

Clinical Question:

A 31-year-old G2P2 woman with a history of well-controlled hypothyroidism delivered a healthy full-term newborn via uncomplicated vaginal delivery during my OB/GYN rotation. During her postpartum stay, she was counseled on infant feeding options but remained unsure whether to exclusively breastfeed for the first 6 months or use formula or mixed feeding. She specifically asked which feeding method would better reduce the risk of infections and improve developmental outcomes during infancy.

PICO Question:

In newborns, does exclusive breastfeeding for the first 6 months compared to formula feeding or mixed feeding reduce infections and improve developmental outcomes?

PICO Search Terms

P	I	C	O
Newborns	Exclusive Breastfeeding	Formula Feeding	Infections
Infants	Breastfeeding for 6 months	Mixed Feeding	Developmental Outcomes
Full-term Infants		Formula Only Feeding	Cognitive Development
Neonates		Partial Breastfeeding	Infant Morbidity
			Immunity

Search tools and strategy used:

Database	Search Terms Used	Filters/Limiters Applied	# of Results
Cochrane	(Newborn) AND (Exclusive Breastfeeding) OR (Mixed Feeding) AND (Infections)	English, Interventions, Pregnancy & Childbirth, Lactation, Duration of breastfeeding	2
Pubmed	(Infants) AND (exclusive breastfeeding) AND (morbidity OR infection) OR (formula feeding)	In the last 5 years, Free full text, Full text, Meta-Analysis, Randomized Controlled Trial, Review, Systematic Review, English, Humans, Child: birth-18 years, MEDLINE	432
Google Scholar	(Infants or Newborns) AND (exclusive breastfeeding) AND (formula OR "mixed feeding) AND (Cognitive development)	Review articles, English language, published within the last 10 years, sorted by relevance	39
Trip Database	(Infant) AND (Exclusive Breastfeeding) OR (Mixed Feeding) AND (Immunity)	In the last 5 years, Primary research, ongoing systemic reviews, systemic reviews, guidelines	7

Articles were selected using a structured search across multiple databases, including Cochrane, PubMed, Google Scholar, and TRIP, with search terms based on the PICO question focusing on exclusive breastfeeding, infections, and developmental outcomes. I prioritized higher-level evidence such as systematic reviews and meta-analyses when available, and then included well-designed cohort studies to support areas where higher-level evidence was limited. Filters such as recent publication dates, human studies, and relevant age groups were used to narrow down results and improve relevance.

One of the main challenges during the search was finding studies that directly addressed the entire PICO question. Most of the available literature focused on either infection outcomes or developmental outcomes, but not both together, which made it necessary to piece together evidence from different types of studies. It was also difficult to find recent systematic reviews that specifically compared exclusive breastfeeding to formula or mixed feeding (and if there were, the studies are still ongoing). In addition, randomized controlled trials in this area are limited due to ethical concerns, which means a lot of the evidence is observational and comes with potential confounding. Because of this, the final selection reflects a balance between using the highest level of evidence available and choosing studies that were still relevant and applicable to the clinical question. Although one article falls outside the typical 10-year range, it was included because it represents the highest level of evidence available on this topic and remains foundational in guiding current clinical recommendations.

Articles Chosen

Article 1	Optimal duration of exclusive breastfeeding
Citation	Kramer, M. S., & Kakuma, R. (2012). Optimal duration of exclusive breastfeeding. The Cochrane database of systematic reviews, 2012(8), CD003517. https://doi.org/10.1002/14651858.CD003517.pub2
Abstract	<p>Background: Although the health benefits of breastfeeding are widely acknowledged, opinions and recommendations are strongly divided on the optimal duration of exclusive breastfeeding. Since 2001, the World Health Organization has recommended exclusive breastfeeding for six months. Much of the recent debate in developed countries has centred on the micronutrient adequacy, as well as the existence and magnitude of health benefits, of this practice.</p> <p>Objectives: To assess the effects on child health, growth, and development, and on maternal health, of exclusive breastfeeding for six months versus exclusive breastfeeding for three to four months with mixed breastfeeding (introduction of complementary liquid or solid foods with continued breastfeeding) thereafter through six months.</p> <p>Search methods: We searched The Cochrane Library (2011, Issue 6), MEDLINE (1 January 2007 to 14 June 2011), EMBASE (1 January 2007 to 14 June 2011), CINAHL (1 January 2007 to 14 June 2011), BIOSIS (1 January 2007 to 14 June 2011), African Index Medicus (searched 15 June 2011), Index Medicus for the WHO Eastern Mediterranean Region (IMEMR) (searched 15 June 2011), LILACS (Latin American and Caribbean Health Sciences) (searched 15 June 2011). We also contacted experts in the field. The search for the first version of the review in 2000 yielded a total of 2668 unique citations. Contacts with experts in the field yielded additional published and unpublished studies. The updated literature review in December 2006 yielded 835 additional unique citations.</p> <p>Selection criteria: We selected all internally-controlled clinical trials and observational studies comparing child or maternal health outcomes with exclusive breastfeeding for six or more months versus exclusive breastfeeding for at least three to four months with continued mixed breastfeeding until at least six months. Studies were stratified according to study design (controlled trials versus observational studies), provenance (developing versus developed countries), and timing of compared</p>

