Review Article

The Assessment of Nutrient Requirements and Risk of Deficiency: Evaluation of Folate Intake in Rajasthan

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ABSTRACT

The recommended dietary allowances have been used to evaluate and plan diets, and to measure the risk of deficiency in individuals and populations. The terms Average Nutrient Requirement (ANR) or Estimated Average Requirement (EAR), Recommended Nutrient Intake (RNI) or Recommended Dietary Allowance (RDA) and Upper Nutrient Level (UNL) or Tolerable Upper Limit (TUL) are important terms used while defining intakes, particularly since they are used in the statistical evaluation of risk in populations. It is important to recognize that the ANR/EAR is used to assess the diets and risk of inadequate intakes of populations while the RDA is specifically used to assess the diet of individuals in a clinical setting. Since the risk of over nutrition, or of a particular nutrient exceeding the TUL in a population is possible with fortification strategies, decisions on supplementation or fortification should ideally be taken after diets are evaluated, such that a clear risk-benefit profile of each fortification can be evaluated. Further biochemical investigations should also be done to substantiate findings on intakes, by the evaluation of biomarkers. As an example, these concepts were used to evaluate the risk of inadequate intake of folate in Rajasthan. The risk of folate inadequacy ranged from 3.3% in girls 13 to 15 years of age to 29.8% in adult women. Since supplementation with folate is already operational for the vulnerable populations in India, it is worth considering whether fortification is also required to avoid adverse effects on health.

INTRODUCTION

Diets in India are diverse across regions and need to be evaluated and monitored for their adequacy as a preliminary step to understand if populations require any interventions to address the problem of nutrient deficiency. The recommended dietary allowances (RDA) has been used to evaluate diets of Indians over the years, as is done across several countries. Currently, this is a single term used for India[1], whereas, some other countries have included other terms which is relevant in the present-day world considering vast changes that have occurred in the variety of foods available. Nutrient requirements are derived through experiments on individuals of the same gender, age, body size and in the case of energy and protein, the weight and physical activity. These values are then summarized for a population to obtain the average requirement and variability.[2]

In the initial years, dietary standards were largely set for planning and procuring food supplies.[3,4,5] Subsequently, over the years several terms have been used to define requirements and to plan diets, evaluate the adequacy of intake of individuals and/or populations, planning national food supplies, nutrition labelling and food regulations, nutrient density and nutritional quality of foods, and for development of nutritional policies (for example, regulatory policies on fortification). In the present food environment, these terms become relevant as they address both inadequate intakes and upper limits of intake beyond which it could lead to risk for a nutrient. Assessing the diets of populations becomes necessary before more invasive biochemical tests are conducted to substantiate the findings related to inadequate intakes.

This review aims to understand these concepts further by analyzing data in terms of intake of folate, the vitamin which also contribute to anemia, particularly megaloblastic anemia. The National Iron Plus Initiative [6,7] was launched by the Government of India in the year 2013 to effectively combat anemia and at the same time prevent neural tube defects. Under the current program 100 µg of folic acid supplement for children 0.5 to 5 years of age, 400 µg for children 5 to 10 years of age, 500 µg for adolescents 10 to 19 years, pregnant and lactating women and women of reproductive age are provisions that are recommended. Whether fortification with folic acid for Rajasthan can be considered will also be explored.

The recommended dietary intake:

The recommended dietary intake values differ from country to country and could range from a single value for a population group (as for India[1]), to four different values that define a 'lower reference intake', an 'average requirement', a 'recommended intake' for individuals from a specific population, and an 'upper tolerable intake'.[1,8] Using experimental and epidemiological evidence most of the reference values have been derived. The United States and Canada use the term Dietary Reference Intakes as recommended by the Institute of Medicine (IOM)[9] and other countries use various other terminologies. Thus, the term Nutrient Intake Values (NIV) was formed by the United Nations University's Food and Nutrition Program, in collaboration with the Food and Agriculture Organization (FAO), the World Health Organization (WHO), and the United Nations Children's Fund (UNICEF) to standardize and harmonize the terms used across nations.

