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Original article

Systematic review and meta-analysis approach on vitamin A fortified foods and its effect on retinol concentration in under 10 year children ☆

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SUMMARY

Objective: To carry out a systematic review and meta-analysis of the trials to identify as well as quantify the effect of vitamin A fortified food on serum vitamin A concentration among children under 10 year.
Study design: All the relevant studies has been retrieved by MEDLINE, PubMed, Embase, ProQuest and the Cochrane Library and secondary referencing. A random effects model was applied to compute the pooled effect size of effect of serum retinol. Meta regression was performed to detect the sources of heterogeneity and moderator variables on the study effect. We included all the relevant randomized control trials. These studies were assessed for inclusion and validity, with independent duplication.
Results: Out of 648 published studies, fourteen were included and evaluated. These studies were covering 6153 children and the duration of feeding for the fortified foods ranged between 3 and 12 months. A pooled effect size of vitamin A fortification on retinol in children was estimated (N 6153; Standard Mean Difference = 0.47; 95% CI 0.16, 0.78). However, there was evidence of substantial heterogeneity of estimate on effect ($I^2 = 97\%$, τ^2(tau-squared) = 0.55, $p < 0.01$).
Conclusion: This study suggests that consumption of Vitamin A fortified foods results in increased concentration of retinol and thereby results in reduction of Vitamin A deficiency among the children.

1. Introduction

Vitamin A deficiency (VAD) is the leading cause of preventable childhood blindness in early childhood [1]. According to the World Health Organization (WHO), an estimated 190 million preschool children were suffering from VAD. The prevalence of VAD among under-five children in India is 62% [2–4], which is one of the highest in the world. A decade ago it was estimated that VAD precipitates the deaths of around 0.3 million children every year in India [5] and the prevalence of VAD in the country was higher than the WHO's limit, making it one of the important public health concerns in the country (i.e. Bitot's spots: >0.5%, night blindness in children: >1%) [6]. Vitamin A fortification (VAF) of foods is one of the most effective interventions for reducing the VAD.

VAD is the leading cause of preventable blindness among children. It also significantly increases the risk of severe illness and also results into death due to common childhood infections, particularly diarrheal and measles [3,7]. The changes in vision are sign of severe vitamin A deficiency and milder forms of VAD are best identified by monitoring plasma or serum retinol levels [8]. Worldwide, about 3 million preschool children present ocular signs of VAD and more than 1% prevalence in children aged 24–71 months, or the presence of serum retinol concentrations of less than 0.70 μ mol/l represent night blindness [9]. Several countries have recently initiated national programs to fortify cooking oil with vitamin A [10]. The present review examines the current evidence for the effect of vitamin-A fortified food on retinol concentration in children. Since we expected heterogeneity among studies, we also explored whether factors such as age, duration of the study, and levels of fortification could predict the effects on retinol concentration in children.

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Systematic reviews present a rigorous approach for synthesizing and evaluating the evidence [11], along with minimizing the reporting bias. The methodological quality of the studies included in experimental and control groups enhances the rigor and overall strength of the of evidences. Transparency of the process is ensured through detailed review of the public health nutrition guidelines to the set the required agenda [12,13].

2. Methods

2.1. Literature search

The steps in this process were conducted according to the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) guidelines for meta-analysis [14]. We searched MEDLINE, PubMed, Embase, ProQuest and the Cochrane Library data bases from 1990 to 2016. We also reviewed the reference lists of the articles, by using the keywords 'Vitamin A' or 'retinol' paired with 'food fortification' or 'dual fortification' or 'triple fortification' or 'multiple micronutrient fortification' and 'fortification trial [15,16].

2.2. Selection criteria

All the available literature was searched regardless of their publication status. For inclusion, studies needed to meet the following criteria; 'involve intervention in children, be randomized (RCTs) or quasi-randomized controlled trails' with control group, or before-after studies, reporting changes in retinol levels, or multiple interventions with other micronutrients administered simultaneously, but whose main outcome measure was the effect of VAF on retinol concentration.

