Spring 2016

A Systematic Review: Effects of Breastfeeding on Early and Late Childhood

Kara Campbell
University of Akron, kfc6@zips.uakron.edu

Samantha Fritz
University of Akron, skf14@zips.uakron.edu

A Systematic Review: Effects of Breastfeeding on Early and Late Childhood

Kara Campbell and Samantha Fritz

The University of Akron

Author Note

Kara Campbell and Samantha Fritz, College of Health Professions, School of Nursing, University of Akron. This paper is in fulfillment for the Honors Research Project, due May 2016. Sponsor: Dr. Enlow: DNP, RNC-OB

Abstract

The topic of the long-term impact of breast milk and formula milk composition on the health status of children continues to be a focus of discussion and research. The aim of this systematic review is to describe and critically appraise current evidence regarding the lasting effects of breastfeeding on health outcomes in children throughout early and late childhood. Twenty-one studies focusing on infant feeding were identified using PubMed, CINAHL, and Medline databases. These studies were then categorized according to health outcomes such as: weight, developmental, and immune system effects. Through a critical appraisal of this evidence, it was found that children who were breastfed had improved outcomes compared to those who were formula fed. From these results, recommendations were made in regards to nurses promoting breastfeeding within the clinical setting, which will be further discussed within the systematic review.

Each year, roughly 3,999,400 infants are born in the United States (Martin, Hamilton, Ventura, Osterman, Wilson, & Mathews, 2011). One decision that new mothers must make is whether or not to breastfeed their newborn children. According to the World Health Organization, "breastfeeding" is defined as: the natural way of providing infants with vitamins and nutrients for growth and development (World Health Organization [WHO], 2015). This process involves a mother utilizing her own breast milk to feed her child. Some mothers must choose formula feeding due to certain medical conditions or social situations that may render them incapable of breastfeeding. However, many pregnant women and new mothers who are capable of breastfeeding, may be unaware of the sum of benefits and risks associated with breastfeeding versus formula feeding their newborns. In fact, these mothers, and even some nurses, may not know that breastfeeding during the first year of life is associated with promoting health during childhood and far into adulthood (Yarnoff, Allaire, & Detzel, 2013). This lack of knowledge has a vital relevance to nursing because nurses are one of the healthcare providers of pregnant women, as well as new mothers, and have the potential to greatly affect the education and final decisions about whether or not to breastfeed their newborns. Nurses can make a difference and increase the number of women who have knowledge on the issue so that more individuals are making educated decisions regarding the feeding of their newborns. Nursing interventions and patient education are crucial responsibilities of nurses. This systematic review allows nurses to use evidence to support these educational opportunities about the long-term effects of breastfeeding.

Researchers consistently find countless positive outcomes of exclusive breastfeeding. Currently, gaps exist in the state of science and evidence based practice

related to breastfeeding, especially in regards to the effects of breastfeeding in late childhood and adolescence. Therefore, the aim of this systematic review is to identify, describe, and critically appraise the evidence about breastfeeding on health outcomes in children and adolescents. The PICOT question for this review is as follows: What evidence is available addressing the effect of breastfeeding compared with formula feeding on health outcomes on health outcomes of children from birth through adulthood (the age of eighteen)? Although the benefits of breastfeeding may extend lifelong, this systematic review is focusing solely on the effects that present until the end of late childhood, or within the first eighteen years of life.

Methods

Study Selection/Identification of Studies

The criteria for the selection of studies for this systematic review include accurate and valid research studies regarding the effects of breastfeeding compared with formula feeding. In this case, these studies included any that examined the effect of breastfeeding compared with formula feeding on health outcomes throughout the first eighteen years of life. The subject of the studies were women who gave birth and were given the choice to breastfeed or formula feed, with the decision not being altered by any health issues preventing the individuals from being able to make the decision. In some studies, the women themselves are the subjects. A variety of studies were analyzed and described, excluding any discrimination among race, gender, religion, social class, etc.

Databases were used in the search for these primary sources. Once studies were found, further evaluation was completed in order to determine the quality of the studies. The specific Databases used were CINAHL, Medline, and PubMed. Key words used to

search for articles included words such as “effects of breastfeeding,” “effects of formula feeding,” “breastfeeding versus formula feeding,” “breastfeeding,” “formula feeding,” “health status,” etc. These words were used in multiple forms and phrases in attempts of widening the window of related articles found. Each of these key words was also mixed and changed in order to increase the pool of related articles found. These terms brought results from a variety of categories including diabetes, weight gain, obesity, disease, brain structure, cognitive development, gut maturation, primary teeth lead level, necrotizing enterocolitis, nasopharyngeal microbial communities and effects on lymphocyte subsets, which will be further explained within this systematic review. Additional inclusion criteria were that the studies needed to be published within the past 5 years, written in English, and demonstrated internal validity.

Quality Assessment

It is also crucial that the studies define variables, are absent of bias, and controlled for extraneous variables. Studies were excluded if the examined health effects were experienced after the 18th year of life. Any negative effects of breastfeeding were also included in the review, but there were far more studies found showing positive outcomes of breastfeeding when analyzing the studies.

Review of Literature

Researchers have investigated the effects of breast milk on varied health outcomes and most have identified positive outcomes (Noughabi, Tehrani, Foroushani, Nayeri, & Baheiraei, 2014). The literature review is structured by categorizing studies based on types of study and outcomes. After the prevalence of breastfeeding and factors

associated with breastfeeding are discussed, studies are divided into three general collections: weight and size effects, cognitive development effects, and immunity effects.

Prevalence of Breastfeeding and Factors Affected by Breastfeeding

Many researchers have studied breastfeeding. Noughabi and colleagues (2014) conducted a cross-sectional study of 538 children aged 6-24 months old and examined the prevalence of breastfeeding exclusively within the first six months of life, including the influential factors on the decision to breastfeed or formula feed (2014). These researchers found that the best form of nutrition for the first six months of life for an infant is exclusive breastfeeding. This study also found that women who did not receive support for breastfeeding and received a biased education of feeding options were less likely to breastfeed their infants. Other factors were investigated by Marinelli and colleagues who conducted a neonatal intensive care unit single-center pre-post prospective cohort study, which explored donor daily enteral intake volume, maternal and infant demographics, and infant clinical data (Marinelli , Lussier, Brownell, Herson, and Hagadorn, 2014). Here, it was found that with the implementation of a breastmilk donor policy, the proportion of infants exclusively breastfed will increase (Marinelli et al., 2014).

Effects on Weight and Size

Additional studies have examined the effect of breastfeeding on early detection of a variety of disorders, causing increased risks of obesity and diabetes, effects of body length, weight, various diseases, and in pre-term/ low birth weight infants. Studies completed by Priego, et al., (2013) and Pozo-Rubio et al., (2013) showed how blood-cell transcripts are influenced by breast milk, which creates biomarkers of health in children.

This goal is reached by altering one's activation markers found on blood cells, which can ultimately help to prevent the expression of various T-cell-mediated disorders, such as coeliac disease, more commonly known as celiac disease (Pozo-Rubio et al., 2013). The researchers involved in the Priego et al. (2013) study included 237 children aged 2-9 years old from eight European countries, and found evidence supporting that breast milk shares a protective effect due to its higher expression levels of blood-cell transcripts, SLC27A2, FASN, PPAR, and INSR. These genetic components found in peripheral blood cells lower an individual's risk of insulin resistance, high plasma triglyceride levels and obesity (Priego et al., 2013). Since those children who were breastfed showed results of increased levels of these biomarkers of health, it was concluded that breastfeeding ultimately aids in lowering the risk of medical complications associated with obesity (Priego et al., 2013).

In regards to the topic of obesity, one study's findings support that breastfeeding leads to less excessive weight gain in infancy, ultimately reducing the risk of obesity in children, leading into adulthood (Jwa, Fujiwara, & Kindo, 2014). This may be due to a lower protein supply in breast milk compared to formula milk (Koletzko, et al., 2013). Jwa, et al., (2014) found latent protective effects of breastfeeding on late childhood obesity. This has the greatest effect on boys in late childhood, protecting this population against becoming overweight. This research also shows that the longer a child was breastfed, the lower his/her risk of becoming overweight. It was also found that exclusive breastfeeding leads to increases in body length of infants by 0.75 cm and increases in weight by 0.25 kg (Yarnoff et al., 2013). Overall, most studies found improved outcomes in breastfed infants, especially those infants who were breastfed for

longer periods of time, compared to those receiving other feeding styles. In addition, in a study by Yarnoff, Allaire, & Detzel (2013), some negative effects of formula milk feedings were identified, which include factors such as decreased length and weight, and increased incidence of disease in developing countries.

