

RIVM report 350040001/2005

Quantification of health effects of breastfeeding

Review of the literature and model simulation

CTM van Rossum, FL Büchner, J Hoekstra

Erratum 14 February 2006, see last page

Contact:

CTM van Rossum

Centre for Nutrition and Health

Caroline.van.Rossum@rivm.nl

This investigation has been performed by order and for the account of the Ministry of Public Health, Welfare and Sports, within the framework of project V/350040/AB, Quantitative foundation of food policy: breastfeeding

Abstract

Quantification of health effects of breastfeeding

Review of literature and model simulation

Breastfeeding has positive health effects, with the largest health gain realized through policy that focuses on encouraging all mothers to start breastfeeding.

A literature review shows that breastfeeding has beneficial health effects in both the short and the longer term. There is convincing evidence that the incidence of gastrointestinal infections, inflammation of middle ear, obesity and high blood pressure is reduced in breastfed children. Probably breastfed children suffer less from asthma, wheezing, eczema and among them intellectual and motor development is probably enhanced. Breastfeeding is possibly related to a reduction of incidence in Crohn's disease, atopy, diabetes mellitus type I, and leukaemia. Regarding the mother, there is convincing evidence for a protective effect of breastfeeding on rheumatoid arthritis. The incidence of pre-menopausal breast and ovarian cancer is probably lower among mothers who breastfed their infants longer.

The health effects of several intervention scenarios are simulated and compared to the present situation. The largest public health gain 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 through a policy only focussing on extending the lactation of women already breastfeeding beyond three months.

Keywords: breastfeeding; formula feeding; maternal health; children's health; benefits; risks; modelling

Het rapport in het kort

Kwantificering van de gezondheidseffecten van borstvoeding

Literatuuroverzicht en modelsimulatie.

Borstvoeding heeft positieve effecten op de volksgezondheid. De grootste gezondheidswinst is te behalen door alle pasgeborenen borstvoeding te laten krijgen.

Literatuuronderzoek laat zien dat borstvoeding gezonder is dan flesvoeding. Dit geldt voor de directe gezondheid van de zuigeling, maar werkt voor zowel het kind als de moeder ook langer door. Overtuigend bewijs is aanwezig dat infecties van het maagdarmkanaal, middenoorontsteking, overgewicht en hoge bloeddruk minder voorkomen bij (langer) borstgevoede kinderen. (Langer) borstgevoede kinderen krijgen waarschijnlijk minder last van astma, piepen op de borst en eczeem. Bovendien verbetert borstvoeding waarschijnlijk de intellectuele- en motorische ontwikkeling. Het is mogelijk dat borstvoeding beschermt tegen de ziekte van Crohn, atopie, diabetes en leukemie. Voor de moeder is er overtuigend bewijs dat het geven van borstvoeding beschermt tegen reumatische artritis en mogelijk tegen borstkanker voor de overgang en ovariumkanker.

Door borstvoeding te promoten kan het voorkomen van verschillende ziekten worden verlaagd. De gezondheidseffecten van verschillende beleidsscenario's zijn geschat met een modelsimulatie. De effecten hiervan zijn vergeleken met de huidige situatie. Vanzelfsprekend is de grootste gezondheidswinst te behalen wanneer alle pasgeborenen minimaal zes maanden borstvoeding krijgen. Verder wordt een groter effect bereikt met maatregelen alleen gericht om alle pasgeborenen borstvoeding te laten krijgen dan met maatregelen alleen gericht op het verlengen van de periode van borstvoeding geven van de moeders die dat nu al drie maanden doen.

Trefwoorden: borstvoeding, flesvoeding, gezondheid moeder, gezondheid zuigeling, gezondheidswinst, positieve gezondheidsaspecten, negatieve gezondheidsaspecten, modellering.

Contents

Samenvatting	7
Summary	10
List of abbreviations	13
1. Introduction	15
1.1 Background	15
1.2 Aim of this study	15
1.3 Approach	15
1.4 Outline of this report	16
2. Method of overviewing the literature	17
2.1 Search method	17
2.2 Quality of the literature	17
2.3 Criteria for evidence	17
3. Overview of the literature	19
3.1 Child	19
3.1.1 Infectious diseases	20
3.1.2 Pyloric stenosis and jaundice	20
3.1.3 Asthma and atopic diseases	20
3.1.4 Obesity, cardiovascular disease and diabetes	21
3.1.5 Cancer	21
3.1.6 Growth	21
3.1.7 Intellectual and motor development	22
3.1.8 Others	22
3.2 Mother	22
3.2.1 Cancer	23
3.2.2 Bone density and rheumatoid arthritis	23
3.2.3 Weight gain	24
3.3 Conclusion	24
4. Method of quantifying health effects	25
4.1 Description of the model	25
4.2 Structure and assumptions of the model	26
4.3 Data for the model	26
4.3.1 Breastfeeding	26
4.3.2 Diseases	27
4.3.3 Disease parameters	28
4.4 Breastfeeding scenarios	29
4.4.1 Present situation	29
4.4.2 Best case scenario, all infants 6 months	30
4.4.3 Worst case scenario	30
4.4.4 Policy: 0→ BF	30

4.4.5	Policy: +1 month	30
4.4.6	Policy: +1 month, (excl. 0)	30
4.4.7	Policy: >0-3 months	30
4.4.8	Policy: 3-6 months	30
4.4.9	Policy: 5% shift	30
4.5	<i>Sensitivity analysis</i>	32
5.	Quantification of health effects	33
5.1	<i>Health effects by duration of breastfeeding</i>	33
5.2	<i>Health effects for each scenario</i>	33
5.2.1	Effect on incidences for each scenario	33
5.2.2	Effect on DALYs for each scenario	38
5.3	<i>Conclusion</i>	38
6.	General discussion	39
6.1	<i>Main results</i>	39
6.2	<i>Limitations and strengths of methods</i>	39
6.3	<i>Conclusions and recommendations</i>	41
	Acknowledgement	43
	References	44
	Appendix 1 Health effects child	51
	Appendix 2 Health effects mother	52
	Appendix 3 Assumptions of the BF model	101
	Appendix 4 Regression estimates per modeled disease	105

Samenvatting

Introductie

Op dit moment voldoet slechts 18% van de Nederlandse moeders aan de WHO-richtlijn om ten minste zes maanden exclusief borstvoeding te geven aan elk kind. Daarom is het beleid van de Nederlandse regering, ten aanzien van borstvoeding, erop gericht om het percentage lacterende vrouwen te verhogen. Maar welk beleid heeft het meeste effect?

Het doel van deze studie is tweeledig. Ten eerste, een overzicht geven van de literatuur over de gezondheidseffecten van borstvoeding (positieve en negatieve effecten samengenomen) voor moeders en kinderen. Ten tweede, het kwantificeren van de gezondheidseffecten (gebaseerd op het literatuuroverzicht) van verschillende potentiële beleidsscenario's met behulp van een modelsimulatie.

Methode

De literatuur is op een systematische wijze doorzocht naar gepubliceerde epidemiologische studies in "westerse" populaties over gezondheidseffecten van borstvoeding. Alle gevonden artikelen zijn getoetst op hun kwaliteit aan de hand van vooropgestelde kwaliteitseisen. Voldeed een artikel niet aan de eisen dan is de studie niet meegenomen. In het literatuuroverzicht wordt de mate van bewijs aangegeven met 'overtuigend', 'waarschijnlijk', 'mogelijk' of 'onvoldoende bewijs', volgens de WHO-criteria voor mate van bewijs.

Om de gezondheidseffecten van potentiële beleidsscenario's van borstvoeding te kwantificeren is een model gemaakt waarin de gezondheidswinst en verlies gesimuleerd worden aan de hand van het aantal moeders dat een bepaalde tijd borstvoeding geeft. Elk beleidsscenario wordt weergegeven door een bepaalde verdeling van borstvoedingduur.

Het model is gebaseerd op relatieve risico's of oddsratio's voor de verschillende gezondheidseffecten die in de wetenschappelijke literatuur zijn gepubliceerd. Er wordt aangenomen dat deze relatieve risico's of oddsratio's ook gelden voor de Nederlandse populatie. Gegeven het percentage kinderen dat borstvoeding krijgt voor een bepaalde periode, berekent het model de incidenties van de verschillende gezondheidseffecten voor de kinderen en de moeders. Uiteindelijk worden de incidenties van alle aandoeningen ook gecombineerd in één maat voor de gezondheidseffecten: 'Disability Adjusted Life Years' (DALYs).

De gezondheidseffecten voor verschillende potentiële beleidsscenario's zijn geschat. De huidige situatie is gebruikt als referentiescenario. De negen doorerekende scenario's zijn:

- Huidige situatie;
- Het gunstigste scenario: alle moeders geven hun kinderen tenminste zes maanden borstvoeding;
- Het minst gunstige scenario: geen enkele moeder geeft haar kind borstvoeding;
- Beleid '0'→BF: alle moeders beginnen met borstvoeding. De verdeling van de duur van de borstvoeding is gelijk aan die van de huidige lacterende moeders;
- Beleid '+1 maand': alle moeders geven hun kind één maand langer borstvoeding vergeleken met de huidige situatie;
- Beleid '+1 maand, exclusief '0'': gelijk aan vorig scenario behalve dat de moeders die nu geen borstvoeding geven dat ook in dit scenario niet doen;
- Beleid '>0-3 maanden': moeders die in de huidige situatie minder dan drie maanden borstvoeding geven, geven in dit scenario drie maanden borstvoeding;

- Beleid '3-6 maanden': moeders die in de huidige situatie hun kinderen ten minste drie maanden borstvoeding geven, geven in dit scenario minimaal zes maanden borstvoeding;
- Beleid '5% verschuiving': uit iedere categorie schuift 5% van de moeders een categorie omhoog.

Resultaten

Onze studie laat zien dat in ontwikkelde landen borstvoeding een overtuigend gezondheidsbevorderend effect heeft op zowel moeder als kind, vergeleken met flesvoeding. Tevens, hoe langer de duur van borstvoeding, des te lager de incidenties van verschillende ziekten. Voor de kinderen is er overtuigend bewijs voor de afname in incidentie en ernst van infecties van het spijsverteringskanaal, middenoorontsteking, obesitas en hoge bloeddruk. Borstgevoede kinderen krijgen waarschijnlijk minder last van astma, piepen op de borst en eczeem. Bovendien verbetert borstvoeding de intellectuele- en motorische ontwikkeling. Het is mogelijk dat borstvoeding gerelateerd is met verminderde incidentie van de ziekte van Crohn, atopie, diabetes en leukemie. Voor de moeder is er overtuigend bewijs dat het geven van borstvoeding de kans op reumatoïde artritis verlaagt. Er is mogelijk bewijs voor een lagere incidentie van pre-menopausale borstkanker en ovariumkanker voor moeders die hun kind voor een langere periode borstvoeding geven.

Door borstvoeding te promoten kan de incidentie van verschillende ziekten worden verlaagd. De grootste gezondheidswinst is te halen wanneer alle pasgeborenen minimaal zes maanden borstvoeding krijgen (de gunstigste situatie). Per 1000 persoonsjaren kunnen 49 incidentiegevallen van middenoorontsteking, 46 gevallen van infecties van het spijsverteringskanaal, ongeveer 131 gevallen van luchtweginfecties en 26 gevallen van eczeem voorkomen worden. Tevens kunnen vier incidentiegevallen van astma voorkomen worden als kinderen ten minste zes maanden borstvoeding krijgen. Voor minder voorkomende aandoening als ziekte van Crohn, leukemie of obesitas op jonge leeftijd, is het aantal te voorkomen gevallen respectievelijk: 256, 39 en 273 gevallen per 100.000 persoonsjaren. Als men kijkt naar de gezondheidseffecten voor de moeders kunnen elk jaar 40 incidentiegevallen reumatoïde artritis, vier incidentiegevallen van pre-menopausale borstkanker en één incidentie ovariumkanker per 100.000 persoonsjaren voorkomen worden. Als deze effecten worden gecombineerd, kunnen in het gunstigste geval per 1000 personen 33 DALYs voorkomen worden. Hierin draagt astma het meeste bij vanwege het chronische karakter van deze ziekte.

Ten aanzien van de overige beleidsscenario's verschilt de te behalen gezondheidswinst niet veel van elkaar. De grootste gezondheidswinst is te behalen wanneer alle moeders starten met het geven van borstvoeding vergeleken met de huidige situatie. De kleinste geschatte gezondheidswinst is te behalen als het beleid is om de lactatieperiode te verlengen van drie naar zes maanden borstvoeding.

Sterke en zwakke punten

Binnen de literatuurstudie is getracht zo veel mogelijk bias te voorkomen door gebruik te maken van vooraf opgestelde kwaliteitseisen. Verder wordt de mate van bewijs gedefinieerd op een gelijke wijze als bij de WHO.

Een model is per definitie een versimpelde weergave van de werkelijkheid en heeft daardoor zijn beperkingen, zoals geen onderscheid tussen wel of niet bijvoedingen of exclusief/niet exclusief borstvoeding. Een sterk punt van ons model is dat de gezondheidseffecten kunnen worden bepaald afhankelijk van de duur van borstvoeding. Ondanks dat ons model niet in

staat is een duidelijk onderscheid te maken tussen de verschillende beleidsscenario's, is het model wel een staat een goede indicatie te geven van de te behalen gezondheidswinst.

Aanbevelingen voor verder onderzoek

Dit onderzoek geeft aan dat er nauwelijks Nederlandse studies zijn over de effecten van borstvoeding op verschillende aandoeningen. Daarnaast is het interessant om de invloed van de voeding van de moeder op de samenstelling van de borstvoeding te onderzoeken. Mogelijk is hiermee nog extra gezondheidswinst te behalen. Het ontwikkelde model, eventueel uitgebreid met een kosteneffectiviteitsmodule, kan verder goed gebruikt worden om de gezondheidswinst en zijn economische consequenties van concrete interventies en beleidsvoornemens in kaart te brengen.

Conclusies

Borstvoeding is gezondheidsbevorderend voor moeder en kind in vergelijking met flesvoeding, als alle positieve en negatieve effecten gerapporteerd in de literatuur worden samengenomen. Potentiële negatieve effecten van toxische stoffen, zoals PCB's en moedermelk, worden overheerst door positieve stoffen in borstvoeding. De grootste gezondheidswinst wordt behaald bij de directe gezondheid van het kind. Echter, het literatuuroverzicht laat ook zien dat de gezondheidswinst van borstvoeding ook op latere leeftijd nog zichtbaar is. Voor de moeder zijn alleen effecten op de langere termijn gevonden.

Samengevat, beleid gericht op het verhogen van het percentage borstgevoede kinderen kan worden gezien als een preventieve maatregel. Vanzelfsprekend, is de grootste gezondheidswinst is te behalen wanneer alle pasgeborenen minimaal zes maanden borstvoeding krijgen. Het model geeft aan dat er meer gezondheidswinst te behalen is wanneer beleidsdoelen zijn gericht om alle pasgeborenen borstvoeding te geven al is het van korte duur, dan met maatregelen die zich richten op het verlengen van de lactatieperiode van drie naar zes maanden.

Summary

Introduction

Currently only 18% of the Dutch mothers comply with the WHO recommendation by giving exclusive breastfeeding to every infant for at least six months. Therefore, the policy of the Dutch government related to breastfeeding is to increase the percentage of breastfeeding mothers. But which policy is the most effective?

The aim of this study is bipartite. Firstly, to give an overview of the literature on health effects of breastfeeding (taking the beneficial and harmful effects together) for mother and infant. Secondly, to quantify the health effects (based on the overview of the literature) for several scenarios based on potential policy targets related with breastfeeding.

Methods

A systematic literature search of published epidemiological studies conducted in the general ('western') population was carried out. Every article is tested on its quality. If an article did not fulfill every quality requirement the study is excluded from the literature overview. In the overview the strength of evidence for an association is qualified as 'convincing', 'probable', 'possible' or 'insufficient', based on WHO-criteria for evidence.

To quantify the health effects of breastfeeding and the effects of possible policy targets a model is created in which the gain/loss in health is simulated given the amount of mothers that breastfeed their infant during a certain period. Each policy target corresponds with a certain distribution of duration of breastfeeding.

The model is based on the relative risks or odds ratios for several diseases given the duration of breastfeeding that were derived from the literature. It is assumed that these relative risks or odds ratios are valid in the Dutch population. Those relative risks were used to find a dose-response function for our model population with the aid of regression analyses. 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. Finally, the incidences of the diseases are also combined into one health measure, the Disability Adjusted Life Years (DALY).

Health effects for several potential policy scenarios were estimated. The present situation is used as reference scenario. The nine scenarios are:

- Present situation;
- Best case, 6 months: all mothers breastfeed their infants for at least six months or longer.
- Worst case: none of the mothers breastfeed their infants;
- 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, 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.

Results

Our study shows that in westernised countries breastfeeding has a clear beneficial health effect for the child and the mother as compared to formula feeding. Also, the longer the breastfeeding period, the lower the incidences of several diseases. For the infant, convincing evidence is available about the positive effect of breastfeeding on the incidence and severity of gastrointestinal infections including diarrhoea, otitis media, obesity and high blood pressure. It is probable that breastfed children will suffer less from asthma, wheezing, eczema and have better intellectual and/or motor development. Possibly breastfeeding is negatively related with Crohn's disease, atopy, diabetes mellitus type I, and leukaemia. For the mother, there is convincing evidence for a protective effect of breastfeeding on rheumatoid arthritis. Possibly, the incidence of pre-menopausal breast and ovarian cancer decreases among mothers who breastfed their infants for a longer period.

By increasing the percentage of breastfed infants, the model quantified that the incidences of several diseases decreases. The largest health gain would be achieved when all newborns were breastfed for at least six months (best case scenario). Per 1000 person years 49 incident cases of otitis media, 46 cases of gastrointestinal infections, about 131 cases of respiratory infections and 26 cases of eczema are prevented. Also four incident cases of asthma per 1000 person years could be prevented when every infant were breastfed for a least six months. For uncommon diseases, like Crohn's disease, leukaemia or obesity at young age, the number of prevented incident cases: 256, 39 and 273 per 100,000 person years respectively. Beneficial effects for the mothers are taken into account as well. Each year 40 incident cases of rheumatic arthritis, four new cases of pre-menopausal breast cancer and one incident case of ovary cancer could be prevented in 100,000 persons. Combining these effects gives: 33 DALYs per 1000 persons could be prevented if all mothers would give human milk to their infants for six months. In this measurement, asthma showed the highest contribution.

In regard to the other potential policy scenarios, gained health effects do not differ substantially. The largest estimated health gain is achieved if all mothers start breastfeeding compared to the current situation. The smallest decrease in disease incidences is observed if an intervention would focus on prolonging the lactation period from three to six months.

Strengths and limitations

Potential biases in our literature overview of the health effects of breastfeeding are avoided as much as possible by using quality requirements for the reviewed literature. The degree of evidence is given by adopting the WHO-criteria for the strength of evidence. Modeling is by definition a simplification and has its limitations. A strength of our model simulation is that it takes into account the duration of breastfeeding. Although, the model is not sensitive enough to distinguish between the effects of every scenario, it does give an indication of the potential health gain.

Recommendations for further research

This project showed that hardly any Dutch data on the association between breastfeeding and diseases is available. In addition, it would be interesting to investigate the effects of dietary habits of the mother on human milk in order to increase the beneficial effect of breastfeeding. The BF-model, if desired extended with a cost-effectiveness-module, can be used to quantify the health effects and economic consequences of actual interventions.

Conclusions

Combining all positive and negative effects of breastfeeding reported in the literature, breastfeeding, in comparison to formula feeding, has a beneficial health effect for the child

and the mother. Potential negative effects due to toxic substances, such as PCBs in the human milk are outweighed by the positive substances of human milk. Most epidemiological studies in which the balance between these toxic substances and the beneficial compounds are made showed a beneficial effect. The largest and most obvious benefits of breastfeeding are seen for the immediate health of the infant. However, the overview shows also that some beneficial effects extend beyond infancy. For the health of the mother mainly long-term effects are found.

In summary, a policy aiming at increasing the percentage of breastfed infants can be seen as a preventive measure. The largest health gain can be achieved when all newborns get breastfeeding for at least six months. Our model indicates that more health gain would be achieved when policy targets on the non-breastfeeding mothers to start with breastfeeding instead of extending the lactation period of 3 months of already breastfeeding women.

List of abbreviations

AOM	Acute otitis media
BF	Breastfeeding
BF (mo)	Effect of Breastfeeding per increase of one month
BF _x	Breastfeeding for the period of x months
CBS	Centraal Bureau voor de Statistiek
CI	Confidence interval
CVD	Cardiovascular disease
DALYs	Disability Adjusted Life Years
EBF	Exclusive breastfeeding/exclusively breastfed
EFF	Exclusive formula feeding/exclusively formula fed.
FF	Formula feeding
IDDM	Insulin dependent diabetes mellitus
LA	Linolenic acids
LNA	Alpha-linolenic acid
MBF	Mixed breastfeeding and formula feeding
OR	Odds ratio
PCBs	polychlorinated biphenyls
PCDDs	polychloro-dibenzo-(p)-dioxins
PCDFs	polychloro-dibenzo-furans
PUFAs	polyunsaturated fatty acids
py	Persons years
RIVM	Dutch National Institute of Public Health and the Environment
RR	Relative risk
SES	Socio-economic status
SIDS	Sudden Infant Death Syndrome
VWS	Ministry of Public Health, Welfare and Sports
WHO	World Health Organization
YLD	Years lived with a disease or disability
YLLs	Years of life lost of life years

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.¹⁶⁸ However, in the Netherlands only 18% of the mothers comply with this recommendation by giving exclusive breastfeeding for the first six months.⁸⁶ Policy of the Dutch government related to breastfeeding aims at increasing this percentage of breastfeeding mothers. The question presents itself: what are the health effects of this policy?

Many papers are published describing the health effects of breastfeeding for children and mothers. A majority of these studies shows a beneficial effect of breastfeeding on mother and child compared to formula feeding. In contrast there are also studies showing potential harmful effects, such as the ingestion of dioxin-like substances by the infant via breastfeeding. Nevertheless, a detailed quantitatively weighted balance of the beneficial effects and potential harmful effects on Dutch mothers and children is never made. 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.

1.2 Aim of this study

The aim of this study was bipartite. Firstly, to give an overview of the literature on health effects associated with breastfeeding (taking the beneficial and harmful effects together) for mother and child. This is done in more detail and based on the most recent literature compared to a section on breastfeeding in a previous RIVM-report.⁷⁸ The second aim was, to quantify the health effects of several scenarios based on potential policy targets related to breastfeeding. A quantification of the health effects in terms of costs is scheduled to be performed in 2006.

1.3 Approach

Human milk is a complex mixture of many substances produced by the mother's body, such as lipids, proteins, antibodies, hormones, vitamins, minerals and nucleotides. Additionally, substances introduced to the mother's body by ingestion of food, drink, pharmaceutical agents, drugs or inhalation of chemicals or via dermal exposure can also be found in human milk. Some of these substances have possible beneficial effects other possible harmful effects.⁸⁴ Theoretically, in order to quantify the health effects of breastfeeding all beneficial effects and harmful effects of each substance in human milk should be compared with all beneficial and harmful effects of formula feeding. However, studies on the health effects for each compound in human milk and in formula are not available. Some studies evaluate the health effects within cohorts of mother-infant pairs where concentrations of specific chemicals have been measured in the mother's milk. For several environmental chemicals the health effects are evaluated by using a risk-assessment approach. But are these risk-assessment assumptions valid for the Dutch situation? In addition, how can these studies be compared with the beneficial health effects of breastfeeding? And how can potential risks from exposure to environmental chemicals in human milk be compared to potential risks of that in formula feeding?

For these reasons, the overview of the literature and the risk-benefit assessment in this study was focussed on *epidemiological studies*, in which the net health effect of the beneficial and harmful effects of breastfeeding versus the effects of formula feeding are given. Therefore invalid extrapolations from animal models to the human situation were not an issue.

Furthermore, the assessment was 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.

To quantify the health effects of breastfeeding a model was developed. The model simulates the health gain/loss given the amount of mothers that breastfeed their infant during a certain period of time. The model was 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.

1.4 Outline of this report

Chapter 2 describes the method of the literature overview. Chapter 3 comprises the overview on the positive and negative health effects. The next two chapters focus on the model simulation. First, the choice of the model for the quantification of the health effects with its general assumptions, the parameters and the data used to construct them, or the selected scenarios are described in Chapter 4. The results of the different scenarios are shown in Chapter 5. Finally, Chapter 6 comprises a general conclusion and some recommendations.

2. Method of overviewing the literature

2.1 Search method

A systematic computerized literature search of published studies was carried out within two steps. First in Augustus/September 2004 all available articles were searched within Medline from 1980 until then. The following search terms were used: 'breastfeeding', 'lactation', or 'human milk'. Also combinations of these terms with known health effects were made like 'infections', 'otitis media', 'obesity' etcetera. Review articles and meta-analyses were used to find important articles that were missed with the computerized literature search. Secondly, the most recent articles were searched from Augustus 2004 until February 2005.

The search was limited to articles published in English or Dutch. In addition, only study populations from Western Europe, North America, Australia and New Zealand were included in the overview.

2.2 Quality of the literature

Every article was tested on its quality according to the following points:

- Time of assessing breastfeeding data (ideally no longer then twelve months after birth). Validity studies have found that parents' memories of breastfeeding initiation is good, but that memory of breastfeeding duration and supplementary feeding is less reliable.²⁵
- Clear definition of (exclusive) breastfeeding and clear statements about the duration of (exclusive) breastfeeding.
- Blind assessment of breastfeeding data as well as blind assessment of the health outcome(s).
- Well-defined health outcome(s).
- Correction for relevant confounders.

When an article did not fulfil the quality requirements named above, but was thought to have a significant impact on the literature overview a note was made about the weak point. When an article did not fulfil any quality requirements the study was excluded from the literature overview.

