



## Breastfeeding 1

# Breastfeeding in the 21st century: epidemiology, mechanisms, and lifelong effect

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The importance of breastfeeding in low-income and middle-income countries is well recognised, but less consensus exists about its importance in high-income countries. In low-income and middle-income countries, only 37% of children younger than 6 months of age are exclusively breastfed. With few exceptions, breastfeeding duration is shorter in high-income countries than in those that are resource-poor. Our meta-analyses indicate protection against child infections and malocclusion, increases in intelligence, and probable reductions in overweight and diabetes. We did not find associations with allergic disorders such as asthma or with blood pressure or cholesterol, and we noted an increase in tooth decay with longer periods of breastfeeding. For nursing women, breastfeeding gave protection against breast cancer and it improved birth spacing, and it might also protect against ovarian cancer and type 2 diabetes. The scaling up of breastfeeding to a near universal level could prevent 823 000 annual deaths in children younger than 5 years and 20 000 annual deaths from breast cancer. Recent epidemiological and biological findings from during the past decade expand on the known benefits of breastfeeding for women and children, whether they are rich or poor.

### Introduction

“In all mammalian species the reproductive cycle comprises both pregnancy and breast-feeding; in the absence of latter, none of these species, man included, could have survived”, wrote paediatrician Bo Vahlquist in 1981.<sup>1</sup> 3 years earlier, Derek and Patrice Jelliffe in their classic book *Breast Milk in the Modern World*<sup>2</sup> stated that “breast-feeding is a matter of concern in both industrialised and developing countries because it has such a wide range of often underappreciated consequences”.<sup>3</sup> The Jelliffes anticipated that breastfeeding would be relevant to “present-day interest in the consequences of infant nutrition on subsequent adult health”.<sup>3</sup> These statements were challenged by the American Academy of Pediatrics, which in its 1984 report on the scientific evidence for breastfeeding stated that “if there are benefits associated with breast-feeding in populations with good sanitation, nutrition and medical care, the benefits are apparently modest”.<sup>4</sup>

In the past three decades, the evidence behind breastfeeding recommendations has evolved markedly (appendix p 3). Results from epidemiological studies and growing knowledge of the roles of epigenetics, stem cells, and the developmental origins of health and disease lend strong support to the ideas proposed by Vahlquist and the Jelliffes. Never before in the history of science has so much been known about the complex importance of breastfeeding for both mothers and children.

Here, in the first of two Series papers, we describe present patterns and past trends in breastfeeding throughout the world, review the short-term and long-term health consequences of breastfeeding for the child and mother, estimate potential lives saved by scaling up breastfeeding, and summarise insights into how

breastfeeding might permanently shape individuals' life course. The second paper in the Series<sup>2</sup> covers the determinants of breastfeeding and the effectiveness of promotion interventions. It discusses the role of breastfeeding in HIV transmission and how knowledge about this issue has evolved in the past two decades, and examines the lucrative market of breastmilk substitutes, the environmental role of breastfeeding, and its economic implications. In the context of the post-2015 development agenda, the two articles document how essential breastfeeding is for building a better world for future generations in all countries, rich and poor alike.

### Search strategy and selection criteria

We obtained information about the associations between breastfeeding and outcomes in children or mothers from 28 systematic reviews and meta-analyses, of which 22 were commissioned for this review. See appendix pp 23–30 for the databases searched and search terms used. We reviewed the following disorders for young children: child mortality; diarrhoea incidence and admission to hospital; lower respiratory tract infections incidence, prevalence, and admission to hospital; acute otitis media; eczema; food allergies; allergic rhinitis; asthma or wheezing; infant growth (length, weight, body-mass index); dental caries; and malocclusion. For older children, adolescents, and adults, we did systematic reviews for systolic and diastolic blood pressure; overweight and obesity; total cholesterol; type 2 diabetes; and intelligence. For mothers, we did systematic reviews covering the following outcomes: lactational amenorrhoea; breast and ovarian cancer; type 2 diabetes; post-partum weight change; and osteoporosis.

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This is the first in a [Series](#) of two papers about breastfeeding

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See [Online](#) for appendix

For the **Demographic and Health Surveys** see <http://www.measuredhs.com/aboutsurveys/dhs/start.cfm>

For the **Multiple Indicator Cluster Surveys** see <http://mics.unicef.org/surveys>

### Key messages

- Children who are breastfed for longer periods have lower infectious morbidity and mortality, fewer dental malocclusions, and higher intelligence than do those who are breastfed for shorter periods, or not breastfed. This inequality persists until later in life. Growing evidence also suggests that breastfeeding might protect against overweight and diabetes later in life.
- Breastfeeding benefits mothers. It can prevent breast cancer, improve birth spacing, and might reduce a woman's risk of diabetes and ovarian cancer.
- High-income countries have shorter breastfeeding duration than do low-income and middle-income countries. However, even in low-income and middle-income countries, only 37% of infants younger than 6 months are exclusively breastfed.
- The scaling up of breastfeeding can prevent an estimated 823 000 child deaths and 20 000 breast cancer deaths every year.
- Findings from studies done with modern biological techniques suggest novel mechanisms that characterise breastmilk as a personalised medicine for infants.
- Breastfeeding promotion is important in both rich and poor countries alike, and might contribute to achievement of the forthcoming Sustainable Development Goals.

### Breastfeeding indicators and data sources for this review

WHO has defined the following indicators for the study of feeding practices of infants and young children:<sup>6</sup> early initiation of breastfeeding (proportion of children born in the past 24 months who were put to the breast within an hour of birth); exclusive breastfeeding under 6 months (proportion of infants aged 0–5 months who are fed exclusively with breastmilk. This indicator is based on the diets of infants younger than 6 months during the 24 h before the survey [to avoid recall bias], not on the proportion who are exclusively breastfed for the full 6-month period); continued breastfeeding at 1 year (proportion of children aged 12–15 months who are fed breastmilk); and continued breastfeeding at 2 years (proportion of children aged 20–23 months who are fed breastmilk).

Because few high-income countries report on the aforementioned indicators, we calculated additional indicators to allow global comparisons: ever breastfed (infants reported to have been breastfed, even if for a short period); breastfed at 6 months (in high-income countries, the proportion of infants who were breastfed from birth to 6 months or older; in low-income and middle-income countries [LMICs] with standardised surveys, the proportion of infants aged 4–7 months [median age of 6 months] who are breastfed); and breastfed at 12 months (in high-income countries, the proportion of children breastfed for 12 months or longer;

in LMICs, the proportion of children aged 10–13 months [median age of 12 months] who are breastfed).

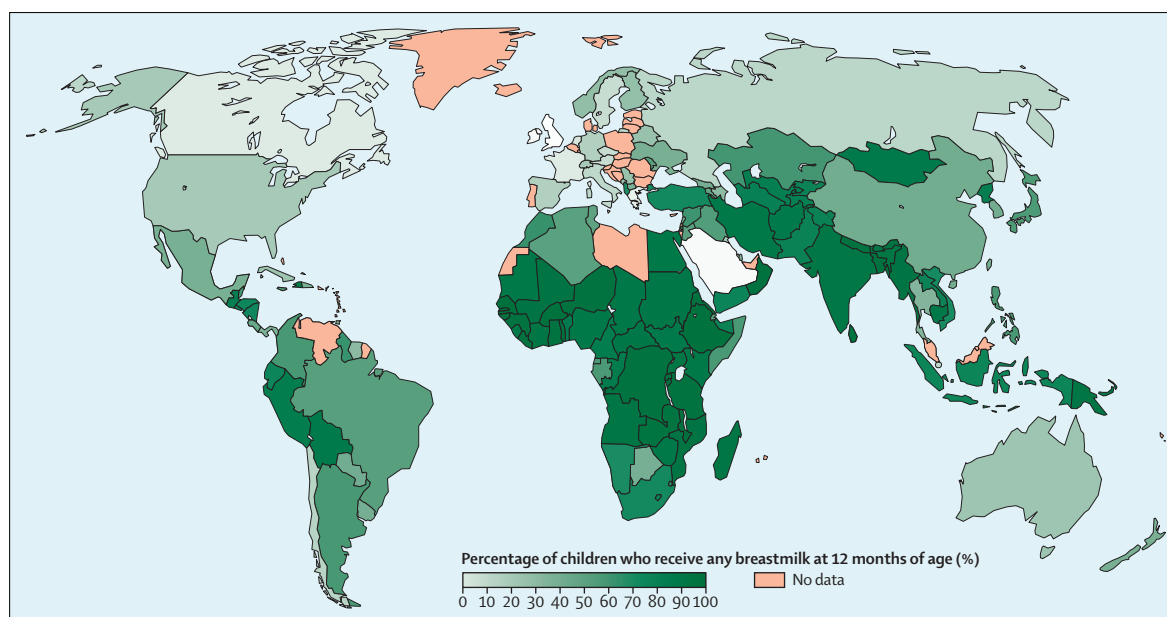
For this review, we used the last three, additional indicators for comparisons between high-income countries and LMICs only. Otherwise, we reported on the standard international indicators (appendix p 4).

