. A total of 489,302 households from the NFHS (recipient) could be matched with 70,762 households from the NSSO (donor). Within the households, data on 693,756 WRA were used for analysis. The validation from the *k*-fold cross-validation for the multivariate linear regression models of household-level per-capita food intake on the matching variables used in the statistical matching technique (**Supplemental Figure 2**) gave correlation coefficients ranging from 0.59 to 0.85 for foods associated with iron intake, which implied that ∼35–72% variation of the per-capita food intake could be accounted for by the matching variables.

Anemia prevalence and iron intake

The all-India anemia prevalence across districts was 53.1% (range: 22.4–80.0%). The urban prevalence was 50.9% (range: 11.5–75.4%), whereas it was 54.3% (range: 9.2–83.9%) in rural India, with large state- and district-level variations. The lowest prevalence was in Nagaland at 23% (range: 9–36% across districts) and the highest was in Jharkhand at 65% (range: 54–79% across districts), as shown in **Supplemental Figure 3**A. A similar variability in iron intake was also observed across states (Supplemental Figure 3B), as well as across districts within states. The national per-capita daily iron intake was 14.1 mg/d, ranging from 6.8 mg/d (95% CI: 5.8, 7.6 mg/d) in Manipur to 21.7 mg/d (95% CI: 19.6, 23.9 mg/d) in Rajasthan. The national per-capita bioavailable iron intake was 0.40 mg/d (95% CI: 0.38, 0.41 mg/d), varying across states (union territories were not considered as the sample size in these locations was small) from 0.17 mg/d (95% CI: 0.14, 0.21 mg/d) in Chhattisgarh to 0.94 mg/d (95% CI: 0.73, 1.21 mg/d) in Kerala.

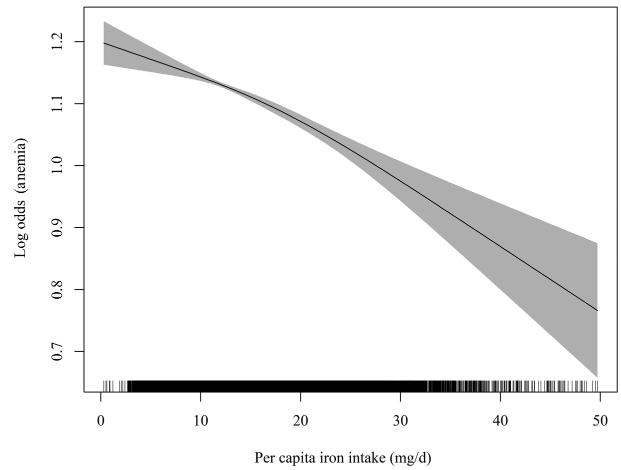

FIGURE 1 Dose-response relation of anemia against dietary iron intake among WRA in India. The line represents the log odds of anemia with dietary iron intake adjusted for sociodemographic factors of wealth index, source of drinking water, toilet facility, years of education, BMI, family size, place of residence (rural/urban), and religion. The vertical lines on the *x*-axis (rug plot) indicate the density of the data across the scale of *x*-axis. The shaded region represents the 95% CI (n = 693,756). WRA, women of reproductive age.

A logistic regression model of anemia among WRA on daily dietary iron intake estimated a 0.8% decrease in odds of anemia per mg increase in daily dietary iron intake (OR: 0.992; 95% CI: 0.991, 0.994), after adjusting for sociodemographic risk factors such as wealth index, source of drinking water, toilet facility, year of education, BMI, family size, place of residence (rural/urban), and religion. The association of odds of anemia with wealth index was the strongest where the $OR_{unadjusted}$ for the highest quintile of wealth was 0.65 (95% CI: 0.64, 0.66). In the entire data set, the dose-response curve for the odds of anemia with daily dietary iron intake was almost linear, except for a mild slope change visually approximated at an iron intake of 15 mg/d (**Figure 1**). This effect was small, but robust and statistically significant. The same analysis, when performed with calculated values of bioavailable iron, resulted in a nonlinear dose response, first increasing the odds of anemia up to an intake of 1.5 mg/d, then decreasing the odds until 4 mg/d, and finally flattening out with higher intakes (**Supplemental Figure 4**). Because the bioavailable iron intake was calculated with many assumptions, in a prediction model that was not validated in India, the effect of total iron intake on the odds of anemia was considered for further analyses.