2.3 Criteria for evidence

For each health outcome the strength of evidence was given, based on the criteria given by the WHO in the report 'Diet, Nutrition and the prevention of chronic diseases' from 2003.¹⁷⁰ The strength of evidence was qualified as 'convincing', 'probable', 'possible' or 'insufficient'. The criteria used to make this distinction were:

- *Convincing evidence*: evidence based on epidemiological studies showing consistent associations between exposure and disease, with little or no evidence to the contrary. The available evidence is based on a substantial number of studies including prospective observational studies. The association should be biologically plausible.
- *Probable evidence*: evidence based on epidemiological studies showing fairly consistent associations between exposure and disease, but where there are perceived shortcomings in the available evidence or some evidence to the contrary. Shortcomings in the evidence may be any of the following: insufficient duration of trials (or studies); insufficient trials (or studies) available; inadequate sample sizes; incomplete follow-up. Again, the association should be biologically plausible.

- *Possible evidence*: evidence based mainly on findings from case-control and cross-sectional studies. Insufficient randomised controlled trials, observational studies or non-randomised controlled trials are available. More trials are required to support the tentative associations, which should also be biologically plausible.
- *Insufficient evidence*: evidence based on findings of a few studies which are suggestive, but are insufficient to establish an association between exposure and disease. More well designed research is required to support the tentative associations.

In addition to these four categories the following qualifications were used:

- *Conflicting evidence*: several studies with sufficient power show opposite effects, so it is impossible to conclude whether breastfeeding has a positive, negative or no effect on the disease outcome.
- *No evidence*: one or two studies with little power so no clear statement can be given about the strength of evidence.

3. Overview of the literature

This chapter gives an overview of the literature on health effects of breastfeeding versus formula feeding. Firstly the health effects for the infant and secondly, the health effects for the mother are presented.

3.1 Child

A summary of the health effects for children who are breastfed compared to those who got formula is given in Table 3.1. This table also shows the strength of the evidence ('convincing', 'probable', 'possible', 'insufficient', 'conflicting' or 'no evidence'; see section 2.3) and the references of the studies on which this evidence was based. More detail about each study, is given in Appendix 1, for example how breastfeeding was measured, how the duration of breastfeeding was taken into account, or the lack of coherence between the different studies. In general, enough evidence was found only for beneficial effects. These health effects are described in the next sections.

Table 3.1 Short overview of the effects of breastfeeding compared to formula feeding on the child.

Health effect	References	Strength of evidence	See also:
Gastrointestinal infections including diarrhoea	10,28,39,43,52,53,58,74,77,126,135,136,141,172	Convincing +	3.1.1
Otitis media	4,7,23,28-30,58,74,77,118,126,136,141,154,157,172	Convincing +	3.1.1
Respiratory infections	4,10,58,74,77,113,115,126,136,148,172	Possible +	3.1.1
Urinary tract infections	96,124	Insufficient	3.1.1
Crohn's disease	69,71,129	Possible +	3.1.1
Ulcerative colitis	69,129	Insufficient	3.1.1
Haemophilus influenza	146	X	3.1.1
Fever	119,172	X	3.1.1
Pyloric stenosis	123	X	3.1.2
Jaundice	14,41,172	Conflicting +	3.1.2
Asthma	20,27,38,48,51,77,81,82,111,113,114,137,144,147,153,161,171,174,176	Probable +	3.1.3
Wheezing	20,74,77,82,111,113-115,126,144,147,161,171,173-176	Probable +	3.1.3
Eczema	12,37,48,58,65,68,74,77,82,87,142,147,150,153,161,165	Probable +	3.1.3
Atopy	19,42,77,82,111,114,138,144,147,153,165,177,178	Possible +	3.1.3
Obesity	8,9,11,40,47,56,70,90,91,121,127,128,156,163	Convincing +	3.1.4
Cardiovascular disease	97,99	X	3.1.4
Blood pressure	88,89,98,99,117,127,152	Convincing +	3.1.4
Diabetes I	60,63,101,110,139,140	Possible +	3.1.4
Leukaemia	54,61,83,85,143,145,158	Possible +	3.1.5
Lymphomas	54,158	Insufficient	3.1.5
All childhood cancers	24,26,54,85,158	X	3.1.5
Growth	75-77	Insufficient	3.1.6
Intellectual and motor development	6,32,44,49,57,62,73,95,104,112,122,125,132,155,162,164	Probable +	3.1.7
Sudden infant death syndrome	33,77,100	Insufficient	3.1.8
Hospitalization	119	X	3.1.8

+ = beneficial effect

x = no evidence

3.1.1 Infectious diseases

One of the substances of human milk thought to have beneficial effects on the breastfed infant are antibodies. Antibodies are an explanation for the protective effect found for several infectious diseases. There is convincing evidence that breastfeeding has a beneficial effect on *gastrointestinal infections* and consequently on the prevalence of diarrhoea. Also for the protective effect of breastfeeding against *otitis media* (ear infections) is convincing evidence. Although, there is only possible evidence for recurrent otitis media. Colostrum, first milk after birth, in particular is thought to be responsible for these effects. It contains a high concentration of secretory IgA, which may protect through the enteromammary and bronchomammary pathways. This may also explain the possible evidence found for the protective effect on respiratory infections in general. For upper *respiratory infections* probable evidence is present. However, for the *lower respiratory infections* there was insufficient evidence for an effect of breastfeeding. Insufficient evidence exists also for a protective effect of breastfeeding on *urinary tract infections*.

Crohn's disease and *ulcerative colitis* are the most common inflammatory bowel diseases. However, the aetiology of both Crohn's disease and ulcerative colitis remains elusive. For Crohn's disease there is possible evidence for a protective effect whereas for ulcerative colitis still insufficient evidence is available. A possible underlying mechanism is the immunological substances of breast milk, just as with other inflammatory diseases.¹²⁹

Because of the general introduction of *Haemophilus influenza* type b (Hib) the effect of breastfeeding on *Haemophilus influenza* is not looked at very closely. In Appendix 1 one study is mentioned which looked at the relationship between *Haemophilus influenza* in a population where the Hib vaccination is very rare. This study found a protective effect for each extra week of breastfeeding.¹⁴⁶

Fever is a common symptom of infectious diseases. However, only two studies investigated the relationship between fever in general and breastfeeding. This number is too small to make a statement about the strength of the evidence.

3.1.2 Pyloric stenosis and jaundice

Pyloric stenosis is characterized by enlarged pyloric musculature and gastric outlet obstruction. Just one case-control study was found which looked at the effect of breastfeeding in relation to pyloric stenosis that makes it impossible to make a pronouncement about the level of evidence.

Neonatal *jaundice* remains the most common problem in full-term infants during the immediate postnatal period. There is conflicting evidence for the role of breastfeeding; whereas a large cohort study from Italy found a protective effect, a smaller cohort study from the USA found a large increasing effect.

3.1.3 Asthma and atopic diseases

The role of breastfeeding in the protection against asthma and atopic diseases is controversial. There are five reasons to expect that breastfed children may show a reduced occurrence of asthma and atopic disease: (1) breastfed children are less exposed to foreign dietary antigen, (2) human milk contains factors that promote gastrointestinal mucosa maturation, thereby allowing early 'closure' of macromolecular absorption, (3) by decreasing the incidence of infection and possibly altering the gut micro flora that can act as an adjuvant for ingested

food proteins, the possibility of sensitisation may be reduced, (4) human milk has functional immunomodulatory and anti-inflammatory factors that curtail macromolecular uptake, (5) cytokines and growth factors in human milk may play an important role in modulating the development of asthma.¹¹²

Within the literature search, probable evidence exist that breastfeeding protects against *asthma, wheezing and eczema*. For atopy in general there is only possible evidence of a protective effect. The majority of the reported effects are relatively small. A general problem with these studies is the lack of stratification by family background of atopy or asthma, which is thought to play a significant role within these disorders.

3.1.4 Obesity, cardiovascular disease and diabetes

Breastfeeding might protect against *obesity* through several probable mechanisms and include behavioural and hormonal mechanisms and differences in macronutrient intake.⁸ Combining all studies together, residual confounding and publication bias cannot be excluded definitely in this association, but convincing evidence is present for a small protective effect of breastfeeding.

No evidence of an effect of breastfeeding on *cardiovascular diseases* (CVD) was found. The studies found are all based on old birth cohorts, with limitations in collecting breastfeeding data. Moreover, the formula feeding used in that time (\pm 1920) differs from the formula feeding used at present. Therefore extrapolation of those results to the present situation is impossible. However, recent literature shows convincing evidence of a positive effect of breastfeeding on blood pressure, an intermediary of CVD. A variety of mechanisms are suggested by which breastfeeding could influence blood pressure, including (1) reducing sodium intake in infancy, (2) increasing intake of long-chain polyunsaturated fatty acids, and (3) protecting against hyperinsulinemia in infancy and insulin resistance in early life, adolescence and adulthood.⁹⁸

Numerous studies have explored the role of possible environmental influences such as viral infections, life stress, and dietary factors within the development of insulin dependent *diabetes mellitus* (IDDM). The current etiologic model suggest that environmental factors are triggers for onset of IDDM in genetically susceptible children.²⁵ For breastfeeding possible evidence is found for an effect on IDDM.

3.1.5 Cancer

Infections are suspected to play a role in the aetiology of childhood leukaemia. Greaves⁴⁵ has suggested that the pattern and timing of non-specific infections may be important; early stimulation of the immune system would promote adequate modulation, increasing the appropriateness of the response to later infections. In some possibly susceptible individuals, an inappropriate response of the immune system could increase the proliferation of pre-malignant clones and enhance the risk of leukaemia.⁶¹ The literature presents possible evidence of an effect of breastfeeding on childhood *leukaemia* and insufficient evidence for an effect on the development of *lymphomas*. Insufficient evidence was found for *all cancer morbidity* and for other specific cancers such as breast³⁵ and testicle²¹.

3.1.6 Growth

Size at birth and rate of growth in infancy are important indicators of infant mortality and morbidity; smaller size being a major risk factor for mortality, particularly due to infectious disease. More recently, early growth patterns have also been linked to metabolic and

cardiovascular diseases in adulthood that are exacerbated by excessive weight gain and obesity.¹¹⁶ However, insufficient evidence of an effect of breastfeeding on *growth* is found. Possibly because our search was not comprehensive. Because growth is not considered a disease, the literature search was not primary focussed on this subject.

3.1.7 Intellectual and motor development

Discussion on nutrition and brain development has highlighted the importance of polyunsaturated fatty acids (PUFA). Breast milk contains a range of PUFA whereas standard bottle milk formulae, at least until recently, were only fortified with the precursors LA and LNA.⁴⁹ On the other hand, it is suggested the presence of PCBs (=polychlorinated biphenyl), PCDDs (=polychloro-dibenzo-(p)-dioxins) and PCDFs (=polychloro-dibenzo-furans) in human milk hampers cognitive development and is altogether harmful for children. Studies address the relationship between exposure to PCBs, PCDFs or PCDDs and functional effects, including delays in psychomotor and cognitive functions, thyroid hormone changes, immune alterations, low birth weight, birth defects, spontaneous abortion, pre-term birth and boy-girl ratio. Besides the postnatal exposure via breastfeeding, infants are exposed prenatal to PCBs, PCDFs or PCDDs. Prenatal exposure, seems to be more important than postnatal exposure in causing health effects. The positive effects of breastfeeding seem to compensate for possible negative effects of PCBs, PCDFs or PCDDs in breast milk. In fact, high-exposed breastfed children perform better in neurodevelopmental tests than low-exposed formula-fed children. Thus, there is probable evidence for a favorable effect of breastfeeding on intellectual and motor development. With breastfed children scoring higher than formula-fed children. Limited information is available on postnatal exposure for other health end-points related to pollution in human milk. Therefore, no conclusions can be drawn for these other health end-points.

3.1.8 Others

Sudden Infant Death Syndrome (SIDS) or cot death is a rare, multifactorial diagnosis of exclusion. It is thus difficult to clearly establish risk factors for this. SIDS cases are often associated with acute upper respiratory or diarrheal infections. Breastfeeding plays a preventive role in the etiology of these diseases. However, insufficient evidence of an effect of breastfeeding on SIDS is found.

Hospitalization is an indication for the severity of a disease. Only one study was found which examines the effect of breastfeeding on hospitalization rate (all admission causes). Therefore, no statement about the strength of the evidence can be made.

3.2 Mother

The health effects for the mother are summarized in Table 3.2. Again this table shows enough evidence only for beneficial effects for mothers giving breastfeeding compared to mothers giving no breastfeeding. Additional information about the studies can be found in Appendix 2.

A general problem that was encountered was that the majority of studies that investigate the effect of breastfeeding on the mother's health had a case-control design. Thus, considering the strength of the evidence, the conditions for 'convincing' and 'probable' evidence could not be fulfilled.

Table 3.2 Short overview of the effects of breastfeeding compared to formula feeding on the mother.

Health effect	References	Strength of evidence	See also:
Pre-menopausal breast cancer	13,17,31,36,67,94,106,108,151,159,180	Possible +	3.2.1
Post-menopausal breast cancer	36,67,94,106-108,151,180	Insufficient	3.2.1
Ovarian cancer	16,46,50,55,130,131,149,166	Possible +	3.2.1
Cervical cancer	109	x	3.2.1
Glioma	59	x	3.2.1
Hip fracture	22,80,103	Insufficient	3.2.2
Rheumatoid arthritis	18,64,66	Convincing +	3.2.2
Weight gain	133,134	Insufficient	3.2.3

+ = beneficial effect

x = no evidence

3.2.1 Cancer

A hypothesis for the protective effect of breastfeeding on breast cancer risk is that lactation causes long-term endogenous hormonal changes which may decrease a woman's cumulative exposure to estrogens, thereby inhibiting the initiation or growth of breast cancer cells. This effect would be more pronounced among pre-menopausal woman.⁹³ For *pre-menopausal breast cancer* risk possible evidence is found for a protective effect of lactating. The effect increases with the total time of lactation (over all children). However, there is insufficient evidence for an effect on *post-menopausal breast cancer* risk.

Ovarian cancer risk is also related with endogenous hormonal changes. Possible evidence was found for an effect of breastfeeding on this type of cancer. Furthermore, *cervical cancer* is thought to be related with endogenous hormonal status. Yet, only one study was found looking at this effect. Hence, the strength of evidence is inconclusive. The study did find a modest inverse effect of breastfeeding on cervical cancer risk.

Glioma is the most common primary malignant brain tumour in adults. Sex differences in incidence suggest that hormonal factors may play a role in the aetiology of this tumour. The one study found reported that cases were more likely than controls to report breastfeeding for a long period of time. The authors do emphasize the importance of caution in interpreting the results of a single study showing this association for brain cancer.⁵⁹

3.2.2 Bone density and rheumatoid arthritis

Pregnancy and lactation involve intense physiologic changes that may be important for bone development. Both states cause pronounced changes in sex steroids and other hormones involved in calcium homeostasis. They also impose calcium losses that could reduce maternal bone mass. On the other hand, calcium absorption becomes more efficient during pregnancy, a change that tends to preserve maternal bone.¹⁰³ Insufficient evidence is found for an effect of breastfeeding on *bone mass and/or hip fracture* with two studies finding no effect^{80,103} and one case-control study finding a decrease in risk with a significant trend by number of months breastfeeding.²²

Also the incidence and clinical expression of rheumatoid arthritis is related with steroid hormones which might explain why *rheumatoid arthritis* occurs 2-4 times more often in women than in men.⁶⁶ There is convincing evidence for the effect of breastfeeding on rheumatoid arthritis.

3.2.3 Weight gain

Although a biologic mechanism is suspected for the effect of breastfeeding on weight loss after pregnancy, insufficient evidence for such an effect is found within this literature overview.

3.3 Conclusion

Thus, the literature overview shows that breastfeeding appears to have a beneficial health effect for the child and mother, compared to formula feeding. Regarding the child, much evidence is available about a positive effect of breastfeeding on the incidence and severity of gastrointestinal infections including diarrhoea, otitis media, obesity and blood pressure. It is probable that breastfed children suffer less from asthma, wheezing, eczema and that intellectual and motor development is enhanced. It is possible that breastfeeding is positively related with Crohn's disease, atopy, diabetes mellitus type I, and leukaemia. The overall positive effect suggest that potential negative effects due to toxic substances, such as PCBs in human milk are dominated by the positive substances of human milk.

Regarding the mother, there is convincing evidence for a protective effect of breastfeeding on rheumatoid arthritis. Possible evidence is available that the incidence of pre-menopausal breast and ovarian cancer is lower among mothers who (longer) breastfed their infants.

4. Method of quantifying health effects

This chapter describes the model that is used for the quantification of the health effects, its assumptions in detail, the parameters, and the data used to construct. Furthermore, this chapter shows the selected scenarios for which the health effects were estimated, as well as the method of sensitivity analyses.

4.1 Description of the model

The aim of the model is to simulate the gain/loss in health given the amount of mothers that breastfeed their infant during a certain period. Breastfeeding influences the incidence of particular diseases in the child as well as in the mother herself. The model is divided in two parts. The first part focuses on the effect of breastfeeding on the children's health. Given the fraction of infants that is breastfed for a particular period, the model computes the incidences of several diseases. The second part focuses on the effect of breastfeeding on the mothers' health. Given the fractions of mothers that breastfed their infants for a particular period, the model computes the incidences of several diseases that the mothers suffer from. This part is analogous to that used for the child, it differs only in the selected diseases and the categories of breastfeeding period. The breastfeeding period for the mother is based on the total period that a mother gave breastfeeding in her life. These categories are not based on the period that she has breastfed only one infant, but they are based on the total period that she has breastfed her infants.

Subsequently, the incidences are aggregated in one public health measure, DALYs (Disability Adjusted Life Years). This measure essentially takes into account premature death and in case of illness, the physical impairment due to ill health and the duration of illness. The breastfeeding prevalence and the incidence of diseases together with its associated DALY value constitute a scenario. Figure 4.1 shows shortly the input and output factors of the model. In practice, to estimate the health effects for a specific scenario the fractions of infants that are breastfed for each period should be put into the model. Subsequently, the health effects in terms of incidences and DALYs are estimated (see Table 4.1).

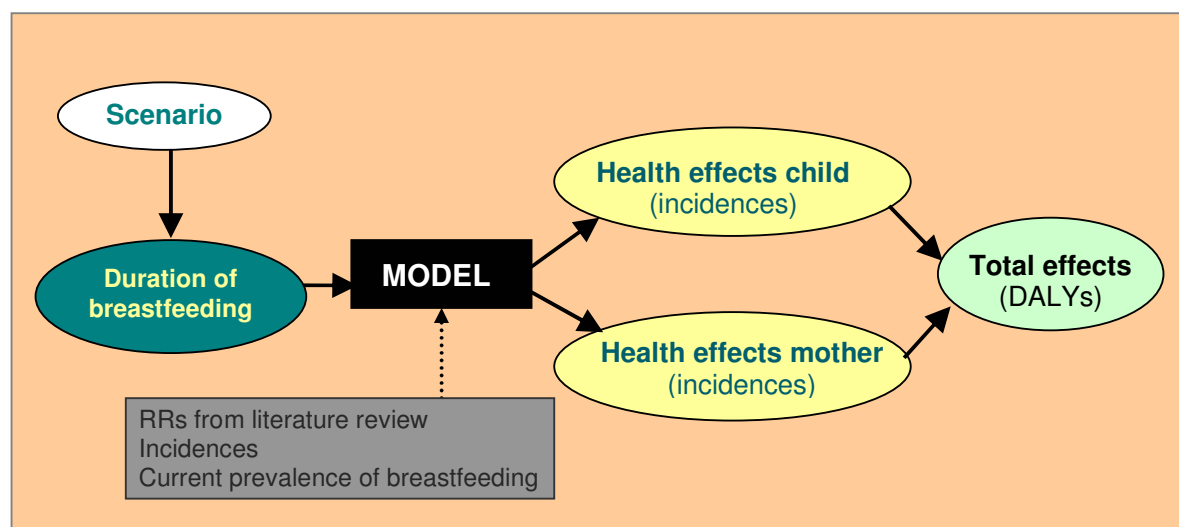


Figure 4.1 Schematic illustration of the model.

Table 4.1 Illustration of a scenario i.e. the in- and output of the model. The fraction of infants that is breastfed for a particular period should be put into the model. The resulting estimated health effects (incidences and DALYs) for that scenario are shown in last two columns.

Disease	Duration of breastfeeding*					Total Incidences	Total DALYs
	0	1	2-4	5	6 +		
	input %	input %	input %	input %	input %		
<i>Child</i>							
Otitis media	incidence	incidence	..	incidence	incidence	∑incidence	∑DALYs
Gastrointestinal infection	incidence	incidence	..	incidence	incidence	∑incidence	∑DALYs
Eczema	incidence	incidence	..	incidence	incidence	∑incidence	∑DALYs
Etc.	incidence	incidence	..	incidence	incidence	∑incidence	∑DALYs
<i>Mother</i>							
Pre-menopausal breast cancer	incidence	incidence	..	incidence	incidence	∑incidence	∑DALYs
Etc.	incidence	incidence	..	incidence	incidence	∑incidence	∑DALYs
Total effects							∑DALYs

* 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.

4.2 Structure and assumptions of the model

From the literature (see Chapter 3), relative risks or odds ratios for several diseases given the duration of breastfeeding could be deduced. The model is based on the assumption that these relative risks or odds ratios are valid in the Dutch population (see Appendix 3-A Transferable relative risks). Those relative risks were used to find a dose-response function for our model population with the aid of regression analyses (see Appendix 3-B Relative risks, dose-response estimation). Knowing the dose-response function, the present incidence of the disease and the prevalence of breastfeeding, we were able to deduce the probability of children and mothers suffering from the disease for any given duration of breastfeeding (see Appendix 3-C From relative risk to incidence or Appendix 3-D From odds ratio to incidence). Finally, the incidences of the diseases were combined into one health measure, the DALY (see Appendix 3-E From incidence to DALY).

4.3 Data for the model

In this paragraph the data that were used to construct parameters in the model is described. The values and the sources of these data are presented.

4.3.1 Breastfeeding

The model uses data from the literature (see Appendix 1) to estimate the association expressed as RRs or ORs between breastfeeding and specific diseases. Therefore, it needs to be clear what one understands by breastfeeding. Furthermore, the present prevalence of breastfeeding is input for the calculations of the model. Section 4.3.1.2 describes how the prevalence, $r(n)$ is estimated from available data.

4.3.1.1 Definition of breastfeeding

Unfortunately not all researchers have used the same definition of breastfeeding. Breastfeeding is sometimes defined as exclusive breastfeeding, sometimes it includes water. In other papers breastfeeding includes supplementary formula feeding or even anything else.

Furthermore, no breastfeeding usually means formula of unspecified type, or possibly cow's milk. We also experienced a definition problem with the duration of breastfeeding. It is not uniquely defined. In some papers duration is defined as longer than a certain period, while in other papers shorter than a certain period. Furthermore, different cut-off points to measure the duration of breastfeeding were used.

These discrepancies are solved as follows. We defined breastfeeding in the broadest sense. Thus, as long as the infant receives human milk we consider it breastfeeding. We made no distinction between exclusive and partial breastfeeding. Finally, we estimated the duration of breastfeeding to be closest to one of several one-month periods. A sensitivity analysis was applied afterwards to disclose some of the uncertainties

4.3.1.2 *Present breastfeeding prevalence*

Necessary information for the model is $\bar{r}(n)$, the fraction of infants that is breastfed for n months. This fraction is based on the prevalence of breastfeeding among infants aged between 0-6 months in the Netherlands which is measured by TNO's division Quality of Life (see appendix 3-F).⁸⁶ We distinguished six categories for the effects for the infant:

- 0=the fraction of infants that have never been breastfed;
- 1=the fraction of infants who are breastfed between one day and 1.5 month;
- 2=the fraction of infants who are breastfed ≥ 1.5 -<2.5 months;
- 3= the fraction of infants who are breastfed ≥ 2.5 -<3.5 months;
- 4= the fraction of infants who are breastfed ≥ 3.5 -<4.5 months;
- 5= the fraction of infants who are breastfed ≥ 4.5 -<5.5 months;
- 6= the fraction of infants who are breastfed ≥ 5.5 months.

The present duration of breastfeeding, based on the described procedure and data from TNO is shown in Table 4.3.

For the effects of the mother, we assumed that each mothers breastfeed all their infants equally long and that no relation exists between the duration of breastfeeding and the number of infants. In addition we assumed that the average number of infants per mother was 1.75.¹ The six categories for the effects of the mother are:

- 0=the fraction of mothers that have never breastfed;
- 1=the fraction of mothers who give breastfeeding to each child on average between one day and 1.5 months (cumulative >0 -<2.6 months);
- 2=the fraction of mothers who give breastfeeding to each child on average ≥ 1.5 -<2.5 months (cumulative $= \geq 2.6$ -<4.4 months);
- 3=the fraction of mothers who give breastfeeding to each child on average ≥ 2.5 -<3.5 months (cumulative $= \geq 4.4$ -<6.1 months);
- 4=the fraction of mothers who give breastfeeding to each child on average ≥ 3.5 -<4.5 months (cumulative $= \geq 6.1$ -<7.9 months);
- 5=the fraction of mothers who give breastfeeding to each child on average ≥ 4.5 -<5.5 months (cumulative >7.9 -<9.6 months);
- 6=the fraction of mothers who give breastfeeding to each child on average ≥ 5.5 months (cumulative >9.6 months).

4.3.2 **Diseases**

In general only those diseases could be incorporated in the model for which the available literature allows the extraction of data and parameters that are necessary for the model. This means that the diseases that are incorporated in the model must satisfy the following criteria

- There is evidence for at least a possible association between breastfeeding and the disease.
- The duration of breastfeeding is stated.
- The health effect measure, either relative risk or odds ratio, and definition of the disease is consistent.
- The age at which the disease is diagnosed is consistent.
- The reference group for the relative risk or odds ratio calculation is formula feeding or no breastfeeding.
- The results are adjusted for confounders.
- The disease is expressed as a dichotomous state. This excludes health effects such as blood pressure and intellectual development.

