Final report

The effect of consumption of animal milk compared to infant formula for non-breastfed/mixed-fed infants 6-11 months of age. A systematic review and meta-analysis

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Executive Summary

Background

The World Health Organization (WHO) and United Nations Children's Fund (UNICEF) recommend that infants should be exclusively breastfed for the first six months of life with continued breastfeeding for up to 2 years of age or beyond alongside complementary feeding. For women who do not breastfeed, WHO recommends using infant formula for the first six months of life or expressed heat-treated breast milk; however, there are conflicting opinions on whether feeding animal milk is a safe alternative to breast milk during 6-11 months of age. Therefore, the objective of this review is to synthesize the most recent evidence on the effects of the consumption of animal milk compared to infant formula in non-breastfed or mixed breastfed infants aged 6-11 months.

Objective

For non-breastfed or mixed-fed (breastmilk and formula) infants 6-11 months of age, is the consumption of animal milk, compared to infant formula, associated with beneficial or adverse outcomes for health and development?

Search Methods

In September 2020, we searched PubMed, EMBASE, the Cochrane Central Register for Controlled Trials, Web of Science, CINHAL, Scopus, WHO Global Index Medicus. We also searched the reference section of the included studies and relevant reviews.

Selection Criteria

We included randomized controlled trials (RCTs) and observational studies with a control group that assessed animal milk use and compared it with formula milk in apparently healthy infants 6-11 months of age. We excluded case-control studies, case series, and case reports.

Data Collection and Analysis

Two review authors screened the titles and abstracted the data from selected studies. We used the Cochrane risk of bias tool (RoB 2) and the risk of bias in non-randomized studies of interventions (ROBINS-I) tool to assess the risk of bias for each outcome from the included studies. The primary outcomes were anemia, gastrointestinal blood loss, weight for age, length for age, and weight for length; the secondary outcomes included those related to iron indices, gut health, and neurodevelopment. We analyzed the data from cohort studies and randomized controlled trials separately. We assessed the overall certainty of evidence using the GRADE approach.

Main Results

We screened 4340 titles and included nine studies in this review with a total of 2536 participants. Four studies were RCTs and five were observational cohort studies. All but one included study was conducted in a high-income country. All included studies used cow's milk as the animal milk, but there was variability in the type of formula milk used. Seven studies contributed data for meta-analysis, but all the studies did not contribute data for each outcome. The data from two cohort studies and two randomized trials showed low certainty of evidence that the use of cow's milk increased the risk of anemia compared to formula milk (Cohort studies RR: 2.26, 95% CI: 1.15, 4.43, No. of studies: 2; p= 0.02, I^2 = 0%, Grade certainty: Low: Randomized controlled trials: RR: 4.03, 95% CI: 1.68, 9.65, No. of studies: 2; p = 0.002, I^2 = 0%; Grade certainty: Low). Data from a cohort study and a randomized trial showed a low certainty evidence that the use of cow's milk may increase the blood loss from the gastrointestinal tract compared to formula milk (Cohort study RR: 1.52, 95% CI: 0.73, 3.16, No. of studies: 1; p = 0.27; Grade certainty: very Low: Randomized controlled trial: RR: 3.14, 95% CI: 0.98, 10.04, No. of studies: 1; p = 0.05; Grade certainty: Low). There was no significant effect of use of animal milk versus formula milk

on weight for age (Randomized Controlled Trials: SMD: -0.02, 95% CI: -0.26, 0.21, No. of studies: 3; p = 0.84, I^2 = 19%, GRADE certainty: low) or length for age (Randomized Controlled Trials: SMD: 0.07, 95% CI: -0.15, 0.30, No. of studies: 2; p = 0.51, I^2 = 17%, Grade certainty: low). The use of animal milk seemed to increase the risk of iron deficiency anemia ((Cohort studies: RR: 2.26, 95% CI: 1.15, 4.43, No. of studies: 2; p = 0.02, I^2 = 0%, GRADE certainty: low) and was associated with lower level of blood hemoglobin (Cohort studies SMD = -0.37, 95% CI: -0.78, 0.05, No. of studies: 2; p = 0.09, I^2 = 52%; Grade certainty: Low: Randomized Controlled Trials: SMD -0.32, 95% CI: -0.59, -0.05, No. of studies: 3; p = 0.02, I^2 = 0%, Grade certainty: Low). Data from a single RCT did not show a significant difference in neurodevelopmental outcomes for PDI (Psychomotor developmental index) scores (SMD 0.18, 95 % CI -0.02, 0.37, p=0.10, 1 study, total participants 428, GRADE certainty: low) or MDI (Mental developmental index) scores (SMD 0.16, 95 % CI -0.03, 0.36, p=0.10, 1 study, total participants 428, GRADE certainty: low). A single observational study reported an increased incidence of constipation (RR 3.31, 95 % CI 0.89,12.37, GRADE certainty: very low) and diarrhea (RR 1.86, 95 % CI 1.05-33.10, GRADE certainty: very low) in the animal milk group compared to formula milk.

Conclusions

The use of cow's milk in infants aged 6-11 months who are non-breastfed/mixed breastfed may increase the risk of anemia but is unlikely to affect growth outcomes. Further studies are needed from low- and middle-income countries to assess the optimal milk-type for non-breastfed infants 6-11 months of age.

Keywords: Animal's milk, infant formula, anemia, cow's milk

Full report:

Introduction

The World Health Organization (WHO) and United Nations Children's Fund (UNICEF) recommend exclusive breastfeeding for the first six months of life with the continuation of breastfeeding for up to 2 years or beyond with complementary feeding beginning at 6 months of age[1,2]. However, many infants do not receive breastmilk exclusively through 6 months of age, or breastfeeding might be stopped before the recommended duration of 2 years[3]. According to the Lancet Breastfeeding series, 37% of children aged 6-24 months do not receive breast milk, with variation in rates of 18% in the lower-income countries, 34 % in the lower-middle-income countries, and 55% in the upper-middle-income countries[4]. Instead, alternative milk beverages are often used, including infant formula and raw animal milk products[3-5]. The use of cow's milk in infancy has been associated with gastrointestinal blood loss, iron deficiency anemia, and increased solute load for kidneys[3,6-8]. Despite these adverse effects, there are conflicting opinions on the safety of feeding cow's milk between 6 and 12 months of age. The WHO's guiding Principles for Feeding Non-breastfed Children 6-24 Months of Age states that feeding animal milk and appropriate complementary foods is a safe choice since the adverse effect of iron deficiency provoked by gastrointestinal blood loss resolves by 12 months of age[3,8]. Furthermore, the same effects are not seen if the milk is heat-treated, and iron deficiency can be avoided by using iron supplements or supplementary foods with adequate bioavailability of iron[3,8]. Alternatively, the Dietary Guidelines for Americans (2020) states that infants should not consume cow's milk before age 12 months as their primary milk drink[9]. Additionally, there have been improvements made to infant formula over the last 20 years that may further increase its benefits compared to cow's milk[10]. Therefore, this review's objective was to synthesize the most

recent research on the effects of the consumption of animal milk compared to infant formula in non-breastfed or mixed breastfed infants aged 6-11 months of age.

Objective

For non-breastfed or mixed-fed (breastmilk and formula) infants 6-11 months of age, is the consumption of animal milk, compared to infant formula, associated with beneficial or adverse outcomes for health and development?

Methods and Analysis

We followed the Cochrane Collaboration's standard guidelines for this review, and we followed the PRISMA guidelines to report our results. The review's detailed methods were published in a protocol[11], and the protocol was also pre-registered on the PROSPERO registry (ID: CRD42020210925).

We included individual and cluster randomized trials, quasi-randomized experimental design studies, and prospective and retrospective cohort studies with a control group.

The study population was apparently healthy infants 6-11 months of age who were non-breastfed or mixed fed (breast milk and formula) irrespective of gestational age and birth weight. We excluded studies with participants who have chronic diseases such as bronchopulmonary dysplasia, genetic disorders, aerodigestive problems, or congenital anomalies.

The intervention of interest was the use of animal milk in infants 6-11 months of age. We included studies in which animal milk was the main milk drink as defined by study authors, or more than 50% of the infant's milk intake was animal milk. We included studies irrespective of whether the animal milk was boiled, pasteurized, or unpasteurized, or if the animal milk was full-fat, reduced-fat, or skim milk. The comparison group in the included studies was formula feeding or mixed feeding (i.e., breastfeeding and formula feeding). We included studies irrespective of

the type of formula used; this could include cow's milk-based formula, partially or extensively hydrolyzed formula, or plant-based formulas such as soy formula. The Food and Drug Administration (FDA) of the United States Federal Food, Drug, and Cosmetic Act (FFDCA) define infant formula as "a food which purports to be or is represented for special dietary use solely as a food for infants by reason of its simulation of human milk or its suitability as a complete or partial substitute for human milk"[12].

The primary outcomes of interest were: Any anemia (dichotomous, as defined by authors); Gastrointestinal blood loss (dichotomous, based on stool occult testing); Weight for age (continuous, kg or Z scores); Length for age (continuous, cm or Z scores); and Weight for length Z score. The secondary outcomes were: Iron deficiency anemia (dichotomous); Serum iron level (continuous); Serum ferritin level (continuous); Stool hemoglobin concentration (continuous); Blood hemoglobin concentration (continuous); Serum triglycerides (continuous); Diarrhea (dichotomous, defined as > 3 loose stools per day); Constipation (dichotomous, defined <3 bowel movements per week); Pneumonia (dichotomous as defined by authors); Allergy (dichotomous IgE-Mediated and non-IgE Mediated and mixed); Obesity (dichotomous); Overweight (dichotomous); Neurodevelopmental outcomes (continuous). We considered the time of follow-up for these outcomes at 7 months, 9 months, 12 months, and the longest follow-up.

We conducted systematic electronic searches on multiple databases, including PubMed, EMBASE, the Cochrane Central Register for Controlled Trials, Web of Science, CINHAL, Scopus, and WHO Global Index Medicus. There were no restrictions applied to the searches based on outcomes, study design, publication status, publication date, or language. The last date

of the search was September 30th, 2020. Our search strategy for all the databases is shown in Annex 1 of the supplementary document.

Searches from all the databases were combined in bibliographic software (EndNote)[13], and duplicates were removed. Two authors (either JE, AI, JC, or MZ) screened the titles using software Covidence [14]. Two authors (JE, JC, or MZ) independently extracted the data from the included studies and compared their findings. Any conflict was resolved by discussion and with the help of the senior author (AI) on the team if needed. The risk of bias was assessed using the Cochrane risk of bias tool-2 (ROB 2.0)[15] for RCTs and using the Cochrane risk of bias in non-randomized studies (ROBINS-I) tool for non-randomized studies[16]. The risk of bias was assessed by two authors for each study included in a pooled analysis.

We reported findings from all included studies in a narrative synthesis and also conducted meta-analyses to synthesize evidence across studies quantitatively. Meta-analyses were conducted when data were available from more than one study and clinical and methodological homogeneity was present in the included studies. Dichotomous outcomes were pooled to obtain an average relative risk (RR). For continuous outcomes, we pooled the data to obtain a standardized mean difference (SMD). All study-level and average effect sizes are reported alongside their 95 % confidence intervals (CIs). We used the generic inverse variance weighting method for meta-analysis. We used a random-effects model for meta-analysis, given that there might be heterogeneity in effects due to variability in the study populations and interventions used. We analyzed randomized controlled trials and cohort studies, separately. We used RevMan[17] software for the statistical analysis.

Statistical heterogeneity in the pooled analysis was assessed using Tau^2, $\chi^{2,}$ and I^2 statistics, and it was considered substantial if the P-value for the Chi^2 test was less than 0.10, the I^2 value

exceeded 50%, and inspection of forest plots showed substantial variability in the effect of the intervention.

We aimed to assess small study and publication bias using funnel plots and regression tests; however, the number of included studies in the meta-analysis was less than ten, so no testing was performed for publication and small study bias (per the analysis protocol)[11].

We assessed the overall certainty of evidence for the effect of the intervention on each primary outcome and select secondary outcomes using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) using the software GradePro[18]. We rated the overall body of evidence to certainty level as very low (we have very little confidence in the effect estimate), low (we have limited confidence in the effect estimate), moderate (we have moderate confidence in the effect estimate; the true effect is likely close to the estimate of the effect), or high (we have high confidence that the true effect lies close to that of the estimate of the effect). We present the results of the GRADE assessment in the form of GRADE Evidence Profiles for the primary outcomes and the following secondary outcomes: blood hemoglobin concentration, iron deficiency anemia, constipation, diarrhea, and neurodevelopmental outcomes.

We aimed to compare effects for the following subgroups when possible: Age group: Age of initiation at 7 months vs. 9 months; Country: Low and middle-income country vs. high-income country; Type of Feeding: Non-breastfeeding vs. mixed feeding; Type of Animal Milk: cow, goat, buffalo, camel, sheep. Finally, we considered the following sensitivity analyses: Studies with a high overall risk of bias excluded; Type of model: Random vs. fixed-effect meta-analysis model.

