Hot Topics in Nutrition – 75 Years Later

Editor
Ferdinand Haschke, Salzburg

Editorial Board
Jatinder Bhatia, Augusta, GA
Carlos Lifschitz, Buenos Aires
Weili Lin, Chapel Hill, NC
Andrew Prentice, Banjul/London
Frank M. Ruemmele, Paris
Hania Szajewska, Warsaw
Fred Were, Nairobi

Supported by Nestlé Nutrition Institute
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 latest medical and scientific information to health professionals in the field of pediatric and adult 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 Editor
F. Haschke is an executive board member of the Nestlé Nutrition Institute.
Contents

5 Foreword
Saavedra, J.M. (Vevey)

6 Editorial
Haschke, F. (Salzburg)

8 Timeline of Annales Nestlé

Hot Topics in Nutrition

12 Focus/Summary

13 Evidence-Based Medicine and Clinical Research: Both Are Needed, Neither Is Perfect
Szajewska, H. (Warsaw)

24 Focus/Summary

25 Nutrition for Preterm Infants: 75 Years of History
van Goudoever, J.B. (Amsterdam)

32 Focus/Summary

33 Food Allergy Prevention and Treatment by Targeted Nutrition
Heine, R.G. (Vevey)

46 Focus/Summary

47 The Double Burden of Malnutrition in Countries Passing through the Economic Transition
Prentice, A.M. (London/Banjul)

55 Focus/Summary

56 Nutrition for the Next Generation: Older Children and Adolescents
Das, J.K. (Karachi); Lassi, Z.S. (Adelaide, SA); Hoodbhoy, Z. (Karachi); Salam, R.A. (Karachi/Adelaide, SA)

The above articles were originally published as a supplementary issue of Annals of Nutrition and Metabolism and are reprinted here with permission.
Policy Statement

Annales Nestlé appears three times a year. Each article is supported by a Focus Page, and each issue by an Infographic illustrating the core topic. Published on www.nestlenutrition-institute.org as well as in print, Annales Nestlé 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 regard it enjoys in medical and scientific circles. The editorial board sets the editorial policy, identifies topics to be addressed, selects authors, and oversees the review process for each issue.

Every issue of Annales Nestlé initially appears as a supplement to Annals of Nutrition and Metabolism – a journal from Karger Publishers, Basel, Switzerland – and is listed in all major bibliographic services, such as Medline, PubMed, and Web of Science. This has been our practice since 2011.

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

Natalia Wagemans, MD
Global Head
Nestlé Nutrition Institute
Vevey (Switzerland)
Foreword

We are proud to present to you the 75th anniversary issue of Annales Nestlé.

The origins of Nestlé, exemplified by Henri Nestlé’s first commercial product, are rooted in infant and childhood nutrition guided by the scientific knowledge of the time. And since its very beginnings, the dissemination of knowledge in pediatric health and nutrition guided the progress and development of the enterprise.

Annales Nestlé, a continuously running publication dedicated to the propagation of this knowledge, began when Nestlé was marking 75 years of its 150-year history. The contents of each issue of Annales reflect the topics of interest and the state of the art and knowledge of the time, providing historical insights into the evolution of infant health and nutrition, as explained in the Editorial of this issue by Prof. Ferdinand Haschke.

As such, Annales Nestlé epitomizes this longstanding commitment to education in nutrition. Annales today constitutes the longest standing pillar of the Nestlé Nutrition Institute, which was created to consolidate and further expand this commitment. The Nestlé Nutrition Institute is dedicated to providing the most up-to-date information in nutrition science as well as clinical and public health nutrition, using all channels, including print and digital technologies, to enhance its reach, and serve all those devoted to supporting the healthy growth and development of infants and children worldwide.

Prof. Jose M. Saavedra, MD
Chairman of the Board
Nestlé Nutrition Institute
This edition of Annales Nestlé is a significant milestone in the history of pediatric medical communications. It is the 75th year in the international series that was originally launched in 1942, following on from an exclusively French-language version that first appeared in 1935.

Although eminent exceptions do exist, few publications manage to survive in continuous form for as long as three-quarters of a century. That Annales Nestlé has reached this anniversary is a tribute to the editors-in-chief, editorial board members, and contributors who have given the publication purpose, direction, and authority over the seven and a half decades since its first inception. It is also a tribute to the many healthcare professionals who have read Annales Nestlé over the years, using its content to keep abreast of new directions in the rapidly evolving field of pediatric medicine in general and, more recently, pediatric nutrition in particular. Last but not least, it is a tribute to the vision and commitment of Nestlé, which has consistently supported the review through its various incarnations, and which continues to do so today via the Nestlé Nutrition Institute.

The editorial decision to focus exclusively on nutrition, which dates from 1995, was taken in response to the speed of developments taking place in pediatric medicine as a whole. This focus has been maintained ever since. The subject of pediatric nutrition was always an important concern of Annales Nestlé, however, with articles on breast milk (1950), rickets (1951), vitamins (1951), pre-term nutrition (1953), and nutrition and eczema (1953) appearing alongside papers on topics as diverse as whooping cough, rheumatism, and premature pneumonia during the review’s early years. The social and emotional context of pediatric medicine has also featured on occasions, with contributions on, for example, social influences on the physiopathology of children (1951), the beaten child (1968), and accidents in children (1968).

Writing in the Foreword to the milestone 40th edition, which appeared in October 1982, the Editorial Committee observed: “The review enjoys a wide readership, with a print run of 60,000 being distributed in many countries, and this in five languages (English, German, Spanish, French and Portuguese). This considerable success obliges us to continually strive for further improvements.” In their preface to the 60th anniversary edition (volume 60, number 3, 2002), the Editorial Committee provided an update: “More than 120,000 copies of this review are distributed three times per year in five languages (English, French, German, Spanish and, more recently, Chinese).” They went on to observe: “Its objective is to keep updated the pediatric community and others interested in infancy by relating research progress in the fields of epidemiology, diagnostic, prevention and treatment of the principal illnesses that strike children in different parts of the industrialized and developing world. Thus, it addresses a varied public whose preoccupations are not necessarily the latest developments in molecular biology or imaging devices, but the means to fight malnutrition, infections and their consequences for the development of the child.”

Today, the content of Annales Nestlé is initially published in Annals of Nutrition and Metabolism, a leading international peer-reviewed journal (current impact factor 2.42). It then appears as Annales Nestlé, being mainly distributed in online form via the Nestlé Nutrition Institute (www.nestlenutrition-institute.org). The journal therefore addresses a global readership, bringing state-of-the-art thinking on pediatric nutrition to the scientific
community as well as to many pediatricians who work in remote parts of the world. The Editorial Board of *Annales Nestlé* would like to thank Prof. Bert Koletzko, the Editor of *Annals of Nutrition and Metabolism*, for his excellent support and cooperation during the past years.

The evidence-based, holistic, and global view of pediatric nutrition that characterizes *Annales Nestlé* is well represented in this 75th issue, with contributions from authors based in The Gambia, Pakistan, Poland, the Netherlands, Switzerland, and Australia. Topics which were burning decades ago and are still sensitive were selected for this issue.

In his paper “The Double Burden of Malnutrition in Countries Passing through the Economic Transition,” Andrew Prentice outlines how, although many low- and middle-income countries (LMICs) are undergoing economic advancement, the accompanying “nutrition transition” occurring within their populations is triggering a new health challenge. Increasingly sedentary lifestyles and energy-dense diets have led to a rapid increase in the prevalence of overweight and obesity. Improvements in nutrition in many LMICs have succeeded in reducing rates of stunting, but in Africa, rapid population growth has led the absolute number of children suffering from stunting to rise. The populations of many parts of Africa, as of many other LMICs, are faced with the “double burden” of malnutrition, whereby under- and overnutrition are simultaneously present in the same population, and sometimes even in the same individual. Prentice hopes that these countries will at least have the benefit of learning from the experience of other countries that have previously undergone the “nutrition transition” and all it entails.

Focusing on the nutritional requirements of older children, adolescents, and young women of childbearing age, Jai K. Das and fellow contributors note that supplementation of the diet with iron and multiple micronutrients has been shown to reduce levels of anemia, but that evidence for effective strategies to prevent and control malnutrition and obesity is lacking, especially in developing countries. The diet and nutritional status before and during pregnancy can have a long-term effect on the nutritional status, growth, and health of offspring. Stressing the intergenerational link between adequate nutrition before and during pregnancy and the health of future generations, the authors argue that guidelines are needed to support nutrition interventions targeting these sections of the population.

Hans B. van Goudoever’s contribution focuses on a much younger demographic – preterm infants – and discusses the crucial role played by human milk in delivering adequate nutrition to support growth and health during this vulnerable life stage. Placing his observations within the context of the history of modern preterm care, van Goudoever references the first article that *Annales Nestlé* published on the subject of the nutrition of neonates, which appeared in 1983. van Goudoever discusses the development of human milk fortifiers, essential for meeting the high nutritional requirements of infants born premature, and also outlines improved methods for pasteurizing human donor milk.

Given the steadily rising prevalence of food allergies, food allergy prevention has become a global health priority. Breastfeeding is a key pillar of primary allergy prevention, and in recent years, research has encouraged the proactive introduction of hypoallergenic formulas in non-breastfed infants and of food allergens from the age of 4 months. Ralf G. Heine discusses this in his contribution, “Food Allergy Prevention and Treatment by Targeted Nutrition,” and also assesses the transformations that have recently taken place in the treatment of food allergies, with immunotherapy via the oral or epicutaneous route offering the promise of effective future treatment strategies.

None of the above articles – or indeed any of the articles that have appeared in *Annales Nestlé* during the past 75 years – would have been possible without the contribution of evidence-based medicine (EBM) and clinical research. Hania Szajewska argues that although EBM had a positive influence on medical practice in the last quarter of the 20th century, it still needs further refinement, and that considerably more rigor is required in the design, execution, analysis, and reporting of clinical research. Szajewska’s belief is that the collation, combination, distribution, and analysis of data from new sources – “big data” and “real-world data” – have the potential to bring about significant improvements in both EBM and clinical research, which are both likely to be transformed in the process.

From the perspective of this 75th anniversary issue of *Annales Nestlé*, it is intriguing to ponder which issue of this review might carry a discussion of how the changes envisaged by Szajewska have come about, and what improvements they have made to pediatric practice. The 100th, perhaps?

Thanks to Jonathan Steffen, who helped with the research, and thanks to all who have made this milestone issue of *Annales Nestlé* possible, along with all the many issues that preceded it.

*Prof. Ferdinand Haschke, MD*

Guest Editor of the 75th issue of *Annales Nestlé*

April 2018
Ever since its inception, **Annales Nestlé** has disseminated best practice in the treatment of critical pediatric conditions. The following timeline is a selection from among the many topics covered by the journal over the years. Considerations of space preclude the presentation of all the papers published, but our thanks go out to all the contributors and editors who have created this ground-breaking body of work in the field of pediatric medicine.
1949

Weller isolates the varicella virus, leading to a greater understanding of chickenpox.

1950


1951

Enders and colleagues create the world’s first measles vaccine.

1952

The WHO launches the Intensified Smallpox Eradication Programme.

1953

Great Ormond Street Hospital leads the first UK clinical trials of the rubella vaccine.

1954

The first heart and lung bypass machine for children is used at Great Ormond Street.

1955

Del Mundo establishes the first pediatrics department in the Philippines.

1956

Nestlé launches the first infant formula with demineralized whey.

1957

The Indian Academy of Pediatrics is established in Mumbai.

1958

Nestlé launches the first infant formula with demineralized whey.

1959

Nestlé infant cereal is rebranded as Cerelac.

1960

The first leukemia research unit in Britain is established, at Great Ormond Street Hospital (London).

1961

The first live poliovirus vaccine, developed by Sabin, is licensed.

1962

The first live poliovirus vaccine, developed by Sabin, is licensed.

1963

The first live poliovirus vaccine, developed by Sabin, is licensed.

1964

The role of infection in mortality of premature babies.

1965

The role of infection in mortality of premature babies.

1966

1967

1968

1969

1970

1971

1972

1973

1974

1975

1976

1977

1978

1979

1980

1981

1982

1983

1984

1985

1986

1987

1988

1989

1990

1991

1992

1993

1994

1995

1996

1997

1998

1999

2000

2001

2002

2003

2004

2005

2006

2007

2008

2009

2010

2011

2012

2013

2014

2015

2016

2017

2018
Renamed Nestlé S.A., the company continues its diversification strategy outside the nutrition sector.

The Nestlé Nutrition Council is founded.

Nestlé is one of the first companies to develop policies based on the WHO code on breast milk substitutes and to apply them across its business.

Maternal Nutrition in pregnancy: eating for two?, based on the workshop held in the previous year, is published.

Nestlé introduces the first infant formula with probiotics.

Nestlé develops the first partially hydrolyzed infant formula.

The first Nestlé Nutrition Workshop is held in Vaucluse, France.

Annales Nestlé is edited in 5 languages (English, French, German, Spanish, Portuguese).

The World Health Assembly formally adopts the international code of marketing of infant formula and other products used as breast-milk substitutes, following initial endorsement in 1980.

The 27th World Health Assembly establishes the Expanded Programme on Immunization.

Maternal Nutrition in pregnancy: eating for two?, based on the workshop held in the previous year, is published.

WHO confirms that HIV can be passed from mother to child during breastfeeding.

In the USA, a major advance in the prevention of HIV infection is achieved by treating infected mothers with zidovudine during pregnancy.

The last case of indigenous polio in the Western Hemisphere occurs (in Peru).

The First International Conference on Nutrition produces a World Declaration on Nutrition.

The 27th World Health Assembly establishes the Expanded Programme on Immunization.

The UN hosts the first World Food Conference.

The World Health Assembly formally adopts the international code of marketing of infant formula and other products used as breast-milk substitutes, following initial endorsement in 1980.

The 27th World Health Assembly establishes the Expanded Programme on Immunization.

The UN hosts the first World Food Conference.
Nestlé acquires Wyeth Nutrition, the infant formula division of Pfizer.

Creation of Nestlé Skin Health.

Nestlé develops formula with Human Milk Oligosaccharides.

The first National Immunization Days against polio begin in Sudan.

A new alternative to open heart surgery for children is invented at Great Ormond Street.

Pediatric Emergency Medicine Switzerland (PEM) is founded in Fribourg, Switzerland.

The WHO establishes a high-level Commission on Ending Childhood Obesity.

UN Secretary-General Ban Ki-moon launches the ‘Zero Hunger Challenge’.

The Scaling Up Nutrition (SUN) movement releases ‘Scaling Up Nutrition – what will it cost?’


The American Academy of Pediatrics finds that breastfeeding can help protect against sudden infant death syndrome (SIDS).


Pediatric Emergency Medicine Switzerland (PEM) is founded in Fribourg, Switzerland.
To avoid wasting time and resources, research needs to be not only well performed, but also adequately reported

**Evidence-Based Medicine and Clinical Research: Both Are Needed, Neither Is Perfect**  
by Hania Szajewska

---

**Key insights**

Evidence-based medicine (EBM) embodies clinical expertise and the judicious application of the latest best evidence towards the care of individual patients. If available, the evidence base relies on data obtained from randomized controlled trials and meta-analyses. However, if not available, moving to a lower level of evidence from observational studies to basic research is needed. Each type of study that contributes to the larger body of knowledge has its own specific flaws. Problems with sample size, over-reliance on p values, lack of methodological rigor, and the tendency to emphasize only “positive” findings are some of the common limitations. The information explosion also poses a serious challenge, as clinicians face the problem of how to deal with the sheer volume of data.

---

**Current knowledge**  
The application of EBM towards patient treatment involves 4 basic steps. Beginning with identifying the question or problem, this is followed by gathering the best evidence to help answer the question. Then, the available evidence needs to be critically appraised before it can be applied to help in clinical decision-making. The overarching goal should be to improve health outcomes for the patient.

---

**Practical implications**  
A number of actions can be taken to overcome the limitations of healthcare research. Overall, the solutions can be broadly classified into 3 domains. First, initial efforts should focus on proper design and conduct of studies, in order to maximize the key learnings that can be derived from the data. Next, the results need to be reported in an accurate and timely manner, to facilitate the dissemination and uptake of the latest findings. Finally, the old “publish or perish” mentality needs to be overhauled to emphasize the quality of publications rather than mere quantity.