In short this means that enough good quality data had to be available to estimate a dose-response function. In Appendix 1 and Appendix 2 the studies that are excluded from use in the model are denoted by a highlighted footnote that expresses the motivation for exclusion.

The model incorporated the following diseases for the child:

- Otitis media, at age 0-12 months
- Gastrointestinal disorders, at age 0-12 months
- Asthma, at age 0-7 years
- Respiratory morbidity, at age 0-12 months
- Eczema, at age 0-18 months
- Crohn's disease, at age 6 months
- Acute lymphatic leukaemia between 0 and 15 years of age
- Obesity/overweight, between age 3 and 10.

For the mother:

- Rheumatic arthritis
 - Pre-menopausal breast cancer
 - Ovary cancer
- have been incorporated in the model.

4.3.3 Disease parameters

The parameters that were needed in the model for each disease are:

- β_d , the regression estimate of the dose-response function of disease d
- p_d , the present incidence of disease d
- w_d , the DALY weight of disease d
- s_d , the conditional mortality rate, provided one suffers from disease d
- AD_d , the average age at the onset of disease d
- LE_d , the life expectancy at AD_d

The following table shows the values of the parameters that were used in the model. Appendix 4 shows graphically the data and the regression estimates of the relative risks and odds ratios of the modelled diseases.

Table 4.2 Disease parameters of the model.

	β^a	RR*	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 ^{b,c}	0.13646	0.030 ^c			
Asthma	-0.039	0.789	0.02356 ^{b,c}	0.02739	0.070 ^{c,e}	0.00001 ^c	79.1	4.5
Respiratory Infection	-0.051	0.734	0.54955 ^b	0.66559	0.020 ^c			
Eczema	-0.048	0.748	0.11370 ^{b,c}	0.13631	0.043 ^{c,f}			
Crohn's Disease	-0.111	0.512	0.00005 ^b	0.00008	0.200 ^c	0.005 ^c	79.3	8.5
Leukaemia	-0.025	0.862	0.00003 ^h	0.00004	0.098 ^c	0.212 ^h	79.2	7.5
Obesity	-0.017	0.901	0.00033 ^b	0.00035	0.035 ⁱ			
Mother								
Rheumatic Arthritis	-0.020	0.889	0.00248 ^c	0.00283	0.530 ^c	0.012 ^c	85.3	68.5
Premenopausal Breast Cancer	-0.007	0.960	0.00070 ^c	0.00074	0.148 ^{c,e}	0.183 ^c	82.2	40.0
Ovary Cancer	-0.007	0.960	0.00017 ^{g,h}	0.00017	0.084 ^c	0.128 ^h	82.8	50.0

RR* The relative risk for breastfeeding 6 months versus never breastfeeding.

Sources: ^a=journal papers (see Appendix 1 and Appendix 2; ^b=NIVEL 2nd study⁹²; ^c=RIVM-kompas²; ^d=CBS¹; ^e=WHO¹⁰⁵; ^f=MIDAS¹⁵; ^g=IARC¹²⁰; ^h=IKC³; ⁱ=estimated between athlete's foot (0.01) and acne (0.06).

When multiple sources are mentioned, the average over all values is used.

4.4 Breastfeeding scenarios

A scenario shows the effects on public health (incidences and DALYs) for a situation where the distribution of the duration that infants are breastfed is presupposed. The following subsections describe the scenarios with the presupposed distribution of duration of breastfeeding. Table 4.3 and Figure 4.2 summarize these scenarios. For each scenario we estimated the incidences of each relevant disease and compared the health effects with the present situation. The present situation was used as reference scenario, the best case and worst case scenarios were used to indicate the maximum health effect that can be gained or lost. Others represent possible interventions.

4.4.1 Present situation

This scenario reflects the present situation and is used as reference scenario. Breastfeeding prevalence was as it was measured in the Dutch population,⁸⁶ see also section 4.3.1.2.

Table 4.3 Distribution of breastfeeding for each scenario, fractions r (%).

	Duration of breastfeeding (months)*						
Scenario	0	1	2	3	4	5	6+
Present situation	22	19	9	8	4	3	35
Best case	0	0	0	0	0	0	100
Worst case	100	0	0	0	0	0	0
0→BF	0	25	11	10	5	4	45
+1 month	0	22	19	9	8	4	38
+1 month (excl 0)	22	0	19	9	8	4	38
>0-3 months	22	0	0	36	4	3	35
3-6 months	22	19	9	8	0	0	42
5% shift	17	19	9	8	4	3	40

* No distinction between exclusive and nonexclusive breastfeeding is made.

4.4.2 Best case scenario, all infants 6 months

The best possible scenario is the situation if all mothers breastfeed their infants for at least six months.

4.4.3 Worst case scenario

The worst possible scenario reflects the situation in which all mothers give formula feeding to their infants; in other words none of the mothers breastfeed their infants.

4.4.4 Policy: 0→ BF

The policy of VWS is to promote breastfeeding. The focus of potential intervention strategies can be different. This scenario depicted the results if the intervention strategy is focussed on those who feed their infant formula at birth. In this scenario we assume that all of these mothers initiate breastfeeding. The duration of breastfeeding was assumed to be similar to that of the current breastfeeding mothers. So, that if in the current situation 25% of all breastfeeding mothers breastfeeds their infant for six months, then in this scenario 25% of all mothers will breastfeed their infant for six months.

4.4.5 Policy: +1 month

This scenario depicts the results if all mothers breastfeed their infant one month longer compared to the present situation. Consequently, the number of infants who are never breastfed were assigned to the 1 month category.

4.4.6 Policy: +1 month, (excl. 0)

This scenario depicts the results if only breastfeeding mothers breastfeed their infants one month longer compared to the present situation. In this scenario, the percentage of never breastfed infants equals the current situation.

4.4.7 Policy: >0-3 months

An alternative policy is to focus on mothers that stop breastfeeding during the first three months. In this scenario, we assumed that mothers who currently breastfeed their infant less than three months, continue to breastfeed their infant up to three months. The prevalence of never breastfed infants and prevalences in the categories of three months and more remain the same.

4.4.8 Policy: 3-6 months

This scenario focuses on mothers who are already enthusiastic about breastfeeding. In this scenario, every mother who currently breastfeeds her infant for three months or more, breastfeeds her infant more than six months.

4.4.9 Policy: 5% shift

In this scenario an absolute 5% in each category prolongs breastfeeding with one month. This means that each category, except the first and the last, gains 5% and loses 5% so that effectively the category never breastfed decreases by 5% and the category 6+ increases by 5%. Although this model does not differentiate between exclusively and partial breastfeeding, this scenario corresponds roughly with the current policy goal of the Dutch government

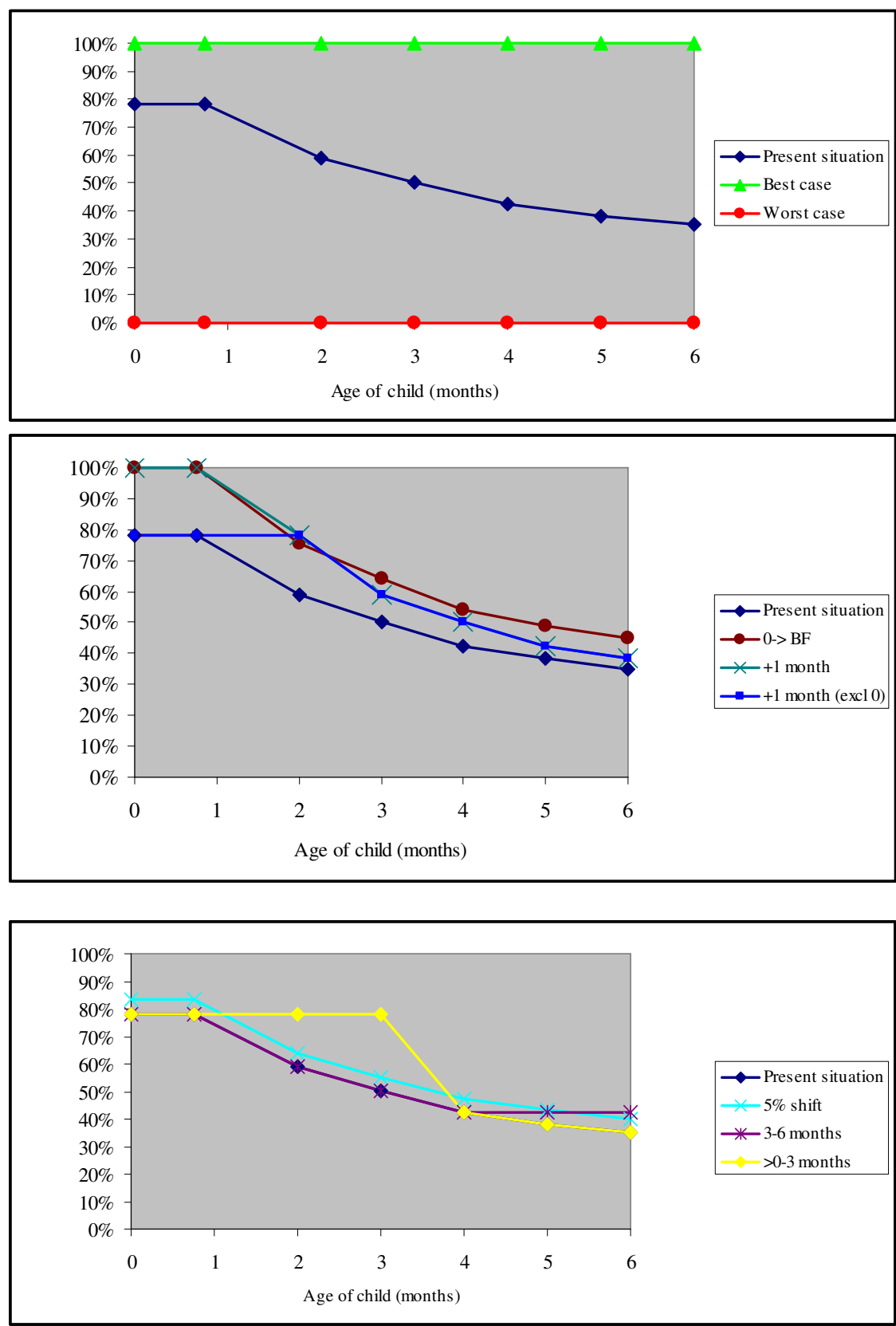


Figure 4.2 Percentage of infants who are breastfed at a certain age for each scenario.

stating that 23% instead of 18% of all mothers give exclusively breastfeeding for at least 6 months.

4.5 Sensitivity analysis

The model's parameters, β_d , w_d , $\overline{p_d}$, $\overline{r(n)}$, are all uncertain. Therefore, a sensitivity analysis for these parameters was done by applying a Monte-Carlo approach. The model was simulated 5000 times, each time with a randomly chosen value for each parameter between its minimum and maximum value. The minimum and maximum were set at plus or minus 10% change of the default value. Note that 10% is considered a small deviation. Parameter estimates from different sources often show much more than 10% difference.

The result is a probability distribution of the incidences of each disease and the combined health effect expressed in DALYs per scenario. The probability distributions reflect the uncertainty in one or more parameter estimates. The sensitivity analysis was performed for each parameter separately and for all parameters together.

5. Quantification of health effects

This chapter describes the quantified health effects. First, the health effects by duration of breastfeeding, second the health effects in incidences and DALYs for each scenario. This chapter is finished with a conclusion.

5.1 Health effects by duration of breastfeeding

Similar to the qualitative overview, the model showed that breastfeeding is associated with a lower incidence of the specified diseases. Intrinsic to the model, in which we estimated log linear regression lines for each disease, a dose-response function was observed between breastfeeding and all modelled diseases of the infant and the mother; those in the category of more than six months breastfeeding had the lowest incidences. Figure 5.1 shows these functions. For children 10-51% of all incident cases among the group who never got breastfeeding could be prevented if the children in this group had got breastfeeding for six months (RRs for at least six months breastfeeding versus never breastfeeding varied between 0.49 to 0.90). The RRs are shown in Table 4.3. The strongest association was found for gastrointestinal infections (RR=0.49). In general, the associations between diseases among children were stronger compared to that of the mothers. For mothers the RRs varied between 0.86 to 0.96.

5.2 Health effects for each scenario

For each scenario in which we assumed a certain distribution of duration of breastfeeding we estimated the incidences for all relevant diseases. Subsequently, the absolute difference between each scenario and the present situation was calculated. Besides the increase or decrease in incidences, the health effects were also expressed in DALYs, in order to sum up all the different health effects in one measure, in which the duration of the disease is taken into account. Again these effects were expressed as a difference with the present situation as reference. The results are described in the following paragraphs.

5.2.1 Effect on incidences for each scenario

Figure 5.2 shows that if all children will be breastfed for at least six months (*scenario best case*), per 1000 person years 49 incident cases of otitis media, 46 cases of gastrointestinal infections, 131 cases of respiratory infections and 26 cases of eczema would be prevented. 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. Also four incident cases of asthma per 1000 person years could be prevented if all children get at least six months breastfeeding. For the less incident diseases, like Crohn's disease, leukaemia or obesity at young age, the number of prevented cases was: 256, 39 and 273 per 100,000 person years. For example for Crohn's disease this would be 47% of the total incidence of Crohn's disease and around 10% for leukaemia or obesity.

If the opposite will happen: all mothers would give only formula feeding to their children (*worst case scenario*), similar changes in incidences of these diseases, but in this case increases of these incidences (or health losses), would be observed.

In Figure 5.3 the different policy scenarios are shown. The expected changes in incidences in these scenarios were much lower than in the best-case scenario. The largest differences in incidences would be achieved if all mothers start at birth of their infants with breastfeeding

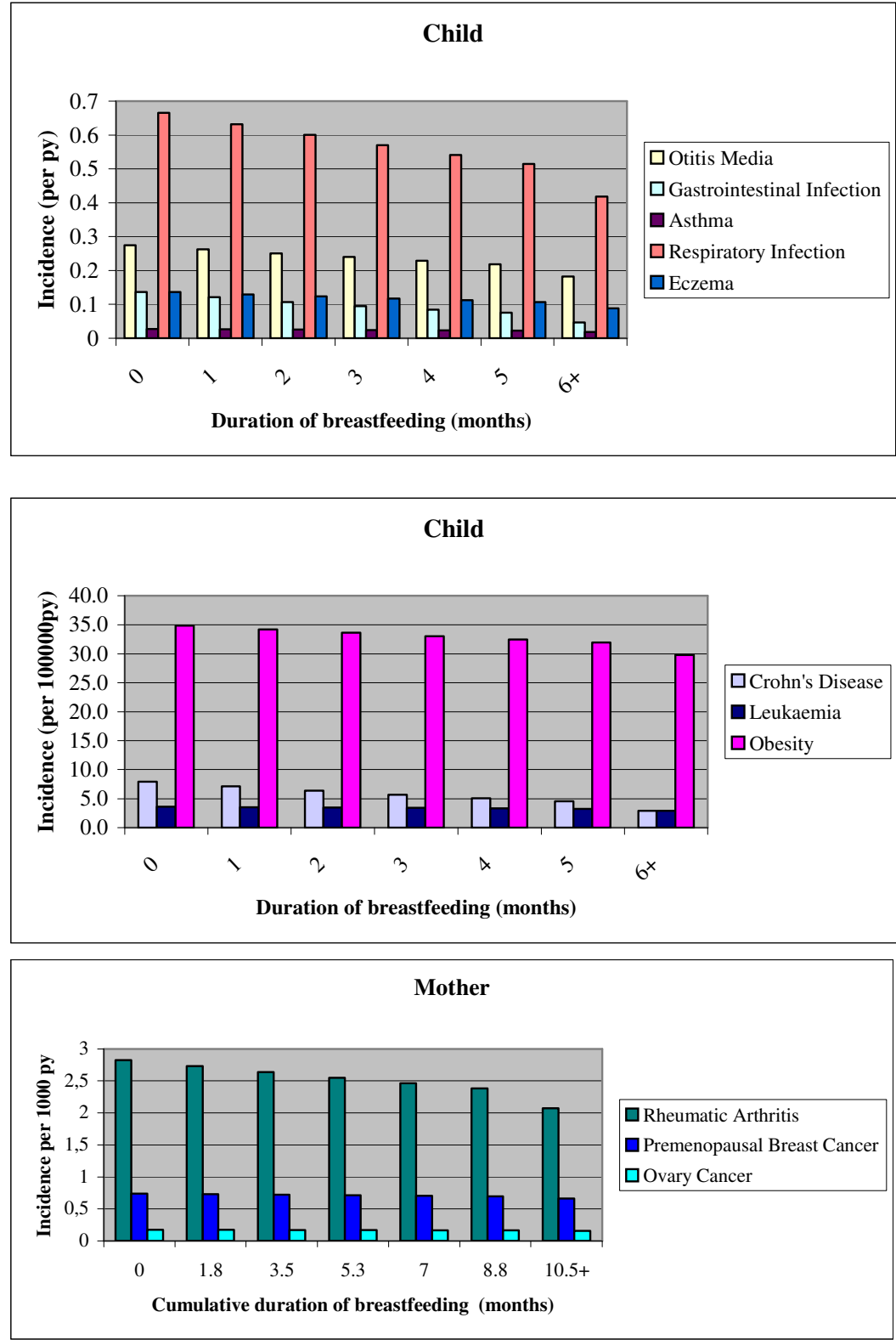


Figure 5.1 Incidences of diseases for the infant and mother by duration of breastfeeding.

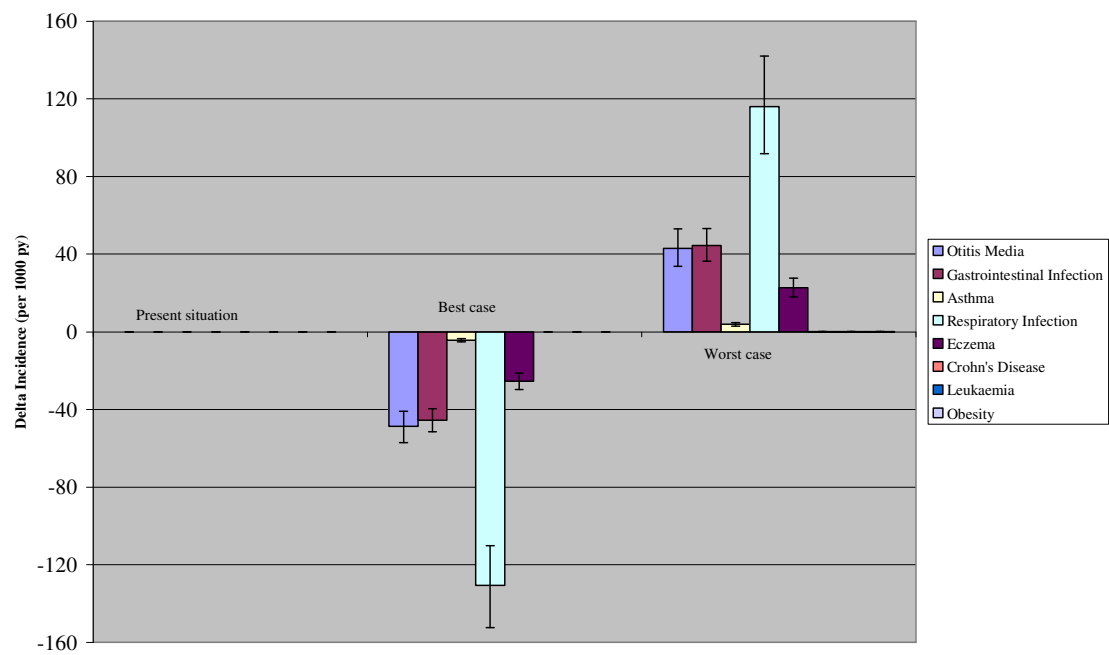


Figure 5.2 Estimated effects on the incidences of diseases for the child for the best case and worst-case scenario compared to the present situation. The error bars represent the probability distribution of the incidences of each disease due to the uncertainty in the used parameters.

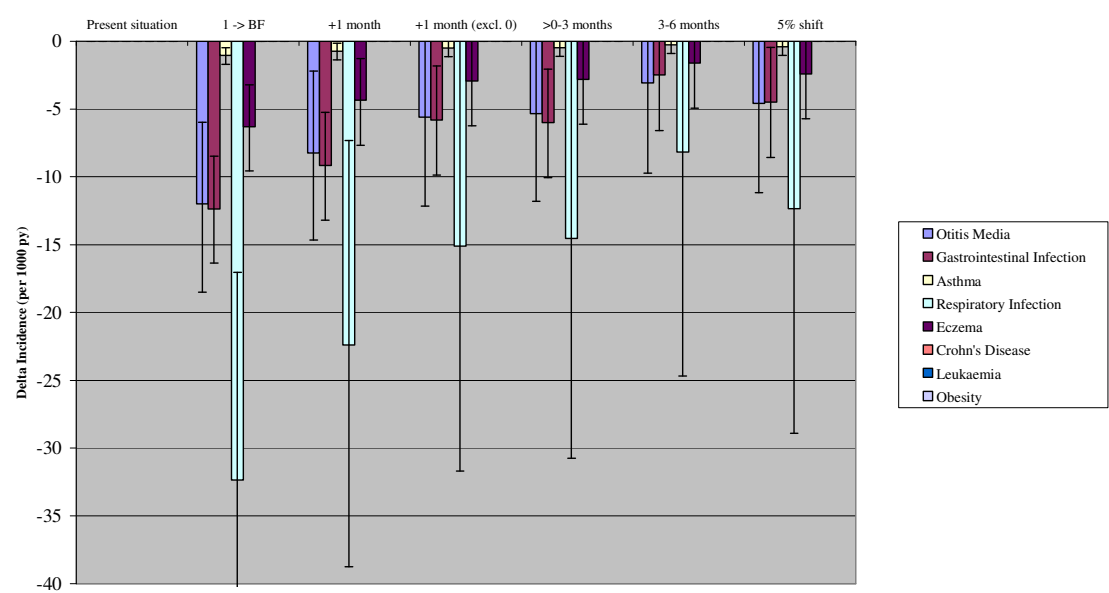


Figure 5.3 Estimated effects on the incidences of diseases for the child per possible intervention scenario compared to the present situation. The error bars represent the probability distribution of the incidences of each disease due to the uncertainty in the used parameters.

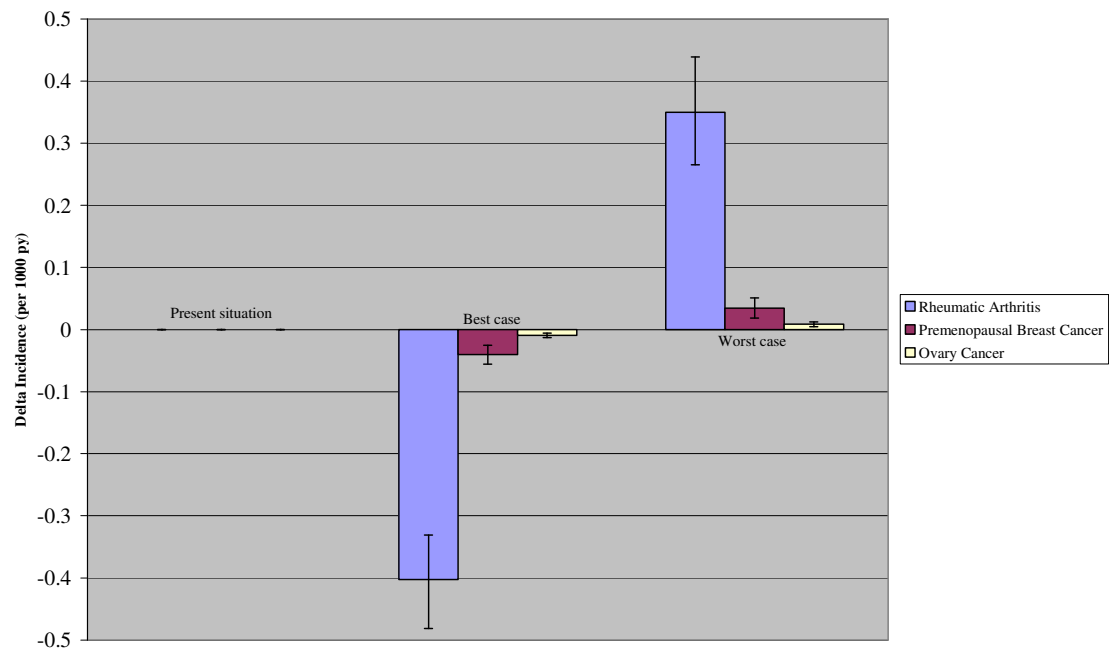


Figure 5.4 Estimated effects on the incidences of diseases for the mother for the best case and worst-case scenario compared to the present situation. The error bars represent the probability distribution of the incidences of each disease due to the uncertainty in the used parameters.