For LMICs, we reanalysed national surveys done since 1993, including Demographic and Health Surveys, Multiple Indicator Cluster Surveys, and others (appendix pp 5–12). Nearly all surveys had response rates higher than 90% and used standardised questionnaires and indicators.

For all high-income countries with 50 000 or more annual births, we did systematic reviews of published studies and the grey literature and contacted local researchers or public health practitioners when data from a particular country were not available or when there was ambiguity (appendix pp 13–17). Information about breastfeeding from national samples was not available from many countries. Although 27 out of 35 countries had some information about breastfeeding at a national level, response rates were often in the 50–70% range, indicators were rarely standardised, and recall periods tended to be long. We used administrative or other data when surveys were not available. If necessary, we estimated the proportion of infants breastfed at 12 months on the basis of information available for breastfeeding at 6 months and vice versa. We calculated time trends using multilevel linear regression models (hierarchical mixed models) that take into account that two or more surveys were included in the analyses for each country. We explored departures from linearity with fractional polynomial regression models.<sup>7</sup> In all analyses, we weighted country data by their populations of children younger than 2 years of age (see appendix pp 18–22 for statistical methods).

We did systematic searches of the published literature, and, when possible, meta-analyses for outcomes postulated to be associated with breastfeeding (appendix pp 23–30). These systematic reviews and meta-analyses were specially commissioned by WHO to provide background information for this Series.

We used the Lives Saved Tool<sup>8</sup> to predict how many deaths of children younger than 5 years would be prevented if breastfeeding patterns as of 2013 were scaled up in the 75 countries that are part of the Countdown to 2015 effort,<sup>9</sup> which account for more than 95% of all such deaths worldwide. We assumed that 95% of children younger than 1 month and 90% of those younger than 6 months would be exclusively breastfed, and that 90% of those aged 6–23 months would be partly breastfed. We applied the relative risks for the protection against all infectious causes of death obtained from our new meta-analyses<sup>10</sup> to all infectious causes of death in children younger than 2 years, and also to the 15% of deaths caused by complications of prematurity that occur after the first week of life



**Figure 1: Global distribution of breastfeeding at 12 months**  
Data are from 153 countries between 1995 and 2013.

(appendix pp 31–36). We also estimated the potential number of deaths from breast cancer that could have been prevented by extending the duration of breastfeeding (appendix pp 37–38).

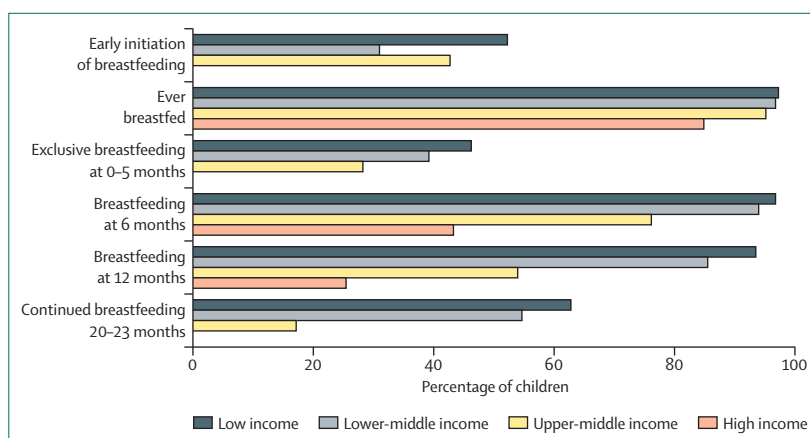
### Epidemiology: levels and trends

We obtained complete information about 127 of the 139 LMICs (appendix pp 5–12), accounting for 99% of children from such countries. For high-income countries, we obtained data for 37 of 75 countries, but for several countries, only a subset of the indicators were available (appendix pp 13–17); these data should, therefore, be interpreted with caution.

Globally, the prevalence of breastfeeding at 12 months is highest in sub-Saharan Africa, south Asia, and parts of Latin America (figure 1). In most high-income countries, the prevalence is lower than 20% (appendix pp 13–17). We noted important differences—eg, between the UK (<1%) and the USA (27%), and between Norway (35%) and Sweden (16%).

We assessed breastfeeding indicators according to country income groups (figure 2). Information about early initiation or exclusive or continued breastfeeding at 2 years was not available for most high-income countries. We noted a strong inverse correlation (Pearson's  $r=-0.84$ ;  $p<0.0001$ ; appendix p 39) between breastfeeding at 6 months and log gross domestic product per person; our regression analyses showed that for each doubling in the gross domestic product per head, breastfeeding prevalence at 12 months decreased by ten percentage points.

Most mothers in all country groups started breastfeeding; only three countries (France, Spain, and the USA) had rates below 80% for ever breastfeeding. However, early



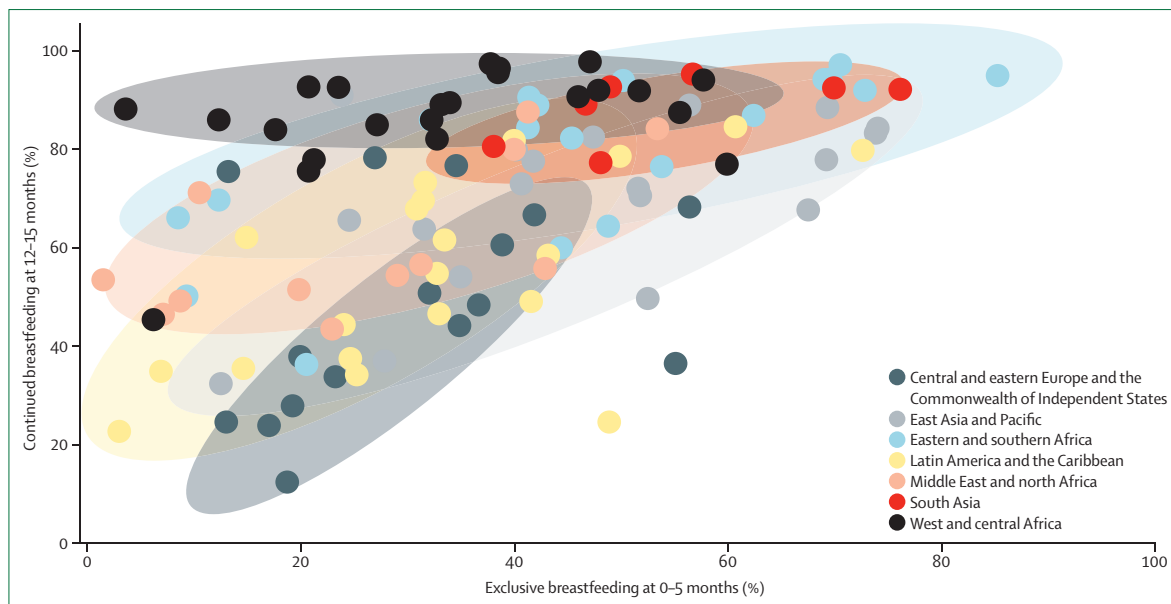
**Figure 2: Breastfeeding indicators by country income group in 2010**

Data are from national surveys that used standard indicators, and were weighted by national populations of children under 2 years. Data for up to 153 countries.

initiation was low in all settings, as was exclusive breastfeeding (figure 2). Breastfeeding at 12 months was widespread in low-income and lower-middle-income settings, but uncommon elsewhere.

Except for early initiation, prevalence of all indicators decreased with increasing national wealth. Low-income countries had a high prevalence of breastfeeding at all ages, but the rates of initiation and exclusive breastfeeding are unsatisfactory even in these countries.