---

**Recommended reading**  
Evidence-Based Medicine and Clinical Research: Both Are Needed, Neither Is Perfect

Hania Szajewska
Department of Pediatrics, The Medical University of Warsaw, Warsaw, Poland

Key Messages
- Over the past 25 years, evidence-based medicine (EBM), defined as individual clinical expertise, best research evidence, and patient values and circumstances, has reshaped medical practice. EBM, however, is not perfect, and the concept is evolving in response to its critics.
- Much of clinical research is poorly designed, conducted, analyzed, and/or reported. Strategies for the development of high-quality research have been developed. If strictly adhered to by all stakeholders, this should lead to more valid and trustworthy findings.
- In the future, considering that new ways of obtaining health data will continue to emerge, the world of EBM and clinical research is likely to change. The ultimate goal, however, will remain the same: improving health outcomes for patients.

Keywords
Science · Research · Methodology · Evaluation · Critical appraisal

Abstract
Currently, it is impossible to think of modern healthcare that ignores evidence-based medicine (EBM), a concept which relies on 3 pillars: individual clinical expertise, the values and desires of the patient, and the best available research. However, EBM is not perfect. Clinical research is also far from being perfect. This article provides an overview of the basic principles, opportunities, and controversies offered by EBM. It also summarizes current discussions on clinical research. Potential solutions to the problems of EBM and clinical research are discussed as well. If there were specific issues related to pediatric nutrition, an attempt was made to discuss the basic principles and limitations in this context. However, the conclusions are applicable to EBM and clinical research in general. In the future, considering that new ways of obtaining health data will continue to emerge, the world of EBM and clinical research is likely to change. The ultimate goal, however, will remain the same: improving health outcomes for patients.

Introduction
Currently, it is impossible to think of modern healthcare that ignores evidence-based medicine (EBM), a concept which relies on 3 pillars: individual clinical expertise, the values and desires of the patient, and the current best evidence (Fig. 1). However, EBM is not perfect. A widely cited expert, John Ioannidis, professor of epidemiology at Stanford University, claims that EBM is “becoming an industry advertisement tool.” Clinical research, one of the EBM pillars, is also far from perfect. Among the prominent figures in medicine who questioned research is
Richard Horton, editor of The Lancet, who stated: “The case against science is straightforward: much of the scientific literature, perhaps half, may simply be untrue. Afflicted by studies with small sample sizes, tiny effects, invalid exploratory analyses, and flagrant conflicts of interest, together with an obsession for pursuing fashionable trends of dubious importance, science has taken a turn towards darkness” [1]. Marcia Angell, who served as the editor of The New England Journal of Medicine for over 2 decades, wrote: “It is simply no longer possible to believe much of the clinical research that is published, or to rely on the judgment of trusted physicians or authoritative medical guidelines” [2]. Ioannidis, based on a theoretical model, concluded that “most published research findings are probably false” [3]. Earlier, he also argued that as much as 30% of the most influential original medical research papers later turn out to be mistaken or overstated [4].

The situation in pediatric research is particularly difficult. Interventions tested in adults but used in infants/children may be ineffective, inappropriate, or harmful. A 2008 review, found in 6 leading journals, such as The New England Journal of Medicine, The Journal of the American Medical Association, Pediatrics, Archives of Pediatrics and Adolescent Medicine, Annals of Internal Medicine, and Archives of Internal Medicine, that compared studies in children with those in adults found that studies in children were significantly less likely to be randomized controlled trials (RCTs), systematic reviews, or studies of therapies. If such studies viewed as sources of the highest evidence are lacking, this has major implications for medical practice and the quality of care for children [5].

Even if the choice of journals and the time period assessed (3 months only) are unlikely to reflect all of the published literature, it points out a problem of many pediatric studies.

This article provides an overview of the basic principles, opportunities, and controversies offered by EBM. It also summarizes current discussions on clinical research, and how to overcome problems with EBM and clinical research. If there were specific issues related to pediatric nutrition, an attempt was made to discuss the basic principles and limitations in this context. However, all conclusions are applicable to EBM and clinical research in general.

**History of EBM**

More than a quarter of a century ago, in 1991, Gordon Guyatt, at that time a young resident at McMaster University, first coined the term “scientific medicine” (which euphemistically speaking was not well accepted by his senior colleagues), and then, the term “evidence-based medicine” [6]. Soon after, in 1996, his mentors, David Sackett and colleagues, all considered the fathers of EBM, defined it as “the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients” [7] (Fig. 1). The concept which revolutionized clinical practice worldwide was born. It has changed and, in many ways, continues to change the medical world, providing healthcare professionals a tool to determine which treatments work and which do not. Thus, it is not surprising that, in 2007, when The BMJ chose the top 15 milestones in medicine over the last 160 years, EBM was one of them, next to achievements as anesthesia, antibiotics, the discovery of DNA structure, sanitation, vaccines, and oral rehydration solution [8].

**Steps for Practicing EBM**

The following 4 steps are needed for practicing EBM (Table 1): (1) formulation of an answerable question (the problem); (2) finding the best evidence; (3) critical appraisal of the evidence; and (4) applying the evidence to the treatment of patients.

**Hierarchy of Evidence**

Although only a general guideline, a hierarchy (levels) of evidence provides useful guidance about which types of evidence, if well done, are more likely to provide trust-
worthy answers to clinical questions. Which hierarchy is appropriate depends upon the type of clinical question asked (Table 2). An extended hierarchy (levels) of evidence that includes diagnostic, prognostic, and screening studies in addition to therapeutic studies has been published by the Oxford Center for Evidence-Based Medicine [9]. Of note, irrespective of the type of question, systematic reviews are considered to offer the strongest evidence.

For intervention questions, systematic reviews and meta-analyses are followed by (in descending order of evidence strength) RCTs, cohort studies, case-control studies, case series studies, and lastly, expert opinions or theories, basic research, and animal studies (Fig. 2). Thus, if available, RCTs and meta-analyses should be used in support of clinical decision-making. If the best level of evidence is not available, moving to a lower level of evidence is needed. However, the lower a methodology ranks, the less robust the results and the less likely the findings of the study represent the objective findings; thus, there is less confidence that the intervention will result in the same health outcomes if used in clinical practice. At the base of the hierarchy is animal and basic research (cell/laboratory studies). Discussing methodological problems of animal and cell research is beyond the scope of this article. However, a number of studies have revealed that animal experiments often fail to predict outcomes in humans. Tests on isolated cells can also produce different results to those performed in the body. On the other hand, many of the remarkable discoveries would not have been possible without vital experiments on animals (e.g., organ transplantation). Moreover, since 1901, nearly every Nobel Laureate in physiology or medicine, if not all, has relied on basic/animal data for their research!

### Criticism of EBM

From the first publications related to EBM, accusations that EBM is “cookbook medicine” [10], “denigrates clinical expertise” [11], or “ignores patient’s values” [12] have been commonly used by critics. In a 2000 commentary, all of these criticisms (many of which were considered misperceptions of EBM) were addressed by Straus and McAlister [13]. However, the passage of time did not ease the criticism. Even more, nowadays, are concerns about the current direction of EBM being raised by many “EBM insiders.” Recently, Ioannidis challengingly stated that “evidence-based medicine has been hijacked” [14]. He says: “As EBM became more influential, it was also hijacked to serve agendas different from what it originally aimed for.” He also claims that clinical evidence is “becoming an industry advertisement tool.” In brief, one of

---

**Table 1. Steps for practicing EBM [48]**

<table>
<thead>
<tr>
<th>Step</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Formulation of an answerable question (PICO)</td>
</tr>
<tr>
<td>2</td>
<td>Finding the best evidence (hierarchy of evidence)</td>
</tr>
<tr>
<td>3</td>
<td>Critical appraisal of the evidence</td>
</tr>
<tr>
<td>4</td>
<td>Applying the evidence to the treatment of patients</td>
</tr>
</tbody>
</table>
the concerns is the impact of industry on the way in which research is performed and reported, and consequently, the way in which medicine is practiced, and even the definition of what constitutes health or disease. Overuse and misuse of the term EBM is another concern. As Ioannidis pointed out, there are “eminence-based experts and conflicted stakeholders who want to support their views and their products, without caring much about the integrity, transparency, and unbiasedness of science.”

In 2014, Greenhalgh et al. [15], on behalf of the Evidence-Based Medicine Renaissance Group, provocatively asked in The BMJ: “Evidence based medicine: a movement in crisis?” The group provided a number of arguments to support this view. First, it includes misappropriation of EBM by vested interests. Indeed, under certain circumstances, industry involvement/funding (i.e., commercial interests) can introduce this bias. Second, the unmanageable volume of evidence, especially clinical guidelines, being produced represents a challenge. Third, statistically significant but clinically irrelevant benefits are being exaggerated. Fourth, contrary to the original concept, EBM is currently not patient-centered. Finally, the failure of EBM guidelines to properly address patients with multiple conditions (multi-morbidity) is a problem. The coexistence of 2 or more long-term conditions in 1 patient presents unique challenges. A “one size fits all” approach with evidence targeted to a single condition and treatment option is clearly inappropriate. In the pediatric setting, many diseases that were once deadly are now cured by modern medicine; however, these patients may face multiple, lifelong health problems.

**Fig. 2.** The hierarchy (levels) of evidence (in descending order of evidence strength). RCTs, randomized controlled trials.

**Table 2.** Different types of clinical questions require different types of research

<table>
<thead>
<tr>
<th>Type of clinical question</th>
<th>Best type of study to answer the question</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapy</td>
<td>RCT; systematic review/meta-analysis of RCTs</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Controlled trial; systematic review/meta-analysis of controlled trials</td>
</tr>
<tr>
<td>Harm</td>
<td>Cohort studies; case-control studies; case studies</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Cohort studies; case-control studies; case studies</td>
</tr>
<tr>
<td>Etiology</td>
<td>Cohort studies</td>
</tr>
<tr>
<td>Prevention</td>
<td>RCT; cohort studies</td>
</tr>
<tr>
<td>Quality improvement</td>
<td>RCT</td>
</tr>
<tr>
<td>Quality of life</td>
<td>Qualitative study</td>
</tr>
<tr>
<td>Cost-effectiveness</td>
<td>Economic evaluation</td>
</tr>
<tr>
<td>Clinical examination</td>
<td>Prospective, blind comparison to gold standard</td>
</tr>
</tbody>
</table>

RCT, randomized controlled trial.

**Criticism of RCTs**

Among the most heavily criticized aspects of EBM is the use of RCTs and meta-analyses. A *randomized controlled trial* is defined as an experiment in which 2 or more interventions are compared by being randomly allocated to participants. Large, well-designed, and well-implemented RCTs are considered the gold standard for
evaluating the efficacy of healthcare interventions (therapy or prevention). RCTs are the best way to identify causal relationships and can determine efficacy (establish definitively which treatment methods are superior). The fact that they are less likely to be biased by known and unknown confounders is an added strength relative to all other study designs. However, there are some concerns with regard to RCTs. In addition to internal validity, which is the extent to which the design and conduct of a study is likely to have prevented bias or systematic error, the external validity, defined as the extent to which results may be generalized to other circumstances and beyond study populations [16], is one of the major concerns and is considered to be the Achilles’ heel of RCTs. One such example is studies carried out in term infants with results that may not be extrapolated to very-low-birth-weight infants.

**RCTs in Pediatric Nutrition**

With the increasing number of RCTs, investigators have recognized limitations of RCTs in the field of pediatric nutrition. First, critically relevant outcomes that relate to nutritional practices in infants/children may take years to become apparent. Therefore, it is difficult to design and implement RCTs that last for a sufficient time to cover more than just a small fraction of the process leading to the final outcome. Second, diet/nutritional and related exposures are complex and interrelated, and in most cases, short-term effects do not persist in the medium to long term. Most studies assess responses to single macro- or micronutrient changes, which may not reflect real-life conditions in which multiple exposures (deficiencies or potential excesses) coexist and interact to define specific outcomes. Third, the outcome of a trial is to show (or to fail to demonstrate) efficacy in achieving a desired outcome. Results of such trials can be simply and robustly interpreted in light of the specific intervention and the given study population. However, extrapolation to other populations or to interventions not exactly the same as those tested in the trial may be inappropriate. Table 3 summarizes main barriers to the conduct of randomized clinical trials.

Still, the results of RCTs may change medical practice. In pediatric nutrition research, one example of a clinical question that has been addressed by an RCT is: Does the fortification of human milk with either human milk-based human milk fortifier or bovine milk-based human milk fortifier (*intervention*) have an effect on the risk of necrotizing enterocolitis (NEC) (*outcome*) in extremely premature infants (*population*)? This RCT, involving 207 infants (birth weight: 500–1,250 g), showed that the groups receiving exclusively human milk had a significantly reduced risk of NEC and NEC needing surgical interventions.

<table>
<thead>
<tr>
<th>Table 3. Main barriers to the conduct of randomized clinical trials</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Barriers affecting all clinical trials</strong>¹</td>
</tr>
<tr>
<td>- Inadequate knowledge of clinical research and trial methodology</td>
</tr>
<tr>
<td>- Lack of funding</td>
</tr>
<tr>
<td>- Excessive monitoring</td>
</tr>
<tr>
<td>- Restrictive privacy law and lack of transparency</td>
</tr>
<tr>
<td>- Complex regulatory requirements</td>
</tr>
<tr>
<td>- Inadequate infrastructures</td>
</tr>
<tr>
<td><strong>Barriers to research in the field of nutrition</strong>¹</td>
</tr>
<tr>
<td>- Testing a nutrient</td>
</tr>
<tr>
<td>- Testing a food intervention</td>
</tr>
<tr>
<td>- Assessing dietary intake</td>
</tr>
<tr>
<td>- Selection of outcomes</td>
</tr>
<tr>
<td><strong>Additional barriers to research in children</strong></td>
</tr>
<tr>
<td>- Unethical to randomize breastfed infants into an infant formula-feeding group</td>
</tr>
<tr>
<td>- The threshold for gaining consent is often higher and more complex because parents have to make decisions about trial participation on behalf of their child</td>
</tr>
<tr>
<td>- Ethical issues (infants/small children cannot give consent)</td>
</tr>
</tbody>
</table>

¹ Identified by the European Clinical Research Infrastructure Network (ECRIN) panel in the context of the ECRIN-IA project.
intervention. Lack of blinding was one of the limitations of the study. Still, the findings strongly support the use of human milk for reducing the risk of NEC in preterm infants [17].

**Criticism of Meta-Analyses**

A meta-analysis begins with a systematic review, i.e., a review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research, and to collect and analyze data from studies that are included in the review. However, in contrast to a systematic review alone, statistical techniques are then utilized to pool the results of all of the RCTs, so that they can be analyzed together. The primary reasons for performing a meta-analysis are to increase statistical power, thus, increasing the chance to reliably detect a clinically important difference, if such a difference exists, and to improve precision in estimating effects, enabling the confidence interval around the effects to be narrowed. When determining whether results of individual trials should be pooled or kept separate, it is important to consider if the studies are sufficiently homogeneous in terms of both the question and the methods. The “PICO” acronym should ideally be the same (or very similar) across studies to be pooled: population, intervention, comparison, and outcome. Thus, it is always appropriate to perform a systematic review, and every meta-analysis should be preceded by a systematic review. However, not every systematic review should be finalized with a meta-analysis; it is sometimes erroneous and even misleading to perform a meta-analysis.

Since the beginning, meta-analyses have received criticism, being labeled as “mega-silliness” [18], “shmeta-analysis” [19], “statistical alchemy” [20], or “mixing apples and oranges” [21]. Despite these criticisms, the number of meta-analyses (including those in the field of pediatric nutrition) is increasing rapidly, and they are unlikely to disappear. However, hand in hand with the increasing number of meta-analyses is an increase in criticism. For example, concerns have been raised about the exponential increase in the number of meta-analyses. For some topics, there are more systematic reviews than individual trials included in these reviews. Ioannidis recently stated “The production of systematic reviews has reached epidemic proportions. Possibly, most systematic reviews are unnecessary, misleading and/or conflicting” [22]. Possible flaws in a meta-analysis include failure to identify all relevant studies (that is why searching one database is never enough); risk of bias in the included trials (any meta-analysis is only as good as the constituent studies); exclusion of unpublished data (inclusion of unpublished data reduces the risk of publication bias); opposite conclusions (differences in the review question, search strategy, etc. may be responsible for this); and inconclusiveness (frustrating statements such as “no clear evidence” or “further research is needed”) [23].

**Meta-Analyses in Pediatric Nutrition**

Is this accusation of overproduction of systematic reviews/meta-analyses true for pediatric nutrition? In just 2 years (2016–2017), at least 14 published meta-analyses aimed to evaluate the effect of probiotics in reducing the risk of NEC, adding to a substantial number of previously published meta-analyses on the same topic [24]. Still, as most existing meta-analyses fail to adequately account for strain-specific effects, it remains unclear which probiotic strain(s) to use. This example shows that overproduction of systematic reviews/meta-analyses may be a problem in pediatric nutrition as well. Considering that there are too many meta-analyses, perhaps it is time to go back to conducting large, multicenter, well-planned, and well-executed trials with well-defined outcomes. Something to be seriously considered by the co-authors of many published meta-analyses (such as myself!).