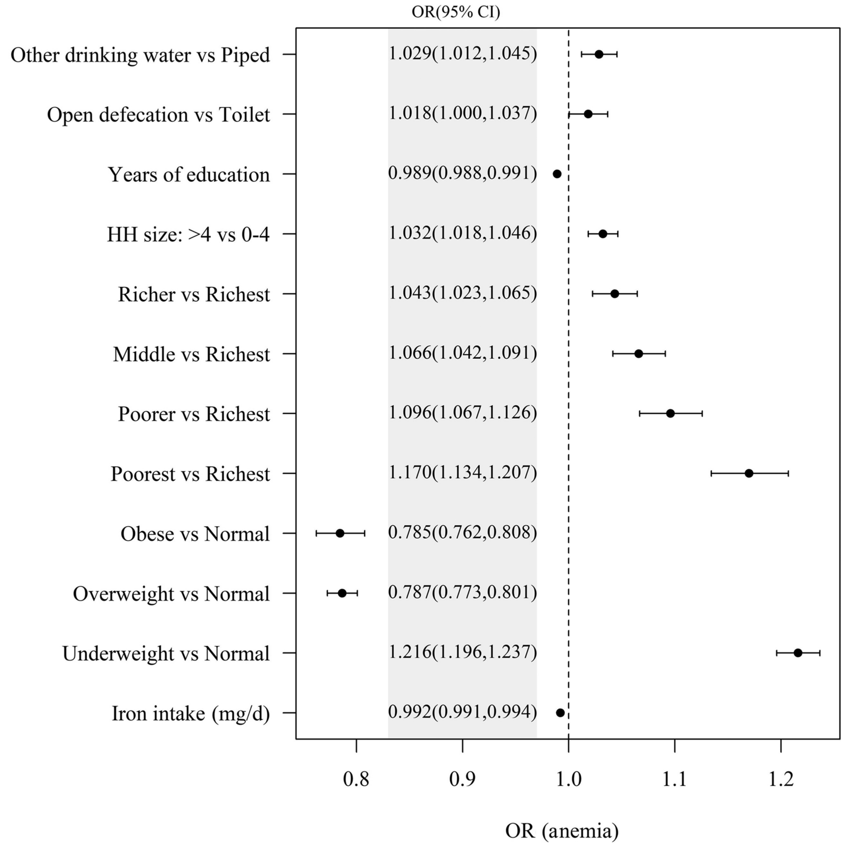

FIGURE 2 Factors associated with anemia among WRA in India. The wealth categories ranging from "poorest" to "richest" correspond to the first to the fifth national wealth quintiles, respectively, compiled by assigning the household score to each usual household member, ranking each person in the household population by their score. The NFHS-4 survey households are scored based on the number and kinds of consumer goods they own. The scores are derived from principal component analysis. Weight categories are based on BMI (kg/m ^{2}): underweight <18.5; normal 18.5–24.9; overweight 25–29.9; obese ≥30. Values are adjusted ORs of anemia with 95% CIs. Model includes all variables presented in the figure (n = 693,756). HH, household; NFHS, National Family Health Survey; WRA, women of reproductive age.

All other risk factors considered in this model, other than years of education of the woman, resulted in greater effect on the OR for anemia, compared with the daily iron intake. The underweight status of WRA (OR:1.22; 95% CI: 1.20,1.24), followed by the lowest wealth quintile (OR:1.17; 95% CI: 1.14,1.21), demonstrated higher OR for anemia than for the normal-weight and highest-wealth quintiles, respectively (**Figure 2**). The effect modification of covariates on iron intake was further examined by stratified analysis (**Figure 3**). Iron intake was not significantly associated with anemia in WRA who were underweight or in the lowest quintile of wealth, demonstrating that although poor nutritional status and poverty were strong predictors of anemia, iron intake independently did not have a significant additional effect. For all other categories of covariates, the effects of iron intake were further enhanced and found to be strongest among overweight and obese WRA, and in those in the highest wealth quintile.

A stratified analysis (by state) demonstrated differential effects of iron intake on the odds of anemia (**Figure 4**). The effect of iron intake on reducing the odds of anemia was strongest in the northeastern states of Manipur, Nagaland, Mizoram, and Sikkim, as well as in Goa (OR: 0.88; 95% CI: 0.84, 0.91 to OR: 0.96; 95% CI: 0.93, 0.99). The possible calculated improvement in anemia prevalence, when the iron intake was increased by 1 mg/d (**Table 1**), ranged from 12% in Manipur to 4% in Goa. It is worth pointing out that the northeastern states of Manipur, Nagaland, and Mizoram had a low prevalence of anemia (<35%), yet also had a low per-capita daily iron intake (<10 mg/d).