	<p>feeding groups (three to seven months versus later).</p> <p>Main results: We identified 23 independent studies meeting the selection criteria: 11 from developing countries (two of which were controlled trials in Honduras) and 12 from developed countries (all observational studies). Definitions of exclusive breastfeeding varied considerably across studies. Neither the trials nor the observational studies suggest that infants who continue to be exclusively breastfed for six months show deficits in weight or length gain, although larger sample sizes would be required to rule out modest differences in risk of undernutrition. In developing-country settings where newborn iron stores may be suboptimal, the evidence suggests that exclusive breastfeeding without iron supplementation through six months may compromise hematologic status. Based on the Belarusian study, six months of exclusive breastfeeding confers no benefit (versus three months of exclusive breastfeeding followed by continued partial breastfeeding through six months) on height, weight, body mass index, dental caries, cognitive ability, or behaviour at 6.5 years of age. Based on studies from Belarus, Iran, and Nigeria, however, infants who continue exclusive breastfeeding for six months or more appear to have a significantly reduced risk of gastrointestinal and (in the Iranian and Nigerian studies) respiratory infection. No significant reduction in risk of atopic eczema, asthma, or other atopic outcomes has been demonstrated in studies from Finland, Australia, and Belarus. Data from the two Honduran trials and from observational studies from Bangladesh and Senegal suggest that exclusive breastfeeding through six months is associated with delayed resumption of menses and, in the Honduran trials, more rapid postpartum weight loss in the mother.</p> <p>Authors' conclusions: Infants who are exclusively breastfed for six months experience less morbidity from gastrointestinal infection than those who are partially breastfed as of three or four months, and no deficits have been demonstrated in growth among infants from either developing or developed countries who are exclusively breastfed for six months or longer. Moreover, the mothers of such infants have more prolonged lactational amenorrhea. Although infants should still be managed individually so that insufficient growth or other adverse outcomes are not ignored and appropriate interventions are provided, the available evidence demonstrates no apparent risks in recommending, as a general policy, exclusive breastfeeding for the first six months of life in both developing and developed-country settings.</p>
<p>Why I chose this article</p>	<p>I chose the Cochrane systematic review by Kramer and Kakuma (2012) because it directly addresses my PICO question by comparing exclusive breastfeeding for six months versus shorter durations with mixed feeding, while evaluating key outcomes such as infections, growth, and development. This article represents a high level of evidence, as it synthesizes findings from multiple studies, including both controlled trials and observational data, allowing for a broader and more comprehensive understanding of the topic. It was particularly useful because it examines both short-term outcomes, like gastrointestinal and respiratory infections, and longer-term developmental measures, which aligns well with my focus on both morbidity and developmental outcomes. Additionally, the inclusion of studies from both developed and developing countries increases the generalizability of the findings. Although the review is somewhat older (2012) and includes variability in how exclusive breastfeeding was defined across studies, I still selected it because of its strong methodology and its direct relevance to the clinical question, providing a solid evidence-based foundation for my analysis.</p>
<p>Link</p>	<p>https://www-cochranelibrary-com.york.ezproxy.cuny.edu/cdsr/doi/10.1002/14651858.CD003517.pub2/full?highlightAbstract=duration%7Cbreastfeed%7Coptimal%7Cof%7Coptim%7Cexclusive%7Cexclus%7Cbreastfeeding%7Cexclusiv%7Cdurat</p>

