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Merryn Netting and Maria Makrides

Effects of early diet on childhood allergy

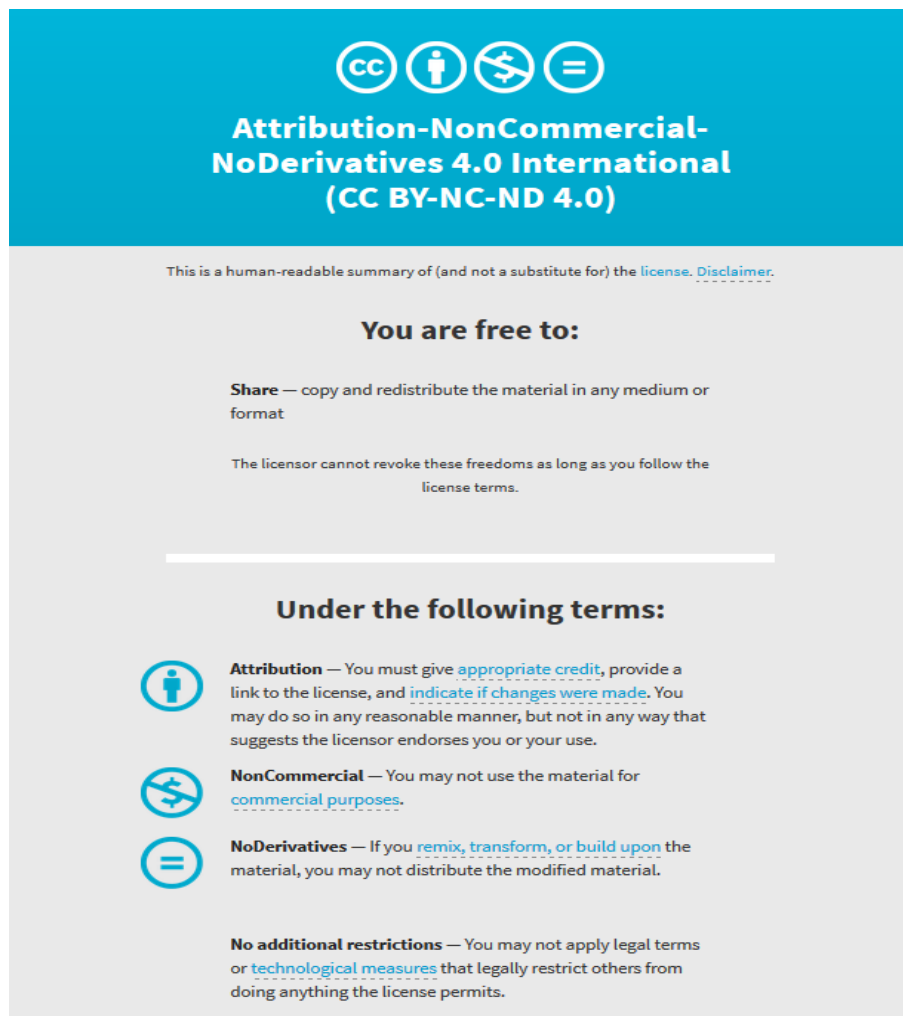
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21 Effects of Early Diet on Childhood Allergy

Merryn Netting and Maria Makrides

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INTRODUCTION

Food allergies are classified into two categories: those that are mediated by immunoglobulin E (IgE) antibodies and those mediated by immune cells (non-IgE mediated) [1]. Although it is possible to develop an IgE-mediated allergy to any food, most individuals with allergies react to one, or a combination, of nine common foods: cow's milk, soy, egg, wheat, peanut, tree nuts, sesame, fish, and shellfish [2]. The most common symptoms associated with food allergy in children include urticaria (hives), angioedema, eczema, enterocolitis, enteropathy, irritability, vomiting, diarrhea, and anaphylaxis [1].

