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Health gain and economic evaluation of breastfeeding policies
Model simulation

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Abstract

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A policy aiming at increasing the percentage of breasted infants can be seen as a preventive measure, which can save health care costs.

A literature review shows that breastfeeding has beneficial health effects in both the short en the longer term. Convincing evidence is found for a protective effect of breastfeeding on gastrointestinal infections, otitis media, obesity and high blood pressure for the child and on rheumatoid arthritis for the mother. The health effects and economic consequences of several intervention scenarios are simulated and compared to the present situation. The largest health gain and savings of health care costs can be achieved when all newborns get breastfeeding for at least six months. Greater public health gain can be achieved by introducing breastfeeding to all newborns than trough a policy only focussing on extending the lactation of women already breastfeeding beyond three months.

The model simulation is also used to calculate the effects of the Masterplan Breastfeeding and the new targets of the Dutch Government on breastfeeding (the government intends to stimulate that 85% of Dutch mothers start breastfeeding and that after six month still 25% of the mothers breastfeed exclusively). Although many assumptions had to be made, the calculations show that the Master plan 2002-2006 was a successful intervention. In addition, if the new objective is achieved possibly an additional 1200 DALYs could be gained and 10 million euro net present value could be saved each year.

Keywords: breastfeeding; formula feeding; modelling; health benefits; health risks; costs

Rapport in het kort

Gezondheidswinst en kosten-batenanalyse van interventies op het gebied van borstvoeding
Modelberekeningen

Het beleid om het aantal pasgeborenen dat borstvoeding krijgt te verhogen is niet alleen een maatregel die tot preventie van ziekten leidt maar ook besparingen in de gezondheidszorg kan opleveren.

Literatuuronderzoek laat zien dat borstvoeding gunstige gezondheidseffecten heeft, zowel op korte termijn als op lange termijn. Overtuigend bewijs is aanwezig dat borstvoeding bij het kind een beschermend effect heeft op infecties van het maagdarmkanaal, middenoorontsteking, overgewicht en hoge bloeddruk en voor de moeder op reumatische artritis. De gezondheidseffecten en de besparingen in de gezondheidszorg van verschillende interventies op het gebied van borstvoeding zijn gesimuleerd en vergeleken met de huidige situatie. De grootste gezondheidswinst en besparingen kunnen worden bereikt wanneer alle pasgeborenen minimaal zes maanden borstvoeding krijgen. Verder wordt een groter effect bereikt met maatregelen gericht om alle pasgeborenen borstvoeding te laten krijgen dan met maatregelen alleen gericht op het verlengen van de periode van borstvoeding door moeders die dat nu al drie maanden doen.

De effecten van het Masterplan Borstvoeding en de nieuwe doelstelling van de Nederlandse overheid voor borstvoeding (de overheid wil promoten dat 85% van de Nederlandse moeders starten met borstvoeding geven en dat na zes maanden nog steeds 25% van de moeders exclusieve borstvoeding geven) zijn ook berekend. Hoewel er vele aannames hierbij gemaakt zijn, is het Masterplan een succesvolle interventie. Wanneer de nieuwe doelstelling van het ministerie voor VWS wordt bereikt, zullen naar verwachting per jaar 1200 DALYs worden gewonnen en 10 miljoen euro netto contante waarde aan kosten van de gezondheidszorg worden bespaard.

Trefwoorden: borstvoeding; flesvoeding; modelleren; gezondheidseffecten; gezondheidskosten

Contents

Summary

Introduction
Because breastfeeding is associated with all sorts of positive health effects, the policy of the Dutch government is to increase the percentage of breastfeeding mothers. In order to underpin the Dutch policy related to breastfeeding the Dutch National Institute for Public Health and the Environment (RIVM) was asked to perform a risk-benefit analysis regarding several breastfeeding policies.

In 2005 RIVM has published a first report[197] on health effects of breastfeeding and breastfeeding policies. It is a review of the scientific literature on health effects associated with breastfeeding and describes the development of a model with which health effects of policies on breastfeeding can be simulated. The report at hand is an update that incorporates the most recent findings from the scientific literature. Furthermore, it describes the extension of the model with a module on health care costs. This allows for the computation of health care cost savings and costs effectiveness of policies on breastfeeding in addition to health gains.

The model is used to evaluate the health effects and health care costs of some hypothetical scenarios, as in the 2005 report, but also that of the new policy targets and some specific interventions.

Methods
Medline was used to search literature on health effects of breastfeeding from February 2005 until July 2006. As in the 2005 report, search terms were: 'breastfeeding', 'lactation' or 'human milk'. But we used combinations with known health outcomes like 'otitis media', 'asthma', or 'obesity' as well. The search was limited to articles published in English or Dutch and included only study populations from Western Europe, North America, Australia and New Zealand. The studies are classified according to quality and strength of the evidence.

Based on the reported relative risks or odds ratios for several diseases and given the fraction of infants that is breastfed for a particular period, the model computes the incidences of several diseases for children as well as mothers, and a combined health measure, the Disability Adjusted Life Years (DALY).
The updated literature resulted in an update of some parameters in the model. In addition an extra module was added to simulate health care costs. Dutch data[183] on health care costs were added to the model. This allowed for the computation of associated costs with each simulated disease episode or incident case. Consequently, the model can simulate health care costs. Costs are expressed as net present value for which we used a discount rate of 4%. This is a method to represent the total costs spend during the lifetime of mother and child in one number. If the costs of a scenario/intervention is known, the cost effectiveness ratio can also be computed.

Several scenarios are simulated. We simulated a best-case scenario, a worse case scenario and some other hypothetical scenarios to investigate the realm of possibilities. Furthermore, scenarios were made to evaluate policies such as the Masterplan and certification of health care centers.

Results
An update of the literature shows that convincing evidence is found for an association between breast feeding and gastrointestinal infections, otitis media, obesity or high blood pressure for the child. For the mother convincing evidence is found for the protective effect of breastfeeding on rheumatoid arthritis. The longer the duration of breastfeeding the larger the health effect.

Although many new studies were found, the strength of evidence has only changed in four health outcomes. Additionally, two new health outcomes were added to the overview, *celiac disease* for children and *diabetes mellitus type 2* for mothers. The protective effect of breastfeeding has become more evident. No evidence was found to bring down the protective effect of breastfeeding on any of the health outcomes.

Model simulations showed that maximally 50 million euro net present value could be saved on health care costs annually if all mothers would breastfeed for at least six months. A more realistic estimate would be 4 million euro annually, when we assume a much more moderate change, like a 5% shift, from the present behaviour resulting in health care costs savings of some 20 euro per newborn. If the target of the new policy could be achieved it would result in costs savings of 10 million euro net present value each year.

Although many assumptions are made, the model simulation shows that the Masterplan Breastfeeding was a successful intervention. Through the Masterplan health gain is achieved of 0.002 DALYs per newborn and health care costs decreased with 20 euro net present value per newborn.

Strengths and limitations
The report shows a comprehensive overview of the literature. The model development allows for quantified evaluation of (potential) policies that would not have been possible otherwise.
Of course uncertainties remain. Model simulation uses many assumptions to simplify the real world. First of all, in the quantification of the health effects and savings, we had to define which health effects were included in the calculations. All diseases with at least possible evidence for an association with breastfeeding are included in the model simulation. Secondly, we assumed that the associations between breastfeeding and health outcomes that are recently found in other developed countries are also valid for the general Dutch population. Another assumption is that the residual confounding for the association between breastfeeding and health outcomes is limited, although it never can be excluded.

In addition, many model parameters had to be estimated. Although a lot of research is done on this topic, still some parameters are estimated with only a small number of studies or some detail is not taken into account. For example, not all results from the literature overview could be incorporated in the model, because of the differences in study population, study design, in definition of breastfeeding, or in that of disease qualification. Or for instance no distinction is made between exclusive and mixed breastfeeding.

Additionally, it is important to consider in the evaluation of the costs, only the health care costs are taken into account. Even in these calculations, lack of data, for instance the health care costs of overweight children, could have lead to an underestimation of the health care costs.

Although the exact results in terms of health gain and savings are rather uncertain, the model approach does allow for ranking of most successful and cost effective policies. Therefore modelsimulation is a good method to underpin breastfeeding policy.

Conclusions
Our conclusion that breastfeeding has beneficial health effects for the mother and child has not changed since the last report. This concerns both the short term and the longer term.
Model simulations showed that if the new Masterplan of 2007-2010 is succesfull reaching the new targets of the Dutch Government on this topic, about and about 21% of the maximum health gain (*best-case scenario*) attainable with breastfeeding will be achieved.
Finally, a policy aiming at increasing the percentage of breasted infants can be seen as a preventive measure, which can also save health care costs.

List of abbreviations

BF	Breastfeeding
FF	Formula feeding
EBF	Exclusive breastfeeding
MBF	Mixed breastfeeding
DALY	Disability Adjusted Life Year
VWS	Ministry of Health, Welfare and Sport
ISRHML	The International Society for Research in Human Milk and Lactation
RIVM	Dutch National Institute for Public Health and the Environment
YLD	Years Lived with the Disease
YLL	Years of Life Lost
CER	Cost Effectiveness Ratio
WHO	World Health Organization

1. Introduction

1.1 Background

The World Health Organization (WHO) and UNICEF recommend exclusive breastfeeding from birth until the first six months of life and sustained breastfeeding together with adequate complementary foods thereafter for up to two years of age or beyond.[206] However, in the Netherlands only one out of four mothers comply with this recommendation by giving exclusive breastfeeding for the first six months.[105] Policy of the Dutch government related to breastfeeding aims at increasing this percentage of breastfeeding mothers. In order to underpin the Dutch policy related to breastfeeding the Dutch National Institute for Public Health and the Environment (RIVM) was asked to perform a risk-benefit analysis for breastfeeding.

In 2005, a literature review was performed by the RIVM[197] (report titled 'Quantification of health effects of breastfeeding') shows that breastfeeding has beneficial health effects compared to formula feeding on both the short and the longer term. Secondly, a model was created to quantify these health effects of breastfeeding for mother and infant for different theoretical policy issues on breastfeeding.[197] For example, to calculate the health gain if more mothers give breastfeeding or for a longer period.

Recently, new targets for the percentage of breastfeeding mothers are defined by the policy makers. It would be interesting to know what the health gain and also the economic consequences would be of this new policy. In the last report the health gain of only theoretical scenarios are estimated. The question arises what health gain and saving of health care costs is and should be reached with specific interventions.

1.2 Aim of this study

The aim of this study is bipartite. Firstly, the health effects of the new policy targets and some specific interventions are quantified in terms of the health gain. Secondly, the health care costs are evaluated for different interventions on breastfeeding.

Before these aims can be reached the breastfeeding model is updated with the most recent literature, as since the last report, new studies have been published. In addition, the module which simulates the health care cost is added to the model.

1.3 Approach

To quantify the health effects and economic consequences of interventions on breastfeeding a model simulation is used. As described in the last report[197], this model is programmed in Microsoft Excel. Based on a extensive literature study, dose-response functions are estimated for eight infant diseases or disorders related to breastfeeding. This is also done for three diseases related to breastfeeding for the mother. In this way the model describes the risk of disease development related to the duration of breastfeeding (in months). Besides incidence

estimations, also estimations about the burden of the eleven diseases, expressed in Disability Adjusted Life Years (DALYs) were determined. The model contains information about the mean life expectancy, the age at which the disease generally occurs, the influence on (preliminary) death, and the influence on quality of life to make good estimations about DALYs possible. The model simulates the health gain/loss given the amount of mothers that breastfeed their infant during a certain period of time. The model can be used to quantify the health effects in the present situation, but also for different scenarios based on different potential policies. Each policy target corresponded with a certain distribution of duration of breastfeeding.

For the economic evaluation of the interventions, only health care costs are taken into account. This means that only the direct and indirect costs related to the health care sector are considered. The costs related to the different diseases included in the model are derived from the RIVM report 'Costs of illness in the Netherlands'[183] considering the incidence and duration of the different diseases.

The assessment is based on the general Dutch population. Thus health effects under certain specific conditions were not taken into account, such as extreme exposure to environmental chemicals, hepatitis C, HIV/AIDS, illicit drug use, implants and breast surgery, metabolic disorders, or use of drugs such as anti-anxiety or anti-depressant. Under such specific conditions the risk-benefit analyses should differ from our risk-benefit assessment.

1.4 Outline of this report

In chapter 2 an update of the most recent literature is described. Where appropriate, the conclusions in our last report are updated. In chapter 3 the improvements of the breastfeeding model are described. As the module for the economic evaluation is a substantial part of that, this is described in a separate chapter (chapter 4). In chapter 5 the health gain in terms of diseases and costs are described. Finally, chapter 6 comprises a general conclusion and some recommendations.

2. Overview literature – an update

In the 2005 report[197] a extensive literature search was carried out until February 2005. In this chapter we give an update of this literature overview until July 2006 and also an update of the strength of evidence for each disease.

2.1 Method of overviewing the literature

Equal to the 2005 report[197], Medline was used to search literature on health effects of breastfeeding from February 2005 until July 2006. Search terms used were: 'breastfeeding', 'lactation' or 'human milk'. But also combinations with known health outcomes like 'otitis media', 'asthma', or 'obesity' were used. A check was made with the publication overviews published by The International Society for Research in Human Milk and Lactation (ISRHML) which gives an overview of recently published studies about several aspects of human milk. Again, the search was limited to articles published in English or Dutch and only study populations from Western Europe, North America, Australia and New Zeeland were included and were considered as representative for the Dutch situation.

The same quality guidelines[197] were used to select the articles presented in the overview. In short, the time of assessing breastfeeding data should ideally be in the first year of life, clear definitions of breastfeeding and health outcome and correction for relevant confounders.

The strength of evidence is based on the WHO criteria for strength of evidence[207]. For each health outcome for which new evidence was found, the strength of evidence was once again determined.

2.2 Overview of the literature

Since our last overview, 37 studies have been published on the association between breastfeeding and diseases for the child or the mother. These studies covered 20 diseases, of which 2 health outcomes were not present in our previous report. Based on the currently available literature, the evidence is slightly changed. The actual evidence will be discussed in the following paragraphs.

2.2.1 Child

In Table 2.1 the health outcomes for the child are given with their references and the strength of evidence. Appendix 1 gives an complete description of all studies used.

Although a lot more studies have been added, only a couple of changes regarding the strength of evidence have been made. The evidence for a protective effect of breastfeeding on 'respiratory infections' is now considered probable instead of possible. And for 'ulcerative colitis', 'sudden infant death syndrome' and 'hospitalization' there was insufficient evidence, but with the additional studies on this topic, there is now possible evidence for a protective effect of breastfeeding.

Table 2.1 Short overview of the effects of breastfeeding compared to formula feeding on the child.

Health effect	References	Strength of evidence report 2005[197]	Current strength of evidence
Gastrointestinal infections including diarrhoea	13, 18, 43, 54, 59, 68, 69, 76, 93, 96, 154, 155, 166, 167, 173, 210	Convincing +	Convincing +
Otitis media	4, 8, 31, 38, 43, 45, 46, 76, 93, 96, 142, 155, 167, 173, 189, 193, 210	Convincing +	Convincing +
Respiratory infections	4, 12, 18, 31, 36, 44, 76, 93, 96, 130, 138, 140, 155, 167, 181, 209, 210	Possible +	Probable +
Celiac disease	148		Insufficient
Urinary tract infections	117, 150	Insufficient	Insufficient
Crohn's disease	17, 34, 89, 91, 159	Possible +	Possible +
Ulcerative colitis	34, 89, 159	Insufficient	Possible +
Haemophilus influenza	179	Insufficient	Insufficient
Fever	143, 210	Insufficient	Insufficient
Pyloric stenosis	149	Insufficient	Insufficient
Jaundice	22, 57, 210	Conflicting	Conflicting
Asthma	33, 42, 53, 64, 67, 96, 98, 99, 136, 138, 139, 168, 177, 180, 188, 196, 209, 212, 214	Probable +	Probable +
Wheezing	13, 31, 33, 93, 96, 99, 136, 138-140, 155, 177, 180, 196, 209, 211-214	Probable +	Probable +
Eczema	20, 52, 64, 76, 84, 88, 93, 96, 99, 106, 115, 153, 175, 180, 184, 188, 196, 203	Probable +	Probable +
Atopy	30, 58, 64, 96, 99, 126, 136, 139, 169, 177, 180, 180, 188, 203, 215, 216	Possible +	Possible +
Obesity	9, 10, 19, 24, 29, 50, 56, 63, 72, 85, 90, 100, 110-112, 146, 156, 157, 191, 200,204	Convincing +	Convincing +
Cardiovascular disease	108, 118, 120, 156, 158	Insufficient	Insufficient
Blood pressure	107-109, 119, 120, 141, 156, 174, 187	Convincing +	Convincing +
Diabetes mellitus type 1	79, 82, 121, 123, 135, 170, 172, 199	Possible +	Possible +
Leukaemia	70, 80, 101-103, 176, 178, 194	Possible +	Possible +
Lymphomas	70, 194	Insufficient	Insufficient
All childhood cancers	39-41, 70, 103, 171, 194	Insufficient	Insufficient
Growth	14, 94-96	Insufficient	Insufficient
Intellectual and motor development	7, 48, 60, 61, 65, 74, 75, 81, 92, 128, 137, 147, 151, 163, 190, 198, 201, 208	Probable +	Probable +
Sudden infant death syndrome	5 ,49, 55, 96, 122	Insufficient	Possible +
Hospitalization	143, 144	Insufficient	Possible +

2.2.1.1 Infectious diseases

The protective effect of breastfeeding on infectious diseases is one of the most consistent finding in the literature about breastfeeding. Because of the high content of antibodies in breastfeeding, especially in the colostrum, it is also understandable why breastfeeding protects against these infectious diseases.

There is convincing evidence for a protective effect of breastfeeding on *gastrointestinal infections*, including diarrhoea. Also the evidence for the effect of breastfeeding on *otitis media* is convincing, although for the effect on recurrent otitis media probable evidence was found. Probable evidence is also found for the positive effect of breastfeeding on *respiratory tract infections*.

For the most common inflammatory bowel disease, *Crohn's disease* and *ulcerative colitis*, possible evidence effect is found for a protective effect of breastfeeding. For *celiac disease* only insufficient evidence is found. Also celiac disease most probably is due to immunological causes on which breastfeeding can have effect.

For the less intensive investigated infectious diseases: *urinary tract infections*, *Haemophilus influenza* and *fever* in general, insufficient evidence is found for an association with breastfeeding.

2.2.1.2 Pyloric stenosis and jaundice

No new studies have been found for the effect of breastfeeding on either *pyloric stenosis* or *jaundice*. So there is still insufficient evidence for on effect on pyloric stenosis and conflicting evidence for jaundice.

2.2.1.3 Asthma and atopic diseases

For *asthma* no new evidence is found, so the evidence for an protective effect of breastfeeding on the development of asthma is still probable. For *wheezing* there is new evidence found. However the strength of evidence is still probable. Also the strength of evidence for *eczema* is still probable in spite of the new studies found. In spite of the new evidence found for an effect of breastfeeding on atopy in general, the strength of evidence for such an association is still possible.

Still no good distinction can be made about the effect of breastfeeding on children with and without family history of atopy and or asthma. This is the major shortcoming in a large number of studies published on this subject until now.

2.2.1.4 Obesity, cardiovascular disease and diabetes mellitus

New studies have been found for *obesity*, *cardiovascular disease* and *diabetes mellitus type 1 (IDDM)*, but for these health effects the strength of evidence has not changed. So there is convincing evidence for a small protective effect of breastfeeding on obesity and high blood pressure. However the biological mechanism is unclear and residual confounding can not be definitely excluded. The evidence on cardiovascular disease is insufficient and possible evidence is found for the effect on *diabetes mellitus type 1*.

2.2.1.5 Cancer

In addition to the health effects mentioned in the above paragraphs, also despite of new studies found for the effect of breastfeeding on several cancers, especially childhood *leukemia* and *lymphomas*, the strength of evidence has not changed. Therefore the evidence

for a protective effect of breastfeeding on childhood leukemia is possible and for lymphomas and childhood cancer in general insufficient evidence is found for a protective role of breastfeeding.

2.2.1.6 Growth and intellectual and motor development

New available studies on *growth* and *intellectual and motor development* did not change the strength of evidence for an association between breastfeeding and these health outcomes. For growth there is a insufficient evidence and for intellectual and motor development there is possbile evidence for an protective association with breastfeeding.

2.2.1.7 Others

For *sudden infant death syndrome* more studies reported about a protective effect of breastfeeding on this health outcome. Therefore the strength of the evidence for a protective effect is possible. The same goes for *hospitalisation*.

2.2.2 Mother

In Table 2.2 the health outcomes for the mother are given with their references and the strength of evidence as given in the 2005 report and the update of the strength of evidence. Appendix 2 gives an complete description of all studies used.

Table 2.2 Short overview of the effects of breastfeeding compared to formula feeding on the mother.

Health effect	References	Strength of evidence report 2005[197]	Current strength of evidence
Premenopausal breast cancer	21, 27, 47, 51, 87, 114, 116, 131, 133, 186, 195, 217	Possible +	Possible +
Postmenopausal breast cancer	51, 87, 114, 131-133, 186, 217	Insufficient	Insufficient
Ovarian cancer	26, 32, 62, 66, 71, 78, 160, 161, 182, 205	Possible +	Possible +
Cervical cancer	134	Insufficient	Insufficient
Glioma	77	Insufficient	Insufficient
Hip fracture	35, 97, 125	Insufficient	Insufficient
Rheumatoid arthritis	28, 83, 86	Convincing +	Convincing +
Weight gain	164, 165	Insufficient	Insufficient
Diabetes mellitus type 2	185		Possible +

Although new studies were found to support the effect of a protective effect of breastfeeding on premenopausal breast cancer and ovarian cancer, for none of the health outcomes of the mother, the strength of evidence changed compared to the previous report. This was attributable to the fact that still no cohort studies but only case-control studies were found to support the effect.

A new health outcome has been introduced in this overview, namely *type 2 diabetes mellitus (NIDDM*). One recent study reported an association found in two large cohorts, 'Nurses Health study I and II'.[185] Based on these associations we considered possible evidence for a protective effect of breastfeeding on NIDDM.[185] The investigators state that residual confounding of other health behaviours is unlikely to explain the association observed. Human studies suggest that lactation affects insulin and glucose homeostasis.

2.3 Conclusion

Although many new studies were found, the strength of evidence has only changed in four health outcomes. Additionally, two new health outcomes were added to the overview, *celiac disease* for children and *diabetes mellitus type 2* for mothers. The protective effect of breastfeeding has become more evident. No evidence was found to bring down the protective effect of breastfeeding on health outcomes. Therefore, our conclusion that breastfeeding has beneficial health effects for the general population has not changed since the last report. This concerns both the short term and the longer term. Convincing evidence is found for an protective affect of breastfeeding on gastrointestinal infections, otitis media, obesity and high blood pressure for the child. For the mother only convincing evidence is found for the protective effect of breastfeeding on rheumatoid arthritis.

3. Quantified health effects - an update

In 2005 a model was developed that describes health gain and loss depending on the duration of breastfeeding. This model was used to predict health effects of several hypothetical breastfeeding interventions. Besides adding a module to the model to describe costs related to health effects of breastfeeding and breastfeeding interventions, the input data of the model is updated.

3.1 Method of quantifying health effects

The basic principles of the model are unchanged. The model simulates the gain/loss in health given the prevalence of infants that are breastfed during a certain period. The model is based on dose-response functions for several diseases that express the risks of developing a specific disease depending on the duration of breastfeeding. The dose-response functions are based on data (relative risks or odds ratios) that were derived from the literature. It is assumed that the relative risks or odds ratios are valid in the Dutch population. The model computes the incidences of several diseases for children as well as mothers. Finally, the incidences of the diseases are combined into one health measure, the Disability Adjusted Life Years (DALY). The model description and parameter estimation method is reported fully in the previous report[197].

3.1.1 Present prevalence of breastfeeding

In March 2006, TNO reported[105] measurements of the prevalence of breastfeeding in the Netherlands in 2005. However, it was not possible to use this recent data to update our model for three reasons. First, in the population in which breastfeeding was measured highly educated mothers were overrepresented and therefore the numbers probably overestimate the duration that mothers nurse their children. Furthermore, TNO measured the prevalence of breastfeeding by asking the age of a baby and whether the baby was breastfed (cross-sectional research design). From this information it is impossible to extract exactly the duration of breastfeeding. Therefore the data must be converted. The method for this is described in the 2005 report[197]. Unfortunately this method makes some assumptions that were not met by the reported data from TNO, leading to the illogical conclusions that more infants were breastfed longer than four months than there were infants that were breastfed longer than three months. Thirdly, consistency would require that also the disease prevalence data had to be updated to 2005. Unfortunately these data are not (yet) readily available.

3.1.2 Relative risks and other model parameters

Because the literature overview is updated, new data have become available. Consequently, some dose-response functions are changed. However, as described earlier not all (new) articles report data that are suitable for the estimation of the dose-response functions. In Appendix 1 and 2, it is indicated for each article whether it is used to establish a dose-response function or why it was not used.

Table 3.1 shows the updated model parameters. The changes are small, the relative risk for leukaemia has increased slightly and the relative risk for obesity is slightly decreased. Also the relative risk of premenopausal breast cancer for the mother is slightly decreased whereas her ovary cancer risk is slightly increased.

Furthermore, in contrast with the earlier report we have chosen to use RIVM data on disability weights, incidences, and mortality, when available instead of averaging over data of all available sources. Therefore, the disability weight for asthma is slightly increased and the disability weight for premenopausal breast cancer is decreased. Furthermore, the incidences of asthma, eczema, and rheumatic arthritis have changed.

Table 3.1 Disease parameters of the model.

	β [a]	RR6 *	p	p_0	w	s	LE [d]	AD [a]
CHILD								
Otitis Media	-0.045	0.762	0.23145 [b]	0.27444	0.008 [f]			
Gastrointestinal Infection	-0.120	0.488	0.09210 [c]	0.13646	0.030 [c]			
Asthma	-0.039	0.789	0.01530 [c]	0.01778	0.080 [c]		79.1	4.5
Respiratory Infection	-0.051	0.734	0.54955 [b]	0.66559	0.020 [c]			
Eczema	-0.048	0.748	0.04059 [c]	0.04865	0.070 [c]		78.8	1.0
Crohn's Disease	-0.111	0.512	0.00005 [b]	0.00008	0.200 [c]	0.005 [c]	79.3	8.5
Leukaemia	-0.023	0.871	0.00003 [h]	0.00004	0.098 [e]	0.212 [h]	79.2	7.5
Obesity	-0.020	0.885	0.00033 [b]	0.00035	0.035 [i]		78.8	5.0
MOTHER								
Rheumatic Arthritis	-0.020	0.889	0.00461 [c]	0.00526	0.530 [c]	0.006 [c]	85.3	68.5
Premeno. Breast Cancer	-0.010	0.944	0.00070 [c]	0.00075	0.210 [c]	0.183 [c]	82.2	40.0
Ovary Cancer	-0.005	0.971	0.00017 [g,h]	0.00017	0.084 [e]	0.128 [h]	82.8	50.0

* The relative risk for breastfeeding 6 months versus never breastfeeding.
Sources: [a] =journal papers (see Appendix 1 and Appendix 2; [b]=NIVEL 2nd study[113]; [c]=RIVM-kompas[1]; [d]=CBS[3]; [e]=WHO[129]; [f]=MIDAS[25]; [g]=IARC[145]; [h]=IKC[2]; [i]=estimated between athlete's foot (0.01) and acne (0.06).

3.2 Quantified health effects

According to the model simulation, per 1000 person years 49 incident cases of otitis media, 46 cases of gastrointestinal infections, 131 cases of respiratory infections and 9 cases of eczema would be prevented if all children were breastfed for at least six months (*best-case scenario*). This is a considerable part of the incidences of these diseases at the specified ages, about 20% for otitis media, respiratory infections and eczema, and almost 50% for all gastrointestinal infections. Furthermore, possibly three incident cases of asthma per 1000 person years could be prevented if all children were breastfed for at least six months. For less incident diseases, like Crohn's disease, leukaemia or obesity at young age, the number of prevented cases would be: 26, 4 and 32 per 1,000,000 person years. For Crohn's disease this would be a reduction of 47% of the total incidence and around 10% for leukaemia or obesity. For the mothers per 1.000.000 person years, 750, 57, and 7 cases of rheumatic arthritis, premenopausal breast cancer, and ovary cancer, respectively, could be prevented. This is a reduction of 16%, 8%, and 4% of each of these diseases. Summarizing all these incidences, with the best-case scenario 28 DALYs per 1000 newborns can be gained. When none of the mothers breastfeed their children (*worst-case scenario*) results are of the same magnitude as for the best-case scenario but in the opposite direction, 25 DALYs per 1000 newborns can be lost. These figures are very similar to those in the former report.

As in the former report, the breastfeeding model was used to estimate the health effects for several potential policy scenarios. The eight scenarios are:

- Present situation as reference scenario;
- Policy '0→BF': all mothers initiate breastfeeding. The duration of breastfeeding is assumed to be similar to that of the current breastfeeding mothers;

- Policy '+1 month': all mothers breastfeed their infant one month longer compared to the present situation;
- Policy '+1 month', (excl. '0'): similar to previous scenario, but the percentage of never breastfed infants equals the current situation;
- Policy '>0-3 months': mothers who currently breastfeed their infant less than three months, starts and continue to breastfeed their infant up to three months;
- Policy '3-6 months': every mother who currently breastfeeds her infant for three months or more, breastfeeds her infant more than six months;
- Policy '5% shift': in each category 5% prolongs breastfeeding with one month

Additionally, one new scenario was created:
- Policy 'FF→1': Al formula feeding mothers initiate breastfeeding for 1 month.

Figure 3.1 summarises the health gain in DALYs due to these different theoretical scenarios. Also the newly estimated health effects of the different scenarios are comparable with those in the former report. The largest health effect can be expected when formula feeding mothers start breastfeeding in comparison with mothers who already breastfeed for three months prolong breastfeeding until at least six months.

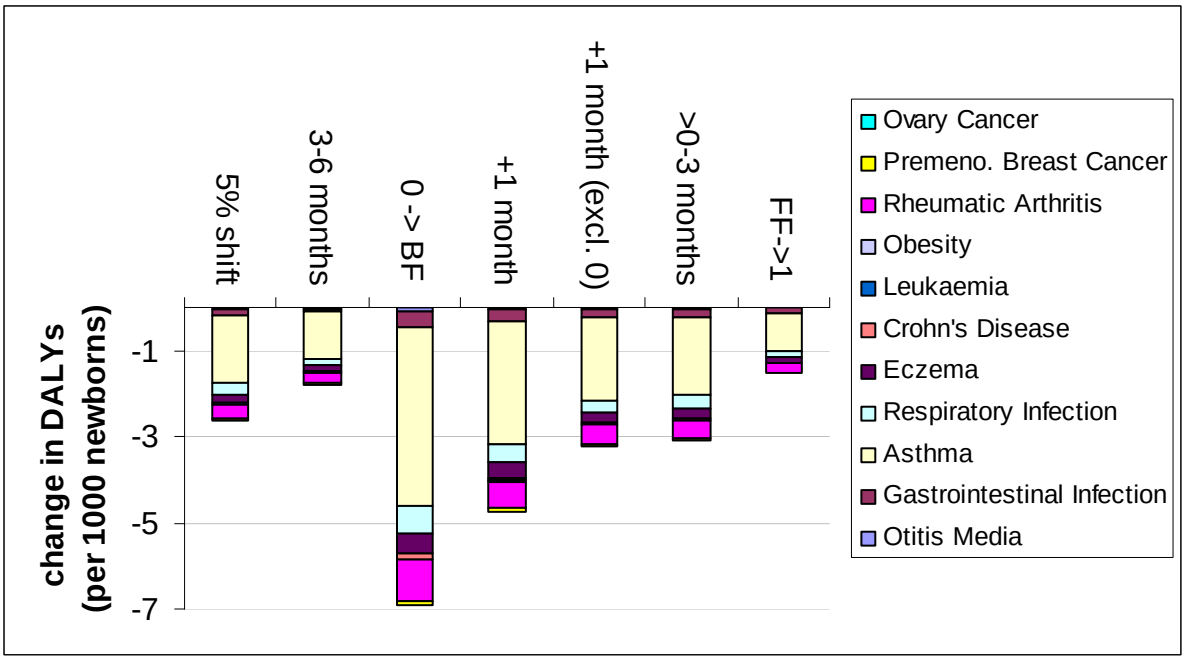

Figure 3.1 The simulated health effect expressed in a change in DALYs compared to the present situation for seven hypothetical policy scenarios classified per disease.

3.3 Conclusion

The basic conclusions drawn in the previous report are not changed due to the updated literature review and parameter estimates: breastfeeding has positive health effects for mother and child. A larger health effect can be expected when all mothers who give formula feeding already in the first month start with breastfeeding in stead, compared to the scenario that mothers who already breastfeed for three months prolong giving breastfeeding until six months. Of course the largest health gain will be achieved when all mothers would fulfil the recommendation of the WHO, to breastfeed their children for at least six months.