The terms that are used with the corresponding terms used by the IOM are:

1. **The average nutrient requirement (ANR)** equivalent to the term Estimated Average Requirement (EAR) used by IOM, which is used to evaluate intakes of populations or groups refers to the average daily nutrient intake level estimated to meet the requirements of half of the healthy individuals in a particular life stage and gender group.
2. **Recommended Nutrient Intake (RNI)** equivalent to the term Recommended Dietary Allowance (RDA) of the IOM and which is used specifically to evaluate individuals, refers to the daily dietary nutrient intake level sufficient to meet the nutrient requirements of nearly all (97–98 percent) healthy individuals of a specific life stage and gender group.
3. **Upper Nutrient Level (UNL)** equivalent to the term Tolerable Upper Level (TUL) refers to the highest average daily nutrient intake level likely to pose no risk of adverse health effects to almost all individuals in the general population.
4. **Safe Intake** or Adequate Intake (AI) are values that are used when ANR or RDA cannot be determined. It is the recommended average daily intake level based on observed or experimentally determined approximations or estimates of nutrient intake by a groups of apparently healthy people that are assumed to be adequate. Particularly for infants, they are set as nutrient targets based on the nutrient content of breast milk.
5. **Lower reference nutrient intake (LRNI)** or Lower threshold intake (LTI) refers to a value derived from the ANR/EAR and evaluates nutrient insufficiency. It is calculated as the ANR/EAR minus 2 SD of the distribution of requirements and is sufficient to meet the needs of the bottom 2% (in some countries 5% or 10%) of individuals.
6. **Acceptable Macronutrient Distribution Ranges (AMDR)** is a range of macronutrient intakes that is associated with a reduced risk of chronic diseases, while providing adequate intakes of essential nutrients. It is usually expressed as a percentage of energy, with a lower and upper limit. In the US and Canada (IOM, 2006), the AMDR's refer to appropriate ranges of usual intakes of individuals, whereas the WHO standards are population mean intake goals. As per the WHO, the mean intake goal for total fat intake is 15% to 30% of the energy intake, and implies that it is acceptable for half of the individuals in a population to have intakes below 15%.[10, 11]

Evaluation of diets using ANR/EAR, RNI/RDA and UNL/TUL

ANR or EAR:

The ANR is specifically used to evaluate diets of populations or groups. This is particularly relevant as each individual has a particular requirement and thus in a population a range of requirements are covered when the average intake level of the population is considered. If the distribution of a nutrient requirement is known in a healthy population (representing individuals in this populations), the ANR/EAR can be estimated.

From a public health and policy perspective it becomes necessary to estimate the level of adequacy or inadequacy of diets of a population of a specific life stage and gender and the existing level of malnutrition in a population. In such situations using intake estimates of populations or groups, the proportion whose usual intake of a nutrient is less than their requirement for the same nutrient can be calculated and hence prevalence of inadequate intakes can be estimated.

RNI or RDA:

The RNI is a derived measure from the ANR/EAR using the distribution or variance of the requirements, which yields a standard deviation (SD). The RNI is thus calculated as[9]- $RNI/RDA=ANI/EAR+2SD_{EAR/ANI}$

The term is inappropriate for dietary assessment of groups as it is the intake level that exceeds the requirement of a large proportion of individuals within the group. Although the RNI for each nutrient is specified for a healthy population, it can be used to evaluate and plan diets in the clinical setting by modification or adjustment of these requirements for the disease process, such as for tuberculosis, and for nutrient metabolism as there are no other standards available.

UNL or TUL:

Although the best way to prevent micronutrient malnutrition is through a balanced diet, this is not always a feasible immediate solution given that adequate access to food and appropriate dietary habits need to be achieved. Thus, both fortification and supplementation strategies have been used. Given that food fortification has been able to deliver nutrients to large populations using foods that are routinely taken by the population either mass fortification to reach the general population where a micronutrient deficiency is inordinately high or targeted fortification which is designed for specific population subgroups is used to alleviate some of the micronutrient deficiencies.[12,13,14] The use of the term UNL or TUL is particularly relevant, more so now with multiple foods being fortified and enriched and in addition, for the vulnerable populations, supplementation being provided. With increasing intakes above the UNL or TUL level, the possibility of adverse effects increases. One of the nutrients where some concerns have been raised on requirements of the population exceeding the upper limit is folic acid.