Results

Literature search

The literature search revealed 4340 titles after the exclusion of duplicates. Figure 1 shows the results of the literature search. After screening the full texts of 96 studies for eligibility, we ultimately included nine studies[6,19-26] available in 11 publications (complete list in Annex 2). We excluded 87 studies, and reasons for exclusion for each study can be found in table of excluded studies in Annex 3.

Characteristics of included studies

Tables 1 and 2 display characteristics of include studies for participant and intervention, respectively.

Study type and Location

Four of the included studies were RCTs[19,20,23,26], and five were prospective observational cohort studies[6,21,22,24,25]. Four studies were conducted in the United States[6,19,25,26], two were from the United Kingdom[21,23], one from Iceland[24], and one from Peru[20]. One study had a multicenter design and took place in 10 countries, including Greece, Spain, Hungary, Ireland, Italy, Portugal, Germany, Chile, Sweden, and Austria[22].

Study population

The studies' median sample size was 133 participants with a range from 15 participants[20] to 971 participants[21]. The mean age of initiation of cow's milk feeding was 6.95 months of age with the range of 3.6 months[6] to 10 months of age[22].

Type of animal milk and Comparators

All studies compared cow's milk feeding as the animal's milk group and formula feeding only as the comparison. Five studies[6,19,20,23,26] used pasteurized homogenized cow's milk. One study[26] used fortified cow's milk. Another study used heat-treated cow's milk[6]. For the comparison

groups, six studies[6,19,20,23,25,26] used cow's milk-based infant formulas. One study[6] used Enfamil as the formula group. Two studies[19,20] used Similac with iron and Carnation follow-up formula as the two formula groups. One study[26] used a specially prepared formula similar in composition to commercially prepared Enfamil, except it contained no added iron. Two studies used iron-supplemented standard cow milk formulas[23,25]. Three of the studies were non-specific about the types of milk or formula used in studies [22-24].

Studies with multiple intervention arms and missing data

Five studies had multiple intervention arms that we combined to obtain a single pairwise comparison[6,20,21,23,27]. For one study[6] we combined whole milk and heat-treated cow's milk for males and females. For three studies[19,20,23], we combined the formula groups. For two studies[20,21], we used standard deviations from studies with similar populations and sample sizes. Annex 4 gives further details on studies where data was converted for this review.

Co-interventions

Four studies included co-interventions. One studies had infants in the cow's milk feeding group eat iron-fortified cereal daily[19] while another study had both the cow's milk feeding group and the formula feeding group eat iron-fortified cereal daily[25]. One study had all infants take a supplement that contained ascorbic acid, iron from ferrous sulfate, and fluoride from sodium fluoride[6]. Another study had infants fed cow's milk take a supplement of ascorbic acid and fluoride in the form of sodium fluoride. At the same time, the formula group received a daily supplement of only fluoride[26].

Confounding variables included in analysis

Four studies (1 RCT and 3 observational studies) included confounding variables in their analysis[21-24]. One study[23] from the United Kingdom randomized infants from the Indian

subcontinent separately due to the high risk for iron deficiency in this population. Additionally, it adjusted for the following variables: breastfeeding, the median duration of breastfeeding, first child, mother education, non-manual social class for neurodevelopmental outcomes expressed as Bayley psychomotor development index (PDI). A prospective cohort study[21] adjusted results for: maternal education, smoking in pregnancy, parity as confounding variables for mean weight. Another cohort study[22] used multiple regression analysis to test associations between hemoglobin, serum ferritin, mean corpuscular volume, transferrin saturation, transferrin as dependent variables, and demographic and dietary factors, growth, and morbidity as independent variables. One cohort study[24] used a linear model which was adjusted for gender, birth weight, and length of exclusive breastfeeding. Two observational studies did not adjust for any confounding variables[6,25].

Effects of interventions

In the section below, we report the meta-analysis and GRADE analysis results for each primary outcome and select secondary outcomes at the longest follow-up. The results for the primary outcomes at other durations of follow up such as at 7, 9, and 12 months are available in Table 3. Table 4 shows GRADE evidence profiles for the primary outcomes and select secondary outcomes. All of the included studies contributed data to an outcome for meta-analysis except two cohort studies[21,22] where the data were reported in a way that could not be meta-analyzed. The results for these studies were reported individually in this review.

Primary Outcomes

Anemia at the longest follow-up

Two RCTs[23,27], and two cohort studies[24,25] reported data on anemia. Each study used slightly different definitions of anemia (please see Annex 5 for definitions). Data from the two cohort

studies included 327 participants with 155 in the milk feeding group and 172 in the formula feeding group. Data from the two RCT studies included 209 participants with 60 in the milk feeding group and 149 participants in the formula feeding group. Three of the studies had the longest follow-up time as 12 months[24,25,27] while one study had the longest follow-up time as 18 months[23]. The results showed a low certainty of evidence that cow's milk as the main milk drink leads to a significant increase in anemia when compared to formula feeding in infants 6-11 months of age (Cohort studies RR: 2.26, 95% CI: 1.15, 4.43, No. of studies: 2; p= 0.02, I^2 = 0%, Grade certainty: Low: Randomized controlled trials: RR: 4.03, 95% CI: 1.68, 9.65, No. of studies: 2; p = 0.002, I^2 = 0%; Grade certainty: Low: figure 2). We downgraded the GRADE certainty for risk of bias (One observational study had a high risk of bias[25] and another[24] had 'moderate' risk of bias and one RCT[19] had 'some concerns') and indirectness (all the studies were conducted in high-income countries) (Table 4).

Subgroup and sensitivity analysis

The *a priori* subgroup analyses based on the type of country (Low and middle-income country vs. high-income country), (type of animal milk cow, goat, buffalo, camel, sheep), and type of feeding in the comparison group (Non-breastfeeding vs. mixed feeding) were not done as all the studies were conducted in high-income countries and used cow's milk as the animal milk. A subgroup analysis based on the age of initiation did not show any significant difference between the groups at 7 months and 9 months of age (p-value for subgroup difference 0.61, supplementary figure 1). Sensitivity analysis based on the type of model used showed the same results for the fixed vs. random model of meta-analysis. One of the cohort studies[25] had a high risk of bias due to lack of adjustment of confounding variables. Exclusion of this study from meta-analysis of the cohort studies changed the summary estimate and the statistical significance

of the summary estimate (RR 6.28, 95 % CI 0.33, 119.77). One RCT had “some concerns’ for risk of bias[19] and exclusion of this study from meta-analysis of RCTs did not change the direction or the statistical significance of the summary estimate (RR 3.77, 95 % CI 1.52, 9.36).

Gastrointestinal blood loss

Two studies reported data on gastrointestinal blood loss. One study was a cohort study[6], and the other was an RCT[26]. The Cohort study included a total of 81 participants with 60 participants in the milk feeding group and 21 participants in the formula feeding group. The RCT included 43 participants with 21 in the milk feeding group and 22 in the formula feeding group. Both the studies quantified gastrointestinal blood loss using the guaiac stool test. The cohort study had the longest follow-up time of 6.54 months[6] while the RCT had the longest follow-up time of 8.28 months[26]. The results showed a very low to low certainty of evidence that cow’s milk leads to increased gastrointestinal blood loss (Cohort study RR: 1.52, 95% CI: 0.73, 3.16, No. of studies: 1; p = 0.27; Grade certainty: very Low: Randomized controlled trial: RR: 3.14, 95% CI: 0.98, 10.04, No. of studies: 1; p = 0.05; Grade certainty: Low: Figure 3). We downgraded the GRADE certainty to very low for cohort study because of the risk of bias (cohort study had 'high’ risk of bias), Imprecision (wide confidence intervals and they included a null effect) and indirectness (study was conducted in high-income country) (Table 4). We downgraded the certainty to low for RCT because of ‘some concerns’ for risk of bias and indirectness (study was conducted in high-income country) (Table 4).

Weight for age

Three RCTs reported weight for age and included 556 participants, with 194 in the animal milk feeding group and 362 in the formula feeding group[20,23,28]. Two studies had a follow-up time of 12 months[20,28]. One study had a follow-up time of 18 months[23]. All three studies included in the

meta-analysis were RCTs[20,23,28]. Two[23,27] of the RCTs had 'some concerns' for risks of bias, and the other a 'high' risk of bias[20]. The pooled results showed no evidence that cow's milk compared to formula feeding had an effect on weight for age (Randomized Controlled Trials: SMD: -0.02, 95% CI: -0.26, 0.21, No. of studies: 3; p = 0.84, I^2 = 19%, Figure 4, GRADE certainty: low). We downgraded the GRADE certainty to low due to the risk of bias and indirectness (all, other than one, of the included studies were conducted in high-income countries) (Table 4).

Subgroup and sensitivity analysis

The subgroup analysis based on the age of initiation of animal milk did not show any significant difference between the age groups of 7 and 9 months (p-value for subgroup difference: 0.42, supplementary figure 2).

A sensitivity analysis based on a fixed-effect model did not change the direction or statistical significance of the summary estimate (SMD 0.00, 95 % CI -0.18, 0.18). Removal of one study[20] with a high risk of bias did not change the direction or statistical significance of the summary estimate (SMD 0.11; 95 % CI -0.03, 0.25).

Length for age

Two RCTs reported length for age and included a total of 529 participants, with 185 in the cow milk feeding group and 344 in the formula feeding group[23,28]. One study had a follow-up time of 12 months[28]. One study had a follow-up time of 18 months[23]. The results showed no evidence that cow's milk compared to formula feeding had an effect on length (Randomized Controlled Trials: SMD: 0.07, 95% CI: -0.15, 0.30, No. of studies: 2; p = 0.51, I^2 = 17%, figure 5, Grade certainty: low). We downgraded the GRADE certainty of evidence to low because of the risk of

bias (one of the two studies had 'some concerns' for risk of bias) and indirectness (all studies were conducted in high-income countries) (Table 4).

Weight for length

No studies reported data on weight for length.

Secondary outcomes

Table 5 includes data on secondary outcomes. We describe the results of selected secondary outcomes for which the GRADE analysis was conducted (Table 4). The results for all the secondary outcomes at the longest follow-up are available in table 5.

Blood hemoglobin concentration

Three RCTs[23,26,27] and two cohort studies[6,24] reported data on hemoglobin concentration in the blood. The two cohort studies had a total number of 246 participants with 148 in the milk feeding group and 98 in the formula feeding group. Three RCTs had a total number of 250 participants with 82 in the milk feeding group and 168 in the formula feeding group. The results showed low certainty evidence that use of animal milk reduces the hemoglobin concentration in blood compared to formula (Cohort studies SMD = -0.37, 95% CI: -0.78, 0.05, No. of studies: 2; p = 0.09, I^2 = 52%; Grade certainty: Low: Randomized Controlled Trials: SMD -0.32, 95% CI: -0.59, -0.05, No. of studies: 3; p = 0.02, I^2 = 0%, Grade certainty: Low, Figure 6). We downgraded the GRADE certainty to low because of the risk of bias and indirectness (Table 4).

Iron deficiency anemia

Two cohort studies reported iron deficiency anemia with 327 participants, 155 in the cow's milk group and 172 in the formula group[24,25]. The pooled results showed a low certainty evidence that the use of animal milk increases the risk of iron deficiency anemia (Cohort studies: RR: 2.26,

95% CI: 1.15, 4.43, No. of studies: 2; p = 0.02, I^2 = 0%, Figure 7). We downgraded the evidence for the risk of bias and indirectness (Table 4).

Neurodevelopmental outcomes

One RCT [23] reported data on neurodevelopmental outcomes and the results did not show a significant difference in neurodevelopmental outcome for PDI (psychomotor developmental index) scores (SMD 0.18, 95 % CI -0.02, 0.37, p=0.10, No. of study: 1, total participants 428, GRADE certainty: low) or MDI (Mental developmental index) scores (SMD 0.16, 95 % CI -0.03, 0.36, p=0.10, No. of study: 1, total participants 428, GRADE certainty: low).

Gut health (diarrhea and constipation)

Data from one cohort study[25] showed very low certainty evidence that the use of animal milk might increase the risk of diarrhea (RR 1.86, 95 % CI: 1.05, 33.10) and constipation (RR 3.31, 95 % CI: 0.89, 12.37) (Table 4).

Other outcomes

Four studies reported data on serum ferritin level, one cohort study and three RTCs. The cohort study had a total number of 165 participants with 87 in the milk feeding group and 78 in the formula feeding group. The RCTs had a total number of 406 participants with 141 in the milk feeding group and 265 in the formula feeding group. The results showed a decrease of serum ferritin level in the animal milk group compared to formula-fed infants (Cohort study SMD: -0.81, 95% CI: -1.13, -0.49, No. of studies: 1 p < 0.00001; Randomized controlled trial: SMD: -0.30, 95% CI: -0.94, 0.34, No. of studies: 3 p = 0.35, Figure 8). Two studies reported data on hemoglobin concentration in the stool with a total of 223 participants, with 93 in the cow's milk group and 135 in the formula feeding group. The pooled results did not show a significant

difference in the stool hemoglobin concentration between the two groups (SMD: 0.22, 95% CI: -0.16, 0.59, p = 0.26, No. of studies: 2; I^2 =41%, Figure 9).

