Health effects of breastfeeding: an update

Systematic literature review

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Colophon

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Gezondheidseffecten van borstvoeding: een update

Borstvoeding is gunstiger voor de gezondheid van kinderen en moeders dan flesvoeding. Zo is overtuigend aangetoond dat borstgevoede zuigelingen minder kans op bepaalde infectieziekten hebben. Het gunstige effect werkt bovendien door nadat met borstvoeding is gestopt. Borstgevoede kinderen hebben waarschijnlijk een lager risico op overgewicht, astma en een piepende ademhaling, en hun moeders op diabetes, reuma en een hoge bloeddruk. Dit blijkt uit onderzoek van het RIVM op basis van wetenschappelijke studies naar gezondheidseffecten van borstvoeding.

Het RIVM heeft in 2005 en 2007 over de gezondheidseffecten van borstvoeding gerapporteerd. Een groot deel van de nu gerapporteerde gezondheidseffecten komt overeen met de resultaten uit de vorige rapporten, al is de sterkte van het bewijs soms net anders. Nieuw is dat moeders die borstvoeding hebben gegeven, waarschijnlijk minder vaak een hoge bloeddruk hebben. Het eerder beschreven beschermende effect van borstvoeding op eczeem bij kinderen is nu minder duidelijk.

De update is uitgevoerd in opdracht van het ministerie van VWS. De Nederlandse overheid wil over objectieve informatie over de gezondheidseffecten van borstvoeding beschikken. Deze informatie wordt gebruikt om zwangere vrouwen hierover te informeren.

Kernwoorden: borstvoeding, gezondheid, kinderen, moeder, systematische literatuur review, Westerse landen

Synopsis

Health effects of breastfeeding: an update

Breastfeeding has a beneficial effect on the health of both the child and the mother compared to formula feeding. There is convincing evidence that breastfed infants run a lower risk of contracting certain infectious diseases. The beneficial effect is maintained after breastfeeding is stopped. Breastfeeding may also reduce the risk of developing obesity, asthma and wheezing in children and diabetes, rheumatoid arthritis and hypertension in their mothers. These are some conclusions of an update of a systematic literature review of epidemiological studies on the health effects of breastfeeding.

Some ten years ago, RIVM reported for the first time on the health effects of breastfeeding (2005 and 2007). Most of the reported health effects were already reported back then, with only some changes in the strength of the evidence. New is the finding that breastfeeding might have a protective effect on hypertension among mothers. The probable protective effect of breastfeeding on eczema in children could not be confirmed.

The present review was commissioned by the Dutch ministry of Health, Welfare and Sport. The Dutch government seeks to provide objective information on breastfeeding and its health effects to be used in the information to pregnant women.

Keywords: breastfeeding, health, children, maternal health, systematic literature review, western countries

Contents

Summary

Introduction
The World Health Organization (WHO) recommends exclusive breastfeeding in the first six months of life. Based on a recent study, 39% of Dutch mothers comply with these recommendations. Policy of the Dutch government related to breastfeeding aims to supply up-to-date and accurate information on the health effects of breastfeeding.

The Dutch National Institute for Public Health and the Environment (RIVM) published two reports on the health effects of breastfeeding in 2005 and 2007. Since then, many studies have been published on this topic, which might have led to new insights. Therefore, the Dutch ministry of Health, Welfare and Sport asked the RIVM to perform a literature search to summarize the current evidence on the health effects of breastfeeding on mother and child.

Methods
A comprehensive literature search on the health effects of breastfeeding was performed in Medline on 11 June 2014. As in the previous reports, search terms were: 'breastfeeding', 'lactation' or 'human milk' combined with known health outcomes like 'otitis media', 'asthma', or 'obesity'. The search was limited to articles published after July 2006 in English or Dutch and focussed on study populations from Western Europe, North America, Australia and New Zealand. First, relevant systematic literature reviews and meta-analyses were selected. In addition, for each outcome primary articles published after the search date of the included systematic literature review (SLR) or meta-analysis (MA) were included. Included studies were classified according to quality. Based on these peer-reviewed articles published since the former report, together with the former report, strength of the body of evidence for each outcome was evaluated following WHO criteria as 'convincing', 'probable', 'possible', 'insufficient', 'conflicting', or 'no evidence', combined with the direction of the effect (reduced risk, increased risk, or absence of an association).

Results
In total, 44 recent peer-reviewed articles were added to the earlier evidence that was summarised in the previous reports. Health effects on the child were described in 22 of these articles (12 SLRs/MAs and 10 primary articles); health effects on the mother in another 22 articles (4 SLRs/MAs and 18 primary articles). The strength of the evidence for health effects of breastfeeding was evaluated, based on the evidence presented in the previous RIVM reports, in combination with the evidence from these 44 new articles.

Health effects on the child
Convincing evidence was found for a protective effect of breastfeeding on gastrointestinal infections, respiratory tract infections and otitis media in early childhood. Probable evidence for a protective effect was found on obesity, asthma and wheezing, with stronger effects in young children than in older children. Possible evidence was found for a protective effect on childhood cancers in general and specifically for

leukaemia, inflammatory bowel disease, Crohn's disease, ulcerative colitis, diabetes mellitus type 1 and type 2 and sudden infant death syndrome. The strength of evidence was insufficient for adult cancers, neonatal weight loss, metabolic syndrome, urinary tract infections, haemophilus influenza, fever, lymphomas, dental caries, and pyloric stenosis. Probable evidence was found for the absence of an association between breastfeeding and growth in the first year of life and cardiovascular disease in later life. Furthermore, possible evidence for no effect was found for Hodgkin lymphoma and Helicobacter pylori infection. Conflicting evidence was found for atopic diseases, eczema, coeliac disease, lung function and jaundice. Finally, no evidence was found for multiple sclerosis.

Health effects on the mother
No convincing evidence was found for an effect of breastfeeding on any of the investigated health outcomes in mothers. However, probable evidence for a protective effect was found for diabetes mellitus type 2, rheumatoid arthritis and hypertension. The review showed possible evidence for a protective effect of breastfeeding on ovarian cancer, postpartum weight retention and hip fractures. The evidence was insufficient for metabolic syndrome, osteoporosis, gallbladder disease, Alzheimer's disease, macular degeneration, obesity, myocardial infarction, wrist fractures, cardiovascular disease, weight gain, glioma and cervical cancer. Conflicting evidence was found for both postmenopausal and premenopausal breast cancer. Finally, no evidence was found for postpartum fatigue, depressive symptoms and benign breast disease (fibroadenoma).

Comparison with previous reports
In the previous reports no indication for a protective effect of breastfeeding on hypertension among mothers was found, while recent studies indicate a probable protective effect of breastfeeding on hypertension among mothers. Furthermore, the addition of recent evidence to the evidence available in the previous reports resulted in changes in the classification of the strength of evidence for a number of health outcomes. For example, the protective effects on obesity of the child and on rheumatic arthritis of the mother are now less convincing than previously, whereas the evidence became more convincing for respiratory tract infections among children. For eczema the evidence is now conflicting, while it was assessed as probable (positive association) based on the literature available for the previous reports.

Discussion
A strength of the current review is the systematic approach to collect and extract the data, making the process transparent and the review of the literature rigorous and reliable. Results of the included reviews could be affected by weaknesses inherent in the included articles. These quality aspects are taken into account as much as possible in the evaluation of the strength of the evidence.

Our study focussed on the epidemiological literature on health effects of breastfeeding. It did not investigate toxic substances which might have negative health effects. Current consencus is that potential negative

effects due to toxic substances are outweighed by the positive substances of human milk.

Conclusions
Breastfeeding has a beneficial health effect on both the child and the mother compared to formula feeding. There is convincing evidence that breastfed infants for example, run a lower risk of contracting certain infectious diseases. The beneficial effect is maintained after breastfeeding is stopped. Breastfeeding may reduce the risk of developing obesity, asthma and wheezing in children and diabetes, rheumatoid arthritis and hypertension in their mothers. For a number of other diseases, the strength of the evidence for a beneficial effect is limited. These are some conclusions of an update of a systematic literature review of epidemiological studies on the health effects of breastfeeding.

List of abbreviations

aHR	Adjusted hazard ratio
aOR	Adjusted odds ratio
aRR	Adjusted relative risk
BF	Breastfeeding
BFD	Breastfeeding duration
CC	Case control
CI	Confidence Interval
CH	Cohort
CS	Cross sectional
EBF	Exclusive breastfeeding
EBFD	Exclusive breastfeeding duration
FF	Formula feeding
HR	Hazard ratio
IQR	Interquartile range
MA	Meta-analysis
MBF	Mixed breastfeeding
Mdn	Median
NA	Not available
NR	Not reported
OR	Odds Ratio
PBF	Paeertial breastfeeding
pCH	Prospective cohort study
rCH	Retrospective cohort study
RCT	Randomized controlled trial
RIVM	National Institute for Public Health and the Environment
RR	Relative risk
SD	Standard deviation
SLR	Systematic literature review
SOR	Summary odds ratio
SRR	Summary relative risk
WHO	World Health Organization

1 Introduction

1.1 Background

WHO recommends exclusive breastfeeding in the first six months of life [1]. Based on a recent study, 39% of Dutch mothers comply with these WHO recommendations [2]. The Dutch government wants to have access to up-to-date and accurate information on the health effects of breastfeeding, which can be used for policy related to breastfeeding and health education.

In the past 10 years, the RIVM published two reports on the associations between breastfeeding and health outcomes for mother and child. In 2005, a literature review was performed on the health effects of breastfeeding compared to formula feeding [3]. Additionally, a model was created to quantify these health effects of breastfeeding for mother and infant for different theoretical policy measures on breastfeeding [3]. The report of 2007 [4] gave an update of the literature and quantified health effects of the policy targets and some specific interventions in terms of health gain. Secondly, the health care costs were evaluated for different interventions on breastfeeding.

Since 2007, new research on the health effects of breastfeeding might have led to new insights. Therefore, the ministry of Health, Welfare and Sport asked the RIVM to update the scientific evidence by a new systematic literature review. A considerable part of the work was subcontracted to Pallas (Rotterdam, The Netherlands). The findings of this review are outlined in this report, presenting the health effects of breastfeeding on mother and child.

1.2 Aim of this study

The aim of this study is to give an up-to-date overview of the peer-reviewed literature on health effects of breastfeeding for mother and child. The overview was used to re-evaluate the strength of evidence published in the 2007 report [4] of the possible health effects of breastfeeding on mother and child.

1.3 Outline of this report

In chapter 2, the methods of the review are described. In chapter 3, the results of the literature search and an updated overview of the strength of evidence for the health effects of breastfeeding are described. Finally, chapter 4 comprises a discussion and a general conclusion.

2 Methods

2.1 Literature search

In the reports of 2005 [3] and 2007 [4], an extensive literature search was performed, including studies published from 1980 till July 2006. For the current report, we searched for relevant systematic literature reviews (SLRs) and meta-analyses (MAs) until December 2014, and complemented these with additional primary studies not included in the SLRs and MAs. The database search and hand search for this report is described below.

2.1.1 Database search

A comprehensive literature search on the health effects of breastfeeding was performed in Medline on 11 June 2014. As in the previous reports, search terms were: 'breastfeeding', 'lactation' or 'human milk', combined with health outcomes like 'otitis media', 'asthma', or 'obesity'. The search was limited to articles published from 2006 onwards in English or Dutch, based on studies in human and based on mainly western study populations which were considered representative for the Dutch situation. An extended literature search was performed on 20 October 2014 and 9 December 2014 in order to find additional SLRs and MAs. The search strings are presented in APPENDIX A

2.1.2 Hand search

To complement the literature database search, a hand search for additional relevant articles was performed by:
- A quick scan in PubMed
- Google search

2.2 Selection procedure

Relevant references were selected using specific in- and exclusion criteria, based on the study subject, study design, study population and characteristics (Table 1). Articles that fulfilled the inclusion criteria were included in the evidence tables (see section 2.4). The selection was done by a three-step selection:

1. Screening of title and abstract: this step yielded the articles that were assessed in full text. The major topics of the articles were checked for relevance for the objectives by the title and abstract. Abstracts that did not contain information relevant to the research objectives were not selected for full text assessment. In case of doubt, an abstract was considered for full-text selection.
2. Screening of full article: in this step the full-text articles selected in step 1 were assessed. First, SLRs and MAs were assessed and selected, followed by primary study designs. For each outcome, only relevant primary articles published after the search date of included systematic literature reviews (SLR) or meta-analyses (MA) were included.
3. Screening during data-extraction phase: further scrutiny of the article during the data-extraction phase may have led to exclusion, when results of the study appeared to be not relevant.

Table 1: Inclusion and exclusion criteria

	Inclusion	**Exclusion**
Study subject	• Health effects of breastfeeding on mother and/or child	• Other subjects
Study designs	• SLRs or Mas • Primary studies for specific health outcomes [1]: - RCTs - Nonrandomized, prospective comparative studies or interventions - Prospective, longitudinal observational studies - Prospective, nested case-control studies - Retrospective, longitudinal observational studies - Retrospective case-control studies - Cross-sectional studies	• Animal studies, in vitro studies, expert opinions, editorials, letters to the editor • Case studies/case series • Narrative (non-systematic) reviews
Study characteristics	• Published between January 2006 and December 2014 • Published in Dutch or English	• Other
Population	• General population • Western population	• Other

[1] Only included when no SLRs or MAs are available, or when primary articles are found that are published after the search date of identified SLRs or MAs

2.3 Registration of the process

The entire process of selection and in- and exclusion of articles was recorded in an Endnote library by one of the researchers. In this way, a clear overview of all the selection steps was maintained at all phases.

2.4 Data extraction

2.4.1 Data extraction tables

For each selected article, the relevant information was extracted into a data extraction table. This included study characteristics, items relevant for the health outcomes included in the review and items relevant for assessment of the quality of included articles (see section 2.5) and the strength of evidence based on the review (see section 2.7).

Data extraction tables for all included articles are presented in a separate ANNEX, consisting of two parts: A. for health outcomes related to the child and B. for health outcomes related to the mother. In each part, first the tables for reviews are presented, followed by the tables for the primary articles. The tables are sorted alphabetically on author's name. Abbreviations specific to the article are presented under the evidence tables; other, more general abbreviations are presented in the list of abbreviations included in this report.

In case an article presented relevant figures or tables from which data cannot be incorporated in data extraction tables, the figure or table itself was copied, without any modifications, and placed under the data extraction tables.

In case more than one SLR or MA was available for one health outcome, overlap between articles included in these reviews was reported in a marginal note below the table.

2.5 Quality assessment

Primary articles were tested on the quality according to the same quality guidelines used in the previous reports [3] [4]:
1. Time of assessing breastfeeding data (ideally no longer than twelve months after birth).
2. Clear definition of (exclusive) breastfeeding and clear statements about the duration of (exclusive) breastfeeding.
3. Blind assessment of breastfeeding data (i.e. before health outcome assessment) and health outcome(s) (i.e. without knowledge on breastfeeding data).
4. Well-defined health outcome(s).
5. Adjustment for relevant confounders.

For SLRs and MAs, comparable criteria were used, combined with four additional criteria originating from the CoCanCPG checklist [5] and AMSTAR tool [6]:
1. Was time of assessing breastfeeding data reported?
2. Were a clear definition of (exclusive) breastfeeding and clear statements about the duration of (exclusive) breastfeeding reported?
3. Did the authors report if studies had blind assessment of breastfeeding data (i.e. before health outcome assessment) and health outcome(s) (i.e. without knowledge on breastfeeding data)?
4. Were health outcome(s) well-defined?
5. Did the author report whether adjustment for relevant confounders was done?
6. Was an appropriate and clear review question/design addressed?
7. Was a sufficiently rigorous comprehensive literature search performed?
8. Was scientific/methodological quality of included studies assessed and taken into account?
9. Were methods of combining data/statistical pooling/meta-analysis (where applicable) appropriate?

When an article did not meet one or more of the above mentioned quality criteria, a remark on the quality was made by the researcher in the evidence table (see section 2.5). No articles were excluded based on the quality criteria.

2.6 Summarising the evidence

For each health outcome, the results were summarised in summary tables. In these tables, a note of the quality of each included primary study was presented (see section 2.5) based on the main quality criteria according to *Tabel 2* below.

Table 2: Predefined quality criteria of primary studies

Predefined criteria	1. Recall BF	2. Definition of BF, exclusivity & duration	3. Blinding	4. Definition of health outcome	5. Adjustment for confounders
Satisfied	≤12 months	Clear definition breastfeeding exclusivity & duration	Outcome assessment after exposure assessment	Well defined	Adjusted for multiple confounders relevant for the health outcome
Partly satisfied	>1 year ≤5 years	Poorly defined (no clear information on either exclusivity or duraction)	Outcome and exposure assessment simultaneously	Poorly defined	Adjusted for only a few confounders or less relevant for the health outcome
Not satisfied	>5 years	No information at all	Outcome assessment before exposure assessment	Not defined	Not adjusted for any confounders

2.7 Strength of evidence

The strength of evidence is based on the WHO criteria for strength of evidence [7]. The strength of evidence was qualified as 'convincing', 'probable', 'possible', 'insufficient', 'conflicting', or 'no evidence', combined with the direction of the effect (reduced risk, increased risk, or absence of an association). The criteria used to make this distinction are presented in Table 3. In order to reach an agreement on the strength of evidence per health outcome, all team members from both Pallas and RIVM completed the assessment for the health outcomes individually. After that, two subsequent meetings were held to discuss any disagreements and to reach consensus.

For the qualification of the strength of evidence, the level of evidence as reported in the previous RIVM reports was re-assessed for each health outcome. Based on he included new evidence, it was considered if the level of evidence stayed the same, of should be up- or downgraded. For the assessment of the evidence base for each health outcome, the included articles in the newly found reviews and meta-analyses were considered individually if necessary (based on information presented in the review), and any overlap between reviews and meta-analyses was taken into account.

Table 3: Strength of evidence based on WHO-criteria for strength of evidence [7]

Classification of evidence	Criteria
Convincing*	Evidence based on epidemiological studies showing consistent associations between exposure and disease, with little or no evidence to the contrary. The available evidence is based on a substantial number of studies including prospective observational studies. The association should be biologically plausible.
Probable*	Evidence based on epidemiological studies showing fairly consistent associations between exposure and disease, but there are perceived shortcomings in the available evidence or some evidence to the contrary. Shortcomings in the evidence may be any of the following: insufficient duration of trials (or studies); insufficient trials (or studies) available; inadequate sample sizes; incomplete follow-up. The association should be biologically plausible.
Possible*	Evidence based mainly on findings from case-control and cross-sectional studies. Insufficient randomised controlled trials, observational studies or non-randomised controlled trials are available. More trials are required to support the tentative associations. The association should be biologically plausible.
Insufficient*	Evidence based on findings of a few studies which are suggestive, but are insufficient to establish an association between exposure and disease. More well-designed research is required to support the tentative associations.
Conflicting*	Several studies with sufficient power show opposite effects, so it is impossible to conclude whether breastfeeding has a positive, negative or no effect on the disease outcome.
No evidence	One or two studies with little power so no clear statement can be given about the strength of evidence.

* Each of these classifications must be combined with an interpretation of the direction of effect: reduced risk (+; protective effect), increased risk (-) or absence of an association (0)

2.8 Quality control of the review process

The following quality control measures were taken:
- Screening of title and abstract: The first 25% of titles and abstracts were screened in duplicate by two independent researchers. The results were compared and discussed before the remaining references were assessed by one researcher.
- Screening of full article: The first 10% of full text articles were appraised in duplicate by two independent researchers. The results of these researchers were compared and discussed. Any disagreements were adjudicated by a third researcher, if necessary.
- Data extraction: the evidence and summary tables were peer-reviewed.
- Assessment strength of evidence: peer-review of individual assessments by Pallas and RIVM project team members in two subsequent discussion meetings (see section 2.7).

3 Results

This chapter gives an overview of the included literature on health effects of breastfeeding compared to no breastfeeding, or longer compared to shorter duration of breastfeeding. First, a general overview of the search results is presented. Secondly, the health effects for the child are presented, followed by the health effects for the mother.

3.1 Search results

The original search in June 2014 and an extended search in October 2014 resulted in 614 hits (including 156 SLRs and MAs). The extended search in December 2014 for SLRs and MAs resulted in 118 hits. In total, this resulted in 716 unique hits.

In Figure 1 a schematic representation of the selection procedure is presented, including the number of articles retrieved from Medline and via hand search.
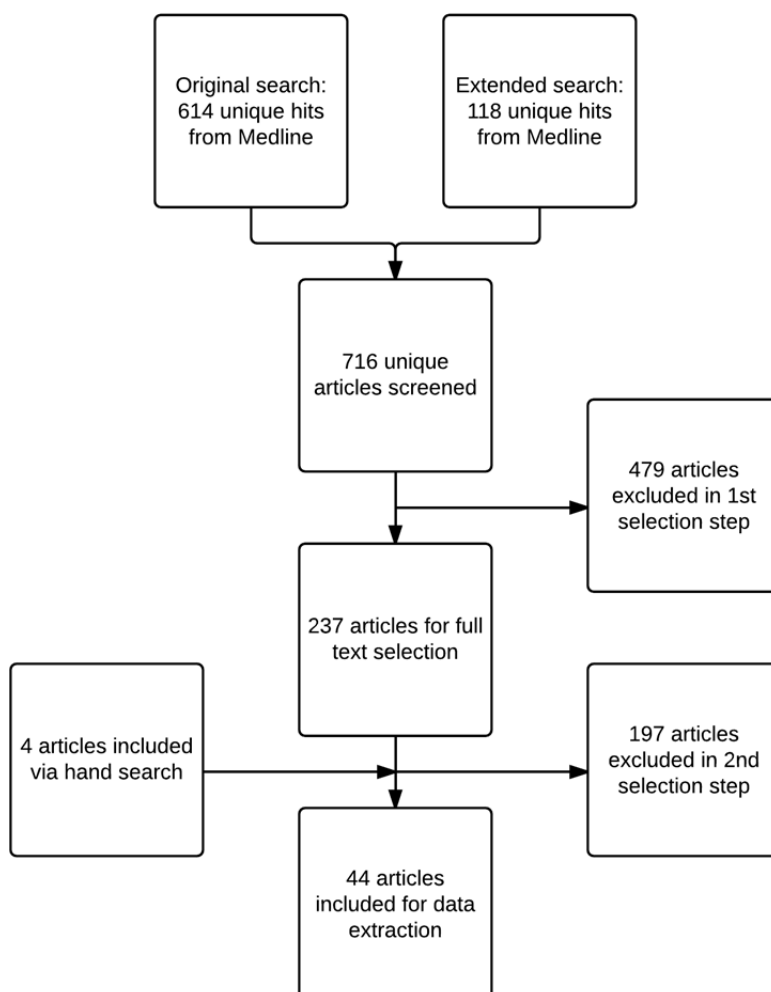

Figure 1: Selection procedure and number of included articles

From 716 unique hits from Medline, 237 articles were selected for full text selection. Main reasons for exclusion in this selection step were the following:
- Articles without relevant information
- Articles outside the geographical scope
- Non-relevant publication types, such as animal studies, case studies, narrative reviews

In total, 44 peer-reviewed articles published since the former report [4] were, together with the former report, included in the current review, of which four were retrieved from hand search. Reasons for exclusion of each article assessed in full text are presented in APPENDIX B. Details of the included articles are presented in evidence tables (ANNEXES A and B).

In total, 34 health outcomes related to the child are described in this report. Of these, ten health outcomes were not covered in the previous reports. The update is based on 12 SLRs/MAs and 10 primary articles covering 27 health outcomes. For seven health outcomes covered in the previous reports, no new evidence was found.

Furthermore, 23 health outcomes related to the mother are described in this report. Of these, 14 health outcomes were not covered in the previous reports. Four SLRs/MAs and 18 primary articles covered 20 health outcomes of the mother. For three of the nine health outcomes covered in the previous reports no new evidence was found. The up-to-date evidence is discussed in the following paragraphs.