The United States had begun the process of folic acid fortification of flour and grain products from the year 1998 primarily to reduce the incidence of neural tube defects, a condition.[15,16,17] The level of fortification chosen was to eventually provide an additional 100 µg of folic acid (1.4 mg/kg of grain) with the likelihood of a very small proportion of population exceeding > 1 mg of folic acid intake.[16,18] The cut off of 1 mg folic acid was chosen as the upper level of intake as above 1 mg masking of vitamin B_{12} deficiency was observed particularly in the elderly.[16] Subsequent analysis indicated that mandatory fortification with folic acid fortification of grains resulted in a reduction in folate deficiency (plasma concentration 6.8 nmol/L)), and decrease in homocysteine concentration (> 13 mol/L), a substantial decrease of 19% in neural tube defects.[18,19] The anticipated increase in serum or plasma folate concentration was predicted to be 1.9 and 3.5 µg/L with a folic acid intake of 70 to 130 µg /day.[18,20] Using reverse prediction, by using extrapolated data from two published studies on increase in fasting plasma folate in populations not taking supplements after fortification Quilivan and Gregory III[18] reported an increase in folate consumption by about 215 to 240 µg/day. This has led to a further concern as intakes over 200 µg/day could lead to the presence of unmetabolized folic acid in the plasma as efficient metabolism of oral folic acid to 5-methyltetrahydrofolate before entering the portal blood is affected. In normal circumstances, this form of folate gets converted to tetrahydrofolate before retention in the cell as a polyglutamate occurs or before conversion to other folate coenzymes. Modulation of the enzyme methionine synthase (the only enzyme substrate for 5-methyltetrahydrofolate) is one mechanism by which folate homeostasis is regulated. Cobalamin is the coenzyme in this process and vitamin B_{12} deficiency could therefore decelerate the process of methionine synthase activity, and disrupt the pathways of utilization of the folate substrate.[18] The sustained presence of this unmetabolized folate occurs with just small doses below 200 µg /day which could thus mask vitamin B_{12} deficiency.[18] In the elderly, it was found that in those with normal vitamin B_{12} status, high serum folate was associated with protection from cognitive impairment, but with low vitamin B_{12} status, cognitive impairment was greater.[21]

To equate the different sources of folate consumed, the term dietary folate equivalent (DFE) was introduced to adjust for the increase in absorption of free folic acid compared to naturally occurring folates in foods. Thus, 1 µg of food folate is equivalent to 0.6 µg of folate added to foods or taken with food or 0.5 µg of folate supplements taken on an empty stomach.[15] An additional intake of about 220 µg of folic acid through fortified foods as observed post fortification in the US, would amount to about approximately 380 µg of food folate which is close to the RNI/RDA value for adults of 400 µg/day even without taking supplements.[14]

Estimation of the risk of inadequate intakes

The risk of inadequate intakes can be calculated if the population/group level data on usual intakes and the requirement are available for a specific nutrient.[7] It is important to define if these intakes are normally distributed, as the techniques given below apply only to normally distributed nutrient intakes. Statistical techniques are used to assess this risk. Two methods are used (1) the EAR cut point method and (2) the probability method. The latter is used when the distribution of the requirement is skewed as for iron in menstruating women. The EAR cut point method is a short method that has been derived from the probability method and is calculated as:

Probability of inadequacy = NORMDIST (EAR, Mean intake, SD of intake, TRUE).

Where, NORMDIST returns the cumulative probability that the observed value of a normal random variable with mean and standard deviation (i.e. intake) will be less than or equal to EAR.

The assumptions used to derive this are that intakes and requirements are not correlated, distribution of requirements is symmetrical, distribution of intakes is more variable than the requirement of the particular nutrient, true prevalence is less than 8% or above 92%.

