Epidemiological Research Drives a Paradigm Shift in Complementary Feeding – The Celiac Disease Story and Lessons Learnt

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Abstract
Breast milk is the initial natural food for infants, but already during the second half year complementary feeding is essential. Epidemiological research, first on celiac disease and later on atopic diseases, has driven a paradigm shift with respect to most favorable age to introduce complementary feeding. Simplified, this implies a shift from later to earlier introduction, which is now taken into account in recommendations on infant feeding. Complementary feeding, including all foods, should not be initiated for any infant before 4 months of age, and not later than around 6 months, including infants with elevated disease risk (e.g. for celiac disease or atopic diseases). Motivating reasons could be that ongoing breastfeeding provides an ‘immunological umbrella’ and/or a different age interval gives a ‘window of opportunity’ for developing oral tolerance towards gluten and other food antigens. This will for some infants be in conflict with recent WHO recommendations on exclusive breastfeeding for 6 months. Epidemiology has evolved over time and could, if increasingly used, contribute even more to innovations in pediatric nutrition and other phenomena related to population health.

Introduction
Maternal and infant food habits deserve attention, since early nutrition, during intrauterine and infant life, is important not only for a child’s health, but also throughout adult life [1, 2]. Flavors experienced early in life, including amniotic fluid, breast milk and complementary foods, are likely to guide lifelong food preferences and choices [3].
Breast milk offers nutritional, antimicrobial, and immune-modulating advantages over infant formula to the recipient infant [4–6]. The World Health Organization (WHO) recommends that infants should be exclusively breast-fed for the first 6 months of life, and thereafter receive nutritionally adequate and safe complementary feeding while breastfeeding continues for up to 2 years or beyond [4]. Introduction of foods and liquids in conjunction with breast milk or infant formula – referred to here as complementary feeding – is essential for the nutritional needs of the infant, fostering normal growth and development and enabling the transition to family food [7]. Evidence-based knowledge on how best to feed infants is growing, although many unknowns remain. Dissemination of this knowledge and implementation in daily practice is occurring at a slow pace. Across the globe, complementary feeding practices vary according to culture and available resources, and there is potential for improvement in many settings.

Celiac disease (CD), also called gluten intolerance, has emerged as a global public health problem, from previous perceptions as a rare disease only affecting European children [8]. Classically, the disease presents during the first years of life with diarrhea and failure to thrive, but nowadays atypical presentations at any age are increasingly recognized. Symptoms and signs are often misinterpreted, leading to delayed or missed diagnosis, with extensive short- and long-term negative health consequences. CD is effectively treated with life-long exclusion of foods containing any gluten-bearing cereals (wheat, rye, or barley). Epidemiological research has revealed that infant food habits play a role in development of autoimmune diseases, such as CD [9], and also influence the risk of atopic disease, another increasingly common health problem [10]. Such findings have been taken into account in recent revisions of European and American infant feeding recommendations [6, 7, 10], and are also likely to be relevant for infant health in other parts of the world.

In this chapter, we show how epidemiological research has driven a paradigm shift in complementary feeding. We describe this paradigm shift and the reasoning behind it with illustrations from epidemiological research on CD and also partly from research on atopic disease. We give a brief overview of epidemiology from a methodological perspective again using CD research as the example. We hope that this will inspire other researchers to embark on multidisciplinary research involving epidemiological approaches, for example in pediatric nutrition.

A Paradigm Shift Concerning Complementary Feeding

The Prevailing Thinking Was ‘Later Is Better’

During the 1920s and following decades, it became normal to introduce solid foods to infants only a few months old, which is still the practice in many low- and middle income countries. During the 1970s, concerns were
raised about possible adverse effects arising from the early introduction of solids, which thereafter were reflected in several guidelines on infant feeding. European infant feeding recommendations in 1982 stated that: (a) solid foods should not be introduced earlier than 3 months or later than 6 months; (b) gluten-containing foods (wheat, rye and barley) should not be introduced before 4 months and postponement until 6 months may be advisable, and (c) certain foods known to be highly allergenic such as eggs and fish are probably best deferred until 5–6 months [11]. When WHO in 2001 launched their recommendation of exclusive breastfeeding for 6 months, this influenced infant feeding habits in many countries towards further delay in introducing solids [4]. Over the same period, other guidelines were launched that recommended avoiding food allergens such as peanuts, fish, and eggs up to 1 year of age, or even longer, as this was expected to reduce the risk for atopic diseases [12]. The postponed introduction of gluten was expected to delay the onset of CD, or even possibly to reduce the risk of the disease. The prevailing thinking about introducing solids seemed to be ‘later is better’.

