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*A Century of*
*Nutritional Discovery for*
*Public Health*


# MMS: Biological and Impact Gaps

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# MMS Impact and Biological Gaps

Nutritional Exposures Coexist

- **Protein-energy deficits**
- **Energy Excess**
- **Micronutrient deficiencies**
  **Vitamins A, E, D,**
  **B-complex, folate,**
  **zinc, iron, iodine, others**
- **Behavioral Causes**
  Breast /complementary feeding
  SES, hygiene, education, etc
- **Food Systems Causes**
  Agricultural/animal husbandry,
  seasonality, infrastructure,
  Markets
- **Societal and Political Causes**

**Chronic disease, disabilty, mortality**

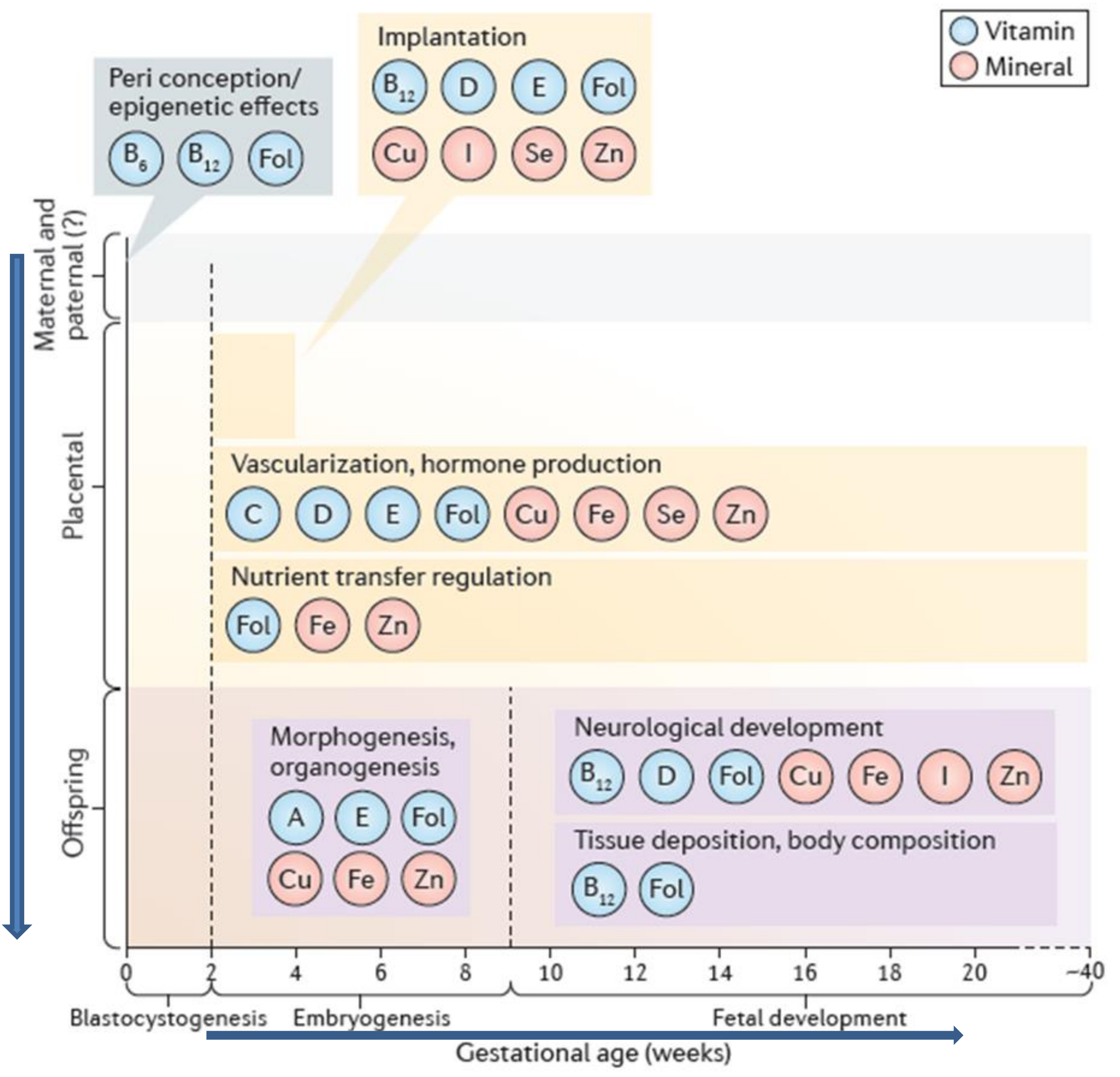
Photos: Paul Joseph Brown

Child and Maternal Health Problems

- **Infant or Child**
- Infection
- Inflammation
- Poor growth
- Impaired cognition, motor development
- Mortality

- **Adolescent or Maternal**
- Short stature
- Thinness…. overweight
- Infection/sepsis
- Obstetric problems
- Anemia
- Mortality

# Micronutrients are Essential Throughout Pregnancy & Gestation




Gernand A et al Nature Rev Epidemiol 2016

WORLD HEALTH ORGANIZATION

ORGANISATION MONDIALE DE LA SANTE

EB89/27

27 December 1991

EXECUTIVE BOARD

Eighty-ninth Session

Provisional agenda item 10.2

# NATIONAL STRATEGIES FOR OVERCOMING MICRONUTRIENT MALNUTRITION

## Vitamin A Deficiency, Iodine Deficiency and Iron Deficiency Anemia

**TABLE 1. POPULATIONS AT RISK OF AND AFFECTED BY MICRONUTRIENT MALNUTRITION, BY WHO REGION, 1991**

(millions)

| Region | Iodine deficiency disorders | | Vitamin A deficiency | | Iron-deficient or anaemic |
|---|---|---|---|---|---|
| | At risk | Affected | At risk | Affected (xerophthalmia) | |
| Africa | 150 | 39 | 18 | 1.3 | 206 |
| Americas | 55 | 30 | 2 | 0.1 | 94 |
| South-East Asia | 280 | 100 | 138 | 10.0 | 616 |
| Europe | 82 | 14 | - | - | 27 |
| Eastern Mediterranean | 33 | 12 | 13 | 1.0 | 149 |
| Western Pacific | 405 | 30 | 19 | 1.4 | 1 058 |
| Total | 1 005 | 225 | 190 | 13.8 | 2 150 |

