PROGRAMA DOUTORAL EM SAÚDE PÚBLICA

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BREAST MILK FEEDING PRACTICES AMONG VERY PRETERM INFANTS:

EFFECTS ON HEALTH-RELATED OUTCOMES DURING CHILDHOOD

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Em cumprimento com o disposto no referido Regulamento, declaro que colaborei na definição das hipóteses em estudo e dos objetivos a responder em cada um dos artigos, bem como na recolha e interpretação dos dados que reportam, em todos os trabalhos que constituem esta tese. Fui responsável pela análise dos dados, interpretação dos resultados e redação da versão inicial de todos os manuscritos de que sou primeira autora e colaborei ativamente na preparação das suas versões finais.

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Aos meus pais e ao meu irmão,

que são as minhas pessoas-sol e me ensinaram o

verdadeiro segredo para um caminho de luz…

"Apenas se vê bem com o CORAÇÃO*.*

O ESSENCIAL *é invisível aos olhos."*

Antoine de Saint-Exupéry

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"O caminho faz-se caminhando", mas não se chega até aqui sozinho… e, por isso, "agradecer" é o "verbo-força" que aqui conjugo mais vezes!

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Breastfeeding

"Possibly, no other health behaviour can affect such varied outcomes in the two individuals who are involved: the mother and the child."

Victora C.G. et al (2016), Lancet.

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ACRONYMS AND ABBREVIATIONS

AAP	American Academy of Pediatrics
ASQ	Ages & Stages Questionnaire
BFHI	Baby-Friendly Hospital Initiative
BMF	Breast milk feeding
BPD	Bronchopulmonary dysplasia
CA	Corrected age
CBCL	Child Behaviour Checklist
CI	Confidence interval
EMBA	European Milk Bank Association
EPICE	Effective Perinatal Intensive Care in Europe
ESPGHAN	European Society for Pediatric Gastroenterology Hepatology and Nutrition
EU	European Union
GA	Gestational age
GXXI	Generation XXI birth cohort
HMOs	Human milk oligosaccharides
IBFAN	International Baby Food Action Network
IPW	Inverse probability weighting
IVH	Intraventricular haemorrhage
LCPUFAs	Long-chain polyunsaturated fatty acids
MI	Multiple imputation
MOM	Mother's own milk
MOSAIC	Models of Organising Access to Intensive Care for Very Preterm Births
MPT	Muito pré-termo
NEC	Necrotizing enterocolitis
NICU	Neonatal Intensive Care Unit
aOR	Adjusted odds ratio
OR	Odds ratio
PARCA-R	Parent Report of Children's Abilities-Revised
PDA	Patent ductus arteriosus
ROP	Retinopathy of prematurity

aRR	Adjusted risk ratio
RR	Risk ratio
SGA	Small for gestational age
UNICEF	United Nations International Children's Emergency Fund
UK	United Kingdom
USA	United States of America
VLBW	Very low birth weight
VPT	Very preterm (<32 weeks)
WHA	World Health Assembly
WHO	World Health Organization

ABSTRACT

Introduction

The use of breast milk feeding (BMF) in very preterm infants (VPT, <32 weeks of gestation) is well recognized to be of the utmost prognostic importance. However, providing BMF to these infants is a complex and challenging process. There is a wide disparity in BMF practices between and within countries that are not entirely explained by maternal and infant characteristics. This suggests that substantial gains are possible if the role of policies and practices operating in neonatal units is understood. Also, the research gap in the effect of BMF practices on medium- and long-term health-related outcomes of children born VPT deserves further investigation. Thus, this thesis aimed to study BMF practices in infants born VPT, and to prospectively assess the effect of such practices on neurodevelopmental and mental health outcomes measured during childhood.

Methods

Cross-sectional and longitudinal data of the prospective population-based cohort of children born VPT, the "*Effective Perinatal Intensive Care in Europe*" (EPICE) cohort, recruited in 2011/2012, from 11 European countries (7 900 live births and 6 792 infants discharged alive), were used. In Portugal, the study involved all of the maternity and neonatal units from two regions (Northern and Lisbon and Tagus Valley), and identified 724 live births (607 discharged alive). Data on demographic and clinical characteristics, medical interventions, and neonatal outcomes were collected until discharge from hospital using standardised protocols, data on the unit´s policies and practices were gathered from health professionals. Finally, information on health and development at two years of corrected age (CA) was obtained for the entire cohort, and additionally at three years in Portugal, using parental structured questionnaires.

Results

Two-thirds of the Portuguese cohort infants born VPT received any BMF at discharge, 25% of them exclusively, with a wide disparity among units (range: 3%-50% for exclusive, 21%-62% for mixed). The major determinant of exclusive BMF at discharge was the presence of a designated staff member to support mothers *(Paper I)*. Policies towards parental presence and involvement in neonatal units varied at the European level between and within countries, and infants cared for in units with more liberal parental policies were found to be about two-fold significantly more likely to be discharged on exclusive BMF *(Paper II)*. The duration of BMF was observed to fall short of international recommendations among this vulnerable population. In Portugal, only 10% of infants received exclusive BMF for at least six months and 10% received any BMF for 12 months or more. Worldwide, based on a systematic literature review, the prevalence of exclusive BMF at six months ranged from 1% to 27%, and varied between 8% and 12% for any BMF at 12 months *(Paper III)*. Across European countries, one-third of ever breastfed VPT infants were found to be breastfed at six months, which varied from 25% to 50%. The probability of being breastfed until the age of six months was lower among infants of mothers with a lower educational level *(Paper IV)*. Additionally, the management of mother´s own milk was observed to vary widely across European countries. In 22% of the inquired units, all VPT infants whose mothers expressed breast milk received their own mother's pasteurised milk (country range: 0%-73%) *(Paper V)*.

Our results stress the importance of BMF on health-related outcomes in childhood, particularly neurodevelopmental and mental health outcomes. Never breastfed children born VPT presented a higher risk of suboptimal non-verbal and verbal cognition at two years of CA compared to those who had ever been breastfed, independent of multiple relevant perinatal and socio-demographic characteristics *(Paper VI)*. BMF potentially play an important role in protecting adverse behavioural and emotional outcomes at preschool age, as shown by the reduced risk of externalizing problems, somatic complaints, aggressive behaviour, as well as autism spectrum and attention deficit/hyperactivity symptoms *(Paper VII)*.

Conclusion

The main findings of our research revealed that neonatal unit characteristics exert a key role in BMF rates at discharge in infants born VPT, as well as in its continuation to six months. The duration of BMF falls short of international recommendations across European countries, including Portugal, and low BMF continuation rates were marked by strong social inequalities. Our results reinforce BMF as a key factor in promoting neurodevelopment and better mental health among children born VPT when evaluated at preschool age.

Implications for public health

Neonatal units' characteristics are to a large extent modifiable and amenable to intervention. Parents are key actors for successful BMF in the neonatal unit environment. Changes in policies and practices in units towards more family-centred and integrated care might be expected to cost-effectively increase BMF and, consequently, mitigate adverse health outcomes in the medium- and long-term in children born VPT.

RESUMO

Introdução

É reconhecido que o uso de leite materno em recém-nascidos muito pré-termo (MPT, <32 semanas de idade gestacional) é de extrema importância prognóstica. No entanto, providenciar leite materno a recém-nascidos MPT é um processo complexo e desafiante. Há uma grande disparidade nas práticas de leite materno entre e dentro de diferentes países que não é inteiramente explicada pelas características maternas e da criança. Este facto sugere que são possíveis ganhos substanciais se o papel das políticas e práticas que operam nas unidades neonatais for compreendido. Além disso, a lacuna que existe sobre o efeito das práticas de aleitamento materno nos resultados em saúde a médio e longo prazo de crianças nascidas MPT merece uma investigação mais aprofundada. Assim, esta tese teve como objetivo estudar as práticas de aleitamento materno em crianças nascidas MPT e avaliar prospetivamente o efeito dessas práticas no neurodesenvolvimento e saúde mental medidos durante a infância.

Métodos

Foram utilizados dados transversais e longitudinais da coorte prospetiva de base populacional de crianças nascidas MPT, coorte "*Efetividade dos Cuidados Intensivos Perinatais na Europa*" (EPICE), recrutada em 2011/2012, em 11 países europeus (7 900 nados-vivos e 6 792 crianças com alta hospitalar). Em Portugal, o estudo envolveu todas as maternidades e unidades de neonatologia de duas regiões (Norte e Lisboa e Vale do Tejo) e identificou 724 nados-vivos (607 com alta hospitalar). Os dados sobre características demográficas e clínicas, intervenções médicas e desfechos neonatais foram recolhidos até ao momento da alta hospitalar, usando protocolos padronizados, e os dados sobre as políticas e práticas da unidade foram obtidos através de questionários aplicados aos profissionais de saúde. Por fim, recolheu-se informação sobre a saúde e o desenvolvimento das crianças aos dois anos de idade corrigida em toda a

coorte, e adicionalmente aos três anos de idade em Portugal, através de questionários estruturados aplicados aos pais.

