Association between funding source, methodological quality and research outcomes in randomized controlled trials of synbiotics, probiotics and prebiotics added to infant formula: A Systematic Review

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Abstract

Background: There is little or no information available on the impact of funding by the food industry on trial outcomes and methodological quality of synbiotics, probiotics and prebiotics research in infants. The objective of this study was to compare the methodological quality, outcomes of food industry sponsored trials versus non industry sponsored trials, with regards to supplementation of synbiotics, probiotics and prebiotics in infant formula.

Methods: A comprehensive search was conducted to identify published and unpublished randomized clinical trials (RCTs). Cochrane methodology was used to assess the risk of bias of included RCTs in the following domains: 1) sequence generation; 2) allocation concealment; 3) blinding; 4) incomplete outcome data; 5) selective outcome reporting; and 6) other bias. Clinical outcomes and authors’ conclusions were reported in frequencies and percentages. The association between source of funding, risk of bias, clinical outcomes and conclusions were assessed using Pearson’s Chi-square test and the Fisher’s exact test. A p-value < 0.05 was statistically significant.

Results: Sixty seven completed and 3 on-going RCTs were included. Forty (59.7%) were funded by food industry, 11 (16.4%) by non-industry entities and 16 (23.9%) did not specify source of funding. Several risk of bias domains, especially sequence generation, allocation concealment and blinding, were not adequately reported. There was no significant association between the source of funding, risk of bias, clinical outcomes and conclusions were assessed using Pearson’s Chi-square test and the Fisher’s exact test. A p-value < 0.05 was statistically significant.

Conclusion: In RCTs on infants fed infant formula containing probiotics, prebiotics or synbiotics, the source of funding did not influence the majority of outcomes in favour of the sponsors’ products. More non-industry funded research is needed to further assess the impact of funding on methodological quality, reported clinical outcomes and authors’ conclusions.

Keywords: Synbiotics, Probiotics, Prebiotics, Funding source, Methodological quality

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Background

There are numerous studies that explore the relationship between industrial sponsorship of biomedical research and published outcomes [1]. Several reviews have documented how trials funded by industry are more likely to report results in favour of the sponsor’s products [2-5]. These reviews focused on trials sponsored by the pharmaceutical industry. Few reviews have explored the impact of funding by the food industry on outcomes of research trials [6,7]. A review by Nkansah et al. also found that majority of trials investigating the effects of calcium supplementation in healthy children were industry funded and all supported calcium supplementation, in favour of the sponsor [8]. Similarly, a review by Lesser et al. found that scientific nutrition related articles (intervention trials, observational studies and scientific reviews) on common consumed beverages (soft drinks, juice, milk) funded by the food industry, were more likely to be favourable to the sponsor than articles that did not have industry funding [6].

Reporting only positive outcomes in a research trial significantly reduces a sponsors’ financial risk. Pressure to show a food product causes favourable outcomes in a specific population, may result in biases in trial design (methodology) and reporting of outcomes in industry sponsored research. This type of bias in nutrition research could adversely affect public health. Results from nutrition research also influence policy formulation, professional dietary guidelines, design of public health interventions and regulation of food product health claims. In addition, findings from nutrition research often receive publicity from the media, which influences consumer behaviour [6].

More studies are needed to explore the relationship between the food industry and nutrition research [7]. There is little or no information available on the impact of funding by the food industry on trial outcomes and methodological quality of trials on synbiotics, probiotics, or prebiotics used in infants. Methodological quality may be compromised when insufficient information is provided regarding sequence generation, allocation concealment, blinding, bias introduced from other sources and incomplete outcome reporting.

Hypothesis

The source of funding in research trials using probiotics, prebiotics or synbiotics supplemented formula in infants is associated with outcomes in favour of the sponsor’s products and authors’ conclusions.

Methods

Criteria for considering studies for this review

Types of studies

All randomized controlled trials (RCTs) conducted from 1980 to 2012 (irrespective of language) on synbiotics, probiotics, or prebiotics added to infant formula were included. Study participants were healthy full term infants (>37 weeks gestation or > 2.5 kg birth weight, 0–12 months old), preterm infants (born < 37 weeks gestation), low birth weight (<2.5 kg at birth) and extreme low birth weight infants (<1000 g at birth). Infants were fed either infant formula (preterm or full term formula), mixed feeds (breast milk with infant formula) with added synbiotics, probiotics or prebiotics or conventional infant formula with or without placebo. RCTs were excluded if they included infants with cardiac defects, pulmonary diseases, gastrointestinal diseases, major congenital abnormalities or chromosomal abnormalities. Commentaries, editorials, letters to the editor and studies that were not RCTs were excluded.

Types of outcome

The outcomes included: 1) Source of funding, 2) Methodological quality (Risk of bias), 3) Clinical outcomes in RCTs, 4) Conclusions (Overall study conclusions and conclusions on reported clinical outcomes) and 5) Association between...
source of funding and methodological quality, clinical outcomes and author’s conclusions.

Search methods for identification of studies
A literature search regardless of language was conducted on electronic databases including The Cochrane CENTRAL Register for Controlled Trials (2012), EMBASE (1980+), Scopus (1980 to 2012), EBSCO host (1960 to 2012), PUBMED / MEDLINE (1966 to 2012), OVID (1950 to 2012), SPORTDiscus (1960 to 2012), Web of Science (1970 to 2012), Science Direct (1950 to 2012), CINAHL (1980 to 2012), Science citation index (1970 to 2012), Latin American Caribbean Health Sciences literature (LILACS) (1965 to 2012), NLMGateway (1950–1966). RCTs published in non-English language journals were translated by independent translators who were familiar with the subject matter.

The search strategy used to search PUBMED for studies on full term infants is: (synbiotic* and probiotic* OR prebiotic*) AND (FOS or fructooligosaccharide or inulin or GOS or galactooligosaccharide) AND (infant formula* OR infant feeding OR formula OR formula milk) AND (infant* OR baby or babies) NOT (preterm or premature or low birth weight babies or allergy or eczema) AND (randomized controlled trial* OR controlled clinical trial* OR random allocation*) Limits: Humans. This search strategy was modified to search other electronic databases and for studies on preterm infants. A hand search was conducted on abstracts of major conference proceedings such as the Pediatric Academic Society meetings from 1990 (www.pas-meetings.org), cross checked references cited in RCTs and in recent reviews (published from 2003 to 2012) for additional RCTs not identified by electronic searches and specialty journals which were not included in any database such as Pediatrika and Chinese Journal of Microecology. To identify on-going and unpublished trials, experts in the field, manufacturers of infant formula containing probiotics and prebiotics were contacted. Web sites of companies that have conducted or were conducting RCTs on probiotics and prebiotics were searched.

Examples: Pfizer (www.pfizerpro.com/clinicaltrials), Chris Hansen Laboratory (www.chr-hansen.com/research_development/documentation.html). A search was conducted on prospective trial registries such as World Health Organization (WHO) International Clinical Trials Registry Platform Search Portal (www.who.int/trialsearch), Clinical Trials.gov register (www.clinicaltrials.gov), Current Controlled Trials metaRegister of Controlled Trials [mRCT] (www.controlled-trials.com/mrct) and www.clinicaltrialresults.org.

Selection of studies
One reviewer (MM) independently reviewed all abstracts, citations and identified potentially eligible RCTs. The full reports of eligible RCTs were retrieved by one reviewer (MM) and the pre-specified selection criteria applied independently by two reviewers (MM, ML) using a study eligibility form designed for this review. If more than one publication of a study existed, all reports of the study were grouped together under one name. Any disagreements between the reviewers were resolved through discussion. Unresolved disagreements were resolved by a third party (RB).

Data extraction and management
Two reviewers (MM, ML) independently extracted data using a pretested data extraction form that was designed for this review. The reviewers (MM, ML) cross checked data and resolved any differences through discussion. Unresolved disagreements were resolved by a third party (RB). One reviewer (MM) entered the data in SPSS version 19 and the other reviewer (AM) conducted quality control checks. The data obtained from each RCT included:

A) Source of funding or support of RCTs
The source of funding or support of the RCTs was defined and categorized as:

1) Industry included:
   • For – profit company, donation of study product by a for – profit company which manufactured the study product,
   • Not – for profit company that promoted the consumption of synbiotics, probiotics or prebiotics,
   • Mixed sources (for-profit company and other source).

2) Non – industry included:
   • Government: National, regional (provincial, county) government body with NO industry association.
   • Foundation / Philanthropies: examples include Rockefeller foundation, Bill and Melinda Gates foundation.
   • Institution: University, Research centres, teaching and academic hospitals.
   • Other source of funding.

3) None: No source of funding was disclosed in study report.