WHO, December 1991

Ann. N.Y. Acad. Sci. ISSN 0077-8923

ANNALS OF THE NEW YORK ACADEMY OF SCIENCES
Special Issue: Annals *Reports*
ORIGINAL ARTICLE

# Setting research priorities on multiple micronutrient supplementation in pregnancy

Filomena Gomes,[1] Megan W. Bourassa,[1] Seth Adu-Afarwuah,[2] Clayton Ajello,[3] Zulfiqar A. Bhutta,[4,5] Robert Black,[6] Elisabete Catarino,[7] Ranadip Chowdhury,[8] Nita Dalmiya,[9] Pratibha Dwarkanath,[10] Reina Engle-Stone,[11] Alison D. Gernand,[12] Sophie Goudet,[13] John Hoddinott,[14] Pernille Kæstel,[15] Mari S. Manger,[16] Christine M. McDonald,[16] Saurabh Mehta,[14] Sophie E. Moore,[17] Lynnette M. Neufeld,[18] Saskia Osendarp,[19] Prema Ramachandran,[20] Kathleen M. Rasmussen,[14] Christine Stewart,[11] Christopher Sudfeld,[21] Keith West,[6] and Gilles Bergeron[1]

**Table 2.** Research questions ranked according to the final unweighted research priority score (RPS)

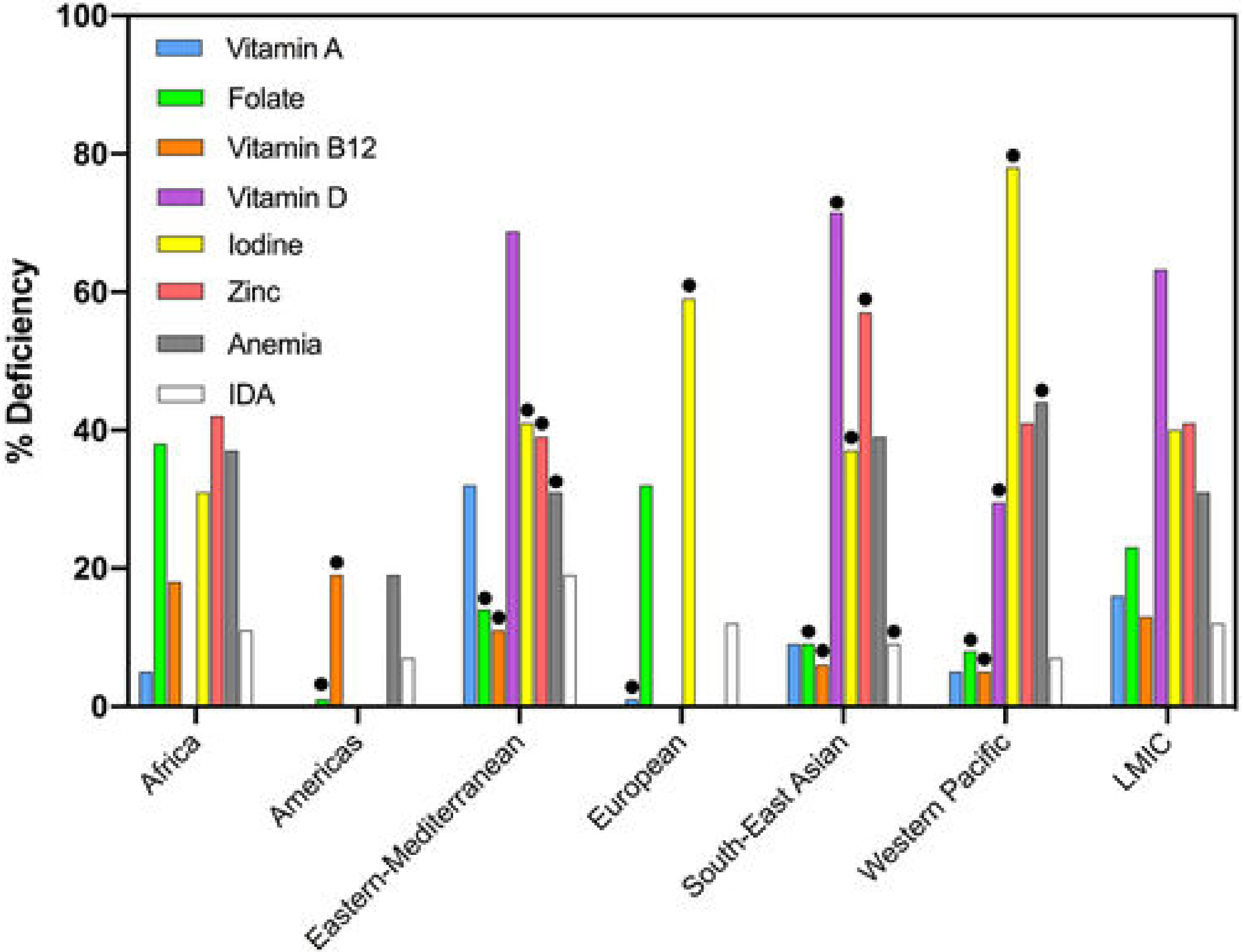
| Research priority score, unweighted (%) | Rank | AEA score | Question | Domain | Subdomain |
|---|---|---|---|---|---|
| 83.2 | 1 | 0.47 | What strategies (cash transfers, easier ANC access, free MMS, pharmacy vouchers, quality service delivery, mass media, social and behavior change communication interventions, SMS text messages, etc.) can best increase ANC attendance and adherence to MMS, including in hard-to-reach populations? | Delivery | Coverage |
| 82.8 | 2 | 0.50 | What limited set of biomarkers of nutritional status (e.g., hemoglobin) and their cutoffs can be used to identify populations that will benefit from prenatal MMS? | Description | Assessment |
| 81.1 | 3 | 0.53 | If MMS were continued through lactation, are there additional benefits for the mother and child (e.g., reduced mortality, infection, improved development, etc.)? | Discovery | Impact |
| 80.8 | 4 | 0.49 | Can community workers help identify pregnancies in the first trimester and facilitate timely ANC attendance that leads to an earlier initiation of MMS? | Delivery | Coverage |
| 79.0 | 5 | 0.43 | What is the burden of micronutrient deficiencies among pregnant women? | Description | Prevalence |