**Problems with Clinical Research**

In the era of EBM, the quality of clinical research, one of the pillars of EBM, is of paramount importance. However, as stated earlier, there are concerns that much of clinical research is poorly designed, conducted, analyzed, and/or reported. Consequently, the conclusions drawn from clinical research are probably false. Among the first to address this issue was Altman [25]. In a 1994 *BMJ* Editorial, he stated that “less research, better research, and research done for the right reasons” is needed. More recently, Ioannidis (alone or with colleagues) has published a large number of papers on this subject, including a highly cited publication “Why Most Published Research Findings Are False” [3]. Based on a mathematical model,
Ioannidis concluded that more than 50% of published biomedical research findings with a \( p \) value of less than 0.05 are likely to be false positive. However, not everyone agrees. For example, Jager and Leek \[26\] in another paper (again, based on a statistical model) argued that only 14% of \( p \) values are likely to be false positive. While the discussions in regard to the extent of bias may continue, it nevertheless indicates that problems exist.

Why does the quality of clinical research remain suboptimal? Important factors to consider include the following \[3\] (see also Table 4).

<table>
<thead>
<tr>
<th>Sample size</th>
<th>When the studies conducted are smaller</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effect size</td>
<td>When effect sizes are smaller</td>
</tr>
<tr>
<td>Analysis</td>
<td>When there is a greater number and less pre-selection of tested relationships</td>
</tr>
<tr>
<td>Flexibility in research design</td>
<td>When there is greater flexibility in designs, definitions, outcomes, and analytical modes</td>
</tr>
<tr>
<td>Conflict of interest</td>
<td>When there are greater financial and other interests and prejudice</td>
</tr>
<tr>
<td>“Hotness” of the research field</td>
<td>The “hotter” (more competitive) the research field</td>
</tr>
</tbody>
</table>

Table 4. Interpretation of the research findings (when they are less likely to be true) (based on \[3\])

Sample Size and Underpowered Studies
The smaller the studies, the less likely the research findings are to be true. Low statistical power weakens the purpose of scientific research and reduces the chance of detecting a true effect. It also lowers the likelihood that a statistically significant result reflects a true effect.

Effect Size
When effect sizes are smaller (often the case in underpowered studies), the research findings are less likely to be true.

Unjustified Reliance on the \( p \) Value of 0.05.
Sole reliance on \( p \) values may be problematic. Both false-positive and false-negative results are possible. Of note, in March 2016, the American Statistical Association (ASA) warned against the misuse of \( p \) values. In its statement, the ASA advises researchers to avoid drawing scientific conclusions or making policy decisions based on \( p \) values alone \[27\].

Lack of Confirmation (Replication)
The reproducibility of research is a critical component of the scientific process. There are various factors that discourage simple repetition of studies, such as a lack of scientific novelty and/or a lack of interest in interventions that have been proven effective in a single study. Still, as a rule, repeat studies are needed, as a single study is, rightly, never sufficient to change clinical practice. If research findings cannot be replicated, it means they are less likely to be true. Discordance of findings does not indicate which results are correct. Both may be incorrect; however, it indicates that difficulties exist in replicating the original findings. Publishing of both positive and negative results is important.

Pre-Selection
The greater the number of hypotheses tested, the more likely it is to find false-positive results. Similarly, the lesser the selection of tested relationships, the less likely the research findings are to be true.

Flexibility in Analysis
The more flexibility in study designs and in definitions, outcomes, and analyses, the less likely the research findings are true. Methodological rigor is likely to reduce the risk of biased findings.

“Hot” Areas of Science
The hotter the research field, the more scientific teams are likely to be involved in a particular field; this greater competition to find impressive results increases the likelihood of false findings.

Financial Interest
The greater the financial (and other) interests and prejudices in a scientific field, the less likely the research findings are to be true. In addition to financial and non-financial conflicts of interest (discussed below), this also includes manipulation of research data and fraud and/or selective outcome reporting.
In Bed with Industry

Ideally, the authors of any type of research should have no conflicts of interest. In the real world, however, this is not always the case. In many settings, research collaboration between academic investigators and industry is even encouraged by universities, public funding bodies, and governmental organizations. For example, Horizon 2020, the biggest EU Research and Innovation program, promotes collaboration with the ultimate goal of making it easier to deliver innovations.

In medicine, conflict of interest generally implies financial ties of the authors with industry. However, conflict of interest is a much broader matter. Examples of nonfinancial conflicts of interest include strongly held personal beliefs related to the research topic, personal relationships, institutional relationships, or a desire for career development [28]. Other players might also not be free of conflict of interest, either financial or nonfinancial. For example, lobbyists, patients’ associations, researchers, lawyers, medical writers, advertising and social networking specialists, physicians, administrators, and policy makers may also be industry supported [29]. Taken together, while eliminating any conflict of interest of all parts involved might be an unrealistic goal, moving toward greater transparency and disclosure of potential or factual conflicts of interest should be a priority. Compared with non-industry-sponsored studies, industry-sponsored studies tended to have more favorable effectiveness and harm findings and more favorable conclusions [30].

In pediatric nutrition, funding of research by manufacturers of infant formulae may be considered even more controversial because of the need for protection and promotion of breastfeeding. However, in the case of studies involving infant formulae, industry involvement is unavoidable, as investigators lack the means to manufacture quality infant products. Still, independently funded research to obtain reliable evidence on the effects, safety, and benefits of drugs and other commercial products and services is a desirable goal.

What Can Be Done to Solve Problems with EBM?

As a response to “systematic bias, wastage, error and fraud relevant to patient care,” a group of prominent individuals published the “EBM Manifesto for Better Health” (Table 5) [31]. Thus, the problems were not only identified, but an agenda for fixing EBM was proposed. The list of proposed solutions may not be complete. Thus, as part of the “EBM Manifesto,” anyone can contribute with suggestions through an online form.

Overall, the solutions proposed by the authors of the “EBM Manifesto” are similar to those proposed by others [16]. EBM should have the care of an individual patient as the top priority. In line with the original understanding of EBM as the integration of the best research evidence with clinical expertise and patient values, individualized application of evidence to patients, with less reliance on following guidelines, is emphasized. Research should be clinically relevant, better reported, and applied. Critical appraisal skills training, while important, should not be done in isolation; shared decision-making skills are needed. The language, format, and presentation of evidence summaries and clinical guidelines should serve those who use the evidence-based information in real practice. Publishers and journal editors have the responsibility for ensuring that published materials can be used by healthcare professionals.

What Can Be Done to Improve Clinical Research?

Standards for Conducting Research

which they discussed: (1) setting research priorities so that funding is based on issues relevant to users of research [32]; (2) research design, conduct, and analysis (key problems include poor protocols and designs, poor utility of information, statistical power and outcome misconception, and insufficient consideration of other evidence) [33]; (3) biomedical research regulation and management [34]; (4) the role of fully accessible research information [35]; and (5) incomplete or unusable research [36].

Standards for Conducting Pediatric Research

Independently, significant developments have taken place in recent years to strengthen pediatric clinical research. In 2009, the Standards for Research (StaR) in Child Health initiative was founded [37]. This initiative addressed the current paucity of and scarcities in pediatric clinical trials. The aim of the StaR is to improve the quality of the design, conduct, and reporting of pediatric clinical research by promoting the use of modern research standards, so that the evidence is methodologically robust and important.

Standards for Reporting Clinical Research

To avoid wasting time and resources, research needs to be not only well performed, but also adequately reported. There is evidence that incomplete and/or poor and/or inaccurate reporting of clinical research is a problem, thus, reducing its role in clinical decision-making. Frequent shortcomings in reporting include non-reporting or delayed reporting of whole studies; selective reporting of only some outcomes in relation to study findings; the omission of crucial information in the description of research methods and interventions; omissions or misinterpretation of results in the main article and abstract; inadequate or distorted reporting of harms; and confusing or misleading presentations of results, data, and graphs [38]. Being aware of the reporting problems, journal editors, together with other stakeholders such as methodologists, researchers, clinicians, and members of professional organizations, have developed a number of standards for reporting clinical research to ensure that all details of design, conduct, and analysis are included in the manuscript. Among others, these standards (all available at the EQUATOR Network website: www.equator-network.org) include the following: CONSORT (Consolidated Standards of Reporting Trials) [39]; PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [40]; STARD (Standards for the Reporting of Diagnostic Accuracy Studies) [41]; and MOOSE (Meta-

<table>
<thead>
<tr>
<th>Table 6. The Leiden Manifesto for research metrics: 10 principles to guide research evaluation [43]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Quantitative evaluation should support qualitative, expert assessment</td>
</tr>
<tr>
<td>2. Measure performance against the research missions of the institution, group, or researcher</td>
</tr>
<tr>
<td>3. Protect excellence in locally relevant research</td>
</tr>
<tr>
<td>4. Keep data collection and analytical processes open, transparent, and simple</td>
</tr>
<tr>
<td>5. Allow those evaluated to verify data and analysis</td>
</tr>
<tr>
<td>6. Account for variation by field in publication and citation practices</td>
</tr>
<tr>
<td>7. Base assessment of individual researchers on a qualitative judgment of their portfolio</td>
</tr>
<tr>
<td>8. Avoid misplaced concreteness and false precision</td>
</tr>
<tr>
<td>9. Recognize the systemic effects of assessment and indicators</td>
</tr>
<tr>
<td>10. Scrutinize indicators regularly and update them</td>
</tr>
</tbody>
</table>

Analysis of Observational Studies in Epidemiology) [42]. Endorsement of these reporting guidelines by journals is highly variable. However, increasingly, the editors now require that authors follow these standards when submitting a manuscript for publication.

Initiatives to Change How Scientists Are Evaluated

The current science evaluation system relies heavily on bibliometrics; thus, it promotes quantity over quality of research. However, there are a number of initiatives focusing on how to improve research quality by changing how scientists are evaluated and rewarded. One example is “The Leiden Manifesto” published in 2015 by a group of experts on altmetrics who identified 10 principles to guide better research evaluation [43] (Table 6). If followed, these criteria are likely to improve the integrity of research. At least some scientific institutions are already developing policies to encourage quality over quantity [44].

The Changing Face of Clinical Trials

Clinical research is evolving. In 2016, The New England Journal of Medicine published a collection of articles called “The Changing Face of Clinical Trials” that examine the current challenges in the design, performance, and interpretation of clinical trials written by trialists for trialists. Among others, this series covers new trial designs. Recognition of the limitations of current research methods leads towards newer research designs. Examples include pragmatic trials (the major strength is that participants are broadly representative of people who
will receive a treatment or diagnostic strategy, and there is potential for high generalizability) or adaptive trial designs (used by the investigators to alter basic features of an ongoing trial).

**“Big Data” and “Real-World Data”**

In the future, decision-making may be influenced by “big data” and “real-world data.” “Big data” (often characterized by 3 Vs: volume, velocity, and variety) is a term that describes the collection of extremely large sets of information, which require specialized computational tools to enable their analysis and exploitation [45]. A subset of “big data” is “real-world evidence” (also known as “real-world data”), defined as data derived from sources such as electronic health records, registries, hospital records, and health insurance data [46] (Fig. 3). “Real-world” data allow one to see whether a treatment works in “real” patients outside of clinical study settings [47]. However, as attractive as “big data” and “real-world data” may be, their real value and whether the evidence is unbiased remain unclear. As with a meta-analytical approach, these data will be only as good as they are accurate.

**Concluding Remarks**

All health decisions should be based on high-quality scientific data. Thus, both EBM and clinical research are needed. However, neither EBM nor clinical research is perfect. Clinical research varies significantly in quality and, therefore, in the trustworthiness of the yielded evidence. A better understanding of the strengths and limitations of EBM and clinical research is vital. Solutions to fix EBM have been proposed. Similarly, strategies for the development of high-quality research have been developed. If strictly adhered to by researchers, academia, funding bodies, industry, journals, and publishers, this should lead to more valid and trustworthy findings. In the future, considering that new ways of obtaining health data will continue to emerge, the world of EBM and clinical research is likely to change. The ultimate goal, however, will remain the same: improving health outcomes for patients.

**Disclosure Statement**

H.S. has participated as a clinical investigator, and/or advisory board member, and/or consultant, and/or speaker for Arla, Biocodex, Danone, Dicofarm, Hipp, Nestlé, Nestlé Nutrition Institute (NNI), Nutricia, Mead Johnson, Merck, and Sequoia. The writing of this article was supported by NNI.

**References**


22 Ioannidis JP: The mass production of redundant, misleading, and conflicted systematic reviews and meta-analyses. Milbank Q 2016;94:485–514.


Since the early days of caring for preterm infants, it has been widely held that human milk was the food of choice for these infants.

**Key insights**

Early nutrition has a tremendous impact on the health and developmental outcomes of preterm infants. Unlike term infants, those who are born preterm have specific nutritional requirements. For example, preterm and low-birth-weight infants are at high risk of iron deficiency, due to their lower internal iron stores at birth and higher iron demands during catch-up growth. The survival rates of preterm infants have greatly improved over the last few decades, largely due to advances in neonatal care and feeding research.

**Current knowledge**

An understanding of the key role played by folate in neural tube development was a landmark in maternal and infant nutrition. This led to the implementation of maternal folic acid supplementation policies across many countries. The development of enteral formulas and the establishment of donor milk banks were also significant advances in preterm infant nutrition. However, the ideal composition of formulas remains to be determined, and new techniques are needed to optimize the storage of human donor milk. Another key question that remains is to define the protein requirements for preterm infants.

**Practical implications**

The best practices for feeding preterm infants have evolved over the past decades. Recent studies have shown that breast milk feeding reduces the incidence of necrotizing enterocolitis and nosocomial infections in preterm infants. However, there is great variability in the composition of human milk. Current evidence supports the use of a fortifier alongside human milk to support the growth and development of these infants. Iron supplementation is also recommended at a dose of 1–3 mg/kg/day to prevent iron deficiency.

**Recommended reading**

Nutrition for Preterm Infants: 75 Years of History

Johannes B. van Goudoever

Emma Children’s Hospital – AMC & VU University Medical Center, Amsterdam, The Netherlands

Key Messages

- Early nutrition has a huge impact on the short- and long-term health of preterm infants.
- Human milk has been and is again the preferred enteral supply, although fortification is required to meet the requirements.

Keywords

Iron · Folate · Human milk · Donor milk · Fortifier · Probiotics

Abstract

As technology has advanced, survival rates of preterm infants have improved dramatically. Human milk was the primary source of enteral nutrition during the early days of neonatology, but the HIV/AIDS epidemic resulted in an increased use of preterm formula. More recently, the benefits of human milk were rediscovered, resulting in increased use of donor human milk as well. The awareness that human milk does not contain the amounts of nutrients to meet the high requirements of infants born premature resulted in the development of human milk fortifiers. The development of these fortifiers is still ongoing, as are alternative methods of pasteurization of donor milk. Those initiatives will increase the use of human milk with consequently short- and long-term benefits for preterm infants.

Introduction

Modern preterm infant care has its origins at the Hôpital de la Charité in Paris. Pierre Budin, influenced by the former head midwife of the Maternité, Madame Henry, installed the first specialized care unit for “weaklings,” as underweight infants were then referred to, in 1893 (Fig. 1). Budin was then called as head of Obstetrics at Hôpital de la Maternité in 1898. Under his direction, both hospitals became the world’s first centers of specialized study on caring for preterm infants. In his lectures to students, published in 1890, Baudin highlighted 3 main basic problems for preterm infants:

- Risk of hypothermia through cooling
- Vulnerability to infections
- Feeding

© 2018 Nestlé Nutrition Institute, Switzerland/
S. Karger AG, Basel
Although the first neonatal unit was already opened in 1893, it took a long time before anything was published on preterm nutrition in the scientific literature and especially in this journal.

The First Article on Preterm Nutrition in Annales Nestlé (Annals of Nutrition and Metabolism)

The first article that appeared in the *Annals of Nutrition and Metabolism* which was somehow related to nutrition and neonates was published by Zittoun et al. [1] from France in 1983. They investigated the effect of iron supplementation during pregnancy, and this placebo-controlled (!) trial demonstrated that iron supplements to iron-deprived mothers had no effect on the ferritin status of the newborn, on the folate status of the mothers or infants, or on the frequency of obstetrical complications. A significant relationship was found between maternal folate levels and length of gestation. The authors concluded that folate supplementation during pregnancy might reduce the incidence of preterm delivery.