3.2 Child

A summary of the health effects for children who are breastfed compared to those who were (partly) formula feed, or who received breastfeeding for a longer duration compared to a shorter duration, is given in Tabel 4. This table also shows the assessed strength of the evidence ('convincing', 'probable', 'possible', 'insufficient', 'conflicting' or 'no evidence'; see section 2.7) and the references of the studies on which this evidence was based. More detail about each study is given in ANNEX A (Data extraction tables) and APPENDIX C (Summary tables), for example, how breastfeeding was measured, how the duration of breastfeeding was taken into account, or remarks on the quality of the study. All identified potential effects of breastfeeding on health outcomes in children were found to be protective.

For 15 health outcomes the current strength of evidence was in line with the strength of evidence in the previous review reports [3][4]. In addition, several changes in the strength of evidence were noted for the remaining health outcomes.

For four health outcomes, the strength of evidence was slightly upgraded compared to the strength of evidence in the previous reports. On respiratory tract infections, two additional SLRs were found. With this, the strength of evidence was adapted from probable to convincing for a protective effect of breastfeeding. No new studies were found for CVD. However, after re-evaluation of the existing evidence, the evidence

Table 4: Short overview of the effects of breastfeeding compared to no breastfeeding, or longer compared to shorter duration of breastfeeding on the child

Health outcome	References of current report	Strength of evidence report 2007[4]	Current strength of evidence
Infectious and inflammatory diseases			
Gastrointestinal infections	8 9	Convincing +	Convincing + (in children <2 yrs)
Otitis media	8 9	Convincing +	Convincing + (in young children)
Respiratory tract infections	8 9	Probable +	Convincing + (in young children)
Inflammatory bowel disease	10	NA	Possible +
Crohn's disease	10	Possible +	Possible +
Ulcerative colitis	10	Possible +	Possible +
Helicobacter pylori infection	11	NA	Possible 0 (for high income countries)
Urinary tract infections	NA	Insufficient	Insufficient +
Haemophilus influenza	NA	Insufficient	Insufficient +
Fever	NA	Insufficient	Insufficient +
Celiac disease	9 12 13	Insufficient	Conflicting 0/+ Possible + for delayed onset after BF during gluten introduction
Pyloric stenosis and jaundice			
Pyloric stenosis	NA	Insufficient	Insufficient +
Jaundice	NA	Conflicting	Conflicting +/0
Asthma and atopic diseases			
Asthma	8 9 14-16	Probable +	Probable + (less strong with older age)
Wheezing	8 9 14 16	Probable +	Probable +
Atopic diseases	8 9	Possible +	Conflicting 0/+
Eczema	8 9 16	Probable +	Conflicting -/0/+
Weight, cardiovascular disease, diabetes and metabolic syndrome			
Obesity/BMI	8 9 15 17-19	Convincing +	Probable +*
Cardiovascular disease	NA	Insufficient	Probable 0
Diabetes mellitus type 1	9 20	Possible +	Possible +
Diabetes mellitus type 2	9	NA	Possible +
Metabolic syndrome	21	NA	Insufficient 0
Cancer			
Childhood cancers	9 22	Insufficient	Possible +
Leukaemia	9	Possible +	Possible +
Adult cancers	9 23	NA	Insufficient +
Lymphomas	NA	Insufficient	Insufficient +
Hodgkin lymphoma	9 24	NA	Possible 0
Intellectual and motor development and growth			
Growth in 1st year of life	8 9	Insufficient	Probable 0

Health outcome	References of current report	Strength of evidence report 2007[4]	Current strength of evidence
Intellectual & motor development	8 9 15 25	Probable +	Possible +
Other			
Sudden infant death syndrome	26	Possible +	Possible +
Neonatal weight loss	27	NA	Insufficient +
Dental caries	8	NA	Insufficient 0
Lung function	28	NA	Conflicting 0/+
Multiple sclerosis	29	NA	No evidence

+ = Reduced risk (Protective effect);
0 = No effect; - = Increased risk;
NA = Not available.
*= The current strength of evidence did not change due to inclusion of a study which is published after the search date of our review. [67]

was revised from insufficient evidence for an effect to probable evidence to no effect. The strength of evidence of breastfeeding on childhood cancers was adapted from insufficient to a possible protective effect based on two new studies. The evidence for the role of breastfeeding on growth appeared to be probable for the absence of an association, rather than insufficient after two additional SLRs were found.

For five health outcomes, the strength of evidence was slightly downgraded. The evidence of a protective effect of breastfeeding on atopic diseases was adapted from possible to conflicting based on the new evidence found in two SLRs. A similar change was observed for eczema: the earlier evidence for a probable beneficial effect was now conflicting. This change is mainly due to a large prospective cohort study [16]. In this study, family history of atopic disease was taken into account and no substantial influence of breastfeeding on the long-term risk of asthma and atopic diseases in children was found. Also, one large SLR describing earlier systematic reviews found conflicting results for the association between breastfeeding and eczema and atopic disease [9]. The evidence for a protective effect of breastfeeding on obesity described in the 2007 report was slightly downgraded from convincing to probable evidence. The main reason for this change is a large prospective cohort study [15] in which sibling comparisons showed absence of an association between breastfeeding and obesity. Four new studies have been found discussing the association between breastfeeding and intellectual and motor development. In combination with the literature of the previous RIVM reports, the strength of evidence was adapted from probable to possible for a protective effect of breastfeeding on intellectual and motor development. For celiac disease, the evidence changed from insufficient to conflicting based on three new studies. However, the literature shows possible evidence for delayed onset of celiac disease if gluten were introduced while still breastfeeding. Two outcomes described in the previous reports (i.e. hospitalization and blood pressure) were not included in this review. The mentioned outcomes were unclear or were considered as risk factor for a disease instead of a specific health outcome.
The health effects are described in sections 3.2.1 to 3.2.7.

3.2.1 Infectious and inflammatory diseases

Convincing evidence was found for a protective effect of breastfeeding on gastrointestinal infections, otitis media (ear infections), and respiratory infections in young children. This may be explained by the presence of antibodies in breast milk and the colostrum, mainly IgA which may protect through the enteromammary and bronchomammary pathways [30] [31].

There is possible evidence for a protective effect of breastfeeding on inflammatory bowel disease. For the most common inflammatory bowel diseases, Crohn's disease and ulcerative colitis, there is also possible evidence for a protective effect of breastfeeding. Possible underlying mechanism is via the immunological substances of breast milk [32].

Possible evidence was found suggesting absence of an association between breastfeeding and *Helicobacter pylori* infections in high income countries.

For urinary tract infections, Haemophilus influenza and fever in general, evidence on the role of breastfeeding is insufficient. Conflicting evidence is found for the effect of breastfeeding on celiac disease, although possible evidence of a protective effect is found for delayed onset after breastfeeding during gluten introduction.

3.2.2 Pyloric stenosis and jaundice

The evidence found for pyloric stenosis is insufficient, while for neonatal jaundice conflicting evidence is found.

3.2.3 Asthma and atopic diseases

There are several reasons to expect that breastfed children may show a reduced occurrence of asthma and atopic disease, mostly based on the beneficial presence of high content of antibodies in breastfeeding [30]. Indeed, from the literature probable evidence was found for a protective effect of breastfeeding on asthma and wheezing. For asthma, the effect appears to decrease with older age.

The evidence for an effect of breastfeeding on atopic diseases and eczema is conflicting.

3.2.4 Weight, cardiovascular disease, diabetes and metabolic syndrome

Breastfeeding might protect against obesity through several probable mechanisms, e.g. behavioural and hormonal mechanisms and differences in macronutrient intake [33]. Although confounding cannot be ruled out completely, probable evidence is found for a protective effect of breastfeeding on obesity. For cardiovascular disease, probable evidence for the absence of an association with breastfeeding is found. Possible evidence for a protective effect was found for diabetes mellitus type 1 and type 2. Whereas the current etiologic model suggest that diabetes mellitus type 1 is triggered by environmental factors in genetically susceptible children [34], obesity is seen as one of the main causes of diabetes mellitus type 2. The association between breastfeeding and diabetes mellitus type 2 may largely depend on the protective effect of breastfeeding on obesity in later life [35].

For metabolic syndrome, insufficient evidence was found.

3.2.5 Cancer

The literature suggested that the pattern and timing of non-specific infections may play a role in the aetiology of childhood leukaemia [36]. The antibodies in breast milk have a protective effect on infections. This could explain the possible evidence that was found for a protective effect of breastfeeding on leukaemia and childhood cancers in general.

Insufficient evidence is found for an association between breastfeeding and the development of lymphomas and adult cancers like breast cancer and testicle cancer. For Hodgkin lymphoma, possible evidence for the absence of an association with breastfeeding is found.

3.2.6 Intellectual and motor development and growth

Long-chain polyunsaturated fatty acids (LCPUFA) in breast milk, specifically docosahexaenoic acid (DHA), are important for infant brain development [37]. On the other hand, it is suggested that the presence of PCBs (=polychlorinated biphenyl), PCDDs (=polychloro-dibenzo-(p)-dioxins) and PCDFs (=polychloro-dibenzo-furans) in human milk hampers cognitive development and might altogether be harmful for children [38]. The positive effects of breastfeeding seem to compensate for possible negative effects of PCBs, PCDFs or PCDDs in breast milk as the literature shows possible evidence for a protective effect of breastfeeding on intellectual and motor development.

Probable evidence was identified for the absence of an association between breastfeeding and growth in infancy.

3.2.7 Other

The review identified possible evidence for a protective effect of breastfeeding on sudden infant death syndrome (SIDS). The composition of breast milk (e.g. immunoglobulins and cytokines) protects infants from infections during the vulnerable period for SIDS, when their production of antibodies is low. Infants who die from SIDS often have had a minor infection in the days preceding death [26]. Although these infections alone will not have caused death, they may have induced proinflammatory cytokines that may cause respiratory or cardiac dysfunction, fever, shock, hypoglycaemia, and arousal deficits [39] [40]. Even more, breastfed infants are more easily aroused from active sleep than formula-fed infants at 2 to 3 months of age, which is within the 2- to 4-month peak age during which SIDS occurs [41].

Insufficient evidence was found for neonatal weight loss and dental caries, conflicting evidence for lung function and no evidence for multiple sclerosis.

3.3 Mother

The health effects for the mother are summarized in Table 5, with their references and the strength of evidence. Additional information about the studies can be found in ANNEX B (Evidence tables) and APPENDIX D (Summary tables).

Table 5: Short overview of the effects of breastfeeding compared to no breastfeeding, or longer compared to shorter duration of breastfeeding on the mother

Health outcome	References of current report	Strength of evidence report 2007 [4]	Current strength of evidence
Cancer			
Ovarian cancer	[42]	Possible +	Possible +
Glioma	NA	Insufficient	Insufficient +
Cervical cancer	NA	Insufficient	Insufficient +
Premenopausal breast cancer	[43 44]	Possible +	Conflicting 0/+ Insufficient + for subjects with family history of BC
Postmenopausal breast cancer	[44]	Insufficient	Conflicting 0/+
Fractures, osteoporosis and rheumatoid arthritis			
Rheumatoid arthritis	NA	Convincing +	Probable + (for long total BFD)
Hip fractures	[45]	Insufficient	Possible +
Osteoporosis	[46]	NA	Insufficient +
Wrist fractures	[45]	NA	Insufficient 0
Weight, diabetes, metabolic syndrome and cardiovascular diseases			
Hypertension	[47-49]	NA	Probable +
Diabetes mellitus type 2	[50 51]	Possible +	Probable + (for longer durations)
Postpartum weight retention	[52 53]	NA	Possible +
Cardiovascular disease	[48]	NA	Insufficient 0
Metabolic syndrome	[47]	NA	Insufficient +
Obesity/BMI	[47 48 52 54-56]	NA	Insufficient 0 Possible + for long term BF
Myocardial infarction	[43]	NA	Insufficient 0
Weight gain	[55 56]	Insufficient	Insufficient +
Other health outcomes			
Gallbladder disease	[57]	NA	Insufficient +
Alzheimer's disease	[58]	NA	Insufficient +
Macular degeneration	[59]	NA	Insufficient +
Postpartum fatigue	[60]	NA	No evidence
Depressive symptoms	[61]	NA	No evidence
Benign breast disease-fibroadenoma	[62]	NA	No evidence

+ = Reduced risk (Protective effect);
0 = No effect;
NA = Not available.

In total, 23 health outcomes for the mother are described in this report, of which 14 had not been described in the previous review reports [3][4]. No increased risk of breastfeeding for mothers' health was found.

For ovarian cancer, glioma, cervical cancer and weight gain the current strength of evidence was in line with the strength of evidence in the previous reports. However, several changes in the strength of evidence were noted for the remaining health outcomes. For two health outcomes, the strength of evidence was slightly upgraded compared to the strength of evidence in the previous reports. The strength of evidence for diabetes mellitus type 2 was upgraded from possible to probable, as two new MAs found a protective effect of longer durations of lifetime breastfeeding. The strength of evidence for hip fractures was upgraded from insufficient to possible, due to a new prospective cohort study. For three health outcomes the strength of evidence was slightly downgraded. Even though no new evidence was found, the strength of evidence for rheumatoid arthritis was downgraded from convincing to probable for longer durations of breastfeeding after re-evaluation of the evidence included in the previous reports. The strength of evidence for postmenopausal and premenopausal breast cancer was downgraded from insufficient and possible, respectively, to conflicting (i.e. absence of an association versus a protective effect), because new evidence did not show a clear indication for a protective effect. However, for subjects with a family history of breast cancer breastfeeding may have a protective effect on premenopausal breast cancer, though the evidence is still insufficient.

The health effects are described in sections 3.3.1 to 3.3.5.

3.3.1   Cancer
Possible evidence was found for a protective effect of breastfeeding on ovarian cancer. Breastfeeding is investigated as a potential factor related to the development of ovarian cancer, because it causes gonadotropin suppression. This suppression leads to low oestrogen concentrations and anovulation resulting in a period of lactational amenorrhea [42][63].

The evidence for glioma and cervical cancer was insufficient, but suggestive for a protective effect of breastfeeding.

For both premenopausal and postmenopausal breast cancer the evidence was conflicting, as studies showed either absence of an association or a protective effect. However, for subjects with a family history of breast cancer there appears to be a protective effect of breastfeeding on premenopausal breast cancer, though the evidence for this effect was insufficient.

3.3.2   Fractures, osteoporosis and rheumatoid arthritis
Probable evidence was found for a protective effect of lifetime breastfeeding for a long duration on rheumatoid arthritis. The biologic mechanism for this is unclear [64].

For a protective effect of breastfeeding on hip fractures possible evidence was found. Pregnancy and lactation involve intense physiologic

changes that may be important for bone development. Both states cause pronounced changes in sex steroids and other hormones involved in calcium homeostasis. They also impose calcium losses that could reduce maternal bone mass. However, the latter appears to return to baseline levels after weaning. On the other hand, calcium absorption becomes more efficient during pregnancy, a change that tends to preserve maternal bone [4].

The evidence for osteoporosis and wrist fractures was insufficient, but appeared to be in the direction of a protective effect for osteoporosis and absence of an association for wrist fractures.

3.3.3 Weight, diabetes, metabolic syndrome and cardiovascular diseases

Probable evidence was found for a protective effect of breastfeeding on hypertension and diabetes mellitus type 2. However, the effect on diabetes mellitus type 2 appeared to be for longer breastfeeding durations only. A possible explanation for the effect on hypertension may be the activation of central neuroendocrine pathways, including oxytocin and prolactin by lactation. These hormones have been associated with blood pressure regulation and incident hypertension risk in animal and human studies [65][66]. Furthermore, human studies suggest that lactation affects insulin and glucose homeostasis, which could explain the association with diabetes mellitus type 2 [50].

For cardiovascular disease insufficient evidence was found, suggesting the absence of an association with breastfeeding.

Although possible evidence was found for a protective effect on postpartum weight retention, which could be explained by the use of energy of the mother for breastfeeding, the evidence for BMI/obesity was insufficient (but suggesting the absence of an association). Still, for longterm breastfeeding, possible evidence was found for a protective effect on obesity/BMI.

The evidence for weight gain, metabolic syndrome and myocardial infarction was also insufficient, but suggested a protective effect for weight gain and metabolic syndrome. Myocardial infarction did not seem to be associated with breastfeeding.

3.3.4 Other health outcomes

Insufficient evidence was found for gallbladder disease, Alzheimer's disease and macular degeneration, though breastfeeding seemed protective for these outcomes in the included studies.

No evidence was found for postpartum fatigue, depressive symptoms and benign breast disease (fibroadenoma).

4   Discussion

The purpose of this review report was to summarize the available evidence published since the 2007 RIVM report [4] on the association between breastfeeding and health effects for mother and child, and to re-evaluate the strength of evidence for these effects.
In total, 44 peer-reviewed articles were included. Health effects on the child were described in 22 articles (16 SLR/MA and 28 primary articles), which covered 27 health outcomes of the child and 20 health outcomes of the mother. This report also describes seven health outcomes of the child and three of the mother which have been covered in the previous reports, but for which no new evidence was found.

4.1   Main findings

4.1.1   *Health effects on the child*
In total, 34 health outcomes for the child are described in this report. In summary, convincing evidence was found for a protective effect of breastfeeding on gastrointestinal infections, respiratory tract infections and otitis media in early childhood. Probable evidence for a protective effect was found on obesity and on asthma and wheezing, with stronger effects in young children than in older children. Possible evidence was found for a protective effect on childhood cancers, inflammatory bowel disease, Crohn's disease, ulcerative colitis, diabetes mellitus type 1, diabetes mellitus type 2, sudden infant death syndrome and leukaemia. The strength of evidence was insufficient for adult cancers, neonatal weight loss, metabolic syndrome, urinary tract infections, haemophilus influenza, fever, lymphomas, dental caries, and pyloric stenosis. Probable evidence was found for the absence of an association between breastfeeding and growth in the first year of life and cardiovascular disease in later life. Furthermore, possible evidence for no effect was found for Hodgkin lymphoma and Helicobacter pylori infection. Conflicting evidence was found for atopic diseases, eczema, coeliac disease, lung function and jaundice. Finally, no evidence was found for multiple sclerosis.

Compared to the previous reports, ten health outcomes had not been described before. For 15 health outcomes the current strength of evidence was in line with the strength of evidence in the previous review reports [3][4]. In addition, several changes in the strength of evidence were noted for the remaining health outcomes. For example, the protective effect on obesity of the child is now less convincing, while it became more convincing for respiratory tract infections among children. For eczema the evidence is now conflicting.

4.1.2   *Health effects on the mother*
In total, 23 health outcomes for the mother are described in this report. In summary, no convincing evidence was found for an effect of breastfeeding on any of the investigated health outcomes in mothers. However, probable evidence for a protective effect was found for diabetes mellitus type 2, rheumatoid arthritis and hypertension. The review showed possible evidence for a protective effect of breastfeeding

on ovarian cancer, postpartum weight retention and hip fractures. The evidence for an effect of breastfeeding was insufficient for metabolic syndrome, osteoporosis, gallbladder disease, Alzheimer's disease, macular degeneration, obesity, myocardial infarction, wrist fractures, cardiovascular disease, weight gain, glioma and cervical cancer. Conflicting evidence was found for both postmenopausal and premenopausal breast cancer. Finally, no evidence was found for postpartum fatigue, depressive symptoms and benign breast disease (fibroadenoma).

Compared to the earlier studies [3,4], 14 health outcomes had not been described in the previous review reports. New evidence was found for a probable protective effect of breastfeeding on hypertension among mothers. Furthermore, the protective effect on rheumatic arthritis of the mother is now less convincing.

4.2 Strengths and limitations

4.2.1 Process of systematic review

A strength of the current review is the systematic approach to collect and extract the data, making the process transparent and the review of the literature rigorous and reliable. By applying clear and relevant inclusion criteria, relevant literature could be identified. The quality of the review process was assured by double selection of 25% of the articles by two independent researchers and a critical appraisal of the quality of the articles in duplicate for 10%. The evidence tables and summary tables were 100% peer-reviewed and checked for quality. Furthermore, the quality of included articles (e.g. recall of breastfeeding data and adjustment for confounding) was assessed using a standardized list of criteria and taken into account with the evaluation of the strength of the evidence. Due to the inclusion of reviews, it was not possible to use a presently common systematic assessment for the evaluation of the strength of the body of evidence, such as GRADE. However, by applying the same method that was used in the previous RIVM reports [3,4], we were able to compare the newly identified evidence with the evidence from the earlier RIVM reports.

4.2.2 Completeness of review

In order to keep the number of articles identified reasonable, search terms for relevant health outcomes were included in the search string rather than searching for all articles reporting on breastfeeding regardless of the outcome. Furthermore, the search was limited to articles published in Dutch and English. This may imply that some relevant articles or articles published in other languages were missed. However, as the focus of the review was on western countries it can be assumed that most data are published in English and no important articles were missed. Given the number of new publications each month on this topic, it is possible that studies published after the search date of our review are missed. Furthermore, except for terms for breastfeeding, all terms were only included as MeSH terms. Articles which have not been indexed in the MeSH database could therefore have been missed. A hand search was performed to overcome these limitations

The focus of the review was a search for SLRs and MAs. To be sure that most recent evidence was taken into account for the identified health outcomes, primary studies which were published after the search date of SLRs/MAs were included and added to the body of evidence. The completeness of our review was dependent on the quality of the inclusion criteria and the completeness of the the included SLR's and MA's. Theoretically, articles may have been missed. Another issue with a "review of reviews" is the overlap of the included primary articles between included SLRs/MAs. However, existing overlap was reported in the evidence and summary tables, and taken into account during the evaluation of the strength of the evidence.

4.2.3   *Quality of included articles*
Few results specific for the Dutch population were available. Therefore, the review focused on studies from western countries, assuming that recent evidence from these countries is also valid for the Dutch situation. However, the dietary habits of the mother may differ between countries or could have changed over time, which could affect the composition of breast milk. Also the ingredients of formula feeding may differ between countries.

The results of the included reviews could be affected by weaknesses inherent in the included articles. Often, the quality of included articles was not assessed by the authors of the SLR, or the quality of some of the articles was assessed as being poor. In addition, due to the retrospective nature of some of the included primary studies, results are subject to recall bias. Furthermore, the use of interviews and questionnaires could lead to misclassification of breastfeeding status. Definitions of exclusive breastfeeding can vary slightly between included articles and the methodology used to assess breastfeeding was not always clear. Even more importantly, adjustment for confounding varied between studies and some results were not adjusted. However, by checking and commenting on criteria of quality (both pre-specified and additional criteria based on information found in the articles) these aspects were taken into account with assessing the body of evidence, as stated above.

4.2.4   *Epidemiological studies*
Our study focused on the epidemiological literature on health effects of breastfeeding. It did not investigate specific substances in human milk, such as toxic substances which might have adverse health effects. In collaboration with the United Nations Environmental Programme the RIVM is currently monitoring the occurrence of 18 Persisten Organic Polluatants (POPs) in human milk in order assess the health risk associated with human milk consumption. However, as most epidemiological studies showed a beneficial effect of human milk, current consencus is that potential adverse effects due to toxic substances are outweighed by the healthy substances of human milk.

4.2.5   *Distinction between exclusive and mixed breastfeeding*
The WHO recommends exclusive breastfeeding in the first half year of life. Ideally, we would have made also a distinction in our reviews between exclusive and mixed breastfeeding and even whether the human milk is directly drunk from the breast or given to the child with a

bottle (expressed milk). Unfortunately, this was not possible with the current available data, but would be interesting to investigate.

4.3 Conclusion

Breastfeeding has a beneficial health effect on both the child and the mother compared to formula feeding. There is convincing evidence that breastfed infants for example, run a lower risk of contracting certain infectious diseases. The beneficial effect is maintained after breastfeeding is stopped. Breastfeeding may reduce the risk of developing obesity, asthma and wheezing in children and diabetes, rheumatoid arthritis and hypertension in their mothers. For a number of other diseases, the strength of the evidence for a beneficial effect is limited. These are some conclusions of an update of a systematic literature review of epidemiological studies on the health effects of breastfeeding. This updated information can be used for policy related to breastfeeding and health education.