Association between other nutrients and anemia

The interaction effect of folate with iron intake on the odds of anemia was not significant, although vitamin B-12 and vitamin C intake (from fruits alone) interacted significantly in the subset of the states that exhibited a significant association between iron intake and OR of anemia (Figure 4). These nutrients were evaluated together for their effect on this relation. For vitamin B-12, the OR of anemia for every 1 mg/d increase in iron intake decreased to 0.986 (95% CI: 0.983, 0.988) and 0.985 (95% CI: 0.983, 0.988), respectively, or a reduction of 1.4% and 1.5%, respectively, if the vitamin B-12 intake was set at 1 or 2 μg/d when vitamin C intake was at its recommended level of 40 mg/d (4). A similar effect was observed for vitamin C, where the OR of anemia for every 1 mg/d increase in iron intake decreased to 0.986 (95% CI: 0.983, 0.988) and 0.982 (95% CI: 0.979, 0.985), or a reduction of 1.4% and 1.8%, respectively, if vitamin C intake was set at 40 or 80 mg/d when vitamin B-12 intake was at its recommended level of 1 μg/d (4) (**Figure 5**A, B).

Further, the interaction of phytate with iron intake was explored with and without the vitamin C and iron interaction term. The model estimated a significant positive interaction

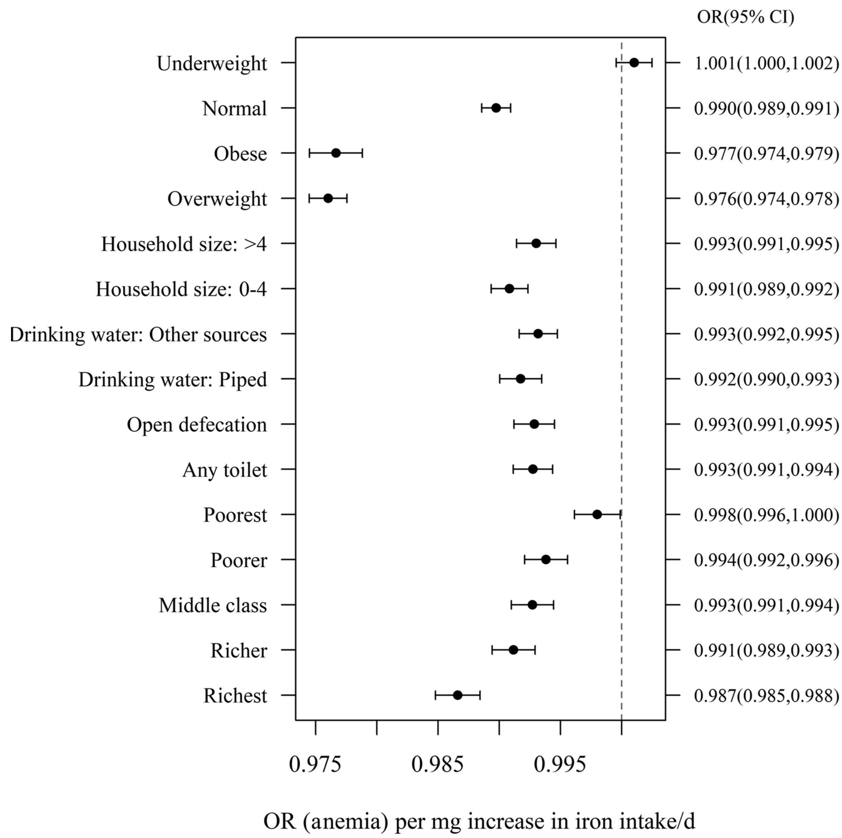

FIGURE 3 Effect of iron intake on odds of anemia in WRA in India. Adjusted OR of anemia with 95% CI per mg iron intake/d is presented. Model includes all variables presented in the figure (*n* = 693,756). WRA, women of reproductive age.

effect with iron on odds of anemia, such that the OR of anemia for every 1 mg/d iron intake further decreased to 0.970 (95% CI: 0.965, 0.976) when phytate intake was assumed to be zero, but increased to 0.977 (95% CI: 0.974, 0.982) and 0.979 (95% CI: 0.976, 0.982) when the phytate intake was set to its median (1.7 g/d) and upper quantile (2.2 g/d) of distribution, respectively. When a model with both phytate and vitamin C was considered, it was found that the OR of anemia for every 1 mg/d iron intake was reduced to 0.971 (95% CI: 0.967, 0.976) when the vitamin C intake was set at 80 g/d and phytate intake was set to its median (1.7 g/d).