One study[26] reported data on blood iron level with serum iron of 4.60 mg/dl in the cow's milk feeding group and 4.49 mg/dl in the formula feeding group (not significant). One study[25] reported data on triglyceride level. The cow's milk feeding group had a triglyceride level of 107.5 mg/dl, and the formula feeding group had a triglyceride level of 117.5 mg/dl (not significant). One study[25] reported data on allergies but reported it as the level of IgE (continuous variable) rather than as a number of infants presenting with allergies (dichotomous value). IgE level in the cow's milk group was 8.3 IU (international unit) and the IgE level in the formula group was 11.1 IU (not significant). No study reported data on pneumonia, obesity, or overweight.

Male et al. 2001[22] was not included in the meta-analysis because their data was not presented in a way that would allow us to compare cow's milk to formula directly. Instead, the authors presented the effects of cows' milk feeding as a function of time. They reported that the duration of feeding cows' milk decreased hemoglobin levels by 2g/L for every month fed cows' milk. Additionally, authors found that each month of cow's milk feeding increased anemia by 23%, iron deficiency by 18%, and iron deficiency anemia by 39% (p<0.001; p<0.01; p<0.001, respectively).

Hopkin's et al was also not included in the meta-analysis due to differences in reporting of data. The study aimed to assess the weight gain in infants who were fed cow's milk, formula milk or breastmilk. The participants were followed to a maximum of 10 years. There was no difference in weight gain velocity during infancy; however, infants who were fed high volumes of cow's milk (> 600 ml/day) in early infancy had higher weight and height gain after infancy. The study

had more than 30 % loss to follow up, and the study did not adjust for missing data, so we had low confidence in the reported results.

Discussion

Summary of Main Results

This systematic review and meta-analysis evaluated the effect of animal milk vs. infant formula as the main milk drink for non-breastfed/mixed fed infants 6-11 months of age. Results from this evidence synthesis suggest that there is low certainty evidence that the use of animal milk compared to infant formula may increase the risk of anemia and blood loss in the gastrointestinal tract and decrease the levels of blood hemoglobin and serum ferritin. Furthermore, low certainty evidence showed that use of animal milk may not have a differential effect on growth outcomes of weight and length for age compared to formula milk. Limited data were available for neurodevelopmental outcomes and adverse events such as constipation and diarrhea, and no conclusive statements could be made in this regard.

Overall completeness and applicability of evidence

This review summarized evidence from both RCTs and observational cohort studies. We included nine studies comprising 2536 participants; however, data were not available for all outcomes in all the included studies. There were not enough studies to perform all the a priori subgroup analyses so that no conclusions can be drawn for any differential effects of animal milk based on country, or type of animal milk. And because all the included studies used cow’s milk for the animal milk, findings from this review cannot be generalized to other types of animal milk such as goat or buffalo milk. Further, given limited variability in the literature, we could not examine any differential effects based on the treatment of cow's milk, such as heated vs. non-heated, pasteurized vs. non-pasteurized, or diluted vs. non-diluted milk. The subgroup analyses

based on age did not have enough studies to make any conclusive statements about the differential effect of animal milk given at different ages (table 3).

Overall, findings from this review suggest that the use of cow's milk between 6-11 months of age may increase the risk of anemia during infancy. All the measured outcomes related to anemia in this review showed a negative association with cow's milk use compared to infant formula. And the effect seems homogenous as statistical heterogeneity measured based on I^2 was non-significant in almost all the anemia-related outcomes. This finding is interesting to note as at least three studies either fortified the cow's milk or supplied additional iron with the help of fortified complementary foods[6,19,26]. However, these three studies did not contribute data to all the anemia-related outcomes, and their relative contribution to overall summary estimates varied from outcome to outcome. Therefore, we cannot comment with great confidence if the risk of anemia could be averted with additional supplementation by fortifying cow's milk and complementary feedings and future studies might be needed to further elaborate on this aspect of the intervention. The proposed mechanisms by which cow's milk may increase anemia's risk are related to decreased amount of iron in cow's milk, decreased bioavailability of iron, and potentially increased blood loss from the gastrointestinal tract[3].

The use of cow's milk does not seem to have a differential effect on growth outcomes, although the certainty of evidence for growth outcomes was low. One RCT[23] reported data for the neurodevelopmental outcomes, and no difference was found between the two groups for PDI or MDI scores so that no solid conclusion can be drawn about the beneficial or adverse effect of cow's milk in this regard. One cohort study[25] reported data on an increased risk of constipation and diarrhea in the cow's milk group compared to formula milk. However, the number of

participants with these outcomes were small, and no solid conclusion can be drawn that cow's milk increases the risk of constipation or diarrhea compared to formula milk.

Certainty of Evidence

Overall, the number of included studies in each analysis was small. As a result, most of the outcomes received certainty of evidence rating as low or very low. We downgraded the certainty of evidence for most of the outcomes for indirectness because all but one[20] of the included studies were conducted in high-income countries and may not represent low- and middle-income populations. For instance, the risk of anemia might be higher in low- and middle-income countries where the use of animal milk is higher in infants, and there is an increased incidence of diarrhea illness leading to less oral intake and increase losses from the gastrointestinal tract[29]. Two observational cohort studies did not adjust for confounding variables and were rated at high risk of bias[6,25]. One of the RCTs was at high risk of bias due to inadequate methods of randomization[20]. We downgraded the certainty ratings for the risk of bias where applicable.

Potential bias in the review process

We followed the standard guidelines of the Cochrane Collaboration to conduct this review. We adopted a broad search strategy, used multiple databases, and examined 4340 titles and abstracts, including published and ongoing studies. We performed our analysis according to an a priori plan, and the protocol was published in a peer-reviewed journal[11]. We analyzed the data separately for randomized controlled trials and cohort studies. Most of the analyses from observational cohort studies mirrored the evidence from randomized controlled trials, suggesting a true increased risk of anemia with use of cow’s milk in non-breastfed infants greater than six months of age. Some of the included did not provide the data needed for meta-analysis. We adopted the standardized methods to use data from other published studies in case of missing

data such as standard deviations for continuous outcomes. Some studies had more than two study groups and we combined certain groups to avoid double counting of the control group. We were transparent about any decisions made related to missing data and data analysis (Annex 4).

Agreement and disagreement with other studies or review

To the best of our knowledge, no prior study has attempted a meta-analysis for the use of animal milk vs. formula milk in infants 6-11 months. One review published in 2015 included children up to 3 years of age and reported an increased risk of anemia with the use of cow's milk[30]. Recent guidelines for healthy American infants recommend avoiding the use of cow's milk in infants less than 12 months of age, based on a qualitative synthesis of the evidence[31]. Our review added to the literature the qualitative and quantitative synthesis of the data for use of animal milk during 6-11 months of age.

Implication for practice

Use of cow's milk compared to formula milk in infants 6-11 months of age in non-breastfed/mixed-fed infants seems to increase the risk of anemia. However, it is important to note that all the included studies in this review were conducted in high-income countries except for one conducted in Peru[20], an upper-middle-income country. Thus, the generalization of these results to low- and middle-income settings should be considered with caution. Furthermore, a standardized infant formula may not be readily available in low- and middle-income countries and might be expensive compared to cow's milk[32,33]. Other strategies to mitigate the anemia in this age group, such as fortified complementary foods should be studied further in non-breastfed infants [3].

Implication for research

Most of the studies included in this review were relatively old, and there was a paucity of data from the last two decades. Also, only one study was from an upper-middle-income country, and there was a paucity of data from low and middle-income countries. Future research might be warranted to examine the effect of animal milk in low- and middle-income countries and to assess if there is a difference in the type of animal milk and the age when animal milk is first introduced. Furthermore, future studies are needed to assess if the risk of anemia with cow's milk could be reduced with the fortification of cow's milk and complementary feeding with iron. Also, future studies should assess the risk of anemia when the cow's milk is pasteurized, heated, vs diluted.

Conclusions

Low certainty evidence showed that feeding cow's milk to infants 6-11 months of age as the main milk drink, as opposed to formula, seems to increase the risk of anemia and indices of anemia, including iron deficiency anemia and decreased blood hemoglobin and ferritin. There was no differential effect of cow's milk on weight or length compared to infant formula based on low certainty of evidence. Limited data were available for the outcome of neurodevelopment and adverse effects such as diarrhea and constipation, and no solid conclusions could be drawn for these outcomes. Most of the available studies were conducted in high-income countries, and future studies are needed from low- and middle-income countries to assess the optimal milk-type use in non-breastfed/mixed fec infants 6-11 months of age.

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Acronyms and abbreviations

World Health Organization (WHO)

The Federal Food, Drug, and Cosmetic Act (FFDCA)

Confidence Interval (CI)

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)

Grading of Recommendations Assessment, Development, and Evaluation (GRADE)

Psychomotor developmental index (PDI)

Mental developmental index(MDI)