In the probability method where adjustments are made because of the skewness of the distribution, the probability of inadequacy of usual intake of each person in the group is first determined, and then the mean of the individual probabilities (by dividing the intake distribution into intervals or bins) obtained to estimate prevalence of inadequacy. Thus:

Cumulative probability= NORMDIST (EAR, Mean intake, SD of intake, TRUE).

The assumptions used for this method is that intakes and requirements are not correlated and that the distribution of requirements are known.

Dietary intake of folate and risk of inadequate intake in Rajasthan

The National Sample Survey Organization (NSSO) provides food consumption data for all 29 states and 6 union territories of India. For this analysis, the ninth quinquennial survey of the Household Consumer Expenditure Surveys of the 68th round of the National Sample Survey Office (NSSO)[22] conducted between July 2011 to June 2012 was utilized. Household food consumption of 223 food items (recall over 30 days) collected through this survey, was used to calculate the dietary intake of folate. The quantities of food consumed by a household were converted to the nutrients of interest using the Indian food composition table[23] for folate. For some items in the food list which were based on number or cost, conversions to weight in grams was first performed before nutrient calculations were done. The folate calculated is the natural folate present in foods. The household nutrient intake was then converted to individual nutrient intake using Consumer Units (CU) based on the listing of the members of the household. The consumer unit assigned to a sedentary man, aged over 20 years and of weight 60 kg was 1.0 while that of a woman of similar age was assigned 0.8, a value of 1.0 for both males and females between 12 to 20 years, 0.8 between 9 to 11 years, 0.7 between 7 to 8 years, 0.6 between 5 to 6 years, 0.5 between 3 to 4 years, 0.4 between 1 to 2 years.[24] Mapping of the intake of dietary folate was done using the NSSO data (Figure 1).

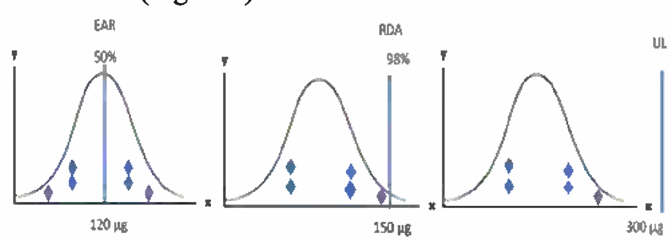

Figure 1: Folate requirement for children 1 to 3 years of age.

The per capita mean daily folate intake in the state of Rajasthan is 238.3 ± 64.7 µg. Mapping of intakes indicated that Barmer district had the highest intakes of dietary folate at 281.0 ± 64.7 µg, while Sirohi district had the lowest intake at 155.4± 41.9 µg followed by Dungarpur at 188.8 ± 48.2 µg. The variability across districts in the per capita intakes of the population therefore is evident (Figure 2).