B) Assessment of methodological quality of evidence (Risk of bias)
Two reviewers (MM, ML) independently assessed the risk of bias of included RCTs as described in the Cochrane Handbook for Systematic Reviews for Interventions according to the following 6 components:
1) sequence generation; 2) allocation concealment; 3)
| Included studies | On-going studies |
|------------------|------------------|
| **Author publication year** | **Full term/Preterm infant** | **Sponsor** | **Author publication year** | **Full term/Preterm infant** | **Sponsor** | **Author, Year study commenced** | **Full term/Preterm infant** |
| Allen 2010 [18] | Full Term | Knowledge exploitation fund, collaborative industrial research, others | Soh 2009 [19] | Full Term | National Medical Research Council, Singapore | Jacobs 2007 [20] | Pre-Term |
| Alliet 2007 [21] Scholtens 2008 [22] | Full Term | Numico | Urban 2008 [23] | Full Term | Nestle | Patole 2009 [24] | Pre-Term |
| Ashley 2012 [25] | Full Term | Mead Johnson | Velaphi 2008 [26] | Full Term | Nestle | Underwood 2009 [27] | Pre-Term |
| Bakker-Zierzikzee 2005 [28] Bakker-Zierzikzee 2006 [29] | Full Term | None/Not clear | Vendt 2006 [30] | Full Term | Valio Ltd | |
| Bettler 2006 [31] | Full Term | Wyeth Nutrition | Vlieger 2009 [32] | Full Term | Friesland | |
| Brunser 2006 [33] | Full Term | None/Not clear | Weizman 2005 [34] | Full Term | Materna Laboratories | |
| Bruzese 2009 [35] | Full Term | Numico | Weizman 2006 [36] | Full Term | Materna Laboratories | |
| Chouraqui 2004 [37] | Full Term | Nestle | Xiao-Ming 2004 [38] | Full Term | Friesland | |
| Chouraqui 2008 [39] | Full Term | Nestle | Xiao-Ming 2008 [40] | Full Term | None / Not clear | |
| Copper 2010 [41] | Full Term | Nestle | Ziegler 2007 [41] | Full Term | Mead Johnson | |
| Costalos 2008 [42] | Full Term | Numico | Bin-Nun 2005 [44] | Pre-Term | Mr and Mrs Stephen Hammerman, Mirsky Research fund | |
| Decsi 2005 [45] | Full Term | Numil Ltd | Boehm 2002 [46] | Pre-Term | Numico | |
| Fanaro 2005 [49] | Full Term | None / Not clear | Chrzanoskiw-Liszewska 2012 [50] | Pre-Term | None/Not clear | |
| Fanaro 2008 [51] | Full Term | Humana GmbH | Costalos 2003 [52] | Pre-Term | None/Not clear | |
| Gibson 2009 [53] | Full Term | Nestle | Dani 2002 [54] | Pre-Term | None/Not clear | |
| Gil-Campos 2012 [55] | Full Term | Puleva | Indri 2008 [56] | Pre-Term | Bio Gaia | |
| Hascoet 2011 [57] | Full Term | Nestle | Indri 2009 [58] | Pre-Term | Numico | |
| Holscher 2012a [59] | Full Term | Nestle | Kapki 2007 [60] | Pre-Term | None/Not clear | |
| Holscher 2012b [61] | Full Term | Nestle | Kitajima 1992 [62] | Pre-Term | None/Not clear | |
| Kim 2010 [63] | Full Term | Ministry of Health, Welfare and family affairs. Republic of Korea | Lin H-C 2008 [64] | Pre-Term | National Science Council of Taiwan | |
| Knol 2005 [65] | Full Term | Numico | Mihatsch 2006 [66] | Pre-Term | Milupa GmbH | |
| Magne 2008 [67] | Full Term | Numico | Mihatsch 2010 [68] | Pre-Term | Nestle | |
| Mah 2007 [69] | Full Term | National Medical Research Council Singapore | Millar 1993 [70] | Pre-Term | Wessex Regional Health Authority and childrens Research fund | |
| Maldonado 2010 [72] | Full Term | Puleva | Modi 2010 [73] | Pre-Term | Danone | |
| Study                | Term     | Formula     | Study                | Term     | Formula     |
|---------------------|----------|-------------|---------------------|----------|-------------|
| Moro 2002 [74]      | Full     | None/Not clear | Mohan 2006 [76]     | Pre-Term | None/Not clear |
| Moro 2003 [75]      | Full     | None/Not clear | Reuman 1986 [78]    | Pre-Term | None/Not clear |
| Moro 2005 [77]      | Full     | None/Not clear | Riskin 2009 [84]    | Pre-Term | None/Not clear |
| Moro 2006 [79]      | Full     | Numico      | Reuman 1986 [78]    | Pre-Term | None/Not clear |
| Arslanoglu 2007 [80] | Full     | None/Not clear | Reuman 1986 [78]    | Pre-Term | None/Not clear |
| Van Hoffen 2009 [82] | Full     | Nestle    | Reuman 1986 [78]    | Pre-Term | None/Not clear |
| Schouten 2011 [83]  | Full     | Danone      | Reuman 1986 [78]    | Pre-Term | None/Not clear |
| Piemontese 2011 [85] | Full     | Nestle      | Reuman 1986 [78]    | Pre-Term | None/Not clear |
| Puccio 2007 [87]    | Full     | Nestle      | Reuman 1986 [78]    | Pre-Term | None/Not clear |
| Rautava 2006 [89]   | Full     | Academy of Finland, Turku University Central Hospital Research Funds | Westerbeek 2010 [93] | Pre-Term | Danone |
| Rautava 2009 [90]   | Full     | Academy of Finland, Turku University Central Hospital Research Funds | Westerbeek 2011a [94] | Pre-Term | Danone |
| Rinne 2005 [92]     | Full     | Academy of Finland, Turku University Central Hospital Research Funds | Westerbeek 2011b [95] | Pre-Term | Danone |
| Saavedra 2004 [96]  | Full     | Nestle      | Yong 2009 [97]      | Pre-Term | None/Not clear |
| Scalabrin 2009 [98] | Full     | Mead Johnson | Yong 2009 [97]      | Pre-Term | None/Not clear |
| Scalabrin 2012 [99] | Full     | Mead Johnson | Yong 2009 [97]      | Pre-Term | None/Not clear |
| Schmelde 2003 [100] | Full     | Numico      | Yong 2009 [97]      | Pre-Term | None/Not clear |
Figure 1 Process of study selection.
Table 2 Table of 56 Excluded studies with reasons for exclusion

| Use of Exclusive breast milk or Other milk feeds (buffalo, goat milk) | Type of feed not clear/specified | Probiotic administered in water, saline or other fluid that is not infant formula | No use of probiotic, prebiotic | Not RCT, (Cross over, Follow up, Observational study) | Different inclusion criteria | Lack of suitable/knowledgeable translator | Data presentation inappropriate | Out dated (published before 1980) |
|---|---|---|---|---|---|---|---|---|
| Agarwal 2003 [101] | Al Hosni 2012 [102] | FengJuan 2008 [103] | Morisset 2011 [104] | Huet 2006 [105] | Agustina 2007 [106] | Akiyama1994a [107] (Japanese) | Grzéskowak 2012 [108] | Andrews 1969 [109] |
| Baldeon 2008 [110] | Campeotto 2011 [111] | Kuutunen 2009 [112] | Patole 2005 [113] | Bongers 2007 [114] | Correa 2005 [115] | Akiyama1994b [116] (Japanese) | | Robinson 1952 [117] |
| Braga 2011 [118] | Cukrowska 2002 [119] | Kukkonen 2007 [120] | Rochat 2007 [121] | Chou I-C 2009 [122] | Hol 2008 [123] | | | |
| Chandra 2002 [124] | *Karonen 1999 [125] | Kukkonen 2008 [126] | Taipale 2011 [127] | Euler 2005 [128] | Isolauri 2000 [129] | | | |
| Lin H-C 2005 [130] | *Karonen 2001 [131] | Taylor 2009 [132] | | Hoyos 1999 [133] | Nopchinda 2002 [134] | | | |
| Marzioni [135] | *Karonen 2002 [136] | Thibault 2004 [137] | | | | | | |
| Rinne 2006 [140] | Li 2004 [141] | Lee 2007 [142] | | Urao 1999 [143] | | | | |
| Samanta 2009 [144] | Panigrahi 2008 [145] | Lidesteri 2003 [146] | | Van der Aa 2010 [147] | | | | |
| Rojas 2012 [148] | Taylor 2007 [151] | Marini 2003 [149] | | Waliogora-Dupriet 2007 [150] | | | | |
| Underwood 2009 [154] | | Rigo 2001 [152] | | Wang 2007 [153] | | | | |
| Savino 2003 [155] | | Sepp 1993 [156] | | | | | | |

Key: * Unpublished trials.
blinding; 4) incomplete outcome data; 5) selective outcome reporting; and 6) other sources of bias [17]. Each domain was assessed as having either a low risk of bias, high risk of bias or unclear to permit judgment. Any disagreements regarding risk of bias were resolved through discussion between MM, ML and RB. The association between risk of bias (domains) and type of funding (industry, non–industry, none declared) was explored.

C) Assessment of clinical outcomes
The primary and secondary outcomes from each study report were evaluated and categorized as:

1. Positive: synbiotic, probiotic or prebiotic supplementation had a statistically significant effect, p < 0.05. Examples of positive outcomes included: adequate growth (weight gain, length gain, head circumference), tolerance (no feeding problems), microflora (increase in colony forming units of bifidobacteria, lactobacillus, decrease in pathogens), decreased infections (decrease in frequency, incidence of infections).

2) Negative: synbiotic, probiotic or prebiotic supplementation had a statistically significant effect in an adverse event / negative outcome such as weight loss, diarrhoea, p < 0.05

3) Neutral: synbiotic, probiotic or prebiotic supplementation did not have a statistically significant effect, p > 0.05, no significant differences between study groups. Clinical outcomes included: growth parameters, gastrointestinal parameters (tolerance to feed, stool characteristics, microflora); immune response, infections and mortality.

D) Overall study conclusions and conclusions on reported outcomes
The authors’ overall study conclusion and conclusions on reported clinical outcomes were evaluated and categorized as:

1. Positive: The author’s conclusion preferred the sponsor’s products over control/placebo. Interpretation of data supported the sponsor’s products over control.

2. Negative: The sponsors’ products were not preferred over control / placebo. Interpretation of data did NOT support the sponsors’ products.