Benefits and risks of iron fortification of foods

The risk of an inadequate dietary intake of iron (less than the EAR) among WRA varied from 23% in Rajasthan to 94% in Manipur and risk prevalence was >50% for a majority (23 states and union territories) (**Supplemental Figure 5**). With an iron fortification of 10 mg/d, only 12 states were identified (Figure 4) where iron fortification presented the possibility of a reduction in the odds of anemia; however, the magnitude of reduction varied, ranging from 0.3% to 12% (Table 1). Equally, with an iron fortification of 10 mg/d (as is provided through the fortification of 1 staple food), there was hardly any risk of an excess intake (greater than the TUL) in WRA (**Supplemental Table 1**). However, when the iron delivered by fortification increased to 20 mg/d (through the fortification of 2 staple foods), the risk of an excess intake rose to 25% for Rajasthan; this risk increased substantially (>5%) in most states when the iron intake through fortification was 30 mg/d (through the fortification of 3 staple foods), except for low iron–intake states such as Manipur (Supplemental Figure 5). The risk of an excess intake is even greater when iron fortification and supplementation are simultaneously rolled out in the same population; for example, in the state of Rajasthan, the proportion of WRA at risk can be as high as 81% (Supplemental Table 1).

Discussion

In this unique triangulated data set, constructed from 2 national Indian surveys, there was only a small effect size in the relation between daily iron intake and odds of anemia, such that for every 1 mg/d increase in dietary iron intake, only a small (0.8%) reduction could be predicted at the individual level, after adjusting for sociodemographic confounders and unobserved heterogeneity across the states and union territories. This translates to a population preventive fraction of 0.6%, or a 6% reduction in the prevalence of anemia through the provision of an additional 10 mg Fe/d by, for example, the intake of a single staple food that was fortified to provide 30–50% of the daily iron requirement (22). A similar weak relation between iron intake and anemia has been found in other analyses. In a survey of 10 states in India, state-level aggregated iron intakes did not correlate with the prevalence of anemia in WRA (25). In a recent study of pregnant women in India, a decrease in district-level prevalence of anemia (from District Level Health Surveys 2–4) was only weakly associated with an increase in district-level average consumption of iron (from NSSO-61 to NSSO-68) (26).

The potentially small anemia odds reduction with an increasing iron intake was not uniform across India. For

