Sponsor Note
This publication was supported by an unrestricted educational grant by the Nestlé Nutrition Institute. The institute is a not-for-profit association which was created to provide medical and scientific information to health professionals in the field of pediatric, adult and sports nutrition with latest information on nutrition and nutrition-related disorders (available at www.nestlenutrition-institute.org).
Any liability of the sponsors for the content of the papers is hereby expressly excluded.

Disclosure Statement Guest Editors
Jacob C. Seidell has no conflicts of interest to declare. Jörg Spieldenner is employed by Nestec SA at the Nestlé Research Center, Lausanne, Switzerland.
Contents

5 Editorial
Seidell, J.C. (Amsterdam)

6 Focus on: The Global Burden of Obesity and the Challenges of Prevention
Seidell, J.C.; Halberstadt, J. (Amsterdam)

7 The Global Burden of Obesity and the Challenges of Prevention
Seidell, J.C.; Halberstadt, J. (Amsterdam)

13 Focus on: Gestational Diabetes Mellitus and Macrosomia: A Literature Review
KC, K.; Shakya, S.; Zhang, H. (Chongqing)

14 Gestational Diabetes Mellitus and Macrosomia: A Literature Review
KC, K.; Shakya, S.; Zhang, H. (Chongqing)

21 Focus on: The Epidemiology of Global Micronutrient Deficiencies
Bailey, R.L. (Bethesda, Md./Baltimore, Md.); West, K.P.; Black, R.E (Baltimore, Md.)

34 Focus on: Food Fortification for Addressing Iron Deficiency in Filipino Children: Benefits and Cost-Effectiveness
Detzel, P. (Lausanne); Wieser, S. (Zürich)

35 Food Fortification for Addressing Iron Deficiency in Filipino Children: Benefits and Cost-Effectiveness
Detzel, P. (Lausanne); Wieser, S. (Zürich)

The above articles were originally published as a supplementary issue of Annals of Nutrition and Metabolism and are reprinted here with permission.
The Nestlé Nutrition Institute was created to provide health professionals with up-to-date information on nutrition and nutrition-related disorders in order to enable them to continuously improve patient care based on the latest medical and scientific developments.

One of the key pillars of the Nestlé Nutrition Institute is *Annales Nestlé*, a pediatric journal that has been published on a regular basis since 1942. It contains review articles on clinical practice and research in all fields of pediatrics with focus on nutrition.

*Annales Nestlé* comprises 3 issues each year and with around 50,000 copies per issue, it is one of the most widely read pediatric journals in the world.

*Annales Nestlé* is edited by an independent editorial board of opinion leaders in pediatric research, thus guaranteeing the medical and scientific impartiality of the journal, and hence the high level of respect and appreciation in medical and scientific circles. The editorial board sets the editorial policy, identifies topics to be addressed, selects authors and is in charge of the review process of each publication.

As of 2011, *Annales Nestlé* is published as a supplement of *Annals of Nutrition and Metabolism* and can be accessed online in PubMed.

We are pleased to offer you our innovative design, which results from a creative and effective cooperation with *Karger Publishers, Switzerland*.

*Natalia Wagemans, MD*
Head of
Nestlé Nutrition Institute
Vevey (Switzerland)
In this issue, the proceedings of a meeting on global nutritional problems are presented. They deal with several problems that long were thought to be mutually exclusive: undernutrition and overnutrition. The first was considered to be a problem related to poverty which may result in inadequate intake of energy and/or micronutrients and strenuous labor. Chronic noncommunicable diseases were associated with affluence and related overconsumption of food and sedentary lifestyles. The papers in this issue show that this is no longer a useful distinction. In fact, in many circumstances, especially in low- and middle-income countries, people have access to energy-dense but, at the same time, nutrient-poor foods. There is an increasing trend in developing countries, where the demographic and socioeconomic transition imposes more constraints on dealing with the double burden of infectious and noninfectious diseases as well as malnutrition in a poor environment, characterized by ill-health systems. It is predicted that, by 2020, noncommunicable diseases will cause seven out of every ten deaths in developing countries. Among noncommunicable diseases, special attention is devoted to cardiovascular disease, diabetes, cancer and chronic pulmonary disease. The burden of these conditions affects countries worldwide but with a growing trend in developing countries. Preventative strategies must take into account the growing trend of risk factors correlated to these diseases. In parallel, despite the success of vaccination programs for polio and some childhood diseases, other diseases like AIDS, tuberculosis, malaria and dengue are still out of control in many regions of the world. In addition, preventing and combatting micronutrient deficiencies is of great importance.

A life course approach to combatting under- and overnutrition is essential. This is illustrated by the paper by KC et al. that focuses on gestational diabetes and macrosomia. Many noncommunicable diseases have their origins in utero. Intrauterine growth retardation resulting in low-birth-weight babies as well as macrosomia (high birth weight) are associated with an increased risk of obesity, type 2 diabetes and cardiovascular disease in the offspring. The paper by Seidell and Halberstadt shows that obesity is an increasing problem in children around the world. Similarly, the paper by Bailey et al. shows that the global problem of micronutrient deficiencies starts early in life with lifelong consequences.

Both under- and overnutrition greatly contribute to the global burden of disease with severe global economic consequences. These do not only relate to the direct costs associated with the medical consequences of malnutrition but also to the indirect costs of reduced productivity of those affected. The paper by Detzel and Wieser in this issue illustrates that combatting iron deficiency by food fortification can be cost-effective.

Jacob C. Seidell
The occurrence of obesity in an individual or in populations is a result of combinations of factors at multiple levels of influence.

Reprinted with permission from: Ann Nutr Metab 2015;66(suppl 2):7–12
The Global Burden of Obesity and the Challenges of Prevention
by Jacob C. Seidell and Jutka Halberstadt

Key insights
The occurrence of obesity in an individual or in a population is the result of a combination of factors acting at multiple levels. The simultaneous increase in obesity around the world appears to be driven by changes in the global food supply, which is offering more processed, affordable and nutrient-dense foods. This, in combination with sociocultural, environmental and economic factors, affects eating behavior and physical activity. These multifactorial drivers of obesity suggest the need for interventions that reset the environmental and societal norms, to facilitate healthy behaviors.

Current knowledge
During the 28-year period from 1980 to 2008, the worldwide prevalence of obesity has nearly doubled. In 2008, an estimated 1.5 billion adults had a body mass index (BMI) of 25 or more, and of these, around 500 million are considered obese. No longer an affliction of the wealthy, obesity has risen dramatically in developing countries and, furthermore, is becoming increasingly prevalent in children and adolescents.

Practical implications
The most recent classification of overweight adults by the WHO applies BMI cutoff points as the universally accepted measure of degree of overweight. However, these measures need to be tailored for specific populations: for example, at a given BMI, Asians may have vastly different levels of fatness and a distinct fat distribution compared to Caucasians. Research has suggested that abdominal fat distribution needs to be taken into account for an accurate classification of overweight and obesity with respect to actual health risks. Effective treatment for obesity employs a combination of lifestyle intervention and, when appropriate, additional medical therapies such as medication and bariatric surgery.

Recommended reading
The Global Burden of Obesity and the Challenges of Prevention

Jacob C. Seidell    Jutka Halberstadt

Department of Health Sciences, VU University, Amsterdam, The Netherlands

Key Words
Obesity · Prevalence · Epidemiology · Prevention

Abstract
The prevalence of obesity is increasing at an alarming rate in many parts of the world. About 2 billion people are overweight and one third of them obese. The plight of the most affected populations, like those in high-income countries in North America, Australasia and Europe, has been well publicized. However, the more recent increases in population obesity in low- and middle-income countries that are now increasingly being observed have been less recognized.

Based on the existing prevalence and trend data and the epidemiological evidence linking obesity with a range of physical and psychosocial health conditions, it is reasonable to describe obesity as a public health crisis that severely impairs the health and quality of life of people and adds considerably to national health-care budgets. Intersectoral action to manage and prevent obesity is urgently required to reverse current trends.

Global Prevalence of Obesity
Over the last three to four decades, overnutrition and obesity have been transformed from relatively minor public health issues that primarily affected the most affluent societies to a major threat to public health that is being increasingly seen throughout the world. The plight of the most affected populations, like those in high-income countries in North America, Australasia and Europe, has been well publicized. However, the more recent increases in population obesity in low- and middle-income countries that are now increasingly being observed have been less recognized.

Two relatively recent papers documented the global prevalence of obesity [1, 2]. The Global Burden of Metabolic Risk Factors of Chronic Diseases Collaborating Group analyzed data from 199 countries and territories and 9.1 million adults with respect to the prevalence of overweight and obesity between 1980 and 2008 [1]. During that 28-year period, the prevalence of obesity nearly doubled worldwide. In 2008, about 1.5 billion adults were...
estimated to have a body mass index (BMI) of 25 or more (about 34%). Of these, 500 million were considered obese (about 10% in men and 14% in women).

In 2008, the highest rates of obesity in women were observed, in descending order of magnitude, in Southern Africa, North Africa and the Middle East, Central Latin America, North America (US and Canada) and Southern Latin America. In men, the top 5 regions were North America (US and Canada), Southern Latin America, Australasia, Central Europe and Central Latin America. Note that many of these regions comprise low- or middle-income countries.

More recently, the analyses for the Global Burden of Disease Study 2013 [2] further documented that worldwide, the proportion of adults with a BMI of 25 or greater increased between 1980 and 2013 from about 29 to 37% in men and from about 30 to 38% in women. These estimates are slightly higher than those calculated by Finucane et al. [1]. The estimates by Ng et al. [2] may reflect further increases between 2008 and 2013, but this may also be due to methodological differences between the two studies. In adults, the estimated prevalence of obesity exceeded 50% in men in Tonga (Polynesia) and in women in some countries in the Middle East, Polynesia and Micronesia. Since 2006, the increase in adult obesity seems to have leveled off in several high-income countries, but the incidence generally remains higher than in most low- and middle-income countries.

**The proportion of adults with a BMI of 25 or greater increased between 1980 and 2013 from about 29 to 37% in men and from about 30 to 38% in women.**

In the analyses for the Global Burden of Disease Study [2], estimates were also made of the global prevalence of overweight and obesity in children and adolescents. Ng et al. [2] showed that among children and adolescents in developed countries, the prevalence in 2013 was high; about 24% of boys and 23% of girls were either overweight or obese. In general, the prevalence of overweight and obesity had increased considerably since 1980. There were, however, large differences in the prevalence of obesity and secular trends. The prevalence of overweight and obesity had also increased in children and adolescents in developing countries, from about 8% in 1980 to 13% in 2013 for boys and girls.

Ng et al. [2] estimated that in 2013, more than 2 billion people in the world were overweight or obese and about 671 million of them were obese.

About 25 years ago, obesity was considered to be particularly a problem of high-income countries. In those high-income countries, as illustrated by Molarius et al. [3], an inverse association was seen between obesity and socioeconomic status, particularly in women. In contrast, in low- and middle-income countries, the prevalence of obesity tended to be low and was confined to those with relatively high socioeconomic status [4]. Monteiro et al. [4] were among the first to show that this was no longer true in 2003 and that obesity had also become a problem of lower socioeconomic groups, particularly of women in middle-income countries. More recently, Dinsa et al. [5] observed that by 2012, the association between socioeconomic status and obesity remained positive for both men and women in low-income countries. However, in middle-income countries, the association varied greatly in men and was generally negative in women. In children and adolescents, however, obesity remained predominantly a problem of those with relatively high socioeconomic status in low- and middle-income countries.