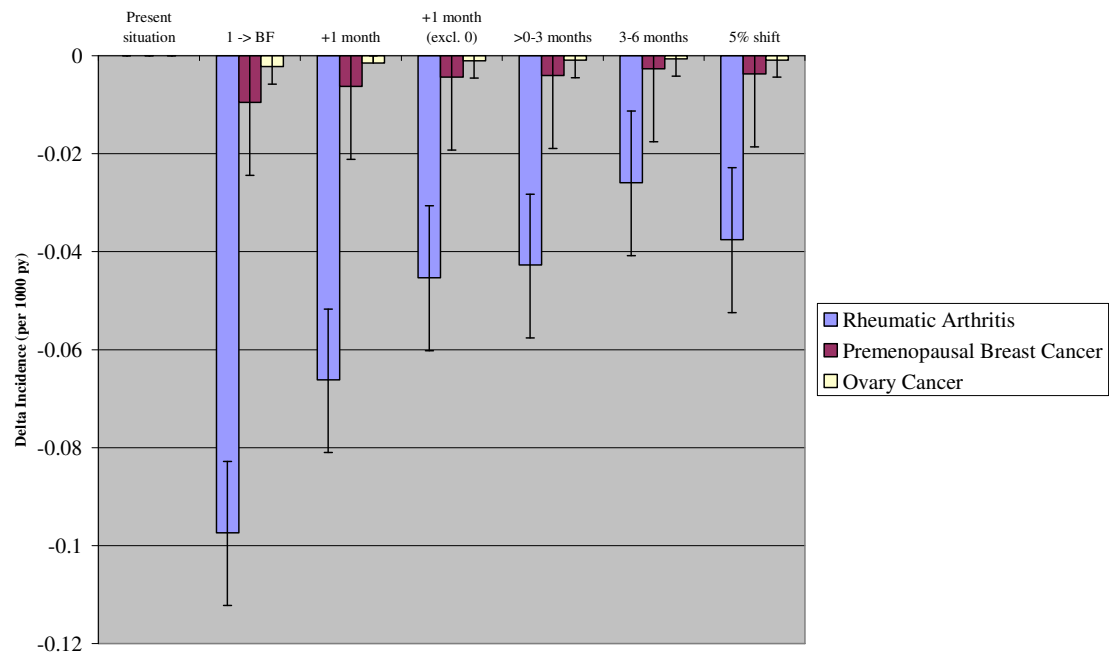


Figure 5.5 Estimated effects on the incidences of diseases for the mother per possible intervention scenario compared to the present situation. The error bars represent the probability distribution of the incidences of each disease due to the uncertainty in the used parameters.

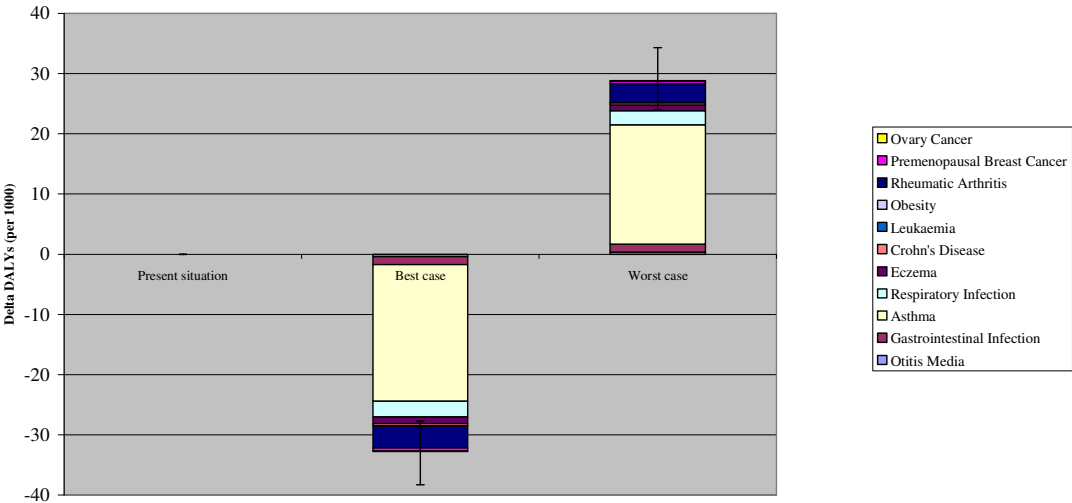


Figure 5.6 Estimated effects on DALYs for the mother and child together per scenario for the best case and worst-case scenario compared to the present situation. The error bars represent the probability distribution of DALYs due to the uncertainty in the used parameters.

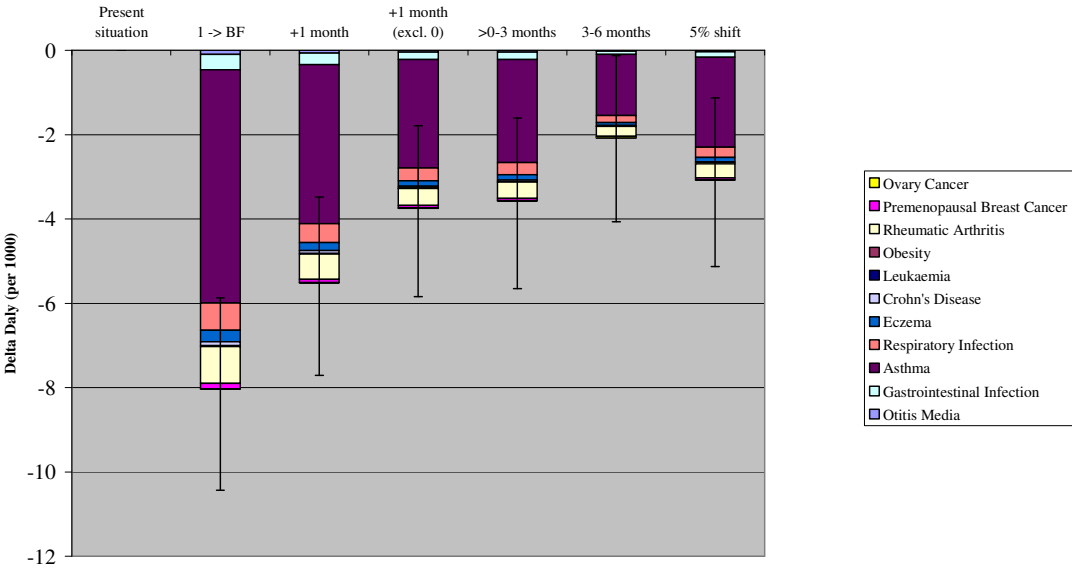


Figure 5.7 Estimated effects on DALYs for the mother and child together per scenario compared to the present situation. The error bars represent the probability distribution of the DALYs due to the uncertainty in the used parameters.

(*scenario 0-> BF*). About 25% of all preventable incidences are prevented with this scenario. Also large health gain would be achieved if all mothers would breastfeed their infants one month longer compared to the current situation (about 17%). In this scenario, all non-breastfeeders initiate breastfeeding for on average 1 month. Of course, if the non-breastfeeders were excluded from these changes the health gain would be lower: about 11% (*scenario + 1 month (excl. 0)*). The smallest decrease in incidences would be observed if the interventions would be focussed on only the already enthusiastic breastfeeding-giving women: to prolong the period from 3 to 6 months (*scenario 3-6 months*). Compared to the best-case scenario only 6% of the preventable incidences could be prevented with this policy.

Figure 5.4 shows the changes in incidences for the mothers. These changes were smaller than those among children. In the *best case scenario*, each year four incident cases of rheumatic arthritis or one incident case of ovary cancer could be prevented in 100,000 person years. This is 16%, 6% or 6% respectively of the total incidence of these diseases in these women. Furthermore, pre-menopausal breast cancer would decrease with ten incident cases per 100,000 person years if all mothers would breastfeed their infants for six months. However, this would be utopia. The different policy scenarios showed the same pattern compared to the health gain for the children: The lowest incidences would be achieved if the policy would be successfully focused on the formula feeders at day 0. Less health gain would be achieved if the intervention concentrates on those who otherwise breastfeed already more than three months.

5.2.2 Effect on DALYs for each scenario

DALYs should be interpreted with care. They need to be compared to the results of a benchmark or reference scenario. Figures 5.6 and 5.7 show the gain in DALYs for the different scenarios. The difference in DALYs between a scenario and the reference scenario are the life years adjusted for disability that are gained or lost when the scenario becomes true instead of the reference.

In the *best-case scenario*, 33 DALYs per 1000 persons could be prevented compared to the *present situation*. Asthma among children and rheumatic arthritis among the mothers contributed the largest gain in DALYs. The largest gain in DALYs was observed for scenario '*0->BF*' and for scenario '*+1 month*': 8.0 and 5.5 DALYs, respectively, compared to the present situation. Besides scenario '*3-6 months*', the other scenarios showed similar gain in health: about 3.5 DALYs per 1000 persons.

5.3 Conclusion

Thus, a weigh up of all health effects, showed a unanimously beneficial effect of breastfeeding compared to formula feeding. Also the longer breastfeeding the lower the incidences of several diseases. If all mothers would fulfil the recommendation of the WHO of giving six months breastfeeding, then per 1000 person years 48 incident cases of otitis media, 46 cases of gastrointestinal infections and about 131 cases of respiratory infections and 25 cases of eczema, four incident cases of asthma and per 100,000 py: 256, 39 or 273 cases of Crohn's disease, leukaemia or obesity at young age would be prevented. Although the health effects for the different policy scenarios did not differ so much, the largest estimated health gain was achieved if all mothers would start at birth of their infants with breastfeeding (*scenario 0-> BF*) or if all mothers would breastfeed their infants one month longer compared to the current situation. The smallest decrease in incidences would be observed if the interventions would be focussed on prolonging the breastfeeding period of 3 to 6 months.

6. General discussion

6.1 Main results

Our study showed that in westernised countries breastfeeding seems to have a unanimously beneficial health effect for the child and the mother, compared to formula feeding. Also, the longer the breastfeeding period, the lower the incidences of several diseases. For the infant, convincing evidence is available about the positive effect of breastfeeding on the incidence and severity of gastrointestinal infections including diarrhoea, otitis media, obesity and blood pressure. It is probable that breastfed children will get less asthma, wheezing, eczema or less intellectual or motor development. Possibly that breastfeeding is positively related with Crohn's disease, atopy, diabetes mellitus type I, and leukaemia. For the mother, there is convincing evidence for a protective effect of breastfeeding on rheumatoid arthritis. Possible evidence was available that the incidence of pre-menopausal breast or ovarian cancer is lower among mothers who (longer) breastfed their infants.

In the model in which the health effects are quantified, we estimated that if all children will be breastfed for at least six months (*scenario best case*), per 1000 person years the largest decreases in incidences are seen for the immediate health of the infant, such as infections. However, the beneficial effects extend beyond infancy immediate health. Although these effects concerns only a few incident cases of chronic diseases, such as asthma, these cases contribute to a large extend to the DALYs as they are prevented for the whole life of a sibling. Also the beneficial effects for the maternal health would happen in the longer term. In total, per 1000 persons 33 DALYs could be prevented if all mothers would give for six months human milk to their infants.

Also the health effects for several potential policy scenarios were estimated. The largest health gain would be achieved when all newborns were breastfed for at least six months (best case scenario). However, this figure could never be reached. Comparing the different policy scenarios with each other the largest estimated health gain was achieved if all mothers would start at birth of their infants with breastfeeding (*scenario 0-> BF*). The smallest decrease in incidences was observed if the interventions would be focussed on prolonging the breastfeeding period of three to six months.

6.2 Limitations and strengths of methods

Before, we can draw final conclusions, we would like to discuss some limitations and strengths of this study. First for the overview of the literature and secondly for the method of modeling.

Overview

In our overview, it is notable that almost no Dutch studies are present. Therefore, 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. This restriction of taking also developing countries into account was not made in previous overviews.^{78,168} But in our view this restriction was necessary for valid conclusions for the Dutch situation.

A strength of our overview was that articles which did not fulfil all quality requirements, the study was excluded from the literature overview in order to ascertain good quality of our conclusions. For example, we selected only peer-reviewed manuscripts. 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.

An issue that was still not taken into account in our study is the variation in constituents of formula feeding between the several studies. The ingredients of formula feeding differ over the countries, but also over the course of time. For that reason only recent studies are suitable for a correct balancing of the effects of breastfeeding compared to formula feeding, as in most cases the formula feeding has been improved over time.

Though, this kind of variation is not only an issue for formula feeding. Also dietary habits of the mother differ over the countries or have also changed over time, which could affect the composition of breastfeeding. It would be interesting to elucidate the effects of dietary habits of the mother on human milk in further research. This knowledge could then be used to increase the health benefits of breastfeeding.

Some part of the associations found might be explained by (residual) confounding as different studies took different confounders into account or corrected for confounders in a different way. We tried to avoid this kind of bias by using the selection criteria of correction for most relevant confounders. Although an overestimation of the effects cannot fully be excluded.

Model

A model is always per definition a simplification of the reality. But as far as we know this model is the first model in which the health effects of breastfeeding are quantified in such detail. Compared to a previous report more, and more recently known health effects are taken into account, not only for the child but also for the mother.⁷⁹ In addition, not only a distinction between breastfeeding and formula feeding is made, but also the duration of breastfeeding is taken into account. Ideally, we would have made also a distinction between exclusive and mixed breastfeeding and even whether the human milk is immediately drunk from the breast or given to the child with a bottle. Unfortunately, this was not possible with the current available data, but would be interesting to investigate.

The designed model was based on several assumptions that could be discussed. First of all, in the quantification of the health effects, we could not include all health effects in the model, even when there was convincing evidence for an association with breastfeeding. For example cognitive development, or the blood pressure. This led to an underestimation of the beneficial effect of breastfeeding. However, the conclusion of the comparison of the health effects of the several policy scenarios would not be different when these disorders were included in some way. On the other hand, in the model also diseases with possible evidence are taken into account, which could have led to an overestimation of the effect. The main reason to do this was the inclusion of diseases with a long period between the moment of breastfeeding and the diagnose of the diseases. Evidence for such an association was mainly assessed with case-control studies. Cohort studies for elucidating these associations should have even been less valid as the ingredients of formula feeding have dramatically changed over time.

Secondly, many 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. 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. Because of the uncertainty in the parameters, we performed a sensitivity analyses. These analyses showed that the model could distinguish between the most diverse scenarios. But unfortunately, it was impossible to distinguish between the health benefits of all scenarios.

Furthermore, DALYs are not without discussion⁵ 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.¹⁰² For example, as no cure is possible for a disease, it contributes many DALYs. Therefore, asthma is the most contributing disease in terms of DALYs. Apart from the fact that it is a relatively severe disease this is due to the model assumption that no cure is possible. This means children/people live with the disease for the largest part of their lives. Nevertheless, from the perspective of a policymaker 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.

6.3 Conclusions and recommendations

In line with the Dutch RIVM rapport 'Ons eten gemeten',⁷⁹ we conclude that potential negative effects due to toxic substances, such as PCBs and dioxins in the human milk are dominated by the positive substances of human milk. Most epidemiological studies look at the beneficial effects of breastfeeding in general, not at specific beneficial or harmful substances within the human milk. But in fact, breastfeeding looked at in these epidemiological studies represents a mix of all the beneficial and harmful substances present in the milk. This predominance of the beneficial effect would even increase as during the last decades the levels of some toxic substances in human milk, such as dioxins en PCBs decreased in the Netherlands¹⁶⁰ and are expected to go down further in the coming years.^{34,179} The greatest and most obvious benefits of breastfeeding are seen for the immediate health of the infant. However, the overview showed also that beneficial effects extend beyond infancy immediate health and showed also beneficial effects for the maternal health in the longer term.

We focussed our assessment on the general Dutch population. Thus our conclusion of preferences of breastfeeding above formula feeding is not valid for specific conditions, such as mothers with an 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, anti-depressant. Under such specific conditions the risk-benefit analyses should be made at an individual level.

The impact of alcoholic beverages, smoking etc, more general drug use, such as mild analgesics or contraception drugs are not taken into account in our model. However, it would be interesting to elucidate the effects of these substances and dietary habits of the mother on human milk in further research. As it is likely that knowledge on the impact of these factors could increase the beneficial effect of breastfeeding.

Given the beneficial effect of breastfeeding it is recommended that all infants be fed with breastfeeding for the first six months of life. As currently only a small part of the Dutch mothers comply with the WHO recommendation by giving exclusive breastfeeding to every infant for at least six months, it is obvious that the policy of the Dutch government is focussed on an increase of this percentage. Our model illustrated that the best policy after the WHO recommendations would be initiation of all mothers with breastfeeding, even for a short duration. Of course, this is not feasible for all mothers because of certain conditions, but figures in other countries show that a higher percentage could be reached.

In the report the chosen scenarios were based on theoretical interventions. In the future, our model could be used for evaluating the health effects of conducted interventions or to estimate the health effects of several potential policies based on several interventions or focussed on specific subpopulations, such as low-SES groups. For such calculations it is necessary to know the effectiveness of the interventions; in other words what would be the change in distribution of duration of breastfeeding due to the intervention. Kools mentioned that there are interventions which were effective in many trials, but also ineffective in many others.⁷² Thus, information on the effectiveness is not yet available. However, in 2006 more data on the effectiveness of current actual interventions would become available, which can be used for a quantification of the health effects of these interventions.

Thus in summary, a policy by which an increase in the percentage of breastfeeding infants would be achieved can be seen as a preventive measure. Although this model is not sensitive enough to distinguish between all potential policies, it indicates that the most health gain would be achieved if the policy would be focussed on getting all mothers initiating breastfeeding. In addition to this quantification of the health effects, presumably the health effects in terms of costs will be performed in 2006.

Acknowledgements

We wish to thank our colleagues Diane van Houweling, Nancy Hoeymans, Cathy Rompelberg, Martine Bakker, Rudolf Hoogenveen, Marco Zeilmaker, Alet Wijga and Wout Slob for their contribution to this report, by giving critical notes and advise.

References

1. Available at <http://statline.cbs.nl>.
2. Available at <http://www.nationaalkompas.nl>.
3. Available at <http://www.ikcnet.nl/>.
4. Alho OP, Koivu M, Sorri M, Rantakallio P. Risk factors for recurrent acute otitis media and respiratory infection in infancy. *Int J Pediatr Otorhinolaryngol* 1990; 19(2):151-61.
5. Anand S, Hanson K. Disability-adjusted life years: a critical review. *J Health Econ* 1997; 16(6):685-702.
6. Anderson JW, Johnstone BM, Remley DT. Breast-feeding and cognitive development: a meta-analysis. *Am J Clin Nutr* 1999; 70(4):525-35.
7. Aniansson G, Alm B, Andersson B *et al*. A prospective cohort study on breast-feeding and otitis media in Swedish infants. *Pediatr Infect Dis J* 1994; 13(3):183-8.
8. Arenz S, Ruckerl R, Koletzko B, Von Kries R. Breast-feeding and childhood obesity-a systematic review. *Int J Obes Relat Metab Disord* 2004.
9. Armstrong J, Reilly JJ. Breastfeeding and lowering the risk of childhood obesity. *Lancet* 2002; 359(9322):2003-4.
10. Beaudry M, Dufour R, Marcoux S. Relation between infant feeding and infections during the first six months of life. *J Pediatr* 1995; 126(2):191-7.
11. Bergmann KE, Bergmann RL, Von Kries R *et al*. Early determinants of childhood overweight and adiposity in a birth cohort study: role of breast-feeding. *Int J Obes Relat Metab Disord* 2003; 27(2):162-72.
12. Bergmann RL, Diepgen TL, Kuss O *et al*. Breastfeeding duration is a risk factor for atopic eczema. *Clin Exp Allergy* 2002; 32(2):205-9.
13. Bernier MO, Plu-Bureau G, Bossard N, Ayzac L, Thalabard JC. Breastfeeding and risk of breast cancer: a metaanalysis of published studies. *Hum Reprod Update* 2000; 6(4):374-86.
14. Bertini G, Dani C, Tronchin M, Rubaltelli FF. Is breastfeeding really favoring early neonatal jaundice? *Pediatrics* 2001; 107(3):E41.
15. Bonsel GJ, Janssen , Birnie E. Mild Disability and Ailment Study. 2003; CVZ report 176.
16. Booth M, Beral V, Smith P. Risk factors for ovarian cancer: a case-control study. *Br J Cancer* 1989; 60(4):592-8.
17. Brinton LA, Potischman NA, Swanson CA *et al*. Breastfeeding and breast cancer risk. *Cancer Causes Control* 1995; 6(3):199-208.
18. Brun JG, Nilssen S, Kvale G. Breast feeding, other reproductive factors and rheumatoid arthritis. A prospective study. *Br J Rheumatol* 1995; 34(6):542-6.
19. Chandra RK, Hamed A. Cumulative incidence of atopic disorders in high risk infants fed whey hydrolysate, soy, and conventional cow milk formulas. *Ann Allergy* 1991; 67(2 Pt 1):129-32.
20. Chulada PC, Arbes SJ Jr, Dunson D, Zeldin DC. Breast-feeding and the prevalence of asthma and wheeze in children: analyses from the Third National Health and Nutrition Examination Survey, 1988-1994. *J Allergy Clin Immunol* 2003; 111(2):328-36.
21. Coupland CA, Forman D, Chilvers CE, Davey G, Pike MC, Oliver RT. Maternal risk factors for testicular cancer: a population-based case-control study (UK). *Cancer Causes Control* 2004; 15(3):277-83.
22. Cumming RG, Klineberg RJ. Breastfeeding and other reproductive factors and the risk of hip fractures in elderly women. *Int J Epidemiol* 1993; 22(4):684-91.
23. Daly KA, Brown JE, Lindgren BR, Meland MH, Le CT, Giebink GS. Epidemiology of otitis media onset by six months of age. *Pediatrics* 1999; 103(6 Pt 1):1158-66.
24. Davis MK. Review of the evidence for an association between infant feeding and childhood cancer. *Int J Cancer Suppl* 1998; 11:29-33.
25. Davis MK. Breastfeeding and chronic disease in childhood and adolescence. *Pediatr Clin North Am* 2001; 48(1):125-41, ix.
26. Davis MK, Savitz DA, Graubard BI. Infant feeding and childhood cancer. *Lancet* 1988; 2(8607):365-8.
27. Dell S, To T. Breastfeeding and asthma in young children: findings from a population-based study. *Arch Pediatr Adolesc Med* 2001; 155(11):1261-5.
28. Dewey KG, Heinig MJ, Nommsen-Rivers LA. Differences in morbidity between breast-fed and formula-fed infants. *J Pediatr* 1995; 126(5 Pt 1):696-702.
29. Duffy LC, Faden H, Wasielewski R, Wolf J, Krystofik D. Exclusive breastfeeding protects against bacterial colonization and day care exposure to otitis media. *Pediatrics* 1997; 100(4):E7.

30. Duncan B, Ey J, Holberg CJ, Wright AL, Martinez FD, Taussig LM. Exclusive breast-feeding for at least 4 months protects against otitis media. *Pediatrics* 1993; 91(5):867-72.
31. Enger SM, Ross RK, Henderson B, Bernstein L. Breastfeeding history, pregnancy experience and risk of breast cancer. *Br J Cancer* 1997; 76(1):118-23.
32. Florey CD, Leech AM, Blackhall A. Infant feeding and mental and motor development at 18 months of age in first born singletons. *Int J Epidemiol* 1995; 24 Suppl 1:S21-6.
33. Ford RP, Taylor BJ, Mitchell EA *et al.* Breastfeeding and the risk of sudden infant death syndrome. *Int J Epidemiol* 1993; 22(5):885-90.
34. Freijer JJ, Hoogerbrugge R, van Klaveren JD, Traag WA, Hoogenboom L, Liem AKD. Dioxins and dioxin-like PCBs in foodstuff: Occurrence and dietary intake in The Netherlands at the end of the 20th century. Bilthoven: RIVM, 2001; RIVM report 639102022.
35. Freudenheim JL, Marshall JR, Graham S *et al.* Exposure to breastmilk in infancy and the risk of breast cancer. *Epidemiology* 1994; 5(3):324-31.
36. Furberg H, Newman B, Moorman P, Millikan R. Lactation and breast cancer risk. *Int J Epidemiol* 1999; 28(3):396-402.
37. Gdalevich M, Mimouni D, David M, Mimouni M. Breast-feeding and the onset of atopic dermatitis in childhood: a systematic review and meta-analysis of prospective studies. *J Am Acad Dermatol* 2001; 45(4):520-7.
38. Gdalevich M, Mimouni D, Mimouni M. Breast-feeding and the risk of bronchial asthma in childhood: a systematic review with meta-analysis of prospective studies. *J Pediatr* 2001; 139(2):261-6.
39. Gianino P, Mastretta E, Longo P *et al.* Incidence of nosocomial rotavirus infections, symptomatic and asymptomatic, in breast-fed and non-breast-fed infants. *J Hosp Infect* 2002; 50(1):13-7.
40. Gillman MW, Rifas-Shiman SL, Camargo CA Jr *et al.* Risk of overweight among adolescents who were breastfed as infants. *JAMA* 2001; 285(19):2461-7.
41. Golding J, Emmett PM, Rogers IS. Does breast feeding have any impact on non-infectious, non-allergic disorders? *Early Hum Dev* 1997; 49 Suppl:S131-42.
42. Golding J, Emmett PM, Rogers IS. Eczema, asthma and allergy. *Early Hum Dev* 1997; 49 Suppl:S121-30.
43. Golding J, Emmett PM, Rogers IS. Gastroenteritis, diarrhoea and breast feeding. *Early Hum Dev* 1997; 49 Suppl:S83-103.
44. Golding J, Rogers IS, Emmett PM. Association between breast feeding, child development and behaviour. *Early Hum Dev* 1997; 49 Suppl:S175-84.
45. Greaves MF. Aetiology of acute leukaemia. *Lancet* 1997; 349(9048):344-9.
46. Gregg S, Parazzini F, Paratore MP *et al.* Risk factors for ovarian cancer in central Italy. *Gynecol Oncol* 2000; 79(1):50-4.
47. Grummer-Strawn LM, Mei Z. Does breastfeeding protect against pediatric overweight? Analysis of longitudinal data from the Centers for Disease Control and Prevention Pediatric Nutrition Surveillance System. *Pediatrics* 2004; 113(2):e81-6.
48. Gruskay FL. Comparison of breast, cow, and soy feedings in the prevention of onset of allergic disease: a 15-year prospective study. *Clin Pediatr (Phila)* 1982; 21(8):486-91.
49. Gustafsson PA, Duchon K, Birberg U, Karlsson T. Breastfeeding, very long polyunsaturated fatty acids (PUFA) and IQ at 6 1/2 years of age. *Acta Paediatr* 2004; 93(10):1280-7.
50. Gwinn ML, Lee NC, Rhodes PH, Layde PM, Rubin GL. Pregnancy, breast feeding, and oral contraceptives and the risk of epithelial ovarian cancer. *J Clin Epidemiol* 1990; 43(6):559-68.
51. Halken S. Prevention of allergic disease in childhood: clinical and epidemiological aspects of primary and secondary allergy prevention. *Pediatr Allergy Immunol* 2004; 15 Suppl 16:4-5, 9-32.
52. Hanson LA. Breastfeeding provides passive and likely long-lasting active immunity. *Ann Allergy Asthma Immunol* 1998; 81(6):523-33; quiz 533-4, 537.
53. Hanson LA. Human milk and host defence: immediate and long-term effects. *Acta Paediatr Suppl* 1999; 88(430):42-6.
54. Hardell L, Dreifaldt AC. Breast-feeding duration and the risk of malignant diseases in childhood in Sweden. *Eur J Clin Nutr* 2001; 55(3):179-85.
55. Harlow BL, Weiss NS, Roth GJ, Chu J, Daling JR. Case-control study of borderline ovarian tumors: reproductive history and exposure to exogenous female hormones. *Cancer Res* 1988; 48(20):5849-52.
56. Hediger ML, Overpeck MD, Kuczmarski RJ, Ruan WJ. Association between infant breastfeeding and overweight in young children. *JAMA* 2001; 285(19):2453-60.
57. Horwood LJ, Darlow BA, Mogridge N. Breast milk feeding and cognitive ability at 7-8 years. *Arch Dis Child Fetal Neonatal Ed* 2001; 84(1):F23-7.