Folate and Iron: Present Knowledge and Advice

That folate was important became more obvious in the following years, but not so much with regard to anemia, but as an actor in prevention of neural tube defects. Unambiguous evidence of the effectiveness of periconceptional folic acid in preventing neural tube defects has been available since 1991 [2] and is still undisputed [3]. The first governments to formulate a periconceptional folic acid supplementation policy were the United Kingdom (1992), Ireland (1993), and the Netherlands (1993); six more (Switzerland 1996, Denmark 1997, Norway 1998, Portugal 1998, France 2000, and Spain 2001) followed. Despite firm evidence, adherence is low.

Many studies have appeared regarding maternal iron supplementation since 1983, and at present it is clear that iron supplementation reduces maternal anemia incidence in pregnancy but the effects on infant outcomes are less clear [4]. Compared with controls, women taking iron supplements less frequently had low-birth-weight newborns (8.4 vs. 10.3%, average RR 0.84, 95% CI 0.69–1.03, 11 trials, 17,613 women; low-quality evidence) and preterm babies (RR 0.93, 95% CI 0.84–1.03, 13 trials, 19,286 women; moderate-quality evidence).

Fig. 1. “Maternité de Paris” from The Illustrated London News, March 8th, 1884.
Preterm and low-birth-weight infants are at high risk of iron deficiency due to low iron stores at birth and higher iron requirements due to rapid growth. Already in 1971, Lundstrom et al. [5] demonstrated that 2 mg/kg was adequate to prevent anemia in infants with a birth weight of 1,000–2,000 g at 3 months of age. The randomization procedure was that infants with odd birth dates received 2 mg iron as ferrous sulfate/kg/day starting at 0.5 months; those with even birth dates received no additional iron unless they developed anemia. Interestingly, almost 50 years later, with many additional randomized controlled trials performed, the most recent recommendation (published in the Annals of Nutrition and Metabolism December 2017 issue) is almost identical: 1–3 mg/kg/day (1–2 mg for marginally low birth weight and 2–3 mg for very low birth weight) is needed to effectively prevent iron deficiency [6]. There is some recent evidence that these levels of iron intake will prevent some of the negative health consequences associated with low birth weight, especially behavioral problems and other neurodevelopmental outcomes and possibly even hypertension.

**Milestones in Enteral Preterm Nutrition**

**Preterm Formula**

Since the early days of caring for preterm infants, it has been widely held that human milk was the food of choice for these infants. This belief, however, has not prevented some pediatricians from suggesting that human milk might not in fact be the ideal food on the grounds that its low protein content is insufficient for growth requirements. Especially the lack of adequate protein content to meet the requirements has driven the development of formulas especially designed for preterm infants. One of the earlier publications on protein content of preterm formula originated from Professor Peter Davies in 1975 [7]. He acknowledged that adequate protein intake in the early weeks of life is necessary if growth is to proceed normally. The question of optimum protein requirements for preterm infants is therefore an important one. He investigated 106 preterm infants who were fed 1 of 3 isocaloric milks for a period of 2 months. Milk A was high-protein milk (21% calories as protein), milk B was medium-protein milk (15% calories as protein), and milk C was human breast milk (7% calories as protein). Changes in weight, length, head circumference, and triceps skinfold thickness were evaluated. The results suggested that though human milk was adequate for the growth needs of the more mature preterm infants (33–36 weeks’ gestation), less mature infants (28–32 weeks’ gestation) fed human milk failed to achieve adequate growth rates compared with infants on higher protein intakes. At the same time, a landmark paper by Goldman et al. [8] appeared in the Journal of Pediatrics, warning about very high protein intake because of deleterious effects on IQ development. This study was a follow-up of an earlier double-blinded study, performed in 1963 [9], where less edema was observed in infants fed 6 g/kg/day of cow’s milk protein, but more fever, lethargy, and poor feeding behavior as well as higher levels of plasma protein than the infants fed 3 g/kg/day of cow’s milk protein in the direct postnatal phase. Specifically infants with a birth weight <1,300 g were at risk of developing strabismus and low IQ scores.

As product development enhanced, casein whey fractions were modified to increase tolerability, many studies addressed the optimal intake and relationship between energy and protein intakes.

Cow’s milk contains approximately 20% whey protein and 80% casein proteins, whereas formulas were gradually modified to a ratio of whey proteins to caseins of 60:40. These modifications resulted in a plasma amino acid pattern more resembling that of a fully breastfed infant [10]. Pivotal in that development were the studies by Kashyap and Heird [11, 12] who studied the effects of varying protein and energy intakes. These studies followed the observation that premature infants have high rates of energy expenditure, using different techniques [13, 14]. Acknowledging that sufficient energy must be provided for maintaining high rates of protein synthesis, many studies were undertaken to determine the optimal protein energy ratio in various groups [15]. This resulted in recommendations that enteral feeding infants should receive 110–135 kcal/kg/day and at least 3.6 g/kg/day of proteins [16].

While the breast milk of mothers who deliver preterm contains higher amounts of proteins, this effect diminishes after approximately 1 month. The quality of the milk may also be different, especially with regard to the immune proteins [17, 18]. These observations led to a general belief that human milk did not meet the requirements of rapidly developing preterm infants with subsequent effects on growth and development. This led to the development of formulas specifically designed for pre-
term infants. An important paper published in *The Lancet* in 1990 [19] suggested that infants fed a higher nutrient density formula for a period as short as 1 month had long lasting effects on neurodevelopment and regional brain volumes [19–21]. Preterm formula became standard feeding in many neonatal units, and rates of infants fed own mother’s milk declined significantly. Editorials with suggestive titles such as “Breast Not Necessarily Best” appeared in 1998, in an era in which AIDS and its effects became very apparent [22]. However, already 5 years later, arguments were made to use own mother’s milk because of evidence that human milk reduced rates of infections and necrotizing enterocolitis (NEC) and enhanced the developmental outcome of preterm infants [23].

**Donor Milk**

Approximately 75 years ago, human donor milk became increasingly popular throughout Europe. Especially after the Second World War, many countries started a human milk bank. Figure 2 shows the workflow in these days. Milk was collected at home, brought to a central place (blood bank or hospital) and vacuum dried. Powdered human milk was available for preterm born infants and neonates with gastrointestinal problems.

With the discovery of HIV and knowing that breast milk could serve as transmitter, many milk banks closed throughout Europe. Concomitantly, preterm formula was developed. Although preterm formula administration results in higher in-hospital growth rates than own mother’s milk, the use of cow’s milk-based preterm formula when own mother’s milk was not available has not been without controversy. Already in 1990, Lucas and Cole [24] reported that in exclusively formula-fed babies, NEC was 6–10 times more common than in those fed breast milk alone and 3 times more common than in those who received formula plus breast milk. Numerous
papers report also an association with a lower incidence of nosocomial infections when own mother’s milk is fed instead of preterm formula [e.g., 25]. Following these observations and implementing methods to prevent the transmission of contagious microbes in human milk, the use of donor milk as substitute for own mother’s milk became increasingly popular again. At present, more than 500 donor milk banks are operating around the world, most of them in Europe and South America. Processing techniques have been optimized and guidelines on the preferential use have been issued [26]. Preservation techniques have been optimized (Fig. 3), increasing the length of storage and therewith the price [27].

The exact mechanism as to how human milk exerts a beneficial effect on the prevalence of NEC is at present unknown. Many factors might contribute to the particularly increased risk of preterm infants to develop NEC (Table 1). The altered microbiome in addition to an altered immune response may be the two most important mechanisms.

The colonization of the gut of the preterm infant is progressing slower than that of a term infant, while the numbers of microbiota are reduced and less diverse. That may be influenced by the high prevalence of antibiotic use in the first period of life [28], the environment (a NICU with many selected pathogens [29]), the altered mucin production rates and quality [30], the motility [31], and the immune system.

The fetal immune system is generally characterized as tolerogenic to prevent graft-versus-host responses during pregnancy. T cells in the fetal intestinal mucosa allow for early compartmentalization of TH1 responses, predominated by TNF-α and IL-2-producing T cells early in human development [32, 33]. These fetal mucosal TH1 cells can contribute to mucosal development by producing TNF-α, which promotes the outgrowth of fetal intestinal epithelial stem cells. However, when this process is disturbed by preterm birth, preferential induction of TH1 cells may instigate an inflammatory cascade providing the underlying conditions for NEC, which might explain why premature infants are more susceptible to NEC than term infants are.

Cow’s milk protein might cause an immunomodulatory effect, for instance an increased production of TNF-α, which subsequently may result in a disturbed outgrowth of these intestinal epithelial stem cells with consequently an inflammatory bowel condition. Some evidence was provided by small studies suggesting that an exclusive human milk diet would result in lower NEC rates [34]. A recent randomized controlled trial, however, did not suggest that cow’s milk protein exposure resulted in a higher rate of NEC, when compared to pasteurized donor milk provided in the first 10 days of life [35].

Thus, most likely, several factors present, especially in unpasteurized milk, exert a beneficial effect, although results from the available high-quality studies are not overwhelming. Schanler et al. [36] did not find an effect on NEC in their blinded randomized controlled trial, but the most recent blinded randomized controlled trial did find a significant association between donor milk and the incidence of NEC [37]. These developments, the cost-effectiveness of human donor milk [38], and the potential benefits in the long term will probably lead to a policy where the use of preterm formula will only be limited to those infants of whom the parents do not want to use donor milk [39–41]. New techniques of pasteurization will increase the effectiveness of donor milk [42].

Fortification of Human Milk

With the knowledge that human milk reduces NEC and nosocomial infections and the fact that nutrient re-
quirements are not met with human milk alone, the usage of fortifiers became increasingly popular at the end of the 20th century. Variability in the composition of human milk and the high nutrient demands of preterm infants was acknowledged and commercial fortifiers became in vogue.

The first study on the use of human milk fortification was published in 1986 by Modanlou et al. [43]. They compared small groups of infants fed either preterm human milk (n = 10), fortified preterm human milk (n = 8), or premature formula (n = 12) and concluded that weight gain rates were similar in the infants fed preterm formula and fortified human milk, but infants fed preterm mother’s milk had lower rates of weight gain. Fourteen high-quality studies followed and current practice is that preterm infants receive fortified human milk. The observation is that fortification leads to higher in-hospital growth, but there are no effects on growth or neurodevelopment observed beyond infancy [44]. As time will proceed, not only cow’s milk proteins, vitamins, and minerals are supplied, but also fat and one might think of specific bioactive products. Lactoferrin is such a promising substance that might be added to the fortifiers in the future [45].

**Probiotics**

The knowledge that human milk contains bacteria originates from the 1950s [e.g., 46]. The first study that showed an effect of adding specific strains to preterm formula originated in the previous century [47]. Prior to that study, some reported the effect of adding probiotics on the microbiome [48–50]. Despite many trials that followed, and an overall clear effect of probiotic supplementation on reducing NEC incidence, probiotics were not used at all units. The heterogeneity of organisms and dosing regimens studied have prevented a species-specific treatment recommendation from being made so far [51–54]. Furthermore, quality control of the available products remains an issue [55].

In conclusion, tremendous developments, both technological and nutritional, have been made, enabling higher survival rates but also higher quality of life. The revival of the use of human milk in the NICU will affect both these outcomes, certainly when the appropriate additives will be used.

**Disclosure Statement**

J.B. van Goudoever is a member of the National Health Council and director of the National Donor Milk Bank. The writing of this article was supported by Nestlé Nutrition Institute.

**Table 1. Contributing factors to the increased risk of preterm infants developing NEC**

<table>
<thead>
<tr>
<th>Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Delayed and altered microbial colonization</td>
</tr>
<tr>
<td>- Altered mucin barrier</td>
</tr>
<tr>
<td>- Decreased gut motility</td>
</tr>
<tr>
<td>- Increased gut permeability</td>
</tr>
<tr>
<td>- Altered immune system</td>
</tr>
</tbody>
</table>

**References**


30 Reprinted with permission from: Ann Nutr Metab 2018;72(suppl 3):25–31

DOI: 10.1159/000487378

J.B. van Goudoever
Nutrition for Preterm Infants


In view of the dramatic rise in the prevalence of food allergy globally, effective prevention strategies have become a public health priority.

**Key insights**
Nutritional interventions play a key role in promoting healthy immune development, particularly in infants. A range of strategies have been explored in the prevention of food allergies. In addition to the promotion of breastfeeding, these have included the use of partially hydrolyzed whey-based formula in non-breastfed infants. Formula supplementation with probiotics or prebiotics has been shown to reduce the risk of atopic dermatitis in several studies. Maternal allergen elimination diets play a role in the treatment of breastfed infants with established food allergies but have no role in allergy prevention. Extensively hydrolyzed and amino acid-based formulas remain the main treatment options for infants with cow’s milk allergy who are not breastfed.

**Current knowledge**
Prevention strategies are based on 3 main hypotheses on the etiology of food allergies: the hygiene hypothesis, the dual allergen exposure hypothesis, and the vitamin D hypothesis. According to the hygiene hypothesis, aberrant T-helper 2 immune responses arise from a lack of environmental microbial stimulation and reduced diversity of the gut microbiome. The dual allergen exposure hypothesis (via skin and gut) suggests that infants may become sensitized via eczematous skin before tolerance has been achieved by introducing the food allergen into the infant’s diet. The vitamin D hypothesis is based on the observation that vitamin D deficiency is associated with food allergies. However, this finding requires further research.

**Practical implications**
The prolonged avoidance of food allergens beyond 12 months of age is no longer recommended. Instead, the early introduction from 4–6 months is one of the most promising food allergy prevention strategies in infants deemed at high risk of allergies.

**Prevention**
Goal: Reduce the risk of allergic sensitization to foods
- Exclusive breastfeeding
- Partially hydrolyzed whey formula (in high-risk infants, if not breastfed)
- Introduction of weaning foods from 4–6 months
- Introduction of food allergens between 4 and 11 months (in high-risk infants)
- Probiotics and prebiotics

**Treatment**
Goal: Prevent allergic reactions to food (until tolerance has developed)
- Strict food allergen avoidance (while maintaining a nutritionally adequate diet)
- Maternal elimination diet (if breastfed infant reacts to food allergens in breastmilk)
- Hypoallergenic infant formula (if not breastfed), e.g., extensively hydrolyzed or amino acid-based formula
- Oral or epicutaneous immunotherapy likely to be available soon (for children and adolescents with peanut allergy)


It remains unclear if this strategy can be applied at the population level. Strict allergen avoidance remains the key treatment principle in infants and children with established food allergies. Oral and epicutaneous immunotherapy may soon become additional treatment options in children and adolescents with peanut allergy. These novel treatment modalities aim for a clinical state of desensitization (non-reactivity) to a food allergen through regular exposure (under strict specialist supervision). However, food immunotherapy does not induce lasting tolerance, and the allergic phenotype generally recurs after the treatment is stopped.

**Recommended reading**
Food Allergy Prevention and Treatment by Targeted Nutrition

Ralf G. Heine

Paediatric Care, Nestlé Health Science, Vevey, Switzerland

Key Messages

- In view of the dramatic rise in the prevalence of food allergy globally, effective prevention strategies have become a public health priority.
- The early introduction of complementary diet and food allergens from 4 months of age is currently one of the most promising approaches in the prevention of food allergies.
- While the strict food allergen avoidance remains the main treatment strategy for food allergies, immunotherapy via the oral or epicutaneous route have emerged as effective and feasible future treatment strategies.

Keywords

Allergy · Atopy · Breastfeeding · Infant formula · Microbiome · Prevention

Abstract

In view of the dramatic rise in the prevalence of food allergy globally, effective prevention strategies have become a public health priority. Several models have emerged around the etiology of food allergy, including the hygiene hypothesis, dual allergen exposure hypothesis, and vitamin D hypothesis. These form the basis for current and potential prevention strategies. Breastfeeding remains a key pillar of primary allergy prevention. Other nutritional interventions, including the use of whey-based, partially hydrolyzed formula in non-breastfed infants, also play an important role. In recent years, there has been a shift away from prolonged food allergen avoidance to the proactive allergen introduction from 4 months of age. This approach is supported by 2 pivotal randomized clinical trials showing that the early introduction of peanut and other food allergens significantly reduces the risk of food allergy. However, the implementation of this strategy at the population level still raises significant logistic problems, including patient selection and development of suitable food formats for young infants. Other prevention strategies, including vitamin D supplementation, are currently under evaluation. Maternal elimination diets during pregnancy and lactation are not recommended for allergy prevention. The treatment of food allergies has also seen major transformations. While strict allergen avoidance is still the key treatment principle, there is a greater focus on desensitization and tolerance induction by oral and epicutaneous immunotherapy. In addition, specialized hypoallergenic infant formulas for the treatment of infants with cow's milk allergy have undergone reformulation, including the addition of lactose and probiotics in order to modulate the gut microbiome and early immune responses. Further research is needed to inform the most effective food allergy prevention strategies at the population level. In addition, the wider application of food allergen immunotherapy may provide better health outcomes and improved quality of life for families affected by food allergies.
**Introduction**

Over the past 2 decades, the prevalence of allergic disorders has increased dramatically [1–3]. The greatest increase has been observed in infants and children with food allergies or atopic eczema [4, 5]. In Europe and Northern America, food allergy is estimated to occur in 1–5% of the population [1]. In Australia, a population-based study found a prevalence of challenge-proven food allergy of over 10% which is the highest rate globally [6]. Overall, prevalence figures for food allergy and anaphylaxis appear to be steadily rising [7]. Effective allergy prevention has therefore become a global public health priority [8].