| | | | | | |
|---|---|---|---|---|---|
| 78.5 | 6 | 0.46 | What field-friendly methods can be used to assess multiple micronutrient deficiencies among pregnant women? (contrast all methods along cost-effectiveness, invasiveness, and training requirements) | Description | Assessment |
| 76.0 | 7 | 0.42 | Which essential micronutrients (e.g., biomarkers or intake) beyond iron should be routinely monitored for pregnant women? | Description | Assessment |
| 75.2 | 8 | 0.39 | Are MMS in pregnancy effective in women with low intakes of energy and protein? | Discovery | Impact |
| 74.4 | 9 | 0.49 | What are the most effective counseling strategies about the benefits of MMS in pregnancy that lead to increased adherence to the MMS regimen? | Delivery | Adherence |
| 73.6 | 10 | 0.42 | What MMS dosage (timing and duration) should be recommended in prepregnancy and pregnancy to achieve maximum adherence and benefits on outcomes? | Development | Implementation |
| 73.0 | 11 | 0.50 | Can human-centered design principles (focused on the needs, contexts, behaviors, and emotions of the people) be used to increase the effectiveness of behavior-change programs and increase adherence to prenatal MMS? | Delivery | Adherence |
| 73.0 | 12 | 0.47 | How can a policy framework be strengthened within a country to ensure the availability of MMS supplements? | Development | Implementation |
| 72.7 | 13 | 0.40 | To what extent do MMS benefit maternal health (not just anemia or pregnancy outcomes)? | Discovery | Impact |

| | | | | | |
|---|---|---|---|---|---|
| 71.3 | 16 | 0.42 | What is the most cost-effective packaging of MMS (i.e., blister packs or bulk packaging; 30-, 90-, or 180-count bottles, etc.) that will optimize both cost and adherence, without adversely affecting ANC attendance? | Delivery | Packaging |
| 70.9 | 17 | 0.43 | In pregnant women taking MMS who develop iron deficiency anemia, what is the ideal amount and duration of additional iron supplements? | Development | Dosage |
| 70.2 | 18 | 0.49 | What data commonly available in national surveys can be used to identify populations that will benefit from prenatal MMS? | Description | Prevalence |
| 70.2 | 19 | 0.40 | What indicators can be measured through routine health information systems to best monitor program performance in relation to MMS delivery during pregnancy (through ANC contacts)? | Delivery | Coverage |
| 69.7 | 20 | 0.42 | To what extent do infections blunt the impact of prenatal MMS in preventing anemia? | Discovery | Impact |
| 69.3 | 21 | 0.51 | What are the predictive risk factors of micronutrient deficiencies among pregnant women? | Description | Prevalence |
| 68.3 | 22 | 0.40 | Is fortification of food staples or ensuring intake of fortified foods (such as lipid-based nutrient supplements) better than providing MMS at scale, on maternal and birth outcomes? | Discovery | Formulation |
| 68.0 | 23 | 0.48 | Would pregnancy outcomes be further improved by the addition of calcium to MMS, given WHO recommendations for calcium supplementation during pregnancy to reduce the risk of preeclampsia? How would this affect adherence, costs, and stability (given iron and calcium interaction)? | Discovery | Formulation |
| 67.9 | 24 | 0.47 | Would outcomes be further improved by the addition of choline to MMS, especially with regard to child development? What would be the cost implications? | Discovery | Formulation |