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Figures and Tables

Figure 1: PRISMA Flow Diagram showing results of the literature search

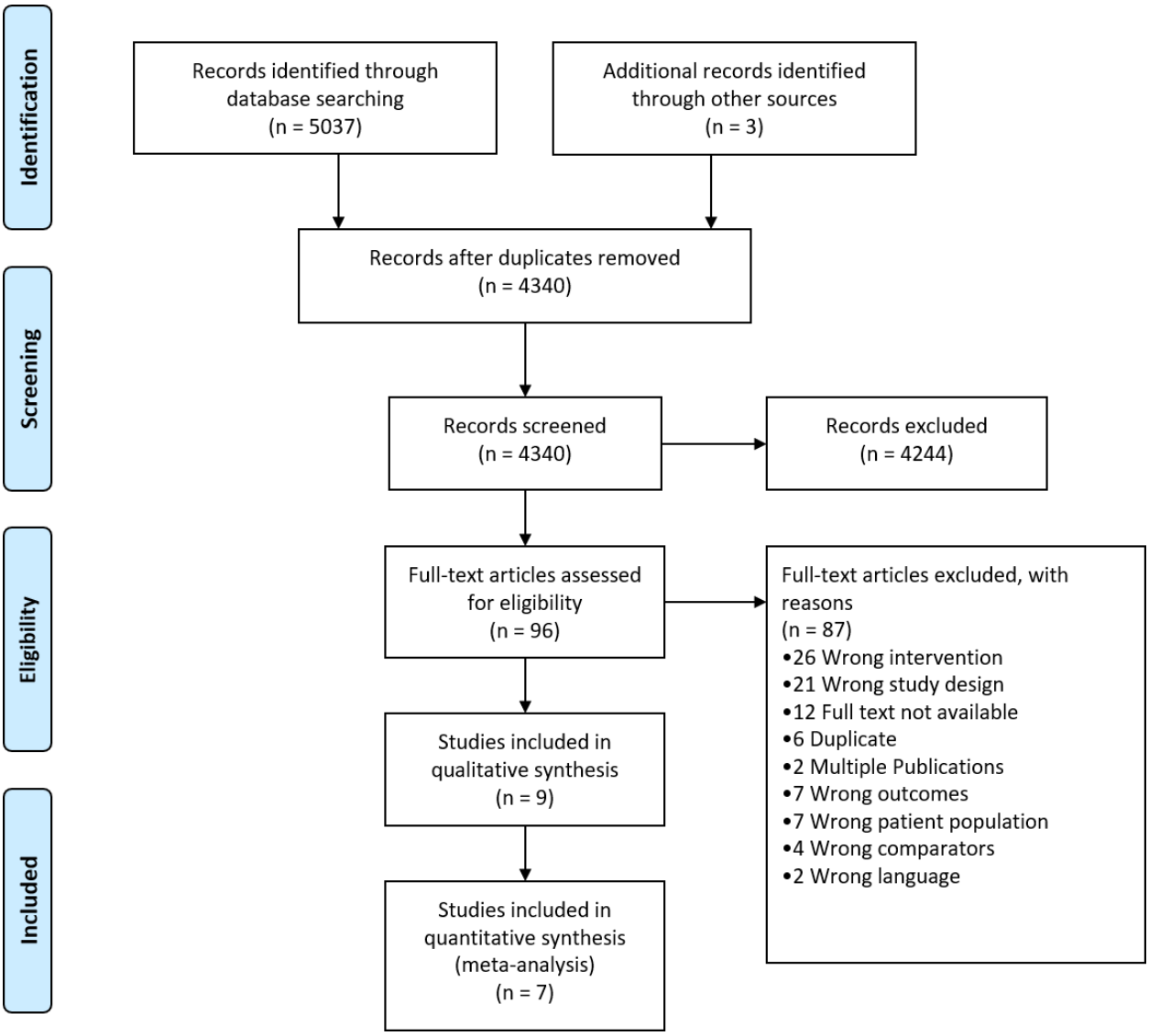
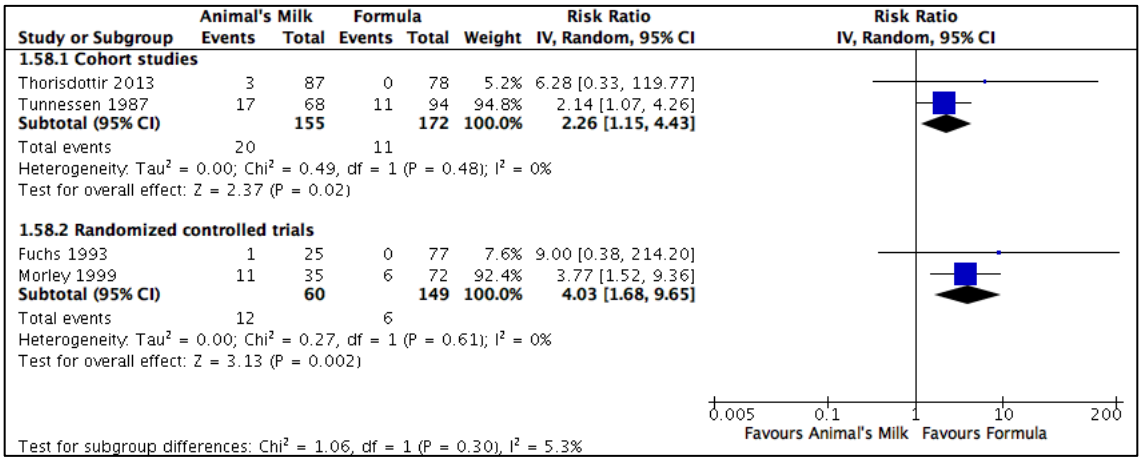
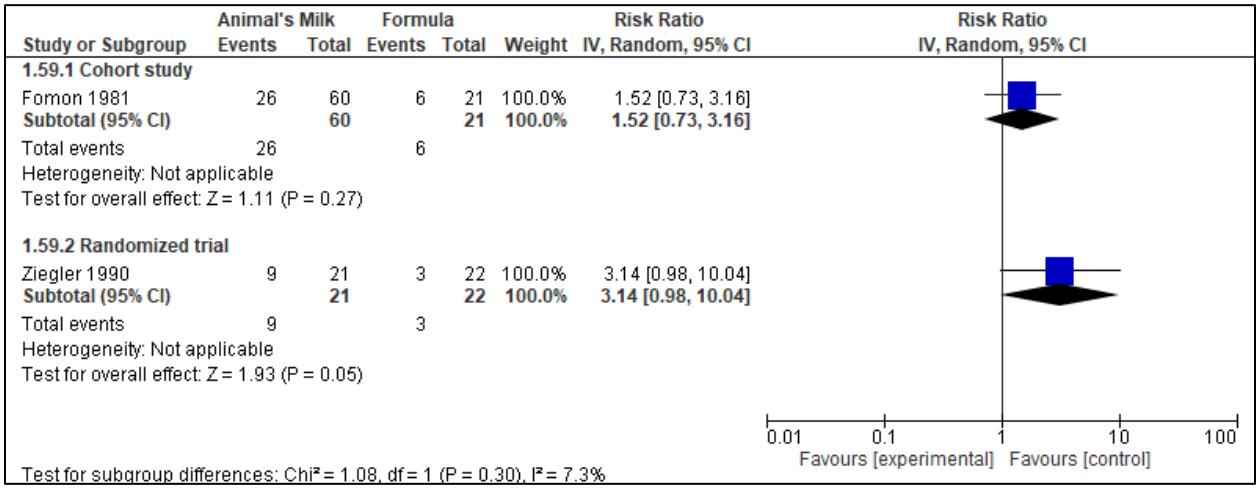


Figure 2: Effect of animal's milk vs formula milk intake in infants 6-11 months of age on Anemia



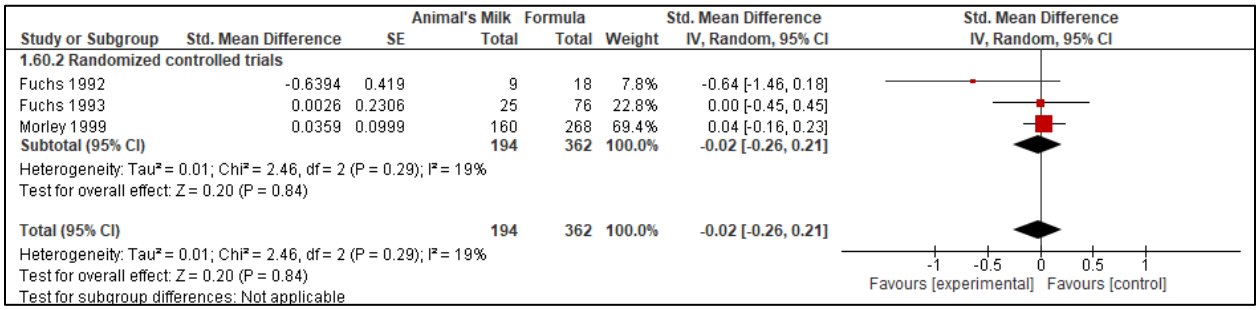
Footnotes: The figure shows results of meta-analysis for use animal milk vs. formula milk for non-breastfed infants based on study type. Only subtotals were calculated as we had decided a priori to pool data from observational studies and randomized controlled trials separately. The direction of effect from both the studies mirror each other and data from randomized trials seems to be confirmatory of effect seen from cohort studies.
Abbreviations: CI: Confidence interval, IV: Inverse variance

Figure 3: Effect of animal's milk vs formula milk intake in infants 6-11 months of age on gastrointestinal blood loss



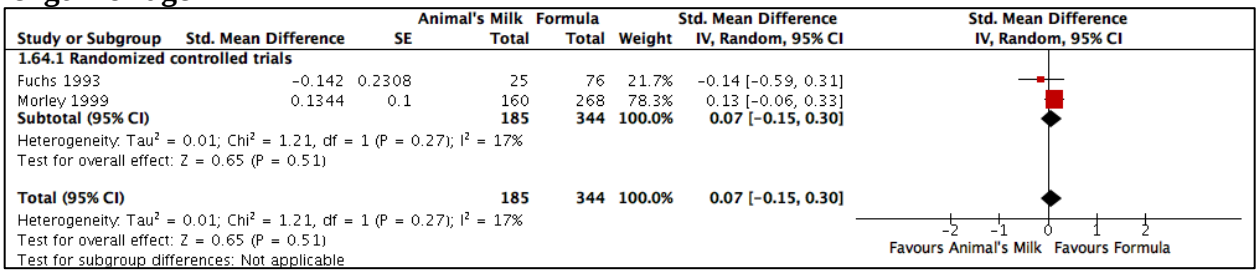
Footnotes: The figure shows results of meta-analysis for use animal milk vs. formula milk for non-breastfed infants based on study type. Only subtotals were calculated as we had decided a priori to pool data from observational studies and randomized controlled trials separately. Number of included studies were small and confidence interval around the summary estimate were wide.
Abbreviations: CI: Confidence interval, IV: Inverse variance

Figure 4: Effect of animal's milk vs formula milk intake in infants 6-11 months of age on weight for age



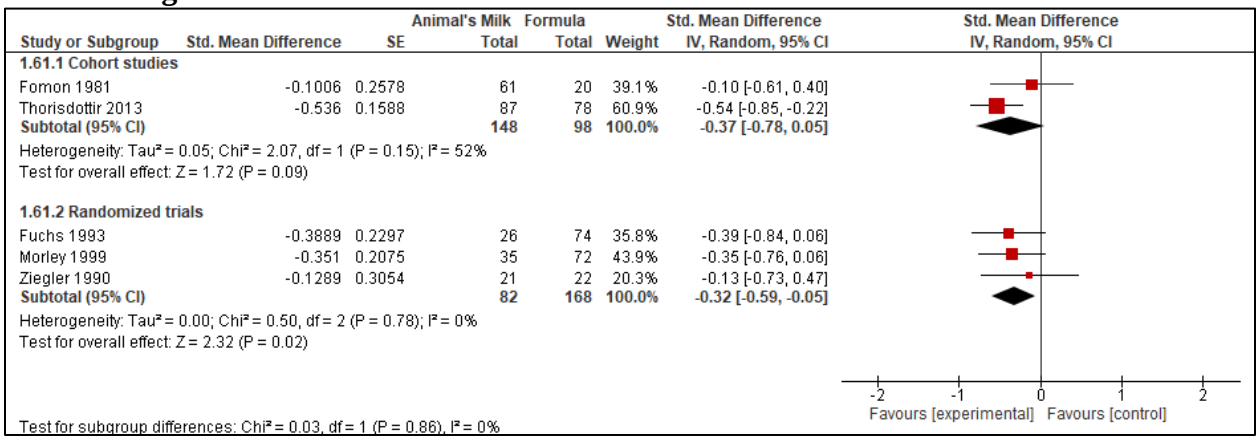
Footnotes: The figure shows results of meta-analysis for use animal milk vs. formula milk for non-breastfed infants based on study type. All the studies were randomized controlled trials.
Abbreviations: CI: Confidence interval, IV: Inverse variance, SE: standard error

Figure 5: Effect of animal's milk vs formula milk intake in infants 6-11 months of age on length for age



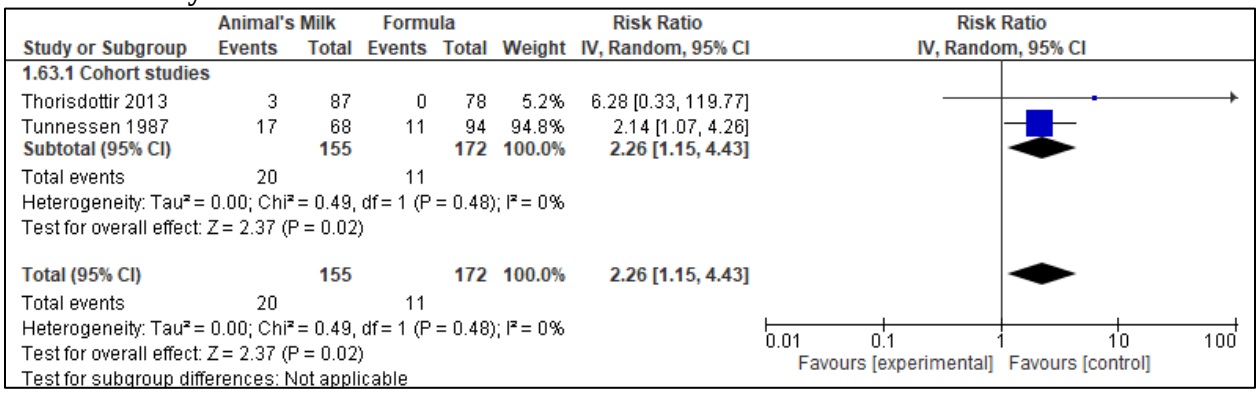
Footnotes: The figure shows results of meta-analysis for use animal milk vs. formula milk for non-breastfed infants based on study type. All the studies were randomized controlled trials.
Abbreviations: CI: Confidence interval, IV: Inverse variance, SE: standard error

Figure 6: Effect of animal's milk vs formula milk intake in infants 6-11 months of age on blood hemoglobin level



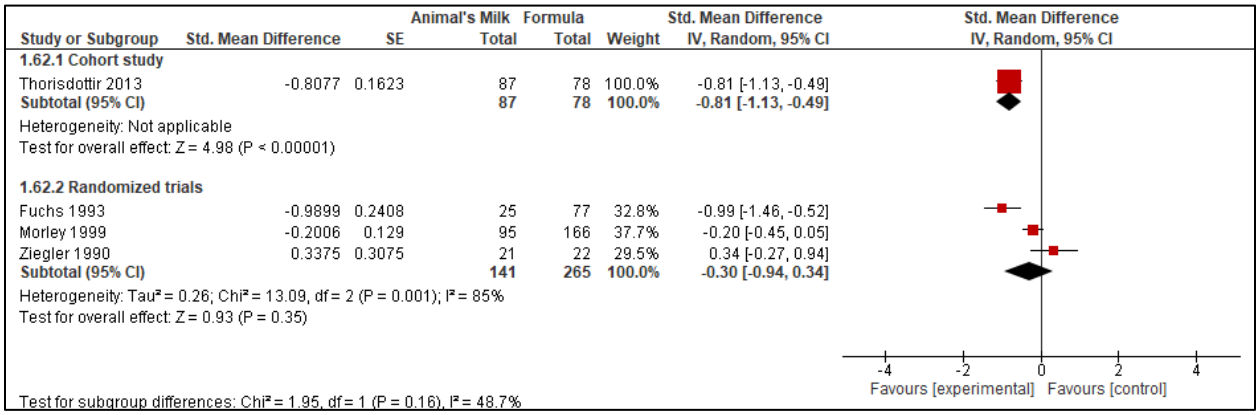
Footnotes: The figure shows results of meta-analysis for use animal milk vs. formula milk for non-breastfed infants based on study type. Only subtotals were calculated as we had decided a priori to pool data from observational studies and randomized controlled trials separately.
Abbreviations: CI: Confidence interval, IV: Inverse variance, SE: standard error

