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Systematic Review with Meta-Analysis

Safety of soya-based infant formulas in children

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Abstract

Soya-based infant formulas (SIF) containing soya flour were introduced almost 100 years ago. Modern soya formulas are used in allergy/intolerance to cows' milk-based formulas (CMF), post-infectious diarrhoea, lactose intolerance and galactosaemia, as a vegan human milk (HM) substitute, etc. The safety of SIF is still debated. In the present study, we reviewed the safety of SIF in relation to anthropometric growth, bone health (bone mineral content), immunity, cognition, and reproductive and endocrine functions. The present review includes cross-sectional, case–control, cohort studies or clinical trials that were carried out in children fed SIF compared with those fed other types of infant formulas and that measured safety. The databases that were searched included PubMed (1909 to July 2013), Embase (1988 to May 2013), LILACS (1990 to May 2011), ARTEMISA (13th edition, December 2012), Cochrane controlled trials register, Bandolier and DARE using the Cochrane methodology. Wherever possible, a meta-analysis was carried out. We found that the anthropometric patterns of children fed SIF were similar to those of children fed CMF or HM. Despite the high levels of phytates and aluminium in SIF, Hb, serum protein, Zn and Ca concentrations and bone mineral content were found to be similar to those of children fed CMF or HM. We also found the levels of genistein and daidzein to be higher in children fed SIF; however, we did not find strong evidence of a negative effect on reproductive and endocrine functions. Immune measurements and neurocognitive parameters were similar in all the feeding groups. In conclusion, modern SIF are evidence-based safety options to feed children requiring them. The patterns of growth, bone health and metabolic, reproductive, endocrine, immune and neurological functions are similar to those observed in children fed CMF or HM.

Key words: **Soya infant formulas: Safety: Infants: Children**

Soya is a product of the Asian plant *Glycine max*, and it has been part of human nutrition in different parts of the world for more than 2000 years. Soya-based infant formulas (SIF) are products derived from soya, which also have a long history of use around the world[1]. They were used for the first time in the USA in 1909 as food alternatives for infants who had allergy or intolerance to cows' milk-based formulas (CMF). Since that report and until 1960s, these infant formulas have been products entirely derived from soya flour, with different protein availability, digestibility, fibres, phytates and protease inhibitors[2]. The limitations of formulas based on soya flour spurred the development of SIF, in which proteins isolated from soya replaced soya flour during the 1960s. Soya protein isolate (SPI) was extracted from the flake using a slightly alkaline solution and was precipitated at the isoelectric point. The resulting isolate had a purity

Abbreviations: AAP, American Academy of Pediatrics; CMF, cows' milk-based formula; HM, human milk; SIF, soya-based infant formula; SMD, standardised mean difference; SPI, soya protein isolate.

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Table 1. Studies excluded from the review

References	Description
Fomonm, 1959[15]	Only four children assigned sequentially to receive a soyabean infant formula
Shepard, 1960[16]	Three cases of hypothyroidism potentially associated with soya intake reported
Cowan, 1969[17]	Thirty children, 2–15 months, enrolled in a before–after study; all received a soya infant formula
Ament, 1972[18]	Case report of a child with flat intestinal lesions after the use of soya
Halpin, 1977[19]	Analysis of soya diets in children with persistent diarrhoea
Powell, 1978[20]	Report of the use of soya and cows' milk formulas and enterocolitis
Naude, 1979[21]	Preterm study with only 1 month of follow-up
Zoppi, 1979[22]	Non-randomised clinical trial in thirty-nine term babies assigned to a soya flour infant formula with different amounts of protein
Shenai, 1981[23]	Metabolic study in preterm babies
Callenbach, 1981[24]	Aetiological studies of rickets in preterm babies
Gruskay, 1982[25]	Analysis of the risk of developing atopy in 15 years
Poley, 1983[26]	Electron microscopy analysis of intestinal damage induced by soya
Hall, 1984[27]	Study of soya formulas for preterm babies
Dagan, 1984[28]	Treatment for acute diarrhoea; short-term administration
Kulkarni, 1984[29]	Case series of preterm babies with rickets fed subfortified soya formulas
Sutton, 1968[30]	Treatment for acute diarrhoea; short-term administration
Sampson, 1988[31]	Possible aetiological mechanisms for atopic dermatitis
Nutrition Review Committee, 1988[32]	Narrative review of some articles related to soya
Iyngkaran, 1988[33]	Study of the intestinal absorption effects of soya in children with diarrhoea
Conway, 1989[34]	Treatment for acute diarrhoea; short-term administration
Chandra, 1989[35]	Comparison of cows' milk *v.* soya *v.* casein to prevent atopic dermatitis; no report of side effects
Cantani, 1990[36]	Sequential use of soya; no comparison
Bock, 1990[37]	Reactions during double-blind challenge tests
Willoughby, 1990[38]	Neurodevelopment study in children fed soya chloride-deficient *v.* soya chloride-normal formulas
Malloy, 1990[39]	Follow-up study of neurodevelopment in 9-year-old children fed soya chloride-deficient *v.* soya chloride-normal formulas
Giampietro, 1992[40]	Sensitisation to soya; no other safety parameters reported
Buts, 1993[41]	Use of soya in children aged 6 months to 3 years; follow-up only for 2 months
Churella, 1994[42]	Analysis of two different soya formulas with different protein contents
Brown, 1994[43]	Meta-analysis of soya and lactose-free milks for acute diarrhoea
Burks, 1994[44]	Study of sensitisation to soya and enterocolitis induced
Chorazy, 1995[45]	Case report of a child with persistent congenital hypothyroidism while being fed soya
Magnolfi, 1996[46]	Study of allergy to soya; no other safety parameters reported
Essex, 1996[12]	Short narrative report on cautions about soya; not evidence based
Bruno, 1997[47]	Report of allergy to soya; no other safety parameters reported
Jabbar, 1997[48]	Case report of three children with hypothyroidism while being fed soya
Cantani, 1997[49]	Narrative review of sensitisation to soya use; no other safety parameters reported
Vanderhoof, 1997[50]	Soya in acute diarrhoea; no report on safety parameters
Kuiper, 1998[51]	Basic analysis of interactions of soya with tissue receptors
Businco, 1998[52]	Reported use of soya formulas for the treatment or prevention of CMPA
Quak, 1998[53]	Use of soya in Asia; no safety parameters reported
Irvine, 1998[54]	Twenty-five children fed a cows' milk-based infant formula and four fed a soya infant formula; measurement of genistein and daidzein levels in urine; no measurement of levels in cows' milk-fed children
Setchell, 1998[10]	Observations derived from one clinical study in children and *in vitro* studies
Lucassen, 1998[55]	Systematic review of soya for colic; no safety parameters reported
Burks, 1998[56]	Soya and atopic dermatitis and food hypersensitivity; no safety parameters reported
American Academy of Pediatrics, 1998[4]	Narrative review of efficacy and safety
Sheehan, 1998[57]	Narrative description of potential effects; evidence in children not included
Irvine, 1998[58]	Measurement of isoflavone content in food products; evidence in children not included
Fayad, 1999[59]	Soya in acute diarrhoea; no report on safety parameters
Zeiger, 1999[60]	Soya use and allergy to soya; no report on other safety parameters
Badger, 2002[61]	Narrative discussion on experimental and adult studies; some non-systematic comments on the effects of growth and bone in children fed a soya infant formula
Zoppi, 1999[62]	Narrative review of safety; no evidence-based analysis
Setchell, 2000[63]	Editorial about the potential effects of isoflavones; not including evidence in children
Goldman, 2001[64]	Letter to editor
Barret, 2002[65]	Narrative review of basic and some clinical studies related to soya; non-systematic evidence analysis
Mendez, 2002[66]	Narrative review of safety of soya formula use
Ostrom, 2002[67]	Effect of palmolein added to soya or hydrolysate on Ca and PO_4 intestinal absorption Main analysis focus on palm oil; no safety parameters on soya reported
Klemola, 2002[68]	Focus on the frequency of allergy to soya; no other safety parameters reported
Miniello, 2003[69]	Narrative discussion on experimental and adult studies; some comments on effects on growth and bone; some non-systematic comments on effects on growth and bone in children fed a soya infant formula
Tuohy, 2003[11]	Narrative review of clinical and basic papers on soya toxicity
Ahn, 2003[70]	Prevalence of soya protein hypersensitivity; no other safety parameters reported
Stettler, 2005[71]	Retrospective cohort study on adults to analyse the risk of obesity using different infant formulas
Chen, 2004[9]	Narrative review of soya infant formulas; includes studies considered in this review
Hoey, 2004[72]	Correlation between the use of soya and microbiota
Giampetro, 2004[73]	Forty-eight children fed with soya; no one with precocious puberty; no control group
Merritt, 2004[74]	Narrative review of soya infant formulas; includes studies considered in this review
Hays, 2005[75]	Use of extensively hydrolysed formulas in allergy
Berger-Achituv, 2005[76]	Indications of soya formulas; no safety issues analysed
Klemola, 2005[77]	Analysis of allergy to soya; no other safety parameters analysed