Resultados

Dois terços das crianças MPT da coorte portuguesa receberam algum leite materno à data da alta, 25% exclusivamente, com uma grande disparidade entre as unidades (variação: 3%-50% para leite materno exclusivo, 21%-62% para misto). O principal determinante de leite materno exclusivo à data da alta foi a presença de um membro da equipa designado para apoiar as mães *(Artigo I)*. A nível europeu, as políticas para a presença e envolvimento dos pais nas unidades neonatais variaram entre e dentro dos países, e verificou-se que crianças internadas em unidades com políticas parentais mais liberais tinham cerca de duas vezes mais probabilidade de receber leite materno exclusivo à data da alta *(Artigo II)*. Observou-se que a duração do leite materno ficou aquém das recomendações internacionais nesta população vulnerável. Em Portugal, apenas 10% das crianças receberam leite materno exclusivo durante pelo menos seis meses e 10% receberam algum leite materno durante 12 meses ou mais. Em todo o mundo, com base numa revisão sistemática da literatura, a prevalência de leite materno exclusivo aos seis meses variou entre 1% e 27%, e entre 8% e 12% para algum leite materno aos 12 meses *(Artigo III)*. Entre os países europeus, verificou-se que um terço das crianças MPT que alguma vez foram amamentadas recebiam leite materno aos seis meses, variando entre 25% e 50%. A probabilidade de ser amamentado até aos seis meses de idade foi menor nas crianças cujas mães tinham um nível de escolaridade mais baixo *(Artigo IV)*. Além disso, observou-se que a gestão do leite da própria mãe variou consideravelmente. Em 22% das unidades inquiridas, todos os recém-nascidos MPT cujas mães faziam a extração do seu leite receberam o leite das próprias mães pasteurizado (variando entre 0% e 73% entre os países) *(Artigo V)*.

Os nossos resultados enfatizam a importância do leite materno nos resultados em saúde durante a infância, particularmente no neurodesenvolvimento e saúde mental. As crianças MPT que nunca receberam leite materno apresentaram maior risco de capacidades de cognição não-verbal e verbal subótimas aos dois anos de idade corrigida, em comparação com aquelas que alguma vez receberam leite materno, independentemente de múltiplas características perinatais e sociodemográficas relevantes *(Artigo VI)*. O leite materno desempenha um papel potencialmente relevante na proteção de desfechos comportamentais e emocionais adversos em idade pré-escolar, como demonstrado pela redução do risco de problemas de externalização, queixas somáticas, comportamento agressivo, bem como sintomas do espectro do autismo e déficit de atenção/hiperatividade *(Artigo VII)*.

Conclusão

Os principais resultados da nossa investigação revelaram que as características das unidades neonatais exercem um papel fundamental na prevalência de leite materno à data da alta em crianças nascidas MPT, bem como na sua continuação até aos seis meses. A duração do leite materno fica aquém das recomendações internacionais em países europeus, incluindo Portugal, e as baixas prevalências na continuação leite materno foram associadas a significativas desigualdades sociais. Os nossos resultados reforçam o leite materno como um fator chave na promoção do neurodesenvolvimento e melhor saúde mental em crianças nascidas MPT quando avaliadas em idade pré-escolar.

Implicações para a Saúde Pública

As características das unidades neonatais são em grande medida modificáveis e passíveis de intervenção. Os pais são os principais atores para o sucesso do aleitamento materno no ambiente da unidade de neonatologia. É expectável que mudanças nas políticas e práticas das unidades, direcionadas a cuidados mais centrados e integrados na família, possam ser uma forma de aumentar o aleitamento materno em termos de custo-eficácia e, consequentemente, mitigar resultados adversos em saúde a médio e longo prazo em crianças MPT.

1. INTRODUCTION

1.1. BREASTFEEDING

1.1.1. Historical context

Human milk has been revered since prehistoric times as being considered essential to assure the survival of infants (1, 2). Worldwide, the importance of breastfeeding has been reflected in its depiction in mythology, philosophy, art and religion from antiquity until the present day (1).

In ancient societies and over the previous centuries, before the introduction of bottle feeding and formula, when a woman could not produce milk or breastfeed for any reason, the most common alternative route for feeding a newborn was through a "wet nurse" – a woman who breastfeeds another woman's infant (1, 2). Wet nurses were frequently paid, even considered to be an organized profession, although it was in some contexts a form of slavery (ancient Rome). Wet nursing was very common between the 16th and the 18th century in Europe, mostly among wealthy families among whom breastfeeding was unacceptable, as it was associated with poor and unsophisticated population groups (1, 2). During this period, paediatricians began to strongly argue in favour of the mother's own milk. By the end of the 18th century, the practice of wet nursing had become more common among lower-income families, as mothers had to work to contribute to the family´s income (1, 2).

Infant formula was introduced in 1865, when the chemist Justus von Liebig created, patented and marketed the first liquid form of infant formula, and shortly thereafter, a powdered form (1, 2). Eighteen years later, there were 27 patented brands of infant formula (1, 2). The early 20th century, with advances in the development of milk formula, witnessed a steady decline in breastfeeding in high-income countries, as well as among more highly educated and wealthier women in low- and middle-income countries (3). The global decrease in breastfeeding in many countries was attributed to the promotion of infant formula, including aggressive and inappropriate marketing strategies by companies directed at both parents and health professionals (3, 4).

In this context, in the 1970s, a movement began to promote and protect breastfeeding, which included the World Health Organization (WHO), the United Nations Children's Fund (UNICEF) and non-governmental organizations, such as the International Baby Food Action Network (IBFAN) (2, 4). In 1981, the World Health Assembly (WHA) of the WHO adopted the

International Code of Marketing of Breastmilk Substitutes, which is an international health policy framework regarding the provision of adequate information on appropriate infant feeding, and the regulation of the marketing and distribution of breastmilk substitutes (4). The International Code had subsequent WHA resolutions that clarified or extended certain provisions. The code applies to governments, manufacturers and distributors of breast milk substitutes, health system and health workers, and enjoins them to avoid conflicts of interests (4).

In 1989, the WHO and UNICEF announced the *Ten Steps* to Successful Breastfeeding (the *Ten Steps*), within a package of policies and procedures that health facilities providing maternity and newborn services should implement to support breastfeeding (5). The Innocenti Declaration on the protection, promotion and support of breastfeeding was adopted, in 1990, by policymakers and international agencies from over 30 countries (6). This Declaration stated that all governments should guarantee that every facility fully practices all of the *Ten Steps* (6). In the same year, the United Nations Convention on the Rights of the Child declared breastfeeding to be a legal right of the child and its promotion to be a legal obligation of countries that ratified the Convention (7).

A few years later, in 1991, the WHO and UNICEF launched the Baby-Friendly Hospital Initiative (BFHI) as a global programme to encourage health facilities providing maternity and newborn services worldwide to implement the *Ten Steps*. Additionally, in 2003, the WHO and UNICEF jointly developed the Global Strategy for Infant and Young Child Feeding to revitalize the world´s attention to the impact that feeding practices have on the nutritional status, growth and development, health, and thus on the very survival of infants and young children (8). This global strategy also reinforced the importance of BFHI. More recently, in 2018, a revised and updated version of the *Ten Steps* and an implementation guidance was published, enlarging its scope to include preterm, low-birth-weight and newborns admitted to Neonatal Intensive Care Units (NICUs) (9). Table 1 presents the 2018 revised *Ten Steps* for successful breastfeeding. Facilities that reported full adherence to the *Ten Steps*, as well as compliance with the International Code of Marketing of Breast-milk Substitutes, could become designated as a "Baby-Friendly Hospital" (9). Nevertheless, in 2017, only 10% of births occur in facilities designated as Baby-Friendly globally (10). For instance, there are currently 15 maternity facilities accredited in Portugal (11), representing less than 40% of those available.

Table 1. WHO/UNICEF *Ten Steps* to Successful Breastfeeding [revised 2018; (9)].

Critical management procedures	
1a.	Fully comply with the International Code of Marketing of Breast-milk Substitutes and relevant World Health Assembly resolutions.
1b.	Have a written infant feeding policy that is routinely communicated to staff and parents.
1c.	Establish ongoing monitoring and data-management systems.
2.	Ensure that staff have sufficient knowledge, competence and skills to support breastfeeding.
Key clinical practices	
3.	Discuss the importance and management of breastfeeding with pregnant women and their families.
4.	Facilitate immediate and uninterrupted skin-to-skin contact, and support mothers to initiate breastfeeding as soon as possible after birth.
5.	Support mothers to initiate and maintain breastfeeding, as well as manage common difficulties.
6.	Do not provide breastfed newborns any food or fluids other than breast milk, unless medically indicated.
7.	Enable mothers and their infants to remain together and to practise rooming-in 24 hours a day.
8.	Support mothers to recognize and respond to their infants' cues for feeding.
9.	Counsel mothers on the use and risks of feeding bottles, teats and pacifiers.
10.	Coordinate discharge so that parents and their infants have timely access to ongoing support and care.