Nutritional interventions play a central role in the prevention and treatment of food allergies (Table 1). In recent years, clinical approaches have undergone significant changes [3]. In the food allergy prevention space, greater focus has been placed on the early introduction of the complementary diet in infancy [9] (Fig. 1). This is in contrast to the previous approach of prolonged food allergen avoidance which, in hindsight, may have paradoxically increased the rate of food allergies [10–12]. In the area of food allergy treatment, there have also been major advances, including a shift from mere food allergen avoidance to proactive food allergen immunotherapy [13]. In addition, there is renewed interest in the role of gut microbiome-modifying therapies in an attempt to promote immunological tolerance development via the gut-associated immune system [14–16]. This review summarizes the previous and current approaches to dietary food allergy prevention and treatment and highlights areas of uncertainty or controversy, as well as priorities for future research.

**Breastfeeding**

Breastfeeding is one of the main pillars in both food allergy prevention and treatment [17–21]. Breast milk provides the most appropriate source of nutrition for the young infant as it contains a specific nutrient mixture, growth factors, and protective maternal antibodies. The World Health Organization (WHO) guidelines on complementary feeding of 2001 recommend exclusive breastfeeding for at least 6 months. However, this recommendation has been challenged in countries with a high prevalence of food allergies, as the early dietary introduction of allergens appears to protect from food allergies [22, 23]. Recent guidelines on the prevention of food allergies from Europe, the USA, and Australia have recommended the introduction of solids from 4–6 months of age [24–28].

**Table 1. Nutritional strategies for the prevention of food allergy**

<table>
<thead>
<tr>
<th>General</th>
</tr>
</thead>
<tbody>
<tr>
<td>– Exclusive breastfeeding for 4–6 months</td>
</tr>
<tr>
<td>– Use of whey-based, partially hydrolyzed formula (if exclusive breastfeeding is not possible)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Introduction of complementary diet from 4 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>– Early introduction of food allergens (peanut, egg, and others) in infants at high risk of developing food allergies</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Microbiome-modifying interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>– Probiotics (e.g., <em>Lactobacillus rhamnosus</em> GG)</td>
</tr>
<tr>
<td>– Prebiotics (e.g., fructo-oligosaccharides, galacto-oligosaccharides)</td>
</tr>
<tr>
<td>– Human milk oligosaccharides (e.g. 2′-fucosyllactose and lacto-N-neotetraose)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Immune-modulating nutrients</th>
</tr>
</thead>
<tbody>
<tr>
<td>– Maternal omega-3 polyunsaturated fatty acid supplementation (docosahexaenoic acid, eicosapentaenoic acid)</td>
</tr>
<tr>
<td>– Vitamin D (under investigation)</td>
</tr>
</tbody>
</table>

Breastfeeding is associated with the establishment of fecal microbiota high in Bifidobacteria [29]. Human milk oligosaccharides (HMO) promote the colonization of the gut with Bifidobacteria which is thought to promote mucosal tolerance via interaction with regulatory T-lymphocytes and Toll-like receptors [30]. Breastfeeding itself does not appear to confer a strong protective effect against food allergies [21]. However, the duration of exclusive breastfeeding appears to influence the risk of allergic disease [31, 32]. The protective effect of breastfeeding on eczema in the first 2 years of life appears to be modified by maternal allergy status [33]. Exclusively breastfed infants can express clinical manifestations of food allergy, including food protein-induced proctocolitis and multiple food intolerance of infancy [34–37]. These often respond to treatment with hypoallergenic maternal elimination diets which eliminate cow’s milk or other food allergens [38, 39]. In some infants who failed a trial of maternal dietary elimination, treatment with a hypoallergenic formula may be required [40–42]. Maternal elimination diets during pregnancy and lactation for the purpose of allergy prevention are not recommended [18, 43].

**Prevention**

Primary food allergy prevention aims to reduce the infant’s risk of sensitization to food allergens [44]. By contrast, secondary prevention aims to prevent the clinical expression of allergic disease in individuals who are either...
allergen sensitized or who already manifest other allergic disorders, such as atopic dermatitis or asthma. The prevention of food allergies and atopic dermatitis by nutritional interventions has been explored for the past 2 decades with a broad range of approaches. In addition to the promotion of breastfeeding, these have included the use of partially hydrolyzed formula (PHF) and a range of maternal elimination diets [43, 45]. Supplementation with probiotics, prebiotics, and specific nutrients has also been explored [46, 47]. Some of these interventions have been trialed in high-risk populations, either in families with a history of allergies, or in infants who are showing evidence of food sensitization or eczema. Other studies have assessed the preventive effect of interventions at the population level without selecting for allergic history. This distinction is important when the findings of prevention trials are translated into population-based health policies [22, 48].

Prevention strategies have been developed around 3 main hypotheses on the etiology of food allergies: the hygiene hypothesis, the dual allergen exposure hypothesis, and the vitamin D hypothesis [11, 49, 50]. The following sections will summarize current preventive strategies in the context of these hypotheses.

**Hygiene Hypothesis**

Gut microbiota and environmental microbial burden play a central role in early immune development and are likely to influence immunological events that lead to allergy [49, 51, 52]. The hygiene hypothesis assumes that there is an immune deviation to T-helper 2 reactions due to reduced early microbial exposure and a lack of fecal microbial diversity [53, 54]. For example, growing up in a rural farm environment has been shown to significantly reduce the risk of asthma and allergic disease in children [49, 55]. There are significant differences in the gut microbiota profiles between allergic and nonallergic infants and children [56, 57]. Infants with IgE-associated eczema have significantly reduced fecal microbial diversity in the first month of life, compared to nonatopic infants [54, 58]. Modification of early gut colonization and fecal microbial diversity in infancy may thus provide an avenue for preventive or therapeutic strategies [59]. Probiotic or prebiotic supplementation has been shown to modify the risk of allergies, particularly for atopic dermatitis in infancy [60–62]. The World Allergy Organization Guidelines recommend the use of probiotics and prebiotics for the prevention of eczema and allergies, but caution that the available evidence is of very low certainty [63, 64].

**Probiotics**

Infants with allergies have been shown to have significantly lower numbers of fecal Bifidobacteria, compared to healthy infants [65]. Allergy prevention via supplementation with probiotic bacteria therefore appears to be a promising approach. The effects of probiotics are mainly mediated via the innate immune system (Toll-like receptors), resulting in the promotion of T-helper 1 differentiation, production of regulatory cytokines (IL-10 and TGF-beta) and enhanced intestinal IgA responses [66]. Several studies have demonstrated that perinatal administration of probiotics to mothers in the last weeks of pregnancy and to infants in the first few months of life was associated with a significant reduction in atopic ec-
Prebiotics

HMO are complex, nondigestible oligosaccharides with prebiotic properties in breast milk which provide a specialized substrate for Bifidobacteria. In the past, infant formulas were devoid of prebiotic oligosaccharides [71]. Over the past decade, several manufactured prebiotics have been added to infant formula, including plant-based long-chain fructo-oligosaccharides (FOS) and short-chain galacto-oligosaccharides (GOS). GOS and FOS have been shown to increase counts of fecal Bifidobacteria in formula-fed infants [72, 73]. A randomized study examined the effects of a FOS/GOS-supplemented hydrolyzed formula on atopic eczema in formula-fed infants during the first 6 months of life [74]. In that study, the FOS/GOS group had significantly lower rates of eczema compared to the placebo group, although eczema severity was similar for both treatment arms. A more recent European multi-center randomized controlled trial assessed the effect of prebiotics in healthy, low-risk infants from 8 weeks to 12 months [75]. Prebiotics reduced the incidence of atopic dermatitis by 44% at 12 months. Again, disease severity was not affected. Further studies are needed to assess the role of GOS and FOS in allergy prevention [62].

HMO in breast milk provide the substrate for specific microbes and significantly influence early microbial gut colonization [76, 77]. Recently, 2 manufactured HMO (2′-fucosyllactose and lacto-N-neotetraose) have been added to standard cow’s milk-based formula [78]. In preclinical studies, HMO have been shown to attenuate allergic responses in cow’s milk-sensitized mice [79]. The role of HMO in the prevention and treatment of food allergies is at this stage not clearly defined but represents a promising area for future research [80, 81].

Dual Allergen Exposure Hypothesis

The dual allergen exposure hypothesis (via skin and gut) is based on the observation that infants with eczema have a high risk of developing IgE-mediated food allergies [11]. While allergen contact via eczematous skin may cause allergic sensitization, the exposure via the gastrointestinal tract is more likely to induce immunological tolerance [11, 82, 83]. Prolonged avoidance of a food allergen in infants with eczema may paradoxically increase the risk of food allergies [12, 84]. Previously, the delayed introduction of common food allergens (cow’s milk after 12 months, egg after 2 years, and peanut after 3 years) was recommended in an attempt to prevent food allergy [10]. Findings from several small studies provided support for the concept of a “window period” for tolerance induction, whereby tolerance is more likely to be achieved if weaning solids are introduced between 4 and 6 months of age. This reflects feeding practices in many European countries, but is not supported by the WHO guidelines on complementary feeding.

The Australian HealthNuts Study showed that the risk of developing egg allergy increased significantly if egg was introduced after 12 months of age [85]. This finding prompted to question the recommendation of delaying the introduction of egg beyond 12 months of age. The LEAP (Learning Early about Peanut) study was the pivotal study demonstrating that the early introduction of peanut into the infants diet from 4 months conferred a protective effect against peanut allergy in high-risk infants [86]. This study was based on the observation that infants in Israel who were exposed to peanut in a teething snack had a low risk of peanut allergy, while Jewish infants in the United Kingdom who introduced peanut generally after 12 months of age had a high risk. The subsequent clinical study enrolled infants with pre-existing egg allergy or eczema and randomized them to introduce peanut from 4 months, or to continue strict peanut avoidance. The study showed overwhelming evidence of a protective effect against peanut allergy (70–86% relative incidence reduction) in those who introduced peanut early between 4 and 11 months of age. A supplementary analysis found that the skin prick test wheal diameter at the time of peanut introduction predicted the tolerance development in those who avoided peanut, with the greatest benefit seen between 6 and 11 months [87]. This analysis provided additional insights on the best timing of the dietary introduction of food allergens in high-risk infants.

A second study, the Enquiring about Tolerance (EAT) study, prospectively examined if the early introduction of
6 food allergens (from 4 months of age) while breastfeeding could reduce the risk of food allergy in a nonallergic population [88]. On per-protocol analysis, there was a significant protective effect against food allergy. However, the study overall failed on intention-to-treat analysis due to a large proportion of participants who were unable to adhere to the study regimen. This raised questions around the logistics of introducing foods early in infancy, including finding suitable food formats that would allow the delivery of food proteins in adequate doses to breastfed infants [22, 27].

**Partially Hydrolyzed Formula**

The role of hydrolyzed formula in allergy prevention has been studied for more than 2 decades. Several studies have explored the tolerogenic potential of cow’s milk peptides in hydrolyzed formula. The German Infant Nutritional Intervention (GINI) study is to date the largest, quasi-randomized trial examining the role of hydrolyzed formula in the prevention of allergies [89]. Infants with a family history of allergies were randomized to receive cow’s milk-based formula, whey-based PHF, whey-based extensively hydrolyzed formula (EHF), or casein-based EHF at the time of weaning. That study found a sustained protective effect against atopic eczema for whey-based PHF and casein-based EHF [89]. Follow-up studies of the GINI cohort have demonstrated a sustained preventive effect of hydrolyzed formulas until 10 years of age, compared to cow’s milk-based formula [90]. A Cochrane review on hydrolyzed formulas in allergy prevention found a limited beneficial effect, compared to cow’s milk-based formula, in “high-risk” infants with a family history of atopy [91]. Two other meta-analyses also confirmed a preventive effect, mainly for atopic dermatitis [92, 93]. Others have questioned the role of PHF and cautioned against overstating its preventive effects [94, 95]. Boyle et al. [96] in their meta-analysis found no support for a preventive effect of PHF against allergic disease. However, pooling of data on hydrolyzed formulas in meta-analyses may be problematic due to significant heterogeneity of PHF products. A more recent meta-analysis addressed this issue and only included studies using 100%-whey PHF [97]. That study found a preventive effect for all allergies and eczema, but acknowledged limitations in the certainty of available data. The current Allergy Prevention Guidelines by the European Academy of Allergy and Clinical Immunology (EAACI) recommend the use of PHF with a documented preventive effect in infants at high-risk of allergy if breastfeeding is insufficient or not possible [98].

**Vitamin D Hypothesis**

Several studies have demonstrated an association between low vitamin D levels and food allergy [99, 100]. An Australian study showed that vitamin D insufficiency (serum level <50 nmol/L) was associated with a significantly increased risk of egg and/or peanut allergy [101]. This finding concurred with the observation that the prevalence of food allergy and eczema follows a north-south gradient, being more common in regions with less sun exposure and lower skin-derived vitamin D levels [102]. Adequate vitamin D levels in the first year of life may therefore provide protection against the development of food allergies. By contrast, vitamin D may also have undesirable immune-modulating effects and, in high doses, increase the risk of allergic sensitization. Vitamin D has been shown to inhibit the maturation of dendritic cells and impede the development of T-helper 1 responses. In theory, vitamin D therefore could increase the risk of allergic disorders in infancy [103]. This is supported by a recent German birth cohort study (LINA study) which found that high vitamin D levels during pregnancy and at birth were associated with an increased risk of food allergy [104]. The varying effects of vitamin D on allergy risk have been explained by a U-shaped dose response curve, i.e., normal vitamin D levels may confer a protective effect while abnormally high or low levels may increase the allergy risk [100]. The aforementioned studies suggest that both vitamin D insufficiency and oversupplementation are risk factors for allergies [99]. The VITALITY trial, a prospective randomized trial, is currently underway to assess the role of postnatal vitamin D supplementation as a preventive strategy against IgE-mediated food allergy, eczema, and lower respiratory tract infections [105].

**Omega-3 Long-Chain Polyunsaturated Fatty Acids**

Maternal diets high in omega-3 long-chain polyunsaturated fatty acids (LCPUFA) are thought to have a protective effect against the development of allergies in the newborn [106]. Supplementation with docosahexaenoic acid and eicosapentaenoic acid during pregnancy has been shown to increase LCPUFA concentrations in breast milk [107]. A large randomized clinical trial of maternal
fish oil supplementation during pregnancy demonstrated a significant decrease in cord blood concentrations of Th-2 cytokines (IL-4 and IL-13) as well as increased levels of oral tolerance-inducing TGF-beta [108]. Palmer et al. [109] assessed the effect of high-dose fish oil supplementation in high-risk infants (with a positive family history of atopy). Pregnant mothers were randomized to receive either 800 mg docosahexaenoic acid plus 100 mg eicosapentaenoic acid or vegetable oil from 21 weeks’ gestation until delivery. Primary outcomes were infantile eczema and food sensitization at 12 months of age. Infants in the fish oil-supplemented group had significantly lower rates of atopic eczema and egg sensitization. In another study by the same group [110], high-risk infants were randomized to 280 mg docosahexaenoic acid plus 110 mg eicosapentaenoic acid daily or olive oil (control) from birth to 6 months of age. In that study, between-group comparisons revealed no differences in allergic sensitization, eczema, asthma, or food allergy. In summary, fish oil supplementation during pregnancy reduced the risk of atopy. Pregnant mothers were randomized to receive either 800 mg docosahexaenoic acid plus 100 mg eicosapentaenoic acid or vegetable oil from 21 weeks’ gestation until delivery. Primary outcomes were infantile eczema and food sensitization at 12 months of age. Infants in the fish oil-supplemented group had significantly lower rates of atopic eczema and egg sensitization. In another study by the same group [110], high-risk infants were randomized to 280 mg docosahexaenoic acid plus 110 mg eicosapentaenoic acid daily or olive oil (control) from birth to 6 months of age. In that study, between-group comparisons revealed no differences in allergic sensitization, eczema, asthma, or food allergy. In summary, fish oil supplementation during pregnancy reduced the risk of atopic eczema and food sensitization, whereas dietary supplementation after birth appeared to be ineffective.