Table 1. *Continued*

References	Description
Agostoni, 2006[78]	Narrative review of soya infant formulas; includes studies considered in this review
Pedrosa, 2006[79]	Analysis of palatability of soya and other infant formulas
D'Auria, 2006[80]	Letter to editor related to paper by Seppo on the impact of soya formulas on growth
Osbron, 2006[81]	Systematic review of the efficacy of soya in preventing allergy
Ostrom, 2006[82]	RCT on soya infant formula efficacy for regurgitation treatment
Ballmer-Weber, 2007[83]	Clinical characteristics of allergy to soya
Fortres, 2007[84]	Portuguese paper on phyto-oestrogen intake and thelarche
Halm, 2007[85]	Comparison of phyto-oestrogen levels in urine between children and adults eating soya nuts
Turck, 2007[86]	Narrative review of indications of soya and safety issues
Song, 2007[87]	Narrative review of the positive and negative effects of soya; studies on soya formula already considered
Agostoni, 2007[88]	Effects of soya on weight/age and length/age in children aged 6–12 months; does not include reports on the basal and final measurements of weight-only and height-only differences
Wolff, 2008[89]	Cohort study related to puberty in girls analysing exposure to soya, but not to a soya infant formula
Zuidmeer, 2008[90]	Prevalence of plant allergies, including allergy to soya, across countries; no safety parameters on infant formulas reported
Johnson, 2008[91]	Narrative review of some articles that describe safety issues regarding soya infant formulas, already considered in this review
Ngamphaiboon, 2008[92]	Description of CMPA in Thai children
Mehr, 2008[93]	Food choices for CMPA; no safety parameters on soya analysed
Boucher, 2008[94]	Epidemiological study of the early intake of soya and protective effect against breast cancer
Kemp, 2008[95]	Consensus about the best treatment for CMPA; no safety parameters on soya analysed
Bernbaum, 2008[96]	Pilot study to evaluate the validity of different techniques to measure breast bud, testicular volume and breast adipose tissue in children; no correlationship study between soya intake and maturation abnormalities
Koplin, 2008[97]	Use of soya and allergy to peanuts; no other safety parameters analysed
Caminiti, 2009[98]	Analysis of cross-reaction to soya; no other safety parameters analysed
Antunes, 2009[99]	Analysis of allergy to soya and extensively hydrolysed formulas; no other safety parameters reported
Badger, 2009[100]	Narrative review of some basic and clinical studies of the effects of soya on health; includes some papers considered in this review
Lee, 2009[101]	Epidemiological study of the intake of soya during adolescence and protective effect against breast cancer
Korde, 2009[102]	Epidemiological study of the early intake of soya and protective effect against breast cancer
Guest, 2009[103]	Health economics model of treatment for CMPA; safety parameters on soya not evaluated
Palmer, 2009[104]	Urogenital effects of *in utero* exposure to diethylstilbestrol in males; does not include studies on infant formulas
Cederroth, 2009[105]	Effects of soya on male reproductive function; animal studies; does not include paediatric studies on soya infant formulas
Vandenplas, 2011[106]	Narrative review on the safety of soya infant formulas; some papers cited are analysed in this review
Dias, 2010[107]	Persistence of CMPA and use of different infant formulas; no safety parameters on soya reported
Bolca, 2010[108]	Soya isoflavones in breast tissue of women under breast resection
Cheng, 2010[109]	Cohort study of soya ingestion during adolescence; not related to infant formulas
Terracciano, 2010[110]	Analysis of soya allergy; no other safety parameters reported
Tillet, 2010[111]	Informative letter of toxicology classification
Nacmias, 2010[112]	Paper related to allergy to soya in neonates; no other safety parameters reported
Sladkevicius, 2010[113]	Health economics analysis of soya use
Katz, 2010[114]	Paper related to allergy to soya; no other safety parameters reported
Patisaul, 2010[115]	Narrative description of biochemical, basic, clinical and epidemiological studies of soya; includes analysis of papers related to soya infant formulas, already considered in this review
Donovan, 2010[116]	Description of soya effects on intestinal cell proliferation and antirotavirus effect; no safety parameters on soya reported
Dinsdale, 2010[117]	Narrative review focused on animal and human studies on potential soya toxicity; non-systematic analysis concludes that there is no evidence of soya infant formula toxicity in children
Wada, 2011[118]	Cross-sectional study of the correlationship between soya in diet and urinary level of sex hormones in boys/girls aged 4–6 years; no history about soya infant formulas is recorded
McCarver, 2011[119]	Exhaustive narrative review focused on animal and human studies; non-systematic analysis concludes that there is no evidence of soya infant formula toxicity in children
Kim, 2011[120]	Case–control study in 7–10·2-year-old girls to establish a correlationship between isoflavones in serum and precocious puberty; no diet history analysed; does not include a discussion on soya infant formulas
Kattan, 2011[121]	Narrative review of soya allergy; no safety parameters on soya reported
Dabeka, 2011[122]	Comparative analysis of aluminium in different food products for children; no safety parameters reported
Degen, 2011[123]	Measurements of isoflavones in urine of 6–18-year-old children; no history about soya infant formulas reported
Nguyen, 2011[124]	US measurements of different organs in children fed soya, cows' milk or HM; no mathematical data reported; only graphs and *P* values reported
Jefferson, 2011[125]	Narrative review of basic, clinical and epidemiological studies of the effects of soya in animal models and human subjects; describes some important papers included in this review
Durham, 2011[126]	Analysis of food allergy; no safety parameters on soya reported
Levi, 2012[127]	Utility of atopy patch in atopic dermatitis; no safety parameters on soya reported
Jefferson, 2012[128]	Narrative review of basic, clinical and epidemiological studies of the effects of soya in animal models and human subjects; describes some important papers included in this review
Blom, 2012[129]	Analysis of allergy to soya; no other safety parameters reported
Crinella, 2012[130]	Narrative review of different hypotheses related to ADHD, with focus on manganese toxicity; brief description of possible association of soya, manganese and ADHD

CMPA, cows' milk protein allergy; RCT, randomised controlled trial; HM, human milk; ADHD, attention deficit hyperactivity disorder.

≥90 %, a high protein digestibility and a balanced high concentration of essential amino acids[3].

During the 1970s, SIF were updated and fortified with L-methionine, L-carnitine and taurine. L-Methionine improved the biological quality of the protein (one of the major criticisms on soya formulas). Other criticisms on SIF are the high levels of aluminium (500–2500 μg/l *v.* 15–400 and 4–65 μg/l in CMF and human milk (HM)) and the presence of phytates (SIF contain approximately 1·5 % of phytates), which may impair the absorption of minerals and trace elements[4].

Table 2. Evidence from studies included in the review (weight, length, bone health and other nutritional parameters)
(Standardised mean difference (SMD) values and 95 % confidence intervals)

Quality assessment							Summary of findings				
							No. of patients		Effects		
No. of studies	Design	Limitations in design	Inconsistency	Indirectness	Imprecision	Other considerations	Soya group	Control group	Absolute SMD	95 % CI	Recommendation
1. Soya infant formula and weight gain (Fig. 1)											
14 ⊕⊕◯◯	RCT	Moderate	Low to moderate	Not serious	Low to moderate	Possible publication bias	983	1798	SMD 0·20	−0·08, 0·48	Similar weight gain in the groups
2. Soya infant formula and height gain (Fig. 2)											
15 ⊕⊕◯◯	RCT	Moderate	Low to moderate	Not serious	Low to moderate	Possible publication bias	1023	1852	SMD 0·18	−0·16, 0·52	Similar height gain in the groups
3. Soya infant formula and Hb values (Fig. 3)											
4 ⊕⊕◯◯	RCT	Moderate	Low to moderate	Not serious	Low to moderate	Possible publication bias	239	237	SMD −0·14	−0·52, 0·24)	No clinical effect on Hb values
4. Soya infant formula and total protein values (Fig. 4)											
3 ⊕◯◯◯	RCT	Low to moderate	Low to moderate	Not serious	Low to moderate	Possible publication bias	63	57	SMD −0·08	−1·12, 0·97	Potentially no effect on total protein levels
5. Soya infant formula and albumin levels											
2 ⊕◯◯◯	RCT	Low to moderate	Low to moderate	Not serious	Low to moderate	Possible publication bias	105	88	SMD −0·97	−1·28, −0·67	Potentially lower albumin levels in the soya intake group
6. Soya infant formula and Zn values (Fig. 5)											
2 ⊕⊕◯◯	RCT	Moderate	Low to moderate	Not serious	Low to moderate	Possible publication bias	136	144	SMD −0·15	−0·49, 0·19	No clinical effect on Zn levels
7. Soya infant formula and total Ca values (Fig. 6)											
3 ⊕⊕◯◯	RCT	Moderate	Low to moderate	Not serious	Low to moderate	Possible publication bias	176	169	SMD −0·50	−0·93, −0·08	Lower levels of Ca only in children fed non-supplemented soya infant formulas
8. Soya infant formula and bone mineral content (gm/cm^2) (Fig. 7)											
6 ⊕⊕◯◯	RCT	Moderate	Low to moderate	Not serious	Low to moderate	Possible publication bias	195	211	SMD −0·41	−0·91, 1·73	No clinical effect on bone mineral density

RCT, randomised controlled trial.

Modern SIF contain P and Ca at concentrations that are about 20 % higher than those present in CMF. These formulas are supplemented with Fe and Zn, and the protease inhibitor activity has been removed by up to 90 %. In fact, a soyabean protease inhibitor with the properties of an antitrypsin, antichymotrypsin and antielastin as heated for infant formulas removes majority of this protease inhibitor activity and renders it nutritionally irrelevant.[4,5]

SIF have been indicated for use in children with cows' milk protein allergy and post-infectious diarrhoea due to lactose intolerance and galactosaemia, for use as a vegan HM substitute, and for the treatment of common feeding problems, such as fussiness, gas and spit-up. The American Academy of Pediatrics (AAP) supports the use of SPI-based formulas as safe and effective alternatives to provide appropriate nutrition for the normal growth and development of term infants whose nutritional needs are not being met by HM or formulas based on cows' milk[6].

Another important topic of discussion is phyto-oestrogens (isoflavones) present in SIF. Commercially, SIF contain 32–47 mg/l of isoflavones, while mother's milk contains only 1–10 μg/l. The three main aglycones found in SIF are genistein, daidzein and, to a smaller extent, glycitein. Concerns have been raised about the genistein content of soya formulas because of its potential negative effects on sexual development and reproduction, neurobehavioural development, immune function and thyroid function[7,8].

However, soya formulas and other soya-based foods contain many components, of which genistein is only one. Chen & Rogan[9] reported that only 3·2–5·8 % of total isoflavones in soya formulas consist of unconjugated genistein and daidzein and that amounts can vary by batch. The majority (>65 %) of isoflavones detected in soya formulas are conjugated to sugar molecules to form glycosides[10]. The levels of isoflavones in cord blood, amniotic fluid, HM, and infant plasma and urine have been measured, providing evidence that isoflavones pass from the mother to the infant and that they are absorbed from infant formulas[9–12]. An international group of paediatricians and statisticians decided to conduct a meticulous review of available evidence to determine whether there is solid scientific evidence that SIF are not safe for infants. Therefore, the aims of the present study were to