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APPENDIX A: Search strings

Introduction

Original search		June 2014	103 SLR/MA	614
			458 other studies	
Additional search	Same as original search, but less exclusions (line 24)	October 2014	53 SLR/MA	
Additional search	Same as original search but even less exclusions	December 2014	118 SLR/MA	118

Original search and additional search October 2014.* *numbers in brackets are based on results in October 2014.*

Database: MEDLINE 1950 to present, MEDLINE In-Process & Other Non-Indexed Citations
Search Strategy:
----
1   exp *Breast Feeding/ae [Adverse Effects] (622)
2   exp *Breast Feeding/ or exp *Milk, Human/ or exp *Lactation/ (43071)
3   exp *"bacterial infections and mycoses"/ or exp *virus diseases/ or exp *parasitic diseases/ or exp *neoplasms/ or exp *musculoskeletal diseases/ or exp *digestive system diseases/ or exp *stomatognathic diseases/ or exp *respiratory tract diseases/ or exp *otorhinolaryngologic diseases/ or exp *nervous system diseases/ or exp *eye diseases/ or exp *male urogenital diseases/ or exp *"female urogenital diseases and pregnancy complications"/ or exp *cardiovascular diseases/ or exp *"hemic and lymphatic diseases"/ or exp *"congenital, hereditary, and neonatal diseases and abnormalities"/ or exp *"skin and connective tissue diseases"/ or exp *"nutritional and metabolic diseases"/ or exp *endocrine system diseases/ or exp *immune system diseases/ or exp *"disorders of environmental origin"/ or exp *animal diseases/ or exp *"pathological conditions, signs and symptoms"/ or exp *occupational diseases/ or exp *chemically-induced disorders/ or exp *"wounds and injuries"/ (10710219)
4   exp Health Promotion/ (57031)
5   exp Child Welfare/ (50631)
6   2 and 3 (10257)
7   1 or 6 (10359)
8   2 and (4 or 5) (1793)
9   exp africa/ or exp caribbean region/ or exp central america/ or exp "gulf of mexico"/ or exp latin america/ or exp south america/ or exp antarctic regions/ or exp arctic regions/ or exp asia/ or exp atlantic islands/ or exp borneo/ or exp indian ocean islands/ or exp indonesia/ or exp japan/ or exp macau/ or exp pacific islands/ or exp philippines/ or exp prince edward island/ or exp svalbard/ or exp taiwan/ or exp west indies/ or exp oceania/ (994770)
10   exp HIV/ or exp HIV Infections/ (275985)
11   exp *Nipples/ (2475)

12   exp Smoking/ (128395)
13   exp *"chemicals and drugs (non mesh)"/ (9862818)
14   exp Substance-Related Disorders/ (238808)
15   exp Practice Guideline/ (19951)
16   exp Practice Guidelines as Topic/ (84109)
17   (breastfe$ or (breast adj fe$) or lactat$).ti. (44540)
18   sn.fs. (546834)
19   ep.fs. (1256375)
20   pc.fs. (1068226)
21   (7 or 8) not 9 (10157)
22   limit 21 to humans (7818)
23   22 and 17 and (18 or 19 or 20) (1964)
24   23 not (10 or 11 or 12 or 13 or 14 or 15 or 16) (1403)
25   limit 24 to animals (52)
26   24 not 25 (1351)
27   limit 26 to (dutch or english) (1209)
28   limit 27 to yr="2006 -Current" (641)
29   remove duplicates from 28 (576)

30   limit 29 to "review articles" (96)
31   exp Meta-Analysis/ (53540)
32   29 and 31 (15)
33   30 or 32 (99)
34   review$.ti. (281487)
35   29 and 34 (31)
36   35 not 33 (4)
37   "Meta-Analysis as Topic"/ (14488)
38   29 and 37 (9)
39   33 or 36 or 38 (106)   (*June* **103 SLR/MA)**
40   29 not 39 (470)   (*June* **458 Other studies)**

42   23 (1964)
43   limit 42 to animals (82)
44   42 not 43 (1882)
45   limit 44 to (dutch or english) (1694)
46   limit 45 to yr="2006 -Current" (911)
47   remove duplicates from 46 (815)
48   47 not 29 (239)
49   limit 48 to "review articles" (51)
50   48 and (31 or 37) (4)
51   49 or 50 (**53**)   (*October* **53 SLR/MA***)

Extended search SLRs and MAs 9-12-2015

Database: MEDLINE 1950 to present
Search Strategy:
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1   exp *Breast Feeding/ae [Adverse Effects] (630)
2   exp *Breast Feeding/ or exp *Milk, Human/ or exp *Lactation/ (43314)
3   exp *"bacterial infections and mycoses"/ or exp *virus diseases/ or exp
*parasitic diseases/ or exp *neoplasms/ or exp *musculoskeletal diseases/ or
exp *digestive system diseases/ or exp *stomatognathic diseases/ or exp
*respiratory tract diseases/ or exp *otorhinolaryngologic diseases/ or exp
*nervous system diseases/ or exp *eye diseases/ or exp *male urogenital
diseases/ or exp *"female urogenital diseases and pregnancy complications"/ or
exp *cardiovascular diseases/ or exp *"hemic and lymphatic diseases"/ or exp
*"congenital, hereditary, and neonatal diseases and abnormalities"/ or exp
*"skin and connective tissue diseases"/ or exp *"nutritional and metabolic
diseases"/ or exp *endocrine system diseases/ or exp *immune system

diseases/ or exp *"disorders of environmental origin"/ or exp *animal diseases/ or exp *"pathological conditions, signs and symptoms"/ or exp *occupational diseases/ or exp *chemically-induced disorders/ or exp *"wounds and injuries"/ (10797008)
4   exp Health Promotion/ (57610)
5   exp Child Welfare/ (50899)
6   2 and 3 (10341)
7   1 or 6 (10447)
8   2 and (4 or 5) (1800)
9   exp africa/ or exp caribbean region/ or exp central america/ or exp "gulf of mexico"/ or exp latin america/ or exp south america/ or exp antarctic regions/ or exp arctic regions/ or exp asia/ or exp atlantic islands/ or exp borneo/ or exp indian ocean islands/ or exp indonesia/ or exp japan/ or exp macau/ or exp pacific islands/ or exp philippines/ or exp prince edward island/ or exp svalbard/ or exp taiwan/ or exp west indies/ or exp oceania/ (1004929)
10   exp HIV/ or exp HIV Infections/ (277782)
11   exp *Nipples/ (2767)
12   exp Smoking/ (129471)
13   exp *"chemicals and drugs (non mesh)"/ (9935215)
14   exp Substance-Related Disorders/ (240553)
15   exp Practice Guideline/ (20143)
16   exp Practice Guidelines as Topic/ (85192)
17   (breastfe$ or (breast adj fe$) or lactat$).ti. (42629)
18   sn.fs. (554865)
19   ep.fs. (1269724)
20   pc.fs. (1078310)
21   (7 or 8) not 9 (10237)
22   limit 21 to humans (7886)
23   22 and 17 and (18 or 19 or 20) (1977)
24   23 not (10 or 11 or 12 or 13 or 14 or 15 or 16) (1410)
25   limit 24 to animals (53)
26   24 not 25 (1357)
27   limit 26 to (dutch or english) (1215)
28   limit 27 to yr="2006 -Current" (647)
29   remove duplicates from 28 (580)
30   limit 29 to "review articles" (97)
31   exp Meta-Analysis/ (54959)
32   29 and 31 (16)
33   30 or 32 (100)
34   review$.ti. (254298)
35   29 and 34 (32)
36   35 not 33 (4)
37   "Meta-Analysis as Topic"/ (14638)
38   29 and 37 (9)
39   33 or 36 or 38 (107)
40   29 not 39 (473)
41   exp *Child Development/ (29800)
42   exp *Cognition/ (65669)
43   exp *Psychomotor Performance/ (45153)
44   exp Overweight/ (157290)
45   exp Maternal Welfare/ (6319)
46   exp Infant Welfare/ (2519)
47   3 or 41 or 42 or 43 or 44 or 45 or 46 (10917372)
48   2 and 47 (11199)
49   1 or 48 or 8 (12756)
50   49 not 9 (10797)
51   limit 50 to humans (8432)
52   51 and (breastfe$ or (breast adj fe$) or lactat$).ti,ab. (6376)
53   ph.fs. (3045333)
54   52 and (18 or 19 or 20 or 53) (3183)

55   54 not (10 or 11 or 13 or 14) (2248)
56   limit 55 to animals (106)
57   55 not 56 (2142)
58   limit 57 to (dutch or english) (1928)
59   limit 58 to yr="2005 -Current" (1116)
60   remove duplicates from 59 (1011)
61   limit 60 to "review articles" (190)
62   60 and (31 or 34 or 37) (76)
63   61 or 62 (202)
64   60 not 63 (809)
65   63 not 39 (95)
66   64 not 40 (336)
67   (1 or 2) and (exp *Health Promotion/ or exp *Child Welfare/ or exp
*Overweight/ or exp *Maternal Welfare/ or exp *Infant Welfare/) (1698)
68   67 not (10 or 11 or 13 or 14) (1548)
69   limit 68 to animals (39)
70   68 not 69 (1509)
71   70 not 9 (1220)
72   limit 71 to humans (1197)
73   limit 72 to yr="2005 -Current" (716)
74   limit 73 to "review articles" (98)
75   73 and (31 or 34 or 37) (39)
76   74 or 75 (108)
77   73 not 76 (608)
78   63 or 76 (248)
79   64 or 77 (1155)
80   78 not 39 (141)
81   79 not 40 (682)
82   remove duplicates from 80 (137)
83   remove duplicates from 81 (665)
84   39 (107)
85   limit 84 to yr="2014 -Current" (6)
86   40 (473)
87   limit 86 to yr="2014 -Current" (20)
88   82 or 85 (143)
89   83 or 87 (685)
90   limit 89 to yr="2006 -Current" (617)
91   88 (143)
92   limit 91 to yr="2006 -Current" **(118)**   *(December **118 SLR/MA**)*

APPENDIX B: Exclusion list

Reference	Reason for exclusion
Abrahams and Labbok, 2011	Narrative review: limited description of methodology included
Ahmed and Sands, 2010	Not relevant for review objective: effect of interventions on breastfeeding duration
Ahnfeldt-Mollerup et al., 2012	Not relevant for review objective: association between infections and continuation of breastfeeding
Akobeng and Heller, 2007	Outcome measure not relevant
Akobeng et al., 2006	Included in review by Hörnell, 2013
Alves et al., 2008	Non-western country (Brazil)
Amir et al., 2007	Outcome not relevant: mastitis
Andrieu et al., 2006	Only BRCA1 and BRCA2 mutation carriers were included
Anonymous, 2009	Non-pertinent publication type
Anonymous, 2010	Narrative review: no description of methodology included
Anonymous, 2013	Non-pertinent publication type
Anonymous, 2013	Non-pertinent publication type
Anonymous, 2014	Non-pertinent publication type
Arenz and Von Kries, 2009	Narrative review: no description of methodology included
Beyerlein and von Kries, 2011	Narrative review: no description of methodology included
Binns et al., 2013	Narrative review: no description of methodology included
Bjorksten et al., 2011	Included in review by Dogaru, 2014
Boskabadi et al., 2010	Not relevant for review objective
Bosnjak and Grguric, 2007	Article in Croatian
Bovbjerg et al., 2013	Non-pertinent publication type
Bramuzzo and Davanzo, 2010	Non-pertinent publication type: letter to the editor
Burdette and Whitaker, 2007	Not relevant for review objective (effect by race/ethnicity)
Burdette et al., 2006	Included in review by Moorcroft, 2011 which was included in Hörnell, 2013
Burgess et al., 2006	Included in review by Dogaru, 2014
Caplan et al., 2008	Due to low number of EBF children (7/175) only comparisons of EFF with children breasted part of the time were made
Chang et al., 2011	Taiwanese population
Chantry et al., 2006	Included in review by Dogaru, 2014
Chapman, 2011	Non-pertinent publication type
Chapman, 2013	Non-pertinent publication type
Chertok, 2007	Narrative review: no description of methodology included
Chmielewska et al., 2013	Narrative review: no description of methodology included
Cohen and Celedon, 2011	Non-pertinent publication type
Colebatch and	Narrative review: no description of methodology included

Reference	Reason for exclusion
Edwards, 2011	
Crepinsek et al., 2010	Not relevant for review objective: effect of BF trials (i.e. BF education and specialist BF advice)
Crume et al., 2012	Results presented by offspring diabetic pregnancies vs offspring non-diabetic pregnancies
Danforth et al., 2007	Included in review by Luan, 2013
de Jonge et al., 2010	Not relevant for review objective: only risk factors of cardiovascular disease (left cardiac structures and blood pressure)
De Kroon et al., 2011	Included in review by Hörnell, 2013
Delgado and Matijasevich, 2013	Not relevant for review objective: review based on data from non-western countries
Dieterich et al., 2013	Narrative review: no description of methodology included
do Carmo Franca-Botelho et al., 2012	Narrative review, no description of methodology included
Dogaru et al., 2012	Included in review by Waidyatillake, 2013
Dorea, 2009	Non-pertinent publication type
Dowling, 2009	Non-pertinent publication type
Duijts et al., 2010	Included in review by Kramer, 2012
Duncan and Sears, 2008	Narrative review, no description of methodology included
Farrukh and Mayberry, 2008	Narrative review; no description of methodology included
Fewtrell, 2011	Narrative review; no description of methodology included
Fewtrell, 2011	Narrative review: no description of methodology included
Fisk et al., 2011	Included in review by Hörnell, 2013
Fleischer et al., 2013	Narrative review: no description of methodology included
Flohr et al., 2011	Published before search date of Hörnell, 2013
Flores-Quijano et al., 2008	Study in Mexico
Fonseca et al., 2010	Included in review by Dogaru, 2014
Fredriksson et al., 2007	Included in review by Dogaru, 2014
Gahagan, 2007	Non-pertinent publication type
Galson, 2008	Non-pertinent publication type
Giwercman et al., 2010	Included in review by Hörnell, 2013
Goelz and Hamprecht, 2008	Narrative review: no description of methodology included
Goldfield et al., 2006	Not relevant for review objective: association between breastfeeding and weight change in a family-based obesity treatment program
Gouveri et al., 2011	Narrative review: limited description of methodology included
Grainger, 2006	Non-pertinent publication type
Gubbels et al., 2011	Included in review by Hörnell, 2013
Guilbert and Wright, 2012	Non-pertinent publication type
Guilbert et al., 2007	Included in review by Waidyatillake, 2013
Gunderson et al., 2007	Not relevant for review objective

Reference	Reason for exclusion
Gunderson, 2008	Narrative review: no description of methodology included
Gunderson, 2009	Non-pertinent publication type
Gunnarsdottir et al., 2010	Published before search date of Hörnell, 2013
Heine and Tang, 2008	Narrative review: no description of methodology included
Hogendorf, 2011	Narrative review, no description of methodology included
Hunsberger and Consortium, 2014	Narrative review: no description of methodology included
Iacovou et al., 2012	Not relevant for review objective: relationship between maternal diet and symptoms of infantile colic in breastfed infants
Iorio et al., 2009	Non-pertinent publication type
Ip et al., 2007	Included in review by Hörnell, 2013
Ip et al., 2009	Summary of Ip, 2007
Jordan et al., 2010	Included in review by Luan, 2013
Jordan et al., 2012	Included in review by Luan, 2013
Juliusson et al., 2011	Published before search date of Hörnell, 2013
Kasonka et al., 2009	Narrative review: no description of methodology included
Khan et al., 2009	Not relevant for review objective: only health marker reported (microvascular function), not disease
Kneepkens and Brand, 2010	Narrative review: no description of methodology included
Kobayashi et al., 2012	Narrative review: no description of methodology included
Koletzko et al., 2009	Narrative review: no description of methodology included
Koletzko, 2006	Narrative review: no description of methodology included
Kramer et al., 2007	Published before search date of Hörnell/Dogaru/Yang
Kramer et al., 2007	Outcome not relevant: study compared intervention (sign. longer BF duration) vs control-group, not BF or BF duration
Kramer et al., 2009	Summary of previously published article
Kramer, 2010	Non-pertinent publication type
Kramer, 2011	Narrative review; no description of methodology included
Kuhn and Aldrovandi, 2010	Narrative review: no description of methodology included
Kusuma et al., 2009	Study population not relevant: late preterm new-borns
Lanari et al., 2012	Narrative review: no description of methodology included
Langan and Fewtrell, 2011	Non-pertinent publication type
Lawrence, 2009	Non-pertinent publication type
Le Doare and Kampmann, 2014	Narrative review: no description of methodology included
Leon and Ronalds, 2009	Narrative review: no description of methodology included
Levy et al., 2009	Study population not relevant: preterm infants
Li et al., 2008	Published before search date of Hörnell, 2013
Libster et al., 2009	Non-healthy population (Acute Respiratory Infection)
Liu et al., 2010	Included in review by Aune, 2014
Loof-Johanson et al., 2011	Not relevant for review objective: only prognostic markers of breast cancer

Reference	Reason for exclusion
Mai et al., 2007	Included in review by Dogaru, 2014
Malcova et al., 2006	Included in review by Cardwell, 2012
Martens, 2012	Articles included in this review are also included in the review by Kramer, 2012. Kramer, 2012 is included as it includes more articles.
Martin et al., 2009	Narrative review: no description of methodology included
Matheson et al., 2007	Included in review by Dogaru, 2014
Matheson et al., 2012	Narrative review: no description of methodology included
Mayer-Davis et al., 2008	Published before search date of Hörnell, 2013
McClure et al., 2012	Not relevant for review objective: only continuous rates of BMI, no ORs
McCrory and Layte, 2012	Included in review by Lefebvre, 2014
Metzger and McDade, 2010	Included in review by Lefebvre, 2014
Michaelsen et al., 2009	Narrative review: no description of methodology included
Mikhailov and Furner, 2009	Narrative review: no description of methodology included
Misak, 2011	Narrative review: no description of methodology included
Monasta et al., 2010	Included in review by Hörnell, 2013
Morris, 2008	Non-pertinent publication type
Mortensen and Tawia, 2013	Narrative review: no description of methodology included
Narbutyte et al., 2013	Not relevant for review objective: focus on mechanism of BF and FF and the impact on the growth of e.g. jaws or dental arches
Nejat et al., 2008	Diseased population (children with hydrocephalus)
Nishimura et al., 2009	Study in Japan
Nobili et al., 2009	Non-healthy study population
Oddy, 2009	Non-pertinent publication type
Oddy, 2009	Narrative review: limited description of methodology included
Ogg et al., 2011	Narrative review; no description of methodology included
Ong and Forouhi, 2007	Author perspective
Ortega-Garcia et al., 2008	Published before search date of Hörnell, 2013
Ostbye et al., 2010	Not relevant for review objective: difference in weight between 1st and 2nd pregnancy
O'Tierney et al., 2009	Published before search date of Hörnell, 2013
Owen et al., 2006	Included in review by Ip, 2007 which is included in review by Hörnell, 2013
Owen et al., 2011	Narrative review: no description of methodology included
Panagiotakos et al., 2008	Published before search date of Hörnell, 2013
Paricio Talayero et al., 2006	Published before search date of Hörnell, 2013. Focus on hospitalizations
Parikh et al., 2009	Not relevant for review objective: continuous data of BMI,

Reference	Reason for exclusion
	no ORs
Pearce et al., 2013	Not relevant for review objective: timing of the introduction of complementary feeding
Pelleboer et al., 2009	Not relevant for review objective: only incidence rate of dehydration among breastfed infants reported
Plenge-Bonig et al., 2010	Both cases and controls have gastroenteritis, no clear definition of breastfeeding reported
Pohlabeln et al., 2010	Published before search date of Hörnell, 2013
Prameela and Vijaya, 2012	Narrative review: no description of methodology included
Prameela, 2011	Narrative review: no description of methodology included
Preer et al., 2012	Not relevant for review objective: in-hospital weight loss in exclusively breastfed infants delivered by caesarean birth
Pritham, 2013	Narrative review: no description of methodology included
Procter and Holcomb, 2008	Only low-income children were included in the study
Quigley et al., 2006	Included in review by Ip, 2007 which is included in Hörnell, 2013
Quigley et al., 2007	Published before search date of Hörnell, 2013
Radtke, 2011	Not relevant for the review objective: late preterm infants
Redondo et al., 2012	Case-case analysis (only different types of breast cancer compared)
Risch, 2012	Narrative review: no description of methodology included
Rudnicka et al., 2007	Included in review by Owen, 2008 which is included in Hörnell, 2013
Rudnicka et al., 2008	Old data in combination with late exposure assessment
Ryan, 2007	Narrative review: no description of methodology included
Rzehak et al., 2009	Included in review by Hörnell, 2013
Saddlemire et al., 2006	Included in RIVM, 2007 report
Samano et al., 2013	Study in Mexico
Sariachvili et al., 2007	Published after search date of Hörnell, 2013
Savilahti, 2008	Narrative review: no description of methodology included
Savino et al., 2009	Narrative review: no description of methodology included
Schack-Nielsen and Michaelsen, 2006	Narrative review: no description of methodology included
Schack-Nielsen et al., 2010	Included in review by Moorcroft, 2011 which is included in Hörnell, 2013
Scholtens et al., 2008	Included in review by Hörnell, 2013
Scholtens et al., 2009	Included in review by Dogaru, 2014
Schwarz et al., 2010	Not relevant for review objective: only measures of subclinical cardiovascular disease as outcome measure
Schwarz, 2013	Narrative review: no description of methodology included
Shields et al., 2010	Published before search date of Hörnell, 2013
Silvers et al., 2007	Non-pertinent publication type
Singhal and Lanigan, 2007	Narrative review; no description of methodology included
Singhal, 2007	Narrative review: no description of methodology included

Reference	Reason for exclusion
Snijders et al., 2007	Non-pertinent publication type
Soldi et al., 2011	Narrative review: no description of methodology included
Soldi et al., 2012	Narrative review: no description of methodology included
Sonnenschein-van der Voort and Duijts, 2013	Non-pertinent publication type
Sonnenschein-van der Voort et al., 2012	Published before search date of Dogaru, 2014
Soto-Ramirez et al., 2012	Included in review by Waidyatillake, 2013
Speller and Brodribb, 2012	Narrative review: no description of methodology included
Stendell-Hollis et al., 2013	Too specific study population: women who were posthysterectomy (observational study) and women received hormone therapy (trial)
Taveras et al., 2006	Published before search date of Hörnell, 2013
Tawia and McGuire, 2014	Narrative review: no description of methodology included
Thomaz et al., 2012	Study in Brazil
Titus-Ernstoff et al., 2010	Included in review by Luan, 2013
Toma and Rea, 2008	Article in Portuguese
Trabulsi and Mennella, 2012	Narrative review: no description of methodology included
Turck, 2007	Narrative review: no description of methodology included
Twells and Newhook, 2010	Published before search date of Hörnell, 2013
van Rossem et al., 2011	Included in review by Hörnell, 2013
Vennemann et al., 2009	Included in review by Hauck, 2011
Viner et al., 2008	Published before search date of Hörnell, 2013
Vogazianos et al., 2007	Published before search date of Hörnell, 2013 and Kramer, 2012
Vukusic and Confavreux, 2013	Narrative review: no description of methodology included
West et al., 2010	Narrative review: no description of methodology included
Weyermann et al., 2006	Included in review by Lefebvre, 2014
Wright et al., 2006	Published before search date of Hörnell, 2013
Wright et al., 2011	Primary article (found in extended search for SLRs and Mas)
Wu and Chen, 2009	Narrative review: no description of methodology included
Xu et al., 2009	Included in review by Dogaru, 2014
Yang et al., 2009	Included in review by Hörnell, 2013
Zeiger and Friedman, 2006	Narrative review: no description of methodology included
Ziegler, 2006	Narrative review: no description of methodology included