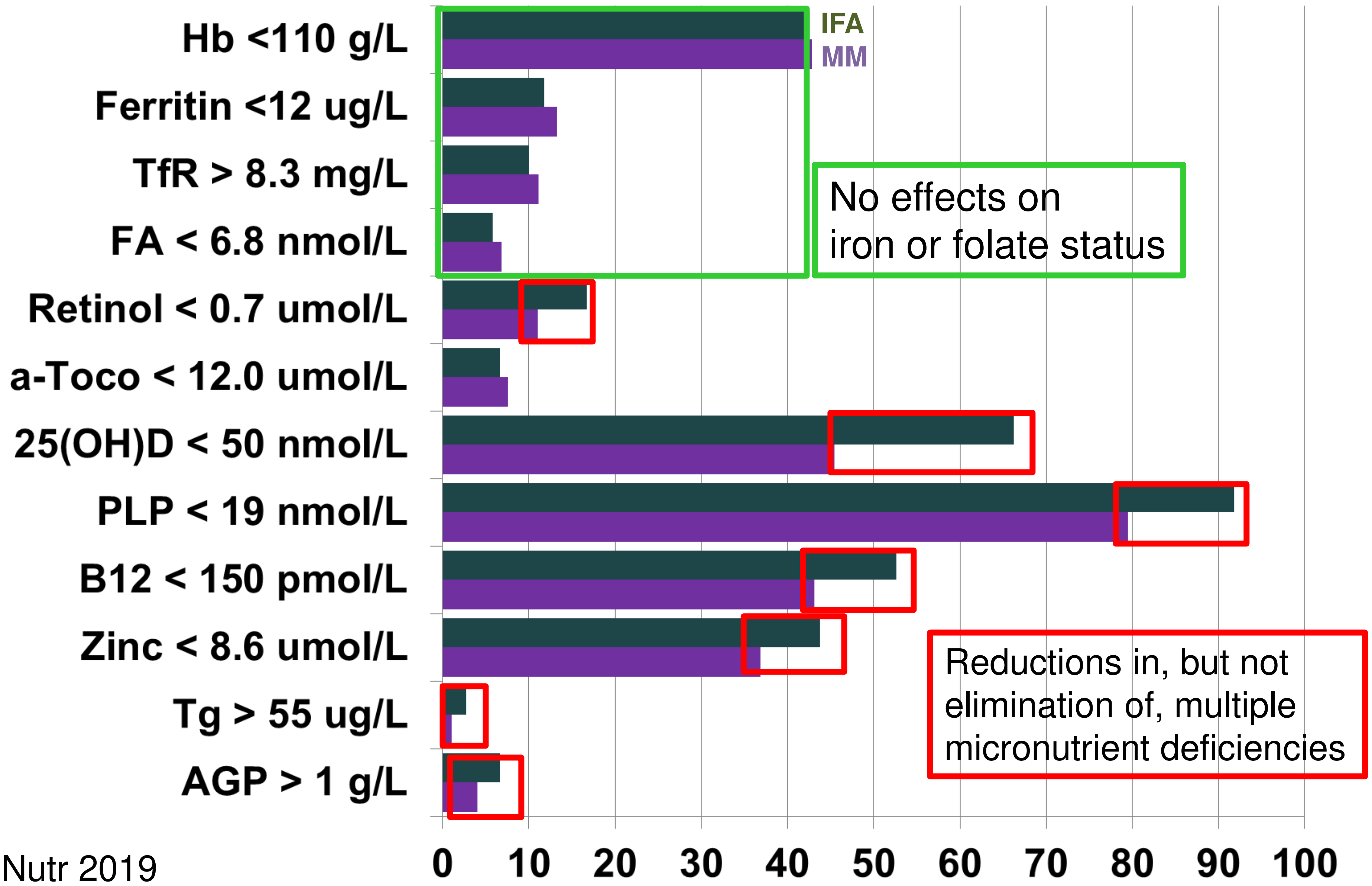
| | | | | | |
|---|---|---|---|---|---|
| 66.3 | 27 | 0.39 | Would birth outcomes be further improved by the addition of n-3 LC-PUFA to MMS, given a recent Cochrane meta-analysis showing reduction in preterm delivery with n-3 LC-PUFA supplementation? What would be the cost implications? | Discovery | Formulation |
| 65.2 | 28 | 0.35 | Are there subpopulations at risk of adverse outcomes with MMS, such as stillbirths or perinatal asphyxia? | Discovery | Impact |
| 65.1 | 29 | 0.40 | Would outcomes be further improved by the addition of magnesium to MMS? What would be the implications on adherence and costs? | Discovery | Formulation |
| 64.8 | 30 | 0.41 | Is selenium deficiency independently associated with prematurity and small-for-gestational-age? | Discovery | Impact |
| 64.3 | 31 | 0.37 | When compared with UNIMMAP, are there more cost-effective formulations? | Development | Dosage |
| 61.8 | 32 | 0.32 | What is the most appropriate dosage for each micronutrient, other than iron? | Discovery | Formulation |

# Micronutrient Deficiencies among Women of Reproductive Age – A Global View




Source: Annals NY Acad Sci, Volume: 1444, Issue: 1, Pages: 6-21, First published: 27 May 2019

# Micronutrient Deficiencies in 3rd Trimester by Supplement Group, JiVitA-3, Bangladesh




Schulze et a J Nutr 2019

# Preconception vitamin E deficiency occurs in LMICs

Animals suffering from sterility do not differ so profoundly from normal in their ovarian function as they do in placental behavior.
… the placentas are abnormal…
Resorption invariably overtakes the products of conception

Ninety-six years ago… Factor "X" was found to restore fertility in rats fed purified diets



## ON THE EXISTENCE OF A HITHERTO UNRECOGNIZED DIETARY FACTOR ESSENTIAL FOR REPRODUCTION[1]

The fact has been abundantly demonstrated that rats may be reared on a dietary regime consisting of "purified" protein, fat and carbohydrate to which an appropriate salt mixture and adequate doses of the growth vitamines Fat Soluble A and Water Soluble B have been added. We have employed a ration of casein (18), cornstarch (54) and lard (15) to which butterfat (9) and salts (4) are added, the animals receiving separately and daily .4 gram each of dried whole yeast.

Such animals are sterile. They are chiefly so in the first generation and wholly so in the next succeeding one. The sterility of dietary origin yields a highly characteristic picture. Animals suffering from it do not differ so profoundly from normal ones in their ovarian function as they do in placental behavior. Approximately the same number of Graafian follicles mature and rupture per ovulation and the ova are fertilized and implanted. The placentæ are abnormal. They may persist almost throughout gestation but show as early as the second day of their establishment beginning blood extravasations which increase in extent. Resorption invariably overtakes the products of conception.

Natural foodstuffs contain a substance, X, which prevents such a sterility or which cures the disorder occasioned by the purified dietary regime. We have thus been able to witness a comparatively sudden restoration of fertility to animals of proven sterility, and whose controls continued sterile, by the administration of fresh green leaves of lettuce. Even the dried leaves of alfalfa appear to possess a similar potency. The proven efficacy of leaves invites inquiry into the certainty of segregation of the new dietary factor from vitamines A and C. As regards A, it is conceivable that amounts of A adequate for normal growth, freedom from eye disease and, indeed, vigorous health might still be inadequate for the reproductive function. Such a conception is apparently strengthened by the reappearance of fertility which we have discovered to take place when the butterfat quota in the above diet is increased so as to constitute 24 per cent. by weight.[2] A sufficient answer to this conception, however, is afforded by our demonstration that in some dietaries reproduction may be unhindered when the A content is lower than in

[1] University of California, aided by the Dairy Division of the Bureau of Animal Industry of the United States Department of Agriculture, the Committee for Research on Sex Problems of the National Research Council and the California Central Creameries. The writers desire also to express their especial thanks to Mr. C. E. Gray, of San Francisco, and Dr. C. W. Larson, of Washington.

[2] Drummond (*Biochem. Jour.*, xiii, 77) has, for instance, reported two generations of animals reared on 20 per cent. butter in this diet.