1.1.2. Human milk composition

Human milk, as the natural food for infants starting at birth, possesses unique characteristics. It is a bioactive fluid derived from a complex biological secretion of the mammary gland with a dynamic composition that changes over the course of lactation and varies within feeds, with the time of the day, between mothers, as well as according to the mother's diet and parity (12, 13). The composition of human milk is also influenced by the length of gestation, along with the method of expression and management (e.g., storage and pasteurization) (12).

Human milk contains all of the nutrients that an infant needs for proper growth and development in the first six months of life. Its composition includes water, carbohydrates (lactose), lipids (fat), proteins, vitamins, minerals, electrolytes and trace elements (12, 13). Human milk oligosaccharides (HMOs) are a key component of human milk and are the third most abundant solid component, following lactose and fat. HMOs favour the growth of specific intestinal bacteria and play an important role in preventing infections (13). Moreover, human milk comprises non-nutritive bioactive factors, including human cells, anti-infectious and anti-inflammatory agents, hormones, growth factors, prebiotics, and probiotics (12, 13). Bioactive factors are important for protection against infections and immune-mediated diseases, and modulate immunological development (12, 13).

The first milk secretions are called colostrum and are produced in low quantities during the first few days following birth. Colostrum is strikingly different from transitional and mature milk, as it is rich in protein, immunologic components and growth factors (12, 13). Transitional milk typically occurs from five days to two weeks postpartum, and has increased lactose and fat to meet the needs of a growing infant. By four to six weeks postpartum, milk is considered to be fully mature and remains relatively similar in its composition (12).

The composition of breast milk from mothers delivering preterm differs from that of mothers who deliver at full-term, with preterm milk tending to be higher in protein and fat (12, 14, 15). This suggests an adaptation resulting from the greater requirements for nutrients in preterm infants (12).

1.1.3. Recommendations for breastfeeding practices

In 2001, as a global public health recommendation, the WHO and UNICEF advised the adoption of three breastfeeding practices (Figure 1). First, early initiation of breastfeeding, placing newborns skin-to-skin with their mother immediately after birth and initiating breastfeeding within the first hour of birth. Second, to provide exclusive breastfeeding for the first six months of life (with no other foods or liquids, including water). Third, after six months, children should begin to eat safe and adequate complementary foods while continuing to breastfeed for up to two years or longer (8, 16).

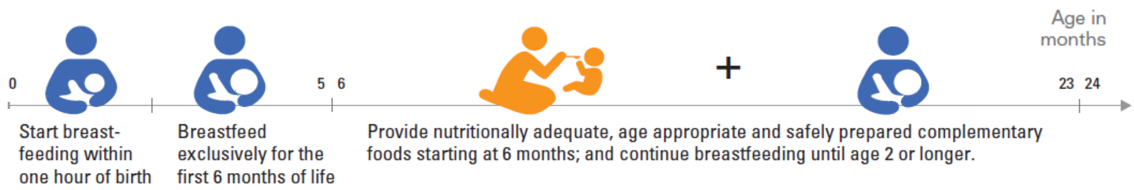


Figure 1. Recommendations for breastfeeding practices. Adapted from UNICEF, 2020 (17).

In line with these recommendations, in 2012, the Nutrition Commission of the Portuguese Society of Paediatrics considered that breast milk should be the "*only source of food during the first six months of life*", while it is "*necessary to diversify food from 5-6 months of life taking into account the nutrition and development of the infant*" (18). In 2019, the Portuguese National Programme for the Promotion of Healthy Eating of the Directorate-General for Health reinforced the importance of exclusive breastfeeding for the first six months of life, starting within an hour of birth, and its continuation for 12 to 24 months (19).

1.1.4. Prevalence and time trends of breastfeeding practices

As observed in Figure 2, there are important differences in the prevalence of breastfeeding worldwide. Independently of the country's income group, more than 80% of children were ever breastfed in 2010 (20). However, early initiation of breastfeeding, that is put to the breast within an hour of birth, was low in all contexts (<50%). Nevertheless, it was slightly higher in low-income countries, which was observed for exclusive breastfeeding as well. However, early initiation of breastfeeding was higher in upper-middle compared with lower-middle income countries, but an inverse trend occurred for exclusive breastfeeding (20).

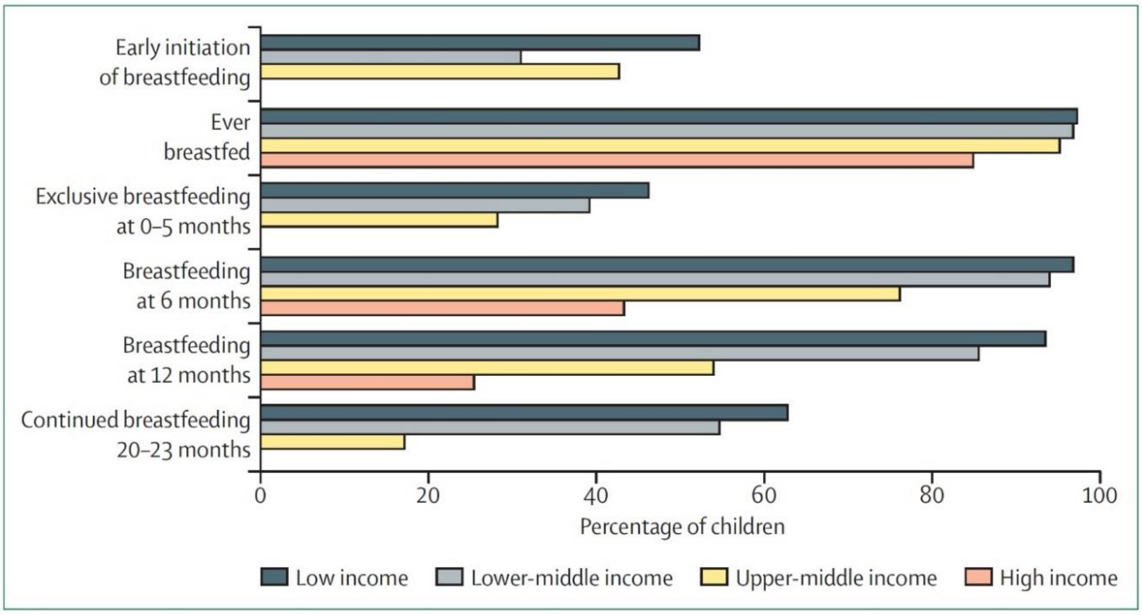


Figure 2. Breastfeeding indicators by country income group in 2010 (data for up to 153 countries). Reproduced from Victora et al., 2016 (20).

Recent data derived from 2014-2019 in the UNICEF global databases revealed that the world is still far from achieving the recommendations for breastfeeding practices. Less than half of all newborns were put to the breast within the first hour of life and only 44% of infants with less than six months of age were exclusively breastfed (17).

According to 2010 data from the European Perinatal Health Report, published in 2013, the percentage of newborns breastfed at birth ranged from 54% to 99% in 19 European countries (Figure 3) (21). More than 95% of babies received some breast milk at birth in the Czech Republic, Latvia, Portugal and Slovenia. Rates were lowest in Ireland, Scotland, Cyprus, France and Malta, ranging between 54% and 69%. Among countries with very high proportions of breastfeeding, exclusiveness varied between 7.2% (Luxembourg) and 48.9% (Cyprus) (21).