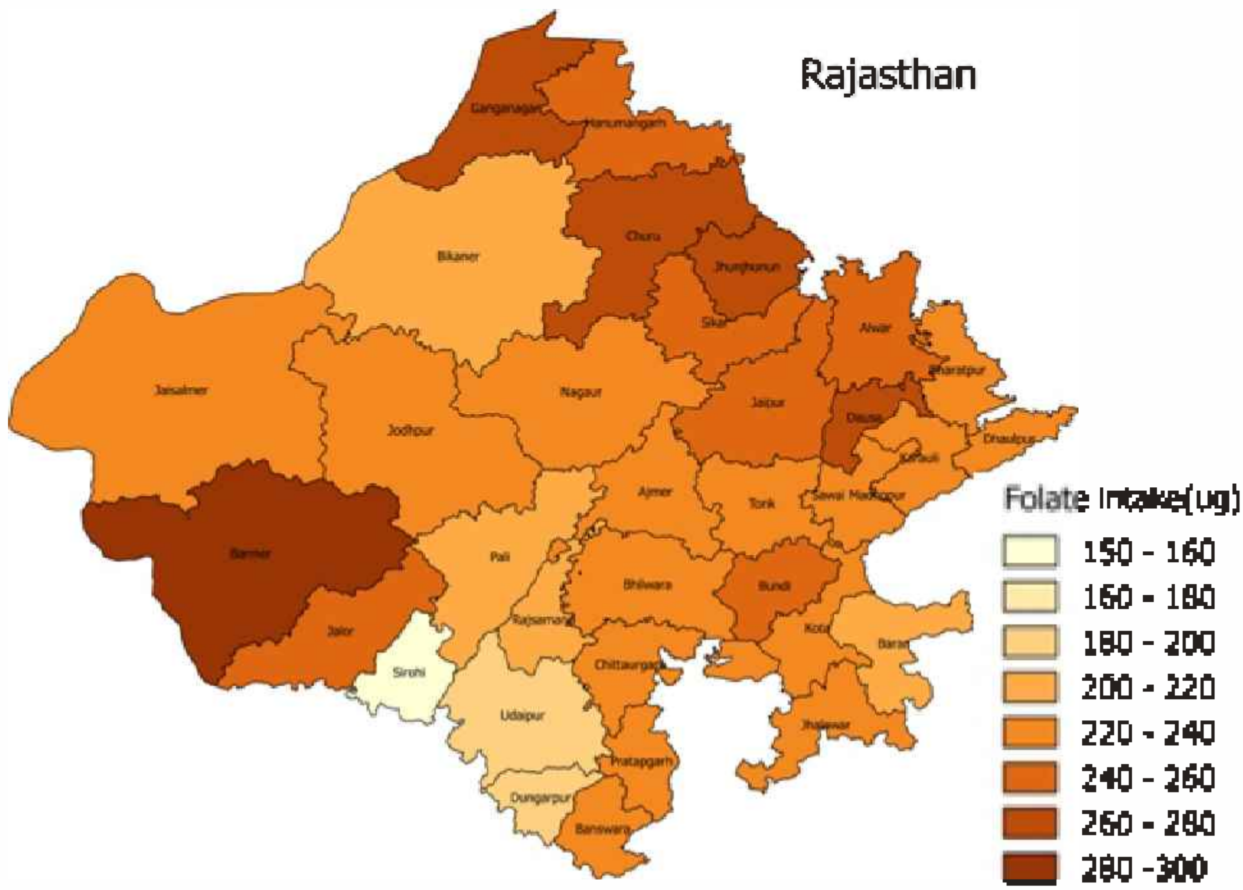

Figure 2: Folate intake in Rajasthan.

The risk of inadequate intakes was calculated for adult men, women and children above the age of 1 year of age (Table1). The lowest risk of inadequacy was in girls 13 to 15 years of age at 3.3% and the highest among adult women at 29.8 %. Between the ages of 4 and 15 years of age the risk of inadequate intake was below 10%. The population groups with risk of inadequate intakes of over 10% were adult men and women, children 1 to 3 years and girls and boys 16 to 17 years of age.

Synthesis

Nutrient requirements include several terms while the Indian recommended dietary allowances have a single term. The methods to evaluate diets of individuals and populations differ and must be used appropriately. To ensure that the population does not exceed the upper limit of intake due to the various supplementation and fortification programs, the first step required is to assess the diet of the population and determine the extent of inadequacy in the diet. This helps in determining the extent of supplementation or fortification required if inadequacy of intake is high.

As an example, the intake of folate in Rajasthan was examined for risk of inadequate intake of folate. Results indicated that the risk of inadequacy for dietary folate in Rajasthan ranged from 3.3% to 29.8% depending on the sub-population studied. With the highest risk of inadequate folate intake being observed in adult women, the risk must be even higher in pregnant and lactating women as requirements increase during these vulnerable periods. More data on the biochemical folate status needs to be studied to corroborate the results obtained on intakes.