The epidemiology of obesity has for many years been difficult to study because many countries had their own specific criteria for the classification of different degrees of overweight. Gradually, during the 1990s, however, the BMI (weight/height²) became a universally accepted measure of the degree of overweight, and now, identical cutoff points are generally recommended. This most recent classification of overweight in adults by the World Health Organization (WHO) is given in table 1 [6]. In many community studies in affluent societies, this scheme has been simplified and cutoff points of 25 and 30 are used for descriptive purposes. Both the prevalence of a very low BMI (<18.5) and of a very high BMI (40 or higher) is usually low, in the order of 1–2% or less.

A WHO expert consultation [7] acknowledged that, at a given BMI, people from Asian populations may have vastly different levels of fitness and a different fat distribution compared to Caucasian populations. This, at least in part, may result in similar health risks in Asians at lower levels of BMI than in Caucasian populations. The consultation concluded that the proportion of Asian people with a high risk of type 2 diabetes and cardiovascular disease is substantial at BMIs lower than the existing WHO cutoff point for overweight (BMI ≥25). However, available data do not necessarily indicate a clear BMI cutoff point for all Asians for overweight or obesity. The cutoff point for moderate health risk varies with a...
BMI of 22–25 in different Asian populations; for high risk, it varies with a BMI of 26–31. Because of the large variations in associations between BMI and health risks in Asian populations, no attempt has been made, therefore, to redefine cutoff points for each population separately.

However, the Asia Pacific Cohort Studies Collaboration has proposed that the international classification of obesity should be adapted for Asian countries [8]. They indicated that, in Asian populations, overweight should be classified as a BMI above 23 and obesity as a BMI of 25 or higher. If such a classification was applied, the prevalence of obesity (BMI ≥ 25) in Japan would be substantially higher (over 20% rather than 2–3%) [9]. The global prevalence of obesity may, therefore, be vastly underestimated because many people in Asia may be inappropriately classified by their level of BMI.

Several countries such as China have adopted their own cutoff points for the classification of BMI. Xi et al. [10], for example, defined obesity in China as a BMI >27.5. They analyzed data from the China Health and Nutrition Survey which was conducted from 1993 to 2009. The prevalence of obesity increased during this period from about 3 to 11% in men and from 5 to 10% in women. Similar trends were seen in all age groups and regions.

Not only is the classification of BMI problematic because of ethnic variations in body composition, but much research over the last decade has suggested that, for an accurate classification of overweight and obesity with respect to the health risks, one needs to factor in abdominal fat distribution as well. Traditionally, this has been indicated by a relatively high waist-to-hip circumference ratio. It has been proposed that the waist circumference alone may be a better and simpler measure of the health risks associated with abdominal fatness [11]. In 1998, the US National Institutes of Health (National Heart, Lung, and Blood Institute) adopted the BMI classification and combined this with waist cutoff points [12]. In this classification, the combination of overweight (BMI between 25 and 30) and moderate obesity (BMI between 30 and 35) with a large waist circumference (≥102 cm in men or ≥88 cm in women) is proposed to carry additional risk [12]. Also, these waist cutoff points may have to be ethnicity specific [7].

### Health Consequences of Obesity

The increase in obesity worldwide has an important impact on health impairment and reduced quality of life [13, 14]. In particular, obesity has an important contribution to the global incidence of cardiovascular disease, type 2 diabetes mellitus, cancer, osteoarthritis, work disability and sleep apnea. Obesity has a more pronounced impact on morbidity than on mortality. Visscher and Seidell [13] predicted in 2001 that disability due to obesity-related cardiovascular diseases would increase particularly in industrialized countries, as patients survive cardiovascular diseases in these countries more often than in nonindustrialized countries. Disability due to obesity-related type 2 diabetes, they argued, would also increase, particularly in low- and middle-income countries, as insulin supply is usually insufficient in these countries. As a result, in these countries, an increase in disabling nephropathy, arteriosclerosis, neuropathy and retinopathy is expected. Increases in the prevalence of obesity will potentially lead to an increase in the number of years that subjects suffer from obesity-related morbidity and disability [13]. The Global Burden of Disease Study and the WHO have recently documented that obesity is indeed a major contributor to ill-health, disability and mortality in many regions of the world [15, 16].

### Prevention of Obesity

Adequate management of obesity as a chronic condition for those who are already obese is important and requires the principles of integrated care for disease management [17]. An example of a national approach towards the management of obesity is the integrated health-care standard for obesity in the Netherlands. This standard involves strategies for early detection, diagnosis and treatment of obesity. Following the principles of stepped care, the preferred treatment is a combined lifestyle intervention and, when appropriate, additional medical therapies such as medication and bariatric surgery can be applied.

<table>
<thead>
<tr>
<th>Classification</th>
<th>BMI</th>
<th>Associated health risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt;18.5</td>
<td>Low (but risk of other clinical problems increased)</td>
</tr>
<tr>
<td>Normal range</td>
<td>18.5–24.9</td>
<td>Average</td>
</tr>
<tr>
<td>Overweight</td>
<td>25.0 or higher</td>
<td></td>
</tr>
<tr>
<td>Preobese</td>
<td>25.0–29.9</td>
<td>Increased</td>
</tr>
<tr>
<td>Obese class I</td>
<td>30.0–34.9</td>
<td>Moderately increased</td>
</tr>
<tr>
<td>Obese class II</td>
<td>35.0–39.9</td>
<td>Severely increased</td>
</tr>
<tr>
<td>Obese class III</td>
<td>40 or higher</td>
<td>Very severely increased</td>
</tr>
</tbody>
</table>
Combined lifestyle interventions target physical activity as well as diet and include psychological techniques such as motivational interviewing and cognitive behavioral therapy. The intervention phase, with a focus on behavior change and weight loss, is followed by a phase of relapse prevention and, if necessary, long-term behavioral and weight maintenance support. Implementation of such a standard transcends traditional boundaries of conventional health-care systems and health-care professions but, instead, focuses on competences of groups of health professionals who organize care from a patient-oriented perspective [17].

From a public health perspective, a sustainable approach towards effective prevention is a more affordable strategy. In order to adequately prevent obesity, the upstream causal factors need first to be identified. Swinburn et al. [18] have pointed out that the simultaneous increases in obesity in almost all countries seem to be driven mainly by changes in the global food supply, which is offering more processed, affordable and effectively marketed food than ever before. Energy-dense palatable foods lead to overconsumption which, in turn, contributes to weight gain and obesity. Factors in the global food system combined with local environmental factors result in large differences in obesity prevalence between populations.

Individuals respond to local environmental factors like sociocultural and economic factors and the physical environment (fig. 1). Glass and McAtee [19] constructed a multilevel model that is useful for addressing the complex, interacting contexts for obesity prevention. This integrates biological and socioenvironmental (economics, culture, social networks and features of the physical environment) influences on behaviors such as eating and physical activity [19, 20].

The purchase and consumption of foods are influenced by many factors such as price, palatability and habits shaped by culture and ethnicity. These factors interact not only linearly but influence each other in many different ways. The multilevel model views obesity as a result of individuals who interact with each other and with environmental factors as organisms in an ecosystem. Such a systems approach illustrates that a single cause of the obesity epidemic is unlikely. It also suggests that the occurrence of obesity in an individual or in populations is a result of combinations of factors at multiple levels of influence [20]. How many people become obese is usually a consequence of environmental factors; who becomes obese is usually more strongly related to biological (i.e., genetic) factors. This lack of one single causal factor also implies that single interventions are unlikely to have more than only a small overall impact on their own. A systemic, sustained portfolio of initiatives, delivered at scale, is needed to address obesity prevention. Interventions are needed that rely less on education and personal responsibility of individuals but more on changes to the environment and societal norms. Such interventions ‘reset the defaults’ to make healthy behaviors easier. In a recent report of the McKinsey Global Institute [21], it was suggested that such interventions should include reducing default portion sizes, changing marketing practices and restructuring urban and educational environments to facilitate physical activity. In the report, it was argued that ‘no individual sectors in society, whether they are governments, retailers, consumer-goods companies, restaurants, employers, media organizations, educators, health-care providers, or individuals, can address obesity on their own’ [21].

A combination of top-down corporate and government interventions with bottom-up community-led ones is most likely to be successful. One of the existing integrated approaches which combine top-down and bottom-up community activities is the EPODE initiative [22]. EPODE (Ensemble Prévenons l’Obésité Des Enfants or Together Let’s Prevent Childhood Obesity) is a large-scale, centrally coordinated, capacity-building approach.

Fig. 1. Graphic representation of environmental influences interacting with individual biology and the effects on behavior and body weight.
for communities to implement effective and sustainable strategies to prevent childhood obesity. Since 2004, EPODE has been implemented in over 500 communities in 6 countries. This approach is based on four pillars [22]:

1. Political commitment: gaining formal political commitment at central and local levels from the leaders of the key organization(s), which influence national, federal or state policies as well as local policies, environments and childhood settings;

2. Resources: securing sufficient resources to fund central support services and evaluation, as well as contributions from local organizations to fund local implementation;

3. Support services: planning, coordinating and providing the social marketing, communication and support services for community practitioners and leaders;

4. Evidence: using evidence from a wide variety of sources to inform the delivery of EPODE and to evaluate process, impact and outcomes of the EPODE program.

Many countries are now adopting this approach. In each country, EPODE combines a top-down and a bottom-up approach. EPODE methodology promotes the involvement of multiple stakeholders coordinated at the national level (e.g. with endorsement from ministries and support from health groups, nongovernmental organizations and private partners), and the program benefits

---

**Fig. 2.** Methodology of EPODE in the form of a concise logic model covering four critical components: political commitment, public and private partnerships, social marketing and evaluation (source: Van Koperen et al. [23]; reproduced with permission from Wiley Publishers).
from a scientific advisory committee (a group of specialists and academics from different disciplines) [22]. Its core, however, is a local approach targeting families and schools in neighborhoods. Van Koperen et al. [23] described the methodology in the form of a concise logic model (fig. 2) covering four critical components: political commitment, public and private partnerships, social marketing and evaluation. Such a logic model suggests a series of activities and inputs that follow a linear causal path, but this is not the case. There are many feedback loops in the different stages of the model. The EPODE logic model presented here can be used as a reference for future and follow-up research; to support future implementation of EPODE in communities; as a tool in the engagement of stakeholders and to guide the construction of a locally tailored evaluation plan.

Because of the large impact of obesity on population health across the world, an effective strategy to prevent and manage the epidemic is urgently needed. No single country has been able to show a significant decrease in the prevalence of obesity as a result of comprehensive policies. Intersectoral action to manage and prevent obesity is urgently required to reverse current trends.

**Disclosure Statement**
The authors have no conflicts of interest to declare.

---

**References**


Macrosomic fetuses in diabetic pregnancies develop a unique pattern of overgrowth, involving the central deposition of subcutaneous fat in the abdominal and interscapular areas.


**Gestational Diabetes Mellitus and Macrosomia: A Literature Review**

by Kamana KC et al.

---

**Key insights**

Fetal macrosomia is a term used to define newborns who are significantly larger than average (birth weight ≥4,000 g). Between 15 and 45% of newborns of mothers with gestational diabetes mellitus (GDM) are macrosomic (in comparison to 12% of newborns of normal mothers). Macrosomic infants of women with GDM have a higher risk of becoming overweight or obese at a young age and are more likely to develop type II diabetes later in life. The findings from several studies suggest that epigenetic alterations in different fetal genes could result in the transmission of GDM and type II diabetes from mothers to their offspring.