Figure 7: Effect of animal's milk vs formula milk intake in infants 6-11 months of age on iron deficiency anemia



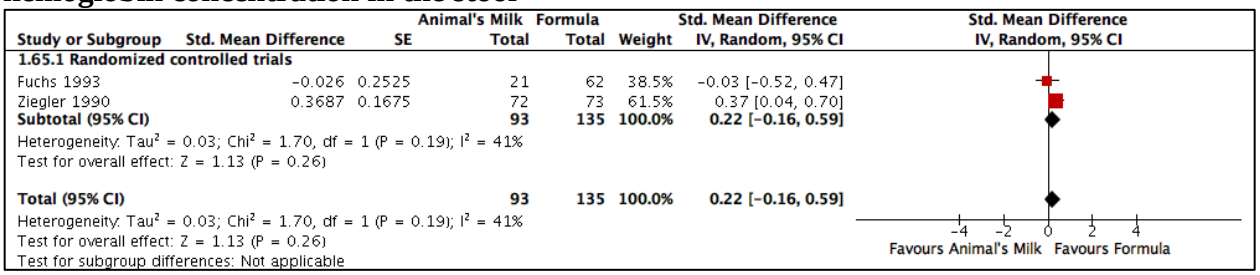
Footnotes: The figure shows results of meta-analysis for use animal milk vs. formula milk for non-breastfed infants based on study type. Both the included studies were cohort studies.
Abbreviations: CI: Confidence interval, IV: Inverse variance,

Figure 8: Effect of animal's milk vs formula milk intake in infants 6-11 months of age on serum ferritin level



Footnotes: The figure shows results of meta-analysis for use animal milk vs. formula milk for non-breastfed infants based on study type. Only subtotals were calculated as we had decided a priori to pool data from observational studies and randomized controlled trials separately.
Abbreviations: CI: Confidence interval, IV: Inverse variance, SE: standard error

Figure 9: Effect of animal's milk vs formula milk intake in infants 6-11 months of age on hemoglobin concentration in the stool



Footnotes: The figure shows results of meta-analysis for use animal milk vs. formula milk for non-breastfed infants based on study type. Both the included studies were randomized controlled trials.
Abbreviations: CI: Confidence interval, IV: Inverse variance, SE: standard error

Table 1: Participant characteristics in the included studies

Author	Type of study	Country	Number of participants in study	Inclusion criteria	Age initiation of animal milk feedings (months)
Fomon 1981[6]	Observational	United States	81	Infants with birth weights >2,450 gm within four days of 112 days of age	3.6 months
Fuchs 1993, 1993, 1996[19,27,28]	RCT	United States	104	Healthy, full term, exclusively bottle-fed infants	6 months
Ziegler 1990[26]	RCT	United States	52	Full term infants with birth weights of 2500 grams	5.5
Tunnessen 1987[25]	Observational	United States	169	Infants previously been fed an iron-supplemented proprietary cow milk formula from birth; no whole cow milk before 6 months of age; born at >38 weeks' gestation, no underlying systemic disease or prior hospital admissions, with a mother who was at least 16 years of age	6 months
Morley 1999[23]	RCT	United Kingdom	493	Healthy infants born at > 36 weeks' gestation, weighing > 2500 g, and either singletons or sole survivors from a multiple pregnancy	9 months
Thorisdottir 2013[24]	Observational	Iceland	165	Icelandic parents, singleton birth; gestational length of 37–41 weeks, birth weight within the10th and 90th percentiles, no birth defects or congenital long-term diseases; early and regular antenatal care of the mother.	3.3 % received whole milk at 6 months, 40 % at 9 months and 56 % at 12 months
Male 2001[22]	Observational	Greece, Spain, Hungary, Ireland, Italy, Portugal, Germany, Chile, Sweden, Austria	488	Birthweight 2500 g, gestational age 37 weeks, single birth, Caucasian origin, no language barrier with parents, known father, and high probability of successful participation for 36 mo.	10 months
Fuchs 1992[20]	RCT	Peru	15	Infants 6-12 months old, recovering from malnutrition; free of diarrhea, parasites and other apparent infections; were gaining weight at an appropriate rate for their height age; free of edema, skins lesions or other signs of specific nutrient deficiencies and had serum albumin levels of at least 3.4 g/dl.	7.5 months
Hopkins 2015[21]	Observational	United Kingdom	925	Resident in a geographically defined area of South-West England; expected date of delivery between April 1991 and December 1992; singleton children born at term with dietary information at 8 months of age.	Data is available based on what the child was consuming at 8 months of age

Table 2: Treatment characteristics in the included studies

Author	Author	Type of milk	Amount of milk	Frequency of milk drinking	Type of comparator (formula, mixed feeding)	Amount of formula	Frequency of formula drinking	Fortification/ measured iron levels	Co-interventions
Fomon 1981[6]	Fomon 1981	Cow's milk[1]	Ad libitum	Daily	Cow's milk based infant formula[2]	Not stated	Ad libitum	Enfamil provided 1.5 mg iron/L, whereas cow milk provided only trace amounts of iron	All infants received daily 1.0 ml of a solution that provided 50 mg ascorbic acid, 12 mg iron from ferrous sulfate, and 0.5 mg fluoride from sodium fluoride.
Fuchs 1993, 1993, 1996[19,27,28]	Fuchs 1993, 1996	Cow's milk[3]	7 months = 810 mL, 12 months = 720 mL	Daily	Cow's milk based infant formula[4]	7 months = 810 mL, 12 months = 720 mL	Daily	The mothers in the WCM + C (cereal) group were additionally provided with iron-fortified rice, oat or mixed rice-oat cereal and counseled to feed their infants 135 mL (9 tbsp) cereal/d mixed in formula, milk, or water (but not in juice) to achieve the recommended dietary allowance (RDA) of iron of 10 mg (11). The mothers of infants in the formula groups were not given specific instructions about the use of infant cereal or other supplemental foods. Iron composition of 4 groups: WCM + Cereal (before supplementation) :0.38 mg/MJ FUF2: 4.54 mg/MJ FUF1: 4.30 mg/ MJ IF: 4.30 mg/ MJ	The infants in the cow's milk group were supplied with dry iron-fortified infant cereal throughout the study period.
Ziegler 1990[26]	Ziegler 1990	Cow's milk[5]	Not stated	Not stated	Cow's milk based infant formula[6]	Not stated	Not stated	The measured iron concentration of Enfamil formula without added iron: 0.83 mg/L. Iron concentration of cow milk, determined on several occasions by atomic absorption spectrophotometry after dry ashing, averaged 0.98 mg/L.	Infants fed cow milk received a daily supplement of 35 mg ascorbic acid and 0.25 mg fluoride in the form of sodium fluoride. The formula group received a daily supplement of 0.25 mg fluoride
Tunnessen 1987[25]	Tunnessen 1987	Whole cow's milk (non-specific)[7]	Not Stated	Daily	Cow's milk based formula[8]	Not Stated	Daily		Parents were encouraged to feed iron-fortified cereal throughout the study period.
Morley 1999[23]	Morley 1999	Cow's milk[9]	Not stated	Daily	Cow's milk based formula[10]	Not stated	Daily	Milk: estimated to contain 0.05 mg iron/litre Formula containing 0.9 mg iron/litre Identical formula with 1.2 mg iron/litre as ferrous sulphate	None
Thorisdottir 2013[24]	Thorisdottir 2013	Cow's milk (non-specific)	332.5 ml/d	Per Day	Follow-on formula (mainly, non-specific)	378.3 ml/d	Per Day	Cow Milk: Median 3.5 mg/d Formula: 7.9 mg/d	No information
Male 2001[22]	Male 2001	Cow's milk (non-specific)	Not stated	Not stated	Formula (non-specific)	Not stated	Not stated	Not given	No information

Fuchs 1992[20]	Fuchs 1992	Whole cow's milk[3]	219 ml/kg/day	ad libitum	Cow's milk based infant formula[11]	219 ml/kg/day	ad libitum	Not given	None
Hopkins 2015[21]	Hopkins 2015	Cow's milk (non-specific)	<600 mL cow milk/d (CMlow); >600 mL cow milk/d (CMhigh)	daily	Formula (non-specific)[12]	<600 mL formula milk/d (FMlow); >600 mL formula milk/d (FMhigh)	Daily	Not given	No information

1 "Whole cow milk" designates pasteurized, homogenized cow milk obtained from a local dairy; "Heat-treated cow milk" designates whole cow milk prepared by the manufacturer of Enfamil at the same time as the batch of Enfamil used in the study and using identical time and temperature treatment.
2 Enfamil
3 WCM signifies pasteurized homogenized cow milk obtained from a local dairy.
4 A ready-to feed infant formula signifies Similac With Iron or one of two ready-to-feed follow- up formulas, an investigational formula or Carnation Follow-up Formula
[5] Locally purchased pasteurized, homogenized whole cow milk fortified with vitamin D, 400 lUlL.
6 Specially prepared formula similar in composition to commercially prepared Enfamil, except that it contained no added iron. The measured iron concentration of this formula was 0.83 mg/L. The protein was unmodified (Le. casein predominant) cow milk protein.
7 Parents were given coupons to buy whole cow's milk
8 Iron-supplemented proprietary cow milk formula
9 Pasteurized
10 With .9 mg of iron/ liter OR identical formula with 1.2 mg iron/ liter as ferrous sulfate.
11 Carnation Follow-up Formula, Carnation Nutritional Products, Glendale, California (FUF), Similac with iron, Ross Laboratories, Columbus, Ohio (IF)
12 Formula group defined as formula with or without some BM and/or cow milk

Table 3: Primary outcome results at different timepoint of follow up

Outcome	Time point	No. of studies	Study Type	RR	95% CI	I2
Anemia	9 months	1	RCT	0.59	0.03,11.92	Not applicable
	12 months	1	Cohort	2.26	1.15,4.43	0%
		2	RCT	9.00	0.38,214.20	0%
Gastrointestinal Blood Loss	7 months	1	Cohort	1.52	0.73,3.16	0%
		1	RCT	2.78	0.83,9.25	
	9 months	1	RCT	3.14	0.98, 10.04	Not applicable
Weight for age	12 months	1	RCT	0.00	-0.45,0.45	NA
Length for age	12 months	1	RCT	-0.14	-0.59, 0.31	Not applicable

Table 4: GRADE Evidence Profile for Certainty Assessment of primary outcomes and selected secondary outcomes

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Animal Milk	Infant Formula	Relative (95% CI)	Absolute (95% CI)	
Anemia at longest follow up-Randomized Controlled Trials											
2	randomised trials	serious[a]	not serious[b]	serious[c]	not serious[d]	none	12/60 (20.0%)	6/149 (4.0%)	**RR 4.03** (1.68 to 9.65)	**122 more per 1,000** (from 27 more to 348 more)	⨁⨁◯◯ Low
Any anemia at the longest follow up-Cohort studies											
2	observational studies	serious[e]	not serious[f]	serious[c]	not serious	none	20/155 (12.9%)	11/172 (6.4%)	**RR 2.26** (1.15 to 4.43)	**81 more per 1,000** (from 10 more to 219 more)	⨁⨁◯◯ Low
Gastrointestinal blood loss at longest follow up - Randomized Controlled Trials											
1	randomised trials	serious[g]	not serious	serious[c]	not serious[h]	none	9/21 (42.9%)	3/22 (13.6%)	**RR 3.14** (0.98 to 10.04)	**292 more per 1,000** (from 3 fewer to 1,000 more)	⨁⨁◯◯ Low
Gastrointestinal blood loss - Cohort study											
1	observational studies	serious[i]	not serious	serious[j]	serious[k]	none	26/60 (43.3%)	6/21 (28.6%)	**RR 1.52** (0.73 to 3.16)	**149 more per 1,000** (from 77 fewer to 617 more)	⨁◯◯◯ Very low
Weight for age at longest follow up-Randomized Controlled Trials											
3	randomised trials	serious[l]	not serious[m]	serious[n]	not serious[o]	none	194	362	-	SMD **0.02 SD lower** (0.26 lower to 0.21 higher)	⨁⨁◯◯ Low
Height for age at the longest follow up-Randomized Controlled Trials											
2	randomised trials	serious[p]	not serious[q]	serious[n]	not serious[r]	none	185	344	-	SMD **0.07 SD higher** (0.15 lower to 0.3 higher)	⨁⨁◯◯ Low
Serum hemoglobin concentration at the longest follow up - Randomized Controlled Trials											

