



United States Department of Agriculture

Vitamin D from Supplements Consumed during Infancy and Toddlerhood and Bone Health: A Systematic Review

2020 Dietary Guidelines Advisory Committee,
Birth to 24 Months Subcommittee

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Nutrition Evidence Systematic Review
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This systematic review was conducted by the 2020 Dietary Guidelines Advisory Committee in collaboration with the Nutrition Evidence Systematic Review (NESR) team at the Center for Nutrition Policy and Promotion, Food and Nutrition Service, U.S. Department of Agriculture (USDA). All systematic reviews from the 2020 Advisory Committee Project are available on the NESR website: <https://nesr.usda.gov/2020-dietary-guidelines-advisory-committee-systematic-reviews>.

Conclusion statements drawn as part of this systematic review describe the state of science related to the specific question examined. Conclusion statements do not draw implications, and should not be interpreted as dietary guidance. This portfolio provides the complete documentation for this systematic review. A summary of this review is included in the 2020 Advisory Committee's Scientific Report available at www.DietaryGuidelines.gov.

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USDA and HHS implemented a process to identify topics and scientific questions to be examined by the 2020 Dietary Guidelines Advisory Committee. The Committee conducted its review of evidence in subcommittees for discussion by the full Committee during its public meetings. The role of the Committee members involved establishing all aspects of the protocol, which presented

ⁱ Under contract with the Food and Nutrition Service, United States Department of Agriculture.

the plan for how they would examine the scientific evidence, including the inclusion and exclusion criteria; reviewing all studies that met the criteria they set; deliberating on the body of evidence for each question; and writing and grading the conclusion statements to be included in the scientific report the 2020 Committee submitted to USDA and HHS. The NESR team with assistance from Federal Liaisons and Project Leadership, supported the Committee by facilitating, executing, and documenting the work necessary to ensure the reviews were completed in accordance with NESR methodology. More information about the 2020 Dietary Guidelines Advisory Committee, including the process used to identify topics and questions, can be found at www.DietaryGuidelines.gov. More information about NESR can be found at NESR.usda.gov.

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TABLE OF CONTENTS

Acknowledgements	3
Table of contents	5
Introduction	6
What is the relationship between vitamin D from supplements consumed during infancy and toddlerhood and bone health?	8
Plain language summary	8
Technical abstract	10
Full review	12
Systematic review question	12
Conclusion statements and grades	12
Summary of the evidence	12
Description of the evidence.....	13
Synthesis and assessment of the evidence	16
Research recommendations	30
Included articles	30
Methodology	31
Analytic framework	32
Literature search and screening plan	33
Inclusion and exclusion criteria	33
Electronic databases and search terms	36
Literature search and screening results.....	38
Excluded articles.....	39
Table 1. Infant feeding and dietary and environmental sources of vitamin D	14
Table 2. Evidence examining the relationship between vitamin D from supplements consumed during infancy and toddlerhood and bone health	19
Table 3. Risk of bias for randomized controlled trials examining consumption of vitamin D from supplements during infancy and toddlerhood and bone health	29
Table 4. Inclusion and exclusion criteria	33
Table 5. Articles excluded after full text screening with rationale for exclusion	39
Figure 1: Analytic framework.....	32
Figure 2: Flow chart of literature search and screening results.....	38

INTRODUCTION

This document describes a systematic review conducted to answer the following question: What is the relationship between vitamin D from supplements consumed during infancy and toddlerhood and bone health? This systematic review was conducted by the 2020 Dietary Guidelines Advisory Committee, supported by USDA's Nutrition Evidence Systematic Review (NESR).

More information about the 2020 Dietary Guidelines Advisory Committee is available at the following website: www.DietaryGuidelines.gov.

NESR specializes in conducting food- and nutrition-related systematic reviews using a rigorous, protocol-driven methodology. More information about NESR is available at the following website: NESR.usda.gov.

NESR's systematic review methodology involves developing a protocol, searching for and selecting studies, extracting data from and assessing the risk of bias of each included study, synthesizing the evidence, developing conclusion statements, grading the evidence underlying the conclusion statements, and recommending future research. A detailed description of the systematic reviews conducted for the 2020 Dietary Guidelines Advisory Committee, including information about methodology, is available on the NESR website: <https://nesr.usda.gov/2020-dietary-guidelines-advisory-committee-systematic-reviews>. In addition, starting on page 31, this document describes the final protocol as it was applied in the systematic review. A description of and rationale for modifications made to the protocol are described in the 2020 Dietary Guidelines Advisory Committee Report, Part D: Chapter 6. Nutrients from Dietary Supplements During Infancy and Toddlerhood.

List of abbreviations

Abbreviation	Full name
25(OH)D	25-Hydroxy Vitamin D
AI	Adequate Intake
ALP	Alkaline Phosphatase
BMC	Bone Mineral Content
BMD	Bone Mineral Density
CNPP	Center for Nutrition Policy and Promotion
CTX	C-Terminal Telopeptides
FNS	USDA Food and Nutrition Service
HHS	U.S. Department of Health and Human Services
IU	International Units
NESR	Nutrition Evidence Systematic Review
NIH	National Institutes of Health
ONGA	Office of Nutrition Guidance and Analysis
PINP	Procollagen I N-Terminal Propeptide
RDA	Recommended Dietary Allowance
USDA	U.S. Department of Agriculture

WHAT IS THE RELATIONSHIP BETWEEN VITAMIN D FROM SUPPLEMENTS CONSUMED DURING INFANCY AND TODDLERHOOD AND BONE HEALTH?

PLAIN LANGUAGE SUMMARY

What is the question?

- The question is: What is the relationship between vitamin D from supplements consumed during infancy and toddlerhood and bone health?

What is the answer to the question?

- 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 1600 IU per day, and biomarkers of bone metabolism in children up to age 36 months.
- 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.
- 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.
- 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.
- 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.

Why was this question asked?

- This important public health question was identified by the U.S. Departments of Agriculture (USDA) and Health and Human Services (HHS) to be examined by the 2020 Dietary Guidelines Advisory Committee.

How was this question answered?

- The 2020 Dietary Guidelines Advisory Committee, Birth to 24 Months Subcommittee, conducted a systematic review to answer this question with support from the Nutrition Evidence Systematic Review (NESR) team.

What is the population of interest?

- Vitamin D supplementation was examined in healthy infants and toddlers (birth to 24 months) with outcomes measured at birth through age 18 years.

What evidence was found?

- This review includes 6 articles.

- The articles compared infants and toddlers who consumed different dosages of vitamin D from supplements. Most articles compared infants supplemented with 400 International Units (IU) per day (which is the Adequate Intake for infants) with infants supplemented with higher dosages.
- The outcomes of interest were bone mass, biomarkers of bone metabolism, rickets, and fracture from birth to age 18 years. Most articles examined bone mass and biomarkers of bone metabolism in children up to age 36 months.
- Limited evidence suggests that infants who are supplemented with 400 IU per day and infants who are supplemented with higher dosages of up to 1600 IU per day do not have differences in biomarkers of bone metabolism up to age 36 months, but the evidence related to bone mass was inconsistent.
- There are limitations in the evidence as follows:
 - There were not a lot of articles, and some of the articles studied groups of infants and toddlers that may have been too small to detect a relationship between iron supplementation and growth or size.
 - The studies examined infants who were given supplements for different lengths of time, examined different biomarkers of bone metabolism, and measured the biomarkers at different ages, so comparing the findings of the studies was difficult.
 - In the studies that reported race, most or all infants were white. The findings may or may not be the same in other racial or ethnic groups.

How up-to-date is this systematic review?

- This review searched for studies from January, 2000 to January, 2020

TECHNICAL ABSTRACT

Background

- This important public health question was identified by the U.S. Departments of Agriculture (USDA) and Health and Human Services (HHS) to be examined by the 2020 Dietary Guidelines Advisory Committee.
- The 2020 Dietary Guidelines Advisory Committee, Birth to 24 Months Subcommittee conducted a systematic review to answer this question with support from the Nutrition Evidence Systematic Review (NESR) team.
- The goal of this systematic review was to examine the following question: What is the relationship between vitamin D from supplements consumed during infancy and toddlerhood and bone health?

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 1600 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)

Methods

- A literature search was conducted using 4 databases (PubMed, Cochrane, Embase, and CINAHL) to identify articles that evaluated the intervention or exposure of vitamin D from supplements consumed during infancy and toddlerhood and bone health outcomes. A manual search was conducted to identify articles that may not have been included in the electronic databases searched. Articles were screened by two NESR analysts independently for inclusion based on pre-determined criteria.
- Data extraction and risk of bias assessment were conducted for each included study, and both were checked for accuracy. The Committee qualitatively synthesized the body of evidence to inform development of conclusion statements, and graded the strength of evidence using pre-established criteria for risk of bias, consistency, directness, precision, and generalizability.

Summary of the evidence

- Six articles met the inclusion criteria for this systematic review, which presented evidence from 5 independent randomized controlled trials (1 research group published 2 articles about the same trial).
- The intervention of interest was vitamin D from supplements consumed during infancy or toddlerhood. *Dietary supplements* are products that contain one or more dietary ingredients (in this case, vitamin D) intended to be taken by mouth to supplement the diet. 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 of age is 600 IU per day. To meet this need, the American Academy of Pediatrics 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 6000 IU per day; 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 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 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 study 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 study 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.

FULL REVIEW

Systematic review question

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

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 1600 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,¹⁻⁶ which presented evidence from 5 independent randomized controlled trials (1 research group published 2 articles about the same trial).
- The intervention of interest was vitamin D from supplements consumed during infancy or toddlerhood. *Dietary supplements* are products that contain one or more dietary ingredients (in this case, vitamin D) intended to be taken by mouth to supplement the diet.ⁱⁱ 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 of age is 600 IU per day. To meet this need, the American Academy of Pediatrics 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 6000 IU per dayⁱⁱⁱ; 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

ⁱⁱ National Institutes of Health Office of Dietary Supplements. Dietary Supplement Health and Education Act of 1994 Public Law 103-417 103rd Congress: Sec. 3. Definitions. https://ods.od.nih.gov/About/DSHEA_Wording.aspx#sec3 Published October 25, 1994. Accessed May 18, 2020

ⁱⁱⁱ Golden NH, Abrams SA. Optimizing bone health in children and adolescents. *Pediatrics*. 2014;134(4):e1229-1243. doi:10.1542/peds.2014-2173.