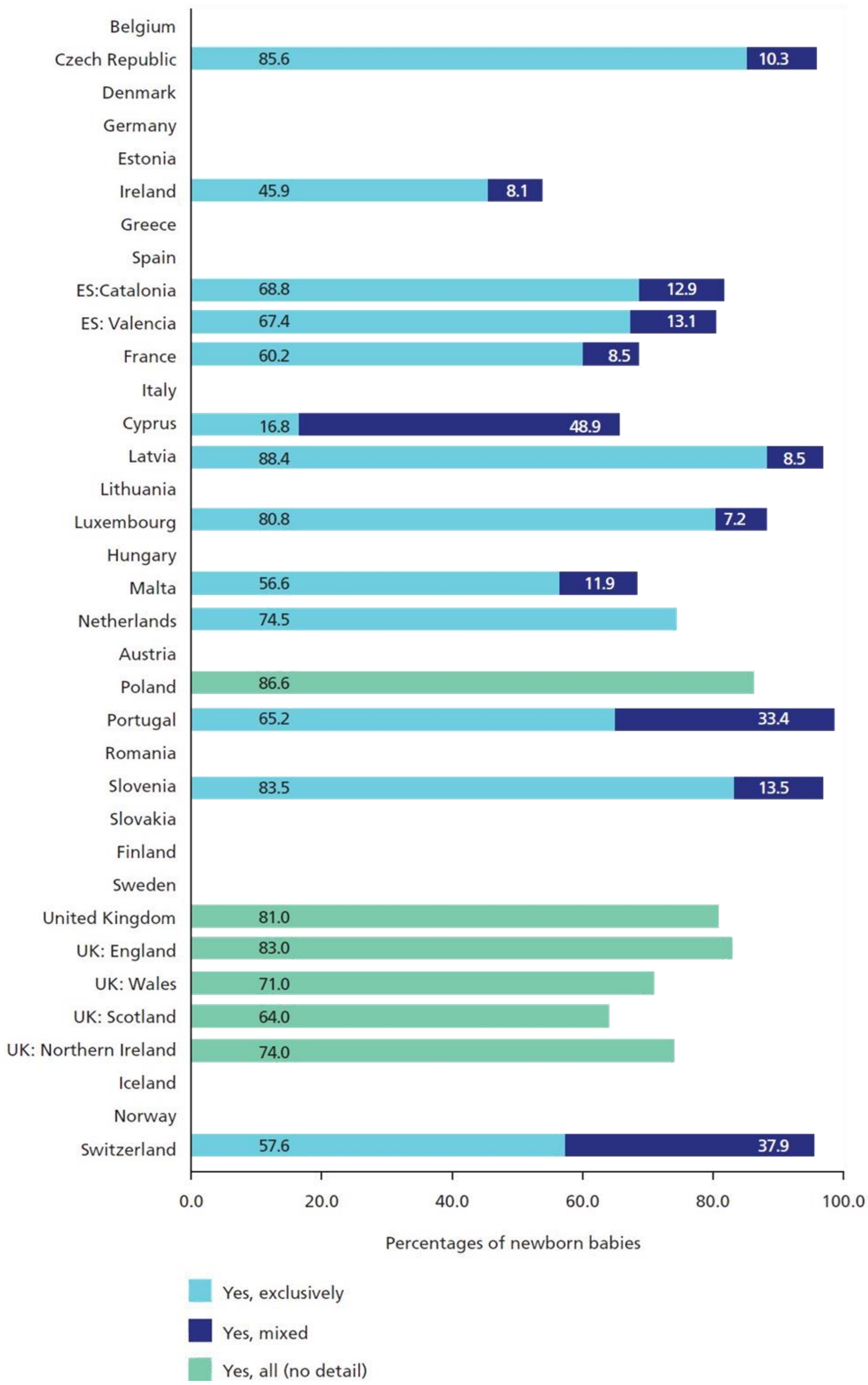


Figure 3. Distribution of breastfeeding for the first 48 hours in 2010, in European countries. Reproduced from the *European Perinatal Health Report*, 2013 (21).

In terms of breastfeeding duration worldwide, high-income countries have a shorter duration than low- and middle-income countries (Figure 2) (20). As observed in Figure 4, the highest prevalence of breastfeeding at 12 months was observed in sub-Saharan Africa, South Asia and parts of Latin America (20). In most high-income countries, the prevalence at 12 months was lower than 20% and considerable differences were observed even among these countries. For example, between the United Kingdom (UK; <1%) and the United States of America (USA; 27%), and between Norway (35%) and Sweden (16%) (20). Globally, based on the UNICEF databases (2014-2019), 65% of children continued to be breastfed during at least 12 months (17).

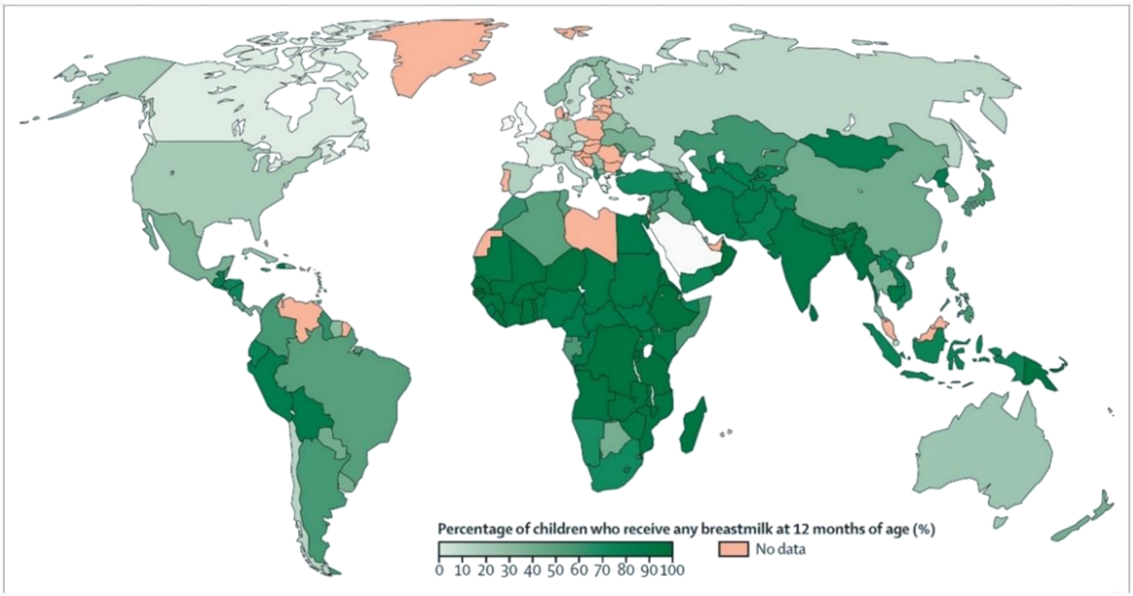


Figure 4: Global distribution of any breastfeeding at 12 months. Data are from 153 countries between 1995 and 2013. Reproduced from Victora et al., 2016 (20).

In Portugal, a national Breastfeeding Registry was set up in 2010 (22). This registry covered 65% of all public hospitals in 2013. However, it excluded preterm infants and infants who were hospitalized for more than six days. In the most recent publication, in 2014, which reports data from 2013, 98.6% (n=30 651/31 097) of newborns initiated breastfeeding before hospital discharge and 84.1% within one hour of birth (22). Nearly 77% of newborns were exclusively breastfed until hospital discharge, but only 22.1% (n=47/213) continued to be exclusively breastfed for at least five months (22). This proportion was higher than that observed in the Portuguese birth cohort Generation XXI (GXXI), which recruited children at birth in 2005/2006, and found that 16.6% of native mothers exclusively breastfed for at least six months and the prevalence of any breastfeeding for 12 months or more was 25.9% (23).

Data from the Portuguese National Health Surveys provided by mothers of infants born between 1982 and 2014 (n=9 172) revealed a positive increase in breastfeeding practices over time (24). The prevalence of infants ever breastfed varied between 71.7% in 1982 and 86.7% in 2014. Exclusive breastfeeding at three months increased by 9.5% per three-year period, ranging from 41.3% in 1982/84 to 62.4% in 2012/14. At six months, exclusive breastfeeding went from 23.5% in 1982/84 to 31.9% in 2012/14, increasing by over 5% per three-year period (24).

1.1.5. Determinants of breastfeeding

Breastfeeding practices are influenced by a wide range of historical, socio-economic, cultural and individual factors (25). In 2016, Rollins and colleagues presented a conceptual model, based on a systematic review, which illustrates the determinants that operate and affect breastfeeding decisions and its practices over time, at multiple levels (Figure 5) (25).

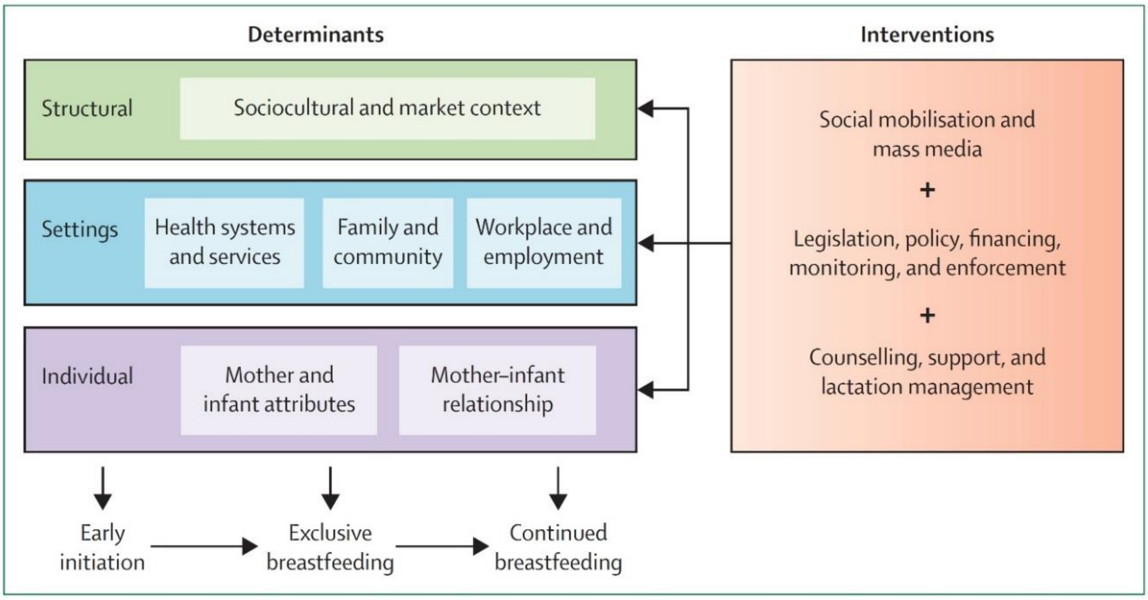


Figure 5. The components of an enabling environment for breastfeeding – a conceptual model. Reproduced from Rollins et al., 2016 (25).

