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Iron, zinc, vitamin A and selenium status in a cohort of Indonesian infants after adjusting for inflammation using several different approaches

Aly Diana[1,2]*, Jillian J. Haszard[2], Dwi M. Purnamasari[3], Ikrimah Nurulazmi[1], Dimas E. Luftimas[1], Sofa Rahmania[3], Gaga I. Nugraha[1], Juergen Erhardt[4], Rosalind S. Gibson[2] and Lisa Houghton[2]

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Abstract

Inflammation confounds the interpretation of several micronutrient biomarkers resulting in estimates that may not reflect the true burden of deficiency. We aimed to assess and compare the micronutrient status of a cohort of Indonesian infants (*n* 230) at aged 6, 9 and 12 months by ignoring inflammation (unadjusted) and adjusting four micronutrient biomarkers for inflammation with C-reactive protein (CRP) and *α*-1-glycoprotein (AGP) using the following methods: (1) arithmetic correction factors with the use of a four-stage inflammation model; and (2) regression modelling. Prevalence of infants with any inflammation (CRP > 5 mg/l and/or AGP > 1 g/l) was about 25 % at each age. Compared with unadjusted values, regression adjustment at 6, 9 and 12 months generated the lowest ($P < 0{\cdot}001$) geometric mean (GM) for serum ferritin (26·5, 14·7, 10·8 μg/l) and the highest GM for serum retinol-binding protein (0·95, 1·00, 1·01 μmol/l) and Zn (11·8, 11·0, 11·5 μmol/l). As a consequence, at 6, 9 and 12 months regression adjustment yielded the highest prevalence of Fe deficiency (20·3, 37·8, 59·5 %) and the lowest prevalence of vitamin A (26·4,16·6, 17·3 %) and Zn (16·9, 20·6, 11·0 %) deficiency, respectively. For serum Se, irrespective of adjustment, GM were low (regression: 0·73, 0·78, 0·81 μmol/l) with prevalence of deficiency >50 % across all ages. In conclusion, without inflammation adjustment, Fe deficiency was grossly under-estimated and vitamin A and Zn deficiency over-estimated, highlighting the importance of correcting for the influence of such, before implementing programmes to alleviate micronutrient malnutrition. However, further work is needed to validate the proposed approaches with a particular focus on assessing the influence of varying degrees of inflammation (i.e. recurrent acute infections and low-grade chronic inflammation) on each affected nutrient biomarker.

Key words: Biomarkers: Indonesia: Inflammations: Iron: Selenium: Vitamin A: Zinc

Micronutrient deficiencies are widespread in many low-income countries[1], especially among infants and children under 5 years of age. The most common micronutrient deficiencies are vitamin A, Fe, and Zn[1,2], although Se deficiency is an increasing concern[3]. Deficiency of these four micronutrients compromise the immune system[4,5], resulting in increases in morbidity and mortality during early childhood. Fe and Zn deficiency are also associated with an increased risk of impaired growth and cognition[6–8].

Micronutrient biomarkers in serum can be used to assess status of these four micronutrients. However the presence of inflammation or infection confounds their assessment[5,9–11]. Consequently, the resulting deficiency prevalence estimates may not reflect the true burden unless inflammation or infection has been taken into account.

During the acute phase response initiated by inflammatory cytokines, the hepatic synthesis of several proteins, termed acute phase proteins (APP), increases[5]. Some of these APP respond to the acute phase response by increases in circulating plasma levels (i.e., positive APP) such as ferritin, and others (e.g. retinol-binding protein (RBP), Zn and selenoprotein P) by decreases (i.e. negative APP). Some APP, notably C-reactive protein (CRP) and *α*-1-glycoprotein (AGP), are recommended as inflammatory biomarkers by the World Health Organization[12], providing a measure of the severity and duration of inflammation, respectively[5].

In the past, estimates of micronutrient deficiencies have often been based on excluding participants with an elevated CRP and/or AGP concentration[13]. However, such an approach may reduce the sample size and/or introduce a sampling bias in low-income settings where the burden of inflammation is often high[5]. As a result, several approaches to adjust the concentrations of micronutrient biomarkers affected by the inflammatory response have been developed[9,13–17]. Recently a new approach involving regression modelling has been recommended by the Biomarkers Reflecting Inflammation and

Abbreviations: AGP, *α*-1-glycoprotein; APP, acute phase proteins; BRINDA, Biomarkers Reflecting Inflammation and Nutritional Determinants Anemia; CRP, C-reactive protein; GM, geometric mean; RBP, retinol-binding protein; sTfR, soluble transferrin receptor.

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