3. Neutral: The author’s conclusion was neutral to the sponsor’s products.

4. No clear conclusion was offered by author.

In this review, the “conclusions on reported outcomes” referred to the authors’ conclusions on individual reported RCTs outcomes. Examples include conclusions on weight gain, length gain, vomiting, necrotizing enterocolitis, sepsis.

Statistical Analysis
All the outcomes in this review were dichotomous and are described in frequencies and percentages. The association between source of funding (industry/non-industry/none) and methodological quality (low/un-clear/high risk of bias), clinical outcomes and author’s conclusions were assessed using both the Pearson’s Chi-square test and the Fisher’s exact test. A p-value of less than 0.05 was considered statistically significant. SPSS version 19 statistical software was used. A statistician (AM) was consulted throughout the review process.

Ethics
The Human Research Ethics Committee at Stellenbosch University, South Africa reviewed the protocol for this review, ruled that all data to be collected for this review was from the public domain and was therefore exempt from ethical approval.

Results
Results of the search and description of studies
Electronic search of available databases yielded 290 citations. After reading titles and abstracts, duplicate reports were removed, 226 articles were screened and 100 articles were excluded. A hand search yielded 6 more articles. Potentially relevant full text reports were retrieved, reviewed for eligibility and a further 56 RCTs were excluded. Studies that had multiple publications were considered as one trial. Sixty seven RCTs and three on-going RCTs were

Table 3 Source of funding and study participants

| Sponsor          | Study participants |          |          |          |          |
|------------------|--------------------|----------|----------|----------|----------|
|                  | Full term infant   | Preterm Infant | Total   |          |          |
|                  | n                  | n        | n (%)    |          |          |
| Industry         | 33                 | 7        | 40 (59.7)|          |          |
| None / Not Clear| 6                  | 10       | 16 (23.9)|          |          |
| Non Industry     | 6                  | 5        | 11 (16.4)|          |          |
| Total            | 45                 | 22       | 67 (100.0)|         |          |

Table 4 Methodological quality (Risk of bias)

| Quality of studies N = 67 | Low risk | High risk | Unclear |
|---------------------------|----------|-----------|---------|
| Sequence generation       | 42 (62.7)| 25 (37.3) |          |
| Allocation concealment    | 32 (47.8)| 35 (52.2) |          |
| Blinding                  | 31 (46.3)| 36 (53.7) |          |
| Incomplete Outcome data   | 52 (77.6)| 1 (1.5)   | 14 (20.9)|
| Selective reporting       | 57 (85.1)| 7 (10.4)  | 3 (45)   |
| Other bias                | 53 (79.1)| 14 (20.9) |          |
| Variable                          | N= | Overall study conclusion | Conclusion on reported outcomes |
|----------------------------------|----|--------------------------|--------------------------------|
| Weight gain                      | N= | 67                       | 67                             |
| Length gain                      | N= | 40                       | 40                             |
| Head circumference               | N= | 31                       | 31                             |
| Colic                            | N= | 13                       | 13                             |
| Spitting up/Regurgitation        | N= | 26                       | 26                             |
| Vomiting                         | N= | 31                       | 31                             |
| Crying/Fussiness                 | N= | 22                       | 22                             |
| Gastric Residuals, Abdominal distension | N= | 5             | 5                              |
| Volume of formula consumed       | N= | 31                       | 31                             |
| Time to full enteral feeds       | N= | 9                        | 9                              |
| Stool frequency                  | N= | 37                       | 37                             |
| Stool consistency                | N= | 37                       | 37                             |
| Stool pH                         | N= | 13                       | 13                             |
| Short chain fatty acids          | N= | 9                        | 9                              |
| Flatulence/Gas                   | N= | 16                       | 16                             |
| Diarrhoea, Diarrhoea episodes    | N= | 19                       | 19                             |
| Constipation                     | N= | 3                        | 3                              |
| Microflora - Bifidobacteria      | N= | 31                       | 31                             |
| Microflora - Lactobacillus       | N= | 19                       | 19                             |
| Microflora - Pathogens           | N= | 25                       | 25                             |
| Immune response CRP, IL6, Cytokines | N= | 0          | 0                              |
| Immunoglobulins (IgA, IgG, Ig-Fc, IgE) | N= | 10       | 10                             |
| Allergy                          | N= | 3                        | 3                              |
| Eczema, Dermatitis, Rash, Skin Alterations | N= | 7       | 7                              |
| Infections - Acute Otitis Media  | N= | 3                        | 3                              |
| Respiratory Infections           | N= | 9                        | 9                              |
| Gastrointestinal infections      | N= | 6                        | 6                              |
| Total infections, other unspecified infections | N= | 8       | 8                              |
| Urinary tract infections         | N= | 2                        | 2                              |

* N= values reflect the total number of evaluations for each variable.
| Table 5 Reported outcomes and conclusions (Continued) |
|-----------------------------------------------------|
| Necrotizing Enterocolitis   | 11  | 2 (18.2) | 9 (81.8) | Necrotizing Enterocolitis | 12  | 7 (58.3) | 3 (25) | 2 (16.7) |
| Sepsis                   | 10  | 10 (100) |          | Sepsis                    | 10  | 9 (90)   | 1 (10) |
| Fever, Febrile Episodes   | 4   | 2 (50)   | 2 (50)   | Fever, Febrile Episodes   | 2   | 2 (100)  |         |
| Antibiotic use            | 19  | 4 (21.1) | 15 (78.9)| Antibiotic use            | 16  | 13 (81.3)| 3 (18.8)|         |
| Hospitalization           | 12  | 12 (100) |          | Hospitalization           | 10  | 10 (100) |         |
| Biochemical measures      | 9   | 9 (100)  |          | Biochemical measures      | 6   | 5 (83.3) | 1 (16.7)|         |
| Adverse events            | 18  | 2 (11.1) | 16 (88.9)| Adverse events            | 17  | 13 (76.5)| 4 (23.5)|         |
| Death / Mortality         | 7   | 1 (14.3) | 6 (85.7) | Death/Mortality           | 8   | 7 (87.5) | 1 (12.5)|         |
| Intestinal permeability   | 3   | 1 (33.3) | 2 (66.7) | Intestinal permeability  | 3   | 1 (33.3) | 2 (66.7)|         |
| Duration of TPN           | 5   | 5 (100)  |          | Duration of TPN           | 5   | 4 (80)   | 1 (20) |

- **Positive**: synbiotic, probiotic or prebiotic supplementation had a statistically significant effect, \( p < 0.05 \).
- **Neutral**: synbiotic, probiotic or prebiotic supplementation did not have a statistically significant effect, \( p > 0.05 \).
- **Negative**: synbiotic, probiotic or prebiotic supplementation had a statistically significant increase in an adverse event / negative outcome, \( p < 0.05 \).
included in this review. (Table 1) The selection process is shown in Figure 1. Table 2 gives a list of 56 RCTs which were excluded for: use of exclusive breast or non-formula milk (8 RCTs), type of feed not clear (11 RCTs), probiotic administered in saline, water or other fluid (4 RCTs), no use of probiotic or prebiotic (6 RCTs), not RCT (12 studies), different inclusion criteria (10 studies), lack of suitable translator (2 RCTs), data presentation inappropriate (1 RCT) and out of date [published before1980] (2 RCTs). Three excluded RCTs were unpublished trials.

### Characteristics of included studies

Table 1 lists included and on-going trials. Sixty seven RCTs were included, 45 (67.2%) on full term infants, 22 (32.8%) on preterm infants. All included RCTs were published trials. All trials were conducted on healthy full

### Table 6 Association between Sponsor and methodological quality (risk of bias)

| Methodological quality | Source of funding | Yes (Low risk) n (%)<sup>ss</sup> | No (High risk) n (%)<sup>ss</sup> | Unclear n (%)<sup>ss</sup> | Chi-square p value | Fisher’s exact p value |
|------------------------|-------------------|---------------------------------|---------------------------------|--------------------------|----------------------|------------------------|
| Sequence generation    | Industry          | 26 (38.8)                      | 14 (20.9)                      | 8 (11.9)                 | 0.435                | 0.465                  |
|                        | None/Not clear    | 8 (11.9)                       | 8 (11.9)                       | 3 (4.5)                  | 0.007                | 0.011                  |
|                        | Non industry      | 8 (11.9)                       | 8 (11.9)                       | 3 (4.5)                  | 0.007                | 0.011                  |
| Allocation concealment | Industry          | 21 (31.3)                      | 19 (28.4)                      | 5 (7.5)                  | 0.023*               | 0.005*                 |
|                        | None/Not clear    | 5 (7.5)                        | 11 (16.4)                      | 2 (3.0)                  | 0.023*               | 0.005*                 |
|                        | Non industry      | 6 (9.0)                        | 5 (7.5)                        | 2 (3.0)                  | 0.023*               | 0.005*                 |
| Blinding               | Industry          | 18 (26.9)                      | 22 (32.8)                      | 10 (14.9)                | 0.039                | 0.045                  |
|                        | None/Not clear    | 6 (9.0)                        | 10 (14.9)                      | 1 (1.5)                  | 0.039                | 0.045                  |
|                        | Non industry      | 7 (10.4)                       | 4 (6.0)                        | 1 (1.5)                  | 0.039                | 0.045                  |
| Incomplete outcome data| Industry          | 36 (53.7)                      | 1 (1.5)                        | 3 (4.5)                  | 0.023*               | 0.005*                 |
|                        | None/Not clear    | 9 (13.4)                       | 7 (10.4)                       | 1 (1.5)                  | 0.023*               | 0.005*                 |
|                        | Non industry      | 7 (10.4)                       | 4 (6.0)                        | 1 (1.5)                  | 0.023*               | 0.005*                 |
| Selective reporting    | Industry          | 36 (53.7)                      | 2 (3.0)                        | 2 (3.0)                  | 0.024                | 0.018                  |
|                        | None/Not clear    | 11 (16.4)                      | 4 (6.0)                        | 1 (1.5)                  | 0.024                | 0.018                  |
|                        | Non industry      | 10 (14.9)                      | 1 (1.5)                        | 0                       | 0.024                | 0.018                  |
| Free of other bias     | Industry          | 35 (52.2)                      | 5 (7.5)                        | 7 (10.4)                 | 0.033*               | 0.038*                 |
|                        | None/Not clear    | 9 (13.4)                       | 7 (10.4)                       | 1 (1.5)                  | 0.033*               | 0.038*                 |
|                        | Non industry      | 8 (13.4)                       | 1 (1.5)                        | 2 (3.0)                  | 0.033*               | 0.038*                 |

<sup>ss</sup>Significant p < 0.05.