APPENDIX C: Summary tables – Health effects on the child

Table C-1: Effect of breastfeeding on obesity

Health outcome	Author, year	Design	Study population	Age group	Type of BF	Results	Remarks
Obesity	Lefebvre, 2014	SLR	-Studies: n=21: 8 pCH 13 other -Subjects: n=107,177	Enrolment: 0-19 yrs (25-42 yrs in one study) Outcome: childhood-19 yrs (25-42 yrs in one study)	BF BFD	-10/21 studies: no significant effect -11/21 studies: significant protective Effect. See below. Protective effect on childhood obesity provided by BF is dependent on duration (n=9); protective effect found for: • BFD $_{\geq 4\ mo.\ vs\ <4\ mo.}$ (n=4) • BFD $_{\geq 6\ mo.\ vs\ <3\ mo/\ /\ NS}$ (n=2) • BFD $_{1-3\ mo.}$ (n=1) • BFD $_{9\ mo.\ vs.\ <3\ mo.}$ (n=1; effect in girls only) • BFD $_{\geq 24\ mo.\ vs.\ 12-24\ mo.}$ and BFD $_{12-24\ mo.\ vs.\ <12\ mo.}$ (n=1)* (no ORs/RRs reported) Author conclusion: while it is possible that there are protective benefits of BF on childhood obesity, it is difficult to prove because of confounding maternal, child, cultural, genetic and environmental variables.	-Jan 2005-March 2012 -2/21 studies were included in the RIVM report (2007). 3/21 studies were included in Hörnell (2014). -13/21 studies were from western countries (1 NR). -Each of the included studies controlled for some confounding variables; 3 studies adjusted for ≤5 confounders: none of the studies controlled for all confounders considered relevant by the authors *Note: 24 mo. of BF not relevant for western countries (study from Iran) Quality criteria Partly fulfilled: 1, 3, 4, 5 Not fulfilled: 2
Obesity	Hörnell, 2013	SLR	-Studies: n=14: 1 SLR 13 pCH -Subjects: n=48,527 (subjects of SLR not included)	Enrolment: NR Outcome: NR	EBF BFD	2/2 SLRs found a lower risk of overweight/obesity with longer duration of EBF. 1/1 CH study found no consistent association between BFD/EBF and overweight/obesity. 1/1 CH study found BMI triceps skinfold thickness and hip circumferences at 6.5 y were higher among EBF for 6 mo. compared to EBF for 3 mo. 1/1 SLR found that BF may be a protective factor against overweight and obesity. 8/9 CH studies show lower risk of overweight/obesity with longer BFD. 1/9 CH study found no significant association between BF intervention and growth indices. Author conclusion: - Probable evidence that EBF >4 mo. associated with slower weight gain during later infancy compared with EBF<4 mo. - Convincing evidence that longer duration of EBF or any BF is associated with a protective effect against overweight and obesity in childhood and adolescence. - Limited-suggestive evidence that BF is associated with lower risk of overweight/obesity in adulthood.	- January 2000-June 2011 - 1/14 studies was included in the RIVM report (2007). 3/14 studies were included in Lefebvre (2014). 3/14 studies were included in Kramer (2012). - All prospective CH were from western regions. Of the SLR, 5 reviews include some from developing countries and 5 more include studies from China and Japan. - All studies were graded A or B (out of A-C) Quality criteria Partly fulfilled: 1, 2, 3, 4, 5 Not fulfilled: -

Health outcome	Author, year	Design	Study population	Age group	Type of BF	Results			Remarks
Obesity	Colen, 2014	pCH	USA Full sample: n=8,237 Sibling sample: n=7,319 Discordant sibling sample: n=1,773[1]	Enrolment: 4-14 yrs Outcome: 4-14 yrs	BF vs. FF BFD in weeks	Full sample **β (SE)= -0.342 (0.066) P<0.001** **β (SE)= -0.007 (0.002) P<0.01**	Sibling sample **β (SE)= -0.369 (0.074) P<0.001** **β (SE)= -0.006 (0.002) P<0.05**	Discordant sibling sample β (SE)= -0.173 (0.164) NS β (SE)= 0.001 (0.004) NS	Adjustment for age, sex, race, marital status, region, insurance coverage, family income, mother's education, and mother's employment. Controls measured at the time of birth include: preterm birth, birth order, mother's age, family income, mother's education, mother's employment, smoked during pregnancy, drank during pregnancy, and timely prenatal care (all models) Within-family estimates (discordant sibling sample): also for within family fixed effects. Quality criteria Partly fulfilled: 1, 2 Not fulfilled: -
Obesity	RIVM, 2007	SLR	-Studies: n=20 (21 publications): 1 SLR 13 CH* 6 CS -Subjects: n=458,255 *unclear whether pCH or rCH	Enrolment: NR Outcome: NR. Included age groups 1-53 yrs	BF	Convincing evidence for a small protective effect of BF on obesity			-1980-September 2004, September 2004-February 2005 and February 2005 until July 2006 -All but one study was from western countries (Czech Republic). Countries from one review NR. -Health outcomes: Obesity, elevated weight gain, BMI
BMI	Kramer, 2012	SLR+ pooled analysis	-Studies: n=1: 1 pCH -Subjects: n=2,951	Enrolment: NR Outcome: 6.5 yrs	EBF 6 mo. vs. EBF 3-4 mo. with MBF thereafter	MD=**0.20 (0.02-0.38)** Author conclusion: authors do not provide conclusions specific for the health outcomes in western countries.			-1966-2011 -3/9 publications of the study were included in the RIVM report (2007). 3/9 publications of the study were included in Hörnell (2013). -All studies were from western countries. -MD: Mean difference -Results are unadjusted. Quality criteria Partly fulfilled: - Not fulfilled: 1, 3, 4, 5

[1] Full sample: all respondents who were interviewed at least once between 1986 and 2010; Sibling sample: cohort children for which a sibling was also assessed; Discordant sibling sample: siblings who were differently fed in infancy (comparison within rather than across families).

Health outcome	Author, year	Design	Study population	Age group	Type of BF	Results			Remarks
BMI	Colen, 2014	pCH	USA Full sample: n=8,237 Sibling sample: n=7,319 Discordant sibling sample: n=1,773	Enrolment: 4-14 yrs Outcome: 4-14 yrs	BF vs. FF BFD in weeks	Full sample **β (SE)= -0.449 (0.094) P<0.001** **β (SE)= -0.007 (0.002) P<0.01**	Sibling sample **β (SE)= -0.413 (0.101) P<0.001** **β (SE)= -0.007 (0.003) P<0.01**	Discordant sibling sample β (SE)= -0.141 (0.188) NS β (SE)= 0.005 (0.003) NS	Adjustment for age, sex, race, marital status, region, insurance coverage, family income, mother's education, and mother's employment. Controls measured at the time of birth include: preterm birth, birth order, mother's age, family income, mother's education, mother's employment, smoked during pregnancy, drank during pregnancy, and timely prenatal care (all models) Within-family estimates (discordant sibling sample): also for within family fixed effects. Quality criteria Partly fulfilled: 1, 2 Not fulfilled: -
BMI	Peneau, 2014	pCH	France n=73	Enrolment: New-borns Outcome: 20 yrs	BF vs no BF	*Results per adjustment* 1. Sex: β = -0.029 (-1.73-1.67) 2. Model 1 + mother's BMI + father's profession: β = -0.413 (-2.12-1.29) 3. Model 2 + energy 4. Model 3 + proteins 5. Model 3 + lipids 6. Model 3 + carbs	*Adjustment for nutritional intake at age 10 mo.* β = -0.431 (-2.11-1.25) β = -0.228 (-1.95-1.49) β = -0.606 (-2.26-1.05) β = -0.618(-2.32-1.09)	*Adjustment for nutritional intake at age 2 yrs* β = -0.772 (-2.39-0.85) β = -0.771 (-2.36-0.92) β = -0.891(-2.52-0.74) β = -0.865(-2.51-0.78)	- Adjustments presented in results column Quality criteria Partly fulfilled: 4 Not fulfilled: -

Health outcome	Author, year	Design	Study population	Age group	Type of BF	Results				Remarks
BMI	Jiang, 2013	rCH	USA n=3,271	Enrolment: 4 mo.-13 yrs Outcome: 5-18 yrs	BFD in months	Unadjusted **β (SE) = -0.120 (0.030)** **P<0.0001**	Linear regression adjusted β (SE) = 0.004 (0.036) P=0.92	GPS adjusted linear regression β(SE) = -0.0004 (0.041) P=0.99	GPS adjusted GAM P=0.99	- GPS: Generalized propensity score - GAM: Generalized additive model Adjustment for: - Child's age at the 1997 survey, race and ethnicity, child's gender, number of siblings, first born to the mother, preterm, born small for gestational age, mother-rated child's health at birth as compared to other babies, HOME scale (measure of cognitive stimulation and emotional support that parents provide to their children) - Maternal characteristics: IQ, education, age at time of child's birth, enrolment in WIC program of Medicaid during pregnancy, employment, marital status, head of household (yes/no), household income. Quality criteria Partly fulfilled: 1 Not fulfilled: 2
BMI	RIVM, 2007	Not available								

Table C-2: Effect of breastfeeding on asthma and wheezing

Health outcome	Author, year	Design	Study population	Age group	Type of BF	Results			Remarks
Asthma	Dogaru, 2014	SLR+ MA	-Studies: n=75: 39 CH* 36 CS&CC -Subjects**: Median (range): 2,144 (50-168,283); Mean: 7,111 *unclear whether pCH or rCH studies **Median and mean for all 117 studies	Enrolment: perinatal to ≥7 yrs Outcome: 0 to ≥7 yrs	EBF ever vs. never EBF <3 vs. ≥3 mo. EBF <6 vs. ≥6 mo. BF ever vs. never BF <3 vs. ≥3 mo. BF <6 vs. ≥6 mo. BF more vs. less BF more vs. less BF more vs. less BF more vs. less BF more vs. less	<u>0-2 yrs</u> OR=N/A **OR=0.62 (0.51-0.74)** **OR=0.69 (0.58-0.81)** **OR=0.65 (0.51-0.82)** **OR=0.59 (0.50-0.70)** **OR=0.61 (0.50-0.74)** **OR=0.63 (0.57-0.69)** <u>All ages</u> *Western countries* **OR=0.80 (0.74-0.85)** *Cohort studies* **OR=0.82 (0.76-0.89)** *High quality studies* OR=0.81 (0.61-1.06) *Studies after 1990* **OR=0.73 (0.67-0.79)**	<u>3-6 yrs</u> OR=N/A OR=0.81 (0.59-1.11) OR=0.51 (0.24-1.08) **OR=0.79 (0.68-0.91)** **OR=0.84 (0.76-0.92)** **OR=0.57 (0.38-0.86)** **OR=0.77 (0.67-0.87)** *Non-western* **OR=0.72 (0.52-0.99)** *Non cohorts* **OR=0.75 (0.67-0.83)** *Medium quality* **OR=0.76 (0.68-0.96)** *Studies before 1990* OR=0.92 (0.84-1.01)	<u>≥7 yrs</u> OR=N/A OR=0.73 (0.39-1.36) OR=*dropped* **OR=0.79 (0.68-0.91)** **OR=0.84 (0.76-0.92)** **OR=0.57 (0.38-0.86)** **OR=0.83 (0.77-0.89)** *Low quality* **OR=0.80 (0.74-0.87)** **Author conclusion:** a positive association of BF with reduced asthma is supported by the combined evidence of existing studies.	-1983- 2012 -Dogaru et al. included 117 studies in the SLR and 113 in the MA, for asthma ever, asthma recent, and wheezing. -11/113 studies were included in the RIVM (2007). 1/113 studies was included in Kramer (2012). 1/113 studies was included in both Hörnell (2013) and Waidyatillake (2013). 1/113 studies was included in Waidyatillake (2013). 6/113 studies were included in Hörnell (2013). -Western(n=89/117): Europe, North- and South-America, Australia, New Zealand -40/117 studies did not adjust for confounders, the others included up to 24 confounders in their analyses - Quality score was based on 1) whether a study reported at least 3 of 7 important potential confounders and 2) whether it satisfied at least 4 of 7 of the selected quality standards suggested by Kramer et al., 1988 -Results for "asthma ever"; results for "recent asthma" are comparable. -More vs. less BF: priority to highest cut-offs in article, exclusive breastfeeding and school-aged subjects -N/A: the groups "EBFD, ever vs. never" were not considered. If reported in a study, these results were relocated to "any BFD, ever vs. never". <u>Quality criteria</u> Partly fulfilled: 1, 2, 5 Not fulfilled: -
Asthma	Hörnell, 2013	SLR	-Studies: n=12: 2 SLRs 10 pCH -Subjects: n=74,738	Enrolment: NR Outcome: NR	BF	1/2 SLR found that BF (>3 mo.) was associated with reduced risk of asthma compared to no BF. 1/2 SLR found no association between BF and risk of asthma. 2/10 CH studies found no association between BF and later risk of allergic disease. 1/10 CH study found a u-shaped association between BF and wheeze, asthma or lung function. 6/10 CH studies found association between BF and reduced risk of asthmatic symptoms. 1/10 CH study found no reduction in risk of asthma when comparing BF intervention with control areas.			- January 2000-June 2011 - 1/12 studies was included in RIVM (2007). 2/12 studies were included in Kramer (2012). 1/12 studies was included in both Dogaru (201X) and Waidyatillake (2013). 6/12 studies were included in Dogaru (2014). - Included studies were from western countries. 1 SLR included 11 studies from developing countries out of 22 studies. - All studies were graded A or B (out of A-C) - Only combined results for asthma and wheezing were presented in this SLR.

Health outcome	Author, year	Design	Study population	Age group	Type of BF	Results			Remarks
						Author conclusion: limited evidence and no conclusions can be drawn for the association between BF and asthma/wheezing. *Complementary search (n=3):* did not change the conclusion as they had differing results.			Quality criteria Partly fulfilled: 1, 2, 3, 4, 5 Not fulfilled: -
Asthma	Kramer, 2012	SLR+ Pooled analysis	-Studies: n=3: 3 pCH -Subjects: wheezing n=3,993; asthma n=4,023	Enrolment: NR Outcome: 5-7 yrs	EBF $_{6 \text{ mo.}}$ vs. EBF $_{3\text{-}4 \text{ mo. with}}$ $_{\text{MBF thereafter}}$	RR=1.02 (0.72-1.44) Author conclusion: authors do not provide conclusions specific for the health outcomes in western countries.			-1966-2011 -5/13 publications of the three studies were included in the RIVM report (2007). 2/13 publications were included in Hörnell (2013). 1/13 publications was included in both the RIVM report (2007) and Dogaru (2014). -All studies were from western countries. -RR: Risk ratio -Results are unadjusted. -Overlap between asthma and wheezing population unknown. Quality criteria Partly fulfilled: - Not fulfilled: 1, 3, 4, 5
Asthma	Colen, 2014	pCH	USA Full sample: n=8,237 Sibling sample: n=7,319 Discordant sibling sample: n=1,773	Enrolment: 4-14 yrs Outcome: 4-14 yrs	BF vs. FF BFD $_{\text{in weeks}}$	Full sample **β (SE)= 0.261 (0.106 P<0.05** **β (SE)= 0.004 (0.002) P<0.05**	Sibling sample **β (SE)= 0.237 (0.117) P<0.05** β (SE)= 0.004 (0.002) P<0.10	Discordant sibling sample β (SE)= 0.023 (0.164) NS β (SE)= 0.006 (0.008) NS	Adjustment for age, sex, race, marital status, region, insurance coverage, family income, mother's education, and mother's employment. Controls measured at the time of birth include: preterm birth, birth order, mother's age, family income, mother's education, mother's employment, smoked during pregnancy, drank during pregnancy, and timely prenatal care (all models) Within-family estimates (discordant sibling sample): also for within family fixed effects. Quality criteria Partly fulfilled: 1, 2 Not fulfilled: -
Asthma	Nwaru, 2013	pCH	UK n=1,924	Enrolment: At birth Outcome: At ages 1, 2, 5, and 10 yrs	BF $_{\text{ever vs. never}}$ BF $_{<2.25 \text{ mo. vs.}}$ $_{\text{never}}$ BF $_{\geq2.25 \text{ mo. vs.}}$ $_{\text{never}}$ EBF $_{<3.73 \text{ mo. vs.}}$ $_{\text{never}}$ EBF $_{\geq3.75 \text{ mo. vs.}}$ $_{\text{never}}$	OR=0.81 (0.59-1.13) OR=0.90 (0.61-1.35) OR=0.76 (0.53-1.09) OR=0.77 (0.52-1.11) OR=0.87 (0.60-1.28)			Adjustment for maternal smoking during pregnancy, maternal atopy, birth order, child's gender, maternal age at booking, maternal SIMD at recruitment and crown-heel length; breastfeeding ever included in models for formula feeding and introduction of complementary foods. Quality criteria Partly fulfilled: 4 Not fulfilled: -

Health outcome	Author, year	Design	Study population	Age group	Type of BF	Results			Remarks
Asthma	RIVM, 2007	SLR	-Studies: n=18, 19 publications: 4 SLR 14 CH* -Subjects: n=44,976 (two reviews: NR) *unclear whether pCH or rCH	Enrolment: NR Outcome: NR Included age groups: 0-15 yrs	BF	Probable evidence of a protective effect of BF on asthma			-1980-September 2004, September 2004-February 2005 and February 2005 until July 2006. -All studies were from western countries (for three reviews NR).
Wheezing	Dogaru, 2014	SLR+ MA	-Studies: n=94: 44 CH* 50 CS&CC -Subjects**: Median (range): 2,144 (50-168,283); Mean: 7,111 *unclear whether pCH or rCH **Median and mean for all 117 studies	Enrolment: perinatal to ≥7 yrs Outcome: 0 to ≥7 yrs	EBF _ever vs. never_ EBF _<3 vs. ≥3 mo._ EBF _<6 vs. ≥6 mo._ BF _ever vs. never_ BF _<3 vs. ≥3 mo._ BF _<6 vs. ≥6 mo._ BF _more vs. less_ BF _more vs. less_ BF _more vs. less_ BF _more vs. less_	0-2 yrs OR=N/A **OR=0.64 (0.55-0.75)** **OR=0.69 (0.58-0.81)** **OR=0.69 (0.57-0.84)** **OR=0.61 (0.54-0.69)** **OR=0.61 (0.47-0.78)** **OR=0.70 (0.65-0.76)** All ages _Western countries_ **OR=0.84 (0.79-0.88)** _Cohort studies_ **OR=0.79 (0.73-0.85)** _High quality studies_ **OR=0.85 (0.77-0.95)** _Studies after 1990_ **OR=0.80 (0.74-0.87)**	3-6 yrs OR=N/A **OR=0.80 (0.69-0.93)** **OR=0.73 (0.56-0.96)** OR=89 (0.73-1.07) **OR=0.75 (0.71-0.80)** **OR=0.73 (0.59-0.89)** **OR=0.81 (0.72-0.89)** _Non-western_ **OR=0.75 (0.62-0.91)** _Non cohorts_ **OR=0.83 (0.74-0.92)** _Medium quality_ **OR=0.81 (0.72-0.90)** _Studies before 1990_ **OR=0.86 (0.78-0.95)**	≥7 yrs OR=N/A OR=0.84 (0.57-1.24) OR=_dropped_ OR=0.95 (0.87-1.04) OR=0.92 (0.82-1.03) OR=1.02 (0.96-1.07) **OR=0.88 (0.79-0.97)** _Low quality_ **OR=0.80 (0.72-0.89)**	-1983- 2012 -Dogaru et al. included 117 studies in the SLR and 113 in the MA, for asthma ever, asthma recent, and wheezing. -12/113 studies were included in the RIVM report (2007). 113 is the total number of studies included in the review by Dogaru, 2014 (asthma ever, asthma recent, and wheezing). -Western(n=89/117): Europe, North- and South-America, Australia, New Zealand -40/117 studies did not adjust for confounders, the others included up to 24 confounders in their analyses. - Quality score was based on 1) whether a study reported at least 3 of 7 important potential confounders and 2) whether it satisfied at least 4 of 7 of the selected quality standards suggested by Kramer et al., 1988 -More vs. less BF: priority to highest cut-offs in article, exclusive breastfeeding and school-aged subjects -N/A: the groups "EBFD, ever vs. never" were not considered. If reported in a study, these results were relocated to "any BFD, ever vs. never". Quality criteria Partly fulfilled: 1, 2, 5 Not fulfilled: -
						Author conclusion: a positive association of BF with reduced wheezing illness is supported by the combined evidence of existing studies.			
Wheezing	Kramer, 2012	SLR+ Pooled analysis	-Studies: n=3: 3 pCH -Subjects: wheezing n=3,993;	Enrolment: NR Outcome: 1 yr	EBF _6 mo._ vs. EBF _3-4 mo. with MBF thereafter_	≥2 episodes of wheezing in first 12 months RR=0.79 (0.49-1.28)			-1966-2011 -5/13 publications of the three studies were included in the RIVM report (2007). 2/13 publications were included in Hörnell (2013).

