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Infant milk-feeding practices and cardiovascular disease outcomes in offspring: a systematic review

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ABSTRACT

Background: During the Pregnancy and Birth to 24 Months Project, the US Departments of Agriculture and Health and Human Services initiated a review of evidence on diet and health in these populations.

Objectives: The aim of these systematic reviews was to examine the relation of *1*) never versus ever feeding human milk, *2*) shorter versus longer durations of any human milk feeding, *3*) shorter versus longer durations of exclusive human milk feeding, and *4*) lower versus higher intensities of human milk fed to mixed-fed infants with intermediate and endpoint cardiovascular disease (CVD) outcomes in offspring.

Methods: The Nutrition Evidence Systematic Review team conducted systematic reviews with external experts. We searched CINAHL, Cochrane, Embase, and PubMed for articles published January 1980–March 2016, dual-screened the results using predetermined criteria, extracted data from and assessed the risk of bias for each included study, qualitatively synthesized the evidence, developed conclusion statements, and graded the strength of the evidence.

Results: The 4 systematic reviews included 13, 24, 6, and 0 articles, respectively. The evidence was insufficient to draw conclusions about endpoint CVD outcomes across all 4 systematic reviews. Limited evidence suggests that never versus ever being fed human milk is associated with higher blood pressure within a normal range at 6–7 y of age. Moderate evidence suggests there is no association between the duration of any human milk feeding and childhood blood pressure. Limited evidence suggests there is no association between the duration of exclusive human milk feeding and blood pressure or metabolic syndrome in childhood. Additional evidence about intermediate outcomes for the 4 systematic reviews was scant or inconclusive.

Conclusions: There is insufficient evidence to draw conclusions about the relationships between infant milk-feeding practices and endpoint CVD outcomes; however, some evidence suggests that feeding less or no human milk is not associated with childhood hypertension. *Am J Clin Nutr* 2019;109(Suppl):800S–816S.

Keywords: breastfeeding, human milk, infant nutrition, systematic review, cardiovascular disease, cholesterol, blood pressure, metabolic syndrome, hypertension

Introduction

The Pregnancy and Birth to 24 Months Project was an initiative of the US Departments of Agriculture and Health and Human Services (1–3). During the Project, the US Department of Agriculture Nutrition Evidence Systematic Review (NESR) team (previously the Nutrition Evidence Library, or NEL) collaborated with external experts to complete a series of de novo systematic reviews (SRs) of primary evidence that examined food

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Abbreviations used: CVD, cardiovascular disease; DBP, diastolic blood pressure; NESR, Nutrition Evidence Systematic Review; SBP, systolic blood pressure; SR, systematic review; TEC, Technical Expert Collaborative.

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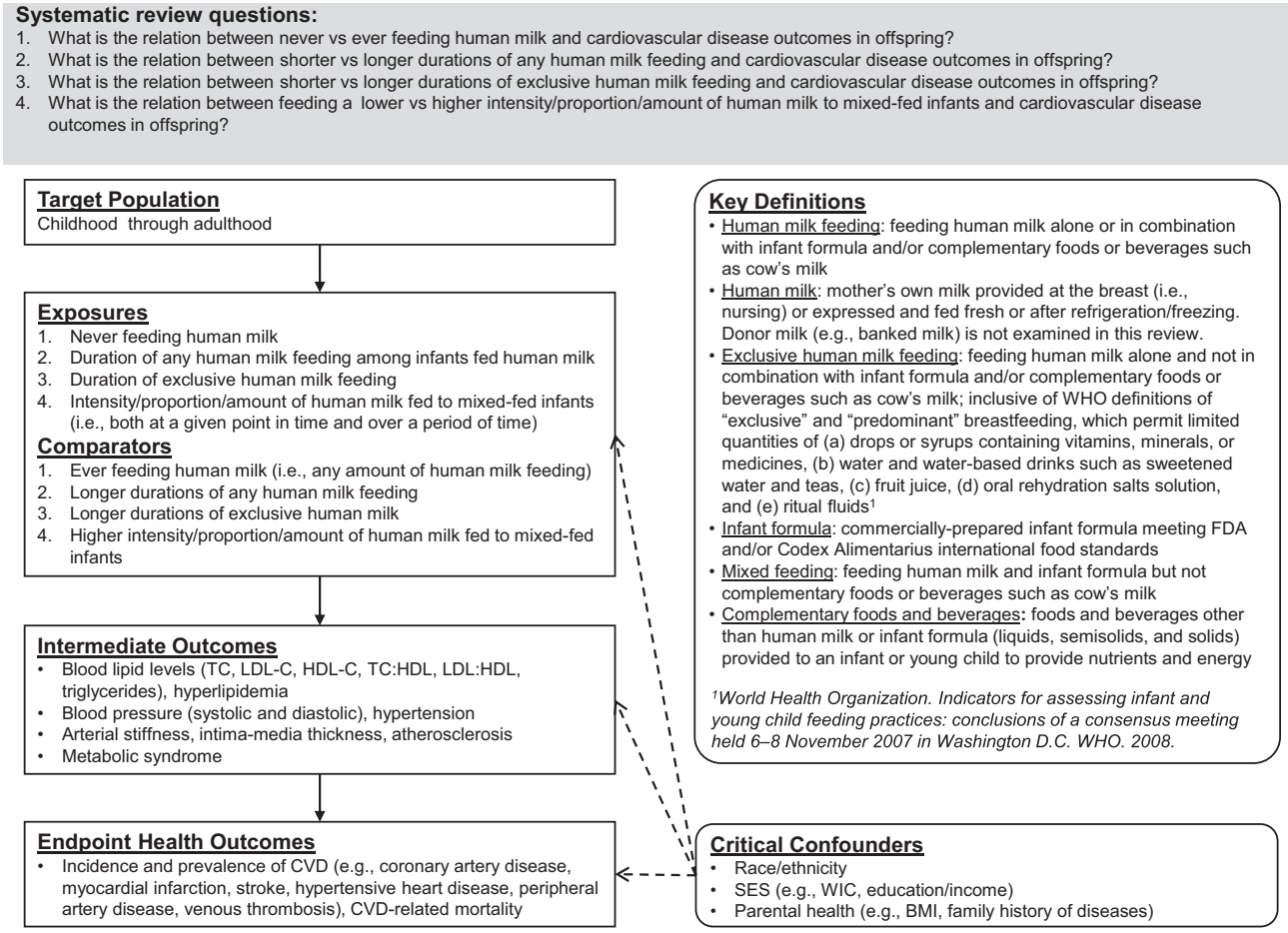

FIGURE 1 The analytic framework for the SRs conducted to examine the relation of infant milk-feeding practices with CVD outcomes in offspring. This framework illustrates the overall scope of the project, including the population, exposures and comparators, and outcomes of interest. It also includes definitions for key terms and identifies key confounders considered in the SR. CVD, cardiovascular disease; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; SES, socioeconomic status; SR, systematic review; TC, total cholesterol; WIC, Special Supplemental Nutrition Program for Women, Infants, and Children.

and nutrition topics relevant to women during pregnancy and offspring during the first 2 y of life.

The SRs in this article examine the relationships between infant milk-feeding practices and cardiovascular disease (CVD) outcomes in offspring. According to the CDC, heart disease is the leading cause of death for both men and women, and for people of most racial and ethnic groups in the United States (4). Although CVD typically manifests in adulthood, cardiovascular risk may begin much earlier and can be evaluated by examining intermediate outcomes such as blood lipids and blood pressure in children and adolescents (5).

The purpose of this article is to summarize the results of 4 SRs conducted to answer the following questions:

- What is the relationship between never versus ever feeding human milk and CVD outcomes in offspring?
- What is the relationship between shorter versus longer durations of any human milk feeding and CVD outcomes in offspring?
- What is the relationship between shorter versus longer durations of exclusive human milk feeding and CVD outcomes in offspring?
- What is the relationship between feeding a lower versus higher intensity, proportion, or amount of human milk to mixed-fed infants and CVD outcomes in offspring?

Methods

NESR analysts and librarians, who were trained in SR methodology and had advanced degrees in fields such as nutrition and library science, collaborated with a group of subject matter experts, called a Technical Expert Collaborative (TEC), to complete SRs using methods that are described in detail in this supplement (6). TEC members provided individual input on SR materials developed by the NESR staff, but did not provide formal group advice or recommendations to the government.

Scope of the SR

TEC members specified the target population, exposures and comparators, intermediate and endpoint health outcomes, critical confounding variables, and key definitions for these SRs using the analytic framework shown in **Figure 1**. In the SRs, *infant milk-feeding practices* referred to the feeding of human milk, infant formula, or a combination of both. TEC members chose

to use the term *human milk feeding* instead of *breastfeeding* for precision. *Breastfeeding* may be understood to mean feeding human milk at the breast when, in fact, feeding method was rarely distinguished by the authors of studies included in the SRs. TEC members intended to examine the feeding of human milk whether or not it was fed at the breast.

For the comparison of never with ever feeding human milk, TEC members did not define any minimum amount for *ever feeding human milk*. Likewise, for the comparisons of shorter with longer durations of any and exclusive human milk feeding, TEC members did not define thresholds for *shorter duration* or *longer duration*. They examined all comparisons of never with ever feeding human milk (or vice versa) and of shorter with longer durations (or vice versa) as defined by the authors of the studies included in the SRs.

TEC members specified both intermediate and endpoint outcomes for CVD, collectively referred to in this article as *CVD outcomes*. Outcomes from birth to 24 mo were not examined because of uncertainty regarding whether and how they relate to subsequent cardiovascular risk.

Literature search, screening, and selection

The librarians developed a literature search strategy that used exposure terminology but not outcome terminology (available at https://nesr.usda.gov) so that 1 search could be used to identify literature in support of SRs examining infant milk-feeding practices with several different outcomes (3). The librarians conducted a broad search in CINAHL, Cochrane, Embase, and PubMed using a search date range of January 1980–March 2016. The search excluded articles published before 1980 because the US Congress passed the Infant Formula Act in 1980, which established nutrient requirements for commercial infant formulas in the United States, and thus health effects associated with formula consumption before 1980 might be different (7).

TEC members defined inclusion and exclusion criteria a priori (**Table 1**), which NESR analysts used to dual-screen the search results and the results of a manual search of the references of included articles and existing SRs. TEC members reviewed the search terms and list of included articles to ensure completeness of the body of evidence.

