

PART D. CHAPTER 6: NUTRIENTS FROM DIETARY SUPPLEMENTS DURING INFANCY AND TODDLERHOOD

INTRODUCTION

From birth to approximately 6 months of age, infants are generally expected to obtain all of their required nutrients from human milk or infant formula. Between ages 6 and 24 months, the combination of human milk (or infant formula, up to age 12 months) and nutrient-rich complementary foods and beverages is expected to meet nutrient needs. However, in some cases nutrients from dietary supplements may be recommended.

The original questions related to this topic were:

- What is the relationship between specific nutrients from supplements and/or fortified foods consumed during infancy and toddlerhood and nutrient status?
- What is the relationship between specific nutrients from supplements and/or fortified foods consumed during infancy and toddlerhood and growth, size, and body composition?
- What is the relationship between specific nutrients from supplements and/or fortified foods consumed during infancy and toddlerhood and bone health?

The specific nutrients identified for investigation were iron, vitamin D, vitamin B₁₂, and omega-3 fatty acids. Subsequently, the scope of these reviews was reduced to focus on 2 of these nutrients, iron and vitamin D, because of existing recommendations for use of iron and vitamin D supplements for breastfed infants.^{1,2} The Committee's reviews also were restricted to supplements only, not fortified foods, because existing reviews^{3,4} had already examined associations between types of complementary foods (inclusive of fortified foods) and the outcomes of interest (see **Part D. Chapter 5: Foods and Beverages Consumed During Infancy and Toddlerhood**). Finally, the reviews were restricted to examining relationships of: a) iron supplements to growth, size, and body composition, and b) vitamin D supplements to bone health.

Iron Supplements

An American Academy of Pediatrics (AAP) policy statement published in 2010¹ recommended iron supplementation for breastfed infants beginning at age 4 months and

continuing until iron-containing complementary foods are introduced in the diet. However, the issue of routine iron supplementation of breastfed infants has been controversial,⁵⁻⁷ and since that time, other authoritative organizations in Canada, the United Kingdom, Europe, and New Zealand have recommended against routine iron supplementation of all breastfed infants.⁸⁻¹¹ Instead, those organizations only recommend iron supplements for certain infants, such as those with a diagnosis of iron deficiency,¹⁰ or for high-risk groups (e.g., low socioeconomic status or living in areas with a high prevalence of iron-deficiency anemia).⁹ Some of these organizations^{8,9,11} noted the importance of delayed umbilical cord clamping to optimize iron stores at birth and reduce the risk of iron deficiency before age 6 months.¹²

Although providing iron supplements can be highly beneficial for iron-deficient infants, for those who are iron-replete, supplementation may have adverse consequences, such as reduced growth, alterations in absorption of other trace minerals, and gastrointestinal effects such as diarrhea, vomiting, and changes to the gut microflora.^{13,14} For this reason, it is important to understand the potential effects of routine iron supplementation on growth, size, and body composition.

Vitamin D Supplements

Adequate intake of vitamin D is important because of its role in the regulation of calcium and phosphorus metabolism and bone health. Vitamin D deficiency can result in rickets among infants and young children, particularly between the ages of 3 and 18 months.² Although vitamin D can be synthesized in the skin through exposure to sunlight, this is limited during the winter months in most of the United States and for most of the year in northern latitudes. Deficiency is most likely among those living at high latitudes, those with dark skin, and those with inadequate sunlight exposure. The Adequate Intake (AI) for infants is 400 International Units (IU) (10 mcg) per day and the Recommended Dietary Allowance (RDA) for children ages 1 year and older is 600 IU (15 mcg) per day.¹⁵ The average human milk vitamin D concentration is only about 20 IU per liter.²

Although maternal supplementation with high doses of vitamin D can increase milk vitamin D concentrations,¹⁶ the potential risks and benefits of this approach for ensuring adequate vitamin D status of breastfed infants have not been fully evaluated. For this reason, the AAP currently recommends vitamin D supplements for breastfed infants. The recommendation states: “Because human milk contains inadequate amounts of vitamin D (unless the lactating mother is taking supplements of approximately 6,000 IU/d), breastfed and partially breastfed infants should be supplemented with 400 IU of vitamin D per day beginning in the first few days of life

and continued until the infant has been weaned and is drinking at least 1 L/d of vitamin D-fortified infant formula or cow milk”.² Because bone development is the clinical outcome most likely to be influenced by vitamin D (due to its critical role in calcium absorption for bone mineralization), the Committee focused its review on the relationship between vitamin D supplements and outcomes related to bone health.