58. Howie PW, Forsyth JS, Ogston SA, Clark A, Florey CD. Protective effect of breast feeding against infection. *BMJ* 1990; 300(6716):11-6.
59. Huang K, Whelan EA, Ruder AM *et al.* Reproductive factors and risk of glioma in women. *Cancer Epidemiol Biomarkers Prev* 2004; 13(10):1583-8.
60. Hyponen E, Kenward MG, Virtanen SM *et al.* Infant feeding, early weight gain, and risk of type 1 diabetes. *Childhood Diabetes in Finland (DiMe) Study Group. Diabetes Care* 1999; 22(12):1961-5.
61. Infante-Rivard C, Fortier I, Olson E. Markers of infection, breast-feeding and childhood acute lymphoblastic leukaemia. *Br J Cancer* 2000; 83(11):1559-64.
62. Jacobson SW, Chiodo LM, Jacobson JL. Breastfeeding effects on intelligence quotient in 4- and 11-year-old children. *Pediatrics* 1999; 103(5):e71.
63. Jones ME, Swerdlow AJ, Gill LE, Goldacre MJ. Pre-natal and early life risk factors for childhood onset diabetes mellitus: a record linkage study. *Int J Epidemiol* 1998; 27(3):444-9.
64. Jorgensen C, Picot MC, Bologna C, Sany J. Oral contraception, parity, breast feeding, and severity of rheumatoid arthritis. *Ann Rheum Dis* 1996; 55(2):94-8.
65. Kajosaari M, Saarinen UM. Prophylaxis of atopic disease by six months' total solid food elimination. Evaluation of 135 exclusively breast-fed infants of atopic families. *Acta Paediatr Scand* 1983; 72(3):411-4.
66. Karlson EW, Mandl LA, Hankinson SE, Grodstein F. Do breast-feeding and other reproductive factors influence future risk of rheumatoid arthritis? Results from the Nurses' Health Study. *Arthritis Rheum* 2004; 50(11):3458-67.
67. Katsouyanni K, Lipworth L, Trichopoulou A, Samoli E, Stuver S, Trichopoulos D. A case-control study of lactation and cancer of the breast. *Br J Cancer* 1996; 73(6):814-8.
68. Kerkhof M, Koopman LP, van Strien RT *et al.* Risk factors for atopic dermatitis in infants at high risk of allergy: the PIAMA study. *Clin Exp Allergy* 2003; 33(10):1336-41.
69. Klement E, Cohen RV, Boxman J, Joseph A, Reif S. Breastfeeding and risk of inflammatory bowel disease: a systematic review with meta-analysis. *Am J Clin Nutr* 2004; 80(5):1342-52.
70. Koletzko B, von Kries R. Are there long term protective effects of breast feeding against later obesity? *Nutr Health* 2001; 15(3-4):225-36.
71. Koletzko S, Sherman P, Corey M, Griffiths A, Smith C. Role of infant feeding practices in development of Crohn's disease in childhood. *BMJ* 1989; 298(6688):1617-8.
72. Kools EJ. Promotion and support of breastfeeding. Maastricht University, 2004.
73. Koopman-Esseboom C, Weisglas-Kuperus N, de Ridder MA, Van der Paauw CG, Tuinstra LG, Sauer PJ. Effects of polychlorinated biphenyl/dioxin exposure and feeding type on infants' mental and psychomotor development. *Pediatrics* 1996; 97(5):700-6.
74. Kramer MS, Chalmers B, Hodnett ED *et al.* Promotion of Breastfeeding Intervention Trial (PROBIT): a randomized trial in the Republic of Belarus. *JAMA* 2001; 285(4):413-20.
75. Kramer MS, Guo T, Platt RW *et al.* Infant growth and health outcomes associated with 3 compared with 6 mo of exclusive breastfeeding. *Am J Clin Nutr* 2003; 78(2):291-5.
76. Kramer MS, Guo T, Platt RW *et al.* Breastfeeding and infant growth: biology or bias? *Pediatrics* 2002; 110(2 Pt 1):343-7.
77. Kramer MS, Kakuma R. Optimal duration of exclusive breastfeeding. *Cochrane Database Syst Rev* 2002; (1):CD003517.
78. Kramers PGN, Van Leeuwen FXR. De afweging gezond versus veilig in gewone voedingsmiddelen. In: *Ons eten gemeten. Gezonde voeding en veilig voedsel in Nederland. RIVM rapportnr. 20555007.* Houten: Bohn Stafleu Van Loghum, 2004: 222-3.
79. Kreijl CF, Knaap AGAC, Busch MCM *et al.* *Ons eten gemeten.* Houten: Bohn Stafleu Van Loghum, 2004; RIVM-rapport 270555007.
80. Kritz-Silverstein D, Barrett-Connor E, Hollenbach KA. Pregnancy and lactation as determinants of bone mineral density in postmenopausal women. *Am J Epidemiol* 1992; 136(9):1052-9.
81. Kull I, Almqvist C, Lilja G, Pershagen G, Wickman M. Breast-feeding reduces the risk of asthma during the first 4 years of life. *J Allergy Clin Immunol* 2004; 114(4):755-60.
82. Kull I, Wickman M, Lilja G, Nordvall SL, Pershagen G. Breast feeding and allergic diseases in infants-a prospective birth cohort study. *Arch Dis Child* 2002; 87(6):478-81.
83. Kwan ML, Buffler PA, Abrams B, Kiley VA. Breastfeeding and the risk of childhood leukemia: a meta-analysis. *Public Health Rep* 2004; 119(6):521-35.
84. LaKind JS, Amina Wilkins A, Berlin CM Jr. Environmental chemicals in human milk: a review of levels, infant exposures and health, and guidance for future research. *Toxicol Appl Pharmacol* 2004; 198(2):184-208.
85. Lancashire RJ, Sorahan T. Breastfeeding and childhood cancer risks: OSCC data. *Br J Cancer* 2003;

- 88(7):1035-7.
86. Lanting CI, Herschderfer K, Wouwe van JP, Reijneveld SA. Effect van invoering van het 'Baby Friendly Hospital Initiative' op het geven van borstvoeding in Nederland. Leiden: TNO , 2003; PG/Jeugd 2003.212.
 87. Laubereau B, Brockow I, Zirngibl A *et al.* Effect of breast-feeding on the development of atopic dermatitis during the first 3 years of life--results from the GINI-birth cohort study. *J Pediatr* 2004; 144(5):602-7.
 88. Lawlor DA, Najman JM, Sterne J, Williams GM, Ebrahim S, Davey Smith G. Associations of parental, birth, and early life characteristics with systolic blood pressure at 5 years of age: findings from the Mater-University study of pregnancy and its outcomes. *Circulation* 2004; 110(16):2417-23.
 89. Leeson CP, Kattenhorn M, Deanfield JE, Lucas A. Duration of breast feeding and arterial distensibility in early adult life: population based study. *BMJ* 2001; 322(7287):643-7.
 90. Li L, Parsons TJ, Power C. Breast feeding and obesity in childhood: cross sectional study. *BMJ* 2003; 327(7420):904-5.
 91. Liese AD, Hirsch T, von Mutius E, Keil U, Leupold W, Weiland SK. Inverse association of overweight and breast feeding in 9 to 10-y-old children in Germany. *Int J Obes Relat Metab Disord* 2001; 25(11):1644-50.
 92. Linden MWvd, Westert GP, Bakker DHd, Schellevis FG. Tweede Nationale Studie naar ziekten en verrichtingen in de huisartspraktijk: klachten en aandoeningen in de bevolking en in de huisartspraktijk. Utrecht, Bilthoven: NIVEL, Rijksinstituut voor Volksgezondheid en Milieu, 2004; NIVEL W1.100.
 93. Lipworth L, Bailey LR, Trichopoulos D. History of breast-feeding in relation to breast cancer risk: a review of the epidemiologic literature. *J Natl Cancer Inst* 2000; 92(4):302-12.
 94. London SJ, Colditz GA, Stampfer MJ *et al.* Lactation and risk of breast cancer in a cohort of US women. *Am J Epidemiol* 1990; 132(1):17-26.
 95. Lucas A, Morley R, Cole TJ, Lister G, Leeson-Payne C. Breast milk and subsequent intelligence quotient in children born preterm. *Lancet* 1992; 339(8788):261-4.
 96. Marild S, Hansson S, Jodal U, Oden A, Svedberg K. Protective effect of breastfeeding against urinary tract infection. *Acta Paediatr* 2004; 93(2):164-8.
 97. Martin RM, Davey Smith G, Mangtani P, Tilling K, Frankel S, Gunnell D. Breastfeeding and cardiovascular mortality: the Boyd Orr cohort and a systematic review with meta-analysis. *Eur Heart J* 2004; 25(9):778-86.
 98. Martin RM, Gunnell D, Smith GD. Breastfeeding in infancy and blood pressure later in life: Systematic review and meta-analysis. *American J Epidemiology* 2005; 161(1):15-26.
 99. Martin RM, Ness AR, Gunnell D, Emmett P, Davey Smith G. Does breast-feeding in infancy lower blood pressure in childhood? The Avon Longitudinal Study of Parents and Children (ALSPAC). *Circulation* 2004; 109(10):1259-66.
 100. McVea KL, Turner PD, Pepler DK. The role of breastfeeding in sudden infant death syndrome. *J Hum Lact* 2000; 16(1):13-20.
 101. Meloni T, Marinaro AM, Mannazzu MC *et al.* IDDM and early infant feeding. Sardinian case-control study. *Diabetes Care* 1997; 20(3):340-2.
 102. Melse JM, Essink-Bot ML, Kramers PG, Hoeymans N. A national burden of disease calculation: Dutch disability-adjusted life-years. Dutch Burden of Disease Group. *Am J Public Health* 2000; 90(8):1241-7.
 103. Michaelsson K, Baron JA, Farahmand BY, Ljunghall S. Influence of parity and lactation on hip fracture risk. *Am J Epidemiol* 2001; 153(12):1166-72.
 104. Mortensen EL, Michaelsen KF, Sanders SA, Reinisch JM. The association between duration of breastfeeding and adult intelligence. *JAMA* 2002; 287(18):2365-71.
 105. Murray CJ, Lopez AD. The global burden of disease: a comparative assessment of mortality and disability from disease, injuries, and risk factors in 1990 and projected to 2020. Cambridge, Mass: Harvard School of Public Health, on behalf of the WHO and the World Bank, 1996.
 106. Negri E, Braga C, La Vecchia C, Levi F, Talamini R, Franceschi S. Lactation and the risk of breast cancer in an Italian population. *Int J Cancer* 1996; 67(2):161-4.
 107. Newcomb PA, Egan KM, Titus-Ernstoff L *et al.* Lactation in relation to postmenopausal breast cancer. *Am J Epidemiol* 1999; 150(2):174-82.
 108. Newcomb PA, Storer BE, Longnecker MP *et al.* Lactation and a reduced risk of premenopausal breast cancer. *N Engl J Med* 1994; 330(2):81-7.
 109. Newcomb PA, Trentham-Dietz A. Breast feeding practices in relation to endometrial cancer risk, USA. *Cancer Causes Control* 2000; 11(7):663-7.
 110. Norris JM, Scott FW. A meta-analysis of infant diet and insulin-dependent diabetes mellitus: do biases

- play a role? *Epidemiology* 1996; 7(1):87-92.
111. Oddy WH. Breastfeeding and asthma in children. A prospective cohort study. *Adv Exp Med Biol* 2000; 478:393-4.
 112. Oddy WH. A review of the effects of breastfeeding on respiratory infections, atopy, and childhood asthma. *J Asthma* 2004; 41(6):605-21.
 113. Oddy WH, de Klerk NH, Sly PD, Holt PG. The effects of respiratory infections, atopy, and breastfeeding on childhood asthma. *Eur Respir J* 2002; 19(5):899-905.
 114. Oddy WH, Holt PG, Sly PD *et al.* Association between breast feeding and asthma in 6 year old children: findings of a prospective birth cohort study. *BMJ* 1999; 319(7213):815-9.
 115. Oddy WH, Sly PD, de Klerk NH *et al.* Breast feeding and respiratory morbidity in infancy: a birth cohort study. *Arch Dis Child* 2003; 88(3):224-8.
 116. Ong KK, Preece MA, Emmett PM, Ahmed ML, Dunger DB. Size at birth and early childhood growth in relation to maternal smoking, parity and infant breast-feeding: longitudinal birth cohort study and analysis. *Pediatr Res* 2002; 52(6):863-7.
 117. Owen CG, Whincup PH, Gilg JA, Cook DG. Effect of breast feeding in infancy on blood pressure in later life: systematic review and meta-analysis. *BMJ* 2003; 327(7425):1189-95.
 118. Paradise JL, Rockette HE, Colborn DK *et al.* Otitis media in 2253 Pittsburgh-area infants: prevalence and risk factors during the first two years of life. *Pediatrics* 1997; 99(3):318-33.
 119. Pardo-Crespo R, Perez-Iglesias R, Llorca J *et al.* Breast-feeding and risk of hospitalization for all causes and fever of unknown origin. *Eur J Public Health* 2004; 14(3):230-4.
 120. Parkin DM, Whelan SL, Ferlay J, Teppo L, Thomas DB. *Cancer Incidence in Five Continents: Volume VIII.* Oxford: Oxford University Press, 2003.
 121. Parsons TJ, Power C, Manor O. Infant feeding and obesity through the lifecourse. *Arch Dis Child* 2003; 88(9):793-4.
 122. Patandin S, Lanting CI, Mulder PG, Boersma ER, Sauer PJ, Weisglas-Kuperus N. Effects of environmental exposure to polychlorinated biphenyls and dioxins on cognitive abilities in Dutch children at 42 months of age. *J Pediatr* 1999; 134(1):33-41.
 123. Pisacane A, de Luca U, Criscuolo L *et al.* Breast feeding and hypertrophic pyloric stenosis: population based case-control study. *BMJ* 1996; 312(7033):745-6.
 124. Pisacane A, Graziano L, Mazzarella G, Scarpellino B, Zona G. Breast-feeding and urinary tract infection. *J Pediatr* 1992; 120(1):87-9.
 125. Pollock JI. Long-term associations with infant feeding in a clinically advantaged population of babies. *Dev Med Child Neurol* 1994; 36(5):429-40.
 126. Raisler J, Alexander C, O'Campo P. Breast-feeding and infant illness: a dose-response relationship? *Am J Public Health* 1999; 89(1):25-30.
 127. Ravelli AC, van der Meulen JH, Osmond C, Barker DJ, Bleker OP. Infant feeding and adult glucose tolerance, lipid profile, blood pressure, and obesity. *Arch Dis Child* 2000; 82(3):248-52.
 128. Reilly JJ, Armstrong J, Dorosty AR *et al.* Early life risk factors for obesity in childhood: cohort study. *BMJ* 2005.
 129. Rigas A, Rigas B, Glassman M *et al.* Breast-feeding and maternal smoking in the etiology of Crohn's disease and ulcerative colitis in childhood. *Ann Epidemiol* 1993; 3(4):387-92.
 130. Riman T, Dickman PW, Nilsson S *et al.* Risk factors for epithelial borderline ovarian tumors: results of a Swedish case-control study. *Gynecol Oncol* 2001; 83(3):575-85.
 131. Riman T, Dickman PW, Nilsson S *et al.* Risk factors for invasive epithelial ovarian cancer: results from a Swedish case-control study. *Am J Epidemiol* 2002; 156(4):363-73.
 132. Rogan WJ, Gladen BC. Breast-feeding and cognitive development. *Early Hum Dev* 1993; 31(3):181-93.
 133. Rogers IS, Golding J, Emmett PM. The effects of lactation on the mother. *Early Hum Dev* 1997; 49 Suppl:S191-203.
 134. Rooney BL, Schauburger CW. Excess pregnancy weight gain and long-term obesity: one decade later. *Obstet Gynecol* 2002; 100(2):245-52.
 135. Rowe SY, Rocourt JR, Shiferaw B *et al.* Breast-feeding decreases the risk of sporadic salmonellosis among infants in FoodNet sites. *Clin Infect Dis* 2004; 38 Suppl 3:S262-70.
 136. Rubin DH, Leventhal JM, Krasilnikoff PA *et al.* Relationship between infant feeding and infectious illness: a prospective study of infants during the first year of life. *Pediatrics* 1990; 85(4):464-71.
 137. Rust GS, Thompson CJ, Minor P, Davis-Mitchell W, Holloway K, Murray V. Does breastfeeding protect children from asthma? Analysis of NHANES III survey data. *J Natl Med Assoc* 2001; 93(4):139-48.

138. Saarinen UM , Kajosaari M. Breastfeeding as prophylaxis against atopic disease: prospective follow-up study until 17 years old. *Lancet* 1995; 346(8982):1065-9.
139. Sadauskaite-Kuehne V, Ludvigsson J, Padaiga Z, Jasinskiene E, Samuelsson U. Longer breastfeeding is an independent protective factor against development of type 1 diabetes mellitus in childhood. *Diabetes Metab Res Rev* 2004; 20(2):150-7.
140. Samuelsson U, Johansson C, Ludvigsson J. Breast-feeding seems to play a marginal role in the prevention of insulin-dependent diabetes mellitus. *Diabetes Res Clin Pract* 1993; 19(3):203-10.
141. Scariati PD , Grummer-Strawn LM, Fein SB. A longitudinal analysis of infant morbidity and the extent of breastfeeding in the United States . *Pediatrics* 1997; 99(6):E5.
142. Schoetza A , Filipiak-Pittroff B, Franke K *et al.* Effect of exclusive breast-feeding and early solid food avoidance on the incidence of atopic dermatitis in high-risk infants at 1 year of age. *Pediatr Allergy Immunol* 2002; 13(4):234-42.
143. Schuz J, Kaletsch U, Meinert R, Kaatsch P, Michaelis J. Association of childhood leukaemia with factors related to the immune system. *Br J Cancer* 1999; 80(3-4):585-90.
144. Sears MR, Greene JM, Willan AR *et al.* Long-term relation between breastfeeding and development of atopy and asthma in children and young adults: a longitudinal study. *Lancet* 2002; 360(9337):901-7.
145. Shu XO, Linet MS, Steinbuch M *et al.* Breast-feeding and risk of childhood acute leukemia. *J Natl Cancer Inst* 1999; 91(20):1765-72.
146. Silfverdal SA, Bodin L, Hugosson S *et al.* Protective effect of breastfeeding on invasive *Haemophilus influenzae* infection: a case-control study in Swedish preschool children. *Int J Epidemiol* 1997; 26(2):443-50.
147. Siltanen M, Kajosaari M, Poussa T, Saarinen KM, Savilahti E. A dual long-term effect of breastfeeding on atopy in relation to heredity in children at 4 years of age. *Allergy* 2003; 58(6):524-30.
148. Sinha A, Madden J, Ross-Degnan D, Soumerai S, Platt R. Reduced risk of neonatal respiratory infections among breastfed girls but not boys . *Pediatrics* 2003; 112(4):e303.
149. Siskind V, Green A, Bain C, Purdie D. Breastfeeding, menopause, and epithelial ovarian cancer. *Epidemiology* 1997; 8(2):188-91.
150. Stabell Benn C, Wohlfahrt J, Aaby P *et al.* Breastfeeding and Risk of Atopic Dermatitis, by Parental History of Allergy, during the First 18 Months of Life. *Am J Epidemiol* 2004; 160(3):217-23.
151. Stuver SO, Hsieh CC, Bertone E, Trichopoulos D. The association between lactation and breast cancer in an international case-control study: a re-analysis by menopausal status. *Int J Cancer* 1997; 71(2):166-9.
152. Taittonen L , Nuutinen M, Turtinen J, Uhari M. Prenatal and postnatal factors in predicting later blood pressure among children: cardiovascular risk in young Finns. *Pediatr Res* 1996; 40(4):627-32.
153. Tariq SM, Matthews SM, Hakim EA, Stevens M, Arshad SH, Hide DW. The prevalence of and risk factors for atopy in early childhood: a whole population birth cohort study. *J Allergy Clin Immunol* 1998; 101(5):587-93.
154. Teele DW, Klein JO, Rosner B. Epidemiology of otitis media during the first seven years of life in children in greater Boston: a prospective, cohort study. *J Infect Dis* 1989; 160(1):83-94.
155. Thorsdottir I, Gunnarsdottir I, Kvaran MA, Gretarsson SJ. Maternal body mass index, duration of exclusive breastfeeding and children's developmental status at the age of 6 years. *Eur J Clin Nutr* 2005; 59(3):426-31.
156. Toschke AM, Vignerova J, Lhotska L, Osancova K, Koletzko B, Von Kries R. Overweight and obesity in 6- to 14-year-old Czech children in 1991: protective effect of breast-feeding. *J Pediatr* 2002; 141(6):764-9.
157. Uhari M, Mantysaari K, Niemela M. A meta-analytic review of the risk factors for acute otitis media. *Clin Infect Dis* 1996; 22(6):1079-83.
158. UK Childhood Cancer Study Investigators. Breastfeeding and childhood cancer. *Br J Cancer* 2001; 85(11):1685-94.
159. United Kingdom National Case-Control Study Group. Breast feeding and risk of breast cancer in young women. *BMJ* 1993; 307(6895):17-20.
160. Van Leeuwen FXR, Malisch R. Results of the third round of the WHO coordinated exposure study on the levels of PCBs, PCDDs and PCDFs in human milk. *Organohalogen Compounds* 2002; 56: 311-6.
161. Van Odijk J , Kull I, Borres MP *et al.* Breastfeeding and allergic disease: a multidisciplinary review of the literature (1966-2001) on the mode of early feeding in infancy and its impact on later atopic manifestations. *Allergy* 2003; 58(9):833-43.
162. Vestergaard M, Obel C, Henriksen TB, Sorensen HT, Skajaa E, Ostergaard J. Duration of breastfeeding and developmental milestones during the latter half of infancy. *Acta Paediatr* 1999; 88(12):1327-32.

163. Von Kries R , Koletzko B, Sauerwald T *et al.* Breast feeding and obesity: cross sectional study . BMJ 1999; 319(7203):147-50.
164. Vreugdenhil HJ, Lanting CI, Mulder PG, Boersma ER, Weisglas-Kuperus N. Effects of prenatal PCB and dioxin background exposure on cognitive and motor abilities in Dutch children at school age. J Pediatr 2002; 140(1):48-56.
165. Wetzig H, Schulz R, Diez U, Herbarth O, Viehweg B, Borte M. Associations between duration of breast-feeding, sensitization to hens' eggs and eczema infantum in one and two year old children at high risk of atopy. Int J Hyg Environ Health 2000; 203(1):17-21.
166. Whittemore AS, Harris R, Itnyre J. Characteristics relating to ovarian cancer risk: collaborative analysis of 12 US case-control studies. II. Invasive epithelial ovarian cancers in white women. Collaborative Ovarian Cancer Group. Am J Epidemiol 1992; 136(10):1184-203.
167. WHO. World Health Report 2000: Health Systems: Improving performance. Geneva: WHO, 2000.
168. WHO. The optimal duration of exclusive breastfeeding [Web Page]. 2001;
169. WHO. The European health report 2002. European Series no. 97. Copenhagen: WHO Regional Office for Europe, 2002.
170. WHO/FAO expert consultation. Diet, Nutrition and the prevention of chronic diseases. 2003; WHO technical report series; 916.
171. Wilson AC, Forsyth JS, Greene SA, Irvine L, Hau C, Howie PW. Relation of infant diet to childhood health: seven year follow up of cohort of children in Dundee infant feeding study. BMJ 1998; 316(7124):21-5.
172. Wright AL, Bauer M, Naylor A, Sutcliffe E, Clark L. Increasing breastfeeding rates to reduce infant illness at the community level. Pediatrics 1998; 101(5):837-44.
173. Wright AL, Holberg CJ, Martinez FD, Morgan WJ, Taussig LM. Breast feeding and lower respiratory tract illness in the first year of life. Group Health Medical Associates. BMJ 1989; 299(6705):946-9.
174. Wright AL, Holberg CJ, Taussig LM, Martinez F. Maternal asthma status alters relation of infant feeding to asthma childhood. Adv Exp Med Biol 2000; 478:131-7.
175. Wright AL, Holberg CJ, Taussig LM, Martinez FD. Relationship of infant feeding to recurrent wheezing at age 6 years. Arch Pediatr Adolesc Med 1995; 149(7):758-63.
176. Wright AL, Holberg CJ, Taussig LM, Martinez FD. Factors influencing the relation of infant feeding to asthma and recurrent wheeze in childhood. Thorax 2001; 56(3):192-7.
177. Wright AL, Sherrill D, Holberg CJ, Halonen M, Martinez FD. Breast-feeding, maternal IgE, and total serum IgE in childhood. J Allergy Clin Immunol 1999; 104(3 Pt 1):589-94.
178. Wright AL, Stern DA, Halonen M. The association of allergic sensitization in mother and child in breast-fed and formula-fed infants. Adv Exp Med Biol 2001; 501:249-55.
179. Zeilmaker MJ, Houweling DA, Cuijpers CEJ, Hoogerbrugge R, van Eijkeren JCH, Baumann BA. Verontreiniging van moedermelk met gechloreerde koolwaterstoffen in Nederland: niveaus in 1998 en tijd-trends. Bilthoven: RIVM.
180. Zheng T, Holford TR, Mayne ST *et al.* Lactation and breast cancer risk: a case-control study in Connecticut. Br J Cancer 2001; 84(11):1472-6.