**Current knowledge**

In mothers with GDM, the higher levels of blood glucose pass through the placenta into the fetal circulation. From the second trimester onwards, the fetal pancreas responds to the hyperglycemia by secreting insulin, resulting in hyperinsulinemia. This combination of hyperinsulinemia and hyperglycemia leads to an increase in the fat and protein stores of the fetus, resulting in macrosomia. Many studies have explored the impact of GDM and fetal macrosomia and shown the effects on maternal and fetal health.

**Practical implications**

For the infant, macrosomia increases the risk of shoulder dystocia, clavicle fractures and brachial plexus injury and increases the need for admission to neonatal intensive care units. For the mother, the risks associated with macrosomia are caesarean delivery, postpartum hemorrhage and vaginal lacerations. There are several recommendations for the management of macrosomia to prevent maternal and fetal birth trauma, including induction of labor and elective caesarean section. Strict regulation of maternal blood glucose levels can limit perinatal adverse outcomes. Newborns of GDM mothers should undergo full physical examination including evaluation for congenital anomalies, hypoglycemia, polycythemia, hyperbilirubinemia and electrolyte abnormalities.

---

**Recommended reading**

Gestational Diabetes Mellitus and Macrosomia: A Literature Review

Kamana KC, Sumisti Shakya, Hua Zhang

Department of Obstetrics and Gynecology, Canada-China-New Zealand Joint Laboratory of Maternal and Fetal Medicine, The First Affiliated Hospital of Chongqing Medical University, and Department of Obstetrics and Gynecology, The Second Affiliated Hospital of Chongqing Medical University, Chongqing, PR China

Abstract

Background: Fetal macrosomia, defined as a birth weight ≥4,000 g, may affect 12% of newborns of normal women and 15–45% of newborns of women with gestational diabetes mellitus (GDM). The increased risk of macrosomia in GDM is mainly due to the increased insulin resistance of the mother. In GDM, a higher amount of blood glucose passes through the placenta into the fetal circulation. As a result, extra glucose in the fetus is stored as body fat causing macrosomia, which is also called ‘large for gestational age’. This paper reviews studies that explored the impact of GDM and fetal macrosomia as well as macrosomia-related complications on birth outcomes and offers an evaluation of maternal and fetal health.

Summary: Fetal macrosomia is a common adverse infant outcome of GDM if unrecognized and untreated in time. For the infant, macrosomia increases the risk of shoulder dystocia, clavicle fractures and brachial plexus injury and increases the rate of admissions to the neonatal intensive care unit. For the mother, the risks associated with macrosomia are cesarean delivery, postpartum hemorrhage and vaginal lacerations. Infants of women with GDM are at an increased risk of becoming overweight or obese at a young age (during adolescence) and are more likely to develop type II diabetes later in life. Besides, the findings of several studies that epigenetic alterations of different genes of the fetus of a GDM mother in utero could result in the transgenerational transmission of GDM and type II diabetes are of concern.

Key Messages

- Fetal macrosomia, resulting from fetal hyperinsulinemia in response to maternal diabetes, might be a predictor of later glucose intolerance.
- Maternal diabetes during pregnancy can lead to a transgenerational transmission of diabetes risk.
- Fetuses of obese women with gestational diabetes mellitus have a higher risk of developing macrosomia than those of nonobese women with gestational diabetes mellitus.

Key Words

Gestational diabetes mellitus · Large for gestational age · Macrosomia · Hyperglycemia · Obesity · Pregnancy · Epigenetics

Introduction

Gestational diabetes mellitus (GDM) is defined as glucose intolerance of variable degrees with an onset, or first recognized, during pregnancy. About 15–45% of babies born to diabetic mothers can have macrosomia, which is
a 3-fold higher rate when compared to normoglycemic controls. Macrosomia is typically defined as a birth weight above the 90th percentile for gestational age or >4,000 g.

Unlike maternal hyperglycemia, maternal obesity has a strong and independent effect on fetal macrosomia [1]. Gestational age at delivery, maternal pre-pregnancy body mass index (BMI), pregnancy weight gain, maternal height, hypertension and cigarette smoking also have a significant impact. When obese women were compared to normal-weight women, the newborns of obese women had more than double the risk of macrosomia compared to those of women with normal weight [2].

In addition, there appears to be a role for excessive fetal insulin levels in causing accelerated fetal growth. In a study which compared umbilical cord sera in infants of diabetic mothers and controls, the heavier, fatter babies from diabetic pregnancies were also hyperinsulinemic [7].

Pathophysiology of GDM
The exact mechanisms behind GDM still remain unclear. The following maternal and fetal-placental factors are interrelated and act in an integrated manner in the development of insulin resistance and GDM.

The Role of the Fetal-Placental Unit in the Development of GDM
During pregnancy, as gestational age progresses, the size of the placenta increases. There is a rise in the levels of pregnancy-associated hormones like estrogen, progesterone, cortisol and placental lactogen in the maternal circulation [8, 9] accompanied by an increasing insulin resistance. This usually begins between 20 and 24 weeks of gestation. As the mother goes through parturition and delivers the fetus, the placental hormone production stops, and so does the illness of GDM, which strongly suggests that these hormones cause GDM [10].

Human placental lactogen raises approximately 10-fold in the second half of the pregnancy. It stimulates lipolysis, which leads to an increase in free fatty acids in order to provide a different fuel to the mother and to conserve glucose and amino acids for the fetus. In turn, the increase in free fatty acid levels directly interferes with the insulin-directed entry of glucose into cells. Therefore, human placental lactogen is considered as a potent antagonist of insulin action during pregnancy.

The Role of Adipose Tissue in the Development of GDM
Adipose tissue produces adipocytokines, including leptin, adiponectin, tumor necrosis factor-α (TNF-α) and interleukin-6, as well as the newly discovered resistin, visfatin and apelin [11, 12]. The roles of adipocytokines and elevated lipid concentrations in pregnancy have also been associated with the changes in insulin sensitivity in non-pregnant women [13] as well as in pregnant women [14]. Evidence suggests that one or more of these adipokines might impair insulin signaling and cause insulin resistance [12]. Specifically, TNF-α has a potential role in decreasing insulin sensitivity [15].

Data from the Diabetes in Early Pregnancy Study indicate that fetal birth weight correlates best with second- and third-trimester postprandial blood sugar levels and not with fasting or mean glucose levels [3]. When postprandial glucose values average 120 mg/dl or less, approximately 20% of infants can be expected to be macrosomic, and if the glucose values are as high as 160 mg/dl, the rate of macrosomia can reach up to 35%. Macrosomic fetuses in diabetic pregnancies develop a unique pattern of overgrowth, involving the central deposition of subcutaneous fat in the abdominal and interscapular areas [4]. They have larger shoulder and extremity circumferences, a decreased head-to-shoulder ratio, significantly higher body fat and thicker upper-extremity skinfolds. Because fetal head size is not increased, but shoulder and abdominal girth can be markedly augmented, the risk of Erb’s palsy, shoulder dystocia and brachial plexus trauma is more common. However, skeletal growth is largely unaffected.

Data from the Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) demonstrated a positive relationship between the severity of maternal fasting hyperglycemia and the risk of shoulder dystocia, with a 1-mmol increase in fasting glucose leading to a 2.09 relative risk for shoulder dystocia [5].

Macrosomia is associated with excessive rates of neonatal morbidity. Macrosomic neonates have 5-fold higher rates of severe hypoglycemia and a doubled increase in neonatal jaundice in comparison with the infants of mothers without diabetes [6].

The newborns of obese women had more than double the risk of macrosomia compared to those of women with normal weight.
Modified Pedersen’s Hypothesis

The pathophysiology of macrosomia can be explained based on Pedersen’s hypothesis of maternal hyperglycemia leading to fetal hyperinsulinemia and increased utilization of glucose and, hence, increased fetal adipose tissue. When maternal glycemic control is impaired and the maternal serum glucose level is high, the glucose crosses the placenta. However, the maternal-derived or exogenously administered insulin does not cross the placenta. As a result, in the second trimester, the fetal pancreas, which is now capable of secreting insulin, starts to respond to hyperglycemia and secrete insulin in an autonomous fashion regardless of glucose stimulation. This combination of hyperinsulinemia (insulin being a major anabolic hormone) and hyperglycemia (glucose being a major anabolic fuel) leads to an increase in the fat and protein stores of the fetus, resulting in macrosomia (fig. 1).

Macrosomia-Related Complications

Maternal Complications

If the baby is atypically large, vaginal birth will be more complicated. There is a risk of prolonged labor in which the fetus might be stuck in the birth canal, instrumental delivery (with forceps or vacuum) may be needed, and even unplanned or emergency cesarean section may be necessary. During birth, there is a greater risk of laceration and tear of the vaginal tissue than when the baby is of normal size, and the muscle between the vagina and the anus might tear (perineal tear).

There is also a high chance of uterine atony. The uterus muscle may not properly contract, resulting in heavy bleeding and postpartum hemorrhage. The risk of postpartum bleeding and genital tract injury was about 3–5 times higher in macrosomic deliveries [16]. Besides, if the mother has had a previous cesarean section, there is a higher chance of uterus tear along the scar line of the previous surgery.

Fetal Complications

Immediate Complications

Premature Birth. Due to early induction of labor before 39 weeks of gestation and/or premature rupture of membranes, there is a risk of preterm delivery. Although all the necessary precautions are undertaken prior to induction of early labor, newborns are still under the risk of complications associated with prematurity, including difficulties in respiration and feeding, infection, jaundice, neonatal intensive care unit admission and perinatal death.

Shoulder Dystocia and Erb’s Palsy. One of the most serious complications of vaginal delivery in macrosomic babies is shoulder dystocia which is associated with birth trauma. Newborns with a birth weight of 4,500 g or more carry a 6 times higher risk of birth trauma [17], and the risk of brachial plexus injury is approximately 20 times higher when the birth weight is above 4,500 g [18].

Hypoglycemia at Birth. One of the most common metabolic disorders of the neonate of a GDM mother is hypoglycemia. It occurs due to the hyperinsulinemia of the fetus in response to the maternal hyperglycemia in utero. Hypoglycemia can lead to more serious complications like severe central nervous system and cardiopulmonary disturbances. Major long-term sequelae include neurologic damage resulting in mental retardation, recurrent seizure activity, developmental delay and personality disorders.

Neonatal Jaundice. Factors which may account for jaundice are prematurity, impaired hepatic conjugation of bilirubin and increased enterohepatic circulation of bilirubin resulting from poor feeding. In macrosomia, neonates have a high oxygen demand causing increased erythropoiesis and, ultimately, polycythemia. Therefore, when these cells break down, bilirubin (a byproduct of red blood cells) increases resulting in neonatal jaundice.

Congenital Anomalies. Heart defects and neural tube defects, such as spina bifida, are the most common types of birth defects. The high blood sugar level of women with GDM can damage the developing organs of the fetus, leading to congenital anomalies.
Later Complications

Childhood Obesity and Metabolic Syndrome. Many studies suggest that one of the reasons of childhood obesity is GDM. There has been evidence of fetal programming of later adiposity amongst offspring exposed to existing diabetes in utero. The offspring of Pima Indian women with preexisting type II diabetes and GDM were larger for gestational age at birth and, after approximately 5 years of age, were heavier than the offspring of prediabetic or nondiabetic women [19]. The Exploring Perinatal Outcomes among Children (EPOCH) study found that exposure to maternal GDM was associated with a higher BMI, a greater waist circumference, more visceral and subcutaneous adipose tissue and a more centralized fat distribution pattern in 6- to 13-year-old multiethnic youth [20]. Moreover, youth exposed to maternal GDM in utero had an overall higher average BMI growth from 27 months through 13 years of age and a higher BMI growth velocity starting at age 10–13 years [21]. These findings suggest that the long-term effects of in utero GDM exposure are not always evident in early childhood, but rather emerge during puberty, another sensitive period for the development of obesity. Offspring of diabetic mothers is also susceptible to the onset of metabolic syndromes such as increased blood pressure, hyperglycemia, obesity and abnormal cholesterol levels that occur together and increase the risk of heart disease, stroke and diabetes.