2.3. Data extraction and quality assessment

The title and abstracts of the studies were identified in the web search and irrelevant studies were excluded. Full texts of the remaining studies were retrieved. Only peer-reviewed published studies were included to avoid publication bias. The extraction of the data was pertained for obtaining the sample size, age, duration of intervention, levels of fortification and mean change and standard deviation (SD) of retinol concentration in the intervention and control groups [15–17]. The search, data extraction and quality assessment were completed independently by two content experts according to the inclusion criteria and confirmed by using recommended criteria for RCT [18,19]. Concealment of allocation was classified as 'adequate', 'unclear',' inadequate' or 'not used', based on randomization, blinding and reporting of withdrawals.

Blinding was classified as 'single blinding', 'double blinding', 'no blinding' or 'unclear'. In designs employing two or more different intervention groups (different levels of fortification or administration regimens) and a single control group [16]. The sample size of the control group was equally allotted to the number of intervention groups while retaining the same mean value for the change and its SD. In reporting such designs, each intervention subgroup was analyzed separately. Thus, some studies contributed more than one intervention component with a single control group for the statistical analysis and resulted in a greater number of trials than the number of studies included [15].

2.4. Statistical analysis

The effect size for the primary outcome, which is the difference in means between the vitamin A fortified (experimental) and the control groups, is referred as the standard mean difference (SMD), which was calculated for the selected trials. The overall effect size was assessed by the Q statistic to measures the extent of inconsistency among studies. The Q test was computed under the assumption of homogeneity among the effect size and the statistic follows the chi-square distribution with k-1 degrees of freedom, where, k being the number of trials [15].

Another strategy for quantifying the heterogeneity in meta-analysis consists of estimating the variance (τ^2) between studies. The parameter I^2 quantifies the extent of heterogeneity from a collection of effect sizes, which is interpreted approximately as the percentage of total variation in study estimates due to heterogeneity rather than the sampling error. The overall SMD of these results were assessed for sampling error (homogeneous, $\tau^2 = 0$). A fixed-effects model was applied to obtain the pooled effect size with 95% confidence interval (CI), and further random-effects model was applied (if heterogeneous, $\tau^2 > 0$) [20,21].

An I^2 value was also calculated, where if the value $I^2 > 50\%$, then its considered to indicate significant heterogeneity between the trials [20–22]. If heterogeneity existed ($I^2 > 50\%$), a meta-regression approach was used to identify it by relating study characteristics. Publication bias was assessed by using the funnel plot and Egger regression test [20], which is equivalent to a weighted, linear ordinary least square (OLS) regression model with standard error (SE) as a covariate [23]. Statistical analyses were performed with Review Manager software version 5.3, IBM SPSS version 24, and Comprehensive Meta-Analysis (CMA).

3. Results

A total of 648 articles were identified, out of which 595 were excluded as they were not RCTs or their interventions were not relevant for the purpose of the current analysis. Fifty-three potentially relevant articles were selected for full text evaluation, out of which fourteen relevant articles [24–37] were included for analysis after employing the inclusion and exclusion criteria (Fig. 1).

3.1. Study characteristics and data quality

Characteristics of the fourteen studies are given in Table 1. All these studies were RCTs and have reported retinol concentrations in intervention as well as in the control groups. These studies have reported on a total of 6153 children who aged from 6 months to 9.5 years with the intervention duration ranging between 3 and 12 months. These studies were carried out over the past two decades (1993–2016). All 14 studies evaluated the effect of various levels of

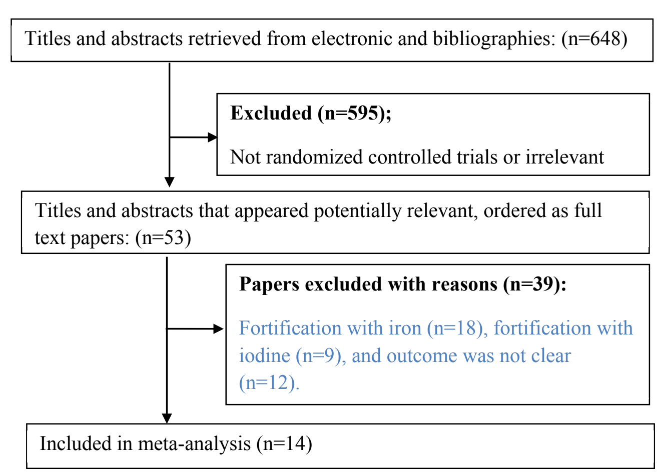

Fig. 1. Flow diagram for inclusion of randomized controlled trials (RCTs).