Health outcome	Author, year	Design	Study population	Age group	Type of BF	Results		Remarks
			asthma n=4,023			Author conclusion: authors do not provide conclusions specific for the health outcomes in western countries.		-All studies were from western countries. -RR: Risk ratio -Results are unadjusted. -Overlap between asthma and wheezing population unknown. <u>Quality criteria</u> Partly fulfilled: - Not fulfilled: 1, 3, 4, 5
Wheezing	Nwaru, 2013	pCH	UK n=1,924	Enrolment: At birth Outcome: At ages 1, 2, 5, and 10 yrs	BF $_{ever\ vs.\ never}$ BF $_{<2.25\ mo.\ vs.\ never}$ BF $_{\geq2.25\ mo.\ vs.\ never}$ EBF $_{<3.73\ mo.\ vs.\ never}$ EBF $_{\geq3.75\ mo.\ vs.\ never}$	<u>Wheeze</u> OR=0.99 (0.78-1.26) OR=1.11 (0.84-1.49) OR=0.90 (0.69-1.17) OR=0.91 (0.70-1.19) OR=1.09 (0.82-1.43)	<u>Wheeze without cold</u> OR=1.02 (0.72-1.45) OR=1.30 (0.86-1.96) OR=0.86 (0.58-1.28) OR=0.97 (0.66-1.44) OR=1.09 (0.73-1.65)	Adjustment for maternal smoking during pregnancy, maternal atopy, birth order, child's gender, maternal age at booking, maternal SIMD at recruitment and crown-heel length; breastfeeding ever included in models for formula feeding and introduction of complementary foods. <u>Quality criteria</u> Partly fulfilled: 4 Not fulfilled: -
Wheezing	RIVM, 2007	SLR	-Studies: n=18, 19 publications 2 SLR 1 RCT 15 CH* -Subjects: n=63,413 (NR in 1 SLR) *unclear whether pCH or rCH	Enrolment: NR Outcome: NR. Included age groups: 0-21 yrs	BF	Probable evidence exist that breastfeeding protects against wheezing.		-1980-September 2004, September 2004-February 2005 and February 2005 until July 2006. -All studies were from western countries (for one review NR)

Table C-3: Effect of breastfeeding on intellectual and motor development

Health out-come	Author, year	Design	Study population	Age group	Type of BF	Results			Remarks
IQ, neurodevelop-mental out-comes	Hörnell, 2013	SLR	-Studies: n=7: 1 SLR 6 pCH -Subjects: n=44,253 (subjects of 1 SLR NR)	Enrolment: NR Outcome: NR	BF	1/1 SLR found little or no evidence for positive association between BF and later cognitive performance of the child. 4/6 CH studies found positive association between BF and increased IQ or developmental scores. 2 CH studies found stepwise increase with longer duration of BF with highest IQ points or developmental scores with BF >6 mo. Positive results were found in the PROBIT-study. 2/6 CH found no association between EBF or BF and increased IQ or developmental scores			- January 2000-June 2011 - None of the included studies were included in the RIVM report (2007). 1/7 studies was included in Kramer (2012). - 6/7 studies were from western countries (1 from Poland). - All studies were graded A or B (out of A-C). Quality criteria Partly fulfilled: 1, 2, 3, 4 ,5 Not fulfilled: -
						Author conclusion: probable evidence that BF is beneficial for IQ and development scores of children, with increase benefit with increasing duration. *Complementary search (n=1):* Supported the conclusion that BF is beneficial for neurodevelopment.			
Cogni-tive ability	Kramer, 2012	SLR+ pooled analysis	-Studies: n=1: 1 pCH -Subjects: n=2,944	Enrolment: NR Outcome: 6.5 yrs	EBF $_{6 mo.}$ vs. EBF $_{3-4 mo. with}$ $_{MBF thereafter}$	Wechsler cognitive ability test *Vocabulary:* MD=0.50 (-0.57-1.57) *Similarities:* MD=0.30 (-0.56-1.16) *Matrices:* MD=-0.20 (-1.07-0.67) *Block designs:* **MD=1.30 (0.40-2.20)*** *Verbal IQ:* MD=0.50 (-0.95-1.95) *Performance IQ:* MD=0.80 (-0.55-2.15) *Full-scale IQ:* MD=0.80 (-0.58-2.18)	Teacher's academy rating *Reading:* **MD=-0.10 (-0.19- -0.01)*** *Writing:* **MD=-0.12 (-0.20- -0.04)*** *Mathematics:* MD=-0.04 (-0.12-0.04) *Other subjects:* **MD=-0.10 (-0.17- -0.03)***	Teacher's and parent's behaviour rating Total difficulties Emotional symptoms Conduct problems Hyperactivity/ inattention Peer problems Prosocial behaviour MD=all non-significant for both teacher's and parent's rating	-1966-2011 -3/9 publications of the one study were included in the RIVM report (2007). 1/9 publications was included in Hörnell (2013). -All studies were from western countries. -MD: Mean difference -Results are unadjusted Quality criteria Partly fulfilled: - Not fulfilled: 1, 3, 4, 5 *Result no longer significant after adjustment for clustering and for other potential confounders.
						Author conclusion: authors do not provide conclusions specific for the health outcomes in western countries.			
Cogni-tive ability	Colen, 2014	pCH	USA Full sample: n=8,237 Sibling sample: n=7,319 Discordant sibling sample: n=1,773	Enrolment: 4-14 yrs Outcome: 4-14 yrs	BF vs. FF BFD $_{in weeks}$ BF vs. FF	Full sample *Hyperactivity* **β (SE)= -0.631 (0.314) P<0.05** **β (SE)= -0.020 (0.007) P<0.01** *Parental attachment* **β (SE)= 0.277 (0.113) P<0.05**	Sibling sample β(SE)= -0.355 (0.348) NS **β(SE)= -0.017 (0.008) P<0.05** β (SE)= 0.223 (0.122) P<0.10	Discordant sibling sample β (SE)= -0.572 (0.549) NS β (SE)= -0.015 (0.012) NS β (SE)= -0.047 (0.205) NS β (SE)= 0.005 (0.004)	Adjustment for age, sex, race, marital status, region, insurance coverage, family income, mother's education, and mother's employment. Controls measured at the time of birth include: preterm birth, birth order, mother's age, family income, mother's education, mother's employment, smoked during pregnancy, drank during pregnancy, and timely prenatal care

Health out-come	Author, year	Design	Study population	Age group	Type of BF	Results			Remarks
					BFD _{in weeks}	**β (SE)= 0.009 (0.003) P<0.001**	**β (SE)= 0.008 (0.003) P<0.01**	NS	(all models) Within-family estimates (discordant sibling sample): also for within family fixed effects. <u>Quality criteria</u> Partly fulfilled: 1, 2 Not fulfilled: -
					BF vs. FF BFD _{in weeks}	*Behavioural compliance* β (SE)= 0.227 (0.119) P<0.10 β (SE)= 0.005 (0.003) P<0.10	**β (SE)= 0.307 (0.129) P<0.05** β (SE)= 0.006 (0.003) P<0.10	β (SE)= -0.204 (0.221) NS β (SE)= 0.009 (0.005) P<0.10	
					BF vs. FF BFD _{in weeks}	*Reading comprehension* **β (SE)= 2.019 (0.346 P<0.001** **β (SE)= 0.047 (0.009) P<0.001**	**β (SE)= 2.001 (0.370) P<0.001** **β (SE)= 0.048 (0.009) P<0.01**	β (SE)= 0.868 (0.690) NS β (SE)= 0.008 (0.014) NS	
					BF vs. FF BFD _{in weeks}	*Vocabulary recognition* **β (SE)= 3.250 (0.444) P<0.001** **β (SE)= 0.084 (0.012) P<0.001**	**β (SE)= 3.181 (0.474) P<0.001** **β (SE)= 0.087 (0.013) P<0.001**	β (SE)= 0.686 (0.865) NS β (SE)= 0.007 (0.021) NS	
					BF vs. FF BFD _{in weeks}	*Math ability* **β (SE)= 2.175 (0.312) P<0.001** **β (SE)= 0.059 (0.008) P<0.001**	**β (SE)= 2.066 (0.331) P<0.001** **β (SE)= 0.056 (0.008) P<0.001**	β (SE)= 0.646 (0.601) NS β (SE)= 0.012 (0.012) NS	
					BF vs. FF BFD _{in weeks}	*Memory based intelligence* **β (SE)= 0.329 (0.084) P<0.001** **β (SE)= 0.007 (0.002) P<0.001**	**β (SE)= 0.311 (0.092) P<0.01** **β (SE)= 0.006 (0.002) P<0.05**	β (SE)= 0.221 (0.178) NS β (SE)= -0.005 (0.003) NS	
					BF vs. FF BFD _{in weeks}	*Scholastic competence* **β (SE)= 2.789 (1.204) P<0.05** **β (SE)= 0.119 (0.029) P<0.001**	β (SE)= 2.363 (1.304) P<0.10 **β (SE)= 0.126 (0.032) P<0.001**	β (SE)= -5.353 (2.757) NS β (SE)= 0.015 (0.058) NS	
Develop-mental delay	Sacker, 2006	CS	UK n=14,660	Enrolment: NR Outcome: 9 months on average	BF _{<2 mo. vs. never} BF _{2-4 mo. vs. never} PBF _{≥4 mo. vs. never} EBF _{≥4 mo. vs. never}	*Fine motor delay* OR=0.94 (0.75–1.17) OR=0.84 (0.61–1.16) OR=0.78 (0.58–1.04) OR=0.93 (0.74–1.16) *Gross motor delay*			Adjustment for - Biological: birth weight, gestation in weeks, mother's age in years, and smoking during pregnancy - Socioeconomic: the National Statistics Socio-economic Class, mother's educational qualifications,

Health out-come	Author, year	Design	Study population	Age group	Type of BF	Results	Remarks
					BF <2 mo. vs. never BF 2-4 mo. vs. never PBF≥4 mo. vs. never EBF≥4 mo. vs. never	**OR=0.81 (0.69–0.96)** **OR=0.75 (0.58–0.96)** **OR=0.80 (0.65–0.98)** **OR=0.67 (0.54–0.84)**	mother's employment status, and partnership status - Psychosocial: mother's Malaise Inventory score (a measure of psychological distress), mother's postnatal attachment score, and the mother's attitude toward child care, other caregivers, and the child's time spent being cared for by others. <u>Quality criteria</u> Partly fulfilled: 3 Not fulfilled: -
Intellec-tual and motor develop ment	RIVM, 2007	SLR	-Studies: n=18: 2 SLR 15 CH* 1 case-CH -Subjects: n ranged between 11,899-13,849 *unclear whether pCH or rCH	Enrolment: NR Outcome: NR Included age groups: 3 mo.-27.2 yrs	BF	There is possible/probable evidence for a favourable effect of BF on intellectual and motor development, with BF children scoring higher than formula-fed children.	-1980-September 2004, September 2004-February 2005 and February 2005 until July 2006 -2 SLRs did not report number of subjects, origin or age groups. -All studies were from western countries. -Health outcomes: WAIS, BPP, McCarthy GCI, PPVT-R, WISC-R, Woodcock, BAS, Bayley, K-ABC, RDLS, Rey complex figure test, SRTT, AVLT, TOL, cognitive development score, Icelandic developmental inventory and development milestones

Table C-4: Effect of breastfeeding on atopic diseases

Health outcome	Author, year	Design	Study population	Age group	Type of BF	Results			Remarks
Atopic disease	Hörnell, 2013	SLR	-Studies: n=9: 2 SLR 7 pCH -Subjects: n=85,832	Enrolment: NR Outcome: NR	BF	1/2 SLRs found a protective effect of EBF >3 mo. on the risk for atopic disease. 1/2 SLRs found no effect of EBF >3 mo. on the risk for atopic disease. 6/7 CH studies found no protective effect of EBF on the development of atopic disease. 1/7 CH study found that EBF increased the risk of eczema after adjustment for demographics, filaggrin variants, parents' eczema and pets at home. Author conclusion: very limited evidence and no conclusion can be drawn for any preventive effects of BF on atopic diseases, including eczema, in children.			- January 2000-June 2011 - 1/9 studies was included in RIVM (2007). 2/9 studies were included in Kramer (2012). - Included studies were from western countries. In 1 SLR NR, but probably from developed countries. -Health outcomes are atopic dermatitis, eczema, atopy and allergic symptoms. - All studies were graded A or B (out of A-C). - Eczema is included in atopic diseases in this review. Quality criteria Partly fulfilled: 1, 2, 3, 4, 5 Not fulfilled: -
Atopic disease	Kramer, 2012	SLR+ pooled analysis	-Studies: n=3: 3 pCH -Subjects: n unclear	Enrolment: NR Outcome: at 1 yr and 5-7 yrs	EBF $_{6\ mo.}$ vs. EBF $_{3-4\ mo.\ with}$ $_{MBF\ thereafter}$	Food allergy *1 yr (by history):* **RR=0.19 (0.08-0.48)** *1 yr (by double challenge):* RR=0.77 (0.25-2.41) *5 yrs:* RR=0.61 (0.12-3.19)	Positive skin-prick test at 6.5 yrs *House dust mite:* RR=0.86 (0.62-1.20) *Cat dander:* RR=0.86 (0.60-1.24) *Birch pollen:* RR=0.80 (0.55-1.18) *Mixed northern grasses:* RR=0.71 (0.50-1.01) *Alternaria:* RR=0.74 (0.47-1.17) *Any positive test:* RR=0.95 (0.81-1.11)	Other allergies *Hay fever at 5-7 yrs:* RR=0.80 (0.39-1.65) *Allergy to animal dander at 5 yrs:* RR=0.81 (0.24-2.72)	-1966-2011 -5/13 publications of the three studies were included in RIVM (2007). 2/13 publication of the three studies were included in Hörnell (2013). -All studies were from western countries. -RR: Risk ratio -Results are unadjusted. Quality criteria Partly fulfilled: - Not fulfilled: 1, 3, 4, 5
						Author conclusion: authors do not provide conclusions specific for the health outcomes in western countries.			

Health outcome	Author, year	Design	Study population	Age group	Type of BF	Results		Remarks
Atopic disease	RIVM, 2007	SLR	-Studies: n=15: 3 SLR 12 CH* -Subjects: n ranged between 18,385-18,603 (1 review: NR) *unclear whether pCH or rCH	Enrolment: NR Outcome: NR Included age groups: 0-21 yrs	BF	Possible evidence for a protective effect of BF on atopy		-1980-September 2004, September 2004-February 2005 and February 2005 until July 2006 -All studies were from western countries (three reviews NR). -Health outcomes: Atopy, IgE, skin prick test, allergic rhinitis, sensitive to inhalation allergens, food allergy.
Eczema	Kramer, 2012	SLR+ pooled analysis	-Studies: n=2: 2 pCH -Subjects: n=3,618	Enrolment: NR Outcome: first 12 mo. and 5-7 yrs	EBF $_{6\ mo.}$ vs. EBF $_{3-4\ mo.}$ with MBF thereafter	First 12 mo. RR=0.65 (0.27-1.59)	Age 5-7 yrs RR=0.86 (0.47-1.58)	-1966-2011 -4/12 publications of the two studies were included in the RIVM report (2007). -All studies were from western countries. -Results are unadjusted. Quality criteria Partly fulfilled: - Not fulfilled: 1, 3, 4, 5
						Author conclusion: authors do not provide conclusions specific for the health outcomes in western countries.		
Eczema	Nwaru, 2013	pCH	UK n=1,924	Enrolment: At birth Outcome: At ages 1, 2, 5, and 10 yrs	BF $_{ever\ vs.\ never}$ BF $_{<2.25\ mo.\ vs.\ never}$ BF $_{\geq2.25\ mo.\ vs.\ never}$ EBF $_{<3.73\ mo.\ vs.\ never}$ EBF $_{\geq3.75\ mo.\ vs.\ never}$	OR=1.06 (0.83-1.35) OR=1.12 (0.84-1.51) OR=1.04 (0.81-1.35) OR=0.93 (0.71-1.21) OR=1.25 (0.95-1.64)		Adjustment for maternal smoking during pregnancy, maternal atopy, birth order, child's gender, maternal age at booking, maternal SIMD at recruitment and crown-heel length; breastfeeding ever included in models for formula feeding and introduction of complementary foods. Quality criteria Partly fulfilled: 4 Not fulfilled: -

Health outcome	Author, year	Design	Study population	Age group	Type of BF	Results	Remarks
Eczema	RIVM, 2007	SLR	-Studies: n=18: 3 SLR 1 RCT 12 CH* 1 nested case-CH 1 CC -Subjects: n ranged between 55,884-59,389; (2 SLRs: NR) *unclear whether pCH or rCH	Enrolment: NR Outcome: NR Included age groups: 0-15 yrs	BF	Probable evidence for a protective effect of BF on eczema	-1980-September 2004, September 2004-February 2005 and February 2005 until July 2006 -All studies were from western/developed countries (for two reviews NR).

Table C-5: Effect of breastfeeding on metabolic syndrome

Health outcome	Author, year	Design	Study population	Age group	Type of BF	Results		Remarks
Metabolic syndrome	Martin, 2014	Long-term follow up of RCT	Belarus n=13,616	Enrolment: at birth Outcome: Median 11.5 yrs (SD: 0.50; IQR: 11.3-11.8)	EBF $_{3\ to\ <6\ mo.}$ vs. $_{<3\ mo}$ EBF $_{\geq6\ mo.}$ vs. $_{<3\ mo}$	Instrumental variable analysis OR=1.91 (0.72-5.05) OR=2.33 (0.52-9.68)	Observational analysis OR=1.09 (0.86-1.39) OR=1.14 (0.68-1.89)	Adjustment for stratum-level variables (urban vs. rural and East vs. West Belarus), and child age at follow-up, sex, birth weight, and both maternal and paternal education Quality criteria Partly fulfilled: - Not fulfilled: -
Metabolic syndrome	RIVM, 2007	Not available						

Table C-6: Effect of breastfeeding on cancer

Health outcome	Author, year	Design	Study population	Age group	Type of BF	Results		Remarks
Childhood cancer – neuroblastoma	Hörnell, 2013	SLR	-Studies: n=1: 1 SLRs -Subjects: n NR	Enrolment: NR Outcome: NR	BF	1/1 SLR found that BF was associated with lower risk for neuroblastoma. Author conclusion: limited but suggestive evidence that BF reduced the risk of childhood cancers.		- January 2000-June 2011 - None of the studies were included in RIVM (2007) -1 SLR: Most studies from based in Europe or North America (including non-western countries) -SLR was graded C Quality criteria Partly fulfilled: 1, 2, 3, 4, 5 Not fulfilled: -
Childhood cancer - CNS tumours	Harding, 2007	CC	UK Cases: n=633 Control: n=7,621	Enrolment: NR Outcome: NR	BF $_{ever\ vs\ never}$ BF $_{<1\ mo.\ vs.\ never}$ BF $_{1-6\ mo.\ vs.\ never}$ BF $_{>6\ mo.\ vs.\ never}$	OR (95% CI) = 1.01 (0.85-1.21) OR (95% CI) = 1.11 (0.86-1.42) OR (95% CI) = 0.94 (0.75-1.19) OR (95% CI) = 1.03 (0.83-1.28) P for trend= 0.72		Adjustment for age, sex, region, and deprivation index Quality criteria Partly fulfilled: - Not fulfilled: 1, 2, 3
Childhood cancer	RIVM, 2007	SLR	-Studies: n=7: 1 SLR 1 CH* 5 CC -Subjects: n ranged between 21,838-23,461 (subjects of 1 SLR NR) *unclear whether pCH or rCH	Enrolment: NR Outcome: NR Included age groups: 0-85 yrs	BF	Insufficient evidence was found for all cancer morbidity and for other specific cancers such as breast and testicle.		-1980-September 2004, September 2004-February 2005 and February 2005 until July 2006 -All studies were from western countries (countries from one review NR). -Health outcomes: childhood cancers, neuroblastoma, brain cancer, Wilms tumour
Adult cancers – breast cancer	Nichols, 2008 USA	CC	USA Cases: n=2,016 Controls: n=1,960	Enrolment: 20-69 yrs Outcome: 20-69 yrs	No BF BF	All women OR= 1 **OR= 0.83 (0.72-0.96)**	Restricted to first-born women (Cases: n=557; Controls: n=514) OR= 1 OR= 0.97 (0.74-1.29)	Adjustment for age, birth order, age at menarche, age at first birth, parity, menopausal status, age at menopause, postmenopausal hormone use, family history of breast cancer in a mother or sister, height, weight at age 20, weight gain since age 20 and mammography screening. Quality criteria Partly fulfilled: 4 Not fulfilled: 1, 2, 3

Health outcome	Author, year	Design	Study population	Age group	Type of BF	Results	Remarks
Adult cancers – several cancers	Hörnell, 2013	SLR	-Studies: n=1: 1 SLRs -Subjects: n NR	Enrolment: NR Outcome: NR	BF	1/1 SLR found that BF was not associated with prostate, colorectal, gastric, smoking-related cancers, nor overall breast cancer. BF women had a reduced risk of premenopausal breast cancer.	- January 2000-June 2011 - None of the studies were included in RIVM (2007) -1 SLR NR. -1 SLR was graded C Quality criteria Partly fulfilled: 1, 2, 3, 4, 5 Not fulfilled: -
						Author conclusion: limited but suggestive evidence that BF reduced the risk of childhood cancers.	
Leu-kaemia	Hörnell, 2013	SLR	-Studies: n=2: 2 SLRs -Subjects: n=3,266 (subjects of 1 SLR NR)	Enrolment: NR Outcome: NR	BF	1 SLR found an association between a history of BFD ≥6 mo. and a reduction in the risk of ALL and AML. 1 SLR found lower risk for ALL when ever BF or EBF vs. never BF.	- January 2000-June 2011 - None of the studies were included in RIVM (2007) - 1 SLR: studies from developed countries; 1 SLR: Most studies from based in Europe or North America (including non-western countries) - 1 SLR graded A, 1 SLR graded C Quality criteria Partly fulfilled: 1, 2, 3, 4, 5 Not fulfilled: -
						Author conclusion: limited but suggestive evidence that BF reduced the risk of childhood leukaemia. The effect on childhood leukaemia seems larger with longer BFD (>6 mo).	
Leu-kaemia	RIVM, 2007	SLR	-Studies: n=8: 1 SLR 7 CC -Subjects: n=13,817-21,324 (one review NR)	Enrolment: NR Outcome: NR Included age groups: 0-18 yrs	BF	Possible evidence for a protective effect of BF on leukaemia	-1980-September 2004, September 2004-February 2005 and February 2005 until July 2006 -All studies were from western countries (one review NR) -Health outcomes: Leukaemia, acute leukaemia, acute myeloid leukaemia and acute lymphatic leukaemia

Table C-7: Effect of breastfeeding on weight loss

Health outcome	Author, year	Design	Study population	Age group	Type of BF	Results		Remarks
Neonatal weight loss	Davanzo, 2013	rCH	Italy n=1,003	Enrolment: Directly after birth Outcome: NR	FF vs BF	**Mean ± SD or %: 255 ± 93g or 7.5% ± 2.4% vs 215 ± 73g or 6.3% ± 2.0% (P < 0.001)**		Adjustment for season, type of delivery, birth weight, jaundice treated and not treated with phototherapy, length of hospital stay, hypernatremia (>150 mEq/L), and hypoglycaemia (blood glucose < 45 mg/dL) <u>Quality criteria</u> Partly fulfilled: - Not fulfilled: 3
					FF vs BF	<u>NWL ≥8% before discharge among all children</u> **OR=3.65 (2.67-4.99)**	<u>NWL ≥8% before discharge among vaginal deliveries (n=795)</u> **OR=4.81 (3.32-6.98)**	
Neonatal weight loss	RIVM, 2007	Not available						

Table C-8: Effect of breastfeeding on multiple sclerosis

Health outcome	Author, year	Design	Study population	Age group	Type of BF	Results	Remarks
MS	Conradi, 2012	CC	Germany 245 Cases 296 Controls	Enrolment: median age Cases: 46 years Controls: 40 years Outcome: NR	No BF BF BF $_{≤4 mo}$ BF $_{>4 mo}$	OR= 1 **OR= 0.58 (0.35-0.94)** OR= 0.87 (0.49-1.52) **OR= 0.51 (0.29-0.88)**	Adjustment for age, gender, number of older siblings, number of inhabitants in place of domicile at age 0-6, day-care attendance between ages 0 and 3. <u>Quality criteria</u> Partly fulfilled: 5 Not fulfilled: 1, 2, 3
MS	RIVM, 2007	Not available					

Table C-9: Effect of breastfeeding on gastrointestinal disorders

Health outcome	Author, year	Design	Study population	Age group	Type of BF	Results	Remarks
Coeliac disease	Hörnell, 2013	SLR	-Studies: n=1: 1 SLR -Subjects: n=4,624	Enrolment: NR Outcome: NR	BF	1/1 SLR found protective effect of BF on coeliac disease. The risk was especially reduced if the child was still BF when gluten was introduced. Author conclusion: probable evidence for BF as protective factor for celiac disease, if gluten is introduced in small amounts while still BF. Unclear whether the protection only delays the onset of celiac disease or if it provides permanent protection.	-January 2000-June 2011 -The article was not included in RIVM (2007). -Included study was from western country. -The studies was graded A (out of A-C). <u>Quality criteria</u> Partly fulfilled: 1, 2, 3, 4, 5 Not fulfilled: -
Coeliac disease	Henriksson, 2013	SLR	-Studies: n=4: two retrospective studies* 1 pCH 1 CC -Subjects: n=3,527 *design unclear	Enrolment: 14 mo-8.4 yrs Outcome: 14 mo-8.4 yrs	BFD BF during gluten introduction	2/3 studies: significant association between longer duration of BF and later onset of coeliac disease 1/3 studies: no association between longer BFD and later onset of coeliac disease 3/3 studies: BF during gluten introduction significantly delayed the onset of coeliac disease. Author conclusion: BF seems to offer a protection against the development of coeliac disease in predisposed infants.	-June 2004-April 2011 -1/4 studies was included in RIVM (2007). 1/4 studies was included in Szajewska (2012). -Studies were of moderate or high risk of bias. <u>Quality criteria</u> Partly fulfilled: 1, 4 Not fulfilled: 2, 3
Coeliac disease	Szajewska, 2012	SLR	-Studies: n=11 3 pCH 7 CC One record linkage study -Subjects: n=266,844	Enrolment: directly after birth-14.9 yrs Outcome: NR, but at last 14.9 yrs old	EBF vs. any PBF or FF BF_{ever} vs. BF_{never} Long BFD Short BFD $BF_{at\ time\ gluten\ introduced}$ vs. no BF at time gluten introduced	3/3 studies: no evidence that EBF reduces the risk of coeliac disease or delays the onset of symptoms 1/2 studies: no association between BF and the risk of coeliac disease 1/2 studies: lower risk of coeliac disease in ever BF children vs. never BF children 5/6 studies: longer duration of BF protects against coeliac disease 1/6 studies: no association found 5/5 studies: no association between short term BF and coeliac disease 3/5 studies: significantly reduced risk of coeliac disease of children who were BF when started receiving gluten 2/5 studies: no association found Author conclusion: whether or not BF protects or delays the clinical presentation of coeliac disease remains controversial. This does not mean that BF does not have a significant effect in preventing coeliac disease, but it could be due to methodological inadequacy of investigating BF in ways that take into account all the complexity of interactions	-Up to July 2012 -1/11 studies was included in the RIVM report (2007). 1/11 studies was included in Henriksson (2013). -All studies were from western regions. -6Sixstudies were at moderate risk of bias. Other not reported <u>Quality criteria</u> Partly fulfilled: 1, 2 Not fulfilled: 3

Health outcome	Author, year	Design	Study population	Age group	Type of BF	Results	Remarks
Coeliac disease	RIVM, 2007	SLR	-Studies: n=1: 1 CC -Subjects: n=280	Enrolment: NR Outcome: NR, but mean age 6.4 yrs	BF	Insufficient evidence for a protective effect of BF on coeliac disease	-1980-September 2004, September 2004-February 2005 and February 2005 until July 2006 -Study from western country
Inflammatory bowel disease	Barclay, 2009	SLR+ MA	-Studies: n=7: 7 CC -Subjects: 1,324 cases 2,282 controls	Enrolment: <22 yrs Outcome: <22 yrs	No BF BF Excluding Gilat et al[2]	1 **0.69 (0.51-0.94)** **0.60 (0.39-0.91)** Author conclusion: possible protective effect for breast milk in the development of early onset inflammatory bowel disease	-Start of database - Jan 2008 -3/7 studies were included in the RIVM report (2007) -Overall quality of the data is poor. -6/7 studies were from western countries (remaining from Japan) Quality criteria Partly fulfilled: 1, 2 Not fulfilled: 3, 5
Inflammatory bowel disease	RIVM, 2007	Not available					
Crohn's disease	Barclay, 2009	SLR+ MA	-Studies: n=6: 6 CC -Subjects: 802 cases 1,424 controls	Enrolment: <22 yrs Outcome: <22 yrs	No BF BF Excluding Gilat et al[3]	1 0.64 (0.38-1.07) 0.65 (0.26-1.15) Author conclusion: no conclusion specific for CD reported	-Start of database - Jan 2008 -3/6 studies were included in the RIVM report (2007) -Overall quality of the data is poor. -5/6 studies were from western countries (remaining from Japan) Quality criteria Partly fulfilled: 1, 2 Not fulfilled: 3, 5
Crohn's disease	RIVM, 2007	SLR	-Studies: n=5: 1 SLR 4 CC -Subjects: n=8,674	Enrolment: NR Outcome: NR Included age groups: 0-65 yrs	BF	Possible evidence for a protective effect of BF on CD	

[2] Meta-analysis combining these results was hindered by the lack of OR and CIs for exposure to breast milk in one published study. A random effects model therefore was applied, including this study and assuming an OR of one for each group in the Gilat et al study. A second analysis was then performed excluding the Gilat et al study from the analysis, because the OR for this study was only a crude estimate.
[3] Meta-analysis combining these results was hindered by the lack of OR and CIs for exposure to breast milk in one published study. A random effects model therefore was applied, including this study and assuming an OR of one for each group in the Gilat et al study. A second analysis was then performed excluding the Gilat et al study from the analysis, because the OR for this study was only a crude estimate.