Epidemiological Research Drives a Paradigm Shift towards ‘Earlier Is Better’

Many were surprised when Sweden, in the mid 1980s, was struck by an abrupt fourfold increase in CD occurrence among children under 2 years of age, leading to levels higher than ever previously reported [13, 14] (fig. 1). This unusual cumulation of newly diagnosed CD cases was observed by most pediatricians in their clinical practice. Strict diagnostic criteria involving small intestinal biopsies were followed throughout the epidemic [15] (fig. 2).

The start of the epidemic followed nationally launched recommendations to delay the introduction of all gluten-containing foods to infants until 6 months of age, in line with changes at that time in many European countries [13]. This was the starting point for extensive epidemiological research with findings that initially were met with skepticism [9], but later accepted and often referred to as a benchmark in CD research.

Our findings about this CD epidemic, in a genetically stable population, illustrated that the disease must have a multifactorial etiology going beyond genetic disposition and exposure to gluten in the diet. In studying 12-year-old children born during the peak of the epidemic (in 1993) as part of a CD screening program (using serological markers, followed by evaluation of the small intestinal biopsy in suspected cases), who as infants had been introduced quite abruptly to gluten often without ongoing breastfeeding, we revealed a CD prevalence of 3% (95% CI: 2.5–3.3) [16]. This should be seen alongside the often assumed universal prevalence of around 1%. The highest recorded prevalence, 5.6%, was reported among Saharawi children in Algeria (95% CI: 4.2–7.1) [17]. It is worth noting that CD cases have been reported from all continents, with rising incidence in many places.
This has stimulated us and others to pursue research for identifying strategies for primary prevention, thus avoiding disease development at least for some people [9, 18, 19]. Most importantly, we showed that CD risk is lower if breastfeeding is still ongoing when gluten-containing foods are introduced, and if gluten is given in small to medium amounts (as compared to large amounts) during the introductory period [13, 20]. We also showed that further prolonged breastfeeding reduced CD risks even more. This is in line with the theoretical thinking that breast milk with its immunological properties is likely to promote oral tolerance [21]. Notably, almost half of the CD cases that occurred during the Swedish epidemic would have been avoided if infant feeding practices had been as favorable as possible (table 1) [20].

Our findings did not pinpoint a certain age interval associated with increased or reduced risk of developing the disease, but subsequent studies suggested the optimal age for introducing gluten as being 4–6 months [22]. By the mid-1990s, Swedish national infant feeding recommendations changed in line with these findings, and at that time the CD epidemic also abated [13]. Thus, the message from CD research regarding introduction of gluten is that ‘earlier is better’, as long as the mother is still breastfeeding, possibly provid-

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**Fig. 1.** Annual incidence rates of CD in children from 1973 to 2003. From Olsson et al. [14], with permission.
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Fig. 2. The intestinal mucosa of a healthy child (left column) and one with active CD (right column). Top row shows scanning electron micrographs and bottom row histological sections.