Data extraction and risk of bias assessment

NESR analysts assembled a table of systematically extracted data from each article included in the SRs (i.e., study characteristics, sample characteristics, exposures and outcomes, risks of bias, and funding sources). Two NESR analysts independently completed the NEL Bias Assessment Tool for each article to identify the risks of bias [(6), https://nesr.usda.gov].

Evidence synthesis, conclusion statement development, and grading the strength of the evidence

NESR analysts and TEC members engaged in a series of conference calls to review, discuss, and synthesize the evidence by age group. TEC members examined both significant and nonsignificant associations (e.g., ORs and CIs) for a thorough synthesis of the evidence. To answer the SR questions, conclusion statements were carefully constructed to accurately reflect the synthesis of evidence. Conclusion statements do not draw implications, nor should they be interpreted to be dietary guidance. The strength of the evidence underlying each conclusion statement was graded *strong*, *moderate*, *limited*, or *grade not assignable* using the NESR grading rubric [(6), https://nesr.usda.gov], which takes into consideration the internal validity, consistency, adequacy, impact, and generalizability of the evidence. Finally, TEC members identified research recommendations.

Results

The literature search yielded 31,335 articles and the bodies of evidence for the 4 SRs on infant milk-feeding practices and CVD outcomes in offspring comprise 35 articles. A table of articles excluded during full-text screening, with the rationale for exclusion, is available at https://nesr.usda.gov.

None of the included articles examined lower versus higher intensities, proportions, or amounts of human milk fed to mixed-fed infants. Herein, we present evidence for the remaining 3 SRs:

- What is the relationship between never versus ever feeding human milk and CVD outcomes in offspring?
- What is the relationship between shorter versus longer durations of any human milk feeding and CVD outcomes in offspring?
- What is the relationship between shorter versus longer durations of exclusive human milk feeding and CVD outcomes in offspring?

Never versus ever feeding human milk and CVD outcomes in offspring

Thirteen articles met the inclusion criteria for this SR question (8–20). None examined endpoint CVD outcomes. In addition, evidence about metabolic syndrome (20) and arterial stiffness (12, 19) throughout the lifespan, and about blood pressure (14) and blood lipids (18) beyond childhood was scant. Additional information about these topics is available at https://nesr.usda.gov. Evidence about childhood blood pressure and blood lipids is presented below.

Blood pressure in childhood.

Six articles examined childhood blood pressure (**Table 2**) (8–13). There were 2 nonrandomized controlled trials (10, 13) and 3 independent prospective cohort studies (8, 9, 11, 12) because de Jonge et al. (11, 12) presented evidence from the Generation R Study across 2 articles. The prospective cohort studies collected infant-feeding data by parent report via questionnaire. Both experimental studies randomized formula-fed infants to groups fed an experimental formula (which was not examined in this SR) or a standard infant formula, and included a comparison of the standard infant formula group with a nonrandomized group of infants fed human milk. The studies measured blood pressure using a sphygmomanometer (9) or automatic device (8, 10–13). Some studies specified that measurements were taken when children were seated (10, 11, 13) or supine (12), and de Jong et al. (13) specified that children had a resting period prior to having their blood pressure measured.

TABLE 1 Inclusion and exclusion criteria established for the selection of studies to include in SRs on infant milk-feeding practices and CVD outcomes in offspring[1]

Category	Inclusion criteria	Exclusion criteria
Study design	Randomized controlled trials Nonrandomized controlled trials Prospective cohort studies Retrospective cohort studies Case-control studies	Cross-sectional studies Before-and-after studies Uncontrolled studies Narrative reviews Systematic reviews Meta-analyses
Publication status	Published in peer-reviewed journals	Grey literature, including unpublished data, manuscripts, reports, abstracts, and conference proceedings
Language	Published in English	Published in languages other than English
Date range	Published from 1980 to December 2015[2]	Published prior to 1980
Source of foods, beverages, or nutrients	Human milk: mother's own milk (MOM), i.e., human milk fed at the breast or expressed and fed fresh or after refrigeration/freezing Infant formula: commercially prepared infant formula meeting FDA (21) or Codex Alimentarius (22) food standards	Human milk from third parties (e.g., banked/donor milk) Infant formulas that are not commercially prepared or that do not meet FDA (21) or Codex Alimentarius (22) food standards
Study setting	Countries listed as Very High or High on the 2014 Human Development Index[3] (23)	Countries listed as Medium or Low on the 2014 Human Development Index (23)
Study participants	Human participants Males Females	Nonhuman participants (e.g., animal studies, in vitro studies) Hospitalized patients, not including birth and immediate postpartum hospitalization of healthy babies
Age of study participants	Exposure age: infants (0–12 mo), toddlers (12–24 mo) Outcome age: children (2–12 y), adolescents (13–18 y) adults (≥19 y)	Outcome age: infants (0–12 mo) and toddlers (12–24 mo)
Size of study groups	Studies with ≥30 participants per study group or a power analysis indicating that the study is appropriately powered for the outcome(s) of interest	Studies with <30 participants per study group with no power analysis indicating that the study is appropriately powered for the outcome(s) of interest
Health status of study participants	Studies done in generally healthy populations Studies done in populations where infants were full term (≥37 and 0/7 wk gestational age) Studies done in populations with elevated chronic disease risk, or that enroll some participants with a disease or with the health outcome of interest	Studies that exclusively enroll participants with a disease or the health outcome of interest Studies done in hospitalized participants (except for birth and immediate postpartum hospitalization of healthy babies) or malnourished participants Studies of exclusively pre-term babies (gestational age <37 wk), exclusively babies that have low birth weight (<2500 g) or exclusively babies that are small for gestational age

[1]CVD, cardiovascular disease SR, systematic review.
[2]In 1980 the Infant Formula Act was passed and December 2015 was when the literature search occurred.
[3]When a country was not included in the Human Development Index ranking, country classification from the World Bank was used instead.

Three of the 5 studies reported statistically significant associations that were consistent in showing that never being fed human milk is associated with higher blood pressure at 6–7 y of age (8–10). Specifically, Martin et al. (8) found that 7 y olds who were ever fed human milk had significantly lower mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) than 7 y olds who were never fed human milk. Additional analyses divided the group ever fed human milk by duration and exclusivity. In comparison with children who were never fed human milk, children who were fed human milk for <2 mo or fed human milk exclusively for <2 mo had significantly lower mean SBP and DBP, and children fed human milk exclusively for ≥2 mo had significantly lower SBP and a lower DBP that was nonsignificant. Forsyth et al. (10) found a significantly lower mean DBP in 6 y olds who were ever fed human milk (i.e., from a nonrandomized human milk-feeding group) than in 6 y olds who were never fed human milk (i.e., from a group randomized to be fed standard infant formula). The corresponding analysis for SBP was not significant. Finally, Wilson et al. (9) reported that 7 y olds who were never fed human milk had higher SBP and DBP than 7 y olds who were fed human milk exclusively until weaning and who were fed human milk in addition to infant formula and/or complementary foods or beverages prior to weaning. Of note, in all 3 studies the mean SBP and DBP values of all the groups were below screening cutoffs for hypertension (i.e., SBP <105–106 mm Hg and DBP <66–68 mm Hg, which is based on the 90th percentile for age- and sex-specific blood pressure in children at the 5th percentile for height so that the negative predictive value is >99%) (24). The associations from 2 additional studies that measured outcomes at 2, 6, and 9 y of age were not statistically significant (11–13).

Blood lipids in childhood.

Two prospective cohort studies (16, 17) and 1 retrospective cohort study (15) examined blood lipids in children (**Table 3**). The evidence was inconclusive. Across the 3 studies, the associations of never versus ever feeding human milk with HDL cholesterol, the ratio of total to HDL cholesterol, LDL cholesterol, and triglycerides were nonsignificant and inconsistent in direction, as were all but 1 of the associations with total

TABLE 2 Evidence examining the relationship between never versus ever feeding human milk and blood pressure in childhood[1]

Author and year (ref.)	Study design (study/cohort name where applicable)	Country	Notable sample characteristics	Never vs ever feeding human milk exposures[2]	Significant associations with blood pressure	Nonsignificant associations with blood pressure
de Jong 2011 (13)	Nonrandomized controlled trial[3] (Groningen LCPUFA study)	Netherlands	$n = 241$ Baseline: birth Race/ethnicity NR	Control formula group vs BF group	None	SBP at 9 y (mm Hg): mean 104.59 (SD = 7.9) vs mean 105.17 (SD = 7.8) DBP at 9 y (mm Hg): mean 63.78 (SD = 7.6) vs mean 63.77 (SD = 8.0)
de Jonge 2010 (11)	Prospective cohort (Generation R Study)	Netherlands	$n = 555$ Baseline: birth Race/ethnicity NR	Never BF vs ever BF	None	SBP at 2 y (mm Hg): β 1.50 (95% CI: −1.85, 4.85) DBP at 2 y (mm Hg): β −0.33 (95% CI: −3.02, 3.68)
				Never BF vs BF ≥6 mo	None	SBP at 2 y (mm Hg): β 2.00 (95% CI: −1.59, 5.60) DBP at 2 y (mm Hg): β −0.17 (95% CI: −3.79, 3.44)
				Never BF vs EBF ≥4 mo	None	SBP at 2 y (mm Hg): β 2.64 (95% CI: −1.11, 6.39) DBP at 2 y (mm Hg): β 0.86 (95% CI: −2.90, 4.62)
de Jonge 2013 (12)	Prospective cohort (Generation R Study)	Netherlands	$n = 5033$ Baseline: birth Race/ethnicity NR	Never BF vs ever BF	None	SBP at 6 y (mm Hg): β 0.00 (95% CI: −0.79, 0.80) DBP at 6 y (mm Hg): β 0.21 (95% CI: −0.48, 0.89)
Forsyth 2003 (10)	Nonrandomized controlled trial[3]	UK, Belgium, Italy	$n = 154$ Baseline: birth Sex NR Race/ethnicity NR	BF group vs control formula group	DBP at 6 y (mm Hg): mean difference −3.4 (95% CI: −6.8, −0.01), $P = 0.02$	SBP at 6 y (mm Hg): NS (data NR)
Martin 2004 (8)	Prospective cohort (ALSPAC)	UK	$n = 7142$ Baseline: birth Race/ethnicity: 95% white, 5% nonwhite	Ever BF vs never BF	SBP at 7 y (mm Hg): mean difference −0.8 (95% CI: −1.5, −0.1), $P = 0.03$ DBP at 7 y (mm Hg): mean difference −0.6 (95% CI: −1.0, −0.1), $P = 0.03$	None —
				Partially BF (stopped BF or non-EBF by 2 mo) vs never BF	SBP at 7 y (mm Hg): mean difference −0.8 (95% CI: −1.5, −0.03), $P = 0.04$ DBP at 7 y (mm Hg): mean difference −0.6 (95% CI: −1.2, −0.1), $P = 0.03$	None —
				EBF ≥2 mo vs never BF	SBP at 7 y (mm Hg): mean difference −0.9 (95% CI: −1.7, −0.1), $P = 0.02$	DBP at 7 y (mm Hg): mean difference −0.6 (95% CI: −1.2, 0.03), $P = 0.06$
Wilson 1998 (9)	Prospective cohort (Dundee Infant Feeding Study)	UK	$n = 301$ Baseline: birth Race/ethnicity NR	Bottle feeding vs partial BF	SBP at age 7 y (mm Hg): mean estimated values 94.2 (95% CI: 93.5, 94.9) vs 90.9 (95% CI: 90.2, 91.6), $P < 0.05$ DBP at age 7 y (mm Hg): mean estimated values 58.5 (95% CI: 58.0, 59.0) vs 56.5 (95% CI: 56.1, 56.9)[4]	None —
				Bottle feeding vs EBF	SBP at 7 y (mm Hg): mean estimated values 94.2 (95% CI: 93.5, 94.9) vs 90.3 (95% CI: 89.5, 91.1), $P < 0.05$ DBP at 7 y (mm Hg): mean estimated values 58.5 (95% CI: 58.0, 59.0) vs 56.2 (95% CI: 55.7, 56.7)[4]	None —