Health outcome	Author, year	Design	Study population	Age group	Type of BF	Results		Remarks
Ulcerative colitis	Barclay, 2009	SLR+ MA	-Studies: n=5: 5 CC -Subjects: 522 cases 1,060 controls	Enrolment: <22 yrs Outcome: <22 yrs	No BF BF Excluding Gilat et al[4]	1 0.72 (0.51-1.02) **0.61 (0.44-0.84)**		-Start of database - Jan 2008 -2/5 studies were included in the RIVM report (2007). -Overall quality of the data is poor. -4/5 studies were from western countries (remaining from Japan). <u>Quality criteria</u> Partly fulfilled: 1, 2 Not fulfilled: 3, 5
						Author conclusion: no conclusion specific for UC reported		
Ulcerative colitis	RIVM, 2007	SLR	-Studies: n=3: 1 SLR 2 CC -Subjects: n=7,586	Enrolment: NR Outcome: NR Included age groups: 0-65 yrs	BF	Possible evidence for a protective effect of BF on UC		-1980-September 2004, September 2004-February 2005 and February 2005 until July 2006 -All studies were from western countries (one review NR)
Helicobacter pylori	Chak, 2009	SLR+ MA	-Studies: n=14: 3 CH* 10 CS 1 CC -Subjects: n NR *unclear whether pCH or rCH	Enrolment: NR Outcome: NR	BF _{any vs. none} BF _{≥4 mo vs. none} BF _{NS vs. none}	<u>All countries</u> **OR=0.78 (0.61-0.99)** OR=0.81 (0.40-1.66) **OR=0.76 (0.59-0.99)**	<u>High income countries</u> OR=0.93 (0.73-1.19)	-1984-2007 -0/14 studies were included in the RIVM report (2007). -6/14 studies were from western countries (7/14 from high income countries: includes Japan). - Authors used adjusted ORs if provided in the article. No adjustment in 5/14 studies. <u>Quality criteria</u> Partly fulfilled: 1, 2, 5 Not fulfilled: 3
						Author conclusion: BF is protective against *H. pylori.*		
Helicobacter pylori	RIVM, 2007	Not available						

[4] Meta-analysis combining these results was hindered by the lack of OR and CIs for exposure to breast milk in one published study. A random effects model therefore was applied, including this study and assuming an OR of one for each group in the Gilat et al study. A second analysis was then performed excluding the Gilat et al study from the analysis, because the OR for this study was only a crude estimate.

Health outcome	Author, year	Design	Study population	Age group	Type of BF	Results	Remarks
Gastrointestinal infections	Kramer, 2012	SLR+ pooled analysis	-Studies: n=1: 1 pCH -Subjects: n=3,483	Enrolment: NR Outcome: first 12 mo	EBF $_{6 mo}$ vs. EBF $_{3-4 mo with}$ $_{MBF thereafter}$	≥1 episodes of GI: **RR=0.67 (0.46-0.97)*** Hospitalization for GI: RR=0.79 (0.42-1.49) * aOR (95% CI)=**0.61 (0.41-0.93)** Age 0-3 mo (when both groups received EBF): aIDR=0.97 (0.46-2.04) Age 3-6 mo (feeding differed): aIDR: 0.35 (0.13-0.96) Author conclusion: authors do not provide conclusions specific for the health outcomes in western countries.	-1966-2011 -3/9 publications of the one study were included in the RIVM report (2007). 1/9 publications were included in Hörnell (2012). -All studies were from western countries. -RR: Risk ratio -IDR: Incidence density ratio -Only the result of episodes of GI was adjusted (see asterisk): geographic region, urban versus rural location, maternal education, and number of siblings in the household. Quality criteria Partly fulfilled: - Not fulfilled: 1, 3, 4, 5
Gastrointestinal infections	Hörnell, 2013	SLR	-Studies: n=7: 3 SLRs 4 pCH -Subjects: n=59,354	Enrolment: NR Outcome: NR	BF	2/3 SLRs found a protective effect of BF on gastrointestinal infections. 1/3 SLR found conflicting results of the effect of BF on gastrointestinal infections. 3/4 CH studies found a protective dose/duration-response effect of BF or EBF on gastrointestinal infections. 1/4 CH study found a protective effect of BF on all infections, including gastrointestinal infections. Author conclusion: convincing evidence that BF protects infants in industrialized countries against gastrointestinal infections. *Note: Hörnell based this conclusion on overall infections (AOM, gastrointestinal and respiratory tract infections).	-January 2000-June 2011 -1/7 studies was included in RIVM (2007). 1/7 studies was included in Kramer (2012). -Included studies were from western countries, except 1 SLR which included 11 studies from developing countries out of 22 studies. -All studies were graded A or B (out of A-C). Quality criteria Partly fulfilled: 1, 2, 3, 4, 5 Not fulfilled: -

Health outcome	Author, year	Design	Study population	Age group	Type of BF	Results	Remarks
Gastrointestinal infections	RIVM, 2007	SLR	-Studies: n=15, 16 publications: 3 SLR 1 trial 9 CH* 2 CC -Subjects: n ranged between 41,276-41,415 (two reviews: NR) *unclear whether pCH of rCH	Enrolment: NR Outcome: NR Included age groups: 0-24 mo	BF	Convincing evidence for a protective effect of breastfeeding on gastrointestinal infections	-1980-September 2004, September 2004-February 2005 and February 2005 until July 2006 -All studies were from western countries (3 SLRs NR) -Health outcomes: gastrointestinal infections, Salmonella B/D, Rotavirus infection, diarrhoea

Table C-10: Effect of breastfeeding on respiratory infections

Health outcome	Author, year	Design	Study population	Age group	Type of BF	Results			Remarks
Respiratory infections	Hörnell, 2013	SLR	-Studies: n=6: 3 SLRs 3 pCH -Subjects: n=72,266	Enrolment: NR Outcome: NR	BF	2/3 SLRs found a protective dose/duration-response effect of BF or EBF on gastrointestinal or respiratory tract infections. 1/3 SLR found no effect. 3/3 CH studies found a protective effect of dose/duration-response of BF or EBF on respiratory tract infections. Author conclusion: convincing evidence that BF protects infants in industrialized countries against respiratory tract infections. *Note: Hörnell based this conclusion on overall infections (AOM, gastrointestinal and respiratory tract infections).			- January 2000-June 2011 - 1/6 studies was included in RIVM (2007). 1/6 studies was included in Kramer (2012). - Included studies were from western countries, except 1 SLR which included 11 studies from developing countries out of 22 studies. - All studies were graded A or B (out of A-C). <u>Quality criteria</u> Partly fulfilled: 1, 2, 3, 4, 5 Not fulfilled: -
Respiratory infections	Kramer, 2012	SLR+ pooled analysis	-Studies: n=2: 2 pCH -Subjects: n=3,993	Enrolment: NR Outcome: first 12 months	EBF $_{6\ mo}$ vs. EBF $_{3-4\ mo\ with\ MBF\ thereafter}$	<u>RTI</u> ≥2 episodes: RR=0.90 (0.79-1.03) <u>Hospitalizations:</u> **RR=0.75 (0.60-0.94)*** * aOR (95% CI)=0.96 (0.71-1.30)	<u>URTI</u> ≥1 episodes: RR=1.07 (0.96-1.20) ≥2 episodes: RR=0.91 (0.82-1.02) ≥4 episodes: RR=0.82 (0.52-1.29)	<u>LRTI</u> ≥1 episodes: RR=1.07 (0.86-1.33)	-1966-2011 -4/9 publications of the two studies were included in the RIVM report (2007). 1/9 publications was included in Hörnell (2012). -All studies were from western countries. -RR: Risk ratio -Results are unadjusted. -Crude risk in 1/2 studies on RTI hospitalizations became non-significant after adjustment for geographic region, urban versus rural location, maternal education and cigarette smoking, and number of siblings in the household (see asterisk). <u>Quality criteria</u> Partly fulfilled: - Not fulfilled: 1, 3, 4, 5
						Author conclusion: authors do not provide conclusions specific for the health outcomes in western countries.			
Respiratory infections	RIVM, 2007	SLR	-Studies: n=19: 2 SLR 1 RCT 15 CH 1 CC -Subjects: n ranged between 45,205-48,825 (1 SLR: NR)	Enrolment: NR Outcome: NR Included age groups: 0-7 yrs	BF	Probable evidence for a protective effect of BF on respiratory infections Probable evidence for a protective effect of BF on upper respiratory infections Insufficient evidence for an effect of BF on lower respiratory tract infections			-1980-September 2004, September 2004-February 2005 and February 2005 until July 2006 -All studies were from western countries or developed countries (SLR) (for one review NR) -Health outcomes: Respiratory infection, upper respiratory tract Infection, disorder lower respiratory tract

Table C-11: Effect of breastfeeding on diabetes

Health outcome	Author, year	Design	Study population	Age group	Type of BF	Results			Remarks
Type 1 diabetes	Cardwell, 2012	SLR+ pooled analysis	-Studies: n=43: 40 CC 3 CH* -Subjects: n=9,874 *unclear whether pCH or rCH	Enrolment: 0-25 yrs Outcome: NR	EBF $_{any\ vs.\ none}$ EBF $_{≥2\ vs\ <2\ wks}$ EBF $_{≥3\ vs\ <3\ mo}$ BF $_{any\ vs.\ none}$ BF $_{≥2\ vs\ <2\ wks}$ BF $_{≥3\ vs\ <3\ mo}$ EBF $_{≥2\ vs\ <2\ wks}$ EBF $_{≥3\ vs\ <3\ mo}$ BF $_{≥2\ vs\ <2\ wks}$ BF $_{≥3\ vs\ <3\ mo}$	<u>All countries</u> **OR=0.74 (0.64-0.84)** **OR=0.75 (0.64-0.88)** OR=0.87 (0.75-1.00) **OR=0.81 (0.72-0.92)** OR=0.93 (0.81-1.07) OR=0.88 (0.78-1.00) <u>Under 5 yrs</u> **OR=0.73 (0.58-0.91)** OR=0.86 (0.71-1.03) OR=0.84 (0.65-1.08) OR=0.86 (0.69-1.08)	<u>European countries (n=28)</u> **OR=0.79 (0.70-0.88)** **OR=0.79 (0.71-0.88)** OR=0.91 (0.78-1.05) **OR=0.82 (0.73-0.91)** **OR=0.85 (0.74-0.98)** **OR=0.86 (0.76-0.98)** <u>Over 5 yrs</u> **OR=0.75 (0.60-0.95)** OR=0.90 (0.76-1.05) OR=0.95 (0.81-1.11) OR=0.90 (0.79-1.02)	<u>Studies with low risk of bias (n=17; 2 non-European countries)</u> OR=0.89 (0.78-1.02) **OR=0.86 (0.75-0.99)** OR=01.13 (0.96-1.33) OR=1.00 (0.89-1.11) OR=1.00 (0.87-1.15) OR=0.99 (0.86-1.14)	-January 1996-1 May 2011 -3/43 studies were included in the RIVM report (2007). -28 included studies were from Europe, 2 from the USA, 1 from Australia and 1 from Canada. Other studies were from non-western countries. -Presented results are unadjusted, however in additional analyses for the associations BF and EBF ≥2 vs. <2 wks authors found little alteration by adjustment for the following confounders: maternal diabetes, birth weight, gestational age, maternal age, birth order, Caesarean section and socioeconomic status. <u>Quality criteria</u> Partly fulfilled: 3 Not fulfilled: 1, 5
						Author conclusion: EBF in early weeks of life could reduce the risk of childhood onset type 1 diabetes by 15% based upon the highest quality studies. Little evidence that longer exclusive or nonexclusive BF has a protective effect. Firm conclusions are difficult to reach because of marked heterogeneity in the observed associations between studies and the weaknesses inherent in many of the included studies.			
Type 1 diabetes	Hörnell, 2013	SLR	-Studies: n=2: 1 SLR 1 pCH -Subjects: n=48,952	Enrolment: NR Outcome: NR	BF BFD	1/1 SLR found that longer duration of BF may contribute to risk reduction in the development of diabetes mellitus type 1. 1/1 CH study found no effect of BF on risk of islet cell autoimmunity in children.			-January 2000-June 2011 -None of the studies were included in the RIVM report (2007). -Included studies were from western countries. -Outcome of the CH was Islet autoimmunity which predict the risk of later development of T1DM in later life. -The studies were graded A and B (out of A-C). <u>Quality criteria</u> Partly fulfilled: 1, 2, 3, 4, 5 Not fulfilled: -
						Authors conclusion: Probable evidence that any BF had a protective effect against diabetes mellitus type 1 Limited but suggestive evidence that BFD is associated with protective effect against diabetes mellitus type 1			

Health outcome	Author, year	Design	Study population	Age group	Type of BF	Results	Remarks
Type 1 diabetes	RIVM, 2007	SLR	-Studies: n=8: 1 SLR 7 CC -Subjects: n=6,436 (+1 SLR: NR)	Enrolment: NR Outcome: NR Included age groups: 0-20yrs	BF	Possible evidence for a beneficial effect of BF on diabetes type 1	-1980-September 2004, September 2004-February 2005 and February 2005 until July 2006 -All studies were from western countries (for one review NR). -Health outcomes: Insulin dependent diabetes mellitus
Type 2 diabetes	Hörnell, 2013	SLR	-Studies: n=1 (SLR with pooled analysis) -Subjects: n=76,744	Enrolment: NR Outcome: NR	BF vs. FF	1/1 SLR found a protective effect of BF on type 2 diabetes mellitus: Pooled OR= 0.61 (0.44-0.85). Author conclusion: probable evidence that any BF had a protective effect against diabetes mellitus type 2. Limited but suggestive evidence that BF duration is associated with protective effect against diabetes mellitus type 2.	-January 2000-June 2011 -None of the studies were included in the RIVM report (2007). -Article from western countries -Pooled results based on 7 single studies - Outcome is T2DM in later life. - The study was graded A (out of A-C). Quality criteria Partly fulfilled: 1, 2, 3, 4, 5 Not fulfilled: -
Type 2 diabetes	RIVM, 2007	Not available					

Table C-12: Effect of breastfeeding on SIDS

Health outcome	Author, year	Design	Study population	Age group	Type of BF	Results	Remarks
SIDS	Hauck, 2011	SLR + MA	-Studies: n=18: 18 CC -Subjects: n unclear	Enrolment: NR Outcome: NR	BF $_{any\ vs.\ none}$ BFD $_{\geq 2\ mo.\ vs.\ none}$ EBF $_{any\ vs.\ no\ BF}$	**OR=0.55 (0.44-0.69)** **OR=0.38 (0.27-0.54)** (unadjusted) **OR=0.27 (0.24-0.31)** (unadjusted) Author conclusion: BF is protective against SIDS, and this effect is stronger when BF is exclusive	-Jan 1996-Dec 2009 -1/18 studies was included in RIVM (2007). -All studies were from western countries. -Multivariable ORs were presented in eight studies: adjustment varied between studies. Use of adjusted OR not possible for BFD and EBF (too few studies) Quality criteria Partly fulfilled: 5 Not fulfilled: 3
SIDS	RIVM, 2007	SLR	-Studies: n=5: 2 SLR 3 CC -Subjects: n=7,136 (NR of 1 SLR of 23 studies)	Enrolment: NR Outcome: NR Included age groups: 0-12 mo (two articles: NR)	BF	Possible evidence for an effect of BF on SIDS	-1980-September 2004, September 2004-February 2005 and February 2005 until July 2006 -All studies were from western countries (for two reviews NR).

Table C-13: Effect of breastfeeding on otitis media

Health outcome	Author, year	Design	Study population	Age group	Type of BF	Results	Remarks
Acute otitis media	Kramer, 2012	SLR+ pooled analysis	-Studies: n=2: 2 pCH -Subjects: n=3,762	Enrolment: NR Outcome: first 12 mo.	EBF $_{6\ mo}$ vs. EBF $_{3-4\ mo}$ with MBF thereafter	N episodes of otitis media: MD=-0.04 (-0.49-0.41) ≥1 episodes of otitis media: **RR=1.28 (1.04-1.57)** Frequent otitis media: RR=0.81 (0.43-1.52) Author conclusion: authors do not provide conclusions specific for the health outcomes in western countries.	-1966-2011 -4/10 publications of the two studies were included in the RIVM report (2007). -All studies were from western countries. -MD: Mean difference -RR: Risk ratio -Results are unadjusted. <u>Quality criteria</u> Partly fulfilled: - Not fulfilled: 1, 3, 4, 5
Acute otitis media	Hörnell, 2013	SLR	-Studies: n=4: 2 SLRs 2 pCH -Subjects: n between 6,752-21,452	Enrolment: NR Outcome: NR	BF	1/2 SLR found that BF was associated with significant reduction in AOM. 1/2 SLR found varying results of the effect of BF on AOM. 2/2 CH studies found no significant association between BF and AOM. Authors conclusion: convincing evidence that BF protects infants in industrialized countries against AOM* *Note: Hörnell based this conclusion on overall infections (AOM, gastrointestinal and respiratory tract infections).	- January 2000-June 2011 - 1/4 studies was included in the RIVM report (2007). - Included studies were from western countries. - All studies were graded A or B (out of A-C). <u>Quality criteria</u> Partly fulfilled: 1, 2, 3, 4, 5 Not fulfilled: -
Acute otitis media	RIVM, 2007	SLR	-Studies: n=17: 2 SLR 1 RCT 14 CH -Subjects: n=38,344-44,777	Enrolment: NR Outcome: NR Included age groups: 0-3 yrs (1 SLR: NR)	BF	The evidence for the effect of breastfeeding on otitis media is convincing, although for the effect on recurrent otitis media probable evidence was found.	-1980-September 2004, September 2004-February 2005 and February 2005 until July 2006 -All studies were from western countries (for two reviews NR) -Health outcomes: Otitis Media, acute Otitis Media, recurrent Otitis Media

Table C-14: Effect of breastfeeding on growth

Health outcome	Author, year	Design	Study population	Age group	Type of BF	Results			Remarks
Weight and length gain	Kramer, 2012	SLR+ pooled analysis	-Studies: n=5: 5 pCH -Subjects: n unclear	Enrolment: NR Outcome: 3-12 mo and 6.5 yrs	EBF 6 mo vs. 3-4 mo with MBF thereafter	<u>3-8 mo</u> *Monthly weight gain (g/mo.)* MD=-7.95 (-31.84-15.93) *Monthly length gain (cm/mo)* MD=-0.03 (-0.11-0.06)	<u>6-9 mo</u> MD=21.11 (-44.70-86.91) MD=-0.04 (-0.10-0.01)	<u>8-12 mo</u> MD=-1.82 (-16.72-13.08) **MD=0.09 (0.03-0.14)**	-1966-2011 -4/18 publications of the five studies were included in the RIVM report (2007). 1/18 publications was included in Hörnell (2012). -All studies were from western countries. -MD: Mean difference -RR: Risk ratio -Results are unadjusted. <u>Quality criteria</u> Partly fulfilled: - Not fulfilled: 1, 3, 4, 5
					EBF 6 mo vs. 3-4 mo with MBF thereafter	<u>6 mo</u> *Weight-for-age z-score <-2* RR=0.92 (0.04-19.04) *Length-for-age z-score <-2* RR=1.53 (0.84-2.78)	<u>9 mo</u> RR=1.52 (0.16-14.62) RR=1.46 (0.80-2.64)	<u>12 mo</u> RR=1.15 (0.13-10.31) RR=0.66 (0.23-1.87)	
					EBF 6 mo vs. 3-4 mo with MBF thereafter	*Weight-for-length z-score<-2* RR=0.31 (0.02-5.34) <u>Height at 6.5 yrs</u> MD=0.10 (-0.40-0.60)	RR=1.14 (0.24-5.37)	RR=1.15 (0.13-10.31)	
						Author conclusion: authors do not provide conclusions specific for the health outcomes in western countries.			
Growth	Hörnell, 2013	SLR	-Studies: n=7: 1 SLR 6 pCH -Subjects: n=38,557	Enrolment: NR Outcome: NR	EBF	1/1 SLR no association between EBF and growth 3/6 CH studies found no association between BF, BFD, EBF and growth. 1/6 CH studies found an association between EBF and slower growth. 1/6 CH studies found that smaller size was strongly associated with increased risks of subsequent weaning and discontinuing EBF. 1/6 CH studies found that those EBF <4 mo showed higher weight-for-length z-scores at 6-7 months compared to those EBF for ≥4 mo			- January 2000-June 2011 - 1/7 studies was included in the RIVM report (2007). 1/7 studies was included in Kramer (2012). - All prospective cohorts were form western regions. 11 out of 22 studies from the SLR were developing countries. - All studies were graded A or B (out of A-C). <u>Quality criteria</u> Partly fulfilled: 1, 2, 3, 4, 5 Not fulfilled: -
						Author conclusion: growth in infancy varied only a little between those EBF for 4 mo or 6 mo.			