Table 1. Dietary patterns during infancy and risk for CD before 2 years of age, and an estimate of public health impact

<table>
<thead>
<tr>
<th>Dietary patterna</th>
<th>Relative riskb</th>
<th>Prevalence of exposure %</th>
<th>AFpc %</th>
</tr>
</thead>
<tbody>
<tr>
<td>breastfeeding at introduction of flour</td>
<td>amount of flour at introduction</td>
<td>cases (n = 392)</td>
<td>referents (n = 626)</td>
</tr>
<tr>
<td>Continuing</td>
<td>Small-medium</td>
<td>1.0</td>
<td>28</td>
</tr>
<tr>
<td>Continuing</td>
<td>Large</td>
<td>2.0 (1.4–3.0)</td>
<td>18</td>
</tr>
<tr>
<td>Discontinued</td>
<td>Small-medium</td>
<td>2.8 (1.9–4.0)</td>
<td>24</td>
</tr>
<tr>
<td>Discontinued</td>
<td>Large</td>
<td>3.3 (2.3–4.8)</td>
<td>30</td>
</tr>
</tbody>
</table>

Adapted from Ivarsson et al. [20].

a Breastfeeding status (continued or discontinued) at the time gluten-containing flour was introduced into their diets, and amount of flour given (small to medium or large amounts).
b Relative risk estimates were based on odds ratios with 95% CIs from conditional logistic regression with 392 matched sets of cases and referents.
c Public health impact was estimated by the population attributable fraction $AF_p = p_c (OR – 1)/OR$, where $p_c$ is the prevalence of the studied exposure among the cases.
ing an ‘immunological umbrella’ and/or a different age interval gives a ‘win-
dow of opportunity’ for developing oral tolerance.

However, the evidence can still be challenged, and we are now continuing
our research along two main lines within a European collaborative project
(www.preventcd.com): (a) a CD screening program for Swedish 12-year-olds
born when the epidemic had abated (in 1997), during a period when gluten
was usually introduced gradually from 4 months of age, with ongoing breast-
feeding (to compare the prevalence in the 1993 and 1997 cohorts), and (b)
a randomized, blinded field trial among pregnant women carrying potentially
high-risk infants, who are allocated either to careful introduction of gluten at
4 months of age, or to infant feeding according to country and family prac-
tices (carefully recorded for both groups) [19].

Recently, the same shift in thinking to ‘earlier is better’ for infant feed-
ing practices has been reflected in publications on atopic disease risk. This
thinking also includes solids that are considered highly allergenic such as
fish, eggs, and foods containing peanut protein. A systematic review of
available evidence up to 2005 concluded that there was little evidence sup-
porting an association between early solid feeding and allergic conditions,
other than eczema [12]. In a recent birth cohort study (LISA) with follow-
up to 6 years of age, delayed introduction of solids (beyond 4–6 months)
was not associated with a decreased risk for asthma, allergic rhinitis, or
sensitization against food or inhaled allergens [23]. However, with respect
to eczema there are still conflicting results [12, 23, 24]. Now, this research
field calls for epidemiological studies addressing the role of early exposure
to allergenic foods, rather than avoidance, and their role in atopic disease
expression.

A Change in Infant Feeding Recommendations

As evident from the Swedish experience of a CD epidemic, changes in
national infant feeding recommendations can have far-reaching consequences.
Our experience also illustrates the value of epidemiological surveillance – as
in the Swedish Prospective Incidence Register of Celiac Disease in Children
[14] – that allows long-term follow-up of consequences for health and disease
after changes in exposure, either on purpose or unintentionally.

Recently, current evidence on the benefits of breastfeeding, and on when
and how to introduce complementary feeding, resulted in revised European
recommendations [6, 7]. It was concluded, as advocated by WHO [4], that
exclusive breastfeeding for around 6 months is desirable but partial breast-
feeding, even for a shorter duration, is also valuable. In addition, continu-
ation of breastfeeding after introducing complementary feeding should be
encouraged. Complementary feeding should not be initiated for any infant
before 4 months of age, and not later than around 6 months. This recommen-
dation was given for all foods, including gluten-containing foods and potent
food allergens such as fish and eggs. Recommendations with similar messages
have followed from the American Academy of Pediatrics [10]. Further revisions will be required as evidence evolves.

