It should be noted that the prevalence of subclinical vitamin A deficiency (VAD) was 21.5% among 5- to 10-y-old children, making it a severe public health problem in 15 states in India (2), and a high prevalence of Bitot's spot (1.4%) was also reported in the same age group (3). In contrast, a low prevalence of subclinical VAD (17.6%) (2) and Bitot's spot (0.3%) (3) was reported among the children 1–5 y old. At the same time, the proportion of children <5 y old covered by a massive dose of VAS increased from 25% in 2003 (8) to 60.2% in 2015–2016 (9). Hence, the low prevalence of VAD in children <5 y old as compared with that of 5- to 10-y-old children could definitely be attributed to the coverage of under-5 children for VAS. Therefore, there should not be any haste to modify the existing universal VAS program in India, solely based on the assumptions and findings derived from the grossly inadequate sample covered under the CNNS.

Hence, before arriving at any hasty decisions, a well-designed study with an adequate nationally representative sample, considering the parameters of serum retinol, Bitot's spot, and dietary vitamin A intake, should be carried out. Until then, we should not deny children's right to receive VAS until their vitamin A intake has improved optimally because its deprivation during their formative years can be detrimental to the growth and development of the child, resulting in morbidity and mortality (10).

The author reports no conflicts of interest.

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Reply to J Sheftel et al. and N Arlappa

Dear Editor:

In answering Sheftel et al. we do appreciate the insightful work of the Tanumihardjo group in evaluating vitamin A (VA) overconsumption with multiple interventions. They express concern about our statement (1) that the universal VA supplementation (VAS) program should be discontinued in India. This concern is misplaced, as we have stated that there is now need for a targeted VAS in India, given the recently available national data on serum retinol, wide socioeconomic variations, improving food access, and mandatory food VA fortification, with attendant risks of VA overconsumption.

With regard to our estimate of the potential impact of VAS on mortality: the mortality estimate was restricted to the 6th–59th month, when VAS is operationalized in India (2), and we estimated mortality reduction based on the Cochrane global estimate (3) to be 1.7/1000 live births in trial settings, potentially even lower programmatically. This impact was small in relation to the financial resources allocated to universal VAS, relating to priority setting in disease-specific mortality reduction (4). Further, the Cochrane global analysis was dominated by studies in the last century, when VA deficiency (VAD) was substantial. A more relevant subanalysis restricted to 5 Indian intervention studies revealed no significant mortality risk reduction (0.96; 95% CI: 0.85, 1.03) with VAS, which reaffirms our point (1).

Next, Sheftel et al. refer to the uncertainty of the use of serum retinol as a VAD marker. We agree this should be interpreted with caution for the reasons stated in their letter. However, it is worth noting that the broader context of population VAD, as defined by several conditions in their WHO reference (5), largely does not exist in present day India. While we agree that more sensitive measurements like the relative dose response and retinol body stores are required in addition to the contextual evaluation of serum retinol (), the feasibility of doing these sensitive and expensive tests at scale in large low- and middle-income countries (LMICs) needs some consideration. In reality, over the last decade, several LMICs have not generated national prevalence data for serum retinol–based VAD in under-5 children. They also object to our acceptance of the WHO guideline for framing VAD while not adhering to the Global Alliance for Vitamin A (GAVA) framework. When multiple stakeholders and economic interests are involved with policy (6; with subsequent commentaries), choosing another recommendation over the existing WHO guideline requires robust reasoning and local validation. Surprisingly, they do not accept our use of uncertainty estimates (CI) when evaluating population prevalence. This was used to confirm the hypothesis that VAD prevalence was >20% in specific states, which required the 95% CI to be >20%. This may have been misinterpreted to mean that we are proposing a new cutoff. We are not.

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Abbreviations used: EAR, Estimated Average Requirement; GAVA, Global Alliance for Vitamin A; NNMB, National Nutrition Monitoring Bureau; RDR, relative dose response; RID, retinol isotope dilution; VA, vitamin A; VAD, vitamin A deficiency; VAS, vitamin A supplementation.

They also take issue with our approach to defining the risk of dietary inadequacy. Specifically, that "in a healthy population, the risk of dietary inadequacy would be 50%." We should first point out that their interchangeable use of the terms "risk of inadequacy" and "inadequacy" is incorrect. Here, we are only referring to the risk of inadequacy, which is determined with simple probability theory when evaluating the distributions of nutrient intake and requirement. When these superimpose on each other in normal populations, the intake of half the population will be lower than the Estimated Average Requirement (EAR), yielding a risk, but not a deterministic measure, of inadequacy. Indeed, Sheftel et al. go on to suggest that populations should consume the RDA (97.5th percentile of the requirement distribution). It is not clear whether they mean that the average intake of the population should be the RDA, or even more. Both positions are incorrect, since they conflate individual and population approaches to risk, and are unjustified on many levels, since setting the threshold of population adequacy to the RDA could magnify nutrient deficiencies, and interventions to increase population retinol intakes to the RDA will increase the risk of overconsumption, and create health inequity.