However, with most of the population of Rajasthan being vegetarian, there is a likelihood that there is a high degree of vitamin B_{12} deficiency and further studies on vitamin B_{12} status is required. A high folate and low vitamin B_{12} intake during pregnancy has been shown to be associated with birth of small for gestational age infants in a study conducted in India.[28] Any decision to improve folate status needs to be taken with lessons learned from other parts of the world. Over 52 countries, except the European

Table 1: Risk of deficient intakes of folate in the population of Rajasthan

Causes	Population number	Mean	Requirement	Risk of deficient intake of folate (%)
Adult men	6264	278.3 (74.6)	200	14.7
Adult women	3898	232.7 (61.6)	200	29.8
Children 1-3 years	952	122.0 (34.1)	80	10.9
Children 4-6 years	1125	166.4 (45.1)	100	7.0
Children 7 to 9 years	1078	204.4 (52.0)	120	5.2
Boys 10 to 12 years	851	245.0 (66.8)	140	5.8
Girls 10 to 12 years	620	238.2 (61.4)	140	5.5
Boys 13 to 15 years	718	269.8 (72.0)	150	4.8
Girls 13 to 15 years	574	260.4 (60.0)	150	3.3
Boys 16 to 17 years	456	258.6 (74.3)	200	21.5
Girls 16 to 17 years	399	266.0 (67.8)	200	16.5

countries, use mandatory flour fortification with folic acid.[25] India needs to make an informed choice based on more detailed studies being conducted to assess diets and deficiency status across India as regional differences could be present. Supplementation programs such as Iron and Folic acid supplementation in India, particularly for children below the age of 5 years, pregnant and lactating women and for adolescents are operational in India with folic acid being added to reduce neural tube defects.[27] Unfortunately, in India records of birth defects are not routinely collected. In a meta-analysis of 19 studies, it was reported that pooled prevalence of neural tube defects was about 4.5 per 1000 total births (95%CI 4.2 to 4.9), with prevalence in the Western region (which included Rajasthan) reporting a pooled prevalence of 2.5 per 1000 total births (95% CI 1.6 to3.5).[26]

CONCLUSION

An informed decision therefore needs to be taken on whether supplementation and/or fortification is required. In case fortification is being considered, the decision on whether it should be mandatory or voluntary or whether any food fortified with folic acid needs to be provided along with vitamin B_{12} needs to be carefully examined based on appropriate evidence generated. Caution in simultaneous roll out of multiple programs is essential and regulatory aspects need to be put in place to avoid adverse effects on health as intakes could cross the upper limit of intake.

REFERENCES

1. Indian Council of Medical Research. Nutrient requirements and recommended dietary allowances for Indians. A Report of the expert group of the Indian Council of Medical Research. National Institute of Nutrition, Hyderabad, 2010.
2. FAO/WHO/UNU. Energy and protein requirements (1985). Report of a Joint FAO/WHO/UNU Expert Consultation. World health organization technical report series 724. WHO, Geneva.
3. Harper AE. Origin of the recommended dietary allowances. An historic overview. American Journal of Clinical Nutrition 1985; 41: 140-148.
4. Swaminathan S, Raj R, Thomas T, Kurpad AV. RDA for Indians-what more do we need, and do these fit requirements? NFI Bulletin Vol 36 (5). Oct 2015.