Allergic disease, and in particular food allergies, significantly impact general health perception, parental emotional distress, and family activities [3]. Young children are particularly at risk of developing food allergy, and it is estimated that up to 10% of toddlers have food allergy, compared with 1% to 2% of adults [1,4]. Why young children are becoming increasingly sensitized to food allergens is the focus of ongoing research. The development of tolerance to multiple foods during early life is essential to survival, and the immune mechanisms that enable the development

of tolerance are highly developed and regulated. Food allergy in an infant or child represents a failure to develop tolerance to a food protein and is associated with aberrant T helper cell 2 (Th2) balance [5]. Environmental factors such as maternal dietary patterns and micronutrient supplements, as well as postnatal factors such as the mode of birth, feeding type, early infections, timing, and type of solid foods, and exposure to allergens all influence the developing immune system [6]. However, it has become clear that these environmental factors may exert differing effects, depending on genetic predisposition, and are modulated by epigenetic effects on gene expression.

Fewer allergies are observed in low-income countries; however, rates appear to be increasing as these countries adopt more Westernized lifestyle patterns [7,8]. There also appear to be important migration effects; the HealthNut cohort in Melbourne had a high rate of food allergy and eczema among children born to Asian immigrants [9]. This difference in allergy rate was significantly higher than that in children born in Asia who migrated to Australia with their parents [9]. The reasons for this increased incidence is unclear, and is likely to be due to multiple mechanisms. In this chapter, following an overview of the hypotheses of allergy development, we examine the evidence relating to dietary influences on development of food allergy, and discuss the most recent infant feeding guidelines for allergy prevention.

HYPOTHESES OF ALLERGY DEVELOPMENT

The reasons why some individuals develop allergies are complex and multifactorial. The main hypotheses about the etiology of allergy include the hygiene and dual allergen exposure hypotheses.

HYGIENE HYPOTHESIS

The hygiene hypothesis is based on the observation that people living in European farming communities have lower rates of food allergy and asthma compared to those in the city [10]. It is hypothesized that the farming environment and lifestyle leads to greater exposure during infancy to bacterial markers called endotoxins that influence the microbiome, which in turn promotes tolerogenic immune pathways.

In a Swedish study, washing dishes by hand was associated with a lower incidence of allergic disease as compared with using automated dishwashers [11]. The protective effect of dishwashing by hand was stronger in children eating fermented foods and foods purchased from the farm door [11]. This effect may be related to exposure to beneficial microbial exposures not destroyed by high-temperature machine dishwashing. In Westernized countries, there has been an increased consumption of virtually sterile processed foods. The influence of the consumption of highly processed foods on the gut microbiome may be one of the mechanisms by which Western-style diets are associated with increases in atopy [12]. The hygiene hypothesis has been further supported by observations that birth by cesarean section is associated with an increased risk of food allergy or atopy [13], with the mechanism postulated to be related to the lack of inoculation with maternal gut flora that occurs during a normal vaginal delivery.

DUAL ALLERGEN EXPOSURE HYPOTHESIS

The dual exposure to allergen hypothesis proposes that tolerance to antigens occurs in the neonate through high-dose oral exposure, and that allergic sensitization occurs through low-dose cutaneous exposure [14]. It is hypothesized that there is a balance between these processes and is an issue particularly for babies with eczema who have filament aggregating protein (filaggrin) mutations, resulting in altered skin barrier function and abnormal immune reactivity [14]. It is proposed that food proteins (from the household environment) pass through the disrupted skin barrier, leading to Th2 responses, IgE production, and sensitization to the allergen [15]. This may be particularly problematic for infants at risk of developing allergy (including babies with eczema), where allergenic foods are consumed by household members but avoided in the infant's diet as the baby is exposed to the allergen via their skin, but not the potentially protective oral route.

DIETARY INFLUENCES ON DEVELOPMENT OF ALLERGY

Our diet has the potential to alter the tendency toward allergy by immunomodulatory effects of dietary components and exposures to allergens. Infants may be exposed to nutritional influences via the maternal diet while they are *in utero*, during breastfeeding, or as they start consuming solid foods [16].

Maternal dietary patterns associated with decreased sensitization in their children include Mediterranean diets, and the consumption of fruits, vegetables, and fish [12]. These nutrient-rich foods and dietary patterns contain immunomodulatory factors, including polyunsaturated fatty acids, antioxidants, vitamin D, prebiotics, and probiotics. These factors may foster a healthy immune system by modifying the immune response or the functioning of the immune system. It is also possible that women who consume these types of diets have other associated lifestyle factors that are associated with a reduced risk of allergy development, such as the avoidance of tobacco smoke, and less exposure to environmental pollutants [17].