4. Economic evaluation of breastfeeding

Apart from the health gain, there is an interest to quantify the economic consequences of breastfeeding as well. Once the costs and savings of interventions are estimated it is possible to rank different types of interventions on their cost-effectiveness ratios. This allows a policy maker to choose those interventions that realise the most health gain per euro spend. Different types of costs can be considered such as the costs involved with treatment of disease that are related to breastfeeding (direct health care costs), indirect non health care costs like the time, productivity and purchasing costs of formula feeding. In this chapter we will discuss which assumptions were made to perform an economic evaluation of policy scenarios with the breastfeeding model. In addition, the health care costs for the several breastfeeding scenarios are estimated.

4.1 Breastfeeding related costs

Economic evaluations within health care can have different perspectives. For example, the economic benefits of breastfeeding can be analysed from a societal welfare point of view, or from the view point of the mother who chooses to breastfeed her infant. In general for policy development and evaluation, it is recommended to use the societal perspective. In this way all costs and all effects are taken into account, regardless of who is responsible for the costs or who receives the benefits[37].

Social costs can be separated into four different categories:

1) Direct costs within health care; costs related to health care use related to diseases now and in the future
2) Indirect costs within health care; costs related to health care concerning all diseases presented in the gain life years due to the intervention
3) Direct costs outside the health care; costs defrayed by other parties, for example patients, employers
4) Indirect costs outside the health care; costs due to absence and production loses as result from illness or death.

In practice it is difficult to quantify all relevant social costs and effects. Therefore often a health care perspective is chosen. Also the RIVM has made an explicit choice to use the health care perspective for the research by order of the Ministry of Health, Welfare and Sport (VWS)[11]. Within this perspective the direct and the indirect costs of health care are included in the analyses, non-health care costs are in general excluded from the analyses. However, with regard to breastfeeding, non-health care costs are of interest. In Table 4.1 an overview is given of the direct and indirect costs that are relevant in relation to breastfeeding. Ideally, analyses from the social welfare perspective include all costs given in Table 4.1. Experience teaches that in general direct costs within health care (I) and indirect costs outside health care (IV) are the largest expenditures. So, it is understandable that in health-economic studies most attention is paid primarily to these costs.

Table 4.1 Direct and indirect costs related to breastfeeding either within or outside the health care perspective.

Direct costs within the health care costs related to health care use related to diseases now and in the future	**Ia.** Diagnostic and treatment costs of diseases related to breastfeeding, for example GP consultation, admission to an hospital, medication and laboratory research
	Ib. Intervention costs to promote breastfeeding, for example training of maternity caretakers or lactation consultant and costs of intervention within hospitals
Direct costs outside the health care Costs defrayed by other parties, for example patients, employers	**IIa**. Costs of mass media campaigns to promote breastfeeding
	IIb. Costs for the parents, for example purchasing costs of formula feeding, breast pump, additional feeding mother, own contribution care costs, transportation costs related to breastfeeding disorders
	IIc. Employers costs to make breast pumping possible, for example a special lactation room and refrigerator to store expressed milk
Indirect costs within health care Costs related to health care concerning all diseases presented in the gain life years due to the intervention	**III**. Health care costs made in life years gained by breastfeeding
Indirect costs outside the health care Indirect costs outside the health care; costs due to absence and production loses as result from illness or death	**IVa**. Costs due to loss of time of parents when attending an ill child
	IVb. Costs due to loss of time of mother while expressing milk or giving breastfeeding
	IVc. Production losses due to illnesses related to breastfeeding
	IVd. Production losses due to breast pumping at the work

Source: among others. Ball et al., 2001[15]

4.2 Literature on economic effects of breastfeeding

The economic effects of breastfeeding are evaluated in several, mainly American, studies. Two studies evaluate the relation between breastfeeding and the incidence of disease (observed in for example Duffy et al.[45]) that is translated to saving medical costs by means of 'cost-of-illness' studies[192,23].

Several studies find possible savings of breastfeeding that vary between $1.1 billion[162] up to $3.6 billion for the American situation[202]. These estimations take into account direct and indirect, medical and non-medical costs. Because these are American studies, they can not be easily transposed to the Dutch situation. Nevertheless, these results do indicate that major savings in costs are possible.

Furthermore, there are some observational studies which identify the costs and effects of breastfeeding. In these kind of studies, medical visits and medications are monitored during a specific amount of time. Simultaneously the costs of the feeding practice are also monitored. Montgomery and Splett[127] describe the difference in costs between two cohorts of babies that receive either exclusive breastfeeding or exclusive formula feeding. They found that for

formula fed children the costs of feeding (about $300) and the costs of medical care (well over $100) were higher than for breastfed children. However, most children are not exclusively breastfed or formula fed, but receive a mixture of breast- en formula feeding. Ball and Wright[16] tried to give a realistic description of avoidable health costs within a population of infants. Within the study population breastfeeding status and the incidence of three common illnesses (respiratory infections, diarrhoea and otitis media) and the health costs are made. The study estimated the additional costs as consequence of inadequate breastfeeding within formula fed infants up to $330-475 within the first year of life.

Little research has been done on the effectiveness in general or cost-effectiveness more specifically, of interventions promoting breastfeeding. Pugh et al. (2002)[152] showed that an intervention where breastfeeding was stimulated by nurse counselling (n=41, costs per patient $301) largely pays for itself. Every two weeks mothers where interviewed about their breastfeeding status, time schedule and care use. The data showed that the intervention costs of $301 per patient is partly compensated by savings in formula feeding ($247). Additionally, when the savings on health services are taken into account (1.4 less medical treatments and 0.6 less prescribed medications) the intervention seems to pay for itself. However the costs and savings accrue to different parties. Savings on the longer term due to lower disease prevalences were not considered within this study.

Only one study investigated the economic effects of breastfeeding in the Netherlands. This is a thesis (1998) from the 'Vrije Universiteit Amsterdam'. It showed a considerable costs savings when the number of children that is breastfed for six months is increased. In this study is stated that a 5% increase of breastfed infants can lead to a annual saving in health services of 1.7 million guilder (=0.8 million euro). This estimation is based on a few diseases (gastrointestinal disorders, respiratory infections and otitis media) in the first year of life. When all breastfeeding related diseases are taken into account we assume that the actual savings could be even higher.

Thus, from the literature no conclusion can be drawn about the current economic effects of breastfeeding in the Dutch population, taking into account all available data on the association between breastfeeding and diseases.

4.3 Economic evaluation in the breastfeeding model

The breastfeeding model, as described earlier, is extended to make economic evaluation possible. In several steps, in line with the fact that the health care perspective is the primary perspective of the 'Ministry of Health, Welfare and Sport', this adjustment is made. A social welfare perspective will also be discussed, however a complete analysis from this perspective is not achievable due to lack of data.

Successively, the following steps are made:

1) Define costs of treatment of diseases and hospitalisation (category Ia) for all relevant diseases. These can be obtained from the in 2006 published 'RIVM-report 'Costs of diseases'.[183] Not for all diseases suitable data can be extracted from this report, and other references have to be found. This is further discussed in paragraph 4.3.3.
2) Establish a discount rate. Costs resulting from diseases that are affected by breastfeeding will not only be made in the first year but can be made during the entire lifetime of the newborn. Therefore, all these costs are expressed as a net present value in the reference (first) year. To compute a net present value one needs a discount rate.

3) Consider the costs of different breastfeeding interventions (category Ia, IIa-IIc).
4) Consider other cost categories from Table 4.1 (category III and IV). Especially costs due to production loss are important to consider because they can be of great influence.

The first two steps are sufficient to simulate the health care savings that can be achieved theoretically, in line with the calculated health effects in the 2005 report. Adding the third step allows the calculation of cost-effectiveness of breastfeeding interventions from a health care perspective. For a societal perspective, step 4 is crucial. However, data to make this step possible are hard to collect and is, at this time, not available. So, here we will only take the health care perspective into account

4.3.1 Description of the module

With the economic module in the breastfeeding model it is possible to simulate the total health care costs given the amount of mothers that breastfeed their infant during a certain period of time. The costs are the sum of all health care costs incurred during the time a person suffers from a disease. The calculation is analogue to YLD_d (Years lived with the disease) in the DALY computation. But now, the disability weight, w_d, is replaced by the averaged annual costs, k_d. The total costs are represented as a net present value for which we use a discount rate, δ. The DALYs are currently not discounted i.e. $\delta = 0$. The following formula (formula 1) describes the computation of the net present value of the costs for a chronic disease:

$$C_d = \sum_{i=AD_d}^{AD_d+LE_d} \frac{1}{(1+\delta)^i} k_d (1-s_d) inc_d \qquad \text{Formula 1}$$

where,

C_d	net present value of the heath care costs of disease d
k_d	average annual costs of disease d
δ	discount rate
s_d	mortality rate of disease d
inc_d	incidence of disease d
AD_d	average age at the time of onset of the disease
LE_d	life expectancy at AD_d

For a non-chronic disease, LE_d must be substituted by the duration of the disease. The total health care costs of a scenario, HCC_s, then simply become:

$$HCC_s = \sum_d C_d \qquad \text{Formula 2}$$

Figure 4.1 and Table 4.2 shows the concept of the breastfeeding model including the economic evaluation.

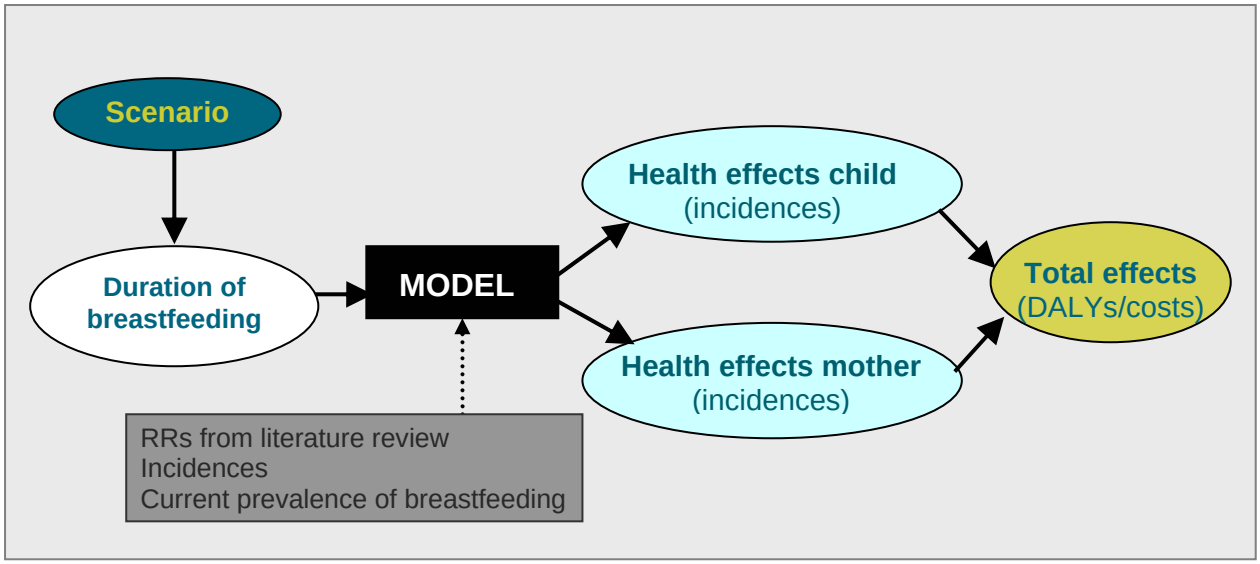

Figure 4.1 Schematic illustration of the model. From the literature relative risks or odds ratios for several diseases given the duration of breastfeeding could be deduced. Those relative risks were used to find a dose-response function for our model population with the aid of regression analyses. Knowing the dose-response function, the present incidence of the disease and the prevalence of breastfeeding, is it possible to deduce the probability of children and mothers suffering from the disease for any given duration of breastfeeding. Finally, the incidences of the diseases were combined into one health measure, the DALY and the health care costs.

Table 4.2 Illustration of a scenario i.e. the in- and output of the model. The fraction of infants that is breasted for a particular period should be put into the model. The resulting estimated health effects (incidences, DALYs and costs) for that scenario are shown in the last three columns.

	Duration of breastfeeding*							
	0	***1***	***2-4***	***5***	***6 +***	***Total***	***Total***	
Disease	***input %***	***input %***	***input %***	***input %***	***input %***	***Incidences***	***DALYs/costs***	
Child							∑DALYs	∑costs
Otitis media	incidence	incidence	..	incidence	incidence	**∑incidence**	∑DALYs	∑costs
Gastrointestinal Infection	incidence	incidence	..	incidence	incidence	**∑incidence**	∑DALYs	∑costs
Eczema	incidence	incidence	..	incidence	incidence	**∑incidence**	∑DALYs	∑costs
Et cetera	incidence	incidence	..	incidence	incidence	**∑incidence**	∑DALYs	∑costs
Mother							∑DALYs	∑costs
Premenopausal Breast cancer	incidence	incidence	..	incidence	incidence	**∑incidence**	∑DALYs	∑costs
Et cetera.	incidence	incidence	..	incidence	incidence	**∑incidence**	∑DALYs	∑costs
Total effects							**∑DALYs**	**∑costs**

* 0= 100% FF; 1 = >0-<1.5; months BF; 2= ≥1.5-<2.5 months BF; 3=≥2.5-<3.5 months BF; 4=≥3.5-<4.5 months BF; 5=≥4.5-<5.5 months BF; 6=≥5.5 months BF.

4.3.1.1 Calculating savings of health care costs

The breastfeeding model simulates the health gain/loss and costs given the amount of mothers that breastfeed their infant during a certain period of time. The model can be used to quantify the effects in the present situation, but also for different scenarios. Each scenario is defined with a certain distribution of duration of breastfeeding. By subtracting the costs of a certain scenario with the costs for the scenario representing the current situation, the possible savings due to these scenarios can be estimated.

4.3.1.2 Calculating cost-effectiveness of breastfeeding interventions

An intervention aimed to persuade more mothers to breastfeed, presumably costs money. The intervention can be expressed in a new breastfeeding scenario from which the health effects and health care costs can be simulated with our model. The savings that are realised when more mothers breastfeed due to an intervention are subtracted from the intervention costs to establish the total costs of an intervention. Because the health effect is also simulated we can now define the cost-effectiveness ratio i.e. the euro per DALY that results from a scenario.

$$CER_s = \frac{COST_s + HCC_s - HCC_0}{E_s - E_0} \qquad \text{Formula 3}$$

where,

CER_s	the cost effectiveness ratio of intervention *s*
$COST_s$	the net present value of the direct costs of intervention *s*
HCC_s, HCC_0	the health care costs due to the intervention, *s* and the reference scenario, *0*
E_s, E_0	the effect in DALYs of the intervention, *s* and the reference scenario, *0*

4.3.2 Data for module

4.3.2.1 Costs of illness

The RIVM-report 'Costs of illness in the Netherlands 2003'[183] describes health care related costs, divided by diagnosis, age and gender. The study takes only the direct medical costs into account. So indirect costs like production losses and informal care by friends and family are not considered.

Besides assumptions about the different diseases, also the differences in study design makes several assumptions unavoidable. 'Costs of illness in the Netherlands 2003'[183] has a cross-sectional design. While we are interested in the costs per patient during the years the patient is ill. The basic assumption is made that the differences in costs in the different stages of a disease average out through the cross-sectional design of the 'Costs of illness' study[183]. Hence, if we divide the total costs per year reported in the study by the prevalence of the disease we find the average annual cost per patient. Sometimes we must make further assumptions about how the costs are allocated between different age groups, or between patients that do and do not become hospitalised et cetera. In Appendix 3 the assumptions and details of the cost estimation is further explained. Tables 4.3 and 4.4 show the annual average cost per patient. These costs are parameters for the model. The cost per year per case of obesity are not taken into account in this module, because obesity is an intermediary for several chronic disease as cardiovascular disease and diabetes mellitus type 2. The costs per obesity case is therefore subject to the relationship between obesity and obesity related diseases. This can lead to an underestimation of the costs that can be saved when more mothers breastfeed their children.

4.3.2.2 Discount rate

Cost savings do not only occur in the base year, but also approximately eighty years thereafter during the entire lifetime of the newborn that is (not) breastfed. Time differences, with current interventions or investments and the savings in the future are taken into account in health-economic evaluations by discounting all costs and savings and express them as net present value in the reference year. According to Dutch guidelines, a discount rate of 4% is used for costs as well as savings[37].

Table 4.3 The annual costs per patient for each of the diseases of the child.

Health effect Child	Strength of evidence	Age group (diagnosis)	Costs per patient per year (euro)
Gastrointestinal infections including diarrhoea	Convincing	0-12 months	161.30
Otitis media	Convincing	0-12 months	465,19
Respiratory infections	Probable	0-12 months	199.73
Crohn's disease	Possible	6 months	2138.59
Asthma	Probable	0-7 year	3180.83
Eczema	Probable	0-18 months	230.68
Obesity	Convincing	3-10 years	?
Leukaemia	Possible	0-15 year	6088.86

Table 4.4 The annual costs per patient for each of the diseases of the mother.

Health effect Mother	Strength of evidence	Age group	Costs per patient per year (euro)
Premenopausal breast cancer	Possible	Premenopausal	2418.74
Ovarian cancer	Possible	All	3381.36
Rheumatoid arthritis	Convincing	All	1152.59

4.4 Health gain in terms of costs or savings due to breast feeding

Table 4.5 shows the simulated health effects and costs that can maximally be lost (*worst-case scenario*) or gained (*best-case scenario*) through breastfeeding. It shows that on average 250 euro could be saved in health care costs per newborn if all children were breastfed for six months compared to the present situation.

Table 4.5 The health care costs and health effects in the best-case and worst-case scenario.

	Best-case (100% BF 6+ mo)	Worst-case (100% FF)
Δ DALY per 1000 newborns	28	-25
Δ health care costs per newborn	€ -250	€ 220

Figure 4.2 shows the costs for each of the potential policy scenarios (see section 3.2). Considering the costs, the most favourable scenario would be the scenario '0->BF'; in which all women breastfeed. In terms of costs as well as in terms of health, the scenario '3-6 months' is less favourable. In this scenario, mothers who already breastfeed for three months, prolong breastfeeding until six months. Note that, that would have about the same effect as scenario 'FF->1' in which each formula feeding mother changes her behaviour and breastfeeds for just one month.

In each scenario, it is clear that asthma contributes most to the costs as well as to the quality of life expressed in DALYs (see also Figure 3.1). The health care costs of rheumatic arthritis are relatively low, while it is a severe disease which decreases the quality of life considerably. Therefore, this disease contributes substantially to the gain in quality of life, but less to the savings. In contrast, otitis media is a relatively mild disease, and thus contributes less to the total number of DALYs, but contributes a substantial part of the savings in each scenario.

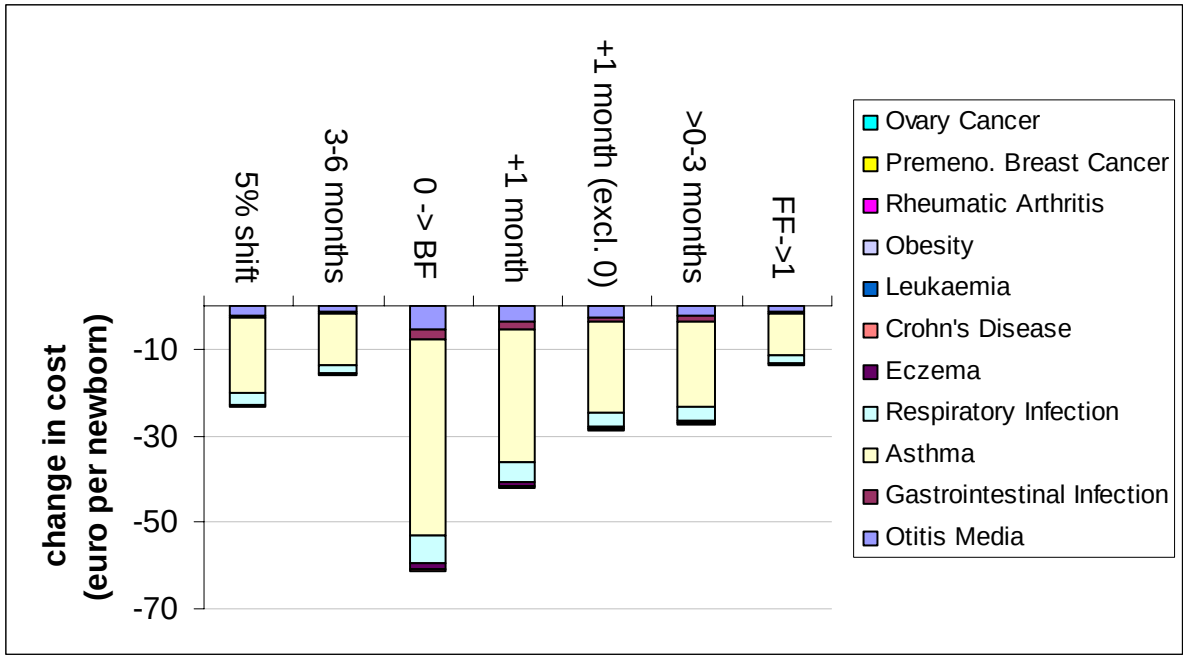

Figure 4.2 The simulated health care costs expressed as a change in euro compared to the present situation for seven hypothetical policy scenarios classified per disease.

4.5 Conclusion

Besides the positive health effects of breastfeeding found in chapter 3, results in this chapter show that breastfeeding can provide savings in health care costs. In the last decade approximately 200,000 children were born annually. In 2003, the number of babies born was 200,297 and in 2005 the number was 187,910 according to CBS[3]. If we assume the same number of births in the future and ideally all children would be breastfed for six months or longer, about 50 million euro net present value could be saved on health care costs per year maximally. A more realistic estimate, like a 5% shift, would be 4 million euro net present value annually, when much more moderate change from the present behaviour resulting in savings of some 20 euro per newborn (see Figure 4.2). That is a fair amount more than the estimates from the VU.[73] However, that study did, among others, not include asthma, which is the disease that is responsible for the largest amount of costs savings (see Figure 4.2).

The ranking of the total health care costs and the health gain in terms of DALYs of the different theoretical breastfeeding scenarios is identical. However there is a difference in which disease contributes the most to either health gain and health care costs savings. Asthma contributes the most DALYs and the most savings. The relative contribution to the DALYs differs from the relative contribution to savings. Obviously, this depends on how severe a disease is rated (ranking of the DALY weights) and how expensive an disease is (ranking of the health care costs). Some diseases can be very expensive like otitis media but causes relatively mild suffering in terms of DALYs whereas rheumatic arthritis is a disease that causes much pain and distress but is relatively inexpensive.

With the expansion of the breastfeeding model with the health care cost module, it is a small step to determine cost-effectiveness of breastfeeding interventions. Only the costs of the interventions are needed. In the next chapter we will give a few examples.

5. Effects of breastfeeding interventions

Besides the theoretical scenarios given in the last chapter, the model is also suitable to calculate health effects and health related costs of actual interventions. However, the effects of the intervention on the duration of breastfeeding is necessary. As an example the health care effects of the 'Masterplan of breastfeeding' as a whole and the new objective of the Dutch Ministry of Health, Welfare and Sport has been estimated.

5.1 'Masterplan Breastfeeding'

In 1991 WHO and UNICEF initiated worldwide the 'Baby Friendly Hospital Initiative'. In the Netherlands this initiative is carried out by 'Stichting Zorg voor Borstvoeding' and main focus is on counselling health professionals. These activities are since 2002 a component of the campaign 'Borstvoeding verdient tijd' conducted by 'The Netherlands Nutrition Centre' (Voedingscentrum).

5.1.1 Description of intervention

In 2002 the 'Masterplan breastfeeding' started. The campaign is called 'Borstvoeding verdient tijd' with translates in breastfeeding deserves time. The main focus is on extending the duration of breastfeeding. In the first phase, which will finish in 2006, the main target was to develop methods to increase the number of mothers that give breastfeeding for six months or longer. Within the second phase, from 2007 until 2010, these methods should be implemented in the governmental policy.

Within this plan it is considered important to put breastfeeding on the agenda and especially making breastfeeding socially more acceptable. Mothers and their partners, employers and the society as a whole have to be aware that breastfeeding is the most natural way of feeding an infant. And by making it socially more acceptable, stimulating mothers the extend the breastfeeding period.

Besides stimulating the duration of breastfeeding, certification of maternity care providers is also implemented within the 'Masterplan', although certification started already in 1996. Maternity care providers are certificated when they implement the 'Ten steps to successful breastfeeding' formulated by the WHO and UNICEF. The ten steps are:

1) Have a written breastfeeding policy that is routinely communicated to all health care staff.
2) Train all health care staff in skills necessary to implement this policy.
3) Inform all pregnant women about the benefits and management of breastfeeding.
4) Help mothers initiate breastfeeding within half an hour after birth.
5) Show mothers how to breastfeed and how to maintain lactation even if they should be separated from their infants.
6) Give newborn infants no food or drink other than breast milk, unless medically indicated.
7) Practice rooming-in, allow mothers and infants to remain together-24 hours a day.
8) Encourage breastfeeding on demand.
9) Give no artificial teats or dummies to breastfeeding infants.
10) Foster the establishment of breastfeeding support groups and refer mothers to them on discharge from hospital.

But also after the maternity care, child health centres are involved in the plan, as the are considered the next in line to stimulate mothers to prolong their breastfeeding period. For the youth health services seven separate steps have been developed to stimulate breastfeeding. These steps are:

1) Have a written breastfeeding policy that is routinely communicated to all health care staff.
2) Train all health care staff in skills necessary to implement this policy.
3) Inform all pregnant women about the benefits and management of breastfeeding.
4) Stimulate and support women that breastfeed their children by given attention to prevent and answer possible problems.
5) Explain to women that in general infants do not need supplementary feeding in the first six months when giving breastfeeding. After these six months breastfeeding can continue, in combination with supplementary feeding, until mother and child want to stop.
6) Inform women about the possibilities to combine breastfeeding with school or work outdoors.
7) Stay in contact with other organisations who guide breastfeeding and to point these organisations to young parents.

With these steps, child care health centres can also be certified. The aim of the certification of maternity care and child health centres is that they better guide and support breastfeeding mothers.

5.1.2 Assumptions for modelling effects

TNO regularly monitors breastfeeding prevalence. In theory, this data allow the comparison between breastfeeding prevalence before (in 2002) and after introduction of the Masterplan (in 2007). However, the data from 2007 and 2002 from TNO for monitoring breastfeeding could not be incorporated in our model (see also paragraph 3.1.1).
For the Masterplan as a whole, we consider the breastfeeding prevalence of before 2002 with the current breastfeeding prevalence, both data from TNO, as given in Table 5.1.

Table 5.1 Distribution of duration of breastfeeding for the reference scenario and scenario Masterplan.

	Duration of breastfeeding (months)*						
Scenario	**0**	**1**	**2**	**3**	**4**	**5**	**6+**
2000-2002 (reference)	21	20	8	8	6	3	34
2005 (Masterplan)	20	20	9	4	3	3	41

* No distinction between exclusive and nonexclusive breastfeeding is made.

In the monitoring data of TNO also information was collected whether the mother has received maternity care from a certified or a non certified organisation. Based on that TNO calculated odds ratios' (OR) in order to determine the effect of certification on the number of women starting breastfeeding. Over the period of 2000-2003 they found an OR of 1.25 with a confidence interval of 1.07 till 1.46. However, the monitoring in 2005 showed no effect of certification. This was explained by the fact that by this time many initiatives where launched, due to the campaign, to promote breastfeeding. This resulted in the fact that even if an organisation was not certified, it would stimulate breastfeeding anyway.
We used the data over the period 2000-2002 to indicate the effect of certification (see Table 5.2). The percentage of formula feeders is based on calculations with the estimated OR. The estimate contains measurement errors and therefore the percentage formula feeders appears to be lower than in the scenario of the overall Masterplan which is based on actual

measurements. Obviously, this is incorrect but because it hardly influences the results in DALYs and health care costs savings we have not considered some sort of correction.

Table 5.2 Distribution of duration of breastfeeding for the reference scenario and the two scenario's for the effect of certification.

	Duration of breastfeeding (months)*						
Scenario	**0**	**1**	**2**	**3**	**4**	**5**	**6+**
2000-2002	21	20	8	8	6	3	34
Certification min	19	24	8	8	6	3	34
Certification max	19	20	8	8	6	3	38

* No distinction between exclusive and nonexclusive breastfeeding is made.

The scenarios 'Certification' present the situation in which only the maternity care is certified. Certification mostly effects the breastfeeding rate in the first week. This means that the number of mothers who start breastfeeding increases. The scenario 'Certification min' assumes that the extra breastfeeding mothers breastfeed for 1 month. The scenario 'Certification max' assumes that all these mothers breastfeed 6 months or more. The actual effect of certification will be somewhere between these extremes.

Besides certification of maternity care, other health care institutes, such as the child health care centres can be certified. That will stimulate prolonged duration of breastfeeding. Unfortunately, at this point there are no accurate data available that show how much longer mothers will breastfeed.

5.1.3 Health gain and cost-effectiveness

The Masterplan results, according to our simulation to a reduction in health care costs of 20 euro net present value per newborn and a gain in DALYs of 0.002 per newborn compared with the 2000-2002 scenario. The certification results in a reduction of costs between 2 and 19 euro net present value and a gain in health between 0 and 0.002 DALYs per newborn. Table 5.3 shows the relative reduction in incidences for the modelled diseases and the relative reduction in DALYs and in health care costs compared to the situation in 2000-2002.

Table 5.3 The relative reduction in incidences, DALYs and health care costs for the Masterplan and certification scenarios compared to scenario '2000-2002'.

	Masterplan	**Certification min**	**Certification max**
Incidences			
Otitis Media	1.7%	0.2%	1.6%
Gastrointestinal Infection	3.7%	0.7%	3.9%
Asthma	1.5%	0.2%	1.4%
Respiratory Infection	1.9%	0.2%	1.8%
Eczema	1.8%	0.2%	1.7%
Crohn's Disease	3.5%	0.6%	3.7%
Leukaemia	0.9%	0.1%	0.8%
Obesity	0.8%	0.1%	0.7%
Rheumatic Arthritis	1.3%	0.2%	1.2%
Premenopausal Breast Cancer	0.7%	0.1%	0.6%
Ovary Cancer	0.3%	0.0%	0.3%
DALYs	**1.5%**	**0.2%**	**1.4%**
Costs	**1.6%**	**0.2%**	**1.5%**

The intervention costs for the Masterplan are estimated at € 360,000 per year during three years of which certification costs are estimated at € 200,000 per year (personal communication, Van Drongelen). The net present value at a discount rate of 4% amounts to

€ 577,219 and € 1,038,994 respectively. We assume the annual number of newborns at 200,000 which is roughly the number of newborns in the Netherlands, the last decade. With these numbers and formula 3 (section 4.3.1.2) we can compute cost-effectiveness ratios (CER) for the Masterplan and certification scenarios.

Table 5.4 shows the cost effectiveness ratio and the numbers needed to compute them. We assume that the costs and the resulting benefits of the intervention both last three years. It is clear that the savings in health care costs outweigh the intervention costs resulting in a negative CER. This means that the Masterplan and certification are successful interventions. They save money while at the same time these interventions improve health.

Table 5.4 The costs and savings, DALYs and resulting CER for the Masterplan and certification scenarios.

	Intervention costs (€)	**Health care costs (€)**	**DALYs**	**CER (€/DALY)**
Masterplan	1,038,994	3*200,000*20	3*200,000*0.002	-9,999
Certification min	577,219	3*200,000*2	3*200,000*0	-0
Certification max	577,219	3*200,000*19	3*200,000*0.002	-9,500

These results must be interpreted with some caution. Calculations of the health effects and cost-effectiveness of the Masterplan and the certification of health centres more specifically depend on a single measurement by TNO. This data are highly subject to the population in which the measurements were carried out. This means that the results can only be seen as an indication because they involve large uncertainties.

5.2 New objective Ministry of Health, Welfare and Sport

Within the priorities of governmental policy from the Ministry of Health, Welfare and Sport (VWS), as stated in the National Budget 2007, the government wants to promote that 85% of Dutch mothers start breastfeeding, 60% of the mothers give breastfeeding at one month and that after six month still 25% of the mothers give breastfeeding exclusively.

5.2.1 Assumptions for modelling effects

Because the government policy focuses on exclusive breastfeeding and the model calculates with total breastfeeding (exclusive breastfeeding plus mixed breastfeeding), assumptions have to be made about the proportion of exclusive breastfeeding within the total number of breastfeeding women at one and six months.

We consider that the proportion exclusive versus total breastfeeding in the period 2000-2003 does not change over time. The ratio EBF/(EBF+MBF) over the period 2000-2003 to start breastfeeding equals 1 and in the sixth month 17.7/(17.7+15.5)=0.53. The drop from starting breastfeeding and breastfeeding at the first months is also considered stable. These assumptions result in the scenario presented in Table 5.5.

Table 5.5 Scenario new objective VWS and the present situation.

	Duration of breastfeeding (months)*						
Scenario	**0**	**1**	**2**	**3**	**4**	**5**	**6+**
Present situation	22	19	9	8	4	3	35
New objective VWS	15	17	8	6	4	3	47

* No distinction between exclusive and nonexclusive breastfeeding is made.