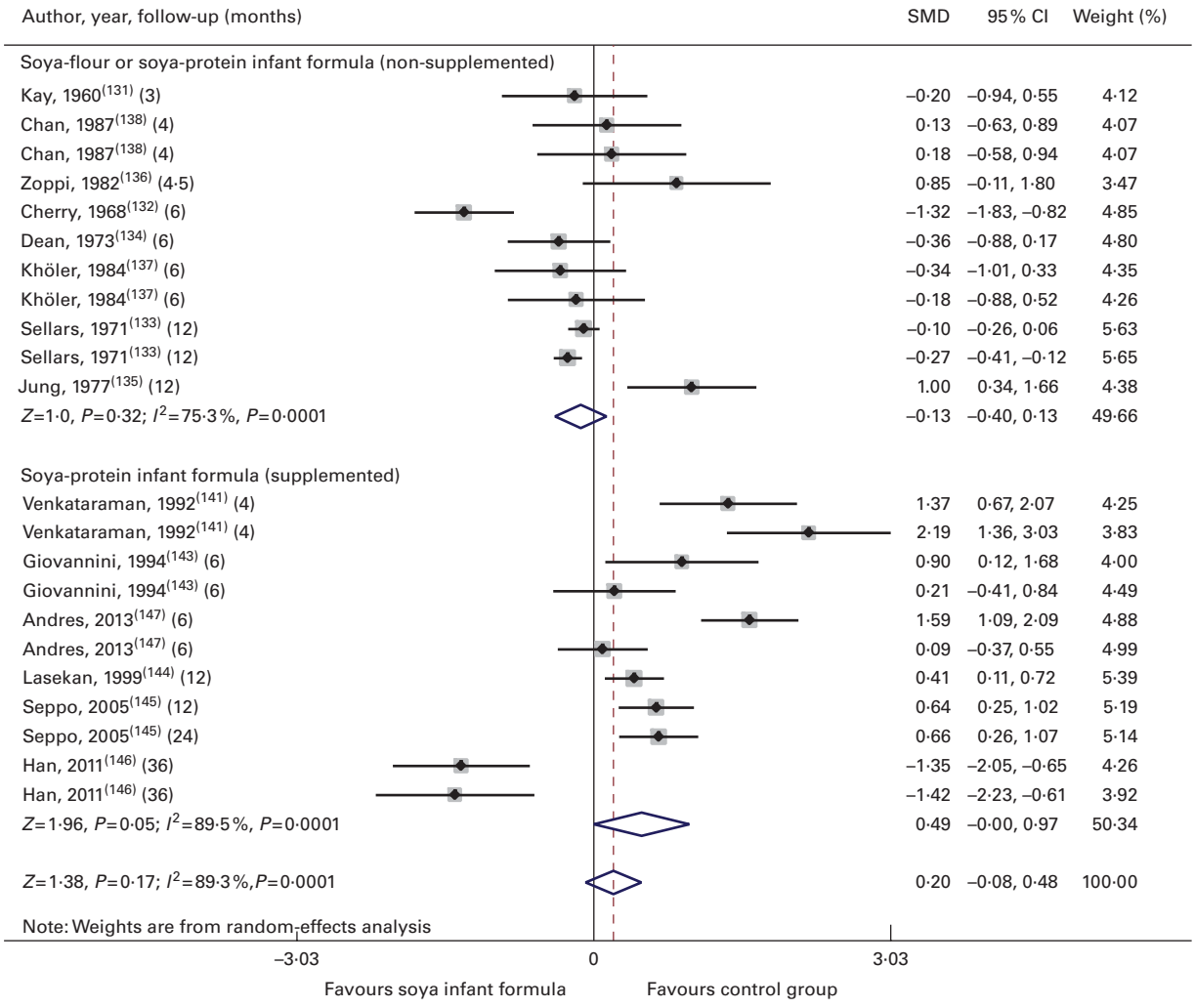

Fig. 1. Effect of soya infant formula on weight gain. SMD, standardised mean difference. (A colour version of this figure can be found online at http://www.journals.cambridge.org/bjn).

search for and evaluate all the available publications on the safety profile of SIF in children, with emphasis on the potentially negative effects on anthropometric growth, bone health, reproductive, endocrine and immune functions, and behaviour. The present review does not include an analysis of the safety of SIF in patients with cows' milk protein allergy. That topic will be discussed in a different publication.

Materials and methods

Studies included and their characteristics

Cross-sectional, case–control, cohort studies or clinical trials were included in the present systematic review if they were carried out in newborns, infants or children aged up to 18 years, independent of country of origin, language or clinical condition. For inclusion, papers were required to (1) be published in English or Spanish, (2) include the use of any type of SIF in at least one arm and (3) include a comparison with another type of infant formula for feeding purposes and measure/compare the effects of SIF on one or more of the following parameters: weight or height changes; Ca metabolism and/or bone mineral density; phyto-oestrogen levels in blood or urine (genistein, daidzein or equol); the effects of phyto-oestrogens on reproductive or endocrine functions (thyroid parameters); the effects on cognition and/or behaviour. We also included papers that analysed the health effects of phytates and aluminium.

Search strategies

Highly sensitive evidence search strategies were employed as described by Wilczynski *et al.*[13] for the identification of observational studies and by Atkins *et al.*[14] for clinical trials, adding the keywords '(soy or soy and infant and formula) or (weight gain) or (height gain) or (hemoglobin changes) or (total and protein changes) or (albumin or globulin levels) or (zinc or calcium values) or (bone and mineral and content) or (genistein or daidzein; or equol levels) or (precocious and puberty) or (breast and bud) or (breast and

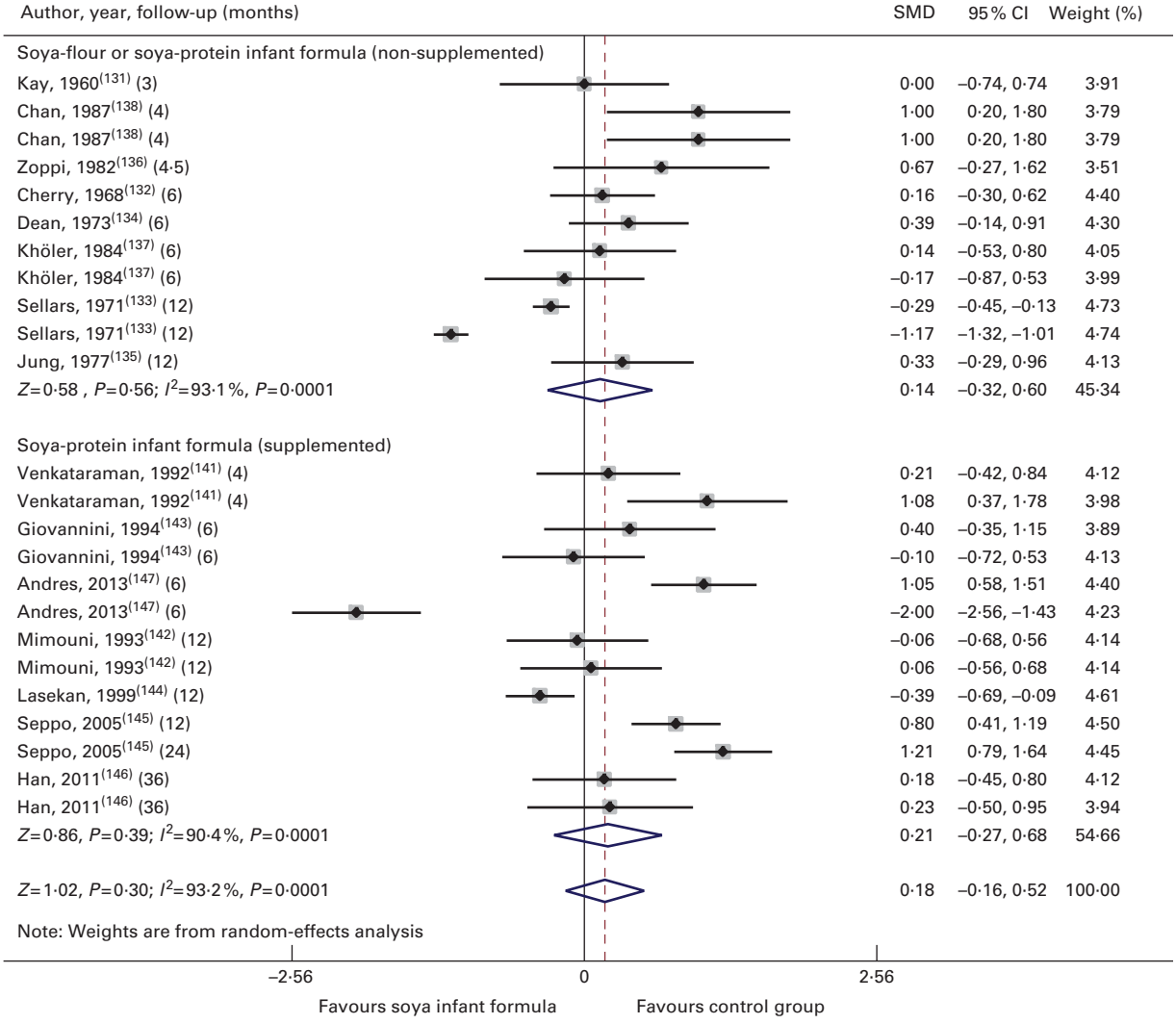

Fig. 2. Effect of soya infant formula on height gain. SMD, standardised mean difference. (A colour version of this figure can be found online at http://www.journals.cambridge.org/bjn).

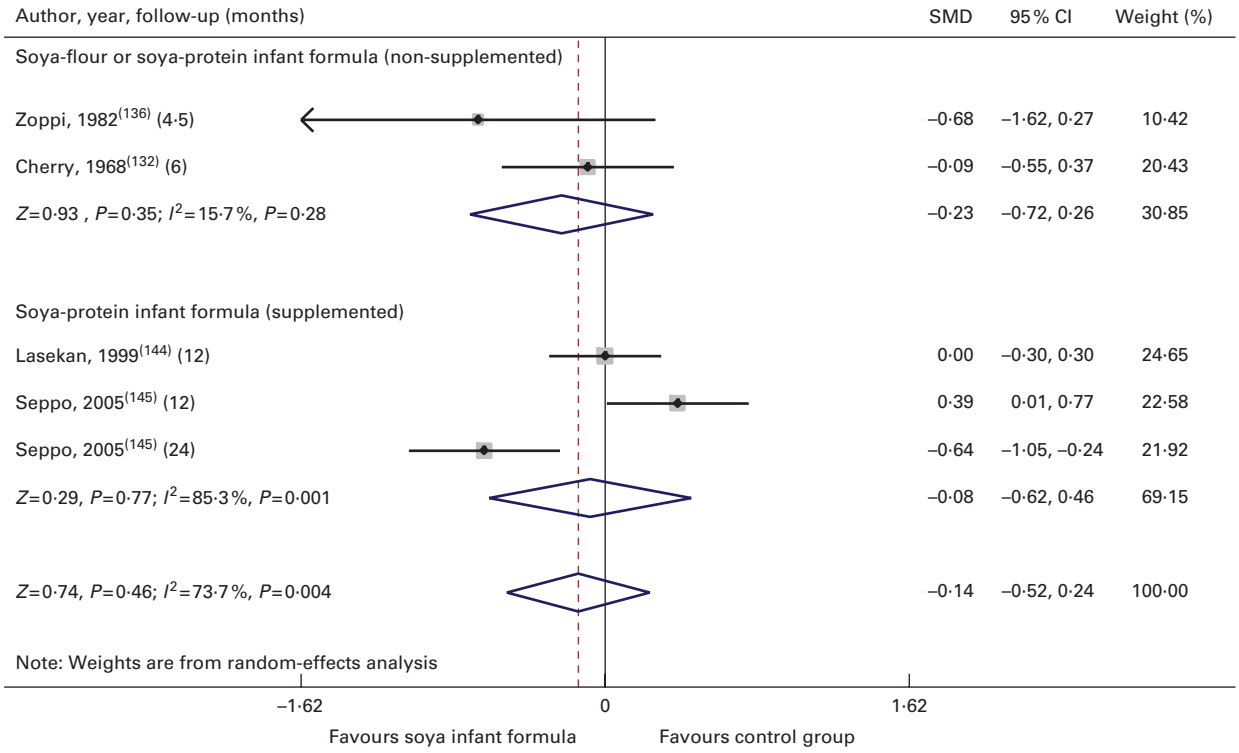

Fig. 3. Effect of soya infant formula on Hb values. SMD, standardised mean difference. (A colour version of this figure can be found online at http://www.journals.cambridge.org/bjn).