LONG-CHAIN POLYUNSATURATED FATTY ACIDS

Omega-3 long-chain polyunsaturated fatty acids (LCPUFA), found predominantly in marine oils, modulate the immune system by the inhibition of inflammatory pathways and may be the reason diets containing fish are associated a lower risk of atopic disorders [12]. Diets rich in omega-3 LCPUFA may alter the immune system by affecting Th cell balance, specifically inhibiting Th2 cell differentiation, and thereby reducing IgE-mediated allergy. The effect of omega-3 LCPUFA in the maternal diet during pregnancy and lactation on development of childhood allergy has been tested in many randomized controlled trials (RCTs), with inconsistent results. The most recent *Cochrane Review* of maternal supplementation with omega-3 LCPUFA concluded that, although there was little effect of omega-3 supplementation during pregnancy and/or breastfeeding in the reduction of allergic disease in children, there were some reductions in atopic disease outcomes, including food allergy and eczema in the first year in children born to women at high risk of allergy [18]. Since this review,

the results of the Copenhagen Prospective Studies on Asthma in Childhood₂₀₁₀ (COPSAC₂₀₁₀) have been published [19]. In the COPSAC₂₀₁₀, pregnant women were randomized to large doses (2.4 g) of omega-3 LCPUFA or a placebo (olive oil) per day during the last trimester of pregnancy, and their offspring were followed to 5 years of age. The study reported that, for children born to the intervention group, the absolute risk of a persistent wheeze or asthma was reduced by one-third, with further analysis suggesting that this effect was strongest in the children of women whose blood eicosapentaenoic acid and docosahexaenoic acid levels were in the lowest third of the trial population. Supplementation with omega-3 LCPUFA may be not recommended for all women, but might be useful for subgroups, such as those with a family history of food allergy or with poor omega-3 LCPUFA status. LCPUFA have many effects, and supplementation may be not without risk, as it has been associated with longer gestational length [20].

The effect of direct supplementation of infants' diets with omega-3 LCPUFA has also been investigated. The Childhood Asthma Prevention Study (CAPs) was an RCT conducted in children with a family history of asthma, which supplemented diets with omega-3 LCPUFA and restricted the dietary intake of dietary omega-6 fatty acids from 6 months of age to 5 years of age [21]. The study found no effect on asthma, eczema, or atopy at 5 years of age. Schindler et al. [22] reviewed nine more studies, including a total of 2,704 infants, that assessed the effect of higher versus lower intake of LCPUFA on allergic outcomes in infants for the Cochrane database. The *Cochrane Review* concluded that there is no evidence that PUFA supplementation in infancy has an effect on infant or childhood allergy, asthma, dermatitis/eczema, or food allergy; however, the authors noted that the studies were of variable quality and heterogeneous in nature.

ANTIOXIDANTS

There is an association between maternal fruit and vegetable intake and less atopy in their babies [12], which may be due to the antioxidant content of diets rich in fruits and vegetables. The antioxidant vitamins (C, A, and E) and minerals (zinc and selenium) present in fruit and vegetables may protect against atopic disease of the airway by protection against oxidant damage and inflammation of the airways [23]. However, there have been no antioxidant supplementation trials to test the link between antioxidants in the maternal diet and atopy development.

VITAMIN D

Vitamin D is a fat-soluble vitamin and hormone with many roles, including immunomodulation, a process in which the immune response is altered. Vitamin D is obtained through the action of sunlight on skin and, in smaller amounts, through diet. Interest in poor vitamin D status and increased allergy risk began with the observation that people living at lower latitudes with greater sun exposure have fewer allergies; this has been shown in the United States and Australia [24]. However, this association has not been demonstrated in cohort studies or RCTs with vitamin D supplementation. The Barwon infant study [25] found no association between low

vitamin D levels at 6 months of age and egg allergy at 1 year of age. Higher cord blood vitamin D was associated with less eczema, but not with food sensitization or food allergy at 1 year of age in a subset of infants enrolled in an RCT comparing the effect of fish oil supplementation during infancy on allergic outcomes [26].