<sup>ss</sup>Overall percentage.

### Table 7 Association between Sponsor and clinical outcomes: Growth

| Growth                  | Source of funding | Assessment of outcome | Chi-square p value | Fisher’s exact p value |
|-------------------------|-------------------|-----------------------|---------------------|------------------------|
|                         | Positive<sup>ss</sup> n (%)<sup>ss</sup> | Neutral<sup>ss</sup> n (%)<sup>ss</sup> |                     |                        |
| Weight gain N = 56      | Industry          | 2 (3.6)               | 35 (62.5)           | 0.309                  | 0.266                  |
|                        | None/Not clear    | 2 (3.6)               | 10 (17.9)           | 0.309                  | 0.266                  |
|                        | Non industry      | 0                    | 7 (12.5)            | 0.309                  | 0.266                  |
| Length gain N = 40      | Industry          | 3 (7.5)               | 29 (72.5)           | 0.667                  | 1.00                   |
|                        | None/Not clear    | 6 (15)                | 2 (5)               | 0.667                  | 1.00                   |
|                        | Non industry      | 2 (5)                 |                     | 0.667                  | 1.00                   |
| Head Circumference N = 31| Industry        | 4 (12.9)              | 23 (74.2)           | 0.712                  | 1.00                   |
|                        | None /Not clear   | 3 (9.7)               |                     | 0.712                  | 1.00                   |
|                        | Non industry      | 1 (3.2)               |                     | 0.712                  | 1.00                   |

<sup>ss</sup>Overall percentage.

<sup>ss</sup>Positive: synbiotic, probiotic or prebiotic supplementation had a statistically significant effect, p < 0.05. There were significant differences between study groups (in favour of experimental group).

<sup>ss</sup>Neutral: synbiotic, probiotic or prebiotic supplementation did not have a statistically significant effect, p > 0.05, No significant differences between study groups.
term or preterm infants and used standard (full term or preterm) infant formula (Table 3).

Funding
Out of 67 trials, 40 (59.7%) were funded by food industry, 11 (16.4%) were funded by non-industry entities, and 16 (23.9%) did not specify their source of funding, 10 RCTs on preterm infants, 6 RCTs on full infants (Table 3).

Methodological quality (Risk of bias)
In this review, several domains were not adequately reported, particularly, the domains of sequence generation, allocation concealment and blinding. Out of 67 RCTs, 25 (37.3%) failed to report sequence generation, 35 (52.2%) failed to report allocation concealment and 36 (53.7%) did not report blinding. Majority of the RCTs were assessed as having a low risk of bias in the domains of incomplete outcome data 52 (77.6%), selective reporting 57 (85.1%) and other bias 53 (79.1%) (Table 4).

Outcomes and study conclusions
In most RCTs, majority of outcomes were assessed as neutral, (intervention did not have a statistically significant effect, p > 0.05). A total of 49 (73.1%) of RCTs had a positive overall study conclusion in favour of the sponsors’ products, while 7 (10.4%) had negative, 7 (10.4%) had neutral conclusions and 4 (6%) had no clear conclusion. The included RCTs either did not provide any conclusion on their reported clinical outcomes or, they provided a positive conclusion for their reported outcome in favour of the sponsors’ products. Few RCTS had either negative or neutral conclusions on their reported clinical outcomes (Table 5).

Association between source of funding (sponsor) and methodological quality of studies
There was no significant association between the source of funding and the domains of sequence generation (Chi–square p = 0.435, Fisher exact p = 0.465), allocation concealment (Chi–square p = 0.315, Fisher exact p = 0.338), blinding (Chi–square p = 0.395, Fisher exact p = 0.457)

Table 8 Association between Sponsor and clinical outcomes: Tolerance symptoms

| Tolerance                     | Source of funding | Positive* n (%) | Negative* n (%) | Neutral* n (%) | Chi-square p value | Fisher’s exact p value |
|-------------------------------|-------------------|-----------------|-----------------|----------------|--------------------|------------------------|
| Colic N = 13                  | Industry          | 1 (7.7)         | 11 (84.6)       | 0.764          | 1.00               |
|                               | None/Not clear    |                 |                 |                |                    |
|                               | Non industry      | 1 (7.7)         |                 |                |                    |
| Spitting up/Regurgitation N = 26| Industry         | 2 (7.7)         | 1 (3.8)         | 0.907          | 1.00               |
|                               | None/Not clear    | 4 (15.4)        |                 |                |                    |
|                               | Non industry      | 2 (7.7)         |                 |                |                    |
| Vomiting N = 31               | Industry          | 1 (3.2)         | 23 (74.2)       | 0.860          | 1.00               |
|                               | None/Not clear    | 5 (16.1)        |                 |                |                    |
|                               | Non industry      | 2 (6.5)         |                 |                |                    |
| Crying fussiness N = 22       | Industry          | 3 (13.6)        | 1 (4.5)         | 0.581          | 1.00               |
|                               | None/Not clear    | 4 (18.2)        |                 |                |                    |
|                               | Non industry      | 0               |                 |                |                    |
| Gastric residuals, Abdominal distension N = 5 | Industry | 1 (20)          |                 | 0.659          | 1.00               |
|                               | None/Not clear    | 1 (20)          |                 |                |                    |
|                               | Non industry      | 1 (6.7)         | 2 (40)          |                |                    |
| Volume of formula consumed/daily intake N = 31 | Industry | 3 (9.7)         | 1 (3.2)         | 0.758          | 1.00               |
|                               | None/Not clear    | 4 (12.9)        |                 |                |                    |
|                               | Non industry      | 5 (16.1)        |                 |                |                    |
| Days to full enteral feeding N = 9 | Industry | 4 (44.4)        |                 | 0.325          | 0.444              |
|                               | None/Not clear    | 1 (11.1)        |                 |                |                    |
|                               | Non industry      | 1 (11.1)        | 2 (22.2)        |                |                    |

*Overall percentage.
*Positive: synbiotic, probiotic or prebiotic supplementation had a statistically significant effect, p < 0.05. There were significant differences between study groups (in favour of experimental group).
*Neutral: synbiotic, probiotic or prebiotic supplementation did not have a statistically significant effect, p > 0.05. No significant differences between study groups.
*Negative: synbiotic, probiotic or prebiotic supplementation had a statistically significant increase in an adverse event / negative outcome, p < 0.05.
### Table 9: Association between sponsor and clinical outcomes: stool characteristics

| Stool characteristics | Source of funding | Positive* (n (%)) | Negative* (n (%)) | Neutral* (n (%)) | Chi-square p value | Fisher’s exact p value |
|-----------------------|-------------------|-------------------|-------------------|-----------------|-------------------|------------------------|
| Stool Frequency N = 37| Industry          | 7 (18.9)          | 22 (59.5)         | 1 (2.7)         | 0.501             | 0.540                  |
|                       | None/Not clear    | 3 (8.1)           | 4 (10.8)          |                 |                   |                        |
|                       | Non industry      | 1 (2.7)           |                   |                 |                   |                        |
| Stool Consistency n = 37| Industry       | 14 (37.8)         | 15 (40.5)         | 1 (2.7)         | 0.562             | 1.00                   |
|                       | None/Not clear    | 4 (10.8)          | 3 (8.1)           |                 |                   |                        |
|                       | Non industry      | 1 (2.7)           |                   |                 |                   |                        |
| Stool pH N = 13       | Industry          | 7 (33.8)          | 2 (15.4)          |                 | 0.305             | 1.00                   |
|                       | None/Not clear    | 4 (30.8)          |                   |                 |                   |                        |
|                       | Non industry      |                   |                   |                 |                   |                        |
| Stool Short Chain Fatty Acids N = 9 | Industry | 2 (22.2) | 4 (44.4) | 1 (11.1) | 0.687 | 1.00 |
|                       | None / Not clear  | 1 (11.1)          |                   |                 |                   |                        |
|                       | Non industry      | 1 (11.1)          |                   |                 |                   |                        |
| Flatulence / Gas N = 16| Industry       | 15 (93.8)         |                   |                 |                   | Not valid               |
|                       | None/Not clear    | 1 (6.3)           |                   |                 |                   |                        |
|                       | Non industry      | 0                 |                   |                 |                   |                        |
| Diarrhoea, Diarrhoea episodes N = 19 | Industry | 3 (15.8) | 1 (5.3) | 10 (52.6) | 0.771 | 1.00 |
|                       | None/Not clear    | 2 (10.5)          |                   |                 |                   |                        |
|                       | Non industry      | 3 (15.8)          |                   |                 |                   |                        |
| Constipation N = 3    | Industry          | 1 (33.3)          |                   |                 | 0.386             | 1.00                   |
|                       | None/Not clear    | 1 (33.3)          |                   |                 |                   |                        |
|                       | Non industry      | 0                 |                   |                 |                   |                        |

*Overall percentage.