tissue) or (breast and enlargement) or (thelarche or menarche) or (menstrual and cycle and length) or (pregnancy) or (abortion or miscarriage) or (ectopic and pregnancy) or (preterm and birth) or (antibodies) or (lymphocytes) or (infectious and episodes) or (thyroid) or (cancer)'. We limited the search strategy to studies conducted in human beings. Mostly as a result of research in animal models, concerns have been expressed regarding the safety of isoflavones in SIF. However, application to human populations is limited by differences in isoflavone metabolism among animal species. In fact, multiple studies have shown that there is no conclusive evidence from animals that indicates that dietary isoflavones may adversely affect the health of children. That is why we focused only on studies carried out in human subjects. The search was carried out electronically and manually in the following databases: PubMed (1909 to July 2013); Embase (1988 to May 2013); LILACS (1990 to May 2011); ARTEMISA (13th edition to December 2012); Cochrane controlled trials register; Bandolier; DARE.

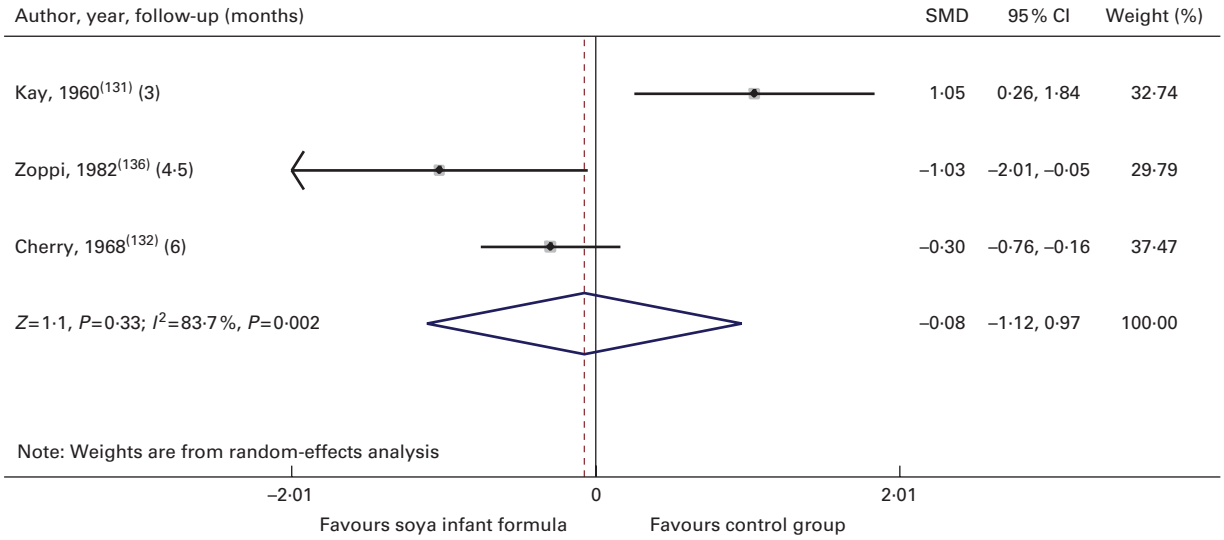

Fig. 4. Effect of soya infant formula on serum total proteins. SMD, standardised mean difference. (A colour version of this figure can be found online at http://www.journals.cambridge.org/bjn).

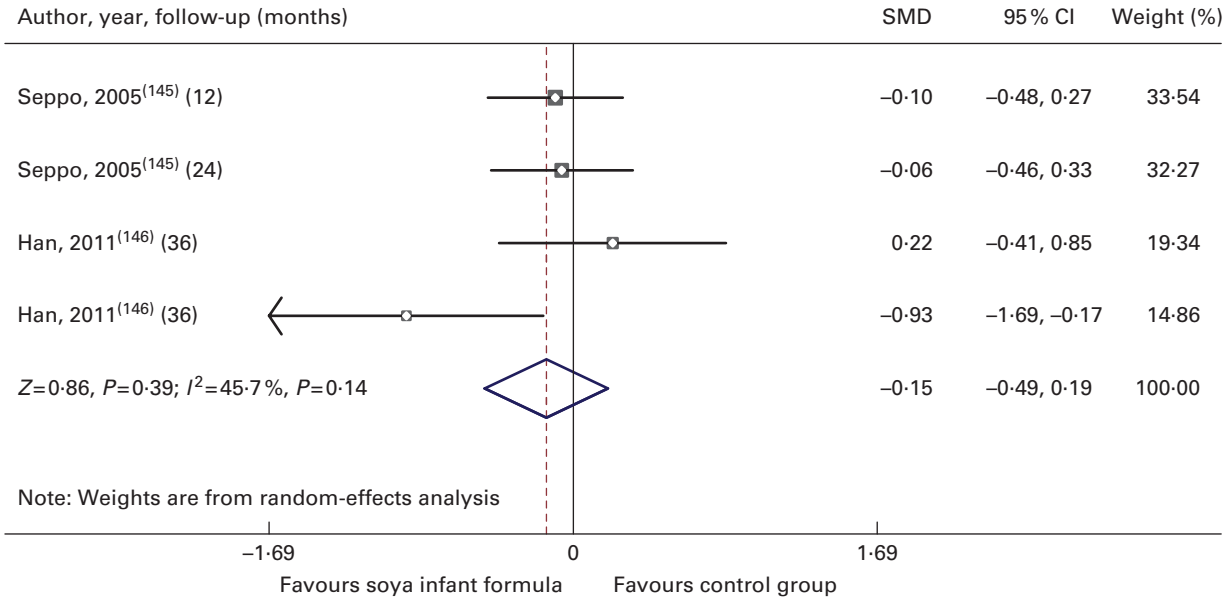

Fig. 5. Effect of soya infant formula on serum zinc values. SMD, standardised mean difference. (A colour version of this figure can be found online at http://www.journals.cambridge.org/bjn).

Evidence quality evaluation

We used the standardised methods described by the Cochrane Collaboration for preparing the protocol, applying the criteria of inclusion, evaluating the quality of publications and extracting information. The quality of publications was determined using the GRADE system[14]. The GRADE approach specifies four levels of quality of the evidence: HIGH (randomised trials or double-upgraded observational studies); MODERATE (downgraded randomised trials or upgraded observational studies); LOW (double-downgraded randomised trials or observational studies); VERY LOW (triple-downgraded randomised trials or downgraded observational studies or case

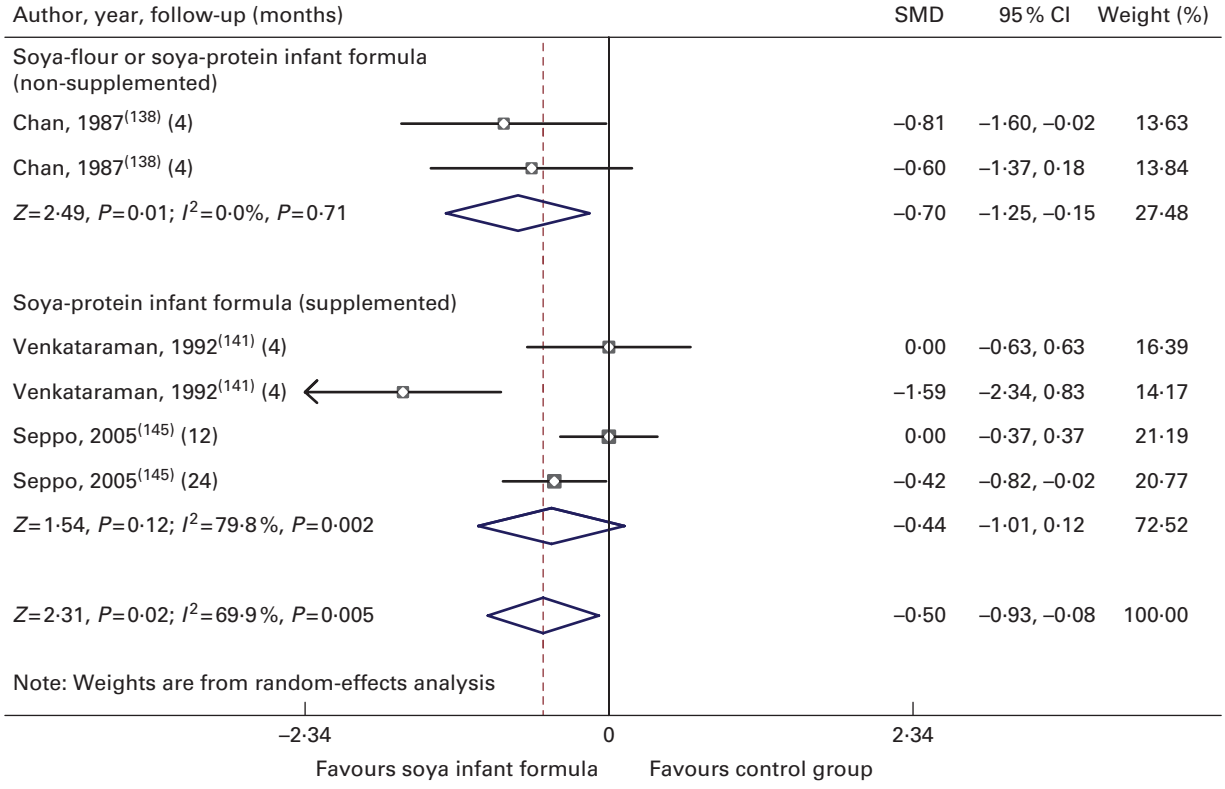

Fig. 6. Effect of soya infant formula on total calcium values. SMD, standardised mean difference. (A colour version of this figure can be found online at http://www.journals.cambridge.org/bjn).

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series/case reports)[14]. Using a double-blind and independent strategy, two authors extracted and evaluated the quality of relevant information in formats designed *a priori* for this purpose. Any disagreement in data collated was resolved by discussion and analysis of the information.