As previously mentioned, there are also mixed findings about the effects of breastfeeding compared with formula feeding, thereby contradicting the majority of study findings. The contradictive studies include a retrospective cohort study, an observational study, and a clinical trial whose results show no difference between the effects of formula feeding versus breastfeeding. Andres, Badger, Casey and Cleves (2013) studied 185 children aged 4-7 years old and found no differences in nutrition and body composition in infants who were fed with breast milk and infants who were fed with other foods within the first six months of life. Yarnoff, Allaire, and Detzel (2013) studied 37,750 children aged 0-6 months and 34,816 children aged 6-12 months from 20 developing countries in Africa, Asia, and Latin America. They found no statistically significant association between breastfeeding and improved infant health for the 6-12 month age group (Yarnoff et al., 2013). Other researchers have analyzed lipid needs in infants and concluded that the amounts of long-chain polyunsaturated fatty acids can be adjusted in formula milk to similarly match that of breast milk (Lapillonne, et al., 2010).

However, in general, researchers have consistently found better outcomes throughout early and late childhood in breastfed infants (Lapillonne, et al., 2010). There are various limitations that exist within any systematic review. One factor to remember when assessing the contradicting studies at hand is to note that each study included a

different variable, such as population, sample size, and setting, which could alter the results between studies.

Effects on Cognitive Development

Tawia (2013) studied the effect of breastfeeding on neurological outcomes, such as brain structure and cognitive development. The author studied the effect of breastfeeding on cognitive development in children aged 7 weeks, 3, 6, 9, and 12 months, 1-5 years old, 4-6 years old, and 7 years old, and found that those who were breastfed had higher IQ (intelligence quotient) scores than those who were not breastfed. In a longitudinal study on neuropsychological development, or the development of brain pathways that lead to psychological function, Beaver, Vaughn, Delisi, and Higgins (2010) found an inverse relationship in length of breastfeeding and neuropsychological deficits in the adolescent population. It has been concluded that adolescents who were exclusively breastfed during infancy had greater levels of intelligence than those who were formula fed, or were not exclusively breastfed (Kafouri, et al., 2013). The reason for this is linked to increased cortical thickness in both the superior and inferior parietal lobes of the brain in association with breastfeeding. The parietal lobes are critical areas of the brain for performance IQ, meaning the part of the brain responsible for integrating "perceptual stimuli with appropriate motor responses," evaluating "visuospatial information and—in general—" working "quickly and efficiently with information present in the surrounding physical and social environment" (Kafouri et al., p. 156, 2013).

Furthermore, Deoni et al., (2013) studied the effects of breastfeeding on early white matter development in the brain. These researchers found a positive association

between early exclusive breastfeeding and increased white matter development. Especially in pathways related to high-order cognition or more complex thinking, this area involves the parts of the brain linked to language, planning, and emotional functioning. This helps with verbal communication, the ability to plan ahead, and better express felt emotions. Jenkins and Foster (2014) found advantageous effects of exclusive breastfeeding on motor ability at age two years, along with increased fine motor skills (such as easily tying a shoe), accelerated reading ability and impressive math ability at age four years (Jenkins & Foster, 2014). Those who were formula fed typically did not reach these milestones as quickly as the breastfed group. Overall, researchers support that breast milk may optimize brain and cognitive development in countless ways (Tawia, 2013).

On the contrary, some researchers have found minimal cognitive improvements to be associated with breastfeeding. In a study with contradicting findings, Magalhaes, Viera, Priore, Ribeiro, Lamounier, Franceschini, and Sant'Ana (2012) analyzed breastfeeding and neurological development. This study, performed on 1,218 children aged 9 years old, found that breastfeeding is not necessarily associated with any advantages on IQ levels, arguing that maternal and socio-economic factors have the greatest impact.

Effects on Immune System

Researchers have also studied breastfeeding and immunity effects of breast milk, as well as gut maturation, lead levels in primary teeth, risk of developing necrotizing enterocolitis, nasopharyngeal microbial communities, and lymphocyte subsets. In general, they found that breastfeeding had positive effects on immune system

development. A retrospective clinical study about the impact of breast milk on primary teeth lead levels was completed involving 22 Lebanese boys and 31 Lebanese girls aged 9-12 years old (Khoury Freiha, Daou, El Osta, Sukhn, and Nehme, 2014). Khoury Freiha and colleagues (2014) uncovered a significant difference in the teeth lead level in breastfed and formula fed infants. As this study explained, a lower teeth lead level is indicative of a healthier nutritional status. With high levels of ingestion, lead can have toxic effects on the immune system. If an infant's teeth lead level is high, it may indicate a high level of lead ingestion and toxic immune system exposure. Therefore, the results of the study are in favor of breastfeeding, as breastfed infants were found to have lower teeth lead levels than formula fed infants. This study also found a statistically significant decrease in lead levels in breast milk compared to formula milk (Khoury Freiha et al., 2014).

In randomized or quasi-experimental designs, two research articles discovered that formula feeding results not only in a higher rate of short-term growth, but also results in a higher risk of developing necrotizing enterocolitis (Reisinger, de Vaan, Kramer, Wolfs, van Heum, & Derikx, 2014; Quigley & McGuire, 2014). Further, Biesbroek, et al., (2014) found a strong connection between breast milk and microbial composition in the upper respiratory systems of infants aged 6 weeks to 6 months. This association dealt with decreased levels of Staphylococcus and anaerobic bacterial communities, including Prevotella and Veillonella in those who were breastfed, and has been found to contribute to protection against respiratory infections and wheezing throughout early infancy (Biesbroek et al., 2014).

In regards to lymphocyte subsets (blood cell membrane surface markers), in a comparative study of infants at risk of coeliac disease, Pozo-Rubio and colleagues (2013) found positive immunomodulatory effects on lymphocyte subsets in infants who were breastfed. These lymphocyte subsets were found to have increased activation of health biomarkers on the infants' blood cells (Pozo-Rubio et al., 2014). This finding suggests that infants who are breastfed have more mature immune systems than formula fed infants (Pozo-Rubio, et al., 2013).

Diabetes Mellitus

Researchers have also considered the effects of breastfeeding on the development of Type I Diabetes Mellitus (DM) in children. Lund-Blix and colleagues (2015) studied the association of breastfeeding with islet autoimmunity and Type I DM in children who were genetically susceptible to DM. These researchers found that infants who were breastfed for 12 months or longer were associated with a lower risk of developing Type I DM and a decreased likelihood of progressing from islet autoimmunity to Type I DM (Lund-Blix, Stene, Rasmussen, Torjesen, Andersen, & Renningen, 2015). This information further indicates a positive association between breastfeeding and the development and maintenance of the immune systems of infants.

Critical Appraisal of Evidence

General Findings

In a systematic review, it is important to incorporate information from valid and reliable studies, using good designs, thereby generating high levels of evidence. Seventeen of the research studies used descriptive designs. These designs did not include experiments on their subjects, but rather were descriptive, identifying the relationships

between variables, predictive variables, and prevalence of conditions, behaviors, health, and other attributes. Further, in the case of infant feeding styles, it would not be ethically sound to randomly assign infants to different types of feeding groups, as researchers have found that feeding style may affect infants' lifelong development. Therefore, most studies used for this systematic review were non-experimental in nature.

Most researchers have used descriptive and correlational designs (Yarnoff et al., 2013; Priego et al., 2013; Lund-Blix et al., 2015; Andres et al., 2013; Noughabi et al., 2014; Beaver et al., 2010; Marinelli et al., 2014; Pozo-Rubio et al., 2013; Khoury Freiha et al., 2014; Deoni et al., 2013; Reisinger et al., 2014; Foster et al., 2014; Jwa et al., 2014; Herson, 2014; Kafouri et al., 2013; Lamounier et al., 2012). Using the Levels of Evidence provided by Schmidt and Brown (2012), these studies generated evidence categorized as Level VIII. Multiple publications were categorized as syntheses. For example, those by Tawia (2013), Quigley and McGuire (2014), and Lapillonne et al. (2013) were included in this category as either systematic reviews or meta-analyses. According to Schmidt and Brown (2012), these publications generate evidence categorized as Level IV sources. Only one study by Koletzko et al. (2013) was experimental in nature as a multicentric clinical trial, generated evidence categorized at Level VI.