5.2.2 Health gain and cost-effectiveness

The new objective results in a DALY gain of 0.006 and in a reduction in health care costs of 50 euro net present value per newborn. Incidences of leukaemia and obesity decrease with about 2% and incidence of Crohn's disease and gastrointestinal infections decrease as far as 10%. Thus, with the new objective from the Ministry of Health, Welfare and Sport the results of the model simulation show that health and health care costs could be saved. If we assume again that approximately 200,000 children are born each year, then if an intervention that fulfils the new policy objective costs less than 10 million euro (200,000 times 50 euro), the intervention will probable save costs and health.

5.3 Conclusion

Policies that aim to increase the percentage of breasted infants are a preventive measure that gain health and can save health care costs. The Masterplan breastfeeding was a cost-effective intervention. If with the new Masterplan of 2007-2010 the new targets on breastfeeding would be reached, about 21% of the maximum health gain (best-case scenario) can be achieved.

Although the exact results in terms of health gain and savings are rather uncertain, the model approach does allow for ranking of most successful and cost effective policies.

6. Discussion and conclusions

6.1 Main findings

Our study shows that in westernised countries breastfeeding has an unanimously beneficial health effect for the child and the mother, compared to formula feeding. The longer the breastfeeding period, the lower the incidences of several diseases and the higher the amount of savings of health care costs.

Convincing evidence is found for gastrointestinal infections, otitis media, obesity and high blood pressure for the child. For the mother only convincing evidence is found for the protective effect of breastfeeding on rheumatoid arthritis. There is probable evidence for a protective effect of breastfeeding on respiratory infections, asthma, wheezing, eczema and intellectual and motor development for the child. Possible evidence of a protective effect of breastfeeding on Crohn's disease, ulcerative colitis, atopy, diabetes mellitus type 1, leukaemia, sudden infant death syndrome and hospitalization in general for children and on premenopausal breast cancer, ovarian cancer and diabetes mellitus type 2 for mothers. There is insufficient evidence of a protective effect of breastfeeding on celiac disease, urinary tract infections, Haemophilus influenza, fever, pyloric stenosis, cardiovascular, lymphomas, all childhood cancers and growth for children and for the mother for post-menopausal breast cancer, cervical cancer, Glioma, hip fracture and weight gain.

As with the former report, health effects of specific interventions are simulated with a model. Additionally health care costs are evaluated for the different interventions on breastfeeding. These calculations suggest that most health could be won and health care costs could be saved when more women start breastfeeding in stead of prolonging the breastfed period for women who already give breastfeeding.

Although many assumptions are made, model simulation suggests that the Masterplan Breastfeeding was a successful intervention. Through the Masterplan health gain is achieved and health care costs decreased.

Since 2006 new targets for the prevalence of breastfeeding mothers are set by the Dutch government. If the new objectives will be achieved, the model simulation shows that additional about 10 million euro health care cost can be saved each year, and about 21% of the maximum health gain (*best-case scenario*) attainable with breastfeeding will be achieved.

6.2 Limitations and strengths

Of course these figures are achieved with model simulation, using many assumptions to simplify the real world. First of all, in the quantification of the health effects and savings, we had to define which health effects were included in the calculations. All diseases with at least possible evidence for an association with breastfeeding are included in the model simulation. Secondly, we assumed that the associations between breastfeeding and health outcomes that are recently found in other developed countries are also valid for the general Dutch population. Another assumption is that the residual confounding for the association between breastfeeding and health outcomes is limited, although it never can be excluded.

A strength of our overview was that articles which did not fulfil all quality requirements, was excluded from the literature overview in order to ascertain good quality of our conclusions. Theoretically, due to potential publication bias, the beneficial effect of breastfeeding could be overestimated. However, as the evidence for an association was based on more studies, conform the WHO criteria, we assumed that we have precluded this kind of bias as much as possible.

In addition, many model parameters had to be estimated. Although a lot of research is done on this topic, still some parameters are estimated with only a small number of studies or some detail is not taken into account. For example, not all results from the literature overview could be incorporated in the model, because of the differences in study population, study design, in definition of breastfeeding, or in that of disease qualification. Or for instance no distinction is made between exclusive and mixed breastfeeding.

Furthermore, DALYs are not without discussion.[6] Notably the weights that are given to particular diseases can vary between countries and populations but also between individuals or focus groups. It makes a difference whether a weight is attributed to a disease by a medical doctor, by a patient or a layman who does not suffer from the illness. Especially for mild short-lasting diseases, disability weights are difficult to estimate.[124] Breastfeeding has particularly effect on such short-lasting diseases as gastrointestinal infections and otitis media. Nevertheless, from the perspective of a policy maker in public health a measure in which all incidences of diseases are combined with each other can be useful. The DALY serves that purpose, but should be interpreted with care.

Also for the cost module in the breastfeeding model assumptions are made. We focussed, for this moment, only on the health care costs and did not take other relevant costs for the society into account, like for instance productivity loses. But also for the health care costs the results of the model depends on the quality of the data and can always be discussed. Additionally, the cost of obesity is not included in the model, as the health care costs related to obesity are mainly due to obesity related diseases. This can have lead to an underestimation of the real costs which can be saved.
For all these reasons, the figures should be therefore interpreted as an indication.

Although these model simulations are a good method for ranking of most successful and cost-effective policies on breastfeeding. Comparisons with model simulations of other lifestyle interventions are difficult to make, as each model has its own assumptions and sensitivity.

6.3 Conclusion

First of all, model simulation is a good method to estimate effects of breastfeeding interventions on both health and health related costs. Therefore it is a good method to underpin breastfeeding policy.

Policies that aim to increase the percentage of breasted infants are a preventive measure that gain health and can save health care costs. The Masterplan breastfeeding 2002-2006 was a cost-effective intervention. If with the new Masterplan of 2007-2010 the new targets on breastfeeding would be reached, about 21% of the maximum health gain (best-case scenario) can be achieved. The expected savings of health care costs could be about 10 million euro net present value per year.

Finally, as breastfeeding has beneficial health effects for the mother and child, a policy aiming at increasing the percentage of breasted infants can be seen as a preventive measure, which can also save health care costs.

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Appendix 1 Health effects child

Meaning of the footnotes in the next tables:

Motivation for not including the results of a study in the model.
a: disease not modelled
c: duration of breast feeding unclear or reference duration not zero (FF)
d: endpoint measure not consistent e.g. OR instead of RR or disease at a different age.
e: relevant original studies of review incorporated
f: no adjustment for confounders

Table A1.1: Effect of breastfeeding on fever

Intermediary of health effect	Authors, Year of publication	Design	Study population	Age group	Breastfeeding	Effect size		Remarks
>38°C [a]	(Wright et al., 1998)	Cohort	USA n= 977/ 858	0-12 mo	FF BF	Before BFHI introduction RR=1 **RR=0.74 (0.35-0.98)**	After BFHI RR=1 **RR=0.65 (0.52-0.81)**	Different ethnic group (Indian reservation). Correction for possible confounders had no effect on the risk estimates. EBF*:± 3 mo EBF, then solids are given, no formula.
Hospitalisation Fever of unknown origin (FUO) [a]	(Pardo-Crespo et al., 2004)	Case-control	Spain 52 Cases 52 Controls	0-24 mo	FF BF $BF_{1\text{-}45\ days}$ $BF_{46\text{-}90\ days}$ $BF_{91\text{-}180\ days}$	OR=1 OR=1.05 (0.34-3.22) OR=1.03 (0.31-3.49) OR=1.66 (0.40-6.82) OR=0.54 (0.10-2.84)		Corrected for SES, smoking, and use of incubator after delivery.

Table A1.2: Effect of breastfeeding on gastrointestinal disorders

Intermediary of health effect	Authors, Year of publication	Design	Study population	Age group	Breastfeeding	Effect size				Remarks
Gastrointestinal infection	(Kramer et al., 2001) [c]	Randomized controlled trial	Belarus n=17,046	0-12 mo	Control group Intervention group	OR=1 **OR=0.60 (0.40-0.91)**				Part of the PROBIT-study. Intervention=BFHI. Intervention group: 3 mo 43% EBF, 6 mo 8% EBF. Control group: 3 mo 6% EBF, 6 mo 1% EBF. Corrected for birth weight and number of siblings.
	(Wright et al., 1998)	Cohort	USA n= 977/858	0-12 mo	FF BF	Before introduction BFHI RR=1 **RR=0.42 (0.21-0.83)**	After BFHI RR=1 **RR=0.52 (0.32-0.86)**			Different ethnic group: Indian reservation. Correction for possible confounder had no effect on the risk estimates. EBF*: solids were introduced after ± 3 months, no formula.
	(Beaudry et al., 1995) [D]	Cohort	Canada n=776	0-6 mo	FF BF	IDR=1 IDR=0.53 (0.27-1.04)				Correction for age child, SES, age mother, and smoking mother had no effect on the IDR.
	(Rubin et al., 1990)	Cohort	Denmark n=500	0-12 mo	FF+MBF(BF≤FF) EBF+MBF(BF>FF)	IDR=1.07 (0.98-1.22) IDR=1				Corrected for birth weight, SES, number of children, day-care, family history, and age child. Large drop-out during follow-up.
	(Howie et al., 1990)	Cohort	Scotland n=618	0-13 wk 14-26 wk 27-39 wk 40-52 wk	$FF_{>3}$ $EBF_{>3}$	0-13 wk RR=1 **RR=0.18**	14-26 wk RR=1 **RR=0.49**	27-39 wk RR=1 **RR=0.39**	40-52 wk RR=1 **RR=0.29**	Corrected for SES, age mother, and smoking (other confounders no effect).
	(Kramer and Kakuma, 2002) [C]	Review	n=3,483	0-12 mo	$MBF_{3\text{-}7}$ $EBF_{3\text{-}7}$	≥ 1 episode RR=1 **RR=0.67 (0.46-0.97)**		Hospitalisation RR=1 RR=0.79 (0.42-1.49)		Based on one study (Kramer et al., 2001).

Table A1.2 continued: Effect of breastfeeding on gastrointestinal disorders

Intermediary of health effect	Authors, Year of publication	Design	Study population	Age group	Breastfeeding	Effect size	Remarks
Gastrointestinal infection continued	(Hanson, 1998;Hanson, 1999) C	Review				Demonstrate significant protection during breastfeeding against diarrhoea and infections in general.	Based on (Howie et al., 1990) and studies from developing countries.
Diarrhoea	(Raisler et al., 1999) D	Cohort	USA n=7,092	0-6 mo	FF MBF (BF< FF) MBF (BF= FF) MBF (BF>FF) EBF	OR=1 OR=0.95 (0.78-1.16) OR=0.87 (0.65-1.18) **OR=0.83 (0.69-0.99)** **OR=0.54 (0.43-0.66)**	Corrected for age mother, ethnicity, SES, birth weight, number of siblings, day-care, age child (mo), smoking, and recall interval. Breastfeeding was defined every month.
	(Baker et al., 1998) D	Cohort	United Kingdom n=8488	6 mo	FF BF<3 BF≥3	OR=1 **OR=0.82 (0.72-0.93)** **OR=0.42 (0.37-0.48)**	Corrected for SES, housing tenure, number of persons in household, siblings, mother smokes
	(Scariati et al., 1997) D	Cohort	USA n=1,743	0-7 mo	FF_{2-7} MBF_{2-7}(1-57% BF) MBF_{2-7} (58-88%BF) MBF_{2-7}(89-99% BF) EBF_{2-7}	**OR=1.8 (p<0.05)** OR=1.3 OR=1.1 OR=0.9 OR=1	Corrected for additional feeding (solids & fluids), age child, gender, SES, smoking, number of siblings, and day-care.
	(Quigley et al., 2006) d	Case-control	United Kingdom 167 cases 137 controls	0-12 mo	FF BF	**OR= 2.74 (1.35-5.57)** 1	≤6 mo: OR=2.21 (0.81-6.01); 1 ≥6 mo: **OR=3.74 (1.39-10.03)**; 1 Matched on age group, Jarman score for the practise, location practise Corrected for age, weaning, SES, contact with person in household/outside household, sex, travel
	(Dewey et al., 1995)	Matched cohort	USA n=87	0-12 mo 12-24 mo	FF BF FF BF	Incidence /100 days at risk 0-12 mo: **i=0.31** **i=0.14** 12-24 mo: i=0.44 i=0.50 Prevalence (days diseased/yr) 0-12 mo: P=6.3 P=2.6 12-24 mo: P=11.2 P=10.7	BF and FF matched on SES, ethnicity, anthropometrical characteristics, gender, and birth weight. Corrected for day-care and number of siblings. Solids were introduced after four months (both BF and FF).
Rotavirus infection a	(Gianino et al., 2002)	Hospital based cohort	Italy n=220	1-18 mo	FF BF	P=66% P=0%	Children hospitalized for gastrointestinal disorders. Followed during hospitalisation and 72 hr after discharge.
	(Golding et al., 1997c)	Review				4 studies find less and/or milder symptoms	Only 4 studies from developed countries.
Salmonella B / D a	(Rowe et al., 2004)	Case-control	USA 22 Cases 39 Controls	0-12 mo	FF BF	0-12 mo: OR=1; **OR=0.05 (0-0.30)** 0-6 mo: 1; **0.05 (0-0.33)** 6-12 mo: 1; 0.83 (0-10.65)	Matched by age and region. Not further corrected. Within the 6-11 mo group: only 5 cases and 15 controls.

Table A1.2 continued: Effect of breastfeeding on gastrointestinal disorders

Intermediary of health effect	Authors, Year of publication	Design	Study population	Age group	Breastfeeding	Effect size		Remarks
Crohn's disease	(Baron et al., 2005) [c]	Case-control	France 222 Cases 222 Controls	0-17 year	FF BF	OR=1 **OR=2.1 (1.3-3.4)**		Cases and controls matched on age (2year), sex and living area. Adjusted for mother's education level, family history, eczema, bacilli Chalmette-Guerin vaccine, drinking tap water.
	(Corrao et al., 1998) [d]	Case-control	Italy 225 Cases 225 Controls	18-65 yr	 FF BF	<u>Male</u> OR=1.9 (0.2-3.7) OR=1	<u>Female</u> **OR=2.2 (1.0-4.8)** OR=1	Matched on age and gender. Adjusted for smoking and oral contraceptive use.
	(Rigas et al., 1993)	Case-control	USA 68 Cases 202 Controls	0-17 yr	FF $BF_{\leq 5}$ $BF_{6\text{-}11}$ $BF_{\geq 12}$	OR= 1 OR=0.7 (0.3-1.5) OR=0.6 (0.2-1.5) OR=0.1 (0.01-1.10) **(p-trend=0.04)**		Corrected for smoking mother, gender, age at diagnosis, number of siblings, ethnicity, and place of birth. Possible information bias in definition breastfeeding.
	(Koletzko et al., 1989) [c]	Case-control	Canada 114 Cases 180 Controls	15-18 yr	FF No BF BF	OR=1.4 (0.5-4.5) OR=3.0 (1.0-9.4) OR=1		Corrected for earlier episodes of diarrhoea (gender, premature birth, way of feeding, age solids, duration EBF, and total duration BF played no significant role). No clear definition breastfeeding; information bias.
	(Klement et al., 2004) [c]	Meta-analysis	3,190 Cases 4,026 Controls		FF BF	OR=1 **OR= 0.67 (0.52-0.86)**		Medline & EMBASE…-Nov 2003. 14 studies including (Rigas et al., 1993) and (Koletzko et al., 1989); other studies had non relevant study populations.
Ulcerative colitis [a]	(Corrao et al., 1998) [c]	Case-control	Italy 594 Cases 594 Controls	18-65 yr	 FF BF	<u>Male</u> OR=1.2 (0.6-1.7) OR=1	<u>Female</u> **OR=2.1 (1.0-3.5)** OR=1	Matched on age and gender Adjusted for smoking and oral contraceptive use
	(Rigas et al., 1993)	Case-control	USA 68 Cases 202 Controls	0-17 yr	FF $BF_{\leq 5}$ $BF_{6\text{-}11}$ $BF_{\geq 12}$	OR=1 OR=0.7 (0.3-1.6) OR=0.5 (0.2-1.5) OR=0.2 (0.03-2.2) (p-trend:0.07)		Corrected for smoking mother, gender, age diagnosis, number of siblings, ethnicity, and place of birth. Possible information bias definition breastfeeding.
	(Klement et al., 2004) [c]	Meta-analysis	2,577 Cases 3,551 Controls		FF BF	OR=1 **OR= 0.77 (0.61-0.96)**		Medline & EMBASE…-Nov 2003. If only 'high quality' studies were included: effect stronger. 14 studies including ((Rigas et al., 1993)); other studies had non relevant study populations..

Table A1.2 continued: Effect of breastfeeding on gastrointestinal disorders

Intermediary of health effect	Authors, Year of publication	Design	Study population	Age group	Breastfeeding	Effect size	Remarks
Celiac disease [a]	(Peters et al., 2001)	Case-control	Germany 143 Cases 137 Controls	Mean age 6.4 yr	FF $BF_{>0-<3\ mo}$ $BF_{\geq 3-<7\ mo}$ $BF_{\geq 7\ mo}$ BF /mo	OR=1 OR=0.39 (0.15-1.02) **OR=0.22 (0.08-0.59)** **OR=0.18 (0.06-0.52)** **OR=0.89 (0.54-0.95)**	Matched on gender and age. Adjusted for age, sex, number of inhabitants of residence, family history, age gluten introduction.
Pyloric stenosis [a]	(Pisacane et al., 1996)	Case-control	Italy 102 Cases 204 Controls	± 1 yr	$FF_{1\ wk}$ $MBF_{1\ wk}$ $EBF_{1\ wk}$	**OR=2.74(1.36-5.52)** **OR=2.04 (1.1-3.76)** OR=1	Corrected for gender, number of siblings, SES, age, smoking, and complications at birth. Definition breastfeeding based on situation first week.

Table A1.3: Effect of breastfeeding on urinary tract morbidity

Intermediary of health effect	Authors, Year of publication	Design	Study population	Age group	Breastfeeding	Effect size			Remarks
Urinary tract Infection [a]	(Marild et al., 2004)	Case-control	Sweden 200 Cases 336 Controls	0-2 yr	 FF BF	Girls and boys **OR=2.30 (1.56-3.39)** OR=1	girls OR=3.78 OR=1	boys OR=1.63 OR=1	Matched on age and gender. Possible information bias in definition breastfeeding.
	(Pisacane et al., 1992)	Case-control	Italy 128 Cases 128 Controls	0-6 mo	FF BF $BF_{\text{at admission}}$	RR=1 **RR=0.38 (0.22-0.65)** **RR=0.18 (0.09-0.36)**			Way of feeding was determined at hospitalisation.

Table A1.4: Effect of breastfeeding on otitis media

Intermediary of health effect	Authors, Year of publication	Design	Study population	Age group	Breastfeeding	Effect size		Remarks
Otitis Media	(Kramer et al., 2001) c	Randomized controlled trial	Belarus N=17,046	0-12 mo	Control group Intervention group	OR=1 OR=1.01 (0.54-1.88)		Part of the PROBIT-study. Intervention=BFHI. Intervention group: 3 mo 43% EBF, 6 mo 8% EBF Control group: 3 mo 6% EBF, 6 mo 1% EBF. Corrected for birth weight, number of siblings, and smoking during pregnancy.
	(Chantry et al., 2006) d	Cohort	USA N=1,993	6-12 mo	FF $EBF_{<1\ mo}$ $EBF_{1-3\ mo}$ $EBF_{4-5\ mo}$ $EBF_{\geq 6\ mo}$	OR=1.57 (0.91-2.71) OR=1.44 (0.81-2.57) **OR=1.87 (1.07-3.26)** OR=1.25 (0.69-2.27) OR=1		Adjusted for ethnicity, day care, head of household, education, poverty index, smoke exposure.
	(Raisler et al., 1999) d	Cohort	USA n=7,092	0-6 mo	FF MBF (BF<FF) MBF (BF=FF) MBF (BF>FF) EBF	No siblings present OR=1 OR=0.88 (0.67-1.17) **OR=0.55 (0.34-0.89)** **OR=0.74 (0.59-0.95)** **OR=0.49 (0.36-0.66)**	Siblings present OR=1 OR=1.07 (0.88-1.30) OR=0.85 (0.63-1.16) OR=1.06 (0.89-1.25) OR=0.85 (0.70-1.05)	Corrected for age mother, ethnicity, SES, birth weight, number of siblings, day-care, age child (month), smoking, and recall interval. Breastfeeding is defined every month.
	(Wright et al., 1998)	Cohort	USA n= 977/858	0-12 mo	FF BF	Before introduction BFHI RR=1 RR=0.75 (0.56-1.00)	After introduction BFHI RR=1 **RR=0.70 (0.56-0.88)**	Different ethnic group: Indian reservation. Correction for possible confounder had no effect on the risk estimates. EBF*:± 3 mo EBF, then solids are given, no formula.
	(Duffy et al., 1997) d	Cohort	USA N=306	0-24 mo	FF_3 vs. EBF_3 FF_6 vs. EBF_6 FF_6 vs. MBF_6 FF_{12} vs. MBF_{12}	Otitis Media **OR=2.53 (1.11-5.81)** **OR=4.57 (1.72-12.18)** **OR=3.06 (1.28-7.31)** **OR=3.00 (1.36-6.69)**	Otitis Media with effusion OR=2.48 (0.85-7.17) **OR=6.23 (1.55-24.78)** **OR=3.00 (1.02-8.76)** **OR=3.29 (1.18-9.12)**	Health effect= risk for first OM episode/OM episode with effusion during the first 24 months. Corrected for gender, day care, smoking mother, age of pathogen colonization.
	(Scariati et al., 1997) d	Cohort	USA n=1,743	0-7 mo	FF_{2-7} MBF_{2-7}(1-57% BF) MBF_{2-7}(58-88% BF) MBF_{2-7} (89-99%BF) EBF_{2-7}	**OR=1.7** (p=0.05) **OR=1.6** (p=0.05) OR=1.4 OR=1.2 OR=1		Corrected for additional feeding, age child, gender, SES, smoking, number of siblings and day-care. Risk of otitis media related to the way of feeding in the preceding month.

Table A1.4 continued: Effect of breastfeeding on otitis media

Intermediary of health effect	Authors, Year of publication	Design	Study population	Age group	Breastfeeding	Effect size		Remarks
Otitis Media continued	(Paradise et al., 1997) c	Cohort	USA N=2,253	2-12 mo 13-24 mo	$BF_{<2}$ BF_2 BF_4 BF_6 BF_8 $BF_{\geq 12}$	2-12 mo mean cum. % of days (n) 21.7 (1629) 19.8 (137) 17.6 (121) 16.8 (83) 14.5 (156) 16.2 (127) **(p-trend <.001)**	13-24 mo mean cum. % of days (n) 17.3 (1629) 15.0 (137) 15.1 (121) 17.2 (83) 13.9 (156) 13.3 (127) **(p-trend <.001)**	Health effect = mean cumulative percent of days with middle ear effusion. No correction.
	(Dewey et al., 1995)	Matched cohort	USA n=87	0-12 mo 12-24 mo	FF BF FF BF	Incidence /100 days at risk 0-12 mo: **i=0.53** **i=0.45** 12-24 mo: i=0.45 i=0.43	Prevalence (days diseased/yr) 0-12 mo: **P=15.8** **P=10.0** 12-24 mo: P=11.1 P=17.3	BF and FF matched on SES, ethnicity, anthropometrical characteristics, gender, birth weight. Corrected for day-care and number of siblings. Solids were introduced after four months (both BF and FF).
	(Rubin et al., 1990)	Cohort	Denmark n=500	0-12 mo	FF+MBF(BF≤FF) EBF+MBF(BF>FF)	IDR=1.28 (0.97-1.7) IDR=1		Corrected for birth weight, SES, number of children, day-care, family history, and age child. Large drop-out during follow-up.
	(Kramer and Kakuma, 2002) e	Review/ meta-analysis	n=3,762	0-12 mo	MBF_{3-7} EBF_{3-7}	RR=1 **RR=1.28 (1.04-1.57)**		Based on two studies (Duncan et al., 1993) and (Kramer et al., 2001).
Acute Otitis Media	(Daly et al., 1999) d	Cohort	USA n=596	0-6 mo	EBF_6 vs. No EBF_6 EBF_3 vs. No EBF_3	**RR=0.7 (0.5-0.98)**; corrected: RR=0.8 (0.5-1.3) **RR=0.8 (0.6-0.96)**		Corrected, where noticed, for day-care, respiratory infection, conjunctivitis, number of siblings, family history OM, number of smokers in family, season of birth, and intake Vitamin C by mother (otherwise no correction).
	(Duffy et al., 1997) d	Cohort	USA n=306	0-24 mo	FF_3 vs. EBF_3 FF_6 vs. EBF_6 FF_6 vs. MBF_6 FF_{12} vs. MBF_{12}	**OR=2.69 (1.12-6.55)** **OR=4.57 (1.61-12.93)** **OR=3.29 (1.34-8.17)** **OR=3.10 (1.32-7.24)**		Health effect= risk for first AOM episode during the first 24 months. Corrected for gender, day care, smoking mother, age of pathogen colonization.

Table A1.4 continued: Effect of breastfeeding on otitis media

Intermediary of health effect	Authors, Year of publication	Design	Study population	Age group	Breastfeeding	Effect size				Remarks
Acute Otitis Media continued	(Aniansson et al., 1994) f	Cohort	Sweden n=400	0-12 mo	FF_{1-3} MBF_{1-3} EBF_{1-3} $FF_{<7}$ MBF_{4-7} $EBF_{<7}$ $FF_{<12}$ MBF_{8-12} $EBF_{<12}$	<3 mo (%) 1 **5** 6 0 1 3 0 0 2	<7 mo (%) 8 12 **19** 4 7 14 0 3 9	<12mo (%) 21 20 28 13 20 26 0 13 **25**		**Bold**=p<0.05 compared with breastfed children. No correction.
	(Duncan et al., 1993)	Cohort	USA n=1,013	0-6 mo 6-12 mo 0-12 mo	FF $BF_{<4}$ $MBF_{\geq4}$ & $FF_{<4}$ $MBF_{\geq4}$ & FF_{4-6} $EBF_{\geq6}$	0-6 mo RR=1 RR=0.84 RR=0.84 RR=0.49 RR=0.53	6-12 mo RR=1 RR=0.96 RR=0.82 RR=0.83 RR=0.78	0-12 mo RR=1 RR=0.92 RR=0.83 RR=0.71 RR=0.69		Effect is manually calculated by means of the given mean numbers of episodes of AOM per infant in the first year (sd) in the article (Table 2). No correction.
	(Howie et al., 1990)	Cohort	Scotland n=618	0-13 wk 14-26 wk 27-39 wk 40-52 wk	$FF_{>3}$ $EBF_{>3}$	0-13 wk RR=1 RR=1.13	14-26 wk RR=1 RR=2.17	27-39 wk RR=1 RR=1.05	40-52 wk RR=1 RR=0.89	Corrected for SES, age mother, and smoking (other confounders no effect).
	(Alho et al., 1990) d	Cohort	Finland n=2130	0-24 mo	$BF_{<3}$ BF_{3-6} BF_{7-11} $BF_{\geq12}$	≥ 3 AOM episodes OR=1 **OR=1.4 (1.2-1.6)** **OR=1.5 (1.3-1.8)** **OR=1.6 (1.3-2.0)**		≥ 3 AOM episodes with effusion OR=1 OR=1.2 (0.9-1.6) **OR=1.4 (1.1-1.8)** **OR=1.5 (1.1-2.0)**		Corrected for allergy, family care, ≥2 siblings, gender, smoking parents. The effect of breastfeeding was more significant in the 'otitis-prone' cases (≥3 episodes).
	(Teele et al., 1989) d	Cohort	USA n=877	0-1 yr 0-3 yr	FF BF	≥1episode ≥3episode	0-1 year OR=1 **OR=0.64 (0.44-0.91)** **OR=0.51 (0.30-0.89)**	0-3 year OR=1 **OR=0.48(0.30-0.76)** NS		Corrected for gender and sibling history of ear infection. Only significant results are mentioned. ≥ 3 episodes within the first 3 years NS also no significant effect within the first 7 years. Enrolment in 1975.

Table A1.4 continued: Effect of breastfeeding on otitis media

Intermediary of health effect	Authors, Year of publication	Design	Study population	Age group	Breastfeeding	Effect size	Remarks
Acute Otitis Media continued	(Uhari et al., 1996) c	Meta-analysis	n=2,548-3,384		BF vs. FF $BF_{\geq 3}$ vs. $BF_{<3}$ $BF_{\geq 6}$ vs. $BF_{<6}$	**RR=0.74 (0.52-0.94)** **RR=0.87 (0.79-0.95)** **RR=0.85 (0.74-0.93)**	Medline 1966-1994. $BF_{>3\ mo}$ six studies (including (Howie et al., 1990), (Aniansson et al., 1994) and (Teele et al., 1989)); n=2,548. $BF_{>6\ mo}$ seven studies (including (Duncan et al., 1993), (Aniansson et al., 1994) and (Teele et al., 1989)); n=3,384. $BF_{ves/no}$ five studies (including (Howie et al., 1990) and (Teele et al., 1989)); n=2,193. Other studies had non relevant study populations.
Recurrent Otitis Media	(Chantry et al., 2006) d	Cohort	USA N=1,963	6-24 mo	FF $EBF_{<1\ mo}$ $EBF_{1-3\ mo}$ $EBF_{4-5\ mo}$ $EBF_{\geq 6\ mo}$	OR=2.30 (1.12-4.71) OR=1.80 (0.88-3.64) OR=2.07 (1.12-3.79) OR=1.95 (1.06-3.59) OR=1	Adjusted for ethnicity, day care, head of household education, poverty index, family size, smoke exposure, birth weight, age.
	(Daly et al., 1999) d	Cohort	USA n=596	0-6 mo	No EBF_6 EBF_6	RR=1 RR=1.2 (0.6-2.2)	Corrected for day-care, respiratory infection, conjunctivitis, number of siblings, family history OM, number of smokers in family, season of birth, and intake vitamin C by mother.
	(Duncan et al., 1993) d	Cohort	USA n=440	0-12 mo	FF & $BF_{<4}$ $MBF_{\geq 4}$ & $FF_{<4}$ $MBF_{\geq 4}$ & FF_{4-6} $EBF_{>6}$	OR=1 **OR=0.73 (0.60-0.90)** **OR=0.54 (0.35-0.81)** **OR=0.39 (0.21-0.73)**	Controls in the analyses never had AOM. Controlled for parental history of allergy, siblings, day-care, maternal smoking, gender, ethnic group, SES.
	(Kramer and Kakuma, 2002) e	Review/ meta-analysis	n=279	0-12 mo	MBF_{3-7} EBF_{3-7}	RR=1 RR=0.81 (0.43-1.52)	Based on one study (Duncan et al., 1993).
	(Uhari et al., 1996) c	Meta-analysis	n=1,156-1,331		BF vs. FF $BF_{\geq 3}$ vs. $BF_{<3}$ $BF_{\geq 6}$ vs. $BF_{<6}$	**RR=0.48 (0.32-0.72)** RR=0.69(0.46-1.03) **RR=0.69 (0.49-0.97)**	Medline 1966-1994. $BF_{ves/no}$ two studies (incl (Teele et al., 1989)); n=1,156. $BF_{>3\ mo}$ three studies (incl (Teele et al., 1989)); n= 1,331. $BF_{>6\ mo}$ three studies (incl (Teele et al., 1989)); n=1,331. Other studies had non relevant study populations.

Table A1.5: Effect of breastfeeding on respiratory infections

Intermediary of health effect	Authors, Year of publication	Design	Study population	Age group	Breastfeeding	Effect size			Remarks
Respiratory infection	(Kramer et al., 2001) d	Randomised controlled trial	Belarus n=17,046	0-12 mo	Control group Intervention group	OR=1 OR=0.87 (0.59-1.28)			Part of the PROBIT-study. Intervention=BFHI. Intervention group: 3 mo 43% EBF, 6 mo 8% EBF. Control group: 3 mo 6% EBF, 6 mo 1% EBF. Corrected for birth weight, number of siblings, and smoking during pregnancy. Respiratory infection includes upper respiratory, otitis media, croup, wheezing, and pneumonia.
	(Chantry et al., 2006) d	Cohort	USA N=2,190	6-24 mo	FF $EBF_{<1\ mo}$ $EBF_{1-3\ mo}$ $EBF_{4-5\ mo}$ $EBF_{>6\ mo}$	Pneumonia OR=2.02 (0.64-6.34) OR=1.34 (0.39-4.62) OR=1.97 (0.53-7.27) OR=4.27 (1.27-14.35) OR=1	Recurrent URI OR=1.41 (0.74-2.70) OR=1.49 (0.76-2.92) OR=1.34 (0.67-2.69) OR=1.53 (0.63-3.68) OR=1		Adjusted for ethnicity, day care, head of household education, poverty index, family size, smoke exposure, birth weight, age, two-parent household, gender.
	(Raisler et al., 1999) d	Cohort	USA n=7,092	0-6 mo	FF MBF (BF< FF) MBF (BF= FF) MBF (BF>FF) EBF	OR=1 OR=1.01 (0.3-1.92) OR=0.27 (0.04-1.85) OR=0.87 (0.47-1.60) OR=0.77 (0.44-1.33)			Corrected for age mother, ethnicity, SES, birth weight, number of siblings, day-care, age child (mo), smoking, and recall interval. Breastfeeding is defined every month.
	(Wright et al., 1998)	Cohort	USA n= 977/858	0-12 mo	FF BF		Before BHFI RR=1 RR=0.51 (0.20-1.13) RR=0.75 (0.10-5.76) RR=0.22 (0.03-1.58) RR= --- **RR=0.59(0.39-0.90)**	After BHFI RR=1 **RR=0.39(0.19-0.79)** RR=0.51 (0.06-4.51) RR=0.29 (0.06-1.26) RR=0.21 (0.03-1.58) **RR=0.77(0.60-0.98)**	Different ethnic group, Indian reservation. Correction for possible confounders had no effect on the risk estimates. EBF*:± 3 mo EBF, then solids are given, no formula.
	(Cushing et al., 1998) d	Cohort	USA n=1,051	0-6 mo	FF MBF EBF	OR=1 OR=1.05 (0.93-1.19) OR=0.98 (0.88-1.08)			Mother kept a diary; once every two weeks interview by telephone. Feeding was defined every two weeks. Corrected for birth number, gender, ethnicity, family history asthma, SES, and day-care.
	(Beaudry et al., 1995) d	Cohort	Canada n=776	0-6 mo	FF BF	IDR=1 **IDR=0.78 (0.61-1.00)**			Corrected for age child, SES, age mother, and smoking mother. Includes also ear infections.
	(Douglas et al., 1994)	Cohort	Australia n=836	0-12 mo 12-24 mo	FF BF_{1-3} BF_{4-6} BF_{7-12} $BF_{>12}$	1st yr 6.10 5.67 6.61 6.19 6.34	2nd yr 5.58 6.09 6.54 6.48 7.02 **(p=0.006)**		Effect measurement is mean value of respiratory episodes.