Synthesis and analysis of information

According to the GRADE system[14], evidence obtained is presented in tables that report limitations in design, inconsistency, indirectness, imprecision, summary of findings and recommendations. The effects of soya on growth and development, reproductive and endocrinological functions, and immunity were meta-analysed using a Mantel–Haenszel fixed-effects model, and they are presented graphically by a forest plot. For all the estimates, a CI of 95 % was calculated. A heterogeneity test was carried out in all cases using the I^2 test, with a significant value of $P<0{\cdot}05$. In the case of suspected bias of publication, a funnel plot is presented. A sensitivity analysis was carried out, where necessary.

Results

Description and quality of studies

The initial search strategy yielded 156 potential studies[4,9–12,15–165] to be included. Upon careful review of the abstracts of each article, 121[4,9–12,15–130] were eliminated (Table 1), leaving a total of thirty-five articles for further analysis[131–165]. The articles were eliminated because they covered topics not related to our safety analysis, were narrative reviews of the evidence, lacked sufficient congruence between what was described in the objectives and what was reported in the analysis, and/or did not contain sufficient extractable information to contribute to the goals of the present review.

Quantitative synthesis of results

Growth and development. Through the present systematic review, we identified fourteen randomised controlled trials[131–138,141,143–147], which led us to identify the nutritional equivalence of SIF compared with that of HM and CMF regarding weight gain (standardised mean difference (SMD) 0·13, 95 % CI −0·15, 0·41, *P*=NS) and length gain (SMD 0·24, 95 % CI −0·10, 0·57, *P*=NS) during the first year of life. At the same time, through this evidence analysis, we found no effects of these formulas on the levels of Hb (SMD 0·14, 95 % CI −0·52, 0·24, *P*=NS), total protein (SMD −0·08, 95 % CI −1·12, 0·97, *P*=NS) and Zn (SMD 0·13, 95 % CI −0·15, 0·41, *P*=NS). The analysis of total Ca levels led us to establish a negative effect of old soya formulas (non-supplemented) on this mineral (SMD −0·50, 95 % CI −0·93, 0·08, *P* 0·01). This effect disappeared with the use of improved and supplemented SIF (SMD −0·44, 95 % CI −1·01, 0·12,

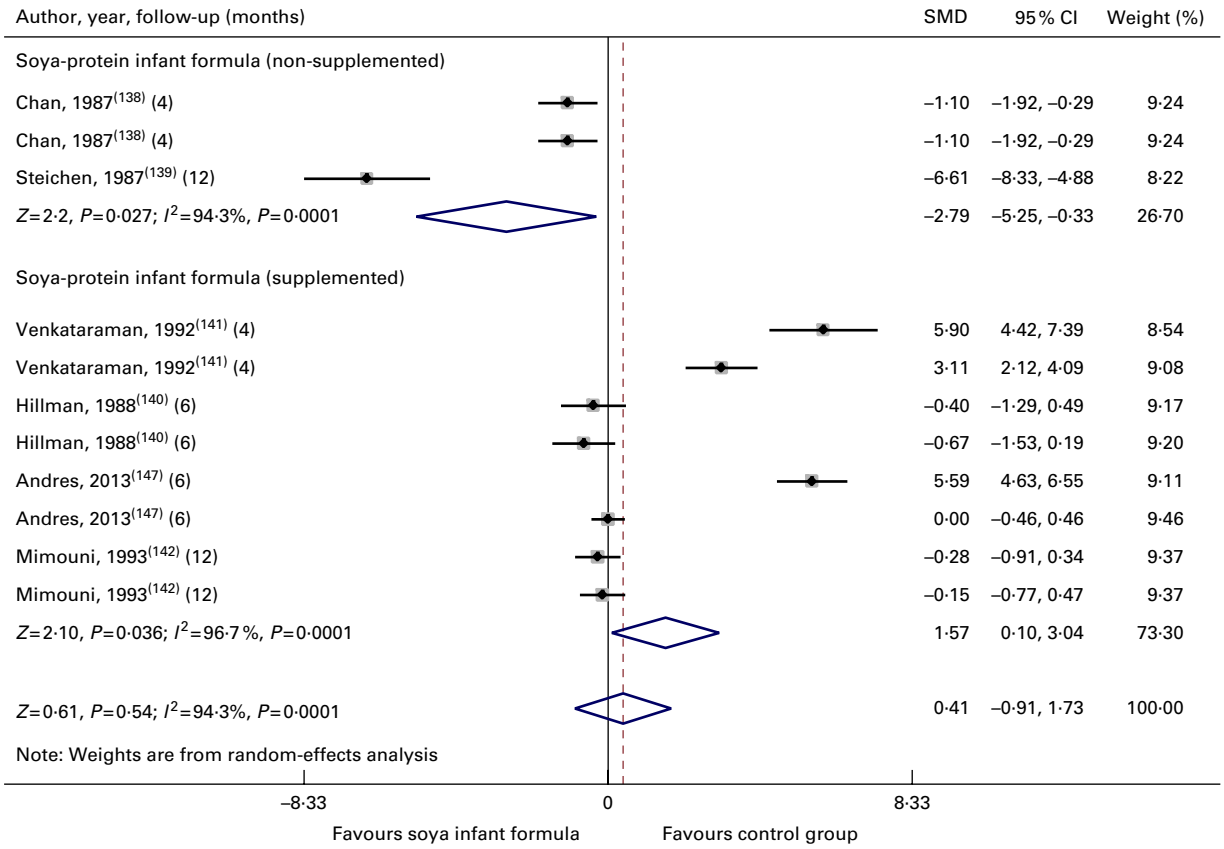

Fig. 7. Effect of soya infant formula on bone mineral content (gm/cm^2). SMD, standardised mean difference. (A colour version of this figure can be found online at http://www.journals.cambridge.org/bjn).

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Table 3. Evidence from studies included in the review (immunity and infection risk)
(Standardised mean difference (SMD) values and 95 % confidence intervals)

Quality assessment							Summary of findings				
							No. of patients		Effects		
No. of studies	Design	Limitations in design	Inconsistency	Indirectness	Imprecision	Other considerations	Soya group	Control group	Absolute SMD	95 % CI	Recommendation
1. Soya infant formula and polio 1 antibodies in serum											
2 ⨁⨁◯◯	RCT	Low to moderate	Low to moderate	Not serious	Low to moderate	Possible publication bias	43	44	SMD −5·95	−8·93, −2·97	Moderate-quality evidence suggests lower levels of polio 1 antibodies in children with a history of soya intake
2. Soya infant formula and polio 2 antibodies in serum											
1 ⨁⨁◯◯	Cohort	Low to moderate	Low to moderate	Not serious	Low to moderate	Possible publication bias	43	44	SMD −4·37	−5·8, −2·94	Moderate-quality evidence suggests lower levels of polio 2 antibodies in children with a history of soya intake
3. Soya infant formula and polio 3 antibodies in serum											
1 ⨁⨁◯◯	Cohort	Low to moderate	Low to moderate	Not serious	Low to moderate	Possible publication bias	43	44	SMD −0·39	−4·8, 4·01	Moderate-quality evidence suggests no effect of soya on the levels of polio 3 antibodies in children
4. Soya infant formula and diphtheria antibodies in serum (Fig. 9)											
1 ⨁⨁◯◯	Cohort	Low to moderate	Low to moderate	Not serious	Low to moderate	Possible publication bias	76	100	SMD −8·10	−25·1, 8·89	Moderate-quality evidence suggests no effect of soya on the levels of diphtheria antibodies in children
5. Soya infant formula and infectious episodes/child (Fig. 10)											
1 ⨁⨁◯◯	Cohort	Low to moderate	Low to moderate	Not serious	Low to moderate	Possible publication bias	117	127	SMD 1·25	−0·16, 2·33	Moderate-quality evidence suggests no effect of soya on the number of episodes of respiratory or gastrointestinal infections in children

RCT, randomised controlled trial.

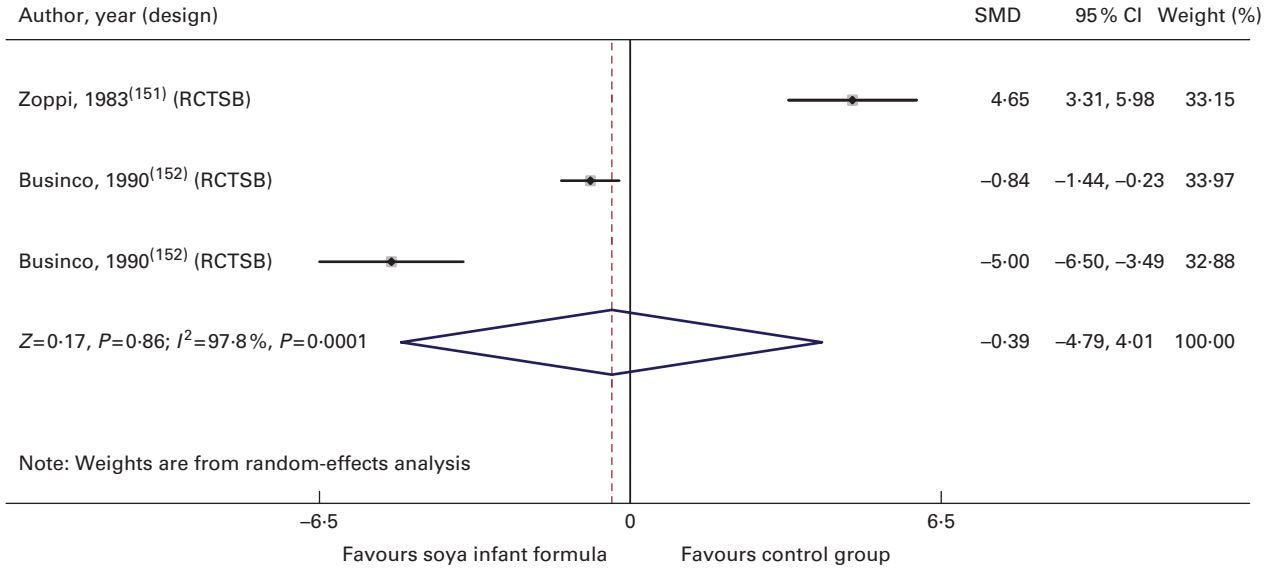

Fig. 8. Effect of soya infant formula on polio antibodies. SMD, standardised mean difference; RCTSB, randomised controlled trial, single blind. (A colour version of this figure can be found online at http://www.journals.cambridge.org/bjn).

P=NS). Moreover, six randomised controlled trials[138–142,147] allowed us to establish a safe profile for modern supplemented formulas with regard to bone mineral density (SMD −0·12, 95% CI −1·46, 1·22, *P*=NS; Table 2; Figs. 1–7).