Internal Validity

Attrition. One aspect of a study that can be a threat to the study's internal validity is the attrition, or dropout, rate. If attrition is high, then the internal validity of a study will be questioned. One study (Andres et al., 2013) reported a significant attrition

rate. This study began with a sample size of 119 children, and 61 children (51% of the original sample) dropped out before the end of the study, leaving only 58 participants.

Sample size. Another important factor for ensuring internal validity is adequate group size to ensure statistical conclusion validity. To examine adequate sample sizes, a power analysis is performed. If a power analysis is not conducted, the researchers should have provided information and rationale for determining sample size and representativeness. Yarnoff et al. (2013) tested the sample for representativeness and found that nearly all mean indicators, such as percentage of non-exclusive breastfeeding and exclusive breastfeeding infants, were identical between the sample and the population. Priego et al. (2014), Andres et al (2013), Jwa et al. (2014), Jenkins and Foster (2014), Beaver et al. (2010), and Lund-Blix et al. (2015) also stated their samples to be representative of the populations without utilizing a power analysis.

Khoury Freiha et al. (2014) stated that their sample may not be representative, but should be expanded utilizing a National Database in order to include more children and be truly representative. Pozo-Rubio et al. (2013), Koletzko et al. (2013), Noughabi et al. (2014), Biesbroek et al. (2014), Reisinger et al. (2014), Lapillonne et al. (2013), Marinelli et al. (2014), Deoni et al. (2013), and Kafouri et al. (2013) did not conduct a power analysis and it is unclear if their sample sizes were made representative of the population by some other means. Only Holme et al. (2009) and Magalhaes et al. (2012) stated that their sample size was not representative of their population due to bias. Studies that are not representative of their populations should be repeated using a larger scale and sampling methods that decrease the incorporation of bias.

Statistical analysis. Researchers used statistical analysis to determine if their findings are significant. Levels of statistical significance vary depending on the topic of study; however, typical levels of statistical significance are smaller than p- values of 0.05, meaning a 95% confidence interval is usually used. A 95% confidence interval indicates that researchers wanted statistical results be "true" 95% of the time. Additional levels of significance are: p values < 0.01 and < 0.001, with smaller values indicating the differences were much less likely to occur by chance alone. In the studies reviewed, all researchers who used levels of statistical significance used p values smaller than 0.05. The methods used by Priego et al., (2013) and Koletzko et al., (2013) for statistical analysis were unclear or unable to be obtained. For details about studies, see Appendix A.

Sampling methods. Researchers must protect against bias in all areas of research, including sampling methods. In order to avoid sampling bias, sample are selected to be as representative of the population as possible (Schmidt and Brown, 2012). Researchers must also provide details on their sampling methods for readers to determine the reliability of findings affected by sampling methods. In this systematic review, studies were examined using various means, such as the type of sampling used and the possibility of bias associated with the sampling method. Across studies, researchers used random sampling (Koletzko et al., 2013), cluster sampling (Pozo-Rubio et al., 2013; Noughabi et al., 2014), stratified sampling (Beaver et al., 2010; Khoury Freiha et al., 2014; Biesbroek et al., 2014), convenience sampling through voluntary response (Jwa et al., 2014; Holme et al., 2010; Lund-Blix et al., 2015; & Kafouri et al. 2013), convenience sampling through including entire samples utilized in previous research studies (Yarnoff

et al., 2013; Priego et al., 2013; Andres et al., 2013; Magalhaes et al., 2012; & Jenkins & Foster, 2014), and convenience sampling through including entire populations admitted to hospitals during a time period (Marinelli et al., 2014). The sampling methods utilized by Reisinger et al. (2014); Lapillonne et al. (2013); and Deoni et al. (2013) were unclear. See Appendix B for details about each study. Regardless of sampling approach, the majority of researchers found that subjects who exclusively breastfed during infancy had improved outcomes compared to those who were partially breastfed, formula fed, or were fed other forms of supplementation.

Data collection methods, reliability, and validity of findings. In every study, it was important for researchers to explain their exact methods for data collection for future researchers to be able to determine the validity, reliability, and duplicability of the study. Data collection methods in systematic reviews must also be explained through discussing the search engines used and the types of articles used in the study. Nearly every study in this systematic review included extensive details regarding the methods of data collection. These details are so extensive, in fact, that future researchers could easily replicate the study with the proper tools. Therefore, these studies, as a whole, are transparent and include systematic methods, which allows readers to critically appraise validity and reliability. Most studies included within this systematic review provided details of the tools used for data collection, describing tools as standardized and well-known. Therefore, these studies have maintained instrument internal validity as a whole. An additional concern regarding the chosen studies deals with the researchers and authors involved. For example, it should be disclosed that a potential for bias exists in the

included studies authored by Nestle, a company associated with the production of formula milk. For details about each study, see Appendix C.

Ethics related to experimental methods. Nearly every study was approved by an ethical committee and researchers consistently obtained informed consent from the parents of infants and children included in the studies. One study, however, had some questionably ethical methods. Khoury Freiha et al. (2014) stated that the protocol was submitted to the Saint-Joseph University research committee in Beirut, Lebanon. However, researchers did not state whether or not the protocol was approved by this review board. This study involved extracting the molars of children ages 9-12 years, a method that some may deem to be unethical. However, written and informed consent was obtained from the parents, or guardians, of the subjects. While the methods of this study may be questionable, the information provided by the study is significant to the effects of breastfeeding versus formula feeding. Therefore, the information provided by Khoury Freiha et al. (2014) is still utilized in this systematic review. Another study by Jwa et al. (2014) did not receive approval from the Institutional Review Board (IRB) because the data used in this study was collected by the Ministry of Health, Labour, and Welfare without identifiable parameters.

External validity

A study's external validity is the degree to which the study's results can be applied and generalized to other studies (Schmidt and Brown, 2012). External validity may first be threatened by samples that do not properly represent the population, or are affected by the effects of selection (Schmidt and Brown, 2012). For example, Khoury Freiha et al. (2014) studied the population of Lebanese children born between 1990 and

2000, aged 9-12 years old, but only studied Beruit, Lebanon and its suburbs. Noughabi et al. (2014) studied the population of Iranian women with infants aged 6-24 months, but most of the sample was from the most largely populated area of Tehran, Islamic Republic of Iran. Therefore, these studies may not be able to be generalized to all Lebanese children (Khoury Freiha et al., 2014) or Iranian children (Noughabi et al., 2014), but rather only to children in the most populated, urbanized areas of the countries being studied. This would make it difficult to accurately replicate these studies in areas other than highly populated, urbanized cities.

Along with obtaining samples that are representative of the population, researchers must also explain the methods used to obtain data. These methods may include sampling methods, inclusion criteria, and exclusion criteria. In other words, researchers must provide information on how they conducted the research in order for the research to be able to be duplicated in the future. A general weakness with nearly every study was that most studies lack regulation of the length and intensity of breastfeeding intervals. The researchers were unable to control how frequently the women breastfed, and whether or not exclusive breastfeeding was maintained, or if supplement feedings were used with other foods. This is because the information used within the studies was not intended to be controlled, rather just collected similar to a survey form in order to be more organic. Therefore, one infant may have been breast fed for twenty-minute intervals, six times a day, while another infant in the same study may have fed for fifteen-minute intervals, ten times a day. The variable of length of breastfeeding sessions may not have been included due to the fact that it is difficult to measure exactly how much breast milk an infant ingests during a feeding. Some mothers may excrete milk faster

than others, and some infants may have a stronger sucking reflex than others, thereby obtaining more milk with each feeding than infants with a weak sucking reflex. However, it is acceptable that these studies did not regulate breastfeeding intervals, as it may have been unethical to limit infants to regulated amounts of milk and nutrition.

Most studies included in this systematic review provided information about the site and sample inclusion and exclusion criteria. "Inclusion criteria clearly identify the characteristics of subjects included in a study, while exclusion criteria decrease the risk of other identifiable characteristics affecting the results of the study" (Schmidt and Brown, p. 250, 2012). These criteria improve studies through providing precision of sample selection and controlling for confounding or extraneous variable, thereby providing stronger and more relevant evidence. Research studies included in this review described inclusion and exclusion criteria, except for any included systematic reviews and meta-analyses. Researchers studied the effect of breastfeeding in a variety of sites in the US and other countries. The inclusion criteria for Beaver et al. (2013), Koletzko et al. (2013) and Biesbroek et al. (2014) were unclear. However, these studies present significant material regarding the effects of breastfeeding on infant and child development, so their findings cannot be disregarded. See Appendix D for detailed description about each study.