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 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) 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)	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. Corrected for SES, smoking, and use of incubator after delivery.
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 _{1-45 days} BF _{46-90 days} BF _{91-180 days}		

Table 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 ^c	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 ₃₋₃ EBF ₃₋₃	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 ₃₋₇ EBF ₃₋₇	≥ 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).
	Hanson, 1998; Hanson, 1999 ^b	Review				Demonstrate significant protection during breastfeeding against diarrhoea and infections in general.	Based on (Howie et al., 1990) and studies from developing countries.

Table 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
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.
	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	<u>0-12 mo</u> OR=1 OR=0.05 (0-0.30)	<u>0-6 mo</u> 1 0.05 (0-0.33)	<u>6-12 mo</u> 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.
Crohn's disease	Rigas et al., 1993	Case-control	USA 68 Cases 202 Controls	0-17 yr	FF BF≤5 BF6-11 BF>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.

Table 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
Ulcerative colitis 	Rigas et al., 1993	Case-control	USA 68 Cases 202 Controls	0-17 yr	FF BF _{≤5} BF ₆₋₁₁ BF _{≥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	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...
Pyloric stenosis 	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 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 	Marild et al., 2004	Case-control	Sweden 200 Cases 336 Controls	0-2 yr	FF BF	<u>Girls and boys</u> OR=2.30 (1.56-3.39) OR=1 <u>girls</u> OR=3.78 OR=1 <u>boys</u> 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 _{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 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.
	Raisler et al., 1999 d	Cohort	USA n=7,092	0-6 mo	FF MBF (BF<FF) MBF (BF=FF) MBF (BF>FF) EBF	<u>No siblings present</u> 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)	<u>Siblings present</u> 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	<u>Before introduction BFHI</u> RR=1 RR=0.75 (0.56-1.00)	<u>After introduction BFHI</u> 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	<u>Otitis Media</u> 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)	<u>Otitis Media with effusion</u> 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.
	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 _{≥12}	<u>2-12 mo</u> 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)	<u>13-24 mo</u> 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	<u>Incidence /100 days at risk</u> 0-12 mo: i=0.53 i=0.45 12-24 mo: i=0.45 i=0.43	<u>Prevalence (days diseased/yr)</u> 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).

Table 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	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	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	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	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.
	Aniansson et al., 1994	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 ≤12 mo (%) 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 _{≥4} & FF _{<4} MBF _{≥4} & FF ₄₋₆ EBF _{≥6}	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.
Alho et al., 1990	Howie et al., 1990	Cohort	Scotland n=618	0-13 wk 14-26 wk 27-39 wk 40-52 wk	FF ₅₃ EBF ₅₃	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	Cohort	Finland n=2130	0-24 mo	BF _{<3} BF ₃₋₆ BF ₇₋₁₁ BF _{≥12}	≥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)

Table 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	Teele et al., 1989 	Cohort	USA n=877	yr 0-3 yr	FF BF	≥1episod e	0-1 year OR=1 OR=0.64 (0.44-0.91) OR=0.51 (0.30-0.89)	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
						≥3episod e	0-3 year OR=1 OR=0.48(0.30-0.76) NS	
Recurrent Otitis Media	Uhari et al., 1996 	Meta-analysis	n=2,548-3,384		BF vs. FF BF _{>3} vs. BF _{<3} BF _{>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.
	Daly et al., 1999 	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 	Cohort	USA n=440	0-12 mo	FF & BF _{<4} MBF _{>4} & FF _{<4} MBF _{>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 	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 	Meta-analysis	n=1,156-1,331		BF vs. FF BF _{>3} vs. BF _{<3} BF _{>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 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.
	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	Bronchiolitis Bronchitis Pneumonia Croup Nasopharyngitis	<u>Before BHF</u> RR=1 RR=0.51 (0.20-1.13)	<u>After BHF</u> RR=1 RR=0.51 (0.06-4.51) RR=0.29 (0.06-1.26) RR=0.21 (0.03-1.58)	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.	
	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.	
	Howie et al., 1990	Cohort	Scotland n=618	0-13 wk 14-26 wk 27-39 wk 40-52 wk	FF _{>3} EBF _{>3}		<u>0-13 wk</u> RR=1 RR=0.69	<u>14-26 wk</u> RR=1 RR=0.87	<u>27-39 wk</u> RR=1 RR=0.92	<u>40-52 wk</u> RR=1 RR=0.83
	Alho et al., 1990 d	Cohort	Finland N=2,130	0-24 mo	BF _{<3} BF ₃₋₆ BF ₇₋₁₁ BF _{>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	<u>Girls and boys</u> OR=1 OR=0.83 (0.58-1.20) OR=0.70 (0.49-0.99)	<u>Girls</u> 1 0.6 (0.34-0.93) 0.50 (0.29-0.79)	<u>Boys</u> 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 a	Review	n=3,483	0-12 mo	MBF ₃₋₇ EBF ₃₋₇	<u>≥ 2 episodes</u> RR=1 RR=0.90 (0.79-1.03)		<u>Hospitalization</u> RR=1 RR=0.75 (0.60-0.94)	Based on one study (Kramer et al., 2001).	

Table 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	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)	Part of the PROBIT-study. Intervention=BFHL. 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	Cohort	Australia n=2,456	0-12 mo	EBF _{≥2} vs. EBF _{<2} MBF _{≥6} vs. MBF _{<6}	OR=1 OR=0.86 (0.38-1.94)	Corrected for gender, gestational age, smoking during pregnancy, older siblings, SES, and age mother (other confounders had no effect).
	Oddy et al., 2002	Cohort	Australia n=2,602	0-12 mo	FF vs. EBF _{≥0} EBF _{<2} vs. EBF _{≥2} EBF _{<4} vs. EBF _{≥4} EBF _{<6} vs. EBF _{≥6}	Hospitalization OR=1.85 (0.79-4.34) OR=2.05 (0.88-4.76)	Corrected for gender, gestational age, and smoking during pregnancy.
	Kramer and Kakuma, 2002	Review	n=492-3,993	0-12 mo	MBF ₃₋₇ EBF ₃₋₇	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.
	Rubin et al., 1990	Cohort	Denmark n=500	0-12 mo	FF+MBF(BF≤FF) EBF+MBF(BF>FF)	≥1 episode RR=1 RR=1.07 (0.96-1.20)	≥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).
	Oddy et al., 2002	Cohort	Australia n=2,602	0-12 mo	FF vs. EBF _{≥0} EBF _{<2} vs. EBF _{≥2} EBF _{<4} vs. EBF _{≥4} EBF _{<6} vs. EBF _{≥6}	≥2 episodes RR=1 RR=0.91 (0.82-1.02)	Corrected for birth weight, SES, number of children, day-care, family history, and age child. Large drop-out during follow-up.
	Nafstad et al., 1996	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	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.
	Kramer and Kakuma, 2002	Review	n=492	0-12 mo	MBF ₃₋₇ EBF ₃₋₇	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)	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)	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)	Based on one study (Oddy et al., 1999).

Table 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	Wilson et al., 1998 d	Cohort	Scotland n=545	0-7 yr	EBF _{≥15wk} , no solids EBF _{≥15wk} , solids EBF _{≥15wk} MBF _{≥15wk} , no solids MBF _{≥15wk} , solids MBF _{≥15wk} FF _{≥15wk} , no solids FF _{≥15wk} , solids FF _{≥15wk}	<u>Respiratory disorder</u> 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)	<u>Cough</u> 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.	
	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.
	Dewey et al., 1995	Matched cohort	USA n=87	0-12 mo 12-24 mo	FF BF FF BF	<u>Incidence /100d at risk</u> 0-12 mo: i=1.7 i=2.1 12-24 mo: i=2.0 i=2.0	<u>Prevalence (day diseased/yr)</u> 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).	
	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}	<u>1st yr</u> 6.10 5.67 6.61 6.19 6.34	<u>2nd yr</u> 5.58 6.09 6.54 6.48 7.02 (p=0.006)	Effect measurement is mean value of respiratory episodes.	
Disorder upper respiratory tract	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.
Disorder lower respiratory tract a	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.
	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}	<u>≤ 4 mo</u> i=2.0 i=3.8 i=2.7	<u>4-6 mo</u> i=2.7 i=2.0 i=2.1	<u>6-12 mo</u> i=7.0 i=7.3 i=2.9	Definition breastfeeding based on prospective and retrospective collection. Not corrected.
	Bachrach et al., 2003 c	Meta-analysis	Developed countries	0-24 mo	EBF _{≥4} vs. none EBF _{≥4} vs. none MBF _{≥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

Table 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 _{≥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 7: Effect of breastfeeding on jaundice

Intermediary of health effect	Authors, Year of publication	Design	Study population	Age group	Breastfeeding	Effect size	Remarks
Jaundice b	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 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	Cohort	Sweden n=3,384	4 yr	EBF ₀₋₂ EBF ₃₋₄ EBF _{≥5} EBF ₀₋₂ EBF ₃₋₄ EBF _{≥5}	<table><tr><td>Total OR=1 OR=0.67 (0.43-1.03) OR=0.61 (0.42-0.86)</td><td>No hereditary OR=1 OR=0.61 (0.36-1.06) OR=0.48 (0.30-0.77)</td><td>Hereditary OR=1 OR=0.76 (0.37-1.54) OR=0.81 (0.46-1.44)</td></tr><tr><td></td><td>Mother no asthma OR=1 OR=0.61 (0.38-0.98) OR=0.57 (0.39-0.84)</td><td>Mother with asthma OR=1 OR=1.04 (0.35-3.09) OR=0.79 (0.32-1.90)</td></tr></table>	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)	Hereditary OR=1 OR=0.76 (0.37-1.54) OR=0.81 (0.46-1.44)		Mother no asthma OR=1 OR=0.61 (0.38-0.98) OR=0.57 (0.39-0.84)	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.
	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)	Hereditary OR=1 OR=0.76 (0.37-1.54) OR=0.81 (0.46-1.44)										
	Mother no asthma OR=1 OR=0.61 (0.38-0.98) OR=0.57 (0.39-0.84)	Mother with asthma OR=1 OR=1.04 (0.35-3.09) OR=0.79 (0.32-1.90)											
	Chulada et al., 2003	Cohort	USA n=8,261	2-71 mo	FF BF BF _{<4} BF _{≥4} EBF ₀ EBF _{<4} EBF _{≥4}	<table><tr><td>HR=1 HR=0.85 (0.64-1.13) HR=0.89 (0.59-1.34) HR=0.82 (0.58-1.17)</td><td></td><td></td></tr><tr><td>HR=1 HR=0.97 (0.57-1.65) HR=0.56 (0.29-1.11)</td><td></td><td></td></tr></table>	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.
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)													
	Siltanen et al., 2003	Cohort	Finland n=456	4 yr	FF _{cow in first 2wk} EBF _{≥3}	<table><tr><td>Family history OR=1 OR=1.42 (0.40-5.11)</td><td>No family history OR=1 OR=1.89 (0.32-10.99)</td><td></td></tr></table>	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.			
Family history OR=1 OR=1.42 (0.40-5.11)	No family history OR=1 OR=1.89 (0.32-10.99)												
	Sears et al., 2002	Cohort	New Zealand n=1,037	0-9 yr 9 yr 11 yr 13 yr 15 yr 18 yr 21 yr 26 yr	FF BF _{≥4 wk}	<table><tr><td>OR=1 Asthma_{<9} OR=1.93 (1.18-3.17) Asthma₉ OR=2.54 (1.45-4.44) Asthma₁₁ OR=2.23 (1.42-3.52) Asthma₁₃ OR=2.93 (1.83-4.69) Asthma₁₅ OR=1.69 (1.17-2.45) Asthma₁₈ OR=1.68 (1.15-2.47) Asthma₂₁ OR=1.50 (1.06-2.13) Asthma₂₆ OR=1.74 (1.26-2.40)</td><td></td><td></td></tr></table>	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 Zealand 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.			
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)													
	Kull et al., 2002	Cohort	Sweden n=3,791	0-2 yr	EBF _{≥4} vs. EBF _{<4} MBF _{≥6} vs. MBF _{<6}	<table><tr><td>Asthma OR=0.66 (0.49-0.90)</td><td>Asthma with other allergic manifestations OR=0.69 (0.49-0.97) OR=0.77 (0.54-1.1)</td></tr></table>	Asthma OR=0.66 (0.49-0.90)	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.				
Asthma OR=0.66 (0.49-0.90)	Asthma with other allergic manifestations OR=0.69 (0.49-0.97) OR=0.77 (0.54-1.1)												
	Wright et al., 2001; Wright et al., 2000	Cohort	USA n=1,043	6 yr 9 yr 11 yr 13 yr	EBF _{≥4} vs. EBF _{<4} + FF	<table><tr><td>Asthma_{6,13} with asthmatic mother OR=8.7 (3.4-22.2) Asthma₆, 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) Asthma₁₃ OR=1</td></tr></table>	Asthma _{6,13} 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.					
Asthma _{6,13} 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													

Table 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	Rust et al., 2001	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	Cohort	Canada n=2,184 (weighted n=331,100)	12-23 mo	BF ₂ vs. BF _{≥2} BF _{≤6} vs. BF _{≤6} BF _{≤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	Cohort	Australia n=2,602	6 yr	EBF ₄ EBF _{≥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	Cohort	Australia n=2,602	6 yr	EBF _{≥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	Cohort	Australia n=2,602	6 yr	EBF ₃ vs. EBF _{≥3} EBF ₄ vs. EBF _{≥4} EBF _{≤6} vs. EBF _{≥6}	OR=1.20 (0.98-1.48) OR=1.25 (1.02-1.52) OR=1.26 (1.02-1.54)	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 _{≥15wk} , no solids EBF _{≥15wk} , solids EBF _{≤15wk} MBF _{≥15wk} , no solids MBF _{≥15wk} , solids MBF _{≤15wk} FF _{≥15wk} , no solids FF _{≥15wk} , solids FF _{≤15wk}	OR=1.12 (0.91-1.34) OR=1.18 (0.97-1.45) 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) p=17.1% (p<0.01) p=10.3%	Data on way of feeding was collected prospectively in the 1 st two years. Corrected for family history, gender, and SES. Within MBF mean duration of breastfeeding was 9.5 wk.
	Tariq et al., 1998	Cohort	United Kingdom n=1,086	4 yr	FF before 3 mo BF	No correction.	No correction.
	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	<u>3 yr</u> i=13/502 i=0/78 <u>5 yr</u> i=7/390 i=0/57 <u>8 yr</u> i=0/368 i=0/44 <u>15 yr</u> i=0/368 i=0/41 i=10/192 i=7/76 i=0/44 i=1/143 i=1/66 i=0/31	No correction.

Table 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	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 <u>With family background of atopy</u> 2 retrospective studies; protective effect BF 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 ₃₋₇ EBF ₃₋₇	RR=1 RR=0.91 (0.61-1.36)	Based on two studies (Kajosaari and Saarinen, 1983, Oddy et al., 1999).
	Gdalevich et al., 2001b c	Meta-Analysis	n=8,183		EBF _{≥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 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.
	Chulada et al., 2003 d	Cohort	USA n=8,261	2-71 mo	FF BF BF _{<4} BF _{≥4} EBF ₀ EBF _{<4} EBF _{≥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 _{cow} in first 2wk EBF _{≥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 _{≥4} vs. EBF _{<4} MBF _{≥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 Zealand 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 Zealand Plunket Nurse programme. Different cut-point for breastfeeding (0, 8, 12 wks) had no effect on the results. Health effect = wheezing with hypersensitive reaction.
	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).

Table 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., 2002 d	Cohort	Australia n=2,602	0-12 mo	FF vs. EBF _{>0} EBF _{<2} vs. EBF _{≥2} EBF _{<4} vs. EBF _{≥4} EBF _{<6} vs. EBF _{≥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 _{≥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 _{≥3} EBF _{<4} vs. EBF _{≥4} EBF _{<6} vs. EBF _{≥6} BF _{<3} vs. BF _{≥3} BF _{<6} vs. BF _{≥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 _{≥4} vs. EBF _{<4} + FF	Wheezing _{<3} OR= ±0.36 ; Wheezing _{≥3} OR= ±1 for children without an asthmatic mother and for children with an asthmatic mother but without atopy Wheezing _{≥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.
	Baker et al., 1998	Cohort	United Kingdom n=8450	6 mo	FF BF _{<3} BF _{≥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 _{≥15wk} , no solids EBF _{≥15wk} , solids EBF _{≥15wk} MBF _{≥15wk} , no solids MBF _{≥15wk} , solids MBF _{≥15wk} FF _{≥15wk} , no solids FF _{≥15wk} , solids FF _{≥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.

Table 9 continued: Effect of breastfeeding on wheezing

Intermediary of health effect	Authors, Year of publication	Design	Study population	Age group	Breastfeeding	Effect size			Remarks
						Age 0-4 mo	Age 4-6 mo	Age 6-12 mo	
Wheezing continued	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}	12.3 8.1 5.2 (p=0.005) OR=1.7 (p=.05) OR=1	6.9 4.7 7.4	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 Odiijk 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; Wright et al., 1995; Wilson et al., 1998; Oddy et al., 1999; Wright et al., 2001; Wright et al., 1989; Raisler et al., 1999). Other studies inadequate study design, or non relevant study populations.
	Kramer and Kakuma, 2002 a	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 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 	Randomised controlled trial	Belarus n=17,046	0-12 mo	Control group Intervention group	<u>Rash</u> OR=1 OR=0.56 (0.38-0.81)	<u>Atopic eczema</u> OR=1 OR=0.54 (0.31-0.95)	<u>Non-eczema rash</u> 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.	
	Stabell Benn et al., 2004	Cohort	Denmark n=15,430	4-18 mo	Not EBF _{≥4} EBF _{≥4}	<u>Non-allergic parents</u> IRR=1 IRR=1.29 (1.06-1.55)	<u>One allergic parent</u> IRR=1 IRR=1.11 (0.94-1.31)	<u>Both parents allergic</u> IRR=1 IRR=0.88 (0.67-1.13)	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.	
	Laubereau et al., 2004 	Cohort	Germany n=3,903	0-3 yr	(MBF + FF) EBF _{≥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 	Cohort	Finland n=456	4 yr	FF _{cow} in first 2wk EBF _{≥3}	<u>family history</u> OR=1 OR=0.68 (0.34-1.35)	<u>no family history</u> 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 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 _{≥4} vs. EBF _{<4} MBF _{≥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 	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 	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.	
	Wetzig et al., 2000 	Cohort	Germany n=325	0-2 yr	EBF _{≥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 	Cohort	United Kingdom n=1,086	4 yr	FF _{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}	<u>0-13 wk</u> RR=1 RR=0.65	<u>14-26 wk</u> RR=1 RR=0.30	<u>27-39 wk</u> RR=1 RR=1.21	<u>40-52 wk</u> RR=1 RR=1.16	Corrected for SES, age mother, and smoking (other confounders no effect). Small numbers (2-16) per group.

Table 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	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	<u>No family history</u> FF _{cow} BF <u>Family history</u> FF _{cow} FF _{soy} BF	<u>3 yr</u> i=22/502 i=0/78 i=24/201 i=9/79 i=4/48	<u>5 yr</u> i=1/390 i=0/57 i=0/192 i=0/76 i=0/44	<u>8 yr</u> i=1/368 i=0/44 i=0/167 i=0/69 i=0/38	<u>15 yr</u> 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.
	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 <u>atopic background family</u> 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	<u>0-12 mo</u> RR=1 RR=0.73 (0.49-1.08)		<u>5 yr</u> 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 _{≥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)			

Table 11: Effect of breastfeeding on atopy

Intermediary of health effect	Authors, Year of publication	Design	Study population	Age group	Breastfeeding	Effect size		Remarks		
Atopy [3]	Siltanen et al., 2003	Cohort	Finland n=456	4 yr	FF _{cow} in first 2wk EBF _{≥3}	Atopy	family history OR=1 OR=0.74 (0.37-1.49)	No family history OR=1 OR=2.40(0.77-7.53)	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 Zealand 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 Zealand 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.		
	Saarininen and Kajosaari, 1995	Cohort	Finland n=150	1, 3, 5, 10, 17 yr	EBF _{≤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)
	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. Based on one study (Kajosaari and Saarinen, 1983).
	Kramer and Kakuma, 2002	Review	n=113	5 yr	MBF ₃₋₇ EBF ₃₋₇	RR=1 RR= 0.91 (0.61-1.36)				
	Golding et al., 1997b	Review				The data in the literature show lirtle 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.		

Table 11 continued: Effect of breastfeeding on atopy

Intermediary of health effect	Authors, Year of publication	Design	Study population	Age group	Breastfeeding	Effect size				Remarks
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 _{≥4} <u>Mother high IgE</u> FF BF _{<4} BF _{≥4}	<u>Birth</u> 0.08 (0.07-0.10) 0.11 (0.09-0.13) 0.10 (0.09-0.12) <u>Mother high IgE</u> FF 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 _{≥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 _{≥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 _{≥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 _{≥3} EBF _{<4} vs. EBF _{≥4} EBF _{<6} vs. EBF _{≥6} BF _{<3} vs. BF _{≥3} BF _{<6} vs. BF _{≥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).
Allergic rhinitis a	Siltanen et al., 2003	Cohort	Finland n=456	4 yr	FF _{cow} in first 2wk EBF _{≥3}	<u>family history</u> OR=1 OR=0.41 (0.18-0.95)		<u>no family history</u> 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.

Table 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 continued a	Kull et al., 2002	Cohort	Sweden n=3,791	0-2 yr	EBF _{≥4} vs. EBF _{<4} MBF _{≥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 5 yr i=4/390 i=2/57 8 yr i=4/368 i=0/44 15 yr i=7/368 i=0/41 i=6/201 i=11/192 i=1/167 i=3/143 i=0/79 i=7/76 i=2/69 i=1/66 i=0/48 i=0/44 i=0/38 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 _{≥4} vs. EBF _{<4} MBF _{≥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 _{≥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 _{≥4} vs. EBF _{<4} MBF _{≥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.
	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 12: Effect of breastfeeding on obesity

Intermediary of health effect	Authors, Year of publication	Design	Study population	Age group	Breastfeeding	Effect size		Remarks
Obesity	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 > 95 th percentile. Corrected for SES, energy intake at 3 year and gender
	Grummer-Strawn and Mei, 2004	Cohort	USA n=177,304	4 yr	FF BF _{<1} BF _{1-2.9} BF _{3-5.9} BF _{6-11.9} BF _{≥12}	<u>full cohort (n=177,304)</u> 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)	<u>Sub-cohort (n=12,587)</u> 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 > 95 th 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}	<u>Males</u> OR=1 OR=0.93 (0.74-1.17)	<u>Females</u> 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}	<u>Overweight</u> OR=1 OR=0.53 (0.31-0.89)	<u>Obesity</u> OR=1 OR=0.46 (0.23-0.92)	Overweight defined as BMI-for-age-and-gender > 90 th percentile; obesity > 97 th 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	<u>Obesity</u> OR=1 OR=0.72 (0.65-0.79)	<u>Severe obesity</u> 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 > 95 th percentile (18.4 kg/m ²), severe obesity > 98 th 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 _{≤2} EBF ₃₋₅ EBF ₆₋₈ EBF _{≥9}	<u>At risk for overweight</u> 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)	<u>Overweight</u> 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 85-94 th percentile; overweight > 97 th percentile. Corrected for birth weight, ethnicity, gender, age, BMI mother, and time when solids were introduced.
	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}	<u>4-8 yr</u> 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)	<u>9-18 yr</u> 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 > 95 th 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.

