PART D. CHAPTER 4: DURATION, FREQUENCY, AND VOLUME OF EXCLUSIVE HUMAN MILK AND/OR INFANT FORMULA FEEDING

INTRODUCTION

Birth to 24 months of postnatal life is a critical phase of the first 1,000 days of life, and how and what infants are fed contributes to developmental programming.[1] Breastfeeding is the biological norm and provides health benefits for both the mother and the infant.[2] Infants fed human milk have reduced risks of communicable diseases in infancy and non-communicable diseases later in life, including ear, gastrointestinal, and respiratory infections, asthma, and sudden infant death syndrome, compared to infants who were not breastfed or, in some cases, breastfed for shorter durations.[3-6] Dissimilarities in growth trajectories have been documented in breast- vs formula-fed infants in the first year of life.[7,8] Breastfeeding has been associated with a 12 percent to 14 percent reduction in the risk of childhood obesity,[6,9] although associations are substantially attenuated in studies that have been able to control for important confounding factors (such as maternal socio-economic status) and in studies comparing siblings within the same family.[10]

The American Academy of Pediatrics (AAP) recommends exclusive breastfeeding for about the first 6 months of life and continued breastfeeding with complementary foods through at least the first year of life.[3,11] The 2020 Healthy People breastfeeding goals are that 81.9 percent of infants will initiate breastfeeding at birth and 60.6 percent and 34.1 percent will continue any breastfeeding at 6 and 12 months, respectively.[12] Surveillance data from the 2017-2018 National Immunization Survey, for infants born in 2016, show that national breastfeeding rates are generally meeting these goals, with 83.8 percent initiation and 57.3 percent and 36.2 percent breastfeeding at 6 and 12 months, respectively.[13] Likewise, exclusive breastfeeding rates of 47.5 percent and 25.4 percent at 3 and 6 months are meeting the 2020 Healthy People targets of 46.2 percent and 25.5 percent, respectively.[12] However, these percentages represent national data and marked disparities in infant feeding exist in the United States based on geography, income, education, and race and ethnicity.[14]

For infants who are not exclusively breastfed, the AAP recommends the use of iron-fortified infant formula for healthy infants for the first year of life.[15] Approximately 75 percent of infants in the United States are receiving formula at age 6 months: 42.7 percent are exclusively formula-fed, and 31.9 percent receive human milk supplemented with infant formula (mixed-feeding).[13]

Thus, in the first year of life, infants may consume human milk and/or infant formula at varying levels of exclusivity, timing, and duration, which may influence growth and body composition, nutritional status, neurocognitive development, and both short-term and long-term health outcomes, including the risk of diabetes, cardiovascular disease (CVD), and food allergies and atopic diseases. This chapter describes the findings of the reviews conducted to examine these relationships.

Background

Previous editions of the *Dietary Guidelines for Americans*, since 1990, began at age 2 years. The systematic reviews included in this report of the 2020 Dietary Guidelines Advisory Committee are the first to examine questions that specifically explore relationships between feeding in the first 2 years of life and short and long-term health outcomes. This chapter focuses on the duration, frequency, and volume of exclusive human milk and/or infant formula consumption. Other chapters report evidence on the timing and composition of complementary feeding (***Part D. Chapter 5: Foods and Beverages Consumed during Infancy and Toddlerhood***) and iron and vitamin D supplements (***Part D. Chapter 6: Nutrients from Dietary Supplements During Infancy and Toddlerhood***) with respect to child outcomes.

The nutrient composition and biological context of human milk and infant formula are dramatically different. Human milk is a complex biological fluid that is the product of maternal genetics, physiological status, dietary intake (for some nutrients), and environmental exposures.[16] The nutrient composition of human milk changes within a feeding and across the course of lactation, and transmits flavors from the maternal diet.[17] In addition to providing nutrients to the infant, human milk provides a bridge from the intrauterine to extrauterine environment by immunological protection through bioactive proteins, antibodies, cytokines, immune cells, and human milk oligosaccharides (HMO).[18,19] Human milk also contains microbes[20] and HMO that seed and feed the infant gut microbiota,[21,22] which, in turn, educates the developing immune system.[21-24] Recent studies have shown associations between microbiome composition in early life and health outcomes that are also linked with human milk feeding, including growth and body composition[25,26] and atopic diseases.[27,28] Because the microbiome of breast and formula-fed infants differs,[21,22] these observations suggest that the microbiome may be a mediator or modulator of the associations between human milk feeding and these health outcomes. For neurocognitive development, links are proposed through the microbiome-gut-brain axis,[29,30] and compelling preclinical data support this hypothesis.[31]

However, human studies have not shown consistent associations between infant feeding, microbiome composition, and neurocognitive outcomes.[32] Therefore, more research is needed in this area to determine causality.

Human milk meets all the nutritional requirements of the breastfed infant for the first 6 months of life, with the exception of vitamin D. As explained in ***Part D. Chapter 6: Nutrients from Dietary Supplements During Infancy and Toddlerhood***, vitamin D supplements are recommended for breastfed infants.[33] Infant formulas are designed to meet the nutritional needs of human infants in the first year of life and their nutrient content is regulated by law.[34,35] The nutrient content and composition of infant formula differs from that of human milk, which can lead to differences in nutrient absorption and nutrient status. For example, infant formulas contain higher protein content than does human milk[36] and most minerals and trace elements also are present in higher concentrations in formula than in human milk and in different forms (e.g., salts vs bound to carrier proteins).[37]

Human milk consumption also has been associated with reduced risk of developing certain atopic diseases. Atopic diseases (atopic dermatitis, food allergies, allergic rhinitis, and asthma) occur due to environmental triggers in genetically susceptible individuals.[38] Over the past 2 decades, atopic diseases have emerged as among the most common chronic conditions in childhood. Skin sensitization presenting as atopic dermatitis is often the first manifestation of atopic disease and often appears to precede the subsequent development of the other allergic conditions.[39] For example, about 30 percent of all children with atopic dermatitis have a food allergy, and a child with moderate to severe atopic dermatitis has a 50 percent risk of developing asthma, either concomitantly or in later life.[39] Although induction of tolerance can be achieved for selected foods and other environmental antigens, for those who remain symptomatic, the management of symptoms can significantly reduce quality of life for the individuals and their families. Therefore, a major focus in control of allergic diseases has been on primary prevention.[40] Given that human milk contains immunomodulatory components, and that cow milk is one of the most common food allergens in infancy, it has been hypothesized that breastfed infants would have a lower incidence of atopic diseases than formula-fed infants. Evidence for associations between breastfeeding, components of human milk, and the development of atopic diseases has been conflicting, however,[41] and previous reviews have not addressed exclusivity, timing, and duration of human milk exposure.

The 2020 Committee also investigated links between breastfeeding and risk of diabetes mellitus (DM) and CVD. Type 1 and type 2 diabetes are among the most common chronic diseases in people younger than age 20 years.[42] From 2002 to 2012, type 1 and type 2 diabetes

incidence increased 1.4 percent and 7.1 percent, respectively, among U.S. youths. Onset of diabetes in childhood and adolescence is associated with numerous short- and long-term complications, including damage to the kidneys (nephropathy), eyes (retinopathy), and nerves (peripheral neuropathy).[42] Type 1 diabetes results from the autoimmune destruction of the insulin-secreting pancreatic islets of Langerhans.[43] Environmental factors, including infant diet, are proposed to influence the risk of type 1 diabetes in genetically susceptible individuals.[44] A meta-analysis of data from approximately 10,000 individuals in 43 studies demonstrated that compared to never being breastfed, breastfeeding exclusively for more than the first 2 weeks of life reduced the risk of childhood onset type 1 diabetes by 14 percent (12 studies; odds ratio [OR]=0.86, 95% confidence interval [CI]: 0.75, 0.99), based upon the highest quality studies. Pooled analysis provided little evidence that being exclusively breastfed for less than 2 weeks or longer than 6 months or non-exclusive breastfeeding reduced the risk of type 1 diabetes.[45] Type 2 diabetes is a disorder of insulin resistance and its increased prevalence has tracked with the increase in childhood obesity.[46] Two systematic reviews[47,48] have suggested that breastfeeding is associated with a lower risk of type 2 diabetes, but they lacked detailed investigations into duration and exclusivity of human milk feeding.

According to the World Health Organization,[49] CVD is the leading cause of death globally and an estimated 17.9 million lives are lost each year to CVD. In the United States, CVD accounts for 1 in every 4 deaths, resulting in 1 person dying every 37 seconds from CVD-related outcomes.[50] Four out of 5 CVD deaths are due to heart attacks and strokes, and one-third of these deaths occur prematurely in people younger than age 70 years.[49] Among younger individuals (ages 18 to 50 years), the incidence of CVD over the past 2 decades has either been steady or has increased.[51] Although CVD outcomes typically affect adults, risk factors can begin as early as infancy[52] and breastfeeding has been postulated to be protective against CVD outcomes.[53]

Two new systematic reviews were conducted by the 2020 Committee to examine the evidence on overweight and obesity and on nutrient status. In addition, systematic reviews completed by the U.S. Departments of Agriculture and of Health and Human Services as part of the Pregnancy and Birth to 24 Months (P/B-24) Project[54,55] that examined infant milk-feeding practices and risk of atopic outcomes,[56] diabetes,[57] and CVD[58] were adopted by the 2020 Committee. Due to time constraints, the Committee was unable to investigate the relationship between the duration, frequency, and volume of exclusive human milk and/or infant formula consumption and developmental outcomes.

LIST OF QUESTIONS

1. What is the relationship between the duration, frequency, and volume of exclusive human milk and/or infant formula consumption and overweight and obesity?
2. What is the relationship between the duration, frequency, and volume of exclusive human milk and/or infant formula consumption and long-term health outcomes?
3. What is the relationship between the duration, frequency, and volume of exclusive human milk and/or infant formula consumption and nutrient status?
4. What is the relationship between the duration, frequency, and volume of exclusive human milk and/or infant formula consumption and food allergies and atopic allergic diseases?

METHODOLOGY

All questions in this chapter were answered using systematic reviews conducted with support from USDA's Nutrition Evidence Systematic Review (NESR) team. NESR's systematic review methodology provided a rigorous, consistent, and transparent process for the Committee to search for, evaluate, analyze, and synthesize evidence.