Reliability

Across all studies, results were consistent regarding the effects on breastfeeding on outcomes in infancy and early and late childhood. In spite of differing settings, populations, and methods of data collection, the overall results were consistent; breastfeeding has positive outcomes on many aspects of physical and cognitive

development. A few studies, such as Jenkins and Foster (2014), showed no difference in health outcomes related to infant feeding styles, but did not show any negative effects of breastfeeding. Mostly, studies that did not express positive outcomes of breastfeeding showed no difference in outcomes relative to feeding styles of breastfeeding and formula feeding.

Applicability of Findings to Practice

Nearly every study used in this systematic review can be applied to practice. Due to the fact that the results in the studies overall indicated a support of breastfeeding, it can be concluded that the promotion of breastfeeding in the clinical setting may assist in improving the health status of infants and children through early adulthood. Findings from studies with questionable reliability, inclusion criteria, sampling methods, or any other possible weakness, must still be considered. While these findings may be limited, their potential significance cannot be completely forgotten. Before applying these weaker findings to the clinical settings, studies must be repeated or comparable research must be discovered.

Synthesis of Evidence

The current state of science relative to the outcomes of breastfeeding in early and late childhood indicates that this form of feeding promotes a prophylactic intervention that can be initiated by mothers across the world. The act of breastfeeding has been proven to have a range of positive outcomes on one's life. This systematic review focuses solely on the first eighteen years of life. It is evident that within this timespan, weight and size, cognitive ability, and immunity have been positively affected. The studies included within this systematic review provided prime examples of how these

areas are influenced. This influence on human development has been proven to be mainly positive, with only minimal reports of opposing findings. A small number of studies included within this systematic review argued little to no difference among those who were breastfed versus formula fed, however, the prevalence of these studies remains significantly lower than those promoting the utilization of breastfeeding, and all of the positive health outcomes it entails.

First, weight and size in children are affected by the presence or absence of breastfeeding in multiple ways. One aspect deals with a lower incidence of excessive weight gain in infancy (Jwa et al., 2014). In addition, breastfeeding was found to have a protective effect against obesity and delayed growth in both childhood and adulthood. This may be due to lower protein supply in breast milk compared to formula (Koletzko et al., 2013). Typically, individuals would believe that less protein would produce a negative effects, however, the researchers who performed this study concluded that the lower protein levels in breast milk compared to formula milk help to "lower insulin-releasing amino acid concentrations and thereby decrease circulating insulin and IGF-I levels, resulting in lesser early weight gain and reduced later obesity risk" (Koletzko et al., p. 11, 2013). The longer an infant is breastfed, the lower the risk of developing obesity throughout early and late childhood (Jwa et al., 2014).

Second, breastfeeding affects outcomes in regards to cognitive development throughout childhood. Breastfeeding in infancy is associated with higher IQ levels in infancy through school age (Tawia, 2013). In addition, there is an inverse relationship between breastfeeding and the development of neuropsychological deficits in adolescents (Beaver et al., 2010). Breastfeeding is also positively associated with early white matter

development in infants (Deoni et al., 2013). This promotes quicker neural growth and maturation of the frontal lobe and association brain regions, which allows for improved cognitive and behavioral performance (Deoni et al., 2013). Finally, breastfeeding causes a positive effect on the development of fine and gross motor skills in toddlers and preschoolers (Jenkins & Foster, 2014).

Third, breastfeeding affects the development of immunity throughout early and late childhood. Breastfeeding has been found to have positive immunomodulatory effects in infants, allowing breastfed children have more mature immune systems than formula fed children (Pozo-Rubio et al., 2014). Formula fed children have been found to have higher lead levels than those who are breastfed (Khoury Freiha et al., 2014). "Lead exposure is a global environmental problem inducing lifelong adverse health effects" (Khoury Freiha et al., p. 14, 2014). This problem can be easily prevented, since the main lead supply within the first 6 months of life is dominated by dietary sources (Khoury Freiha et al., 2014). Breastfeeding also decreases the risk of the development of necrotizing enterocolitis, a devastating gastrointestinal condition, in infants (Reisinger et al., 2014). In regards to the development of autoimmune diseases, genetically susceptible breastfed children are less likely to develop Type I Diabetes Mellitus than those who are formula fed (Anderson et al., 2015).

Overall, breastfeeding has been found to have positive effects on the growth and development of children through all developmental levels. The results in these studies add evidence to the question of the long-term benefits of breastfeeding on healthcare outcomes in children. This information can assist healthcare providers in understanding the importance of a woman's decision regarding how to feed her infant. The overall

outcome from gaining additional evidence is that nurses would be more proactive in educating women to promote breastfeeding.

Recommendations

Due to the great amount of research supporting the positive effects of breastfeeding on the growth and development of children, it can be stated that nurses should promote breastfeeding in the clinical setting. This promotion can, and should, occur in multiple ways. Nurses should educate new mothers on the effects of breastfeeding on children through providing specific facts and statistics. Nurses should also teach these mothers how to initiate breastfeeding through providing demonstrations and visual aids.

While it is important for nurses to encourage breastfeeding, it must be acknowledged that some physical deformities, of the child or mother, may prevent the mother from being able to breastfeed her child. In these cases, the nurse should encourage the mother to administer breast milk via bottles if possible, as this method will still provide the child with the nutrients and antibodies that allow for positive developmental outcomes. If a mother cannot breastfeed due to carrying a disease such as HIV/AIDS, or due to a physical deformity that prevents her from producing breast milk, this mother should not be discouraged. While breastfed children are found to be more advanced in terms of development across studies, formula fed children are often not far behind. In other words, a mother who cannot breastfeed should not be worried that her child will not fully develop solely because of the lack of breast milk in her child's diet. If a patient cannot breastfeed, or has chosen not to breastfeed, then the nurse must assist the patient in finding the best and most nutritious feeding option for the child. While

breastfeeding is the best feeding option for optimal growth and development of a child, many other feeding options do exist, and should be presented when educating the patient on feeding selections.

While performing this Systematic Review, a gap in the literature was found in the adolescent age group. Much research has been conducted on the effects of breastfeeding on the growth and development of infants, preschoolers, and school age children. However, it was very difficult to find any literature regarding the effects of this feeding style on adolescent health. In fact, only two studies included in this Systematic Review focus on the adolescent age group: Beaver et al. (2010) and Kafouri et al. (2013). This gap in literature may be due to the numerous confounding variables that increasingly affect health status throughout one's life. Regardless, more research should be conducted on the effect of breastfeeding on adolescent growth, immunity, and cognitive development in order to gain a better understanding of the long-term effects of breastfeeding on child development.

Reference List

Andres, A., Casey, P., Cleves, M., Badger, T. (2013). Body fat and bone mineral content of infants fed breast milk, cow's milk formula, or soy formula during the first year of life. *The Journal of Pediatrics,* 163(1). 49-54. doi: 10.1016/j.jpeds.2012.12.067

Beaver, K., Vaughn, M., Delisia, M., Higgins, G., (2010). The Biosocial Correlates of Neuropsychological Deficits: Results From the National Study of Adolescent Health. *International Journal of Offender Therapy and Criminology,* 54 (6). 878-894. doi: DOI: 10.1177/0306624X09345993

Biesbroek, G., Bosch, A., Wang, X., Keijser, B., Veenhoven, R., Sanders, E., & Bogaert, D., (2014). The impact of breastfeeding on nasopharyngeal microbial communities in infants. *The American Journal of Respiratory and Critical Care Medicine,* 190(3). 298-308. doi: 10.1164/rccm.201401-0073OC

Deoni, S., Dean, D., Piryatinsky, I., O'Muircheartaigh, J., Waskiewicz, N., Lehman, K., Han, M., & Dirks, H.(2013). Breastfeeding and early white matter development: A cross-sectional study. *Neuroimage,* 82. 77-86. doi:10.1016/j.neuroimage.2013.05.090

Holme, A., MacArthur, C., & Lancashire, R. (2010). The effects of breastfeeding on cognitive and neurological development of children at 9 years. *Child: Care, Health & Development*, *36*(4), 583-590. doi:10.1111/j.1365-2214.2009.01068.x

Jenkins, J. & Foster, E. (2014). The Effects of Breastfeeding Exclusivity on Early Childhood Outcomes. *American Journal of Public Health,* 104(1). 128-134.doi:10.2105/AJPH.2013.301713

Jwa, S., Fujiwara, T., & Kondo, N. (2014). Latent protective effects of breastfeeding on

late childhood overweight and obesity. *Obesity (Silver Spring),* 22(6). 1527-37. doi: 10.1002/oby.20735

Kafouri, S. , Kramer, M., Leonard, G., Perron, M., Pike, B., Richer, L., Toro, R., Veillette, S., Pausova, Z., and Paus1, T. (2013). Breastfeeding and Brain Structure in Adolescence. *International Journal of Epidemiology, 42*, 150-159. doi:10.1093/ije/dys172

Khoury Freiha, M., Daou, M., El Osta, N., Sukhn, C., and Nehme, E. (2014). Impact of breast vs. formula feeding mode on primary teeth lead level. *The Lebanese Medical Journal,* 62(1). 14-21.