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Animal Milk	Infant Formula	Relative (95% CI)	Absolute (95% CI)	
3	randomised trials	serious[s]	not serious[b]	serious[c]	not serious	none	82	168	-	SMD **0.32 SD lower** (0.59 lower to 0.05 lower)	⨁⨁◯◯ Low
Serum hemoglobin level - Cohort studies											
2	observational studies	serious[t]	not serious	serious[j]	not serious[u]	none	148	98	-	SMD **0.37 SD lower** (0.78 lower to 0.05 higher)	⨁⨁◯◯ Low
Iron deficiency anemia at the longest follow up-Cohort studies											
2	observational studies	not serious	not serious[f]	serious[c]	not serious	strong association	20/155 (12.9%)	11/172 (6.4%)	**RR 2.26** (1.15 to 4.43)	**81 more per 1,000** (from 10 more to 219 more)	⨁⨁◯◯ Low
Constipation-Cohort study											
1	observational studies	not serious	not serious	serious[j]	serious[v]	strong association	7/69 (10.1%)	3/98 (3.1%)	**RR 3.31** (0.89 to 12.37)	**71 more per 1,000** (from 3 fewer to 348 more)	⨁◯◯◯ Very low
Diarrhea-Cohort study											
1	observational studies	not serious	not serious	serious[j]	not serious	none	21/69 (30.4%)	16/98 (16.3%)	**RR 1.86** (1.05 to 33.10)	**140 more per 1,000** (from 8 more to 1,000 more)	⨁◯◯◯ Very low
Neurodevelopment outcome (PDI scores) at the longest follow-Randomized Controlled Trial											
1	randomised trials	not serious	not serious	serious[j]	serious[w]	none	160	268	-	SMD **0.18 SD higher** (0.02 lower to 0.37 higher)	⨁⨁◯◯ Low
Neurodevelopment outcome (MDI score) at the longest follow up-Randomized Controlled Trial											
1	randomised trials	not serious	not serious	serious[j]	serious[x]	none	160	268	-	SMD **0.16 SD higher** (0.03 lower to 0.36 higher)	⨁⨁◯◯ Low

CI: confidence interval; **RR:** risk ratio; **SMD:** standardised mean difference

Explanations

a. One of the two randomized trial studies had "some concerns' for the risk of bias from the Cochrane risk of bias tool (2).
b. No statistical heterogeneity was found in the pooled data. I2 = 0%. There was clinical heterogeneity in the type of formula and animal milk use. We did not downgrade the grade level for clinical heterogeneity as there is no consensus on the type of formula or animal milk that should be used when the breastmilk is not available and that multiple options are available for infant formula and animal milk in the community.
c. All the included studies were from high-income countries. This might limit the applicability of the results to populations from low and middle-income countries. We however think that the direction of effect might remain the same if there were eligible studies from low and middle-income countries and the magnitude of the effect might increase against animal milk.
d. Results were statistically significant and the confidence interval is fairly narrow around the summary estimate.
e. One cohort study had high risk of bias and the second one had some concerns for risk of bias.
f. The I2 statistics was 0 %
g. Study had "some concerns" for risk of bias based on Cochrane risk of bias tool (2).
h. Even though the confidence interval around the summary estimate included 1, the lower limit of the confidence interval was 0.98.
i. The study had 'high risk of bias' from the ROBINS tool.
j. The only include study for this outcome was conducted in high-income country
k. The confidence interval around the summary estimate inlcuded 1 and risk of increased or decreased risk cannot be excluded.
l. All three studies were randomized trials. One of the three randomized trial studies had 'high' and another has "some concerns' for the risk of bias from Cochrane risk of bias tool-2 (ROB 2).
m. The overall unexplained statistical heterogeneity based on 12 statistics was 19 %. The visual inspection of the forest plot showed that three of the included studies had an effect in the same direction and around the mean summary estimate. We did not downgrade the grade level for inconsistency for this outcome.
n. All other than one of the included studies were from high-income countries. This might limit the applicability of the results to populations from low and middle-income countries.
o. The overall magnitude of the effect for the weight for age was small (SMD 0.06). This small statistical effect is not meaningful clinically. Also, even though the confidence interval included 0, the total sample size from the pooled studies was 1216. We think there was optimal information size (OIS) from the sample size of the pooled studies that if there was a true effect, that should have been picked up by this much of sample size. We, therefore, did not downgrade for imprecision.
p. Two studies were randomized trials. One of the two randomized trial studies had "some concerns' for the risk of bias from the Cochrane risk of bias tool-2(ROB 2).
q. Unexplained statistically heterogeneity based on 12 statistics was 17 % only.
r. The overall magnitude of the effect for the weight for age was small (SMD 0.07) and the confidence interval included 0. This is a very small effect clinically. The total sample size in the analysis was 529 which should have been enough to pick a clinically meaningful effect. We, therefore, did not downgrade the level for imprecision.
s. The randomized trial studies had "some concerns' for the risk of bias from the Cochrane risk of bias tool-2.
t. One of the observational studies had 'high' risk of bias and the other had a 'moderate' risk of bias from the ROBINS-1 tool
u. Even though the confidence interval around the summary estimate included a null effect, the upper limit was almost toward the threshold of statistical significance. The data from RCTs showed a similar direction of effect and was statistically significant.
v. The 95 % CI around the summary estimate included 1. The total sample size was 167 which is not large enough to be confident about the summary estimate.
w. The overall magnitude of the effect was small (SMD 0.18) and the confidence interval included 0.
x. The overall magnitude of the effect was small (SMD 0.16) and the confidence interval included 0.

Table 5: Use of animal milk vs. formula milk: Results of Secondary Outcomes

Outcome	No. of studies	Type of studies	Total participants	SMD/RR (95 % CI)	I^2
Iron deficiency anemia	2	Cohort	327	RR = 2.26 (1.15, 4.43)	0%
Blood ferritin at longest follow up	1	Cohort	165	SMD = -0.81 (-1.13, -0.49)	0%
	3	RCT	406	SMD=-0.30 (-0.94,0.34)	85%
Hemoglobin concentration in the stool	2	RCT	228	SMD = 0.22 (-0.16, 0.59)	41%
Hemoglobin concentration in the blood	2	Cohort	246	SMD = -0.37 (-0.78, -0.05)	0%
	3	RCT	250	SMD = -0.32 (-0.59, -0.05)	
Serum iron level	1	Cohort	43	SMD=-0.13 (-0.73, 0.46)	NA
Diarrhea	1	Cohort	167	RR=1.86 (1.05-33.1)	NA
Constipation	1	Cohort	167	RR=3.31 (0.89,12.37)	NA
Neurodevelopmental outcome	1	RCT	428	SMD=0.18 (-0.02, 0.37)	NA

Footnotes: RR: relative risk, SMD: Standardized mean difference

Supplementary Information:

The effect of consumption of animal milk compared to infant formula for non-breastfed/mixed-fed infants 6-11 months of age. A systematic review (protocol)

Aamer Imdad, Julie Ehrlich, Joseph Catania, Emily Tanner Smith, Abigail Smith, Olivia Tsistinas, Zulfiqar Ahmed Bhutta,

Table of Content:

Annex 1: Search Strategy for electronic data bases

PubMed

((("cow milk"[tiab] OR "cow's milk*"[tiab] OR "cows milk*"[tiab] OR "bovine milk*"[tiab] OR "bovine's milk*"[tiab] OR "goat milk*"[tiab] OR "goat's milk*"[tiab] OR "goats milk*"[tiab] OR "caprine milk*"[tiab] OR "buffalo milk*"[tiab] OR "buffalo's milk*"[tiab] OR "camel milk*"[tiab] OR "camel's milk*"[tiab]OR "camels milk*"[tiab] OR "sheep milk*"[tiab] OR "sheep's milk*"[tiab] OR "ewe milk*"[tiab] OR "ewe's milk*"[tiab] OR "ewes milk*"[tiab] OR "ovine milk*"[tiab]) AND ("Infant Formula"[Mesh] OR formula*[tiab])) AND ("Infant"[Mesh] OR infant*[tiab] OR infancy[tiab] OR baby[tiab] OR babies[tiab] OR neonat*[tiab] OR "neo nat*"[tiab] OR newborn*[tiab] OR "new born*"[tiab] OR "newly born*"[tiab] OR "Child"[Mesh] OR child*[tiab] OR youth[tiab] OR juvenile*[tiab])) NOT ("Animals"[Mesh] NOT ("Animals"[Mesh] AND "Humans"[Mesh]))*

CINAHL

(TI ("cow milk" OR "cow's milk*" OR "cows milk*" OR "bovine milk*" OR "bovine's milk*" OR "goat milk*" OR "goat's milk*" OR "goats milk*" OR "caprine milk*" OR "buffalo milk*" OR "buffalo's milk*" OR "camel milk*" OR "camel's milk*" OR "camels milk*" OR "sheep milk*" OR "sheep's milk*" OR "ewe milk*" OR "ewe's milk*" OR "ewes milk*" OR "ovine milk*") OR AB ("cow milk*" OR "cow's milk*" OR "cows milk*" OR "bovine milk*" OR "bovine's milk*" OR "goat milk*" OR "goat's milk*" OR "goats milk*" OR "caprine milk*" OR "buffalo milk*" OR "buffalo's milk*" OR "camel milk*" OR "camel's milk*" OR "camels milk*" OR "sheep milk*" OR "sheep's milk*"OR "ewe milk*" OR "ewe's milk*" OR "ewes milk*" OR "ovine milk*"))*

AND

((MH "Infant Formula") OR (TI formula OR AB formula*))*

AND

(((MH "Child") OR (MH "Infant+")) OR (TI (infant OR infancy OR baby OR babies OR neonat* OR "neo nat*" OR newborn* OR "new born*" OR "newly born*" OR child* OR youth OR juvenile*) OR AB (infant* OR infancy OR baby OR babies OR neonat* OR "neo nat*" OR newborn* OR "new born*" OR "newly born*" OR child* OR youth OR juvenile*)))*

NOT

(((MH "Animals+") OR (MH "Animal Studies") OR (TI "animal model")) NOT (MH "human"))*

Exclude Medline Records

SCOPUS

(TITLE-ABS ("cow milk" OR "cows milk*" OR "bovine milk*" OR "bovine's milk*" OR "goat milk*" OR "goats milk*" OR "caprine milk*" OR "buffalo milk*" OR "buffalo's milk*" OR "camel milk*" OR "camels milk*" OR "sheep milk*" OR "sheep's milk*" OR "ewe milk*" OR OR "ewes milk*" OR "ovine milk*")) AND (TITLE-ABS (formula*)) AND (TITLE-ABS (infant* OR infancy OR baby OR babies OR neonat* OR "neo nat*" OR newborn* OR "new born*" OR "newly born*" OR child* OR youth OR juvenile*)) AND NOT INDEX (medline)*

Embase

1 'cow milk'/exp OR 'goat milk'/exp OR 'buffalo milk'/exp OR 'camel milk'/exp OR 'sheep milk'/exp

2 'cow milk':ti,ab OR 'cows milk*':ti,ab OR 'cow s milk*':ti,ab OR 'bovine milk*':ti,ab OR 'bovine s milk*':ti,ab OR 'goat milk*':ti,ab OR 'goat s milk*':ti,ab OR 'goats milk*':ti,ab OR 'caprine milk*':ti,ab OR 'buffalo milk*':ti,ab OR 'buffalo s milk*':ti,ab OR 'camel milk*':ti,ab OR 'camel s milk*':ti,ab OR 'camels milk*':ti,ab OR 'sheep milk*':ti,ab OR 'sheep s milk*':ti,ab OR 'ewe milk*':ti,ab OR 'ewes milk*':ti,ab OR 'ewe s milk*':ti,ab OR 'ovine milk*':ti,ab*
3 #1 OR #2
4 'artificial milk'/exp
5 formula:ti,ab*
6 #4 OR #5
7 'infant'/exp OR 'infancy'/exp OR 'baby'/exp OR 'newborn'/exp OR 'child'/exp OR 'juvenile'/exp
8 infant:ti,ab OR infancy:ti,ab OR baby:ti,ab OR babies:ti,ab OR neonat*:ti,ab OR 'neo nat*':ti,ab OR newborn*:ti,ab OR 'new born*':ti,ab OR 'newly born*':ti,ab OR child*:ti,ab OR youth:ti,ab OR juvenile*:ti,ab*
9 #7 OR #8
10 #3 AND #6 AND #9
11 #10 NOT ([animals]/lim NOT [humans]/lim)
12 #11 NOT [medline]/lim