In response to Arlappa, we wish to rebut several factually incorrect statements. First, with regard to the conflicting "measurement numbers" that he quotes from the survey report and from our paper (1); his 'number' quoted from the survey report is incorrect, as it is adjusted for the survey weight and is not the true sample size. We have correctly reported the true sample size in our paper as the number of valid measurements (1). With regard to his contention that the survey was underpowered and not nationally representative, the true national representativeness of a sample should be assessed from the precision of the eventual estimate. Arlappa simply quotes the tentative sample size decided prior to the survey but does not evaluate the precision of the national VAD prevalence estimate. Up to 5% precision is usually acceptable, and the absolute precision of our reported VAD estimate was 0.55% while the relative precision was ~3.5%. Further, a comparison of the demographic characteristics of samples with valid measurements and with missing/invalid measurements did not indicate any bias. We agree a few states did not have sufficient samples, but then the 95% CI should be interpreted for any state-level analyses. Therefore, the primary contentions of this letter are invalid.

With regard to Arlappa's statement that VAS should continue because the (dated) National Nutrition Monitoring Bureau (NNMB) surveys show "dietary VA inadequacy" of >86%, it is sufficient to point out that these estimates are incorrectly calculated against the RDA, which is almost twice the EAR (1, 7). Therefore, raising the specter of a "gross deficit" is imprudent unless it is correctly quantified (1). With regard to the inaccuracy of a monthly food-basket recall, this is likely to be better in poorer sections, with more monotonous purchases. In contrast, the NNMB daily food recall has its own biases. Arlappa goes on to imply that oil fortification will do nothing for VA nutrition based on a notion of 100% inadequacy of oil intake in rural areas and local oil procurement in villages. This is also incorrect for many reasons: first, our data-based estimate of retinol intake from fortified oil (1) showed that even if low (8.8 g oil/d for the poorest quintile of 1- to 3-y-old children), the consumption of fortified oil could provide up to a third of the EAR of VA; and second, the Food Safety and Standards Authority of India (FSSAI) has regulated the mandatory fortification for all cooking oils (8), while prohibiting the sale of unpackaged local oil. He also incorrectly refers to VA deprivation resulting in morbidity and mortality, and to the children's right to receive VAS. This appears ideological, and we can only point him specifically to the Cochrane subanalyses of Indian data showing no effect of VAS on mortality (3) and to our evidence-based considerations of equity (1) and doing no harm (overconsumption). Indeed, even the mandatory fortification of all cooking oil might be a step too far in violating considerations of autonomy as well as equity.

A famous economist said: "When the facts change, I change my mind. What do you do?" Our data-driven, granular, and local-context approach (1) is a reasonable alternative to the "one-size-fits-all" approach. Even so, we advocate abundant caution when transitioning from universal VAS, in continued and intensive population monitoring through, for example, sentinel (ophthalmological) surveillance and vital statistics. To the authors of both letters, we say this with conviction: when settings struggle to provide adequate allocations for competing health budgets, and public health frameworks seek to do no harm, as in India, the need for moving from universal to targeted VAS has never been more appropriate.

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The homeoviscous adaptation to dietary lipids (HADL) hypothesis is probably incorrect

Dear Editor:

Zinöcker, Svendsen, and Dankel recently presented their homeoviscous adaptation to dietary lipids (HADL) model (1). Briefly, their model can be summarized as follows: high dietary SFA and low PUFA intake causes changes to plasma membrane fluidity that drive transfer of free cholesterol frommembranes to lipoproteins, whereas a low dietary SFA and high PUFA intake does the opposite. The authors suggest several immediate implications for how we now should understand biology and the connection between diet and health.

In the following, we address issues and topics which suggest that the presented hypothesis is incorrect.

First, let us discuss the key questions posed by the authors, concerning the origin and disposal of LDL cholesterol, as this is established scientific knowledge (2). Cholesterol in plasma is transported in lipoproteins, and in humans, the majority is found in apoB-100-containing LDL particles. All apoB-100-containing lipoprotein particles originate from VLDLs, which are being continuously secreted by the liver. The main function of VLDL particles is to transport lipids, mainly triglycerides (energy), from the liver to peripheral tissues. LDL particles are the smallest VLDL remnants from which most of the triglycerides have been depleted via the function of lipoprotein lipase and hepatic lipase. Furthermore, LDL particles are continuously removed from circulation by hepatocytes via the LDL-receptor (LDLR)-dependent pathway; LDL particles can therefore accumulate in the plasma because of increased VLDL secretion and residence time or reduced LDL clearance. After degradation in lysosomes, LDL particle contents will be dispersed into various cellular pools. Cholesterol, for example, will be deposited as lipid droplets, incorporated into membranes, used for VLDL particle biosynthesis, or secreted into the bile ducts either as cholesterol or as bile salts to reach the gut for reabsorption or ultimate excretion (2).