Koletzko, B., Beyer, J., Brands, B., Demmelmair, H., Grote, V., Haile, G., Gruszfeld, D., Rzehak, P., Socha, P., & Weber, M. (2013). Early influences of nutrition on postnatal growth. *Nestle Nutrition Institute Series,* 71(1). 11-27. doi: 10.1159/000342533

Lapillonne, A., Groh-Wargo, S., Gonzalez, C., & Uauy, R. (2013). Lipid needs of preterm infants: updated recommendations. *The Journal of Pediatrics,* 162(3). 37-47. doi: 10.1016/j.jpeds.2012.11.052

Lund-Blix, N., Stene, L., Rasmussen, T., Torjesen, P. Andersen, L., & Renningen, K. (2015). Infant Feeding in Relation to Islet Autoimmunity and Type I Diabetes in Genetically Susceptible Children: The MIDIA Study. *Diabetes Care*, 38, 257-263. doi: 10.2337/dc14-1130

Magalhaes, T., Vieira, S. Priore, S., Ribeiro, A., Lamounier, J., Franceschini, S., & Sant'Ana, L. (2012). Exclusive breastfeeding and other foods in the first six

months of life: effects on nutritional status and body composition of Brazilian children. *The Scientific World Journal, 1-15.* doi: 10.1100/2012/468581

Marinelli, K., Lussier, M., Brownell, E., Herson, V., & Hagadorn, J. (2014). The effect of a donor milk policy on the diet of very low birth weight infants. *Journal of Human Lactation,* 30(3). 310-316. doi: 10.1177/0890334414530511

Martin, J., Hamilton, B., Ventura, S., Osterman, M., Wilson, E., & Mathews, T. (2011). Births: Final data for 2010. *National Vital Statistics Reports, 61,* 1–72. Retrieved November 21, 2014, from http://www.cdc.gov/nchs/data/nvsr/nvsr61/nvsr61_01.pdf#table01

Noughabi, Z., Tehrani, S., Foroushani, A., Nayeri, F., & Baheiraei., A. (2014). Prevalence and factors associated with exclusive breastfeeding at 6 months of life in Tehran. *Eastern Mediterranean Health Journal*, 20(1). 24-32.

Pozo-Rubio, T., Capilla, A., Mujico, J. R., de Palma, G., Marcos, A., Sanz, Y., & ... Nova, E. (2013). Influence of breastfeeding versus formula feeding on lymphocyte subsets in infants at risk of coeliac disease: the PROFICEL study. *European Journal Of Nutrition, 52*(2), 637-646. doi:10.1007/s00394-012-0367-8

Priego, T., Sanchez, J., Pico, C., Ahrens, W., Bammann, K., De Henauw, S., Fraterman, A., Iacoviello, L., Lissner, L., Molnar, D., Moreno, L., Siani, A., Tornaritis, M., Veidebaum, T., & Palou, A. (2013). Influence of breastfeeding on blood-cell transcript-based biomarkers of health in children. *Pediatric Obstetrics.* doi: 10.1111/j.2047-6310.2013.00204.x

Quigley, M. & McGuire, W. (2014). Formula versus donor breast milk for feeding preterm or low birth weight infants. *The Cochrane Database of Systematic Reviews,* 4(1). doi: 10.1002/14651858.CD002971.pub3

Reisinger, K., de Vaan, L., Kramer, B., Wolfs, T., van Heurn, L., & Derikx, J. (2014). Breastfeeding improves gut maturation compared to formula feeding in preterm babies. *Journal of Pediatric Gastroenterology and Nutrition,* 59(6). 720-724. doi: 10.1097/MPG.0000000000000523

Schmidt, N. & Brown, J. (2011). Evidence based practice for nurses: *Appraisal and application of research (2nd ed.).* Sudbury, MA: Jones & Bartlett Learning.

Tawia, S. (2013). Breastfeeding, brain structure and function, cognitive development and educational attainment. *Breastfeeding Review, 21*(3), 15-20.

World Health Organization (2015). *Breastfeeding*. Retrieved from http://www.who.int/topics/breastfeeding/en/

Yarnoff. B., Allaire, B., & Detzel, P. (2013). Associations between infant feeding practices and length, weight, and disease in developing countries. *Frontiers Pediatrics.* doi: 10.3389/fped.2013.00021

Appendix A

The Purposes and Findings of Individual Studies

Author	Purpose	Findings and p-values
Andres et al. (2013)	To identify the differences in fat mass, free fat mass, and bone mineral content in infants fed cows' milk formula, soy milk formula, and breast milk.	Compared with infants fed cows' milk formula and soy milk formula, those fed breast milk had higher fat mass at three months of age (p=.001) and lower free fat mass (p=.001) between six months and one year of age.
Beaver et al. (2010)	To examine the factors that contribute to deficits in neuropsychological states of adolescents.	The impact of breastfeeding on neuropsychological deficits was statistically significant (p-value=.05). This was an inverse relationship, meaning that the longer an infant breastfed, the less likely that infant would be to develop neuropsychological deficits.
Biesbroek et al. (2014)	To study the association between breastfeeding and nasopharyngeal microbial communities, including all cultivable and non-cultivable bacteria.	The p-values for four different types of bacteria were less than .001, indicating a significant difference between the levels of bacteria in formula fed infants and breastfed infants. Breastfed children under age six months had increased levels of Corynebacterium and Dolosigranulum, and decreased levels of Staphylococcus and Veillonella.
Deoni et al. (2013)	To investigate the effect of breastfeeding/breast milk on brain development, namely early white matter, and myelin.	Compared to formula-fed infants and infants of mixed feeding styles, exclusively breastfed infants showed greater white matter and myelin development throughout many areas of the brain (p-value=.05).
Holme et al. (2010)	To examine whether breastfeeding is associated with later differences in children's cognitive and neurological development.	The average total IQ for a breastfed infant was 106.6, while the average total IQ for a formula fed infant was 101.1. Initially, these findings were statistically significant. (P=0.00) However, after adjustment, Holme et al. (2010) found that these findings were not significant, and indicate that breast feeding is not associated with an increase in IQ.
Jenkins & Foster (2014)	To examine a relationship between exclusive breastfeeding, duration of breastfeeding, physical health,	Breastfeeding exclusivity had positive effects on mental/cognitive outcomes and motor outcomes at all levels of exposure (p-value=0.01). Body mass index was not affected significantly by breastfeeding exclusivity.

	and cognitive health in children at 2 and 4 years.	
Jwa et al. (2014)	To investigate the latent effect of breastfeeding on overweight and obesity in late childhood.	Researchers utilized a main p-value of .002, finding that formula fed boys had higher BMI at aged 7 and 8. Breastfed girls also had lower BMI at ages 7 and 8 than formula fed girls. While the findings regarding the male subjects were statistically significant, the findings regarding female subjects were not.
Kafouri et al. (2013)	To evaluate the association between the structure of cortical regions/general intelligence and duration of exclusive breastfeeding.	The duration of exclusive breastfeeding predicted the cortical thickness of the superior and inferior parietal lobules ($p=0.021$). Non-breastfed adolescents were more likely to have been exposed to secondhand smoking during the prenatal period ($p<0.0001$).
Khoury Freiha et al. (2014)	To detect the level of lead in the first primary molar of a group of Lebanese children born between 1990 and 2000, living in Beircut and suburbs, and to compare the amount of lead according to gender and feeding mode.	At a p-value of .044, researchers found a significant increase in teeth lead level in formula fed children when compared to breastfed children.
Koletzko et al. (2013)	To test the hypothesis that reduced infant formula protein contents will lower insulin-releasing amino acid concentrations and thereby decrease circulating insulin and IGR-I levels, resulting in lesser early weight gain and reduced obesity risk later in life.	Lowered protein in infant formula induces similar metabolic and endocrine responses and normalizes weight and BMI, relative to breastfed controls, at the age of 2 years. Methods for statistical analysis were unclear.
Lapillonne et al. (2013)	To further refine adequate intake for groups of preterm infants and to analyze the impact of long-chain polyunsaturated fatty acids	Overall, studies show that providing larger amounts of DHA supplements, especially to small infants, is associated with better neurologic outcomes in early life. Systematic review; no p-value.