Article 2	Exclusive Breastfeeding and Childhood Morbidity: A Narrative Review
Citation	Hossain, S., & Miharshahi, S. (2022). Exclusive Breastfeeding and Childhood Morbidity: A Narrative Review. <i>International journal of environmental research and public health</i> , 19(22), 14804. https://doi.org/10.3390/ijerph192214804
Abstract	<p>Background: Globally, diarrheal diseases and acute respiratory infections are the leading causes of morbidity and mortality in children under 5 years old. The benefits of exclusive breastfeeding in reducing the risk of gastrointestinal and respiratory infections are well documented. Optimal breastfeeding may potentially save the lives of about 800,000 children in low-income settings. Despite the evidence, around 63% of infants from birth to 6 months are not exclusively breastfed worldwide.</p> <p>Methods: We searched the literature published between 2010 and 2022 in Medline, Embase, and Scopus on the association between exclusive breastfeeding and infectious diseases. We selected and reviewed 70 relevant studies.</p> <p>Results: Our findings expand and confirm the positive association between exclusive breastfeeding and reduced risk of a number of gastrointestinal, respiratory, and other infections in 60 out of 70 studies observed in both low- and high-income settings. Several studies analyzing exclusive breastfeeding duration reported that a longer exclusive breastfeeding duration is protective against many infectious diseases. This review also reported a lack of standardized definition for measuring exclusive breastfeeding in many studies.</p> <p>Conclusions: Overall, the results highlight the benefits of exclusive breastfeeding in many studies and suggest reporting exclusive breastfeeding in future studies using a consistent definition to enable better monitoring of exclusive breastfeeding rates.</p>
Why I chose this article	I chose the narrative review by Hossain and Miharshahi (2022) because it directly supports my PICO question by examining the relationship between exclusive breastfeeding and childhood morbidity, particularly infections such as diarrhea and acute respiratory illnesses. This article was useful because it includes a large body of more recent literature (2010–2022), reviewing 70 studies across both low- and high-income settings, which strengthens the relevance and applicability of the findings to current clinical practice. It aligns well with my outcomes of interest, as the review consistently demonstrates that exclusive breastfeeding is associated with a reduced risk of gastrointestinal and respiratory infections, which are key components of my PICO. I also selected this article because it highlights trends across multiple study designs, giving a broad overview of existing evidence rather than focusing on a single population. While it is a narrative review rather than a systematic review or meta-analysis and includes variability in definitions of exclusive breastfeeding, it still provides valuable, up-to-date context and reinforces the overall evidence supporting exclusive breastfeeding for reducing childhood infections.
Link	https://pmc.ncbi.nlm.nih.gov/articles/PMC9691199/

Article 3	Exclusive Breastfeeding, the Early-life Microbiome and Immune Response, and Common Childhood Respiratory Illnesses
Citation	Rosas-Salazar, C., Shilts, M. H., Tang, Z. Z., Hong, Q., Turi, K. N., Snyder, B. M., Wiggins, D. A., Lynch, C. E., Gebretsadik, T., Peebles, R. S., Jr, Anderson, L. J., Das, S. R., & Hartert, T. V. (2022). Exclusive breast-feeding, the early-life microbiome and immune response, and common childhood respiratory illnesses. <i>The Journal of allergy and clinical immunology</i> , 150(3), 612–621.