Table A1.5 continued: Effect of breastfeeding on respiratory infections

Intermediary of health effect	Authors, Year of publication	Design	Study population	Age group	Breastfeeding	Effect size				Remarks
Respiratory infection continued	(Howie et al., 1990)	Cohort	Scotland n=618	0-13 wk 14-26 wk 27-39 wk 40-52 wk	$FF_{>3}$ $EBF_{>3}$	0-13 wk RR=1 **RR=0.69**	14-26 wk RR=1 RR=0.87	27-39 wk RR=1 RR=0.92	40-52 wk RR=1 **RR=0.83**	Corrected for SES, age mother, and smoking (other confounders no effect).
	(Alho et al., 1990) [d]	Cohort	Finland N=2,130	0-24 mo	$BF_{<3}$ BF_{3-6} BF_{7-11} $BF_{\geq 12}$	OR=1 OR=1.2 (1.0-1.6) OR=1.2 (1.0-1.4) **OR=1.3 (1.1-1.6)**				Corrected for allergy, family care, ≥2 siblings, gender, smoking parents. The effect of breastfeeding was more significant in the 'otitis-prone' cases (≥3 episodes).
	(Sinha et al., 2003) [d]	Case-control	USA 237 Cases 1,205 Controls	0-30 days	FF MBF EBF	Girls and boys OR=1 OR=0.83 (0.58-1.20) **OR=0.70 (0.49-0.99)**	Girls 1 **0.6 (0.34-0.93)** **0.50 (0.29-0.79)**	Boys 1 1.4 (0.78-2.4) 1.1 (0.64-2.0)		Corrected for birth year, age mother, season of birth, number of siblings, SES, and ethnicity.
	(Kramer and Kakuma, 2002) [e]	Review	n=3,483	0-12 mo	MBF_{3-7} EBF_{3-7}	≥ 2 episodes RR=1 RR=0.90 (0.79-1.03)	Hospitalization RR=1 **RR=0.75 (0.60-0.94)**			Based on one study (Kramer et al., 2001).
Upper respiratory tract infection	(Kramer et al., 2001)	Randomised controlled trial	Belarus n=17,046	0-12 mo	Control group Intervention group	OR=1 OR=0.87 (0.58-1.30)	Croup OR=1 OR=0.86 (0.38-1.94)			Part of the PROBIT-study. Intervention=BFHI. Intervention group: 3 mo 43% EBF, 6 mo 8% EBF. Control group: 3 mo 6% EBF, 6 mo 1% EBF. Corrected for birth weight, number of siblings, and smoking during pregnancy.
	(Oddy et al., 2003) [c]	Cohort	Australia n=2,456	0-12 mo	$EBF_{\geq 2}$ vs. $EBF_{<2}$ $MBF_{\geq 6}$ vs. $MBF_{<6}$	≥4 medical visits **OR=1.43 (1.02-2.01)** OR=1.46 (1.07-2.00)	Hospitalization OR=1.85 (0.79-4.34) OR=2.05 (0.88-4.76)			Corrected for gender, gestational age, smoking during pregnancy, older siblings, SES, and age mother (other confounders had no effect).
	(Oddy et al., 2002) [c]	Cohort	Australia n=2,602	0-12 mo	FF vs. $EBF_{>0}$ $EBF_{<2}$ vs. $EBF_{\geq 2}$ $EBF_{<4}$ vs. $EBF_{\geq 4}$ $EBF_{<6}$ vs. $EBF_{\geq 6}$	OR=0.80 (0.56-1.13) OR=0.93 (0.73-1.19) OR=0.91 (0.73-1.12) **OR=0.74 (0.60-0.93)**				Corrected for gender, gestational age, and smoking during pregnancy.
	(Wilson et al., 1998) [d]	Cohort	Scotland n=545	0-7 yr	$EBF_{\geq 15wk,\ no\ solids}$ $EBF_{\geq 15wk,\ solids}$ $EBF_{\geq 15wk}$ $MBF_{\geq 15wk,\ no\ solids}$ $MBF_{\geq 15wk,\ solids}$ $MBF_{\geq 15wk}$ $FF_{\geq 15wk,\ no\ solids}$ $FF_{\geq 15wk,\ solids}$ $FF_{\geq 15wk}$	Respiratory disorder P=14.9 (13.7-16.1) P=19.1 (17.4-20.8) P=17.0 (15.9-18.1) P=25.6 (23.0-28.2) P=32.5 (31.1-33.9) P=31.0 (26.8-35.2) P=27.6 (23.9-31.3) P=33.3 (31.7-34.9) P=32.2 (30.7-33.7)	Cough P=11.0 (10.3-11.7) P=11.7 (10.3-12.6) P=11.3 (10.7-11.9) P=21.0 (19.3-22.7) P=22.5 (21.5-23.5) P=22.2 (19.5-24.9) P=23.5 (20.8-26.2) P=24.8 (23.7-25.9) P=24.6 (23.6-25.6)		Way of feeding was collected prospectively during the first and second year. Corrected for family history, gender, SES. Within the MBF group the mean duration of breastfeeding was 9.5 weeks.

Table A1.5 continued: Effect of breastfeeding on respiratory infections

Intermediary of health effect	Authors, Year of publication	Design	Study population	Age group	Breastfeeding	Effect size			Remarks
Upper respiratory tract infection continued	(Cushing et al., 1998) [d]	Cohort	USA n=1,051	0-6 mo	FF MBF EBF	OR=1 OR=1.11(0.98-1.27) OR=1.10(0.98-1.24)			Corrected for birth number, gender, ethnicity, family history asthma, SES, and day-care.
	(Dewey et al., 1995)	Matched cohort	USA n=87	0-12 mo 12-24 mo	FF BF FF BF	Incidence /100d at risk 0-12 mo: i=1.7 i=2.1 12-24 mo: i=2.0 i=2.0	Prevalence (day diseased/yr) 0-12 mo: p=59.6 p=62.3 12-24 mo: p=66.4 p=61.9		BF and FF matched on SES, ethnicity, anthropometrical characteristics, gender, and birth weight. Corrected for day-care, number of siblings. Solids were introduced after 4 mo (both BF and FF).
	(Rubin et al., 1990)	Cohort	Denmark n=500	0-12 mo	FF+MBF(BF≤FF) EBF+MBF(BF>FF)	IDR=0.98 (0.88-1.07) IDR=1			Corrected for birth weight, SES, number of children, day-care, family history, and age child. Large drop-out during follow-up.
	(Kramer and Kakuma, 2002) [c]	Review	n=492-3,993	0-12 mo	MBF_{3-7} EBF_{3-7}	≥1 episode RR=1 RR=1.07 (0.96-1.20)	≥2 episodes RR=1 RR=0.91 (0.82-1.02)	≥4 episodes RR=1 RR=0.82 (0.52-1.29)	≥1 and ≥4 episodes based on one study (Oddy et al., 1999); 2 episodes based on two studies (Oddy et al., 1999) and (Kramer et al., 2001).
Disorder lower respiratory tract [a]	(Oddy et al., 2002) [c]	Cohort	Australia n=2,602	0-12 mo	FF vs. $EBF_{>0}$ $EBF_{<2}$ vs. $EBF_{\geq 2}$ $EBF_{<4}$ vs. $EBF_{\geq 4}$ $EBF_{<6}$ vs. $EBF_{\geq 6}$	OR=0.82 (0.51-1.32) OR=0.89 (0.65-1.22) OR=1.01 (0.77-1.32) OR=0.98 (0.75-1.29)			Corrected for gender, gestational age, and smoking during pregnancy.
	(Cushing et al., 1998) [d]	Cohort	USA n=1,051	0-6 mo	FF MBF EBF	OR=1 OR=0.95(0.78-1.16) **OR=0.79(0.67-0.94)**			Corrected for birth number, gender, ethnicity, family history asthma, SES, and day-care.
	(Nafstad et al., 1996) [c]	Cohort	Norway n=3,238	0-12 mo	$BF_{>6;\ non\ smoking\ mother}$ $BF_{>6;\ smoking\ mother}$ $BF_{0-6;\ non\ smoking\ mother}$ $BF_{0-6;\ smoking\ mother}$	7-12 mo OR=1 OR=1.0 (0.6-1.5) OR=1.4 (1.0-1.8) **OR=1.9 (1.3-2.7)**	0-12 mo OR=1 OR=1.1 (0.7-1.6) OR=1.3 (1.0-1.7) **OR=2.2 (1.6-3.1)**		Corrected for gender, number of sibling, sharing a bedroom, day-care, SES, family history asthma, and smoking.
	(Rubin et al., 1990)	Cohort	Denmark n=500	0-12 mo	FF+MBF(BF≤FF) EBF+MBF(BF>FF)	IDR=1.00 (0.74-1.35) IDR=1			Corrected for birth weight, SES, number of children, day-care, family history, and age child. Large drop-out during follow-up.
	(Wright et al., 1989) [d]	Cohort	USA n=1,246	0-4 mo 4-6 mo 6-12 mo	BF_{0-1} BF_{1-4} $BF_{>4}$	< 4 mo i=2.0 i=3.8 i=2.7	4-6 mo i=2.7 i=2.0 i=2.1	6-12 mo i=7.0 i=7.3 i=2.9	Definition breastfeeding based on prospective and retrospective collection. Not corrected.

Table A1.5 continued: Effect of breastfeeding on respiratory infections

Intermediary of health effect	Authors, Year of publication	Design	Study population	Age group	Breastfeeding	Effect size	Remarks
Disorder lower respiratory tract continued [a]	(Bachrach et al., 2003) [c]	Meta-analysis	Developed countries	0-24 mo	$EBF_{\geq 4}$ vs. none $EBF_{\geq 4}$ vs. none $MBF_{\geq 4}$ vs. none	**RR=0.28 (0.14-0.54)** Corrected for smoking mother **RR=0.43(0.22-0.85)** Corrected for SES **RR=0.53 (0.30-0.93)**	Inclusion criteria: industrialized country, no specific risk groups, duration and exclusivity breastfeeding stated In total nine studies incl. seven cohort studies (including, (Beaudry et al., 1995), (Howie et al., 1990), (Nafstad et al., 1996), (Oddy et al., 1999)). Other studies had inadequate study design
	(Kramer and Kakuma, 2002) [c]	Review	n=492	0-12 mo	MBF_{3-7} EBF_{3-7}	RR=1 RR=1.07 (0.86-1.33)	Based on one study (Oddy et al., 1999).

Table A1.6: Effect of breastfeeding on Haemophilus influenza

Intermediary of health effect	Authors, Year of publication	Design	Study population	Age group	Breastfeeding	Effect size			Remarks
Haemophilus influenza [a]	(Silfverdal et al., 1997)	Case Control	Sweden 54 Cases 139 Controls	0-6 yr	$EBF_{\geq 13\ wk}$ $EBF_{<13\ wk}$ EBF (wk)	OR=1 **OR=3.79 (1.6-8.8)** **OR=0.95 (0.91-0.99)**	≥12 mo OR=1 **OR=7.97 (2.4-26.6)**	≥24 mo OR=1 **OR=4.61 (1.0-21.8)**	Matched on living area, time period, gender and age. Corrected for SES, siblings, day-care, passive smoking, and history of diseases. Definition breastfeeding at time of diagnosis (mean age 21.6 mo). Study performed before introduction Hib vaccination.

Table A1.7: Effect of breastfeeding on jaundice

Intermediary of health effect	Authors, Year of publication	Design	Study population	Age group	Breastfeeding	Effect size		Remarks
Jaundice [a]	(Bertini et al., 2001)	Cohort	Italy n=2,174	3-4 days	FF MBF EBF	OR=1.15 **OR=1.36** OR=1		Possible confounders are measured separately, not corrected.
	(Wright et al., 1998)	Cohort	USA n= 977/858	0-12 mo	FF BF	Before intervention RR=1 **RR=7.59 (1.59-36.26)**	after intervention RR=1 RR=3.08 (0.52-18.04)	Different ethnic group, Indian reservation Correction for possible confounder had no effect on the risk estimates. EBF*:± 3 mo EBF, then solids are given, no formula.
	(Golding et al., 1997a)	Review			BF vs. FF	Seven studies increased risk for BF Two studies decreased risk for BF		Based on nine studies.

Table A1.8: Effect of breastfeeding on asthma

Intermediary of health effect	Authors, Year of publication	Design	Study population	Age group	Breastfeeding	Effect size			Remarks
Asthma	(Kull et al., 2004) d	Cohort	Sweden n=3,384	4 yr	EBF_{0-2} EBF_{3-4} $EBF_{\geq 5}$ EBF_{0-2} EBF_{3-4} $EBF_{\geq 5}$	Total OR=1 OR=0.67 (0.43-1.03) **OR=0.61 (0.42-0.86)**	No hereditary OR=1 OR=0.61 (0.36-1.06) **OR=0.48 (0.30-0.77)** Mother no asthma OR=1 **OR=0.61 (0.38-0.98)** **OR=0.57 (0.39-0.84)**	Hereditary OR=1 OR=0.76 (0.37-1.54) OR=0.81(0.46-1.44) Mother with asthma OR=1 OR=1.04 (0.35-3.09) OR=0.79 (0.32-1.90)	Hereditary was defined as physician-diagnosed asthma, hay fever, or both in combination with allergy to a furred pet, pollen or both in at least one parent. Corrected for age mother, smoking during pregnancy, and hereditary.
	(Chulada et al., 2003)	Cohort	USA n=8,261	2-71 mo	FF BF $BF_{<4}$ $BF_{\geq 4}$ EBF_{0} $EBF_{<4}$ $EBF_{\geq 4}$	HR=1 HR=0.85 (0.64-1.13) HR=0.89 (0.59-1.34) HR=0.82 (0.58-1.17) HR=1 HR=0.97 (0.57-1.65) HR=0.56 (0.29-1.11)			Corrected for gender, birth weight, ethnicity, SES, day-care, history of asthma parents, smoking, and smoking during pregnancy.
	(Siltanen et al., 2003) d	Cohort	Finland n=456	4 yr	$FF_{\text{cow in first 2wk}}$ $EBF_{\geq 3}$	Family history OR=1 OR=1.42 (0.40-5.11)	No family history OR=1 OR=1.89 (0.32-10.99)		FF = > 450 ml on cow milk based formula. Data from the first y was collected prospectively from the birth cohort (questionnaires at 0, 2, 6 and 12 mo). Corrected for gender, season f birth, number of siblings, smoking, furred pets, SES, age introduction solids.
	(Sears et al., 2002) d	Cohort	New Zeeland n=1,037	0-9 yr 9 yr 11 yr 13 yr 15 yr 18 yr 21 yr 26 yr	FF $BF_{>4\ wk}$	OR=1 $Asthma_{<9}$ **OR=1.93 (1.18-3.17)** $Asthma_{9}$ **OR=2.54 (1.45-4.44)** $Asthma_{11}$ **OR=2.23 (1.42-3.52)** $Asthma_{13}$ **OR=2.93 (1.83-4.69)** $Asthma_{15}$ **OR=1.69 (1.17-2.45)** $Asthma_{18}$ **OR=1.68 (1.15-2.47)** $Asthma_{21}$ **OR=1.50 (1.06-2.13)** $Asthma_{26}$ **OR=1.74 (1.26-2.40)**			Possible information bias: Breastfeeding only asked after at age 3 yr, but was verified where possible through the New Zeeland Plunket Nurse programme. Different cut point for breastfeeding (0, 8, 12 wk) had no effect on the results. Asthma with hypersensitive reactions showed more or less the same results.
	(Kull et al., 2002) d	Cohort	Sweden n=3,791	0-2 yr	$EBF_{\geq 4}$ vs. $EBF_{<4}$ $MBF_{\geq 6}$ vs. $MBF_{<6}$	Asthma **OR=0.66 (0.49-0.90)** **OR=0.69 (0.50-0.95)**	Asthma with other allergic manifestations **OR=0.69 (0.49-0.97)** OR=0.77 (0.54-1.1)		Corrected for gender, family history, age mother, smoking during pregnancy /1st 3 mo after birth baby, and date of construction home. Questionnaires at ages 2 mo, 1 yr and 2 yr.

Table A1.8 continued: Effect of breastfeeding on asthma

Intermediary of health effect	Authors, Year of publication	Design	Study population	Age group	Breastfeeding	Effect size	Remarks
Asthma continued	(Wright et al., 2000;Wright et al., 2001) d	Cohort	USA n=1,043	6 yr 9 yr 11 yr 13 yr	$EBF_{\geq 4}$ vs. $EBF_{<4}$ + FF	$Asthma_{6\text{-}13}$ with asthmatic mother **OR=8.7 (3.4-22.2)** $Asthma_{6}$, atopic child, asthmatic mother **OR= ±5**; $Asthma_{9,\ 11,\ 13}$ **OR= ±2,7-3.0** $Asthma_{6,9,11,13}$, only asthmatic mother, only atopic child OR around 1 $Asthma_{6,9,11}$, no atopy or asthma OR= ±0.8 (nss) $Asthma_{13}$ OR=1	Corrected for SES, smoking mother, gender, ethnicity, number of siblings, day-care, and asthma parents. Both studies were based on the same cohort. The study from 2000 has no data on asthma at age 13.
	(Rust et al., 2001) d	Cohort	USA n=6,783	2 mo – 6 yr	FF BF	OR=1 OR=0.89 (0.47-1.66)	Breastfeeding asked after between 2 mo and 6 yr. Linear regression model: duration of breastfeeding is no predictor for age at diagnosis asthma.
	(Dell and To, 2001) d	Cohort	Canada n=2,184 (weighted n=331,100)	12-23 mo	$BF_{<2}$ vs. $BF_{\geq 2}$ $BF_{\leq 6}$ vs. $BF_{>6}$ $BF_{\leq 9}$ vs. $BF_{>9}$	OR=1.11 (0.68-1.83) OR=1.62 (0.86-3.08) OR=2.39 (0.95-6.03)	Corrected for gender, smoking parents, SES, and low birth weight.
	(Oddy et al., 2002) c	Cohort	Australia n=2,602	6 yr	$EBF_{<4}$ $EBF_{\geq 4}$	**OR=1.36 (1.00-1.85)** OR=1	The first yr: feeding dairy, closed with a questionnaire on bf and lung disorders & physical examination. 6-yr follow-up: questionnaire and skin-prick test (n=1.595). Corrected for gender, gestational age, smoking mother, atopy, earlier infections, and asthma mother.
	(Oddy, 2000) c	Cohort	Australia n=2,602	6 yr	$EBF_{\geq 4}$ MBF	OR=1 **OR=1.25 (1.02-1.51)**	MBF = < 4 mo introduction other milk products. Corrected for gender, gestational age, and smoking.
	(Oddy et al., 1999) c	Cohort	Australia n=2,602	6 yr	$EBF_{<3}$ vs. $EBF_{\geq 3}$ $EBF_{<4}$ vs. $EBF_{\geq 4}$ $EBF_{<6}$ vs. $EBF_{\geq 6}$ $BF_{<3}$ vs. $BF_{\geq 3}$ $BF_{<6}$ vs. $BF_{\geq 6}$	OR=1.20 (0.98-1.48) **OR=1.25 (1.02-1.52)** **OR=1.26 (1.02-1.54)** OR=1.12 (0.91-1.34) OR=1.18 (0.97-1.45)	Corrected for gender, gestational age <37 weeks, smoking, and day-care <3 mo. The same cohort as cohort used in study of (Oddy et al., 2002).
	(Wilson et al., 1998)	Cohort	Scotland n=545	0-7 yr	$EBF_{\geq 15wk,\ no\ solids}$ $EBF_{\geq 15wk,\ solids}$ $EBF_{\geq 15wk}$ $MBF_{\geq 15wk,\ no\ solids}$ $MBF_{\geq 15wk,\ solids}$ $MBF_{\geq 15wk}$ $FF_{\geq 15wk,\ no\ solids}$ $FF_{\geq 15wk,\ solids}$ $FF_{\geq 15wk}$	P=10.6 (9.1-12.1) P=13.4 (11.4-15.4) P=12.1 (10.9-13.4) P=18.5 (15.4-21.7) P=22.5 (20.9-24.0) P=21.7 (17.3-26.1) P=14.8 (11.6-17.9) P=19.3 (17.8-20.8) P=18.6 (17.2-20.0)	Data on way of feeding was collected prospectively in the 1st two years. Corrected for family history, gender, and SES. Within MBF mean duration of breastfeeding was 9.5 wk.

Table A1.8 continued: Effect of breastfeeding on asthma

Intermediary of health effect	Authors, Year of publication	Design	Study population	Age group	Breastfeeding	Effect size				Remarks
Asthma continued	(Tariq et al., 1998) c	Cohort	United Kingdom n=1,086	4 yr	FF $_{\text{before 3 mo}}$ BF	**p=17.1%** (p=<0.01) **p=10.3%**				No correction.
	(Gruskay, 1982) c	Cohort	USA n=908	3 yr 5 yr 8 yr 15 yr	<u>No family history</u> FF $_{\text{cow}}$ BF <u>Family history</u> FF $_{\text{cow}}$ FF$_{\text{soy}}$ BF	<u>3 yr</u> i=13/502 i=0/78 i=20/201 i=7/79 i=4/48	<u>5 yr</u> i=7/390 i=0/57 i=10/192 i=7/76 i=0/44	<u>8 yr</u> i=0/368 i=0/44 i=0/167 i=1/69 i=0/38	<u>15 yr</u> i=0/368 i=0/41 i=1/143 i=1/66 i=0/31	No correction.
	(Halken, 2004) e	Review			BF vs. FF, BF, EBF	≥4 months BF protects against asthma; ≤ 4 months increases risk (2 studies) ≤ 3 months EBF increases risk of asthma (2 studies)				Four studies ((Gruskay, 1982), (Oddy et al., 1999), (Oddy et al., 2002) and (Tariq et al., 1998)
	(van Odijk et al., 2003) c	Review	Developed countries			<u>Non selected population</u> 7 prosp. studies; 3 no effect; 4 protective effect BF 1 intervention study; protective effect BF 2 retrospective studies; protective effect BF <u>With family background of atopy</u> 1 prospective study; protective effect BF 4 intervention studies; protective effect				Non selected population: seven prospective studies (including (Wilson et al., 1998))(Oddy et al., 1999;Wright et al., 2001); one intervention study ((Gruskay, 1982)); two retrospective studies. With family background of atopy: one prospective study; four intervention studies (including (Gruskay, 1982)). Other studies had inadequate study design.
	(Kramer and Kakuma, 2002) c	Review /meta-analysis	n=552	5-6 yr	MBF$_{3\text{-}7}$ EBF$_{3\text{-}7}$	RR=1 RR=0.91 (0.61-1.36)				Based op two studies (Kajosaari and Saarinen, 1983),(Oddy et al., 1999).
	(Gdalevich et al., 2001b) c	Meta-Analysis	n=8,183		EBF$_{\geq 3}$ vs. not EBF$_{>3}$	< 2 yr follow-up (n=1788): **OR=0.47 (0.34-0.66)** ≥ 2 yr follow-up (n=6395): **OR=0.72 (0.62-0.84)** long follow-up: **OR=0.70 (0.60-0.81)** with positive family history: **OR=0.52 (0.35-0.79)** with negative family history : **OR=0.73 (0.62-0.86)** without family history: OR=0.99 (0.48-2.03)				12 prospective studies (1966-1999); developed countries; with/without family history (including (Gruskay, 1982), (Wilson et al., 1998), (Tariq et al., 1998) and (Oddy et al., 1999)). Other studies did not control for confounders or had inadequate study design.

Table A1.9: Effect of breastfeeding on wheezing

Intermediary of health effect	Authors, Year of publication	Design	Study population	Age group	Breastfeeding	Effect size		Remarks
Wheezing	(Kramer et al., 2001) c	Randomised controlled trial	Belarus n=17,046	0-12 mo	Control group Intervention group	OR=1 OR=0.70 (0.29-1.70)		Part of the PROBIT-study. Intervention=BFHI. Intervention group: 3 mo 43% EBF, 6 mo 8% EBF. Control group: 3 mo 6% EBF, 6 mo 1% EBF. Corrected for birth weight, and number of siblings.
	(Chantry et al., 2006) d	Cohort	USA N=1,950	6-24 mo	FF $EBF_{<1\ mo}$ $EBF_{1-3\ mo}$ $EBF_{4-5\ mo}$ $EBF_{\geq 6\ mo}$	OR=1.05 (0.60-1.81) OR=1.41 (0.78-2.57) OR=1.07 (0.54-2.12) OR=0.98 (0.49-1.96) OR=1		Adjusted for ethnicity, day care, head of household education, poverty index, smoke exposure, birth weight, two-parent household, parent atopy.
	(Chulada et al., 2003) d	Cohort	USA n=8,261	2-71 mo	FF BF $BF_{<4}$ $BF_{\geq 4}$ EBF_{0} $EBF_{<4}$ $EBF_{\geq 4}$	OR=1 OR=0.81 (0.57-1.14) OR=0.87 (0.57-1.33) OR=0.80 (0.51-1.23) OR=1 OR=0.84 (0.46-1.55) OR=0.82 (0.34-1.98)		Corrected for gender, birth weight, ethnicity, SES, day-care, history of asthma parents, smoking, and smoking during pregnancy.
	(Siltanen et al., 2003) d	Cohort	Finland n=456	4 yr	 $FF_{\text{cow in first 2wk}}$ $EBF_{\geq 3}$	<u>family history</u> OR=1 OR=1.39 (0.60-3.21)	<u>no family history</u> OR=1 OR=3.73 (0.95-14.68)	FF = > 450 ml on cow milk based formula. Data from the first yr was collected prospectively from the birth cohort (questionnaires at 0, 2, 6 and 12 mo). Corrected for gender, season of birth, number of siblings, smoking, furred pets, SES, and age introduction solids.
	(Kull et al., 2002) d	Cohort	Sweden n=3,791	0-2 yr	$EBF_{\geq 4}$ vs. $EBF_{<4}$ $MBF_{\geq 6}$ vs. $MBF_{<6}$	**OR=0.78 (0.65-0.93)** **OR=0.81 (0.67-0.97)**		Corrected for gender, family history, age mother, smoking during pregnancy /1st 3 mo after birth baby, and date of construction home. Questionnaires at ages 2 months, 1 yr and 2 yr.
	(Sears et al., 2002) d	Cohort	New Zeeland n= 1,037	9 yr 11 yr 13 yr 15 yr 21 yr	FF $BF_{>4\ wk}$	OR=1 $Wheezing_{9}$ **OR=2.87 (1.71-4.84)** $Wheezing_{11}$ **OR=2.36 (1.32-4.20)** $Wheezing_{13}$ **OR=4.34 (2.06-9.16)** $Wheezing_{15}$ **OR=1.44 (1.85-2.47)** $Wheezing_{21}$ **OR=1.80 (1.03-3.13)** $Wheezing_{9-21}$ **OR=2.09 (1.42-3.08)**		Possible information bias: Breastfeeding only asked after at age 3 yr, but was verified where possible through the New Zeeland Plunket Nurse programme. Different cut-point for breastfeeding (0, 8, 12 wks) had no effect on the results. Health effect = wheezing with hypersensitive reaction.

Table A1.9 continued: Effect of breastfeeding on wheezing

Intermediary of health effect	Authors, Year of publication	Design	Study population	Age group	Breastfeeding	Effect size		Remarks
Wheezing continued	(Oddy et al., 2003) d	Cohort	Australia n=2,456	0-12 mo	$EBF_{<0}$ vs. $EBF_{>0}$ $EBF_{<2}$ vs. $EBF_{>2}$ $EBF_{<4}$ vs. $EBF_{>4}$ $EBF_{<6}$ vs. $EBF_{>6}$ $EBF_{<8}$ vs. $EBF_{>8}$ $MBF_{<0}$ vs. $MBF_{>0}$ $MBF_{<2}$ vs. $MBF_{>2}$ $MBF_{<4}$ vs. $MBF_{>4}$ $MBF_{<6}$ vs. $MBF_{>6}$ $MBF_{<8}$ vs. $MBF_{>8}$	Policlinic treatment **OR=1.61 (1.05-2.48)** OR=1.36 (0.99-1.88) **OR=1.70 (1.25-2.30)** **OR=2.07 (1.47-2.90)** **OR=1.61 (1.08-2.40)** **OR=1.62 (1.06-2.49)** **OR=1.60 (1.14-2.24)** **OR=1.56 (1.14-2.12)** **OR=1.60 (1.17-2.17)** **OR=1.76 (1.27-2.44)**	Hospitalization OR=1.61 (0.73-3.54) OR=1.66 (0.92-3.01) **OR=2.26 (1.23-4.16)** **OR=2.65 (1.30-5.41)** OR=1.77 (0.78-3.99) OR=1.58 (0.72-3.47) OR=1.43 (0.75-2.73) OR=1.49 (0.83-2.67) **OR=2.39 (1.30-4.42)** **OR=2.89 (1.44-5.80)**	No restriction regarding to water. Corrected for gender, gestational age, smoking during pregnancy, older siblings, SES, and age mother (other confounders had no effect).
	(Oddy et al., 2002) d	Cohort	Australia n=2,602	0-12 mo	FF vs. $EBF_{>0}$ $EBF_{<2}$ vs. $EBF_{\geq 2}$ $EBF_{<4}$ vs. $EBF_{\geq 4}$ $EBF_{<6}$ vs. $EBF_{\geq 6}$	OR=0.83 (0.53-1.30) OR=1.08 (0.81-1.43) OR=1.33 (1.03-1.71) OR=1.26 (0.97-1.64)		During the first a dairy has been kept by the parents. At 6 yr follow-up a questionnaire had to be answered. Corrected for gender, gestational age, and smoking during pregnancy.
	(Oddy, 2000) d	Cohort	Australia n=2,602	6 yr	$EBF_{\geq 4}$ MBF	OR=1 Last yr wheezing: **OR=1.32 (1.06-1.64)** Sleep problems by wheezing: **OR=1.43 (1.08-1.90)**		MBF = introduction other milk products before 4 months. Corrected for gender, gestational age, and smoking.
	(Oddy et al., 1999) d	Cohort	Australia n=2,602	1-6 yr	$EBF_{<3}$ vs. $EBF_{\geq 3}$ $EBF_{<4}$ vs. $EBF_{\geq 4}$ $EBF_{<6}$ vs. $EBF_{\geq 6}$ $BF_{<3}$ vs. $BF_{\geq 3}$ $BF_{<6}$ vs. $BF_{\geq 6}$	Wheezing 1-6 yr **OR=1.32 (1.06-1.65)** **OR=1.41 (1.14-1.76)** **OR=1.49 (1.18-1.88)** OR=1.10 (0.88-1.38) **OR=1.35 (1.08-1.69)**	Wheezing 6 yr OR=1.19 (0.95-1.49) **OR=1.31 (1.05-1.64)** **OR=1.26 (1.00-1.59)** OR=1.12 (0.89-1.41) OR=1.14 (0.91-1.42)	Corrected for gender, gestational age <37 weeks, smoking, and day-care <3 months.
	(Wright et al., 2001); (Wright et al., 2000) d	Cohort	USA n=1,043	0-3 yr ≥ 3 yr	$EBF_{\geq 4}$ vs. $EBF_{<4}$ + FF	$Wheezing_{<3}$ **OR= ±0.36**; $Wheezing_{\geq 3}$ **OR= ±1** for children without an asthmatic mother and for children with an asthmatic mother but without atopy $Wheezing_{\geq 3}$ **OR= ±5** for children with an asthmatic mother and atopy		RR read from figure. Corrected for SES, smoking mother, gender, ethnicity, number of siblings, day-care, and asthma parents. Both studies are based on the same cohort. The study from 2000 has no data on asthma at 13 yr of age.
	(Raisler et al., 1999) d	Cohort	USA n=7,092	0-6 mo	FF MBF (BF< FF) MBF (BF= FF) MBF (BF>FF) EBF	OR=1 OR=1.00 (0.83-1.19) **OR=0.68 (0.51-0.92)** **OR=0.81 (0.68-0.96)** **OR=0.83 (0.70-1.00)**		Corrected for age mother, ethnicity, SES, birth weight, number of siblings, day-care, age child (mo), smoking, and recall interval. Breastfeeding was defined every month.