Transgenerational Transmission of GDM and Epigenetics

In GDM, the abnormal metabolic intrauterine environment affects the development of the fetus by inducing changes in gene expression by epigenetic mechanisms of susceptible cells, leading to the development of diabetes in adulthood. Offspring (F1 generation) of severely and mildly hyperglycemic mothers develops GDM and other metabolic disorders in later life, affecting the second generation (F2 generation) as well. Thus, GDM gives rise to a vicious cycle in which mothers with GDM have babies with epigenetic changes who are prone to develop metabolic disease later in life, which will give rise to a new generation of mothers with GDM. This trend of passing a disease from one generation to another through epigenetic changes is known as transgenerational transmission (fig. 2).

It is now widely accepted that an adverse preconceptional and intrauterine environment is associated with epigenetic malprogramming of the fetal metabolism and predisposition to chronic, and in particular, metabolic disorders later in life [22, 23].

Epigenetics is the study of heritable changes in gene expression that occur without changes in the DNA sequence [24]. DNA methylation and histone modifications are two major epigenetic regulators in mammalian cells, which are functionally linked in transcription and may provide a mechanism for the stable propagation of gene activity from one generation of cells to the next [25]. Biochemical changes, i.e. in the form of DNA methylation and histone modifications, control the spatial, temporal and parent-specific highly coordinated gene expression patterns. As exogenous influences can induce epigenetic modifications, epigenetic variation among individuals may be genetically or environmentally determined [26]. Many different studies have made the observation that early adverse conditions are associated with diabetes and metabolic dysfunction later in life.

Although the mechanisms involved in the epigenetic modifications that lead to the possibility of transgenerational transmission are still unclear, evidence suggests that methylation in germ cells might be responsible [27]. Others suggested that the hyperglycemic uterine environment during pregnancy affects multiple loci in the fetal epigenome initiating metabolic programming, leading not only to transgenerational transmission of GDM but also of several other metabolic diseases [28, 29].

In one study [30], in both F1 and F2 offspring of GDM mothers in a rat model, the expression of imprinted genes Igf2 and H19 was downregulated in pancreatic islets, which was caused by the abnormal methylation status of the differentially methylated region, which may be one of the mechanisms for impaired islet ultrastructure and function. Furthermore, in the same study, altered Igf2 and H19 gene expression was found in sperm of adult F1 GDM offspring, indicating that changes of epigenetics in germ cells contributed to transgenerational transmission.

In another study [28], to test the effects of GDM on the epigenome of the next generation, cord blood and the placenta of mothers with GDM were tested. Here, the maternally imprinted MEST gene, the nonimprinted glucocorticoid receptor NR3C1 gene and interspersed ALU repeats showed significantly decreased methylation levels in GDM groups compared to controls. Significantly de-
increased blood MEST methylation was also observed in adults with morbid obesity compared to normal-weight controls, suggesting that epigenetic malprogramming of MEST may contribute to obesity predisposition throughout life.

Several studies on different genes were carried out in order to understand the epigenetic mechanisms of GDM and transgenerational transformation. All of these studies found epigenetic alterations in the respective genes which had been studied [28, 31–34]. Therefore, from these studies, we can conclude that epigenetic mechanisms predispose offspring to developing type II diabetes, GDM and other metabolic diseases in later stages of life. An increased need for insulin by the fetus to deal with high levels of glucose caused by GDM is an environmental circumstance which probably triggers epigenetic changes in the early stage of life, involving genes critical to pancreatic development and B-cell function, peripheral glucose uptake and insulin resistance.

**Maternal Obesity, GDM and Macrosomia**

The majority of mothers with GDM are obese, and a significant proportion of those who are obese have GDM [35]. One meta-analysis showed that the risk of developing GDM was 2.14-fold higher in overweight pregnant women, 3.56-fold higher in obese pregnant women and 8.56-fold higher in severely obese pregnant women compared to pregnant women with normal weight [36]. An analysis of data from more than 23,000 women in the HAPO (Hyperglycemia and Adverse Pregnancy Outcomes) study [37] showed that the prevalence of macrosomia among 17,244 nonobese women without GDM was 6.7% compared to 10.2% in 2,791 nonobese women with GDM and 20.2% in 935 obese women with GDM.

A study has shown that maternal obesity is a stronger predictor of a large-for-gestational-age infant than maternal hyperglycemia [38]. In the HAPO study [37], the investigators found that the frequency of macrosomia in GDM was increased by 50% compared to non-GDM in both the nonobese and obese groups. Obesity was associated with a 2-fold higher frequency of macrosomia whether in the non-GDM or GDM group. Macrosomia in GDM only was present in 26%, in GDM plus obesity in 33% and in obesity only in 41%. A large prospective study from Spain found that the upper quartile of maternal BMI was responsible for 23% of macrosomia, while GDM accounted for 3.8% [39]. Women who did not have GDM but who were obese had a 13.6% increased risk of macrosomia (defined as a child weighing 4,000 g or more at birth) than nonobese women [37].

From this, we can conclude that although GDM and maternal obesity are independently associated with adverse pregnancy outcomes, the combination of both GDM and maternal obesity has a greater effect on macrosomia.

**Management of Macrosomia**

There are various recommendations for the management of macrosomia varying from expectant management and elective induction of labor before term to elective cesarean section for an estimated fetal weight of ≥4,250 g [40] or >4,500 g [41] depending on the study.

Studies have shown that the chance of vaginal delivery is higher when spontaneous labor occurs than when labor is induced [42]. However, waiting for spontaneous labor to begin is an option limited by gestational age. As the gestational age exceeds 41 weeks of gestation, maternal morbidity and perinatal morbidity and mortality increase. Hence, timely action to induct delivery is needed.

**Early Induction of Labor**

Given that after 37 weeks of gestation the fetus continues to grow at a rate of 230 g/week [43], elective induction of labor before or near term has been proposed to prevent macrosomia and its complications [44]. However, there are two factors necessary for the induction of labor: the first is fetal lung maturation. Fetuses with a diabetic mother have been shown to have delayed lung maturity. Normally, the pulmonary maturation takes place at a
mean gestational age of 34–35 weeks. By 37 weeks, 99% of fetuses are matured. However, in the fetus of a diabetic mother, the lung may not be mature until 38.5 weeks. The second important point is that the patient who is going to undergo induction must have a ripe cervix with a Bishop score of ≥6; otherwise, there is an increased chance of failure of induction, which ultimately leads to a cesarean section [45]. In one study [46], the outcomes of suspected macrosomic infants of mothers who had expectant management of pregnancy versus elective induction of labor were compared. The rate of cesarean sections was found to be very high (57 vs. 31%) in those who were assigned to the electively induced group. In some studies, elective induction of labor for macrosomia was found to increase the rate of cesarean delivery without improvement in perinatal outcomes [42, 47].

Elective Cesarean Section

Many studies suggest offering a cesarean section to patients who are suspected of expecting a macrosomic infant, especially to those with GDM, insulin-dependent diabetes and a previous high-birth-weight infant, so as to prevent maternal and fetal birth trauma. Unfortunately, measures to calculate the weight of the fetus are inaccurate [48]. In one study, it was claimed that, in a general population, it is unreasonable to perform an elective cesarean section to prevent brachial plexopathy [49].

Management of the Neonate

Large-for-gestational-age neonates do not only include postterm infants, but also term or even preterm infants. This should be kept in mind as the management and the main concerns in treatment could differ. A strictly regulated maternal blood sugar level decreases the perinatal adverse outcomes.

Neonates with a diabetic mother should undergo a full physical examination from head to toe, congenital anomalies (congenital heart defects, tracheoesophageal fistula and central nervous system abnormalities) and birth trauma being of more concern. They should receive intensive observation and care and should be evaluated for hypoglycemia, polycythemia, hyperbilirubinemia and electrolyte abnormalities.

The blood glucose level should be examined within 1 h of life, then every hour for the next 6–8 h and then as needed. Oral feeding, ideally breast feeding, is recommended as soon as possible, and if oral feeding is insufficient, an intravenous infusion of glucose should be started.

Disclosure Statement

None of the authors has any conflicts of interest in connection with this study.

References

Like poverty, undernutrition and micronutrient deficiencies often occur as part of an intergenerational cycle

Reprinted with permission from: Ann Nutr Metab 2015;66(suppl 2):22–33

The Epidemiology of Global Micronutrient Deficiencies
by Regan L. Bailey et al.

**Key insights**
Micronutrient deficiencies (MNDs) have a direct impact on individuals and on societies, resulting in poorer health, lower educational attainment and decreased work capacity and earning potential. Nutrition is the most powerful adaptable environmental factor that can be targeted in order to reduce the burden of disease across an individual’s entire life span. MNDs are preventable and the return on investment for the provision of micronutrients is high. Understanding how to interpret the biomarkers of MNDs alongside clinical and functional indicators is key to characterizing the global burden of MNDs and to identifying the optimal interventions.

**Current knowledge**
Around the world, pregnant women and children under 5 years of age are at the highest risk of MNDs. Iron, iodine, folate, vitamin A, and zinc deficiencies are the most widespread MNDs and are common contributors towards poor growth, intellectual impairment, perinatal complications, and increased risk of morbidity and mortality. Of greatest concern is the fact that the cycle of MNDs perpetuates across the generations, with far-reaching consequences on the future population.

**Practical implications**
Addressing MNDs has traditionally been accomplished through supplementation, fortification, and food-based approaches including dietary diversification. Of note, intervention in the first 1,000 days of life is most effective for breaking the cycle of malnutrition; however, a coordinated, sustainable commitment to scaling up nutritional interventions at the global level is needed. Supplementation is a cost-effective solution but does not address the root cause of the MND. Over the long term, food fortification may offer a more effective means to address MNDs, as it enables a larger segment of a population to be targeted.

**Recommended reading**

---

Micronutrient deficiencies have consequences throughout an individual’s life span and are perpetuated across the generations.