Cochrane CENTRAL
1 cow NEXT milk*:ti,ab OR bovine* NEXT milk*:ti,ab OR goat* NEXT milk*:ti,ab OR caprine NEXT milk*:ti,ab OR buffalo* NEXT milk*:ti,ab OR camel* NEXT milk*:ti,ab OR sheep* NEXT milk*:ti,ab OR ewe* NEXT milk*:ti,ab OR ovine NEXT milk*:ti,ab*
2. MeSH descriptor: [Infant Formula] explode all trees
3. formula:ti,ab*
4. #2 OR #3
5. MeSH descriptor: [Child] explode all trees
6. MeSH descriptor: [Infant] explode all trees
7. infant:ti,ab OR infancy:ti,ab OR baby:ti,ab OR babies:ti,ab OR neonat*:ti,ab OR neo NEXT nat*:ti,ab OR newborn*:ti,ab OR new NEXT born*:ti,ab OR "newly born":ti,ab OR child*:ti,ab OR youth:ti,ab OR juvenile*:ti,ab*
8 #5 OR #6 OR #7
9 MeSH descriptor: [Animals] explode all trees
10 MeSH descriptor: [Humans] explode all trees
11 (#9 NOT(#9 AND #10))
12 #1 AND #4 AND #8
13 #12 NOT #11
14 "accession number" near pubmed
15 #13 NOT #14

LILACS
ti:("cow milk" OR "cow's milk*" OR "cows milk*" OR "bovine milk*" OR "bovine's milk*" OR "goat milk*" OR "goat's milk*" OR "goats milk*" OR "caprine milk*" OR "buffalo milk*" OR "buffalo's milk*" OR "camel milk*" OR "camel's milk*" OR "camels milk*" OR "sheep milk*" OR "sheep's milk*" OR "ewe milk*" OR "ewe's milk*" OR "ewes milk*" OR "ovine milk*") OR (ab:("cow milk*" OR "cow's milk*" OR "cows milk*" OR "bovine milk*" OR "bovine's milk*" OR "goat milk*" OR "goat's milk*" OR "goats milk*" OR "caprine milk*" OR "buffalo milk*"*

OR "buffalo's milk" OR "camel milk*" OR "camel's milk*" OR "camels milk*" OR "sheep milk*" OR "sheep's milk*" OR "ewe milk*" OR "ewe's milk*" OR "ewes milk*" OR "ovine milk*")) AND (((ti:(formula*)) OR (ab:(formula*))) OR ((mh:("infant formula")))) AND (((ti:(infant* OR infancy OR baby OR babies OR neonat* OR "neo nat*" OR newborn* OR "new born*" OR "newly born*" OR child* OR youth OR juvenile*)) OR (ab:(infant* OR infancy OR baby OR babies OR neonat* OR "neo nat*" OR newborn* OR "new born*" OR "newly born*" OR child* OR youth OR juvenile*))) OR ((mh:("infant")) OR ((mh:("child"))))) AND NOT ((mh:("animals")) AND NOT ((mh:("animals")) AND ((mh:("humans")))))*

Global Index Medicus

ti:("cow milk" OR "cow's milk*" OR "cows milk*" OR "bovine milk*" OR "bovine's milk*" OR "goat milk*" OR "goat's milk*" OR "goats milk*" OR "caprine milk*" OR "buffalo milk*" OR "buffalo's milk*" OR "camel milk*" OR "camel's milk*" OR "camels milk*" OR "sheep milk*" OR "sheep's milk*" OR "ewe milk*" OR "ewe's milk*" OR "ewes milk*" OR "ovine milk*") OR (ab:("cow milk*" OR "cow's milk*" OR "cows milk*" OR "bovine milk*" OR "bovine's milk*" OR "goat milk*" OR "goat's milk*" OR "goats milk*" OR "caprine milk*" OR "buffalo milk*" OR "buffalo's milk*" OR "camel milk*" OR "camel's milk*" OR "camels milk*" OR "sheep milk*" OR "sheep's milk*" OR "ewe milk*" OR "ewe's milk*" OR "ewes milk*" OR "ovine milk*")) AND (((ti:(formula*)) OR (ab:(formula*))) OR ((mh:("infant formula")))) AND (((ti:(infant* OR infancy OR baby OR babies OR neonat* OR "neo nat*" OR newborn* OR "new born*" OR "newly born*" OR child* OR youth OR juvenile*)) OR (ab:(infant* OR infancy OR baby OR babies OR neonat* OR "neo nat*" OR newborn* OR "new born*" OR "newly born*" OR child* OR youth OR juvenile*))) OR ((mh:("infant")) OR ((mh:("child"))))) AND NOT ((mh:("animals")) AND NOT ((mh:("animals")) AND ((mh:("humans")))))AND (db:("WPRIM" OR "IMEMR" OR "IMSEAR" OR "AIM"))*

Web of Science

1
TI=(“cow milk*" OR "bovine* milk*" OR "goat* milk*" OR "caprine milk*" OR "buffalo* milk *" OR*
“camel milk*" OR "sheep* milk*" OR “ewe* milk*” OR "ovine milk*")*
2
AB=(“cow milk*" OR "bovine* milk*" OR "goat* milk*" OR "caprine milk*" OR "buffalo* mil k*" OR "camel* milk*" OR "sheep* milk*" OR “ewe* milk*” OR "ovine milk*")*

3 #2 OR #1

4 TI=(formula)*

5 AB=(formula)*

6 #5 OR #4
7 TI=(infant OR infancy OR baby OR babies OR neonat* OR "neo nat*" OR newborn* OR "new* born*" OR child* OR youth OR juvenile*)*

8

9 #8 OR #7

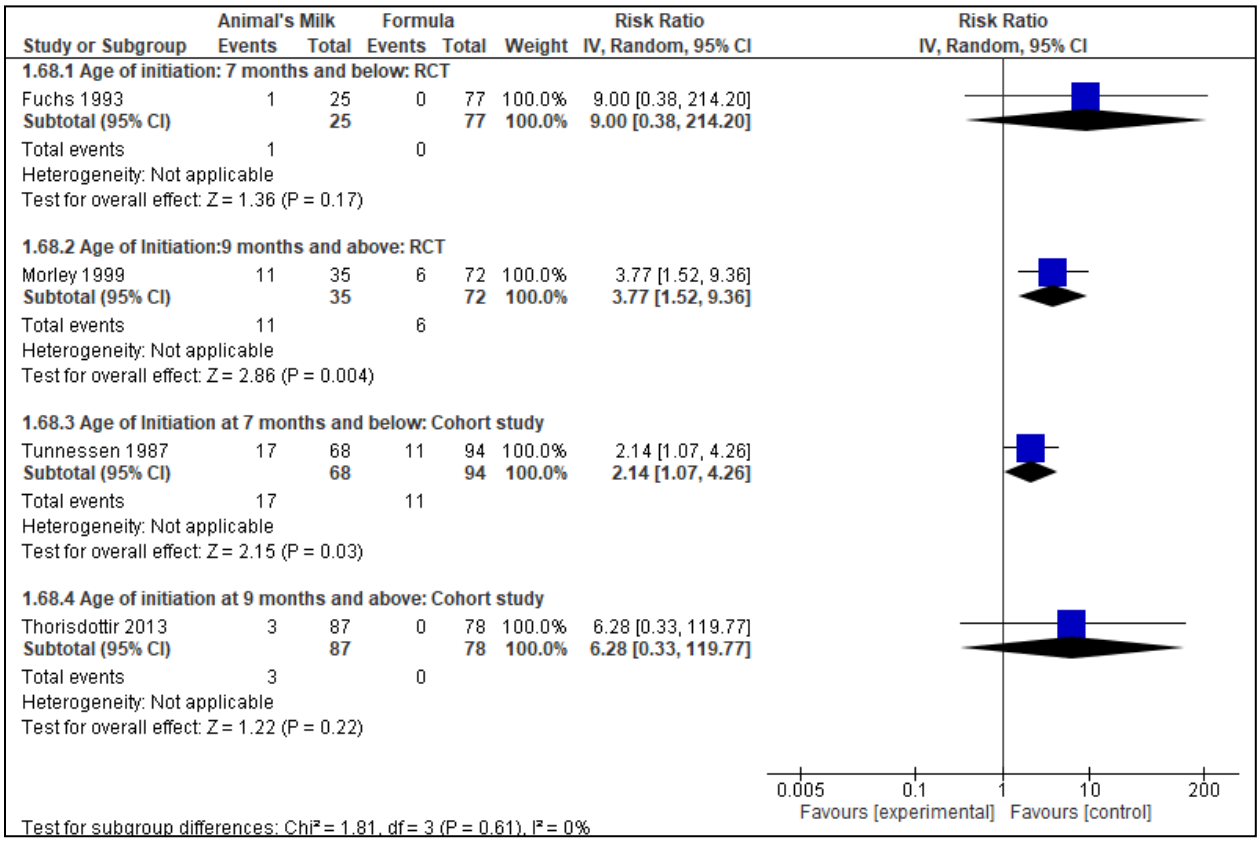
10 #9 AND #6 AND #3

11 #9 AND #6 AND #3 Exclude Medline

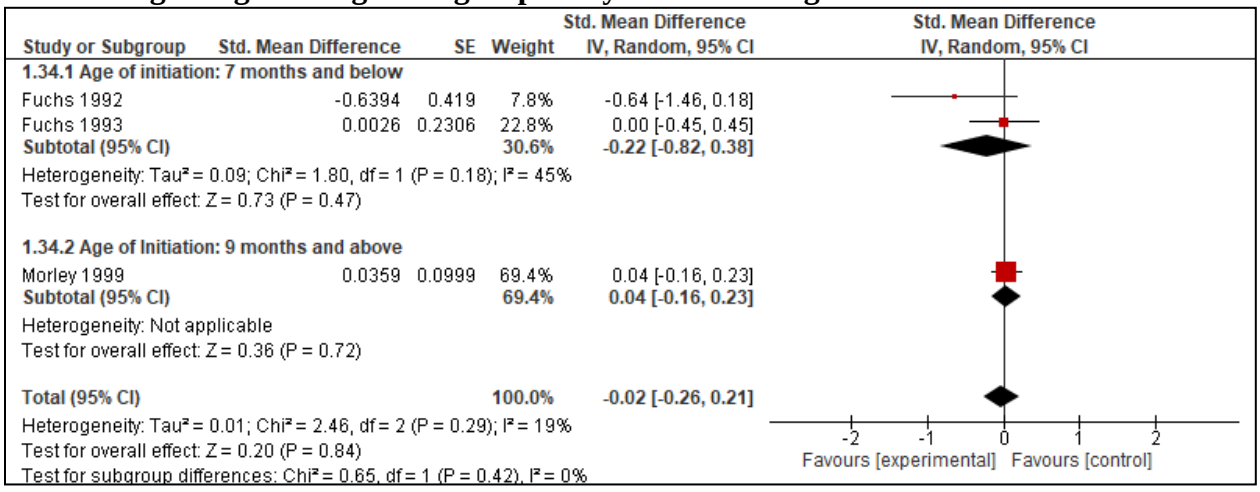
Annex 2: List of publications of included studies

Title	Authors	Published Year	Merged Citation Title
Cow milk feeding in infancy: gastrointestinal blood loss and iron nutritional status.	Fomon SJ; Ziegler EE; Nelson SE; Edwards BB	1981	
Iron status and intake of older infants fed formula vs cow milk with cereal	Fuchs, G. J.; Farris, R. P.; DeWier, M.; Hutchinson, S. W.; Warrier, R.; Doucet, H.; Suskind, R. M.	1993	Fuchs G, DeWier M, Hutchinson S, Sundeen M, Schwartz S, Suskind R. Gastrointestinal blood loss in older infants: impact of cow milk versus formula. J Pediatr Gastroenterol Nutr. 1993 Jan;16(1):4-9 Fuchs GJ, Farris RP, DeWier M, et al. Iron status and intake of older infants fed formula vs cow milk with cereal. Am J Clin Nutr 1993;58:343-8. Fuchs, G. J. Clemens, R. A. Hutchinson, S. W. et al, Growth of older infants fed low-fat formula: Nutrition Research, Volume 16, Issue 3, 1996, Pages 391-400,
Cow milk feeding in infancy: further observations on blood loss from the gastrointestinal tract	Ziegler, E. E.; Fomon, S. J.; Nelson, S. E.; Rebouche, C. J.; Edwards, B. B.; Rogers, R. R.; Lehman, L. J.	1990	
Consequences of starting whole cow milk at 6 months of age	Tunnessen, W. W., Jr.; Oski, F. A.	1987	
Iron fortified follow on formula from 9 to 18 months improves iron status but not development or growth: a randomised trial	Morley, R.; Abbott, R.; Fairweather-Tait, S.; MacFadyen, U.; Stephenson, T.; Lucas, A.	1999	
Iron status of one-year-olds and association with breast milk, cow's milk or formula in late infancy	Thorisdottir, A. V.; Ramel, A.; Palsson, G. I.; Tomassson, H.; Thorsdottir, I.	2013	
Prevalence of iron deficiency in 12-mo-old infants from 11 European areas and influence of dietary factors on iron status (Euro-Growth study)	Male, C.; Persson, L. A.; Freeman, V.; Guerra, A.; van't Hof, M. A.; Haschke, F.	2001	
Comparative Metabolic Study of Older Infants Fed Infant Formula, Transition Formula, or Whole Cows Milk	Fuchs, G. J.; Gastanaduy, A. S.; Suskind, R. M.	1992	
Effects on childhood body habitus of feeding large volumes of cow or formula milk compared with breastfeeding in the latter part of infancy	Hopkins, D.; Steer, C. D.; Northstone, K.; Emmett, P. M.	2015	