	(LCPUFAs) on central nervous system development.	
Lund-Blix et al. (2015)	To examine the association between breastfeeding duration and the introduction of solid foods with the development of Type I DM and islet autoimmunity in children who are genetically susceptible.	The development of Type 1 Diabetes did not significantly differ according to breastfeeding duration (p-value of .44). However, through utilizing the Kaplan- Meier method, researchers predicted a lowered risk of developing Type 1 Diabetes in children who breastfed for 12 months or longer compared to those who were breastfed for less than 12 months.
Magalhaes et al. (2012)	To evaluate the effect of exclusive breastfeeding and consumption of other foods in the first six months of life in the nutritional status and body composition of children.	Researchers found that exclusive breastfeeding was not directly connected to nutritional status. Cow's milk and dairy formulas also did not influence nutritional growth in infants.
Marinelli et al. (2014)	To compare very low birth weight (VLBW) enteral intake type in the first 28 days of life versus after establishing a donor milk (DM) policy.	The amount of babies fed formula significantly decreased, while the amount of babies fed exclusively human milk significantly increased after the initiation of a donor milk policy. These findings indicate that a donor milk policy may increase the proportion of infants being fed breast milk.
Noughabi et al. (2014)	To determine the prevalence of exclusive breastfeeding in Tehran, Islamic Republic of Iran in the first 6 months of life, and the influencing factors, with focus on postpartum factors.	In the categories of formula supplementation after birth, mother's intention to breastfeed, and family and spouse support of breastfeeding, the p-values were less than .05.
Pozo-Rubio et al. (2013)	To assess the effects of infant feedings on lymphocyte subsets of CD4+ and CD25+ lymphocyte development.	Percentages of CD4 + and CD25+ lymphocytes were higher in breastfed infants compared to formula fed infants (p=-0.026).
Priego et al. (2013)	To examine the relation between transcriptional biomarkers of	Protective effects of breastfeeding are reflected in higher expression levels of multiple blood cells. These biomarkers may serve to discriminate the

	metabolic health and types of infant feeding in a subset of children from the IDEFICS (Identification and Prevention of Dietary and Lifestyle-Induced Health Effects in Children and Infants) cohort.	formula-fed children that are at high risk for metabolic alterations. Methods for statistical analysis are unclear.
Quigley & McGuire (2014)	To determine the effect of feeding with formula compared with donor breast milk on growth and development in preterm or low birth weight infants.	In preterm and low birth weight infants, formula feeding, compared with donor breast milk, results in a higher rate of short-term growth and a higher risk of developing necrotizing enterocolitis. Systematic Review; no p-value.
Reisinger et al. (2014)	To assess the effects of breastfeeding on intestinal maturation in prematurely born babies by evaluating postnatal changes in urinary intestinal Fatty Acid Binding Protein (I-FABP) levels.	Breastfeeding increased the urinary fatty acid binding protein (I- FABP) levels between 5 and 12 days after birth (Reisinger et al., 2014). However, formula fed babies had increased concentrations of I-FABP between 12 and 19 days after birth. These findings indicate that formula fed babies may have delayed gut maturation in comparison to breastfed babies. (p-value=.002).
Tawia (2013)	To review the most recent evidence for an effect of breastfeeding on cognitive development.	Both breast milk and being breastfed are required for the optimal development of brain structure and function. Infants who are not breastfed, or are breastfed for short durations, have detrimental effects on brain development throughout their lifetimes. Systematic review; no p-value.
Yarnoff et al. (2013)	To examine the effects of feeding types on length, weight, diarrhea incidence, fever, and cough in infants younger and older than six months.	In infants younger than 6 months, breastfed infants were longer in length (p=0.14) and weighed more than those not exclusively breastfed (p=0.12). Exclusively breastfed infants had fewer incidence of diarrhea (p= 0.04) than non-exclusively breastfed infants (p=0.04). Exclusive breastfeeding did not have a statistically significant association with the age group of 6 months to 1 year. For the age group of 6 months to 1 year, no feeding type had a significant association with infant health.

Appendix B

Sampling Methods and Bias of Individual Studies

Source	Sampling Method	Introduction of Bias
Andres et al. (2013)	Convenience Sampling: the entire sample from the Beginnings Study was used as the population in this study.	Because the entire population was studied, except for subjects who were excluded in relation to defined exclusion criteria, researchers in this study avoided sampling bias.
Beaver et al. 2012	Researchers obtained their initial data from the National Longitudinal Study of Adolescent Health, which they utilized to obtain a stratified, random sample of middle and high schools across the United States.	Through the voluntary response of participants, a moderate amount of bias may have been introduced into the study. However, the stratified, random sampling of schools allows for a low risk of sampling bias to be associated with this study (Schmidt and B8own, p.253, 2012).
Biesbroek et al. (2014)	Stratified random sampling to identify 101 subjects who had received exclusive breastfeeding and 101 subjects who had received exclusive formula feeding for the first six weeks of life.	Due to the randomization of selection of subjects, there is a low chance of sampling bias associated with this study.
Deoni et al. (2013)	Sampling methods were unclear.	Unable to determine if sampling bias was incorporated into the study.
Holme et al. (2010)	Voluntary response sampling from the population.	With this type of convenience sampling, a moderate amount of sampling bias may have been introduced into this study.

Jenkins & Foster (2014)	Utilized information from the early Childhood Longitudinal Study-Birth Cohort, in which data was collected through parent interviews and child assessments.	With this type of convenience sampling, a moderate amount of sampling bias may have been introduced into this study.
Jwa et al. (2014)	Voluntary response survey sampling, which is a type of convenience sampling.	Due to the fact that participants in this study were asked to voluntarily respond to the survey, the likelihood of sampling bias is moderate in this study.
Kafouri et al. (2013)	Voluntary recruitment from high schools around the region of Saguenay-Lac-Saint-Jean of Quebec, Canada. Data was collected through medical questionnaires and telephone interviews with parents.	Due to the fact that participants in this study were asked to voluntarily respond to the survey, there is a moderate likelihood of sampling bias in this study.
Khoury Freiha et al. (2014)	Stratified random sampling through dividing the population into strata of males and females.	According to Schmidt and Brown (p.253, 2012), the likelihood of sampling bias through using this method with randomization of selection is low.
Koletzko et al. (2013)	A system of double-blinded, random assignment was used to place subjects in the groups of high-protein and low-protein formula groups.	Due to the incorporation of random assignment, there is a low likelihood of bias in this study.
Lapillonne et al. (2013)	Systematic review; methods of choosing studies were not stated.	Unable to determine bias.
Lund-Blix et al. (2015)	Utilized information from the MIDIA study, which obtained subjects through seemingly voluntary parental recruitment from the Norwegian general population.	Through utilizing voluntary recruitment and voluntary response of subjects, researchers may have introduced a moderate amount of sampling bias into this study.