There is a notable conflict between the WHO recommendation of exclusive breastfeeding for at least 6 months [4], and other guidelines that recommend introduction of complementary feeding within the age interval of 4–6 months [6, 7, 10]. It has been discussed that delaying introduction of solids until 6 months of age is difficult to justify in richer parts of the world, in the face of emerging evidence that this may be detrimental [6, 21]. There are also other reasons for adapting the WHO recommendations to specific country situations or individual needs, such as maternal infection with the human immunodeficiency virus, where mixed feeding confers the greatest risk of maternal to child transmission after birth [6]. The changing, and potentially confusing, recommendations pose challenges for health care personnel, parents and other caregivers, and some efforts have been made to also give guidance in this respect [25].

### Current Epidemiological Research

It is evident that epidemiological research has contributed to an improved understanding of the role infant feeding habits have on the development of CD and atopic disease, and on many other phenomena related to health in populations. In our opinion, epidemiology should be more appreciated and utilized, also within the field of pediatric nutrition, because of its potential to contribute to future innovations. We therefore briefly describe how this discipline has evolved over time, and share our experience of epidemiological research applied to CD from a methodological perspective.

In the past, epidemiology was mainly concerned with communicable disease epidemics, but nowadays contributes to increased understanding of many phenomena related to health in populations. A commonly used definition is 'The study of the distribution and determinants of health-related states or events in specified populations, and the application of this study to control of health problems' [26]. The emphasis is on taking advantage of the often underutilized potential of observational studies, but experimental study designs for complex community interventions are also being developed in parallel. Importantly, it is becoming increasingly evident that the highly valued experimental randomized controlled trial (RCT) is not a sufficient method for many research questions related to human health. Consequently, taking advantage of optimized observational designs is also important. Supporting guidelines are, for example, TREND (Transparent Reporting of Evaluations in Nonrandomized Designs) [27], and GRADE [28], which can help when grading quality of evidence and strength of recommendations both for observational and experimental studies.

In approaching a certain phenomenon, a step-wise use of different epidemiological research designs is often advisable, moving from observational
descriptive and analytical studies towards experimental designs when feasible. This is illustrated by the epidemiological approach to CD research from the early 1980s until now [18] (fig. 3). Clinical case reports, followed by observational surveillance studies and cross-sectional screening studies, revealed complex epidemiological patterns relating to person, time and place. Based on these findings, and with ecological studies added (also called correlation studies), hypotheses on causality were generated. Thereafter observational analytical studies, such as case-referent and cohort designs, were used to assess causality. Recently, further steps have been taken to field trials, basically RCTs involving healthy persons.

It is important to recognize that multidisciplinary research teams are needed, encompassing epidemiological and statistical skills as well as knowledge in other sciences. Different study designs are listed and briefly described below, with some strengths and weaknesses. Further details can be found in epidemiology textbooks [29].

Observational Descriptive and Analytical Studies

Observational studies, also called non-experimental, imply that the researcher does not intervene except to collect information for statistical analyses. Thus, the researcher observes and takes advantage of natural courses of health and disease to learn more about the studied phenomena.

Observational descriptive studies report the occurrence of diseases and other health-related characteristics in population, often under the headings of person, time and place. Such studies are useful for disease surveillance and

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**Fig. 3.** An epidemiological approach to CD research. Adapted from Ivarsson et al. [18], with permission.
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dimensioning for health care services, and for generating hypotheses about disease causality. A next step can be ecological study designs where data on exposure and disease are compared for populations or groups of people (but not for single individuals), which can give valuable insights even though causality cannot be proven. The cross-sectional design, with data on individuals at one particular time, can further increase our understanding, but cannot be used to prove causality as information about the temporal sequence of cause and effect is lacking.

In contrast, the purpose of observational analytical studies is to evaluate putative associations or hypothesized causal relationships. The prospective cohort study, often considered to provide the best basis for assessing causality, encompasses a large number of subjects followed over a long period (often years), comparing occurrence of the phenomena under study in groups that differ in exposure. The retrospective cohort design can be as reliable if it is possible to take advantage of exposure data collected and documented far back in time. Importantly, the case-referent study design and interlinked methods for analyses have been extensively developed over the years, and now represent a valuable and cost-effective option for consideration. Persons with the disease or other outcome of interest (cases) are compared with referents (also sometimes called controls) with respect to the exposures of interest, also taking potential confounding factors into account. For valid results, the selection of referents is crucial and careful thought needs to be given as to how referents represent the population giving rise to the cases.