According to Rollins et al., determinants at three important levels influence breastfeeding practices: structural, settings and individual factors (25). Socio-cultural attitudes and market factors that affect the entire population shape structural determinants, such as social trends and media, as well as breast milk substitutes available in stores. The settings level includes factors related to health systems and services (e.g., gaps in knowledge and skills of health-care staff, and long hospital stays), workplace and employment (such as short maternity leave and on-site lactation facilities), as well as family and community (e.g., attitudes and preferences of fathers, and the previous experience of relatives). At an individual level, a woman's breastfeeding behaviour is influenced by their own characteristics, such as age, education, lifestyle behaviours, depression, her confidence and self-efficacy, as well as by her infant´s characteristics, for instance, gestational age, birthweight, well-being and temperament. Additionally, the mother-infant interaction plays an important role in successful breastfeeding (25).

A study from Portugal, which recruited women after delivery in a public maternity unit in Lisbon, showed that the main self-reported causes for stopping breastfeeding were insufficient milk production, bad sucking and returning to work. In fact, mothers introduced formula at three months after medical recommendation in nearly 70% of cases (26), while maintaining breastfeeding at six months was associated with a previous positive experience, a higher educational level and not smoking (26).

1.1.6. Lifelong effects for child and mother

Scientific evidence is robust regarding the benefits of breastfeeding for both children and mothers. The advantages of breastfeeding among children have been observed in numerous nutritional, immunologic, developmental and psychological outcomes (20, 27). Compared to children who are breastfed for shorter periods, or not breastfed at all, those who are breastfed for longer periods have lower risks of mortality and morbidity, such as diarrhoea, respiratory infections, otitis media and dental malocclusions, and better cognitive development (20, 28-31). This protective effect of breastfeeding on health persists throughout adolescence and adulthood (32, 33). Furthermore, cumulative research also suggests that breastfeeding might protect against overweight, obesity and diabetes later in life (20, 34, 35).

Maternal benefits of breastfeeding include decreased risk of breast and ovarian cancer, as well as cardiometabolic disease (hypertension, hyperlipidemia, and type 2 diabetes *mellitus*) (20, 36). Moreover, a longer breastfeeding duration is associated with reduced maternal postpartum weight retention and postpartum depression (20, 37, 38), and also contributes to mother-infant bonding (39). Finally, breastfeeding can also improve birth spacing (20, 36).

1.1.7. Breastfeeding as a public health priority

Breastfeeding is widely recognized as the best option for infant feeding, and as a result, its protection, promotion and support is considered a public health priority (8). Nevertheless, international exclusive breastfeeding rates remain far from the target endorsed by the Global Nutrition Targets, which intends to increase the rate of exclusive breastfeeding for the first six months to at least 50% by 2025 (40).

Besides reducing the burden of disease for both children and mothers, breastfeeding also provides beneficial effects for families, the community, the health and social system, the environment, and society in general. As such, breastfeeding is considered to be an exceptionally cost-effective strategy for child and maternal health and well-being (20, 25).

The scaling up of breastfeeding could prevent around 823 thousand annual child deaths in children under five years of age, corresponding to 13.8% of the deaths under two years of age (20). Additionally, 20 thousand deaths from breast cancer could be prevented each year (20). Also, if every infant was breastfed until at least six months of age, cognitive deficits could be avoided with a consequent global economy savings of US$300 billion annually (25). Recent analyses indicate that over 595 thousand child deaths from diarrhoea or pneumonia are attributed to not breastfeeding, according to recommendations from the WHO and UNICEF, each year (41). Furthermore, there would be nearly 975 thousand less cases of childhood obesity every year. Optimal breastfeeding practices also have the potential to prevent an additional 98 thousand deaths of mothers from cancer and type II diabetes annually. The total global economic losses are estimated to range from US$257 to US$341 billion or between 0.37% and 0.70% of the global gross national income (41).

The literature on the costs associated with sub-optimal breastfeeding practices provides indisputable evidence that breastfeeding should be a public health priority. Additionally, breastfeeding practices have been well document to be highly responsive to interventions delivered in health systems and services, the community, and family, as well as in the work environment, leading to rapid improvements in breastfeeding (Table 2) (25).

Table 2. Effects of interventions on breastfeeding outcome measures, by setting. Reproduced from Rollins et al., 2016 (25).

	Early initiation of breastfeeding (within 1 h of birth)	Exclusive breastfeeding for 0–5 months	Continued breastfeeding for 12–23 months	Any breastfeeding up to 6 months
Health systems and services				
Overall	29 studies: RR 1·11 (1·06–1·16)	51 studies: RR 1·46 (1·37–1·56)	Eight studies: RR 1·18 (1·03–1·35)	47 studies: RR 1·40 (1·30–1·52)
Baby-friendly support	Ten studies: RR 1·20 (1·11–1·28)	15 studies: RR 1·49 (1·33–1·68)	Three studies: RR 1·26 (0·96–1·64)	13 studies: RR 1·66 (1·34–2·07)
Counselling* or education	Ten studies: RR 1·12 (1·05–1·19)	28 studies: RR 1·66 (1·43–1·92)	Five studies: RR 1·15 (0·99–1·35)	24 studies RR 1·47 (1·29–1·68)
Special training of health staff	Three studies: RR 1·09 (1·01–1·18)	Five studies: RR 1·36 (1·14–1·63)	No studies	Five studies RR 1·33 (1·07–1·67)
Family and community				
Home and family	Five studies: RR 1·74 (0·97–3·12)	43 studies: RR 1·48 (1·32–1·66)	Two studies: RR 1·26 (1·05–1·50)	36 studies: RR 1·16 (1·07–1·25)
Counselling* or education	Five studies: RR 1·74 (0·97–3·12)	38 studies: RR 1·58 (1·39–1·80)	One study: HR 1·22 (1·01–1·47)	33 studies: RR 1·17 (1·08–1·27)
Family or social support	No studies	Five studies: RR 0·95 (0·87–1·02)	One study: RR 1·69 (0·95–2·99)	Three studies: RR 1·02 (0·86–1·22)
Community	Five studies: RR 1·86 (1·33–2·59)	Six studies: RR 1·20 (1·03–1·39); one study: OR 1·10 (0·60–1·80)	No studies	No studies
Group counselling* or education	Four studies: RR 1·65 (1·38–1·97)	One study: RR 1·61 (0·95–2·71); one study: OR 1·10 (0·60–1·80)	No studies	No studies
Integrated mass media, counselling, and community mobilisation approach	One study: RR 5·33 (2·33–12·19)	Five studies: RR 1·17 (1·0–1·36)	No studies	No studies
Work environment				
Work environment	No studies	Four studies: RR 1·28 (0·98–1·69)	One study: RR 3·33 (1·43–10·0)	Four studies: RR 1·31 (1·10–1·56)
Maternal leave policy	No studies	Two studies: RR 1·52 (1·03–2·23)	No studies	One study: RR 0·99 (0·8–1·29)
Workplace support	No studies	Two studies: RR 1·08 (0·74–1·60)	No studies	One study: RR 1·25 (1·09–1·43)
Employment status	No studies	No studies	One study: RR 3·33 (1·43–10·0)	Two studies: RR 1·49 (1·12–1·98)
Combination of settings				
Combination of settings	Ten studies RR 1·57 (1·24–1·97)	26 studies RR 1·79 (1·45–2·21)	Seven studies RR 1·97 (1·74–2·24)	30 studies RR 1·30 (1·06–1·61)
Health systems and services and home and family	Six studies: RR 1·36 (1·07–1·73)	16 studies: RR 1·63 (1·27–2·10)	Six studies: RR 1·34 (1·01–1·81)	21 studies: RR 1·23 (1·08–1·40); two studies: OR 2·08 (1·32–3·28)
Home and family and community	Three studies: RR 1·85 (1·08–3·17)	Three studies: RR 1·42 (1·21–1·66)	No studies	Three studies: RR 1·00 (0·89–1·12)
Health systems and services and community	One study: RR 2·09 (1·64–2·67)	Seven studies: RR 2·52 (1·39–4·59)	One study: RR 10·2 (7·66–13·74)	Six studies: RR 1·74 (0·84–3·39)

Data are risk ratio (RR; 95% CI) or odds ratio (OR; 95% CI). All estimates of effect and methods are provided in Sinha and colleagues.[64] *Antenatal counselling focused on infant feeding decision making and preparation for breastfeeding; periodic postnatal home and family encounters focused on establishing exclusive breastfeeding, managing problems and challenges, and continued breastfeeding.

There is robust evidence that adherence to the BFHI *Ten Steps* significantly improves breastfeeding rates. A systematic review of 58 studies, published in 2016, clearly demonstrated that the implementation of the *Ten Steps* impacts early initiation of breastfeeding immediately after birth, exclusive breastfeeding at hospital discharge, as well as the total duration of exclusive and any breastfeeding (42). A dose-response association between the number of BFHI steps women are exposed to and the likelihood of improved breastfeeding outcomes has been observed. In particular, community support (step 10) appears to be of the utmost relevance for sustaining the breastfeeding impacts of BFHI in the long-term (42).