*Positive: synbiotic, probiotic or prebiotic supplementation had a statistically significant effect, *p* < 0.05. There were significant differences between study groups (in favour of experimental group).

*Neutral: synbiotic, probiotic or prebiotic supplementation did not have a statistically significant effect, *p* > 0.05, No significant differences between study groups.

*Negative: synbiotic, probiotic or prebiotic supplementation had a statistically significant increase in an adverse event / negative outcome, *p* < 0.05.

### Table 10: Association between sponsor and clinical outcomes: Microflora

| Microflora                | Source of funding | Positive 4* (n (%)) | Negative 5* (n (%)) | Neutral 6* (n (%)) | Chi-square p value | Fisher’s exact p value |
|--------------------------|-------------------|---------------------|---------------------|---------------------|-------------------|------------------------|
| Bifidobacteria N = 31    | Industry          | 12 (38.7)           | 6 (19.4)            | 0.416               | 0.583             |
|                          | None/Not clear    | 8 (25.8)            | 2 (6.5)             |                     |                   |                        |
|                          | Non industry      | 3 (9.7)             |                     |                     |                   |                        |
| Lactobacillus N = 19     | Industry          | 2 (10.5)            | 6 (31.6)            | 0.155               | 0.176             |
|                          | None/Not clear    | 4 (21.1)            | 5 (26.3)            |                     |                   |                        |
|                          | Non industry      | 2 (10.5)            | 0                   |                     |                   |                        |
| Pathogens N = 25         | Industry          | 2 (8.0)             | 11 (44.0)           | 0.532               | 0.612             |
|                          | None/Not clear    | 3 (12.0)            | 1 (4.0)             | 6 (24.0)            |                   |                        |
|                          | Non industry      | 2 (8.0)             |                     |                     |                   |                        |

*Overall percentage.

*Positive: synbiotic, probiotic or prebiotic supplementation had a statistically significant effect, *p* < 0.05. There were significant differences between study groups (in favour of experimental group).

*Neutral: synbiotic, probiotic or prebiotic supplementation did not have a statistically significant effect, *p* > 0.05, No significant differences between study groups.

*Negative: synbiotic, probiotic or prebiotic supplementation had a statistically significant increase in an adverse event / negative outcome, *p* < 0.05.
and selective reporting (Chi–square \( p = 0.224 \), Fisher exact \( p = 0.188 \)) (Table 6).

There was a significant association between funding and the domains of incomplete outcome data (Chi–square \( p = 0.023 \), Fisher exact \( p = 0.033 \)) and free of other bias (Chi–square \( p = 0.038 \)) (Table 6). The association between source of funding and incomplete outcome data was such that industry-funded trials had significantly less missing data than non-industry funded trials. The association between source of funding and free of other bias (such as outcomes bias) was such that a significantly higher percentage of industry-funded trials were free of other bias compared to non-industry-funded trials.

### Association between source of funding (sponsor) and clinical outcomes

There was no significant association between source of funding and reporting of clinical outcomes: Growth parameters, stool characteristics, microflora, infections (Tables 7, 8, 9, 10 and 11), immune parameters, adverse events and mortality (data not shown). There was a significant association between the source of funding and reporting of antibiotic use in formula fed infants (Chi-square \( p = 0.031 \), Fisher exact \( p = 0.039 \)) such that industry funded trials were more likely to decrease the use of antibiotics than non-industry funded trials (Table 11).

### Association between source of funding (sponsor) and overall study conclusion

There was no significant association between sources of funding and overall study conclusion (Chi-square \( p = 0.505 \), Fisher exact \( p = 0.373 \)). Majority of RCTs, 49 (73.1%), had a positive study conclusion; 32 (47.8%) of these RCTs, were industry sponsored, 7 (10.4%) non-industry and 10 (14.9%) which did not declare their source of funding (Table 12). A sensitivity analysis was conducted with respect to combining industry sponsored studies with those that had not declared their source of funding. There was no change in the results. There was no significant association between source of funding and overall study conclusion (Chi-square \( p = 0.483 \), Fisher exact \( p = 0.425 \)).

### Association between source of funding (sponsor) and conclusion on reported clinical outcomes

There was a significant association between source of funding and conclusion on weight gain (Chi-square \( p = 0.037 \), Fisher exact \( p = 0.024 \)) such that industry-funded

| Source of funding | Positive* n (%) | Neutral* n (%) | Chi-square p value | Fisher’s exact p value |
|-------------------|-----------------|----------------|-------------------|------------------------|
| Necrotising enterocolitis N = 11 | Industry | 4 (36.4) | 0.118 | 0.273 |
| | None/Not clear | 3 (27.3) | |
| | Non industry | 2 (18.2) | |
| Sepsis N = 10 | Industry | 2 (20) | Not Valid | |
| | None/Not clear | 3 (30) | |
| | Non industry | 5 (50) | |
| Antibiotic use N = 19 | Industry | 4 (21.1) | 0.031* | 0.039* |
| | None/Not clear | 5 (26.3) | |
| | Non industry | 6 (31.6) | |

*Overall percentage.

*Positive: synbiotic, probiotic or prebiotic supplementation had a statistically significant effect, \( p < 0.05 \). There were significant differences between study groups (in favour of experimental group).

*Neutral: synbiotic, probiotic or prebiotic supplementation did not have a statistically significant effect, \( p > 0.05 \). No significant differences between study groups.

* Significant \( p < 0.05 \).
trials were more likely to report positive conclusions on weight gain than non-industry-funded trials (Table 13). There was no significant association between source of funding and conclusion on other reported clinical outcomes (Tables 14, 15, 16 and 17).

### Table 13 Association between sponsor and conclusion on reported outcome: Growth parameters

| Authors conclusion on: | Source of funding | No conclusion on reported outcome | Positive | Negative | Chi-square p value | Fisher’s exact p value |
|------------------------|-------------------|----------------------------------|----------|----------|--------------------|-----------------------|
|                        |                   | n (%)                           | n (%)    | n (%)    |                    |                       |
| Weight gain N = 56     | Industry          | 23 (41.1%)                      | 14 (25.0%)| 0.037$$  | 0.024$$            |                       |
|                        | None/Not clear    | 10 (17.9%)                      | 1 (1.8%) | 1 (1.8%) |                    |                       |
|                        | Non industry      | 7 (12.5%)                       | 1 (1.8%) | 1 (1.8%) |                    |                       |
| Length gain N = 40     | Industry          | 18 (45%)                        | 14 (35%) | 0.068    | 0.051              |                       |
|                        | None/Not clear    | 6 (15%)                         | 1 (2.5%) | 1 (2.5%) |                    |                       |
|                        | Non industry      | 2 (5)                           | 1 (2.5%) | 1 (2.5%) |                    |                       |
| Head circumference N = 31 | Industry   | 13 (41.9%)                      | 14 (45.2) | 0.151    | 0.232              |                       |
|                        | None/Not clear    | 3 (9.7)                         | 1 (3.2)  | 1 (3.2)  |                    |                       |
|                        | Non industry      | 1 (3.2)                         | 1 (3.2)  | 1 (3.2)  |                    |                       |

$$Significant p < 0.05, \text{ }$$Overall percentage.

### Discussion

This review revealed that majority of RCTs (from 1980 to 2012) on infants fed formula supplemented with probiotics, prebiotics or synbiotics are funded by the food industry. This is consistent with the trend that

### Table 14 Association between sponsor and conclusion on reported outcome: Tolerance symptoms

| Tolerance                      | Source of funding | No conclusion on reported outcome | Positive | Negative | Chi-square p value | Fisher’s exact p value |
|--------------------------------|-------------------|----------------------------------|----------|----------|--------------------|-----------------------|
|                                |                   | n (%)                           | n (%)    | n (%)    |                    |                       |
| Colic N = 13                   | Industry          | 10 (76.9)                       | 2 (15.4) | 0.657    | 1.00               |                       |
|                                | None/Not clear    | 1 (7.7)                         | 1 (7.7)  | 0.657    | 1.00               |                       |
|                                | Non industry      | 2 (7.7)                         | 2 (7.7)  | 0.657    | 1.00               |                       |
| Spitting up/Regurgitation N = 26| Industry          | 19 (73.1)                       | 1 (3.8)  | 0.032    | 0.062              |                       |
|                                | None/Not clear    | 2 (7.7)                         | 2 (7.7)  | 0.032    | 0.062              |                       |
|                                | Non industry      | 2 (7.7)                         | 2 (7.7)  | 0.032    | 0.062              |                       |
| Vomiting N = 32                | Industry          | 19 (59.4)                       | 5 (15.6) | 0.648    | 1.00               |                       |
|                                | None/Not clear    | 3 (9.4)                         | 3 (9.4)  | 0.648    | 1.00               |                       |
|                                | Non industry      | 2 (6.3)                         | 2 (6.3)  | 0.648    | 1.00               |                       |
| Crying Fussiness N = 20        | Industry          | 10 (50)                         | 6 (30)   | 0.648    | 1.00               |                       |
|                                | None/Not clear    | 2 (10)                          | 2 (10)   | 0.648    | 1.00               |                       |
|                                | Non industry      | 0                               | 0        | 0        | 1.00               |                       |
| Gastric residuals, Abdominal distension N = 6 | Industry | 1 (16.7) | 1 (16.7) | 0.513 | 1.00 | |
|                                | None/Not clear    | 1 (16.7) | 1 (16.7) | 0.513 | 1.00 | |
|                                | Non industry      | 2 (33.3) | 1 (16.7) | 0.513 | 1.00 | |
| Volume of formula consumed/daily intake N = 30 | Industry | 19 (63.3) | 2 (6.7) | 0.867 | 0.733 | |
|                                | None/Not clear    | 3 (10.0) | 1 (3.3) | 0.867 | 0.733 | |
|                                | Non industry      | 4 (13.3) | 1 (3.3) | 0.867 | 0.733 | |
| Days to full enteral feeding N = 8 | Industry | 2 (25) | 1 (12.5) | 0.547 | 1.00 | |
|                                | None/Not clear    | 1 (12.5) | 1 (12.5) | 0.547 | 1.00 | |
|                                | Non industry      | 2 (25) | 1 (12.5) | 0.547 | 1.00 | |

$$Overall percentage.$$

[This is a sample of the text from the document without any graphical elements or images.]
biomedical research is increasingly being funded by industry [1,2]. There was a trend that more RCTs on pre-term infants failed to report their source of funding. The reason(s) for this trend needs to be explored further.