ALLERGEN EXPOSURE: TIMING AND TYPE OF ALLERGENS

MATERNAL ALLERGEN AVOIDANCE DURING PREGNANCY

Avoidance of common allergens in the maternal diet during pregnancy is not recommended as a strategy for allergy prevention in Australia and other countries, including the United States and Europe. Avoiding the consumption of common allergens during pregnancy does not reduce the incidence of sensitization to allergens in children [12], and the restricted diet is associated with lower pregnancy weight gain [27].

DOES BREASTFEEDING PREVENT ALLERGY?

Breast milk is the gold standard for infant feeding, and has many benefits for both the mother and child. In addition to its nutritional benefits, breast milk contains many nonnutritional components, including antibodies, cytokines, and other immunomodulatory components [28]. The evidence that breastfeeding is protective against allergy, specifically food allergy, is weak; however, this may be due to methodological issues. A recent systematic review and meta-analysis including the results of 89 studies reported that breastfeeding is associated with less asthma at 5 years of age, with a greater effect in low- to middle-income countries [29]. This review reported that there is weak evidence for breastfeeding and the prevention of other atopic diseases, including eczema and rhinitis, with no effect of breastfeeding on development of food allergy [29]. The lack of protective results for breastfeeding and food allergy may be due to reverse causality, as highly atopic families are more likely to breastfeed and feed for longer, and the authors note that this should be adjusted for when reporting the results of trials investigating breastfeeding and allergy development. There are other innate issues with studies investigating the effects of breastfeeding, including the inability to randomize exposures. Additionally, the lack of evidence for breastfeeding and protection against food allergy may also be because many of the cohort studies included in the systematic review were conducted prior to the food allergy epidemic [29]. Some of the limitations of the cohort studies have been addressed by the only randomized trial of breastfeeding exposure in Belarus [30]. In the PROBIT study, women were cluster randomized via attendance at maternal health centers that followed the World Health Organization Baby Friendly Hospital Initiative (WHO BHFI) advice or other health centers [30]. Allergic sensitization was assessed using skin prick testing, and allergy symptoms were scored using standardized protocols. A total of 17,046 mother–infant pairs were randomized into the trial, and 13,889 were reviewed at 6.5 years of age. Although infants whose mothers attended the WHO BHFI health centers breastfed for longer, the results of this RCT did not support the protective effect of prolonged breastfeeding against allergic sensitization, and the development of asthma, hay fever, or eczema [30].

Food allergens consumed by the mother appear in her breast milk [31], and avoidance of allergens in the maternal diet during lactation does not reduce the incidence of sensitization in the infant. However, there are emerging data, specific to egg, that the inclusion of egg in the maternal diet during early lactation is associated with increased levels of egg-specific IgG4 in their babies, which may be important for tolerance development [32].

WHAT ABOUT INFANT FORMULA?

Not all infants are breastfed, and many breastfed infants have infant formula top-up feeds. Infant formula is usually based on modified cow's milk protein, and this is often an infant's first exposure to an allergen. For the prevention of allergy, there is insufficient evidence to recommend the use of soy-based formulas, goat-milk-based formulas, formulas containing LCPUFA, or formulas containing pre- or probiotics [17].

Partially hydrolyzed infant formula has been promoted as a means of preventing development of allergy and, until recently, infant feeding guidelines in Europe, America, and Australasia [33–35] supported the use of hydrolyzed formulas for non-breastfed infants in place of standard cow's milk formula if the infant has a family history of allergy. A recent systematic review and meta-analysis by Boyle et al. [36] investigated whether hydrolyzed cow's milk formulas can prevent allergic or autoimmune disease. This review, commissioned by the UK Food Standards Authority, included 37 eligible intervention trials of hydrolyzed formula, with over 19,000 participants. There was evidence of a conflict of interest and a high or unclear risk of bias in most studies of allergic outcomes, and evidence of publication bias for studies of eczema and wheeze. Overall, the authors reported that there was no consistent evidence that partially or extensively hydrolyzed formulas reduced the risk of allergic or autoimmune outcomes, and this is reflected in newer infant feeding guidelines for allergy prevention guidelines [37].

COMPLEMENTARY FOODS: WHEN AND WHICH FOODS?