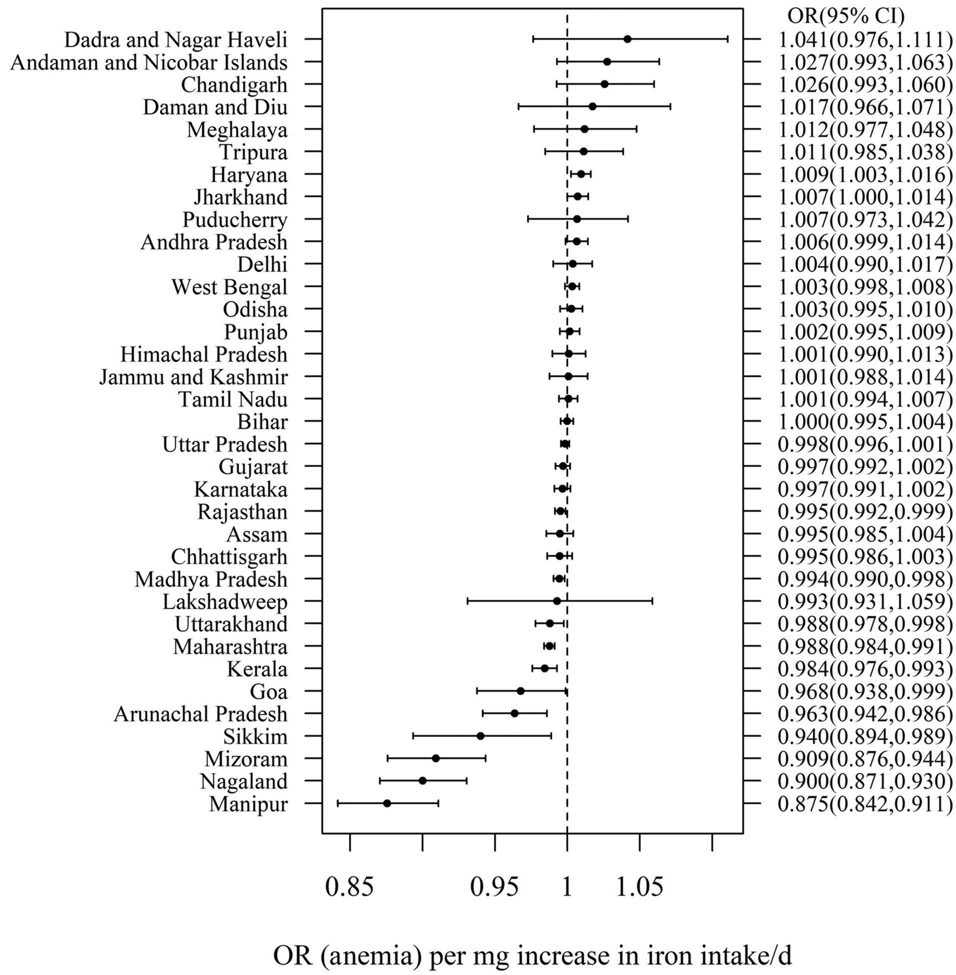

FIGURE 4 Effect of iron intake on odds of anemia among WRA in the different states of India. OR of anemia adjusted for sociodemographic and individual level factors with 95% CI per mg iron intake/d is presented (n = 693,756). WRA, women of reproductive age.

example, the northeastern states of Manipur, Nagaland, and Mizoram had a greater possibility of odds reduction with increasing daily iron intake, and thus could possibly be most amenable to iron fortification strategies (Supplemental Figure 5). On the other hand, Rajasthan, Punjab, Haryana, Madhya Pradesh, Himachal Pradesh, Uttarakhand, and Uttar Pradesh formed a group with relatively high iron intake (>15 mg/d; ≤21 mg/d in Rajasthan), along with a high prevalence of anemia (>45%), but with very small or nonsignificant odds for anemia with iron intake, indicating the potential futility of iron fortification in these states (Figure 4, Supplemental Figure 5).

TABLE 1 Relative benefit of iron fortification among selected states exhibiting a negative association between anemia and iron intake among WRA in India[1]

State	Percentage reduction in odds of anemia per 1 mg iron fortification/d	Prevalence of anemia, %
Manipur	12.4 (8.9,15.8)	23.9
Nagaland	10.1 (7.0,13.0)	26.4
Mizoram	9.1 (5.6,12.4)	19.3
Sikkim	6.2 (1.3,10.8)	55.1
Goa	3.9 (0.8,6.8)	48.3
Arunachal Pradesh	3.5 (1.3,5.7)	54.3
Maharashtra	1.6 (1.3,2)	53.8
Kerala	1.3 (0.5,2.2)	35.6
Uttarakhand	1.3 (0.3,2.2)	59.8
Assam	1.0 (0.1,2)	35.7
Madhya Pradesh	0.8 (0.4,1.1)	68.9
Uttar Pradesh	0.3 (0.04,0.6)	63.2

[1]Values are percentages (95% CIs). WRA, women of reproductive age.

There is enthusiasm for fortification as a method to improve iron intake without behavior change in India. However, there are diminishing returns when fortification is too enthusiastic: fortifying 2 food items to increase the iron intake by 20 mg/d can result in the risk that the intake exceeds the TUL in some states (Supplemental Figure 5). As the newly revised national guidelines for control of anemia (7) include a supplementation of 8.6 mg/d (a theoretical daily value calculated from a weekly supplementation of 60 mg for adolescent girls and women, which may be an oversimplification), then having both fortification and supplementation substantially increases the risk of excess intake (Supplemental Table 1). For example, in the state of Rajasthan the risk increases to ∼22% with iron fortification of only 1 food item (10 mg/d through fortification and 8.6 mg/d from supplementation). The risk is substantially higher (>5%) in most states when iron intake through both fortification of 2 food items and supplementation reached 28.6 mg/d, except for states with low iron intakes (e.g., Manipur).