Questions 1 and 3 in this chapter were answered using new NESR systematic reviews. The Committee developed a systematic review protocol for each question, which described how the Committee would apply NESR's methodology to answer the question. Each protocol included an analytic framework and inclusion and exclusion criteria that were used to guide identification of the most relevant body of evidence to use in answering each systematic review question. Each analytic framework outlined core elements of the systematic review question (i.e., population; intervention and/or exposure and comparator [i.e., the alternative being compared to the intervention or exposure]; and outcomes), and included definitions for key terms, key confounders, and other factors to be considered when reviewing the evidence. The inclusion and exclusion criteria were selected, up front, to operationalize the elements of the analytic framework, and specify what made a study relevant for each systematic review question. Next, a literature search was conducted to identify all potentially relevant articles, and those articles were screened by two NESR analysts independently based on the criteria selected by the Committee. For each included article, data were extracted and risk of bias assessed. The Committee qualitatively synthesized the body of evidence to inform development of a conclusion statement(s), and graded the strength of evidence using pre-established criteria

for risk of bias, consistency, directness, precision, and generalizability. Finally, recommendations for future research were identified. A detailed description of NESR's systematic review methodology is provided in ***Part C. Methodology***, including standard inclusion and exclusion criteria applied in many of the Committee's systematic reviews. Complete documentation of each systematic review, including the protocol, is available on the following website: nesr.usda.gov/2020-dietary-guidelines-advisory-committee-systematic-reviews. Below is a summary of the unique elements of the protocols developed to answer Questions 1 and 3 on the duration, frequency, and volume of exclusive human milk and/or infant formula consumption.

For both Questions 1 and 3, the interventions or exposures were examined in healthy full-term infants (birth to 24 months). The interventions or exposures of interest, and their comparators, were:

- Ever consuming human milk (i.e., any amount of human milk feeding) compared with never consuming human milk,
- Different durations of any human milk consumption among infants fed human milk,
- Different durations of exclusive human milk consumption before the introduction of infant formula, and
- Different intensities/proportions/amounts of human milk consumed by mixed-fed infants.

These interventions or exposures and their comparators were selected to align with the first feeding decisions that caregivers make. First, caregivers must decide whether or not to feed human milk. For caregivers who feed human milk, the next decisions are how long to feed human milk at all and how long to feed human milk exclusively, which align with the second and third comparisons. In this Chapter, duration of exclusive human milk consumption before the introduction of infant formula (not complementary foods and beverages) was examined, to avoid overlap with systematic review Questions 1 and 3 in ***Part D. Chapter 5: Foods and Beverages Consumed During Infancy and Toddlerhood***, which examined how the timing of the introduction of complementary foods is associated with various outcomes (growth, size, and body composition and nutrient status, respectively). The fourth comparison aligns with decisions about the supplementation of human milk with infant formula.

For Question 1, additional comparisons of interest were specified:

- Different intensities, proportions, or amounts of human milk consumed at the breast vs by bottle in infants fed human milk as their only source of milk, and

- Consuming human milk or infant formula (i.e., a single substance) compared with human milk and infant formula (i.e., both substances) during a single feeding session.

The first comparison aligns with decisions caregivers make about the feeding mode they use to feed human milk (i.e., breast, bottle, or both). The second comparison aligns with decisions caregivers may make about "topping up" a human milk feeding with infant formula.

In these systematic reviews, *human milk* refers to mother's own milk provided at the breast (i.e., nursing) or expressed and fed fresh or after refrigeration or freezing. Examinations of donor milk were not included in these reviews. *Exclusive human milk consumption* refers to consuming human milk alone and not in combination with infant formula or complementary foods and beverages. This definition includes the WHO definitions of *exclusive* and *predominant breastfeeding*, which permit limited quantities of: a) drops or syrups containing vitamins, minerals, or medicines, b) water and water-based drinks, such as sweetened water and teas, c) fruit juice, d) oral rehydration salts solution, and e) ritual fluids.[59] *Infant formula* refers to commercially prepared infant formula meeting the FDA and/or Codex Alimentarius[34,35] international food standards. *Mixed feeding* refers to feeding human milk and infant formula but not complementary foods or beverages such as cow milk. *Complementary foods and beverages* refers to foods and beverages other than human milk or infant formula (liquids, semisolids, and solids) provided to an infant or young child to provide nutrients and energy.

For Question 1, the outcomes of interest were divided into 2 groups:

- In all studies, the outcomes of interest were overweight and/or obesity from 2 years of age through adulthood.
- In a subset of studies, which conducted within-family analyses of siblings, additional outcomes of interest were specified: rapid weight gain from birth to 24 months and body mass index (BMI) and measures of body composition (e.g., percent fat mass, waist-to-hip ratio) from age 2 years through adulthood. The within-family analyses of siblings compared discordant siblings (i.e., siblings from the same family who were fed differently during infancy, or who had a different outcome status, or both). The Committee gave such studies special consideration because they reduce the risk of bias from confounding from genetic and environmental factors (i.e., factors that siblings share). Infant-feeding research can be prone to bias from confounding because infant feeding is strongly socially patterned. Therefore, analyses that reduce bias from confounding are important.

Initially, the outcomes of interest included measures of growth, size, and body composition from birth through adulthood for all studies. The outcomes of interest, however, were modified to focus only on overweight and obesity starting at 2 years of age, because the Committee determined that these outcomes were of the greatest public health importance. In addition, the Committee recognized that the relationship between infant feeding and growth and size outcomes was already examined by an expert panel for the CDC.[60] The additional outcomes of interest were still included for the within-family studies of discordant siblings (listed above), because it was thought that they could provide supporting evidence, from a set of studies with reduced risk of bias from confounding, for the conclusions drawn about overweight and obesity from the general body of evidence.

For Question 3, the outcomes of interest were iron status, iron deficiency and anemia, zinc status, iodine status, vitamin D status, vitamin B_{12} status, and fatty acid status from birth to 24 months.

When establishing inclusion and exclusion criteria for the systematic reviews to address Questions 1 and 3, the Committee used standard NESR criteria for study design, publication status, language of publication, study participants, and health status of study participants and country. The Committee also established criteria for the size of study groups for both questions. The criterion on size of study groups required 30 participants per group, or a power analysis indicating that the study was appropriately powered for the outcome(s) of interest.

For Question 1, the Committee added a criterion for confounders that specified that studies would be excluded if they did not account for any of the key confounders selected by the Committee (listed in the analytic framework). Research examining the relationship between infant feeding and overweight and obesity is mostly observational and prone to bias from confounding. Therefore, this criterion was selected to help ensure that only the strongest studies that attempted to reduce the risk of confounding bias would be examined. For within-family studies of discordant siblings, cross-sectional studies were included because of the unique attributes of within-family analyses of siblings related to the reduced risk of confounding.

Two separate literature searches were conducted to identify all potentially relevant articles for Questions 1 and 3. The first search was from the P/B-24 Project (nesr.usda.gov/infant-milk-feeding-practices-technical-expert-collaborative). During the Project, a single literature search was conducted to identify potential studies published from January 1980 to March 2016 for the family of reviews on human milk and infant formula consumption and health outcomes. However, some of the intended reviews, including nutrient status and overweight and obesity, were not completed before the end of the Project. Therefore, the 2020 Committee was able to

use that search to identify studies for their reviews on those outcomes. The second search was done to update the first search and identify relevant articles published from January 2016 to September 2019.

Results of both literature searches were screened by NESR analysts using the inclusion and exclusion criteria established in the Committee's protocols for Questions 1 and 3, and described herein. Initially, the protocols for both Questions 1 and 3 specified that literature published between January 1980 and September 2019 would be included. The publication date criterion for Question 1 was subsequently modified to include studies published between January 2011 and September 2019. The Committee acknowledged that a number of systematic reviews have already been published on this topic.[10] However, such reviews have not captured the most recently published studies. Therefore, the Committee selected their date range in order to fill that gap in evidence. Sibling studies published from January 1980 to September 2019 were included because these were considered to be a unique set of studies not previously examined as a cohesive unit.

Questions 2 and 4 in this chapter were answered using existing systematic reviews that were previously conducted by NESR as part of the P/B-24 Project, which was completed in 2019. The conclusion statements that answer these questions were taken directly from the existing systematic reviews and were not updated to match the slightly different phrasing conventions used by the Committee to write conclusion statements for the new systematic reviews (Questions 1 and 3), to prevent inadvertent changes to the meaning of the conclusion statements. A description of the process the Committee used to determine that these existing systematic reviews were relevant to their questions and timely enough to not require updating is provided in ***Part C. Methodology***. In addition, detailed information about methodology used to complete these systematic reviews can be found at the following website: nesr.usda.gov/project-specific-overview-pb-24-0.

REVIEW OF THE SCIENCE

Question 1. What is the relationship between the duration, frequency, and volume of exclusive human milk and/or infant formula consumption and overweight and obesity?

Approach to Answering Question: NESR systematic review

Conclusion Statements and Grades

Ever vs Never Consuming Human Milk

Moderate evidence from observational studies indicates that ever, compared with never, consuming human milk is associated with lower risk of overweight and obesity at ages 2 years and older, particularly if the duration of human milk consumption is 6 months or longer. Grade: Moderate

Duration of Any Human Milk Consumption Among Infants Fed Human Milk

Insufficient evidence is available to determine the relationship between the duration of any human milk consumption, among infants fed human milk, and overweight and obesity at ages 2 years and older; the available evidence was inconsistent. Grade: Grade Not Assignable

Duration of Exclusive Human Milk Consumption Before the Introduction of Infant Formula

Insufficient evidence is available to determine the relationship between the duration of exclusive human milk consumption before the introduction of infant formula and overweight and obesity at ages 2 years and older. Grade: Grade Not Assignable

Intensity, Proportion, or Amount of Human Milk Consumed by Mixed-Fed Infants

No evidence is available to determine the relationship between the intensity, proportion, or amount of human milk consumed by mixed-fed infants and overweight and obesity at ages 2 years and older. Grade: Grade Not Assignable

Intensity, Proportion, or Amount of Human Milk Consumed at the Breast vs by Bottle in Infants Fed Human Milk as their Only Source of Milk

No evidence is available to determine the relationship between the intensity, proportion, or amount of human milk consumed at the breast vs by bottle in infants fed human milk as their

only source of milk and overweight and obesity at ages 2 years and older. Grade: Grade Not Assignable

Consuming Human Milk or Infant Formula (i.e., a Single Substance) vs Human Milk and Infant Formula (i.e., Both Substances) During a Single Feeding Session

No evidence is available to determine the relationship between consuming human milk or infant formula (i.e., a single substance) vs human milk and infant formula (i.e., both substances, e.g., "topping up") during a single feeding session and overweight and obesity at ages 2 years and older. Grade: Grade Not Assignable

Summary of the Evidence

- This systematic review examined the relationship between the duration, frequency, and volume of exclusive human milk and/or infant formula consumption and overweight and obesity. Specifically, this systematic review examined available evidence that compared:
  - Infants who ever consumed milk (i.e., any amount of human milk) with infants who never consumed human milk,
  - Infants who consumed human milk (i.e., any amount of human milk) for different durations,
  - Infants who consumed human milk exclusively for different durations before the introduction of infant formula,
  - Mixed-fed infants (i.e., consuming both human milk and infant formula, but not complementary foods and beverages) who consumed different intensities, proportions, or amounts of human milk,
  - Infants who consumed human milk as their only source of milk and who consumed different intensities, proportions, or amounts of human milk at the breast vs by bottle, and
  - Mixed-fed infants who consumed a single substance at a single feeding session (i.e., either human milk or infant formula) with mixed-fed infants who consumed both substances at a single feeding session (e.g., "topping up").
- The outcomes of interest were overweight and obesity at ages 2 years and older. Available evidence about rapid weight gain from birth to 24 months and BMI and body composition at ages 2 years and older also were examined from studies that conducted within-family

analyses of discordant siblings (i.e., siblings fed differently during infancy, siblings with differences in outcome status, or both).