Table 1
Summary of studies of assessing the effect of VAF foods on mean retinol concentrations in children (<10 year).

Reference	Year	Duration (Months)	Average Age (years)	Level of fortification(IU)	Food vehicle	Initial sample size	Country
Liu DS et al. [25]	1993	3	1.59	350	Rusks	226	China
Saskia DP et al. [26]	1995	1.2	1.7	350	Stir-fried	562	Netherland
Anna et al. [24]	2000	6	0.75	644	Milk	216	Ghana
Solon FS et al. [27]	2000	7.5	9.5	142	wheat flour bun	922	Philippines
Van Stuijvenberg ME et al. [28]	2001	3	8	144	Biscuits	437	South Africa
Zimmermann MB et al. [31]	2004	10	7	720	fortified capsules	159	Morocco
Luz VC et al. [20]	2006	6	6.9	789	Fortified cooking oil	308	Philippines
Winichagoon P et al. [24]	2006	7.75	9.45	270	Wheat noodles	569	Thailand
Zeba AN et al. [30]	2006	12	8.5	720	Red palm oil	384	Burkina Faso
Varma JL et al. [29]	2007	6	4.25	500	Khichidi	696	India
Nga TT et al. [22]	2009	4	7	300	Biscuits	550	Vietnam
Osei AK et al. [23]	2010	8	8	375	Fortified meals	499	India
Prashanth T et al. [25]	2012	6	9	60	Fortified rice	1506	India
Kumar MV et al. [21]	2014	8	7	900	Fortified meals	646	India

fortification on retinol concentration. Out of these, seven studies which had multiple interventions with multiple micronutrients, we considered only those groups that received VAF [26,27,31–33,36]. The trials were either based on different levels of intervention of food fortification conducted on two occasions (before and after) or they were compared with a placebo. In each trial, the number of participants, mean and SD of retinol concentration were also estimated for conducting meta-analysis.

3.2. Effects of VAF on retinol concentration

The meta-analysis results indicate that the mean change in retinol concentration was significantly higher in the VAF-fortified group than in the control group (N = 6153; SMD = 0.47; 95% CI 0.16, 0.78; P < 0.0001), as depicted in the forest plot (Fig. 2). There was significant heterogeneity for the mean retinol concentration reported among the included trials. All statistical tests of heterogeneity such as the Q statistic (Q = 748.40, df = 22), which was more than df; τ^2 greater than zero ($\tau^2 = 0.55$); and I^2 greater than 50% ($I^2 = 97\%$) were higher than the expected value, indicating heterogeneity among the studies.

Meta-regression analysis was performed to detect the source of heterogeneity and indicated that the dose of the intake of fortified food was positively associated with the effect size. The significant differences in the extent of improvement in retinol levels as reported in the forest plot (Fig. 2) are perhaps due to different dose of the feeding regimens of vitamin A-fortified foods to the children.

3.3. Publication bias

The funnel plot (Fig. 3) was symmetrical, indicating the presence of publication bias. Egger's weighted regression was significant. (Egger test, p < 0.041) [20].