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 36 months.
- Limited evidence from 3 studies 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 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 study 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 study 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.

Description of the evidence

This systematic review examines available evidence about the relationship between vitamin D from supplements consumed during infancy and toddlerhood and bone health from birth through adolescence.

Six articles, published between 2010 and 2018, met the inclusion criteria.¹⁻⁶ The 6 articles present evidence from 5 independent randomized controlled trials; the 2 articles by Gallo et al^{1,2} are from the same study.

Population

Study participants were from the United States,^{4,6} Canada,^{1,2} and Finland.^{3,5} In 3 studies, the participants were predominantly or entirely White,^{1,2,5,6} and the remaining 2 studies did not report race or ethnicity.^{3,4}

Baseline vitamin D status was similar in 3 studies, with serum 25-hydroxy vitamin D [25(OH)D] averaging 50-56 nmol/L.¹⁻⁴ Rosendahl et al⁵ reported that for the majority of infants (52%), the

range was 75-125 nmol/L 25(OH)D. Ziegler et al⁶ did not report baseline vitamin D concentrations.

The studies focused on infants fed human milk. Intake of infant formula, dietary sources of vitamin D, and sun exposure varied between studies (Table 1).

Table 1. Infant feeding and dietary and environmental sources of vitamin D

Study	Human milk and infant formula	Dietary vitamin D	Sun exposure
Gallo et al^{1,2}	<ul style="list-style-type: none"> Recruited infants <1 month consuming ≥80% total milk volume as human milk; 88% and 35% consumed any human milk at 6 and 12 months, respectively Average formula intake increased from 35 g/d at 1 month to 155 g/d at 6 months and 252 g/d by 12 months 	<ul style="list-style-type: none"> Average dietary intake of vitamin D increased from 43 IU/d at 1 month to 84 IU/d at 6 months and 245 IU/d by 12 months Average dietary intake of vitamin D was 247-302 IU/d at 36 months, depending on the group 	<ul style="list-style-type: none"> Average sun exposure (estimated as h/wk * % exposed body surface area) increased from 7 at 1 month to a peak of 71 at 9 months and then decreased to 56 at 12 months; at 36 months it was 1.6-1.7 depending on the group About half (56%) of infants were born during the “synthesizing period” of April to October when cutaneous vitamin D production is possible based on latitude The majority of children (84-96% depending on the group) had fair or very fair skin color
Holmlund-Suila et al³	<ul style="list-style-type: none"> Infant feeding at recruitment not reported At the time of the outcome measure (3 months), 95% of infants were consuming human milk At the time of the outcome measure (3 months) mean formula intake was 2.5 L/wk 	<ul style="list-style-type: none"> Not reported; however, infants were only 3 months old by the end of the study 	<ul style="list-style-type: none"> Not reported; however infants were born in September to February in Finland and followed for 3 months
Ponnapakkam et al⁴	<ul style="list-style-type: none"> Recruited newborns whose mothers intended to feed >50% human milk for 3 months Excluded infants consuming >50% infant formula ≤ 3 months (36% of participants) 	<ul style="list-style-type: none"> Not reported 	<ul style="list-style-type: none"> Not reported; however infants resided in southern Louisiana, and 7 of 25 participants who completed the study were described as “high risk” based on the presence of risk factors such as dark skin color or full-body clothing/draping
Rosendahl et al⁵	<ul style="list-style-type: none"> The majority (79%) of infants were fed human milk >6 months Formula intake was not reported 	<ul style="list-style-type: none"> Average dietary intake of vitamin D was 248 IU/d at 12 months, and not reported at other ages 	<ul style="list-style-type: none"> Not reported; however, authors describe the population as “northern European with limited sunlight exposure” All infants were of northern European ethnicity
Ziegler et al⁶	<ul style="list-style-type: none"> Recruited infants <28 days fed human milk exclusively Caregivers encouraged not to introduce infant formula until >9 months 	<ul style="list-style-type: none"> Not reported 	<ul style="list-style-type: none"> All infants Caucasian Outcomes measured at the end of winter

Interventions and comparators

The intervention was vitamin D from supplements consumed during infancy and toddlerhood. In all 5 studies, vitamin D was provided in the form of vitamin D3 drops.

Four studies compared 400 IU/d of vitamin D with higher dosages:

1. Gallo et al^{1,2} compared dosages of 400, 800, 1200, and 1600 IU/d from 1 to 12 months of age (i.e., nearly 1 year of supplementation)
2. Holmlund-Suila et al³ compared dosages of 400, 1200, and 1600 IU/d from 2 weeks to 3 months of age (i.e., 2.5 months of supplementation)
3. Rosendahl et al⁵ compared dosages of 400 and 1200 IU/d from 2 weeks to 24 months of age (i.e., nearly 2 years of supplementation)
4. Ziegler et al⁶ compared 400, 600, and 800 IU/d from 2 to 9 months (i.e., 7 months of supplementation)

One study compared 400 IU/d with a lower dosage: Ziegler et al⁶ compared 400 and 200 IU/d from 2 to 9 months (i.e., 7 months of supplementation).

One study compared 200 IU/d for different durations with a placebo: Ponnappakkam et al⁴ compared 200 IU/d from birth to 6 months (i.e., 6 months of supplementation), 200 IU/d from 2 to 6 months (i.e., 4 months of supplementation), and placebo from birth to 6 months.

Outcomes

Four studies assessed bone mass outcomes:

1. Gallo et al^{1,2} reported:
 - Femur, lumbar spine, and whole-body bone mineral content (BMC) at 3, 6, 9, and 12 months, and change in femur, lumbar spine, and whole-body BMC from 1 to 3, 3 to 6, 6 to 9, and 9 to 12 months
 - Lumbar spine and whole-body BMC 36 months, change in lumbar spine and whole-body BMC from 12 to 36 and 1 to 36 months, and lumbar spine and whole-body bone mineral density (BMD) and BMD z-score at 36 months
2. Holmlund-Suila et al³ reported:
 - Total and trabecular bone and cortical bone BMD and cross-sectional area at 3 months, and polar stress and strain index (an indicator of bone strength) at 3 months
3. Rosendahl et al⁵ reported:
 - Total bone and cortical bone BMC, BMD, cross-sectional area, and polar moment of inertia at 24 months
4. Ziegler et al⁶ reported:
 - Whole-body BMC and BMD at the end of winter (i.e., infant ages 5.5-9 months) and in subsamples of infants who were 5.5, 7.5, and 9 months at end of winter

Four studies assessed biomarkers of bone formation and bone resorption:

Bone formation biomarkers

- Alkaline phosphatase (ALP) at 2, 4, and 6 months⁴ and 4, 5.5, 7.5, and 9 months⁶

- Osteocalcin at 4, 5.5, 7.5, and 9 months⁶
- Procollagen I N-terminal propeptide (PINP) at 3 months³

Bone resorption biomarkers

- C-terminal telopeptides (CTX) at 3 months³; 4, 5.5, 7.5, and 9 months⁶; and 36 months²

One study assessed rickets: Ponnappakkam et al⁴ reported the incidence of rickets at 2, 4, and 6 months.

Synthesis and assessment^{iv} of the evidence

Comparisons of 400 IU/d with higher dosages of vitamin D

Four of the 5 studies compared 400 IU/d of vitamin D with higher dosages.^{1-3,5,6} The Adequate Intake (AI) for infants is 400 IU/d of vitamin D and the Recommended Dietary Allowance (RDA) for children ages 1 year and older is 600 IU/d.^v To meet this need, the American Academy of Pediatrics currently recommends a supplement of 400 IU/d for human milk-fed infants (with the possible exception of infants whose mothers are taking supplements of about 6000 IU/d).^{vi}

All 4 studies examined bone mass outcomes, and 3 examined biomarkers of bone metabolism.

Bone Mass

The evidence was inconsistent with regard to the statistical significance of the findings and the direction of the statistically significant relationships. These inconsistencies are outlined below.

Holmlund-Suila et al³ reported significant positive relationships and Ziegler et al⁶ reported significant inverse relationships between vitamin D dosage and bone mass in infants:

- Holmlund-Suila et al³ compared infants given 400, 1200, and 1600 IU/d of vitamin D₃ from 2 weeks to 3 months of age. Infants given 1600 IU/d had: (a) significantly higher total and trabecular bone cross-sectional area at 3 months than infants given 400 IU/d (but not 1200 IU/d); (b) significantly higher cortical bone cross-sectional area at 3 months than infants given 400 or 1200 IU/d; and (c) significantly higher polar stress and strain index at 3 months than infants given 400 or 1200 IU/d. There were no significant differences in total and trabecular bone or cortical bone BMD at 3 months.
- Ziegler et al⁶ compared infants given 400, 600, and 800 IU/d of vitamin D₃ from 2 to 9 months of age. Infants given 600 IU/d had: (a) significantly lower whole-body BMC at the end of winter (i.e., 5.5-9 months) than infants given 400 IU/d, and (b) significantly lower whole-body BMD at the end of winter than infants given 400 IU/d. There were also no

^{iv} A detailed description of the methodology used for grading the strength of the evidence is available on the NESR website: <https://nesr.usda.gov/2020-dietary-guidelines-advisory-committee-systematic-reviews> and in Part C of the following reference: Dietary Guidelines Advisory Committee. 2020. *Scientific Report of the 2020 Dietary Guidelines Advisory Committee: Advisory Report to the Secretary of Agriculture and the Secretary of Health and Human Services*. U.S. Department of Agriculture, Agricultural Research Service, Washington, DC.

^v Institute of Medicine. *Dietary Reference Intakes for Calcium and Vitamin D*. Washington, DC: The National Academies Press;2011. doi:10.17226/13050. 978-0-309-16394-1.