	https://doi.org/10.1016/j.jaci.2022.02.023
Abstract	<p>Background: The impact of breastfeeding on certain childhood respiratory illnesses remains controversial.</p> <p>Objective: To examine the effect of exclusive breastfeeding on the early-life upper respiratory tract (URT) and gut microbiome, the URT immune response in infancy, and the risk of common pediatric respiratory diseases.</p> <p>Methods: We analyzed data from a birth cohort of healthy infants with prospective ascertainment of breastfeeding patterns and common pediatric pulmonary and atopic outcomes. In a subset of infants, we also characterized the URT and gut microbiome using 16S ribosomal RNA sequencing and measured 9 URT cytokines using magnetic bead-based assays.</p> <p>Results: Of the 1,949 infants enrolled, 1,495 (76.71%) had 4-year data. In adjusted analyses, exclusive breastfeeding 1) had an inverse dose-response on the α-diversity of the early-life URT and gut microbiome, 2) was positively associated with the URT levels of IFN-α, IFN-γ, and IL-17A in infancy, and 3) had a protective dose-response on the development of a lower respiratory tract infection (LRTI) in infancy, 4-year current asthma, and 4-year ever allergic rhinitis (AR) (OR [95% CI] for each 4 weeks of exclusive breastfeeding = 0.95 [0.91–0.99], 0.95 [0.90–0.99], and 0.95 [0.92–0.99], respectively). In exploratory analyses, we also found that the protective association of exclusive breastfeeding on 4-year current asthma was mediated through its impact in the gut microbiome (p=0.03).</p> <p>Conclusions: Our results support a protective causal role of exclusive breastfeeding on the risk of developing an LRTI in infancy and asthma and AR in childhood. They also shed light on potential mechanisms of these associations, including the effect of exclusive breastfeeding on the gut microbiome.</p>
Why I chose this article	<p>I selected this prospective cohort study because it directly addresses my PICO question by examining how exclusive breastfeeding influences respiratory infections and longer-term respiratory outcomes in children. This article was particularly useful because it follows a large birth cohort (n=1,949) over time, allowing for stronger conclusions about associations and potential causal relationships compared to cross-sectional studies. The findings showed a clear dose-response relationship, where longer durations of exclusive breastfeeding were associated with lower risks of lower respiratory tract infections in infancy, as well as reduced odds of asthma and allergic rhinitis later in childhood. Additionally, I chose this study because it goes beyond just clinical outcomes and explores underlying mechanisms, demonstrating that exclusive breastfeeding influences the infant gut and respiratory microbiome and enhances antiviral immune responses. This adds depth to my PICO by not only showing that breastfeeding reduces infections, but also explaining how it may biologically contribute to improved immune and respiratory health. While the study is observational and cannot fully eliminate confounding, its large sample size, longitudinal design, and adjustment for multiple variables strengthen the reliability of its conclusions and make it a strong piece of evidence for my analysis.</p>
Link	https://pmc.ncbi.nlm.nih.gov/articles/PMC9463089/

Article 4	Association of Breastfeeding and Child IQ Score at Age 5 Years
Citation	Plunkett, B. A., Mele, L., Casey, B. M., Varner, M. W., Sorokin, Y., Reddy, U. M., Wapner, R. J., Thorp, J. M., Jr, Saade, G. R., Tita, A. T. N., Rouse, D. J., Sibai, B., Mercer, B. M., Tolosa, J. E., Caritis, S. N., & for the Eunice Kennedy Shriver National Institute of Child Health and Human

	Development (NICHD) Maternal-Fetal Medicine Units (MFMU) Network (2021). Association of Breastfeeding and Child IQ Score at Age 5 Years. <i>Obstetrics and gynecology</i> , 137(4), 561–570. https://doi.org/10.1097/AOG.0000000000004314
Abstract	<p>Objective: To evaluate whether breastfeeding and its duration are associated with a reduced risk of low IQ scores or other neurodevelopmental problems.</p> <p>Methods: We conducted a secondary analysis of two parallel multicenter, double-blinded randomized controlled trials in which participants with a singleton pregnancy and either subclinical hypothyroidism or hypothyroxinemia were treated with thyroxine or placebo. Our primary outcome was a low IQ score (less than 85 on the WPPSI-III [Wechsler Preschool and Primary Scale of Intelligence III] at age 5 years). Secondary outcomes included performance measures on other validated neurodevelopmental tests. Univariable and multivariable analyses were performed to evaluate the association between breastfeeding and neurodevelopmental outcomes. Stepwise backward proceeding linear and logistic regression models were used to develop the final adjusted models.</p> <p>Results: Of the 772 participants studied, 614 (80%) reported breastfeeding. Of these, 31% reported breastfeeding for less than 4 months, 19% for 4-6 months, 11% for 7-9 months, 15% for 10-12 months and 23% for more than 12 months. IQ scores were available for 756 children; mean age-5 scores were higher with any breastfeeding (96.7±15.1) than without (91.2±15.0, mean difference 5.5, 95% CI 2.8-8.2), and low IQ scores were less frequent with any breastfeeding (21.5%) than with no breastfeeding (36.2%, odds ratio 0.48, 95% CI 0.33-0.71). In adjusted analyses, breastfeeding remained associated with reduced odds of low IQ score (adjusted odds ratio [aOR] 0.62, 95% CI 0.41-0.93), and each additional month of breastfeeding was associated with lower odds of a low IQ scores (aOR 0.97, 95% CI 0.939-0.996). No significant associations between breastfeeding and other neurodevelopmental outcomes were identified in adjusted analyses.</p> <p>Conclusion: Breastfeeding and its duration are associated with lower odds of low IQ score at age 5 years.</p>
Why I chose this article	I selected this study because it directly evaluates the relationship between breastfeeding and cognitive outcomes, which aligns with the developmental component of my PICO question. This article stood out because it uses data from large, multicenter randomized controlled trials and applies a secondary analysis, allowing for a more rigorous and structured dataset compared to many observational studies. The findings showed that children who were breastfed had higher mean IQ scores at age 5 and lower odds of having a low IQ score (< 85), with a clear association between longer breastfeeding duration and reduced risk. Additionally, breastfeeding remained associated with decreased odds of low IQ even after adjusting for multiple confounding variables, which strengthens the validity of the findings. I also found it valuable that the study explored a dose-response relationship, where each additional month of breastfeeding was linked to a small but significant reduction in the risk of lower IQ scores. While this is still an observational analysis and cannot fully establish causation, the large sample size, longitudinal follow-up, and use of standardized neurodevelopmental assessments make it a strong and relevant piece of evidence to support the developmental outcomes aspect of my PICO question.
Link	https://pubmed.ncbi.nlm.nih.gov/33706345/