LIST OF QUESTIONS

1. What is the relationship between iron from supplements consumed during infancy and toddlerhood and growth, size, and body composition?
2. What is the relationship between vitamin D from supplements consumed during infancy and toddlerhood and bone health?

METHODOLOGY

Both questions discussed in this chapter were answered by conducting systematic reviews 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. 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 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 the questions on nutrients from dietary supplements consumed during infancy and toddlerhood.

The intervention or exposure was the consumption of iron from dietary supplements for Question 1 and vitamin D from dietary supplements for Question 2. Dietary supplements are products that contain one or more dietary ingredients (in this case, iron or vitamin D) intended to be taken by mouth to supplement the diet.¹⁷ For both questions, the population of interest for the intervention or exposure was infants and toddlers (birth to age 24 months; in this report 0 to age 6 months refers to 0 to age 5.99 months, ages 6 to 12 months refers to ages 6 to 11.99 months, and ages 12 to 24 months refers to ages 12 to 23.99 months). Initially, the protocols for these questions specified an intervention or exposure of iron, vitamin D, vitamin B₁₂, and omega-3 fatty acids from supplements or fortified foods. However, the Committee modified their protocols to focus solely on iron and vitamin D from supplements, for a few reasons. First, iron and vitamin D are the nutrients of greatest public health concern in this age group with respect to the outcomes being examined (i.e., growth and bone health, respectively). Second, iron and vitamin D supplements are recommended for infants in the United States. Third, two existing NESR systematic reviews examined complementary foods, including fortified foods, and the outcomes of interest (see **Part D. Chapter 5: Foods and Beverages Consumed During Infancy and Toddlerhood**).^{3,4} The comparators were the consumption of iron for Question 1 and vitamin D for Question 2 at a different dosage or frequency from supplements or from fortified foods.

For Question 1, the outcomes of interest were measures of growth, size, and body composition at any age (e.g., weight, length/height, body mass index (BMI)/weight-for-length, body circumferences, body composition and distribution, incidence/prevalence of underweight, failure to thrive, stunting, wasting, healthy weight, overweight, and obesity). For Question 2, the outcomes of interest were measures of bone health from birth to age 18 years (i.e., bone mass, including bone

mineral density and bone mineral content; biomarkers of bone metabolism; rickets; and fracture).

When establishing inclusion and exclusion criteria, the Committee used standard NESR criteria for study design, publication status, language of publication, country, study participants, and health status of study participants. Studies were included if they were published from January 2000 to January 2020.

REVIEW OF THE SCIENCE

Question 1. What is the relationship between iron from supplements consumed during infancy and toddlerhood and growth, size, and body composition?

Approach to Answering Question: NESR systematic review

Conclusion Statements and Grades

Moderate evidence indicates that human milk-fed infants who are supplemented with iron do not have greater growth, and may have slower growth, than human milk-fed infants not supplemented with iron. Grade: Moderate

Insufficient evidence is available to determine the relationship between iron from supplements consumed during infancy and body composition during infancy. Grade: Grade Not Assignable

Insufficient evidence is available to determine the relationship between iron from supplements consumed during infancy and growth, size, and body composition beyond age 12 months. Grade: Grade Not Assignable

Insufficient evidence is available to determine the relationship between iron from supplements consumed after age 12 months and growth, size, and body composition. Grade: Grade Not Assignable