Cochrane guidelines were used to assess the risk of bias of included RCTs. The reporting of several domains was however suboptimal particularly sequence generation, allocation concealment and blinding domains. Considering completed data, there was no significant association between funding source and methodological quality of RCTs in the domains of sequence generation, allocation concealment, blinding and selective reporting. There was a significant association between funding and methodological quality of RCTs in the domains of incomplete outcome data and free of other bias. Industry funded trials had significantly less missing data than non-industry funded trials. A higher percentage of industry funded trials were free of other bias compared to non-industry funded trials. More industry sponsored trials had low risk of bias in 5 out of 6 domains, even though our results did not show a statistical significant association between funding and methodological quality in most domains. Our results confirm findings from previous reviews on infants given enteral feeds with probiotics, prebiotics and synbiotics [157-159].

There was no significant association between funding source and clinical outcomes or majority of authors’ conclusions. There was a significant association between funding and conclusion on weight gain. Regardless of the reported clinical outcomes, nearly all RCTs in this review reported neutral results. That is supplementation with probiotics, prebiotics or synbiotics did not have a significant effect or there were no significant differences between study groups of infants given supplemented formula or placebo. Our findings confirm the results of two

Table 15 Association between sponsor and conclusion on reported outcome: Stool characteristics

| Stool characteristics | Source of funding | No conclusion on reported outcome n (%) | Positive n (%) | Negative n (%) | Pearson’s chi Square | Fisher’s exact p value |
|-----------------------|-------------------|----------------------------------------|----------------|----------------|----------------------|------------------------|
| Stool frequency N = 38| Industry          | 21 (55.3)                              | 9 (23.7)       |               | 0.809               | 1.00                   |
|                       | None / Not clear  | 5 (13.2)                               | 2 (5.3)        |               |                      |                        |
|                       | Non industry      | 1 (2.6)                                |                |               |                      |                        |
|                       | Total             | 27 (71.1)                              | 11 (28.9)      |               |                      |                        |
| Stool consistency n = 39 | Industry          | 18 (46.2)                              | 13 (33.3)      |               | 0.699               | 1.00                   |
|                       | None / Not clear  | 4 (10.3)                               | 3 (7.7)        |               |                      |                        |
|                       | Non industry      | 1 (2.6)                                |                |               |                      |                        |
|                       | Total             | 23 (59)                                | 16 (41)        |               |                      |                        |
| Stool pH N = 12       | Industry          | 5 (41.7)                               | 3 (25)         |               | 0.679               | 1.00                   |
|                       | None / Not clear  | 5 (16.7)                               | 2 (16.7)       |               |                      |                        |
|                       | Non industry      | 2 (2.6)                                |                |               |                      |                        |
|                       | Total             | 27 (71.1)                              | 11 (28.9)      |               |                      |                        |
| Stool short chain fatty acids N = 9 | Industry | 3 (33.3) | 3 (33.3) | 0.638 | 1.00 |
|                       | None / Not clear  | 1 (11.1)                               | 1 (11.1)       |               |                      |                        |
|                       | Non industry      | 1 (11.1)                               |                |               |                      |                        |
|                       | Total             | 7 (58.3)                               | 5 (41.7)       |               |                      |                        |
| Flatulence/Gas N = 15 | Industry          | 10 (66.7)                              | 4 (26.7)       | 0.533         | 1.00                 |
|                       | None / Not clear  | 2 (16.7)                               | 2 (16.7)       |               |                      |                        |
|                       | Non industry      | 1 (6.7)                                |                |               |                      |                        |
|                       | Total             | 11 (73.3)                              | 2 (6.7)        |               |                      |                        |
| Diarrhoea, Diarrhoea episodes N = 18 | Industry | 7 (38.9) | 5 (27.8) | 1 (5.6) | 0.484 | 0.557 |
|                       | None / Not clear  | 2 (11.1)                               | 1 (5.6)        |               |                      |                        |
|                       | Non industry      | 3 (16.7)                               |                |               |                      |                        |
|                       | Total             | 12 (66.7)                              | 5 (27.8)       | 1 (5.6)       |                      |                        |
| Constipation N = 4    | Industry          | 2 (50)                                 | 1 (25)         |               | 0.505               | 1.00                   |
|                       | None / Not clear  | 1 (25)                                 |                |               |                      |                        |
|                       | Non industry      | 1 (25)                                 |                |               |                      |                        |
|                       | Total             | 3 (75)                                 | 1 (25)         |               |                      |                        |

Overall percentage.
systematic reviews which found that supplementation with probiotics, prebiotics or synbiotics did not offer any distinct advantage over placebo [158,159]. However, results of this review did not agree with two nutrition related reviews or reviews on pharmaceutical industry supported RCTs, which reported that industry sponsored RCTs had results and conclusions in favour of the sponsor [2-4,6,8,160-162]. Despite reporting neutral outcomes, authors from industry sponsored RCTs had a tendency to advocate for the consumption of the sponsors’ products. Similar findings were reported by Nestle, who reported that research investigators “who received company grants tended to publish results, give advice and prescribe in favour of the sponsor.” This applied to research that was supported by pharmaceutical and food industries [163].

Effects of sponsorship on overall study conclusion have been equally documented in biomedical literature. Reviews by Lessor and Nkansah reported positive conclusions in favour of the sponsor [6,8]. Although no statistically significant association between funding and authors conclusion was found in this review, more than 70% of RCTs reported positive conclusions, 47.8% of these were industry sponsored. Often, these positive conclusions in the RCTs were not supported by the reported data as demonstrated by the neutral clinical outcomes. Our findings are consistent with those of previous reviews, which found that, results from RCTs may be accurate, but authors may distort the meaning of the results, present conclusions that are more favourable, and that were not supported by the data presented [2,5,163]. Even meta – analyses were not spared from this trend [2,5,163]. Despite overwhelming positive overall study conclusions, majority of RCTs did not have any conclusion on their reported clinical outcomes. The RCTs that reported any conclusion on their clinical outcomes, majority were positive in favour of the sponsors’ products.

Limitations
This review did not document the role of the sponsor in study design, data collection, and analysis. Few RCTs

### Table 16 Association between sponsor and conclusion on reported outcome: Microflora

| Microflora      | Source of funding | No conclusion on reported outcome | Positive | Negative | Neutral | Chi-square p value | Fisher’s exact p value |
|-----------------|-------------------|-----------------------------------|----------|----------|---------|--------------------|------------------------|
| Bifidobacteria  | Industry          | 7 (23.3)                          | 11 (36.7)| 0.249    | 0.195   |                    |                        |
|                 | None/Not clear    | 2 (6.7)                           | 5 (16.7) | 1 (3.3)  | 1 (3.3)  |                    |                        |
|                 | Non industry      | 1 (3.3)                           | 1 (3.3)  | 1 (3.3)  | 1 (3.3)  |                    |                        |
| Lactobacillus   | Industry          | 5 (26.3)                          | 4 (21.1) | 0.084    | 0.294   |                    |                        |
|                 | None/Not clear    | 3 (15.8)                          | 4 (21.1) | 0.084    | 0.294   |                    |                        |
|                 | Non industry      | 1 (5.3)                           | 1 (5.3)  | 1 (5.3)  | 1 (5.3)  |                    |                        |
| Pathogens       | Industry          | 7 (28)                            | 6 (24)   | 0.152    | 0.269   |                    |                        |
|                 | None/Not clear    | 4 (16)                            | 5 (20)   | 0.152    | 0.269   |                    |                        |
|                 | Non industry      | 1 (4)                             | 1 (4)    | 1 (4)    | 1 (4)    |                    |                        |

$^{*}$ Overall percentage.