**Infancy**
- Low birth weight
- Higher mortality rate
- Impaired mental development
- Increased risk of chronic disease

**Childhood**
- Stunted
- Reduced mental capacity and productivity
- Frequent infections
- Inadequate growth
- Higher mortality rate

**Adolescence**
- Stunted
- Reduced mental capacity
- Frequent infections
- Fatigue

**Adulthood**
- Reduced productivity
- Poor socioeconomic status
- Malnourished
- Increased perinatal complications and mortality

**Infancy**
- Low birth weight
- Higher mortality rate
- Impaired mental development
- Increased risk of chronic disease

**Childhood**
- Stunted
- Reduced mental capacity and productivity
- Frequent infections
- Inadequate growth
- Higher mortality rate

**Adolescence**
- Stunted
- Reduced mental capacity
- Frequent infections
- Fatigue

**Adulthood**
- Reduced productivity
- Poor socioeconomic status
- Malnourished
- Increased perinatal complications and mortality
The Epidemiology of Global Micronutrient Deficiencies

Regan L. Bailey\textsuperscript{a, b} Keith P. West Jr.\textsuperscript{b} Robert E. Black\textsuperscript{b}

\textsuperscript{a}Office of Dietary Supplements, National Institutes of Health, Bethesda, Md., \textsuperscript{b}Department of International Nutrition, The Bloomberg School of Public Health, Johns Hopkins University, Baltimore, Md., USA

Key Words
Epidemiology · Micronutrient deficiencies · Vitamins · Minerals

Abstract
Micronutrients are essential to sustain life and for optimal physiological function. Widespread global micronutrient deficiencies (MNDs) exist, with pregnant women and their children under 5 years at the highest risk. Iron, iodine, folate, vitamin A, and zinc deficiencies are the most widespread MNDs, and all these MNDs are common contributors to poor growth, intellectual impairments, perinatal complications, and increased risk of morbidity and mortality. Iron deficiency is the most common MND worldwide and leads to microcytic anemia, decreased capacity for work, as well as impaired immune and endocrine function. Iodine deficiency disorder is also widespread and results in goiter, mental retardation, or reduced cognitive function. Adequate zinc is necessary for optimal immune function, and deficiency is associated with an increased incidence of diarrhea and acute respiratory infections, major causes of death in those <5 years of age. Folic acid taken in early pregnancy can prevent neural tube defects. Folate is essential for DNA synthesis and repair, and deficiency results in macrocytic anemia. Vitamin A deficiency is the leading cause of blindness worldwide and also impairs immune function and cell differentiation. Single
MNDs rarely occur alone; often, multiple MNDs coexist. The long-term consequences of MNDs are not only seen at the individual level but also have deleterious impacts on the economic development and human capital at the country level. Perhaps of greatest concern is the cycle of MNDs that persists over generations and the intergenerational consequences of MNDs that we are only beginning to understand. Prevention of MNDs is critical and traditionally has been accomplished through supplementation, fortification, and food-based approaches including diversification. It is widely accepted that intervention in the first 1,000 days is critical to break the cycle of malnutrition; however, a coordinated, sustainable commitment to scaling up nutrition at the global level is still needed. Understanding the epidemiology of MNDs is critical to understand what intervention strategies will work best under different conditions.

Defining Deficiency

The nutritional status of a micronutrient can be characterized along a continuum from deficiency to excess (fig. 1) [3]. The sufficiency status for micronutrients can be determined along this continuum using biomarkers, dietary intake data, or nonspecific functional indicators, like stunting or low birth weight. Ideally, MND is determined by a valid and reliable biomarker. Biomarkers are typically defined as biological measurements (i.e. blood, urine, etc.) that are used to indicate ‘normal biological processes, pathogenic processes, or pharmacologic responses to therapeutic intervention’ [4]. Unfortunately, biomarkers are not available for all, while other existing biomarkers are not practical or feasible for widespread assessment or for use outside the clinical setting. Furthermore, biomarkers may be influenced by inflammation, infection, hydration status, age, kidney function, and analytical method, all of which make their interpretation difficult. Finally, a number of issues exist concerning the use of cut points for biomarkers to determine deficiency and sufficiency as there is a distribution around the cut point, cut points may differ by many factors (e.g. by age group or by analytical method), and the selection of which cut point to use is problematic. National sur-
veys containing dietary data are not routinely collected in most developing countries. Furthermore, databases needed to analyze reported intakes must be region specific and are often lacking or not up-to-date. The use of functional indicators to characterize the extent of MNDs is problematic because so many factors contribute to these public health problems. MNDs are commonly only one of the root causes of these types of indicators. Thus, in the absence of dietary or biomarker data, we can only assume that countries with a high burden of adverse functional physical indicators also have a high burden of MNDs.

**Causes of MNDs**

MNDs are only one form of undernutrition. Other forms of undernutrition are more readily visible and, for this reason, MNDs are often referred to as hidden hunger [5]. At the most basic level, MNDs, like all forms of undernutrition, occur due to insufficient intake or sufficient intakes combined with impaired absorption due to infection, disease, or inflammation [6, 7]. For infants, MNDs may result from maternal MND in utero or rapid postnatal growth [8]. The antecedents to these immediate causes for undernutrition are complex and can be fully appreciated by examining the 2013 UNICEF Conceptual Framework for the Determinants of Undernutrition (fig. 2) [6]. The underlying causes that contribute to the immediate causes include food insecurity, inadequate care or feeding practices, and an unhealthy environment with inadequate access to health services. Nutritional status is greatly impacted by infection [9]. Infection is the leading cause of child mortality [10]. Acute respiratory infection and diarrhea are the most common causes of infant mortality, and MNDs contribute greatly to the immune response [11]. Undernutrition is the leading cause of immunodeficiency worldwide [7].

The basic root cause of most undernutrition is poverty. As a result, low- and middle-income countries have the highest burden of MNDs; however, MNDs exist even in certain population groups in higher-income countries. The United Nation’s Millennium Development Goals include eradicating extreme poverty and hunger as their priority goal [12]. Like poverty, undernutrition and MNDs often occur as part of an intergenerational cycle (fig. 3). During pregnancy and lactation, there are increased macro- and micronutrient requirements [13]. Pregnant mothers without optimal nutritional intakes have children with suboptimal nutritional status including impaired physical and mental development, setting the infant on a deleterious course of stunting, increased likelihood for infection, and developmental delays [14]. In time, these children themselves enter their reproductive years at a nutritional disadvantage and the cycle continues. Furthermore, adults with nutritional disadvantages often have a lower work capacity due to the early developmental delays mediated through a lack of education [14]. Thus, both malnutrition and poverty often track together and operate synergistically.

**MNDs of Greatest Public Concern**

**Iron**

Iron is a mineral that is an essential component of hemoglobin, myoglobin, enzymes, and cytochromes and is necessary for oxygen transport and cellular respiration [15]. Iron also is critical for optimal growth and cognitive function. Two forms of iron exist, namely heme and non-heme. Heme iron is found in animal sources, whereas nonheme iron is found in plants and used in fortification. Neither form of iron is highly bioavailable; heme iron bioavailability is estimated to be 12–25%, and nonheme iron is <5% bioavailable [1, 15]; however, with the exception of menstruating and pregnant women, iron in vivo is very highly conserved [15].

Acute respiratory infection and diarrhea are the most common causes of infant mortality, and MNDs contribute greatly to the immune response.

Iron deficiency is the most common MND in the world, affecting more than 30% of the world’s population, an estimated 2 billion people [16]. Iron deficiency causes anemia and disrupts optimal function of both the endocrine and immune systems. Iron deficiency is particularly common during pregnancy because of increased requirements for fetal growth and development. Maternal iron deficiency is associated with low birth weight, premature delivery, and a host of perinatal complications, especially hemorrhage. Anemia is estimated to contribute to 20% of maternal deaths [16]. Children born to iron-deficient mothers are more likely to have low iron stores, to suffer from impaired physical and cognitive development, and to have suboptimal immune systems. Early-life iron status substantially influences human potential at the individual and country level [16–18]. Iron deficiency
may also be associated with enhanced absorption of environmental metal toxins such as cadmium [19].

Iron status is typically assessed through plasma ferritin, transferrin saturation, and hemoglobin concentrations. Ideally, all of these biomarkers are available to make an assessment; however, routinely, only 1 or 2 of these are available in screening and assessment. Hemoglobin is most often used to determine anemia. Ferritin is reflective of body iron stores; but, because it is also an acute-phase protein, ferritin will be elevated in acute or chronic disease, and tests may yield misleading results. Globally, the World Health Organization (WHO) estimates that 25% of the population (1.62 billion people; CI 1.50–1.74 billion) has anemia [16]. Preschool children (47.4%) and pregnant women (41.8%) have the highest prevalence overall. Africa (67.6 and 57.1%) and Southeast Asia (65.5 and 48.2%) have the highest burden of anemia in preschool children and pregnant women, respectively [16].

Women in perinatal life stages and their infants (<6 months of age) are considered to be at the highest risk for iron deficiency. Routine iron supplementation in pregnancy and infancy is recommended in areas without endemic malaria [20]. Iron supplementation in those with malaria may exacerbate the falciparum-related complications and mortality [20]. Recently, it has been proposed to dovetail efforts with iron nutriment in conjunction with malaria control programs [21]. Fortification programs with iron exist in several countries with the food vehicles of choice ranging from flours, dairy products, condiments, sugar, and salt to infant formulas. Fortification and supplementation may be appropriate for areas with high concentrations of vegetarians.

Fig. 2. Updated UNICEF Conceptual Framework for the Determinants of Undernutrition (adapted from UNICEF [6]).
Vitamin A

Vitamin A is a fat-soluble vitamin that has multiple roles in the body including vision, cell differentiation, immune function, reproduction, and organ and bone formation and growth. Vitamin A comes from animal sources in the diet preformed as retinol or retinyl esters, or from provitamin A carotenoids found in plant sources. Provitamin A carotenoids, which exhibit differential vitamin A activity, are converted to the active forms of the vitamin (retinal and retinoic acid) for use by the body.

Vitamin A deficiency (VAD) has been associated with increased rates and severity of infections and is a primary cause of childhood morbidity and mortality in the developing world, particularly in Africa and Southeast Asia [22]. VAD is the leading cause of preventable blindness in children. VAD causes xerophthalmia, a series of ocular manifestations like night blindness, Bitot’s spots, and corneal ulcerations and lesions [1]. The WHO estimates that 250–500 million children are blind because of VAD, and half of these children will die within a year of vision loss. VAD is also common in pregnancy in lower-income countries with estimates ranging from 10 to 20%. Very little is known about older children and adults with regard to vitamin A status; however, because VAD tends to cluster in families, communities, and regions, we can assume that vitamin A status is low in areas with child and pregnancy burden. Subclinical VAD affects far greater numbers of individuals, particularly in Africa and Asia [23].

VAD is characterized using serum retinol, with hyporetinolemia defined as concentrations <0.70 μmol/l, clinical parameters determined via eye exam, and/or functional indicators like night blindness. Often, VAD occurs in clusters, so prevention and treatment schedules are in place to provide high-dose oral supplementation intermittently (i.e. semi-annually, every 4–6 months, etc.) based on age (beginning at birth), life stage, and severity of deficiency. Vitamin A can also be added as a fortificant to the food supply. For example, in Guatemala, vitamin A

---

**Fig. 3.** The conceptual framework for the cycle of micronutrient inadequacies across the life span (adapted from ACC/SCN [14]).
is added to sugar [24] in addition to intermittent supplementation programs, together yielding a low rate of VAD determined by serum retinol [25]. Despite the Cochrane reviews limiting maternal, neonatal, and infant vitamin A supplementation in developing countries [26, 27], continued emphasis should be placed on vitamin A supplementation programs in Southeast Asia given the clearly documented effects on ocular health and mortality [22, 28, 29].

**Iodine**

Iodine is a trace mineral, and its primary function is in the synthesis of thyroid hormone. Approximately 60% of the total body pool of iodine is stored in the thyroid gland [30]. Thyroid hormone is necessary for regulation of human growth and development. Iodine in foods and dietary supplements is generally either in a salt or organic form [31]. The iodine content of many foods is dependent upon soil concentration of the element and fertilization and irrigation practices [15]. The iodine content of fish and seaweed is also highly variable [32]. Iodine stores in vivo during a sufficient state are estimated at 60 μg, and during deficiency, stores are much lower in the 10- to 20-μg range [30]. Iodine absorption and utilization can be impaired by the presence of goitrogens [33] or exposure to percolate, disulfides, and thiocyanates (from tobacco exposure) [34]. Hypothyroidism can occur in individuals when dietary intakes are lower than 10–20 μg daily, and it is frequently accompanied by goiter [15].

Thyroid hormones are essential for optimal fetal and postnatal central nervous system growth and development [35, 36]. Maternal iodine requirements increase by more than 50% during pregnancy to meet fetal needs and because of enhanced renal clearance of iodine and alternated iodine metabolism during pregnancy [37]. Maternal iodine deficiency, particularly when it occurs during early pregnancy, can lead to irreversible neurological complications and mental retardation in the offspring referred to as iodine deficiency disorder (IDD) [35]. IDD represents a spectrum of diseases affecting the entire life course. From infancy to adulthood, IDD includes goiters, impaired mental function, and hypo- or hyperthyroidism. At the most severe form, in utero iodine deficiency can result in cretinism [38].