^{vi} Golden NH, Abrams SA. Optimizing bone health in children and adolescents. *Pediatrics*. 2014;134(4):e1229-1243. doi:10.1542/peds.2014-2173.

significant differences between infants given 800 IU/d and smaller dosages.

Gallo et al^{1,2} and Rosendahl et al⁵ did not report significant differences in bone mass between infants given different dosages of vitamin D:

- Gallo et al^{1,2} compared infants given 400, 800, 1200, and 1600 IU/d of vitamin D3 from 1 to 12 months of age. No significant differences were observed in: (a) femur, lumbar spine, and whole-body BMC at 3, 6, 9, and 12 months, (b) change in femur, lumbar spine, and whole-body BMC from 1 to 3, 3 to 6, 6 to 9, and 9 to 12 months, (c) lumbar spine and whole-body BMC 36 months, (d) change in lumbar spine and whole-body BMC from 12 to 36 and 1 to 36 months, and (e) lumbar spine and whole-body BMD and BMD z-score at 36 months. It is possible that the lack of statistical significance is related to power. Study authors calculated that 25 participants per group would be sufficient to detect a 5% difference in whole-body BMD, and at the 36-month outcome measure, the analytic groups had between 6 and 25 participants, depending on the assessment.
- Rosendahl et al⁵ compared infants given 400 and 1200 IU/d of vitamin D3 from 2 weeks to 24 months and reported no significant differences in total bone and cortical bone BMC, BMD, cross-sectional area, and polar moment of inertia at 24 months. It is unlikely that the lack of statistical significance was related to power. Study authors calculated that 210 participants per group would permit detection of 0.2 SD difference in BMC and 297 participants per group would permit detection of 0.2 SD difference in the cross-sectional area; analytic groups were larger than these estimations (N=343 and 361).

Given the small number of studies and the inconsistency in results, there is insufficient evidence to determine the relationship between 400 IU/d of vitamin D from supplements, compared with higher dosages of vitamin D from supplements, and bone mass.

Biomarkers of bone metabolism

The evidence had strong consistency. None of the studies found significant differences in biomarkers of bone metabolism between different dosages and durations of vitamin D supplementation.

Bone resorption biomarkers:

- Holmlund-Suila et al³ compared dosages of 400, 1200, and 1600 IU/d from 2 weeks to 3 months and found no significant differences in CTX at 3 months
- Ziegler et al⁶ compared 400, 600, and 800 IU/d from 2 to 9 months and found no significant differences in CTX at 4, 5.5, 7.5, and 9 months
- Gallo et al² compared dosages of 400, 800, 1200, and 1600 IU/d from 1 to 12 months and found no significant differences in CTX at 36 months

Bone formation biomarkers:

- Holmlund-Suila et al³ compared dosages of 400, 1200, and 1600 IU/d from 2 weeks to 3 months and found no significant differences in PINP 3 months
- Ziegler et al⁶ compared 400, 600, and 800 IU/d from 2 to 9 months and found no significant differences in ALP or osteocalcin at 4, 5.5, 7.5, and 9 months

Although the evidence had strong consistency, the analyses were heterogeneous. The studies assessed different biomarkers of bone formation (i.e., PINP, ALP, and osteocalcin). The studies assessed the same biomarker of bone resorption (i.e., CTX); however, it was assessed at different ages (3, 4, 5.5, 7.5, 9, and 36 months), in relation to different periods of supplementation

(2.5, 7, and 11 months), and during different phases of the study (within the supplementation period, at the end of the supplementation period, and 2 years after the supplementation period).

The evidence had limited precision; it is possible that the lack of statistical significance relates to insufficient statistical power. Two of the studies did not report power analyses,^{3,6} and the third study reported a power analysis related to BMD, but not CTX.²

The evidence has limited generalizability, as the participants in 2 of the 3 studies were predominantly² or entirely⁶ White (the third study did not report race or ethnicity).

There was a moderate likelihood that the design and conduct of the studies prevented or minimized bias. The evidence was from randomized controlled trials, which had some risks of bias that varied between studies ([Table 3](#)).

Given this synthesis of the evidence, limited evidence suggests there is no relationship between consumption of 400 IU/d of vitamin D from supplements in infants younger than 12 months of age, compared with higher dosages of up to 1600 IU/d, and biomarkers of bone metabolism followed up to 36 months of age.

Comparisons of 400 IU/d with lower dosages of vitamin D

One of the 5 studies compared 400 IU/d with a lower dosage. Ziegler et al⁶ compared infants given 400 or 200 IU/d of vitamin D3 from 2 to 9 months of age. There were no significant differences in whole-body BMC or BMD at the end of winter (i.e., 5.5-9 months). There were also no significant differences in alkaline phosphatase, osteocalcin, and CTX at 4, 5.5, 7.5, and 9 months.

This is insufficient evidence to determine the relationship between 400 IU/d of vitamin D from supplements, compared with lower dosages, and bone health.

Comparisons of 200 IU/d for different durations with a placebo

One of the 5 studies compared 200 IU for different durations (i.e., birth to 6 months and 2 to 6 months) with a placebo. Ponnappakkam et al⁴ found no significant differences in ALP at 2, 4, and 6 months, and no cases of rickets in any of the participants.

This is insufficient evidence to determine the relationship between vitamin D from supplements, compared with no vitamin D from supplements, and bone health.

Table 2. Evidence examining the relationship between vitamin D from supplements consumed during infancy and toddlerhood and bone health*

Article, Year Study design Country	Vitamin D from supplements intervention vs comparator†	Bone health outcomes	Significant findings	Nonsignificant findings	
Gallo 2013 ¹ RCT Canada	400 IU/d vitamin D3 from 1 mo to 12 mo vs 800 IU/d vitamin D3 from 1 mo to 12 mo vs 1200 IU/d vitamin D3 from 1 mo to 12 mo vs 1600 IU/d vitamin D3 from 1 mo to 12 mo	Lumbar spine			
		BMC (mean, g)			
		@ 3 mo (N=NR)		~3 for all groups; NS	
		@ 6 mo (N=NR)		~3.5 for all groups; NS	
		@ 9 mo (N=NR)		~4.5 for all groups; NS	
		@ 12 mo (N=NR)		~5.5 for all groups; NS	
		Change in BMC (mean, g/mo)			
		1 to 3 mo (N=NR)		~0.0-0.2 for all groups; NS	
		3 to 6 mo (N=NR)		~0.2 for all groups; NS	
		6 to 9 mo (N=NR)		~0.3 for all groups; NS	
		9 to 12 mo (N=NR)		~0.3 for all groups; NS	
		Femur			
		BMC (mean, g)			
		@ 3 mo (N=NR)		~4.5-5 for all groups; NS	
@ 6 mo (N=NR)		~6-7 for all groups; NS			
@ 9 mo (N=NR)		~7-9 for all groups; NS			
@ 12 mo (N=NR)		~9.5-11.5 for all groups; NS			
Change in BMC (mean, g/mo)					
1 to 3 mo (N=NR)		~0.5-0.7 for all groups; NS			
3 to 6 mo (N=NR)		~0.5 for all groups; NS			

Article, Year Study design Country	Vitamin D from supplements intervention vs comparator†	Bone health outcomes	Significant findings	Nonsignificant findings
		6 to 9 mo (N=NR)		~0.5-0.7 for all groups; NS
		9 to 12 mo (N=NR)		~0.5-1.3 for all groups; NS
		Whole-body		
		BMC (mean, g)		
		@ 3 mo (N=NR)		~130-140 for all groups; NS
		@ 6 mo (N=NR)		~160-180 for all groups; NS
		@ 9 mo (N=NR)		~200 for all groups; NS
		@ 12 mo (N=NR)		~230-250 for all groups; NS
		Change in BMC (mean, g/mo)		
		1 to 3 mo (N=NR)		~15-18 for all groups; NS
		3 to 6 mo (N=NR)		~12-15 for all groups; NS
		6 to 9 mo (N=NR)		~7-12 for all groups; NS
		9 to 12 mo (N=NR)		~7-12 for all groups; NS
Gallo 2016² RCT Canada	400 IU/d vitamin D3 from 1 mo to 12 mo vs 800 IU/d vitamin D3 from 1 mo to 12 mo vs 1200 IU/d vitamin D3 from 1 mo to 12 mo vs 1600 IU/d vitamin D3 from 1 mo to 12 mo	Lumbar spine, vertebrae L1–L4 BMC (mean [95% CI], g) @ 36 mo (N=25, 24, 25, 11)		11.5 [10.8, 12.2] vs 11.4 [10.8, 12.0] vs 11.8 [11.3, 12.3] vs 11.6 [10.3, 12.9]; p=0.865
		BMD (mean [95% CI], g/cm ²) @ 36 mo (N=25, 24, 25, 11)		0.474 [0.450, 0.500] vs 0.463 [0.445, 0.481] vs 0.479 [0.462, 0.496] vs 0.463 [0.429, 0.498]; p=0.655

Article, Year Study design Country	Vitamin D from supplements intervention vs comparator [†]	Bone health outcomes	Significant findings	Nonsignificant findings
		BMD Z-score (mean [95% CI]) @ 36 mo (N=25, 24, 25, 11)		0.46 [0.05, 0.97] vs 0.18 [-0.22, 0.59] vs 0.62 [0.25, 0.98] vs -0.18 [-0.56, 0.92]; p=0.457
		Change in BMC (mean [95% CI], g) from 12 to 36 mo (N=24, 24, 24, 11)		5.71 [4.96, 6.47] vs 5.74 [4.55, 6.93] vs 6.13 [5.61, 6.65] vs 5.89 [4.84, 6.95]; p=0.882
		from 1 to 36 mo (N=25, 24, 25, 11)		8.48 [7.82, 9.14] vs 8.83 [8.29, 9.37] vs 9.00 [8.36, 9.65] vs 8.62 [7.47, 9.76]; p=0.652
		Whole body BMC (mean [95% CI], g) @ 36 mo (N=24, 23, 25, 10)		600.6 [578.9, 622.3] vs 593.1 [575.4, 610.7] vs 593.1 [576.5, 609.6] vs 633.1 [591.5, 674.9]; p=0.110
		BMD (mean [95% CI], g/cm ²) @ 36 mo (N=24, 23, 25, 10)		0.622 [0.607, 0.637] vs 0.626 [0.611, 0.642] vs 0.618 [0.604, 0.633] vs 0.651 [0.615, 0.686]; p=0.133
		BMD Z-score (mean [95% CI]) @ 36 mo (N=24, 23, 25, 10)		2.00 [1.53, 2.47] vs 1.97 [1.58, 2.36] vs 1.83 [1.46, 2.19] vs 2.61 [1.63, 3.59]; p=0.245