Summary of the Evidence

- Ten articles met the inclusion criteria for this systematic review, which presented evidence from 8 randomized controlled trials (RCTs), 1 non-RCT, and 1 study that did not clearly describe its prospective study design.¹⁸⁻²⁷
- The intervention or exposure of interest was iron from supplements consumed during infancy and toddlerhood. Nine studies¹⁹⁻²⁷ examined iron supplementation during infancy, and only 1 study¹⁸ examined iron supplementation during toddlerhood.
- The comparators of interest were different dosages of iron from supplements and iron from fortified foods.
- The outcomes of interest were measures of growth, size, and body composition at any age. However, no articles were identified that examined outcomes beyond 24 months. The articles presented evidence about growth (i.e., change in size between birth or baseline and follow-up) and size (i.e., attained size at follow-up). However, no articles presented evidence about body composition (e.g., percent fat mass, skinfold thickness).
- Moderate evidence, from 5 studies^{21,22,24,26,27} that compared iron from supplements with no iron from supplements, indicated that human milk-fed infants who are supplemented with iron do not have greater growth, and may have slower growth, than human milk-fed infants not supplemented with iron. Inconsistencies in the evidence may be explained by differences in the risk of iron deficiency between the populations studied, differences in participants' consumption of iron-fortified formula or iron-rich foods, and differences in the timing of iron supplementation. This heterogeneity, the small number of studies, and the small sample sizes were the primary factors limiting the ability to draw stronger conclusions.
- Evidence available from 3 studies^{18,20,21} was insufficient to determine whether a relationship exists between iron from supplements, compared with a different dosage or duration of iron from supplements, and growth or size because the studies used heterogeneous interventions that could not be compared.
- Evidence available from 2 studies^{25,26} was insufficient to determine whether a relationship exists between iron from supplements, compared with iron from fortified foods, and growth or size because the studies used heterogeneous interventions that could not be compared.

For additional details on this body of evidence, visit: [nesr.usda.gov/2020-dietary-guidelines-advisory-committee-systematic-reviews/birth-24-months-subcommittee/iron-supplements-infancy-toddlerhood-growth-size-body-composition](https://www.nesr.usda.gov/2020-dietary-guidelines-advisory-committee-systematic-reviews/birth-24-months-subcommittee/iron-supplements-infancy-toddlerhood-growth-size-body-composition)

Question 2. What is the relationship between vitamin D from supplements consumed during infancy and toddlerhood and bone health?

Approach to Answering Question: NESR systematic review

Conclusion Statements and Grades

Limited evidence suggests no relationship between consumption of 400 IU per day of vitamin D from supplements before age 12 months, compared with higher dosages of up to 1,600 IU per day, and biomarkers of bone metabolism in children up to age 36 months. Grade: Limited

Insufficient evidence is available to determine the relationship between 400 IU per day of vitamin D from supplements, compared with higher dosages, and bone mass, rickets, or fracture. Grade: Grade Not Assignable

Insufficient evidence is available to determine the relationship between 400 IU per day of vitamin D from supplements, compared with lower dosages, and bone mass, biomarkers of bone metabolism, rickets, or fracture. Grade: Grade Not Assignable

Insufficient evidence is available to determine the relationship between vitamin D from supplements, compared with no vitamin D from supplements, and bone mass, biomarkers of bone metabolism, rickets, or fracture. Grade: Grade Not Assignable

Insufficient evidence is available to determine the relationship between vitamin D from supplements, compared with vitamin D from fortified foods, and bone mass, biomarkers of bone metabolism, rickets, or fracture. Grade: Grade Not Assignable

Summary of the Evidence

- Six articles met the inclusion criteria for this systematic review,²⁸⁻³³ which presented evidence from 5 independent RCTs (1 research group published 2 articles about the same trial).
- The intervention of interest was vitamin D from supplements consumed during infancy or toddlerhood. In the United States, 400 IU of vitamin D per day is the AI for infants younger than age 12 months, whereas the RDA for ages 12 to 24 months is 600 IU per day. To meet this need, the AAP currently recommends a supplement of 400 IU per day for infants fed

human milk (with the possible exception of infants whose mothers are taking supplements of about 6,000 IU per day²; maternal vitamin D supplementation during lactation was outside of the scope of this systematic review).