5. Swaminathan S, Mani I, Thomas T, Kurpad AV. Recommended dietary allowances-facts and uncertainties. Proc Indian Natn Sci Acad 82. 2016: 1555-1563.
6. MoHFW. Government of India. Guidelines for control of iron deficiency anemia. Available at http://www.unicef.org/india/10. National Iron Plus Initiative Guidelines for Control of IDA.pdf (accessed on 21 Nov 2017).
7. Kapil U, Bhadoria AS. National Iron-plus Initiative guidelines for control of iron deficiency anaemia in India, 2013. National Medical Journal of India 2014 ; 17 (1): 27-29.
8. King JC, Vorster HH, Tome DG. Nutrient intake values (NIVs): A recommended terminology and framework for the derivation of values. Am J Clin Nutr 2007; 81: S16-S26.
9. Institute of Medicine. Dietary reference intakes: The essential guide to nutrient requirements. Otten JJ, Hellwig JP, Meyers LD, Editors. National Academy of Sciences. The National Academies Press, Washington DC. 2006.
10. King JC, Garza C. Harmonization of nutrient intake values. Am J Clin Nutr 2007; 81: S3-S12.
11. World Health Organization. Diet, nutrition and the prevention of chronic diseases. Geneva: World Health Organization, 2003.
12. WHO, FAO (2006) Guidelines on food fortification with micronutrients, Lindsay A, de Benoist B, Omar D, Hurrell R(eds). WHO Publications, USA.
13. Allen L, de Benoist B, Dary O, Hurrell R, editors. Guidelines on food fortification with micronutrients. Geneva: WHO; 2006. p. 137–61.
14. World Health Organization/Food and Agriculture Organization. A model for establishing upper levels of intake for nutrients and related substances. Report of a Joint FAO/WHO Technical Workshop on Nutrient Risk Assessment. Geneva: WHO/FAO, 2006.
15. Rosenberg IH. Science-based micronutrient fortification: which nutrients, how much, and how to know? Am J Clin Nutr 2005;82:279–80.
16. Shane B. Folate fortification: Enough already? Am J Clin Nutr 2003;77:8–9.
17. Institute of Medicine. Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12 , Pantothenic Acid, Biotin, and Choline. A report of the standing committee on the scientific evaluation of dietary reference intakes and its panel on folate, other b vitamins, and choline and subcommittee on upper reference levels of nutrients food and nutrition board, institute of medicine. National Academy Press. Washington, DC.
18. Quinlivan EP, Gregory III JF. Effect of food fortification on folic acid intake in the United States. Am J Clin Nutr 2003;77:221–5.
19. Honein MA, Paulozzi LJ, Mathews TJ, Erickson JD, Wong LC. Impact of folic acid fortification of the US food supply on the occurrence of neural tube defects. JAMA 2001; 258: 2981–6.
20. Food and Drug Administration. Food labeling: health claims and label statements; folate and neural tube defects. Fed Regist 1993; 58: 53254–95.
21. Morris MS, Jacques PF, Rosenberg IH, Selhub J. Folate and vitamin B_{12} status in relation to anemia, macrocytosis, and cognitive impairment in older Americans in the age of folic acid fortification. Am J Clin Nutr 2007 ; January ; 85(1): 193–200.
22. Nutritional intake in India, 2011–12. NSS (68th round) [Internet]. New Delhi (India) National Sample Survey Office, Government of India. 2014 [cited 2017 Feb 2]. Report No.: 560. Available from:
http://www.indiaenvironmentportal.org.in/files/file/nutritional%20intake%20in%20India%202011-12.pdf.
23. Longvah T, Ananthan R, Bhaskarachary K, Venkaiah K. Indian food composition tables. National Institute of Nutrition. Indian Council of Medical Research. Hyderabad. 2017.
24. Gopalan C, Rama Sastri BV, Balasubramanian SC. Nutritive value of Indian foods. Hyderabad (India): National Institute of Nutrition, Indian Council of Medical Research; 1989.
25. Allen LH. Pros and cons of increasing folic acid and vitamin B_{12} intake by fortification. Bhutta ZA, Hurrell RF, Rosenberg IH (eds): Meeting micronutrient requirements for health and development. Nestlé Nutr Inst Workshop Ser. 70:175–183.
26. Allagh KP, Shamanna BR, Murthy GV, Ness AR, Doyle P, Neogi SB, Pant HB; Wellcome Trust- PHFI Folic Acid project team. Birth prevalence of neural tube defects and orofacial clefts in India: a systematic review and meta-analysis. PLoS One.2015 Mar 13;10(3):e0118961.
27. Dwarkanath P, Barzilay JR, Thomas T, Thomas A, Bhat S, Kurpad AV. High folate and low vitamin B-12 intakes during pregnancy are associated with small-for-gestational age infants in South Indian women: a prospective observational cohort study. Am J Clin Nutr 2013;98:1450–8.
28. Ministry of Health and Family Welfare. Govt of India. Guidelines for control of anaemia: national iron plus initiative. Available in: http://www.unicef.org/india/10._National_Iron_Plus_Initiative_Guidelines_for_Control_of_IDA.pdf [Last accessed on 2017 Dec 10].

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