[1] ALSPAC, Avon Longitudinal Study of Parents and Children; BF, breastfed; DBP, diastolic blood pressure; EBF, exclusively breastfed; LCPUFA, long-chain polyunsaturated fatty acid, NR, not reported; NS, nonsignificant; RCT, randomized controlled trial; ref., reference; SBP, systolic blood pressure.

[2] Exposures, as defined by the authors of the studies included in the body of evidence, which address never versus ever feeding human milk or vice versa.

[3] Study was an RCT, but the comparison of interest included a nonrandomized breastfeeding reference group.

[4] The authors did not state that this is statistically significant; however, the CIs do not overlap.

TABLE 3 Evidence examining the relationship between never versus ever feeding human milk and blood lipids in childhood[1]

Author and year (ref.)	Study design (study/cohort name where applicable)	Country	Notable sample characteristics	Never vs ever feeding human milk exposures[2]	Significant associations with blood lipids	Nonsignificant associations with blood lipids
Bekkers 2011 (17)	Prospective cohort (PIAMA birth cohort)	Netherlands	$n = 751$ Baseline: birth Race/ethnicity NR	BF 1–16 wk vs no BF	None	Plasma TC concentration at 8 y (mmol/L): β −0.01 (95% CI: −0.15, 0.13), OR ∼0.9 (95% CI: ∼0.7, ∼1.1) Plasma HDL-C concentration at 8 y (mmol/L): β −0.01 (95% CI: −0.08, 0.06), OR ∼1.0 (95% CI: ∼0.8, ∼1.2) TC:HDL at 8 y: β 0.03 (95% CI: −0.13, 0.18), OR ∼0.9 (95% CI: ∼0.8, ∼1.2)
				BF ≥16 wk vs no BF	None	Plasma TC concentration at 8 y (mmol/L): β 0.003 (95% CI: −0.15, 0.16), OR ∼1.0 (95% CI: ∼0.8, ∼1.2) Plasma HDL-C concentration at 8 y (mmol/L): β −0.002 (95% CI: −0.08, 0.07), OR ∼0.9 (95% CI: ∼0.7, ∼1.2) TC:HDL at 8 y: β 0.04 (95% CI: −0.13, 0.22), OR ∼1.0 (95% CI: ∼0.8, ∼1.2)
Gishti 2014 (16)	Prospective cohort (Generation R Study)	Netherlands	$n = 3417$ Baseline: birth Race/ethnicity NR	Never BF vs ever BF	None	TC at 6 y (mmol/L): SDS −0.06 (95% CI: −0.19, 0.06) HDL-C at 6 y (mmol/L): SDS 0.07 (95% CI: −0.06, 0.19) LDL-C at 6 y (mmol/L): SDS −0.05 (95% CI: −0.18, 0.08) Triglycerides at 6 y (mmol/L): SDS −0.01 (95% CI: −0.14, 0.11)
Plancoulaine 2000 (15)	Retrospective cohort[3] (Fleurbaix Laventie Ville Santé)	France	$n = 461$ Baseline: 5–11 y Race/ethnicity NR	BF vs FF	TC in boys 5–11 y (mmol/L): 4.4 (95% CI: 4.2, 4.6) vs 4.7 (95% CI: 4.5, 4.8), $P = 0.03$	TC in girls 5–11 y (mmol/L): 4.6 (95% CI: 4.4, 4.9) vs 4.6 (95% CI: 4.4, 4.8), $P = 0.59$ Triacylglycerol ≥0.8 mmol/L in boys 5–11 y (%): 43.2 (95% CI: 37.0, 49.4) vs 54.1 (95% CI: 48.9, 59.3), $P = 0.35$ Triacylglycerol ≥0.8 mmol/L in girls 5–11 y (%): 54.5 (95% CI: 47.9, 61.1) vs 55.6 (95% CI: 49.0, 62.2), $P = 0.71$

[1]BF, breastfed; FF, formula fed; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; NR, not reported; PIAMA, Prevention and Incidence of Asthma and Mite Allergy; ref., reference; SDS, standard deviation score; TC, total cholesterol.

[2]Exposures, as defined by the authors of the studies included in the body of evidence, which address never versus ever feeding human milk or vice versa.

[3]The authors call their study a cross-sectional study; however, the exposure data were collected in the past rather than at the time of the outcome.

cholesterol. The only statistically significant association, reported by Plancoulaine et al. (15), found that 5- to 11-y-old boys who were fed human milk had significantly lower total cholesterol than boys who were exclusively fed infant formula; however, the corresponding analysis in girls was nonsignificant. The other studies in childhood did not examine outcomes by sex, so there were no comparable analyses that would allow TEC members to examine whether this association is typical among boys.

Shorter versus longer durations of any human milk feeding and CVD outcomes in offspring

Twenty-four articles met the inclusion criteria for this SR question (9, 11, 12, 16, 25–44). Two articles with evidence from a single retrospective cohort study examined endpoint CVD outcomes, with the endpoint being CVD-related mortality in both articles (34, 44). Evidence about blood pressure beyond childhood (30–33), blood lipids in adolescence (39), and arterial stiffness throughout the lifespan (12, 32, 43) was scant. Additional information about these topics is available at https://nesr.usda.gov. Evidence about blood pressure in childhood, blood lipids in childhood and adulthood, and metabolic syndrome is presented below.

Blood pressure in childhood.

Kramer et al. (25) and Martin et al. (26) provided compelling evidence from the Promotion of Breastfeeding Intervention Trial (PROBIT) that there is no significant relationship between the duration of any human milk feeding and childhood blood pressure (**Table 4**). In this cluster randomized controlled trial of an intervention to promote prolonged duration and exclusivity of human milk feeding among mothers who chose to feed human milk, the intervention group had higher rates of human milk feeding than the control group measured at 3, 6, 9, and 12 mo. The primary, intention-to-treat analysis did not find significant mean differences between the intervention and control groups in SBP or DBP, which were measured in duplicate by study pediatricians using an oscillometric device at 6.5 (25) and 11.5 y of age (26). Prospective cohort analyses of PROBIT study data that were intended to compare extremes of duration found that children fed human milk exclusively for ≥6 mo followed by continued human milk feeding until ≥12 mo had significantly higher SBP at 6.5 y of age than children weaned at ≤1 mo (25). However, there were no significant mean differences in SBP or DPB at 11.5 y of age between children fed human milk 3–<6 mo or ≥6 compared with <3 mo and no significant trend across the 3 categories of duration (<3, 3–<6, and ≥6 mo) (26).

Six independent prospective cohort studies examined blood pressure in children across 8 articles (9, 11, 12, 16, 27–29, 33) [de Jonge et al. (11, 12) and Gishti et al. (16) presented evidence from the Generation R Study across 3 articles]. Data about the duration of any human milk feeding were collected by parent report via questionnaires and assessed as a continuous variable (9, 29, 33) or as a categoric variable, allowing the comparison of heterogeneous ranges of duration (11, 12, 27, 28) or the trend across multiple categories of duration (16). Blood pressure was measured by sphygmomanometer or digital oscillometric device. Amorim et al. (27) and the Generation R Study authors (11, 12, 16) specified that measurements were taken more than once, and Ulbak et al. (29), Hosaka et al. (28), and de Jonge et al. (11) specified that children were seated when measurements were obtained.

The prospective cohort studies did not suggest any discernible relationship between the duration of any human milk feeding and blood pressure in childhood. Specifically, Amorim et al. (27) reported a significant association between being fed human milk <40 d compared with ≥40 d and higher SBP at 8 y of age in a sample in which a large proportion (43.5%) of participants had low birth weight; however, the corresponding analysis for DBP was not significant. The Generation R Study examined blood pressure at 2 y of age (11) and 6 y of age (12, 16). At 2 y of age, de Jonge et al (11) reported that children fed human milk for 2–4 and 4–6 mo had significantly lower DBP than those fed human milk ≥6 mo; however, the corresponding analyses for SBP were not statistically significant. In addition, there were no significant associations between being fed human milk at 0–2 mo compared with ≥6 mo and SBP or DBP at 2 y of age. At 6 y of age, de Jonge et al. (12) found no significant associations between <2 compared with ≥6 mo of human milk feeding and SBP or DBP, and Gishti et al. (16) found no significant trend across the categoric variables 0–1.9, 2–3.9, 4–5.9, and ≥6 mo of human milk feeding. Hosaka et al. (28) reported a significant association between a longer compared with a shorter duration of any human milk feeding (around the median of 8 mo when human milk was reported as a major source of nutrition) and lower SBP and DBP at 7 y of age measured by participants' families at home; however, the corresponding analyses for SBP and DBP measured by study staff lacked statistical significance. Taittonen et al. (33) found no significant association between the duration of human milk feeding and SBP or DBP in male or female participants who were children through young adults at the time of the outcome measure (i.e., 9–24 y of age). Ulbak et al. (29) reported no significant associations between the duration of any human milk feeding and SBP or DBP at 2.5 y of age. Wilson et al. (9) found a significant association between the duration of any human milk feeding, assessed as a continuous variable, and lower SBP at 7 y of age; however, the corresponding association with DBP was not statistically significant.