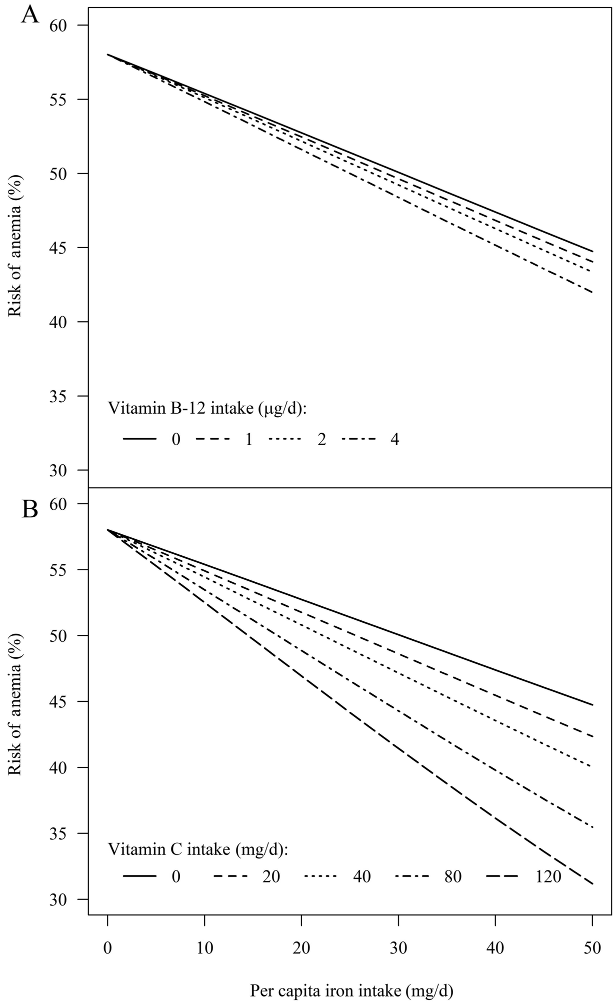

FIGURE 5 Effect of vitamin B-12 and vitamin C intakes on the association of anemia with iron intake for WRA in India. The lines represent the percentage risk of anemia with dietary iron intake adjusted for sociodemographic factors and at different levels of vitamin B-12 (0, 1, 2, 4 μg/d) and vitamin C (0.20, 40, 80, 120 mg/d). (A) At 1 μg vitamin B-12/d, the OR of anemia for every 1 mg/d increase in iron intake is 0.986 (95% CI: 0.983, 0.988) and at 2 μg/d the OR is 0.985 (95% CI: 0.983, 0.988), ($n = 211,066$). (B) At 40 mg vitamin C/d, the OR of anemia for every 1 mg/d increase of iron intake is 0.986 (95% CI: 0.983, 0.988) and at 80 mg/d the OR is 0.982 (95% CI: 0.979, 0.985) ($n = 211,066$). WRA, women of reproductive age.

Excess iron can have adverse effects, as it is an oxidant, and in iron fortification trials has been shown to increase the proportion of potentially enteropathogenic bacterial species and decrease beneficial species such as lactobacilli and bifidobacteria in the microbiome of children (9–11), which may lead to systemic inflammation (27). This may have broader implications in adults as well, as the microbiome is increasingly implicated in good health and longevity (28). This risk, weighed against the possibility of a small improvement in the chances of developing anemia with additional dietary iron, calls into question the wisdom of overfortifying the food chain, particularly in the context of the intensification of iron supplementation programs, via which adolescent girls and women could receive on average an additional 14 mg of supplemental iron per day (29, 30).

The preceding comments do not mean that iron fortification is not required in India. There is no doubt that the density of iron in predominantly vegetarian diets is low, and that iron fortification does benefit iron stores and hemoglobin, as shown in 2 efficacy studies in peninsular and eastern parts of India, which have relatively low iron intakes (31, 32). One study imputed a 5% reduction in the prevalence of anemia after the supply of 10 mg fortified iron per day (31), in agreement with the estimate in this analysis. However, the heterogeneous distributions of iron intake in different states predict a risk of excess intake at lower fortification levels of intake in some states (Supplemental Figure 5). This heterogeneity should caution against a uniform pan-India strategy for mandatory iron fortification of multiple foods; any approach taken needs nuance and restraint, and better strategies to deliver absorbable iron.