Typically, iodine status is assessed via urinary iodine content because it is a reliable indicator of recent intake as approximately 90% of ingested dietary iodine is excreted in urine across the range of dietary intakes [30, 36, 39] and because renal clearance is relatively constant [40]. The WHO defines iodine insufficiency in children and adults as a median urinary iodine concentration of <100 μg/l. During pregnancy, different urinary iodine excretion rates may occur [41]; therefore, during pregnancy, sufficiency status is defined as a median urinary iodine concentration of 150–249 μg/l, with concentrations <150 μg/l defined as insufficient [42]. It is intuitive to think that thyroid hormones may serve as a biomarker of iodine status; however, thyroid hormones, with the exception of thyroglobulin [43], do not appear to be adequately sensitive to change in iodine status [44, 45].

Pregnant females and infants (<24 months of age) are the population groups at highest risk of iodine deficiency. As previously stated, in pregnancy, requirements are greatly increased, and infants have the highest requirements per kg of body weight of any age group [30]. Exclusively breastfed infants may also be at risk if not provided iodine in complementary foods [46]. While iodine is found in breast milk [15], its concentration is dependent on maternal intake and status [47, 48].

Globally, ~2 billion are estimated to have inadequate iodine status [49, 50]. As many as half of the European population (52%, 459.7 million people) is estimated to have inadequate iodine status and more than 500 million individuals are affected in Southeast Asia. While the group of highest concern is pregnant females, we have no global estimation of the burden of iodine deficiency in this group [51]. Approximately 30% (241 million) of the world’s school-aged children have insufficient iodine intakes [52].

---

**Universal salt iodization is the most practical strategy to reduce iodine deficiency globally.**

---

Many countries of the world (~120 countries) have fortified table salt with iodine because iodine is found naturally in very few foods [53]. Salt is traditionally the food vehicle chosen for iodization because it is universally consumed at a relatively consistent intake level; the process of adding iodine to salt is very cheap at less than 5 cents per person per year. Global estimates from the UNICEF indicate that 68% of households have adequate table salt iodine [51]. Universal salt iodization refers to all salts used within a country, regardless if iodine is in table salt or in salt used by the food industry. Very few countries in the world have achieved universal salt iodization, and often, the food industry does not use iodized salt in food production [30]. Iodine can also be found in dietary supplements. Universal salt iodization is the most practical strategy to reduce iodine deficiency globally. Correcting
iodine deficiency does have some health risks for certain populations in terms of thyroid function and should be considered within the context of each country separately [38].

**Folate**

Folate is a generic term for multiple forms of the essential B vitamin. Folate naturally occurs in foods, whereas folic acid is a synthetic form of the vitamin that is used in fortified foods and in dietary supplements. Folic acid is much more bioavailable than folate naturally occurring in foods and when ingested is converted by dihydrofolate reductase to the dihydrofolate and then the tetrahydrofolate form of folate; these reduced compounds are identical to those that would arise from ingestion of natural folate. Folate is essential for synthesis of purines and thymidylate and, therefore, is involved in DNA synthesis, stability, and repair. Folate is also involved in one carbon metabolism and, as such, can alter DNA methylation, which is an important epigenetic determinant in gene expression, in the maintenance of DNA integrity, and in the development of mutations.

Folate deficiency can be determined by serum, plasma, or erythrocyte folate concentrations. Folate deficiency is very low in countries with mandatory or voluntary folic acid fortification programs [52]. Folate deficiency causes megaloblastic or macrocytic anemia and increases the likelihood for pregnancies affected by neural tube defects. The global prevalence of anemia secondary to folate deficiency is very low. Folate deficiency in pregnancy has also been associated with low birth weight, preterm delivery, and fetal growth retardation [53, 54]. Globally, only about 30% of women take folic acid supplements prior to conception [55]. No good estimates of global folate deficiency exist for those considered to be of highest risk: women of reproductive age, pregnant females, and young children [56].

Folic acid supplementation in the periconceptional period unequivocally reduces the occurrence of neural tube defects [57, 58]. For this reason, the governments of both the United States and Canada instituted national fortification programs with folic acid to enhance the diets of reproductive-aged females [59–61], and neural tube defect rates decreased in both the United States [62] and Canada [63–65]. Since this time, more than 75 countries have instituted folic acid fortification programs, and the amount of folic acid added varies by country [66]. Several more countries allow folic acid to be added to flour on a voluntary basis, while other countries fortify with iron and other B vitamins, but not with folic acid [67, 68]. Concerns exist about high exposure to folic acid through fortification practices and supplements among nontarget groups (i.e. females not in the reproductive age) like children, males, and the elderly.

---

**Zinc supplementation during pregnancy is associated with a significant reduction in preterm births without an effect on infant birth weight.**

---

**Zinc**

Zinc is an essential mineral that is involved in multiple aspects of cellular metabolism [69]. Zinc is required for the activity of more than 200 enzymes, and it is critical for immune system function, cell division, and protein and DNA synthesis [15]. Zinc is also required for normal growth and development from in utero until puberty. The human body has no long-term storage system for zinc, so consistent dietary intake is needed to sustain all of these functions and maintain the relatively small exchangeable zinc pool. Because of its diverse functions in vivo, it has been difficult to develop a single biomarker of zinc status; plasma zinc concentrations have been used, but this biomarker is nonspecific [69]. Zinc is primarily found in animal products and seafood. Similar to iron, zinc absorption is impaired by phytates, fiber, and lignins, all of which impair the bioavailability from nonanimal sources of zinc. Calcium and casein may reduce the bioavailability of zinc from cow’s milk. Zinc is present in human breast milk.

Zinc status has been associated with reduced incidence, severity, and mortality due to diarrhea and respiratory and malarial infection (as summarized by Patel et al. [70] and Black et al. [71]). Infection is known to compromise dietary intake and micronutrient absorption, and diarrhea can contribute to losses in key micronutrients. A recent Cochrane review of randomized clinical trials (80 trials with 205,401 participants) in children 6 months to 12 years of age indicates a positive effect for zinc supplementation in reducing all-cause and infectious disease mortality and a small positive impact on linear growth [72]. A recent clinical trial in full-term infants in India receiving placebo or 5 mg zinc daily indicated a significantly higher skinfold thickness for infants in the treatment group when compared to the placebo group, without a difference observed in linear growth [73]. The
effect of zinc on anthropometry, but not linear growth, was also seen in a Peruvian clinical trial in which mothers were supplemented prenatally with zinc; infants born to zinc-supplemented mothers had greater weight gain, higher calf and chest circumference, and more calf muscle area than children born to mothers without zinc supplementation [74]. Zinc supplementation during pregnancy is associated with a significant reduction in preterm births without an effect on infant birth weight [75].

Deficiency in zinc is thought to be one of the primary causes of morbidity in developing countries and, yet, surprisingly little is known about the status of the world [76]. Given the issues concerning the assessment of zinc status by biomarkers, estimates of inadequacy are largely based on the prevalence of child stunting, estimates of dietary intakes, and the availability of zinc from the food supply [76]. Globally, it is estimated that 17.3% of the population has inadequate zinc intakes, with the highest estimates in Africa (23.9%) and Asia (19.4%). Pregnant females and their young children are the highest-risk groups for zinc deficiency. Currently, the WHO and UNICEF recommend provision of zinc supplements for 10–14 days along with oral rehydration therapy for acute diarrhea; however, no routine supplementation recommendations currently exist for the prevention of zinc deficiency.

**Multiple MNDs**

Single MNDs rarely happen in isolation; more often, multiple MNDs are occurring simultaneously [1, 5]. Multiple MNDs appear to be mainly driven by a lack of food security, defined by the Food and Agriculture Organization (1996) at the World Food Summit as follows: ‘when all people at all times have access to sufficient, safe, nutritious food to maintain a healthy and active life’ [77]. Many factors contribute to food security and MNDs, including lack of available quality and diversity of foods, poverty in certain population groups, lack of access to health care and nutrition education, subsistence farming practices, volatile food prices, urbanization, high rates of infection (both acute and chronic), and issues with sanitation, climate change, and access to potable water [5, 78–80].

Estimates of multiple MNDs have been difficult to ascertain due to limitations in the available data. Muthayya et al. [5] estimated global hidden hunger indices for iron, vitamin A, and zinc together and determined that 18 of the 20 countries with the highest burden of multiple MNDs are in Africa, with Afghanistan and India (WHO region Asia) completing the list. Iodine may be the exception to the clustering of MNDs, and iodine deficiency is region specific and does not necessarily track with countries with a high hidden hunger [5]. However, deficiency in other micronutrients, like selenium, iron, and vitamin A, can exacerbate iodine deficiency by altering thyroid function [81–83].

**Strategies and Interventions**

Several options exist to combat MNDs, including supplementation, fortification, and food-based approaches like dietary diversification. The choice of intervention strategy or strategies should depend on the cause, severity, and scope of the MND. The intervention strategy should always try to eliminate the root cause and must be considered within the cultural preferences [2]. Understanding the sustainability and feasibility of interventions is critical a priori. Ensuring continued access to the intervention or strategy is of upmost importance depending on the intervention.

In general, supplementation is the approach to utilize when an MND is severe and requires a therapeutic approach to treatment, or for the purpose of prevention [2]. Supplementation can be daily or intermittently (i.e. 1–2 times per year). Widespread success has been achieved with vitamin A supplementation for the prevention of night blindness and infant mortality; the success is in part due to the intermittent requirements for supplementation (i.e. 1–2 times per year vs. daily). Supplementation as a strategy requires that provision of supplements is feasible and that adequate educational programs are in place to garner compliance. Ideally, supplementation is limited to these purposes because supplementation does not address the root cause of the deficiency. However, supplementation offers a relatively cost-effective short-term solution to MNDs. There are growing concerns that supplemental nutrients may exhibit different physiological responses and absorption than nutrients found in food; this has been noted for folic acid, zinc, and iron.

Food fortification is a more long-term strategy to combat MNDs than supplementation. Fortification differs
from supplementation in that most of the population is exposed to fortification, whereas supplementation is targeted toward certain individuals or groups. Fortification generally requires policy and procedural changes and engagement of the food industry and, thus, requires substantially more time to implement than supplementation. However, if an MND is widespread, fortification is the tool with the greatest capacity to reach the most within a country. The choice of the food vehicle is equally critical as the amount of fortificant to add; ideally, fortification will enhance the intakes at the lowest tail of the intake distribution without causing excessive intakes among those with already high intakes. Using more than one food vehicle and understanding the current intake patterns have been recommended to avoid excessive intakes of nutrients caused by fortification [84]. An emerging option for enhancing micronutrient intakes is by biofortification. Biofortification utilizes recombinant DNA technology or fermentation procedures to alter the micronutrient content, but not the appearance, taste, or smell, of an existing food or crop [85]. The use of nanotechnology to create new delivery systems and storage forms of micronutrients is also a rapidly evolving field [86, 87]. Continued monitoring of any widespread food fortification program is necessary.