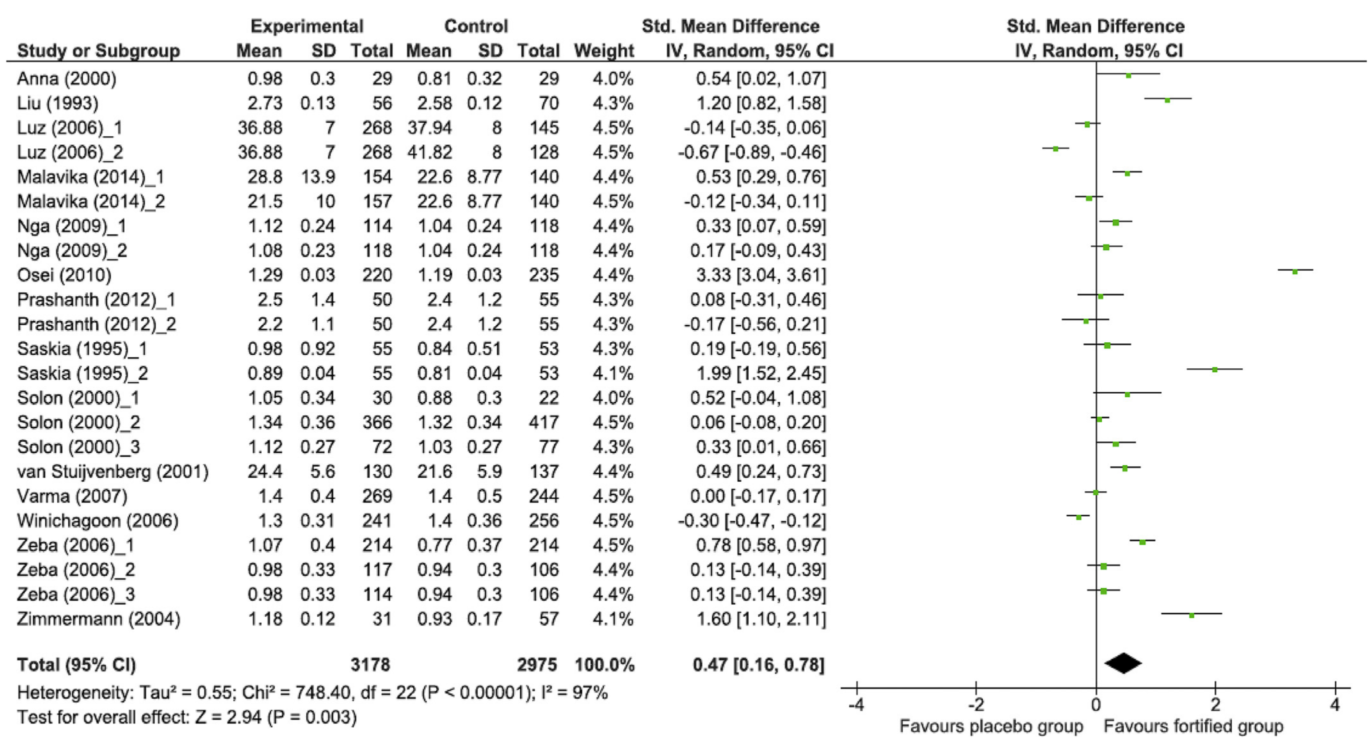

Fig. 2. Forest plot: effect of VAF on mean retinol concentration in comparison with no intervention or placebo control in children. The sizes of data markers indicate the weight of each study in the analysis. Horizontal lines represent 95% CI. Blob indicates best estimate and diamond indicates the summary estimate of the SMD.

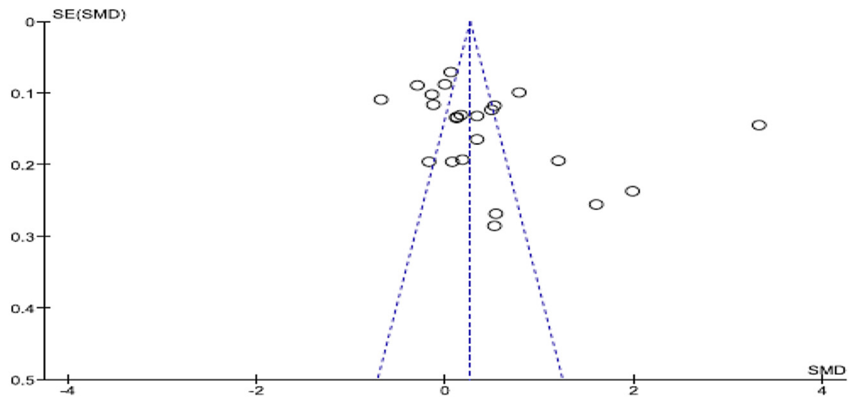

Fig. 3. Funnel plot of all individual studies in the meta-analysis. Studies that evaluated the effect of vitamin A-fortification on retinol concentration in children were plotted with their SMD.