Surprisingly, most national level breastfeeding indicators were not strongly correlated (appendix p 39). We found only a moderate correlation (Pearson's  $r=0.54$ ) between exclusive and continued breastfeeding at 1 year in LMICs. Although the prevalence of



**Figure 3: The relation between exclusive breastfeeding at 0–5 months and continued breastfeeding at 12–15 months, by region**  
Datapoints are countries (values from the most recent survey from 117 countries, 2000–13) and are coloured according to their region. The shaded ellipses include at least 80% of the points in each region.

continued breastfeeding was high throughout west and central Africa, rates of exclusive breastfeeding varied widely (figure 3). Countries from eastern and southern Africa tended to have on average lower rates of continued breastfeeding but higher rates of exclusive breastfeeding than did those in west Africa. In Latin America and the Caribbean, and in central and eastern Europe and the Commonwealth of Independent States, both indicators tended to be lower than in Africa. South Asian countries had high rates of both indicators whereas countries in the Middle East and north Africa had lower rates. Countries from east Asia and the Pacific region had moderate to high prevalence of both indicators.

In children younger than 6 months in LMICs, 36.3 million (63%) were not exclusively breastfed at the time of the most recent national survey. The corresponding percentages were 53% in low-income countries, 61% in lower-middle-income countries, and 63% in upper-middle-income countries. In children aged 6–23 months in LMICs, 64.8 million (37%) were not receiving any breastmilk at the time of the most recent national survey, with corresponding rates of 18% in low-income, 34% in lower-middle-income, and 55% in upper-middle-income countries. 101.1 million children in LMICs were not breastfed according to international recommendations.

In most LMICs, data were available from several surveys over time, making it possible to explore time trends both at the national level and for children in the poorest and richest 20% of families. Our analyses were restricted to surveys for which breakdown of

breastfeeding indicators by wealth quintiles was possible (214 surveys for exclusive and 217 for continued breastfeeding; appendix pp 18–22), accounting for 83% of the total 2010 population of children younger than 2 years of age in LMICs. We reported linear trends because there was no evidence of departures from linearity. Exclusive breastfeeding rates increased slightly from 24.9% in 1993 to 35.7% in 2013 (figure 4). In the richest 20% of families, the increase was much steeper, whereas the poorest 20% followed the general trend. Continued breastfeeding at 1 year (12–15 months) dropped slightly at the global level (from 76.0% to 73.3%), partly due to a decline among the poorest 20% in each country (figure 4).

### Epidemiology: within-country inequalities

We analysed 98 surveys from LMICs to investigate within-country inequalities according to wealth quintile (appendix p 40). Wealth-related inequalities in exclusive breastfeeding were small but disparities in continued breastfeeding rates were consistent: poorer people tend to breastfeed for longer than their richer counterparts in all country groupings, but especially in middle-income countries. Similar results based on 33 countries have been reported elsewhere.<sup>11</sup>

Our review of studies from high-income countries showed that high-income, better-educated women breastfeed more commonly than do those in low-income groups with fewer years of formal education.<sup>12–20</sup> Breastfeeding initiation in the USA was more common in mothers with lower education up until the 1960s, but the social gradient has since reversed.<sup>4</sup>

Breastfeeding is one of few positive health-related behaviours in LMICs that is less frequent in rich people, both between and within countries. The low rates of continued breastfeeding in richer families raises the possibility that poorer mothers will move towards breastmilk substitutes as their income increases, a concern that is reinforced by decreasing rates in poor populations.

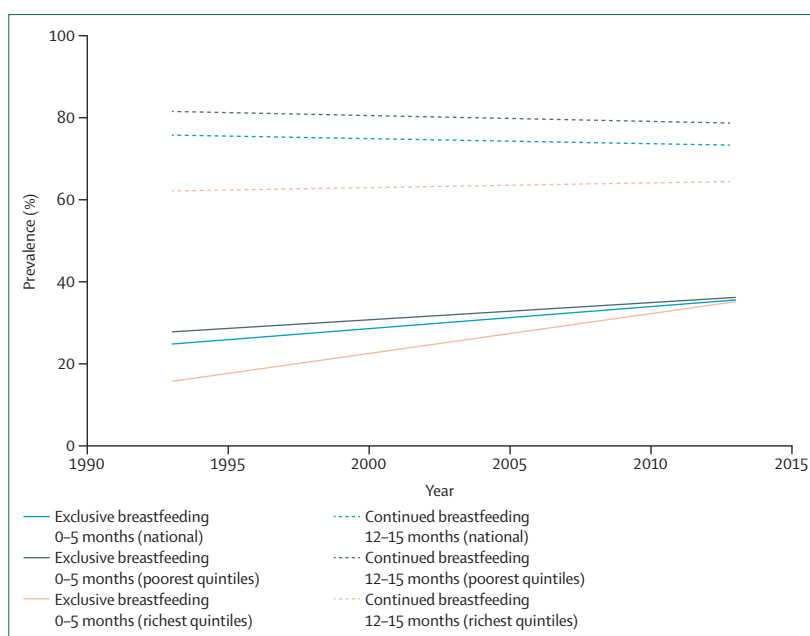
### Short-term effects in children: mortality and morbidity

The results of 28 meta-analyses on the associations between breastfeeding and outcomes in the children and mothers, of which 22 were commissioned for this Series, are summarised in the table. Because studies varied with regard to their feeding classifications, for several outcomes we compared longer versus shorter breastfeeding durations (eg, never vs ever breastfed, breastfed for less or more than a given number of months, and for a few outcomes longer vs shorter durations of exclusive breastfeeding). We tested for heterogeneity due to the type of breastfeeding categorisation, and in its absence we pooled the different studies. We described the results of randomised trials on how breastfeeding promotion affects health, nutrition, or developmental outcomes, but not of trials in which the endpoint was restricted to breastfeeding indicators; these are reviewed in the second article in the Series.<sup>5</sup>

Only three studies in LMICs provide information about mortality according to exclusive, predominant, partial, or no breastfeeding in the first 6 months of life (table). A strong protective effect was evident, with exclusively breastfed infants having only 12% of the risk of death compared with those who were not breastfed.<sup>10</sup> Another three studies in LMICs showed that infants younger than 6 months who were not breastfed had 3.5-times (boys) and 4.1-times (girls) increases in mortality compared with those who received any breastmilk, and that that protection decreased with age.<sup>33</sup> These results are lent support by studies of children aged 6–23 months, in whom any breastfeeding was associated with a 50% reduction in deaths (table).

Breastfeeding might also protect against deaths in high-income countries. A meta-analysis of six high-quality studies showed that ever breastfeeding was associated with a 36% (95% CI 19–49) reduction in sudden infant deaths.<sup>34</sup> Another meta-analysis of four randomised controlled trials showed a 58% (4–82) decrease in necrotising enterocolitis,<sup>34</sup> a disorder with high case-fatality in all settings.<sup>35</sup>

In terms of child morbidity, overwhelming evidence exists from 66 different analyses, mostly from LMICs and including three randomised controlled trials, that breastfeeding protects against diarrhoea and respiratory infections (table).<sup>21</sup> About half of all diarrhoea episodes and a third of respiratory infections would be avoided by breastfeeding. Protection against hospital admissions



**Figure 4: National and wealth quintile-specific time trends in exclusive and continued breastfeeding, 1993–2013**

Data are weighted by national populations of children younger than 2 years at the time of the survey. Analyses restricted to 66 countries with information about household wealth.

due to these disorders is even greater: breastfeeding could prevent 72% of admissions for diarrhoea and 57% of those for respiratory infections. We discuss the risks associated with breastmilk substitutes in terms of biological and chemical contamination in appendix p 41.

Our reviews suggest important protection against otitis media in children younger than 2 years of age, mostly from high-income settings, but inconclusive findings for older children (table).<sup>22</sup> We saw no clear evidence of protection against allergic disorders: no association with eczema or food allergies and some evidence of protection against allergic rhinitis in children younger than 5 years.<sup>23</sup> When we analysed the 29 studies of asthma, we noted statistically significant evidence of a 9% (95% CI 2–15) reduction in asthma with breastfeeding, but effects were smaller and non-significant when we restricted analyses to the 16 studies with tighter control of confounding (a reduction of 5% [–6 to 15]) or to the 13 cohort studies (6% reduction [–11 to 20]).