Summary of the Evidence

Author (Date)	Level of Evidence	Sample/Setting (# of subjects/studies, cohort definition etc.)	Outcome(s) studied	Key Findings	Limitations & Biases
Kramer MS, Kakuma R (2012)	Cochrane Systematic Review	<p>23 independent studies meeting selection criteria: 11 from developing countries (including 2 controlled trials from Honduras) and 12 from developed countries (all observational studies)</p> <p>- Databases searched: Cochrane Library, MEDLINE, EMBASE, CINAHL, BIOSIS, African Index Medicus, LILACS, and other databases through June 2011</p> <p>- Population: healthy term infants and their mothers</p> <p>- Studies stratified by design (RCTs vs. observational), provenance (developing vs. developed countries), and timing of feeding groups</p>	<p>- Compared exclusive breastfeeding for 6 months vs. exclusive breastfeeding for 3-4 months + mixed feeding</p> <p>- Primary outcome: Child health, growth, and development</p> <p>- Specific outcomes: Weight and length gain, gastrointestinal infection, respiratory infection, atopic eczema/asthma, cognitive ability, behavior, dental caries, iron/hematologic status, lactational amenorrhea, postpartum weight loss</p>	<p>- Infections: Infants exclusively breastfed for 6 months had significantly reduced risk of gastrointestinal infection compared to those partially breastfed at 3-4 months</p> <p>- Respiratory infection risk also reduced (in some populations)</p> <p>- Growth: No deficits in weight or length gain demonstrated in either developing or developed countries</p> <p>- No significant long-term differences in: cognition, obesity, allergies</p> <p>- Development: No benefit of 6 months vs. 3 months exclusive breastfeeding on cognitive ability or behavior at 6.5 years (Belarusian study).</p> <p>- Maternal benefits: Prolonged lactational amenorrhea and more rapid postpartum weight loss with 6 months exclusive breastfeeding</p>	<p>- Exclusive breastfeeding defined inconsistently across studies, limiting comparability</p> <p>- Only 2 RCTs (both from Honduras), while the remaining 21 studies were observational with inherent confounding</p> <p>- Most developed-country evidence from observational studies only</p> <p>- Variability in definitions of “exclusive breastfeeding” across studies</p> <p>- In developing countries with suboptimal newborn iron stores, exclusive breastfeeding without iron supplementation may compromise hematologic status</p> <p>- Some studies had small sample sizes and methodological limitations</p> <p>- Potential bias from reverse causality (healthier infants more likely to continue breastfeeding)</p> <p>- Limited data on long-term developmental outcomes</p> <p>- Publication date: 2012 (outside 10-year window, but remains the foundational Cochrane review on this topic)</p>