Table 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	von Kries et al., 1999; Koletzko and von Kries, 2001	Cross-sectional	Germany n=9,357	5-6 yr	EBF _{≤2} EBF ₃₋₅ EBF ₆₋₁₂ EBF _{>12} BF	<u>Overweight</u> 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)		<u>Obesity</u> 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 > 90 th percentile; obesity >97 th 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	<u>Overweight</u> OR=1 OR=0.80 (0.71-0.90)		<u>Obesity</u> OR=1 OR=0.80 (0.66-0.96)		Overweight defined as BMI-for-age-and-gender > 90 th percentile; obesity >97 th 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.
	Gillman et al., 2001 c	Cross sectional	USA n=15,341	9-14 yr	FF ₆ BF ₆ BF _{≤3} BF _{≥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 > 95 th 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 a	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.
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 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)	Sadauskaite-Kuehne et al., 2004	Case-control	Sweden ≥ 165 Cases ≥ 420 Controls	5-9 yr	EBF _{≥5} vs. EBF _{not ≥5} BF _{≥7} vs. BF _{not ≥7} BF _{≥9} vs. BF _{not ≥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, prematurity, 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.
	Hyponen et al., 1999	Case-control	Finland 435 Cases 386 Controls	0-14 yr	EBF _{≥3} EBF _{≥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}	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	Corrected for SES and number of siblings. Matched on age and gender. Breastfeeding determined at later age.
	Jones et al., 1998	Case-control	United Kingdom 315 Cases 1,525 Controls	0-20 yr	BF (mo) BF _{discharge} FF _{discharge}	OR=1.10 (0.99-1.22) RR=1 RR=1.33 (0.76-2.34)	Matched on gender, yr of birth, given birth in which hospital.
	Samuelsson et al., 1993	Case-control	Sweden 297 Cases 792 Controls	0-15 yr	EBF MBF	Non significant	Matched on birth yr, gender and geographic location
	Norris and Scott, 1996	Meta analysis			BF FF (18 studies) BF _{≥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 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 _{≤5} BF ₆₋₁₁ BF _{≥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 _{≤5} BF ₆₋₁₁ BF _{≥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 a	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 _{≤5} BF ₆₋₁₁ BF _{≥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).
Blood pressure (mmHg) a	Martin et al., 2004	Cohort	Great-Britain n=7,276	7 yr	FF BF MBF ₂ EBF ₂	<u>Systolic blood pressure</u> Ref -0.7 (-1.4; -0.22) -0.7 (-1.4; 0.01) -0.8 (-1.5; 0.01)	<u>Diastolic blood pressure</u> 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 _{≥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}	<u>Systolic blood pressure</u> 125.1 124.9	<u>Diastolic blood pressure</u> 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.

Table 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) continued	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).	
	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.	
Elasticity of the blood vessels	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	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.

Table 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 [3]	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 _{>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 _{>1} BF ₁₋₅ BF _{>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 _{>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 181 Controls	1,5-15 yr	FF BF _{<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 [2]	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 _{>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 _{>1} BF ₁₋₅ BF _{>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 _{>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 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 _{≥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)	
	Hardell and Dreifaldt, 2001	Case-control	Sweden 26 Cases 27 Controls	0-14 yr	FF + BF _{<1} BF _{≥1} BF ₁₋₅ BF _{≥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.
Acute myeloid leukaemia ^a	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 _{≥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 _{≤6} BF _{≥6}	<u>SES corrected</u> OR=1 OR=0.90 (0.80-1.02) OR=0.85 (0.73-0.98) 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	Lancashire and Sorahan, 2003	Case-control	United Kingdom 948 Cases 948 Controls	1-15 yr	FF BF BF _{<1} BF ₁₋₆ BF _{≥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 _{≥1} BF ₁₋₅ BF _{≥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.

Table 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	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 _{≥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 491 Controls	0-10 yr	FF BF _{≤3} BF _{>3}	<div> <div> <div><10 yr</div> <div>OR=1</div> <div>OR=0.68 (0.49-0.95)</div> <div>OR=0.67 (0.47-0.94)</div> </div> <div> <div>< 4 yr</div> <div>OR=1</div> <div>OR=0.62 (0.37-1.03)</div> <div>OR=0.63 (0.39-1.03)</div> </div> <div> <div>≥4 yr</div> <div>OR=1</div> <div>OR=0.78 (0.50-1.23)</div> <div>OR=0.68 (0.41-1.14)</div> </div> </div>	Cases and controls matched on gender, age, and region. Corrected for age mother and SES.
	Schuz et al., 1999	Case-control	Germany 682 Cases 2,574 Controls	0-14 yr	BF _{≥6} BF ₂₋₆ BF _{<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 _{≤6} BF _{>6}	<div> <div>All studies</div> <div>OR=1</div> <div>OR=0.90 (0.82-0.99)</div> <div>OR=0.75 (0.67-0.85)</div> </div> <div> <div>SES corrected</div> <div>OR=1</div> <div>OR=0.88 (0.80-0.97)</div> <div>OR=0.76 (0.68-0.84)</div> </div>	Eight case-control studies, including Davis et al., 1988, one study from China and one from Moscow.
Malignant lymphoma	Hardell and Dreifaldt, 2001	Case-control	Sweden 99 Cases 97 Controls	0-14 yr	FF + BF _{<1} BF _{≥1} BF ₁₋₅ BF _{≥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.
Hodgkin's disease	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 _{≥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	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 _{≥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.

Table 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
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 _{≥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 _{≥1} BF ₁₋₅ BF _{≥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 _{≥1} BF ₁₋₅ BF _{≥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.
Breast cancer a	Freudenheim et al., 1994	Case-control	USA 740 Cases 810 Controls	40-85 yr	FF BF	<u>Pre-menopausal</u> OR=1 OR=0.76 (0.52-1.12)	<u>Postmenopausal</u> OR=1 OR=0.73 (0.47-1.13)	<u>All</u> 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 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)) [4]	Kramer et al., 2003	Cohort	Belarus n=3,483	0-12 mo	EBF ₃ EBF ₆	3-6 mo ref	6-9 mo ref	9-12 mo ref	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	3 mo ref	9 mo ref	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	6-9 mo ref	8-12 mo ref	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).
	Kramer et al., 2003	Cohort	Belarus n=3,483	0-12 mo	EBF ₃ EBF ₆	3-8 mo ref	6-9 mo ref	9-12 mo ref	Corrected for region, SES, number of siblings, birth weight or height at birth, weight or height gain from birth until 3 mo.
Height gain (difference in height (cm)) [4]	Kramer et al., 2002	Intervention	Belarus n=17,046	1, 2, 3, 6, 9, 12 mo	Control Experiment	1 mo ref	3 mo ref	9 mo ref	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	6-9 mo ref	8-12 mo ref	3-8 mo four studies (n=4,388); 6-9 mo two studies (n=3,432); 8-12 mo three studies (n=3,450).
	Kramer et al., 2002	Intervention	Belarus n=17,046	1, 2, 3, 6, 9, 12 mo	control Experiment	1 mo ref	3 mo ref	9 mo ref	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	9 mo ref	12 mo ref	Health effect = difference in head circumference (cm). One study (Kramer et al., 2001).

Table 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 _{≤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 _{≤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.
	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	Perceptual performance e -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.
	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.

Table 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	Horwood and Fergusson, 1998	Cohort	New Zealand n=869	8 & 9 yr	FF BF _{<4} BF ₄₋₇ BF _{>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.
	Horwood et al., 2001	Cohort	New Zealand n=280	18 mo	FF BF _{<4} BF ₄₋₇ BF _{>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 _{≥3} EBF _{≥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	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	12 mo	18 mo	24 mo	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.
						-0.6(-4.5;3.2)	-2.5(-6.8;1.7)	-0.8(-5.7;4.2)	-1.2(-7.1;4.8)	
						3.4 (-0.1;6.9)	3.4(-0.4;7.1)	4.4 (0.0-8.9)	6.7(1.4-12.1)	
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)	0.8(-3.0;4.6)	3.7 (-0.8;8.1)	5.6(0.2-11.0)							
2.8 (-0.8;6.3)										

Table 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
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 complex figure test	Vreugdenhil et al., 2004	Cohort	Netherlands N=83	9 year	BF _{short} - FF BF _{long} - BF _{short} BF _{long} - FF	Rev copy -0.26±1.45 0.46±1.65 0.20±1.45 Rev recall 1.53±1.64 0.25±1.87 1.77±1.64 Rev 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
Tower of London (TOL)	Vreugdenhil et al., 2004	Cohort	Netherlands N=83	9 year	BF _{short} - FF BF _{long} - BF _{short} BF _{long} - FF	BF _{short} - FF -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	Pollock, 1994	Case-cohort	United Kingdom n=3,738	5 yr	FF _{≥3} EBF _{≥3}	OR=1 OR=1.5	Corrected.
Icelandic developmental inventory	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).
	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	Vestergaard et al., 1999	Cohort	Denmark n=1,656	8 mo	EBF ₀₋₁ EBF ₂₋₃ EBF ₄₋₅ EBF _{≥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 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 [6]	Ford et al., 1993	Case-control study	New-Zeeland 485 Cases 1,800 Controls	0-12 mo	FF	Discharge hospital OR=1 OR=1.10 (0.59-2.07) OR=0.52 (0.35-0.77)	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.
					MBF	1st 4 weeks OR=1 OR=0.95 (0.58-1.55) OR=0.69 (0.43-1.11)	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.
					EBF	Last 2 days OR=1 OR=0.96 (0.65-1.44) OR=0.65 (0.46-0.91)	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.
					MBF ₃₋₇ EBF ₃₋₇	RR=1 RR=2.30 (0.21-25.37)	
	Kramer and Kakuma, 2002	Review/meta-analysis	n=3,483	0-12 mo	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.
	McVea et al., 2000	Meta-analysis	23 studies				

Table 19: Effect of breastfeeding on hospitalization

Intermediary of health effect	Authors, Year of publication	Design	Study population	Age group	Breastfeeding	Effect size	Remarks
Hospitalisation [6]	Pardo-Crespo et al., 2004	Case-control	Spain 336 Cases 336 Controls	1-24 mo	FF	1-24 mo OR=1 OR=1.14 (0.72-1.79) OR=1.63 (0.97-2.76) OR=0.86 (0.49-1.49) OR=0.80 (0.44-1.45) OR=1.06 (0.44-2.55)	Corrected for SES, smoking, and incubator after delivery.
				1-6 mo	BF	1-6 mo OR=1 OR=0.50-1.63 OR=0.62-2.27 OR=0.28-1.34 OR=0.18-1.19	
				7-24 mo	BF _{1-45 days} BF _{46-90 days} BF _{91-180 days (≥91 days)} BF _{>181 days}	7-24 mo OR=1 OR=0.77-3.34 2.79(1.11-7.01) OR=0.56-2.94 OR=0.67-3.36 OR=0.55-4.70	

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 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	London et al., 1990	Cohort	United States of America n=89,413 (1,262 cases)	40-65 yr	EFF	RR=1	Correction for age, number of children, age first birth, age menarche, family history, benign breast disorder history, oral contraceptive, menopausal status.
					BF _{<7}	RR=0.94 (0.82-1.06)	
					BF ₇₋₁₁	RR=0.83 (0.67-1.03)	
					BF ₁₂₋₂₃	RR=0.90 (0.74-1.09)	
	Meeske et al., 2004	Case-control	United States of America 412 Cases 507 Controls	35-64 yr	BF _{≥24}	RR=0.95 (0.73-1.23) (p-trend: 0.20)	Correction for: age, ethnicity, family history, BMI, number of children, age first birth.
					Life-long BF		
					EFF	OR=1	
					EBF _{<3}	OR=1.02 (0.73-1.43)	
					EBF ₄₋₉	OR=1.30 (0.86-1.95)	
					EBF ₁₀₋₁₄	OR=1.62 (0.56-3.07)	
					EBF _{≥15}	OR=1.71 (0.79-3.67) (p-trend: 0.03)	
					EBF (mo)	OR=1.032 (1.00-1.06)	
					BF _{<3}	OR=1.01 (0.69-1.49)	
					BF ₄₋₉	OR=1.05 (0.69-1.58)	
	Zheng et al., 2001	Case-control	United States of America 522 Cases 511 Controls	30-80 yr	BF ₁₀₋₁₄	OR=1.36 (0.82-2.28)	Correction for age, age first birth, number children, fat intake (g/day), SES, ethnicity, family history cancer, study location, menopausal status.
					BF ₁₅₋₂₃	OR=1.16 (0.64-2.12)	
					BF _{≥24}	OR=2.00 (1.11-3.60) (p-trend: 0.04)	
					BF (mo)	OR=1.014 (1.00-1.03)	
	Tryggvadottir et al., 2001	Case-control	Iceland 993 Cases 9,729 Controls	26-90 yr	EFF	OR=1	Correction for age menarche, age first birth, number children, number children, age first birth, weight.
					BF	OR=0.83 (0.63-1.09)	
					BF ₁₋₆	OR=0.86 (0.61-1.21)	
					BF ₇₋₁₂	OR=0.82 (0.52-1.29)	
					BF ₁₃	OR=0.78 (0.53-1.14) (p-trend: 0.16)	
					Life-long BF		
					BF _{0-4 wks}	OR=1	
					BF _{5-26 wks}	OR=0.67(0.51-0.89)	
					BF _{27-52 wks}	OR=0.79(0.59-1.05)	
					BF _{53-104 wks}	OR=0.70(0.51-0.97)	
					BF _{≥105 wks}	OR=0.48(0.31-0.74)	
					40 yr (84 Cases)	40-55yr (399 c) OR=1 OR=0.51 (0.20-1.30)	
					EFF	OR=1	
					BF	OR=0.09 (0.02-0.45)	
						>55yr (510 c) OR=1 OR=0.32 (0.15-0.66)	

Table 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	Chang-Claude et al., 2000	Case-control family study	Germany 706 Cases 1,381 Controls	< 50 yr	FF BF <u>Life-long BF</u> BF ₁₋₆ BF ₇₋₁₂ BF ₁₃₋₂₄ BF _{>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.
	Furberg et al., 1999	Case-control	United States of America 751 Cases 743 Controls	20-74 yr	EFF BF <u>Life-long BF</u> BF ₁₋₃ BF ₄₋₁₂ BF _{>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 <u>Life-long BF</u> BF ₁₋₅ BF ₆₋₁₁ BF ₁₂₋₁₇ BF ₁₈₋₂₃ BF _{>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 st 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 <u>Life-long BF</u> BF _{<3} BF ₃₋₁₁ BF ₁₂₋₂₃ BF _{>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 FBB 109, 130, 108, 129) Only the 12 studies given who correct for confounders

Table 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
Pre-menopausal	London et al., 1990 [6]	Cohort	United States of America n=89,413 (624 cases)	40-65 yr	EFF	RR=1	Correction for age, nr children, age first delivery, age menarche, family history, benign breast conditions, contraception
					BF _{<7}	RR=1.00 (0.83-1.20)	
					BF ₇₋₁₁	RR=0.85 (0.63-1.14)	
					BF ₁₂₋₂₃	RR=0.90 (0.69-1.18)	
	Zheng et al., 2001	Case-control	United States of America 522 Cases 511 Controls	30-80 yr	BF _{≥24}	RR=1.06 (0.75-1.50) (p-trend: 0.59)	BF retrospectively collected, other data prospectively Correction for age, age first delivery, nr children, fat intake (g/d), SES, ethnicity, family history cancer, study location
					OR=1		
					OR=0.73 (0.40-1.31)		
					OR=0.77 (0.36-1.63)		
	Furberg et al., 1999	Case-control	United States of America 425 Cases 371 Controls	20-49 yr	BF ₁₋₆	OR=0.69 (0.30-1.60)	Correction for age, ethnicity, nr children, age first delivery, family history, BMI, menopausal status
					BF ₇₋₁₂	OR=0.74 (0.36-1.52) (p-trend: 0.39)	
					BF _{≥13}		
					OR=1		
	Stuver et al., 1997	Case-control	Wales, United States of America 1,142 Cases 3,529 Controls	± 41 yr	OR=0.8 (0.5-1.1)		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
					OR=0.8 (0.5-1.3)		
					OR=0.7 (0.4-1.1)		
					OR=0.8 (0.4-1.4)		
	Enger et al., 1997 [6]	Case-control	United States of America 452 Cases 452 Controls	<40 yr	Life-long BF	Age 1 st time BF<25 yr OR=1	Correction for age menarche, family history breast cancer, total month contraception use, ethnicity, alcohol intake, physical activity
					EFF	Age 1 st time BF≥25 yr OR=1	
					BF ₁₋₆	OR=1.34 (0.83-2.16)	
					BF ₇₋₁₅	OR=1.23 (0.72-2.11)	
	Negri et al., 1996	Case-control	Italy 847 Cases 695 Controls	?	BF ₁₂₋₁₇	OR=0.76 (0.41-1.39) (p-trend:0.14)	Correction for age, centre, SES, number of children. (Other variables had no influence on the results)
					BF _{≥16}		
					OR=1		
					OR=1.10 (0.8-1.4)		
	Katsouyanni et al., 1996	Case-control	Greece 270 Cases 505 Controls	?	OR=1.17 (0.9-1.6)		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
					BF ₁₂₋₁₇	OR=1.15 (0.8-1.7)	
					BF _{≥18}	OR=1.11 (0.6-2.0) (non sign trend)	
					OR=1		

Table 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
Pre-menopausal continued	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 _{≥12} BF _{<6} BF ₆₋₁₁ BF ₁₂₋₁₇ BF _{≥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 <u>Life-long BF</u> BF _{≤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	<u>Life-long BF</u> EFF BF ₁₋₃ BF ₄₋₉ BF ₁₀₋₁₅ BF ₁₆₋₂₁ BF _{≥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 pre-menopausal
	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
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 _{≥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

Table 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 continued	Furberg et al., 1999	Case-control	United States of America 326 Cases 372 Controls	50-74 yr	EFF BF <u>Life-long BF</u> BF ₁₋₃ BF ₄₋₁₂ BF _{≥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	<u>Life-long BF</u> EFF BF BF ₁₋₆ BF ₇₋₁₂ BF ₁₃₋₂₄ BF ₂₅₋₃₆ BF _{≥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 _{≥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 <u>Life-long BF</u> BF _{<3} BF ₃₋₁₁ BF ₁₂₋₂₃ BF _{≥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
	Newcomb et al., 1999	Case-control	United States of America 3,633 Cases 3,790 Controls	50-79 yr	EFF BF <u>Life-long BF</u> BF _{<3} BF ₃₋₆ BF ₇₋₁₂ BF ₁₃₋₂₃ BF _{≥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	Case-control	United States of America 4,254 Cases 5,378 Controls	?	EFF BF <u>Life-long BF</u> BF _{<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

Table 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
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 _{≤12} BF _{>12} BF (mo)	<u>BRCA1 mutation (n=685)</u> OR=1 OR=0.89 (0.68-1.17) OR=0.55 (0.38-0.80) OR=0.98 (0.97-0.99)	<u>BRCA2 mutation (n=280)</u> 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 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 <u>Life-long BF</u> BF ₁₋₅ BF ₆₋₁₁ BF ₁₂₋₂₃ BF _{≥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 <u>Life-long BF</u> BF ₁₋₃ BF ₄₋₈ BF ₉₋₁₈ 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 3: Effect of breastfeeding on ovarian cancer risk

Intermediary of health effect	Author of publication	Design	Study population	Age group	Breastfeeding	Effect size	Remarks
Ovarian cancer	Riman et al., 2002	Case-control	Sweden 459 Cases 2,637 Controls	50-74 yr	BF _{<1} BF ₁₋₅ BF ₆₋₁₁ BF _{≥12}	OR=1 OR=0.99 (0.64-1.52) OR=0.77 (0.50-1.19) OR=0.87 (0.56-1.35)	Correction for age, number of children, BMI, age menopause, duration of contraception use, ever use of hormone replacement therapy
	Greggi et al., 2000	Case-control	Italy 330 Cases 721 Controls	13-80 yr	EBF _{≤12} BF _{≤12} BF _{≥12}	OR=1 OR=0.8 (0.5-1.1) OR=0.5 (0.4-0.8)	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?!?)
	Siskind et al., 1997	Case-control	Australia 619 Cases 724 Controls	18-79 yr	Life-long EBF EBF ₁₋₆ EBF ₇₋₁₂ EBF ₁₃₋₂₄ EBF ₂₄₋₃₆ EBF _{≥24} EBF _{≥36}	Pre-menopause OR=1 OR=0.89 (0.65-1.21) OR=0.68 (0.49-0.94) OR=0.84 (0.59-1.20) OR=0.69 (0.38-1.27) OR=0.77 (0.34-1.75)	Correction for number of children, age, use contraceptives, SES, history of smoking, (menopause status)
	Whittemore et al., 1992	Case-control	United States of America 870 Cases 4,624 Controls	25-80	FF BF BF ₁₋₅ BF ₆₋₁₁ BF ₁₂₋₂₃ BF _{≥24}	Postmenopausal OR=1 OR=0.98 (0.65-1.47) OR=0.83 (0.54-1.26) OR=0.88 (0.56-1.38) OR=0.93 (0.46-1.88) OR=1.27 (0.50-3.2)	Correction for age, study parity, oral contraceptive use
	Gwinn et al., 1990	Case-control	United States of America 321 Cases 3,312 Controls	20-54 yr	FF BF ₁₋₂ BF ₃₋₅ BF ₆₋₁₁ BF ₁₂₋₂₃ BF _{≥24}	OR=0 OR=0.6 OR=0.8 OR=0.8 OR=0.7 OR=0.3	Correction for number of pregnancies, use of contraceptives, age, pregnancy*age
	Booth et al., 1989	Case-control	United Kingdom 169 Cases 362 Controls	<65 yr	FF BF _{≤6} BF ₇₋₁₂ BF ₁₃₋₁₈ BF ₁₉₋₂₄ BF _{≥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

Table 3 continued: Effect of breastfeeding on ovarian cancer risk

Intermediary of health effect	Author Yr of publication	Design	Study population	Age group	Breastfeeding	Effect size	Remarks
Borderline ovarian tumours	Riman et al., 2001	Case-control	Sweden 135 Cases 2,637 Controls	50-74 yr	FF BF ₁₋₅ BF ₆₋₁₁ BF _{>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 _{≥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 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> RR=1 RR=1.00 RR=1.00 <u>Radius</u> RR=1 RR=1.01 RR=1.00 <u>Hip</u> RR=1 RR=1.00 RR=1.00 <u>Spine</u> RR=1 RR=0.99	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 _{<3} BF ₄₋₁₁ BF ₁₂₋₂₃ BF _{>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 _{≥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 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 Schauburger, 2002	Cohort	United States of America n=540	26-51 yr	FF BF _{2-12 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’

Appendix 3 Assumptions of the BF-model

A Transferable relative risks

Suppose that for any population of infants the probability, $p_d(n)$ of suffering from disease d , given the duration of breastfeeding, n , and some, m , known and unknown confounders, X_i , is expressed by the following equation:

$$\ln(p_d(n)) = \beta_{d,0} + \beta_d n + \sum_{i=1}^m \beta_{d,i} X_{d,i} . \quad \text{Equation 1}$$

Then the relative risk of n months of breastfeeding versus formula feeding (0 months) of the study population is:

$$\tilde{RR}_d(n) = \frac{\tilde{p}_d(n)}{\tilde{p}_d(0)} = \frac{e^{\beta_{d,0} + \beta_d n + \sum_{i=1}^m \beta_{d,i} \tilde{X}_{d,i}}}{e^{\beta_{d,0} + \sum_{i=1}^m \beta_{d,i} \tilde{X}_{d,i}}} = e^{\beta_d n} , \quad \text{Equation 2}$$

where $\tilde{X}_{d,i}$, denotes the values of the confounders in the study population for disease d .

The relative risk of the model population is:

$$\hat{RR}_d(n) = \frac{\hat{p}_d(n)}{\hat{p}_d(0)} = \frac{e^{\beta_{d,0} + \beta_d n + \sum_{i=1}^m \beta_{d,i} \hat{X}_{d,i}}}{e^{\beta_{d,0} + \sum_{i=1}^m \beta_{d,i} \hat{X}_{d,i}}} = e^{\beta_d n} , \quad \text{Equation 3}$$

where $\hat{X}_{d,i}$, denotes the value of the confounders in the model population.

Hence, the relative risk from the study population equals that of the model population, in this case, the Dutch population.

Note, that if the relative risks, $RR_d(n)$ are transferable over populations the odds ratios, $OR_d(n)$ are not, unless

$$\tilde{p}_d(0) = \hat{p}_d(0) \quad \text{Equation 4}$$

or

$$RR_d(n) = 1. \quad \text{Equation 5}$$

Because

$$\frac{\tilde{p}_d(n)}{\tilde{p}_d(0)} = RR_d(n) = \frac{\hat{p}_d(n)}{\hat{p}_d(0)} , \quad \text{Equation 6}$$

it follows

$$\begin{aligned} \tilde{OR}_d(n) &= \frac{\tilde{p}_d(n)(1 - \tilde{p}_d(0))}{\tilde{p}_d(0)(1 - \tilde{p}_d(n))} = RR_d(n) \frac{(1 - \tilde{p}_d(0))}{(1 - \tilde{p}_d(0)RR_d(n))} \neq \\ &RR_d(n) \frac{(1 - \hat{p}_d(0))}{(1 - \hat{p}_d(0)RR_d(n))} = \frac{\hat{p}_d(n)(1 - \hat{p}_d(0))}{\hat{p}_d(0)(1 - \hat{p}_d(n))} = \hat{OR}_d(n) . \end{aligned} \quad \text{Equation 7}$$

Hence an $OR_d(n)$ which is valid for every population does not exist.

For some diseases notably those of the mother, we assumed the odds ratio is transferable from study populations to the model population. This assumption is forced through the availability of data; all studies that investigated the association of breastfeeding and diseases among mothers are case-control studies. From these studies, only odds ratios could be deduced instead of relative risks. Also for some diseases among the children, mainly odds

ratios are reported (see Chapter 3 or Appendix 1). Therefore it is assumed that for these diseases the odds of suffering from disease d , given the duration of breastfeeding, n and some (m) confounders, X_i , is expressed by the following equation:

$$\ln\left(\frac{p_d(n)}{1-p_d(n)}\right) = \beta_{d,0} + \beta_d n + \sum_{i=1}^m \beta_{d,i} X_{d,i}. \quad \text{Equation 8}$$

Similar to the relative risk transferability it was easy to show that :

$$\tilde{OR}_d(n) = \hat{OR}_d(n). \quad \text{Equation 9}$$

B Relative risks, dose-response estimation

A regression analyses is used to construct an overall dose-response function that incorporates the information from the considered studies. Based on Equation 1 the dose-response function has the following form:

$$\ln(RR_d(n)) = \beta_d n \quad \text{Equation 10}$$

or for some diseases:

$$\ln(OR_d(n)) = \beta_d n. \quad \text{Equation 11}$$

$RR_d(n)$ denotes the relative risk and $OR_d(n)$ denotes the odds ratio of suffering from disease d after n months of breastfeeding relative to formula feeding. The function of equation 10 forces the relative risk to be 1 for 0 months of breastfeeding.