- The comparators of interest were different dosages of vitamin D from supplements and vitamin D from fortified foods. However, no articles were identified that included fortified food comparators.
- The outcomes of interest were bone mass, biomarkers of bone metabolism, rickets, and fracture through adolescence (i.e., birth through age 18 years). However, no articles were identified that examined fracture or outcomes beyond age 36 months.
- Limited evidence from 3 studies^{29,30,33} suggests no relationship between 400 IU per day of vitamin D from supplements, compared with higher dosages, and biomarkers of bone metabolism in children up to age 36 months. The ability to draw a stronger conclusion was primarily limited by a small number of studies, small sample sizes, heterogeneous methods, and limited generalizability.
- Evidence available from 4 studies^{28-30,32,33} was insufficient to determine whether a relationship exists between 400 IU per day of vitamin D from supplements, compared with higher dosages, and bone mass. The ability to draw a conclusion was hindered by inconsistent findings from a small number of studies. No studies were available that examined the relationship between 400 IU per day of vitamin D from supplements, compared with higher dosages, and rickets or bone fracture.
- Evidence available from 1 study³³ was insufficient to determine whether a relationship exists between 400 IU per day of vitamin D from supplements, compared with lower dosages, and bone mass or biomarkers of bone metabolism. No studies were available that examined the relationship between 400 IU per day of vitamin D from supplements, compared with lower dosages, and rickets or fracture.
- Evidence available from 1 study³¹ was insufficient to determine whether a relationship exists between 200 IU per day of vitamin D from supplements for different durations, compared with no vitamin D from supplements, and biomarkers of bone metabolism or rickets. No studies were available that examined the relationship between 200 IU per day of vitamin D from supplements for different durations, compared with no vitamin D from supplements, and bone mass or fracture. No studies were available that compared other dosages of vitamin D from supplements with no supplementation. It is likely that the evidence that led to the current supplementation recommendation pre-dates our literature search date range of January 2000 to January 2020.

For additional details on this body of evidence, visit: nestr.usda.gov/2020-dietary-guidelines-advisory-committee-systematic-reviews/birth-24-months-subcommittee/vitamin-d-supplements-infancy-toddlerhood-bone-health

DISCUSSION

Iron Supplements

This evidence from the Committee's review showed no positive effects, and possibly negative effects, on growth when iron supplements were given to breastfed infants younger than age 9 months, compared with infants not given iron or given a placebo. Of the 5 RCTs included in this comparison,^{21,22,24,26,27} 3 reported significant differences between intervention groups in one or more growth outcomes (all in the same direction, i.e., slower growth among infants given iron supplements)^{21,26,27} and 2 did not.^{22,24}

Several possible explanations may account for the differences in findings among these 5 studies. First, the study populations differed in several characteristics that may be related to risk of iron deficiency and therefore the potential impact of iron supplements on growth. Four studies were conducted among populations with medium to high average socio-economic or educational status,^{21,22,26,27} whereas the study by Lozoff et al²⁴ was conducted in rural China and only about one-third of mothers had a high school education or greater. Risk of iron deficiency appeared to be greater in the study by Lozoff et al²⁴ based on average hemoglobin and serum ferritin concentrations at age 9 months in the control or placebo groups.³⁴

Second, the studies differed in the extent to which the infants were supplemented with iron-fortified infant formula or iron-rich foods, which may have obscured effects of iron supplementation on growth. Although all studies enrolled infants who were initially breastfed, 3 studies reported that a substantial proportion of infants ceased breastfeeding and/or were supplemented with infant formula,^{22,26,27} whereas Dewey et al²¹ enrolled mothers who intended to exclusively breastfeed until 6 months (except for small "tastes" of low-iron foods) and to continue breastfeeding until at least 9 months. In the study by Lozoff et al,²⁴ investigators reported that more than 80 percent of infants were still breastfeeding at 9 months, and more than 50 percent received breast milk as the sole milk source. Lastly, the timing of iron supplementation differed among studies. Of the 3 studies that began iron supplementation at 1 month or 6 weeks, 2 did not report significant differences in growth between intervention groups,^{22,24} and the third reported significant group differences in growth among females but not

among male infants.²⁷ Both studies that began iron supplementation at about age 4 months demonstrated significant group differences in growth.^{21,26}