Health outcome	Author, year	Design	Study population	Age group	Type of BF	Results	Remarks
Growth	RIVM, 2007	SLR	-Studies: n=4: 1 SLR 1 intervention 2 CH* -Subjects: n=27,731-28,685	Enrolment: NR Outcome: NR Included age groups: 0-12 mo	BF	Insufficient evidence of an effect of breastfeeding on growth is found.	-1980-September 2004, September 2004-February 2005 and February 2005 until July 2006 -All studies were from western countries. -Health outcomes: Weight gain, height gain, head circumference

Table C-15: Effect of breastfeeding on lung function

Health outcome	Author, year	Design	Study population	Age group	Type of BF	Results				Remarks
Lung growth and function	Waidyatillake, 2013	SLR	-Studies: n=8, in 10 publications: 7 pCH 3 CS -Subjects: n=21,992	Enrolment: 0-79 yrs Outcome: 4-79 yrs	BFD vs. no BF or shorter BF	FEV$_1$ 3/6 studies: positive association 3/6 studies: no association	FVC 3/4 studies: positive association 1/4 studies: no association	FEV$_1$/FVC 1/4 studies: positive association 3/4 studies: no association	Peak flow 2/4 studies: positive association 2/4 studies: no association	-NR-June 2013 -1/10 articles was included in the RIVM report (2007). 1/10 articles was included in Hörnell (2013) and Dogaru (2014). 1/10 articles was included in Dogaru (2014). -8/10 studies from western countries, 1/10 studies from worldwide, and 1/10 studies country unknown -3/10 studies assessed the evidence of possible effect of mediators: weight gain in the first year of life (may mediate the effect of BF on FVC); birth weight, number of lower respiratory tract infections, smoking pattern, and body fat (no mediating effect found in the BF/lung function relationship); atopy, asthma and lower respiratory tract infections (no evidence found that these factors mediate the effect of BF) -3/10 studies examined total BFD, 2/10 studies EBF duration, and 5/10 studies described BFD without defining it was exclusive or total. Quality criteria Partly fulfilled: 1, 2, 4, 5 Not fulfilled: 3
					BF vs. no BF	1/3 studies: positive association 2/3 studies: no association	1/1 study: no association		1/1 study: positive association	
						Author conclusion: beneficial effect of BF on lung function. No clear evidence that the relationship between BF and lung function was mediated through other factors				
Lung function	RIVM, 2007	Not available								

Table C-16: Effect of breastfeeding on dental caries

Health outcome	Author, year	Design	Study population	Age group	Type of BF	Results	Remarks
Caries	Kramer, 2012	SLR+ pooled analysis	-Studies: n=1: 1 pCH -Subjects: n=2,948	Enrolment: NR Outcome: 6 yrs	EBF $_{6\ mo}$ vs. EBF $_{3-4\ mo\ with\ MBF}$ $_{thereafter}$	Any dental caries (decayed, missing, or filled teeth): RR=0.98 (0.94-1.03) Any incisor caries (decayed, missing, or filled teeth): RR=0.91 (0.72-1.16) Author conclusion: authors do not provide conclusions specific for the health outcomes in western countries.	-1966-2011 -3/9 publications of the one study were included in the RIVM report (2007). -All studies were from western countries. -RR: Risk ratio -Results are unadjusted. Quality criteria Partly fulfilled: - Not fulfilled: 1, 3, 4, 5
Caries	RIVM, 2007	Not available					

Table C-17: Effect of breastfeeding on Hodgkin lymphoma

Health outcome	Author, year	Design	Study population	Age group	Type of BF	Results			Remarks
Hodgkin Lymphoma	Wang, 2013	SLR+ pooled analysis	-Studies: n=10: 10 CC -Subjects: n=1,618 cases and 8,181 controls	Enrolment: between 0-17 yrs Outcome: between 0-17 yrs	BF_{never} BF_{ever} $BFD_{0-6\ mo}$ $BFD_{>6\ mo}$ BF_{never} BF_{ever}	OR=1 OR=0.79 (0.58-1.08) OR=1.03 (0.78-1.37) OR=0.80 (0.46-1.39)			-Search dates not clear -3/10 studies were included in the RIVM report (2007). -7/10 studies were from western regions (3 from Asia). -5 studies scored >7 out of 9 possible stars. <u>Quality criteria</u> Partly fulfilled: 1, 5 Not fulfilled: 2, 4
						North America (n=2) OR=1 **OR=0.66 (0.49-0.89)**	Asia (n=3) OR=1 **OR=0.29 (0.12-0.70)**	Europe (n=5) OR=1 OR=1.10 (0.84-1.45)	
						Author conclusion: limited evidence for an inverse association between BF and risk of childhood Hodgkin lymphoma			
Hodgkin Lymphoma	Hörnell, 2013	SLR	-Studies: n=1: 1 SLRs -Subjects: n NR	Enrolment: NR Outcome: NR	BF	1 SLR found that BF was associated with lower risk for Hodgkin's disease.			- January 2000-June 2011 - The study was not included in RIVM (2007). - 1 SLR: Most studies from based in Europe or North America (including non-western countries) - SLR graded C(!) <u>Quality criteria</u> Partly fulfilled: 1, 2, 3, 4, 5 Not fulfilled: -
						Author conclusion: No conclusion for the effect of breastfeeding on Hodgkin's disease was stated in the article.			
Hodgkin Lymphoma	RIVM, 2007	SLR	-Studies: n=1 1 CC -Subjects: n=7,078	Enrolment: NR Outcome: NR. Included age group: 1-14 yrs	BF	Insufficient evidence was found for all cancer morbidity			-1980-September 2004, September 2004-February 2005 and February 2005 until July 2006 -Included study from western country

Table C-18: Effect of breastfeeding on diseases included in the previous RIVM reports [3 4]

Health outcome	Author, year	Design	Study population	Age group	Type of BF	Results	Remarks
Urinary tract infections	RIVM, 2007	SLR	-Studies: n=2: 2 CC -Subjects: n=792	Enrolment: NR Outcome: NR Included age groups: 0-2 yrs	BF	Insufficient evidence for a protective effect of BF on urinary tract infections	-1980-September 2004, September 2004-February 2005 and February 2005 until July 2006 -All studies were from western countries.
Haemophilus influenza	RIVM, 2007	SLR	-Studies: n=1: 1 CC -Subjects: n=193	Enrolment: NR Outcome: NR Included age groups: 0-6 yrs	BF	Insufficient evidence for a protective effect of BF on haemophilus influenza	-1980-September 2004, September 2004-February 2005 and February 2005 until July 2006 -All studies were from western countries.
Fever	RIVM, 2007	SLR	-Studies: n=2 -Subjects: n=1,939	Enrolment: NR Outcome: NR Included age groups: 0-24 mo	BF	Insufficient evidence for a protective effect of BF on fever	-1980-September 2004, September 2004-February 2005 and February 2005 until July 2006 -All studies were from western countries. -Health outcomes: hospitalisation Fever of unknown origin, >38°C
Pyloric stenosis	RIVM, 2007	SLR	-Studies: n=1: 1 CC -Subjects: n=306	Enrolment: NR Outcome: NR Included age groups: ±1 yr	BF	Insufficient evidence for an effect of BF on jaundice	-1980-September 2004, September 2004-February 2005 and February 2005 until July 2006 -All studies were from western countries.
Jaundice	RIVM, 2007	SLR	-Studies: n=3: 1 SLR 2 CH* -Subjects: n=4,009 (One review NR)	Enrolment: NR Outcome: NR Included age groups: 0-12 mo	BF	Conflicting evidence for an effect of BF on jaundice	-1980-September 2004, September 2004-February 2005 and February 2005 until July 2006 -One review included -All studies were from western countries (One review NR).
Lymphomas	RIVM, 2007	SLR	-Studies: n=2: 2 CC -Subjects: n=7,388	Enrolment: NR Outcome: NR Included age groups: 0-14 yrs	BF	Insufficient evidence for an effect of BF on lymphomas	-1980-September 2004, September 2004-February 2005 and February 2005 until July 2006 -All studies were from western countries. -Health outcomes: Malignant lymphoma, non-Hodgkin's lymphoma
Hospitalizations	RIVM, 2007	SLR	-Studies: n=2: 1 CH* 1 CC -Subjects: n=2,057 *unclear whether pCH or rCH	Enrolment: NR Outcome: NR Included age groups: 0-24 mo	BF	Possible evidence for a protective effect of BF on hospitalization	-1980-September 2004, September 2004-February 2005 and February 2005 until July 2006 -All studies were from western countries.
Cardiovascular disease	RIVM, 2007	SLR	-Studies: n=5: 1 SLR 3 CH* 1 CS -Subjects: n=93,295 (1 SLR: NR) *unclear whether pCH or rCH	Enrolment: NR Outcome: NR Included age groups: 9-68 yrs (1 SLR: NR)	BF	Possible evidence for no effect of BF on cardiovascular disease	-1980-September 2004, September 2004-February 2005 and February 2005 until July 2006 -Most studies were from western countries (Estonia) (1 SLR: NR). -Health outcomes: Cardiovascular disease, coronary heart disease, cholesterol

APPENDIX D: Summary tables – Health effects on the mother

Table D-1: Effect of breastfeeding on postpartum fatigue

Health outcome	Author, year	Design	Study population	Age group	Type of BF	Results	Remarks
Postpartum fatigue	Callahan, 2006	pCH	France n=247	Enrolment: 20-43 yrs (mean ± SD: 29.96 ± 4.55) Outcome: Same age, 12 weeks later	T1 EBF vs. FF T2 EBF vs. FF T2 EBF vs. (FF + quit BF) T3 EBF vs. FF T3 EBF vs. (FF + quit BF):	*BF and Pichot Fatigue Scores, descriptive statistics (BF, FF and those who switched from BF to FF)* |	T1			T2			T3		
	n	Mdn	IQR	n	Mdn	IQR	n	Mdn	IQR
EBF	128	7	3-10	68	4	1-9	25	4	2-6
FF	114	5	2-10	78	4	1-7	41	3	1-5
Quit BF	-			19	4	3-6	23	2	0-7	 Mdn: Median *Mann-Whitney analysis for the groups presented in the table above* U = 6,510, Z = -1.44; P = 0.14 U = 2,637, Z = -1.34; P = 0.17 U = 3,280, Z = -0.05; P = 0.95 U = 411, Z = -1.34; P = 0.17 U = 638, Z = -1.47; P = 0.13	-No adjustment for confounders -Assessment of BF on days 2, 3 or 4 (T1, baseline feeding choice), 6 weeks (T2) and 12 weeks (T3) postpartum <u>Quality criteria</u> Partly fulfilled: 2, 3 Not fulfilled: 5
Postpartum fatigue	RIVM, 2007	Not available					

Table D-2: Effect of breastfeeding on obesity/weight gain

Health outcome	Author, year	Design	Study population	Age group	Type of BF	Results			Remarks
Obesity	Schwarz, 2009	pCH, including historical data	USA n=139,681	Enrolment: median age: 63 yrs Outcome: Prevalent cases: median age 63 yrs Incident cases: NR, but during the median follow-up of 7.9 yrs	*Lifetime BF:* Never BF BF $_{1-6\ mo}$ BF $_{7-12\ mo}$ BF $_{13-23\ mo}$ BF $_{24+\ mo}$	OR=1 OR=1.00 (0.96-1.03) OR=0.96 (0.91-1.00) OR=0.95 (0.90-1.00) OR=1.02 (0.96-1.09)			Corrected for sociodemographic, family history and lifestyle variables Quality criteria Partly fulfilled: 2, 3, 4 Not fulfilled: 1
Obesity	Cohen, 2009	CS	USA n=31,184 (7,986 white and 23,198 black)	Enrolment: Average: early 50s (range 40-79 yrs) Outcome: Same	*Lifetime BF:* BF $_{1-3\ mo\ vs.\ no\ BF}$ BF $_{4-6\ mo\ vs.\ no\ BF}$ BF $_{7-12\ mo\ vs.\ no\ BF}$ BF $_{>12\ mo\ vs.\ no\ BF}$	<u>Overall</u> OR=1.02 (0.93-1.12) OR= 0.97 (0.86-1.09) OR=1.05 (0.94-1.18) OR=0.91 (0.82-1.00)	<u>White women</u> OR=0.95 (0.80-1.13) OR=1.05 (0.84-1.31) OR=0.86 (0.86-1.32) **OR=0.68 (0.56-0.82)**	<u>Black women</u> OR=1.07 (0.96-1.20) OR=0.95 (0.83-1.09) OR=1.07 (0.93-1.23) OR=1.04 (0.93-1.17)	Adjustment for parity, age, BMI at age 21, education, household income, menopausal status, marital status, current occupational status, smoking status, alcohol consumption, fruit and vegetable consumption, total MET-hrs/day of physical activity, depression based on CESD, use of oral contraceptives, and age of menarche Quality criteria Partly fulfilled: 3, 4 Not fulfilled: 1, 2
Obesity	Ram, 2008	CS	USA n=2,516	Enrolment: Mean (SD) Absence of MetSyn: 46.5 (2.2) yrs Presence of MetSyn: 46.7 (2.1) yrs Outcome: Same	BF $_{ever\ vs.\ never}$ Lifetime BFD $_{per\ year}$	**OR=0.70 (0.58-0.86)** **OR=0.86 (0.78-0.96)**			Adjustment for age, smoking history, parity, ethnicity, study site, socioeconomic status, physical activity, daily caloric intake and high school BMI Quality criteria Partly fulfilled: 2, 3 Not fulfilled: 1

Health outcome	Author, year	Design	Study population	Age group	Type of BF	Results			Remarks
BMI	Cohen, 2009	CS	USA n=31,184 (7,986 white and 23,198 black)	Enrolment: Average: early 50s (range 40-79 yrs) Outcome: Same	Lifetime BFD $_{per\ mo\ increase}$	*Current BMI* β ± SE = -0.003 ± 0.003 (p = 0.26)			Adjustment for parity, age, BMI at age 21, education, household income, menopausal status, marital status, current occupational status, smoking status, alcohol consumption, fruit and vegetable consumption, total MET-hrs/day of physical activity, depression based on CESD, use of oral contraceptives, and age of menarche Quality criteria Partly fulfilled: 3, 4 Not fulfilled: 1, 2
BMI	Dujmović, 2014	pCH	Croatia n=159	Enrolment: Mean age ± SD: 30.69 ± 5.05 yrs Outcome: NR, but follow-up for 6 months. Mean age ± SD: 30.69 ± 5.05 yrs	BF vs. no BF	Time since parturition 1 mo* BMI: 25.39 (3.95) vs 27.02 (6.31) (p = 0.250)	Time since parturition 3 mo* **BMI: 25.23 (4.24) vs 26.56 (4.18) (p = 0.048)**	Time since parturition 6 mo* **BMI: 23.43 (4.52) vs 24.96 (4.82) (p = 0.040)**	*No adjustment for confounders Quality criteria Partly fulfilled: 3 Not fulfilled: 5
BMI	Bobrow, 2013	CS	UK n=740,628	Enrolment: 50 – 64 yrs Outcome: 50 - 64 yrs Mean age ± SD: 57.5 ± 4 yrs	Lifetime BFD (mean in mo) No BF BF $_{< 6\ mo\ (2.3)}$ BF $_{6-9\ mo\ (7.3)}$ BF $_{≥10\ mo\ (18.5)}$ Change in mean BMI per 6 mo BF	Reference β = -0.24 (-0.21 to -0.26) β = -0.36 (-0.32 to -0.40) β = -0.53 (-0.50 to -0.57) β = -0.13 (-0.11 to -0.13)			Adjustment for age, region, parity, socioeconomic group, smoking, and physical activity Quality criteria Partly fulfilled: 3 Not fulfilled: 1

Health outcome	Author, year	Design	Study population	Age group	Type of BF	Results							Remarks
BMI	Wiklund, 2011	CS study	Finland n=198	Enrolment: mean age 48 yrs Outcome: mean age 48 yrs	*BF: Total mo/nr of children* SDB MDB LDB	BMI 16–20 years after the last parturition							SDB: Short duration of BF MDB: Medium duration of BF LDB: Long duration of BF Corrected for pre-pregnancy weight and BMI, age at first pregnancy, smoking, menopause status, level of education, previous and current participation in leisure-time physical activity, current dietary energy intake, number of biological children, and duration of exclusive and total BF months. Quality criteria Partly fulfilled: 3 Not fulfilled: 1
							SDB (n=67)	MDB (n=68)	LDB (n=62)	SDB vs. MDB p-value	SDB vs. LDB	MDB vs. LDB	
								Mean (SD)					
						BMI (kg/m^2)	27.3 (5.5)	24.4 (3.7)	24.6 (3.3)	**<0.001**	**0.001**	0.847	
Postpartum weight retention	Dujmović, 2014	pCH	Croatia n=159	Enrolment: Mean age ± SD: 30.69 ± 5.05 yrs Outcome: NR, but follow-up for 6 months. Mean age ± SD: 30.69 ± 5.05 yrs	BF vs. no BF Lactating = 1 Non-lactating = 2	Time since parturition 1 mo* Weight retention (kg): 6.91 (4.85) vs 7.77 (6.61) (p = 0.721) % of pre-pregnancy weight:110.79 (7.39) vs 113.37 (8.17) (p = 0.721)		Time since parturition 3 mo* **Weight retention (kg): 8.48 (5.05) vs 4.28 (4.04) (p = 0.001)** **% of pre-pregnancy weight:109.92 (7.47) vs 106.69 (8.08) (p = 0.009)**		Time since parturition 6 mo* **Weight retention (kg): 1.33 (5.45) vs 4.10 (4.93) (p = 0.001)** **% of pre-pregnancy weight:101.95 (8.21) vs 105.01 (7.39) (p = 0.014)**			*No adjustment for confounders -Regression analysis adjusted for time since parturition, gestational weight gain, average energy intake, average energy from fat, protein and carbohydrate Quality criteria Partly fulfilled: 3 Not fulfilled: 5
						Regression analysis **β = -0.281 (0.040); P < 0.001**							
Postpartum weight retention	Krause 2010	rCH	USA 3 mo postpartum sample: n=14,330/ 6 mo postpartum sample: n=4,922	Enrolment: NR Outcome: At 3 mo postpartum: 23.5 yrs (SD 5.5 yrs) At 6 mo postpartum: 25.2 yrs (SD 5.6 yrs)	MBF vs FF EBF vs FF	At 3 mo postpartum Regression coefficient= 0.18, SE=0.14, p=0.21 Regression coefficient=-0.33, SE=0.19, p=0.09			At 6 mo postpartum **Regression coefficient=-0.84, SE=0.23, p=0.0002** **Regression coefficient=-1.38, SE=0.25, p<0.0001**				Adjustment for age, race, ethnicity, education, parity, gestational weight gain and pre-pregnancy weight. Quality criteria Partly fulfilled: 3, 4 Not fulfilled: -

Health outcome	Author, year	Design	Study population	Age group	Type of BF	Results						Remarks
Weight gain	Wiklund, 2011	CS study	Finland n=198	Enrolment: Mean age 48 yrs Outcome: Mean age 48 yrs	*BF: Total mo/nr of children* SDB MDB LDB	*Weight gain 16–20 years after the last parturition*						SDB: Short duration of BF MDB: Medium duration of BF LDB: Long duration of BF Corrected for pre-pregnancy weight and BMI, age at first pregnancy, smoking, menopause status, level of education, previous and current participation in leisure-time physical activity, current dietary energy intake, number of biological children, and duration of exclusive and total BF months. Quality criteria Partly fulfilled: 3 Not fulfilled: 1
							SDB (n=67)	MDB (n=68)	LDB (n=62)	**SDB vs. MDB**	**SDB vs. LDB**	
								Mean (SD)		p-value		
						Weight gain (kg)	14.0 (9.1)	8.3 (6.5)	7.6 (6.6)	**0.001**	**<0.001**	
Weight change	Cohen, 2009	CS	USA n=31,184 (7,986 white and 23,198 black)	Enrolment: Average: early 50s (range 40-79 yrs) Outcome: Same	Lifetime BFD total mo	*Weight change in kg (weight at time of interview, minus weight at age 21)* $\beta \pm SE = 0.009 \pm 0.09$ (p = 0.92)						Adjustment for parity, age, BMI at age 21, education, household income, menopausal status, marital status, current occupational status, smoking status, alcohol consumption, fruit and vegetable consumption, total MET-hrs/day of physical activity, depression based on CESD, use of oral contraceptives, and age of menarche Quality criteria Partly fulfilled: 3, 4 Not fulfilled: 1, 2
Weight gain	RIVM, 2007	SLR	-Studies: n=2: 1 SLR 1 CH* -Subjects: n=540 (One review NR) *unclear whether pCH or rCH	Enrolment: NR Outcome: NR Included age groups: 25-51 yrs	BF	Insufficient evidence for an effect of BF on weight gain						-1980-September 2004, September 2004-February 2005 and February 2005 until July 2006 -All studies were from western countries.