Blood lipids in childhood and adulthood.

Five prospective cohort studies examined blood lipids in children (16, 35–38), and 1 retrospective and 3 prospective cohort studies presented outcomes in adults (32, 34, 40, 41) (**Table 5**). Evidence across both age groups was inconclusive. Three of the 5 childhood studies reported statistically significant associations between the duration of any human milk feeding and HDL cholesterol that were inconsistent in direction (16, 37, 38), and almost all of the associations between the duration of human milk feeding and total cholesterol, LDL cholesterol, and triglycerides were nonsignificant and inconsistent in direction. In adulthood, there were nonsignificant associations between the duration of any human milk feeding and blood lipid levels at 32 (32), 50 (41), and 62 y of age (40). The remaining study, by Fall et al. (34), found significant associations between being weaned compared with not weaned at 1 y of age and lower fasting total cholesterol, nonfasting total cholesterol, LDL cholesterol, and the ratio of LDL to HDL at 59–70 y of age; however, the corresponding analyses for HDL cholesterol and triglycerides

TABLE 4 Evidence examining the relationship between shorter versus longer durations of any human milk feeding and blood pressure in childhood[1]

Author and year (ref.)	Study design (study/cohort name where applicable)	Country	Notable sample characteristics	Shorter vs longer durations of any human milk feeding exposures[2]	Significant associations with blood pressure	Nonsignificant associations with blood pressure
Amorim 2014 (27)	Prospective cohort	Brazil	$n = 187$ Baseline: birth Race/ethnicity NR 43.5% LBW	BF <40 d vs BF ≥40 d	SBP at 8 y (mm Hg): β 3.46 (95% CI: 0.21, 6.71), $P \leq 0.05$	DBP at 8 y (mm Hg): β 3.84 (95% CI: −1.82, 9.50)
de Jonge 2010 (11)	Prospective cohort (Generation R Study)	Netherlands	$n = 555$ Baseline: birth Race/ethnicity NR	BF 0–2 mo vs BF ≥6 mo	None	SBP at 2 y (mm Hg): β 2.65 (95% CI: −0.09, 5.39) DBP at 2 y (mm Hg): β 0.26 (95% CI: −2.49, 3.01)
				BF 2–4 mo vs BF ≥6 mo	DBP at 2 y (mm Hg): β −2.83 (95% CI: −5.64, −0.01)	SBP at 2 y (mm Hg): β −2.51 (95% CI: −5.31, 0.30)
				BF 4–6 mo vs BF ≥6 mo	DBP at 2 y (mm Hg): β −3.35 (95% CI: −6.69, −0.01)	SBP at 2 y (mm Hg): β −1.18 (95% CI: −4.50, 2.15)
de Jonge 2013 (12)	Prospective cohort (Generation R Study)	Netherlands	$n = 5033$ Baseline: birth Race/ethnicity NR	BF <2 mo vs BF ≥6 mo	None	SBP at 6 y (mm Hg): β −0.24 (95% CI: −0.90, 0.42) DBP at 6 y (mm Hg): β −0.11 (95% CI: −0.68, 0.45)
Gishti 2014 (16)	Prospective cohort (Generation R Study)	Netherlands	$n = 3417$ Baseline: birth Race/ethnicity NR	BF duration trend considering categories 0–1.9 mo, 2–3.9 mo, 4–5.9 mo, and ≥6 mo	None	SBP at 6 y (mm Hg): $P = 0.32$ DBP at 6 y (mm Hg): $P = 0.26$
Hosaka 2013 (28)	Prospective cohort (Tohoku Study of Child Development)	Japan	$n = 377$ Baseline: birth Race/ethnicity NR	Longer BF duration (BF as a major source of nutrition ≥ median 8 mo) vs shorter BF duration (BF as a major source of nutrition < median 8 mo)	SBP at 7 y measured at home (mm Hg): β −1.59, $P = 0.008$ DBP at 7 y measured at home (mm Hg): β −1.11, $P = 0.053$	SBP at 7 y measured conventionally (mm Hg): β −0.83, $P = 0.4$ DBP at 7 y measured conventionally (mm Hg): β 0.08, $P = 0.9$
Kramer 2007 (25)	RCT[3] or prospective cohort, depending on the analysis (PROBIT)	Belarus	$n = 13{,}889$ Baseline: birth Race/ethnicity NR	Intervention group (higher rates of any BF measured at 3, 6, 9, and 12 mo) vs control group	None	SBP at 6.5 y (mm Hg): mean difference 0.2 (95% CI: −2.9, 3.3) DBP at 6.5 y (mm Hg): mean difference 0.2 (95% CI: −1.8, 2.2)
				EBF ≥6 mo with continued BF until ≥12 mo vs weaned <1 mo	SBP at 6.5 y (mm Hg): mean difference 1.5 (95% CI: 0.1, 2.9)	None

(*Continued*)

TABLE 4 (*Continued*)

Author and year (ref.)	Study design (study/cohort name where applicable)	Country	Notable sample characteristics	Shorter vs longer durations of any human milk feeding exposures[2]	Significant associations with blood pressure	Nonsignificant associations with blood pressure
Martin 2014 (26)	RCT[3] or prospective cohort, depending on the analysis (PROBIT)	Belarus	$n = 13{,}616$ Baseline: birth Race/ethnicity NR	Intervention group (higher rates of any BF measured at 3, 6, 9, and 12 mo) vs control group	None	SBP at 11.5 y (mm Hg): mean difference 1.23 (95% CI: −0.58, 3.05) DBP at 11.5 y (mm Hg): mean difference 0.77 (95% CI: −0.69, 2.23)
				BF 3–<6 mo vs BF <3 mo	None	SBP at 11.5 y (mm Hg): mean difference 0.16 (95% CI: −0.24, 0.55) DBP at 11.5 y (mm Hg): mean difference 0.02 (95% CI: −0.29, 0.33)
				BF ≥6 mo vs BF <3 mo	None	SBP at 11.5 y (mm Hg): mean difference 0.14 (95% CI: −0.22, 0.50) DBP at 11.5 y (mm Hg): mean difference 0.11 (95% CI: −0.17, 0.40)
				BF duration trend using the categories <3, 3-<6, and ≥6 mo	None	SBP at 11.5 y (mm Hg): $P = 0.45$ DBP at 11.5 y (mm Hg): $P = 0.42$
Taittonen 1996 (33)	Prospective cohort (Cardiovascular Risk in Young Finns)	Finland	$n = 2014$ Baseline: 3–18 y Race/ethnicity NR	BF duration (mo)	None	SBP in males 9–24 y (mm Hg): β −0.13, $P = 0.13$ SBP in females 9–24 y (mm Hg): β −0.09, $P = 0.32$
Ulbak 2004 (29)	Prospective cohort[4] (Danish National Birth Cohort)	Denmark	$n = 73$ Baseline: birth Race/ethnicity NR 63% male	BF duration (mo)	None	SBP at 2.5 y (mm Hg): β −0.15 (SE = 0.28), $P = 0.590$ DBP at 2.5 y (mm Hg): β −0.08 (SE = 0.28), $P = 0.789$
Wilson 1998 (9)	Prospective cohort (Dundee Infant Feeding Study)	UK	$n = 301$ Baseline: birth Race/ethnicity NR	BF duration	SBP at 7 y (mm Hg): longer BF duration associated with reduction in SBP (data NR)	DBP at 7 y (mm Hg): BF duration not associated with DBP (data NR)

[1]BF, breastfed; DBP, diastolic blood pressure; EBF, exclusively breastfed; LBW, low birth weight; NR, not reported; PROBIT, Promotion of Breastfeeding Intervention Trial; RCT, randomized controlled trial; ref., reference; SBP, systolic blood pressure.

[2]Exposures, as defined by the authors of the studies included in the body of evidence, which address shorter versus longer durations of any human milk feeding or vice versa.

[3]RCT of an intervention to promote prolonged duration and exclusivity of breastfeeding.

[4]Study was an RCT, but the data of interest were pooled and unrelated to randomization.

TABLE 5 Evidence examining the relationship between shorter versus longer durations of any human milk feeding and blood lipids in childhood and adulthood[1]