Supplementary figure 1: Effect of animal's milk vs formula milk intake in infants 6-11 month of age on Anemia: Subgroup analysis based on age of initiation



Supplemental figure 2: Effect of animal's milk vs formula milk intake in infants 6-11 month of age weight for age: Subgroup analysis based on age of initiation



Annex 3: List of excluded studies and reason for exclusion

Abrams 1997[1]	exclude wrong study design: looked at different mineral levels in infants fed just breast milk and solid foods. Does not compare formula or animal's milk.
AfeicheZehil 2017[2]	Excluded for wrong study design as data collection was a 24-hour recall of dietary intake rather than a longitudinal study.
Anderson 1987[3]	Full text was not available.
Balogun 1994[4]	Excluded for wrong study design. They are examining the elemental composition of different milks rather than using the milks in infants. There is no patient population.
Bano 2008[5]	Exclude for wrong study design as this is a descriptive and cross-sectional study on infants up to the age of 6 months being fed either mothers` milk, infant formula or cow/buffalo milk.
Borovik 2017[6]	Excluded for wrong intervention: comparing breastmilk to formula and looking at intervention starting from 0-5 months
Chessare 1988[7]	Excluded for wrong study design: not a study, just a reply to the editor reviewing the Tunnessen and Oski (J PEDIATR 1987;111:813-6) study which we are including
Davidsson 1989[8]	Excluded for wrong study population. The mean age was 28 years (range, 21 to 45 years). We are at looking infants aged 4-11 months.
Donovan 1988[9]	Excluded for wrong study design and wrong intervention as this is a basic science study looking at nutrient and protein differences between cow milk, goat milk and infant formula
Frey 1986[10]	Full text was not available.
Fuchs 1991[11]	Duplicate of study Fuchs 1991 (see below).
Fuchs 1991[12]	Duplicate: abstract of Fuchs 1992 study (included)
Gruskay 1982[13]	Excluded for wrong patient population: started intervention in non-breastfed infants at birth rather than at 4-11 months. Additionally, it is unclear if the milk formula is cow's milk or actually formula as there are no details on how the formula was made in which case it would also be excluded for wrong intervention.
Hachelaf 1993[14]	Excluded for wrong intervention as they are comparing goat's milk to cow's milk rather than animal's milk to formula. Additionally, children are aged 9-72 months of age and the study does not break up results by age groups, so most of these children would be outside of our study range (4-11 months).
Hong-Seok 1997[15]	Full text was not available.
Host 1988[16]	Excluded for wrong patient population and wrong intervention. They are comparing homogenized milk vs non-homogenized milk allergic patients and the median age was 14 months.
Jury 1991[17]	Full text was not available.
Kersting 1988[18]	Full text was not available.
Knip 2018[19]	Excluded for wrong intervention as both groups were fed formula rather than comparing formula to cow's milk. Additionally, the outcomes were only based on diabetes status rather which is not related to our primary or secondary outcomes.
Lapointe 1952[20]	Full text was not available.
Laubereau 2004[21]	Excluded for wrong intervention: studying breastmilk vs milk-based formulas. Also, wrong age group, they started their study at birth and are looking at the first 2 weeks of life rather than at 4-11 months.
Lovell 2019[22]	Excluded for wrong patient population. They are starting the intervention at 12 months rather than at 4-11 months (our inclusion criteria)
Lucas 1990[23]	Excluded for wrong intervention as they are not looking at cow's milk.
MacLean 1978[24]	Excluded for wrong patient population as the mean age was 17 months rather than 4-11 months (our inclusion criteria). Additionally, they are studying cow's milk formula rather than raw animal's milk.
Magalhães 2012[25]	Excluded for wrong patient population as data collection for infant feeding is taken "in first months of life" and does not delineate between the ages. We are specifically looking at comparing formula to animal's milk feedings starting between the ages of 4-11 months of age.
Martin 2003[26]	Exclude for wrong study design as this was a long term follow up study and they were looking at milk supplementation rather than comparing cow's milk to formula
Mennella 2015[27]	exclude wrong intervention: they are not comparing to animals' milk but instead to formula and starting treatment at .5 months rather than at 4-11 months of age
Mennella 2016[28]	This is a duplicate of the above study (Mennella 2016)
Mills 1990[29]	Excluded for wrong study design. Infants were studied with a single screening survey of children aged 8-24 months.
Mimouni 1993[30]	Excluded for wrong intervention: comparing three formula groups: one not animal milk.
Montalto 1985[31]	Excluded for wrong outcomes as they are looking at protein, sodium, potassium, solid food intake, etc. of those fed breast, cow's milk or formula.
Naudé,1979[32]	Excluded for wrong intervention as this study is looking at soy formula vs. milk-based formula.

Nct 2006[33]	Duplicate of Nielsen 2007
Nielsen 2007[34]	Excluded for wrong outcomes: right population and intervention but they are only looking at the microbiota of the infants.
Ozkan 1994[35]	Excluding for wrong intervention as they are looking at formula vs breastfeeding.
Penrod 1988[36]	Excluded as "duplicate" as this is the abstract for Penrod 1990.
Penrod 1990[37]	Excluded for wrong study design: a cross-sectional study.
Penrod 1990[38]	Excluded: duplicate
Pirila 2011[39]	Excluded for wrong patient population as this study is a follow-up of the original cohort study and is focusing on adults rather than on children.
Qudsia 2015[40]	Excluded for wrong comparator. This study is looking at fortified milk fed vs cow's milk fed vs breast feeding. They are not comparing formula vs milk.
Radke 2017[41]	Excluded for wrong intervention: comparing two formulas (one with and one without probiotics) rather than looking at animal's milk
Rapetti 1997[42]	Excluded for wrong population: these infants are 12 - 48 months (our inclusion criteria are infants that started the intervention between ages 4-11 months). Additionally, these infants already have anemia/ iron deficiency.
Riikonen 2016[43]	Excluded for wrong study design as this study is a descriptive study looking at percent of people feeding what foods from birth - 1 year of life and what the first complementary feedings were
Rzehak 2009[44]	Excluded for wrong intervention (they are comparing formulas with partially hydrolyzed whey, extensively hydrolyzed whey, extensively hydrolyzed casein or cow-milk formula and infants exclusively breastfed).
Rzehak 2011[45]	Excluded for wrong intervention (they are comparing formulas with partially hydrolyzed whey, extensively hydrolyzed whey, extensively hydrolyzed casein or cow-milk formula and infants exclusively breastfed).
Rzehak 2013[46]	Excluded for wrong intervention: they were comparing formulas rather than animals milk vs formula
Saarinen 1977[47]	Excluded for wrong intervention as they are looking at cow's milk vs. breastmilk NOT formula and started treatment before 2 months rather than at 4-11 months
Saarinen 1979[48]	Exclude wrong comparator. Says "homemade cow's milk formula" but does not say how it was prepared. Additionally, intervention was started at 2 months rather than at 4-11 months of age.
Saarinen 1979[49]	Excluded wrong comparator. Definition of the formula did not qualify as formula. Only necrose was added to commercially available daily milk.
Saarinen 1979[50]	Excluded for wrong outcomes. We would only be looking at the BII group (short breastfeeding and then switched to cow's milk or formula at 2-6 months) but the paper does not separate results for the BII group into cow's milk vs formula.
Saarinen 1999[51]	Excluded: duplicate
Saarinen 2000[52]	Excluded for wrong intervention: studied cow's milk formula rather than raw cow's milk.
Sacri 2016[53]	Excluded for wrong study design: abstract to a cross-sectional study published a year later.
Sadowitz 1983[54]	Excluded for wrong study design. Only a single sample was taken (iron test) and dietary information was collected form each patient on when age of feeding began. There is no longitudinal component to this study.
Sakihara 2020[55]	Exclude for wrong intervention: they are looking at cow's milk formula.
Saldan 2017[56]	Exclude for wrong study design: cross sectional study.
Schmitz 1992[57]	Excluded for wrong intervention: comparing formula vs. formula.
Schrander 1993[58]	Excluding for wrong study design: cross-sectional study
Shank 1987[59]	Full text not found and based on the abstract this is likely a cross-sectional study.
Shank 1992[60]	Wrong study design: cross sectional study
Sobik 2020[61]	Excluded for wrong intervention: comparing milk-based formula to soy formula (rather than raw animal milk).
Southby 1948[62]	Full text was not available.
Specker 1991[63]	Excluded wrong intervention: studying breastmilk vs milk-based formulas.
Tannock 2013[64]	Excluded wrong intervention: comparing 2 types of formula (cow and goat).
Thomas 1986[65]	Excluded: duplicate of Thomas 1986 (see below)
Thomas 1986[66]	Excluded for wrong study design. This is a cross sectional study in which a single, randomly selected stool sample for determination of FA1AT was obtained from each subject.
Thorisdottir 2011[67]	Exclude for wrong outcomes, wrong study design and wrong intervention. This study does not compare formula to cow's milk. Instead, this is a series of surveys done at 0-4, 4-8 and 8-12 months to study nutrient intakes based on those surveys for the study population.
Ummarino 2003[68]	Excluded for wrong study design as they are looking at the education level of mothers who feed infants inappropriately rather than comparing formula to milk.
Venkataraman 1992[69]	Full text was not available.
Vesikari 1986[70]	Excluded for wrong outcomes as they are only looking at IgG and IgM antibodies after rotavirus vaccination.
Vesikari 1986[71]	Excluded as this is a duplicate of the above study (Vesikari 1986)
Virtanen 1998[72]	Excluded for wrong outcomes: looking at diabetes incidence after starting milk at various ages rather than comparing formula to milk drinking
vonBerg 2003[73]	Excluded for wrong intervention: they are studying three hydrolyzed formulas to a conventional cow's milk-based formula
VonBerg 2009[74]	Excluded: wrong intervention. They are looking at 3 hydrolyzed formulas were compared with standard CMF
Vossenaar 2015[75]	Excluded wrong study design: this is a questionnaire-based study on feeding preferences vs. demographics of infants.
Walter 1990[76]	Full text not available.
Wharton 1992[77]	Full text not available.
Woodruff 1972[78]	Exclude wrong study design: started cow's milk at 2 months of age rather than at 4-11 months of age (the group we are looking at)

Woodruff 1987[79]	Full text was not available.
Yagi 1986[80]	Excluded: wrong outcomes. This only compares the protein and growth factor levels in cow's milk compared to breastmilk and formulas. there is no treatment of infants involved.
Yeung 1982[81]	Excluded for wrong comparator as they are comparing 2% milk to formula + cow's milk together rather than comparing 2% milk to formula alone.
Zhou 2011[82]	Excluded for wrong intervention as both intervention and control are formulas
Ziegler 1999[83]	Excluding for wrong comparator as they are studying hemoglobin levels after all infants start cow's milk after a 2-month period in which they are fed formula. They are also comparing infants who were previously breastfed and then fed cow's milk to infants who are formula fed and start cow's milk feedings.
Zimring 1986[84]	Full text was not available.
COW'S MILK VERSUS HUMAN MILK PROTEIN IN INFANT FEEDING 1962[85]	Excluded for wrong study design: review

Annex 4: Handling of data from individual studies for inclusion in the meta-analysis

Fomon 1981	Combined whole milk and heat-treated cow's milk for boys and girls
Fuchs 1993/1996	Combined the three formula groups (2 low fat follow-up formulas and a standard infant formula) and males/females
Morley 1999	Combined unfortified formula and iron fortified formula groups
Fuchs 1992	Combined follow up formula and standard infant formula. Added the increments and used data at 12 months of age. Used standard deviations from Maldanado 2010.

Annex 5: Study definitions of outcome parameters of anemia and gastrointestinal blood loss

Study	Anemia definition	Gastrointestinal blood loss definition
Morley 1999	haemoglobin value below 110 g/ litre	n/a
Fuchs 1993	Hb < 105 g/L	n/a
Thorisdottir 2013	The cutoff points used for IDA (iron deficiency anemia) were Hb <105 g/l, MCV < 74 fl and SF < 12 lg/l	n/a
Tunnessen 1987	Hemoglobin (g/dL) < 11	n/a
Fomon 1981	n/a	Guaic-positive stools (at 196 days)
Ziegler 1990	n/a	Guaic-positive stools (at 252 days)

Abbreviations: n/a not available

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