- This review identified 42 articles that met the inclusion criteria.[61-102] Thirty of the 42 articles presented evidence about ever, compared with never, consuming human milk, and 21 of the 42 articles presented evidence about different durations of any human milk consumption (i.e., some articles presented evidence about both exposures).
- The 30 articles that examined the relationship between ever, compared with never, consuming human milk, and overweight and/or obesity at ages 2 years and older presented evidence from 21 independent cohorts.
    - The evidence had strong consistency. Fourteen of the 21 studies found significant associations and all of them showed that ever, compared with never, consuming human milk is associated with lower risk of overweight and/or obesity at ages 2 years and older. One study showed a marginal association in the same direction, and some of the remaining studies may have lacked statistically significant associations because they were underpowered.
    - The evidence available from 5 of 7 studies that compared infants who consumed human milk for different durations with infants who never consumed human milk suggested that a longer duration of human milk consumption (e.g., ≥6 months) is most likely to be associated with reduced risk of overweight or obesity, compared to never consuming human milk.
    - In 4 studies, the investigators conducted within-family analyses of siblings, which are designed to reduce bias due to confounding from genetic and environmental factors (i.e., because the siblings share these factors). Some of these analyses showed an attenuation of the significant associations found in full-sample analyses, suggesting that confounding may explain some of the association between ever, compared with never, consuming human milk and overweight and/or obesity at ages 2 years and older.
    - The ability to draw stronger conclusions was primarily limited by the potential for confounding in a body of evidence made up of observational studies, and some concerns about the generalizability of the evidence from the studies conducted outside the United States (because U.S. populations may have higher risk of overweight and obesity than do the populations sampled for the non-U.S. studies).
- The 21 articles that examined the relationship between the duration of any human milk consumption, among infants fed human milk, and overweight and/or obesity at ages 2 years

and older presented evidence from 1 cluster randomized controlled trial (RCT) and 18 independent cohorts.
    - The evidence was inconclusive. Nine of the 19 studies reported significant associations, but they were inconsistent in direction. In addition, potential bias from confounding and the limited generalizability of the evidence from the non-U.S. studies raised concerns (in particular because the prevalence of obesity among the participants of the cluster RCT, conducted in Belarus, was much lower than the prevalence among youth in the United States).
- Evidence available from 2 studies was insufficient to determine the relationship between the duration of exclusive human milk consumption before the introduction of infant formula and overweight and/or obesity at ages 2 years and older.
- No studies were identified that examined the intensity, proportion, or amount of human milk consumed by mixed-fed infants, the intensity, proportion, or amount of human milk consumed at the breast vs by bottle, or the consumption of a single substance (i.e., either human milk or infant formula) vs both human milk and infant formula during a single feeding session.

For additional details on this body of evidence, visit: nesr.usda.gov/2020-dietary-guidelines-advisory-committee-systematic-reviews/birth-24-months-subcommittee/human-milk-infant-formula-overweight-obesity

Question 2. What is the relationship between the duration, frequency, and volume of exclusive human milk and/or infant formula consumption and long-term health outcomes?

Approach to Answering Question: Existing NESR systematic reviews

Conclusion Statements and Grades

Diabetes

Ever vs Never Consuming Human Milk

Limited evidence from observational studies suggests that never versus ever being fed human milk is associated with higher risk of type 1 diabetes. Grade: Limited

There is insufficient evidence to determine whether or not there is a relationship between never versus ever feeding human milk and type 2 diabetes, prediabetes, fasting glucose, HbA1c, insulin resistance, and glucose tolerance throughout the lifespan. Grade: Grade Not Assignable

Duration of Any Human Milk Consumption Among Infants Fed Human Milk

Moderate evidence from observational studies suggests that, among infants fed some amount of human milk, shorter versus longer durations of any human milk feeding are associated with higher risk of type 1 diabetes. Grade: Moderate

Limited but consistent evidence suggests that the duration of any human milk feeding is not associated with fasting glucose or insulin resistance in childhood or during the transition from childhood into adolescence. Grade: Limited

There is insufficient evidence to determine whether or not there is a relationship between shorter versus longer durations of any human milk feeding and type 2 diabetes, prediabetes, or HbA1C throughout the lifespan, and fasting glucose and insulin resistance in adulthood. Grade: Grade Not Assignable

Duration of Exclusive Human Milk Consumption

Limited evidence from observational studies suggests that shorter versus longer durations of exclusive human milk feeding are associated with higher risk of type 1 diabetes. Grade: Limited

Limited evidence, from a single study that used a strong design, also suggests that the duration of exclusive human milk feeding is not associated with fasting glucose or insulin resistance at 11.5 years of age. Grade: Limited

There is insufficient evidence to determine whether or not there is a relationship between shorter versus longer durations of exclusive human milk feeding and type 2 diabetes, prediabetes, and HbA1c throughout the lifespan, and fasting glucose and insulin resistance at ages other than 11.5 years. Grade: Grade Not Assignable

Intensity, Proportion, or Amount of Human Milk Consumed by Mixed-Fed Infants

There is insufficient evidence to determine whether or not there is a relationship between feeding a lower versus higher intensity, proportion, or amount of human milk to mixed-fed infants and diabetes outcomes in offspring. Grade: Grade Not Assignable

Cardiovascular Disease

Ever vs Never Consuming Human Milk

Limited evidence suggests that never versus ever being fed human milk is associated with higher blood pressure, within a normal range, at 6 to 7 years of age. Grade: Limited

Evidence about the relationship of never versus ever being fed human milk with blood lipids in childhood was inconclusive, and there was insufficient evidence to determine the relationship of never versus ever being fed human milk with endpoint cardiovascular disease outcomes, blood pressure and blood lipids in adolescence or adulthood, metabolic syndrome, and arterial stiffness. Grade: Grade Not Assignable

Duration of Any Human Milk Consumption Among Infants Fed Human Milk

Moderate evidence suggests that there is no association between the duration of any human milk feeding and blood pressure in childhood. Grade: Moderate

Evidence about the relationship of shorter versus longer durations of any human milk feeding with blood lipids in childhood and adulthood and with metabolic syndrome was inconclusive, and there was insufficient evidence to determine the relationship of shorter versus longer durations of any human milk feeding with endpoint cardiovascular disease outcomes, blood pressure in adolescence or adulthood, blood lipids in adolescence, and arterial stiffness. Grade: Grade Not Assignable

Duration of Exclusive Human Milk Consumption

Limited evidence suggests that there is no association between the duration of exclusive human milk feeding and blood pressure in childhood or metabolic syndrome at 11.5 years of age. Most of the evidence comes from just one non-U.S. sample assessed using a strong study design. Grade: Limited

There was insufficient evidence to determine the relationship of shorter versus longer durations of exclusive human milk feeding with endpoint cardiovascular disease outcomes, blood pressure in adolescence or adulthood, blood lipids, and metabolic syndrome at ages other than 11.5 years. Grade: Grade Not Assignable

Intensity, Proportion, or Amount of Human Milk Consumed by Mixed-Fed Infants

There is no evidence to determine whether or not there is a relationship between feeding a lower versus higher intensity, proportion, or amount of human milk to mixed-fed infants and cardiovascular disease outcomes in offspring. Grade: Grade Not Assignable

Summary of the Evidence

Diabetes

Ever vs Never Consuming Human Milk

- This systematic review examined comparisons of infants who were never fed human milk with infants who were ever fed human milk (i.e., any amount of human milk feeding).
- This systematic review examined available evidence related to diabetes outcomes in offspring, including fasting glucose, HbA1C, glucose tolerance/insulin resistance, and the incidence and prevalence of prediabetes, type 1 diabetes, and type 2 diabetes.
- Twenty-one articles met the inclusion criteria for this systematic review,57 including 16 with evidence about type 1 diabetes, 2 with evidence about type 2 diabetes, and 3 with evidence about the intermediate diabetes outcomes of fasting glucose, HbA1C, and insulin resistance.
- Evidence about the association between never vs ever feeding human milk and higher risk of type 1 diabetes was limited. Across the 15 independent studies (16 articles) that examined type 1 diabetes, 6 found statistically significant associations. The primary difference between the studies that did and did not report significant associations was statistical power. With one exception, the statistically significant associations suggested that never vs ever being fed human milk is associated with higher risk of type 1 diabetes. The ability to draw stronger conclusions was primarily limited by insufficient sample sizes, risk of bias, such as the potential for confounding, and the retrospective collection of exposure data, which increased the risk of misclassification of the exposure.

- Evidence related to type 2 diabetes and intermediate diabetes outcomes (e.g., fasting glucose, HbA1C, and insulin resistance) was scant.