Magalhaes et al. (2012)	Convenience sampling: As a retrospective cohort study, researchers obtained their sample by including all members of their population.	This sampling method introduces a considerable amount of bias (Schmidt and Brown, p. 257, 2012).
Marinelli et al. (2014)	Convenience sampling through including all infants born within time frames of October 2009-March 2010 or October 2010-September 2012.	As stated by Schmidt and Brown (p. 257, 2012), this sampling method introduces a considerable amount of bias. However, this method makes it easy for researchers to gather significant data in a limited time frame.
Noughabi et al. (2014)	Multi-stage, random cluster technique for distributing questionnaires.	It is unclear if the researchers used a certain percentage or number of subjects from each geographic area. Therefore, there is a slight possibility of sampling bias with this study (Schmidt and Brown (p. 253, 2012).
Pozo-Rubio et al. (2013)	Cluster sampling through dividing Spain geographically into six areas, and recruiting subjects from one hospital in each area.	It is unclear if Pozo-Rubio and colleagues used a defined number of subjects from each area, allowing for a slight possibility of sampling bias (Schmidt and Brown, p.253, 2012).
Priego et al. (2013)	Stratified the population into multiple strata based on country of origin and gender. They then selected roughly 40 subjects from each country studied, aiming for an equal amount of male and female participants.	According to Schmidt and Brown (p.253, 2012), this type of sampling has a low risk of bias if the selection of subjects in randomized. Therefore, there is a low risk of sampling bias associated with this study.
Quigley & McGuire (2014)	Literature search through the Cochrane	Through the use of multiple search

	Central Register of Controlled Trials, MEDLINE, EMBASE, CINAHL, conference proceedings, and reviews.	engines, bias was mostly avoided.
Reisinger et al. (2014)	Methods were unclear.	Without clearly defined sampling methods, it is difficult to determine if researchers took measures to avoid sampling bias. Therefore, there is a possibility to that sampling bias occurred in conducting this study.
Tawia (2013)	Methods for obtaining studies/information remain unclear.	Without clearly defined use of multiple search engines and resources, it is difficult to determine if Tawia took measures to avoid bias when conduction this systematic review. Therefore, there is a possibility to that bias occurred in conducting this study.
Yarnoff et al. (2013)	Convenience sampling: included all surveys from the 20 countries studied.	While convenience sampling was used, researchers tested for representativeness and found that the sample and population were nearly identical in the proportions of feeding types. Therefore, researchers avoided sampling bias when conducting this study.

Appendix C

Topics and Data Collection Methods of Individual Studies

Source	Topic of Study	Data Collection Methods
Andres et al. (2013)	Body fat and bone mineral content in infants fed three different types of milk or formula: breast milk, cow's milk formula, and soy formula.	Study visits were conducted when the infants reached 3 months, 6 months, 9 months, and 12 months of age. At these times, researchers used standardized measures to find weight to the nearest .01kg, length to the nearest .01cm, and found weight-for length z-scores using growth charts by the World Health Organization. Researchers also examined fat mass percentage and bone mineral composition in each infant using dual-energy X-ray absorptiometry (Andres et al., p. 49, 2013). These researchers also estimated familial socioeconomic status using the Hollingshead Four-Factor Index of Social Status.
Beaver et al. (2010)	The effects of multiple factors on neurological and cognitive outcomes in adolescents.	To gather data for length of breastfeeding, researchers conducted a one-item length of breastfeeding during the first wave of analysis. In this step, mothers of subjects were asked whether they breastfed their child and the duration of the breastfeeding. Researchers utilized

		coded numerical responses such as: 0= no breastfeeding, 1=less than three months, 2=three to six months, 3= six to nine months, etc. This scale continued at regular intervals until the highest value of 6, meaning that the infant was breastfed for 24 months or more.
Biesbroek et al. (2014)	Nasopharyngeal microbial makeups in breastfed infants in comparison to formula-fed infants.	Researchers used 16S-based GS-FLX-titanium-pyrosequencing to study various microbes, and nonmetric multidimensional scaling to measure the amount of each microbe.
Deoni et al. (2013)	The effect of breastfeeding on early white matter and myelin development in children 10 months to 4 years of age.	Researchers obtained information regarding feeding status, age, gestation duration, maternal age, and maternal education level from parental interviews. To obtain images of white matter and myelin development, the multicomponent Driven Equilibrium Single Pulse Observation of T1 and T2 (mcDESPOT) was used. All infants were scanned while asleep and were monitored with pulse oximetry and in-fared cameras throughout the scan. Researchers then used a three-pool signal model to essentially create a map of each infant's brain composition. These maps were then aligned to a specified template utilizing the Advanced Normalization Tools

		software package. Developmental differences were examined as logarithmic formulas utilizing a single equation.
Holme et al. (2010)	The long-term effects of breastfeeding on children at 9 years of age.	Psychologists in the children's various schools used the British Ability Scales and Quick Neurological Screening Test (QNST) to assess for both cognitive and neurological development in study subjects. Researchers conducted home interviews of mothers of subjects in order to obtain information on breastfeeding and other unspecified variables related to cognitive advancement. To compare the development of subjects, researchers used standardized IQ and QNST scores.
Jenkins & Foster (2014)	A relationship between exclusive breastfeeding, duration of breastfeeding, physical health, and cognitive health in children at 2 and 4 years.	Information collected included breastfeeding status and inclusion of solid foods. At age 2, cognitive and motor skills zero scores were measured, along with BMI Trained administrators conducted assessments of math, reading, find motor skills, and BMI at age 4. All scores were developed by the National Center for Education Statistics.
Jwa et al. (2014)	Studied the protective effects of breastfeeding on childhood obesity.	Questionnaires were mailed to the parents of study subjects every year, beginning at 6 months of age, and

		continuing until the subjects turned 5.5 years of age. Questionnaires were then mailed at ages 7 and 8 years of age. In the first questionnaire, parents were asked whether they breastfed or formula fed their child. Based on these responses, children were categorized as receiving exclusive breastfeeding, mixed feedings, and exclusive formula feedings. Each questionnaire required parents to include their child's weight to the nearest 0.1 kg and height to the nearest 0.1 cm. BMI was calculated using the formula of weight (kg) divided by height (m^2). Researchers utilized the International Obesity Task Force BMI cut points to define measurements of overweight and obesity, which related to a BMI of 25 for overweight and 30 for obesity in adults.
Kafouri et al. (2013)	The association between the structure of cortical regions/general intelligence and duration of exclusive breastfeeding.	Obtained information regarding pregnancy, birthweight, alcohol use during pregnancy, exposure to second-hand smoking, and other pregnancy related variables through telephone interviews and questionnaires distributes to biological mothers or subjects. Intelligence of children was measured using the Wechsler-Intelligence Scale for Children III

		(WISC-III), which measures both verbal and performance IQ. Magnetic Resonance Imaging (MRI) of the brain was conducted on each subject to obtain and analyze position and size of cortical thickness.
Khoury Freiha et al. (2014)	The association between teeth lead level and breastfeeding versus formula feeding in children aged 9-12 years.	Khoury Freiha et al. (2014) studied the association between teeth lead level and breastfeeding versus formula feeding in children aged 9-12 years. To conduct this study, researchers asked four qualified pediatric dentists to extract the first mandibular molar of every child. For this extraction, a regulated anesthetic was used and all instruments were stainless steel. All teeth were rinsed with a nitric acid solution and deionized water before being sent to the accredited American University of Beruit Environmental Core Laboratory. At this location, scientists performed many steps to calculate the tooth lead level, including an ETHOS microwave program and Ion Coupled Plasma Mass Spectrometry (Khoury Freiha et al., p.16 , 2014).
Koletzko et al. (2013)	The hypothesis that reduced infant formula protein contents lower insulin-releasing amino acid concentrations, resulting in lesser early weight gain	Formula-fed infants were randomly assigned in a double-blind process to be fed formula with high protein or formula with low protein levels. These

	and reduced later obesity risk.	formulas were equal in calorie count. A reference group of fully breastfed infants was also monitored. The BMIs of all infants were measured and compared at 6, 12, and 24 months. Children were then followed up until the age of six years.
Lapillonne et al. (2013)	Systematic review on the updated recommendations of lipid needs in preterm babies.	The articles used are specified throughout this study, however, the search engines used to find articles were not discussed.
Lund- Blix et al. (2015)	The association between breastfeeding duration and the introduction of solid foods with the development of Type I DM and islet autoimmunity in children who are genetically susceptible.	Obtained initial information through distributing questionnaires. Information regarding feeding status, demographic variables, and family history from the first questionnaire, administered at 3 months of age. Delivery type, gestational age, and birth weight were acquired through utilizing The Medical Birth Registry of Norway. The blood tests that were conducted at ages 3, 6, 9 and 12 months were tested at the Ohio University Hospital Hormone Laboratory. At this location, blood was tested for diabetes-associated autoantibodies, such as GADA and the antibody related protein, tyrosine kinase. Islet autoimmunity was determined through high titer levels of one autoantibody or increased levels of