Article, Year Study design Country	Vitamin D from supplements intervention vs comparator†	Bone health outcomes	Significant findings	Nonsignificant findings
		Change in BMC (mean [95% CI], g) from 12 to 36 mo (N=18, 21, 21, 6)		354.2 [329.8, 378.6] vs 362.10 [345.3, 378.9] vs 361.7 [346.0, 377.5] vs 388.7 [333.4, 444.1]; p=0.377
		from 1 to 36 mo (N=24, 23, 25, 10)		497.0 [474.6, 519.5] vs 496.6 [479.0, 514.2] vs 493.5 [475.3, 511.8] vs 534.0 [492.0, 576.0]; p=0.931
		Plasma C-terminal telopeptide of type I collagen (CTX) (mean [95% CI], ng/mL) @ 36 mo (N= NR)		1.13 [1.06–1.20]; NS
Holmlund- Suila 2012³ RCT Finland	400 IU/d vitamin D3 from 2 wk to 3 mo vs 1200 IU/d vitamin D3 from 2 wk to 3 mo vs 1600 IU/d vitamin D3 from 2 wk to 3 mo	Total and trabecular bone BMD (mean ± SE, mg/cm ³) @ 3 mo (N=25, 29, 28)		448 ± 13 vs 430 ± 12 vs 451 ± 12; p=0.387
		Cross sectional area (mean ± SE, mm ²) @ 3 mo (N=25, 29, 28)	72 ± 3 vs 77 ± 3 vs 81 ± 3*; p=0.069	
			Cross sectional area (mm ²) significantly higher in 1600 IU/d group than in 400 IU/d group (p=0.022)	
		Cortical bone BMD (mean ± SE, mg/cm ³) @ 3 mo (N=25, 29, 28)		724 ± 8 vs 716 ± 7 vs 726 ± 7; p=0.609

Article, Year Study design Country	Vitamin D from supplements intervention vs comparator†	Bone health outcomes	Significant findings	Nonsignificant findings
		Cross sectional area (mean ± SE, mm ²) @ 3 mo (N=25, 29, 28)	31 ± 1 vs 32 ± 1 vs 34 ± 1*; p=0.053 Cross sectional area (mm ²) significantly higher in 1600 IU/d group than 400 IU/d group (p=0.027) and 1200 IU/d group (p=0.050)	
		Polar stress and strain index (mean ± SE, mm ³) @ 3 mo (N=25, 29, 28)	48 ± 2 vs 48 ± 2 vs 54 ± 2*; p=0.070 Polar stress and strain index (mm ³) significantly higher in 1600 IU/d group than 400 IU/d group (p=0.043) and 1200 IU/d group (p=0.050)	
		Procollagen I N-terminal propeptide (PINP) (mean, µg/L) @ 3 mo (N=25, 29, 28)		2.2 vs 2.1 vs 2.0; p=0.992
		C-terminal cross-linked telopeptides of type I collagen (mean, µg/L) @ 3 mo (N=25, 29, 28)		1.4 vs 1.4 vs 1.3; p=0.757
Ponnapakkam 2010⁴ RCT United States	200 IU/d vitamin D3 from birth to 6 mo vs 200 IU/d vitamin D3 from 2 mo to 6 mo vs placebo from birth to 6 mo	Serum alkaline phosphatase (mean ± SE, IU/L) @ 2 mo (N=33)		~135 ± 15 vs ~137 ± 15 vs ~125 ± 10; NS
		@ 4 mo (N=22)		~137 ± 25 vs ~100 ± 10 vs ~120 ± 15; NS
		@ 6 mo (N=25)		~140 ± 20 vs ~100 ± 15 vs ~80 ± 10; NS

Article, Year Study design Country	Vitamin D from supplements intervention vs comparator†	Bone health outcomes	Significant findings	Nonsignificant findings
		Incidence of rickets @ 2 mo (N=NR)		No infants with rickets; NS
		@ 4 mo (N=NR)		No infants with rickets; NS
		@ 6 mo (N=NR)		No infants with rickets; NS
Rosendahl, 2018⁵ RCT Finland	400 IU/d vitamin D3 from 2 wk to 24 mo vs 1200 IU/d vitamin D3 from 2 wk to 24 mo	Total bone BMC (mean difference [95% CI], mg/mm) @ 24 mo (N=343, 361)		0.4 [-0.8, 1.6]; NS
		BMD (mean difference [95% CI], mg/cm ³) @ 24 mo (N=343, 361)	.	2.9 [-8.3, 14.2]; NS
		Cross sectional area (mean difference [95% CI], mm ²) @ 24 mo (N=343, 361)	.	-0.9 [-5.0, 3.2]; NS
		Polar moment of inertia (mean difference [95% CI], mm ⁴) @ 24 mo (N=343, 361)		-66.0 [-274.3, 142.3]; NS
		Cortical bone BMC (mean difference [95% CI], mg/mm) @ 24 mo (N=343, 361)		1.0 [-0.4, 2.4]; NS
		BMD (mean difference [95% CI], mg/cm ³) @ 24 mo (N=343, 361)	.	6.0 [-3.2, 15.2]; NS
		Cross sectional area (mean difference [95% CI], mm ²) @ 24 mo (N=343, 361)	.	1.0 [-0.4, 2.4]; NS
		Polar moment of inertia (mean difference [95% CI], mm ⁴) @ 24 mo (N=343, 361)		9.9 [-69.1, 88.9]; NS
Ziegler 2017⁶ RCT United States	200 IU/d vitamin D3 from 2 mo to 9 mo vs 400 IU/d vitamin D3 from 2 mo to 9 mo vs 600 IU/d vitamin D3 from 2 mo to 9 mo vs 800 IU/d vitamin D3 from 2 mo to 9 mo	Bone-specific alkaline phosphatase (mean ± SD, IU/L) @ 4 mo (N=46, 44, 42, 33)		167 ± 42 vs 188 ± 51 vs 168 ± 41 vs 194 ± 56 [‡] ; NS

Article, Year Study design Country	Vitamin D from supplements intervention vs comparator†	Bone health outcomes	Significant findings	Nonsignificant findings
		@ 5.5 mo (N=NR)		145 ± 40 vs 158 ± 41 vs 133 ± 33 vs 161 ± 42‡; NS
		@ 7.5 mo (N=NR)		123 ± 31 vs 140 ± 40 vs 122 ± 38 vs 159 ± 46‡; NS
		@ 9 mo (N=NR)		141 ± 52 vs 160 ± 68 vs 128 ± 40 vs 170 ± 49‡; NS
		Osteocalcin (mean ± SD, mcg/L)		
		@ 4 mo (N=46, 44, 42, 33)		16.8 ± 4 vs 17.4 ± 6.5 vs 18.7 ± 6.0 vs 16.8 ± 5.4; NS
		@ 5.5 mo (N=NR)		16.7 ± 4 vs 15.3 ± 6.3 vs 17.2 ± 5.6 vs 14.4 ± 4.3; NS
		@ 7.5 mo (N=NR)		19.7 ± 5 vs 18.5 ± 6.6 vs 20.5 ± 7.7 vs 17.0 ± 7.0; NS
		@ 9 mo (N=NR)		23.0 ± 6 vs 22.4 ± 6.8 vs 24.8 ± 6.7 vs 19.3 ± 8.4; NS
		C-terminal telopeptides (mean ± SD, mcg/L)		
		@ 4 mo (N=45, 43, 42, 30)		1.21 ± 0.30 vs 1.23 ± 0.26 vs 1.21 ± 0.36 vs 1.32 ± 0.31; NS

Article, Year Study design Country	Vitamin D from supplements intervention vs comparator†	Bone health outcomes	Significant findings	Nonsignificant findings
		@ 5.5 mo (N=NR)		1.16 ± 0.25 vs 1.15 ± 0.28 vs 1.20 ± 0.31 vs 1.21 ± 0.28; NS
		@ 7.5 mo (N=NR)		1.13 ± 0.27 vs 1.12 ± 0.27 vs 1.22 ± 0.39 vs 1.16 ± 0.37; NS
		@ 9 mo (N=NR)		1.25 ± 0.25 vs 1.18 ± 0.26 vs 1.30 ± 0.33 vs 1.13 ± 0.28; NS
		Whole-body BMC (mean ± SD, g) @ the end of winter (i.e., 5.5-9 mo) (N=17, 17, 14, 11)	168.5 ± 20.3 vs 184.7 ± 36.6 vs 166.6 ± 21.9* vs 171.2 ± 25.4; BMC (g) significantly lower in 600 IU/d group than 200 IU/d and 400 IU/d groups, p <0.05	
		in the subsample of infants who were 5.5 mo at the end of winter (N=6, 7, 8, 3)	159.4 ± 20.1 vs 161.9 ± 28.0 vs 157.6 ± 18.7* vs 144.7 ± 29.3; BMC (g) significantly lower in 600 IU/d group than 200 IU/d group, p<0.05	
		in the subsample of infants who were 7.5 mo at the end of winter (N=10, 4, 4, 4)		172.6 ± 20.4 vs 183.2 ± 16.5 vs 175.8 ± 26.1 vs 182.1 ± 10.3; NS
		in the subsample of infants who were 9 mo at the end of winter (N=1, 6, 2, 4)		181.3 ± NR vs 212.3 ± 39.5 vs 184.3 ± 12.1 vs 180.2 ± 22.7; NS