<p>Hossain S, Mirshahi S. (2022)</p>	<p>Narrative Review</p>	<ul style="list-style-type: none"> - Literature review of 70 studies published between 2010–2022 - Databases searched: Medline, Embase, and Scopus - Studies from both low-income and high-income country settings - Focused on infants & children under 5 years 	<ul style="list-style-type: none"> - Gastrointestinal infections (diarrhea) - Respiratory infections (acute respiratory infections, pneumonia) - Other infections (otitis media, urinary tract infections) - Association between exclusive breastfeeding and infectious disease morbidity 	<ul style="list-style-type: none"> - 60 out of 70 studies (86%) confirmed a positive association between exclusive breastfeeding and reduced risk of gastrointestinal, respiratory, and other infections - Longer duration of exclusive breastfeeding → greater protection against infections - Protective effect seen in both low- and high-income countries 	<ul style="list-style-type: none"> - Narrative review (not systematic) – less rigorous methodology than systematic reviews - Lack of standardized definition for measuring exclusive breastfeeding across included studies - Potential for selection bias - Reliance on observational studies with inherent confounding (socioeconomic status, maternal education, healthcare access)
<p>Rosas-Salazar C, Shilts MH, Tang ZZ, et al. (2022)</p>	<p>Prospective Cohort Study</p>	<ul style="list-style-type: none"> - 1,949 healthy infants enrolled at birth; 1,495 (76.7%) had 4-year follow-up data - Birth cohort study conducted in the United States - Subset of infants had URT and gut microbiome characterized using 16S rRNA sequencing → For some babies, they analyzed the bacteria in their nose/throat and gut using a lab method that identifies bacteria - 9 URT cytokines measured using magnetic bead-based assays → They measured 9 immune system proteins (cytokines) 	<p>Primary outcomes:</p> <ul style="list-style-type: none"> - Lower respiratory tract infection (LRTI) in infancy - 4-year current asthma - 4-year ever allergic rhinitis <p>Mechanistic outcomes:</p> <ul style="list-style-type: none"> - URT and gut microbiome α-diversity → Microbiome composition - URT cytokine levels (IFN-α, IFN-γ, IL-17A, and others) → immune response 	<ul style="list-style-type: none"> - Exclusive breastfeeding showed a protective dose-response effect ↓ risk of: <ul style="list-style-type: none"> - LRTI in infancy - Asthma at 4 years - Allergic rhinitis - Each additional 4 weeks of exclusive breastfeeding ↓ risk ~5% - Exclusive breastfeeding had inverse dose-response on α-diversity of URT and gut microbiome - Exclusive breastfeeding positively associated with URT levels of IFN-α, IFN-γ, and IL-17A - Protective association on 4-year asthma was mediated through gut microbiome impact 	<ul style="list-style-type: none"> - Cannot establish causation despite prospective design, so residual confounding is possible - 23% loss to follow-up (1,949 enrolled → 1,495 with 4-year data) may introduce selection bias - Microbiome and cytokine analyses performed on subset of participants, limiting generalizability of mechanistic findings - Breastfeeding patterns and some outcomes were self-reported - Limited data on type of formula and introduction of solid foods

		in the airway to see how the immune system responds			
Plunkett BA, Mele L, Casey BM, et al. (2021)	Prospective cohort design within RCT framework	<ul style="list-style-type: none"> - Secondary analysis of 2 multicenter randomized controlled trials conducted across 33 U.S. hospitals - 772 mother-infant pairs → Breastfeeding: 614 (80%) → No breastfeeding: 158 - Followed up with neurodevelopmental testing up to age 5 - Breastfeeding duration: 31% 4 months, 19% 4-6 months, 11% 7-9 months, 15% 10-12 months, 23% >12 months 	<p>Primary outcome:</p> <ul style="list-style-type: none"> - Low IQ score (defined as 85 on the WPPSI-III [Wechsler Preschool and Primary Scale of Intelligence III]) at age 5 years <p>Secondary outcomes:</p> <ul style="list-style-type: none"> - Performance measures on other validated neurodevelopmental tests → Cognitive development (DAS-II, Bayley III) → Behavioral outcomes (ADHD, CBCL scores) 	<p>IQ scores:</p> <ul style="list-style-type: none"> - Mean age-5 IQ scores were higher with any breastfeeding than without → mean difference 5.5 points <p>Low IQ prevalence:</p> <ul style="list-style-type: none"> - Less frequent with any breastfeeding vs. no breastfeeding <p>Adjusted analysis:</p> <p>Breastfeeding remained associated with reduced odds of low IQ</p> <ul style="list-style-type: none"> - Each additional month of breastfeeding is associated with lower odds of low IQ (~3% per month) - Higher mean IQ scores in breastfed children 	<ul style="list-style-type: none"> - Observational analysis → cannot prove causation - Breastfeeding data based on self-report (recall bias) - Some participants had thyroid abnormalities (subclinical hypothyroidism or hypothyroxinemia), which may limit generalizability to healthy populations - Despite multivariable adjustment, residual confounding possible (e.g., maternal IQ not directly measured) - Cognitive outcome measured only at age 5 years; no long-term follow-up