**Experimental Studies**

In most experimental studies, the exposure is intentionally altered in order to study the outcome. Sometimes, however, the intervention is beyond control of the researcher, for example in the case of naturally occurring events, or impositions following societal decisions. Such quasi-experiments have their limitations as the allocation is not random. Attempts to draw conclusions on causality can still be done, as analyses across different groups can be made and potential confounders taken into account.

In modern usage, the term experimental epidemiology is synonymous with RCTs, i.e. with subjects randomly allocated to the study group receiving the exposure, and the control group usually receiving ‘standard care’. Some suggest the term *RCT* be saved for studies on patients, with the term *field trial* being used when a study involves healthy persons, and the term *community trial* being used when whole groups of people are involved. Many interventions, especially community interventions, are highly complex. Developing and evaluating such interventions poses many additional challenges. Guidelines have recently been launched [30], but standards for such evaluations are still lacking.

For some time, the RCT has been considered the best, or even the only, study design that can link cause and effect. However, this is now increasingly
questioned. The RCT is limited to highly standardized conditions and often by restricted follow-up times. In the field of infant nutrition, such studies are likely to be unrealistic or even impossible to conduct for evaluating the effects of infant dietary exposures on long-term health outcomes.

Conclusions

Breast milk is the initial natural food for infants, but already during the second half year complementary feeding is essential. Epidemiological research has driven a paradigm shift with respect to most favorable age to introduce complementary feeding, that simplified implies a shift from later to earlier introduction, which has been taken into account in recent recommendation changes. Complementary feeding, including all foods, should not be initiated for any infant before 4 months of age and no later than around 6 months, also for those with elevated disease risk (e.g. for CD or atopic diseases). Epidemiology has evolved over time and could, if increasingly used, contribute even more to innovations in pediatric nutrition, and other phenomena related to population health.

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References

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**Discussion**

*Dr. Greer:* Do you have any data from 2003 to 2009? It would appear that the incidence of celiac disease was starting to rise again in 2003?

*Dr. Ivarsson:* The incidence curve I showed is based on our National Swedish Childhood Celiac Disease Register with prospectively collected data from 1991 and onwards. Thus, we also have information from 2003 to 2009, but data from the most recent years need more quality checks before being presented. But even when only including data up to 2003, it is correct that the incidence rate is increasing year by year in all age groups [1].

*Dr. Hernell:* You discussed the possibility that there is an immunological window, perhaps between 4 and 6 months, explaining the advantage of early rather than late introduction of strong food allergens. I think that such a window is easily shown in mice and perhaps other experimental animals, but it's not that easy to show it in humans. This raises an interesting question. Take celiac disease as the example. We have shown that breastfeeding has a preventive effect, or rather, as you mentioned, introducing gluten during breastfeeding reduces the risk for celiac disease. It has never been studied whether introducing other food antigens under the immunologic umbrella of breastfeeding has a similar preventive effect against allergy. So maybe the important thing is to introduce strong food antigens while the mother is still breastfeeding. What we as pediatricians have caused with the recommendations with respect to allergy is to actually postpone the introduction of allergens, so that most mothers, particularly those with allergy in the family, have stopped breastfeeding before the introduction, that is if they have followed the recommendations. The question now is what will happen if we start to introduce those antigens while the mother is still breastfeeding? Is it an important concept to introduce them during breastfeeding, or is there indeed an immunological window in humans? I think that’s still an open question.

*Dr. Ivarsson:* True, I agree. There are many unanswered questions.

*Dr. Mittal:* I think I can take your argument for the introduction of complementary feeding further. We need to look at the WHO guidelines again because in poor countries like ours growth of the infants cannot be sustained with exclusive breastfeeding for 6 months. So, it is not only from an allergic point of view or a celiac point of view but also the nutritional point of view. Secondly, the process of weaning cannot be done in one day, it is a gradual introduction. Thirdly, and this is more of an observation, if you start introducing something new after 6 months, many babies are very reluctant to leave the breast. I will call it breast addiction. So I think we need to look back at these recommendations of exclusive breastfeeding for 6 months.