Article, Year Study design Country	Vitamin D from supplements intervention vs comparator†	Bone health outcomes	Significant findings	Nonsignificant findings
		Whole-body BMC (mean ± SD, g/kg) @ the end of winter (i.e., 5.5-9 mo) (N=17, 17, 14, 11)	22.37 ± 1.47 vs 22.56 ± 1.61 vs 21.02 ± 1.54* vs 22.00 ± 1.48; BMC (g/kg) significantly lower in 600 IU/d group than 200 IU/d and 400 IU/d groups, p <0.05	
		in the subsample of infants who were 5.5 mo at the end of winter (N=6, 7, 8, 3)	22.17 ± 1.58 vs 21.61 ± 1.50 vs 20.30 ± 1.47* vs 20.75 ± 1.19; BMC (g/kg) significantly lower in 600 IU/d group than 200 IU/d group, p<0.05	
		in the subsample of infants who were 7.5 mo at the end of winter (N=10, 4, 4, 4)		22.41 ± 1.53 vs 22.97 ± 0.62 vs 21.98 ± 1.39 vs 21.93 ± 1.65; NS
		in the subsample of infants who were 9 mo at the end of winter (N=1, 6, 2, 4)		23.17 ± NR vs 23.38 ± 1.77 vs 22.00 ± 0.13 vs 23.00 ± 0.867; NS
		Whole-body BMD (mean ± SD, g/cm ²) @ the end of winter (i.e., 5.5-9 mo) (N=17, 17, 14, 11)	0.2688 ± 0.0193 vs 0.2768 ± 0.0311 vs 0.2516 ± 0.0326* vs 0.2668 ± 0.021; BMD (g/cm ²) significantly lower in 600 IU/d group than 200 IU/d and 400 IU/d groups, p <0.05	
		in the subsample of infants who were 5.5 mo at the end of winter (N=6, 7, 8, 3)		0.2645 ± 0.0217 vs 0.2586 ± 0.0287 vs 0.2491 ± .0289 vs 0.2477 ± 0.0136; NS

Article, Year Study design Country	Vitamin D from supplements intervention vs comparator [†]	Bone health outcomes	Significant findings	Nonsignificant findings
		in the subsample of infants who were 7.5 mo at the end of winter (N=10, 4, 4, 4)		0.2709 ± 0.0196 vs 0.2847 ± 0.0177 vs 0.2475 ± 0.0489 vs 0.2732 ± 0.0180; NS
		in the subsample of infants who were 9.0 mo at the end of winter (N=1, 6, 2, 4)		0.2730 ± NR vs 0.2933 ± 0.0329 vs 0.2695 ± 0.0064 vs 0.2755 ± 0.0236; NS

* Abbreviations: BMC – bone mineral content, BMD – bone mineral density, CI – confidence interval, CTX – C terminal telopeptide of type I collagen, IU – International units, L1 – lumbar spine vertebra 1, L4 – lumbar spine vertebra 4, NR – not reported, NS – nonsignificant, PINP – procollagen I N-terminal propeptide, RCT – randomized controlled trial, SD – standard deviation, SE – standard error

[†] Interventions and comparators, from the articles included in the body of evidence, which compare vitamin D from supplements with different dosages of vitamin D from supplements or a placebo.

[‡] Study authors state “*Bone-specific alkaline phosphatase showed a very modest yet statistically significant (p<0.01) increase with the highest dose of VD (800 IU/day)*” however, the results reported in the table are not marked as statistically significant.

Table 3. Risk of bias for randomized controlled trials examining consumption of vitamin D from supplements during infancy and toddlerhood and bone health^{*†}

	Randomization	Identification of participants - randomization	Deviations from intended interventions	Missing outcome data	Outcome measurement	Selection of the reported result
Gallo, 2013 ¹	Low	Low	Low	Some Concerns	Low	Low
Gallo, 2016 ²	Low	Low	Some Concerns	Some Concerns	Low	Some Concerns
Holmlund-Suila, 2012 ³	Low	Low	Low	Low	Some Concerns	Low
Ponnapakkam, 2010 ⁴	High	High	High	High	High	High
Rosendahl, 2018 ⁵	Low	Low	Low	Low	Low	Low
Ziegler, 2017 ⁶	Some Concerns	Low	High	High	Low	High

* A detailed description of the methodology used for assessing risk of bias is available on the NESR website: <https://nesr.usda.gov/2020-dietary-guidelines-advisory-committee-systematic-reviews> and in Part C of the following reference: Dietary Guidelines Advisory Committee. 2020. *Scientific Report of the 2020 Dietary Guidelines Advisory Committee: Advisory Report to the Secretary of Agriculture and the Secretary of Health and Human Services*. U.S. Department of Agriculture, Agricultural Research Service, Washington, DC.

† Possible ratings of low, some concerns, or high determined using the "[Cochrane Risk-of-bias 2.0 \(RoB 2.0\)](#) (August 2016 version)" (Higgins JPT, Sterne JAC, Savović J, Page MJ, Hróbjartsson A, Boutron I, Reeves B, Eldridge S. A revised tool for assessing risk of bias in randomized trials In: Chandler J, McKenzie J, Boutron I, Welch V (editors). *Cochrane Methods. Cochrane Database of Systematic Reviews* 2016, Issue 10 (Suppl 1). dx.doi.org/10.1002/14651858.CD201601.)

Research recommendations

Investigate how much (if any) vitamin D supplementation is needed for bone health under the following circumstances:

- a) When the mother is taking high doses of vitamin D, and
- b) When the infant has short periods of sun exposure in certain latitudes.

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

Included articles

1. Gallo S, Comeau K, Vanstone C, et al. Effect of different dosages of oral vitamin D supplementation on vitamin D status in healthy, breastfed infants: a randomized trial. *JAMA*. 2013;309(17):1785-1792.doi: 10.1001/jama.2013.3404.
2. Gallo S, Hazell T, Vanstone CA, et al. Vitamin D supplementation in breastfed infants from Montreal, Canada: 25-hydroxyvitamin D and bone health effects from a follow-up study at 3 years of age. *Osteoporos Int*. 2016;27(8):2459-2466.doi: 10.1007/s00198-016-3549-z.
3. Holmlund-Suila E, Viljakainen H, Hytinantti T, Lamberg-Allardt C, Andersson S, Makitie O. High-dose vitamin d intervention in infants--effects on vitamin d status, calcium homeostasis, and bone strength. *J Clin Endocrinol Metab*. 2012;97(11):4139-4147.doi: 10.1210/jc.2012-1575.
4. Ponnappakkam T, Bradford E, Gensure R. A treatment trial of vitamin D supplementation in breast-fed infants: universal supplementation is not necessary for rickets prevention in Southern Louisiana. *Clin Pediatr (Phila)*. 2010;49(11):1053-1060.doi: 10.1177/0009922810376320.
5. Rosendahl J, Valkama S, Holmlund-Suila E, et al. Effect of Higher vs Standard Dosage of Vitamin D3 Supplementation on Bone Strength and Infection in Healthy Infants: A Randomized Clinical Trial. *JAMA Pediatr*. 2018;172(7):646-654.doi: 10.1001/jamapediatrics.2018.0602.
6. Ziegler EE, Koo WW, Nelson SE, Jeter JM. Lack of Effect of Graded Doses of Vitamin D on Bone Metabolism of Breastfed Infants. *J Clin Nutr Metab*. 2017;1(1).doi.

METHODOLOGY

The NESR team used its rigorous, protocol-driven methodology to support the 2020 Dietary Guidelines Advisory Committee in conducting this systematic review.

NESR's systematic review methodology involves:

- Developing a protocol,
- Searching for and selecting studies,
- Extracting data from and assessing the risk of bias of each included study,
- Synthesizing the evidence,
- Developing conclusion statements,
- Grading the evidence underlying the conclusion statements, and
- Recommending future research.

A detailed description of the methodology used in conducting this systematic review is available on the NESR website: <https://nesr.usda.gov/2020-dietary-guidelines-advisory-committee-systematic-reviews>, and can be found in the 2020 Dietary Guidelines Advisory Committee Report, Part C: Methodology.^{vii} This systematic review was peer reviewed by Federal scientists, and information about the peer review process can also be found in the Committee's Report, Part C. Methodology. Additional information about this systematic review, including a description of and rationale for any modifications made to the protocol can be found in the 2020 Dietary Guidelines Advisory Committee Report, Chapter 6. Nutrients from Dietary Supplements During Infancy and Toddlerhood.

Below are details of the final protocol for the systematic review described herein, including the:

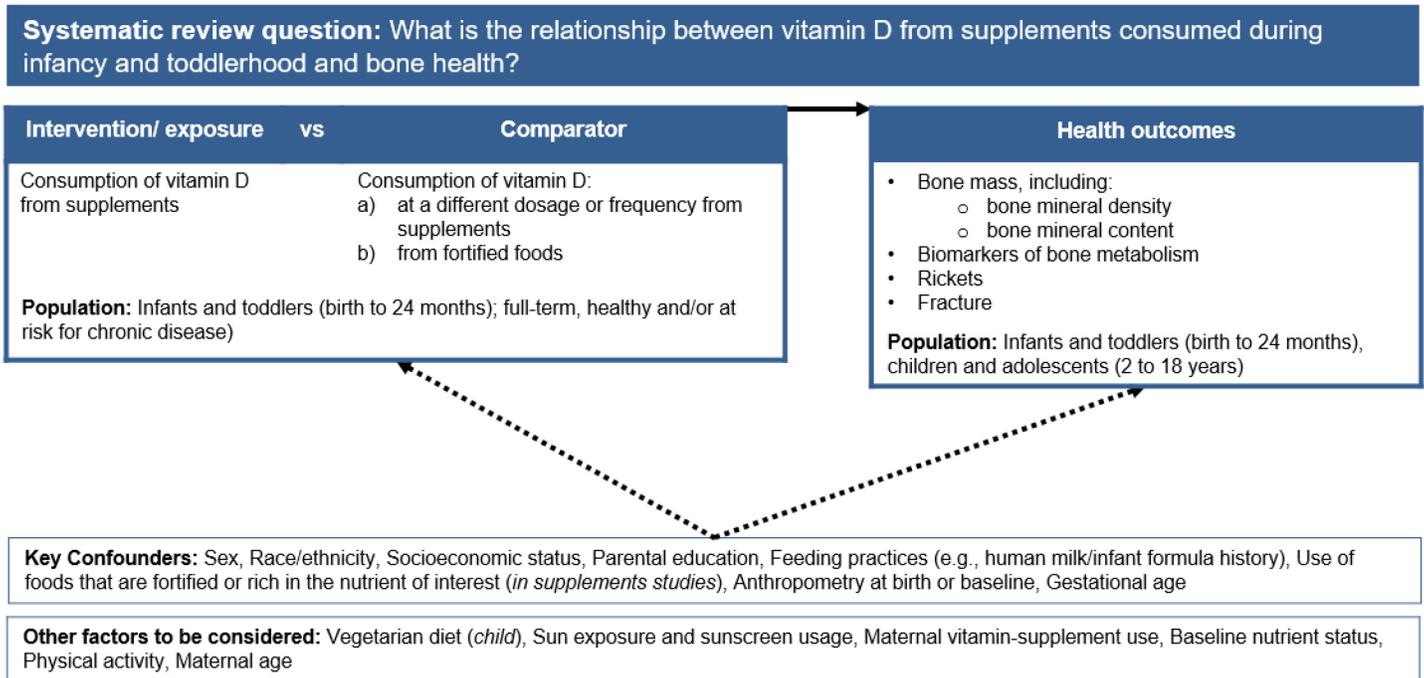
- Analytic framework
- Literature search and screening plan
- Literature search and screening results