An alternative to fortification of the food supply are home-based fortification systems in which micronutrients are added to foods that are already consumed within the home. This strategy, often called ‘home fortification’, avoids the policy and food industry involvement and allows for targeted intervention in individuals in need. Most often, home fortification involves adding multiple micronutrients to a semi-solid food prepared in the home. The micronutrients generally come in packets or sachets. Home-based fortification programs were ongoing in 22 countries as of 2011. In one trial in Pakistan, the use of home fortification with multiple micronutrients in children aged 6–18 months was associated with a significant decline in iron deficiency anemia but was also associated with increased rates of diarrhea [88]. A Cochrane review of home fortification suggests that home fortification with multiple micronutrients is effective for reducing anemia and iron deficiency but cautions that such products be used judiciously in areas with malaria as limited data exist at present. Issues have been raised concerning the compliance to home fortification systems and also concerning an increase in pollution due to the foil-lined packaging needed to preserve the micronutrients [89].

While optimal in terms of sustainability, changing the dietary patterns of individuals and communities may be difficult to achieve. Dietary diversification may not be possible due to limited food availability within certain regions. However, resources could be directed towards agricultural practices to change food availability; this is a sustainable mechanism to ensure access to a particular food or foods. However, a change in dietary patterns usually is not enough to ameliorate certain deficiencies such as iodine deficiency given that the root cause is the geographic location in which foods, animals, and seafood are produced. Food-based approaches can include additions or changes to complementary feeding practices when infants start to consume foods other than breast milk or infant formula. This transition period between liquid and solid nourishment is often accompanied by MND in developing countries. Provision of meals served outside the home, like school lunches, provides one opportunity to enhance micronutrient intakes of school-aged children. Several fortified food products exist to add micronutrients to the diet without changing dietary patterns, such as biscuits or noodles which have been delivered by aid programs either intermittently or consistently depending on the scope of the problem. Finally, if infection is the root cause of an MND, none of these intervention strategies alone would combat the problem of MNDs. In such instances, deworming or other public health control measures are needed [2]. Thus, those instituting interventions must adequately address all root causes of the MND in determining which strategy or combination of strategies to employ.

Resources could be directed towards agricultural practices to change food availability.

Economic Impact of MNDs

Given the widespread impacts that MNDs have across the life span, it is not surprising that they cause tremendous financial burdens to societies [71]. Adequate nutritional status is a primary building block of human capital [90, 91]. Early-life nutrition has long-lasting impacts on the individual and society, including poorer adult health, less educational attainment, diminished work capacity, and lower lifetime earning potential [71, 92]. An estimated 11% of the gross national product in Africa and Asia are lost each year secondary to the high burden of malnutrition. Estimates of increased earning potential due to early-life nutrition interventions are as high as 50% (e.g.
boys in Guatemala). For this reason, the Expert Panel for the Copenhagen Consensus Center determined nutrition through bundled micronutrient interventions as the top recommended global health issue to target resources toward in 2012.

**Disclosure Statement**

Regan L. Bailey and Keith P. West Jr. have no conflicts of interest to disclose. Robert E. Black presides on the governing boards of the Micronutrient Initiative and Vitamin Angels; he is also a member of the Creating Shared Value Advisory Council of Nestlé.

**References**


79 The other oil problem. The world’s growing appetite for cheap palm oil is destroying rain forests and amplifying climate change. Sci Am 2012;307:10.

Reprinted with permission from: Ann Nutr Metab 2015;66(suppl 2):22–33
DOI: 10.1159/000371618

Bailey/West/Black


Current evidence suggests that food fortification is a cost-effective means of addressing iron deficiency at the population level, particularly in infants and young children.

Key insights
Iron deficiency anemia has a profound impact on human health and productivity, with especially pronounced and long-lasting effects in the first 1,000 days of life. The use of fortified foods is a cost-effective tool for addressing iron deficiency in infants and young children in the Philippines. There are three categories of the most commonly used food vehicles employed for this purpose: staple food items (rice, oils and wheat), condiments (fish sauce, soy sauce and sugar) and processed commercial food items (infant complementary foods, dairy products and noodles). For infants and young children, the use of fortified complementary foods has been shown to be safer and more effective compared to supplements.

Current knowledge
In the Philippines, a large percentage of the population suffers from one or more forms of malnutrition including micronutrient deficiencies. The most common form of malnutrition in the Filipino population is iron deficiency, particularly amongst children. Iron deficiency is frequently manifested as iron deficiency anemia. Given the pervasive effects of iron deficiency on all aspects of an individual’s health and throughout the life span, iron is a key target for optimizing health, physical and cognitive potential and economic productivity.

Practical implications
The feasibility and cost-effectiveness of using fortified powdered milk to increase micronutrient intake amongst children were estimated based on a consumer survey of 1,800 Filipino households. Powdered milk was found to be an appropriate vehicle, since it is a widely used food item for children in the Philippines. Not surprisingly, poorer households were more price sensitive, indicating that they would buy more milk if the price was lower. Altogether, the most cost-effective interventions which would result in the greatest health and economic benefits are those targeting the poorest 20% of the population.

Recommended reading
Food Fortification for Addressing Iron Deficiency in Filipino Children: Benefits and Cost-Effectiveness

Patrick Detzel\textsuperscript{a} Simon Wieser\textsuperscript{b}

\textsuperscript{a}Nestlé Research Center, Lausanne, and \textsuperscript{b}Winterthur Institute of Health Economics, Zürich University of Applied Sciences, Zürich, Switzerland

**Key Messages**

- In the Philippines, a large percentage of the population suffers from one or more forms of malnutrition including micronutrient deficiencies.
- Iron deficiency (manifested as iron deficiency anemia) is the most common form of malnutrition in the Filipino population, especially in children.
- Ensuring adequate iron status will enhance individual health, with a positive impact on physical and cognitive productivity; this will increase the individual’s ability to contribute socially and economically.
- The fortification of commonly consumed food items presents an opportunity to increase the nutrient intake of a population, thereby improving nutritional status.
- Safety and compliance aspects indicate that fortification is superior to supplementation.
- Impacts of iron deficiency are measured in health-care costs, productivity losses and disability-adjusted life years.
- The estimated consequences of these deficiencies in childhood throughout the lifetime of the individual, using a health-economic model, are large and significant and vary substantially between socioeconomic strata.
- The feasibility and cost-effectiveness of using fortified powdered milk to increase micronutrient intake amongst children were estimated based on a consumer survey of 1,800 Filipino households.
- The most cost-effective interventions are those targeting the poorest 20% of the population, since the costs of intervention increase more rapidly relative to the additional disability-adjusted life year gains if the intervention is extended to the wealthier segments of the population.

**Key Words**

Micronutrient deficiencies · First 1,000 days · Food fortification · Burden of disease · Cost of illness · Cost-effectiveness analysis · Philippines

**Abstract**

Iron deficiency is one of the most widespread nutritional disorders in both developing and industrialized countries, making it a global public health concern. Anemia, mainly due to iron deficiency, affects one third of the world’s population and is concentrated in women and children below 5 years of age. Iron deficiency anemia has a profound impact on human health and productivity, and the effects of iron deficiency are especially pronounced in the first 1,000 days of life.
life. This critical window of time sets the stage for an individual’s future physiological and cognitive health, underscoring the importance of addressing iron deficiency in infants and young children. This review focuses on the use of fortified foods as a cost-effective tool for addressing iron deficiency in infants and young children in the Philippines.

© 2015 Nestec Ltd., Vevey/S. Karger AG, Basel

**Introduction**

The past few decades have witnessed tremendous socioeconomic growth in the Asia Pacific region [1]. Yet, despite these advances, the benefits of development have not reached all sectors of society. Undernutrition in women and children is still widespread in the Asia Pacific region, and the ongoing cycle of malnutrition, underweight and malnourishment in girls gives rise to a generation of undernourished mothers of underweight babies [2–4]. Early malnutrition affects physical and cognitive health in later life, with far-reaching effects on personal well-being and the economic potential of the future generation [4, 5].

Iron Deficiency: Effects on Health

Iron is an essential micronutrient as it plays key roles in many metabolic processes, such as oxygen transport, DNA synthesis, neurotransmitter synthesis, energy metabolism, cell growth and differentiation and electron transport [11, 12]. Due to its essential role in so many physiological functions, iron homeostasis is tightly regulated. Since the human body lacks specific mechanisms for active iron excretion, iron balance is regulated largely at the level of absorption [11]. In general, iron is conserved in the body and is not readily lost. However, an increased demand occurs during childhood growth and pregnancy and in cases of bleeding or menstruation. The average adult stores between 1–3 g of iron in the body [11].

Iron deficiency occurs when iron supply or absorption are not sufficient to compensate for the individual’s iron requirements and losses [13]. Those with particularly high iron requirements, including pregnant women, infants, young children and adolescents, have a greater risk of being iron deficient [13–17]. The condition of iron deficiency is defined as the state in which no mobilizable iron stores are available in the body, resulting in a compromised iron supply to tissues. Iron deficiency can exist with or without the development of anemia. Anemia is defined as the condition in which the number of red blood cells is low, or if they contain less than the normal amount of hemoglobin [18]. Anemia affects an estimated one third of the world’s population, especially children below 5 years of age and women [2, 3], making it a global public health concern. Half of all anemias is related to iron deficiency [19]. In developing countries, the main cause of iron deficiency is the low iron bioavailability of the diet due to the concomitant presence of substances (such as through prescriptions for iron supplements), rather than through preventive strategies that can be influenced through population awareness and public policy [10].

The purpose of this review is to examine food fortification as a means of addressing iron deficiency in the Philippines. The first part of this review covers the effects of iron on health and the effectiveness of food fortification when used to ameliorate iron status at the population level. This is followed by a discussion of the economic burden related to iron deficiency and the cost-effectiveness of food fortification as a tool for addressing iron deficiency in the Philippines, particularly in infants and young children.

In the Philippines, a large percentage of the population suffers from one or more forms of malnutrition including micronutrient deficiencies [6]. Among Filipino children, the four major deficiency disorders are protein-energy malnutrition, iodine deficiency disorder, vitamin A deficiency and iron deficiency [7]. Iron deficiency (manifested as iron deficiency anemia) is the most common form of malnutrition in the Filipino population, especially in children [6, 8]. Despite its importance in the etiology of so many disorders, iron deficiency anemia has not received the necessary attention in many public health spheres [9]. This is thought to be due to several factors. First, the relatively subtle effects of anemia are less apparent compared to the dramatic effects of vitamin A (night blindness and xerophthalmia) or iodine deficiency (goiter and cretinism), resulting in the misconception that anemia is a consequence of other disease processes rather than a primary target for intervention [3]. Second, another misconception is that iron deficiency anemia should be addressed therapeutically by the medical profession. © 2015 Nestec Ltd., Vevey/S. Karger AG, Basel
like phytate or polyphenols that limit iron absorption [13].

The physiological consequences of iron deficiency affect the individual at many levels (table 1). Iron deficiency has a direct effect on cognitive function [20]. A deficiency in iron during the neonatal period and in early childhood is an important factor in perturbing cognitive development [21, 22]. Depending on the duration and severity of the iron deficiency, these cognitive deficits may be irreversible. The well-known effects of iron deficiency on memory, intelligence and sensory perception have a direct impact on school performance, later translating into decreased economic productivity and earning potential [21, 22]. Iron deficiency also impairs immune function, increasing an individual’s susceptibility to infections [23, 24]. In pregnancy, iron deficiency can cause irreversible changes to fetal biochemical and cellular processes, for example, affecting kidney and neuronal development in the fetus [25, 26].

In the Philippines, the highest prevalence of iron deficiency anemia is seen in infants aged 6–11 months (56.5%), followed by children aged 12–23 months (41%) [6, 27]. The proportion of children up to 5 years of age with iron deficiency anemia remains high, ranging from 20 to 50% depending on the region [7]. Similarly, around half of pregnant women in the Philippines are anemic, a factor which may contribute to the infant mortality rate, one of the highest in Southeast Asia [8]. Not surprisingly, a high incidence of low birth weight and prematurity has also been reported in the Philippines [8]. Studies in birth cohorts from low- to middle-income countries (including the Philippines) have shown that preterm or term small-for-gestational-age birth was associated with deficits in adult height and reduced schooling attainment and that this pattern was consistent across all birth cohorts [28, 29].