Author and year (ref.)	Study design (study/cohort name where applicable)	Country	Notable sample characteristics	Shorter vs longer durations of any human milk feeding exposures[2]	Significant associations with blood lipids	Nonsignificant associations with blood lipids
Childhood						
Gishti 2014 (16)	Prospective cohort (Generation R Study)	Netherlands	$n = 3417$ Baseline: birth Race/ethnicity NR	BF 0–1.9 mo vs BF ≥6 mo	None	TC at 6 y (mmol/L): SDS 0.03 (95% CI: −0.07, 0.14) HDL-C at 6 y (mmol/L): SDS 0.10 (95% CI: −0.01, 0.20) LDL-C at 6 y (mmol/L): SDS −0.05 (95% CI: −0.15, 0.05) Triglycerides at 6 y (mmol/L): SDS 0.00 (95% CI: −0.10, 0.11)
				BF 2–3.9 mo vs BF ≥6 mo	None	TC at 6 y (mmol/L): SDS −0.06 (95% CI: −0.05, 0.16) HDL-C at 6 y (mmol/L): SDS 0.10 (95% CI: −0.01, 0.20) LDL-C at 6 y (mmol/L): SDS 0.03 (95% CI: −0.07, 0.14) Triglycerides at 6 y (mmol/L): SDS 0.01 (95% CI: −0.10, 0.12)
				BF 4–5.9 mo vs BF ≥6 mo	None	TC at 6 y (mmol/L): SDS 0.10 (95% CI: −0.02, 0.22) HDL-C at 6 y (mmol/L): SDS 0.06 (95% CI: −0.07, 0.18) LDL-C at 6 y (mmol/L): SDS 0.07 (95% CI: −0.05, 0.20) Triglycerides at 6 y (mmol/L): SDS 0.03 (95% CI: −0.09, 0.16)
				BF duration trend considering the categories 0–1.9, 2–3.9, 4–5.9, and ≥6 mo	HDL-C at 6 y (mmol/L): $P = 0.03$	TC at 6 y (mmol/L): $P = 0.64$ LDL-C at 6 y (mmol/L): $P = 0.29$ Triglycerides at 6 y (mmol/L): $P = 0.95$
Hoppu 2013 (35)	Prospective cohort	Finland	$n = 185$ Baseline: birth Race/ethnicity NR	Partial BF duration	None	TC at 2 y (mmol/L): NS (data NR) HDL at 2 y (mmol/L): NS (data NR)
Ramirez-Silva 2015 (36)	Prospective cohort (Prenatal Omega-3 Fatty Acid Supplementation and Child Growth and Development Study)	Mexico	$n = 446$ Baseline: birth Race/ethnicity NR	BF <3 mo vs BF >12 mo	None	TC at 4 y (mg/dL): path coefficient (mean difference) 4.50 (95% CI: −2.77, 11.77), $P = 0.23$ Log HDL-C at 4 y (mg/dL): path coefficient (mean difference) 0.014 (95% CI: −0.05, 0.07), $P = 0.64$ LDL-C at 4 y (mg/dL): path coefficient (mean difference) 2.32 (95% CI: −3.94, 8.58), $P = 0.47$ Log triglycerides at 4 y (mg/dL): path coefficient (mean difference) 0.08 (95% CI: −0.06, 0.22), $P = 0.27$
				BF 3–6 mo vs BF >12 mo	None	TC at 4 y (mg/dL): path coefficient (mean difference) 2.13 (95% CI: −3.77, 8.02), $P = 0.48$ Log HDL-C at 4 y (mg/dL): path coefficient (mean difference) −0.002 (95% CI: −0.05, 0.05), $P = 0.94$ LDL-C at 4 y (mg/dL): path coefficient (mean difference) 1.88 (95% CI: −3.20, 6.96), $P = 0.47$ Log triglycerides at 4 y (mg/dL): path coefficient (mean difference) 0.02 (95% CI: −0.09, 0.13), $P = 0.74$
				BF >6-12 mo vs BF >12 mo	None	TC at 4 y (mg/dL): path coefficient (mean difference) −1.24 (95% CI: −6.67, 4.18), $P = 0.65$ Log HDL-C at 4 y (mg/dL): path coefficient (mean difference) −0.004 (95% CI: −0.05, 0.04), $P = 0.88$ LDL-C at 4 y (mg/dL): path coefficient (mean difference) −0.32 (95% CI: −4.99, 4.36), $P = 0.89$ Log triglycerides at 4 y (mg/dL): path coefficient (mean difference) −0.01 (95% CI: −0.11, 0.09), $P = 0.84$

(*Continued*)

TABLE 5 (*Continued*)

Author and year (ref.)	Study design (study/cohort name where applicable)	Country	Notable sample characteristics	Shorter vs longer durations of any human milk feeding exposures[2]	Significant associations with blood lipids	Nonsignificant associations with blood lipids
				BF duration trend considering the categories <3, 3–6, >6–12, and >12 mo	None	TC at 4 y (mg/dL): $P = 0.17$ Log HDL-C at 4 y (mg/dL): $P = 0.74$ LDL-C at 4 y (mg/dL): $P = 0.34$ Log triglycerides at 4 y (mg/dL): $P = 0.30$
Strbak 1991 (37)	Prospective cohort	Country NR (likely Slovakia)	$n = 1034$ Baseline: birth Race/ethnicity NR Sex NR	Weaned <2 wk vs 2 wk–1 mo vs 1–3 mo vs 3–6 mo vs >6 mo	None	TC at 1-7 y (mmol/L): NS decrease with increasing age at weaning
				BF <1 wk vs 1 wk–1 mo vs 1–3 mo vs >6 mo	None	TC at 6 y (mmol/L): NS increase with increasing BF duration
				BF <1 wk vs BF 1 wk–1 mo	None	LDL-C at 6 y (mmol/L): NS higher in group BF <1 wk HDL-C at 6 y (mmol/L): NS higher in group BF <1 wk
				BF <1 wk vs BF 1–3 mo	None	LDL-C at 6 y (mmol/L): NS lower in group BF <1 wk HDL-C at 6 y (mmol/L): NS lower in group BF <1 wk
				BF <1 wk vs BF >6 mo	None	LDL-C at 6 y (mmol/L): NS lower in group BF <1 wk HDL-C at 6 y (mmol/L): NS higher in group BF <1 wk
				BF 1 wk– 1 mo vs BF 1–3 mo	LDL-C at 6 y (mmol/L): lower in group BF 1 wk–1 mo, $P < 0.05$ HDL-C at 6 y (mmol/L): lower in group BF 1 wk–1 mo, $P < 0.02$	None
				BF 1 wk–1 mo vs BF >6 mo	None	LDL-C at 6 y (mmol/L): NS lower in group BF 1 wk–1 mo HDL-C at 6 y (mmol/L): NS lower in group BF 1 wk–1 mo
				BF 1–3 mo vs BF >6 mo	HDL-C at 6 y (mmol/L): higher in group BF 1–3 mo, $P < 0.05$	LDL-C at 6 y (mmol/L): NS lower in group BF 1–3 mo
Thorsdottir 2003 (38)	Prospective cohort	Iceland	$n = 120$ Baseline: birth Race/ethnicity NR	BF duration (mo)	HDL-C at 6 y in female subsample (mmol/L): β 0.03 (SD = 0.01), $P = 0.032$	HDL-C at 6 y in male subsample (mmol/L): NS (data NR) LDL-C at 6 y (mmol/L): NS (data NR) TC at 6 y (mmol/L): NS (data NR) Triglycerides at 6 y (mmol/L): NS (data NR)
Adulthood						
Fall 1992 (34)	Retrospective cohort	UK	$n = 485$ Baseline: mean 64 y (range 59–70 y) Sex: 100% male Race/ethnicity NR	EBF and weaned ≤1 y vs EBF and not weaned ≤1 y	Fasting TC at 59–70 y in men (mmol/L): 6.6 vs 6.9, $P < 0.05$ Nonfasting TC at 59–70 y in men (mmol/L): 6.4 vs 6.9, $P < 0.01$ LDL-C at 59–70 y in men (mmol/L): 4.6 vs 5.0, $P < 0.01$ LDL-C:HDL-C at 59–70 y in men: 3.8 vs 4.2, $P < 0.01$	HDL-C at 59–70 y in men (mmol/L): 1.2 vs 1.2 Triglycerides at 59–70 y in men (mmol/L): 1.4 vs 1.5
Kajantie 2008 (40)	Prospective cohort (Helsinki Birth Cohort)	Finland	$n = 1999$ Baseline: birth Race/ethnicity NR	BF duration trend considering the categories 0–3, 3–6, and ≥6 mo	None	TC at ~62 y (mmol/L): $P \geq 0.2$ HDL-C at ~62 y (mmol/L): $P \geq 0.2$ Triglycerides at ~62 y (mmol/L): $P \geq 0.2$
Pearce 2009 (41)	Prospective cohort (Newcastle Thousand Families cohort)	UK	$n = 406$ Baseline: birth Race/ethnicity NR	Duration of total BF	None	TC at ~50 y (mmol/L): NS (data NR) HDL-C at ~50 y (mmol/L): NS (data NR) LDL-C at ~50 y (mmol/L): NS (data NR) LDL:HDL at ~50 y: NS (data NR) Triglycerides at ~50 y (mmol/L): NS (data NR)
Pirila 2014 (32)	Prospective cohort	Finland	$n = 158$ Baseline: birth Race/ethnicity NR	BF duration (mo)	None	TC at ~32 y (mmol/L): β −0.02 (95% CI: −0.05, 0.04), $P = 0.81$ LDL-C at ~32 y (mmol/L): β −0.01 (95% CI: −0.04, 0.04), $P = 0.88$

[1] BF, breastfed; EBF, exclusively breastfed; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; NR, not reported; NS, nonsignificant; ref., reference; SDS, standard deviation score; TC, total cholesterol.
[2] Exposures, as defined by the authors of the studies included in the body of evidence, which address shorter versus longer durations of any human milk feeding or vice versa.

were not statistically significant. The evidence presented by Fall et al. (34) may not be generalizable because the authors examined outcomes only in the male subsample of the cohort. In addition, the evidence is prone to survivorship bias because the analyses were completed among the subset of the original cohort that was still living; some members of the cohort were deceased due to ischemic heart disease and other causes.

Metabolic syndrome.

Two studies presented conflicting evidence about metabolic syndrome in children (26, 42) (**Table 6**). Martin et al. (26) presented evidence from the PROBIT study (described previously). The intention-to-treat analysis did not find a significant association between intervention group membership and odds of metabolic syndrome at 11.5 y of age. Prospective cohort analyses of PROBIT study data also found no significant associations between being fed human milk 3–<6 mo or ≥6 mo compared with <3 mo and metabolic syndrome and no significant trend across the 3 categories of duration (<3, 3–<6, and ≥6 mo). On the other hand, Huang et al. (42) found that being fed human milk ≥4 mo compared with <4 mo was associated with a significantly lower odds of metabolic syndrome at 8 y of age. The inconsistency in the findings from these studies may have resulted from heterogeneous study designs, outcome assessment methods, or ages at outcome measure. Martin et al. (26) reported experimental evidence from a cluster randomized controlled trial, whereas Huang et al. (42) reported observational evidence from a prospective cohort study that is more prone to residual confounding. Martin et al. (26) assessed metabolic syndrome at 11.5 y of age using recommendations from the European Group for the Study of Insulin Resistance (45), whereas Huang et al. (42) defined metabolic syndrome at 8 y of age as membership in the *high-risk cluster* resulting from a cluster analysis (algorithms maximized between-group variation and minimized within-group variation so that members of the *high-risk cluster* had higher BMI, SBP, serum triglyceride, and glucose than nonmembers).