^{vii} Dietary Guidelines Advisory Committee. 2020. *Scientific Report of the 2020 Dietary Guidelines Advisory Committee: Advisory Report to the Secretary of Agriculture and the Secretary of Health and Human Services*. U.S. Department of Agriculture, Agricultural Research Service, Washington, DC.

ANALYTIC FRAMEWORK

The analytic framework (**Figure 1**) illustrates the overall scope of the systematic review, including the population, the interventions and/or exposures, comparators, and outcomes of interest. It also includes definitions of key terms and identifies key confounders and other factors considered in the systematic review. The inclusion and exclusion criteria that follow provide additional information about how parts of the analytic framework were defined and operationalized for the review.

Figure 1: Analytic framework



Key definitions

- Dietary Supplement**— a product (other than tobacco) that: is intended to supplement the diet; contains one or more dietary ingredients (including vitamins; minerals; herbs or other botanicals; amino acids; and other substances) or their constituents; is intended to be taken by mouth as a pill, capsule, tablet, or liquid; and is labeled on the front panel as being a dietary supplement. (ODS, Dietary Supplement Health and Education Act, 1994)
- Fortification**— as defined by the U.S. Food and Drug Administration (FDA), the deliberate addition of one or more essential nutrients to a food, whether or not it is normally contained in the food. Fortification may be used to prevent or correct a demonstrated deficiency in the population or specific population groups; restore naturally occurring nutrients lost during processing, storage, or handling; or to add a nutrient to a food at the level found in a comparable traditional food. When cereal grains are labeled as enriched, it is mandatory that they be fortified with folic acid

Legend

- The relationship of interest in the systematic review
- Factors that may impact the relationship of interest in the systematic review

LITERATURE SEARCH AND SCREENING PLAN

Inclusion and exclusion criteria

This table provides the inclusion and exclusion criteria for the systematic review. The inclusion and exclusion criteria are a set of characteristics used to determine which articles identified in the literature search were included in or excluded from the systematic review.

Table 4. Inclusion and exclusion criteria

Category	Inclusion Criteria	Exclusion Criteria
Study design	<ul style="list-style-type: none"> • Randomized controlled trials • Non-randomized controlled trials, including quasi-experimental and controlled before and after studies • Prospective cohort studies • Retrospective cohort studies • Nested case-control studies 	<ul style="list-style-type: none"> • Uncontrolled trials • Case-control studies • Cross-sectional studies • Uncontrolled before-and-after studies • Narrative reviews • Systematic reviews • Meta-analyses
Intervention/exposure	<ul style="list-style-type: none"> • Studies that examine consumption of vitamin D from supplements • Studies that specify the dosage/amount of vitamin D received 	<ul style="list-style-type: none"> • Studies that do not specify the dosage/amount level of vitamin D received • Studies that vary nutrients other than vitamin D without controlling for that variation
Comparator	<ul style="list-style-type: none"> • Studies that compare consumption of vitamin D <ul style="list-style-type: none"> ○ at a different dosage or frequency from supplements ○ from fortified foods 	<ul style="list-style-type: none"> • N/A
Outcomes	<ul style="list-style-type: none"> • Bone mass, including: <ul style="list-style-type: none"> ○ bone mineral density ○ bone mineral content • Biomarkers of bone metabolism • Rickets • Fracture 	<ul style="list-style-type: none"> • N/A
Date of publication	<ul style="list-style-type: none"> • January 2000 – January 2020 	<ul style="list-style-type: none"> • Articles published prior to 2000

Category	Inclusion Criteria	Exclusion Criteria
Publication status	<ul style="list-style-type: none"> Articles that have been peer-reviewed 	<ul style="list-style-type: none"> Articles that have not been peer-reviewed and are not published in peer-reviewed journals (e.g., unpublished data, manuscripts, pre-prints, reports, abstracts, and conference proceedings)
Language of publication	<ul style="list-style-type: none"> Articles published in English 	<ul style="list-style-type: none"> Articles published in languages other than English
Country^{viii}	<ul style="list-style-type: none"> Studies conducted in countries ranked as high or higher human development 	<ul style="list-style-type: none"> Studies conducted in countries ranked as medium or lower human development
Study participants	<ul style="list-style-type: none"> Human participants Males Females 	Non-human participants (i.e., animals)
Age of study participants	<ul style="list-style-type: none"> Age at intervention or exposure: <ul style="list-style-type: none"> Infants and toddlers (0-24 months) Age at outcome: <ul style="list-style-type: none"> Infants and toddlers (0-24 months) Children and adolescents (2-18 years) 	<ul style="list-style-type: none"> Age at intervention or exposure: <ul style="list-style-type: none"> Children and adolescents (2-18 years) Adults (19 years and older) Age at outcome: <ul style="list-style-type: none"> Adults (19 years and older)

^{viii} The Human Development classification was based on the Human Development Index (HDI) ranking from the year the study intervention occurred or data were collected (UN Development Program. HDI 1990-2017 HDRO calculations based on data from UNDESA (2017a), UNESCO Institute for Statistics (2018), United Nations Statistics Division (2018b), World Bank (2018b), Barro and Lee (2016) and IMF (2018). Available from: <http://hdr.undp.org/en/data>). If the study did not report the year in which the intervention occurred or data were collected, the HDI classification for the year of publication was applied. HDI values are available from 1980, and then from 1990 to present. If a study was conducted prior to 1990, the HDI classification from 1990 was applied. If a study was conducted in 2018 or 2019, the most current HDI classification was applied. When a country was not included in the HDI ranking, the current country classification from the World Bank was used instead (The World Bank. World Bank country and lending groups. Available from: <https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-country-and-lending-groups>).

Category	Inclusion Criteria	Exclusion Criteria
Health status of study participants	<ul style="list-style-type: none"> • Studies that enroll participants who are healthy and/or at risk for chronic disease, including those with obesity • Studies that enroll some participants diagnosed with a disease or with rickets. • Studies that enroll infants born full-term (≥ 37 weeks and 0/7 days gestational age) 	<ul style="list-style-type: none"> • Studies that exclusively enroll participants diagnosed with a disease. (For this criterion, studies that exclusively enroll subjects with obesity were included.) • Studies that exclusively enroll participants with rickets (i.e., studies that aim to treat participants who have already been diagnosed with the outcome of interest) • Studies that exclusively enroll infants born preterm (gestational age < 37 weeks and 0/7 days), infants with low birth weight (< 2500g), and/or infants born small for gestational age
Source of Foods, Beverages, or Nutrients	<ul style="list-style-type: none"> • Vitamin D supplements (e.g., vitamin D drops) • Mother's own milk • Commercially prepared infant formula meeting FDA^{ix} and/or Codex Alimentarius^x international food standards (e.g., milk-based, soy, partially-hydrolyzed, extensive-hydrolyzed, amino-acid based) • Complementary foods/beverages 	<ul style="list-style-type: none"> • Donor or banked milk • Infant formulas that do not meet FDA and/or Codex Alimentarius standards

^{ix} U.S. Food and Drug Administration. Version 19 December 2013. Internet: <https://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/InfantFormula/ucm136118.htm#manufacture> (accessed March 23, 2018).

^x Food and Agriculture Organization of the United Nations. World Health Organization. Codex Alimentarius. International Food Standards. Standard for infant formula and formulas for special medical purposes intended for infants. Codex Stan 72-1981. 2007.