On the basis of 49 studies done mostly in LMICs, our analyses of oral health outcomes (table) showed that breastfeeding was associated with a 68% reduction (95% CI 60–75) in malocclusions.<sup>26</sup> Most studies were restricted to young children with deciduous teeth, but malocclusion in this age group is a risk factor for malocclusion in permanent (adult) teeth.<sup>36,37</sup> However, breastfeeding for longer than 12 months and nocturnal feeding were associated with 2–3-times increases in dental caries in deciduous teeth, possibly due to inadequate oral hygiene after feeding.<sup>25</sup>



| Outcome   | Types of comparison (breastfeeding categories)         | Studies (n)   | Age range of outcome | Pooled effect (95% CI) | Confounding and effect modification | Other biases   | Conclusions   |  |
|---|--|---|----------------------|------------------------|-------------------------------------|--|---|--|
| <b>Effects on children, adolescents, or adults according to breastfeeding pattern</b> |  |   |                      |                        |                                     |  |   |  |
| Sankar et al (2015) <sup>10</sup>   | Mortality due to infectious diseases                   | Exclusive versus predominant  | 3                    | <6 months              | OR 0.59 (0.41–0.85)                 | All studies from LMICs, where confounding by SEP would probably underestimate the effect of breastfeeding. Confounder-adjusted studies showed similar effects  | Studies that avoided reverse causation (breastfeeding stopped because of illness) showed similar effects. No evidence of publication bias but very few studies available              | Consistent evidence of major protection. Few studies used the four breastfeeding categories in young infants, but evidence from other studies comparing any versus no breastfeeding is very consistent |
| Sankar et al (2015) <sup>10</sup>   | Mortality due to infectious diseases                   | Exclusive versus partial  | 3                    | <6 months              | OR 0.22 (0.14–0.34)                 | See above  | See above   | See above  |
| Sankar et al (2015) <sup>10</sup>   | Mortality due to infectious diseases                   | Exclusive versus none   | 2                    | <6 months              | OR 0.12 (0.04–0.31)                 | See above  | See above   | See above  |
| Sankar et al (2015) <sup>10</sup>   | Mortality due to infectious diseases                   | Any versus none   | 9                    | 6–23 months            | OR 0.48 (0.38–0.60)                 | See above  | See above   | See above  |
| Horta et al (2013) <sup>21</sup>  | Diarrhoea incidence                                    | More versus less breastfeeding (eg, exclusive vs non-exclusive; predominant vs partial; partial vs none; any breastfeeding vs no breastfeeding) | 15                   | <5 years               | RR 0.69 (0.58–0.82)                 | Most studies were from LMICs, where confounding would probably underestimate an effect. Confounder-adjusted studies showed similar effects. Three RCTs of breastfeeding promotion (not included in the meta-analysis) showed protection against diarrhoea morbidity (pooled OR 0.69 [0.49–0.96]) | Few studies that allowed for reverse causation also showed protection. Publication bias is unlikely to explain the findings because results from large and small studies were similar | Strong evidence of major protection against diarrhoea morbidity and admissions to hospital, particularly in young infants, based on a large number of studies  |
| Horta et al (2013) <sup>21</sup>  | Diarrhoea incidence                                    | See above   | 23                   | <6 months              | RR 0.37 (0.27–0.50)                 | See above  | See above   | See above  |
| Horta et al (2013) <sup>21</sup>  | Diarrhoea incidence                                    | See above   | 11                   | 6 months to 5 years    | RR 0.46 (0.28–0.78)                 | See above  | See above   | See above  |
| Horta et al (2013) <sup>21</sup>  | Admission to hospital for diarrhoea                    | See above   | 9                    | <5 years               | RR 0.28 (0.16–0.50)                 | See above  | See above   | See above  |
| Horta et al (2013) <sup>21</sup>  | Lower respiratory infections (incidence or prevalence) | See above   | 16                   | <2 years               | RR 0.68 (0.60–0.77)                 | Most studies were from LMICs, where confounding would probably underestimate the effect of breastfeeding. Confounder-adjusted studies showed similar effects   | Studies that avoided reverse causation showed similar effects. No evidence of publication bias  | Strong evidence of a reduction in severe respiratory infections in breastfed children, based on a large number of studies  |
| Horta et al (2013) <sup>21</sup>  | Admissions to hospitals for respiratory infections     | See above   | 17                   | <2 years               | RR 0.43 (0.33–0.55)                 | The only available RCT showed an RR of 0.85 (0.57–1.27), a non-significant reduction in admissions to hospital   | See above   | See above  |

(Table continues on next page)

Information about breastfeeding and child growth was derived from 17 studies, including 15 randomised controlled trials, mostly from middle-income countries.<sup>24</sup> Attained weight and length at about 6 months did not differ, but there was a small reduction ( $Z$  score  $-0.06$  [95% CI  $-0.12$  to  $0.00$ ]) in body-mass index (BMI) or bodyweight for length in children whose mothers received the breastfeeding promotion intervention compared with those whose mothers did not receive the promotion intervention (table).

### Long-term effects in children: obesity, non-communicable diseases, and intelligence

We updated existing meta-analyses<sup>38</sup> on the associations between breastfeeding and outcomes related to non-communicable diseases (table). Most studies are from high-income settings. Based on all 113 studies identified, longer periods of breastfeeding were associated with a 26% reduction (95% CI 22–30) in the odds of overweight or obesity.<sup>27</sup> The effect was consistent across income classifications. The only breastfeeding promotion trial

|                                    | Outcome            | Types of comparison (breastfeeding categories)   | Studies (n) | Age range of outcome | Pooled effect (95% CI) | Confounding and effect modification  | Other biases   | Conclusions   |
|------------------------------------|--------------------|--|-------------|----------------------|------------------------|--|--|---|
| (Continued from previous page)     |                    |  |             |                      |                        |  |  |   |
| Bowatte et al (2015) <sup>22</sup> | Acute otitis media | More versus less breastfeeding (ever vs never; exclusive breastfeeding at 6 months vs not exclusive breastfeeding at 6 months; any breastfeeding for ≥3–4 months vs <3–4 months) | 11          | ≤2 years             | OR 0.67 (0.62–0.72)    |  | Egger's test for small study effects showed weak evidence for publication bias (p=0.360)                     | Consistent evidence of reduction in acute otitis media during the first 2 years of life associated with longer durations of breastfeeding, based on 11 studies. No evidence of protection after 2 years |
| Bowatte et al (2015) <sup>22</sup> | Acute otitis media | See above  | 5           | >2 years             | OR 1.21 (0.60–2.45)    | Most studies were done in HICs. Several studies did not adjust for important confounders   | High heterogeneity ( <i>I</i> <sup>2</sup> =84%) among the five studies of children older than 2 years       | See above   |
| Lodge et al (2015) <sup>23</sup>   | Eczema             | More versus less breastfeeding (ever vs never; exclusive breastfeeding at 6 months vs not exclusive breastfeeding at 6 months; any breastfeeding for ≥3–4 months vs <3–4 months) | 17          | ≤2 years             | OR 0.95 (0.85–1.07)    | About a third of the studies were from LMICs, and results are similar to those from HICs. Few studies in young children account for reverse causation. Several studies did not adjust for essential confounders  | Some evidence of publication bias, with smaller pooled effect sizes in larger studies                        | No evidence of an association between breastfeeding and eczema  |
| Lodge et al (2015) <sup>23</sup>   | Eczema             | See above  | 20          | >2 years             | OR 1.09 (0.99–1.20)    | See above  | See above  | See above   |
| Lodge et al (2015) <sup>23</sup>   | Food allergies     | See above  | 10          | ≤5 years             | OR 1.07 (0.90–1.26)    | See above  | The ten studies on food allergy in children ≤5 years were highly heterogeneous ( <i>I</i> <sup>2</sup> =88%) | No evidence of an association between breastfeeding and food allergies  |
| Lodge et al (2015) <sup>23</sup>   | Food allergies     | See above  | 4           | >5 years             | OR 1.08 (0.73–1.26)    | See above  | See above  | See above   |
| Lodge et al (2015) <sup>23</sup>   | Allergic rhinitis  | See above  | 5           | ≤5 years             | OR 0.79 (0.63–0.98)    | See above  | See above  | Possible protection against allergic rhinitis in children <5 years, based on only five studies  |
| Lodge et al (2015) <sup>23</sup>   | Allergic rhinitis  | See above  | 9           | >5 years             | OR 1.05 (0.99–1.12)    | See above  | See above  | No evidence for those older than 5 years  |
| Lodge et al (2015) <sup>23</sup>   | Asthma or wheezing | See above  | 29          | 5–18 years           | OR 0.91 (0.85–0.98)    | The protective effect of asthma was smaller and not significant in 16 studies with thorough control for confounders (OR 0.95 [0.85–1.06]) and in the 13 cohort studies (OR 0.94 [0.80–1.11]). There were too few studies to estimate association with asthma in adults | See above  | Inconclusive evidence for the association between breastfeeding and the risk of asthma or wheezing  |