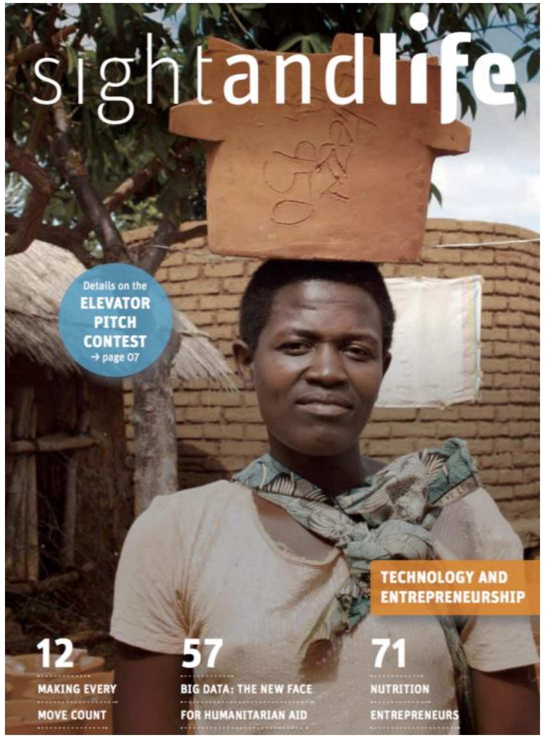
Evans HM, Bishop KS.
On the Existence of a **Hitherto Unrecognized Dietary Factor** Essential for Reproduction.
Science 1922;56:650-1

Fresh Lettuce

Dried Alfalfa

**Hypothesis: Multiple sourced, variably processed, mutli-vendored, environmentally exposed, over-cooked vegetable oils may lack vitamin E**

Photo: Dr. Klaus Kraemer, Kolkata




# Omics Innovations and Applications for Public Health Nutrition: An integrated view


**Sun Eun Lee**
Center for Human Nutrition, Department of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA


## Key messages

- Omics technologies comprise sets of molecular mapping tools that can help us understand and navigate to or from states of health, including nutriture.
- Single omics studies explore sets of genes, epigenetic marks, transcripts, proteins, or metabolites, as well as microbial communities, in an unbiased manner.
- Trans-omics studies offer opportunities to connect, integrate, and map a group of molecules across multiple omics layers to identify pathways, interactions and feedback loops that may more fully reveal the biology and, likely, suites of diagnostic markers, therapeutic targets and pathways to and from disease states.
- Omics approaches are transitioning from the theoretical level to the level of practical application to benefit vulnerable populations.
- Human studies need to be greatly expanded in number and breadth and rigorously designed to overcome methodological, analytical and biological complexities in omics data.

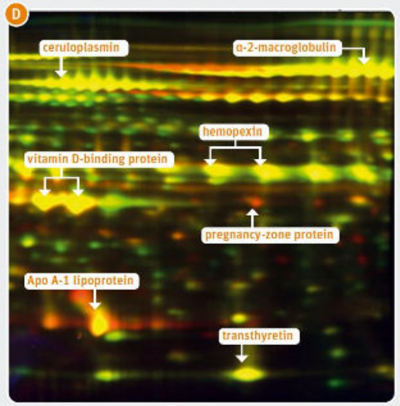
## Introduction

Let's assume that you have been taken to a place you have never been before, and are not sure how you got there. The first thing you might do is look at a Google map, which may reveal several roads leading to the place, each with outlying intersections and roads from other towns. Different overlays may reveal varying terrain, weather or road conditions throughout the region leading to your destination. Now, imagine a health problem affecting a population as your destination, and the plexus of pathways (routes), biochemical networks (towns), function (traffic flow) and other influential conditions (terrain, road upkeep, weather, etc.) that may lead to the health problem, overlaid on the map. Omics technologies comprise sets of molecular mapping tools for each overlay that can help us understand and navigate to or from states of health, including nutriture. This breakthrough approach has become possible due to advances in the development and application of high-throughput technologies, which allow us to analyze large-scale biological data to form new molecular maps to health and disease.

> "Omics technologies can help us understand and navigate to or from states of health"

Conventional hypothesis-driven studies typically focus on a few specific molecules of interest based on prior knowledge: a nutritional deficiency or excess may set into motion a genomic aberration or epigenetic change that affects RNA expression, protein synthesis, metabolite production, or certain bacterial growth (Figure 1A). Single omics studies explore sets (individual *overlays*) of genes, epigenetic marks, transcripts, proteins, or metabolites, or microbial communities, in an unbiased manner. They are data-driven and provide opportunities to discover un-

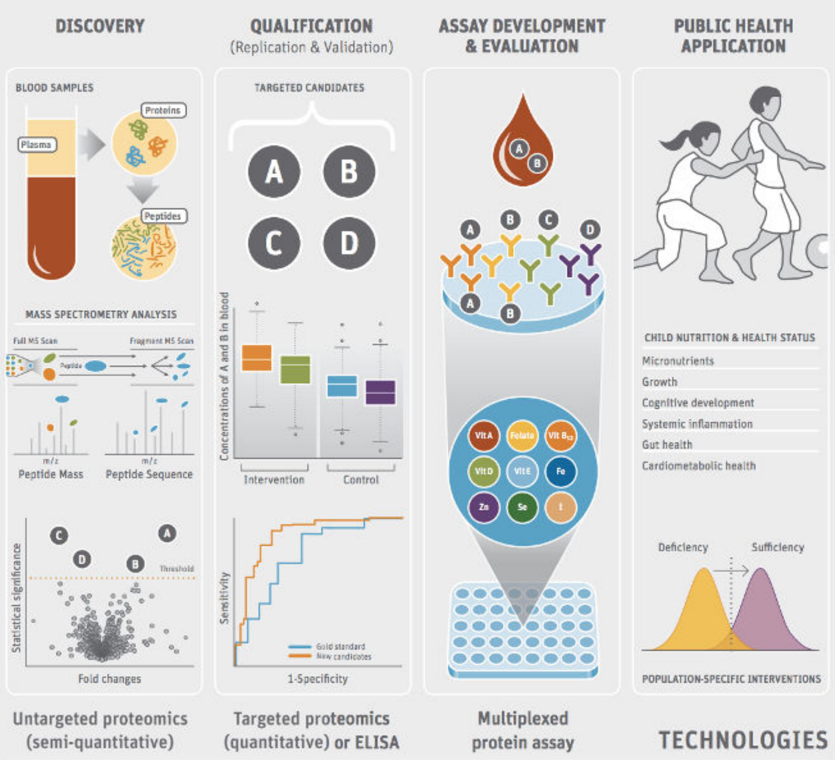



**A and B:** Children in Sarlahi, Nepal were visited in their homes for assessment of nutritional and health status including anthropometric measurements and blood sample collection.
**C:** Blood samples were processed by trained technicians at a local laboratory in Sarlahi.
**D:** Our initial proteomics work was based on two-dimensional difference in-gel electrophoresis analysis of serum samples from pregnant Nepalese women.