Therefore, multiple arguments support the investment for improving iron status. Ensuring adequate iron status will enhance individual health, with a positive impact on physical and cognitive productivity [9]. In turn, this will increase the individual’s ability to contribute socially and economically. The key window of intervention lies during the first 1,000 days of life. This is the critical period of brain development when adequate iron status is crucial for ensuring the optimal morphologic, cellular and biochemical processes that modulate brain function [20, 28]. Addressing the iron status of children will have effects that cascade throughout later life, improving the rates of illness and school dropouts (reducing public expenditure in health and education) and strengthening their long-term economic prospects [9]. The additional benefit of targeting children and pregnant mothers is that this can compensate for cultural biases against girls and facilitate optimal health for both genders [9].

**Food Fortification as a Tool for Addressing Micronutrient Deficiency**

The fortification of commonly consumed food items presents an opportunity to increase the nutrient intake of a population, thereby improving nutritional status [30]. In developed countries, iron fortification of staple food items has long been used to increase the iron intake of the population [31]. There are three categories of the most commonly used food vehicles employed for this purpose: staple food items (rice, oils and wheat), condiments (fish sauce, soy sauce and sugar) and processed commercial food items (infant complementary foods, dairy products and noodles) [32]. The effectiveness of any intervention that seeks to improve the nutritional status of a target population depends upon several factors, including the delivery system, the recipients’ compliance and the perceived benefits [33, 34]. Iron fortification of different food vehicles has been successfully used to deliver iron to large segments of the population, including flours (in Venezuela), fish sauce (in Vietnam), soy sauce (in China) and rice (in the Philippines) [31].

However, these foods are suitable for older children and adults, but targeting infants and young children poses several challenges. This target population requires spe-
cialized food vehicles [1]. In infants and young children, the use of fortified complementary foods has been shown to be more effective compared to supplements [35]. Three large trials in children between 1 month and 4 years of age in Nepal, India and Africa demonstrated that children who received additional iron/folic acid plus zinc in the form of supplements experienced more adverse effects compared to those who received only placebo, raising concerns on potential negative zinc-iron interactions and questioning the safety of this strategy [36–39]. In contrast, no safety issues were raised when iron and zinc were delivered through food, suggesting that these adverse interactions are minimized with this strategy [39, 40]. Another issue that has been raised is compliance, a factor which may have affected the safety outcomes in the iron/folic acid and zinc supplementation trials [40]. A study in northern India evaluated user compliance for two home-based fortification strategies for providing iron and zinc: a rice-based fortified complementary food versus a sprinkle delivered in sachets in children aged 6–24 months [40]. The authors found that the use of the fortified complementary food for 6 months resulted in a significant increase in mean hemoglobin levels and that it had a higher compliance than the use of sprinkles [40]. These findings have been supported by a number of other studies, indicating the advantages of using fortified foods over micronutrient supplements, particularly for infants and young children [41, 42].

Fortified complementary foods for infants older than 6 months typically consist of milk or cereal-based products to be used in combination with continued breastfeeding. One of the problems is that these food items are often excluded from national programs that provide fortified foods for the general population [43]. In comparison to the efficacy of other types of fortified foods, there are relatively little data on the effects of fortified milk and cereals in children. A recent meta-analysis compared the impact of micronutrient-fortified milk and cereal-based products versus similar nonfortified items in children between 6 months and 5 years of age [43]. This analysis included 18 randomized controlled trials and 5,468 children. The study concluded that the use of fortified milk and cereal-based products was more effective in reducing anemia in young children in developing countries compared to nonfortified products. Blood hemoglobin was significantly increased by 6.2 g/l and the risk of anemia was 50% lower in children receiving the fortified milk or infant cereals. Furthermore, results from the study revealed that fortification with iron plus multiple micronutrients was more effective than iron fortification alone for improving hematological parameters [43].

The benefits of fortified complementary foods for reducing iron deficiency have also been demonstrated by several independent groups. One study illustrated the effectiveness of fortified milk and noodles in reducing anemia in Indonesian children aged 6–59 months from a large sample of families (total of 81,885) living in rural and urban slum areas [44]. In this population, consumption of fortified milk and noodles was associated with a significant decrease in the odds of childhood anemia [44] and stunting [45]. A double-blind group-randomized trial assessed the effectiveness of a large-scale iron-fortified subsidized milk program in reducing the rates of anemia and iron deficiency in Mexican children between 12 and 30 months of age [46]. This trial showed a significant reduction in anemia in the study population after 6 and 12 months of the fortified subsidized milk distribution program. Importantly, these effects were biologically significant and were reflected by improved serum levels of ferritin and soluble transferrin receptor, two biomarkers of body iron stores [46]. Similar findings have been reported in a systematic review on the use of iron supplements (including iron-fortified formula) in low-birth-weight infants [47].

Taken together, these data support the benefits and feasibility of using fortified milk and complementary foods to address iron deficiency in infants and young children.

The Economic Impact of Iron Deficiency

There are two ways of expressing the economic impact of a disease (including iron deficiency). First, this may be captured in terms of the ‘cost of illness’, focusing on the health-care costs and productivity losses for the affected individual. Second, the impact of a disease may be expressed in terms of ‘burden of the disease’, which identifies the impact on the affected individual in terms of years lived with disability (disability-adjusted life years; DALYs) and years of life lost [48]. The costs of illness and burden of disease are often used as indicators to reflect the impact
of a disease and thus categorize the importance of addressing each disease for policy makers.

In a study that evaluated the causal relationship between iron deficiency and functional consequences in economic terms for 10 developing countries, the median value of annual losses due to decreased physical productivity was found to be USD 2.32 per capita (0.57% of the gross domestic product) [49]. The median total losses (physical and cognitive losses combined) were USD 16.78 per capita or 4.05% of the gross domestic product. Assuming a cost of USD 1.33 per case of anemia prevented, the authors calculated the benefit-cost ratio for long-term iron fortification programs. The median benefit-cost ratio value was 6:1 for the 10 countries examined, increasing to 36:1 when potential future benefits due to cognitive improvements were included in the estimate [49]. The Asian Development Bank estimated that productivity losses due to iron deficiency anemia in manual laborers are 17% for workers who perform heavy physical labor and 5% for blue-collar workers [50]. In children, decreased cognitive performance due to iron deficiency was associated with a 4% decrease in hourly earnings in later life [50].

A recent study by Wieser et al. [48] used a health-economic model that simulated the consequences of micronutrient deficiencies (specifically iron, vitamin A and zinc) in Filipino children aged 6–23 and 24–59 months. The authors designed a model that enabled them to extrapolate the consequences of these deficiencies in childhood throughout the lifetime of the individual (fig. 1).

The total lifetime costs were reflected in the following three parameters: medical costs, which amounted to USD 30 million, production losses of USD 618 million and other intangible costs of 122,138 DALYs [48]. The bulk of the costs incurred were due to projected lifetime costs, resulting from impaired mental and physical development and the costs of premature deaths. Furthermore, the authors revealed that the burden of micronutrient deficiencies varied substantially between socioeconomic strata: the costs were 5 times higher in the poorest third of the households compared to the wealthiest third. The conclusions from this study are two-fold. First, the results underscore the importance of addressing micronutrient deficiencies in infants and young children in the Philippines. Second, this study confirms that the target population at highest risk consists of children in the very poorest households (fig. 2). This latter finding has important implications when determining the strategy for targeting this population. Not only should the food vehicle be suitable for children, but the means of delivery has to be accessible to families in the lowest socioeconomic strata in the Philippines [48].

**Cost Savings Associated with Food Fortification**

While there is evidence to support the cost-effectiveness of food fortification strategies in general, there is relatively little information on the cost-effectiveness in preschool children. Extending on the findings of previous work on the effectiveness of milk and cereal fortification...
in infants and young children [43] and on the cost burden of iron deficiency in the Philippines [48], Wieser et al. [51] evaluated the feasibility and cost-effectiveness of using fortified powdered milk in 1,800 Filipino households. The authors designed different price-based interventions with fortified powdered milk in order to assess the effectiveness and cost-effectiveness of each intervention in the reduction of iron and vitamin A deficiencies in Filipino children aged 6–23 months. Powdered milk was selected as the most appropriate vehicle, since it is a widely used food item for this age group in the Philippines and is well integrated into the local dietary habits. Using a questionnaire designed for a household survey, the authors obtained results from 1,800 low- to middle-income households with at least one child aged 6–23 months. In these households, the target respondents were mothers who were also the primary decision makers regarding food purchased for the child [51].

The findings from this study have several implications. First, the authors found that a large proportion of the households (32% in the lowest and 83% in the highest socioeconomic quintile) are already using fortified powdered milk on a regular basis. This strengthens the case for using fortified powdered milk as a vehicle for intervention. Second, and not surprisingly, the poorer households were more price sensitive, meaning that they would buy more milk if the price was lower. Third, the authors observed that the nutritional knowledge of the mothers (awareness) had no impact on the demand for fortified powdered milk, that these products were widely available (availability) and that product price was one of the main drivers of demand (affordability). Taken together, these findings suggest that in order to ameliorate nutritional deficiencies using fortified powdered milk, the child’s family must first be in a position to purchase the product. One of the mechanisms by which this can be brought about is through lowering the price of the product [51]. The poorest households also exhibit a greater price elasticity, where a small change in price can effect a larger change in demand, compared to wealthier households. The authors concluded that the most cost-effective interventions are those targeting the poorest 20% of the population, since the costs of intervention increase more rapidly relative to the additional DALY gains if the intervention is extended to the wealthier segments of the population [51].

Other studies have also demonstrated that, in general, cost is a significant factor influencing the purchase of food items, particularly in poorer households. A study in South Africa showed that purchasing healthier food items resulted in 69% higher daily costs and that these cost increases represent a high proportion of the total income for much of the population [52]. A Chinese study found that, in rural populations, food fortification was a cost-effective strategy. The authors compared the costs of supplementation, food fortification and dietary diversifica-
tion per DALY [53]. The results indicated that for iron deficiency, food fortification was the most cost-effective method (expressed in international dollars; $) with a cost of $66 per DALY, whereas supplementation and dietary diversification had estimated costs of $179 and 103 per DALY, respectively. The authors concluded that food fortification is one of the more effective strategies for targeting rural populations [53]. It is important to note that when designing intervention programs that target a specific population, cost may not be the only factor to consider, as consumers are also sensitive to the taste [54], color [55] and texture [56] of the food items involved, showing that acceptance of the fortified product is key.

Conclusions
The effectiveness of any intervention which aims at improving the nutritional status of a population depends on a number of variables, including the delivery system, the recipients’ compliance, as well as the characteristics of the target population [34]. Food fortification remains a promising means of addressing micronutrient deficiencies, particularly for infants and young children. The ideal characteristics of a food vehicle for fortification include the following: (1) it enables the intervention to reach the target population, using existing or improved food delivery systems; (2) it does not require major changes in a population’s dietary patterns, and (3) regular consumption of the fortified item enables the individual to maintain steady body stores of the nutrient in question [32]. Current evidence suggests that food fortification is a cost-effective means of addressing iron deficiency at the population level, particularly in infants and young children.

Disclosure Statement
Partial research funding was received from the Nestlé Research Center, Lausanne, Switzerland, to conduct this study.

References