(Table continues on next page)

that reported on this outcome did not detect an association; in this trial, the investigators reported important early differences between intervention and comparison groups in terms of exclusive breastfeeding, but at 12 months of age only 19% of children in the intervention group and 11% of children in the comparison

group were breastfed.<sup>39,40</sup> A 2005 meta-analysis<sup>41</sup> of breastfeeding and mean BMI included 36 articles of which 11 included adjustment for socioeconomic status, maternal smoking, and maternal BMI; their pooled effect did not suggest an association with breastfeeding. In our review,<sup>27</sup> 23 high-quality studies with sample sizes of

| Outcome                              | Types of comparison (breastfeeding categories) | Studies (n)  | Age range of outcome | Pooled effect (95% CI)                | Confounding and effect modification | Other biases  | Conclusions   |   |
|--------------------------------------|--|--|----------------------|---------------------------------------|-------------------------------------|---|---|---|
| (Continued from previous page)       |  |  |                      |                                       |                                     |   |   |   |
| Giugliani et al (2015) <sup>24</sup> | Length   | Randomised trials or quasi-experiments comparing children receiving breastfeeding promotion interventions with control children                | 17                   | About 6 months (range 3–24)           | Z score 0.03 (–0.02 to 0.08)        | Most studies are from middle-income countries. Confounding is unlikely because 15 of the 17 studies were randomised trials. Analyses were by intent to treat, so that low compliance with breastfeeding promotion might underestimate the magnitude of the effect | Evidence of publication bias for BMI, with small studies showing larger reductions  | No evidence of an effect on breastfeeding promotion on length at 6 months of age                                      |
| Giugliani et al (2015) <sup>24</sup> | Weight   | See above  | 16                   | See above                             | Z scores 0.03 (–0.06 to 0.12)       | See above   | See above   | No evidence of an effect on breastfeeding promotion on weight at 6 months of age                                      |
| Giugliani et al (2015) <sup>24</sup> | BMI or weight for length                       | See above  | 11                   | See above                             | Z scores –0.06 (–0.12 to 0.00)      | See above   | See above   | Some evidence supporting a reduction in BMI or weight for length  |
| Tham et al (2015) <sup>25</sup>      | Dental caries                                  | Breastfeeding >12 months versus ≤12 months   | 4                    | <6 years                              | OR 2.69 (1.28–5.64)                 | Most studies did not control for the introduction of sugary foods and drinks. Most studies were from HICs, where high SEP would be expected to negatively confound the association  | Publication biases veer toward studies that show an association between breastfeeding beyond 12 months or on demand and dental caries                   | Consistent evidence that breastfeeding >12 months has detrimental effects on deciduous teeth                          |
| Tham et al (2015) <sup>25</sup>      | Dental caries                                  | Breastfeeding on demand or nocturnal feeding versus not (in breastfed children)  | 6                    | <6 years                              | OR 2.90 (2.33–3.60)                 | See above   | See above   | Consistent evidence that breastfeeding on demand has detrimental effects on deciduous teeth                           |
| Peres et al (2015) <sup>26</sup>     | Malocclusion                                   | Never versus ever breastfed; longer versus shorter duration of exclusive breastfeeding; or longer versus shorter duration of any breastfeeding | 41                   | Childhood, adolescence, and adulthood | OR 0.32 (0.25–0.40)                 | 80% of the studies were from LMICs. Because malocclusions are not associated with SEP or any other known determinant of breastfeeding patterns, it is unlikely that these results are affected by confounding   | Some evidence of publication bias but the association was also present in the larger and better designed studies  | Consistent evidence of a major, two-thirds reduction in malocclusions in deciduous teeth in breastfed individuals     |
| Horta et al (2015) <sup>27</sup>     | Systolic blood pressure                        | Never versus ever breastfed; or longer versus shorter breastfed duration   | 43                   | Childhood, adolescence and adulthood  | –0.80 mm Hg (–1.17 to –0.43)        | Three-quarters of the studies were from LMICs. Evidence of residual confounding as effect in studies from HIC but not in those from LMICs   | Evidence of publication bias in systolic blood pressure studies   | No evidence of a reduction in blood pressure associated with breastfeeding  |
| Horta et al (2015) <sup>27</sup>     | Diastolic blood pressure                       | Never versus ever breastfed; or longer versus shorter breastfeeding duration   | 38                   | Childhood, adolescence, and adulthood | –0.24 mm Hg (–0.50 to 0.02)         | See above   | Evidence of publication bias in diastolic blood pressure studies  | See above   |
| Horta et al (2015) <sup>27</sup>     | Overweight or obesity                          | Never versus ever breastfed; longer versus shorter duration of exclusive breastfeeding; or longer versus shorter duration of any breastfeeding | 113                  | Childhood, adolescence, and adulthood | OR 0.74 (0.70–0.78)                 | In HICs, residual confounding by SEP is a possibility; however, the effect size was similar in studies from LMICs (a third of all studies). 23 high-quality studies showed a smaller pooled reduction of 13% (95% CI 6–19)  | Some evidence of publication bias with larger effects in small studies, but even large and well controlled studies showed a 20% reduction in prevalence | Suggestive evidence of protection, including high-quality studies and those from low-income or middle-income settings |

(Table continues on next page)



| Outcome                               | Types of comparison (breastfeeding categories) | Studies (n)  | Age range of outcome | Pooled effect (95% CI)                | Confounding and effect modification | Other biases   | Conclusions  |  |
|---------------------------------------|--|--|----------------------|---------------------------------------|-------------------------------------|--|--|--|
| (Continued from previous page)        |  |  |                      |                                       |                                     |  |  |  |
| Horta et al (2015) <sup>27</sup>      | Total cholesterol                              | Never versus ever breastfed; or longer versus shorter breastfeeding duration   | 46                   | Childhood, adolescence, and adulthood | -0.01 mmol/L (-0.05 to 0.02)        | No evidence of heterogeneity with nearly all studies showing small effects. Three-quarters of the studies were from HICs   | No evidence of an association  | No evidence of an association  |
| Horta et al (2015) <sup>27</sup>      | Type 2 diabetes                                | Never versus ever breastfed; longer versus shorter duration of exclusive breastfeeding; or longer versus shorter duration of any breastfeeding | 11                   | Childhood, adolescence, and adulthood | OR 0.65 (0.49-0.86)                 | Only two of 11 studies were from LMICs; these studies showed 14% reduction; residual confounding might have affected HIC studies   | Few available studies; no evidence of publication bias   | Restricted evidence of protection, based on 11 studies   |
| Horta et al (2015) <sup>28</sup>      | Intelligence                                   | Never versus ever breastfed; or longer versus shorter breastfeeding duration   | 16                   | Childhood, adolescence, and adulthood | IQ points: 3.44 (2.30-4.58)         | In HICs (14 of the 16 studies), residual confounding by SEP was a possibility; however, the effect was also present in two studies from LMICs. One high-quality RCT showed a statistically significant increase in IQ of more than 7 points  | Some evidence of publication bias with larger effects in small studies, but even large studies showed an effect. Nine studies with adjustment for maternal IQ showed difference of 2.62 points (1.25-3.98) | Consistent effect of about 3 IQ points in observational studies; also present a large RCT on this topic  |
| <b>Effects on women who breastfed</b> |  |  |                      |                                       |                                     |  |  |  |
| Chowdhury et al (2015) <sup>29</sup>  | Lactational amenorrhoea                        | Highest versus lowest duration of breastfeeding  | 13                   | Women (<1 year post partum)           | RR 1.17 (1.04-1.32)                 | Most studies were from LMICs. Residual confounding unlikely. Strongest effects when exclusive or predominant breastfeeding are compared with partial (RR 1.21) or no breastfeeding (RR 1.23)   | No evidence of publication bias  | Consistent effect on prolonging lactational amenorrhoea, especially for exclusive or predominant breastfeeding   |
| Chowdhury et al (2015) <sup>29</sup>  | Breast cancer                                  | Highest versus lowest duration of breastfeeding  | 76                   | Adult women                           | OR 0.81 (0.77-0.86)                 | Three-quarters of the studies were from HICs. Parity reduces the risk of breast cancer and is also associated with greater lifetime breastfeeding duration. Most studies did not adjust appropriately for parity and therefore tended to exaggerate effect size. A thoroughly adjusted pooled analysis of 47 studies shows an OR of 0.96 for each 12 months of breastfeeding <sup>30</sup> | Some evidence of publication bias but the association was also present in the larger and better designed studies   | Consistent protective effect of breastfeeding against breast cancer in 47 well designed studies, of a 4.3% reduction per 12 months of breastfeeding in the better controlled studies |
| Chowdhury et al (2015) <sup>29</sup>  | Ovarian cancer                                 | Highest versus lowest duration of breastfeeding  | 41                   | Adult women                           | OR 0.70 (0.64-0.75)                 | Only six studies from LMICs. Confounding by parity might affect the results but socioeconomic confounding is unlikely. Studies with fine adjustment for parity and exclusion of nulliparous women showed less protection with an OR of 0.82 (0.75-0.89)  | Some evidence of publication bias, with smaller pooled effect sizes in the 22 studies with samples larger than 1500 women (OR 0.76 [0.69-0.84])  | Suggestive evidence of a protective effect of breastfeeding  |
| Chowdhury et al (2015) <sup>29</sup>  | Osteoporosis (distal radius)                   | Highest versus lowest duration of breastfeeding  | 4                    | Adult women                           | SDS -0.132 (-0.260 to -0.003)       | All studies from HICs. High heterogeneity in the distal radius analyses with the largest study showing no association and smaller studies showing protection   | Not assessed because of small number of studies  | Insufficient evidence  |