Table A1.9 continued: Effect of breastfeeding on wheezing

Intermediary of health effect	Authors, Year of publication	Design	Study population	Age group	Breastfeeding	Effect size			Remarks
Wheezing continued	(Baker et al., 1998) [d]	Cohort	United Kingdom n=8450	6 mo	FF $BF_{<3}$ $BF_{\geq 3}$	OR=1 **OR=0.79 (0.68-0.91)** **OR=0.68 (0.59-0.79)**			Corrected for SES, housing tenure, number of persons in household, siblings, mother smokes.
	(Wilson et al., 1998)	Cohort	Scotland n=545	0-7 yr	$EBF_{\geq 15wk,\ no\ solids}$ $EBF_{\geq 15wk,\ solids}$ $EBF_{\geq 15wk}$ $MBF_{\geq 15wk,\ no\ solids}$ $MBF_{\geq 15wk,\ solids}$ $MBF_{\geq 15wk}$ $FF_{\geq 15wk,\ no\ solids}$ $FF_{\geq 15wk,\ solids}$ $FF_{\geq 15wk}$	P=8.2 (7.0-9.4) P=17.3 (15.0-19.6) P=12.8 (11.3-14.3) P=11.8 (9.3-14.4) P=23.8 (22.1-25.5) P=21.2 (16.2-26.1) P=10.2 (7.5-12.9) P=20.1 (18.4-21.8) P=18.6 (17.0-20.1)			Way of feeding was collected prospectively during the first and second year. Corrected for family history, gender, and SES. Within the MBF group the mean duration of breastfeeding was 9.5 weeks. Conclusion: Early introduction of solids increases risk of wheezing.
	(Wright et al., 1995) [d]	Cohort	USA n=988	6 yrs	FF BF	OR=1.49 (0.80-2.77) OR=1.00	Atopic children **OR=3.03 (1.05-8.69)** OR=1	Non-atopic children OR=1.36 (0.49-3.73) OR=1	Corrected for SES, ethnicity, hay fever mother, and wheezing first 6 months. Group BF includes $BF_{<1\ mo}$ tot $BF_{>6\ mo.}$
	(Wright et al., 1989) [d]	Cohort	USA n=1,246	0-4 mo 4-6 mo 6-12 mo	BF_{0-1} BF_{1-4} $BF_{>4}$ BF_{0-1} $BF_{1-4} + BF_{>4}$	Age 0-4 mo 12.3 8.1 5.2 **(p=0.005)** **OR=1.7 (p=.05)** OR=1	Age 4-6 mo 6.9 4.7 7.4	Age 6-12 mo 6.3 13.1 7.0	Incidences are not corrected. OR's are corrected for shared bedroom, SES, smoking, family history, ethnic group, and gender.
	(van Odijk et al., 2003) [d]	Review	Developed countries			Non selected population 9 prospective studies → 1 no effect; 7 protective effect BF; 1 protective effect non-atopic children; no effect atopic children 3 retrospective studies → protective effect BF Family background of atopy 4 prospective studies → seems to be a protective effect of BF 6 intervention studies → protective effect BF 1 retrospective study → protective effect BF			Non selected population: twelve studies (including (Wright et al., 1995), (Wright et al., 2001), (Baker et al., 1998), (Wilson et al., 1998), (Oddy et al., 1999;Oddy et al., 1999;Wilson et al., 1998;Wright et al., 1995;Wright et al., 2001), (Raisler et al., 1999;Wright et al., 1989)). Other studies inadequate study design, or non relevant study populations.
	(Kramer and Kakuma, 2002) [e]	Review	n=3,993	0-12 mo	MBF_{3-7} EBF_{3-7}	RR=1 RR=0.79 (0.49-1.28)			Based on two studies ((Kramer et al., 2000) and (Oddy et al., 1999)).

Table A1.10: Effect of breastfeeding on eczema

Intermediary of health effect	Authors, Year of publication	Design	Study population	Age group	Breastfeeding	Effect size			Remarks
Eczema	(Kramer et al., 2001) c	Randomised controlled trial	Belarus n=17,046	0-12 mo	Control group Intervention group	Rash OR=1 **OR=0.56 (0.38-0.81)**	Atopic eczema OR=1 **OR=0.54 (0.31-0.95)**	Non-eczema rash OR=1 **OR=0.59 (0.38-0.92)**	Part of the PROBIT-study. Intervention=BFHI. Intervention group: 3 mo 43% EBF, 6 mo 8% EBF. Control group: 3 mo 6% EBF, 6 mo 1% EBF. Corrected for family history of atopy.
	(Ludvigsson et al., 2005) d	Cohort	Sweden N=8,784	0-12 mo	$EBF_{<4\ mo}$ $EBF_{\geq 4mo}$	OR=1.07 (0.94-1.21) OR=1	Atopy in family OR=1.16 (0.90-1.48) OR=1	No atopy in family OR=1.04 (0.90-1.21) OR=1	Corrected for smoking, furred pets, preterm birth, maternal education, parity, atopic heredity.
	(Stabell Benn et al., 2004)	Cohort	Denmark n=15,430	4-18 mo	FF EBF_1 EBF_2 EBF_3 EBF_4 EBF_5 EBF_6 $EBF_{\geq 6}$	IRR=1 IRR=0.52 IRR=0.54 IRR=0.53 IRR=0.71 IRR=0.84 IRR=0.87 IRR=0.83			BF asked after at 6 months; eczema at 18 months Corrected for gender, SES, smoking in presence of child, pets, number of siblings, age mother, day-care (6 months), and birth weight. Only non-allergic parents. Specific calculations were made in order to make formula feeding the reference.
	(Laubereau et al., 2004) D	Cohort	Germany n=3,903	0-3 yr	(MBF + FF) $EBF_{\geq 4}$	OR=1 OR=0.95 (0.79-1.14)			Corrected for study location, gender, smoking mother, SES, number of allergic family members, solids during 1st 4 months. Breastfeeding asked after at age 1 yr.
	(Siltanen et al., 2003) D	Cohort	Finland n=456	4 yr	$FF_{\ cow\ in\ first\ 2wk}$ $EBF_{\geq 3}$	family history OR=1 OR=0.68 (0.34-1.35)	no family history OR=1 **OR=2.37 (1.03-5.48)**		FF = > 450 ml on cow milk based formula. Data from the first year was collected prospectively from the birth cohort (questionnaires at 0, 2, 6 and 12 mo). Corrected for gender, season f birth, number of siblings, smoking, furred pets, SES, and age introduction solids.
	(Kull et al., 2002) D	Cohort	Sweden n=3,791	0-2 yr	$EBF_{\geq 4}$ vs. $EBF_{<4}$ $MBF_{\geq 6}$ vs. $MBF_{<6}$	OR=0.85 (0.71-1.00) OR=0.88 (0.72-1.05)			Corrected for gender, family history, age mother, smoking during pregnancy /1st 3 months after birth baby, and date of construction home. Questionnaires at ages 2 mo, 1 yr and 2 yr.
	(Bergmann et al., 2002) D	Cohort	Germany n=1,314	0-7 yr	BF (mo)	OR=1.029 (1.002-1.057)			Every month of breastfeeding increases the risk on eczema with 3%.
	(Schoetzau et al., 2002) D	Cohort	Germany n=1,121	0-1 yr	$FF_{\ cow}$ $EBF_{16\ weeks}$	OR=1 **OR=0.47 (0.30-0.75)** Introduction solids 1-16 weeks OR=0.33 (0.08-1.4) Introduction solids 17-24 weeks **OR=0.48 (0.26-0.91)** Introduction solids >24 weeks OR=0.55 (0.25-1.2)			Corrected for family history of eczema, atopic risk level, gender, ethnicity, smoking mother, pets, and SES.

Table A1.10 continued: Effect of breastfeeding on eczema

Intermediary of health effect	Authors, Year of publication	Design	Study population	Age group	Breastfeeding	Effect size				Remarks
Eczema continued	(Wetzig et al., 2000) D	Cohort	Germany n=325	0-2 yr	$EBF_{\geq 5}$ vs. $EBF_{<5}$	Children with high IgE in umbilical cord and a family history of atopy **OR=2.68 (1.1-6.6);** non significant when only one of the characteristics was true At two yr no effect was seen				
	(Tariq et al., 1998) D	Cohort	United Kingdom n=1,086	4 yr	$FF_{\text{before 3 mo}}$ BF	p=13.2% p=10.7%				No correction.
	(Howie et al., 1990)	Cohort	Scotland n=618	0-13 wk 14-26 wk 27-39 wk 40-52 wk	$FF_{>3}$ $EBF_{>3}$	0-13 wk RR=1 RR=0.65	14-26 wk RR=1 RR=0.30	27-39 wk RR=1 RR=1.21	40-52 wk RR=1 RR=1.16	Corrected for SES, age mother, and smoking (other confounders no effect). Small numbers (2-16) per group.
	(Kajosaari and Saarinen, 1983) D	Cohort	Finland n=135	1 yr	EBF_6 + $solids_3$* EBF_6	p=35% p=14% (p<.01)				Children with an atopic background.
	(Gruskay, 1982) D	Cohort	USA n=908	3 yr 5 yr 8 yr 15 yr	No family history FF_{cow} BF Family history FF_{cow} FF_{sov} BF	3 yr i=22/502 i=0/78 i=24/201 i=9/79 i=4/48	5 yr i=1/390 i=0/57 i=0/192 i=0/76 i=0/44	8 yr i=1/368 i=0/44 i=0/167 i=0/69 i=0/38	15 yr i=0/368 i=0/41 i=0/143 i=0/66 i=0/31	No correction.
	(Kerkhof et al., 2003) C	Nested case-cohort	Netherlands Case=76 Control=228	12 mo	No $EBF_{13\ wk}$ $EBF_{13\ wk}$	OR=1 OR=0.6 (0.3-1.2); Only visible eczema OR=0.4 (0.2-1.0)				Corrected for gender, birth weight, gestational age, age mother, number of siblings, day-care, smoking, pets, region, and SES. All children had allergic mothers.
	(Purvis et al., 2005) d	Case-control study	New-Zeeland N=550	3.5 yr	FF $BF_{<6\ mo}$ $BF_{\geq 6\ mo}$	OR=1 **OR=7.05 (1.44-34.56)** **OR=9.93 (2.18-45.36)**				Corrected for parental atopy, older siblings, cat and/or dog, damp, mould, maternal smoking, antibiotics used in first year of life. Designed as a case-control study with low weight children sampled differently from normal weight children; this study used disproportionate sampling design into account). Measurements at birth, 1 year and 3.5 year.

Table A1.10 continued: Effect of breastfeeding on eczema

Intermediary of health effect	Authors, Year of publication	Design	Study population	Age group	Breastfeeding	Effect size		Remarks
Eczema continued	(van Odijk et al., 2003) d	Review	Developed countries			Non-selected population 8 prospective studies → 2 no effect; 5 protective effect BF; 1 increased risk 2 intervention studies → protective effect BF atopic background family 6 prospective studies → seems to be a protective effect for BF 9 intervention studies → protective effect BF		Non selected population:8 prospective studies (including (Lucas et al., 1990) and (Saarinen and Kajosaari, 1995)); 2 intervention studies ((Gruskay, 1982) and (Kramer et al., 2001)). With familiar background of atopy: six prospective studies (including (Wetzig et al., 2000)); nine intervention studies (including (Gruskay, 1982), (Chandra and Hamed, 1991) and (Halken, 2004)).
	(Kramer and Kakuma, 2002) D	Review	n=113 – 3,618	0-12 mo 5 yr	MBF_{3-7} EBF_{3-7}	0-12 mo RR=1 RR=0.73 (0.49-1.08)	5 yr RR=1 RR=0.97 (0.50-1.89)	Results 0-12 mo based on two studies (Kajosaari and Saarinen, 1983) and (Kramer et al., 2001); results 5 yr based on one study (Kajosaari and Saarinen, 1983)
	(Gdalevich et al., 2001a) D	Review/ meta-analysis			FF $EBF_{\geq 3}$	OR=1 Total: **OR=0.77 (0.60-0.98)** Positive family history: **OR=0.58 (0.41-0.92)** Negative family history: OR=0.84 (0.59-1.19)		At least corrected for age, SES, family history, and smoking.

Table A1.11: Effect of breastfeeding on atopy

Intermediary of health effect	Authors, Year of publication	Design	Study population	Age group	Breastfeeding	Effect size					Remarks
Atopy [a]	(Siltanen et al., 2003)	Cohort	Finland n=456	4 yr	FF $_{cow\ in\ first\ 2wk}$ $EBF_{\geq 3}$	Atopy Severe symptoms of allergic disease	family history OR=1 OR=0.74 (0.37-1.49) **OR=0.66 (0.49-0.90)**	***No family history*** OR=1 OR=2.40(0.77-7.53) **OR=0.69(0.50-0.95)**			FF = > 450 ml on cow milk based formula. Data from the first yr was collected prospectively from the birth cohort (questionnaires at 0, 2, 6 and 12 mo). Corrected for gender, season f birth, number of siblings, smoking, furred pets, SES, and age introduction solids.
	(Sears et al., 2002)	Cohort	New Zeeland n= 1,037	13 yr 21 yr	FF $BF_{>4\ wks}$	Cat House dust mite Grass Alternaria Any allergen positive	Atopy 13 yr OR=1 **OR=2.41 (1.52-3.83)** **OR=1.72 (1.24-2.38)** **OR=2.16 (1.57-2.98)** **OR=1.96 (1.03-3.74)** **OR=1.91 (1.42-2.58)**	Atopy 21 yr OR=1 **OR=1.58 (1.17-2.13)** **OR=1.48 (1.13-1.93)** **OR=1.91 (1.46-2.49)** **OR=1.93 (1.28-2.90)** **OR=1.49 (1.13-1.97)**			Possible information bias: Breastfeeding only asked after at age 3 yr, but was verified where possible through the New Zeeland Plunket Nurse programme. Different cut-point for breastfeeding (0, 8, 12 wks) had no effect on the results. Division according to family history of has little effect on the results.
	(Tariq et al., 1998)	Cohort	United Kingdom n=1,086	4 yr	FF $_{before\ 3\ mo}$ BF	**p=30.0%** (p=<0.01) **p=21.5%**					No correction.
	(Saarinen and Kajosaari, 1995)	Cohort	Finland n=150	1, 3, 5, 10, 17 yr	$EBF_{\geq 6}$ EBF_{1-6} $EBF_{<1}$	1 yr 23 (16-30) 23 (17-29) 11 (5-17)	3 yr 36 (28-44) 24 (17-31) 22 (14-31)	5 yr 46 (37-55) 27 (19-34) 34 (24-44)	10 yr 43 (33-52) 31 (23-39) 29 (19-39)	17 yr 65 (56-74) 36 (28-44) 42 (31-52)	Health effect = % prevalence. In every group started on solids after 3.5 mo.
	(Chandra and Hamed, 1991)	Cohort	Canada n=263	6 mo 12 mo 18 mo	EBF_6 FF $_{whey\ hydrolysate}$ FF $_{soy}$ Cow milk	Total 60 68 68 67	6 mo 12 5 25 24	12 mo 14 12 27 28	18 mo 15 18 30 29		Health effect = cumulative number of children with atopic symptoms, allergic symptoms in family. Statistical significant differences between whey and cow milk and between whey and soy. Whey and mother milk did not differ significantly from each other.
	(Kramer and Kakuma, 2002)	Review	n=113	5 yr	MBF_{3-7} EBF_{3-7}	RR=1 RR= 0.91 (0.61-1.36)					Based on one study (Kajosaari and Saarinen, 1983).

Table A1.11 continued: Effect of breastfeeding on atopy

Intermediary of health effect	Authors, Year of publication	Design	Study population	Age group	Breastfeeding	Effect size				Remarks
Atopy continued [a]	(Golding et al., 1997b)	Review				The data in the literature show little consistent evidence to identify any protective association between BF and either eczema, wheezing/asthma or other types of atopy or allergic response				± 30 studies. The articles included in the review are mostly from debatable quality; relevant studies are already included in this table.
IgE [a]	(Wright et al., 1999)	Cohort	USA n=1,047	9 mo 6 yr 11 yr	<u>Mother low IgE</u> FF $BF_{<4}$ $BF_{\geq 4}$ <u>Mother high IgE</u> FF $BF_{<4}$ $BF_{\geq 4}$	<u>Birth</u> 0.08 (0.07-0.10) 0.11 (0.09-0.13) 0.10 (0.09-0.12) 0.18 (0.13-0.26) 0.15 (0.12-0.19) 0.15 (0.03-0.93)	<u>9 mo</u> 3.0 (2.2-4.0) 3.0 (2.4-3.9) 3.5 (2.9-4.2) 4.2 (2.6-6.9) 5.1 (3.5-7.3) 5.2 (4.0-6.8)	<u>6 yr</u> 44.3 (29-67) **21.4** **(15-31)** **25.8** **(20-34)** 36.2 (22-60) 41.8 (25-71) **97.0** **(66-143)**	<u>11 yr</u> 68.4 (44-107) 45.6 (30-69) 40.8 (31-54) 100 (50-201) 92 (61-141) 122 (82-182)	Health effect in IU/ml.
Skin prick test [a]	(Siltanen et al., 2003)	Cohort	Finland n=456	4 yr	$FF_{cow\ first\ 2wk}$ $EBF_{\geq 3}$	<u>family history</u> OR=1 **OR=0.23-0.31 (0.06-0.96)**		<u>no family history</u> OR=1 OR=1.44 (0.22-9.29)		FF = > 450 ml on cow milk based formula. Data from the first yr was collected prospectively from the birth cohort (questionnaires at 0, 2, 6 and 12 mo). Corrected for gender, season f birth, number of siblings, smoking, furred pets, SES, and age introduction solids.
	(Wright et al., 2001)	Cohort	USA n=702	6 yr	$BF_{<4}$ + FF $BF_{\geq 4}$	<u>mother allergic for mulberry tree</u> OR=1.4 (0.5-3.7) **OR=3.7 (1.14-15.6)**		<u>mother *not* allergic for mulberry tree</u> OR=1 OR=1.6(0.8-3.0)		Health effect = positive skin prick test on mulberry tree (chosen because was most related to breastfeeding).
	(Oddy, 2000)	Cohort	Australia n=2,602	6 yr	$EBF_{\geq 4}$ MBF	OR=1 **OR=1.30 (1.05-1.61)**				Corrected for gender, gestational age, smoking parents.
	(Oddy et al., 1999)	Cohort	Australia n=2,602	6 yr	$EBF_{<3}$ vs. $EBF_{\geq 3}$ $EBF_{<4}$ vs. $EBF_{\geq 4}$ $EBF_{<6}$ vs. $EBF_{\geq 6}$ $BF_{<3}$ vs. $BF_{\geq 3}$ $BF_{<6}$ vs. $BF_{\geq 6}$	OR=1.19 (0.95-1.48) **OR=1.30 (1.04-1.61)** OR=1.11 (0.89-1.38) **OR=1.26 (1.01-1.59)** OR=1.07 (0.86-1.34)				Corrected for gender, gestational age <37 weeks, smoking, and day-care <3 months.
	(Kramer and Kakuma, 2002)	Review	n=331	6 yr	MBF_{3-7} EBF_{3-7}	RR=1 RR= 0.99 (0.73-1.35)				Based on one study (Oddy et al., 1999).

Table A1.11 continued: Effect of breastfeeding on atopy

Intermediary of health effect	Authors, Year of publication	Design	Study population	Age group	Breastfeeding	Effect size				Remarks
Allergic rhinitis [a]	(Siltanen et al., 2003)	Cohort	Finland n=456	4 yr	$FF_{cow\ in\ first\ 2wk}$ $EBF_{\geq 3}$	family history OR=1 **OR=0.41 (0.18-0.95)**		no family history OR=1 OR=1.57 (0.47-5.29)		FF = > 450 ml on cow milk based formula. Data from the first yr was collected prospectively from the birth cohort (questionnaires at 0, 2, 6 and 12 mo). Corrected for gender, season of birth, number of siblings, smoking, furred pets, SES, and age introduction solids.
	(Kull et al., 2002)	Cohort	Sweden n=3,791	0-2 yr	$EBF_{\geq 4}$ vs. $EBF_{<4}$ $MBF_{\geq 6}$ vs. $MBF_{<6}$	**OR=0.73 (0.54-0.99)** OR=0.80 (0.58-1.09)				Corrected for gender, family history, age mother, smoking during pregnancy and first 3 months after given birth, and date of construction home. Questionnaires at ages 2 months, 1 yr and 2 yr.
	(Tariq et al., 1998)	Cohort	United Kingdom n=1,086	4 yr	$FF_{before\ 3\ mo}$ BF	p=6.1% p=4.5%				Not corrected.
	(Gruskay, 1982)	Cohort	USA n=908	3 yr 5 yr 8 yr 15 yr	No family history FF_{cow} BF Family history FF_{cow} FF_{soy} BF	3 yr i=0/502 i=0/78 i=6/201 i=0/79 i=0/48	5 yr i=4/390 i=2/57 i=11/192 i=7/76 i=0/44	8 yr i=4/368 i=0/44 i=1/167 i=2/69 i=0/38	15 yr i=7/368 i=0/41 i=3/143 i=1/66 i=1/31	Not corrected.
	(Mimouni Bloch et al., 2002)	Review/ meta-analysis	n=3,303	Mean follow-up 2.25 yr	$EBF_{<3}$ $EBF_{>3}$	OR=1 OR=0.74 (0.54-1.01) with atopic family history OR=0.87 (0.48-1.58)				Strict inclusion criteria, including breastfeeding recall < 12 mo, developed countries and corrected for confounders (age, SES, family history, and smoking). Six studies including (Gruskay, 1982).
Sensitive to inhalation allergens [a]	(Kull et al., 2002)	Cohort	Sweden n=3,791	0-2 yr	$EBF_{\geq 4}$ vs. $EBF_{<4}$ $MBF_{\geq 6}$ vs. $MBF_{<6}$	**OR=0.66 (0.47-0.92)** OR=0.80 (0.56-1.15)				Corrected for gender, family history, age mother, smoking during pregnancy /1st 3 mo after birth baby, and date of construction home. Questionnaires at ages 2 months, 1 yr and 2 yr.
	(Wetzig et al., 2000)	Cohort	Germany n=325	0-2 yr	FF $EBF_{\geq 5}$	Children with increased IgE in umbilical cord OR=1 **OR=4.9 (1.2-20.4);** not significant for family history or combination 2 yr: no effect				Intermediary of effect is sensitivity for hen's eggs at one yr which is a predictor for allergy to inhalation allergens.
Food allergy [a]	(Kull et al., 2002)	Cohort	Sweden n=3,791	0-2 yr	$EBF_{\geq 4}$ vs. $EBF_{<4}$ $MBF_{\geq 6}$ vs. $MBF_{<6}$	OR=0.91 (0.75-1.1) OR=1.0 (0.85-1.31)				Corrected for gender, family history, age mother, smoking during pregnancy /1st 3 mo after birth baby, and date of construction home. Questionnaires at ages 2 months, 1 yr and 2 yr.
	(Tariq et al., 1998)	Cohort	United Kingdom n=1,086	4 yr	$FF_{before\ 3\ mo}$ BF	p=2.4% p=3.4%				Corrected for gender, low birth weight, winter birth, low cord serum IgE, SES, family history atopy, and maternal smoking, furred pets.

Table A1.11 continued: Effect of breastfeeding on atopy

Intermediary of health effect	Authors, Year of publication	Design	Study population	Age group	Breastfeeding	Effect size			Remarks
Food allergy continued [a]	(Kramer and Kakuma, 2002)	Review	n=135	1 yr 5 yr	 MBF_{3-7} EBF_{3-7}	1 yr (by history) RR=1 **RR=0.19 0.08-0.48)**	1yr(double challenge) RR=1 RR=0.77 (0.25-2.41)	5 yr (by history) RR=1 RR=0.61 (0.12-3.19)	Based on one study (Kajosaari and Saarinen, 1983).

Table A1.12: Effect of breastfeeding on obesity

Intermediary of health effect	Authors, Year of publication	Design	Study population	Age group	Breastfeeding	Effect size		Remarks
Obesity	(Weyerman n et al., 2006) [c]	Cohort	Germany N=839	2 yr	FF BF FF EBF<3 mo EBF3-<6 mo EBF≥6 mo FF BF<3 mo BF3-<6 mo BF 6-<9 mo BF≥9 mo	OR=1 OR=2.2 (0.7-7.2) OR=0.6 (0.2-1.4) OR=1 OR=0.8 (0.4-1.5) **OR=0.4 (0.2-0.9)** **OR=0.3 (0.1-0.9)** OR=1 OR=1.0 (0.5-2.0) **OR=0.4 (0.2-0.8)** **OR=0.4 (0.2-0.8)**		Adjusted for nationality of mother, age mother, education mother, BMI mother, smoking during pregnancy, birth weight. FF-group was a small group and possibly different in other aspects than in breastfeeding habits. Overweight defined as BMI above the 90th age- and sex-specific percentile of the German reference population.
	(Burke et al., 2005)	Cohort	Australia N=1,672	1-8 yr	FF $BF_{\leq 4\ mo}$ $BF_{5-\leq 8\ mo}$ $BF_{9-\leq 12\ mo}$ $BF_{>12\ mo}$	OR=1 OR=1.29 (0.89-1.97) OR=0.81 (0.50-1.31) OR=0.88 (0.54-1.42) OR=0.90 (0.58-1.47)		Adjusted for birth weight, gestational age, ethnicity, sex, maternal BMI, maternal smoking during pregnancy, first child, maternal education.
	(Kvaavik et al., 2005) [d]	Cohort	Norway N=635 (11-16y) N=352 (31-35y)	11-16 yr 31-35 yr	 FF BF_{1-3} $BF_{\geq 4}$	11-16 year OR=1 OR=0.57 (0.23-1.47) **OR=0.15 (0.03-0.72)**	31-35 year OR=1 OR=0.48 (0.20-1.18) OR=0.34 (0.12-1.01)	Adjusted for sex, parents BMI, education, mothers smoking during pregnancy. Breastfeeding asked at mean age 13 year. Also data on overweight and BMI.
	(Li et al., 2005)	Cohort	USA N=2,636	2-14 yr	FF $BF_{1-3\ mo}$ $BF_{\geq 4\ mo}$	OR=1 OR=0.7 (0.5-1.0) **OR=0.6 (0.4-1.0)**		Overweight defined as ≥ 95th percentile. Corrected for sex, ethnicity, age, gestational age, birth order, birth weight, maternal smoking, alcohol use, weight gain during pregnancy, maternal age, highest education at childbirth, annual family net income.
	(Reilly et al., 2005)	Cohort	United Kingdom N=5493	7 yr	FF MBF_2 EBF_2	OR=1 OR=1.08 (0.80-1.45) OR=1.22 (0.87-1.71)		Obesity defined as BMI-for-age-and-gender > 95th percentile. Corrected for SES, energy intake at 3 year and gender.

Table A1.12 continued: Effect of breastfeeding on obesity

Intermediary of health effect	Authors, Year of publication	Design	Study population	Age group	Breastfeeding	Effect size		Remarks
Obesity continued	(Bogen et al., 2004)	Cohort	USA N=73,458	4 yr	FF $BF_{<8\ wk}$ $BF_{8\text{-}15\ wk}$ $BF_{16\text{-}26\ wk}$ $BF_{>26\ wk}$	OR=1 OR=0.97 (0.86-1.09) OR=0.84 (0.69-1.02) OR=0.86 (0.70-1.06) **OR=0.70 (0.61-0.81)**		Obesity defined as ≥ 95th percentile. Only white children whose mothers did not smoke during pregnancy. Corrected for maternal age, education, parity, marital status, pregnancy conditions, delivery method, child sex, birth weight, birth order and birth year.
	(Grummer-Strawn and Mei, 2004)	Cohort	USA n=177,304	4 yr	FF $BF_{<1}$ $BF_{1\text{-}2.9}$ $BF_{3\text{-}5.9}$ $BF_{6\text{-}11.9}$ $BF_{>12}$	full cohort (n=177.304) OR=1 OR=0.98 (0.94-1.03) *OR=0.88 (0.83-0.93)* **OR=0.81 (0.76-0.87)** **OR=0.73 (0.68-0.79)** *OR=0.72 (0.65-0.80)*	Sub-cohort (n=12.587) OR=1 OR=1.12 (0.97-1.30) OR=1.06 (0.91-1.24) OR=0.91 (0.75-1.09) OR=0.93 (0.76-1.12) OR=0.76 (0.53-1.08)	Overweight defined as BMI-for-age-and-gender > 95th percentile. Full cohort, corrected for gender, ethnicity and birth weight. Sub-cohort, corrected for gender, ethnicity, birth weight, age mother, SES, BMI at pregnancy, weight gain during pregnancy, and smoking mother.
	(Parsons et al., 2003) D	Cohort	United Kingdom n=9,287	33 yr	FF $BF_{>1}$	Males OR=1 OR=0.93 (0.74-1.17)	Females OR=1 OR=0.84 (0.67-1.05)	BMI ≥ 30 kg/m^2. Corrected for SES, BMI mother, smoking mother. Other possible confounders had no effect on the model. Breastfeeding asked after at 7 yr of age.
	(Bergmann et al., 2003) C	Cohort	Germany n=918	6 yr	FF + $MBF_{<2}$ $BF_{>3}$	Overweight OR=1 **OR=0.53 (0.31-0.89)**	Obesity OR=1 **OR=0.46 (0.23-0.92)**	Overweight defined as BMI-for-age-and-gender > 90th percentile; obesity >97th percentile. Corrected for overweight mother, smoking during pregnancy, and SES.
	(Armstrong and Reilly, 2002) C	Cohort	Scotland n=32,200	3 - 3.5 yr	FF BF	Obesity OR=1 **OR=0.72 (0.65-0.79)**	Severe obesity OR=1 **OR=0.70 (0.61-0.80)**	BF/FF determined once at 6-8 weeks. Obesity defined as BMI-for-age-and-gender > 95th percentile (18.4 kg/m^2), severe obesity >98th percentile (19.0 kg/m^2). Corrected for SES, gender and birth weight.
	(Hediger et al., 2001)	Cohort	USA n=2,685	3-5 yr	FF BF_{ever} $EBF_{\leq 2}$ $EBF_{3\text{-}5}$ $EBF_{6\text{-}8}$ $EBF_{\geq 9}$	At risk for overweight OR=1 OR=0.63 (0.41-0.96) OR=0.57 (0.32-1.02) OR=0.69 (0.35-1.33) OR=0.55 (0.27-1.12) OR=0.76 (0.32-1.80)	Overweight OR=1 OR=0.84 (0.62-1.13) OR=0.98 (0.67-1.43) OR=0.70 (0.33-1.48) OR=0.65 (0.34-1.24) OR=0.75 (0.29-1.95)	At risk for overweight defined as BMI-for-age-and-gender 85-94th percentile; overweight > 97th percentile. Corrected for birth weight, ethnicity, gender, age, BMI mother, and time when solids were introduced.