Only 1 study provided evidence in adults. Pirila et al. (32) found no association between the duration of any human milk feeding, reported prospectively by parents, and metabolic syndrome at 32 y of age, assessed using the National Cholesterol Education Program's Adult Treatment Panel III criteria (46, 47).

Shorter versus longer durations of exclusive human milk feeding and CVD outcomes in offspring

Six articles met the inclusion criteria for this SR (25, 26, 35, 41, 48, 49). None examined endpoint CVD outcomes. In addition, none examined blood pressure or metabolic syndrome beyond childhood, and evidence about blood lipids was scant (35, 41). Additional information about these topics is available at https://nesr.usda.gov. Evidence about blood pressure and metabolic syndrome in childhood is presented below.

Blood pressure in childhood.

The PROBIT study (25, 26, 48) and a prospective cohort study by Vitolo et al. (49) examined the duration of exclusive human milk feeding and blood pressure in childhood (**Table 7**). As described previously, the intention-to-treat analyses of the PROBIT study did not find significant mean differences in SBP or DBP at 6.5 or 11.5 y of age between the intervention group (which had higher rates of exclusive human milk feeding measured at 3 and 6 mo) and the control group (25, 26). Prospective cohort analyses of PROBIT study data also found no significant mean differences in SBP or DBP at 11.5 y of age between children fed human milk exclusively for 3-<6 mo or ≥6 mo in comparison with children fed human milk <3 mo; however, the trend across the 3 categories of duration (<3, 3–<6, and ≥6 mo) was significant and associated with higher DBP at 11.5 y of age (26). Another prospective cohort analysis compared children fed human milk exclusively for 3 mo followed by partial human milk feeding to ≥6 mo with those who were fed human milk exclusively ≥6 mo and did not find significant associations with SBP or DBP at 6.5 y of age (48). Evidence from a prospective cohort study by Vitolo et al. (49) was consistent with the evidence from the intention-to-treat analyses of the PROBIT study. Infant-feeding data were collected prospectively by interview with mothers, and blood pressure was measured with a sphygmomanometer. The outcome, high SBP at 3–4 y of age, was defined as >90th percentile for age, sex, and height using the 2004 standard from the Task Force on Hypertension Control in Children and Adolescents (50). This study did not find a significant association between being fed human milk exclusively ≥4 mo compared with <4 mo and risk of high SBP at 3–4 y of age (49).

Metabolic syndrome in childhood.

As previously described, the intention-to-treat analysis of the PROBIT study found no relationship between intervention group membership and odds of metabolic syndrome at 11.5 y of age (26). Prospective cohort analyses of PROBIT study data, which compared 3–<6 mo and ≥6 mo of exclusive human milk feeding with <3 mo and evaluated the trend across the 3 categories of duration (<3, 3–<6, and ≥6 mo), also found no significant associations with metabolic syndrome at 11.5 y of age (**Table 8**).

Discussion

The conclusion statements that answer the 4 SR questions, and the grades of the evidence underlying the conclusion statements, are listed in **Table 9**. Two major themes emerged. First, minimal evidence examined how infant milk-feeding practices relate to endpoint CVD outcomes. Second, the evidence was relatively consistent across 3 exposures in suggesting that infant milk-feeding practices do not relate to hypertension in childhood; TEC members concluded that there was evidence of no relationship between the durations of any or exclusive human milk feeding and childhood blood pressure and that, although never versus ever being fed human milk was associated with higher blood pressure at 6–7 y of age, blood pressure remained within a normal range (24). TEC members used the NESR grading rubric to consider the aspects of the consistency, adequacy, impact, generalizability, and internal validity of the evidence underlying their conclusion statements described below.

Experimental evidence from the PROBIT study, which formed the basis for the conclusion statements about the durations of

TABLE 6 Evidence examining the relationship between shorter versus longer durations of any human milk feeding and metabolic syndrome[1]

Author and year (ref.)	Study design (study/cohort name where applicable)	Country	Notable sample characteristics	Shorter vs longer durations of any human milk feeding exposures[2]	Significant associations with metabolic syndrome	Nonsignificant associations with metabolic syndrome
Huang 2007 (42)	Prospective cohort (Raine Cohort)	Australia	$n = 406$ Baseline: birth Race/ethnicity NR Sex NR	BF ≥4 mo vs BF <4 mo	Metabolic syndrome at 8 y: OR 0.6 (95% CI: 0.37, 0.97)	None
Martin 2014 (26)	RCT[3] or prospective cohort, depending on the analysis (PROBIT)	Belarus	$n = 13{,}616$ Baseline: birth Race/ethnicity NR	Intervention group (higher rates of any BF measured at 3, 6, 9, and 12 mo) vs control group	None	Metabolic syndrome at 11.5 y: OR 1.16 (95% CI: 0.81, 1.66)
				BF 3-<6 mo vs BF <3 mo	None	Metabolic syndrome at 11.5 y: OR 1.07 (95% CI: 0.82, 1.39)
				BF ≥6 mo vs BF <3 mo	None	Metabolic syndrome at 11.5 y: OR 1.15 (95% CI: 0.91, 1.46)
				BF duration trend using the categories <3, 3–<6, and ≥6 mo	None	Metabolic syndrome at 11.5 y: $P = 0.24$
Pirila 2014 (32)	Prospective cohort	Finland	$n = 158$ Baseline: birth Race/ethnicity NR	BF duration (mo)	None	Metabolic syndrome at ~32 y: OR 0.95 (95% CI: 0.8, 1.1)

[1] BF, breastfed; NR, not reported; PROBIT, Promotion of Breastfeeding Intervention Trial; RCT, randomized controlled trial; ref., reference.
[2] Exposures, as defined by the authors of the studies included in the body of evidence, which address shorter versus longer durations of any human milk feeding or vice versa.
[3] RCT of an intervention to promote prolonged duration and exclusivity of breastfeeding.

any and exclusive human milk feeding, was likely to have good internal validity. Randomization mitigates selection bias and confounding. Detection bias may have been reduced by collecting infant-feeding data prospectively, and an audit by PROBIT researchers found that a random subset of infant-feeding data showed close agreement with data obtained by maternal interview. Although attrition rose as the follow-up period increased, it was not high (18.5% after 6.5 y of follow-up and 20.1% after 11.5 y). On the other hand, the evidence that examined never versus ever being fed human milk and childhood blood pressure may have lower internal validity (the PROBIT study was not part of this body of evidence because it was a trial of an intervention to promote prolonged duration and exclusivity of human milk feeding among mothers who chose to feed human milk). Forsyth et al. (10) did not control for confounding variables. The remaining studies did control for confounding variables that TEC members identified as being critical confounders for these SRs, including measures of socioeconomic status such as maternal education (8, 11–13) and family household income (11); race and ethnicity (12); and measures of parental health including prepregnancy BMI (8, 11, 12), family history of hypertension (8, 11), and maternal blood pressure (9). Nevertheless, residual confounding from other variables related to infant feeding and CVD risk may have persisted as a source of bias. Attrition also may have biased the evidence because, across the studies, attrition was high (>20%) and differential with respect to variables such as socioeconomic variables (8, 9, 12) and birth weight (8, 10, 12).

The adequacy of the evidence underlying the conclusion statements had limitations with regard to the number and independence of the identified articles. Evidence examining the relationship between never versus ever feeding human milk and childhood blood pressure came from only 5 independent studies, and the primary evidence related to the duration of any and exclusive human milk feeding came from a single study (PROBIT) with supporting evidence from a small number of additional studies.

The consistency of the evidence underlying the conclusion statements varied. The evidence examining never versus ever feeding human milk and childhood blood pressure was reasonably consistent across studies measuring outcomes at 6–7 y of age, as reflected in the conclusion statement. With regard to the relationship between shorter versus longer durations of any human milk feeding and childhood blood pressure, the PROBIT study (25, 26) found evidence of no relationship, and, taken together, the evidence across 5 prospective cohort studies (9, 11, 12, 16, 27–29) provided further evidence of no relationship because it was inconsistent. The consistency of the evidence examining shorter versus longer durations of exclusive human milk feeding and childhood blood pressure and metabolic syndrome could not be assessed because the number of studies was too small.

TEC members had some doubts about the generalizability of the evidence to US populations. On one hand, the samples were all from countries that met the inclusion criterion of being high or very high on the Human Development Index (23) and

TABLE 7 Evidence examining the relationship between shorter versus longer durations of exclusive human milk feeding and blood pressure in childhood[1]

Author and year (ref.)	Study design (study/cohort name where applicable)	Country	Notable sample characteristics	Shorter vs longer durations of exclusive human milk feeding exposures[2]	Significant associations with blood pressure	Non-significant associations with blood pressure
Kramer 2007 (25)	RCT[3] (PROBIT)	Belarus	$n = 13,889$ Baseline: birth Race/ethnicity NR	Intervention group (higher rates of EBF measured at 3 and 6 mo) vs control group	None	SBP at age 6.5 y (mm Hg): mean difference 0.2 (95% CI: −2.9, 3.3) DBP at age 6.5 y (mm Hg): mean difference 0.2 (95% CI: −1.8, 2.2)
Kramer 2009 (48)	Prospective cohort[4] (PROBIT)	Belarus	$n = 2951$ Baseline: birth Race/ethnicity NR	EBF for 3 mo with continued partial BF to ≥6 mo vs EBF ≥6 mo	None	SBP at age 6.5 y (mm Hg): mean difference 0.0 (95% CI: −1.0, 0.9) DBP at age 6.5 y (mm Hg): mean difference −0.3 (95% CI: −1.2, 0.5)
Martin 2014 (26)	RCT[3] or prospective cohort, depending on the analysis (PROBIT)	Belarus	$n = 13,616$ Baseline: birth Race/ethnicity NR	Intervention group (higher rates of EBF measured at 3 and 6 mo) vs control group	None	SBP at 11.5 y (mm Hg): mean difference 1.23 (95% CI: −0.58, 3.05) DBP at 11.5 y (mm Hg): mean difference 0.77 (95% CI: −0.69, 2.23)
				EBF 3-<6 mo vs EBF <3 mo, instrumental variable analysis	None	SBP at 11.5 y (mm Hg): mean difference 3.32 (95% CI: −2.28, 8.92) DBP at 11.5 y (mm Hg): mean difference 2.03 (95% CI: −2.79, 6.84)
				EBF 3–<6 mo vs EBF <3 mo, prospective cohort analysis	None	SBP at 11.5 y (mm Hg): mean difference 0.09 (95% CI: −0.31, 0.48) DBP at 11.5 y (mm Hg): mean difference 0.24 (95% CI: −0.07, 0.55)
				EBF ≥6 mo vs EBF <3 mo, instrumental variable analysis	None	SBP at 11.5 y (mm Hg): mean difference 4.71 (95% CI: −2.86, 12.28) DBP at 11.5 y (mm Hg): mean difference 2.85 (95% CI: −3.93, 9.63)
				EBF ≥6 mo vs EBF <3 mo, prospective cohort analysis	None	SBP at 11.5 y (mm Hg): mean difference 0.73 (95% CI: −0.09, 1.54) DBP at 11.5 y (mm Hg): mean difference 0.58 (95% CI: −0.06, 1.22)
				EBF duration trend using the categories <3, 3–<6, and ≥6 mo	DBP at 11.5 y (mm Hg): $P = 0.03$	SBP at 11.5 y (mm Hg): $P = 0.17$
Vitolo 2013 (49)	Prospective cohort[4]	Brazil	$n = 331$ Baseline: birth Race/ethnicity NR	EBF ≥4 mo vs <4 mo	None	High SBP at 3–4 y: effect 0.31 (95% CI: 0.07, 1.28), $P = 0.1$