(Table continues on next page)

|                                      | Outcome                     | Types of comparison (breastfeeding categories)  | Studies (n) | Age range of outcome         | Pooled effect (95% CI)   | Confounding and effect modification   | Other biases   | Conclusions   |
|--------------------------------------|-----------------------------|---|-------------|------------------------------|--|---|--|---|
| (Continued from previous page)       |                             |   |             |                              |  |   |  |   |
| Chowdhury et al (2015) <sup>29</sup> | Osteoporosis (femoral neck) | Highest versus lowest duration of breastfeeding | 4           | Adult women                  | SDS -0.142 (-0.426 to 0.142)   | All studies from HICs. None of the studies showed an association  | Not assessed because of small number of studies        | Insufficient evidence   |
| Aune et al (2013) <sup>31</sup>      | Type 2 diabetes             | Highest versus lowest duration of breastfeeding | 6           | Adult women                  | RR 0.68 (0.57-0.82)  | Several confounding factors were adjusted for. Significant protection also seen for 3-month and 12-month increases in breastfeeding duration. Five of the six studies were from HICs. All six studies showed protection | Few available studies; no evidence of publication bias | Restricted evidence of protection against type 2 diabetes in women who breastfed for longer periods |
| Neville et al (2014) <sup>32</sup>   | Post-partum weight change   | Qualitative review                              | 45          | Women (<2 years post partum) | Not estimated because of different outcome measures at variable post-partum ages | Studies were highly variable. Most studies saw no association. Of the five studies with high methodological quality, four reported beneficial effects. Nearly all studies from HICs                                     | Not assessed in the published review                   | The role of breastfeeding on post-partum weight change is uncertain                                 |

Data are odds ratio (95% CI), risk ratio (95% CI), Z score (95% CI), mm Hg (95% CI), mmol/L (95% CI), intelligence quotient (95% CI), or standard deviation scores (95% CI). In 22 sets of analyses, the summary effect sizes are the pooled results of studies comparing longer versus shorter breastfeeding durations (either never vs ever breastfed; exclusive breastfeeding for more than a specific number of months vs less than that number of months; or any breastfeeding for more than a specific number of months vs less than that number of months). Separate results for each type of categorisation are available in the appendix. OR=odds ratio. LMICs=low-income and middle-income countries. SEP=socioeconomic position. RR=risk ratio. RCT=randomised controlled trial. HICs=high-income countries. BMI=body-mass index. IQ=intelligence quotient. SDS=SD score.

**Table: Results of meta-analyses on the associations between breastfeeding and outcomes in children and mothers**

more than 1500 participants and adjustment for socioeconomic status, maternal BMI and perinatal morbidity showed a pooled reduction in the prevalence of overweight or obesity of 13% (95% CI 6–19).

For the incidence of type 2 diabetes, the pooled results from 11 studies indicate a 35% reduction (95% CI 14–51). We deemed only three studies to be of high quality, which indicated a potentially important, but not statistically significant, reduction of 24% (95% CI ranging from a 60% reduction to a 47% increase).<sup>27</sup> The direction and magnitude of the association with diabetes are consistent with findings for overweight. An earlier review of six studies indicated a possible protective effect against type 1 diabetes.<sup>34</sup> The meta-analyses for systolic (43 studies) and diastolic (38 studies) blood pressure, and total cholesterol (46 studies) showed no evidence of protective effects of breastfeeding.<sup>27</sup>

Breastfeeding was consistently associated with higher performance in intelligence tests in children and adolescents, with a pooled increase of 3.4 intelligence quotient (IQ) points (95% CI 2.3–4.6) based on the findings of 16 observational studies that controlled for several confounding factors including home stimulation (table).<sup>28</sup> Nine studies also adjusted for maternal intelligence, showing a pooled effect of 2.6 points (1.3–4.0). A large randomised trial reported an increase of more than 7 IQ points at 6.5 years of age,<sup>42</sup> and a similar effect was reported in a non-randomised trial in

which preterm infants were fed formula or breastmilk.<sup>43</sup> Positive associations with attained schooling were reported from the UK,<sup>44,45</sup> New Zealand,<sup>46</sup> and Brazil,<sup>47</sup> but a joint analysis of four cohorts in LMICs showed mixed results.<sup>48</sup> A study in Brazil including 30 years of follow-up suggested an effect of breastfeeding on intelligence, attained schooling, and adult earnings, with 72% of the effect of breastfeeding on income explained by the increase in IQ.<sup>49</sup> A review of 18 studies suggested that breastfeeding is associated with a 19% reduction (95% CI 11–27) in the incidence of childhood leukaemia.<sup>50</sup>

### Effects on the mother

The table shows the results of new reviews (published in July, 2015) on lactational amenorrhoea, breast and ovarian cancer, type 2 diabetes, and osteoporosis.<sup>29</sup> We also cite existing reviews on diabetes, weight retention, and maternal depression. Most studies were from high-income countries, except for those on lactational amenorrhoea.

The role of breastfeeding in birth spacing is well recognised. In 2003, it was estimated that in countries where continued breastfeeding is prevalent, eg, Uganda and Burkina Faso, 50% more births would be expected in the absence of breastfeeding.<sup>51</sup> Our review confirms that increased breastfeeding, and especially exclusive or predominant breastfeeding, were associated with longer periods of amenorrhoea.<sup>29</sup> Findings from randomised controlled trials of breastfeeding promotion interventions also confirm this effect.<sup>52</sup>

Evidence exists of a robust inverse association between breastfeeding and breast cancer (table). The largest individual-level analysis on this topic included about 50 000 patients with cancer from 47 studies,<sup>30</sup> which is about half those included in our meta-analysis. Each 12-month increase in lifetime breastfeeding was associated with a reduction of 4·3% (95% CI 2·9–6·8) in the incidence of invasive breast cancer. This analysis included thorough adjustment parity and other confounders; nulliparous women were excluded. The results did not vary substantially according to menopausal status. Our meta-analysis suggests a higher magnitude of protection, but when restricted to the 14 studies with fine adjustment for parity and exclusion of nulliparous women, the reduction comparing longer versus shorter breastfeeding durations was 7% (95% CI 3–11).<sup>29</sup>

The meta-analysis of 41 studies on breastfeeding and ovarian cancer shows a 30% reduction associated with longer periods of breastfeeding (95% CI 25–36). Confounding by parity might affect the results but socioeconomic confounding is unlikely because socioeconomic status is only weakly associated with ovarian cancer incidence. The pooled reduction, based on studies with fine adjustment for parity and exclusion of nulliparous women, was 18% (14–42).<sup>29</sup> We also reviewed the evidence on osteoporosis, finding no evidence of an association between breastfeeding and bone mineral density in the four studies available (table).<sup>29</sup>

A meta-analysis of six cohort studies on type 2 diabetes showed an odds ratio of 0·68 (95% CI 0·57–0·82).<sup>31</sup> In view of this finding, an association could be predicted with overweight, but a review of 54 articles on the possible role of breastfeeding on postpartum weight change was inconclusive.<sup>32</sup> Few studies are available for the long-term association between nursing and adiposity. After the review of studies on overweight and breastfeeding was published, an analysis of 740 000 British women with long-term follow-up showed that mean BMI was 1% lower for every 6 months that the woman had breastfed.<sup>53</sup> A qualitative review of 48 studies showed clear associations between breastfeeding and reduced maternal depression,<sup>54</sup> but it is more likely that depression affects breastfeeding than the opposite.