Table A1.12 continued: Effect of breastfeeding on obesity

Intermediary of health effect	Authors, Year of publication	Design	Study population	Age group	Breastfeeding	Effect size		Remarks
Obesity continued	(Frye and Heinrich, 2003)	Cross-sectional	Germany N=6,590	5-14 yr	FF EBF≤4 wk 4 wk <EBF≤12 wk EBF> 12 wk BF≤4 wk 4 wk <BF≤12 wk BF> 12 wk	Overweight OR=1 OR=1.0 (0.9-1.3) OR=1.2 (1.0-1.4) OR=1.0 (0.8-1.2) OR=1.1 (0.9-1.2) OR=1.1 (0.9-1.3) OR=0.9 (0.7-1.1)	Obese OR=1 OR=0.9 (0.6-1.2) OR=0.8 (0.6-1.0) **OR=0.7 (0.5-1.0)** **OR=0.8 (0.6-1.0)** **OR=0.7 (0.5-0.9)** **OR=0.6 (0.4-0.9)**	Corrected for age, sex and survey. Three cross-sectional surveys combined.
	(Li et al., 2003)	Cross-sectional	United Kingdom n=2,631	4-8 yr 9-18 yr	$BF_{<1\ wk}$ $BF_{1\ wk-1\ mo}$ $BF_{2-3\ mo}$ BF_{4-6} BF_{7-9} $BF_{>9}$	4-8 yr OR=1 OR=1.04 (0.57-1.90) OR=0.68 (0.34-1.35) OR=0.94 (0.50-1.78) OR=1.14 (0.61-2.16) OR=0.61 (0.28-1.32)	9-18 yr OR=1 OR=1.25 (0.65-2.39) OR=0.69 (0.32-1.52) OR=1.31 (0.62-2.74) OR=2.02 (0.80-5.10) OR=0.73 (0.23-2.27)	Obesity defined as BMI-for-age-and-gender > 95th percentile. Corrected for gender, BMI parents, smoking during pregnancy, birth weight, and SES. Not clear when breastfeeding is asked after, seems that it is asked after at the same time as the health effect.
	(von Kries et al., 1999); (Koletzko and von Kries, 2001)	Cross-sectional	Germany n=9,357	5-6 yr	$EBF_{\leq 2}$ EBF_{3-5} EBF_{6-12} $EBF_{>12}$ BF	Overweight OR=0.89 (0.73-1.07) OR=0.87 (0.72-1.05) *OR=0.67 (0.49-0.91)* OR=0.43 (0.17-1.07) **OR=0.79 (0.68-0.93)**	Obesity OR=0.90 (0.65-1.24) *OR=0.65 (0.44-0.95)* *OR=0.57 (0.33-0.99)* OR=0.28 (0.04-2.04) **OR=0.75 (0.57-0.98)**	Overweight defined as BMI-for-age-and-gender > 90th percentile; obesity >97th percentile. BF inquired at 5-6 yr of age. Corrected for SES, smoking during pregnancy, low birth weight, own bedroom, frequency of butter consumption. (Koletzko and von Kries, 2001) is the same study population.
	(Toschke et al., 2002) [c]	Cross-sectional	Czech Republic n=33,768	6-14 yr	FF BF	Overweight OR=1 **OR=0.80 (0.71-0.90)**	Obesity OR=1 **OR=0.80 (0.66-0.96)**	Overweight defined as BMI-for-age-and-gender > 90th percentile; obesity >97th percentile. Corrected for SES, overweight parents, smoking mother, high birth weight, watching ≥1 h TV a day, number of siblings, and physical activity. No distinction EBF/MBF; BF asked after at 6-14 yr.
	(Liese et al., 2001)	Cross-sectional	Germany N=2108	9-10 year	FF BF EBF<2 EBF2-4 EBF5 - >6 BF<6 BF6- >12	OR=1 **OR=0.66 (0.52-0.87)** **OR=0.70 (0.49-0.99)** **OR=0.68 (0.48-0.98)** **OR=0.51 (0.33-0.80)** **OR=0.71 (0.51-0.98)** **OR=0.56 (0.53-0.90)**		Adjusted for age, sex, city, nationality, SES, environmental tobacco smoke.

Table A1.12 continued: Effect of breastfeeding on obesity

Intermediary of health effect	Authors, Year of publication	Design	Study population	Age group	Breastfeeding	Effect size				Remarks
Obesity continued	(Gillman et al., 2001) C	Cross sectional	USA n=15,341	9-14 yr	FF_6 BF_6 $BF_{\leq 3}$ $BF_{\geq 7}$	OR=1 **OR=0.78 (0.66-0.91)** OR=1 **OR=0.80 (0.67-0.96)**				Overweight defined as BMI-for-age-and-gender > 95th percentile. BF asked after at 9-14 yr of age. Corrected for age, gender, Tanner score (puberty), physical activity, daily energy intake, BMI mother, birth weight, number of siblings, SES, smoking mother, dietary restraint, weight cycling, and weight concerns.
	(Arenz et al., 2004) E	Review/ meta analysis	n= ± 69,000	3-26 yr	FF BF	OR=1 **OR=0.78 (0.71-0.85)**				Nine studies including (Bergmann et al., 2003), (Gillman et al., 2001), (Hediger et al., 2001), (Li et al., 2003), (Toschke et al., 2002) and (von Kries et al., 1999). Corrected for at least three of the following relevant factors: birth weight, overweight parents, smoking, diet factors, physical activity and SES.
Elevated weight gain a	(Kalies et al., 2005)	cohort	Germany N=2,624	2 yr	$EBF_{0\text{-}1\ mo}$ $EBF_{2\text{-}3\ mo}$ $EBF_{4\text{-}5\ mo}$ $EBF_{\geq 6\ mo}$	**OR=1.99 (1.34-2.97)** **OR=1.61 (1.04-2.50)** OR=1.40 (0.93-2.11) OR=1	boys **OR=1.76 (1.01-3.06)** **OR=1.78 (1.00-3.19)** OR=1.60 (0.92-2.79) OR=1	girls **OR=2.35 (1.31-4.21)** OR=1.50 (0.77-2.92) OR=1.20 (0.65-2.23) OR=1		Elevated weight gain was defined as a weight gain greater or equal than the 90th sex-specific percentile of this cohort. Adjusted for introduction and composition of solid food, maternal BMI, maternal smoking during pregnancy, SES, study centre, birth order, (sex).
BMI a	(Parsons et al., 2003)	Cohort	United Kingdom n=9,287	7 yr 11 yr 16 yr 33 yr	<u>males</u> $BF_{>1}$ $BF_{<1}$ FF <u>Females</u> $BF_{>1}$ $BF_{<1}$ FF	<u>7 yr</u> 15,94 15.91 15.99 15.86 15.88 15.95	<u>11 yr</u> 17.31 17.24 17.44 17.63 17.69 17.79	<u>16 yr</u> 20.28 20.23 20.32 20.96 20.96 **21.22***	<u>33 yr</u> 25.52 25.69 **25.87*** 24.39 24.60 **24.88***	* p<0.05 for comparison FF with BF>1 mo. Breastfeeding asked after at 7 yr of age.
	(Ravelli et al., 2000)	Cohort	Netherlands n=625	48-53 yr	$EBF_{10\ days}$ $MBF\&FF_{10\ days}$	26.8 (kg/m^2) 27.2 (kg/m^2)				Breastfeeding determined from hospital discharge papers (approximately 10 days after birth). Corrected for prenatal exposure to famine, age mother, gender, duration of hospitalisation.

Table A1.13: Effect of breastfeeding on diabetes

Intermediary of health effect	Authors, Year of publication	Design	Study population	Age group	Breastfeeding	Effect size	Remarks
Insulin-dependent diabetes mellitus (IDDM) [a]	(Sadauskaite-Kuehne et al., 2004) [c]	Case-control	Sweden ≥ 165 Cases ≥ 420 Controls	5-9 yr	$EBF_{\geq 5}$ vs. $EBF_{not \geq 5}$ $BF_{\geq 7}$ vs. $BF_{not \geq 7}$ $BF_{\geq 9}$ vs. $BF_{not \geq 9}$	**OR= 0.54 (0.36-0.81)** **OR= 0.56 (0.38-0.84)** **OR= 0.61 (0.41-0.92)**	Matched on age and gender. Corrected for age mother, prematurely, treatment hospital < 1 mo, infection < 1 mo, neonatal jaundice first week, infection during last 6 mo, stressful event during last 6 mo, and living in city.
	(McKinney et al., 1999) [c]	Case-control	United Kingdom 196 cases 325 controls	0-16 yr	FF EBF	OR=1 **OR=0.60 (0.41-1.89)**	Matched by sex and age. Corrected for age mother, mother with diabetes mellitus 1, preeclampsia, caesarean delivery and neonatal illnesses. EBF= initial EBF.
	(Hypponen et al., 1999) [c]	Case-control	Finland 435 Cases 386 Controls	0-14 yr	$EBF_{<3}$ $EBF_{\geq 3}$	**OR=1.53 (1.1-2.2)** OR=1	Matched on day of birth and gender. Corrected for individual weight gain curve. Breastfeeding asked at inclusion cohort (mean age 8 yr).
	(Meloni et al., 1997)	Case-control	Italy 100 Cases 100 Controls	0-17 yr	BF FF FF BF_{1-2} BF_{3-5} $BF_{>6}$ BF (mo)	OR=1 **OR=0.41 (0.19-0.91)** **OR=0.36 (0.14-0.94)** OR=0.48 (0.19-1.24) OR=1.18 (0.52-2.68) OR=1 OR=1.10 (0.99-1.22)	Corrected for SES and number of siblings. Matched on age and gender. Breastfeeding determined at later age.
	(Jones et al., 1998) [c]	Case-control	United Kingdom 315 Cases 1,525 Controls	0-20 yr	$BF_{discharge}$ $FF_{discharge}$	RR=1 RR=1.33 (0.76-2.34)	Matched on gender, yr of birth, given birth in which hospital.
	(Virtanen et al., 1993) [c]	Case-control	Finland 690 Cases 690 Controls	0-14 yr	$EBF_{<2\ mo}$ $EBF_{2-3\ mo}$ $EBF_{4-5\ mo}$ $EBF_{\geq 6\ mo}$ $BF_{<2\ mo}$ $BF_{2-3\ mo}$ $BF_{4-5\ mo}$ $BF_{\geq 6\ mo}$	OR=1 OR=1.05 (0.49-2.25) OR=0.76 (0.31-1.85) OR=1.24 (0.46-3.36) OR=1 OR=1.02 (0.59-1.76) OR=1.10 (0.59-2.02) OR=0.87 (0.47-1.63)	Matched on birth date and sex. Adjusted for age at introduction of diary products. Adjustment for mother's education, mother's age, child's birth order, birth weight, prematurely, admission to intensive care or nursery after birth did not affect the results. BF data collection between 0-14 yr after birth.
	(Samuelsson et al., 1993) [c]	Case-control	Sweden 297 Cases 792 Controls	0-15 yr	EBF MBF	Non significant	Matched on birth yr, gender and geographic location.

Table A1.13 continued: Effect of breastfeeding on diabetes

Intermediary of health effect	Authors, Year of publication	Design	Study population	Age group	Breastfeeding	Effect size	Remarks
Insulin-dependent diabetes mellitus (IDDM) continued [a]	(Norris and Scott, 1996) [c]	Meta analysis			BF FF (18 studies) $BF_{\geq 3}$ $BF_{<3}$	OR=1 **OR=1.13 (1.04-1.23)** OR=1 High risk population: **OR=1.39 (1.15-1.68)** Mean risk population: **OR=1.17 (1.05-1.31)** Low risk population: OR=1.34 (0.73-2.46)	19 case-cohort studies.

Table A1.14: Effect of breastfeeding on cardiovascular diseases incidence and intermediary's of cardiovascular diseases

Intermediary of health effect	Authors, Year of publication	Design	Study population	Age group	Breastfeeding	Effect size	Remarks
Cardiovascular diseases [a]	(Martin et al., 2004)	Cohort	Great-Britain n=3,861	66-68 yr	FF BF $BF_{\leq 5}$ $BF_{6\text{-}11}$ $BF_{\geq 12}$	HR=1 HR=1.04 (0.83-1.30) HR=0.96 (0.67-1.35) HR=0.91 (0.67-1.22) HR=1.04 (0.66-1.62)	Corrected for current age, gender, residence, number of siblings, SES during childhood. Stratified for research district. Way of feeding during childhood determined in childhood (Boyd Orr cohort; born between 1918-1939).
	(Martin et al., 2004)	Meta analysis			BF vs. FF Prolonged BF vs. FF	RR=1.06 (0.94-1.20) RR=1.16 (0.99-1.36)	4 Historical cohorts, including Boyd Orr cohort ((Martin et al., 2004)); born between 1904-1939.
Coronary heart disease	(Rich-Edwards et al., 2004)	Cohort	USA n=87.252	56-60 yr	FF BF $BF_{<9}$ $BF_{>9}$	HR=1.0 HR=0.92 (0.80-1.05) HR=0.93 (0.77-1.13) HR=0.84 (0.69-1.03)	Corrected for age, smoking, birth weight. BF asked after at age 46+ yr.
	(Martin et al., 2004)	Cohort	United Kingdom n=3,861	66-68 yr	FF BF $BF_{\leq 5}$ $BF_{6\text{-}11}$ $BF_{\geq 12}$	HR=1 HR=1.02 (0.77-1.36) HR=0.89 (0.56-1.41) HR=0.90 (0.62-1.31) HR=1.07 (0.61-1.87)	Corrected for current age, gender, residence (1998), number of siblings, SES during childhood. Stratified for research district. Way of feeding during childhood determined in childhood (Boyd Orr cohort; born between 1918-1939).
	(Martin et al., 2004) [d]	Meta analysis			FF BF Prolonged BF	RR=1 RR=1.19 (0.89-1.58) RR=1.08 (0.88-1.31)	4 Historical cohorts, including Boyd Orr cohort (Martin et al., 2004); born between 1904-1939.
Cerebral infarction [a]	(Rich-Edwards et al., 2004)	Cohort	USA n=87,252	56-60 yr	FF BF $BF_{<9}$ $BF_{>9}$	HR=1.0 HR=0.91 (0.79-1.06) HR=0.82 (0.66-1.03) HR=1.00 (0.81-1.23)	Corrected for age, smoking, birth weight. BF asked after at age 46+ yr.
	(Martin et al., 2004)	Cohort	Great-Britain n=3,861	66-68 yr	FF BF $BF_{\leq 5}$ $BF_{6\text{-}11}$ $BF_{\geq 12}$	HR=1 HR=1.16 (0.71-1.90) HR=1.56 (0.81-3.00) HR=0.85 (0.42-1.69) HR=1.14 (0.40-3.26)	Corrected for current age, gender, residence (1998), number of siblings, SES during childhood. Stratified for research district. Way of feeding during childhood determined in childhood (Boyd Orr cohort; born between 1918-1939).

Table A1.14 continued: Effect of breastfeeding on cardiovascular diseases incidence and intermediary's of cardiovascular diseases

Intermediary of health effect	Authors, Year of publication	Design	Study population	Age group	Breastfeeding	Effect size		Remarks
Blood pressure (mmHg) [a]	(Martin et al., 2004)	Cohort	Great-Britain n=7,276	7 yr	FF BF MBF_2 EBF_2	Systolic blood pressure Ref *-0.7 (-1.4; –0.22)* -0.7 (-1.4; 0.01) -0.8 (-1.5; 0.01)	Diastolic blood pressure Ref **-0.4 (-1.1; –0.04)** **-0.6 (-1.2; –0.06)** -0.5 (-1.1; 0.1)	BF determined at age 6 months and 15 months. Corrected for age, gender, room temperature, SES, age mother at birth, hypertension mother, birth weight, gestational age, age introduction solids, BMI during pregnancy, height mother, height child, BMI child.
	(Lawlor et al., 2004)	Cohort	United Kingdom n=3,864	5 yr	$BF_{<6}$ + FF $BF_{\geq 6}$	Ref **-1.19 (0.40-1.96)**		Corrected for BMI mother, smoking, SES, number of siblings, marital state, BMI father, birth- weight and -height, weight at 5 yr. Breastfeeding determined at 6 month. Selective follow-up.
	(Ravelli et al., 2000)	Cohort	Netherlands n=625	48-53 yr	$EBF_{10\ days}$ $MBF\&FF_{10\ days}$	Systolic blood pressure 125.1 124.9	Diastolic blood pressure 85.7 84.8	Breastfeeding determined from hospital discharge papers (approximately 10 days after birth). Corrected for prenatal exposure to famine, age mother, gender, duration of hospitalisation.
	(Taittonen et al., 1996)	Cohort	Finland n=2,799	3-18 yr	FF BF_{0-3} $BF_{>3}$	Girls Ref **-3.5 (-6.2,-0.9)** **-4.5 (-7.2,-1.7)**	Boys Ref **-3.6 (-7.0;-0.2)** **-6.5 (-10.1;-3.0)**	Effect measurement is mean change of systolic blood pressure (mm Hg) from the baseline (1980) till now (1986).
	(Lawlor et al., 2005)	Cross-sectional	Estonia and Denmark N=1,557	9-15 yr	FF $EBF_{<1\ mo}$ $EBF_{1-3\ mo}$ $EBF_{4-6\ mo}$ $EBF_{>6\ mo}$	0 -1.12 (-2.87 to 0.61) **-1.85 (-3.24 to -0.45)** **-2.13 (-3.69 to -0.58)** -1.56 (-3.15 to 0.05)		Adjusted difference. Corrected for age child, sex, country, birth weight, pubertal stage, BMI, height, education mother/father, income mother father, smoking mother/father, BMI mother/fathers.
	(Martin et al., 2005)	Meta-analysis	n=17,503	0-12 mo	FF BF	Mean difference sys bp Ref **-1.4 mmHg (-2.2;-0.6)**	Mean difference diast bp Ref **-0.5 mmHg (-0.9;-0.04)**	Medline, EMBASE …-2003. Two randomised trials (Singhal et al., 2001) and (Lucas and Morley, 1994), 8 prosp cohorts (including (Wilson et al., 1998), (Taittonen et al., 1996), (Lawlor et al., 2004), (Kolacek et al., 1993) and (Martin et al., 2004)), one historical cohort (Ravelli et al., 2000) and four case-control studies (including (Leeson et al., 2001)).
	(Owen et al., 2003)	Review			FF BF BF (effect ≤1 yr) BF (effect >1 -16 yr) BF (effect ≥17 yr)	Systolic blood pressure Ref *-0.79 (-1.42; –0.16)* ***-1.43 (-3.69; 0.84)*** *-0.78 (-1.48; -0.07)* ***-1.75 (-3.51; 0.02)***	Diastolic blood pressure Ref -0.39 (-0.90; 0.13) -0.83 (-2.88; 1.22) -0.37 (-0.93; 0.18) -0.45 (-1.27; 0.37)	25 studies including (Leeson et al., 2001) and (Wilson et al., 1998). Possible publication bias.

Table A1.14 continued: Effect of breastfeeding on cardiovascular diseases incidence and intermediary's of cardiovascular diseases

Intermediary of health effect	Authors, Year of publication	Design	Study population	Age group	Breastfeeding	Effect size			Remarks
Elasticity of the blood vessels [a]	(Schack-Nielsen et al., 2005)	Cohort	Denmark N=87	10 yr	BF /mo	PWV (aorto-radial) OR=5.0 (0.5-54.6)	PWV (aorto-femoral) OR=8.2 (1.5-40.4)		PWV in cm/s. Adjusted for gender, height, weight, body fat, systolic and diastolic blood pressure, energy, fat energy, physical activity.
	(Leeson et al., 2001)	Cross sectional	United Kingdom n=331	20-28 yr	BF	**-3.93 µm/month (-7.29; -0.57)** men: -2.9 women:-4.3			Corrected for heartbeat, age, gender, cholesterol concentration, BMI, and SES.
Cholesterol [a]	(Ravelli et al., 2000)	Cohort	Netherlands n=625	48-53 yr	$EBF_{10\ days}$ $MBF\&FF_{10\ days}$	LDL 3.96 4.15	HDL 1.34 1.27 **(p=0.03)**	LDL/HDL ratio 2.86 3.14 **(p=0.01)**	Breastfeeding determined from hospital discharge papers (approximately 10 days after birth). Corrected for prenatal exposure to famine, age mother, gender, and duration of hospitalisation.
	(Lawlor et al., 2005)	Cross-sectional	Estonia and Denmark N=1,557	9-15 yr	FF $EBF_{<1\ mo}$ $EBF_{1-3\ mo}$ $EBF_{4-6\ mo}$ $EBF_{>6\ mo}$	0 -0.04 (-0.09 to 0.02) -0.01 (-0.05 to 0.04) -0.01 (-0.06 to 0.04) **-0.05 (-0.10 to 0.00)**			Adjusted difference HDL. Corrected for age child, sex, country, birth weight, pubertal stage, BMI, height, education mother/father, income mother father, smoking mother/father, BMI mother/fathers.

Table A1.15: Effect of breastfeeding on cancer incidence

Intermediary of health effect	Authors, Year of publication	Design	Study population	Age group	Breastfeeding	Effect size	Remarks
All cancers [a]	(Lancashire and Sorahan, 2003)	Case-control	United Kingdom 3,376 Cases 3,376 Controls	1-15 yr	FF BF $BF_{<1}$ BF_{1-6} $BF_{\geq 7}$	OR=1 OR=1.01 (0.91-1.12) OR=1.05 (0.90-1.22) OR=0.98 (0.87-1.11) OR=1.06 (0.85-1.31) (p-trend: 0.77)	Matched on age, gender, and region. Corrected for SES, age mother at birth, and number of siblings.
	(Hardell and Dreifaldt, 2001)	Case-control	Sweden 835 Cases 860 Controls	0-14 yr	FF + $BF_{<1}$ $BF_{\geq 1}$ BF_{1-5} $BF_{\geq 6}$	OR=1 OR=1.0 (0.7-1.3) OR=0.9 (0.7-1.3) OR=1.0 (0.7-1.4)	Gestational age, number of siblings, birth weight, age mother, and smoking during pregnancy did not differ between cases and controls, so no correction has been carried out.
	(UK Childhood Cancer Study Investigators, 2001)	Case-control	United Kingdom 3,500 Cases 6,964 Controls	1-14 yr	FF BF $BF_{<1}$ BF_{1-6} $BF_{\geq 7}$	OR=1 OR=0.92 (0.84-1.00) OR=1.01 (0.89-1.14) **OR=0.88 (0.79-0.98)** OR=0.89 (0.79-1.01)	Corrected for age diagnose, gender, region, number of siblings, and SES. Same dataset as (Lancashire and Sorahan, 2003), but different analyse methods.
	(Davis et al., 1988)	Case-control	USA 201 Cases 181Controls	1,5-15 yr	FF $BF_{\leq 6}$ $BF_{>6}$	**OR=1.75 (1.08-2.83)** **OR=1.89 (1.09-3.22)** OR=1	No correction
	(Davis, 1998)	Review				3 studies all cancers: 2 BF protective effect; 1 no effect 5 studies ALL: 5 no effect 3 studies n-Hodgkin: 3 no effect 2 studies Hodgkin: 2 BF protective effect 2 studies ANLL: 2 no effect 2 studies lymphoma: 1 BF protective; 1 no effect 1 studies leukaemia: no effect	Nine case-control studies; seven in developed countries.
Leukaemia [a]	(Lancashire and Sorahan, 2003)	Case-control	United Kingdom 1,342 Cases 1,342 Controls	1-15 yr	FF BF $BF_{<1}$ BF_{1-6} $BF_{\geq 7}$	OR=1 OR=1.00 (0.85-1.18) OR=1.14 (0.89-1.45) OR=0.95 (0.79-1.15) OR=0.98 (0.71-1.37) (p-trend: 0.70)	Cases and controls age- gender- and region matched. Corrected for SES, age mother at birth, and number of siblings.
	(Hardell and Dreifaldt, 2001)	Case-control	Sweden 235 Cases 237 Controls	0-14 yr	FF + $BF_{<1}$ $BF_{\geq 1}$ BF_{1-5} $BF_{\geq 6}$	OR=1 OR=0.9 (0.5-1.6) OR=0.9 (0.5-1.7) OR=0.9 (0.5-1.7)	Gestational age, number of siblings, birth weight, age mother, and smoking during pregnancy did not differ between cases and controls so no correction has been carried out.
	(UK Childhood Cancer Study Investigators, 2001)	Case-control	United Kingdom 1,637 Cases 6,964 Controls	1-14 yr	FF BF $BF_{<1\ mo}$ BF_{1-6} $BF_{\geq 7}$	OR=1 OR=0.89 (0.80-1.00) OR=0.96 (0.81-1.14) OR=0.88 (0.77-1.02) OR=0.85 (0.73-1.00)	Corrected for age diagnose, gender, region, number of siblings, and SES. Same dataset as (Lancashire and Sorahan, 2003), but different method of analysis.

Table A1.15 continued: Effect of breastfeeding on cancer incidence

Intermediary of health effect	Authors, Year of publication	Design	Study population	Age group	Breastfeeding	Effect size		Remarks
Acute leukaemia [a]	(Schuz et al., 1999)	Case-control	Germany 1,001 Cases 1,001 Controls	≤14 yr	$BF_{>6}$ BF_{2-6} $BF_{<1}$	OR=1 OR=1.2 (0.9-1.5) OR=1.2 (0.9-1.6)		Cases and Controls matched on age and gender. Corrected for SES.
	(Shu et al., 1999)	Case-control	USA & Canada 2,200 Cases 2,418 Controls	1 - 18yr	FF BF BF_{1-3} BF_{4-6} BF_{7-9} BF_{10-12} $BF_{>12}$	OR=1 **OR=0.79 (0.70-0.91)** OR=0.88 (0.74-1.05) OR=0.80 (0.70-1.03) **OR=0.65 (0.51-0.83)** **OR=0.63 (0.49-0.81)** OR=0.81 (0.64-1.03)		
Acute myeloid leukaemia [a]	(Hardell and Dreifaldt, 2001)	Case-control	Sweden 26 Cases 27 Controls	0-14 yr	$FF + BF_{<1}$ $BF_{\geq 1}$ BF_{1-5} $BF_{\geq 6}$	OR=1 OR=0.3 (0.0-2.2) OR=0.2 (0.0-2.0) OR=0.3 (0.0-3.2)		Gestational age, number of siblings, birth weight, age mother, and smoking during pregnancy did not differ between cases and controls, so no correction has been carried out.
	(UK Childhood Cancer Study Investigators, 2001)	Case-control	United Kingdom 214 Cases 6,964 Controls	1-14 yr	FF BF $BF_{<1\ mo}$ BF_{1-6} $BF_{\geq 7}$	OR=1 OR=0.78 (0.58-1.05) OR=0.82 (0.53-1.26) OR=0.85 (0.60-1.20) OR=0.65 (0.43-1.00)		Corrected for age diagnose, gender, region, number of siblings, and SES.
	(Shu et al., 1999)	Case-control	USA & Canada 456 Cases 539 Controls	1 - 18yr	FF BF BF_{1-3} BF_{4-6} BF_{7-9} BF_{10-12} $BF_{>12}$	OR=1 OR=0.77 (0.57-1.03) OR=1.12 (0.73-1.72) OR=0.81 (0.54-1.23) **OR=0.48 (0.28-0.82)** OR=0.69 (0.39-1.23) OR=0.58 (0.31-1.08)		
	(Kwan et al., 2004)	Meta-analysis			FF $BF_{\leq 6}$ $BF_{>6}$	<u>All studies</u> OR=1 OR=0.90 (0.80-1.02) **OR=0.85 (0.73-0.98)**	<u>SES corrected</u> OR=1 OR=0.91 (0.80-1.04) **OR=0.85 (0.73-0.98)**	8 case-control studies, including (Davis et al., 1988) and one study from China.
Acute lymphatic leukaemia	(Kwan et al., 2005)	Case-control	USA 311 Cases 400 Controls	1-14 yr	FF $EBF_{\leq 3}$ EBF_{4-6} EBF_{7-12} $EBF_{\geq 13}$	<u>1-14 year</u> OR=1 OR=1.06 (0.65-1.71) OR=0.97 (0.55-1.71) OR=0.98 (0.55-1.75) OR=0.86 (0.38-1.92) (p-trend: 0.64)	<u>2-5 year</u> OR=1 OR=1.75 (0.91-3.34) OR=1.32 (0.63-2.77) OR=1.14 (0.53-2.44) OR=2.04 (0.69-6.07) (p-trend: 0.74)	EBF does not exclude solid foods, only formula or other milk

Table A1.15 continued: Effect of breastfeeding on cancer incidence

Intermediary of health effect	Authors, Year of publication	Design	Study population	Age group	Breastfeeding	Effect size			Remarks
Acute lymphatic leukaemia continued	(Lancashire and Sorahan, 2003)	Case-control	United Kingdom 948 Cases 948 Controls	1-15 yr	FF BF $BF_{<1}$ BF_{1-6} $BF_{\geq 7}$	OR=1 OR=0.99 (0.82-1.20) OR=1.10 (0.83-1.46) OR=0.96 (0.77-1.20) OR=0.90 (0.60-1.34) (p-trend: 0.55)			Cases and controls age- gender- and region matched. Corrected for SES, age mother at birth, and number of siblings.
	(Hardell and Dreifaldt, 2001) [c]	Case-control	Sweden 204 Cases 202 Controls	0-14 yr	FF + $BF_{<1}$ $BF_{\geq 1}$ BF_{1-5} $BF_{\geq 6}$	OR=1 OR=1.0 (0.5-1.9) OR=1.0 (0.5-2.0) OR=0.9 (0.5-1.8)			Gestational age, number of siblings, birth weight, age mother, and smoking during pregnancy did not differ between cases and controls, so no correction has been carried out.
	(UK Childhood Cancer Study Investigators, 2001)	Case-control	United Kingdom 1,401 Cases 6,964 Controls	1-14 yr	FF BF $BF_{<1}$ BF_{1-6} $BF_{\geq 7}$	OR=1 OR=0.91 (0.81-1.04) OR=0.98 (0.82-1.17) OR=0.90 (0.77-1.04) OR=0.89 (0.75-1.05)			Corrected for age diagnose, gender, region, number of siblings, and SES. Same dataset as (Lancashire and Sorahan, 2003), but different method of analysis.
	(Infante-Rivard et al., 2000)	Case-control	Canada 491 Cases 491Controls	0-10 yr	FF $BF_{\leq 3}$ $BF_{>3}$	<u>≤10 yr</u> OR=1 **OR=0.68 (0.49-0.95)** **OR=0.67 (0.47-0.94)**	<u>< 4 yr</u> OR=1 OR=0.62 (0.37-1.03) OR=0.63 (0.39-1.03)	<u>≥4 yr</u> OR=1 OR=0.78 (0.50-1.23) OR=0.68 (0.41-1.14)	Cases and controls matched on gender, age, and region. Corrected for age mother and SES.
	(Schuz et al., 1999) [c]	Case-control	Germany 682 Cases 2,574 Controls	0-14 yr	$BF_{>6}$ BF_{2-6} $BF_{\leq 1}$	OR=1 OR=1.2 (0.9-1.6) OR=1.3 (1.0-1.7)			Cases and controls frequency matched. Corrected for SES.
	(Shu et al., 1999)	Case-control	USA & Canada 1,744 Cases 1,879 Controls	1 - 15yr	FF BF BF_{1-3} BF_{4-6} BF_{7-9} BF_{10-12} $BF_{>12}$	OR=1 **OR=0.80 (0.69-0.93)** OR=0.85 (0.70-1.03) OR=0.87 (0.68-1.08) **OR=0.70 (0.53-0.92)** **OR=0.61 (0.46-0.80)** OR=0.85 (0.66-1.11)			
	(Kwan et al., 2004)	Meta-analysis			FF $BF_{\leq 6}$ $BF_{>6}$	<u>All studies</u> OR=1 **OR=0.90 (0.82-0.99)** **OR=0.75 (0.67-0.85)**	<u>SES corrected</u> OR=1 **OR=0.88 (0.80-0.97)** **OR=0.76 (0.68-0.84)**		Eight case-control studies, including (Davis et al., 1988), one study from China and one from Moscow.
Malignant lymphoma [a]	(Hardell and Dreifaldt, 2001)	Case-control	Sweden 99 Cases 97 Controls	0-14 yr	FF + $BF_{<1}$ $BF_{\geq 1}$ BF_{1-5} $BF_{\geq 6}$	OR=1 OR=1.9 (0.7-4.7) OR=1.9 (0.7-4.7) OR=1.8 (0.7-5.0)			Gestational age, number of siblings, birth weight, age mother, and smoking during pregnancy did not differ between cases and controls, so no correction has been carried out.