### Table 17 Association between sponsor and conclusion on reported outcome: Necrotising Enterocolitis Sepsis and antibiotic use

| Source of funding | No conclusion on reported outcome | Positive | Negative | Pearson’s chi Square | Fisher’s exact p value |
|-------------------|-----------------------------------|----------|----------|----------------------|------------------------|
| NEC N = 12        | Industry                          | 3 (25)   | 1 (8.3)  | 0.511                | 0.782                  |
|                   | None/Not clear                    | 2 (16.7) | 1 (8.3)  |                      |                        |
|                   | Non industry                       | 2 (16.7) | 2 (16.7) |                      |                        |
|                   |                                    | 7 (58.3) | 3 (25)   |                      |                        |
| Sepsis N = 10     | Industry                          | 2 (20)   | 1 (10)   | 0.274                | 0.500                  |
|                   | None/Not clear                    | 2 (20)   | 1 (10)   |                      |                        |
|                   | Non industry                       | 5 (50)   |          |                      |                        |
| Antibiotic use N = 16 | Industry                          | 4 (25)   | 3 (18.8)| 0.093                | 0.141                  |
|                   | None/Not clear                    | 4 (25)   |          |                      |                        |
|                   | Non industry                       | 5 (31.3) |          |                      |                        |

$^{*}$ Overall percentage.
reported this. More detailed documentation and disclosure in RCT reports would help evaluate if there was an association between funding and reported outcomes or conclusions. Many RCTs had missing data especially on the domains of sequence generation, allocation concealment and blinding. Attempts were made to contact authors for missing information but none responded. The sample size (number of RCTs) was small and skewed towards industry.

Conclusion
This study assessed the impact of funding by the food industry on trial outcomes and methodological quality of synbiotics, probiotics and prebiotics research in infants. There was no significant association between source of funding and methodological quality of study in the domains of sequence generation, allocation concealment and blinding. Industry funded trials had less missing data and were free of other bias than non-industry funded trials.

There was no significant association between funding and majority of reported clinical outcomes or authors’ conclusions. However, there was a significant association between funding source and reported antibiotic use and conclusion on weight gain. Majority of RCTs were industry funded, more non-industry funded research is needed to further assess the impact of funding on methodological quality, reported clinical outcomes and authors’ conclusions.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
The reviewers contributed the following: MW: Developed review protocol (unpublished); selected RCTs; conducted data extraction, assessment of risk of bias in included RCTs, developed, edited and critically reviewed the manuscript. ML: Selected RCTs, conducted data extraction, assessment of risk of bias in included RCTs, critically reviewed the manuscript. AM: Conducted the statistical analysis, interpretation of results and critically reviewed the manuscript. TY: Contributed to designing the review methodology and critically reviewed the manuscript. RB: Contributed to designing the review, acted as third party arbitrator and critically reviewed the manuscript. All authors read and approved the final manuscript.

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References
1. Khan NA, Lombieda JI, Singh M, Spencer HU, Torralba KD: Association of industry funding with the outcome and quality of randomized controlled trials of drug therapy for rheumatoid arthritis. Arthritis Rheum 2012, 64:2059–2067.
2. Leschin J: Those who have the gold make the evidence: How the pharmaceutical industry biases the outcomes of clinical trials of medications. Sci Eng Ethics 2012, 18:247–261.
3. Sirondo S: Pharmaceutical company funding and its consequences: A qualitative systematic review. Contemp Clin Trials 2008, 29:109–113.
4. Bekelman JE, Li Y, Gross CP: Scope and impact of financial conflicts of interest in biomedical research: A systematic review. JAMA 2003, 289:654–666.
5. Als-Nielsen B, Chen W, Gluud C, Jørgensen H: Association of funding and conclusions in randomized drug trials: A reflection of treatment effect or adverse effects. J Am Med Assoc 2003, 290:921–928.
6. Lessler J, Ebbeling CB, Gozzer M, Wypij D, Ludwig DS: Relationship between funding source and conclusion among nutrition-related scientific articles. PLoS Med 2007, 4:e61–e006.
7. Katan MB: Does industry sponsorship undermine the integrity of nutrition research? PLoS Med 2007, 4:e003–e004.
8. Niamah N, Nguyen T, Raninzhad H, Boro L: Randomized trials assessing calcium supplementation in healthy children: Relationship between industry sponsorship and study outcomes. Public Health Nutr 2009, 12:1931–1937.
9. Shah NP: Functional cultures and health benefits. Int Dairy J 2007, 17:126–1277.
10. Gibson GR, Delzenne N: Inulin and oligofructose: New scientific developments. Nutr Today 2008, 43:54–59.
11. Gibson GR: Fibre and effects on probiotics (the prebiotic concept). Clin Nutr Suppl 2004, 1:25–31.
12. Tuohy KM, Prentice RM, Smijekel CW, Gibson GR: Using probiotics and prebiotics to improve health. Curr Opin Clin Nutr Metab Care 2003, 6:693–700.
13. Macfarlane GT, White CA, Macfarlane S: Bacterial metabolism and health-related effects of galactooligosaccharides and other prebiotics. J Appl Microbiol 2008, 104:305–344.
14. Losada MA, Olleros T: Towards a healthier diet for the colon: The influence of fructooligosaccharides and lactobacilli on intestinal health. Nutr Res 2002, 22:71–84.
15. Watel B, Gribache S, Roller M: Inulin, oligofructose and immunomodulation. Br J Nutr 2005, 93(Suppl 1):S49–S55.
16. Torres DP, Gonçalves M, Teixeira JA, Rodrigues LR: Galactooligosaccharides: Production, properties, applications, and significance as prebiotics. Compr Rev Food Sci Food Saf 2010, 9:438–454.
17. Higgins JPT, Green S: Cochrane handbook for systematic reviews of interventions. John Wiley & Sons Ltd: Chichester, West Sussex; 2008.
18. Acuin SJ, Jordan S, Storey M, Thornton CA, Graevenor M, Garcia-I, Plummer AF, Wang D, Morgan G: Dietary supplementation with lactobacilli and bifidobacteria is well tolerated and not associated with adverse events during late pregnancy and early infancy. J Nutr 2010, 140:483–488.
19. Suh SE, Aw M, Gerez I, Chong YS, Rauff M, Ng YPM, Wong HB, Pai N, Lee BW, Shek LP: Probiotic supplementation in the first 6 months of life in at risk infants – effects on eczema and atopic sensitization at the age of 1 year. Clin Exp Allergy 2009, 39:571–578.
20. Jacobs S: The use of probiotics to reduce the incidence of sepsis in premature infants. : Australian New Zealand Clinical Trials Registry. 2007. ACTRN12607001444155 26/02/2007 [http://www.anzctr.org.au].
21. Alliet P, Scholtens P, Raes M, Hensen K, Jongen H, Rummens J, Boehm G, Vandenplas Y: Effect of probiotic galacto-oligosaccharide, long-chain fructo-oligosaccharide infant formula on serum cholesterol and triacylglycerol levels. Nutrition 2007, 23:19–723.
22. Scholtens PAMJ, Alliet P, Raes M, Alves MS, Koos H, Boehm G, Kröpflis LM, Knol J, Vandenplas Y: Fecal secretory immunoglobulin A is increased in healthy infants who receive a formula with short-chain galacto-oligosaccharides and long-chain fructo-oligosaccharides. J Nutr 2008, 138:1141–1147.
23. Urban MF, Bolton KD, Mokhachane M, MPHalehe RE, Bomela HN, Monaheng L, Beck-Arnold E, Cooper PA: Growth of infants born to HIV-infected women when fed a biologically acidified starter formula with and without probiotics. South Afr J Clin Nutr 2008, 21:28–32.
24. Patole S: A randomized placebo controlled trial on the safety and efficacy of a probiotic product in reducing all case mortality and definite necrotising enterocolitis in preterm very low birth weight neonates.
In Australian New Zealand Clinical Trials Registry. 2009. ACTRN1260900374268.

27/05/2009 [http://www.anzctr.org.au].

25. Ashley C, Johnston WH, Harris CL, Stolz SI, Wampler JL, Bersest CL. Growth and tolerance of infants fed formula supplemented with polydextrose (PDX) and/or galactooligosaccharides (GOS): Double-blind, randomized, controlled trial. *Nutr* 2012, 11:38. doi:10.1186/1475-2891-11-38.

26. Velghe SC, Cooper PA, Bolton KD, Mokhtarani M, Mohahsheh RM, Beck-Arnold E, Monaheng L, Haschke-Becher E. Growth and metabolism of infants born to women infected with human immunodeficiency virus and fed acidified whey-adapted starter formulas. *Nutrition* 2008, 24:203–211.

27. Underwood M. The impact of oligosaccharides and bifidobacteria on the intestinal microflora of Premature infants. Clinical trials registry. . .NTIC00010605 05/11/2009 (http://www.clinicaltrials.gov).

28. Bakker-Ziekenhuis AM, Alles MS, Knol J, Kok FJ, Tollboon JM, Bindels JG. Effects of infant formula containing a mixture of galacto- and fructo-oligosaccharides or viable bifidobacterium animals on the intestinal microflora during the first 4 months of life. *Br J Nutr* 2005, 94:783–790.

29. Bakker-Ziekenhuis AM, Van Tol EAF, Kroes H, Alles MS, Kok FJ, Bindels JG. Faecal SigA secretion in infants fed on pre- or probiotic infant formula. *Pediatr Allergy Immunol* 2006, 17:34–140.

30. Vlieger AM, Robroch A, Van Buuren S, Kiers J, Rijkers G, Benninga MA, Te Biesebeke Beusekom CM, Schaafsma A. Acidified milk formula of preterm infants. *Acta Paediatr* 2005, 94:186–190.

31. Bettler J, Euler AR: Prebiotics improve gastric motility in preterm newborns. *JPediatr* 2008, 156:387–390.

32. Decsi T, Ataró A, Balogh M, Dolinay T, Kanjo AH, Szabó É, Várkonyi Á. Randomised placebo controlled double blind study on the effect of prebiotic oligosaccharides on intestinal flora in healthy infants. *Orv Hetil* 2005, 146:2445–2450.