The potentially adverse effects of iron supplements on growth of infants and children younger than age 2 years are consistent with other findings. In a systematic review and meta-analysis focused on children ages 4 to 24 months,¹⁴ infants and children randomized to receive iron supplements had less length gain (SMD -0.83 cm, -1.53 to -0.12) and weight gain (-1.12 kg, -1.19 to -0.33) than those who did not receive iron. These analyses included children from both high-income (3 studies) and lower-income (5 studies) countries. In addition, among the trials with illness data, vomiting and fever were more prevalent among children receiving iron.¹⁴ For iron-deficient children, providing sufficient iron (from food, supplements, or fortified foods) is important for reducing iron-deficiency anemia and its consequences, including impaired neurobehavioral development.³⁵ However, iron is a “double-edged sword” in the sense that excess iron intake among iron-replete individuals may be harmful. In the meta-analysis described above,¹⁴ stratified analyses based on the initial iron status of the children were not possible. The potential mechanisms by which iron may adversely affect growth among iron-replete children include increased gastrointestinal illness, impaired zinc or copper status, pro-oxidative or pro-inflammatory effects, and disturbances in the gut microbiota.¹³ Among infants younger than age 6 months, iron homeostasis appears to be absent or limited, which has been attributed to lack of regulation of the iron transporters DMT1 and ferroportin.³⁶ As a result, supplemental iron is likely to be absorbed even if the infant is iron-replete and does not need it. After 6 months, infants appear to be able to downregulate iron absorption appropriately,³⁶ as is the case for older children and adults.

Vitamin D Supplements

All of the studies included in this review were RCTs. A single study³¹ compared vitamin D supplementation to placebo, while all other studies compared the impact of various doses of vitamin D supplementation on bone health indicators from birth to 36 months of age. The groups showed little to no evidence of statistically significant differences in bone health indicators based on dose of Vitamin D supplementation. Of the studies that examined bone health outcomes,^{29-31,33} 2 identified statistically significant differences,^{30,33} but these differences were small in magnitude while the number of comparisons conducted was large and sample sizes in each group were quite small. None of the studies that examined impact of vitamin D supplementation on biomarkers of bone metabolism identified any significant differences. Because only 1 study³¹

examined the impact of vitamin D supplementation on incidence of rickets, and not a single event was observed in that study, no conclusions could be drawn regarding that outcome.

Information on race and/or ethnicity of the participants was not provided in most of the studies. The countries of study origin were Canada, the United States, and Finland, but without knowing more about the characteristics of the participants, it is difficult to judge the potential risk factors for vitamin D deficiency that may have been present.

SUMMARY

The evidence suggesting slower growth among infants given iron supplements suggests that routine iron supplementation of all breastfed infants may not be advisable. An alternative could be to screen for iron deficiency among higher-risk infants younger than age 6 months, and provide iron supplements only to those with biomarkers indicating iron deficiency. However, screening for iron deficiency using appropriate biomarkers, such as serum ferritin, could be challenging because it is not as simple as measuring hemoglobin.³⁷ Iron supplementation is routinely advised for low birthweight and preterm infants beginning at age 1 month,¹ who are born with low iron stores. Apart from those subgroups, infants at higher risk for iron deficiency before age 6 months are those with birth weight less than 3,000 grams, male infants,³⁸ and those for whom the umbilical cord was clamped immediately.¹² After age 6 months, other sources of iron can be provided, such as iron-rich or iron-fortified complementary foods, so iron supplementation is generally not needed. Further research is needed to: a) evaluate how to best identify and treat infants who become iron deficient before age 6 months, including populations with racial and ethnic diversity, and b) investigate the biological mechanisms by which iron supplementation during infancy may affect growth, including potential effects on morbidity, the microbiome, zinc and copper status, and oxidative stress or lipid peroxidation.

Existing recommendations regarding vitamin D supplementation during infancy are based on a body of evidence compiled largely before 2000, the starting date for this review. The limited evidence available since 2000 suggests that doses higher than 400 IU per day (the current AAP recommendation for infants²) do not result in differences in biomarkers of bone metabolism in infancy or early childhood. Thus, at this time, the current body of evidence does not provide a basis for recommending vitamin D supplementation above 400 IU per day during infancy. Further research is needed to investigate how much (if any) vitamin D supplementation is needed for breastfed infants when the mother is taking high doses of vitamin D. Future studies

should be appropriately powered, include racially and ethnically diverse samples, and report baseline infant vitamin D status, human milk vitamin D content, and sun exposure.

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