The parameter β_d is found through a weighted regression of equation 10 on the reported $RR_d^i(n)$ in the relevant studies, i . The software package S-plus, version 6.2 is used to perform the regression. The weights were either the number of subjects in the study population (cohort studies) or the number of cases in the study population (case-control studies), depending on the study design.

C From relative risk to incidence

The relative risk of disease d for n months duration of breastfeeding, $RR_d(n)$, follows from the dose-response function (Equation 10). From this relative risk the incidence or the probability of suffering from the disease for each period of breastfeeding can be derived.

We distinguished seven classes of breastfeeding, one for never breastfeeding, one for each month of breastfeeding up to five months, and one class for at least six months.

The incidence is expressed by

$$p_d = \sum_{i=0}^6 r(i) p_d(i), \quad \text{Equation 12}$$

Where,

p_d : the probability of becoming ill, or the incidence in the present population

$r(n)$: the fraction of the population that is breastfed for n months.

A dash over a variable denotes the value of the variable in the present population. Now, $p_d(n)$ and $p_d(0)$ can be expressed in terms of \bar{p}_d , $\bar{r}(n)$, and $RR_d(n)$.

Hence,

$$p_d(0) = \frac{\bar{p}_d}{r(0) + \sum_{i=1} \bar{r}(i) RR_d(i)} \quad \text{Equation 13}$$

and

$$p_d(n) = RR_d(n) p_d(0) = \frac{\bar{p}_d RR_d(n)}{r(0) + \sum_{i=1} \bar{r}(i) RR_d(i)}. \quad \text{Equation 14}$$

With these equations the incidence of the disease of an infant that is breastfed for n months and who belongs to the model population characterized by p_d and $r(n)$ could be computed.

D From odds ratio to incidence

For a number of diseases, such as different types of cancer of the mother, or leukaemia of the infant, odds ratios characterize the association with breastfeeding. The odds ratios follow from the estimated dose-response function (Equation 10). The incidence or the probability of suffering from the disease is derived analogous to the previous section. From the definition of the odds ratio we could write $p_d(n)$ as

$$p_d(n) = \frac{OR_d(n) p_d(0)}{1 + p_d(0)(OR_d(n) - 1)}. \quad \text{Equation 15}$$

Hence, combining equation 15 and equation 12:

$$\bar{p}_d = p_d(0) \left(r(0) + \sum_{i=1}^N \frac{\bar{r}(i) OR_d(i)}{1 + p_d(0)(OR_d(i) - 1)} \right). \quad \text{Equation 16}$$

Equation 16 can be solved numerically for $p_d(0)$. The model uses the goal seek function in Microsoft Excel. Once $p_d(0)$ is known the other risks, $p_d(n)$ follow from equation 15.

E From incidence to DALY

In order to compare the health effects of different scenarios with each other, the incidences of the different diseases must be comparable to each other. Therefore, the incidence of every disease needs to be converted in a similar unit. In this project was chosen for disability adjusted life years (DALYs). DALYs as a measure for the burden of disease are well documented in the literature.^{105,167,169} A DALY is measured in years and consists of two parts. These are the years of life lost (YLLs) due to premature death and years lived with the disease or disability (YLDs). The last part is weighted for the gravity of the disease. In this way, years with a disease and death can be compared. For example if a disease is weighted with a factor 0.5, it means that living with the disease for one year is considered as bad as losing half a year of one's life. A DALY is defined for each disease d as follows:

$$DALY_d = YLD_d + YLL_d. \quad \text{Equation 17}$$

The total health effect is the summation of DALYs over all diseases (from mother and infant).

$$DALY = \sum_d DALY_d \quad \text{Equation 18}$$

For the children, we dealt mostly with mild and short-lasting diseases. For these kinds of diseases we interpreted the weighing of YLD as a year in which an episode of the disease is experienced. It is expressed as:

$$YLD_d = w_d p_d, \quad \text{Equation 19}$$

in which w_d is the disability weight of the disease and p_d is the incidence of the disease. YLL depends on the average age at time of death, AD_d , the life expectancy, LE , and the number of people dying of the disease, M_d . It is expressed as:

$$YLL_d = (LE - AD_d)M_d. \quad \text{Equation 20}$$

The number of people dying of the disease is estimated with s_d , the conditional probability of death caused by the disease, conditional on already having the disease.

$$M_d = s_d p_d = s_d \sum_{n=0}^N r(n) p_d(n) \quad \text{Equation 21}$$

The conditional mortality is estimated from the mortality and the incidence of the disease in the present/reference population according to.

$$s_d = \frac{\overline{M}_d}{p_d}, \quad \text{Equation 22}$$

where \overline{M}_d is the mortality through disease d , in the present population.

The diseases of the mother and some of the infant's are not short-lasting (< 1 year) which means that the years lived with the disease could not be computed by equation 19. The number of years lived with the disease is weighted by the disability weight, w_d of the disease.

$$YLD_d = w_d (LE - AD_d)(1 - s_d) \sum_{n=0}^N r(n) p_d(n) \quad \text{Equation 23}$$

We assumed that the life expectancy of those who obtain the disease but die of other causes is not affected. Moreover, they are not cured either. They live with the disease for the rest of their lives. The first assumption could cause an underestimation of the DALYs because death is worse than the disease. The second assumption causes an overestimation because living with disease is worst than being healthy.

Furthermore, we assumed that those who die of the disease do so immediately. Thus, we used AD_d both for the age at time of death and the age at time of obtaining the disease. This results in an underestimate of the DALYs.

F Breastfeeding prevalence

Necessary information for the model is $\bar{r}(n)$, the fraction of infants that is breastfed for n months. TNO's division Quality of Life, has measured the prevalence of breastfeeding among infants aged between 0-6 months in the Netherlands.⁸⁶ In this cross-sectional study performed between 2000-2003 the age of an infant and whether it was breastfed has been measured. The variable, $prev(a)$ is the fraction of infants that received mother's milk at age a where a denotes the age of the infant in months. The variable, $prev(0)$ denotes the fraction of infants that are 1 day old and who are breastfed, so that:

$$1 - prev(0) = r(0), \quad \text{Equation 24}$$

where $\bar{r}(0)$ is the fraction of infants that have never been breastfed. We deduce $\bar{r}(n)$ from $prev(a)$. Now for instance, suppose 40% of the three month old infants, 30% of the four month old infants and 60% of the two month old infants are breastfed. Then we can conclude that 10% (40-30) of the mothers breastfeed their infants somewhere between three and four months and 20% of the mothers breastfeed their infants between two and three months. We assign half of the infants that are breastfed between two and three months, to being breastfed three months. Half of those that are breastfed between three and four months are also assigned to being breastfed three months, and so on.

Using this procedure we could compute the $\bar{r}(n)$ as follows:

$$\bar{r}(0) = 1 - prev(0) = 1 - \sum_{i=1}^{6+} r(i) \quad \text{Equation 25}$$

$$\bar{r}(1) = prev(0) - prev(1) + \frac{prev(1) - prev(2)}{2} \quad \text{Equation 26}$$

$$\bar{r}(n) = \frac{(prev(n-1) - prev(n))}{2} + \frac{(prev(n) - prev(n+1))}{2}, n = 2 \dots 5 \quad \text{Equation 27}$$

$$\bar{r}(6^+) = prev(6^+) + \frac{prev(5) - prev(6^+)}{2} \quad \text{Equation 28}$$

Infants who are breastfed between one day and one month are assigned to $r(1)$. Hence, $r(0)$ means exactly those infants that have never been breastfed.

For the categories of the mother, we assumed mothers breastfeed all their infants equally long and that no relation exists between the duration of breastfeeding and the number of infants. Thus,

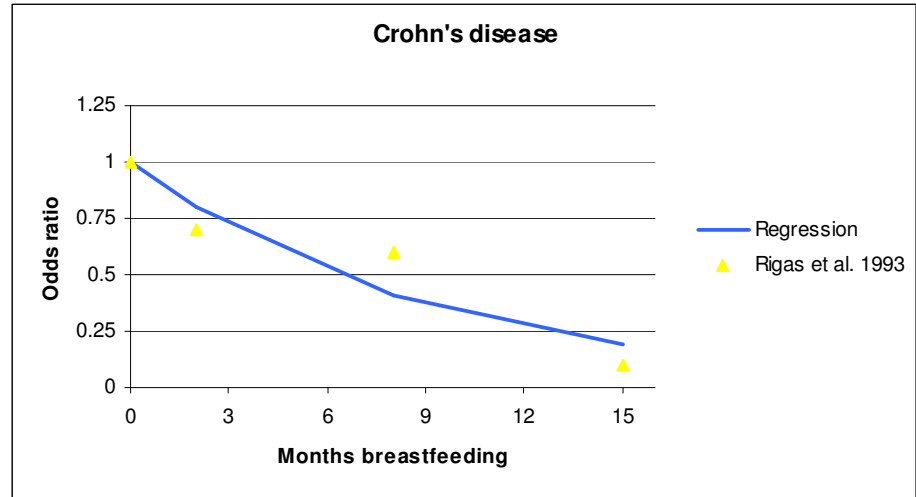
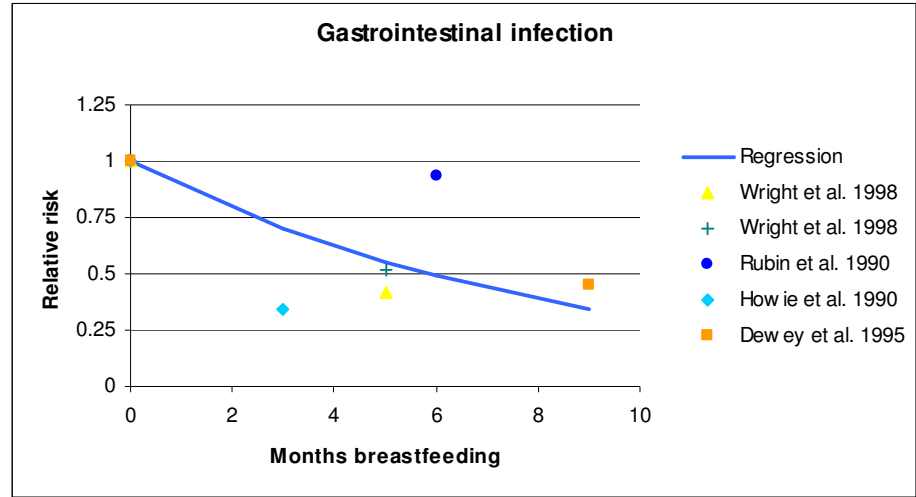
$$\bar{r}_m(nk) = \bar{r}(n), \quad \text{Equation 29}$$

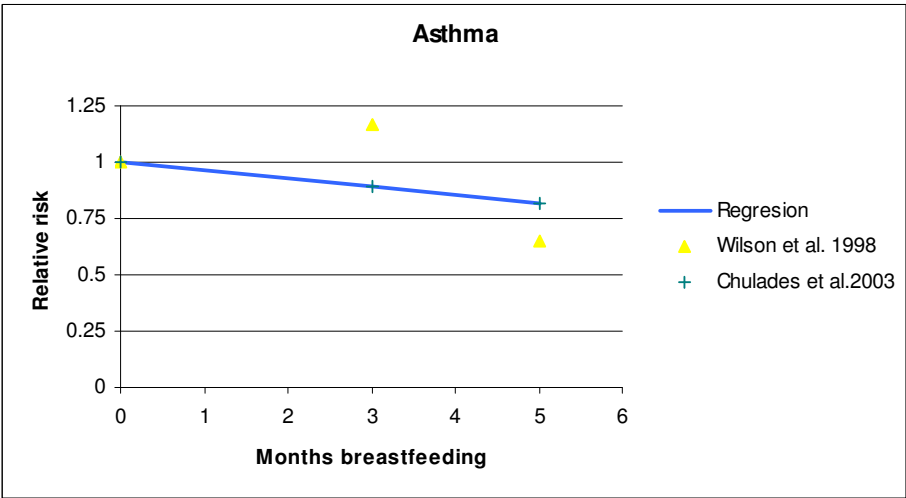
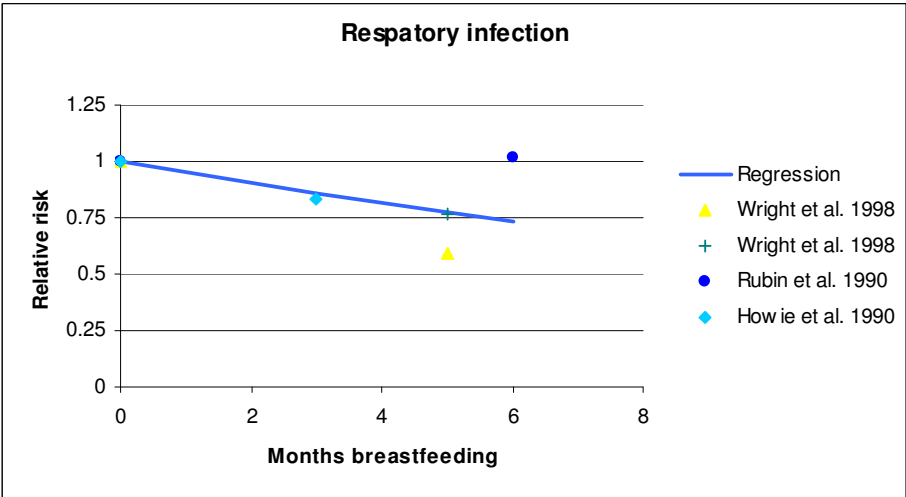
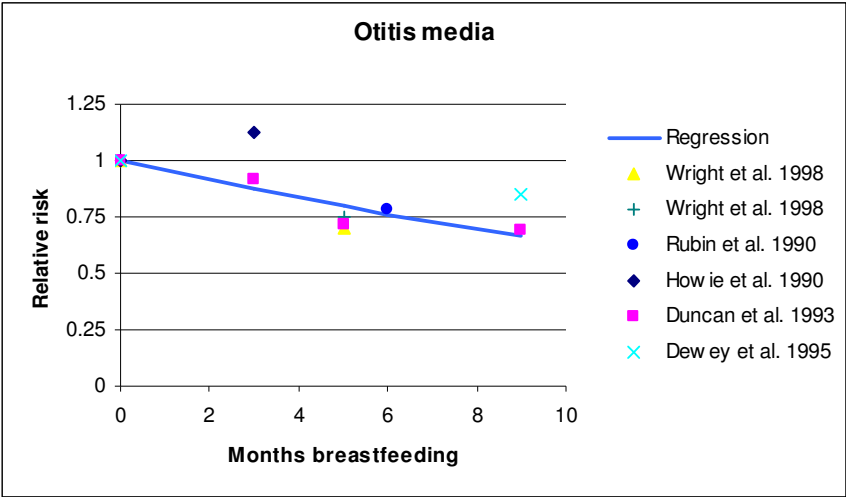
where k is the average number of infants per mother. Fertility data from CBS show that k equals 1.75.¹

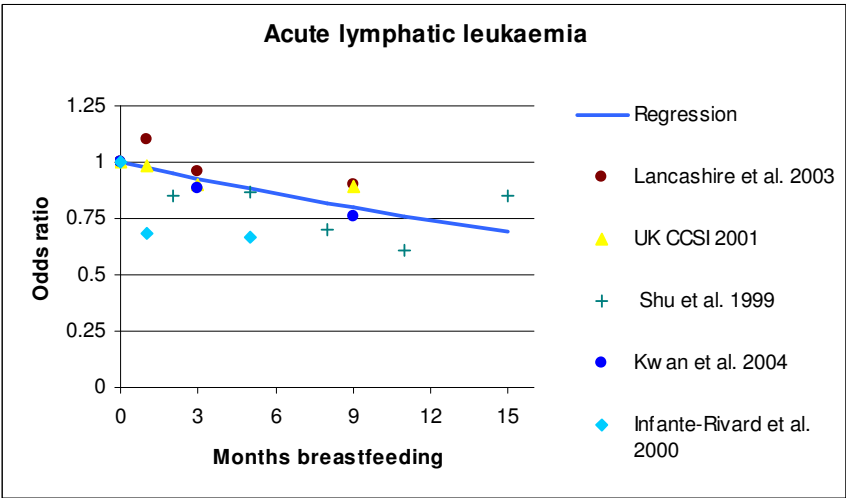
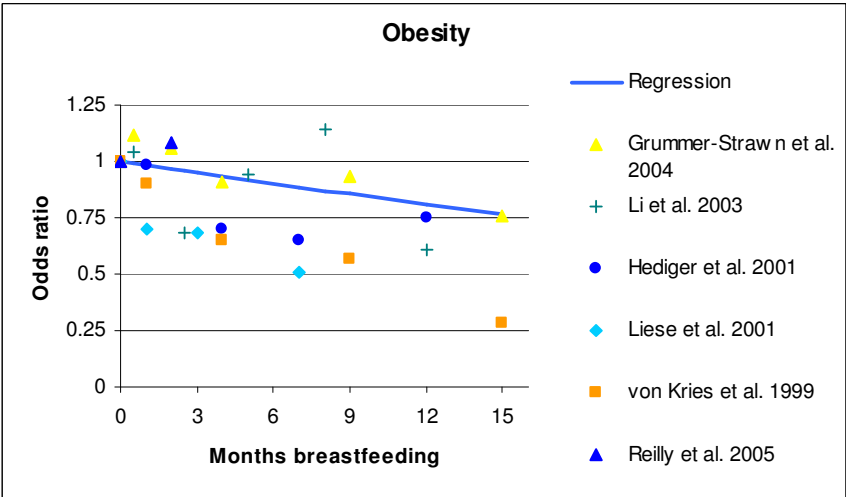
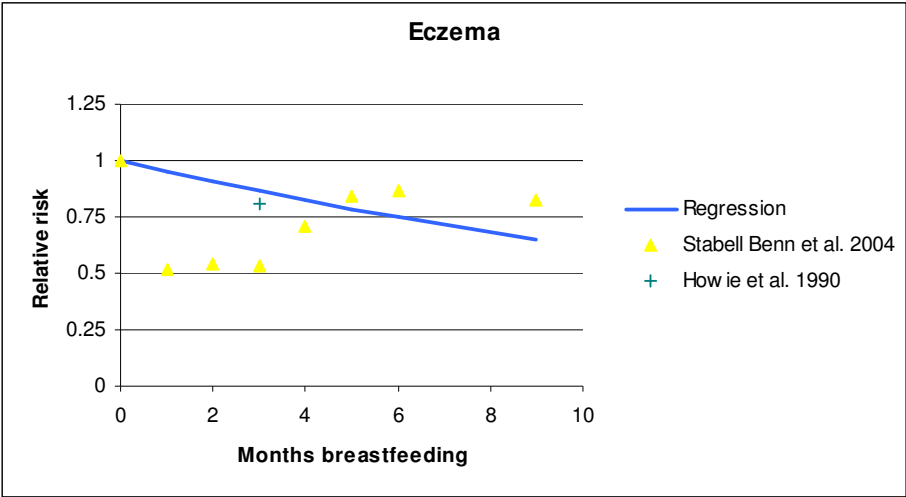
Appendix 4 Regression estimates per modeled disease

This appendix shows graphically the data and the regression estimates of the relative risks and odds ratios of the modeled diseases.

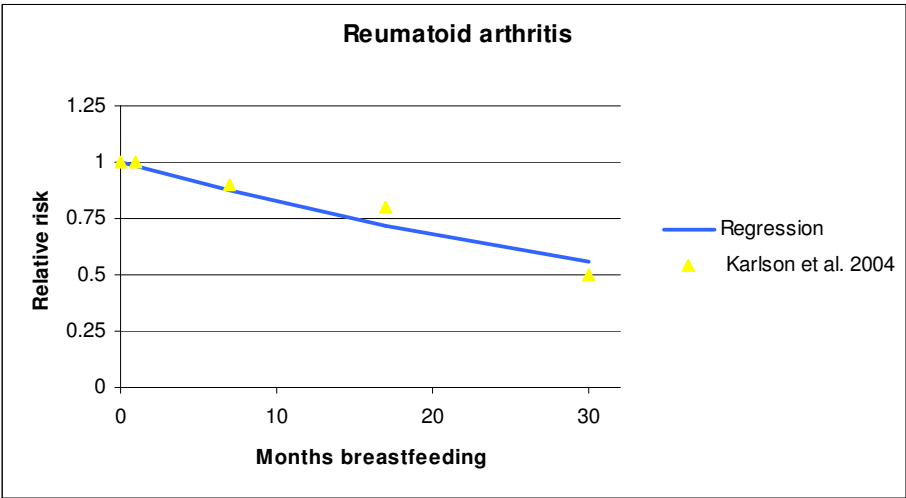
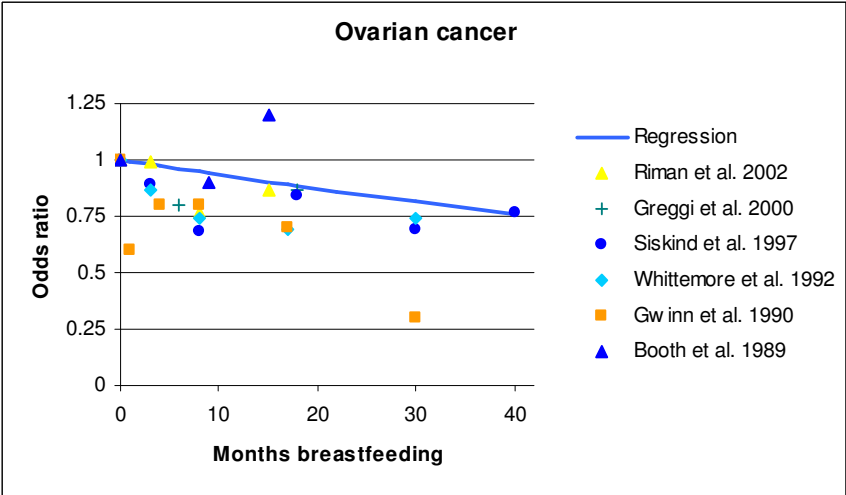
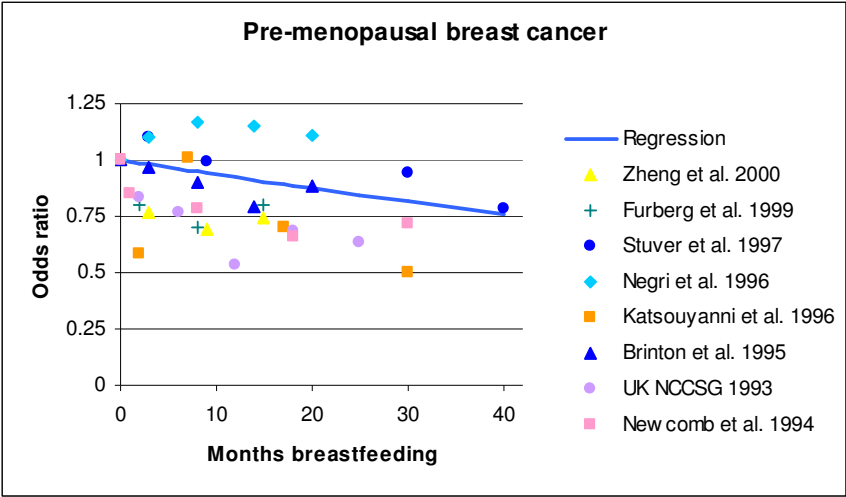
Diseases of the child.







Diseases of the mother.



Datum

Error! Unknown

document property name.

Ons kenmerk

Error! Unknown

document property name.

Blad

1/1

Erratum

Quantification of health effects of breastfeeding, Review of the literature and model simulation Report 350040001/2005

Due to a mistake, the incidences of some rare diseases are reported incorrect. The reported incidences are 100-fold too high. This has to be corrected at the following pages:

1. page 8:

Voor minder voorkomende aandoening als ziekte van Crohn, leukemie of obesitas op jonge leeftijd, is het aantal te voorkomen gevallen respectievelijk: 256, 39 en 273 gevallen per 100.000 persoonsjaren.

Should be replaced with:

Voor minder voorkomende aandoening als ziekte van Crohn, leukemie of obesitas op jonge leeftijd, is het aantal te voorkomen gevallen respectievelijk: 26, 4 en 27 gevallen per 1.000.000 persoonsjaren.

2. page 11:

For uncommon diseases, like Crohn's disease, leukaemia or obesity at young age, the number of prevented incident cases: 256, 39 and 273 per 100,000 person years respectively.

Should be replaced with:

For uncommon diseases, like Crohn's disease, leukaemia or obesity at young age, the number of prevented incident cases: 26, 4 and 27 per 1,000,000 person years respectively.

3. page 33:

For the less incident diseases, like Crohn's disease, leukaemia or obesity at young age, the number of prevented cases was: 256, 39 and 273 per 100,000 person years.

Should be replaced with:

For the less incident diseases, like Crohn's disease, leukaemia or obesity at young age, the number of prevented cases was: 26, 4 and 27 per 1,000,000 person years.

4. page 38:

If all mothers would fulfil the recommendation of the WHO of giving six months breastfeeding, then per 1000 person years 48 incident cases of otitis media, 46 cases of gastrointestinal infections and about 131 cases of respiratory infections and 25 cases of eczema, four incident cases of asthma and per 100,000 py: 256, 39 or 273 cases of Crohn's disease, leukaemia or obesity at young age would be prevented.

Should be replaced with:

If all mothers would fulfil the recommendation of the WHO of giving six months breastfeeding, then per 1000 person years 48 incident cases of otitis media, 46 cases of gastrointestinal infections, about 131 cases of respiratory infections, 25 cases of eczema, and 4 incident cases of asthma and per 1,000,000 person years: 26, 4 or 27 cases of Crohn's disease, leukaemia or obesity at young age would be prevented.