With regard to the potential negative effects of SIF on neurodevelopment, a study with an acceptable quality of evidence was conducted in 9- to 10-year-old children who were fed either SIF or HM during their first year of life. After adjusting for covariates, including ingestion of a chloride-deficient SIF, the authors did not find differences in intelligence quotient, behavioural problems, learning impairment or emotional problems[148]. Another study was conducted in 1999 among adults aged 20–34 years, who, as infants, participated in controlled feeding studies from 1965 to 1978. The percentage of men or women who achieved some level of college or trade school education, whether fed SIF or CMF, did not differ[149]. A more recently published prospective cohort study compared the developmental status (i.e. mental, motor and language) of breast-fed (HM), CMF-fed and SIF-fed infants during the first year of life. A total of 391 healthy infants were assessed longitudinally at ages 3, 6, 9 and 12 months. Development was evaluated using the Bayley Scales of Infant Development and the Preschool Language Scale-3. Mixed-effects models were used while adjusting for socio-economic status, mother's age and intelligence quotient, gestational age, sex, birth weight, head circumference, race, age and diet history. No differences were found between the CMF-fed and SIF-fed infants. The HM-fed babies had a small benefit in cognitive development compared with the formula-fed infants[150].

With regard to immune function and the risk of respiratory and gastrointestinal infections, we identified two randomised controlled trials[151,153,154] and one cohort study[152] with a

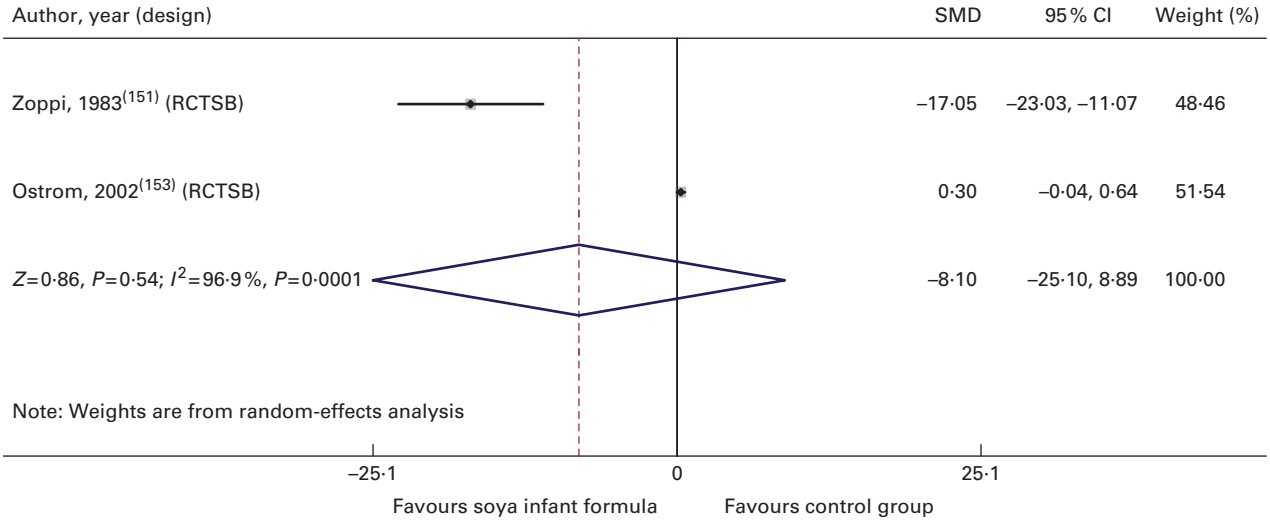

Fig. 9. Effect of soya infant formula on diphtheria antibodies. SMD, standardised mean difference; RCTSB, randomised controlled trial, single blind. (A colour version of this figure can be found online at http://www.journals.cambridge.org/bjn).

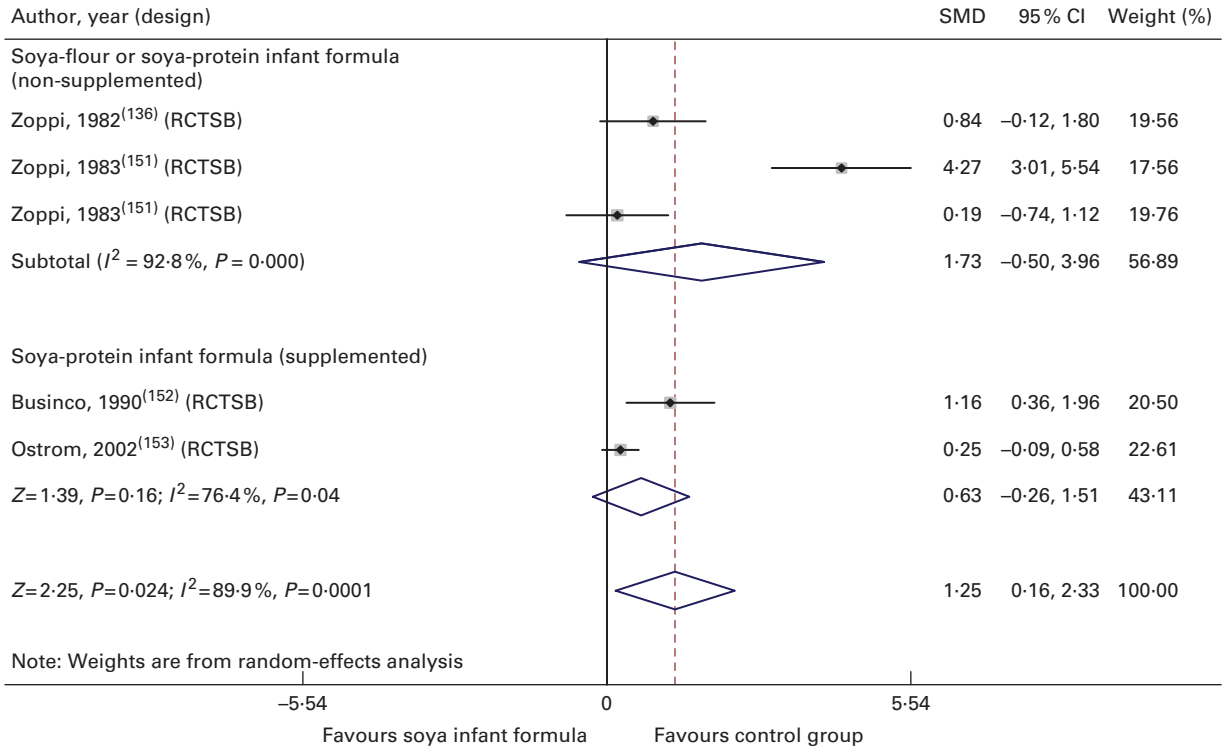

Fig. 10. Effect of soya infant formula on infectious episodes/child. SMD, standardised mean difference; RCTSB, randomised controlled trial, single blind. (A colour version of this figure can be found online at http://www.journals.cambridge.org/bjn).

low-to-moderate quality of evidence of similar behaviour between HM-fed, CMF-fed and SIF-fed children in relation to the percentage of B lymphocytes, T lymphocytes or natural killer cells, levels of IgA, IgG and IgM, and titration of antibodies against polio virus (SMD −0·39, 95% CI −4·8, 4·01), diphtheria (SMD −8·10, 95% CI −25·1, 8·89) or *Haemophilus influenzae*. We also found that the number of episodes/child of respiratory infections or acute diarrhoea was similar between the groups (SMD 1·25, 95% CI −0·16, 2·33; Table 3; Figs. 8–10).

Phytate and aluminium toxicity. It is known that phytates can interfere with the intestinal absorption of Zn, Ca, Fe and P. None of the studies that we reviewed showed any negative impact of the content of phytates in SIF on anthropometric growth, Hb levels, and Ca and Zn serum levels in SIF-fed, CMF-fed children or breast-fed infants[132,136–138,141,144–146] (Figs. 1–7).

As has been described above, SIF contain higher levels of aluminium than CMF and HM. However, daily aluminium intake does not exceed 1 mg/kg, which is considered to be a tolerable level by the FAO/WHO[78]. Before the present systematic review, no published evidence has shown a negative health effect of aluminium in full-term infants fed modern SIF. In 2008, the AAP concluded that aluminium in SIF is not a safety issue, except when fed to preterm infants or infants with renal failure[155].

Reproductive and endocrine functions. We identified one randomised controlled trial and one cross-sectional study that demonstrated with a very low quality of evidence that there is an association of SIF intake with higher serum and urine levels of genistein (SMD 2·54, 95% CI 2·07, 3·01, P 0·0001) and daidzein (SMD 4·68, 95% CI 3·48, 5·87, P 0·0001) *v.* other feedings, but with similar equol levels (SMD 0·24, 95% CI −9·34, 9·38, P=NS). These authors did not find significant correlations between the concentrations of isoflavones and the levels of certain hormones in children fed soya formulas[156,157]. Despite convincing evidence of relatively high exposures, whether the isoflavones in SIF are biologically active in infants is an open question. If genistein, daidzein and equol are all oestrogenic in cell receptors and animals, the question appears to be primarily one of dose[157]. It is not conclusive what levels are biologically active and can produce organic effects. Importantly, some authors demonstrated that most of the phyto-oestrogens present in the plasma of SIF-fed infants are in a conjugated form and are therefore unable to exert hormonal effects. Our analysis of clinical evidence also produced inconclusive results[158] (Table 4; Figs. 11 and 12).