Photo credits: Keith P West Jr. (A, B, and C) and Robert N Cole (D)

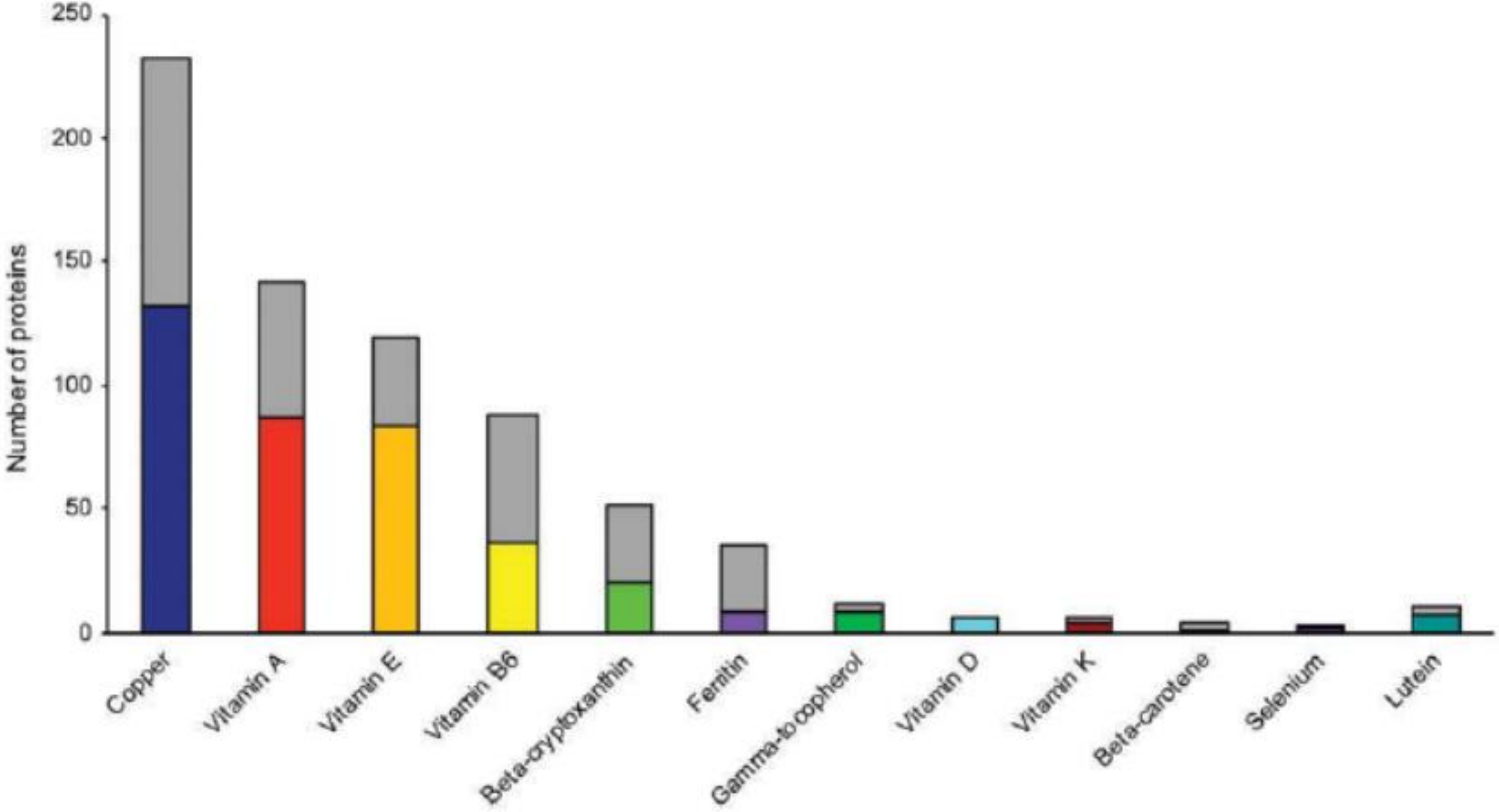
**FIGURE 2:** Conceptual workflow of the proteomics-driven development of nutrition and health assays for populations



# Plasma Proteomics

## A Future Approach to Assess Micronutrient Status and Health for Public Health Application

# Plasma Nutriproteome in Nepalese Children




Lee SE, Schulze KJ, West KP Jr Food Nutr Bull 2019

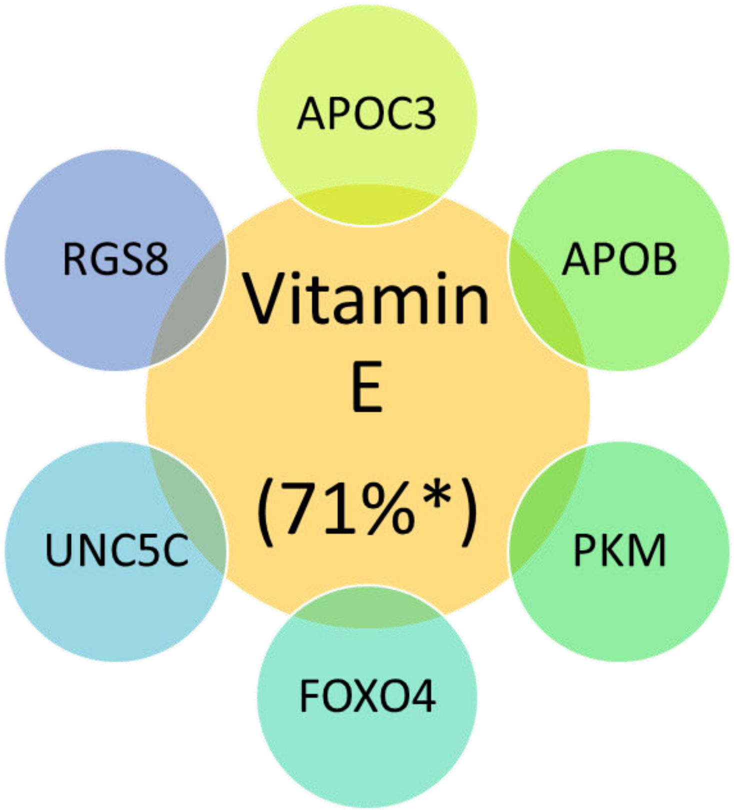
# Plasma Alpha-Tocopherome (n=119 proteins; q <0.10) in 500 Nepalese Children, 6-8 Yr of Age