Table A1.15 continued: Effect of breastfeeding on cancer incidence

Intermediary of health effect	Authors, Year of publication	Design	Study population	Age group	Breastfeeding	Effect size			Remarks
Hodgkin's disease [a]	(UK Childhood Cancer Study Investigators, 2001)	Case-control	United Kingdom 114 Cases 6,964 Controls	1-14 yr	FF BF $BF_{<1}$ BF_{1-6} $BF_{\geq 7}$	OR=1 OR=1.01 (0.67-1.53) OR=1.50 (0.88-2.57) OR=0.85 (0.51-1.40) OR=0.90 (0.50-1.60)			Corrected for age diagnose, gender, region, number of siblings, and SES.
Non-Hodgkin's lymphoma [a]	(UK Childhood Cancer Study Investigators, 2001)	Case-control	United Kingdom 228 Cases 6,964 Controls	1-14 yr	FF BF $BF_{<1}$ BF_{1-6} $BF_{\geq 7}$	OR=1 OR=1.03 (0.77-1.38) OR=1.04 (0.68-1.59) OR=1.12 (0.80-1.50) OR=0.90 (0.60-1.34)			Corrected for age diagnose, gender, region, number of siblings, and SES.
Neuroblastoma [a]	(Daniels et al., 2002)	Cohort	USA & Canada 393 Cases 376 Controls	6 mo-19 yr	FF BF MBF EBF BF_{0-3} BF_{4-6} BF_{7-9} BF_{9-12} $BF_{\geq 13}$	OR=1 **OR=0.6 (0.5-0.9)** OR=0.7 (0.5-1.2) **OR=0.6 (0.5-0.9)** OR=0.7 (0.4-1.0) OR=0.7 (0.5 (1.2) OR=0.6 (0.4-1.1) OR=0.6 (0.3-1.1) **OR=0.5 (0.3-0.9)**			Matched on day of birth (±6 mo). Age mother, SES, ethnicity, smoking and alcohol consumption, number of siblings and day-care were no confounders so no correction has been carried out. Breastfeeding determined at later age.
	(Hardell and Dreifaldt, 2001)	Case-control	Sweden 34 Cases 38 Controls	0-14 yr	FF + $BF_{<1}$ $BF_{\geq 1}$ BF_{1-5} $BF_{\geq 6}$	OR=1 OR=0.6 (0.1-2.5) OR=0.6 (0.1-2.8) OR=0.5 (0.1-2.6)			Gestational age, number of siblings, birth weight, age mother, and smoking during pregnancy did not differ between cases and controls, so no correction has been carried out.
Brain cancer [a]	(Hardell and Dreifaldt, 2001)	Case-control	Sweden 246 Cases 274 Controls	0-14 yr	FF + $BF_{<1}$ $BF_{\geq 1}$ BF_{1-5} $BF_{\geq 6}$	OR=1 OR=0.8 (0.4-1.3) OR=0.8 (0.4-1.4) OR=0.7 (0.4-1.3)			Gestational age, number of siblings, birth weight, age mother, and smoking during pregnancy did not differ between cases and controls so no correction has been carried out.
Wilms tumour (childhood kidney tumour) [a]	(Saddlemire et al., 2006)	Case-control	USA & Canada 501 Cases 480 Controls	0-15 yr			≤ some post-high school education	≥ college graduate	Matched on age of diagnosis and region. Overall analysis adjusted for age, region, household income, mothers education. Models stratified by mothers education adjusted for age, region, household income.
					FF BF EBF MBF	OR=1 **OR=0.7 (0.5-0.9)** **OR=0.6 (0.4-0.9)** OR=0.7 (0.5-1.0)	OR=1 **OR=0.6 (0.4-0.8)** OR=0.6 (0.4-1.0) **OR=0.5 (0.4-0.8)**	OR=1 OR=1.1 (0.6-1.9) OR=0.8 (0.4-1.6) OR=1.1 (0.6-2.1)	
					$BF_{0-3\ mo}$ $BF_{4-6\ mo}$ $BF_{7-9\ mo}$ $BF_{10-12\ mo}$ $BF_{\geq 13\ mo}$	OR=0.7 (0.5-1.1) OR=0.5 (0.3-0.7) OR=0.7 (0.4-1.3) OR=0.7 (0.4-1.2) OR=0.6 (0.4-1.0)	OR=0.7 (0.4-1.0) **OR=0.3 (0.2-0.5)** OR=0.4 (0.2-1.0) **OR=0.4 (0.2-0.9)** OR=0.7 (0.4-1.4)	OR=1.0 (0.5-2.1) OR=1.1 (0.5-2.4) OR=1.3 (0.5-3.4) OR=1.9 (0.8-4.8) OR=0.8 (0.4-1.8)	

Table A1.15 continued: Effect of breastfeeding on cancer incidence

Intermediary of health effect	Authors, Year of publication	Design	Study population	Age group	Breastfeeding	Effect size			Remarks
Breast cancer [a]	(Freudenheim et al., 1994)	Case-control	USA 740 Cases 810 Controls	40-85 yr	FF BF	Premenopausal OR=1 OR=0.76 (0.52-1.12)	Postmenopausal OR=1 OR=0.73 (0.47-1.13)	All OR=1 **OR=0.74** **(0.56-0.99)**	Not population based due to large lack of response. BF determined later in life, participants who did not know if they were breastfed excluded from the analyses (27%). Corrected for age, education, menarche, age 1st pregnancy, number of pregnancies, family history, history of benign breast disorders, BMI, and height.
Testicle cancer [a]	(Coupland et al., 2004)	Case-control	United Kingdom 446 Cases 422 Controls	15-49 yr	FF BF	OR=1 OR=0.81 (0.59-1.11)			Matched on yr of birth (within a yr). Only mothers younger than 70 yr, breastfeeding was asked after. Corrected for age, region, SES, undescended testis or inguinal hernia before 15 yr and age mother during pregnancy.

Table A1.16: Effect of breastfeeding on growth

Intermediary of health effect	Authors, Year of publication	Design	Study population	Age group	Breastfeeding	Effect size						Remarks
Weight gain (weight difference (g)) [a]	(Baker et al., 2004)	Cohort	Denmark N=3,768	0-12 mo	BF<20wk BF 30-31wk BF 32-40wk BF>40wk	258.7 206.4 153.3 ref		Complementary food <16 wk 365.1 -43.5 -102.5 271.0		Complementary food ≥16 wk ref ref ref ref		Weight gain from birth to 1 year. Corrected for prepregnant BMI, primiparity, smoking during pregnancy, gestational weight gain, gestation duration, sex, birth weight, infant length.
	(Kramer et al., 2003)	Cohort	Belarus n=3,483	0-12 mo	EBF_3 EBF_6	3-6 mo ref **-28 (12, 44)**		6-9 mo ref -5 (-11, 21)		9-12 mo ref -1 (-15, 17)		Corrected for region, SES, number of siblings, birth weight, weight or height gains from birth until 3 month.
	(Kramer et al., 2002)	Intervention	Belarus n=17,046	1, 2, 3, 6, 9, 12 mo	Control Experiment	1 mo ref **61**	2 mo ref **88**	3 mo ref **106**	6 mo ref **89**	9 mo ref **58**	12 mo ref -7	Controls also give breastfeeding but less (PROBIT study). Intervention=BFHI.
	(Kramer and Kakuma, 2002)	Review/ meta-analysis	n=3,432; 3,450; 4,388	3-8 mo 6-9 mo 8-12 mo	MBF_{3-7} EBF_{3-7}	3-8 mo ref -12.5(-23.5; -1.4)		6-9 mo ref -2.3 (-16.9; 12.4)		8-12 mo ref -1.8 (-16.7-13.1)		3-8 months: four studies (n=4,388); 6-9 months two studies (n=3,432); 8-12 months three studies (n=3,450). (Effect should be treated with caution because of heterogeneity studies).
Height gain (difference in height (cm)) [a]	(Kramer et al., 2003)	Cohort	Belarus n=3,483	0-12 mo	EBF_3 EBF_6	3-8 mo ref **-1.1 (0.5- 1.6)**		6-9 mo ref -0.5 (-0.1, 1.1)		9-12 mo ref **0.9 (-1.5, -0.3)**		Corrected for region, SES, number of siblings, birth weight or height at birth, weight or height gain from birth until 3 mo.
	(Kramer et al., 2002)	Intervention	Belarus n=17,046	1, 2, 3, 6, 9, 12 mo	Control Experiment	1 mo ref 0.16	2 mo ref **0.32**	3 mo ref **0.50**	6 mo ref **0.46**	9 mo ref **0.31**	12 mo ref 0.18	Controls also give breastfeeding but less (PROBIT study). Intervention=BFHI.
	(Kramer and Kakuma, 2002)	Review/ meta-analysis	n=3,430; 3,448; 4,385	3-8 mo 6-9 mo 8-12 mo	MBF_{3-7} EBF_{3-7}	3-8 mo ref -0.4 (-0.7; 0.0)		6-9 mo ref -0.4 (-1.0; 0.1)		8-12 mo ref **0.9 (0.3-1.4)**		3-8 mo four studies (n=4,388); 6-9 mo two studies (n=3,432); 8-12 mo three studies (n=3,450).
Head circumference (difference head circumference (cm)) [a]	(Kramer et al., 2002)	Intervention	Belarus n=17,046	1, 2, 3, 6, 9, 12 mo	control Experiment	1 mo ref 0.19	2 mo ref 0.18	3 mo ref 0.18	6 mo ref 0.14	9 mo ref -0.02	12 mo ref -0.18	Controls also give breastfeeding but less (PROBIT study).
	(Kramer and Kakuma, 2002)	Review/ meta-analysis	n=3,440	6 mo 9 mo 12 mo	MBF_{3-7} EBF_{3-7}	6 mo ref -1.0 (-2.3; 0.3)		9 mo ref 0.7 (-0.6; 2.0)		12 mo ref **1.9 (0.6-3.2)**		Health effect = difference in head circumference (cm). One study (Kramer et al., 2001).

Table A1.17: Effect of breastfeeding on intellectual and motor development

Intermediary of health effect	Authors, Year of publication	Design	Study population	Age group	Breastfeeding	Effect size						Remarks
WAIS (=Wechsler Adult Intelligence Scale) [a]	(Mortensen et al., 2002)	Cohort	Denmark n=973	Mean age 27.2 yr	$BF_{\leq 1}$ BF_{2-3} BF_{4-6} BF_{7-9} $BF_{>9}$	verbal IQ 99.7 102.3 102.7 105.7 103.0(**p=0.007**)	Performance IQ 99.1 100.6 101.3 105.1 104.4 **(p=0.02)**	Full scale IQ 99.4 101.7 102.3 106.0 104.0 **(p=0.003)**				Corrected for marital state, SES, height mother, age mother, weight gain during pregnancy, smoking mother, number of pregnancies, gestational age, birth weight, birth height, complications during pregnancy, complications during childbirth, gender, use of medications.
BPP (=Børge Priens Prøve (test at draftee)) [a]	(Mortensen et al., 2002)	Cohort	Denmark n=2,280 (only men)	Mean age 27.2 yr	$BF_{\leq 1}$ BF_{2-3} BF_{4-6} BF_{7-9} $BF_{>9}$	38.0 39.2 39.9 40.1 40.1 **(p=0.01)**						Corrected for marital state, SES, height mother, age mother, weight gain during pregnancy, smoking mother, number of pregnancies, gestational age, birth weight, birth height, complications during pregnancy, complications during childbirth.
McCarthy GCI [a]	(Jacobson et al., 1999)	Cohort	USA n=321	4 yr	FF BF	OR=1 OR=1.06						Corrected for SES, IQ mother, HOME score (=breeding) Way of feeding is determined several times during the first yr of the child's life.
	(Wigg et al., 1998)	Cohort	Australia N=548	4 yr	EBF minus FF EBF minus MBF	1.3 (-2.3; 4.9) 2.8 (-4.1; 9.7)						Adjusted advantage; adjusted for gender, birth rank, parental smoking, parents living together, birth weight, maternal age, Daniel score, HOME score, maternal IQ, blood lead concentration.
	(Rogan and Gladen, 1993)	Cohort	USA n=636	5 yr	BF_{short} – FF BF_{long} – BF_{short} BF_{long} – FF	General cognitive 0.1 **4.7** **4.8**	Verbal 0.5 **2.8** **3.3**	Quantitative -0.4 **3.9** **3.5**	Memory 1.6 **3.2** **4.8**	Percept performance -0.6 2.1 1.5	Motor -0.6 1.8 1.2	BF_{short} = 0-4 weeks predominately BF and <9 wks formula. BF_{long} = 5-19 weeks BF and FF > 19 weeks or >20 weeks BF and < 49 weeks FF. Corrected for age mother, SES, smoking, alcohol consumption, gender child, birth weight, number of siblings, identity researcher.
	(Vreugdenhil et al., 2002)	Cohort	Netherlands N=372	Mean age 6.7 years	FF BF	General **100.8±12.4** **108.2±11.7 (p≤0.01)**		Memory **44.7±7.7** **48.2±7.2 (p≤0.01)**		Motor 52.06±10.5 52.3±9.2		BF: intended to breast-feed for at least 6 weeks mean±SD.
PPVT-R [a]	(Oddy et al., 2004)	Cohort	Australia n=1,450	6 yr	FF $EBF_{<4}$ EBF_{4-6} $EBF_{>6}$	105.19 (12.98) 105.55 (12.73) 107.18 (12.44) 108.67 (13.15) **(p=0.003)**						Effect measurement is mean (sd). Corrected for gestational age, age mother, SES, smoking parents, number of siblings.
	(Jacobson et al., 1999)	Cohort	USA n=321	4 yr	FF BF	OR=1 OR=1.08						Corrected for SES, IQ mother, HOME score (=breeding). Way of feeding is determined several times during the first yr of the child's life.
WISC-R (=Wechsler Intelligence Scale for children) [a]	(Oddy et al., 2004)	Cohort	Australia n=1,450	8 yr	FF $EBF_{<4}$ EBF_{4-6} $EBF_{>6}$	12.14 (3.05) 12.29 (3.12) 12.46 (3.21) 12.53 (3.34) (p=0.223)						Effect measurement is mean (sd). Corrected for gender, gestational age, age mother, SES, smoking parents, and number of siblings.

Table A1.17 continued: Effect of breastfeeding on intellectual and motor development

Intermediary of health effect	Authors, Year of publication	Design	Study population	Age group	Breastfeeding	Effect size				Remarks
WISC-R (=Wechsler Intelligence Scale for children) continued [a]	(Gustafsson et al., 2004)	Cohort	Sweden n=131	6.5 yr	BF (wk)	Verbal IQ **OR=1.23**	Performance IQ OR=1.23	Total IQ **OR=1.33**		Corrected for SES, gender, gestation week, and life events.
	(Jacobson et al., 1999)	Cohort	USA n=280	11 yr	FF BF	Verbal IQ OR=1 OR=1.07	Performance IQ OR=1 OR=1.02	Full scale IQ OR=1 OR=1.06		Corrected for SES, IQ mother, HOME score (=breeding). Way of feeding is determined several times during the first yr of the child's life.
	(Horwood and Fergusson, 1998)	Cohort	New Zeeland n=869	8 & 9 yr	FF $BF_{<4}$ BF_{4-7} $BF_{\geq 8}$	8 yr 98.7 99.7 100.6 101.5 **(p=0.005)**	9 yr 99.0 99.8 100.6 101.4 **(p=0.01)**			Corrected for age mother, SES, number of siblings, and birth weight.
	(Wigg et al., 1998)	Cohort	Australia N=494	7 & 11-13 yr	EBF minus FF EBF minus MBF	7 year 1.2 (-2.0; 4.4) 1.0 (-5.4; 7.4)	11-13 year 0.8 (-1.9; 3.5) 0.1 (-4.7; 4.9)			Adjusted advantage; adjusted for gender, birth rank, parental smoking, parents living together, birth weight, maternal age, Daniel score, HOME score, maternal IQ, blood lead concentration.
	(Horwood et al., 2001)	Cohort	New Zeeland n=280	18 mo	FF $BF_{<4}$ BF_{4-7} $BF_{\geq 8}$	Verbal IQ 96.1 98.1 100.1 102.1 **(p=<0.05)**	Performance IQ 99.6 100.8 102.1 103.3 (p>0.15)			Corrected for gender, birth weight, gestational age, age mother, SES, smoking mother, ethnicity, number of siblings. BF determined at 18 mo. Very low birth weight.
Woodcock [a]	(Jacobson et al., 1999)	Cohort	USA n=277	11 yr	FF BF	Word comprehension OR=1 OR=1.02	Passage comprehension OR=1 OR=1.05	Reading comprehension OR=1 OR=1.04		Corrected for SES, IQ mother, HOME score (=breeding). Way of feeding is determined several times during the first yr of the child's life.
BAS (= British Ability Scales) [a]	(Pollock, 1994)	Case-cohort	United Kingdom n=3,738	10 yr	$FF_{\geq 3}$ $EBF_{\geq 3}$	Total OR=1 OR=1.64	Picture language OR=1 OR=1.49	Word definition OR=1 OR=1.55	Similarities OR=1 OR=1.64	Corrected.
Bayley [a]	(Gomez-Sanchiz et al., 2004)	Cohort	Spain N=238	24 mo	$BF_{\leq 4\ mo}$ minus FF $BF_{>4mo}$ minus $BF_{>4mo}$	Mental development 3.8 (-0.7to 8.3) 3.7 (-0.5 to 7.9)	Psychomotor development **4.3 (0.2 to 8.6)** 2.9 (-1.2 to7.1)			Corrected for living area, smoking mother, SES, education father/mother, number of siblings, mother working outside home, age mother, IQ mothere/father.
	(Wigg et al., 1998)	Cohort	Australia N=601	2 yr	EBF minus FF EBF minus MBF	3.4 (-0.1;6.9) 4.2 (-2.6;11.0)				Adjusted advantage; adjusted for gender, birth rank, parental smoking, parents living together, birth weight, maternal age, Daniel score, HOME score, maternal IQ, blood lead concentration.

Table A1.17 continued: Effect of breastfeeding on intellectual and motor development

Intermediary of health effect	Authors, Year of publication	Design	Study population	Age group	Breastfeeding	Effect size				Remarks
Bayley continued [a]	(Florey et al., 1995)	Cohort	Scotland n=592	18 mo	BF minus FF	Discharge hospital **-3.7 (-6.9;-0.5)**	Health visitor **-5.7 (-9.2;-2.2)**			Health effect = regression coefficient. Corrected for SES, gestational age and gender. Bayley scales of infant Mental and Motor Development.
	(Rogan and Gladen, 1993)	Cohort	USA n=636	6 mo 12 mo 18 mo 24 mo	Mental BF_{short} minus FF BF_{long} minus BF_{short} BF_{long} minus FF Psychomotor BF_{short} minus FF BF_{long} minus BF_{short} BF_{long} minus FF	6 mo -0.6(-4.5;3.2) 3.4 (-0.1;6.9) 2.8 (-0.8;6.3) -0.5(-4.4;3.5) 2.5 (-1.1;6.0) 2.0 (-1.7;5.7)	12 mo -2.5(-6.8;1.7) 3.4(-0.4;7.1) 0.8(-3.0;4.6) -0.6(-5.3;4.1) 2.2(-1.9;6.4) 1.6(-2.6;5.9)	18 mo -0.8(-5.7;4.2) **4.4 (0.0-8.9)** 3.7 (-0.8;8.1) 1.8 (-3.1;6.6) 3.5 (-0.9;7.9) **5.3 (0.9;9.6)**	24 mo -1.2(-7.1;4.8) **6.7(1.4-12.1)** **5.6(0.2-11.0)** 1.8 (-3.9;7.5) 4.1 (-1.0;9.3) **5.9(0.8;11.1)**	BF_{short} = 0-4 wk predominately BF and < 9 wk formula. BF_{long} = 5-19 wk BF and FF after 19 wk or >20 wk BF and < 49 wk FF. Corrected for age mother, SES, smoking, alcohol consumption, gender child, birth weight, number of siblings, and identity researcher.
	(Koopman-Esseboom et al., 1996)	Cohort	Netherlands n=207	3, 7, 18 mo	Mental FF BF Psychomotor FF BF	3 months 126±13 128±13 (p=.21) 117±12 118±12 (p=.92)	7 months **112±9** **115±11 (p=.03)** **111±13** **115±15 (p=.05)**	18 months **107±17** **113±18 (p=.01)** 108±14 110±17 (p=.17)		BF: intended to breast-feed for at least 6 weeks. mean±SD.
K-ABC (Kaufman Assessment Battery for Children (Dutch version)	(Patandin et al., 1999)	Cohort	Netherlands N=373	42 mo	FF BF	Cognitive scale **108±15** **114±12** **(p<0.01)**	Seq proc scale **107±14** **111±13** **(p<0.01)**	Sim proc scale **106±14** **112±11** **(p<0.01)**		BF: intended to breast-feed for at least 6 weeks. mean±SD.
RDLS (Reynell Developmental Language Scales)	(Patandin et al., 1999)	Cohort	Netherlands N=190	42 mo	FF BF	Verbal comprehension scale **101±12** **108±11 (p<0.01)**				BF: intended to breast-feed for at least 6 weeks. mean±SD.
Rey compex figure test	(Vreugdenhil et al., 2004)	Cohort	Netherlands N=83	9 year	BF_{short} – FF BF_{long} – BF_{short} BF_{long} – FF	Rey copy -0.26±1.45 0.46±1.65 0.20±1.45	Rey recall 1.53±1.64 0.25±1.87 1.77±1.64	Rey copy strat. **-0.27±0.12** 0.01±0.14 **-0.25±0.12**		B±SE. Correction for alcohol use during pregnancy, gestational age, sex, parity, parental education level, parental verbal IQ, age at assessment.
SRTT	(Vreugdenhil et al., 2004)	Cohort	Netherlands N=83	9 year	BF_{short} – FF BF_{long} – BF_{short} BF_{long} – FF	SRTT-RT 18.88±13.79 1.53±15.70 20.42±14.03	SRTT-SD 2.48±7.31 -9.44±8.33 -6.95±7.44			B±SE. Correction for alcohol use during pregnancy, gestational age, sex, parity, parental education level, parental verbal IQ, age at assessment.
Auditory-verbal learning test (AVLT)	(Vreugdenhil et al., 2004)	Cohort	Netherlands N=83	9 year	BF_{short} – FF BF_{long} – BF_{short} BF_{long} – FF	AVLT short -2.02±2.35 0.96±2.68 -1.05±2.36	AVLT long -0.89±0.66 1.06±0.76 0.17±0.66			B±SE. Correction for alcohol use during pregnancy, gestational age, sex, parity, parental education level, parental verbal IQ, age at assessment.

Table A1.17 continued: Effect of breastfeeding on intellectual and motor development

Intermediary of health effect	Authors, Year of publication	Design	Study population	Age group	Breastfeeding	Effect size					Remarks
Tower of London (TOL)	(Vreugdenhil et al., 2004)	Cohort	Netherlands N=83	9 year	$BF_{short} - FF$ $BF_{long} - BF_{short}$ $BF_{long} - FF$	-0.39±0.72 -1.42±0.82 **-1.81±0.73**					B±SE. Correction for alcohol use during pregnancy, gestational age, sex, parity, parental education level, parental verbal IQ, age at assessment.
Cognitive development score [a]	(Pollock, 1994)	Case-cohort	United Kingdom n=3,738	5 yr	$FF_{\geq 3}$ $EBF_{\geq 3}$	OR=1 OR=1.5					Corrected.
	(Anderson et al., 1999)	Meta analysis			BF minus FF	total **2,89 (2.41-3.37)**	6-23 mo **3.11 (1.52-4.39)**	2-5 yr **2.53 (1.86-3.20)**	6-9 yr **3.01 (1.99-4.03)**	10-15 yr **3.19 (1.89-4.48)**	Weighted mean difference in cognitive development. Corrected for confounders. Seven studies including (Morrow-Tlucak et al., 1988).
	(Golding et al., 1997d)	Meta analysis			BF versus FF	Six studies find higher IQ and development tests scores for breastfed children Four studies find no significant differences					Ten studies including (Lucas et al., 1992) and (Pollock, 1994).
Icelandic developmental inventory [a]	(Thorsdottir et al., 2005)	Cohort	Iceland n=85	6 yr	EBF (mo)	Learning -0.4	Motor 0.9	Verbal -0.2	Total 0.4		Effect measurement is the regression coefficient. Corrected for BMI mother, birth weight, education mother and father, income and gender.
Development milestones [a]	(Vestergaard et al., 1999)	Cohort	Denmark n=1,656	8 mo	EBF_{0-1} EBF_{2-3} EBF_{4-5} $EBF_{\geq 6}$	Crawling OR=1 OR=0.7 (0.5-1.1) OR=1.2 (0.8-1.7) OR=1.4 (0.9-2.1)	Pincer grip OR=1 OR=1.1(0.7-1.8) **OR=1.4(1.0-2.1)** **OR=2.2(1.3-3.7)**	Polysyllable babblers OR=1 OR=1.1 (0.8-1.7) **OR=1.6 (1.1-2.3)** **OR=2.5 (1.6-3.9)**			

Table A1.18: Effect of breastfeeding on sudden infant death syndrome

Intermediary of health effect	Authors, Year of publication	Design	Study population	Age group	Breastfeeding	Effect size			Remarks
Sudden infant death syndrome [a]	(Alm et al., 2002) [c]	Case-control	Scandinavia 239 cases 841 controls	?	EBF_{0-3wk} EBF_{4-7wk} EBF_{8-11wk} $EBF_{12-15wk}$ $EBF_{\geq 16wk}$ MBF_{0-3wk} MBF_{4-7wk} MBF_{8-11wk} $MBF_{12-15wk}$ $MBF_{\geq 16wk}$	**OR=5.1 (2.3-11.2)** **OR=3.7 (1.6-8.4)** OR=1.6 (0.7-3.6) **OR=2.8 (1.2-6.8)** OR=1 **OR=4.6 (1.9-11.1)** OR=2.3 (1.0-5.4) OR=1.0 (0.4-2.2) OR=1.6 (0.7-3.9) OR=1			Cases and controls matched on sex, age, maternity ward. Adjusted for smoking during pregnancy, paternal employment, sleeping position, age infant.
	(Gilbert et al., 1995) [c]	Case-control	UK 98 cases 190 controls	1wk-1yr	FF MBF EBF	OR=1.8 (0.7-4.8) OR=1.2 (0.5-2.7) OR=1			Cases and controls matched on age and time visit health visitor. Adjusted for sleeping position, maternal smoking, gestation, employment status.
	(Ford et al., 1993) [c]	Case-control	New-Zeeland 485 Cases 1,800 Controls	0-12 mo		Discharge hospital	1st 4 weeks	Last 2 days	Corrected for age, region, season, SES, age mother, number of pregnancies, gender, ethnicity, birth weight, smoking mother, sleeping position, and child shared bed with others.
					FF	OR=1	OR=1	OR=1	
					MBF	OR=1.10 (0.59-2.07)	OR=0.95 (0.58-1.55)	OR=0.96 (0.65-1.44)	
					EBF	**OR=0.52 (0.35-0.77)**	OR=0.69 (0.43-1.11)	OR=0.65 (0.46-0.91)	
	(Kramer and Kakuma, 2002) [c]	Review/ meta-analysis	n=3,483	0-12 mo	MBF_{3-7} EBF_{3-7}	RR=1 RR=2.30 (0.21-25.37)			
	(McVea et al., 2000) [c]	Meta-analysis	23 studies		BF FF	OR=1.00 **OR=2.11 (1.66-2.68)**			Clear statements about why which articles were included. They question the correction for confounders (perhaps BF is a marker for other factor(s) which could be responsible for the sudden death syndrome.

Table A1.19: Effect of breastfeeding on hospitalization

Intermediary of health effect	Authors, Year of publication	Design	Study population	Age group	Breastfeeding	Effect size			Remarks
Hospitalisation [a]	(Paricio Talayero et al., 2006)	Cohort	Spain N=1385	0-12 mo	FF $BF_{<4\ mo}$ $BF_{\geq 4\ mo}$	**OR=4.91 (2.41-9.99)** **OR=2.45 (1.28-4.66)** OR=1			Adjusted for siblings, gender, birth weight, prematurity, smoking mother, birth at public hospital. Hospitalization due to infectious disease.
	(Pardo-Crespo et al., 2004)	Case-control	Spain 336 Cases 336 Controls	1-24 mo 1-6 mo 7-24 mo		1-24 mo	1-6 mo	7-24 mo	Corrected for SES, smoking, and incubator after delivery.
					FF	OR=1	1	1	
					BF	OR=1.14 (0.72-1.79)	0.90(0.50-1.63)	1.60(0.77-3.34)	
					$BF_{1\text{-}45\ days}$	OR=1.63 (0.97-2.76)	1.19(0.62-2.27)	**2.79(1.11-7.01)**	
					$BF_{46\text{-}90\ days}$	OR=0.86 (0.49-1.49)	0.61(0.28-1.34)	1.29(0.56-2.94)	
					$BF_{91\text{-}180\ days\ (\geq 91\ days)}$	OR=0.80 (0.44-1.45)	0.46(0.18-1.19)	1.44(0.67-3.36)	
					$BF_{\geq 181\ days}$	OR=1.06 (0.44-2.55)		1.60(0.55-4.70)	

Motivation for not including the results of a study in the model.
a: disease not modelled
c: duration of breast feeding unclear or reference duration not zero (FF)
d: endpoint measure not consistent e.g. OR instead of RR or disease at a different age.
e: relevant original studies of review incorporated
f: no adjustment for confounders

Appendix 2 Health effects mother

Meaning of the footnotes in the next tables:

Motivation for not including the results of a study in the model.
a: disease not modelled
b: not a consistent study design
c: duration of breast feeding unclear or reference duration not zero (FF)
d: endpoint measure not consistent e.g. RR instead of OR or disease at age 4 instead of 1
e: relevant original studies of Review incorporated

Table A2.1: Effect of breastfeeding on breast cancer risk

Intermediary of health effect	Author Year of publication	Design	Study population	Age group	Breastfeeding	Effect size			Remarks
Combined pre- and post-menopausal breast cancer [a]	(London et al., 1990)	Cohort	United States of America n=89,413 (1,262 cases)	40-65 yr	EFF $BF_{<7}$ BF_{7-11} BF_{12-23} $BF_{\geq 24}$	RR=1 RR=0.94 (0.82-1.06) RR=0.83 (0.67-1.03) RR=0.90 (0.74-1.09) RR=0.95 (0.73-1.23) (p-trend: 0.20)			Correction for age, number of children, age first birth, age menarche, family history, benign breast disorder history, oral contraceptive, menopausal status.
	(Meeske et al., 2004)	Case-control	United States of America 412 Cases 507 Controls	35-64 yr	Life-long BF EFF $EBF_{<3}$ EBF_{4-9} EBF_{10-14} $EBF_{\geq 15}$ EBF (mo) $BF_{<3}$ BF_{4-9} BF_{10-14} BF_{15-23} $BF_{\geq 24}$ BF (mo)	 OR=1 OR=1.02 (0.73-1.43) OR=1.30 (0.86-1.95) OR=1.62 (0.56-3.07) OR=1.71 (0.79-3.67) **(p-trend:0.03)** **OR=1.032 (1.00-1.06)** OR=1.01 (0.69-1.49) OR=1.05 (0.69-1.58) OR=1.36 (0.82-2.28) OR=1.16 (0.64-2.12) **OR=2.00 (1.11-3.60) (p-trend:0.04)** **OR=1.014 (1.00-1.03)**			Correction for: age, ethnicity, family history, BMI, number of children, age first birth.
	(Zheng et al., 2001)	Case-control	United States of America 522 Cases 511 Controls	30-80 yr	EFF BF BF_{1-6} BF_{7-12} BF_{13}	OR=1 OR=0.83 (0.63-1.09) OR=0.86 (0.61-1.21) OR=0.82 (0.52-1.29) OR=0.78 (0.53-1.14) (p-trend: 0.16)			Correction for age, age first birth, number children, fat intake (g/day), SES, ethnicity, family history cancer, study location, menopausal status.
	(Tryggvadottir et al., 2001)	Case-control	Iceland 993 Cases 9,729 Controls	26-90 yr	Life-long BF $BF_{0-4\ wks}$ $BF_{5-26\ wks}$ $BF_{27-52\ wks}$ $BF_{53-104\ wks}$ $BF_{\geq 105\ wks}$ EFF BF	 OR=1 **OR=0.67(0.51-0.89)** OR=0.79(0.59-1.05) **OR=0.70(0.51-0.97)** **OR=0.48(0.31-0.74)** *40 yr (84 Cases)* OR=1 **OR=0.09 (0.02-0.45)**	 *40-55yr (399 c)* OR=1 OR=0.51 (0.20-1.30)	 *>55yr (510 c)* OR=1 **OR=0.32 (0.15-0.66)**	Correction for age menarche, age first birth, number children, oral contraceptive, height, weight.
	(Chang-Claude et al., 2000)	Case-control family study	Germany 706 Cases 1,381 Controls	< 50 yr	FF BF Life-long BF BF_{1-6} BF_{7-12} BF_{13-24} $BF_{\geq 25}$	OR=1 OR=0.9 (0.8-1.2) OR=1.1 (0.8-1.30 OR=0.9 (0.6-1.2) **OR=0.6 (0.4-0.9)** OR=0.5 (0.3-1.1) **(p-trend 0.01)**			Correction for full term pregnancies, age menarche, family history. Other possible confounders had no effect on the estimates.

Table A2.1 continued: Effect of breastfeeding on breast cancer risk

Intermediary of health effect	Author Year of publication	Design	Study population	Age group	Breastfeeding	Effect size	Remarks
Combined pre- and post-menopausal breast cancer continued [a]	(Furberg et al., 1999)	Case-control	United States of America 751 Cases 743 Controls	20-74 yr	EFF BF Life-long BF BF_{1-3} BF_{4-12} $BF_{\geq 13}$	OR=1 **OR=0.7 (0.5-0.8)** **OR=0.7 (0.5-0.9)** **OR=0.6 (0.4-0.9)** OR=0.8 (0.5-1.1)	Correction for age, ethnicity, family history, BMI, number of children, age first birth, family history, menopausal status.
	(Negri et al., 1996)	Case-control	Italy 2,167 Cases 2,208 Controls	20-74 yr	EFF BF Life-long BF BF_{1-5} BF_{6-11} BF_{12-17} BF_{18-23} $BF_{\geq 24}$	OR=1 OR=1.17 (1.0-1.3) OR=1.19 (1.0-1.4) OR=1.15 (1.0-1.4) **OR=1.34 (1.1-1.7)** OR=1.10 (0.8-1.5) OR=0.86 (0.5-1.3) (p-trend>0.05)	Correction for age, study location, SES, , number children, menopausal status, age menopause, age 1[e] birth, family history, benign breast disorder, BMI, marital status.
	(Katsouyanni et al., 1996)	Case-control	Greece 657 Cases 1,164 Controls	Mean age 55 yr	EFF BF Life-long BF $BF_{<3}$ BF_{3-11} BF_{12-23} $BF_{\geq 24}$	OR=1 OR=0.93 (0.67-1.27) OR=0.91 (0.63-1.32) OR=1.00 (0.71-1.42) OR=1.06 (0.70-1.61) **OR=0.64 (0.41-0.99)**	Correction for BMI, number children, age menarche, menopausal status, age menopause, age first birth, daily energy intake, benign breast disorder history, family history, intake vegetables, fruits, olive oil, alcohol, abortion, menopausal oestrogen use.
	(Lipworth et al., 2000)	Review	Medline 1966-1998		Ever vs. never Nr children breastfed Life-long BF Mean duration of breastfeeding	Overall, the evidence with respect to "ever" breastfeeding remains inconclusive, with results indicating either no association or a rather weak protective effect against breast cancer 2 studies found a protective dose-response relation; 4 studies did not 10 'western' studies; no effect; in non-western countries indication protective effect	Only studies with over 200 cases, and correction for number of pregnancies and age first pregnancy. No pooled risk estimation.
	(Bernier et al., 2000)	Meta-analysis	Medline & Embase 1980-1998		EFF BF BF_{0-6} BF_{6-12} $BF_{>12}$	OR=1 **OR=0.84 (0.74-0.96)** OR=1.00 (0.85-1.17) OR=0.97 (0.85-1.10) **OR=0.72 (0.65-0.83)**	23 case control studies; also in China, Costa Rica, Mexico, also including FBB109, 130, 108, 129). Only the 12 studies given who correct for confounders.