### Estimating lives saved for children and mothers

The Lives Saved Tool<sup>8</sup> estimates that 823 000 annual deaths would be saved in 75 high-mortality LMICs in 2015 if breastfeeding was scaled up to near universal levels. This corresponds to 13·8% of the deaths of children under 2 years of age. For preventable deaths, 87% would have occurred in infants younger than 6 months due to a combination of high death rates and low prevalence of exclusive breastfeeding.

We also estimated the potential effect of breastfeeding on breast cancer mortality (appendix pp 31–37). Using the estimates of protection from the pooled study, we estimate

that existing global rates of breastfeeding avert 19 464 annual breast cancer deaths compared with a scenario in which no women breastfed (table).<sup>30</sup> The low-income regions with long breastfeeding durations (Africa and south Asia) account for 58% of currently prevented deaths, despite only accounting for 36% of the global population included in this analysis. We also estimate that an additional 22 216 lives per year would be saved by increasing breastfeeding duration from present levels to 12 months per child in high-income countries and 2 years per child in LMICs. We cannot model the same effect in all countries given the differences in data availability and the fact that very few children in high-income countries are breastfed for longer than 12 months. Latin America, central and eastern Europe, the Commonwealth of Independent States, and high-income countries would benefit most because of their higher incidence of breast cancer and also shorter breastfeeding durations at present.

### Conclusions

The fact that the reproductive cycle includes breastfeeding and pregnancy<sup>1</sup> has been largely neglected by medical practice, leading to the assumption that breastmilk can be replaced with artificial products without detrimental consequences. This neglect is particularly important in high-income countries, where fewer than one in every five children are breastfed by the age of 12 months. For each doubling in national gross domestic product per person, breastfeeding prevalence at 12 months decreases by 10 percentage points.

Findings from epidemiology and biology studies substantiate the fact that the decision to not breastfeed a child has major long-term effects on the health, nutrition, and development of the child and on women's health. Possibly, no other health behaviour can affect such varied outcomes in the two individuals who are involved: the mother and the child. Findings from immunology, epigenetic, microbiome, and stem-cell studies done over the past two decades that elucidate potential mechanisms through which breastfeeding can improve outcomes will probably be followed by other, even more exciting discoveries on the exquisite personalised medicine provided by human milk (panel).

Our global analyses show that more than 80% of neonates receive breastmilk in nearly all countries. However, only about half begin breastfeeding within the first hour of life, even though such a recommendation was issued by WHO more than 25 years ago.<sup>70</sup> Because 60% of the world's children are now delivered by skilled assistants,<sup>9</sup> further promotion of early initiation is possible. In most countries, rates of exclusive breastfeeding are well below 50%, and the correlation with the duration of any breastfeeding is only moderate. This finding signals the need to tailor breastfeeding support strategies to specific patterns recorded in each country. In the poorest countries, late initiation and low rates of exclusive breastfeeding are the main challenges. In middle-income and high-income

**Panel: Breastmilk—a personalised medicine**

The nutritional advantages of breastfeeding and its protection against infection are well known. In the past two decades, the possibility that crucial imprinting events might be modulated during breastfeeding, with potential lifelong effects for the infant, has become apparent.<sup>55</sup> These events might be mediated directly or through effects on the infant microbiome. The ability of the microbiome to regulate host responses in infancy depends on individual bacterial species, which modulate T-cell polarisation and immune regulation, metabolic responses, adipogenesis, and possibly even brain development and cognitive functioning.<sup>56,57</sup> Abnormal colonisation patterns have a deleterious long-term effect on immune and metabolic homeostasis. It is therefore remarkable that a mother's breastmilk transmits elements of her own microbiome and immune responses, and also provides specific prebiotics to support growth of beneficial bacteria.

Delivery mode initially established whether the gut flora of the mother (vaginal delivery) or the skin flora of the birth attendants (caesarean section) dominates the initial colonisers,<sup>58</sup> which induce an important immune response in the infant. Feeding mode is the second fundamental determinant of the infant microbiome. Breastfed infants maintain persistent microbial differences, independent of delivery mode,<sup>59,60</sup> owing to the effects of human milk oligosaccharides (HMOs). Human milk contains a much wider variety of sugars than other mammalian milks: up to 8% of its calorific value is provided in the form of indigestible HMOs, which function as prebiotics to support growth of specific bacteria. They cannot be used by most enteric organisms, but support growth of *Bifidobacterium longum* biovar *infantis*, which has co-evolved to express the enzymes needed for the utilisation of HMOs.<sup>55</sup> Substantial inter-individual variation exists in maternal HMO production, which in turn underpins the pattern of flora acquisition by the infant.<sup>61</sup> Therefore, there is specificity of the interaction between breastmilk and the infant microbiome, causing different bacterially induced effects on the infant's metabolism and immunity.

This specificity of interaction is further underpinned by the mother's enteromammary axis. To maintain her own gut homeostasis, the mother's intestinal dendritic cells take up individual bacteria from the lumen and transport them to gut lymphoid follicles,<sup>56</sup> where T cells are committed to a regulatory phenotype and B cells shifted towards immunoglobulin A. Programmed dendritic cells and lymphocytes then re-enter the circulation before homing back to the gut through interaction between their induced  $\beta 7$  integrins and locally expressed mucosal vascular addressin cell adhesion molecule (MAdCAM-1). MAdCAM-1 is expressed in the mammary

endothelium during pregnancy, allowing selective uptake by the breast of gut-programmed cells.<sup>62</sup> The consequences of enteromammary trafficking include the release of dendritic cells containing live maternal gut bacteria, T cells expressing gut-derived  $\beta 7$  integrins, and plasma cells producing immunoglobulin A specific for maternal gut bacteria into the colostrum and breastmilk. Breastmilk therefore contains a dominance of immune cells of gut-related phenotype ( $\gamma \delta$  cells,  $\beta 7+$  cells) that have matured within the mother's intestine.<sup>63</sup> Breastmilk cytokines also vary depending on the mother's immunological experiences. Therefore, there is coordinated input to the infant's nascent mucosal immune system, specific for the mother's microbiome, in which individual bacterial types are favoured and tolerogenic immune responses are transmitted. Caesarean section, perinatal antibiotics, and failure to breastfeed are the three major factors that affect this co-evolved imprinting process. Findings from a study of flora acquisition and immune responses in primates identified clear differences in both gut bacterial composition and mucosal immune responses in breastfed compared with formula-fed macaques, with the responses persisting into adult life.<sup>64</sup>

In addition to changes mediated through the flora, individual breastmilk components might directly affect epigenetic programming of the infant.<sup>65</sup> The usual adverse effect of peroxisome proliferator-activated receptor- $\gamma$  polymorphisms on adiposity and metabolism is prevented by breastfeeding, possibly due to the content of peroxisome proliferator-activated receptor-modulating constituents such as long-chain polyunsaturated fatty acids and prostaglandin J.<sup>66</sup> Protection against breast cancer for a breastfeeding mother might also be mediated through peroxisome proliferator-activated receptor modulation.<sup>66</sup> Lactoferrin, a major breastmilk component, binds bacterial CpG motifs and blunts mucosal NF- $\kappa$ B responses to the flora. Microvesicles called exosomes are secreted into breastmilk, and might inhibit atopic sensitisation dependent on maternal immune experience.<sup>67</sup> Breastmilk fat globules contain many secreted micro-RNAs, the expression of which is modulated by maternal diet, which are predicted to target several genes in the infant.<sup>68</sup> Evidence also exists that multipotential stem cells are secreted into breastmilk and can persist within infants.<sup>69</sup>

Human breastmilk is therefore not only a perfectly adapted nutritional supply for the infant, but probably the most specific personalised medicine that he or she is likely to receive, given at a time when gene expression is being fine-tuned for life. This is an opportunity for health imprinting that should not be missed.

countries, short overall duration of breastfeeding is an additional challenge.