[1]DBP, diastolic blood pressure; EBF, exclusively breastfed; NR, not reported; PROBIT, Promotion of Breastfeeding Intervention Trial; RCT, randomized controlled trial; ref., reference; SBP, systolic blood pressure.

[2]Exposures, as defined by the authors of the studies included in the body of evidence, which address shorter versus longer durations of exclusive human milk feeding or vice versa.

[3]RCT of an intervention to promote prolonged duration and exclusivity of breastfeeding.

[4]The cohort was sampled from an RCT; however, the data of interest from this article are unrelated to randomization.

therefore had a level of human development likely generalizable to the United States. However, none of the conclusion statements was drawn from evidence that included US samples, and US populations may have higher cardiovascular risk than the populations from which study participants were sampled. A difference in cardiovascular risk could reduce the generalizability of the evidence to the US population of interest.

In the NESR grading rubric, the impact of the evidence takes into consideration the directness with which the study designs examined the link between the exposure and outcome of interest in the SR question, and the clinical significance of the evidence. Two of the studies in the body of evidence examining never versus ever feeding human milk and childhood blood pressure were indirect because they were originally designed to examine the effect of long-chain polyunsaturated fatty acid supplementation in infant formula (10, 13). In the bodies of evidence examining the durations of any and exclusive human milk feeding, the PROBIT study was designed as a cluster randomized controlled trial

TABLE 8 Evidence examining the relationship between shorter versus longer durations of exclusive human milk feeding and metabolic syndrome in childhood[1]

Author and year (ref.)	Study design (study/cohort name where applicable)	Country	Notable sample characteristics	Shorter vs longer durations of exclusive human milk feeding exposures[2]	Significant associations with metabolic syndrome	Nonsignificant associations with metabolic syndrome
Martin 2014 (26)	RCT[3] or prospective cohort, depending on the analysis (PROBIT)	Belarus	$n = 13{,}616$ Baseline: birth Race/ethnicity NR	Intervention group (higher rates of EBF measured at 3 and 6 mo) vs control group	None	Metabolic syndrome at 11.5 y: OR 1.16 (95% CI: 0.81, 1.66)
				EBF 3–<6 mo vs EBF <3 mo	None	Metabolic syndrome at 11.5 y: OR 1.09 (95% CI: 0.86, 1.39)
				EBF ≥6 mo vs EBF <3 mo	None	Metabolic syndrome at 11.5 y: OR 1.14 (95% CI: 0.68, 1.89)
				EBF duration trend using the categories <3, 3–<6, and ≥6 mo EBF	None	Metabolic syndrome at 11.5 y: $P = 0.43$

[1]EBF, exclusively breastfed; NR, not reported; PROBIT, Promotion of Breastfeeding Intervention Trial; RCT, randomized controlled trial; ref., reference.
[2]Exposures, as defined by the authors of the studies included in the body of evidence, which address shorter versus longer durations of exclusive human milk feeding or vice versa.
[3]RCT of an intervention to promote prolonged duration and exclusivity of breastfeeding.

of a breastfeeding promotion intervention, which created study groups with distinct human milk exposures, and the outcomes of interest in this SR were listed as secondary outcomes. The evidence underlying the conclusion statements is unlikely to have clinical significance because it suggested that infant milk-feeding practices do not relate to CVD risk in childhood.

Research recommendations

TEC members identified several areas for future research. There was insufficient evidence to answer 1 of the 4 SR questions (Table 9); no articles met the inclusion criteria that examined the intensity, proportion, or amount of human milk fed to mixed-fed infants. In addition, the available evidence tended to examine intermediate outcomes instead of endpoint CVD outcomes and studied samples outside of the United States that may differ in cardiovascular risk from the US population. Therefore, the primary research recommendation is for future research to focus on these gaps in evidence. Some potential means of accessing data include linking surveillance systems that collect data about infant feeding and noncommunicable diseases and making use of emerging electronic medical record data.

Researchers should move toward collecting infant-feeding data consistently using validated methods, and we propose

TABLE 9 Systematic review questions, conclusion statements, and grades of the evidence supporting the conclusion statements[1]

Systematic review question	Conclusion statements and grades
What is the relationship between never versus ever feeding human milk and CVD outcomes?	Limited evidence suggests that never versus ever being fed human milk is associated with higher blood pressure, within a normal range, at 6–7 y of age. (Grade: Limited) Evidence about the relationship of never versus ever being fed human milk with blood lipids in childhood was inconclusive, and there was insufficient evidence to determine the relationship of never versus ever being fed human milk with endpoint CVD outcomes, blood pressure and blood lipids in adolescence or adulthood, metabolic syndrome, and arterial stiffness. (Grade: Grade not assignable)
What is the relationship between shorter versus longer durations of any human milk feeding and CVD outcomes?	Moderate evidence suggests that there is no association between the duration of any human milk feeding and blood pressure in childhood. (Grade: Moderate) Evidence about the relationship of shorter versus longer durations of any human milk feeding with blood lipids in childhood and adulthood and with metabolic syndrome was inconclusive, and there was insufficient evidence to determine the relationship of shorter versus longer durations of any human milk feeding with endpoint CVD outcomes, blood pressure in adolescence or adulthood, blood lipids in adolescence, and arterial stiffness. (Grade: Grade not assignable)
What is the relationship between shorter versus longer durations of exclusive human milk feeding and CVD outcomes?	Limited evidence suggests that there is no association between the duration of exclusive human milk feeding and blood pressure in childhood or metabolic syndrome at 11.5 y of age. Most of the evidence comes from just 1 non-US sample assessed using a strong study design. (Grade: Limited) There was insufficient evidence to determine the relationship of shorter versus longer durations of exclusive human milk feeding with endpoint CVD outcomes, blood pressure in adolescence or adulthood, blood lipids, and metabolic syndrome at ages other than 11.5 y. (Grade: Grade not assignable)
What is the relationship between feeding a lower versus higher intensity, proportion, or amount of human milk to mixed-fed infants and CVD outcomes?	There was insufficient evidence to determine the relationship between feeding a lower versus higher intensity, proportion, or amount of human milk to mixed-fed infants and CVD outcomes. (Grade: Grade not assignable)

[1]CVD, cardiovascular disease.

studying the duration of human milk feeding among infants fed human milk (i.e., assess infants never fed human milk separately). Researchers should consider effect modification in their study design whenever possible (e.g., participant sex) in case biological or environmental characteristics modify the impact of infant feeding on the outcomes. Infant-feeding research will continue to rely on observational designs; however, researchers should endeavor to minimize bias through sound research design and conduct. For example, baseline differences in critical confounding variables should be assessed. The critical confounding variables proposed by TEC members were race and ethnicity, socioeconomic status, and family history of cardiovascular risk. Additional study designs that further minimize confounding include sib-pair analyses (e.g., comparisons of associations within sibling pairs compared with associations irrespective of sibship), and analyses of cohorts with different confounding structures; the use of instrumental variables such as Mendelian randomization approaches will also be helpful in minimizing confounding (51).