For additional details on this body of evidence, visit: nesr.usda.gov/what-relationship-between-never-versus-ever-feeding-human-milk-and-diabetes-outcomes-offspring#full-review

Duration of Any Human Milk Consumption Among Infants Fed Human Milk

- This systematic review examined comparisons of infants who were fed human milk for shorter durations with infants who were fed human milk for longer durations.
- This systematic review examined available evidence related to diabetes outcomes in offspring, including fasting glucose, HbA1C, glucose tolerance/insulin resistance, and the incidence and prevalence of prediabetes, type 1 diabetes, and type 2 diabetes.
- Thirty-seven articles met the inclusion criteria for this systematic review,[57] including 30 with evidence about type 1 diabetes, 1 with evidence about type 2 diabetes, and 6 with evidence about intermediate diabetes outcomes (i.e., fasting glucose and insulin resistance).
- Evidence about the association between shorter vs longer durations of any human milk feeding and higher risk of type 1 diabetes was moderate. Across 22 independent observational studies (30 articles), 12 reported significant associations. With the exception of 1 study that had limited external validity, the significant associations between the duration of any human milk feeding and type 1 diabetes risk were inverse associations. The ability to draw stronger conclusions was primarily limited by insufficient sample sizes, risk of bias, such as the potential for confounding, and the retrospective collection of exposure data, which increased the risk of misclassification of the exposure.
- Evidence about the duration of any human milk feeding and fasting glucose and insulin resistance during childhood and the transition into adolescence was limited, and suggested no association. One cluster RCT and 3 prospective cohort studies (PCS) provided consistent evidence. The ability to draw stronger conclusions was primarily limited by the small number of studies and the limited evidence from the United States (where metabolic risk may be higher).
- Evidence related to type 2 diabetes, prediabetes, and HbA1C, and about fasting glucose and insulin resistance beyond early adolescence was scant.

For additional details on this body of evidence, visit: nesr.usda.gov/what-relationship-between-shorter-versus-longer-durations-any-human-milk-feeding-and-diabetes#full-review

Duration of Exclusive Human Milk Consumption

- This systematic review examined comparisons of infants who were fed human milk exclusively for shorter durations with infants who were fed human milk exclusively for longer durations.
- This systematic review examined available evidence related to diabetes outcomes in offspring, including fasting glucose, HbA1C, glucose tolerance/insulin resistance, and the incidence and prevalence of prediabetes, type 1 diabetes, and type 2 diabetes.
- Eighteen articles met the inclusion criteria for this systematic review,[57] including 17 with evidence about type 1 diabetes, and 1 with evidence about fasting glucose and insulin resistance.
- Evidence about the association between shorter vs longer durations of exclusive human milk feeding and higher risk of type 1 diabetes was limited. Seven studies found significant associations, all of which were inverse associations between the duration of exclusive human milk feeding and type 1 diabetes risk. However, some of the studies that were most likely to have sufficient statistical power found nonsignificant associations. The ability to draw stronger conclusions was primarily limited by this inconsistency, insufficient sample sizes for some of the studies, risk of bias, such as the potential for confounding, and the retrospective collection of exposure data, which increased the risk of misclassification of the exposure.
- Evidence about the duration of exclusive human milk feeding and fasting glucose and insulin resistance at age 11.5 years was limited, and suggested no association. One cluster RCT provided strong evidence. The ability to draw stronger conclusions was limited by having only 1 study and because the study was not conducted in the United States (where metabolic risk may be higher).
- No evidence was identified that examined how the duration of exclusive human milk feeding was related to type 2 diabetes, prediabetes, and HbA1C, or fasting glucose and insulin resistance other than at age 11.5 years.

For additional details on this body of evidence, visit: nesr.usda.gov/what-relationship-between-shorter-versus-longer-durations-exclusive-human-milk-feeding-and-diabetes#full-review

Intensity, Proportion, or Amount of Human Milk Consumed by Mixed-Fed Infants

- This systematic review examined comparisons of mixed-fed infants fed different intensities, proportions, or amounts of human milk.
- This systematic review examined available evidence related to diabetes outcomes in offspring, including fasting glucose, HbA1C, glucose tolerance/insulin resistance, and the incidence and prevalence of prediabetes, type 1 diabetes, and type 2 diabetes.
- This review included 1 article,[57] which was not enough evidence to draw any conclusions about the relationship between the intensity, proportion, or amount of human milk fed to infants who are fed both human milk and infant formula and diabetes outcomes in offspring.

For additional details on this body of evidence, visit: nesr.usda.gov/what-relationship-between-feeding-lower-versus-higher-intensity-proportion-or-amount-human-milk-2#full-review

Cardiovascular Disease

Ever vs Never Consuming Human Milk

- This systematic review examined comparisons of infants who were never fed human milk with infants who were ever fed human milk (i.e., any amount of human milk feeding).
- This systematic review examined available evidence related to CVD outcomes in offspring from childhood through adulthood, including blood lipids, blood pressure, arterial stiffness, metabolic syndrome, CVD, and CVD-related mortality.
- Thirteen articles met the inclusion criteria for this systematic review,[58] including 4 with evidence about blood lipids, 7 with evidence about blood pressure, 2 with evidence about arterial stiffness, and 1 with evidence about metabolic syndrome (1 article presented evidence for both blood pressure and arterial stiffness). None of the included articles presented evidence about CVD or CVD-related mortality.
- Evidence about the association between never vs ever feeding human milk and higher blood pressure, within a normal range, at age 6 to 7 years was limited. Across the 5 independent

studies (6 articles) that examined blood pressure in children, 3 found statistically significant associations, and all of them showed that never being fed human milk was associated with higher blood pressure within a normal range. The ability to draw stronger conclusions was primarily limited by the small number of studies, the lack of studies from the United States (where CVD risk may be higher), and risk of bias, such as the potential for confounding.

- Evidence about blood lipids in childhood was inconclusive. Across 3 independent studies, the only significant association was in a subsample of boys, no comparable analyses existed with which to compare the significant finding, and the nonsignificant associations were inconsistent in direction.
- Evidence related to outcomes beyond childhood was scant, and no studies examined endpoint health outcomes (i.e., CVD and CVD-related mortality).

For additional details on this body of evidence, visit: nesr.usda.gov/what-relationship-between-never-versus-ever-feeding-human-milk-and-cardiovascular-disease-outcomes#full-review

Duration of Any Human Milk Consumption Among Infants Fed Human Milk

- This systematic review examined comparisons of infants who were fed human milk for shorter durations with infants who were fed human milk for longer durations.
- This systematic review examined available evidence related to CVD outcomes in offspring from childhood through adulthood, including blood lipids, blood pressure, arterial stiffness, metabolic syndrome, CVD, and CVD-related mortality.
- Twenty-four articles met the inclusion criteria for this systematic review,[58] including 13 with evidence about blood pressure, 10 with evidence about blood lipids, 3 with evidence about metabolic syndrome, 3 with evidence about arterial stiffness, and 2 with evidence about CVD-related mortality (some articles included evidence for more than 1 outcome).
- Moderate evidence about shorter vs longer durations of any human milk feeding and blood pressure in childhood suggested no association. Compelling evidence from the Promotion of Breastfeeding Intervention Trial (PROBIT) showed no significant relationship between the duration of any human milk feeding and blood pressure at age 6.5 or 11.5 years, and inconsistent evidence across 6 independent PCSs did not suggest any discernable relationship between the duration of any human milk feeding and blood pressure in childhood. The ability to draw stronger conclusions was primarily limited by the small

number of studies and concern about generalizability of the evidence, because none of the evidence was from the United States and U.S. populations may be at higher risk for CVD than the populations examined by the studies included in the systematic review.

- Evidence about blood lipids in childhood and adulthood and about metabolic syndrome was inconclusive, primarily due to inconsistencies in the direction and statistical significance of the findings.
- Evidence related to outcomes beyond childhood was scant, and only 2 articles, with evidence from the same retrospective cohort study, examined endpoint CVD outcomes (CVD-related mortality in both articles).

For additional details on this body of evidence, visit: nesr.usda.gov/what-relationship-between-shorter-versus-longer-durations-any-human-milk-feeding-and-cardiovascular#full-review

Duration of Exclusive Human Milk Consumption

- This systematic review examined comparisons of infants who were fed human milk exclusively for shorter durations with infants who were fed human milk exclusively for longer durations.
- This systematic review examined available evidence related to CVD outcomes in offspring from childhood through adulthood, including blood lipids, blood pressure, arterial stiffness, metabolic syndrome, CVD, and CVD-related mortality.
- Six articles met the inclusion criteria for this systematic review,[58] including 4 with evidence about blood pressure, 2 with evidence about blood lipids, and 1 with evidence about metabolic syndrome (1 article included evidence about both blood pressure and metabolic syndrome).
- Evidence about shorter vs longer durations of exclusive human milk feeding and blood pressure in childhood and metabolic syndrome at age 11.5 years was limited, and suggested no associations. Most of the evidence came from the PROBIT, which used a strong design to examine blood pressure and metabolic syndrome in children in Belarus. One additional study from Brazil provided supporting evidence about childhood blood pressure. The ability to draw stronger conclusions was primarily restricted by the limited number of studies and the lack of evidence from the United States (where the risk of CVD may be higher).

- Evidence related to other CVD outcomes was scant.

For additional details on this body of evidence, visit: nesr.usda.gov/what-relationship-between-shorter-versus-longer-durations-exclusive-human-milk-feeding-and-0#full-review

Intensity, Proportion, or Amount of Human Milk Consumed by Mixed-Fed Infants

- This systematic review examined comparisons of mixed-fed infants fed different intensities, proportions, or amounts of human milk.
- This systematic review examined available evidence related to CVD outcomes in offspring from childhood through adulthood, including blood lipids, blood pressure, arterial stiffness, metabolic syndrome, CVD, and CVD-related mortality.
- No articles met the inclusion criteria for this systematic review.

For additional details on this body of evidence, visit: nesr.usda.gov/what-relationship-between-feeding-lower-versus-higher-intensity-proportion-or-amount-human-milk-1#full-review

Question 3. What is the relationship between the duration, frequency, and volume of exclusive human milk and/or infant formula consumption and nutrient status?