When considering the introduction to solid foods, issues specific to the prevention of allergy relate to the timing of introduction to solid foods and the type of foods introduced [29,38–40]. In the last 10 years, there has been a reversal of recommendations regarding the introduction to solid foods for prevention of allergy. While guidelines are used to promote delayed introduction to solid foods, and staged and delayed exposure to common allergens, this was not associated with a reduction in the prevalence of food allergy and, in fact, may have contributed to the increasing prevalence. The change in guidelines has occurred as available evidence to inform these recommendations has shifted from population-based cohort studies to RCTs and systematic reviews of RCTs.

Several randomized controlled trials have investigated the timing of including common allergens in an infant's diet. Whereas most of the trials have considered single allergens, peanut [41] and egg [42–45], one trial [46] investigated the effect of adding multiple allergens into an infant's diet before one year of age. The outcomes of the single allergen trials are summarized in Table 21.1.

TABLE 21.1
Summary of Results from Single Allergen Allergy Prevention Studies

Trial	Allergen	Intervention	Result
LEAP [41]	Peanut	RCT Peanut vs. no peanut from 4–11 months Group 1: peanut SPT <1 mm: <i>n</i> = 530 Group 2: peanut SPT 1–4 mm: <i>n</i> = 98	Peanut allergy at five years: Group 1 Peanut group: 1.9% Control group: 13.7% (<i>p</i> < 0.001) Group 2 Peanut group: 10.6% Control group: 35.3% (<i>p</i> = 0.004)
STAR [43]	Egg	DBPC RCT Egg (<i>n</i> = 49) vs. no egg (<i>n</i> = 37) From 4–8 months Infants with eczema	Egg allergy at one year: Egg group: 33% Control group: 51% RR 0.65; 95% CI: 0.38, 1.11; <i>p</i> = 0.11
STEP [42]	Egg	DBPC RCT Egg (<i>n</i> = 407) vs. no egg (<i>n</i> = 410) From 4–10 months Infants with family history of atopy but without eczema	Egg allergy at one year: Egg group: 7.0% Control group: 10.3%; ARR 0.75; 95% CI: 0.48, 1.17; <i>p</i> = 0.20 Egg-specific IgG4 levels: Egg group median: 1.22 mg A/L Control group: 0.07 mg A/L; <i>p</i> < 0.0001
HEAP [44]	Egg	RCT Egg (<i>n</i> = 184) vs. no egg (<i>n</i> = 199) From 4–12 months	Sensitization to hen's egg at one year: Egg group: 5.6% Control group: 2.6% RR 2.20; 95% CI: 0.68, 7.14; <i>p</i> = 0.24 Hen's egg allergy at one year: Egg group: 2.1% Control group: 0.6% RR 3.30; 95% CI: 0.35, 31.32; <i>p</i> = 0.35
BEAT [45]	Egg	RCT Egg (<i>n</i> = 165) vs. no egg (<i>n</i> = 154) From 4–8 months Infants with family history of allergic disease and EW-SPT <2 mm	Egg sensitization at one year (EW-SPT ≥3 mm) Egg group: 11% Control group: 20% OR 0.46; 95% CI: 0.22, 0.95; <i>p</i> = 0.03 IgG4 to egg proteins and IgG4/IgE ratios higher in egg group (<i>p</i> < 0.0001)

Note: A/L, antigen per liter; ARR, adjusted relative risk; DBPC, double-blind placebo-controlled; EW-SPT, egg white skin prick test; IgE, immunoglobulin E; IgG4, immunoglobulin G4; OR, odds ratio; RCT, randomized controlled trial; RR, relative risk; SPT, skin prick test.

The Learning Early About Peanut (LEAP) allergy study [41] compared early (4–11 months) with delayed (5 years) introduction to peanut in children at high risk of peanut allergy defined as preexisting eczema and/or egg allergy. The study demonstrated an 11%–25% absolute reduction in the risk of peanut allergy in high-risk infants (and a relative risk reduction of up to 80%) if peanut was introduced between 4 and 11 months of age [41].