		two or three autoantibodies. These researchers used methods that had been tested by the Norwegian Childhood Diabetes Registry, and estimated to have a100% specificity and 32% sensitivity.
Magalhaes et al. (2012)	The effects of breastfeeding on body composition in children 4-7 years of age.	Data on infant feeding styles was obtained via medical records. Researchers evaluated children in the category of weight (kg), with each child measured on a digital electronic scale. Height (cm) was measured through the use of a vertical stadiometer, which was attached to a wall. Nutritional status was evaluated using the categories of weight for age, height for age, and BMI, as referenced by the World Health Organization (WHO). Researchers used Software WHO Anthro Plus to calculate indices. Body composition was checked using Dual Energy X-Ray absorptiometry. Waist circumference (cm) was measured using a flexible, inelastic tape measure. The average calorie intake of each subject was compared to the Estimated Energy Requirement through using the reported physical activity level.
Marinelli et al. (2014)	The effects of the implementation of a donor milk policy on infants very low	Researchers used a feeding protocol for both breastfed and formula fed

	birth weight infants.	infants. This feeding protocol regulated the amount of breast milk or formula that each infant received (according to weight), the initiation of feedings and fortifications, and the advancement of feedings as time passed. This regulation of feeding sizes allowed each infant to receive proportionally equal amounts of nutrition.
Noughabi et al. (2014)	The prevalence of breastfeeding in Tehran, and why mothers may choose to breastfeed.	Data was collected from subjects via questionnaires and face-to-face interviews with mothers included in the study. Researchers collected many pieces of data, including parental sociodemographic factors, childbirth factors, and postpartum factors. All factors were defined by researchers and collected from each participant. Noughabi et al. (2014) used the definition of exclusive breastfeeding provided by the World Health Organization. Information regarding postpartum depression was utilized through using the Edinburgh Depression Scale.
Pozo-Rubio et al. (2013)	Lymphocyte subsets in infants at risk for coeliac disease.	Researchers classified the infants into three risk groups depending on HLA class II and DQA1 and DQB1 genotypes (Pozo-Rubio et al., p.639, 2013). To identify the genotypes, researchers first extracted DNA from

		the infant's buccal mucosal cells. They then conducted HLA-DQ genotyping through polymerase chain reaction sequence-specific primers analysis (Pozo-Rubio et al., p. 639, 2013). Blood analyses and flow cytometry analysis were then utilized to find the lymphocyte subsets in these infants.
Priego et al. (2013)	The association between biomarkers of metabolic health and infant feeding type in children aged 2-9 years.	Each subject was physically examined for weight during a fasting state, height, and skin-fold thickness using standardized procedures. Infant feeding type was reported by parents of the subjects. Body Mass Index (BMI) of each subject was calculated through dividing weight (kg) by height (m^2). BMIs were then categorized using criteria provided by the International Obesity Task Force. Gene expression analysis was studied using quantitative polymerase chain reactions. Priego and colleagues used evidence from a previous study to determine which genes should be incorporated into the study based on their association with metabolic health.
Quigley & McGuire (2014)	Systematic review on formula feeding versus donor breast milk for preterm infants and infants of low birth weight.	Articles were obtained through searches via the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, CINAHL, and previous systematic reviews. Data was

		gathered using methods provided by the Cochrane Neonatal Group. The authors of this systematic review separately evaluated trial quality and data extraction of each study being utilized.
Reisinger et al. (2014)	The gut maturation of breastfed and formula fed preterm infants.	In order to assess intestinal maturation, researchers obtained urinary fatty acid binding protein (I-FABP) levels. Reisinger et al. (2014) explains that I-FABP is a specific enterocyte marker, or a marker of cells in the small intestine. The urinary levels of I-FABP were obtained from each subject at 5, 12, 19, and 26 days after birth. Researchers were unclear regarding the method of obtaining the urine from the infants.
Tawia et al. (2013)	Systematic review on recent evidence to discover the effects of breastfeeding on cognitive development.	While the articles used are specified throughout the study, the search engines used to find articles are not discussed.
Yarnoff et al. (2013)	Associations of six different types of feedings with five measures of infant health.	Feeding styles and infant health were discovered through questioning of parents. Researchers provided consistency in the variables of weight and height through using z-scores for weight and height for infant age. Researchers then used a regression analysis to estimate an association between breastfeeding and non-

		breastfeeding, and utilized regression coefficients to predict health levels for exclusive breastfeeding, and supplementation of solids, milk, and formula.

Appendix D

Research Sites and Inclusion/Exclusion Criteria for Individual Studies

Source	Site of Research	Inclusion Criteria	Exclusion Criteria
Andres et al. (2013)	Published in Little Rock, AR	Children included in The Beginnings Study.	Unclear.
Beaver et al. (2010)	All U.S. High Schools and Middle Schools	Adolescents currently enrolled in grades 7-12.	Any students who did not participate in each "wave" of research.
Biesbroek et al. (2014)	The Netherlands	Infants aged 6 weeks to 6 months.	Unclear.
Deoni et al. (2013)	United States	Healthy singleton babies, aging 10 months to four years, who were born between 37 and 42 weeks gestation and had APGAR scores of at least 8.	Infants with abnormalities on fetal ultrasound, history of neurological events or disorders, admission to a NICU, sibling history of psychological or neurological disorders, pregnancy complications, and report of illicit drug or alcohol use during pregnancy.
Holme et al. (2010)	United Kingdom	All viable subjects from primary randomized control trial of an intervention to reduce maternal smoking while pregnant.	Any children, who had formed a severe handicap, had emigrated, or who had severe family problems.

Jenkins & Foster (2014)	United States	Children born in the United States in 2001, involved in the Childhood Longitudinal Study-Birth Cohort.	Unclear.
Jwa et al. (2014)	Japan	Babies born in Japan, January 10th- 26th and July 10th-26th, 2010.	Multiple births, pre-term deliveries, unknown gestational age, and missing data on breastfeeding status at six months of age. Children were also excluded if parents did not report weight and height at any time during the follow-up period.
Kafouri et al. (2013)	The Sanguenay-Lac-Saint-Jean region of Canada	Adolescents aged 12-18 years with two or more siblings per family, living in or around Sanguenay-Lac-Saint-Jean, Canada. Involved in Sanguenay Youth Study.	Any subject with alcohol misuse during pregnancy, severe mental illness or mental retardation, and any history of heart disease, brain trauma or tumor, epilepsy, or meningitis.
Khoury Freiha et al. (2014)	Beruit, Lebanon and its suburbs	Children fed exclusively with formula or breast milk for a minimum of six months.	Children with known health problems or medical diagnoses.
Koletzko et al. (2013)	Europe	Infants and children aged 2 years.	Unclear.
Lapillonne et al. (2013)	Paris, France	Pre-term/very low birth weight infants.	Any children that were born full term.
Lund-Blix et al. (2015)	Norway	Subjects with high-risk HLA genotypes for Type 1	Subjects with any missing data from questionnaires that

		Diabetes.	were distributed at ages 3, 6, 9, and 12 months.
Magalhaes et al. (2012)	Southeast Brazil	Children who received breast milk for a minimum of two months, whose residence location was known.	Children who had a low birth weight, macrosomia, or had been weaned during the study follow up.
Marinelli et al. (2014)	Connecticut Children's Medical Center's 32-bed level 4 NICU in Hartford, Connecticut	Infants weighing ≤ 1500 grams, who were admitted during the study periods and remained hospitalized at 28 days of life.	Infants born weighing greater than 1500 grams.
Noughabi et al. (2014)	Tehran, Islamic Republic of Iran	Mothers with a singleton infant aged 6-24 months, living in Tehran for at least one year before the study was conducted.	Unclear.
Pozo-Rubio et al. (2013)	Spain	Infants 4-months old, who were had at least one parent or sibling with Celiac Disease.	Infants born outside of Spain or outside of the time frame of 2006 to 2010.
Priego et al. (2013)	8 European countries (Germany, Hungary, Italy, Cyprus, Spain, Estonia, Sweden, Belgium)	Children from the Identification and Prevention of Dietary- and Lifestyle-Induced Health Effects in Children and Infants cohort.	Any children outside of the age group of 2-9 years.
Quigley & McGuire (2014)	United Kingdom	Infants (1070 were utilized as subjects).	Unclear.

Reisinger et al. (2014)	The Netherlands	Babies who were <37 weeks gestation, had their first enteral feeding within 4 days after birth, and obtained a diet of either completely breast milk or completely formula milk.	Any infants who developed gastrointestinal pathology, thereby requiring treatment during the 30 day study period.
Tawia et al. (2013)	Australia and New Zealand	Children ages two months to seven years.	Unclear.
Yarnoff et al. (2013)	20 developing countries in Africa, Asia, and Latin America	Multiple survey years per country, with each survey including information on maternal features and infant feeding.	Infants greater than one year in age, along with any infants who were not included in the Demographic Health Survey.