From a public health perspective, interventions to improve breastfeeding rates should be multifaceted and context-led, while also addressing the broader determinants of social inequalities. For example, in the UK, neighbourhood deprivation was independently and inversely associated with breastfeeding initiation (43). Compared with the least deprived areas, the likelihood of initiating breastfeeding was 40% lower in the most deprived neighbourhoods. The likelihood of breastfeeding initiation, exclusivity at three months or more, and any breastfeeding for at least six months each reduced by around 20% with the maternal perception of neighbourhoods lacking safe play environments for children compared with neighbourhoods perceived as safe to play in (43).

Data from the Portuguese birth-cohort GXXI showed that migrant mothers, irrespective of their length of residence in Portugal, breastfed (any breastfeeding or exclusive breastfeeding) for longer periods than native mothers (23). Also, data from the GXXI cohort indicated that among women who reported being exposed to physical violence in the last year before delivery, 15.3% never breastfed their children, while the prevalence among women not exposed to physical violence was 6.6%. Those exposed to physical violence were more likely to never breastfeed [Odds Ratio (OR)=2.43; 95% confidence interval (CI): 1.28-4.61], and this association remained statistically significant following adjustment for potential confounders (44).

Thus, there is a high potential for improving breastfeeding rates through enhanced global and community-based policies and programs to effectively protect, promote and support breastfeeding.

1.2. VERY PRETERM INFANTS

1.2.1. Definition, prevalence and trends of very preterm birth

Preterm birth is defined by the WHO as birth before 37 completed weeks of gestation or with fewer than 259 days since the first day of a woman's last menstrual period (45). According to the most recent global estimates, approximately 11% (15 million) of all live births are preterm, with more than 80% occurring in South Asia and sub-Saharan Africa (46). Overall, the preterm birth rate is increasing – from 9.8% to 10.6% in 2000 and 2014, respectively. In 2014, the estimated preterm birth rates ranged from 8.7% in Europe to 13.4% in North Africa (Figure 6) (46).

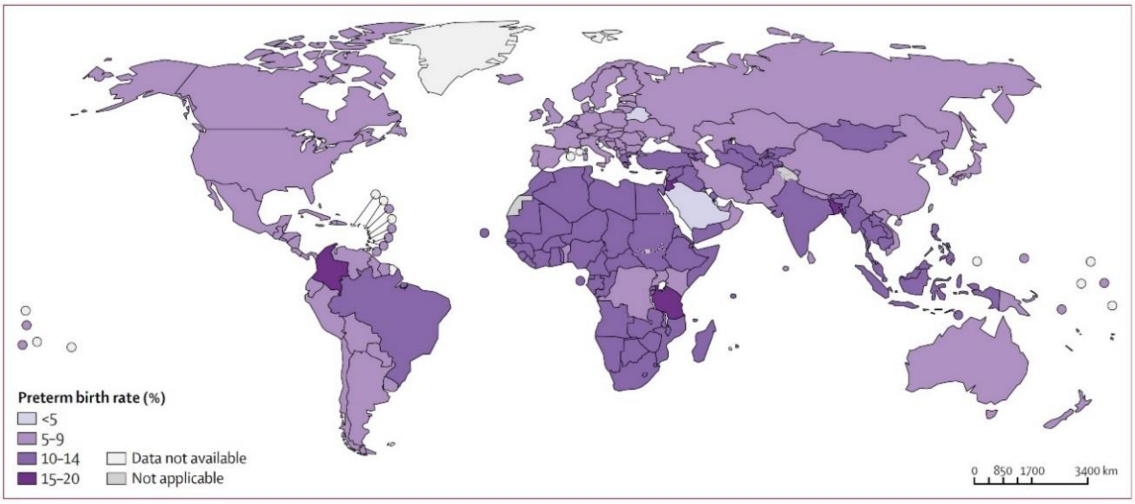


Figure 6. Estimated preterm birth rates in 2014. Reproduced from Chawanpaiboon et al., 2019 (46).

Based on gestational age, preterm birth can be further sub-divided into: late preterm (34-36 completed weeks of gestation); moderate preterm (32-33 weeks), very preterm (28-31 weeks), and extremely preterm (<28 weeks) (47). Births occurring before 32 weeks of gestation account for up to 2% of births worldwide and represent 15% of all preterm births (46, 48). According to the most recent European Perinatal Health Report, in 2015, the prevalence rates of very preterm (VPT) live births (<32 weeks of gestation) range from 0.8% to 1.4% in Europe – an average of 1.0% of all live births (Figure 7) (49). This pattern is similar to that observed in 2010 (21). In Portugal, the prevalence of VPT birth has remained stable in the last two decades (around 1%). According to Statistics Portugal (INE), 896 infants were born VPT in 2019, representing 1.0% of all births and a proportion of 12.8% among preterm births (50).

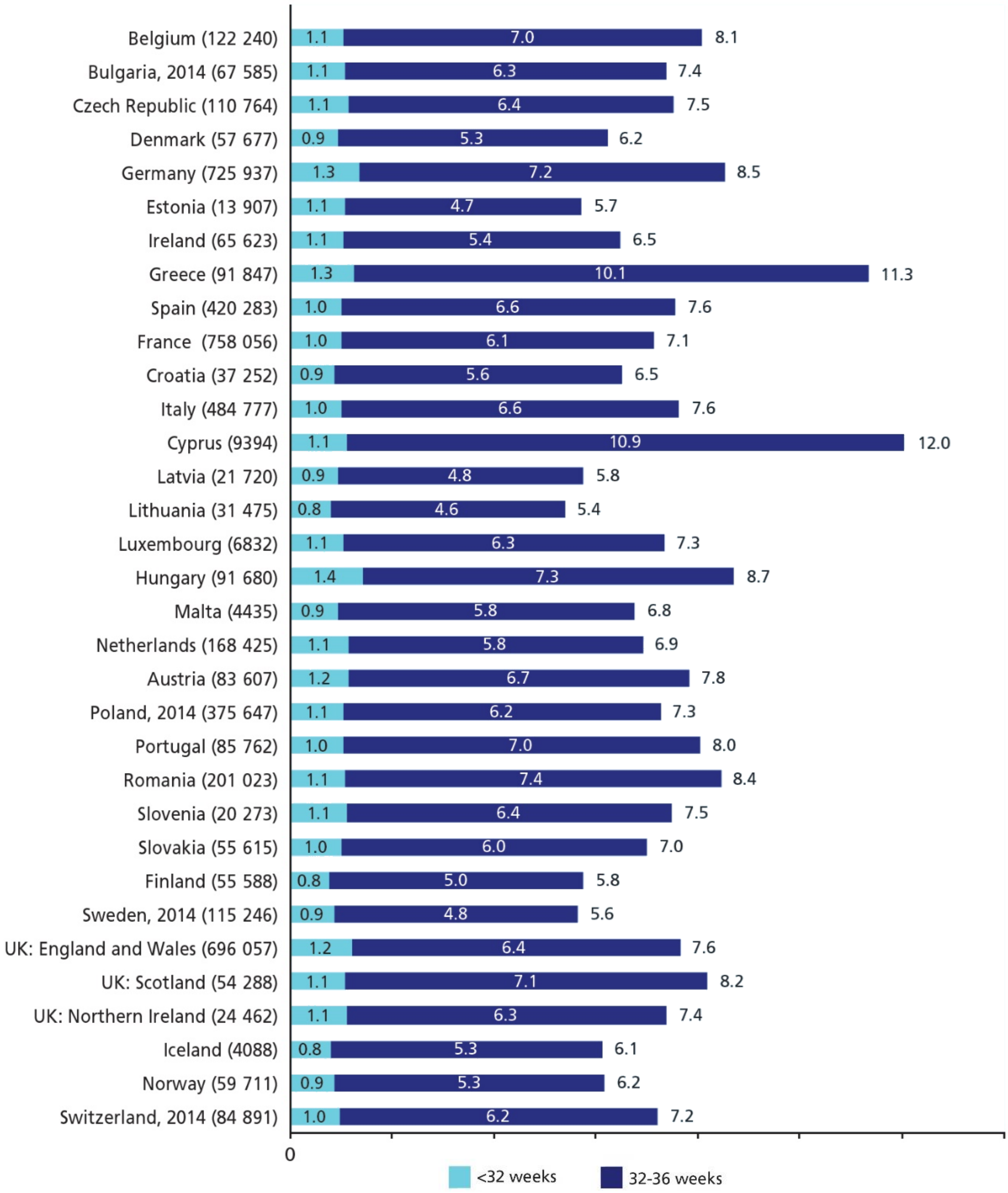


Figure 7. Prevalence of preterm live births overall and by gestational age in 2015. Reproduced from the *European Perinatal Health Report*, 2018 (49). [Note: Number of live births with data for gestational age in parentheses after country name.]

1.2.2. Causes and risk factors of very preterm birth

Preterm birth is considered a syndrome that occurs for a variety of causes, which can be categorized into two subtypes: (1) spontaneous preterm birth (spontaneous onset of labour with intact membranes or following prelabour preterm premature rupture of the membranes); and (2) provider-initiated preterm birth (induction of labour or elective caesarean section for maternal and/or foetal indications, or other non-medical reasons) (47, 51, 52). Two-thirds of preterm births are estimated to occur spontaneously (47, 51, 52).