Four trials investigating the timing of introduction to egg have been published [42–45]. Although none of the trials reported statistically significant differences in rates of egg allergy at 1 year of age in infants fed egg early compared with later introduction to egg, there was a trend toward lower rates of egg allergy in the groups of children introduced earlier to egg. Meta-analysis of the egg trials (including 1,915 participants) showed evidence that egg introduction at 4 to 6 months was associated with a lower risk of egg allergy compared with later egg introduction (RR 0.56; 95% CI: 0.36, 0.87; $p = 0.009$) [39]. The authors concluded that there is moderate certainty that early introduction to egg, compared to delayed introduction to egg, will reduce the risk of IgE-mediated egg allergy by up to 30%. It was of concern, however, that many infants screened for these trials already had clinical egg allergy prior to the introduction of solid foods, indicating that, at least for egg allergy, sensitization and allergy development takes place very early in life, and there may need to be some level of caution for some subgroups of the population, such as babies with severe eczema, when introducing egg into the diet.

The EAT study [46] was the first randomized controlled trial to test the effect of early introduction to solid foods (from 3 months) compared with the UK guidelines on allergy development of exclusive breastfeeding until introduction to solid foods at 6 months. The study found no significant difference in food allergy rates in the primary analysis (intention to treat analysis) between the early and standard introduction groups. There was no difference in breastfeeding rates at 12 months for individuals in the early introduction group, compared with the exclusive breastfeeding group, showing that earlier introduction of allergenic foods did not have an impact on breastfeeding [47].

Meta-analysis of the LEAP and EAT studies showed evidence that peanut introduction at 4 to 11 months of age was associated with a lower risk of peanut allergy when compared to delayed introduction to peanut (RR 0.29; 95% CI: 0.11, 0.74; $p = 0.009$) [39].

UPDATED INFANT FEEDING GUIDELINES FOR PREVENTION OF FOOD ALLERGY

Ten international allergy and immunology bodies released a joint consensus communication in 2015, highlighting new evidence from the LEAP study regarding the potential benefits of early, rather than delayed, peanut introduction during the period of complementary food introduction to prevent peanut allergy in high-risk infants [35]. This has led to the development of Australian Infant Feeding Consensus Guidelines [48] and an addendum to the USA National Institute of Health Feeding Guidelines for Reduction of Peanut Allergy [49] (Box 21.1). Whereas the Australian guidelines provide general information related to inclusion of allergens in the infant diet, the U.S. guidelines provide advice related to the inclusion of peanut into an infant's diet stratified by degree of risk, defined as the presence of eczema and/or egg allergy.

BOX 21.1 INFANT FEEDING GUIDELINES FOR THE PREVENTION OF FOOD ALLERGY

Australian Infant Feeding Consensus Guidelines [37]:

- When your infant is ready, at around 6 months, but not before 4 months, start to introduce a variety of solid foods, starting with iron-rich foods, while continuing breastfeeding.
- All infants should be given allergenic solid foods including peanut butter, cooked egg, and dairy and wheat products in the first year of life. This includes infants at high risk of allergy.
- Hydrolyzed (partially and extensively) infant formula are not recommended for prevention of allergic disease.

U.S. National Institute of Allergy and Infectious Diseases Guidelines, 2010 [50]:

- Restriction of maternal diet during pregnancy or lactation is not recommended as a strategy for preventing the development of food allergy.
- It is recommended that all infants be exclusively breastfed until 4 to 6 months of age (unless contraindicated for medical reasons).
- It is recommended that introduction of solid food should not be delayed beyond 4 to 6 months. Potentially allergenic foods may be introduced at this time as well.

U.S. National Institute of Allergy and Infectious Diseases Addendum Guidelines for Introduction to Peanut, 2017 [49]:

- Addendum guideline 1—For infants with severe eczema, egg allergy, or both:
 - Strongly consider evaluation by specific peanut IgE measurement and/or skin prick testing and, if necessary, an oral food challenge. Based on test results, introduce peanut-containing foods.
 - Earliest age of peanut introduction: 4 to 6 months.

CONCLUSION

The risk factors for developing childhood food allergy are complex and multifactorial, depending on a combination of genetic, nutritional, and environmental factors. Early life nutrition exposures and feeding practices play an important role, as does the maternal diet during pregnancy. The most recent public health guidelines for infant feeding to prevent food allergy promote exposure to common allergens, particularly peanut, in the first year of life. There are many other potential factors,

including the influence of a variety of foods and nutrients, and the role of processing on foods, that are yet to be explored.

There are concerns regarding the potential for increasing incidence of food allergy in low- to middle-income countries as they adopt more Westernized food and lifestyle patterns, and it is possible that early intervention may prevent this increase.

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