Second, we would like to comment on a few of the statements about atherosclerosis. Although endothelial injury ("response-to-injury") may contribute, the real driver of atherosclerotic progression is the subendothelial retention of apoB-100-containing lipoprotein particles ("response-to-retention") which then launches a local, sterile inflammation (3). This means that inflammation is a consequence rather than a cause of lipid accumulation in the arterial wall. In contrast, the cholesterol molecules present in the circulation are not relevant to atherosclerosis per se. Furthermore, all apoB-100-containing particles are potentially atherogenic, and the degree of atherosclerosis progression is driven mainly by the cumulative exposure to atherogenic lipoproteins, which is determined by the absolute plasma concentration and the duration of exposure ("cholesterol burden"). Indeed, a persistently elevated concentration of LDL particles in plasma is harmful regardless of its cause (unfavorable genetic variants or an unhealthy diet), whereas a persistently low concentration is beneficial regardless of its cause [favorable genetic variants, a healthy diet, or pharmacotherapy using statins, proprotein convertase subtilisin-kexin 9 (PCSK9) inhibitors, or ezetimibe] (3).

Third, the authors should have considered the following topics while developing their hypothesis:

1) From basic science, animal models, genetic studies, and intervention trials, we know the most important determinants of the variability in plasma LDL cholesterol (3, 4). For example, number and activity of hepatic LDLRs (relevant genes include *LDLR*, *PCSK9*, *APOE*), LDL binding to LDLRs (*LDLR*, *APOB*), cholesterol biosynthesis [3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (*HMGCR*)], hepatic bile acid synthesis [cholesterol 7 alpha-hydroxylase (*CYP7A1*)], and enterocyte uptake and secretion of cholesterol [Niemann-Pick C1-Like 1, ATP-binding cassette sub-family G member 5 and 8 (*NPC1L1*, *ABCG5/G8*)].

2) All human cells can produce the cholesterol they need, and cellular cholesterol deficiency occurs only when its synthesis is defective (5–7). For example, heterozygous and homozygous familial hypercholesterolemia subjects exhibit 50% and 100% reduced cellular LDL uptake, respectively, but show no symptoms consistent with cholesterol deficiency. In contrast, cholesterol synthesis defects such as Smith–Lemli–Opitz syndrome are detrimental already in fetal life.

3) In contrast to glucose homeostasis, no hormonal system has evolved to keep plasma cholesterol concentration within a narrow range. This is because every cell can synthesize cholesterol and, accordingly, no cell has an absolute requirement for cholesterol uptake (6–8). Therefore, plasma LDL-cholesterol concentrations can be extremely low (although not 0) with few adverse effects.

4) Because free cholesterol is toxic and human cells cannot degrade cholesterol molecules, there is a balance between whole-body cholesterol input through diet and biosynthesis, and output through utilization and excretion (2, 8).

Finally, the HADL hypothesis provides at least two testable implications. The first relates to dose-response. If the physicochemical properties of dietary fatty acids affect membrane fluidity, which then determines cholesterol accretion in membranes, which then causes plasma LDL cholesterol to increase or decrease, we should be able to predict the change in LDL cholesterol based on the physicochemical properties of dietary fatty acids. Theoretically, an incrementally higher melting point of dietary fatty acids would cause incremental increases in plasma LDL cholesterol, whereas an incrementally lower melting point would do the opposite. But from controlled interventions, we find no such relation. Among the SFAs, myristic acid (14:0) increases plasma LDL cholesterol most strongly [+0.071 mM per energy percent (E%) increase in the diet], followed by palmitic acid (16:0, +0.047 mM/E%), then lauric acid (12:0, +0.01 mM/E%) (9). Among the PUFAs, both linoleic acid (18:2n–6) and α-linolenic acid (18:3n–3) reduce plasma LDL cholesterol by equal amounts (−0.017 mM/E%) (9). And importantly, of the long-chain omega-3 fatty acids, neither EPA (20:5n–3) nor DHA (22:6n–3) affects plasma LDL cholesterol (4).

Another testable implication concerns the temporal sequence, an essential part of any cause–effect analysis. If dietary fatty acids affect membrane fluidity, which then determines cholesterol accretion in membranes, and which then causes plasma LDL cholesterol to increase or decrease, we should observe membrane remodeling before the changes in plasma LDL cholesterol. However, that is not what we observe in controlled interventions: whereas plasma LDL cholesterol responds rapidly to dietary change (days to weeks), changes in membrane lipid composition occur slowly (weeks to months) and depend largely on the rate of cell turnover (10).