Approach to Answering Question: NESR systematic review

Conclusion Statements and Grades

Ever vs Never Consuming Human Milk

Moderate evidence indicates that ever, compared with never, consuming human milk may be associated with fatty acid status from birth to 24 months. However, the difference in fatty acid status between infants fed human milk and infants fed infant formula is likely to depend on the composition of the human milk and infant formula consumed. Grade: Moderate

Insufficient evidence is available to determine the relationship between ever, compared with never, consuming human milk and iron and zinc status from birth to 24 months. No evidence is available to determine the relationship between ever, compared with never, consuming human

milk and iodine, vitamin B_{12}, and vitamin D status from birth to 24 months. Grade: Grade Not Assignable

Duration of Any Human Milk Consumption Among Infants Fed Human Milk

Insufficient evidence is available to determine the relationship between the duration of any human milk consumption, among infants fed human milk, and iron, zinc, vitamin D, and fatty acid status from birth to 24 months. No evidence is available to determine the relationship between the duration of any human milk consumption, among infants fed human milk, and iodine or vitamin B_{12} status from birth to 24 months. Grade: Grade Not Assignable

Duration of Exclusive Human Milk Consumption Before the Introduction of Infant Formula

Insufficient evidence is available to determine the relationship between the duration of exclusive human milk consumption before the introduction of infant formula and fatty acid status. No evidence is available to determine the relationship between the duration of exclusive human milk consumption before the introduction of infant formula and iron, zinc, iodine, vitamin B_{12}, or vitamin D status from birth to 24 months. Grade: Grade Not Assignable

Intensity, Proportion, or Amount of Human Milk Consumed by Mixed-Fed Infants

No evidence is available to determine the relationship between the intensity, proportion, or amount of human milk consumed by mixed-fed infants and iron, zinc, iodine, vitamin B_{12}, vitamin D, or fatty acid status from birth to 24 months. Grade: Grade Not Assignable

Summary of the Evidence

- This systematic review examined the relationship between the duration, frequency, and volume of exclusive human milk and/or infant formula consumption and nutrient status. Specifically, this systematic review examined available evidence that compares:
    - Infants who ever consumed milk (i.e., any amount of human milk) with infants who never consumed human milk,
    - Infants who consumed human milk (i.e., any amount of human milk) for different durations,
    - Infants who consumed human milk exclusively for different durations before the introduction of infant formula, and

  - Mixed-fed infants (i.e., consuming both human milk and infant formula, but not complementary foods and beverages) who consumed different intensities, proportions, or amounts of human milk.

- The outcomes of interest were iron status (including iron deficiency and anemia), zinc status, iodine status, vitamin B_{12} status, vitamin D status, and fatty acid status.
- This review identified 23 articles.[103-125]
  - Iron status: Ten articles, published between 1990 and 2019, examined the relationships of: a) ever, compared with never, consuming human milk, and b) different durations of any human milk consumption, among infants fed human milk, with iron status from birth to 24 months.
    - The evidence available from 2 studies did not show a consistent association between ever, compared with never, consuming human milk and anemia. The evidence available from 5 studies did not show consistent associations between ever, compared with never, consuming human milk and hemoglobin, hematocrit, red blood cell count, mean corpuscular volume, red cell distribution width, serum ferritin, or serum iron.
    - The evidence available from 3 studies did not show a consistent association between the duration of any human milk consumption, among infants fed human milk, and iron deficiency or anemia. The evidence available from 4 studies did not show consistent associations between the duration of any human milk consumption, among infants fed human milk, and hemoglobin, hematocrit, serum ferritin, serum iron, mean corpuscular volume, transferrin receptor, or transferrin saturation.
  - Zinc status: Five articles, published between 1986 and 1994, examined the relationships of: a) ever, compared with never, consuming human milk, and b) different durations of any human milk consumption, among infants fed human milk, with zinc status from birth to 24 months.
    - The evidence available from 4 studies did not show a consistent association between ever, compared with never, consuming human milk and zinc status.
    - The evidence available from 2 studies was insufficient to determine whether an association exists between the duration of any human milk consumption, among infants fed human milk, and zinc status.

- Vitamin D status: One article, published in 2014, examined the relationship between the duration of any human milk consumption, among infants fed human milk, and vitamin D status from birth to 24 months. This evidence was insufficient to determine whether an association exists between the duration of any human milk consumption, among infants fed human milk, and vitamin D status.
- Fatty acid status: Nine articles, published between 1986 and 2016, examined the relationships of: a) ever, compared with never, consuming human milk, b) different durations of any human milk consumption, among infants fed human milk, and c) different durations of exclusive human milk consumption before the introduction of infant formula with fatty acid status from birth to 24 months.
  - The evidence available from 7 studies was moderately consistent in showing that ever, compared with never, consuming human milk is related to fatty acid status, but the direction and strength of associations varied depending on the composition of the infant formula fed to participants who never consumed human milk (and also likely due to the composition of human milk, although this could not be assessed), as well as the specific types of fatty acids examined in the blood.
  - The evidence available from 1 study was insufficient to determine whether an association exists between the duration of any human milk consumption, among infants fed human milk, and fatty acid status.
  - The evidence available from 1 study was insufficient to determine whether an association exists between the duration of exclusive human milk consumption before the introduction of infant formula and fatty acid status.
- No studies met the inclusion criteria that examined iodine status or vitamin B_{12} status.

- The ability to draw stronger conclusions was primarily limited by:
  - The small number of studies that presented evidence on each topic,
  - The study designs, as most studies were designed to examine the effect of novel infant formula compositions rather than differences in outcomes between infants ever and never fed human milk,
  - Concerns about the generalizability of the evidence to U.S. infants consuming infant formulas currently on the market, and
  - Concerns about the potential for bias, especially bias due to confounding.

For additional details on this body of evidence, visit: nesr.usda.gov/2020-dietary-guidelines-advisory-committee-systematic-reviews/birth-24-months-subcommittee/human-milk-infant-formula-nutrient-status

Question 4. What is the relationship between the duration, frequency, and volume of exclusive human milk and/or infant formula consumption and food allergies and atopic allergic diseases?

Approach to Answering Question: Existing NESR systematic reviews

Conclusion Statements and Grades

Ever vs Never Consuming Human Milk

Moderate evidence suggests that never, in comparison to ever, being fed human milk is associated with higher risk of childhood asthma. Grade: Moderate

Limited evidence does not suggest a relationship between never versus ever being fed human milk and atopic dermatitis in childhood. Grade: Limited

Evidence about the relationship between never versus ever being fed human milk and atopic dermatitis from birth to 24 months is inconclusive, and there is insufficient evidence to determine the relationship of never versus ever being fed human milk with food allergies throughout the lifespan, allergic rhinitis throughout the lifespan, asthma in adolescence or in adulthood, and atopic dermatitis in adolescence or in adulthood. Grade: Grade Not Assignable

Duration of Any Human Milk Consumption Among Infants Fed Human Milk

Moderate evidence, mostly from observational studies, suggests that, among infants fed human milk, shorter versus longer durations of any human milk feeding are associated with higher risk of asthma in childhood and adolescence. Grade: Moderate

Limited evidence does not suggest a relationship between the duration of any human milk feeding and allergic rhinitis or atopic dermatitis in childhood. Grade: Limited

Evidence about the relationship between shorter versus longer durations of any human milk feeding and atopic dermatitis from birth to 24 months is inconclusive, and there is insufficient evidence to determine the relationship of shorter versus longer durations of any human milk

feeding with food allergies throughout the lifespan; allergic rhinitis from birth to 24 months, in adolescence, or in adulthood; asthma in adulthood; and atopic dermatitis in adolescence or in adulthood. Grade: Grade Not Assignable

Duration of Exclusive Human Milk Consumption Before the Introduction of Infant Formula

There is insufficient evidence to determine the relationship between shorter versus longer durations of exclusive human milk feeding prior to the introduction of infant formula and food allergies, allergic rhinitis, atopic dermatitis, and asthma throughout the lifespan. Grade: Grade Not Assignable

Intensity, Proportion, or Amount of Human Milk Consumed by Mixed-Fed Infants

There is no evidence to determine the relationship between feeding a lower versus higher intensity, proportion, or amount of human milk to mixed-fed infants and food allergies, allergic rhinitis, atopic dermatitis, and asthma throughout the lifespan. Grade: Grade Not Assignable

Intensity, Proportion, or Amount of Human Milk Consumed at the Breast vs by Bottle

There is no evidence to determine the relationship between feeding a higher intensity, proportion, or amount of human milk by bottle versus by breast and food allergies, allergic rhinitis, atopic dermatitis, and asthma throughout the lifespan. Grade: Grade Not Assignable

Summary of the Evidence

Ever vs Never Consuming Human Milk

- This systematic review examined comparisons of infants who were never fed human milk with infants who were ever fed human milk (i.e., any amount of human milk feeding).
- This systematic review examined available evidence related to food allergies, allergic rhinitis, and atopic dermatitis from birth through adulthood and asthma from childhood through adulthood (outcomes before childhood may represent transient recurrent wheeze).[126]
- Forty-four articles met the inclusion criteria for this systematic review,[56] including 5 with evidence about food allergies, 2 with evidence about allergic rhinitis, 24 with evidence about atopic dermatitis, and 22 with evidence about asthma. Almost all of the evidence was from observational studies.

- Evidence about the association between never vs ever feeding human milk and higher childhood asthma risk was moderate. Across the 17 independent studies (19 articles) that examined asthma in children, 9 found statistically significant associations, and all of them showed that never being fed human milk was associated with higher risk. The majority of nonsignificant associations also were consistent in suggesting higher risk of childhood asthma with never vs ever feeding human milk, and some of the inconsistency in statistical significance may be explained by insufficient statistical power. The ability to draw stronger conclusions was primarily limited by the limited statistical power in some studies and concerns about internal validity, such as the potential for confounding in a body of evidence primarily made up of observational studies.
- Evidence about the lack of an association between never vs ever feeding human milk and atopic dermatitis in childhood was limited. Across the 9 studies that examined atopic dermatitis in children, the only significant association was from a study that used a sample in which about half of the participants were born small for gestational age (i.e., which raised concerns about generalizability). The ability to draw stronger conclusions was limited by the small number of studies, limited statistical power in some studies, a potential lack of generalizability of the samples to diverse U.S. populations, and the potential for reverse causality and confounding.
- Evidence about atopic dermatitis from birth to 24 months was inconclusive. Across 14 independent studies (16 articles), the associations were inconsistent in direction. In addition, the outcome assessment methods described by the studies raised concerns that the studies may have detected skin conditions similar to atopic dermatitis in addition to clinical atopic dermatitis.
- Evidence related to food allergies and allergic rhinitis throughout the lifespan and atopic dermatitis and asthma beyond childhood was scant.

For additional details on this body of evidence, visit: nesr.usda.gov/what-relationship-between-never-versus-ever-feeding-human-milk-and-food-allergies-allergic-rhinitis#full-review

Duration of Any Human Milk Consumption Among Infants Fed Human Milk

- This systematic review examined comparisons of infants who were fed human milk for shorter durations with infants who were fed human milk for longer durations.