4. Discussion

The vitamin A fortification intervention impact varied across trials. Out of twenty-three trials included in the meta-analysis, eighteen trials found that VAF was significantly associated with increased retinol concentration in the intervention group as compared to control group. However, there was heterogeneity in the results across the trials. The present study adopted sequential statistical methods to verify that implementation of fortified foods with VAF improves retinol concentration among the children.

The presence of heterogeneity is an important attribute of meta-analysis which can influence the results [38]. It was tested by the Q statistic, τ^2 and I^2, and the results were depicted in the form of a forest plot. Due to the presence of heterogeneity among the trials, fixed-effects model cannot be performed, so a random-effects model was deployed [39]. The random-effects model showed a significant impact of VAF on retinol concentration among the child beneficiaries and provides evidences which shows that food fortification with vitamin A is an ideal strategy to prevent vitamin A deficiency (VAD) among children.

A meta regression analysis was performed to examine whether the study heterogeneity could be explained by one or multiple factors. We examined effect size of retinol concentration as a dependent variable and age, level of fortification and duration of supplementation as moderators. The results indicate that the duration of feeding is positively associated with study heterogeneity ($\beta = 2.15$, $p = 0.02$) [40].

Yet another critical step in meta-analysis is the publication bias which can lead to inflated estimates of efficacy [41]. We observed that there was heterogeneity among trials, as some of the trials did not fit into the funnel Plot. Egger's regression test also suggested that there was presence of publication bias ($p < 0.041$) among trials. Though food fortification has been assumed to be a powerful tool to address micronutrient deficiency, yet there is no compelling evidence as a strategy for addressing VAD. The findings of this study support that introduction of vitamin A fortified food improves serum retinol status in many cases and thereby likely to impact clinical outcomes related to VAD [9,42]. This study also provides evidence that VAF of food does not always have the expected effect in children.

5. Conclusion

Present study suggests that consumption of vitamin A-fortified foods often but not always significantly increases the retinol concentration among the children. However, further studies are required for comparing different doses and type of delivery mechanisms with the longer follow-up trials to resolve the uncertainty regarding the safety and clinical effectiveness.

Conflicts of interest

There are no conflicts of interest.

Ethics

Ethical approval was not required for the present study.

Authors' contribution

Ramesh Athe contributed in the data collection, analysis, and manuscript preparation. Vishnu Vardhana Rao Mendu developed the study protocol, secured funds, supervised the study, and guided in manuscript preparation. Madhavan Nair contributed in the development of study protocol and manuscript writing.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnesp.2019.01.005.

References

[1] UNICEF. Annual results report 2015: Nutrition. 2015. http://www.unicef.org/publicpartnerships/files/2015ARR_Nutrition.pdf.
[2] Gautam K. Nutritional assessment and its associated factors among 6-59 Months children in Dalit community of Bagchaur Municipality, Salyan (Doctoral Dissertation). 2018.
[3] Stevens GA, Bennett JE, Hennocq Q, Lu Y, De-Regil LM, Rogers L, et al. Trends and mortality effects of vitamin A deficiency in children in 138 low-income