From a clinical point of view, we identified two cohort studies[149,153] with a moderate quality of evidence of marginal unfavourable effects of SIF on early menarche (SMD −0·36, 95% CI −0·69, −0·02, P 0·04) and two studies with a very low quality of evidence (one cross-sectional study and one case–control study) where SIF seemed to be a risk factor for the presence of breast tissue during the second year of life (OR 2·44, 95% CI 1·11, 5·39, P 0·01)[160,161]. Additionally, in one of the cohort studies[149], the authors identified an association of SIF intake with 9 h (95% CI 1·5, 16 h) of more menstrual bleeding and more discomfort during menstrual periods (risk ratio 1·77, 95% CI 1·04, 3·0, P 0·001). In other

Table 4. Evidence from studies included in the review (reproductive and endocrine functions).
(Odds ratios, risk ratios (RR) or standardised mean difference (SMD), weighted mean difference (WMD) values and 95 % confidence intervals)

Quality assessment							Summary of findings				
							No. of patients		Effects		
No. of studies	Design	Limitations in design	Inconsistency	Indirectness	Imprecision	Other considerations	Soya group	Control group	Relative (OR, RR) Absolute (SMD, WMD)	95 % CI	Recommendation
1. Soya infant formula and genistein levels in serum (Fig. 11)											
1	RCTSB Cross -sectional	Low	Low	Serious	Low	Possible publication bias	68	64	SMD 2·54	2·07, 3·01	Low-quality evidence suggests an increase in genistein levels in serum
2. Soya infant formula and daidzein levels in serum (Fig. 12)											
1	RCTSB Cross -sectional	Low	Low	Serious	Low	Possible publication bias	68	64	SMD 4·66	3·48, 5·87	Low-quality evidence suggests an increase in daidzein levels in serum
3. Soya infant formula and equol levels in serum											
1	RCTSB	Low	Low	Serious	Low	Possible publication bias	7	14	SMD 0·24	−9·34, 9·83	Low-quality evidence suggests no effect on equol levels in serum
4. Soya infant formula and age of menarche (Fig. 13)											
2	Cohort	Low to moderate	Low to moderate	Not serious	Low to moderate	Possible publication bias	63	57	SMD −0·36	−0·69, −0·02	Potential effect on menarche, 4 months earlier (1–6 months)
5. Soya infant formula and breast tissue											
1	Cross -sectional	Low	Low	Serious	Low	High risk of publication bias	11/50	24/232	OR 2·44	1·11, 5·39	Low-quality evidence suggests more risk for the early development of breast tissue in girls with soya intake
6. Soya infant formula and thelarche (years)											
1	Cohort	Low to moderate	Low to moderate	Not serious	Low to moderate	Possible publication bias	127 12·3 (SD 1·2)	268 12·3 (SD 1·6)	SMD −0·02	−0·33, 0·29	Moderate-quality evidence suggests no effect of soya on thelarche
7. Soya infant formula and cycle length (days between periods)											
1	Cohort	Low to moderate	Low to moderate	Not serious	Low to moderate	Possible publication bias	122 28·1 (SD 5·9)	257 29·0 (SD 10·1)	SMD −0·58	−2·54, 1·38	Moderate-quality evidence suggests no effect of soya on menstrual cycle
8. Soya infant formula and duration of menstrual bleeding (days requiring pads or tampons)											
1	Cohort	Low to moderate	Low to moderate	Not serious	Low to moderate	Possible publication bias	127 5·0 (SD 1·4)	267 4·7 (SD 1·3)	SMD 0·37	0·06, 0·68	Moderate-quality evidence suggests that soya prolongs menstrual bleeding by 9 h (range 1·5–16 h)
9. Soya infant formula and irregular menstrual periods											
1	Cohort	Low to moderate	Low to moderate	Not serious	Low to moderate	Possible publication bias	26/128	54/268	RR 0·91	0·58, 1·44	Moderate-quality evidence suggests no effect of soya on irregular menstrual periods
10. Soya infant formula and heavy menstrual flow											
1	Cohort	Low to moderate	Low to moderate	Not serious	Low to moderate	Possible publication bias	35/128	67/268	RR 0·98	0·67, 1·44	Moderate-quality evidence suggests no effect of soya on heavy menstrual flow
11. Soya infant formula and missed menstrual periods (except during pregnancy)											
1	Cohort	Low to moderate	Low to moderate	Not serious	Low to moderate	Possible publication bias	27/128	66/268	RR 0·91	0·62, 1·33	Moderate-quality evidence suggests no effect of soya on missed menstrual periods
12. Soya infant formula and discomfort during menstrual periods											

Table 4. *Continued*

Quality assessment							Summary of findings				
							No. of patients		Effects		
No. of studies	Design	Limitations in design	Inconsistency	Indirectness	Imprecision	Other considerations	Soya group	Control group	Relative (OR, RR) Absolute (SMD, WMD)	95 % CI	Recommendation
1 ⨁⨁◯◯	Cohort	Low to moderate	Low to moderate	Not serious	Low to moderate	Possible publication bias	23/128	30/268	RR 1·77	1·04, 3·0	Moderate-quality evidence suggests no effect of soya on more discomfort during menstrual periods
13. Soya infant formula and spotting in the middle of menstrual period											
1 ⨁⨁◯◯	Cohort	Low to moderate	Low to moderate	Not serious	Low to moderate	Possible publication bias	41/128	65/268	RR 1·18	0·88, 1·58	Evidence suggests no effect of soya on spotting in the middle of menstrual period
14. Soya infant formula and breast tenderness											
1 ⨁⨁◯◯	Cohort	Low to moderate	Low to moderate	Not serious	Low to moderate	Possible publication bias	12/128	22/268	RR 1·34	0·67, 2·69	Evidence suggests no effect of soya on breast tenderness
15. Soya infant formula and ever pregnant											
1 ⨁⨁◯◯	Cohort	Low to moderate	Low to moderate	Not serious	Low to moderate	Possible publication bias	54/128	128/268	RR 0·94	0·85, 1·04	Evidence suggests no effect of soya on ever pregnant
16. Soya infant formula and miscarriages											
1 ⨁⨁◯◯	Cohort	Low to moderate	Low to moderate	Not serious	Low to moderate	Possible publication bias	15/117	38/249	RR 0·65	0·28, 1·48	Evidence suggests no effect of soya on miscarriage probability
17. Soya infant formula and preterm deliveries											
1 ⨁⨁◯◯	Cohort	Low to moderate	Low to moderate	Not serious	Low to moderate	Possible publication bias	10/79	12/148	RR 2·11	0·84, 5·31	Evidence suggests no effect of soya on preterm deliveries
18. Soya infant formula and uterine fibroids											
1 ⨁⨁◯◯	Cohort	Low to moderate	Low to moderate	Not serious	Low to moderate	Possible publication bias	58/641	1201/16 012	RR 1·25	0·67, 1·91	Evidence suggests no significant effect of soya on the development of uterine fibroids

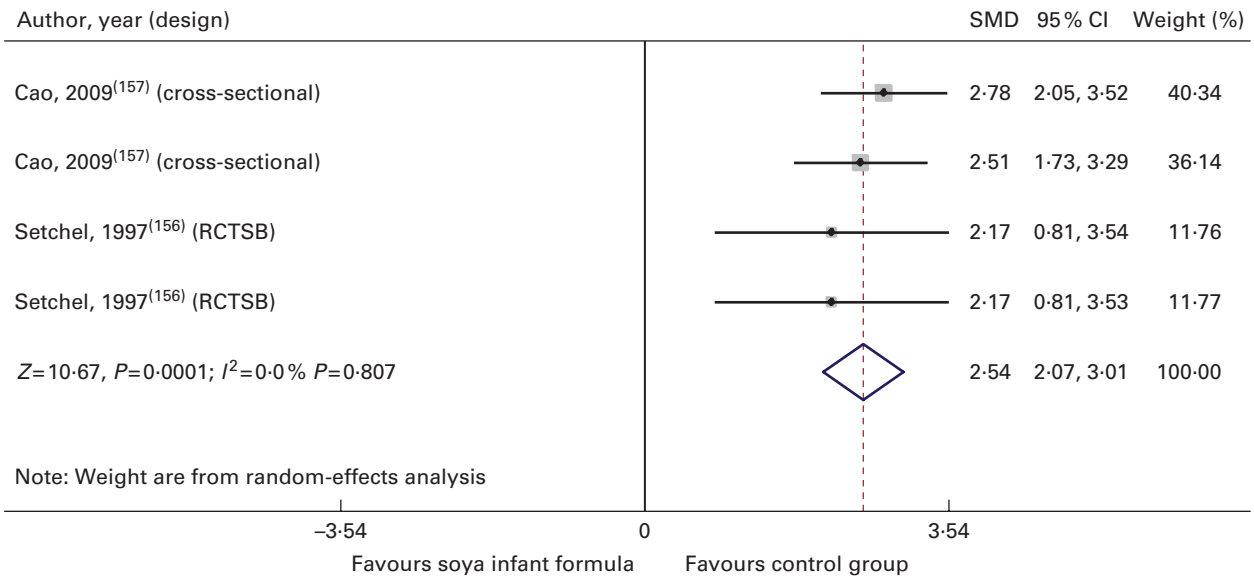

Fig. 11. Effect of soya infant formula on genistein levels in serum. SMD, standardised mean difference; RCTSB, randomised controlled trial, single blind. (A colour version of this figure can be found online at http://www.journals.cambridge.org/bjn).

words, this study found only subtle effects including slight increases in the duration of women's menstrual cycles and the level of discomfort during menstruation. However, this study showed no statistically significant differences between groups in either women or men for more than thirty outcomes (e.g. precocious puberty, early thelarche, modification of cycle length, duration of menstrual bleeding, irregular menstrual periods, heavy menstrual flow, missed menstrual periods, spotting in the middle of a menstrual period, breast tenderness, frequency of pregnancies, and miscarriages or preterm deliveries) (Table 4; Fig. 13).

In 2010, a report about the possible association between uterine fibroids and SIF intake was published. In this cohort study with a low-to-moderate quality of evidence, the authors identified a risk ratio of 1·25, but with a CI of 0·97–1·61, associated with a non-significant *P* value[162]. With regard to SIF intake and potential association with endocrine dysfunction, interestingly, we found that most of these publications were published as case reports[43,163,164]. Messina *et al.*[165] reported no association between SIF intake and thyroid function disturbances in healthy infants with euthyroidism. These investigators identified fourteen trials in which the effects of soya foods or isoflavones on at least one measure of thyroid function were evaluated in healthy subjects: eight included only women; four involved only men; two included both men and women. With only one exception, either no effects or only very limited changes were observed in these trials. Thus together, the findings provide little evidence that in euthyroid, iodine-replete subjects, soya foods or isoflavones adversely affect thyroid function[165].