**Lipid/VE transport/ metabolism**
APOA1
APOA2
APOB
APOC1
APOC2
APOC3
APOC4
APOD
APOE
RBP4
TTR
LCN2
AFM

**Cell Adhesion/ Cell-Cell Interactions**
CDH1
CD44
ICAM2
VCAM1
TGFB1
DSG2
ADAMTS

**Host Defense**
CF1
C2
C9
sCD14
TNFAIP-IP1
ORM1 (AGP)
ORM2 (AGP)
FCGR3A

**Antioxidant**
QSOX1
PKM
GSTO1
PRDX2
TXN
CAT
PON1
PON3
SEPP1




**Growth Regulation**
QSOX1
IGFBP2
IGFBP3
IGFALS

**Coagulation**
PROC
vWF
F2
F11
F13A1

**Transcription**
KLF17
FOXO4
TMF1

* Percent of variance in plasma α-tocopherol

West KP et al J Nutr 2015 doi: 10.3945/jn.115.210682

# Plasma Proteins Predict Selenium Status

Int. J. Vitam. Nutr. Res., 85 (5–6), 2015, xxx–xxx 1

Original Communication

## Plasma Selenium Protein P Isoform 1 (SEPP1): A Predictor of Selenium Status in Nepalese Children Detected by Plasma Proteomics

Kerry J. Schulze[1], Robert N. Cole[2], Raghothama Chaerkady[2], Lee S. F. Wu[1], Bareng A. S. Nonyane[3], Sun Eun Lee[1], James D. Yager[4], John D. Groopman[4], Parul Christian[1], and Keith P West, Jr[1]

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[2]Mass Spectrometry and Proteomics Core Facility, Department of Biological Chemistry, School of Medicine, Johns Hopkins University, Baltimore, MD, USA
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Received: May 19, 2015; Accepted: August 28, 2015

*Table II:* Plasma proteins associated with plasma $\log_2$ selenium in children 6–8 years old (n = 499) in rural Nepal[1].

| Name | gi Accession number[2] | Gene symbol | n | r | $R^2$ | p | q | % change[3] |
|---|---|---|---|---|---|---|---|---|
| Selenoprotein P, plasma 1[4] | 62530391 | SEPP1 | 499 | 0.79 | 0.63 | 3.48E-79 | 5.74E-06 | 106.9 |
| Glutathione peroxidase 3 | 6006001 | GPX3 | 499 | 0.60 | 0.36 | 7.70E-06 | 0.0042 | 30.3 |
| Apolipoprotein A-II | 4502149 | APOA2 | 499 | 0.59 | 0.35 | 0.00014 | 0.039 | 22.8 |

SEPP1 predicts 63% of plasma selenium concentration

Schulze KJ et al Intl J Vit Nutr Res 2016

# Maternal Multiple Micronutrient Supplementation Stabilizes Mitochondrial DNA Copy Number in Pregnant Women in Lombok, Indonesia

J Nutr 2019

Lidwina Priliani,[1,2] Elizabeth L Prado,[3,4] Restuadi Restuadi,[1,5] Diana E Waturangi,[2] Anuraj H Shankar,[3,6] and Safarina G Malik[1]

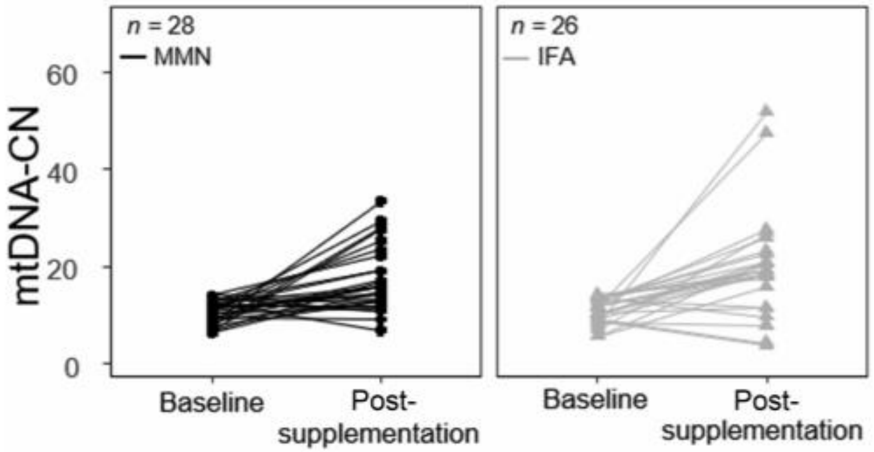
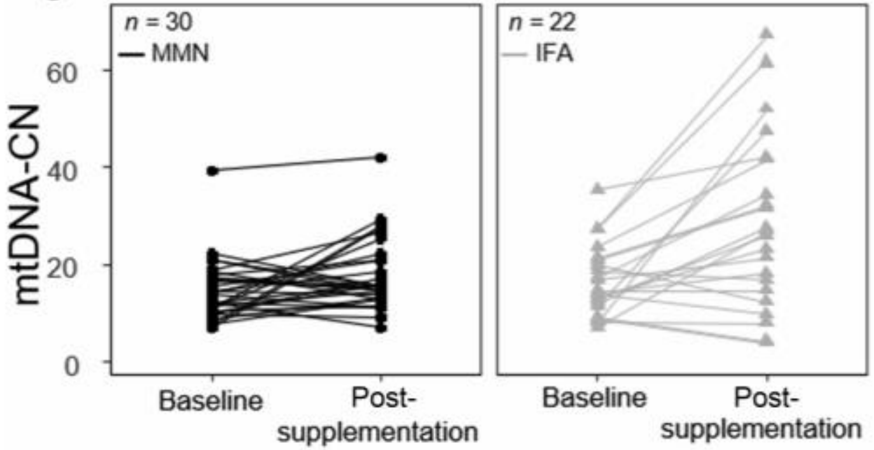