and middle-income countries between 1991 and 2013: a pooled analysis of population-based surveys. Lancet Global Health 2015 Sep 1;3(9):e528–36.
[4] Dong S, Xia H, Wang F, Sun G. The effect of red palm oil on vitamin A deficiency: a meta-analysis of randomized controlled trials. Nutrients 2017 Nov 24;9(12):1281.
[5] Hachinski V, editor. Treatable and potentially preventable dementias. Cambridge University Press; 2018 May 31.
[6] WHO. Global prevalence of vitamin A deficiency in populations at risk 1995–2005: WHO global database on vitamin A deficiency. Geneva: World Health Organization; 2009.
[7] Oxman AD, Sackett DL, Guyatt GH, Browman G, Cook D, Gerstein H, et al. Users' guides to the medical literature: I. How to get started. Jama 1993 Nov 3;270(17):2093–5.
[8] Bailey RL, West Jr KP, Black RE. The epidemiology of global micronutrient deficiencies. Ann Nutr Metabol 2015;66(Suppl. 2):22–33.
[9] Allen LH, De Benoist B, Dary O, Hurrell R, World Health Organization. Guidelines on food fortification with micronutrients. 2006.
[10] Tanumihardjo SA, Mokhtar N, Haskell MJ, Brown KH. Assessing the safety of vitamin A delivered through large-scale intervention programs: workshop report on setting the research agenda. Food Nutr Bull 2016 Jun;37(2_suppl): S63–74.
[11] Current processes of the US Preventive Services Task Force: refining evidence-based recommendation development. Ann Intern Med 2007 Jul 17;147(2): 117–22.
[12] Briss PA, Zaza S, Pappaioanou M, Fielding J, Wright-De Agüero L, Truman BI, et al. Developing an evidence-based guide to community preventive services—methods12. Am J Prev Med 2000 Jan 1;18(1):35–43.
[13] Dybå T, Dingsøyr T. Empirical studies of agile software development: a systematic review. Inf Software Technol 2008 Aug 1;50(9–10):833–59.
[14] Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med 2009 Jul 21;6(7):e1000100.
[15] Athe R, Rao MV, Nair KM. Impact of iron-fortified foods on Hb concentration in children. Public Health Nutr 2014 Mar;17(3):579–86.
[16] Athe R, Mendu VV, Krishnapillai MN. A meta-analysis combining parallel and cross-over randomized controlled trials to assess impact of iodine fortified foods on urinary iodine concentration among children. Asia Pac J Clin Nutr 2015 Sep 1;24(3):496–503.
[17] Oxman AD, Guyatt GH. Guidelines for reading literature reviews. CMAJ Can Med Assoc J 1988 Apr 15;138(8):697.
[18] Balk EM, Horsley TA, Newberry SJ, Lichtenstein AH, Yetley EA, Schachter HM, et al. A collaborative effort to apply the evidence-based review process to the field of nutrition: challenges, benefits, and lessons learned–. Am J Clin Nutr 2007 Jun 1;85(6):1448–56.
[19] Gera T, Sachdev HP. Effect of iron supplementation on incidence of infectious illness in children: systematic review. Bmj 2002 Nov 16;325(7373):1142.
[20] Egger M, Davey-Smith G, Altman D, editors. Systematic reviews in health care: meta-analysis in context. John Wiley & Sons; 2008 Apr 15.
[21] DerSimonian R, Laird N. Meta-analysis in clinical trials. Contr Clin Trials 1986 Sep 1;7(3):177–88.
[22] Borenstein M, Hedges L, Higgin J, Rothstein H. Introduction to meta-analysis. Hoboken, NJ: John Wily & Sons, Ltd; 2009.
[23] Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ: Br Med J 2003 Sep 6;327(7414):557.
[24] Anna L, Manu A, Brown KH, Dewey KG. Predictors of micronutrient status among six-to twelve-month-old breast-fed Ghanaian infants. J Nutr 2000 Jan 1;130(2):199–207.
[25] Liu DS, Bates CJ, Yin TA, Wang XB, Lu CQ. Nutritional efficacy of a fortified weaning rusk in a rural area near Beijing. Am J Clin Nutr 1993 Apr 1;57(4): 506–11.
[26] Luz VC, Magsadia CR, Velasco RE, Pedro MR, Barba CV, Tanchoco CC. The effect of vitamin A-fortified coconut cooking oil on the serum retinol concentration of Filipino children 4-7 years old. Asia Pac J Clin Nutr 2005 Mar 1;14(1):43.