33. Bohem G, Lestedi M, Caspeta P, Jelinké J, Negretti F, Stahl B, Mariní A. Supplementation of a bovine milk formula with an oligosaccharide mixture increases counts of faecal bifidobacteria in preterm infants. *Arch Dis Child Neonatal Ed* 2002, 86:F178–F181.

34. Bohem G, Fanaro S, Jelínké J, Stahl B, Mariní A. Prebiotic concept for infant nutrition. *Acta Paediatr* 2003, 91:64–67.

35. Bruzzese E, Volpicelli M, Squeglia V, Bruzzese D, Salvini F, Bisceglia M, Lionetti P, Mugambi et al. *BMC Medical Research Methodology* 2013, 13:137.

36. Cooper PA, Bolton KD, Mokhtarani M, Mohahsheh RM, Beck-Arnold E, Monaheng L, Haschke-Becher E. Growth of infants born to HIV-positive mothers fed a whey-adapted acidified starter formula with prebiotics and nucleotides. *South Afr J Clin Nutr* 2010, 23:90–95.

37. Ziegler E, Vanderhoof JA, Petchoswka B, Mittresser SH, Stolz SI, Harris CL, Bersest CL. Term infants fed formula supplemented with selected blends of prebiotics grow normally and have soft stools similar to those reported for breast-fed infants. *J Pediatr Gastroenterol Nutr* 2007, 44:359–364.

38. Costalos C, Kapiki A, Apostoloulou M, Papathoma E. The effect of a prebiotic supplemented formula on growth and stool microbiology of term infants. *Early Hum Dev* 2008, 84:45–49.

39. Bin-Nun A, Bromrker R, Wilchanski M, Kaplan M, Rudensky B, Kaplan M, Hamburger C. Oral probiotics prevent necrotizing enterocolitis in very low birth weight neonates. *J Pediatr* 2005, 147:192–195.

40. Decsi T, Ataró A, Balogh M, Dolinay T, Kanjo AH, Szabó É, Várkonyi Á. Randomised placebo controlled double blind study on the effect of prebiotic oligosaccharides on intestinal flora in healthy infants. *Orv Hetil* 2005, 146:2445–2450.

41. Cooper PA, Bolton KD, Mokhtarani M, Mohahsheh RM, Beck-Arnold E, Monaheng L, Haschke-Becher E. Growth of infants born to HIV-positive mothers fed a whey-adapted acidified starter formula with prebiotics and nucleotides. *South Afr J Clin Nutr* 2010, 23:90–95.

42. Ziegler E, Vanderhoof JA, Petchoswka B, Mittresser SH, Stolz SI, Harris CL, Bersest CL. Term infants fed formula supplemented with selected blends of prebiotics grow normally and have soft stools similar to those reported for breast-fed infants. *J Pediatr Gastroenterol Nutr* 2007, 44:359–364.
galacto-oligosaccharides and long-chain fructo-oligosaccharides induces a beneficial immunoglobulin profile in infants at high risk for allergy. *Allergy* 2009, 64:489–487.

82. Vanhoff E, Ruitter B, Faber J, MiSanet L, Knol EF, Stahl B, Arslanoglu S, Moro G, Boehm G. A specific mixture of short-chain oligosaccharides and long-chain fructo-oligosaccharides induces a beneficial immunoglobulin profile in infants at high risk for allergy. *Allergy* 2009, 64:489–487.
efficacy and bifidogenicity of a new infant formula containing partially hydrolyzed protein, a high beta-palmitic acid level and nod digestible oligosaccharides. J Pediatr Gastroenterol Nutr 2003, 36:342–351.

101. Agarwal R, Sharma N, Chaudhry R, Deearai A, Paul VK, Gewobih IH, Panigrahi P: Effects of oral lactobacillus GG on enteric microflora in low birth-weight neonates. J Pediatr Gastroenterol Nutr 2003, 36:397–402.

102. Al-Hosni M, Duran M, Hawk M, Stewart LA, Bongheva RA, Calhoon M, Atwood L, Howard D, Ferrelli K, Soll R: Probiotics-supplemented feeding in extremely low-birth-weight infants. J Perinatol 2011, 32:252–259.

103. Funguan Z, Zheng-yun S, Belti C: Oral probiotics and immune function and digestive tract of premature children. (Chinese). J Shandong Univ Health Sci 2008, 46(11):1–6.

104. Morisset M, Aubert-Jacquin C, Soulaines P, Moneret-Vautrin D, Dupont C: The impact of perinatal probiotic intervention on gut microbiota: Double-blind placebo-controlled trials in Finland and Germany. Anorecon 2012, 18:7–13.

105. Andrews BF, Cook LN: The impact of probiotics on growth and neurodevelopmental outcomes in preterm infants. Int J Pediatr 2005, 40:157–164.

106. Isolauri E, Arvola T, Sutas Y, Moilanen E, Salminen S: Probiotics in the management of atopic eczema. Clin Exp Allergy 2000, 30:1604–1610.

107. Lin H-C, Su B-H, Chen A-C, Lin T-W, Tsal C-H, Yeh T-F, Oh W: Oral probiotics reduce the incidence and severity of necrotizing enterocolitis in very low birth weight infants. Pediatr 2005, 115:1–4.

108. Karvonen AV, Sinkiewicz G, Connolly E, Vesikari T: Safety and colonization of the probiotic Lactobacillus reuteri ATCC 55730 in newborn infants and premature infants. Int J Pediatr 2004, 152:259–263.

109. Kim S, Da HL, Meyer D: Supplementation of infant formula with native LC-PUFA on infants recovery after an infection. [abstract PC28]. J Pediatr Gastroenterol Nutr 2003, 33:S1231–S1234.
140. Rinne M, Kalliomäki M, Salminen S, Isolauri E: Probiotic intervention in the first months of life: Short-term effects on gastrointestinal symptoms and long-term effects on gut microbiota. J Pediatr Gastroenterol Nutr 2006, 43:200–205.

141. Li Y, Shemizu T, Hosaka A, Kaneko N, Ohtsuka Y, Yamashiro Y: Effects of bifidobacterium breve supplementation on intestinal flora of low birth weight infants. Pediatr Int 2004, 46:509–515.

142. Lee SJ, Cho SJ, Park EA: Effects of probiotics on enteric flora and feeding tolerance in preterm infants. Neonatology 2007, 91:174–179.

143. Urao M, Fujimoto T, Lane GJ, Seo G, Miyano T: Long-term colonization of a lactobacillus plantarum synbiotic preparation in the neonatal gut. J Pediatr Gastroenterol Nutr 2008, 47:45–53.

144. Liedstrøm M, Agostini M, Matini A, Boehm G: Oligosaccharides might stimulate calcium absorption in formula-fed preterm infants. Acta Paediatr 2003, 91(441):91–92.

145. Van Der Aa LB, Heymans HS, Van Aalderen WM, Sillevis Smitt JH, Knol J, Ben Amor K, Goossens DA, Sprikkelman AB: Effect of a new synbiotic mixture on atopic dermatitis in infants: A randomized-controlled trial. Clin Exp Allergy 2010, 40:795–804.

146. Rojas MA, Lozano JM, Rojas MX, Rodríguez VA, Rondon MA, Bastidas JA, Perez LA, Rojas C, Ovaille O, García-Harker JE, Tamayo ME, Ruiz GC, Ballesteros A, Archila MM, Arevolo M: Prophylactic probiotics to prevent death and nosocomial infection in preterm infants. Pediatrics 2012, 130:e1113–e1120.

147. Marin A, Negretti F, Boehm G, Li Destri M, Clerici-Bagozzi D, Mosca F, Agosti M: Pro- and pre-biotics administration in preterm infants: Colonization and influence on faecal flora. Acta Paediatr 2003, 91(441):80–81.

151. Mugambi MN, Musekwa A, Lombard M, Young T, Blauw R: Probiotics, prebiotics infant formula use in preterm or low birth weight infants: A systematic review. Nutr J 2012, 11(1):Article number 58. DOI:10.1186/1475-2891-11-58.

152. Rigo J, Pieltain C, Studzinski F: Probiotics for prevention of necrotizing enterocolitis in very low birth weight newborns. J Trop Pediatr 2009, 55:128–131.

153. Mugambi MN, Musekiwa A, Lombard M, Young T, Blauw R: Probiotics, prebiotics infant formula use in preterm or low birth weight infants: A systematic review. Nutr J 2012, 11(1):Article number 58. DOI:10.1186/1475-2891-11-58.

154. Underwood MA, Salzman NH, Bennett SH, Barman M, Mills DA, Marcobal A, Art. No:CD005496.DOI:10.1002/14651858.CD005496.pub2.

155. Savino F, Cresci F, Maccario S, Cavallo F, Dalmaso P, Fanaro S, Oggero R, Vigi V, Silvestro L: “Minor” feeding problems during the first months of life: Effect of a partially hydrolysed milk formula containing fructo- and galacto-oligosaccharides. Acta Paediatr 2003, 91:86–90.

156. Sepp E, Mikkelaar M, Salminen S: Effect of administration of lactobacillus casei strain GG on the gastrointestinal microbiota of newborns. Microb Ecol Health Dis 1993, 6:309–314.

157. Alfaleh KM, Basler D: Probiotics for prevention of necrotizing enterocolitis in preterm infants. In Cochrane Database of Systematic Reviews 2008, Issue 1. Art. No:CD005496.DOI:10.1002/14651858.CD005496.pub2.

158. Mugambi MN, Musekwa A, Lombard M, Young T, Blauw R: Probiotics, prebiotics infant formula use in preterm or low birth weight infants: A systematic review. Nutr J 2012, 11(1):Article number 8. DOI:10.1186/1475-2891-11-81.

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