The treatment of food allergies relies on the strict elimination of the offending allergens

**Treatment**

The treatment of food allergies relies on the strict elimination of the offending allergens. In exclusively breastfed infants who react to allergens via breast milk, maternal elimination diets have been shown to be effective [34, 38]. The complementary diet also needs to be free of the food allergen. In formula-fed infants with cow’s milk allergy (CMA), specialized hypoallergenic formulas are the treatment of choice. The main types of these treatment formulas are EHF and amino acid-based formula (AAF) [40, 111, 112]. Hypoallergenic elimination diets need to be carefully supervised for nutritional adequacy [38]. Despite attempts to strictly eliminate offending food allergens from the diet, accidental reactions are relatively common. The risk of inadvertent allergic reactions and anaphylaxis significantly impacts the quality of life of patients and families [113, 114]. Precautionary allergen labelling is in many instances still confusing or incomplete [115, 116]. Reassuringly, several countries have introduced legislation towards more consistent allergen labelling [117].

**Maternal Elimination Diets**

Food allergens that are secreted into breast milk may elicit allergic symptoms in the infant [118]. While maternal elimination diets have no role in primary food allergy prevention, they have become a widely used intervention in breastfed infants with food allergies [38]. Poorly supervised or broad-based maternal elimination diets are not without nutritional risks for both mother and infant [119]. The nutritional adequacy of the maternal diet should be assessed and monitored by a pediatric dietitian [120]. Calcium supplementation is generally recommended if cow’s milk products are eliminated from the maternal diet.

**Extensively Hydrolyzed Formula**

Whey- or casein-based EHF are considered the first-line treatment of formula-fed infants with CMA [121]. These formulas contain small cow’s milk peptides that are produced via enzymatic breakdown and ultrafiltration of intact cow’s milk proteins. There are significant differences in the molecular weights and profiles of peptides in EHF. This may explain differences in the risk of allergic reactions to various EHF [122, 123]. A task force of the European Academy of Allergy and Clinical Immunology (EAACI) has therefore called for stricter standards for the definition of EHF marketed in Europe, including preclinical testing, quality assurance, and labelling requirements [124]. Some recently developed EHF contain highly purified lactose. Contrary to common perception, lactose is tolerated well by most infants with CMA [125]. The only exception are infants with cow’s milk protein-induced enteropathy and secondary lactase deficiency due to villous damage (Table 2). These infants may develop increased diarrhea after lactose ingestion. However, a lactose-containing EHF can generally be reintroduced once the diarrhea has settled and the small intestinal mucosal integrity has been restored. As young infants do not absorb all ingested lactose, it is considered a prebiotic compound with positive effects on the gut microbiome of infants [126]. Compared to lactose-free formula, lactose-containing formula is associated with increased counts of Bifidobacteria and increased concentrations of short-chain fatty acids. This may confer a protective effect on colonic mucosal integrity and have a beneficial effect on early immune development [53]. There is to date no data showing a direct effect on tolerance development or allergic risk.

EHF contains trace amount of allergenic peptides and therefore has a small residual allergenicity with the risk of allergic reactions [127]. Conversely, the antigenic content in EHF may have the potential to actively promote toler-
ance development [128]. This ability may be further enhanced by the addition of probiotic bacteria or other ingredients. Berni Canani et al. [129] conducted a randomized clinical trial of EHF supplemented with *Lactobacillus rhamnosus* GG (LGG) in infants with CMA. In that trial, infants receiving the probiotic-supplemented formula had a greater chance of achieving tolerance to cow’s milk protein at 6 and 12 months of age. This effect appeared to be, at least in part, modulated by an expansion of butyrate-producing gut microbiota [130]. At the 3-year follow-up of another cohort, there appeared to be a greater rate of resolution of IgE-mediated CMA as well as a lower incidence of other allergic manifestations in response to LGG-supplemented EHF [15]. These studies highlight the potential for probiotic supplementation of EHF to hasten tolerance development as well as the importance of butyrate as a likely key mediator in tolerance acquisition. However, further clinical trials are required to confirm the tolerogenic effects of LGG and assess the potential benefits of other probiotic strains with regard to early immune development.

**Amino Acid-Based Formula**

AAF is a synthetic, nutritionally complete, cow’s milk antigen-free formula containing free amino acids, which is used in the treatment of infants with severe CMA. AAF is therefore not a first-line treatment but recommended for infants who have failed treatment with EHF, as well as infants with cow’s milk anaphylaxis [112], multiple food intolerance of infancy [36, 131], or eosinophilic esophagitis [132]. As tolerance development is thought to be an antigen-driven process [128], AAF is unlikely to promote tolerance development [128]. The addition of prebiotics or probiotics to AAF may have beneficial effects on gut microbiome, but clinical outcome data are not currently available [133].

**Other Potential Formula Options**

Should EHF or AAF not be available, other formula options may be considered. Soy formula is frequently used for economic reasons in countries with limited access to hypoallergenic formulas [134]. However, the role of soy formula in the treatment of infants with CMA remains controversial. Generally, soy formula is not recommended as a first-line treatment in infants with CMA under 6 months of age [112]. Hydrolyzed rice-based formula has become available in recent years as a hypoallergenic formula in infants with CMA [135, 136]. The hydrolysis is required due to the poor solubility and hydrophobic properties of rice protein. These formulas are tolerated well and may have a taste advantage over casein- or whey-based EHF. The exact role of hydrolyzed rice-based formulas needs to be clarified. Importantly, rice-based infant formulas must not be confused with rice “milk” beverages which are low-protein, low-energy cereal milks which are not suitable for infant feeding due to the risk of severe protein-energy malnutrition [137]. Mammalian milks, including goat’s or sheep’s milk formula, are often

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Maternal elimination diet</th>
<th>First-line formula treatment</th>
<th>Second-line formula treatment</th>
<th>Need for lactose restriction</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgE-mediated CMA</td>
<td>Only required if reacting to cow’s milk protein in breast milk</td>
<td>AAF</td>
<td>EHF</td>
<td>No</td>
</tr>
<tr>
<td>With anaphylaxis</td>
<td></td>
<td></td>
<td>EHF¹</td>
<td>No</td>
</tr>
<tr>
<td>Without anaphylaxis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cow’s milk protein-induced enteropathy</td>
<td>Only required if reacting to cow’s milk protein in breast milk</td>
<td>EHF</td>
<td>AAF</td>
<td>Yes, until diarrhea has</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>resolved and normal small</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>intestinal mucosa has been</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>restored</td>
</tr>
<tr>
<td>Cow’s milk protein-induced proctocolitis</td>
<td>Only required if reacting to cow’s milk protein in breast milk</td>
<td>EHF</td>
<td>AAF</td>
<td>No</td>
</tr>
<tr>
<td>Cow’s milk protein-induced enterocolitis syndrome (FPIES)</td>
<td>Generally not required</td>
<td>EHF</td>
<td></td>
<td>No</td>
</tr>
</tbody>
</table>

EHF, extensively hydrolyzed formula; AAF, amino acid-based formula, FPIES, food protein-induced enterocolitis syndrome. ¹ In infants with a history of anaphylaxis, EHF should be first trialed under medical supervision.

---

Food Allergy Prevention and Treatment

Reprinted with permission from: Ann Nutr Metab 2018;72(suppl 3):33–45 DOI: 10.1159/000487380
considered as alternatives to cow’s milk formula but are not suitable due to a high rate of protein homology and allergic cross-reactivity [138]. Cross-contamination with cow’s milk protein during production may also occur. Although often perceived as safe alternatives to cow’s milk formula, these mammalian milk formulas may cause significant allergic reactions, including anaphylaxis [139].

**Food Allergen Immunotherapy**

The concept of food allergen immunotherapy is not new. The concept was first described by Schofield in 1908 in a 13-year-old boy with egg allergy who was successfully desensitized by introducing egg in incremental doses [140]. Since then, 3 main clinical immunotherapy concepts to food allergens have emerged: oral, sublingual, and epicutaneous immunotherapy. The focus has so far mainly been on children with the most prevalent food allergies to peanut, egg, and cow’s milk.

Oral immunotherapy (OIT) involves the stepwise introduction of a food allergen via the oral route, starting with milligram doses [141] (Fig. 2). The administration of initial doses and stepwise updosing occurs under medical supervision, generally with fortnightly intervals, until a maintenance dose has been achieved after about 6 months [13]. For OIT to peanut, 79% of peanut-allergic patients were effectively desensitized to 443 mg of peanut protein [141]. The remaining patients were unable to tolerate the treatment due to significant allergic side effects, ranging from persistent gastrointestinal symptoms to anaphylaxis. Combination therapy of OIT with anti-IgE (omalizumab) or other biologicals is being explored as an avenue to reduce the rate and severity of adverse events during updosing [142]. Importantly, patients generally do not achieve true, lasting immunological tolerance but a state of non-responsiveness, called “desensitization.” The duration of “sustained unresponsiveness” to an allergen after cessation of OIT maintenance treatment varies, but the allergic phenotype generally recurs gradually over weeks to months [13].

Epicutaneous immunotherapy (EPIT) is based on the delivery of food allergens via intact skin [143]. The allergen is bound to a thin plastic membrane that is placed onto the skin under an occlusive patch, similar to the approach for atopy patch testing [144, 145]. The allergen is taken up by Langerhans cells in the epidermis. These are immune-competent antigen-presenting cells that have
the ability to initiate a regulatory T-cell response and communicate with regional lymph nodes. Daily application of EPIT patches containing 250 μg of peanut for 12 months in patients with peanut allergy has been shown to significantly raise the threshold dose for allergic reactions on food challenge [146, 147]. The desensitization effect is not as marked as that of OIT, but the rate of adverse effects is minimal and mainly limited to local skin irritation where the EPIT patch has been applied [143]. Guidelines for the clinical use of OIT versus EPIT in clinical practice still have to be defined.

**Conclusion**

Based on recent research, food allergy prevention and treatment have undergone significant improvements. Further research is needed to inform the most effective food allergy prevention strategies at the population level (Table 1). Effective prevention has the potential to reverse the rising prevalence trends for food allergies. In addition, the wider application of food allergen immunotherapy may provide better health outcomes and improved quality of life for families affected by food allergies.

**Disclosure Statement**

Dr. Ralf G. Heine is an employee of Nestlé Health Science, Switzerland. There are no other disclosures.

**References**


43 Kramer MS, Kukama R: Maternal dietary antigen avoidance during pregnancy or lactation, or both, for preventing or treating atopic disease in the child. Evid Based Child Health 2014;9:447–483.


42 Reprinted with permission from: Ann Nutr Metab 2018;72(suppl 3):33–45 DOI: 10.1159/000487380

Heine


119 Kramer MS, Kakuma R: Maternal dietary antigen avoidance during pregnancy or lactation, or both, for preventing or treating atopic disease in the child. Cochrane Database Syst Rev 2012;9:CD001333.


The poor and emerging nations of the world are, by definition, the least able to bear the health costs of treating serious nutrition-related conditions such as severe acute malnutrition and obesity-related diabetes.

Reprinted with permission from: Ann Nutr Metab 2018;72(suppl 3):47–54

The Double Burden of Malnutrition in Countries Passing through the Economic Transition
by Andrew M. Prentice

Key insights
The economic advancement of low- and middle-income countries (LMICs) has been accompanied by a rise in obesity. These nations must now cope with the severely malnourished plus an increasing number of individuals with obesity-related chronic diseases, especially diabetes. The result is that many countries bear the double burden of under- and overnutrition. Alongside the unfinished agenda of high levels of infectious diseases, this double burden of malnutrition is crippling the healthcare systems of many LMICs, requiring urgent attention.

Current knowledge
The main drivers for undernutrition are all associated with poverty. These, in turn, are linked to low levels of education, particularly among girls and women who end up as the primary caregivers of children. Despite the bleak outlook, developing nations have the opportunity to learn from the mistakes made by other countries that have already experienced this transition.

Practical implications
The metabolic processes that regulate energy balance in humans are greatly influenced by a wide variety of environmental and cultural factors. Therefore, any attempts to combat obesity must address all aspects of human lifestyles, from individual health to hygiene, education, housing, and public transport. An important element is the understanding that childhood undernutrition has prenatal origins and intergenerational consequences. For instance, stunted infants are usually born to small mothers. Furthermore, the malnourished fetus has the tendency to adopt a thrifty phenotype that is specially adapted to accrue fat in later life. In the obesogenic modern world, many such individuals are at risk of weight gain.

Recommended reading
The Double Burden of Malnutrition in Countries Passing through the Economic Transition

Andrew M. Prentice

MRC Unit The Gambia at LSHTM, Banjul, The Gambia; London School of Hygiene & Tropical Medicine, London, UK

Key Messages
- Most low- and middle-income countries that manage to avoid conflict are undergoing economic advancement to a greater or lesser degree.
- The prevalence of undernutrition is strongly correlated with a country’s wealth and hence stunting and underweight tend to disappear as wealth advances. This is the good news.
- The bad news, which should be of great concern to the governments of emerging nations, is that economic advancement seems inevitably associated with a rapidly increasing prevalence of obesity. Without urgent actions to combat these trends, countries will be faced with ever-growing health costs as they try to cope with the obesity-related chronic diseases, especially diabetes.

Keywords
Malnutrition · Obesity · Double burden

Abstract
Undernutrition in both its acute and chronic forms (wasting and stunting) is strongly inversely correlated with the wealth of nations. Consequently, as many low- and middle-income countries (LMICs) achieve economic advancement and pass through the so-called “nutrition transition,” their rates of undernutrition decline. Many countries successfully achieved the Millennium Development Goal of halving undernutrition and whole continents have been transformed in recent decades. The exception is Africa where the slower rates of decline in the prevalence of undernutrition has been overtaken by population growth so that the absolute number of stunted children is rising. In many regions, economic transition is causing a rapid increase in the number of overweight and obese people. The rapidity of this rise is such that many nations bear the simultaneous burdens of under- and overnutrition; termed the “double burden” of malnutrition. This double burden, accompanied as it is by the unfinished agenda of high levels of infectious diseases, is crippling the health systems of many LMICs and thus requires urgent attention. Although the prognosis looks threatening for many poor countries, they have the advantage of being able to learn from the mistakes made by other nations that have passed through the transition before them. Concerted action across many arms of government would achieve huge future dividends in health and wealth for any nations that can grasp the challenge.
the early 2000s (Fig. 1). Sadly, even this good news is tinged with bad; the decline was less than 20% and the very latest data suggests that the decline halted in 2015 and has now reversed. The other bad news is that rates of obesity have been climbing steadily over the past 40 years and that this rise affects all continents (Fig. 2). In Asia, which started with the lowest prevalence of obesity and still has the best statistics, there is nonetheless some evidence that the rate of increase is accelerating.

It is this coexistence of malnutrition at each end of the spectrum that is termed the “double burden” of malnutrition. It represents a major challenge for emerging nations as their governments try to meet the health costs of caring for both conditions simultaneously [2]. This paper will discuss some of the basic etiological drivers and then use some country and regional case studies to try to capture some of the key drivers of the double burden and learn lessons for the future.

**Undernutrition: The Basic Drivers**

Undernutrition is classically defined by a body mass index (BMI) of less than 18.5 kg/m² in adults, and by 3 metrics in children (weight-for-age, WfA; height-for-age, HfA; and weight-for-height, WfH). In children, values less than –2 Z-scores compared to the WHO Anthrops

---

**Fig. 1.** The number of undernourished people in the world has been falling since 2000, but may be rising again. Reproduced with permission from [1].

**Fig. 2.** Adult obesity is rising everywhere at an accelerating pace. Reproduced with permission from [1].
The Double Burden of Malnutrition in LMICs

Reference values are respectively defined as underweight, stunted, or wasted. Wasting is a measure of acute malnutrition and stunting of longer-term chronic malnutrition. It goes without saying that the primary drivers of undernutrition are all associated with poverty, which in turn tends to be associated with low levels of education, especially among girls who become the primary caregivers of children. This simplistic analysis conceals many complexities both in causation and in necessary interventions that are summarized in Figure 3 from the seminal Lancet series on Maternal and Child Undernutrition and Overweight in Developing Countries [3].