Conclusions

1. Kramer & Kakuma (2012) concluded that exclusive breastfeeding for 6 months, compared to exclusive breastfeeding for 3-4 months with continued mixed feeding, significantly reduces the risk of gastrointestinal infections without demonstrating any deficits in infant growth. This Cochrane systematic review of 23 studies found that while infection-related benefits were clear, no significant differences in cognitive ability or behavior were observed at 6.5 years between the two feeding durations. The authors supported exclusive breastfeeding for 6 months as a general policy recommendation.
2. Hossain & Mirhshahi (2022) concluded that the majority of evidence (60 out of 70 studies, or 86%) confirms a positive association between exclusive breastfeeding and reduced risk of gastrointestinal, respiratory, and other infections in children under 5 years. This narrative review emphasized that protective effects were observed across both low- and high-income settings, and that optimal breastfeeding practices could potentially save approximately 800,000 children's lives annually in low-income countries.
3. Rosas-Salazar et al. (2022) concluded that exclusive breastfeeding demonstrates a dose-response protective effect against lower respiratory tract infections in infancy, as well as asthma and allergic rhinitis at 4 years of age. Uniquely, this US-based prospective cohort study identified that these protective associations are mediated through the gut microbiome and enhanced upper respiratory tract immune responses (including increased IFN- α ,

IFN- γ , and IL-17A levels), providing mechanistic evidence for how breastfeeding confers immunological benefits.

4. Plunkett et al. (2021) concluded that breastfeeding is associated with higher IQ scores and reduced odds of low IQ (score <85) at age 5 years, with a dose-response relationship where each additional month of breastfeeding further reduced the odds of low IQ. In this US-based multicenter study, breastfed children had mean IQ scores 5.5 points higher than non-breastfed children, and the association remained significant after adjusting for confounders.

Taken together, these four articles provide consistent, multi-level evidence supporting the benefits of exclusive breastfeeding for the first 6 months of life in reducing infections and modestly improving developmental outcomes. Collectively, the findings demonstrate that exclusive breastfeeding reduces gastrointestinal and respiratory infections through immunological mechanisms involving the microbiome and cytokine responses, while also having cognitive benefits with dose-response relationships. While some studies are observational and subject to confounding, the consistency of findings across multiple high-quality studies strengthens the conclusion that exclusive breastfeeding provides meaningful health benefits in early life.

Clinical Bottom Line:

Weight of the evidence:

The overall weight of the evidence supports the use of exclusive breastfeeding for the first 6 months to reduce infections and improve developmental outcomes. The strongest evidence in this review comes from the Cochrane systematic review by Kramer and Kakuma, which provides high-level evidence demonstrating a clear reduction in gastrointestinal infections without adverse effects on growth. It synthesized 23 studies including 2 RCTs and formed the foundation of my conclusions. The main weakness here is that it is from 2012, but this is the same review that informed the WHO's 6-month exclusive breastfeeding recommendation, so it carries a lot of weight. The two US-based prospective cohort studies (Rosas-Salazar et al. and Plunkett et al.) strengthen the evidence base with recent data (2021-2022) and substantial sample sizes (approximately 2,000 and 772 participants, respectively). The prospective cohort study by Rosas-Salazar et al. demonstrated a dose-response relationship, as well as how it works biologically through immune and microbiome mechanisms. Plunkett et al. supports the developmental component of the PICO question, demonstrating an association between breastfeeding and reduced odds of low IQ at age 5, although causation cannot be established due to its observational design. Finally, the Hossain & Miharshahi narrative review (Level V) is methodologically the weakest article due to its non-systematic approach and potential selection bias. However, its inclusion is justified by its comprehensive synthesis of 70 recent studies, 86% of which demonstrated protective effects of exclusive breastfeeding against infections. This consistency across a large body of literature adds value despite the lower evidence level.

Magnitude of any effects:

The magnitude of effects observed across studies was modest but consistent. For infection-related outcomes, the Rosas-Salazar study demonstrated that each 4 weeks of exclusive breastfeeding reduced odds of lower respiratory tract infections by approximately 5% (OR 0.95, 95% CI 0.91–0.99). To put this in perspective, over a full 6 months of exclusive breastfeeding, this translates to approximately 20-25% reduced odds, which is a more substantial cumulative effect. The same dose-response pattern was observed for 4-year current asthma (OR 0.95, 95% CI 0.90–0.99) and 4-year allergic rhinitis (OR 0.95, 95% CI 0.92–0.99), suggesting that the protective effects extend beyond infancy into early childhood. The Kramer & Kakuma systematic review reported "significantly reduced" gastrointestinal infection risk in infants exclusively breastfed for 6 months compared to those partially breastfed at 3-4 months, based on studies from Belarus, Iran, and Nigeria. The Hossain & Miharshahi review, while not providing pooled effect estimates due to its narrative design, noted that protective effects were observed across the majority of 70 included studies, with some individual studies reporting risk reductions of 50% or greater for specific infections.