- This systematic review examined available evidence related to food allergies, allergic rhinitis, and atopic dermatitis from birth through adulthood and asthma from childhood through adulthood (outcomes before childhood may represent transient recurrent wheeze).[126]
- Thirty-five articles met the inclusion criteria for this systematic review,[56] including 3 with evidence about food allergies, 7 with evidence about allergic rhinitis, 15 with evidence about atopic dermatitis, and 23 with evidence about asthma. Almost all of the evidence was from observational studies.
- Evidence about the association between shorter vs longer durations of any human milk feeding and higher risk of asthma in childhood and adolescence was moderate. Across the 20 independent studies (21 articles), 8 found statistically significant associations and, with 1 exception, they showed that shorter durations of any human milk feeding was associated with higher risk. The majority of nonsignificant associations were also consistent in suggesting higher risk of asthma in childhood and adolescence with shorter durations of any human milk feeding, and some of the inconsistency in statistical significance may be explained by insufficient statistical power. The ability to draw stronger conclusions was primarily limited by the limited statistical power in some studies, potential problems with reverse causality, and risk of bias, such as the potential for confounding in a body of evidence primarily made up of observational studies.
- Evidence about the lack of an association between shorter vs longer durations of any human milk feeding and allergic rhinitis and atopic dermatitis in childhood was limited. Across the 5 independent studies (6 articles) that examined allergic rhinitis in children, the only significant association was from a subsample analysis of African-American children, and no comparable analyses existed with which to compare the result. Likewise, across the 8 independent studies (9 articles) that examined atopic dermatitis in children, the only significant associations were reported by a study with risk of multiple comparison bias. The ability to draw stronger conclusions was primarily limited by the small number of studies, limited statistical power in some studies, limited generalizability of the samples to diverse U.S. populations, and the potential for confounding.
- Evidence about atopic dermatitis from birth to 24 months was inconclusive. Across 8 studies, the associations were inconsistent in direction. In addition, the outcome assessment methods described by the studies raised concerns that the studies may have detected skin conditions similar to atopic dermatitis in addition to clinical atopic dermatitis.

- Evidence related to food allergies throughout the lifespan, and outcomes beyond childhood, in general, was scant.

For additional details on this body of evidence, visit: nesr.usda.gov/what-relationship-between-shorter-versus-longer-durations-any-human-milk-feeding-and-food-allergies#full-review

Duration of Exclusive Human Milk Consumption Before the Introduction of Infant Formula

- This systematic review examined comparisons of infants who were fed human milk exclusively for shorter durations with infants who were fed human milk exclusively for longer durations before being introduced to infant formula. The question examined the duration of exclusive human milk feeding before the introduction of infant formula (not complementary foods and beverages) to avoid overlap with systematic review Question 5 in ***Part D. Chapter 5: Foods and Beverages Consumed During Infancy and Toddlerhood***).
- This systematic review examined available evidence related to food allergies, allergic rhinitis, and atopic dermatitis from birth through adulthood and asthma from childhood through adulthood (outcomes before childhood may represent transient recurrent wheeze).[126]
- This review included 1 article,[56] which provided insufficient evidence to draw any conclusions about the relationship between the duration of exclusive human milk feeding before the introduction of infant formula and food allergies, allergic rhinitis, atopic dermatitis, or asthma.
- A large degree of overlap may exist between current literature examining the duration of exclusive human milk feeding (which may terminate with complementary feeding) and the timing of the introduction of complementary foods and beverages (which may immediately follow a period of exclusive human milk feeding). Yet, the degree of overlap is difficult to ascertain; infant feeding research does not often specify whether exclusive human milk feeding is followed by complementary feeding or formula feeding or both, and complementary feeding research does not often specify whether complementary foods and beverages are introduced to infants fed human milk exclusively or fed infant formula in some amount. It would be beneficial for future researchers to be mindful about this potential ambiguity when designing and conducting research about the duration of exclusive human milk feeding or the timing of the introduction of complementary foods and beverages, and

strive to help clarify any unique contributions of each of the two feeding practices on atopic disease and other outcomes.

For additional details on this body of evidence, visit: nesr.usda.gov/what-relationship-between-shorter-versus-longer-durations-exclusive-human-milk-feeding-prior#full-review

Intensity, Proportion, or Amount of Human Milk Consumed by Mixed-Fed Infants

- This systematic review examined comparisons of mixed-fed infants fed different intensities, proportions, or amounts of human milk.
- This systematic review examined available evidence related to food allergies, allergic rhinitis, and atopic dermatitis from birth through adulthood and asthma from childhood through adulthood (outcomes before childhood may represent transient recurrent wheeze).[126]
- No articles met the inclusion criteria for this systematic review.

For additional details on this body of evidence, visit: nesr.usda.gov/what-relationship-between-feeding-lower-versus-higher-intensity-proportion-or-amount-human-milk-0#full-review

Intensity, Proportion, or Amount of Human Milk Consumed at the Breast vs by Bottle

- This systematic review examined comparisons of mixed-fed infants fed different intensities, proportions, or amounts of human milk by bottle and by breast.
- This systematic review examined available evidence related to food allergies, allergic rhinitis, and atopic dermatitis from birth through adulthood and asthma from childhood through adulthood (outcomes before childhood may represent transient recurrent wheeze).[126]
- No articles met the inclusion criteria for this systematic review.

For additional details on this body of evidence, visit: nesr.usda.gov/what-relationship-between-feeding-higher-intensity-proportion-or-amount-human-milk-bottle-versus#full-review

DISCUSSION

Current infant-feeding practices in the United States encompass a spectrum of human milk exposures of differing durations, intensities, proportions, or amounts. The Committee sought to determine associations between these different levels, durations and intensities of exposure to human milk and infant formula and overweight and obesity, long-term health outcomes, nutrient status, and food allergy and atopic allergic diseases.

Overweight and Obesity

Ever vs Never Consuming Human Milk

Based on evidence from 17 observational cohort studies published between 2011 and 2019, and 4 sibling-pair studies published between 2003 and 2019 that also included cohorts of non-siblings, the Committee concluded that ever, compared with never, consuming human milk is associated with lower risk of overweight and obesity at ages 2 years and older, particularly if the duration of human milk consumption is 6 months or longer. This conclusion statement was graded as "Moderate." The observational cohort studies were strongly consistent, but these studies were limited by potential confounding because none of them controlled for all of the key confounders identified in the analytical framework. In particular, few studies accounted for complementary feeding practices and childhood diet, which are likely to be correlated with whether the child was fed human milk and may also influence risk of overweight and obesity.

Sibling-pair studies greatly reduce the risk of confounding, because siblings share a common environment. The 4 sibling-pair analyses generally showed an attenuation of the significant associations that were found in full-sample analyses in those studies, which suggests that confounding may explain a substantial proportion of the association between ever vs never consuming human milk and subsequent overweight and obesity. Nonetheless, 1 of the sibling-pair analyses[87] did show a significant association between ever, compared with never, consuming human milk and lower odds of overweight or obesity at ages 9 to 19 years. In another sibling-pair analysis,[74] initiating human milk feeding was associated with a significantly lower BMI z-score at age 5 years, though not with risk of overweight or obesity. Sibling-pair studies are often limited by the smaller sample size available for within-family analyses, which makes it less likely to detect associations. Among these 4 studies, several risks of bias also were of concern. For example, in 2 of the cohorts,[70,87,92] mothers were asked to recall how they fed their offspring during infancy when those offspring were between ages 4 and 18 years. In 1 cohort,[63,66] some participants reported their own height and weight, and in another,[70,92] the

methods used to collect outcome data were not reported. In addition, none of these studies had within-family analyses that compared infants who consumed human milk for different durations with infants who never consumed human milk. Therefore, it is not possible to comment on whether the trend described for the other observational studies (i.e., that longer durations of human milk consumption may be important) is observed in sibling-pair analyses.

Because of the risk of confounding in observational studies, and the limitations of the sibling-pair studies described above, it is difficult to determine whether a causal relationship exists between ever vs never consuming human milk and risk of overweight or obesity. Other systematic reviews and meta-analyses on this topic have generally come to similar conclusions. For example, a systematic review of systematic reviews[10] concluded that breastfeeding is consistently associated with a reduction in the odds of overweight or obesity in childhood and adulthood, by about 13 percent in high-quality studies, but residual confounding could not be ruled out.

Duration of Any Human Milk Consumption Among Infants Fed Human Milk

With regard to the relationship between the duration of any human milk consumption, among infants fed human milk, and overweight and/or obesity at age 2 years and older, the Committee concluded that evidence was insufficient. This was based not on a lack of evidence (18 observational cohort studies, including 4 with sibling-pair analyses, and 1 RCT of a breastfeeding promotion intervention were included in the review), but rather on the inconsistency in the findings: Some studies showed inverse associations, some positive associations, and some no association between duration of human milk consumption and risk of overweight or obesity. Notably, all of the sibling-pair analyses showed no association. The systematic review of systematic reviews cited above[10] stated that “there are some indications that breastfeeding of very short duration has a lesser protective effect than breastfeeding of longer duration on the later risk of overweight and obesity, although residential confounding cannot be excluded.”

Duration of Exclusive Human Milk Consumption Before the Introduction of Infant Formula

Only 2 studies[93,98] examined the relationship between the duration of exclusive human milk consumption before the introduction of infant formula and overweight and/or obesity. Thus, the Committee concluded that evidence was insufficient to determine the relationship between the

duration of exclusive human milk consumption before the introduction of infant formula and overweight and obesity at age 2 years and older.

Intensity, Proportion, or Amount of Human Milk Consumed by Mixed-Fed Infants, by Breast vs Bottle, or During a Feeding

No studies were identified that examined whether overweight or obesity was related to: a) the intensity, proportion, or amount of human milk consumed by mixed-fed infants, b) the intensity, proportion, or amount of human milk consumed at the breast vs by bottle in infants fed human milk as their only source of milk, or c) consuming a single substance (i.e., either human milk or infant formula) vs both human milk and infant formula during a single feeding session.