Figure 4 illustrates the very strong association between a country’s level of wealth and stunting rates. Stunting is rare in wealthy nations and where it does occur it is likely driven by a specific pathology within the child or to be confined to recent or second-generation immigrants who have yet to escape from the long-term intergenerational consequences in their parents’ and possibly grandparent’s undernourishment. It is notable that there is wide diversity between stunting levels among the poorer countries on the left-hand side of Figure 4. This emphasizes how progress against malnutrition can be achieved even in the poorest nations.

Nutrition-Specific and Nutrition-Sensitive Causes of Undernutrition

There is an increasing awareness that a child’s nutritional status in not determined by dietary and nutritional factors alone. These operate within a constellation of other environmental influences that can impact their growth and health. For instance, a child’s energy and nutrient status is determined by the cumulative balance between its intake and its utilization or losses. In young children, whose immature immune systems have to learn to cope with the many infectious and antigenic threats that surround them in unhygienic environments, the role of infections is thought to be paramount. This explains why early postnatal growth falls so far below the WHO reference curves in the first 2 years of life, as illustrated in Figure 5 for children in rural Gambia. The pattern shown in

---

**Fig. 3.** Malnutrition often has many immediate and underlying causes and requires investments in solutions across many domains. Reproduced with permission from [2].
Figure 5 is replicated in all low-income settings as shown by Victora et al. [4] in their renowned meta-analysis of data from 54 low- and middle-income countries (LMICs) that formed the basis of the “first 1,000 days” concept. It is notable, at least in our Gambian data, that the children’s nutritional status stops deteriorating at about 2 years of age and starts a partial recovery. The effects of the infections are thought to arise from the excess nutrient and energy drain needed to mount an immune response (especially the adaptive responses), from children’s loss of appetite when sick and from malabsorption secondary to the condition of so-called environmental enteric disease, which is a chronic damage and persistent inflammation of the gut.

This strong link with early childhood infections and environmental enteric disease suggests that improved water, sanitation, and hygiene (WASH) should have a big impact on such outcomes, and large investments have been made to test this hypothesis. The largest trials have been the WASH Benefits trials in Bangladesh and Kenya [5] and the SHINE trial in Zimbabwe [6]. The SHINE results are not yet fully published in peer-reviewed journals, but have been presented at meetings. The WASH Benefits results have been published recently [7, 8]. The trial arms that included improved infant and young child feeding (IYCF) advice showed evidence of improvements in growth, but the effect sizes were very small. Disappointingly, the WASH arms achieved no benefit. A possible interpretation of this is not that the concept is faulty but rather that the interventions were not nearly intensive enough. They improved latrines and educated mothers about hygiene and provided washing stands and soap, but they did not truly re-engineer the environment to give families the wherewithal to make substantive differences to their children’s exposure to dirt and pathogens.

**The Emergence of Overweight and Obesity Worldwide**

Prior to the 1970s, obesity was a relatively rare condition even in the wealthiest of nations, and when it did exist it tended to occur among the wealthy. Then, a confluence of events started to change the human condition. The average BMI of populations in first-world countries started to increase and, consequently, there was a raid in the proportion of people overweight and obese. Serial state-by-state surveys in the USA from the 1980s onwards describe a remarkable transformation and associated surveys of diabetes show delayed but otherwise highly correlated trends. These data can be accessed and
Figure 6 shows that, unsurprisingly, the relationship between obesity (in this case plotted as childhood overweight and obesity) and country wealth is reciprocal to that for undernutrition shown in Figure 4. As noted for the undernutrition statistics, there is a notable spread of prevalence rates among countries with similar levels of wealth. This partly reflects the fact that some countries have undergone very rapid economic improvements and their (predictably rising) obesity rates have not yet caught up, but it also captures true differences that may be related to national behaviors and health policies. For instance, a country such as the Netherlands with, among other things very high rates of cycling which are encouraged by cycle-friendly policies, has consistently lower obesity rates than neighboring countries such as the UK.

The factors leading to the obesity pandemic were several and complex. Food prices declined as a proportion of peoples’ disposable income and the energy density of foods increased rapidly as foods were subjected to higher rates of extraction and refinement. An analysis of these trends in the UK demonstrated that such changes did not seem to greatly increase average per capita food intake, and thus an alternative (or additional) explanation was required. The same analysis showed that sedentary lifestyles and the associated reduction in energy expenditure probably played (and still plays) a major role [9]. Genetic effects cannot explain these rapid population shifts in obesity, though they can help to explain which individuals within any given population will be more or less susceptible. Recent research has revealed that epigenetic effects may explain a much greater proportion of population variance than genetic effects [10, 11] and this has implications for prevention as discussed below.

Fig. 6. Childhood overweight and obesity rates as a function of countries’ per capita gross domestic product (GDP). Overweight and obesity statistics use the latest data available for each country (limited to countries with post 2000 data) collated by the International Obesity Taskforce (http://www.iaso.org/iotf/obesity/?map = children). GDP adjusted for purchasing power parity (PPP) mostly refer to 2012 and were accessed from the International Monetary Fund’s (IMF) World Economic Outlook Database, October 2013.

Fig. 7. Overweight and obese patients queue for a diabetic clinic. Photo credit: Felicia Webb.

Fig. 8. Obesity is now a common sight in urban areas of Africa, especially among middle-aged women. Photo credit: Felicia Webb.

downloaded from the Centers for Disease Control (CDC) website (www.cdc.gov).

Figure 6 shows that, unsurprisingly, the relationship between obesity (in this case plotted as childhood overweight and obesity) and country wealth is reciprocal to that for undernutrition shown in Figure 4. As noted for
The Demographic Switch in Social Groups Most Susceptible to Obesity

In poorer nations, it is generally only the rich who can, and do, become obese, but as nations pass through the demographic transition a switch occurs and the wealthier strata tend to be less likely to be obese and the poorer strata more likely. The photographs in Figures 7 and 8 show relatively wealthy women waiting for their appointments at the diabetes clinic and yet poorer women similarly afflicted; this is from a country in which the switch is in the process of playing out.

Within many poor countries, especially in Africa, there are 2 notable features of obesity distribution as illustrated in Figure 9 for The Gambia [2, 12]. First, there tends to be a strong urban-rural gradient with much more obesity in townships and cities. Second, within those urban areas, women are often much more likely to be obese than men (see the white and light-grey areas at the top right hand of Fig. 9). There are deep social reasons for such trends [13] and an understanding of them is important in designing interventions.

The pace of the demographic transition is such that in some regions of the world it is not uncommon to see stunted children living in households where one or both of their parents (usually the mother) is clinically obese [e.g., 14].

National Challenges Posed by the “Double Burden” of Malnutrition

The poor and emerging nations of the world are, by definition, the least able to bear the health costs of treating serious nutrition-related conditions such as severe acute malnutrition and obesity-related diabetes. As a consequence, treatment facilities are often poorly equipped and staffed, and hence the case fatality rates for such conditions are much higher than in rich nations. The photographs in Figures 10 and 11 were taken on the same day in a tertiary level hospital in urban Africa. The bed-ridden woman was awaiting amputation of her diabetic foot (reported by the surgeons as one of the most common operations they performed). The malnourished child was in a ward directly below the adult ward, graphically illustrating the juxtaposition of the two extremes of malnutrition and the terrible challenges that this poses. When considered in the context of the high additional
The Double Burden of Malnutrition in LMICs

burden of treating infectious diseases, it is no wonder that so many health systems are failing. A visit to such hospitals can be a traumatic experience for visitors used to top-quality first-world medical care.

Solutions

A decade ago, the UK government published the seminal Foresight Report [15] that attempted to collate all the available evidence about the drivers of the obesity epidemic and to use this knowledge to construct recommendations for government action. The report acknowledged that the metabolic mechanisms regulating (or failing to regulate) energy balance in humans were central to all efforts, but that these were influenced by a wide variety of social and environmental determinants that were rapidly changing in our modern world. They drew up a complex “systems map” to describe these influences and used it to press the case that strategies against obesity must be developed by almost every government department from health to transport, housing, education, and sport, and all must have the support of treasury. Though developed for the UK, these lessons are applicable everywhere.

The World Health Organization has convened expert groups on obesity and noncommunicable diseases and is constantly updating the evidence base used to plan recommended initiatives [e.g., 16, 17]. These are backed by ancillary reports on mechanisms to achieve these ends such as fiscal measures against sugary drinks [18] and development of a global action plan to promote physical activity [19]. The report on childhood obesity makes a large number of recommendations [17], indeed probably an overwhelming number for low-income countries that already have major challenges in strengthening their school systems.

A relatively new element of all of these efforts is the recent appreciation of how important it is to consider both ends of the malnutrition spectrum with a life-course lens. In other words, to understand that childhood undernutrition has prenatal and probably intergenerational origins [11, 17]. Most children who are stunted at the age of 2 years were already stunted at birth [19] and were born to small mothers. Likewise, a malnourished fetus may adopt a “thrifty phenotype” [20] that is better able to accrue fat in later life if exposed to an obesogenic environment and is therefore at special risk of inappropriate weight gain.

Prospectus for the Future

The economic advancement and associated demographic transitions that are happening in most countries except those marred by conflict will ultimately bring a natural decline in undernutrition. Progress in recent decades has been good in all continents except Africa as a whole; and even here there were many nations that achieved their Millennium Development Goal of halving malnutrition. However, unless the governments and peoples of these emerging nations are able to learn lessons from the countries that have passed through the transition before them, they will incur a huge burden of overweight and obesity. The challenge therefore is first to recognize the impending

Fig. 10. An overweight patient awaits treatment for her diabetic foot. Photo credit: Felicia Webb.

Fig. 11. A malnourished child in a nearby ward exemplifies the health system’s challenges of the double burden of malnutrition. Photo credit: Felicia Webb.
threat and then to take cross-government actions to halt the epidemic and its associated health crisis. The greatest hope lies in the fact that most governments are at least aware of the threat; finding the bandwidth and resources to tackle it would bring long-term gains in health and wealth to any government that can achieve it.

Disclosure Statement

The writing of this article was supported by Nestlé Nutrition Institute.

References

The nutritional issues of undernutrition and overnutrition among children and adolescents in developing countries are intricately woven together in an intergenerational cycle of malnutrition.

Key insights
Globally, the focus of malnutrition interventions has been on pregnant women and young children under 5 years of age. Older children (aged 6–9 years) and adolescents (aged 10–19 years) have not received as much attention. In addition to undernutrition and obesity, adolescent girls in particular face pregnancy-related risks such as anemia, premature birth, stillbirths, and death. There is thus a need to develop guidelines for nutritional interventions that target this group, particularly in low- and middle-income countries (LMICs).

Current knowledge
Older children and adolescents are at high risk of malnutrition because they experience critical growth spurts which demand essential macro- and micronutrients. Approximately half of adult ideal body weight and approximately 20% of adult height are gained during adolescence, with most of this acquired rapidly in 1–2 years preceding the early stages of sexual maturation. In LMICs, there is a high prevalence of under- and overnutrition in older children and adolescents, compromising growth and cognitive potential while increasing the risk of obesity and cardiovascular diseases in later life.

Practical implications
School feeding programs as well as multiple micronutrient supplementation and fortification have had beneficial outcomes in school-aged children. The World Health Organization (WHO) recommends 3 months of preventive iron supplementation in adolescents living in areas with a high anemia prevalence. Teenage girls should receive folic acid supplementation during the preconception period to prevent neural tube defects in the developing fetus. Schools have been one of the successful platforms used for delivering nutritional interventions, but the use of electronic and social media can also be explored as tools to promote a healthy lifestyle.

Recommended reading
Nutrition for the Next Generation: Older Children and Adolescents

Jai K. Das\textsuperscript{a} Zohra S. Lassi\textsuperscript{b} Zahra Hoodbhoy\textsuperscript{a} Rehana A. Salam\textsuperscript{a,c}

\textsuperscript{a}Division of Women and Child Health, Aga Khan University, Karachi, Pakistan; \textsuperscript{b}Robinson Research Institute, University of Adelaide, Adelaide, SA, Australia; \textsuperscript{c}South Australian Health and Medical Research Institute, University of Adelaide, Adelaide, SA, Australia

Key Messages

- It is critical to ensure adequate nutrition for children and adolescents as this is intrinsically linked to the health of future generations.
- There is a need to make specific guidelines for nutrition requirements and interventions for older children and adolescents across various contexts, including low- and middle-income countries (LMICs).
- There is a need for more evidence around determining the most effective strategies to tackle the rising burden of overweight and obesity, especially from LMICs.

Keywords

Adolescents · Older children · Nutrition · Undernutrition · Overweight · Obesity · Nutrition interventions

Abstract

This paper reviews information on why the nutrition of older children (5–9 years) and adolescents (10–19 years) is important and the consequences that it can have over generations. Developing countries still face a high burden of undernutrition and anemia, while the burden of overweight and obesity is on the rise in both developing and developed countries. There are evidence-based interventions which can improve the nutritional status and these include interventions for a balanced and diverse diet and micronutrient supplementation, especially iron and multiple micronutrient supplementation where there is sufficient evidence to reduce anemia. There is mixed evidence for the effective strategies to prevent and control obesity and a dearth of evidence from developing countries. Adolescent pregnancy also poses greater challenges to the health of mother and child, and advocacy should be rampant to delay the age of marriage and pregnancy. Interventions targeted to improving the nutritional status among “pregnant adolescents” have shown improvement in birth weight and a reduction in low birth weight and preterm delivery. Traditional platforms including school-based and community-based approaches offer a mixed picture of effectiveness, but emerging avenues of mHealth and social media could also be channelized to reach this population. The population of this age group is on the rise globally, and failure to invest in improving the nutrition of older children and adolescents will further increase the number of dependents in coming generations and negatively influence the health of future generations and progress of nations.
Background

Malnutrition encompassing both under- and overnutrition is a major public health crisis for children and adults across the world [1]. Developing countries are now facing the “double burden” of undernutrition and overweight and obesity [2], as the prevalence of overweight and obesity in children and adolescents has increased from 8.1% (7.7–8.6) in 1980 to 12.9% (12.3–13.5) in 2013 for boys and from 8.4% (8.1–8.8) to 13.4% (13.0–13.9) in girls [3]. And during the same period, the prevalence of overweight and obesity has increased remarkably in developed countries: from 16.9% (16.1–17.7) in boys and 16.2% (15.5–17.1) in girls in 1980 to 23.8% (22.9–24.7) in boys and 22.6% (21.7–23.6) in girls in 2013 [3]. There is also a high burden of undernutrition in developing countries and protein-energy malnutrition is responsible for 225,906 deaths (uncertainty level: 168,497–280,129) in children and adolescents aged 0–19 years [4]. Iron deficiency anemia is the leading cause of years lived with disability among children and adolescents, accounting for 619 million (uncertainty level: 618–621 million) prevalent cases in 2013 [4].

Pregnancy in adolescence poses additional risks to the mother and newborn, as adolescent girls are not physically mature enough, and undernutrition further exacerbates these risks. The common risks during adolescent pregnancy include anemia, stillbirth, prematurity, and mortality. It is estimated that around 10% of the global total births occur to adolescent girls between the age of 15 and 19 years [5]. And around three-quarters of these adolescent pregnancies occur in developing countries [5]. Stunted adolescents have further risks of obstetric complications, including obstructed labor and weakened physical capacity [6].

The major global focus of health has been on children under the age of 5 years and pregnant women, while older children (aged 6–9 years) and adolescents (aged 10–19 years) have not received the due attention until lately. Alleviating malnutrition in this age group requires a complex, multifactorial approach and thus addresses a major public health concern.

Consequences of Undernutrition across the Life Course

The nutritional issues of undernutrition and overnutrition among children and adolescents in developing countries are intricately woven together in an intergenerational cycle of malnutrition.

It is essential that women, particularly girls, are nourished well at all stages of growth and development because the risk of malnutrition in women spans a life cycle and also across generations, termed as intergenerational effects of malnutrition [7]. Any nutritional deficiency experienced during this critical period of life can have an effect on the future health of the individual and their offspring (Fig. 1).

Fig. 1. Intergenerational effects of malnutrition. Adapted from the ACC/SCN-appointed Commission on the Nutrition Challenges of the 21st Century.
Addressing nutritional deficiencies in women and girls via life cycle approach can improve their nutritional status. Nutritional deficiencies experienced early on such as in utero, infancy, and childhood have consequences into the adult life. Stunting is often rooted from inadequate fetal growth [8] and it also influences the childhood cognitive tests and educational achievement [9]. Changes in utero nutritional environment are associated with hampered growth and development and increased risk of developing cardiovascular and metabolic disorders in adult life [10]. The same vicious cycle of malnutrition is repeated in children of mothers who were malnourished.