Electronic databases and search terms

PubMed

- Provider: U.S. National Library of Medicine
 - Date(s) Searched: January 13, 2020
 - Date range searched: January 1, 2000 – January 13, 2020
 - Search terms:
 - #1** - vitamin d[Mesh] OR vitamin d [tiab] OR vitamin d3[tiab] OR cholecalciferol[tiab] OR ergocalciferol*[tiab]
 - #2** - ("Bone Density"[Mesh] OR "bone density"[tiab] OR "Bone Development"[Mesh] OR "Bone Development"[tiab] OR osteogenesis[tiab] OR "Fractures, Bone"[Mesh] OR osteitis[tiab] OR bone turnover[tiab] OR bone loss[tiab] OR (bone[tiab] AND fracture*[tiab]) OR rickets [mesh] OR ricket*[tiab] OR bone mineral*[tiab] OR bone mass[tiab] OR bone health[tiab] OR bone demineral*[tiab]) OR ((bone[tiab] OR bones[tiab] OR "Bone and Bones"[Mesh] OR bone diseases[mh] OR bone development[Mesh]) AND (remodel*[tiab] OR form*[tiab] OR osteolysis[tiab] OR ossification[tiab] OR resorption[tiab] OR accretion[tiab] OR bmc[tiab] OR bmd[tiab] OR "Biomarkers"[Mesh] OR biomarker*[tiab]))
 - #3** - dietary supplements[Mesh] OR supplement*[tiab] OR drops[tiab] OR multivitamin*[tiab]
 - #4** - #1 AND #2 AND #3
 - #5** - #4 NOT ("Animals"[Mesh] NOT ("Animals"[Mesh] AND "Humans"[Mesh]))
 - #6** - #4 NOT (editorial[ptyp] OR comment[ptyp] OR news[ptyp] OR letter[ptyp] OR review[ptyp] OR systematic review[ptyp] OR systematic review[ti] OR meta-analysis[ptyp] OR meta-analysis[ti] OR meta-analyses[ti] OR retracted publication[ptyp] OR retraction of publication[ptyp] OR retraction of publication[tiab] OR retraction notice[ti])
- Publication Date Filters: Publication date from 2000/01/01 to 2020/01/13; English

Cochrane Central Register of Controlled Trials (CENTRAL)

- Provider: John Wiley & Sons
 - Date(s) Searched: January 13, 2020
 - Date range searched: January 1, 2000- January 13, 2020
 - Search terms:
 - #1** - "vitamin d" OR [mh "vitamin d"[mj]] OR "vitamin d3" OR cholecalciferol OR ergocalciferol*
 - #2** - ([mh "Bone Density"[mj]] OR "bone density" OR [mh "Bone Development"[mj]] OR "Bone Development" OR osteogenesis OR [mh "Fractures, Bone"[mj]] OR [mh "Bone Diseases"[mj]] OR osteitis OR "bone turnover" OR "bone loss" OR (bone AND fracture*) OR ricket* OR "bone mineral*" OR "bone mass" OR "bone health" OR "bone demineral*") OR ((bone OR bones) NEAR/5 (remodel* OR form* OR osteolysis OR ossification OR resorption OR accretion OR bmc OR bmd OR biomarker* OR [mh "Biological Markers"]):ti,ab,kw
 - #3** - [mh "dietary supplement"] OR supplement* OR drops OR multivitamin*
- Filters: Publication Year from 2000 to 2020, Trials

Embase

- Provider: Elsevier
- Date(s) Searched: January 13, 2020
- Date range searched: January 1, 2000 – January 13, 2020
- Search terms:

#1 - 'vitamin d'/exp/mj OR 'vitamin d*':ab,ti OR 'vitamin d3':ti,ab OR cholecalciferol:ab,ti OR ergocalciferol*:ab,ti

#2 - (((bone OR bones) NEAR/6 (remodel* OR form* OR osteolysis OR ossification OR resorption OR accretion OR bmc OR bmd OR biomarker*)):ab,ti) OR ((bone NEAR/6 fracture*):ab,ti) OR 'bone density':ab,ti OR 'bone development':ab,ti OR osteogenesis:ab,ti OR osteitis:ab,ti OR 'bone turnover':ab,ti OR 'bone loss':ab,ti OR ricket*:ab,ti OR 'bone mineral*':ab,ti OR 'bone mass':ab,ti OR 'bone health*':ab,ti OR 'bone demineral*':ab,ti OR 'bone density'/exp/mj OR 'bone development'/exp/mj OR 'fracture'/exp/mj OR 'bone disease'/exp/mj

#3 - 'dietary supplement'/exp OR supplement*:ti,ab OR drops:ti,ab OR multivitamin*:ti,ab OR 'multivitamin'/exp

#4 - #1 AND #2 AND #3

#5 - #4 AND ([article]/lim OR [article in press]/lim) AND [humans]/lim AND [english]/lim AND [2000-2020]/py NOT ([conference abstract]/lim OR [conference paper]/lim OR [editorial]/lim OR [erratum]/lim OR [letter]/lim OR [note]/lim OR [review]/lim OR [systematic review]/lim OR [meta analysis]/lim)

Cumulative Index to Nursing and Allied Health Literature (CINAHL Plus)

- Provider: Ebscohost
- Date(s) Searched: January 13, 2020
- Date range searched: January 1, 2000- January 13, 2020
- Search terms:

#1 - "vitamin d" OR "vitamin d3" OR (MH "vitamin d") OR cholecalciferol OR ergocalciferol*

#2 - (MH "Bone Density") OR "bone density" OR (MH "Bone Development") OR "Bone Development" OR osteogenesis OR (MH "Fractures, Bone") OR (MH "Bone Diseases") OR osteoporosis OR osteopenia OR osteitis OR "bone turnover" OR "bone loss" OR (bone AND fracture*) OR ricket* OR "bone mineral*" OR "bone mass" OR "bone health*" OR "bone demineral*" OR ((bone OR bones) N5 (remodel* OR form* OR osteolysis OR ossification OR resorption OR accretion OR bmc OR bmd OR biomarker*)) OR (bone* AND (MH "Biological Markers+"))

#3 - (MH "dietary supplements") OR supplement* OR drops OR multivitamin*

#4 - #1 AND #2 AND #3

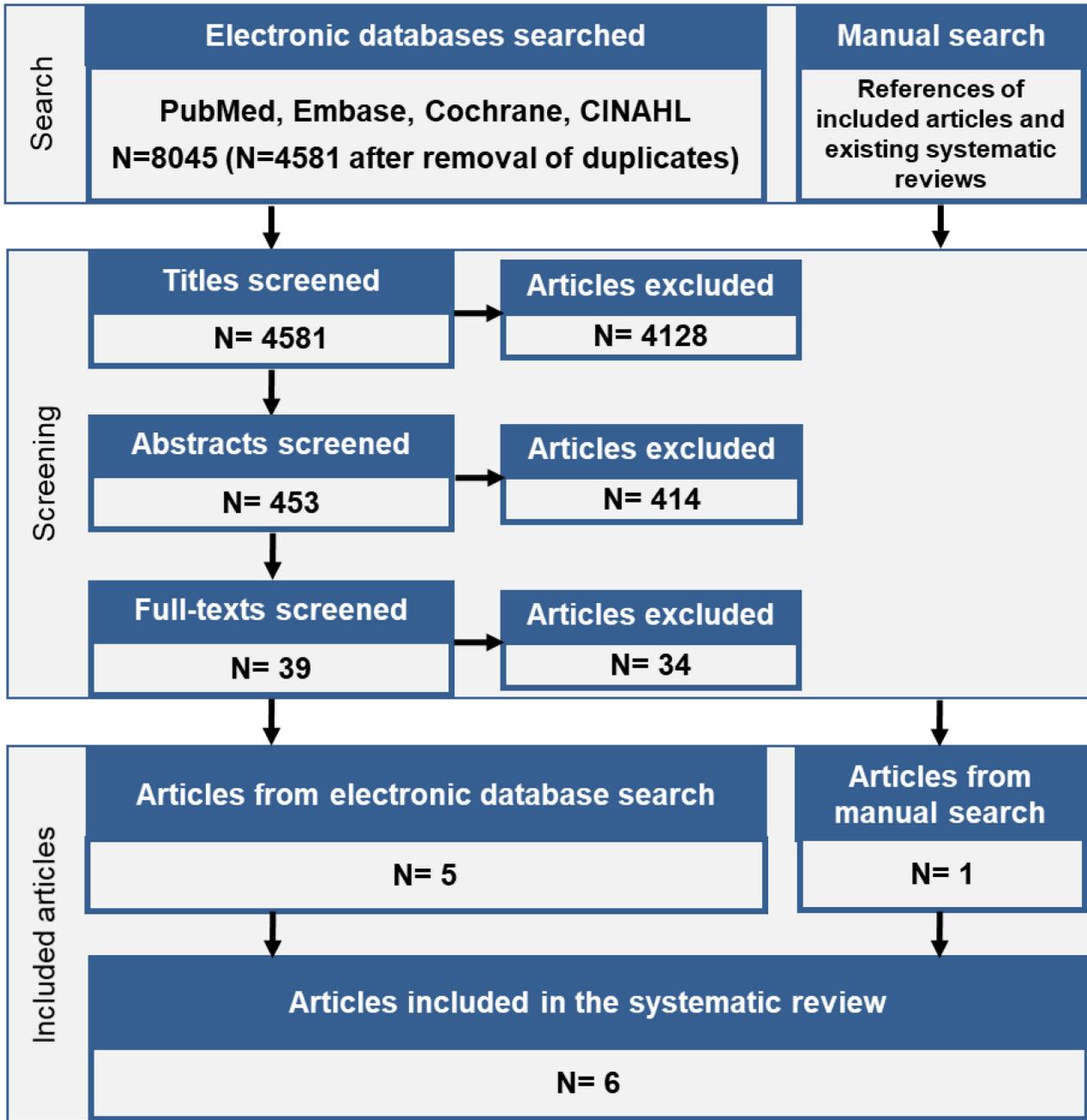
#5 - #4 NOT (MH "Literature Review" OR MH "Meta Analysis" OR MH "Systematic Review" OR MH "News" OR MH "Retracted Publication" OR MH "Retraction of Publication")

Filters: Published Date: 20000101 to 20200113, English, Human

LITERATURE SEARCH AND SCREENING RESULTS

The flow chart (**Figure 2**) below illustrates the literature search and screening results for articles examining the systematic review question. The results of the electronic database searches, after removal of duplicates, were screened independently by two NESR analysts using a step-wise process by reviewing titles, abstracts, and full-texts to determine which articles met the inclusion criteria. Refer to [Table 5](#) for the rationale for exclusion for each excluded full-text article. A manual search was done to find articles that were not identified when searching the electronic databases; all manually identified articles are also screened to determine whether they met criteria for inclusion.

Figure 2: Flow chart of literature search and screening results



Excluded articles

Table 5. Articles excluded after full text screening with rationale for exclusion

The table below lists the articles excluded after full-text screening. At least one reason for exclusion is provided for each article, which may not reflect all possible reasons for exclusion. Information about articles excluded after title and abstract screening is available upon request.