Potential Mechanisms and Research Needs

Despite the challenges of establishing a causal relationship between human milk feeding exposures and risk of overweight or obesity, several lines of evidence suggest potential biological mechanisms for such a relationship. Rapid weight gain during infancy (particularly during the first 6 months) is consistently related to subsequent risk of overweight or obesity,[127-129] and rapid weight gain is more likely among formula-fed than among breastfed infants.[128] Although the reasons for more rapid weight gain among formula-fed infants are not fully understood, infant self-regulation of energy intake may differ between breast- and formula-fed infants.[130] Additionally, higher protein intake among formula-fed infants drives hormonal differences that may stimulate greater weight gain and fat deposition,[131] though the precise mechanisms are not yet clear and this is an active area of investigation. RCTs of reduced protein formulas have demonstrated less rapid infant weight gain and reduced obesity at school age.[132-136] The concentrations of free amino acids in human milk vs formula also may be important. For example, free glutamate, which is much higher in human milk than in conventional infant formulas, is a key signal for satiation. An experimental study comparing extensively hydrolyzed formula, with higher free glutamate content, with a standard infant formula reported a significant difference in early rapid weight gain between the groups.[137]

Overfeeding of formula-fed infants also is a possibility, as feeding by bottle may make it more difficult for the infant to communicate satiety signals, and in some cases the caregiver may urge the infant to finish the bottle so as to avoid wastage.[138,139] The feeding dynamics of breast- and bottle-feeding mothers and their infants may differ. In a small pilot study using a within-subject approach, Whitfield and Ventura[140] assessed maternal responsiveness to infant cues during 2 human milk feeding sessions differing by feeding modality (breastfeeding vs bottle-

feeding). Mothers were more sensitive to infant cues during breastfeeding and the latency from feeding session midpoint to the first satiation cue was significantly longer during breastfeeding compared to bottle-feeding. Shloim et al[141] investigated whether breastfed infants signal more to mothers to facilitate responsive feeding than do formula-fed infants, and, if so, what communication cues are important during the feeding interaction. Breastfeeding infants exhibited more engagement and disengagement cues than did formula-fed infants. The authors suggested that educating mothers to identify engagement and disengagement cues during a milk feed may promote more responsive feeding strategies. Differences in the dyadic approach of mothers and infants during feeding may have longer term implications for programming of appetite regulation. At ages 3 to 6 years, children who were fed human milk in a bottle as infants were less likely to have high satiety responsiveness compared to directly breastfed children, after controlling for child age, child weight status, maternal race/ethnicity, and maternal education.[139] All of the above studies were relatively small, so additional research on satiety signals and responsiveness is needed.

Future research studies on infant milk-feeding practices and health outcomes should be designed to reduce bias from confounding factors as much as possible. Sibling-pair studies are one example of this type of study design, but few such studies have been conducted and they tend to have much smaller sample sizes than do other types of observational studies. Larger sibling-pair studies are needed, and they need to examine siblings who differ in terms of the duration of human milk consumption (e.g., <6 months, ≥6 months), not just with respect to ever vs never consuming human milk.

Another way to approach these questions is with RCTs of breastfeeding promotion, as was done in the PROBIT trial in Belarus.[142] If the trial achieves substantial differences in duration or exclusivity of breastfeeding between intervention groups, this provides an opportunity to examine effects on subsequent overweight or obesity (and many other outcomes).

Observational studies that make use of large datasets, especially those that follow participants longitudinally and, in particular, link children with siblings and parents, also would be very useful for robustly assessing associations and providing more confidence in conclusions regarding causality. This could be achieved by linking surveillance systems that collect data about infant feeding and health outcomes (including overweight and obesity), and making use of emerging electronic medical record data.

In general, observational studies need to take into account all of the key confounders in the analytical framework of this review, including aspects of the child's diet (complementary feeding and later dietary patterns). The use of instrumental variables, such as Mendelian randomization

approaches, also could be helpful in minimizing confounding.[143] In both observational and intervention studies, researchers should consider effect modification in their study design whenever possible (e.g., child sex, parental obesity, socioeconomic status, race or ethnicity, child diets, child activity levels) to examine the impact of infant feeding on these outcomes within key subgroups.

Long-term Health Outcomes

Diabetes Mellitus

The Committee included a systematic review that investigated the relationship between infant milk-feeding practices and the risk of diabetes outcomes in offspring.[57] A total of 53 articles met the inclusion criteria, although only 1 of the included articles examined lower vs higher intensities, proportions, or amounts of human milk fed to mixed-fed infants. Therefore, no conclusions could be drawn about these comparisons. Based on the available evidence the Committee was able to draw conclusions regarding type 1 diabetes and the comparisons of ever vs. never consuming human milk, different durations of any human milk consumption, and different durations of exclusive human milk consumption. Evidence was insufficient to determine whether or not a relationship exists between ever vs never feeding human milk or duration of exposure to human milk and type 2 diabetes, prediabetes, or intermediate outcomes throughout the lifespan.

Ever vs Never Consuming Human Milk

Limited evidence from observational studies suggests that never vs ever being fed human milk is associated with higher risk of type 1 diabetes and that the evidence is consistent and generalizable to the U.S. population. Although the prevalence of type 1 diabetes is low, small increases in the risk of type 1 diabetes may have public health implications.

Duration of Any Human Milk Consumption Among Infants Fed Human Milk

Moderate evidence from observational studies indicates that, among infants fed some amount of human milk, shorter vs longer durations of any human milk feeding are associated with higher risk of type 1 diabetes. Limited, but consistent, evidence suggests that the duration of any human milk feeding is not associated with fasting glucose or insulin resistance in childhood or during the transition from childhood into adolescence.

Duration of Exclusive Human Milk Consumption

Limited evidence from observational studies suggests that shorter vs longer durations of exclusive human milk feeding are associated with higher risk of type 1 diabetes. Limited evidence from long-term follow-up of children in the PROBIT cluster randomized trial also suggests that the duration of exclusive human milk feeding is not associated with fasting glucose or insulin resistance at age 11.5 years.

The research community has been keenly interested in infant feeding practices, including breastfeeding, in modulating the development of islet autoimmunity and type 1 diabetes.[44] The autoimmune destruction of insulin-producing beta cells in the pancreas that results in type 1 diabetes occurs in genetically susceptible individuals, but is likely triggered by environmental agents early in life and progresses over many months or years during which time the individual is asymptomatic.[144] Several disease-related autoantibodies have been identified that are predictive of clinical type 1 diabetes.[145] However, these autoantibodies may be biomarkers of the destructive process rather than being directly involved in beta-cell destruction. A number of mechanisms are proposed to be involved in the protective effect of breastfeeding against the development of type 1 diabetes. A delay in the introduction of cow milk proteins may be one important factor,[146] although recent results from the TRIGR RCT suggest that weaning to a hydrolyzed formula compared with a conventional formula does not reduce the incidence of type 1 diabetes at age 11.5 years.[147] However, that study was not designed to test the effect of exclusive breastfeeding on type 1 diabetes incidence. Recent evidence from 2 large Scandinavian birth cohorts[148,149] and a meta-analysis[45] support a role of breastfeeding in reducing type 1 diabetes risk. Additional mechanisms that may be involved in the protective effect of breastfeeding include the presence of biologically active components in human milk that could play a role in reducing gut permeability and early enterovirus infections as well as promoting a healthier infant gut microbiota.[44]

Breastfeeding has been proposed to reduce the risk of developing type 2 diabetes[150] through mechanisms that involve reduced circulating glucose and insulin concentrations in infancy[47] and reduced risk of obesity later in life.[151] However, evidence to support this contention is sparse. Indeed, the one cluster RCT that has been conducted[152] found no associations between the breastfeeding intervention and intermediate outcomes (related to type 2 diabetes) at age 11.5 years.

Cardiovascular Disease

A systematic review was conducted to investigate the relationship between infant milk-feeding practices and the risk of CVD outcomes and related intermediate outcomes in offspring.[58] A total of 35 articles met the inclusion criteria, none of which examined lower versus higher intensities, proportions, or amounts of human milk fed to mixed-fed infants. All of the studies were conducted in countries with high or very high Human Development Index (HDI) rankings,[153] but not the United States, thus reducing the generalizability to the U.S. population. Overall, the Committee concluded that evidence is inconclusive or insufficient to determine whether infant milk-feeding practices are associated with blood lipids or endpoint CVD outcomes. However, some conclusions could be made with regard to infant milk-feeding practices and blood pressure and metabolic syndrome.

Ever vs Never Consuming Human Milk

Limited evidence indicates that never vs ever being fed human milk is associated with higher blood pressure, within a normal range, at 6 to 7 years of age.

Duration of Any Human Milk Consumption Among Infants Fed Human Milk

Moderate evidence indicates no association between the duration of any human milk feeding and childhood blood pressure. However, evidence about the relationship of shorter vs longer durations of any human milk feeding with blood lipids in childhood and adulthood and with metabolic syndrome is inconclusive.

Duration of Exclusive Human Milk Consumption

Limited evidence suggests no association between the duration of exclusive human milk feeding and blood pressure in childhood or metabolic syndrome at age 11.5 years.

The biological plausibility of a protective effect of breastfeeding on CVD outcomes has as its underpinning the association between breastfeeding and reduced risk of overweight or obesity.[6] The high content of long chain polyunsaturated fatty acids in human milk has been proposed as a potential mediator, as these fatty acids are incorporated into cell membranes of the vascular endothelium and supplementation with these fatty acids lowers blood pressure in hypertensive individuals.[154] Indeed, a non-RCT[155] and PCSs[156,157] support an association between ever being fed human milk and lower blood pressure at ages 6 to 7 years, albeit within the normal range. However, evidence from the large cluster-randomized PROBIT study found no impact of

breastfeeding on blood pressure at ages 6.5, 11.5, or 16 years,[84,152,158] as well as fasting insulin and glucose or metabolic syndrome at 11.5 years.[152]

Nutrient Status

Due to the differences in the concentrations and bioavailability of some nutrients in human milk compared to infant formula, and changes in human milk composition over time as compared to the constant composition of formula (*see **Part D. Chapter 3: Food, Beverage, and Nutrient Consumption During Lactation***), the Committee investigated associations between infant milk-feeding practices and nutrient status of the infant, which included iron, zinc, iodine, vitamin B_{12}, vitamin D, and fatty acids. Across all questions of human milk feeding and nutrient status, only 23 studies met inclusion and exclusion criteria. For most questions regarding human milk feeding and nutrient status, evidence was scant to nonexistent, leading to conclusions of insufficient evidence and grade not assignable. For questions where evidence was available to address a topic, the number of studies was typically small, did not show consistent associations, and most studies were prone to a substantial risk of bias.

Ever vs Never Consuming Human Milk

The only question for which moderate evidence existed was whether ever compared with never consuming human milk is associated with child fatty acid status. Human milk differs in fatty acid composition compared to infant formula. The evidence was consistent in showing that human milk feeding is likely related to fatty acid status but the direction and strength of associations differed as well as the specific types of fatty acids examined. In addition, fatty acid composition of breast milk is dependent on maternal diet, which was not reported in most studies.