For cognitive outcomes, the Plunkett study found that breastfed children scored an average of 5.5 IQ points higher than non-breastfed children (96.7 ± 15.1 vs. 91.2 ± 15.0 ; 95% CI for difference: 2.8 - 8.2). Perhaps more clinically meaningful, the prevalence of low IQ (score < 85) was substantially lower among breastfed infants (21.5%) compared to

non-breastfed infants (36.2%). After adjustment for potential confounders including maternal education, race/ethnicity, and socioeconomic factors, breastfeeding remained significantly associated with reduced odds of low IQ (adjusted OR 0.62, 95% CI 0.41–0.93). The dose-response relationship showed that each additional month of breastfeeding was associated with 3% lower odds of low IQ.

One important caveat to note is that the Kramer & Kakuma systematic review found no significant difference in cognitive ability or behavior at 6.5 years between infants exclusively breastfed for 6 months versus 3-4 months with continued mixed feeding. This suggests that while breastfeeding versus no breastfeeding may confer cognitive benefits, the incremental benefit of extending exclusive breastfeeding from 3-4 months to 6 months specifically for cognitive outcomes may be limited. This is an important nuance when counseling patients.

Clinical Significance:

Clinically, these findings are highly relevant and support current recommendations promoting exclusive breastfeeding as a first-line preventive health strategy. While a 5% reduction in infection risk per month may appear modest at the individual level, the cumulative effect over 6 months and across populations is substantial. Breastfeeding is a low-cost, widely accessible intervention with minimal risk, and its ability to reduce infection rates can decrease healthcare utilization, including clinic visits and hospital admissions. The Hossain & Mirshahi review highlights its global impact, estimating that optimal breastfeeding practices could prevent approximately 800,000 child deaths annually in low-income countries. Additionally, findings from Rosas-Salazar et al. extend the clinical significance beyond infancy by demonstrating protection not only against acute infections but also chronic conditions such as asthma and allergic rhinitis.

The dose-response relationships observed in both infection and cognitive outcomes have important implications for patient counseling in practice. These findings suggest that even partial breastfeeding or shorter durations still provide benefits compared to no breastfeeding. This is particularly relevant given that many mothers face barriers to exclusive breastfeeding for the full 6 months, including work demands, medical issues, or personal circumstances. Rather than presenting breastfeeding as an all-or-nothing recommendation, clinicians can encourage any amount of breastfeeding while still supporting the goal of exclusive breastfeeding when feasible. In clinical practice, these findings support the role of healthcare providers in actively counseling and encouraging exclusive breastfeeding during prenatal and postpartum care. This includes addressing common barriers such as maternal concerns, lack of support, and workplace limitations, as well as providing resources such as lactation support services. However, it is also important to recognize that breastfeeding may not be feasible for all patients, and recommendations should be individualized in a nonjudgmental and supportive manner.

Other considerations important in weighing this evidence to guide practice

Although the available evidence supports exclusive breastfeeding for reducing infections and improving developmental outcomes, several limitations should be considered when applying these findings to practice. Much of the evidence is observational, which introduces potential confounding factors such as maternal education, socioeconomic status, and home environment that may independently influence both breastfeeding practices and child outcomes. No randomized controlled trials directly comparing exclusive breastfeeding to formula feeding exist, nor would such trials be ethical given current recommendations. Additionally, definitions of “exclusive breastfeeding” varied across studies, complicating direct comparisons. While evidence for infection reduction is robust, cognitive outcome data remains somewhat mixed, as the Kramer and Kakuma review found no significant cognitive differences at 6.5 years between 6-month and 3-month exclusive breastfeeding groups. Future research would benefit from larger US-based cohorts with extended follow-up, standardized definitions of exclusive breastfeeding, improved control for confounders such as maternal IQ and home environment, and investigation of which subgroups derive the greatest benefit (e.g., preterm infants, infants with family history of atopy).