Women, in general, are more likely to suffer from nutritional deficiencies than men because of their reproductive biology. However, children and adolescents in developing countries suffer the most with additional underlying factors including poverty, illiteracy, poor social status, and disparity in society. Today, approximately 468 million nonpregnant women in low- and middle-income countries (LMICs) and half of all the pregnant women are anemic [11, 12]. Poor nutritional status increases the risks for morbidity and mortality. For women, anemia is an underlying cause in approximately 20% of maternal deaths [13] and being underweight increases the chances of being stunted and that increases the risk for obstetric complications such as obstructed childbirth [14, 15]. At a macro-level, malnourishment hinders work capacity and leads to further economic disadvantages.

**Physiology and Metabolism**

Malnutrition is the single most common reason for growth retardation. Inadequate nutrition in the early life of a child can delay sexual maturation and physical growth, which is necessary to reach the full development potential as an adult. For a girl, this is also important to prepare for her nutritional demands during pregnancy and lactation in adulthood. There are no standardized anthropometric measures for adolescents [16], and consequently various definitions are used by different studies to measure the burden of underweight and overweight in adolescents, thus hampering the determination of the actual burden of adolescent malnutrition.

The nutritional status has a significant contributing effect on the timing of adolescent sexual maturation, and it is well documented that undernutrition is associated with delayed age of menarche [17]. The growth spurt in adolescence requires rapid tissue expansion with special nutrient requirements, thus it is necessary to ensure that energy and nutrition requirements match the adolescent needs. Approximately half of an adult’s ideal body weight is gained during adolescence, and approximately 20% of adult height is gained during the adolescent age period and most of this is gained rapidly 1–2 years preceding the early stages of sexual maturation [16]. Malnutrition prevents individuals from attaining normal bone structure, strength, and development, and the onset of puberty is delayed in adolescents who are undernourished. This can allow for a longer time to catch up on growth, although there are deliberations on whether young adolescents who are stunted can catch up to their optimal height.

Older children and adolescents are particularly at risk of malnutrition because they experience the growth spurt and need all essential macro- and micronutrients to support the increased demand of the body for attaining puberty and development. Therefore, it is important that children and adolescents, particularly girls, are fed properly and are given all required micronutrients. Young girls who become pregnant during this phase are at greater risk of various complications since their body is supporting their own growth and that of the growing fetus; and the still-growing adolescent mother and her baby may compete for nutrients and increase the infant’s risk of low birth weight and early death [18].

This age group also needs iron for their increased physiologic requirements for growth. Infectious diseases, such as malaria and hookworm, and menstruation in females can also affect iron absorption, use, and loss in adolescents and frequently contributes to iron deficiency. Malaria-related inflammation also reduces iron absorption and incorporation into red blood cells [19].

There is an increase in appetite in this age group and individuals with a sedentary lifestyle have a greater chance to accumulate fat, which contributes greatly to overweight and obesity, especially if they consume high-energy food. The caloric requirement of adolescent males is higher than that of adolescent females, owing to greater increases in height, weight, and lean body mass. Table 1 shows the Dietary Reference Intakes (DRIs) and Adequate Intakes (AIs) for adolescents as recommended by the Institute of Medicine and includes recommendations on energy requirements and requirements for various macro- and micronutrients [20].

**Long-Term Health Impacts of Malnutrition**

Malnutrition in women contributes to the growing burden of cardiovascular and other noncommunicable diseases. Undernutrition leads to numerous physiological and social alterations and is partly due to epigenetic
changes [21]. Undernutrition provokes stress in the body and stimulates the release of adrenaline and noradrenaline and the production of cortisol. The chronic physiological stress due to undernutrition over time weakens the body and leads to fatigue and unproductivity and also poses multiple-fold risks of getting an infection [22]. A study on malnourished children found a higher resting heart rate [23] and an association of nutritional stunting with increased rates of arterial hypertension [24, 25]. Short maternal stature is associated with obesity and type 2 diabetes [26], low birth weight, and stunting in children [27]. Undernutrition is also linked with hyperinsulinemia and reduced sensitivity to insulin, which is responsible for an increased BMI in adult life [28]. Animal studies have also proven that changes in in utero kidney development can occur due to maternal malnutrition and sug-

### Table 1. Examples of population reference nutrient intakes (vitamins and minerals): Dietary Reference Intakes (DRIs) and Adequate Intakes (AIs) for adolescents in the USA [20]

<table>
<thead>
<tr>
<th></th>
<th>Females</th>
<th>Males</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>9–13 years</td>
<td>14–18 years</td>
</tr>
<tr>
<td>Energy, kcal/day</td>
<td>2,071</td>
<td>2,368</td>
</tr>
<tr>
<td>Carbohydrates, g/day</td>
<td>130</td>
<td>30</td>
</tr>
<tr>
<td>Total fiber, g/day</td>
<td>26</td>
<td>28</td>
</tr>
<tr>
<td>n-6 polyunsaturated fat, g/day</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>n-3 polyunsaturated fat, g/day</td>
<td>1.0</td>
<td>1.1</td>
</tr>
<tr>
<td>Protein, g/day</td>
<td>34</td>
<td>46</td>
</tr>
<tr>
<td><strong>Vitamins</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin A, μg/day</td>
<td>600</td>
<td>700</td>
</tr>
<tr>
<td>Vitamin C, mg/day</td>
<td>45</td>
<td>65</td>
</tr>
<tr>
<td>Vitamin D, μg/day</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Vitamin E, mg/day</td>
<td>11</td>
<td>15</td>
</tr>
<tr>
<td>Vitamin K, μg/day</td>
<td>60</td>
<td>75</td>
</tr>
<tr>
<td>Thiamin, mg/day</td>
<td>0.9</td>
<td>1.0</td>
</tr>
<tr>
<td>Riboflavin, mg/day</td>
<td>0.9</td>
<td>1.0</td>
</tr>
<tr>
<td>Niacin, mg/day</td>
<td>12</td>
<td>14</td>
</tr>
<tr>
<td>Vitamin B₆, μg/day</td>
<td>1.0</td>
<td>1.2</td>
</tr>
<tr>
<td>Folate, μg/day</td>
<td>300</td>
<td>400</td>
</tr>
<tr>
<td>Vitamin B₁₂, μg/day</td>
<td>1.8</td>
<td>2.4</td>
</tr>
<tr>
<td>Pantothenic acid, mg/day</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Biotin, μg/day</td>
<td>20</td>
<td>25</td>
</tr>
<tr>
<td>Choline, mg/d ay</td>
<td>375</td>
<td>400</td>
</tr>
<tr>
<td><strong>Elements</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium, mg/day</td>
<td>1,300</td>
<td>1,300</td>
</tr>
<tr>
<td>Chromium, μg/day</td>
<td>21</td>
<td>24</td>
</tr>
<tr>
<td>Copper, μg/day</td>
<td>700</td>
<td>890</td>
</tr>
<tr>
<td>Fluoride, mg/day</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Iodine, μg/day</td>
<td>120</td>
<td>150</td>
</tr>
<tr>
<td>Iron, mg/day</td>
<td>8</td>
<td>15</td>
</tr>
<tr>
<td>Magnesium, mg/day</td>
<td>240</td>
<td>360</td>
</tr>
<tr>
<td>Manganese, mg/day</td>
<td>1.6</td>
<td>1.6</td>
</tr>
<tr>
<td>Molybdenum, μg/day</td>
<td>34</td>
<td>43</td>
</tr>
<tr>
<td>Phosphorus, mg/day</td>
<td>1,250</td>
<td>1,250</td>
</tr>
<tr>
<td>Selenium, μg/day</td>
<td>40</td>
<td>55</td>
</tr>
<tr>
<td>Zinc, mg/day</td>
<td>8</td>
<td>9</td>
</tr>
</tbody>
</table>

Source: data from reports from the Institute of Medicine, Food and Nutrition Board, Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, copyright by the National Academy of Sciences, courtesy of the National Academies Press, Washington, DC, USA (http://www.nap.edu/).
gested delays in intrauterine growth and a reduced number of nephrons [29]. This phenomenon determines poor renal function and increased blood pressure. Studies have also shown the association of pancreatic function with undernutrition in early life [30]. Undernutrition and ensuing anemia can also affect cognitive development, the ability to learn, and hence compromise the standard of living throughout the life cycle [31].

Evidence suggests that a poor maternal BMI before and during pregnancy has significant impacts on adverse pregnancy outcomes. A recent review reported that maternal prepregnancy underweight is significantly associated with preterm births, small-for-gestational-age babies and low birth weight [32]. On the other hand, maternal pre-pregnancy overweight is associated with increased risk of hypertensive disorders, pre-eclampsia, and gestational diabetes. The risk of adverse pregnancy outcomes increases multifold if the mother is obese [32].

Similarly, overweight and obesity among children and adolescents pose an increased risk for cardiovascular and other noncommunicable diseases. There is considerable evidence to show that childhood obesity is a risk factor for type 2 diabetes, hypertension, coronary heart disease, and stroke in adulthood (hazard ratios ranging from 1.1 to 5.4) [33, 34]. A systematic review of 23 studies reported that childhood obesity is significantly associated with adult systolic and diastolic blood pressure and triglycerides and inversely associated with high-density lipoprotein [35]. And hypertension is the leading cause of other noncommunicable diseases, such as high serum cholesterol, diabetes, etc. These also lead to direct (medical) and indirect (nonmedical) costs related to obesity that impose a significant economic burden to individuals and health care infrastructure.

### Nutrition Interventions for Older Children and Adolescents

Intervening in infancy and early childhood is paramount to improving the nutritional status and achieving long-lasting impacts as this is an age group which responds well to the interventions not only to improve physical growth but also cognitive development and attainment of complete physical capacity. Various interventions including optimal breastfeeding, complementary feeding, and micronutrient supplementation have been recommended for infants and young infants. Apart from nutrition-specific interventions, water, sanitation, hygiene, and prevention of infection also play an important role [36]. Although older children and adolescents often do not receive intervention and policy priority, intervening in this age is also vital for improving nutrition and achieving long-term health. A balanced, nutritious diet is the key to promote healthy growth and development of children and adolescents [37], leading to a healthier and productive generation. Below we discuss the evidence-based nutrition-specific interventions for older children (Table 2) and adolescents. Younger adolescents (10–13 years) act as a special group, as they transition from older school-aged children to adolescents.

#### Older Children

The interventions range from addressing under- to overnutrition. A systematic review on school feeding programs reported that balanced school meals provided in LMICs had a significant impact on weight but not on height [38]. Multiple micronutrient supplementation through fortified beverages has shown a significant impact on improving serum hemoglobin level and reducing the risk of anemia in school-aged children in low-resource settings [39]. A systematic review on micronutrient powders suggested an impact on improving serum hemoglobin and reducing the prevalence of anemia in

<table>
<thead>
<tr>
<th>Table 2. Evidence of impact of interventions in older children</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcome</strong></td>
</tr>
<tr>
<td><strong>School feeding programs</strong></td>
</tr>
</tbody>
</table>
| Weight gain | Over 19 months MD: 0.39 kg (95% CI: 0.11 to 0.67)  
Over 11.3 months MD: 0.71 kg (95% CI: 0.48 to 0.95)  
Height gain MD: 0.38 cm (95% CI: –0.32 to 1.08) |
| **Micronutrient powders** |  |
| Anemia RR: 0.53 (95% CI: 0.25 to 1.12)  
Hemoglobin MD: 7.86 g/L (95% CI: –0.76 to 16.49) |
| **Intermittent iron supplementation** |  |
| Anemia RR: 0.54 (95% CI: 0.33 to 0.90)  
Hemoglobin MD: 4.04 g/L (95% CI: 0.30 to 7.78) |
| **Iron fortification** |  |
| Hemoglobin SMD: 0.46 (95% CI: 0.24 to 0.67)  
Anemia RR: 0.60 (95% CI: 0.43 to 0.84) |
| **MMN-fortified beverages** |  |
| Hemoglobin MD: 2.76 g/L (95% CI: 1.19 to 4.33)  
Anemia RR: 0.58 (95% CI: 0.29 to 0.88)  
Iron deficiency anemia RR: 0.17 (95% CI: 0.06 to 0.53) |

MD, mean difference; MMN, multiple micronutrient; RR, risk ratio; SMD, standard mean difference.
children under the age of 5 years but not in older children [40]. A systematic review on intermittent iron supple-
mentation in children aged 5–10 years showed a statistically significant increase in serum hemoglobin but no effect on anemia, and this review also suggested no difference when intermittent iron supplementation was compared to daily supplementation [41]. A review on iron fortification also suggested improvement in serum hemoglobin levels and reduction in anemia in preschool- and school-aged children [42]. There is some evidence suggesting that iodine supplementation in children aged 10–12 years leads to improvement in cognitive functioning and fine motor skills [43].

A recent systematic review of nutrition interventions in adolescents suggested that iron/iron folic acid supple-
mentation alone or in combination with other micronu-
trients leads to a reduction in anemia (risk ratio: 0.69, 95% CI: 0.62 to 0.76) and was associated with improved serum hemoglobin (MD: 1.94 g/dL; 95% CI: 1.48 to 2.41), ferritin (MD: 3.80 μg/L; 95% CI: 2.00 to 5.59), and iron (MD: 6.97 mmol/L; 95% CI: 0.19 to 13.76) [51]. Zinc supple-
mentation led to improved serum zinc concentrations (MD: 0.96 μg/dL; 95% CI: 0.81 to 1.12), while calcium and vitamin D supplementation did not have a clear impact on vitamin D levels or parathyroid hormone [51].

The nutritional effect of large-scale urbanization, often coined the “nutrition transition,” is that as people assume a more sedentary lifestyle, have more ready access to snack or street foods, and reduce the consumption of more traditional foods, the prevalence of overweight and obesity increases substantially. As increased caloric input is one of the key mechanisms for weight gain, nutritional interventions are a key for preventing and managing obesity in adolescents. Interventions targeted to adoles-
cents to improve fruit and vegetable consumption behaviors suggest that these behaviors are dependent on home availability of fruits/vegetables and taste preferences [52]. A positive correlation between milk consumption and bone mineral density has also been reported in young girls [53]. Dietary interventions for obesity management in adolescents include caloric restriction [54] and/or traffic light diet (low added sugar and increased fiber intake) [55], which have shown to have significant reductions in BMI and waist circumference [56]. The NEAT (Nutrition and Enjoyable Activities in Teen Girls) trial to prevent obesity in girls from a low socioeconomic background reported an insignificant effect on body composition but may still have potential clinical importance [57].

**Adolescents**

The World Health Organization (WHO) recommends that 3 months of preventative iron supplementation of 60 mg iron per day be given to adolescents living in areas where the population prevalence of anemia is greater than 40% [48]. Folic acid supplementation in the preconception period has been recommended to reduce the incidence of neural tube defects [49]. Calcium supple-
mentation in girls aged 10–18 years has been essential for achieving optimum bone mineral density and hence preventing osteoporosis [50].

**The combination of various settings can be proposed as one of the solutions to effectively address nutritional interventions in older children and adolescents**
potentiel to improve dietary quality in youth [59]. mHealth technology has also been studied to promote a healthy diet and other lifestyle behaviors in children [60]. A recent systematic review reported that compliance to treatment and self-monitoring has been shown to improve with the use of this technology; however, the effect on outcomes such as BMI was limited [60]. A combination of various platforms such as schools, community, and media has been successful in implementing healthy dietary patterns in elementary-school children [61]. The combination of various settings can be proposed as one of the solutions to effectively address nutritional interventions in older children and adolescents.

**Conclusion**

Adolescent and older children health care is challenging compared to that of children under the age of 5 years and adults, and this is due to various factors mostly related to the ever-evolving physical and mental development. There is still a high burden of malnutrition in older children and adolescents globally, with developed countries facing a huge load of overweight and obesity, while developing countries are engulfed with a traditionally high prevalence of undernutrition and the threats of recent hike in overweight and obesity. There is a greater need to focus exclusively on this population, as improving the nutritional status of adolescents can help break the vicious cycle of intergenerational malnutrition.

National governments together with development partners need to make specific guidelines and recommendations to tackle malnutrition in this age group, albeit this may require more evidence especially around determining strategies to combat obesity. This focus would not only improve the nutritional status of older children and adolescents but may also escalate the mental and cognitive growth and help individuals reach their true potential, which may have far-reaching repercussions by not only increasing the quality of life but influence the growth and productivity of generations to come and countries at large.

**Disclosure Statement**

All authors declare no conflict of interest and received no compensation. The writing of this article was supported by Nestlé Nutrition Institute.

**References**


DOI: 10.1159/000487385