*Dr. Cooper:* In my part of the world, Southern Africa, the staple foods that are first introduced are all maize based and it would be uncommon for children, particularly in the rural areas, to be exposed to wheat before a year of age. Have you any data on how that might affect celiac disease?

*Dr. Ivarsson:* I am surprised about your comment on wheat consumption in South Africa as it isn’t that low according to the official statistics, but of course it might still be low for the infants.

*Dr. Cooper:* The adults eat it.

*Dr. Ivarsson:* What we know for sure is that as long as gluten-containing foods haven’t been introduced into the diet the disease will not develop as the gluten proteins – present in wheat, rye and barley – are the triggers and maintainers of the immunological processes of the disease. However, according to our incident case-referent study the overlap between breastfeeding and introduction of gluten reduced the risk for celiac disease, at least for the first 2 years of life [2]. Delaying introduction of
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gluten up to 1 year of age or later, as you tell is common in South Africa, would according to this reasoning increase the long-term risk for celiac disease. However, more studies are needed to clarify if this is the case or not.

Dr. Thakre: Would you suggest any intervention for the huge majority of patients with subclinical celiac disease?

Dr. Ivarsson: It is evident from clinical experiences that celiac disease cases, also those with vague symptoms, benefit from being diagnosed and treated with a gluten-free diet. In your country, and many other parts of the world, I am quite sure that you could find the celiac disease children among those with chronic diarrhea and among those that are malnourished, for example those stunted. Thus, it is important to increase awareness of the disease, and encourage active case finding by generously testing for celiac disease serological markers. If these diagnostic tools are not available, also a trial period with gluten-free diet could be worth considering. Although most celiac disease cases still remain undiagnosed, there is not yet sufficient evidence for suggesting mass screening of populations. However, through our present studies we will be able to increase knowledge on the consequences of having subclinical celiac disease. In our ongoing population-based screening studies of 12-year-olds, the families are asked to respond to comprehensive questionnaires (well-being, health, etc.) before getting the result of the serological marker analyses [3], which increases reliability of their responses. Thus, this study will enable us to clarify self-reported consequences of having undiagnosed celiac disease up to this age. Other comparable studies on the consequences of this disease in adults are underway.

Dr. S. Koletzko: We just finished a study in Germany in 17,000 randomly selected children in all age groups up to 17 years. They were screened for celiac disease with tTG antibodies. Children with positive antibodies were significantly smaller compared to age- and sex-matched controls and the BMI was also lower. We know from undiagnosed celiac adults that their bone mineral density is decreased and other health problems may occur in spite of absence of GI symptoms. Particularly in countries with a higher prevalence of undernutrition, the effect on length and BMI may even be stronger compared to countries with an ‘overfed’ population like in Germany.

Dr. Ivarsson: Irrespective of clinical signs and symptoms, celiac disease cases have an ongoing inflammatory process in their small intestinal mucosa, as illustrated by some of the slides I showed. Also, today we know that the celiac disease processes are not restricted to the gastrointestinal tract, but can affect any organ in the body. Thus, I would be surprised if the subclinical cases haven’t suffered from long-term negative health consequences. However, further scientific evidence is needed.

Dr. Wang: We are very interested in the research results of the celiac disease. We don’t know what happened in China, because we’ve never done an investigation into the disease before. Still, it has always been believed that celiac disease was not very common in China. But I think that this may not be true. I think perhaps we should do the same investigation as you did in China. My question is what is the protocol and method to be used; do you use a commercial package for the screening?

Dr. Ivarsson: There are several commercially available kits for measuring celiac disease serological markers, and most of them measure anti-human tissue transglutaminase antibodies. However, many laboratories use in-house-developed methods to keep down the costs. In our celiac disease screening studies, we use Celikey (Phadia, GmbH, Freiburg, Germany), which is a test that in our experience performs well [3]. Among the about 7,200 tested children, only 192 had elevated markers, and out of the 180 that accepted a small intestinal biopsy, the celiac disease diagnosis was confirmed in 145. Thus, only few unnecessary small intestinal biopsies were performed. Also, children with elevated markers, but a normal intestinal mucosa, will be checked repeatedly as they might be in the process of developing the disease.
**Dr. Wang:** This means that if you get a positive result of the screening test, you should do the biopsy.