Our time-trend analyses show that, for LMICs as a whole, exclusive breastfeeding has increased by about

0.5 percentage points per year since 1993, reaching 35% in 2013. In 2012, the 56th World Health Assembly set as a target for 2025 to "increase the rate of exclusive breastfeeding in the first 6 months up to at least 50%".<sup>71</sup>

To achieve this goal would need a doubling of the recent annual increase, to more than 1 percentage point a year in the next decade, which is already the rate for the richest 20% of people. In view of the benefits of exclusive breastfeeding and of present achievements by leading countries, could a more ambitious target not be aimed for? The Assembly did not set a goal for continued breastfeeding.

In terms of inequalities, our findings show that breastfeeding is one of the few positive health behaviours that is more prevalent in poor than in rich countries. They also show that poor women breastfeed for longer than rich women in LMICs, whereas in high-income countries the pattern is reversed. These results suggest that breastfeeding patterns are contributing to reducing the health gaps between rich and poor children in LMICs, which would be even greater in the absence of breastfeeding.

In LMICs, there are no inequalities between rich and poor mothers in exclusive breastfeeding rates. Findings from our time-trend analyses suggest that this is because rich mothers are adopting exclusive breastfeeding at a much faster rate than are poor mothers—only 20 years ago, the poorer mothers had substantially higher rates of exclusive breastfeeding. Continued breastfeeding is still more common in poor mothers than in wealthy mothers, but rates seem to be dropping among these while remaining stable in rich mothers. Protecting breastfeeding in the world's poorest populations is therefore a major priority.

Our systematic reviews emphasise how important breastfeeding is for all women and children, irrespective of where they live and of whether they are rich or poor. Appropriate breastfeeding practices prevent child morbidity due to diarrhoea, respiratory infections, and otitis media. Where infectious diseases are common causes of death, breastfeeding provides major protection, but even in high-income populations it lowers mortality from causes such as necrotising enterocolitis and sudden infant death syndrome. Available evidence shows that breastfeeding enhances human capital by increasing intelligence. It also helps nursing women by preventing breast cancer. Additionally, our review suggests likely effects on overweight and diabetes in breastfed children, and on ovarian cancer and diabetes in mothers. The only harmful consequence of breastfeeding we detected was an increase in tooth decay in children breastfed for more than 12 months. In view of the many benefits of breastfeeding, this observation should not lead to discontinuation of breastfeeding but rather to improved oral hygiene.

Findings from our systematic reviews are restricted by the observational nature of most of the available data for breastfeeding and by the limitations of meta-analyses.<sup>72,73</sup> Experimental data are scarce because breastfeeding promotion activities must be highly effective to change feeding patterns to an extent that leads to a measurable

effect on short-term and long-term outcomes. Moreover, confounding can occur because breastfeeding is associated with higher socioeconomic position in high-income countries. Our reviews included subanalyses of studies with tight control for confounding. Whenever possible, we also did separate analyses of studies from LMICs, because poor individuals tend to breastfeed for longer than rich people in these countries (appendix p 40), an association that is reversed in high-income countries. Interpretation of associations is also affected by the fact that non-breastfed infants receive different diets in different countries—eg, animal milk in most poor societies and formula in middle-income and high-income populations. The association between breastfeeding and overweight, for example, is probably affected by the diet of infants who are not breastfed.

No consensus exists about whether or not breastfeeding can protect against a child's later risk of overweight or diabetes,<sup>34,38,41</sup> largely because of potential residual confounding. Although the evidence is not as strong as it is for infections or intelligence, we argue that the evidence linking breastfeeding with protection from later overweight or diabetes is growing. Findings from our meta-analyses showed that the association persisted when restricted to only high-quality studies, and also when restricted to studies from only low-income and middle-income settings. The association seems to be specific—eg, we noted no effect on blood pressure or blood lipid concentrations, for which confounding patterns are similar. Finally, findings from randomised trials of breastfeeding promotion in infancy indicate a reduction in adiposity.

The scaling up of breastfeeding practices to almost universal levels is estimated to prevent 823 000 annual deaths, or 13·8% of all deaths of children younger than 24 months in the 75 Countdown to 2015<sup>9</sup> countries. The target of 95% of all infants younger than 6 months having exclusive breastfeeding is ambitious because at present the highest national prevalences are 85% in Rwanda and 76% in Sri Lanka. We also used a target of 90% for any breastfeeding from 6–23 months, but five countries already have levels that are above this target (Nepal, Rwanda, Ethiopia, Burundi, and Guinea). We acknowledge that these targets are ambitious, but the estimates show the potential for lives saved if mothers and children adhered to international recommendations. Despite differences in methods, our estimates about potential lives saved are consistent with those from the 2013 *Lancet* Nutrition Series (804 000 deaths)<sup>74</sup> but higher than those from the 2010 Global Burden of Disease study (540 000 deaths),<sup>75</sup> in which the assumptions and methods were not sufficiently detailed to understand the reasons for the discrepancy. Breastfeeding is potentially one of the top interventions for reducing under-5 mortality, and the modest changes in breastfeeding rates since 2000 have contributed to the fact that most LMICs did not reach the fourth Millennium Development Goal,



to reduce under-5 mortality by two-thirds.<sup>76</sup> We show that increasing exclusive breastfeeding should be among the top priorities for reducing infant deaths.

As an example of the potential to save women's lives, we estimated that present rates of breastfeeding prevent almost 20 000 annual deaths from breast cancer, and an additional 20 000 are preventable by scaling up breastfeeding practices (appendix). To achieve its full effect, breastfeeding should continue up to the age of 2 years. Protection against mortality and morbidity from infectious diseases extends well into the second year of life—eg, breastfeeding prevents half of deaths caused by infections in children aged 6–23 months. Protection against otitis media, a common childhood illness throughout the world, also extends to 2 years and possibly beyond. Findings from studies of overweight and obesity show that longer durations of breastfeeding are associated with lower risk, as do studies of IQ showing a clear dose-response association with duration. Breast cancer is reduced by lifetime duration of breastfeeding in women, with a 6% reduction for every 12 months.<sup>50</sup> Findings from ethnographical research show that total duration of breastfeeding ranges between 2 and 4 years in most traditional societies,<sup>77</sup> and our review of the literature lends support to international recommendations about the total duration of breastfeeding, in both high-income and low-income countries.

Data availability for breastfeeding patterns shows an unusual distribution. Health authorities and researchers in high-income countries seem to neglect breastfeeding to such an extent that most of these countries are unable to report on reliable, standardised indicators. This situation contrasts sharply with the high quality of data for breastfeeding in LMICs, as a consequence of the regular conduct of standardised surveys such as the Demographic and Health Surveys and Multiple Indicator Cluster Surveys.

Our findings show how essential the protection, promotion, and support of breastfeeding is for the achievement of many of the newly launched Sustainable Development Goals by 2030. Breastfeeding is clearly relevant to the third sustainable goal, which includes not only maternal and child health but also non-communicable diseases such as breast cancer and diabetes as well as overweight and obesity. It is also relevant to the second goal (on nutrition). The effect of breastfeeding on intelligence and on human capital is relevant to the fourth goal (education), the first goal (poverty), and the eighth goal (inclusive economic growth). Finally, by helping close the gap between rich and poor, breastfeeding can contribute to goal number ten—reducing inequalities.

#### Contributors

CGV and NCR had the idea for the paper. CGV was the primary author. The other co-authors contributed specific sections: SM (biological mechanisms), SH (breast cancer cases averted), NW (child lives saved), MJS (meta-analysis on child mortality), and RB (early initiation of breastfeeding). AJDB, GVAF, and JK collected and analysed the data. All authors revised the draft report and approved the final version.

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