[27] Kumar MV, Nirmalan PK, Erhardt JG, Rahmathullah L, Rajagopalan S. An efficacy study on alleviating micronutrient deficiencies through a multiple micronutrient fortified salt in children in South India. Asia Pac J Clin Nutr 2014 Sep 23;23(3):413–22.
[28] Nga TT, Winichagoon P, Dijkhuizen MA, Khan NC, Wasantwisut E, Furr H, et al. Multi-micronutrient–fortified biscuits decreased prevalence of anemia and improved micronutrient status and effectiveness of deworming in rural Vietnamese school children. J Nutr 2009 Mar 25;139(5):1013–21.
[29] Osei AK, Rosenberg IH, Houser RF, Bulusu S, Mathews M, Hamer DH. Community-level micronutrient fortification of school lunch meals improved vitamin A, Folate, and iron status of schoolchildren in Himalayan villages of India–3. J Nutr 2010 Apr 21;140(6):1146–54.
[30] Winichagoon P, McKenzie JE, Chavasit V, Pongcharoen T, Gowachirapant S, Boonpraderm A, et al. A multimicronutrient-fortified seasoning powder enhances the hemoglobin, zinc, and iodine status of primary school children in North East Thailand: a randomized controlled trial of efficacy. J Nutr 2006 Jun 1;136(6):1617–23.
[31] Prashanth T, Rah JH, Thomas T, Selvam S, Amalrajan V, Srinivasan K, et al. Multiple micronutrient-fortified rice affects physical performance and plasma Vitamin B-12 and Homocysteine concentrations of Indian school children–4. J Nutr 2012 Mar 21;142(5):846–52.
[32] de Pee S, West CE, Hautvast JG, Karyadi D. Lack of improvement in vitamin A status with increased consumption of dark-green leafy vegetables. Lancet 1995 Jul 8;346(8967):75–81.
[33] Solon FS, Klemm RD, Sanchez L, Darnton-Hill I, Craft NE, Christian P, et al. Efficacy of a vitamin A–fortified wheat-flour bun on the vitamin A status of Filipino schoolchildren–. Am J Clin Nutr 2000 Sep 1;72(3):738–44.
[34] Van Stuijvenberg ME, Dhansay MA, Lombard CJ, Faber M, Benade AJ. The effect of a biscuit with red palm oil as a source of β-carotene on the vitamin A status of primary school children: a comparison with β-carotene from a synthetic source in a randomised controlled trial. Eur J Clin Nutr 2001 Aug;55(8):657.
[35] Varma JL, Das S, Sankar R, Mannar MG, Levinson FJ, Hamer DH. Community-level micronutrient fortification of a food supplement in India: a controlled trial in preschool children aged 36–66 mo–. Am J Clin Nutr 2007 Apr 1;85(4): 1127–33.
[36] Zeba AN, Prével YM, Somé IT, Delisle HF. The positive impact of red palm oil in school meals on vitamin A status: study in Burkina Faso. Nutr J 2006 Dec;5(1):17.
[37] Zimmermann MB, Wegmueller R, Zeder C, Chaouki N, Biebinger R, Hurrell RF, et al. Triple fortification of salt with microcapsules of iodine, iron, and vitamin A. Am J Clin Nutr 2004 Nov 1;80(5):1283–90.
[38] Polderman TJ, Benyamin B, De Leeuw CA, Sullivan PF, Van Bochoven A, Visscher PM, et al. Meta-analysis of the heritability of human traits based on fifty years of twin studies. Nat Genet 2015 Jul;47(7):702.
[39] Cronin P, Kelly AM, Altaee D, Foerster B, Petrou M, Dwamena BA. How to perform a systematic review and meta-analysis of diagnostic imaging studies. Acad Radiol 2018 May 1;25(5):573–93.
[40] Nakagawa S, Schielzeth H. A general and simple method for obtaining R2 from generalized linear mixed-effects models. Methods Ecol Evol 2013 Feb 1;4(2): 133–42.
[41] Turner EH, Matthews AM, Linardatos E, Tell RA, Rosenthal R. Selective publication of antidepressant trials and its influence on apparent efficacy. N Engl J Med 2008 Jan 17;358(3):252–60.
[42] Burke R, Whitehead R, Figueroa J, Whelan D, Aceituno A, Rebolledo P, et al. Effects of inflammation on biomarkers of vitamin A status among a cohort of bolivian infants. Nutrients 2018 Sep 5;10(9):1240.