Preterm birth results from an interplay of multiple factors (Table 3). The precursors to spontaneous preterm birth vary by maternal age, multiple gestations (most of them associated with assisted reproductive technologies), maternal chronic diseases (e.g., diabetes), as well as social and environmental factors (47, 52). Underlying clinical conditions for provider-initiated preterm birth include maternal and/or fetal complications, such as pre-eclampsia or eclampsia, uterine rupture, fetal distress, or intrauterine growth restriction. Additionally, there is an overlap between provider-initiated preterm birth and the risk factors for spontaneous preterm birth (47, 52).

Table 3. Types of preterm birth and risk factors. Adapted from Blencowe et al., 2013 (47).

Type:	Risk Factors:	Examples:
Spontaneous preterm birth:	Age at pregnancy and pregnancy spacing	Adolescent pregnancy, advanced maternal age, or short inter- pregnancy interval
	Multiple pregnancy	Increased rates of twin and higher order pregnancies with assisted reproduction
	Infection	Urinary tract infections, asymptomatic bactiuria, malaria, HIV, syphilis, chorioamnionitis, bacterial vaginosis,
	Underlying maternal chronic medical conditions	Diabetes, hypertension, anaemia, asthma, thyroid disease
	Nutritional	Undernutrition, micronutrient deficiencies
	Lifestyle/work related	Smoking, excess alcohol consumption, recreational drug use, excess physical work/ activity
	Maternal psychological health	Depression, violence against women
	Genetic and other	Genetic risk, e.g., family history Cervical incompetence Intra-uterine growth restriction Congenital abnormality
Provider-initiated preterm birth:	Medical induction or cesarean birth for: obstetric indication Fetal indication Other - Not medically indicated	Prior classical cesarean section, Placenta accrete. There is an overlap for indicated provider-initiated preterm birth with the risk factors for spontaneous preterm birth

1.2.3. The public health dimension of very preterm birth

Prematurity is a public health issue worldwide (47, 48). Globally, preterm birth is a direct cause of child mortality during the neonatal period (15.9%) and until the age of five years (17.8%) (53). Every year, 1.1 million deaths of children under five occur as a result of preterm birth complications (53). The majority of these deaths happen in low- and middle-income countries due to a lack of adequate newborn care. In high-income countries, the main causes of neonatal death are normally complications associated with VPT birth (<32 weeks). Half of the babies born before 25 weeks may survive in high-income settings, however, half of the babies born at 32 weeks still die due to a lack of basic care in low-income settings (54). In Europe, data from 2015, revealed that 57.3% of neonatal deaths occurred in infants born before 32 weeks of gestation (49).

In the last decades, improvements to antenatal and neonatal care, such as the use of antenatal steroids and surfactant, have led to a dramatic reduction in the mortality and morbidity of these infants, even among those born before 26 weeks of gestation (55-60). Nowadays, the survival rate ranges between 80% and 90% among infants born before 32 weeks in high-income countries (59, 61). However, a wide variation in the mortality rates associated with VPT births across European countries and over time has been observed (62-65). A geographically defined prospective cohort of VPT infants (the EPICE cohort), using data from 16 regions in Europe, showed that the stillbirth and in-hospital mortality rate was 27.7% (range from 19.9% to 35.9% by region), and over four-fifths of the variation observed could not be explained by maternal, pregnancy or infant characteristics (62). In particular, the stillbirth and in-hospital mortality rate in Portugal was 29.6% (28.7% in the Northern region and 30.2% in Lisbon and Tagus Valley) (62). Additionally, considering only live births, 86.0% of infants were discharged alive, which varied between 79.1% in Poland and 92.2% in Estonia (83.8% in Portugal) (66).

Despite the significant medical advances in the last decades, the prevalence of prematurity-related diseases and health problems in the short-, medium- and long-term are substantial among infants born before 32 weeks of gestation, being inversely related to gestational age (Figure 8) (60, 67-71). These infants are at higher risk of respiratory, cardiovascular and gastrointestinal complications (60, 72, 73). Bronchopulmonary dysplasia, infections, necrotising enterocolitis, retinopathy of prematurity, patent ductus arteriosus, periventricular leukomalacia, intraventricular haemorrhage and feeding difficulties are the most common complications experienced during neonatal hospitalization (60, 65, 74). Moreover, several studies have shown that VPT children have an increased risk of neurodevelopmental impairments, including cerebral palsy, motor problems and sensory loss (such as visual and auditory deficits), as well as cognitive delays particularly related to language, memory, attention and executive function, along with learning disabilities and behavioural problems (68, 70, 71, 75-80). A meta-analysis estimated that, worldwide, 52% of extremely preterm and 24% of VPT infants develop a certain degree of neurodevelopmental impairment (81). Growing evidence also suggests that the effects of VPT birth can reach adulthood (71, 75, 82-84).

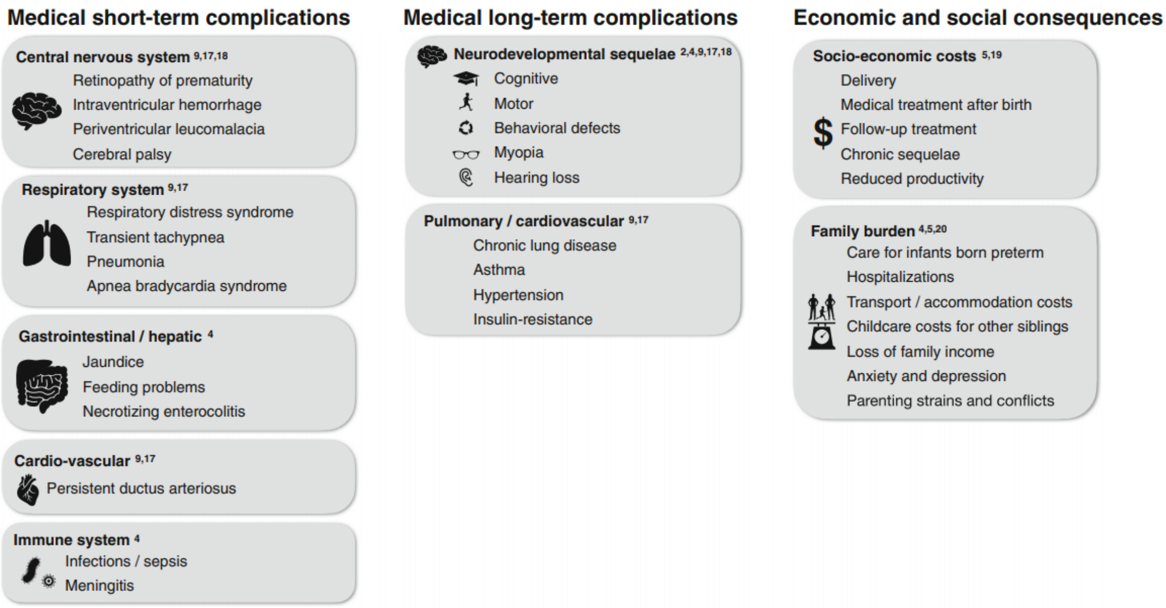


Figure 8. Consequences of preterm birth by medical short-term, medical long-term, and economic and social consequences. Reproduced from Deindl & Diemert, 2020 (85).

There are substantial variations in morbidity between and within countries that remain unexplained by clinical or socio-demographic characteristics (59, 65, 72, 74). A large international cohort from 11 high-income countries compared a composite outcome (including mortality or any grade ≥3 peri-intraventricular haemorrhage, periventricular echodensity/echolucency, bronchopulmonary dysplasia, or treated retinopathy of prematurity), and found that rates varied from 26.4% in Switzerland to 47.3% in the UK (average 39.7%) (59). In Europe, data from the EPICE cohort showed that 13.8% of VPT birth survivors had at least one severe neonatal morbidity, ranging from 10.4% to 23.5% across regions. In Portugal specifically, the prevalence was 13.6% in Lisbon and Tagus Valley and

14.6% in the Northern region (74). Furthermore, a large between-country variability in the use of obstetric and neonatal interventions was observed that is independent of the patient case-mix (86-89), which was also previously observed (90). Nearly 42% of infants did not receive a combination of the four basic evidence-based interventions, and this was found to be associated with significant excess mortality and morbidity (91). Continued variability between European regions was observed in the rates of moderate to severe neurodevelopmental impairment at two years of corrected age (CA), ranging from 10.2% to 26.1% by country, which persists following adjustments for known population, maternal and infant factors (92). These results suggest that substantial gains are possible, particularly in terms of increased survival without severe morbidity, using evidence-based practices in perinatal medicine (91).

VPT birth constitutes an acute disruptive life event with a negative impact on parents' health and well-being (93). Parental stress, anxiety and depression symptoms are frequent among families who experience a VPT birth (94-98). Recently, a Portuguese study showed that mothers and fathers of VPT infants hospitalized in the NICU classified the overall experience of hospitalization as very stressful and stressful, respectively, and the "change in parental role" was the greatest source of stress (97).