Full texts screened	Rationale for exclusion
1 Abrams, S. A., Hawthorne, K. M., Rogers, S. P., Hicks, P. D., Carpenter, T. O. (2012). Effects of ethnicity and vitamin D supplementation on vitamin D status and changes in bone mineral content in infants <i>BMC Pediatr</i> , 12, 6	Intervention/exposure vs comparator
2 Bagnoli, F., Casucci, M., Toti, S., Cecchi, S., Iurato, C., Coriolani, G., Tiezzi, M., Vispi, L. (2013). Is vitamin D supplementation necessary in healthy full-term breastfed infants? A follow-up study of bone mineralization in healthy full-term infants with and without supplemental vitamin D <i>Minerva Pediatr</i> , 65(3), 253-60	Study design
3 Bly, E., Huntington, J., Harper, A. L., Vincent, E. C. (2013). What is the best age to start vitamin D supplementation to prevent rickets in breastfed newborns? <i>Journal of Family Practice</i> , 62(12), 755+763	Study design
4 Czech-Kowalska, J., Pludowski, P., Dobrzanska, A., Kryskiewicz, E., Karczmarewicz, E., Gruszczyńska, D., Pleskaczynska, A., Golkowska, M. (2012). Impact of vitamin D supplementation on markers of bone mineral metabolism in term infants <i>Bone</i> , 51(4), 781-6	Intervention/exposure vs comparator
5 Gallo, S., Rodd, C., Vanstone, C., Agellon, S., L'Abbe, M., Khamessan, A., Weiler, H. (2011). Lumbar spine bone mineral density is enhanced in breast fed infants receiving 800 or 1200 IU of vitamin d daily from 4 to 20 weeks of age <i>Journal of bone and mineral research</i> , 26	Publication status
6 Hazell, T. J., Gallo, S., Vanstone, C. A., Agellon, S., Rodd, C., Weiler, H. A. (2017). Vitamin D supplementation trial in infancy: body composition effects at 3 years of age in a prospective follow-up study from Montréal <i>Pediatric obesity</i> , 12(1), 38-47	Outcome
7 Jackson, R. D., LaCroix, A. Z., Gass, M., Wallace, R. B., Robbins, J., Lewis, C. E., Bassford, T., Beresford, S. A. A., Black, H. R., Blanchette, P., Bonds, D. E., Brunner, R. L., Brzyski, R. G., Caan, B., Cauley, J. A., Chlebowski, R. T., Cummings, S. R., Granek, I., Hays, J., Heiss, G. (2006). Calcium plus vitamin D supplementation and the risk of fractures [corrected] [published erratum appears in <i>N ENGL J MED</i> 2006 Mar 9;354(10):1102] <i>New England Journal of Medicine</i> , 354(7), 669-683	Participant age
8 Jin, J. (2018). Vitamin D and Calcium Supplements for Preventing Fractures <i>Jama</i> , 319(15), 1630	Publication status
9 Jorde, R., Stunes, A. K., Kubiak, J., Joakimsen, R., Grimnes, G., Thorsby, P. M., Syversen, U. (2019). Effects of vitamin D supplementation on bone turnover markers and other bone-related substances in subjects with vitamin D deficiency <i>Bone</i> , 124, 7-13	Participant age

Full texts screened	Rationale for exclusion
10 Jorde, R., Strand Hutchinson, M., Kjærgaard, M., Sneve, M., Grimnes, G. (2013). Supplementation with high doses of vitamin D to subjects without vitamin D deficiency may have negative effects: Pooled data from four intervention trials in Tromsø ISRN Endocrinology, 1(1)	Study design
11 Kim, M. J., Na, B., No, S. J., Han, H. S., Jeong, E. H., Lee, W., Han, Y., Hyeun, T. (2010). Nutritional status of vitamin D and the effect of vitamin D supplementation in Korean breast-fed infants J Korean Med Sci, 25(1), 83-9	Intervention/exposure vs comparator
12 LeFevre, M. K. (2010). Rickets: A Preventable Growth Delay Journal of Pediatric Healthcare, 24(6), 408-412	Publication status, Participant health
13 McAllister, J. C., Lane, A. T., Buckingham, B. A. (2006). Vitamin D deficiency in the San Francisco Bay Area J Pediatr Endocrinol Metab, 19(3), 205-8	Study design
14 Morandi, G., Maines, E., Piona, C., Monti, E., Sandri, M., Gaudino, R., Boner, A., Antoniazzi, F. (2015). Significant association among growing pains, vitamin D supplementation, and bone mineral status: results from a pilot cohort study J Bone Miner Metab, 33(2), 201-6	Participant age
15 Mutlu, G. Y., Kusdal, Y., Ozsu, E., Cizmecioglu, F. M., Hatun, S. (2011). Prevention of Vitamin D deficiency in infancy: daily 400 IU vitamin D is sufficient Int J Pediatr Endocrinol, 2011(1), 4	Intervention/exposure vs comparator, Outcome
16 Ponnappakkam, T., Bradford, E., Gensure, R. (2010). Vitamin D supplementation in breastfed infants: results of a prospective trial in the southern United States Journal of bone and mineral research., 25, S232	Publication status
17 Ponnappakkam, T., Bradford, E., Gensure, R. (2010). A treatment trial of vitamin d supplementation in breast-fed infants: Universal supplementation is not necessary for rickets preventio in southern louisiana Clinical Pediatrics, 49(11), 1053-1060	Duplicate
18 Rangarajan, R., Mondal, S., Thankachan, P., Chakrabarti, R., Kurpad, A. V. (2018). Assessing bone mineral changes in response to vitamin D supplementation using natural variability in stable isotopes of Calcium in Urine Sci Rep, 8(1), 16751	Participant age
19 Rooze, S., Mathieu, F., Claus, W., Yangzom, T., Yangzom, D., Goyens, P., de Maertelaer, V. (2016). Effect of calcium and vitamin D on growth, rickets and Kashin-Beck disease in 0- to 5-year-old children in a rural area of central Tibet Trop Med Int Health, 21(6), 768-75	Intervention/exposure vs comparator
20 Savino, F., Viola, S., Tarasco, V., Lupica, M. M., Castagno, E., Oggero, R., Miniero, R. (2011). Bone mineral status in breast-fed infants: influence of vitamin D supplementation Eur J Clin Nutr, 65(3), 335-9	Study design
21 Sen, S., Penfield-Cyr, A., Hollis, B. W., Wagner, C. L. (2017). Maternal Obesity, 25-Hydroxy Vitamin D Concentration, and Bone Density in Breastfeeding Dyads J Pediatr, 187, 147-152.e1	Intervention/exposure vs comparator
22 Shaikh, U., Alpert, P. T. (2006). Nutritional rickets in Las Vegas, Nevada J Pediatr Endocrinol Metab, 19(3), 209-12	Study design
23 Thorisdottir, B., Gunnarsdottir, I., Steingrimsdottir, L., Palsson, G. I., Thorsdottir, I. (2014). Vitamin D intake and status in 12-month-old infants at 63-66° N Nutrients, 6(3), 1182-1193	Study design

Full texts screened	Rationale for exclusion
24 Torjesen, I. (2018). Vitamin D supplements do not protect bone health, analysis finds <i>Bmj</i> , 363, k4223	Publication status
25 Valkama, S., Holmlund-Suila, E., Enlund-Cerullo, M., Rosendahl, J., Hauta-Alus, H., Helve, O., Hytinantti, T., Viljakainen, H., Andersson, S., Makitie, O. (2017). No Severe Hypercalcemia with Daily Vitamin D3 Supplementation of up to 30 microg during the First Year of Life <i>Horm Res Paediatr</i> , 88(2), 147-154	Outcome
26 Valkama, S., Holmlund-Suila, E., Enlund-Cerullo, M., Rosendahl, J., Hauta-Alus, H., Helve, O., Hytinantti, T., Viljakainen, H., Andersson, S., Makitie, O. (2017). No Severe Hypercalcemia with Daily Vitamin D3 Supplementation of up to 30 µg during the First Year of Life <i>Hormone research in paediatrics</i> , 88(2), 147-154	Duplicate
27 van den Hooven, E. H., Heppe, D. H., Kieft-de Jong, J. C., Medina-Gomez, C., Moll, H. A., Hofman, A., Jaddoe, V. W., Rivadeneira, F., Franco, O. H. (2015). Infant dietary patterns and bone mass in childhood: the Generation R Study <i>Osteoporos Int</i> , 26(5), 1595-604	Intervention/exposure vs comparator
28 Viljakainen, H. T., Korhonen, T., Hytinantti, T., Laitinen, E. K., Andersson, S., Makitie, O., Lamberg-Allardt, C. (2011). Maternal vitamin D status affects bone growth in early childhood--a prospective cohort study <i>Osteoporos Int</i> , 22(3), 883-91	Intervention/exposure vs comparator
29 Viljakainen, H. T., Korhonen, T., Hytinantti, T., Laitinen, E. K. A., Andersson, S., Makitie, O., Lamberg-Allardt, C. (2011). Maternal vitamin D status affects bone growth in early childhood-a prospective cohort study <i>Osteoporosis International</i> , 22(3), 883-891	Duplicate
30 Wicklow, B., Gallo, S., Majnemer, A., Vanstone, C., Comeau, K., Jones, G., L'Abbe, M., Khamessian, A., Sharma, A., Weiler, H., Rodd, C. (2016). Impact of Vitamin D Supplementation on Gross Motor Development of Healthy Term Infants: A Randomized Dose-Response Trial <i>Phys Occup Ther Pediatr</i> , 36(3), 330-42	Outcome
31 (2012). Boning up on calcium and vitamin D. Do you need supplements to preserve your bone health? <i>Johns Hopkins Med Lett Health After 50</i> , 24(9), 1-2	Publication status
32 (2006). Calcium and vitamin D supplements <i>Med Lett Drugs Ther</i> , 48(1240), 61	Study design
33 (2006). Calcium + vitamin D offers small bone improvements. But these supplements do not significantly reduce the risk of fractures <i>Health News</i> , 12(5), 6-7	Publication status
34 (2011). How much vitamin D do you need? <i>Johns Hopkins Med Lett Health After 50</i> , 23(2), 7	Publication status