That many Indian states would not show a significant reduction in anemia with an increase in iron intake is also due to the dominance of other sociodemographic confounders, which have stronger associations (Figure 3). Indeed, the role of dietary iron intake in the reduction of anemia was strongly and positively influenced by socioeconomic status, indicating a path to other logical interventions. This is particularly relevant in poor and thinner subjects, where increasing iron intake is unlikely to address anemia. There was considerable variability in the influence of unexplained latent variables on anemia across states as well, when compared against Manipur which had the strongest association between iron intake and the OR of anemia (**Supplemental Figure 6**).

The shallow slope of the relation between iron intake and the odds of anemia is not altogether surprising, considering the high intake of dietary phytate in this cereal-consuming, vegetarian population; this was particularly relevant in the high-iron, wheat-consuming states. The high-iron-intake states also had a relatively high per-capita procurement of milk (>6500 g/mo), with Haryana having the highest at 11,500 g/mo. Calcium and phytate are potent inhibitors of iron absorption (25, 21), indicating that iron fortification might well be unsuccessful and offer diminishing returns in these states. The effect of phytate and its interaction with fruit-based vitamin C intake on the relation between iron and the odds of anemia was striking. When phytate was set at a theoretical value of 0, there was a 3% decrease in the odds of anemia per milligram increase in iron intake. These odds increased as expected when the phytate intake was set to its observed median intake of 1.7 g/d; however, this effect was nullified with sufficiently increased vitamin C intake such as would be delivered by the consumption of 1–2 servings of vitamin C–rich fruit.

Vitamin B-12 and folate intakes were much lower than the daily requirement across most states. The risk of folate-deficient intakes averaged ∼55% across India, but was not associated with anemia. Vitamin B-12 intake demonstrated the potential for a small and robust beneficial effect on the risk of anemia (Figure 5). Because vitamin B-12 comes from animal food sources, it is possible that the benefit provided could also be due to the intake of heme iron and therefore a higher iron bioavailability. However, milk was the major food contributor to vitamin B-12 intake in this population (168 g/d; 95% CI: 164, 172 g/d), and the meat or heme iron was low (0.20 mg/d; 95% CI: 0.20, 0.21 mg/d). Vitamin C enhances iron absorption strikingly (33); however, the independent effects of vitamin C intake on the odds of anemia were not considered, as vitamin C is heat labile and its intake in the NSSO survey was calculated for raw foods, which is not representative of the true dietary intake. Vitamins C and B-12 were therefore modeled in terms of an interaction of a theoretical increase in their intake on the iron-anemia odds relation. At intakes of 1–2 times the RDA, which can be achieved through dietary means, they had similar effects of reducing the odds of anemia by ∼1.5–2% per 1 mg/d increase in iron intake.

The main strength of this study is that, to our knowledge, statistical matching between 2 major national-level survey data sets has been used for the first time to evaluate the relation between iron intake and anemia in India. The choice of matching variables was acceptable. A limitation was the mismatch in the size of the NSSO survey compared to the NFHS 4 survey, obligating the assignment of ∼7 households of the NFHS survey to a single household of the NSSO survey. Other limitations are that the estimates of risk of inadequate and excess intake in the population are based on an EAR that is derived by a factorial method with assumptions, and on a TUL that is based on reports of adverse events with variable uncertainty factors. Additionally, the relation between iron intake and the odds of anemia may be altered by the addition of highly bioavailable fortificant iron, such as NaFeEDTA. An efficacy study of fortified wheat flour in India showed that the crude bioavailability of this fortificant was 8% (34), similar to values obtained in isotopic measurements with different diets and subjects in India (33, 35). However, NaFeEDTA is not yet used for fortification in any systematic way in India; other salts that have been proposed do not have a greatly enhanced relative bioavailability (36).

In conclusion, anemia relates weakly and nonuniformly to iron intake when examined through the use of triangulated data between 2 major national surveys. On a public health scale, India must carefully evaluate the need for simultaneous iron supplementation and fortification. This applies specifically to the fortification of multiple staple foods, especially for the poor who subsist on the Public Distribution System. Alternative approaches are urgently required, such as improving iron bioavailability through dietary interventions, or the use of iron supplements through test-and-treat approaches, concurrently with improving hygiene, sanitation, and general nutritional status. Precision programming, driven by nationally representative data, rather than a "one size fits all" approach for nutrition interventions, is the current need.

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