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References

1. Obbagy JE, Blum-Kemelor DM, Essery EV, Lyon JMG, Spahn JM. USDA Nutrition Evidence Library: methodology used to identify topics and develop systematic review questions for the birth-to-24-mo population. Am J Clin Nutr 2014;99(3):S 692–6.
2. Raiten DJ, Raghavan R, Porter A, Obbagy JE, Spahn JM. Executive summary: evaluating the evidence base to support the inclusion of infants and children from birth to 24 mo of age in the Dietary Guidelines for Americans—"the B-24 Project." Am J Clin Nutr 2014;99(3):663s–91s.
3. Stoody EE, Spahn JM, Casavale KO. The Pregnancy and Birth to 24 Months Project: a series of systematic reviews on diet and health. Am J Clin Nutr 2019;109(7):685S–97S.
4. Centers for Disease Control and Prevention. Version 28 November 2017. [Internet]. Available from: https://www.cdc.gov/heartdisease/facts.htm [cited 28 February, 2018].
5. National Heart Lung and Blood Institute. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. NIH Publication No. 12-7486. October 2012.
6. Obbagy JE, Spahn JM, Wong YP, Psota TL, Spill MK, Dreibelbis C, Güngör D, Nadaud P, Raghavan R, Callahan EH, et al. Systematic review methodology used in the Pregnancy and Birth to 24 Months Project. Am J Clin Nutr 2019;109(7):951S–7S.
7. Infant Formula Act of 1980. 96-359.
8. Martin RM, Ness AR, Gunnell D, Emmett P, Davey Smith G. Does breast-feeding in infancy lower blood pressure in childhood? The Avon Longitudinal Study of Parents and Children (ALSPAC). Circulation 2004;109(10):1259–66.
9. Wilson AC, Forsyth JS, Greene SA, Irvine L, Hau C, Howie PW. Relation of infant diet to childhood health: seven year follow up of cohort of children in Dundee infant feeding study. BMJ 1998;316(7124):21–5.
10. Forsyth JS, Willatts P, Agostoni C, Bissenden J, Casaer P, Boehm G. Long chain polyunsaturated fatty acid supplementation in infant formula and blood pressure in later childhood: follow up of a randomised controlled trial. BMJ 2003;326(7396):953.
11. de Jonge LL, van Osch-Gevers L, Geelhoed JJ, Hofman A, Steegers EA, Helbing WA, Jaddoe VW. Breastfeeding is not associated with left cardiac structures and blood pressure during the first two years of life. The Generation R Study. Early Hum Dev 2010;86(8):463–8.
12. de Jonge LL, Langhout MA, Taal HR, Franco OH, Raat H, Hofman A, van Osch-Gevers L, Jaddoe VW. Infant feeding patterns are associated with cardiovascular structures and function in childhood. J Nutr 2013;143(12):1959–65.
13. de Jong C, Boehm G, Kikkert HK, Hadders-Algra M. The Groningen LCPUFA study: no effect of short-term postnatal long-chain polyunsaturated fatty acids in healthy term infants on cardiovascular and anthropometric development at 9 years. Pediatr Res 2011;70(4):411–6.
14. Kwok MK, Leung GM, Schooling CM. Breast feeding and early adolescent behaviour, self-esteem and depression: Hong Kong's 'Children of 1997' birth cohort. Arch Dis Child 2013;98(11):887–94.
15. Plancoulaine S, Charles MA, Lafay L, Tauber M, Thibult N, Borys JM, Eschwege E; Fleurbaix Laventie Ville Sante Study g. Infant-feeding patterns are related to blood cholesterol concentration in prepubertal children aged 5–11 y: the Fleurbaix-Laventie Ville Sante study. Eur J Clin Nutr 2000;54(2):114–9.
16. Gishti O, Gaillard R, Durmus B, Hofman A, Duijts L, Franco OH, Jaddoe VW. Infant diet and metabolic outcomes in school-age children. The Generation R Study. Eur J Clin Nutr 2014;68(9):1008–15.
17. Bekkers MB, Brunekreef B, Smit HA, Kerkhof M, Koppelman GH, Oldenwening M, Wijga AH. Early-life determinants of total and HDL cholesterol concentrations in 8-year-old children; the PIAMA birth cohort study. PLoS One 2011;6(9):e25533.
18. Victora CG, Horta BL, Post P, Lima RC, De Leon Elizalde JW, Gerson BM, Barros FC. Breast feeding and blood lipid concentrations in male Brazilian adolescents. J Epidemiol Community Health 2006;60(7):621–5.
19. Evelein AM, Geerts CC, Visseren FL, Bots ML, van der Ent CK, Grobbee DE, Uiterwaal CS. The association between breastfeeding and the cardiovascular system in early childhood. Am J Clin Nutr 2011;93(4):712–8.
20. Sangun O, Dundar B, Kosker M, Pirgon O, Dundar N. Prevalence of metabolic syndrome in obese children and adolescents using three different criteria and evaluation of risk factors. J Clin Res Pediatr Endocrinol 2011;3(2):70–6.
21. US Food and Drug Administration. Version 19 December 2013. [Internet]. Available from: https://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/InfantFormula/ucm136118.htm#manufacture [cited 23 March, 2018].
22. Food and Agriculture Organization of the United Nations. World Health Organization. Codex Alimentarius. International Food Standards. Standard for infant formula and formulas for special medical purposes intended for infants. Codex Stan 72-1981. 2007.
23. United Nations Development Programme. Human Development Report 2014. New York: United Nations: 2014.
24. Flynn JT, Kaelber DC, Baker-Smith CM, Blowey D, Carroll AE, Daniels SR, de Ferranti SD, Dionne JM, Falkner B, Flinn SK, et al. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. Pediatrics 2017;140(3).
25. Kramer MS, Matush L, Vanilovich I, Platt RW, Bogdanovich N, Sevkovskaya Z, Dzikovich I, Shishko G, Collet JP, Martin RM, et al. Effects of prolonged and exclusive breastfeeding on child height, weight, adiposity, and blood pressure at age 6.5 y: evidence from a large randomized trial. Am J Clin Nutr 2007;86(6):1717–21.
26. Martin RM, Patel R, Kramer MS, Vilchuck K, Bogdanovich N, Sergeichick N, Gusina N, Foo Y, Palmer T, Thompson J, et al. Effects of promoting longer-term and exclusive breastfeeding on cardiometabolic risk factors at age 11.5 years: a cluster-randomized, controlled trial. Circulation 2014;129(3):321–9.
27. Amorim Rde J, Coelho AF, de Lira PI, Lima Mde C. Is breastfeeding protective for blood pressure in schoolchildren? A cohort study in northeast Brazil. Breastfeed Med 2014;9(3):149–56.

28. Hosaka M, Asayama K, Staessen JA, Ohkubo T, Hayashi K, Tatsuta N, Kurokawa N, Satoh M, Hashimoto T, Hirose T, et al. Breastfeeding leads to lower blood pressure in 7-year-old Japanese children: Tohoku Study of Child Development. Hypertens Res 2013;36(2):117–22.
29. Ulbak J, Lauritzen L, Hansen HS, Michaelsen KF. Diet and blood pressure in 2.5-y-old Danish children. Am J Clin Nutr 2004;79(6):1095–102.
30. Horta BL, Victora CG, Lima RC, Goncalves H, Guimaraes BE, Barros FC. Breastfeeding duration and blood pressure among Brazilian adolescents. Acta Paediatr 2006;95(3):325–31.
31. Mann KD, Tennant PW, Parker L, Unwin NC, Pearce MS. The relatively small contribution of birth weight to blood pressure at age 49–51 years in the Newcastle Thousand Families Study. J Hypertens 2011;29(6):1077–84.
32. Pirila S, Taskinen M, Viljakainen H, Makitie O, Kajosaari M, Saarinen-Pihkala UM, Turanlahti M. Breast-fed infants and their later cardiovascular health: a prospective study from birth to age 32 years. Br J Nutr 2014;111(6):1069–76.
33. Taittonen L, Nuutinen M, Turtinen J, Uhari M. Prenatal and postnatal factors in predicting later blood pressure among children: cardiovascular risk in young Finns. Pediatr Res 1996;40(4):627–32.
34. Fall CH, Barker DJ, Osmond C, Winter PD, Clark PM, Hales CN. Relation of infant feeding to adult serum cholesterol concentration and death from ischaemic heart disease. BMJ 1992;304(6830):801–5.
35. Hoppu U, Isolauri E, Koskinen P, Laitinen K. Diet and blood lipids in 1–4 year-old children. Nutr Metab Cardiovasc Dis 2013;23(10): 980–6.
36. Ramirez-Silva I, Rivera JA, Trejo-Valdivia B, Martorell R, Stein AD, Romieu I, Barraza-Villarreal A, Ramakrishnan U. Breastfeeding status at age 3 months is associated with adiposity and cardiometabolic markers at age 4 years in Mexican children. J Nutr 2015;145(6):1295–302.
37. Strbak V, Skultetyova M, Hromadova M, Randuskova A, Macho L. Late effects of breast-feeding and early weaning: seven-year prospective study in children. Endocr Regul 1991;25(1-2):53–7.
38. Thorsdottir I, Gunnarsdottir I, Palsson GI. Association of birth weight and breast-feeding with coronary heart disease risk factors at the age of 6 years. Nutr Metab Cardiovasc Dis 2003;13(5):267–72.
39. Kark JD, Troya G, Friedlander Y, Slater PE, Stein Y. Validity of maternal reporting of breast feeding history and the association with blood lipids in 17 year olds in Jerusalem. J Epidemiol Community Health 1984;38:218–25.
40. Kajantie E, Barker DJ, Osmond C, Forsen T, Eriksson JG. Growth before 2 years of age and serum lipids 60 years later: the Helsinki Birth Cohort study. Int J Epidemiol 2008;37(2):280–9.
41. Pearce MS, Relton CL, Parker L, Unwin NC. Sex differences in the association between infant feeding and blood cholesterol in later life: the Newcastle thousand families cohort study at age 49–51 years. Eur J Epidemiol 2009;24(7):375–80.
42. Huang RC, Burke V, Newnham JP, Stanley FJ, Kendall GE, Landau LI, Oddy WH, Blake KV, Palmer LJ, Beilin LJ. Perinatal and childhood origins of cardiovascular disease. Int J Obes (Lond) 2007;31(2):236–44.
43. Schack-Nielsen L, Molgaard C, Larsen D, Martyn C, Michaelsen KF. Arterial stiffness in 10-year-old children: current and early determinants. Br J Nutr 2005;94(6):1004–11.
44. Osmond C, Barker DJ, Winter PD, Fall CH, Simmonds SJ. Early growth and death from cardiovascular disease in women. BMJ 1993;307(6918):1519–24.
45. Balkau B, Charles MA. Comment on the provisional report from the WHO consultation. European Group for the Study of Insulin Resistance (EGIR). Diabet Med 1999;16(5):442–3.
46. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith SC, Jr, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation 2005;112(17):2735–52.
47. Olufadi R, Byrne CD. Clinical and laboratory diagnosis of the metabolic syndrome. J Clin Pathol 2008;61(6):697–706.
48. Kramer MS, Matush L, Bogdanovich N, Aboud F, Mazer B, Fombonne E, Collet JP, Hodnett E, Mironova E, Igumnov S, et al. Health and development outcomes in 6.5-y-old children breastfed exclusively for 3 or 6 mo. Am J Clin Nutr 2009;90(4):1070–4.
49. Vitolo MR, da Costa Louzada ML, Rauber F, Campagnolo PD. Risk factors for high blood pressure in low income children aged 3–4 years. Eur J Pediatr 2013;172(8):1097–103.
50. National High Blood Pressure Education Program Working Group on High Blood Pressure in C, Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. Pediatrics 2004;114(2 Suppl 4th Report):555–76.
51. Brion M-JA, Lawlor DA, Matijasevich A, Horta B, Anselmi L, Araújo CL, Menezes AMB, Victora CG, Smith GD. What are the causal effects of breastfeeding on IQ, obesity and blood pressure? Evidence from comparing high-income with middle-income cohorts. Int J Epidemiol 2011;40(3):670–80.