**TABLE 3** The Δ mtDNA-CN proportions of 108 pregnant women enrolled in the Supplementation with Multiple Micronutrients Intervention Trial study by supplementation group

| MtDNA-CN change[1] | Supplement: MMN ($n = 54$) | Supplement: IFA ($n = 54$) |
|---|---|---|
| >10% decrease | 14 (25.9) | 13 (24.1) |
| No change | 12 (22.2) | 3 (5.6) |
| >10% increase | 27 (51.9) | 38 (70.4) |
| $P$[2] | 0.021 | |

C




# Antenatal Micronutrients and the Mitochondrial Genome: A Glimpse of Future Nutritional Investigation

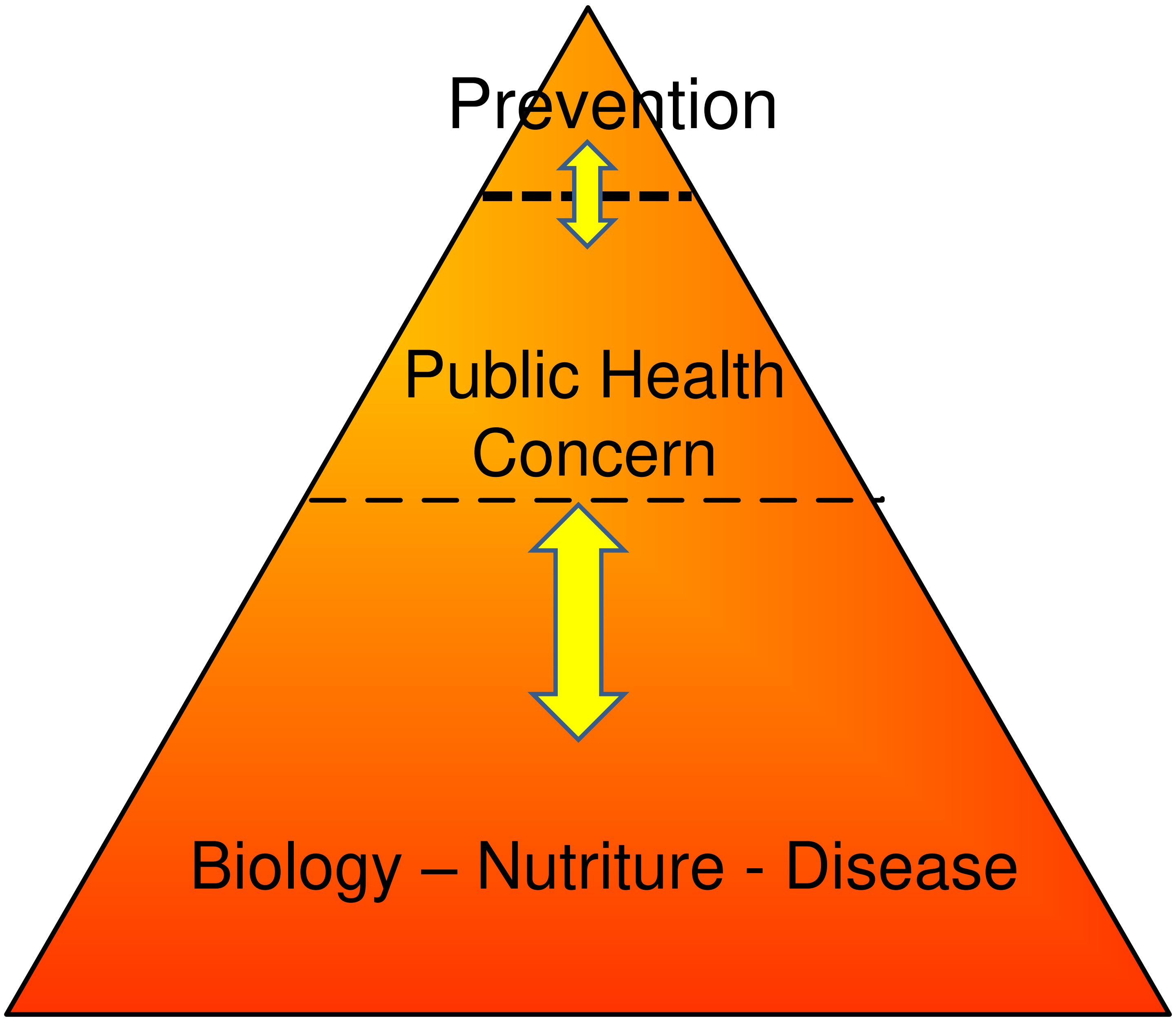
J Nutr 2019

Sun Eun Lee,[1] Michael F Fenech,[2] and Keith P West, Jr[1]

**MMS may improve health of materno-placental mitochondria and, thus, bioenergetics of pregnancy**

# Distillation of Biological & Impact Gaps

- Reveal Hidden Hunger: before, during after pregnancy; children, leading to accurate and timely estimates of extent
- Preconceptional MMS impact
- Optimization of dosage for health: eg 1 or more RDA?
- Contextualization: diet, status, dominant diseases, resources
- Additional nutrient frontiers: Calcium, magnesium, redox agents
- Micronutrient-inflammation interactions/implications
- Extended postnatal, life stage effects of MMS
- Effects of MMS in nutrition transition societies
- Implications of anemia – by cause
- Plausible biological mechanisms/pathways of MMS


Prevention
Public Health
Concern
Biology – Nutriture - Disease