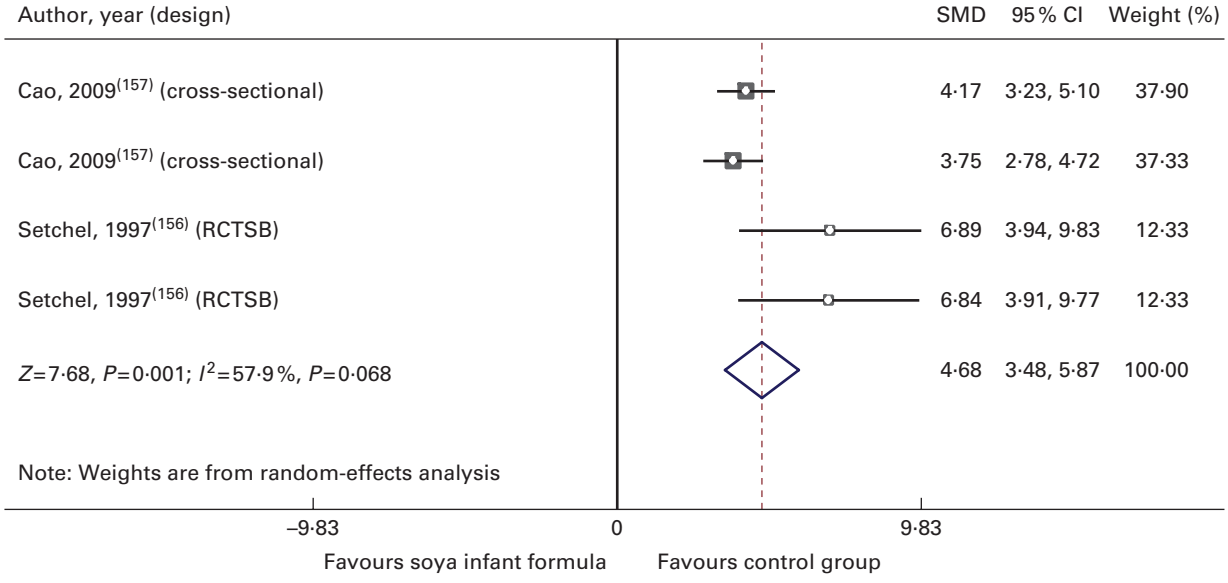

Fig. 12. Effect of soya infant formula on daidzein levels in serum. SMD, standardised mean difference; RCTSB, randomised controlled trial, single blind. (A colour version of this figure can be found online at http://www.journals.cambridge.org/bjn).

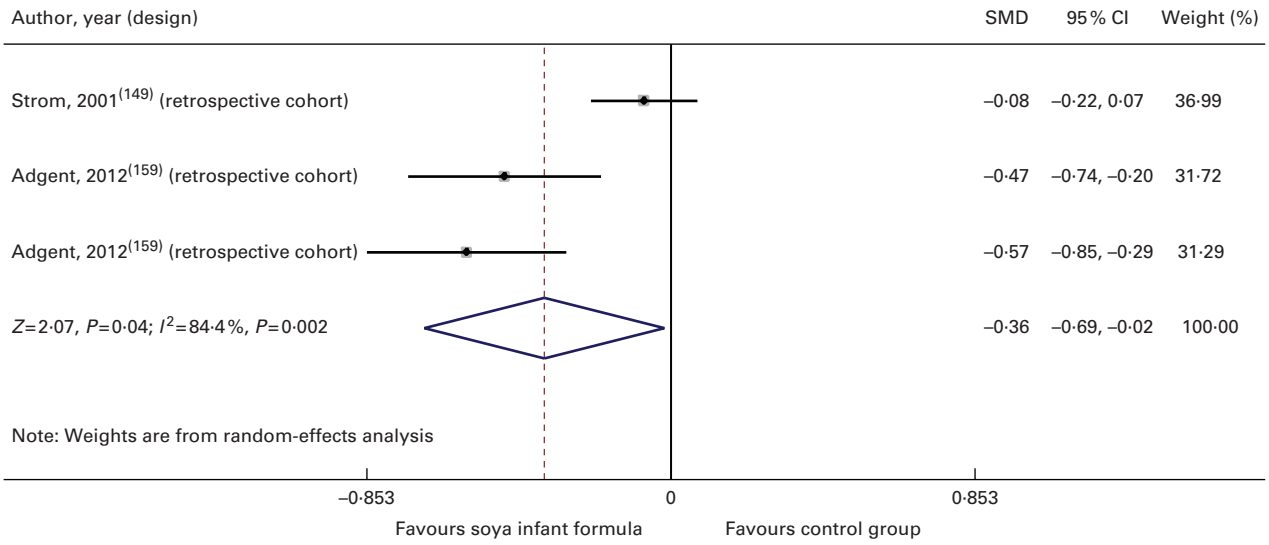

Fig. 13. Effect of soya infant formula on age of menarche. SMD, standardised mean difference. (A colour version of this figure can be found online at http://www.journals.cambridge.org/bjn).

Discussion

Soya has been used as food throughout the world for thousands of years. Ruhräh[1] published the first report on the use of a soyabean-based formula for infants in 1909. Early SIF contained soya flour, a constituent with a poorer protein digestibility and a reduced protein content when compared with the SPI used in modern SIF. SPI replaced soya flour in infant formulas during the early 1960s. In the 1970s, methionine, iodine, carnitine, taurine, choline and inositol were added to standard SIF. Modern SIF meet the AAP recommendations and the Infant Formula Act (1980 and subsequent amendments in 1986) requirements for term infants[1–4].

Approximately 25% of infants in the USA are fed SIF at some point in their first year of life (AAP, 2008)[155]. Recently, some findings generated in animal models or human observations have challenged the use of these formulas in infants and children because of concerns about potential negative effects on growth, bone health, immunity, cognition, and reproductive or endocrine functions[74,106]. The first review about soya was a narrative review published in 1988 that focused on growth and bone mineralisation. It was a result of concerns regarding adequate bone mineralisation when rickets was observed in very-low-birth-weight infants receiving soya-based feedings. This review concluded that children fed a soya isolate formula (old composition) had a pattern of growth similar to that of children fed a CMF and that infants fed a soya isolated formula had significantly lower bone mineral content and bone width at 3, 6, 9 and 12 months of age than those fed CMF, but that their values were similar to those of previously studied infants fed HM with vitamin D supplementation[32]. After the publication of this paper, at least eighteen additional narrative reviews on different aspects of safety and/or efficacy of SIF were published, most of them demonstrating a safety profile for use in children[4,9,49,62,66,69,74,78,86,87,91,100,106,117,121,125,128,130]. In addition to these publications, only three systematic reviews with a meta-analysis were published about the efficacy of soya as an adjuvant in acute diarrhoea, infantile colic or cows' milk protein allergy prevention. In these publications, Brown *et al.*[43] assessed the effects of continued feeding of non-HM or formulas to infants during acute diarrhoea on their treatment failure rates, stool frequency and amount, diarrhoeal duration and body-weight change. They concluded that the vast majority of young children with acute diarrhoea can be successfully managed with continued feeding of undiluted non-HM. Lucassen *et al.*[55] concluded that in infants with infantile colic, the effectiveness of substitution with soya formula milks is unclear when only trials of good methodological quality are considered. Finally, Osborn & Sinn[82] concluded that soya formula feeding cannot be recommended for the prevention of allergy or food intolerance in infants at a high risk of allergy or food intolerance.

To our knowledge, this is the first systematic review with a meta-analysis published with the focus mainly on SIF and safety in infants and children. It has the advantage of covering evidence analysis from 1909 to July 2013 (104 years), including papers published on SIF, non-enriched SIF and supplemented/enriched SIF. This extensive analysis objectively showed that SIF intake in normal full-term infants – even during the most rapid phase of growth – is associated with normal anthropometric growth, adequate protein status, bone mineralisation and normal immune development. The importance of the meta-analysis reported herein is that data demonstrate the negative effects of the 'old/unsupplemented soya formulas' on Ca metabolism and bone mineral content. For example, Chan *et al.*[138] studied the mineral metabolism in healthy term infants fed the old soya formula containing different sources of carbohydrates. Exclusively breast-fed infants served as controls. These investigators found that at 2 and 4 months of age, the breast-fed infants had higher bone mineral content and bone density. On the contrary, more recent studies using modern/

supplemented SIF have shown growth patterns, Ca levels, bone mineral content, serum Hb levels, total protein levels, immune factors, and upper respiratory or diarrhoeic infection risk similar to those found with other types of feedings.

Few studies have evaluated the impact of SIF on neurodevelopment. For example, a study carried out by Malloy & Berendes[148], in school-aged children who were fed either SIF or HM during their first year of life, showed no differences in intelligence quotient, behavioural problems, learning impairment or emotional problems. Strom *et al.*[149] conducted a study among adults aged 20–34 years who, as infants, participated in controlled feeding studies. Results indicated no differences in men or women with regard to the achievements of the level of college or trade school education, whether they were fed SIF or CMF. Andres *et al.*[150], in a more recent study in healthy infants, assessed the Bayley Scales of Infant Development and the Preschool Language Scale-3 during the first year of life. No differences were found between the CMF-fed and SIF-fed infants. We are aware of the debate about differences in behaviour (mental, psychomotor and language) in breast-fed infants and formula-fed infants, which are not necessarily related only to the type of feedings.

SPI contains 1–2% of phytates, which may impair the absorption of minerals and trace elements. Modern SIF contain higher levels of micronutrients (Ca, Zn, Fe, etc.) when compared with CMF or HM. We found that feeding SIF to young infants did not result in any negative impact on the levels of Hb, Zn, Ca and overall growth (Figs. 1–3, 5 and 6). Similarly, we also found that SIF contain significantly higher levels of aluminium than CMF and HM (SIF 500–2500 μg/l, CMF 15–400 μg/l and HM 4–65 μg/l). This systematic review did not find any evidence of a negative health effect of this metal in children. SIF should not be fed to preterm infants or infants with renal failure. Studies have concluded that in term infants with normal renal function, there is no risk of aluminium toxicity from SIF.

Finally, it is known that phyto-oestrogens represent a broad group of plant-derived compounds of non-steroidal structure that are abundant within the plant kingdom, including soya, and have a weak oestrogenic activity. Minimum data are available on the potential effects of exposure to phyto-oestrogens in young children on later sexual and reproductive development. SIF-fed infants may have higher serum and urine levels of genistein and daidzein. As has been mentioned earlier, it seems that most of the phyto-oestrogens present in the plasma of SIF-fed infants are in a conjugated form and are therefore unable to exert hormonal effects[158]. The exhaustive analysis that we conducted in the present systematic review produced inconclusive results. We identified two cohort studies with a moderate quality of evidence of marginal adverse effects of SIF on early menarche. Furthermore, two other studies with a very low quality of evidence (one cross-sectional study and one case–control study) showed that SIF would be a risk factor for the presence of breast tissue during the second year of life. Additionally, one cohort study identified an association of SIF intake with a significant increase in the duration of women's menstrual cycles and more discomfort during menstrual periods. However, the same study did not show any statistical difference between the groups for more than thirty additional outcomes, such as presence of puberty, early thelarche, modification of cycle length, severity of menstrual flow, irregular menstrual periods, heavy menstrual flow, missed menstrual periods, spotting in the middle of a menstrual period, breast tenderness, frequency of pregnancies, and miscarriages or preterm deliveries.

This evidence analysis led us to establish that there is no significant effect of soya on important reproductive functions in human beings. The AAP has emphasised that literature reviews and clinical studies of infants fed SIF raise no clinical concerns with respect to nutritional adequacy, sexual development, thyroid disease, immune function or neurodevelopment. Additional studies confirm that SIF do not interfere with normal immune responses. The US Food and Drug Administration has also approved these formulas to be safe for use in infants.

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