**Dr. Ivarsson:** Yes, so far the diagnosis of celiac disease has been based on evaluation of the small intestinal mucosa, even though the serological markers have shown increasing reliability over time. If the celiac disease prevalence in a population is unknown, a first step could be to determine the prevalence of elevated markers, which also without follow-up biopsies would give an estimate of the celiac disease prevalence. However, for involved individuals a follow-up biopsy is important as it will confirm the diagnosis for most, but also rule the disease for some.

**Dr. Wang:** You just mentioned that you have done an investigation about the timing of solid food introduction in young children. What kind of solid food have you investigated?

**Dr. Ivarsson:** In our incident case-referent study we asked the parents to report at what age different solids (and liquids) were introduced and in what amount, and then 2 weeks later about both frequency and amount. Thus, our study asked for the introduction pattern of all foods, but we restricted the analyses to gluten-containing foods [2].

**Dr. B. Koletzko:** Are there data on the prevalence of celiac disease in Asian populations outside of Asia, for example in Europe or the US?

**Dr. Ivarsson:** The only such population I am aware of are Indian immigrants in Great Britain, who have about the same prevalence as those originally British. Globally, the prevalence nowadays is assumed to be about 1% in the general population; however, it varies between different countries, and within a certain country with respect to age and sex. In Sweden, we recently revealed a prevalence of 3% among 12-year-olds [3], while in an adult screening study in the mid-1990s the determined prevalence was 0.5% [4]. The highest prevalence reported so far is 5.6% among Saharawi children in Algeria [5].

**Dr. Mittal:** We have adequate data from India to say that celiac disease now is almost as prevalent, at least in the northern part, as in the developed countries, and we also share the same HLA antigen.

**Dr. Ivarsson:** The only parts of the world from which I haven’t seen any prevalence estimates, or even case reports in the native population, are from Sub-Saharan Africa and South-East Asia. Thus, screening studies are needed there.

**Dr. De Curtis:** I would like to ask two questions. What is the most appropriate age to give complementary food and gluten to premature infants? Is there a difference in the prevalence of celiac disease between premature and term infants?

**Dr. Ivarsson:** I am not aware of any studies that specifically have addressed these issues in prematurely born children, neither with respect to the celiac disease prevalence nor suitable age for introducing gluten. However, as for all other children introducing gluten while still breastfeeding seems preferable [2], which implies not delaying introduction too much.

**Dr. Shenoi:** I would like to ask a question and make a comment. The question is: would the gluten intake in a breastfeeding mother be a confounder in your studies, because there are certain communities in South India which restrict gluten intake in lactating mothers. The comment is: I concur with Dr. Mittal’s comments about North India. We do find celiac disease in South India, but this is in a segment of children who are failing to thrive and have resistant iron deficiency anemia, resistant to iron therapy. In that subgroup, we find a high incidence of celiac disease.

**Dr. Ivarsson:** There are a few studies clearly showing that breast milk contains both small amounts of gluten and antigliadin antibodies, but the clinical significance of that is unclear. Perhaps Dr. Hernell would like to give a comment?
Dr. Hernell: It’s more likely that the small amounts of gliadin peptides or gliadin in breast milk would induce tolerance rather than celiac disease, and I am not aware of a single case of celiac disease that has been diagnosed before you have introduced gluten as complementary food into the infant’s diet.

Dr. Ivarsson: It is likely that this question can be further clarified by the ongoing European collaborative celiac disease study (www.preventcd.com). More than 1,000 pregnant mothers from high-risk families are recruited with a planned follow-up at least until the child is 2 years of age. Among many things, the breast milk content will be analyzed, and could be put in relation to the risk for celiac development in the child.

References