Table D-3: Effect of breastfeeding on metabolic syndrome

Health outcome	Author, year	Design	Study population	Age group	Type of BF	Results	Remarks
Metabolic syndrome	Ram, 2008	CS	USA n=2,516	Enrolment: Mean (SD) Absence of MetSyn: 46.5 (2.2) yrs Presence of MetSyn: 46.7 (2.1) yrs Outcome: Same	BF $_{ever\ vs.\ never}$ Lifetime BFD $_{per\ year}$	**OR=0.77 (0.62-0.96)** **OR=0.88 (0.77-0.99)**	Adjustment for age, smoking history, parity, ethnicity, study site, socioeconomic status, physical activity, daily caloric intake and high school BMI <u>Quality criteria</u> Partly fulfilled: 2, 3 Not fulfilled: 1
Metabolic syndrome	RIVM, 2007	Not available					

Table D-4: Effect of breastfeeding on osteoporosis

Health outcome	Author, year	Design	Study population	Age group	Type of BF	Results				Remarks
						<u>Overall</u>	<u>Women who were ≥27 yrs at first pregnancy</u>	<u>BF and ≥27 yrs vs. no BF and <27 yrs at first pregnancy</u>	<u>Women who were ≥22 yrs at first pregnancy</u>	
Postmenopausal osteoporosis	Schnatz2010	CS	USA n=619	Enrolment: ≥49 yrs, mean age 61.4 yrs Outcome: Same, CS analysis	BF vs. no BF	Prevalence: **7.6% vs. 18.7%; p <0.001**	Prevalence: **4.6% vs. 25.4%; p <0.001**	Prevalence: **4.6% vs. 16.3%; p = 0.001**	Prevalence: **7.1% vs. 20.6%; p <0.001**	No adjustment for confounders <u>Quality criteria</u> Partly fulfilled: 2, 3 Not fulfilled: 1, 5
Postmenopausal osteoporosis	RIVM, 2007	Not available								

Table D-5: Effect of breastfeeding on gallbladder disease

Health outcome	Author, year	Design	Study population	Age group	Type of BF	Results	Remarks
Hospitalization for gallbladder disease	Liu, 2009	pCH	England and Scotland n=1,289,029	Enrolment: 50 – 64 yrs. Mean age 56.0 yrs (SD 4.7) Outcome: NR, but admissions occurred a mean of 3.4 yrs following recruitment	*Lifetime BF* BF vs. no BF BF $_{<6\ mo\ vs.\ no\ BF}$ BF $_{6-11\ mo\ vs.\ no\ BF}$ BF $_{\geq12\ mo\ vs.\ no\ BF}$ BFD $_{per\ year\ BF}$	**RR=0.92 (0.90-0.96)** RR=0.97 (0.93-1.00) **RR=0.89 (0.85-0.94)** **RR=0.85 (0.81-0.89)** **RR (95% CI) = 0.93 (0.90-0.95)**	Adjustment for age at recruitment, region of recruitment, socioeconomic status, BMI, smoking, hysterectomy, use of oral contraceptives, hormone replacement therapy, and parity. Quality criteria Partly fulfilled: - Not fulfilled: 1, 2
Hospitalization for gallbladder disease	RIVM, 2007	Not available					

Table D-6: Effect of breastfeeding on myocardial infarction

Health outcome	Author, year	Design	Study population	Age group	Type of BF	Results	Remarks
Myocardial infarction	Stuebe, 2009	pCH	USA n=89,326	Enrolment: 30 - 55 yrs Outcome: 40 – 81 yrs	*Lifetime BF* BF $_{0-3\ mo\ vs.\ no\ BF}$ BF $_{3-6\ mo\ vs.\ no\ BF}$ BF $_{6-11\ mo\ vs.\ no\ BF}$ BF $_{11-23\ mo\ vs.\ no\ BF}$ BF $_{>23\ mo\ vs.\ no\ BF}$	HR=1.01 (0.91-1.11) HR=1 (0.88-1.14) HR=1.02 (0.88-1.18) HR=0.93 (0.8-1.07) **HR=0.77 (0.62-0.94)** **P for trend= 0.02**	Adjustment for age, parity, history of stillbirth, BMI at age 18 years, birth weight of subject, parental history of MI before age 60 years, diet quintile, physical activity, smoking, menopausal status, use of aspirin, alcohol multivitamins and postmenopausal hormones Quality criteria Partly fulfilled: 2 Not fulfilled: 1
Myocardial infarction	RIVM, 2007	Not available					

Table D-7: Effect of breastfeeding on Alzheimer's disease

Health outcome	Author, year	Design	Study population	Age group	Type of BF	Results	Remarks
Alzheimer's disease	Fox, 2013	CC	UK 40 Cases 41 Controls	Enrolment: Cases: 86 yrs Controls: 80 yrs Outcome: Cases: 86 yrs Controls: 80 yrs	Total months BF $_{Exp(1)-fold\ higher\ value\ of\ BFSUM}$ BFD-to-pregnancy ratio $_{Exp(1)-fold\ higher\ value\ of\ BFSUM/PMONTHS}$ No BF BF	**HR= 0.78 (P < 0.01)** **HR= 0.77 (P = 0.022)** HR= 1 **HR= 0.36 (P = 0.017)**	BFSUM: total sum of months spent BF BFSUM/PMONTHS: ratio between BFSUM and total sum of months spent pregnant Corrected for age at interview and exponentiated age. <u>Quality criteria</u> Partly fulfilled: - Not fulfilled: 1, 2, 3
Alzheimer's disease	RIVM, 2007	Not available					

Table D-8: Effect of breastfeeding on depressive symptoms

Health outcome	Author, year	Design	Study population	Age group	Type of BF	Results	Remarks
Depressive symptoms	Hahn-Holbrook, 2013	pCH	USA n=205 (cases at -3 mo: 40 -6 mo: 31 -12 mo: 28 -24 mo: 24)	Enrolment: mean age 29 yrs Outcome: NR, but most depressive symptomatology was assessed in the first three months after birth	BF $_{at\ 3\ mo\ vs\ no\ BF}$ EBF vs. FF only, at 3 mo High % vs. low % breast milk at 3 mo* * % breast milk vs. FF	- No significant association between BF at month 3 vs. no BF and absolute levels of depression at 6, 12 or 24 months* - No absolute and change in depressive symptomatology at 3 mo* Covariates had no effect on the pattern of these results - No difference in absolute or change in of depressive symptomatology	* not adjusted Others corrected for maternal age, income, education, marital status, parity, preterm birth, maternal employment, ethnicity and, social support <u>Quality criteria</u> Partly fulfilled: 3 Not fulfilled: -
Depressive symptoms	RIVM, 2007	Not available					

Table D-9: Effect of breastfeeding on diabetes

Health outcome	Author, year	Design	Study population	Age group	Type of BF	Results		Remarks
Diabetes type 2	Aune, 2014	SLR+ MA	-Studies: n=6: pCH: 6 -Subjects: n=273,961	Enrolment: NR Outcome: NR	BFD low BFD high BFD lifetime, per 12 mo BFD per 3 mo per child	<u>Overall</u> RR= 1 **RR= 0.68 (0.57-0.82)** RR= 0.91 (0.86-0.96) (n=4) RR= 0.89 (0.77-1.04) (n=3)	<u>Europe (n=1)-America (n=3)-Australia (n=1)</u> RR= 1 **RR Europe= 0.54 (0.34-0.85)** **RR America = 0.77 (0.63-0.94)** **RR Australia = 0.58 (0.50-0.68)**	-Up to September 19th 2013 -1/6 studies was included in the RIVM report (2007). 2/6 studies were included in the review by Jäger, 2014. -5/6 studies were from western regions (1 from China). -All studies scored 6 to 8 stars out of 9 possible. <u>Quality criteria</u> Partly fulfilled: 4 Not fulfilled: 1, 2, 3
						Author conclusion: The longest duration of breastfeeding compared to no breastfeeding was associated with a 32% reduction in the relative risk of type 2 diabetes, independent of other risk factors.		
Diabetes type 2	Jäger, 2014	SLR+ MA	-Studies: n=4, of which 3 with relevant outcomes pCH: 3 -Subjects: n=220,360	Enrolment: NR Outcome: 4.6-16 yrs	*Lifetime BF* BF vs. no BF BF >0 to 3 mo vs. no BF BF >3 to 6 mo vs. no BF BF >6 to 11 mo vs. no BF BF >11 to 23 mo vs. no BF BF per additional year of BF	HR=0.86 (0.71-1.02) HR=0.98 (0.92-1.05) HR=1.01 (0.93-1.10) HR=0.92 (0.85-1.00) **HR=0.90 (0.83-0.99)** **HR=0.94 (0.91-0.97)**		-Search period: NR -1/3 studies was included in the RIVM report (2007). 2/3 studies were included in the review by Aune (2014). -2/3 studies were from western countries. -Analyses were adjusted for potential confounders (which varied per included cohort) plus baseline BMI. <u>Quality criteria</u> Partly fulfilled: 2, 4 Not fulfilled: 1
						Author conclusion: Longer breast-feeding duration may be related to lower maternal type 2 diabetes risk. However, the role of body weight as a mediator or confounder remains uncertain.		
Diabetes type 2	RIVM, 2007	SLR	-Studies: n=1: 1 CH* -Subjects: n=157,003 *unclear whether pCH or rCH	Enrolment: 25-55 yrs Outcome: NR	BF	Possible evidence for a protective effect of BF on diabetes type 2		-1980-September 2004, September 2004-February 2005 and February 2005 until July 2006 -The study was from a western country.

Table D-10: Effect of breastfeeding on fractures

Health outcome	Author, year	Design	Study population	Age group	Type of BF	Results	Remarks
Wrist fractures	Bjørnerem, 2011	pCH	Norway n=3,748	Enrolment: 63.3 yrs (range 50 to 94 yrs) Outcome: NR	*Lifetime BF* No BF BF BFD $_{1-9\ mo}$ BFD $_{10-19\ mo}$ BFD $_{\geq20\ mo}$	HR= 1 HR= 1.06 (0.68-1.66) HR= 1.08 (0.68-1.73) HR= 1.05 (0.66-1.69) HR= 1.04 (0.65-1.66)	-Corrected for age, BMI, height, current smoking, alcohol use, HRT use, physical activity, a history of diabetes, previous hip or wrist fracture and length of education. <u>Quality criteria</u> Partly fulfilled: 2 Not fulfilled: 1
Hip fractures	Bjørnerem, 2011	pCH	Norway n=3,748	Enrolment: 63.3 yrs (range 50 to 94 yrs) Outcome: NR	*Lifetime BF* No BF BF BFD $_{1-9\ mo}$ BFD $_{10-19\ mo}$ BFD $_{\geq20\ mo}$	HR= 1 **HR= 0.50 (0.32-0.78)** **HR= 0.51 (0.31-0.83)** **HR= 0.49 (0.30-0.80)** **HR= 0.50 (0.31-0.81)**	-Corrected for age, BMI, height, current smoking, alcohol use, HRT use, physical activity, a history of diabetes, previous hip or wrist fracture and length of education. <u>Quality criteria</u> Partly fulfilled: 2 Not fulfilled: 1
Hip fractures	RIVM, 2007	SLR	-Studies: n=3: 1 CH* 2 CC -Subjects: n=3,491 *unclear whether pCH or rCH	Enrolment: NR Outcome: NR Included age groups: ≥60 yrs	BF	Insufficient evidence for an effect of BF on hip fractures	-1980-September 2004, September 2004-February 2005 and February 2005 until July 2006. -All studies were from western countries. -Health outcome: hip fracture and bone density

Table D-11: Effect of breastfeeding on hypertension

Health outcome	Author, year	Design	Study population	Age group	Type of BF	Results		Remarks
Hypertension	Schwarz, 2009	pCH, including historical data	USA n=139,681	Enrolment: median age: 63 yrs Outcome: Prevalent cases: median age 63 yrs Incident cases: NR, but during the median follow-up of 7.9 yrs	*Lifetime BF* Never BF BF 1-6 mo BF 7-12 mo BF 13-23 mo BF 24+ mo	OR= 1 **OR= 0.95 (0.92-0.98)** **OR= 0.88 (0.84-0.92)** **OR= 0.89 (0.84-0.93)** **OR= 0.87 (0.82-0.92)** P for trend < 0.001		Corrected for sociodemographic, family history, lifestyle variables and BMI. Quality criteria Partly fulfilled: 2, 3, 4 Not fulfilled: 1
Hypertension	Stuebe, 2011 USA	pCH, including historical data	USA n=55,636 registered nurses (8,861 incident cases)	Enrolment: mean age 35.1-37.3 yrs Outcome: NR	Never BF BF >0-3 mo BF >3-<6 mo BF 6-<9 mo BF 9-<12 mo BF ≥12 mo Never BF BF, never EBF EBF >0-3 mo EBF >3-<6 mo EBF ≥6 mo	BF for the first child **HR= 1.22 (1.13-1.31)** **HR= 1.24 (1.15-1.33)** **HR= 1.13 (1.05-1.22)** **HR= 1.09 (1.01-1.17)** HR= 1.03 (0.96-1.11) HR= 1 P trend < 0.001 EBF for the first child **HR= 1.22 (1.13-1.31)** **HR= 1.07 (1.00-1.15)** HR= 1.08 (0.99-1.18) HR= 1.04 (0.96-1.13) HR= 1	Mean duration/child* **HR= 1.16 (1.07-1.26)** **HR= 1.13 (1.05-1.22)** **HR= 1.13 (1.05-1.21)** HR= 1.07 (0.99-1.15) HR= 1.08 (0.99-1.17) HR= 1 P trend < 0.001 Mean EBF duration/child* **HR= 1.12 (1.02-1.23)** **HR= 1.09 (1.00-1.19)** HR= 1.07 (0.98-1.16) HR= 1.04 (0.95-1.13) HR= 1	Corrected for age, maternal BMI at age 18 years, year of first birth, self-reported history of preeclampsia, gestational hypertension, gestational diabetes, birth of an infant at <37 weeks' gestation, birth of an infant weighing <2,500 g, miscarriage or stillbirth at >12 weeks' gestation, smoking status, vigorous physical activity, alcohol consumption, DASH diet score quintile, family history of hypertension, current oral contraceptive use, current nonnarcotic analgesic use, self-reported race and current BMI *additionally adjusted for parity. Quality criteria Partly fulfilled: 2, 3, 4 Not fulfilled: 1
Hypertension	Ram, 2008	CS	USA n=2,516	Enrolment: Mean (SD) Absence of MetSyn: 46.5 (2.2) yrs Presence of MetSyn: 46.7 (2.1) yrs Outcome: Same	BF ever vs. never BF Lifetime BFD per year	**OR=0.83 (0.68-0.998)** **OR=0.90 (0.81-0.996)**		Adjustment for age, smoking history, parity, ethnicity, study site, socioeconomic status, physical activity, daily caloric intake and high school BMI Quality criteria Partly fulfilled: 2, 3 Not fulfilled: 1
Hypertension	RIVM, 2007	Not available						

Table D-12: Effect of breastfeeding on macular degeneration

Health outcome	Author, year	Design	Study population	Age group	Type of BF	Results	Remarks
Macular degeneration	Erke, 2013 Norway	CS	n=1,057 (48 cases)	Enrolment: NR, but between 65-87 yrs Outcome: NR, but between 65-87 yrs	BF $_{total\ per\ 3\ mo}$ BF $_{per\ mo}$ BF$_{\geq 3\ mo\ vs.\ not}$ $_{\geq 3\ mo}$ BF$_{\geq 4\ mo\ vs.\ not}$ $_{\geq 4\ mo}$ BF$_{\geq 6\ mo\ vs.\ not}$ $_{\geq 6\ mo}$	**OR= 0.84 (0.73-0.97; P = 0.02)** **OR= 0.80 (0.68-0.94; P = 0.01)** **OR= 0.37 (0.16-0.85; P = 0.02)** **OR= 0.24 (0.09-0.62; P <0.01)** **OR= 0.09 (0.02-0.44; P <0.01)**	Corrected for Age, smoking, systolic blood pressure, BMI, total cholesterol, cardiovascular disease, number of children given birth to, age at first childbirth, physical activity. <u>Quality criteria</u> Partly fulfilled: 2, 3 Not fulfilled: 1
Macular degeneration	RIVM, 2007	Not available					

Table D-13: Effect of breastfeeding on breast disease

Health outcome	Author, year	Design	Study population	Age group	Type of BF	Results			Remarks
Pre- and postmenopausal breast cancer	Yang, 2008	SLR	-Studies: n=31 CC: 30 CH: 1* -Subjects: n=57,307 (2 studies: NR) *unclear whether pCH or rCH	Enrolment: 18-90 yrs* Outcome: NR	BF $_{ever\ vs,\ never}$ BF $_{some\ amount\ of}$ $_{extended\ BFD}$** BF history	11/27 studies: significant protective association 13/24 studies: significant protective association 4/8 studies: no significant effect in either pre- or postmenopausal women 2/8 studies: protective effect in both pre- or postmenopausal women 1/8 studies: significant protective effect only among postmenopausal women 1/8 studies: significant protective effect only among premenopausal women Author conclusion: The systematic review did not yield consistent findings for the association between ever breastfeeding or cumulative breastfeeding duration and breast cancer.			-1999-2007 -5/31 articles were included in the RIVM report (2007). -4/18 studies were from western countries. -Some articles corrected for: menstrual history, reproductive history, reproductive system diseases, endocrine diseases, other health issues, and medication. *For some studies it was only reported that population consisted of adults. **Ranges of durations assessed were not consistent. <u>Quality criteria</u> Partly fulfilled: 5 Not fulfilled: 1, 2, 3, 4
Premenopausal breast cancer	Stuebe, 2009	pCH, including historical data	USA n=60,075	Enrolment: Between 25-42 yrs Outcome: mean age 46.2 yrs	*Lifetime BF* BF $_{never}$ BF $_{ever}$ BFD $_{<1\ mo}$ BFD $_{>1-3\ mo}$ BFD $_{>3-6\ mo}$ BFD $_{>6-12\ mo}$ BFD $_{>12-24\ mo}$ BFD $_{>24-36\ mo}$ BFD $_{>36\ mo}$ BF, never EBF EBF $_{>0-3\ mo}$ EBF $_{>3-6\ mo}$ EBF $_{>6-12\ mo}$ EBF $_{>12-18\ mo}$ EBF $_{>18\ mo}$	<u>Overall</u> HR=1 HR=0.75 (0.56-1.00) HR=0.93 (0.63-1.38) HR=0.72 (0.46-1.11) **HR=0.54 (0.36-0.82)** HR=0.78 (0.56-1.08) HR=0.71 (0.51-1.00) HR=0.92 (0.64-1.32) **HR=0.63 (0.40-0.99)** HR=1 HR=0.94 (0.69-1.28) HR=1.08 (0.82-1.43) HR=1.07 (0.84-1.36) HR=1.09 (0.80-1.48) HR=0.86 (0.54-1.39)	<u>No family history of BC</u> HR=1 HR=0.89 (0.64-1.22) HR=1.08 (0.70-1.67) HR=0.82 (0.50-1.33) HR=0.66 (0.42-1.05) HR=0.90 (0.62-1.30) HR=0.88 (0.60-1.28) HR=1.16 (0.77-1.75) HR=0.68 (0.41-1.12)	<u>Family history of BC</u> HR=1 HR=0.41 (0.22-0.75) HR=0.54 (0.21-1.43) HR=0.51 (0.19-1.36) **HR=0.23 (0.08-0.66)** HR=0.48 (0.24-0.98) **HR=0.35 (0.17-0.74)** **HR=0.33 (0.14-0.79)** HR=0.42 (0.16-1.09)	Height, BMI, BMI at age 18 years, and year of first birth (continuous); family history of first- or second-degree relative with breast cancer, history of benign breast disease, and use of medications to suppress lactation (dichotomous); and birth weight of participant, age at menarche, parity, and age at first birth; physical activity; alcohol consumption; and oral contraceptive use (categorical) <u>Quality criteria</u> Partly fulfilled: 1 Not fulfilled: -

Health outcome	Author, year	Design	Study population	Age group	Type of BF	Results	Remarks
Premeno-pausal breast cancer	RIVM, 2007	SLR	-Studies: n=12: 1 SLR 1 CH* 10 CC -Subjects: n=106,289 (One review: NR *unclear whether pCH or rCH	Enrolment: NR Outcome: NR Included age groups: <80 yrs (6 NR)	BF	Possible evidence for a protective effect of BF on premenopausal breast cancer	-1980-September 2004, September 2004-February 2005 and February 2005 until July 2006 -All studies were from western countries (One review: NR).
Postmeno-pausal breast cancer	RIVM, 2007	SLR	-Studies: n=8: 1 CH* 7 CC -Subjects: n=119,821 *unclear whether pCH or rCH	Enrolment: NR Outcome: NR Included age groups: 40-80 yrs (2 NR)	BF	Insufficient evidence for an effect of BF on postmenopausal breast cancer	-1980-September 2004, September 2004-February 2005 and February 2005 until July 2006. -All studies were from western countries.
Benign breast disease – Fibroadenoma	Bernardi, 2012	CC	Italy n=203 (Cases: 105 Controls: 98)	Enrolment: Mean age Cases: 31.5 yrs Controls: 32.3 yrs Outcome: Mean age Cases: 31.5 yrsControls: 32.3 yrs	Lifetime BF $_{per\ mo\ BFD}$ BF $_{per\ month}$ $_{BFD/child}$	OR=1.01 (0.99-1.09) OR=1.06 (1.00-1.17)	Adjustment for age, parity, BMI, hormonal contraception usage and menarche Quality criteria Partly fulfilled: 1, 2, 3 Not fulfilled: -
Benign breast disease – Fibroadenoma	RIVM, 2007	Not avail-able					

Table D-14: Effect of breastfeeding on ovarian cancer

Health outcome	Author, year	Design	Study population	Age group	Type of BF	Results			Remarks
Ovarian cancer	Luan, 2013	SLR+ MA	-Studies: n=35 CC: 30 pCH: 5 -Subjects: n=14,465 cases and 706,152 non-cases	Enrolment: NR Outcome: NR	*Lifetime BF* BF ever vs. never BF longest vs. shortest BF per 5 mo increase	<u>All countries</u> **RR=0.76 (0.69-0.83)** **RR=0.65 (0.55-0.78)** **RR=0.92 (0.90-0.95)**	<u>Europeans (n=8)</u> RR=0.85 (0.69-1.06) RR=0.81 (0.59-1.10) RR=0.96 (0.90-1.01)	<u>Americans (n=13)</u> **RR=0.71 (0.63-0.81)** **RR=0.55 (0.43-0.71)** **RR=0.89 (0.85-0.93)**	-Database initiation-Dec 31, 2012 -8/35 studies were included in the RIVM report (2007). -24/35 studies were from western countries. -Health outcome: Epithelial ovarian cancer
						Author conclusion: The findings from the meta-analysis suggest that breastfeeding, particularly a longer duration of breastfeeding, was inversely associated with risk of EOC.			<u>Quality criteria</u> Partly fulfilled: 3, 5 Not fulfilled: 1
Ovarian cancer	RIVM, 2007	SLR	-Studies: n=10: 10 CC -Subjects: n=23,460	Enrolment: NR Outcome: NR Included age groups: <80 yrs	BF	Possible evidence for a beneficial effect of BF on ovarian cancer			-1980-September 2004, September 2004-February 2005 and February 2005 until July 2006 -All studies were from western countries. -Health outcomes: ovarian cancer and borderline ovarian tumours

Table D-15: Effect of breastfeeding on cardiovascular disease

Health outcome	Author, year	Design	Study popu-lation	Age group	Type of BF	Results			Remarks
Cardiovascular disease	Schwarz, 2009	pCH, including historical data	USA n=139,681	Enrolment: median age: 63 yrs Outcome: Prevalent cases: median age 63 yrs Incident cases: NR, but during the median follow-up of 7.9 yrs	*Lifetime BF* Never BF BF 1-6 mo BF 7-12 mo BF 13-23 mo BF 24+ mo	Prevalent cardiovascular disease OR=1 OR=1.03 (0.98-1.09) OR=0.95 (0.88-1.02) OR=0.93 (0.85-1.01) **OR=0.89 (0.80-0.98)**	Incident cardiovascular disease OR=1 OR=1.03 (0.98-1.08) OR=0.97 (0.90-1.04) OR=0.98 (0.91-1.05) OR=0.93 (0.85-1.02)		Adjustment for sociodemographic, family history, lifestyle variables and BMI <u>Quality criteria</u> Partly fulfilled: 2, 3, 4 Not fulfilled: 1 *unadjusted results
					Never BF BFD 7-12 mo BFD 13-23 mo BFD ≥24 mo	Women aged 50-59 yrs Prevalent cases OR=1 **OR=0.84 (0.71-0.99)** **OR=0.80 (0.65-0.97)** **OR=0.75 (0.58-0.96)**	Women aged 60-69 yrs Prevalent cases OR= OR=NS OR=0.85 (0.75-0.96) OR=NS	Women aged 70-79 yrsPrevalent cases No significant association found	
					Never BF BFD 7-12 mo BFD 13-23 mo BFD ≥24 mo.	Incident cases HR=1 **HR=0.80 (0.67-0.95)** HR=NS **HR=0.68 (0.52- 0.89)**	Incident cases No significant association found	Incident cases No significant association found	
					Never BF BFD 7-12 mo BFD 13-23 mo BFD ≥24 mo	One live birth* Incident cases HR=1 **HR=0.72 (0.53-0.97)** HR=NS HR=NS	Two live births* Incident cases HR=1 HR=NS HR=NS **HR=0.58 (0.35-0.95)**	Three live births* Incident cases HR=1 HR=NS HR=NS **HR=0.78 (0.63-0.98)**	
Cardiovascular disease	RIVM, 2007	Not available							

Table D-16: Effect of breastfeeding on diseases included in the previous RIVM reports [3] [4]

Health outcome	Author, year	Design	Study population	Age group	Type of BF	Results	Remarks
Cervical cancer	RIVM, 2007	SLR	-Studies: n=1: 1 CC -Subjects: n=2,994	Enrolment: NR Outcome: NR Included age groups: 40-79 yrs	BF	Insufficient for an effect of BF on cervical cancer	-1980-September 2004, September 2004-February 2005 and February 2005 until July 2006 -All studies were from western countries.
Glioma	RIVM, 2007	SLR	-Studies: n=1: 1 CC -Subjects: n=689	Enrolment: NR Outcome: NR Included age groups: 18-80 yrs	BF	Insufficient for an effect of BF on glioma	-1980-September 2004, September 2004-February 2005 and February 2005 until July 2006 -All studies were from western countries.
Rheumatoid arthritis	RIVM, 2007	SLR	-Studies: n=3: 2 CH* 1 CC -Subjects: n=168,084 *unclear whether pCH or rCH	Enrolment: NR Outcome: NR Included age groups: 28-84 yrs	BF	Convincing evidence for a protective effect of BF on rheumatoid arthritis	-1980-September 2004, September 2004-February 2005 and February 2005 until July 2006 -All studies were from western countries.

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