The majority of evidence identified addressed the comparison of ever contrasted with never, consuming human milk and nutrient status outcome. Most studies compared infants who were fed human milk to infants who were fed an infant formula that had a novel composition at the time of the study (such as added DHA, or different levels of iron), and/or a control group who were fed a conventional infant formula. Because nutrient status outcomes in formula-fed infants can vary widely depending on the composition of the formula, which was quite different across studies, the synthesis of evidence was difficult. Other components of infants' diets varied and were often not reported clearly, including the exclusivity of human milk, types and amounts of formula fed in addition to human milk, types and amounts of complementary foods fed in addition to human milk or infant formula, and supplements. These other foods and factors that

could have influenced nutrient status were not described or accounted for in most of the literature identified. The inconsistency in findings may be due to differences between studies in consumption of human milk, infant formula, cow milk, complementary foods, and supplements.

The studies in this body of literature generally examined healthy full-term infants who were recruited at or close to birth and lived in the United States, Australia, Asia, or Europe. Race and ethnicity were not reported in most studies and cultural norms for infant feeding differ widely, leading to concern that the generalizability of the evidence to U.S. infants consuming commercial formulas currently available on the market is limited.

Food Allergy and Atopic Allergic Diseases

Five systematic reviews were completed to investigate the relationship between early infant feeding practices and the risk of atopic dermatitis, food allergies, allergic rhinitis, and asthma.[56] A total of 73 articles met the inclusion criteria. However, there was insufficient evidence to answer 3 of the systematic review questions, namely those comparing lower vs higher intensities, proportions, or amounts of human milk fed to mixed fed infants, or fed by bottle vs by breast. For the remaining 2 comparisons (ever vs. never being fed human milk and shorter vs. longer durations of any human milk feeding), evidence was found for 2 outcomes for specific age groups, but not across the life span.

Ever vs Never Consuming Human Milk

For asthma, moderate evidence indicated that never being fed human milk was associated with a higher risk of childhood asthma risk in childhood, but evidence was insufficient to determine if this relationship persisted into other life stages. Limited evidence did not suggest a relationship between never being fed human milk and atopic dermatitis in childhood. The evidence for birth to 24 months was inconclusive, however, diagnosis of atopic dermatitis can lack specificity in this age group. Evidence was insufficient to determine the relationship between duration of any human milk feeding with atopic dermatitis in adolescence or in adulthood. Insufficient evidence was available to determine a relationship between never vs ever being fed human milk and the risk of developing either allergic rhinitis or food allergy throughout the lifespan.

Duration of Any Human Milk Consumption Among Infants Fed Human Milk

Similar to the findings regarding any human milk feeding, moderate evidence indicated that being fed human milk for shorter durations was associated with higher risk of asthma in

childhood and adolescence, but the evidence was insufficient to determine if this relationship persisted into adulthood. Limited evidence did not suggest a relationship between shorter vs longer duration of any human milk feeding and atopic dermatitis in childhood. Evidence for a relationship between duration of any human milk feeding and atopic dermatitis from birth to 24 months was inconclusive and evidence was insufficient for adolescence or adulthood. In terms of allergic rhinitis in childhood, limited evidence suggested no relationship between the duration of any human milk feeding and evidence is insufficient to determine the relationship from birth to 24 months, in adolescence, or in adulthood. Lastly, evidence was insufficient to determine a relationship between the duration of any human milk feeding with food allergies throughout the lifespan.

Taken together, a protective association between any or longer durations of human milk consumption and lower risk of asthma in childhood was observed, while data for other atopic outcomes were limited or insufficient. These findings are consistent with the most recent conclusions from the American Academy of Pediatrics statement on the impact of breastfeeding on atopic disease.[159] However, a limitation is that nearly all of the evidence in this portfolio was from observational studies. Breastfeeding research may be subject to detection bias, because data are often collected through the use of parent reporting methods that may not be valid and reliable. However, for most studies in this set of evidence, feeding data were collected prospectively, which reduces recall bias. Confounding also can arise because sociodemographic differences between breastfed vs formula-fed groups are rarely mitigated by randomization (the exception is the PROBIT study, which is discussed below) and infant-feeding decisions can be strongly socially patterned. Most studies adjusted for confounding variables deemed important and feasible to control, although the specific adjustment variables varied between studies. Reverse causation can be a major concern for atopy outcomes, because parents may decide, or receive medical advice, to continue or discontinue feeding human milk based on infants' symptoms and because atopic disease in parents or older siblings may influence parents' feeding decisions as they try to prevent asthma. However, the majority of studies found no baseline differences in family history of atopic disease between groups or included family history of atopic disease as an adjustment variable.

The PROBIT cluster RCT was able to overcome many of the above limitations. In this trial,[142] hospitals were randomized to breastfeeding promotion (intervention) or routine care (control). Infants from the intervention sites were significantly more likely than control infants to be breastfed to any degree at age 12 months (19.7 percent vs 11.4 percent) or exclusively breastfed at age 3 (43.3 percent vs 6.4 percent) or 6 (7.9 percent vs 0.6 percent) months.[142] At

age 1 year, the infants in the intervention group were less likely to have atopic eczema than those in the control group (3.3 percent vs 6.3 percent; adjusted OR=0.54; 95% CI: 0.31, 0.95).[142] However, by age 6.5 years, the groups did not differ in ever having atopic dermatitis/eczema, allergic rhinitis or asthma.[160] At age 16 years,[161] adolescents in the intervention group had an approximately 54 percent lowered risk of flexural dermatitis (0.3 percent vs 0.7 percent), but no significant differences in lung function or questionnaire-derived measures of atopic eczema or asthma (note that atopic eczema is much less common at this age).[161] Thus, this study provides evidence for longer-term protective effects of breastfeeding on flexural dermatitis, though the overall incidence in this population was very low.

The conclusion of our review that human milk is related to reduced risk of asthma is supported by previous meta-analyses.[162-164] Gdalevich et al[162] reported that the overall odds ratio for the protective effect of breastfeeding was 0.70 (95% CI: 0.60, 0.81). The importance of genetic susceptibility was evident in that the effect estimate was greater in studies of children with atopic first-degree relatives (OR=0.52; 95% CI: 0.35, 0.79) than in studies that combined children with and without atopic family history (OR=0.73; 95% CI: 0.62, 0.86) or those without a family history (OR=0.99; 95% CI: 0.48, 2.03).[162] A more recent study confirmed that infants who were exclusively breastfed for 4 or more months had a reduced risk of asthma during the first 8 years of life (OR=0.63; 95% CI: 0.50, 0.78]) compared to infants breastfed for less than 4 months.[165] The biological plausibility for a role of breastfeeding in protecting against asthma development includes its demonstrated benefit in reducing the number of respiratory tract infections in infancy, especially among infants in middle- and low-income countries.[166] In addition, exclusive breastfeeding may be beneficial for lung function as evidenced by shorter duration of hospital admission, risk of respiratory failure, and the requirement for supplemental oxygen in infants hospitalized with bronchial inflammation.[41] Indeed, infants exclusively breastfed for 4 months or more had better lung function at age 8 years, as measured by peak expiratory flow, than did infants breastfed less than 4 months.[165] Breastfeeding may mediate these effects through protecting the lungs from viral infections or by promoting maturation of the infant immune system and microbiome.[167]

SUMMARY

The aim of these systematic reviews was to determine how various exposures to human milk are linked to selected outcomes in offspring. The comparisons were structured so as to align with the first feeding decisions that caregivers make: a) whether or not to feed human milk,

b) duration of human milk feeding, and c) feeding human milk exclusively or supplementing with infant formula. The strongest evidence found was in relation to the first of these comparisons. Specifically, the Committee concluded that ever being breastfed may reduce the risk of overweight or obesity, type 1 diabetes, and asthma, compared to never being breastfed. For the second issue, evidence suggested that a longer duration of any breastfeeding is associated with lower risk of type 1 diabetes and asthma, although the optimal duration of breastfeeding with respect to these outcomes is not well understood. For the third issue, exclusivity of breastfeeding was found to be associated with a lower risk of type 1 diabetes.

The outcomes included in these reviews were limited to overweight and obesity, long-term health outcomes (diabetes and CVD), nutrient status, and atopic or allergic diseases in the offspring, and did not include child infectious diseases (e.g., gastrointestinal, respiratory and ear infections), cancer, mortality, or development, nor any maternal outcomes that may be related to initiation or duration of lactation (see ***Part D. Chapter 3: Food, Beverage, and Nutrient Consumption During Lactation***). Implications with regard to recommendations need to be considered in the context of all relevant outcomes, not just those reviewed herein. Nonetheless, the evidence summarized above supports existing recommendations for breastfeeding in the United States[11] and globally,[168] including many other high-income countries.[154,169-173] Those recommendations generally advise exclusive breastfeeding until about age 6 months[11] and continued breastfeeding thereafter, together with appropriate complementary feeding, until at least 12 months[11] or 24 months of age.[168]

Therefore, the Committee supports the following recommendations:

- Encourage exclusive breastfeeding, ideally for the first 6 months of life, with continued breastfeeding through the first year of life or longer as desired by the mother and infant.
- Encourage the broader implementation of policies and programs that promote, protect, and support breastfeeding to benefit both the health of the mother and the infant.

Given the evidence that human milk feeding may be related to infant fatty acid status, depending on maternal diet, the Committee also supports recommendations for lactating women to consume food sources of long-chain polyunsaturated fatty acids (see ***Part D. Chapter 3***).

Despite the importance of the questions examined in this chapter for the long-term health of the child, the available evidence for many questions was insufficient to form conclusion statements, highlighting the critical need for additional research. Generally, much more evidence exists about shorter-term outcomes (e.g., in infancy and early childhood) than for long-

term outcomes (into adulthood), because studies of the latter require such a long timeframe. It also is important to note that no conclusions could be made regarding the effects of the intensity, proportion, or amount of human milk consumed by mixed-fed infants for any outcome investigated. Given the high prevalence of mixed-feeding in the U.S. population, additional research is needed to investigate how the patterns and proportions of human milk feeding across the day and night and within each feeding, in the context of mixed-feeding, are related to health outcomes. Similarly, very little evidence is available on the consequences of feeding human milk by bottle vs from the breast. The composition of human milk varies during the day and within a feeding, which may affect the infant's physiology[174]; bottle-feeding human milk may modify these patterns. As mentioned previously, some evidence suggests that the feeding dynamics of breast- and formula-feeding mothers and their infants differ, which also deserves further investigation.

Specific research needs for the breastfeeding mother-infant dyad are discussed in ***Part E. Future Directions***. However, as mentioned in ***Part D. Chapter 3***, the Committee supports the on-going federal initiative to expand research on human milk composition and how it relates to maternal and infant health.[175]

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