Table A2.1 continued: Effect of breastfeeding on breast cancer risk

Intermediary of health effect	Author Year of publication	Design	Study population	Age group	Breastfeeding	Effect size	Remarks
Premenopausal	(London et al., 1990) [d]	Cohort	United States of America n=89,413 (624 cases)	40-65 yr	EFF $BF_{<7}$ BF_{7-11} BF_{12-23} $BF_{\geq 24}$	RR=1 RR=1.00 (0.83-1.20) RR=0.85 (0.63-1.14) RR=0.90 (0.69-1.18) RR=1.06 (0.75-1.50) (p-trend: 0.59)	Correction for age, nr children, age first delivery, age menarche, family history, benign breast conditions, contraception. BF retrospectively collected, other data prospectively.
	(Ma et al., 2006)	Case-control	United States of America 1161 Cases 315 Controls	20-49 yr	FF $BF_{<1}$ BF_{1-6} BF_{7-23} $BF_{\geq 24}$	OR=1 OR=0.99 (0.56-1.77) **OR=0.58 (0.37-0.91)** **OR=0.52 (0.33-0.82)** **OR=0.51 (0.30-0.86) (p trend:0.001)**	Adjusted for race, age, education, family history, age menarche, full term pregnancies, BMI, COC use, alcohol consumption.
	(Zheng et al., 2001)	Case-control	United States of America 522 Cases 511 Controls	30-80 yr	EFF BF BF_{1-6} BF_{7-12} $BF_{>13}$	OR=1 OR=0.73 (0.40-1.31) OR=0.77 (0.36-1.63) OR=0.69 (0.30-1.60) OR=0.74 (0.36-1.52) (p-trend: 0.39)	Correction for age, age first delivery, nr children, fat intake (g/d), SES, ethnicity, family history cancer, study location.
	(Furberg et al., 1999)	Case-control	United States of America 425 Cases 371 Controls	20-49 yr	EFF BF Life-long BF BF_{1-3} BF_{4-12} $BF_{\geq 13}$	OR=1 OR=0.8 (0.5-1.1) OR=0.8 (0.5-1.3) OR=0.7 (0.4-1.1) OR=0.8 (0.4-1.4)	Correction for age, ethnicity, nr children, age first delivery, family history, BMI, menopausal status.
	(Stuver et al., 1997)	Case-control	Wales, United States of America 1,142 Cases 3.529 Controls	± 41 yr	Life-long BF EFF BF BF_{1-6} BF_{7-12} BF_{13-24} BF_{25-36} $BF_{\geq 37}$	 OR=1 OR=1.16 (0.81-1.66) OR=1.10 (0.72-1.69) OR=0.99 (0.56-1.75) OR=1.71 (0.97-3.04) OR=0.94 (0.30-2.94) OR=0.78 (0.08-7.15)	Correction for age, number of children, age first delivery, age menarche, (age menopause), BMI, SES, study centre. Data divided in a high (United States of America and Wales) mean risk (Greece, Slovenia, Brazil) and low risk (Japan, Taiwan) area. Only results for high risk area presented.
	(Enger et al., 1997) [d]	Case-control	United States of America 452 Cases 452 Controls	<40 yr	Life-long BF EFF BF_{1-6} BF_{7-15} $BF_{\geq 16}$	Age 1[e] time BF<25 yr OR=1 OR=1.34 (0.83-2.16) OR=1.23 (0.72-2.11) OR=0.76 (0.41-1.39) (p-trend:0.14)	Age 1[e] time BF≥25 yr OR=1 OR=1.03 (0.67-1.58) OR=0.66 (0.40-1.08) **OR=0.55 (0.31-0.97)** **(p-trend:0.04)**	Correction for age menarche, family history breast cancer, total month contraception use, ethnicity, alcohol intake, physical activity.
	(Negri et al., 1996)	Case-control	Italy 847 Cases 695 Controls	?	EFF BF_{1-5} BF_{6-11} BF_{12-17} $BF_{\geq 18}$	OR=1 OR=1.10 (0.8-1.4) OR=1.17 (0.9-1.6) OR=1.15 (0.8-1.7) OR=1.11 (0.6-2.0) (non sign trend)	Correction for age, centre, SES, number of children. (Other variables had no influence on the results).

Table A2.1 continued: Effect of breastfeeding on breast cancer risk

Intermediary of health effect	Author Year of publication	Design	Study population	Age group	Breastfeeding	Effect size	Remarks
Premenopausal continued	(Katsouyanni et al., 1996)	Case-control	Greece 270 Cases 505 Controls	?	EFF BF Life-long BF $BF_{<3}$ BF_{3-11} BF_{12-23} $BF_{\geq 24}$	OR=1 OR=0.68 (0.43-1.09) OR=0.58 (0.34-0.98) OR=1.01 (0.61-1.67) OR=0.70 (0.34-1.60) OR=0.50 (0.23-1.41)	Correction for BMI, number of children, age menarche, menopausal status, age menopause, age first delivery, daily energy intake, benign breast history , family history, intake vegetables, fruit, olive oil, alcohol, abortion, menopausal oestrogen use.
	(Brinton et al., 1995)	Case-control	United States of America 433 Cases 371 Controls	<45 yr	EFF $EBF_{<4}$ EBF_{4-7} EBF_{8-11} $EBF_{\geq 12}$ $BF_{<6}$ BF_{6-11} BF_{12-17} $BF_{\geq 18}$	OR=1 OR=0.91 (0.7-1.1) OR=0.89 (0.7-1.2) OR=1.02 (0.7-1.4) OR=0.76 (0.5-1.1) OR=0.97 (0.8-1.2) OR=0.90 (0.7-1.2) OR=0.79 (0.6-1.1) OR=0.88 (0.7-1.2)	Correction for research centre, age, ethnicity, number of children, age first delivery, years of use contraceptives.
	(Newcomb et al., 1994)	Case-control	United States of America 1,180 Cases 2,185 Controls	?	EFF BF Life-long BF $BF_{\leq 3}$ BF_{4-12} BF_{13-24} $BF_{>24}$	OR=1 **OR=0.78 (0.66-0.91)** OR=0.85 (0.69-1.06) **OR=0.78 (0.63-0.97)** **OR=0.66 (0.50-0.87)** **OR=0.72 (0.51-0.99) (p-trend:<0.001)**	Correction for age menarche, age first delivery, number of children, family history, BMI.
	(United Kingdom National Case-Control Study Group, 1993)	Case-control	United Kingdom 755 cases 755 controls	<36 yr	Life-long BF EFF BF_{1-3} BF_{4-9} BF_{10-15} BF_{16-21} $BF_{\geq 22}$ BF (3 mo)	 OR=1 OR=0.83 OR=0.77 OR=0.53 OR=0.68 OR=0.63 **(p-trend 0.026)** **OR=0.94 (0.89-0.99)**	Correction for number of children, age menarche, family history, benign breast disorders, age first delivery, total duration of oral contraceptive use. Assumption that women below the age of 36 are premenopausal.
	(Bernier et al., 2000) c	Meta-analysis	Medline & Embase 1980-1998		EFF BF	OR=1 **OR=0.76 (0.66-0.87)**	23 Case-Control studies; also in China, Costa Rica, Mexico, also including FBB109, 130, 108, 129). Only the 12 studies given who correct for confounders.

Table A2.1 continued: Effect of breastfeeding on breast cancer risk

Intermediary of health effect	Author Year of publication	Design	Study population	Age group	Breastfeeding	Effect size	Remarks
Post-menopausal	(Zheng et al., 2001)	Case-control	United States of America 522 Cases 511 Controls (all women)	30-80 yr (all women)	EFF BF BF_{1-6} BF_{7-12} BF_{13}	OR=1 OR=0.91 (0.66-1.26) OR=0.89 (0.60-1.33) OR=1.03 (0.57-1.85) OR=0.88 (0.54-1.41) (p-trend: 0.61)	Correction for age, age first delivery, number of children, fat intake (g/d), SES, ethnicity, family history cancer, study centre.
	(London et al., 1990) d	Cohort	United States of America n=89,413 (511 Cases)	40-65 yr (all women)	EFF $BF_{<7}$ BF_{7-11} BF_{12-23} $BF_{\geq 24}$	RR=1 RR=0.99 (0.82-1.21) RR=0.93 (0.66-1.31) RR=0.96 (0.70-1.33) RR=0.87 (0.55-1.39) (p-trend: 0.55)	Correction for age, number of children, age first delivery, age menarche, family history, benign breast disorders, use contraceptives, years since menopause. BF collected retrospectively, other variables prospectively.
	(Furberg et al., 1999)	Case-control	United States of America 326 Cases 372 Controls	50-74 yr	EFF BF Life-long BF BF_{1-3} BF_{4-12} $BF_{\geq 13}$	OR=1 **OR=0.7 (0.5-0.9)** **OR=0.6 (0.4-0.9)** OR=0.6 (0.4-1.0) OR=0.9 (0.5-1.4)	Correction for age, ethnicity, number of children, age first delivery, family history, BMI. Selection pre/post menopausal made according to age.
	(Stuver et al., 1997)	Case-control	Wales, United States of America 1,692 Cases 5,508 Controls	± 60 yr	Life-long BF EFF BF BF_{1-6} BF_{7-12} BF_{13-24} BF_{25-36} $BF_{\geq 37}$	 OR=1 OR=1.10 (0.87-1.38) OR=1.06 (0.81-1.40) OR=1.11 (0.82-1.50) OR=1.03 (0.73-1.46) OR=1.27 (0.81-2.00) OR=1.55 (0.92-2.60)	Correction for age, number of children, age first delivery, age menarche, (age menopause), BMI, SES, study centre. Data divided in a high (United States of America and Wales) mean risk (Greece, Slovenia, Brazil) and low risk (Japan, Taiwan) area. Only results for high risk area presented.
	(Negri et al., 1996)	Case-control	Italy 1,318 Cases 1,513 Controls		EFF BF_{1-5} BF_{6-11} BF_{12-17} $BF_{\geq 18}$	OR=1 OR=1.21 (1.0-1.5) OR=1.06 (0.9-1.3) OR=1.32 (1.0-1.7) OR=0.92 (0.7-1.3) (non sign trend)	Correction for age, centre, SES, number of children (other factors had no influence on the outcome).
	(Katsouyanni et al., 1996)	Case-control	Greece 550 Cases 1,041 Controls		EFF BF Life-long BF $BF_{<3}$ BF_{3-11} BF_{12-23} $BF_{\geq 24}$	OR=1 OR=1.18 (0.74-1.88) OR=1.48 (0.85-2.56) OR=1.00 (0.64-1.77) OR=1.32 (0.77-2.27) OR=0.79 (0.45-1.39)	Correction for BMI, number of children, age menarche, menopausal status, age menopause, age first delivery, daily energy intake, history benign breast disorders, family history, intake vegetables, fruit, olive oil, alcohol, abortion, menopausal oestrogen use.

Table A2.1 continued: Effect of breastfeeding on breast cancer risk

Intermediary of health effect	Author Year of publication	Design	Study population	Age group	Breastfeeding	Effect size		Remarks
	(Newcomb et al., 1999)	Case-control	United States of America 3,633 Cases 3,790 Controls	50-79 yr	EFF BF Life-long BF $BF_{<3}$ BF_{3-6} BF_{7-12} BF_{13-23} $BF_{\geq 24}$ BF (3 mo)	OR=1 **OR=0.87 (0.78-0.96)** OR=0.89 (0.78-1.02) **OR=0.77 (0.64-0.93)** OR=1.06 (0.87-1.28) OR=0.81 (0.63-1.04) **OR=0.73 (0.56-0.94)** OR=0.99 (0.97-1.00)		Correction for study centre, number of children, age first delivery, family history, age menopause, BMI, SES.
	(Newcomb et al., 1994) [d]	Case-control	United States of America 4,254 Cases 5,378 Controls	?	EFF BF Life-long BF $BF_{\leq 3}$ BF_{4-12} BF_{13-24} $BF_{>24}$	RR=1 RR=1.04 (0.95-1.14) RR=1.03 (0.93-1.14) RR=1.07 (0.94-1.22) RR=1.01 (0.83-1.21) RR=1.04 (0.82-1.32) (p-trend 0.51)		Correction for age menarche, age first delivery, number of children, family history, BMI, age menopause.
BRCA1 of BRCA2 mutation carriers [a]	(Jernstrom et al., 2004)	Case-control	Canada, Israel, Poland, United Kingdom, Sweden, United States of America 965 Cases 965 Controls	18-71 yr	EFF $BF_{\leq 12}$ $BF_{>12}$ BF (mo)	BRCA1 mutation (n=685) OR=1 OR=0.89 (0.68-1.17) **OR=0.55 (0.38-0.80)** **OR=0.98 (0.97-0.99)**	BRCA2 mutation (n=280) OR=1 OR=1.12 (0.73-1.71) OR=0.95 (0.56-1.59) OR=0.99 (0.98-1.01)	Matched on birth year, age first delivery, age last delivery, smoking during breastfeeding. Correction for contraception use and number of children BRCA1 mutation: 30% Canada, 7% Israel, 17% Poland, 1% UK, 2% Sweden, 43% USA. BRCA2 mutation: 47% Canada, 8% Israel, 0% Poland, 1% UK, 1% Sweden, 43% USA.

Table A2.2: Effect of breastfeeding on cervical cancer risk

Intermediary of health effect	Author Yr of publication	Design	Study population	Age group	Breastfeeding	Effect size	Remarks
Cervical cancer [a]	(Newcomb and Trentham-Dietz, 2000)	Case-control	United States of America 586 Cases 2,408 Controls	40-79 yr	EFF BF Life-long BF BF_{1-5} BF_{6-11} BF_{12-23} $BF_{\geq 24}$	RR=1 RR=0.90 (0.72-1.1) RR=0.95 (0.74-1.2) RR=1.0 (0.70-1.5) RR=0.65 (0.42-1.0) RR=0.84 (0.52-1.4) (trend=0.4)	Correction for age, smoke status, SES, BMI, post-menopausal hormone use, number of children.
Glioma	(Huang et al., 2004)	Case-control	United States of America 191 Cases 498 Controls	18-80 yr	FF BF Life-long BF BF_{1-3} BF_{4-8} BF_{918} $BF_{>18}$	OR=1 OR=1.05 (0.73-1.50) **OR=0.47 (0.24-0.90)** OR=0.75 (0.40-1.43) OR=1.37 (0.81-2.31) **OR=1.81 (1.03-3.20) p-trend:0.006**	Correction for age, age*age, menopausal status, age*menopausal status. Risk estimates for women instead of mothers.

Table A2.3: Effect of breastfeeding on ovarian cancer risk

Intermediary of health effect	Author Yr of publication	Design	Study population	Age group	Breastfeeding	Effect size			Remarks
Ovarian cancer	(Chiaffarino et al., 2005)	Case-control	Italy 1031 Cases 2411 Controls	17-79 yr			Serous cancers	Mucinous	Adjusted for age, study centre, education, parity, oral contraceptive use, first degree family history ovarian/breast cancer: 492 serous cancers; 82 mucinous cancers.
					FF	OR=1	OR=1	OR=1	
					BF	OR=1.16 (0.93-1.43)	OR=1.12 (0.85-1.48)	OR=1.59	
					BF_{1-4}	OR=1.20 (0.91-1.59)	OR=1.29 (0.90-1.85)	(0.82-3.07)	
					BF_{5-8}	OR=1.24 (0.95-1.62)	OR=1.16 (0.81-1.65)		
					BF_{9-16}	OR=1.01 (0.77-1.33)	OR=1.06 (0.74-1.51)		
					$BF_{\geq 17}$	OR=1.21 (0.85-1.71)	OR=0.87 (0.55-1.39)		
	(Riman et al., 2002)	Case-control	Sweden 459 Cases 2,637 Controls	50-74 yr	$BF_{<1}$	OR=1			Correction for age, number of children, BMI, age menopause, duration of contraception use, ever use of hormone replacement therapy.
					BF_{1-5}	OR=0.99 (0.64-1.52)			
					BF_{6-11}	OR=0.77 (0.50-1.19)			
					$BF_{\geq 12}$	OR=0.87 (0.56-1.35)			
	(Greggi et al., 2000)	Case-control	Italy 330 Cases 721 Controls	13-80 yr	EFF	OR=1			Correction for age, SES, number of children, contraception use and duration, family history, spontaneous abortion, abortion, age first delivery. Risk estimates for women instead of mothers (1 case is 13 year?!?).
					$BF_{\leq 12}$	OR=0.8 (0.5-1.1)			
					$BF_{>12}$	**OR=0.5 (0.4-0.8)**			
	(Siskind et al., 1997)	Case-control	Australia 619 Cases 724 Controls	18-79 yr	Life-long EBF		Pre-menopause	Postmenopausal	Correction for number of children, age, use contraceptives, SES, history of smoking, (menopause status).
					EFF	OR=1	OR=1	OR=1	
					EBF_{1-6}	OR=0.89 (0.65-1.21)	OR=0.75 (0.46-1.21)	OR=0.98 (0.65-1.47)	
					EBF_{7-12}	**OR=0.68 (0.49-0.94)**	**OR=0.53 (0.31-0.94)**	OR=0.83 (0.54-1.26)	
					EBF_{13-24}	OR=0.84 (0.59-1.20)	OR=1.03 (0.54-1.95)	OR=0.88 (0.56-1.38)	
					EBF_{24-36}	OR=0.69 (0.38-1.27)	OR=0.29 (0.08-1.04)	OR=0.93 (0.46-1.88)	
					$EBF_{>24}$	OR=0.77 (0.34-1.75)		OR=1.27 (0.50-3.2)	
					$EBF_{>36}$				
	(Whittemore et al., 1992)	Case-control	United States of America 870 Cases 4,624 Controls	25-80	FF	OR=1			Correction for age, study parity, oral contraceptive use.
					BF	OR=0.81 (0.68-0.95)			
					BF_{1-5}	OR=0.87 (0.72-1.1)			
					BF_{6-11}	**OR=0.74 (0.57-0.96)**			
					BF_{12-23}	**OR=0.69 (0.51-0.94)**			
					$BF_{\geq 24}$	OR=0.74 (0.49-1.1)			
	(Gwinn et al., 1990)	Case-control	United States of America 321 Cases 3,312 Controls	20-54 yr	FF	OR=0			Correction for number of pregnancies, use of contraceptives, age, pregnancy*age.
					BF_{1-2}	OR=0.6			
					BF_{3-5}	OR=0.8			
					BF_{6-11}	OR=0.8			
					BF_{12-23}	OR=0.7			
					$BF_{\geq 24}$	OR=0.3			

Table A2.3: Effect of breastfeeding on ovarian cancer risk

Intermediary of health effect	Author Yr of publication	Design	Study population	Age group	Breastfeeding	Effect size	Remarks
Ovarian cancer continued	(Booth et al., 1989)	Case-control	United Kingdom 169 Cases 362 Controls	<65 yr	FF $BF_{\leq 6}$ BF_{7-12} BF_{13-18} BF_{19-24} $BF_{\geq 25}$	OR=1 OR=1.3 (0.8-2.2) OR=0.9 (0.5-1.6) OR=1.2 (0.5-2.5) OR=2.1 (0.7-6.7) **OR=3.4 (1.1-10.8)** (p-trend:1.8)	Correction for SES and age.
Borderline ovarian tumours	(Huusom et al., 2006)	Case-control	Denmark 202 Cases 1564 Controls	35-79 yr	FF BF_{1-5} BF_{6-11} BF_{12-24} $BF_{\geq 25}$ BF /5mo	OR=0.97 (0.50-1.86) OR=1 OR=0.73 (0.48-1.13) OR=0.93 (0.57-1.50) **OR=0.32 (0.11-0.95)** OR=0.90 (0.80-1.00)	Adjusted for age, childbirth, additional birth, age first birth, duration of contraceptives, smoking, intake of milk.
	(Riman et al., 2001)	Case-control	Sweden 135 Cases 2,637 Controls	50-74 yr	FF BF_{1-5} BF_{6-11} $BF_{\geq 12}$	OR=1 OR=0.72 (0.38-1.36) OR=0.52 (0.28-1.00) **OR=0.47 (0.24-0.94)** (p-trend:0.12)	Borderline Ovarian tumours are tumours of a low malignant potential. Correction for age, parity, BMI, age menopause, ever use oral contraceptives.
	(Harlow et al., 1988)	Case-control	United States of America 123 Cases 209 Controls	20-79 yr	$BF_{0-<1}$ $BF_{\geq 1}$ BF_{1-2} BF_{3-9} $BF_{>9}$	RR=1 **RR=0.5 (0.2-0.8)** **RR=0.4 (0.1-0.9)** RR=0.6 (0.3-1.2) **RR=0.3 (0.1-0.7)**	Correction for parity, age at diagnosis, use of oral contraceptives.

Table A2.4: Effect of breastfeeding on skeleton morbidity

Intermediary of health effect	Author Yr of publication	Design	Study population	Age group	Breastfeeding	Effect size	Remarks
Hip fraction [a]	(Michaelsson et al., 2001)	Case-control	Sweden 664 Cases 1,848 Controls	60-80 yr	<u>Life-long BF</u> BF_{1-5} BF_{6-10} BF_{11-16} $BF_{>16}$ BF (3 mo)	 OR=1 OR=0.90 (0.70-1.15) OR=0.95 (0.72-1.26) OR=1.01 (0.75-1.38) OR=1.00 (0.96-1.04)	Correction for number of children, age, hormone use, menopause, contraceptive use, BMI.
	(Cumming and Klineberg, 1993)	Case-control	Australia 131 Cases 107 Controls	≥65 yr	EFF BF mean nr months BF/Child $BF_{0,5-3}$ BF_{3-6} BF_{6-9} $BF_{>9}$	 OR=1 OR=0.55 (0.10-2.90) OR=0.64 (0.13-3.06) OR=0.79 (0.18-3.51) OR=0.41 (0.09-1.82) OR=0.24 (0.04-1.53) **(p-trend<0.01)**	Correction for age, BMI, hormone use menopause, current use of psychotropic medications, smoke status, consumption milk products, mental status, physical activity, health status. Small numbers in the different groups for duration of breastfeeding (7-24).
Bone density [a]	(Kritz-Silverstein et al., 1992)	Cohort	United States of America n=741	60-89 yr	 FF BF BF (mo)	<u>Wrist</u> / <u>Radius</u> / <u>Hip</u> / <u>Spine</u> RR=1 / RR=1 / RR=1 / RR=1 RR=1.00 / RR=1.01 / RR=1.00 / RR=0.99 RR=1.00 / RR=1.00 / RR=1.00 / RR=1.00	Health effect is bone mineral density. Correction for age, obesity, number of yrs postmenopausal, oestrogen use, thiazide use, ever smoking.
Rheumatoid Arthritis	(Karlson et al., 2004)	Cohort	United States of America n=104,642	30-55 yr at baseline (1976; follow-up 2002)	FF $BF_{\leq 3}$ BF_{4-11} $BF1_{2-23}$ $BF_{\geq 24}$	RR=1 RR=1.0 (0.8-1.2) RR=0.9 (0.7-1.1) RR=0.8 (0.6-1.0) **RR=0.5 (0.3-0.8) (p-trend:0.001)**	Correction for age, smoking, BMI, age at menarche, age at first birth, parity, oral contraceptives, menstrual cycle regularity, postmenopausal hormone use.
	(Brun et al., 1995) [d]	Cohort	Norway n=63,090	32-74 yr at baseline	FF BF_{1-9} BF_{10-19} BF_{20-29} $BF_{\geq 30}$	MRR=1 MRR=0.67 (0.42-1.07) MRR=0.72 (0.46-1.15) **MRR=0.38 (0.22-0.67)** **MRR=0.49 (0.28-0.85) (p-trend=0.006)**	MRR=Mortality Rate Ratio. Correction for age, region, SES and parity.
	(Jorgensen et al., 1996) [d]	Case-control	United States of America 176 Cases 176 Controls	28-84 yr	FF BF_{1-6} $BF_{>6}$	OR=1 OR=1.65 (0.71-3.84) OR=0.96 (0.41-2.29)	Health effect is estimated risk for severe RA. Correction for age at birth, OCP use and parity.

Table A2.5: Effect of breastfeeding on body weight

Intermediary of health effect	Author Yr of publication	Design	Study population	Age group	Breastfeeding	Effect size	Remarks
Weight gain [a]	(Rooney and Schauberger, 2002)	Cohort	United States of America n=540	26-51 yr	FF $BF_{2\text{-}12\ wks}$ $BF_{>12\ wks}$	3.73 (1.97-5.49) 2.05 (0.10-4.00) reference	Weight gain ten yrs after "study pregnancy". Correction for weight gain during pregnancy, weight loss by 6 mo, postpartum exercise.
	(Rogers et al., 1997)	Review	Developed countries			3 studies; 2 studies found no effect; 1 study found protective effect	'It may be that the effect of breastfeeding on changes in maternal bodyweight is only apparent when breastfeeding is continued for more than six months'.

Table A2.6: Effect of breastfeeding on diabetes

Intermediary of health effect	**Author Yr of publication**	**Design**	**Study population**	**Age group**	**Breastfeeding**	**Effect size**		**Remarks**
Diabetes mellitus type 2	(Stuebe et al., 2005)	2 Cohorts	United States of America N=83,585 N=73,418	Baseline age 30-55 and 25-42 year	FF BF>0-3 BF>3-6 BF>6-11 BF>11-23 BF>23 Per additional yr BF	Nurses Health Study HR=1 HR=0.98 (0.91-1.05) HR=1.03 (0.94-1.13) HR=0.96 (0.87-1.06) HR=0.92 (0.84-1.02) HR=0.88 (1.78-1.00) **p-trend:0.02** **HR=0.96 (0.82-0.99)**	Nurses Health Study II HR=1 HR=1.04 (0.86-1.26) HR=0.91 (0.73-1.14) HR=0.87 (0.72-1.06) HR=0.88 (0.47-1.06) **HR=0.67 (0.54-0.84)** **p-trend:<0.001** **HR=0.88 (0.82-0.94)**	Adjusted for parity, BMI at age 18 yr, dietary score quintile, physical activity, family history diabetes mellitus, smoking status, birth weight, multivitamin use, Current BMI. Nurses Health Study prospective analysis. Nurses Health Study II retrospective analysis.

Motivation for not including the results of a study in the model.
a: disease not modelled
b: not a consistent study design
c: duration of breast feeding unclear or reference duration not zero (FF)
d: endpoint measure not consistent e.g. RR instead of OR or disease at age 4 instead of 1
e: relevant original studies of Review incorporated

Appendix 3 Assumptions and details of the cost estimation

The diseases taken into account are described in chapter 2.

Children

Gastrointestinal infections including diarrhoea

Only the gastrointestinal infections including diarrhoea occurring in the first year of life are taken into account. In the report from NIVEL, 'Second National Study', the incidence of gastrointestinal infections and diarrhoea are given for the first life-year. Additionally they give information about the percentage of patients which receive medication and the percentage of patients that is referred to the hospital. The RIVM-report 'Costs of illness' can also make an distinction in costs for primary health care, hospital costs, medical costs or other sources. A summary of the available data are given in Table A3.1.

Table A3.1: Incidence and percentage of patient given medication and/or were referred to an hospital plus the related costs per patient (euro)

Incidence gastrointestinal infections incl diarrhoea	Medication	Referred to hospital	Costs of primary care per patient (euro)	Costs of medication per patient (euro)	Costs of hospital care per patient (euro)
26,037	18 %	0.7 %	26.45	3.58	16846.15

When the data from Table A3.1 is combined, the average costs of one gastrointestinal infection event is 161.30 euro per patient.

Otitis media

For otitis media a similar method for data collection was used. However, the specific costs for otitis media were not available. Therefore, the costs of otitis media were considered equal to these of respiratory infections (see next). But the incidence and amount of prescriptions and hospitalizations differ between otitis media and respiratory infections. That is why the costs per patients differ (see Table A3.2 and A3.3).

Table A3.2: Incidence and percentage of patient given medication and/or were referred to an hospital plus the related costs per patient (euro)

Incidence otitis media	Medication	referred to hospital	Costs of primary care per patient (euro)	Costs of medication per patient (euro)	Costs of hospital care per patient (euro)
38,232	68%	1.46%	121.98	10.78	287.26

When the data from Table A3.2 is combined, the average costs of one otitis media infection event is 465,19 euro per patient.

Respiratory infections

The data collection for the costs of respiratory infections was done in a similar way as the costs for gastrointestinal infections. The summary of available data are given in Table A3.3.

When the data from Table A3.3 are combined, the average costs of one respiratory infection event is 199.73 euro per patient.

Table A3.3: Incidence and percentage of patient given medication and/or were referred to an hospital plus the related costs per patient (euro)

Incidence respiratory infections	Medication	Referred to hospital	Costs of primary care per patient (euro)	Costs of medication per patient (euro)	Costs of hospital care per patient (euro)
89,264	35%	0.49%	52.25	13.10	25213.27

Crohn's disease

Crohn's disease is a chronic disease. Ideally, one would like to know the costs of one patient to get diagnosed and treated for the rest of their life. However this information is not available. Only overall costs are known which contain costs to make a diagnosis, but also costs for treatment several years thereafter when possible complications have arrived. 'Nationaal Kompas Volksgezondheid' estimated the prevalence of Crohn's disease given the incidence (see Table A3.4). This makes it possible to make an indication of average costs per patient per year. However, this way, all Crohn's disease patients are considered, not only the patients diagnosed during their childhood. In the RIVM-report 'Costs of Illness' the total costs for inflammatory bowel disease, which consists of Crohn's disease and ulcerative colitis, is given. From the 'Nationaal Kompas Volksgezondheid' the distribution between these two diseases is given (see Table A3.4).

Table A3.4: Prevalence of Crohn's disease and the health related costs per patient (euro)

Prevalence Crohn's disease (2000)*	Total costs inflammatory bowel disease	Ratio CD:UC	Costs Crohn's disease	Costs Crohn's disease per patient per year
15,500	89.5 million euro	1: 1.7	33,148,148	2138.59

Asthma

As Crohn's disease, asthma is also a chronic disease, so a similar method as for Crohn's disease is used. Available data are summarized in Table A3.5. For this calculation age- and sex specific prevalence's and costs were first used and later combined using the demographic data of the Netherlands

Table A3.5: Prevalence of Asthma and the health related costs per patient (euro)

Prevalence Asthma	Total costs Asthma (2003)	Costs asthma per patient per year
519,859	738,5 million euro	3180,83

Eczema

Only eczema in childhood (starting at a age of 0-18 months with a mean duration of 3.1 year) is considered within the model. Again the 'Second National Study' from NIVEL is used to determine the incidence of eczema and the number of prescriptions and hospitalizations. This data are summarized in Table A3.6.

Table A3.6: Incidence and percentage of patient given medication and/or were referred to an hospital plus the related costs per patient (euro)

Incidence eczema	Medication	Referred to hospital	Costs of primary care per patient (euro)	Costs of medication per patient (euro)	Costs of hospital care per patient (euro)
40,009	100%	2.2%	0-12 mo: 109.57 1-4 yr: 186.82	0-12 mo: 16.78 1-4 yr: 121.28	0-12 mo: 33.56 1-4 yr: 181.20

Combining these data, the average costs of one eczema event is 230,68 euro per patient per year.

Obesity
In paragraph 4.3.2.1 is already explained why we do not have the costs for obesity. In short, because obesity itself is not an disease but an intermediary for several chronic disease as cardiovascular disease and diabetes mellitus type 2, the costs per obesity case is subject to the relationship between obesity and obesity related diseases. However the precise effect of (childhood) obesity on these diseases is not yet fully stated.

Leukaemia
Acute Lymphatic Leukaemia (ALL) is one the forms of blood cancer. Only for non-Hodgkin specific health related costs are available. The other forms, including ALL are taken together. Assumed is that all these other forms of blood cancer are equal in costs to diagnose and treat. Taken the age- and sex-specific prevalence of all leukaemia's excluding non-Hodgkin lymphomas and the prevalence of ALL, costs of one ALL patient can be estimated and is 6088.86 euro per patient per year.

Mothers

Premenopausal breast cancer
Patients with breast cancer diagnosed before menopause are often under medical attention for a long time thereafter, many of them even still being treated. However, again it is impossible to retrieve the average costs of one patient being diagnosed and treated.
We do have the number of all breast cancer patients and the costs to treat all of these patients. If presumed that all breast cancer patient costs the same to get diagnosed and treated, cost per patient can be calculated. Calculated is that a breast cancer patient costs 2418.74 euro per year.

Ovarian cancer
With age and sex specific prevalence and costs of ovarian cancer. The costs for one ovarian cancer patient per year is calculated to be 3381.36 euro

Rheumatoid arthritis
With age and sex specific prevalence and costs of rheumatoid arthritis. The costs for one rheumatoid arthritis patient per year is calculated to be 1152.59 euro