Additionally, VPT birth significantly contributes to increased economic costs for families, as well as for health and social systems (Figure 8) (85). Since its adverse effects are often multiple and begin early in life, with lifelong consequences and long-term complex healthcare needs (75), the economic impact is high for initial hospitalization in the NICU, and for health and educational support in the long-term (85, 99, 100).

In that regard, and in line with evidence-based and internationally acknowledged recommendations, global efforts should be made to reduce the risk of extreme and VPT birth, as well as its short- and long-term complications whenever necessary (101). The efforts to improve health outcomes for infants born before 32 weeks include guaranteeing equitable access to human milk, with the mother's own milk being the first choice, in order to achieve optimal growth, development and health for these vulnerable infants (102).

1.3. BREAST MILK FEEDING IN VERY PRETERM INFANTS

1.3.1. Breast milk feeding recommendations for very preterm infants

Feeding with human milk has been recognised as an essential component of newborn care, and is especially important for sick and vulnerable newborns, including those born below 32 weeks of gestation, who are at greatest risk of illness and death. According to the most recent WHO recommendations, every effort should be made to provide the mother's own milk to newborns, either by giving them their mother's expressed breast milk or directly through breastfeeding later (103). Infants who cannot be fed the mother's own milk should receive donor human milk, which should be safely provided through a human milk bank (103). This recommendation was reinforced in 2017, with the brief policy "*Ensuring equitable access to human milk for all infants*" (102).

In their most recent consensus, the American Academy of Pediatrics (AAP), the European Society for Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN), and the European Milk Bank Association (EMBA), stated that "*mother's own milk is the first choice in the feeding of preterm infants. When mother's milk is not available, pasteurized donor human milk should be used*" (104). More recently, the *European Standards of Care for Newborn Health (European Standards)* developed standards for nutrition and strongly encourage the use of the mother's own milk for primary feeding for infants born before 32 weeks of gestation and, when this is not possible, the safe use of human pasteurized donor milk would be the best alternative. Preterm formula should be used, as the last option, when the mother's own milk or donor human milk is not available (105).

Infants born VPT regularly require nutritional support by parenteral and/or enteral nutrition as their digestive tract function is often immature. Also, these infants have fast weight gain and high nutritional requirements per kilogram of body weight. Thus, professional nutritional care management is essential to prevent the early occurrence of nutrient deficits and growth faltering. Several international recommendations are available for neonatal parenteral nutrition (106-108), as well as for enteral nutrition (109-111). Briefly, parenteral nutrition should begin on the first day after birth, usually using standard solutions, and continued until sufficient enteral feeding is established (108). Parenteral nutrition with amino acids and glucose should commence in all VPT infants. Intravenous lipid emulsions are a good source of energy and can be used on day one. Early enteral feeding should be established, based on a standard protocol, preferably with the mother's own milk (109). In Portugal, national guidelines were updated by the Portuguese Neonatal Society, in 2014, for enteral nutrition (112) and, in 2019, for parenteral nutrition (113, 114).

Fresh mother's own milk should be preferred when feeding VPT infants (115). However, there is a risk of bacterial contamination, decreased immunological activity and potentially less nutritional value when a mother's expressed milk is stored and handled. Previous studies revealed differences in mother's own milk management among NICUs and between countries (116, 117). Accordingly, the working group of the French Neonatal Society on fresh human milk use in preterm infants recently advised that specific recommendations are needed to harmonise the provision of fresh mother's milk (115).

Considering that the specific nutritional needs of infants born before 32 weeks are higher compared to full-term infants, human milk does not entirely provide enough nutrition during the first weeks of life (118, 119). To prevent extrauterine growth restriction, which is associated with poor neurocognitive outcomes (120, 121), and to avoid specific nutrient deficiencies, nutrient fortification of human milk is recommended (i.e. calcium, proteins, vitamins, minerals and trace elements) (122, 123). According to the most recent recommendations of the EMBA Working Group on Human Milk Fortification published in 2019, all preterm infants with a birth weight less than 1800 grams should be fed fortified human milk (122). Based on this document, individualized fortification (adjustable or targeted) is recommended for human milk fortification (122). This is in line with the previous joint consensus of the AAP and the ESPGHAN, although they proposed that human milk fortification should start with standard fortification and, if infants do not grow appropriately, individualized fortification is advisable (104). However, the best fortification strategies and the optimal composition of fortifiers remain to be further explored, as there is insufficient evidence (124, 125).

1.3.2. The role of donor human milk and human milk banks

Human milk banks are established institutions that collect, screen, store, process and distribute donor milk, which is expressed by lactating women and voluntarily donated to a human milk bank (126). Donor human milk can supplement or replace the supply of maternal breast milk when it is insufficient or when the mother´s own milk is not available, e.g., due to medical conditions or treatments (126).

The first human milk bank was established in 1909, in Vienna, Austria, and the EMBA was officially launched in 2010 (126). There are currently nearly 250 active human milk banks in Europe operating in 28 countries (127). Bulgaria, Croatia, Estonia, Netherlands and Portugal each have one human milk bank active. France and Italy have the highest number of human milk banks, with 36 and 37, respectively. The only human milk bank available in Portugal opened in 2009, and is located in Lisbon (at the Maternidade Dr. Alfredo da Costa), serving only two NICUs in the country (127).

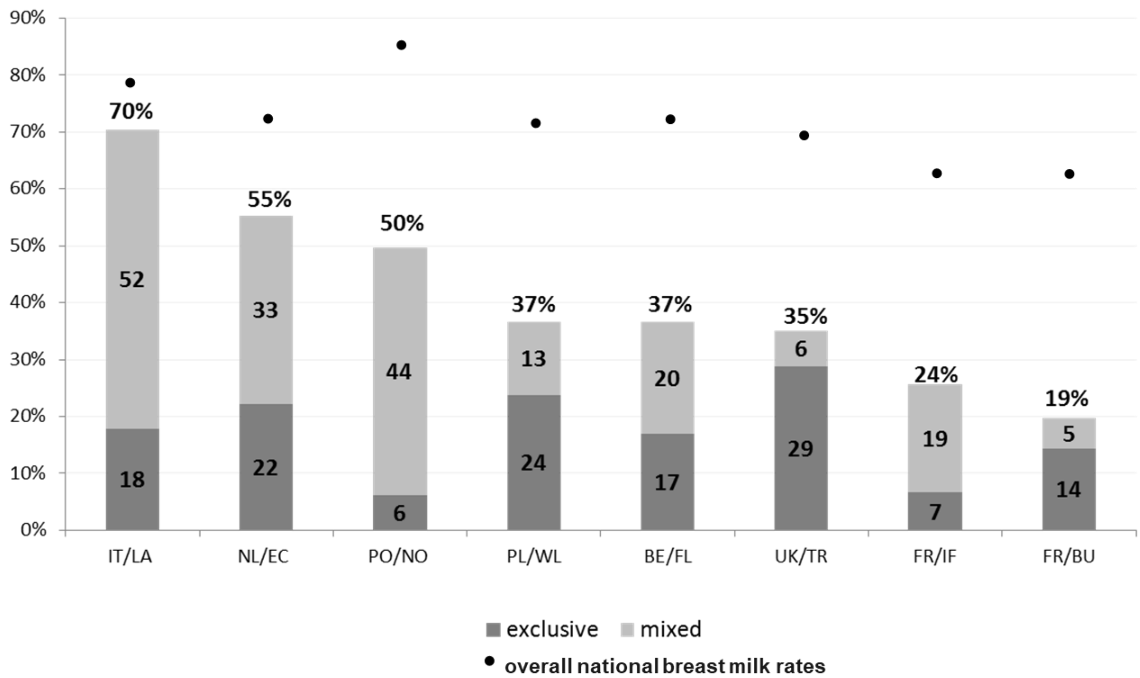
In 2013, the ESPGHAN Committee on Nutrition documented the existing evidence of the benefits and common concerns deriving from the use of donor milk in preterm infants (128). Protection against necrotizing enterocolitis and bronchopulmonary dysplasia were the major clinical benefits deriving from the use of donor human milk compared with infant formula (129, 130). Additionally, the presence of a human milk bank is associated with higher rates of breast milk feeding (BMF) at discharge in NICUs, leading to successful breastfeeding in later on (131-133).

Although several countries have well-regulated human milk banks and national guidelines available (134), differences exist between these guidelines. These are inherent from variations in practices and regulations as well as the organization of human milk banks within each country (126, 135, 136). Furthermore, discrepancies in practices are often due to the lack of evidence. In this context, in 2019, the EMBA developed recommendations and consensus statements for the establishment and operation of human milk banks in Europe (126). However, the need for a common regulation of donor human milk and milk banks at the European level has emerged (135). As such, it has become essential to guarantee that "*human milk's procurement, storage, processing, and distribution meet high quality and safety standards in a harmonized and safe manner*" (135). Considering the health benefits of human milk for infants born VPT, to guarantee equitable access to safe donor human milk is a public health concern.

1.3.3. Prevalence and time trends of breast milk feeding in very preterm infants

Despite the current clinical guidelines and public health policy, the prevalence and duration of BMF in VPT infants is lower than among full-term infants. Additionally, there is a large variation in BMF between and within countries.

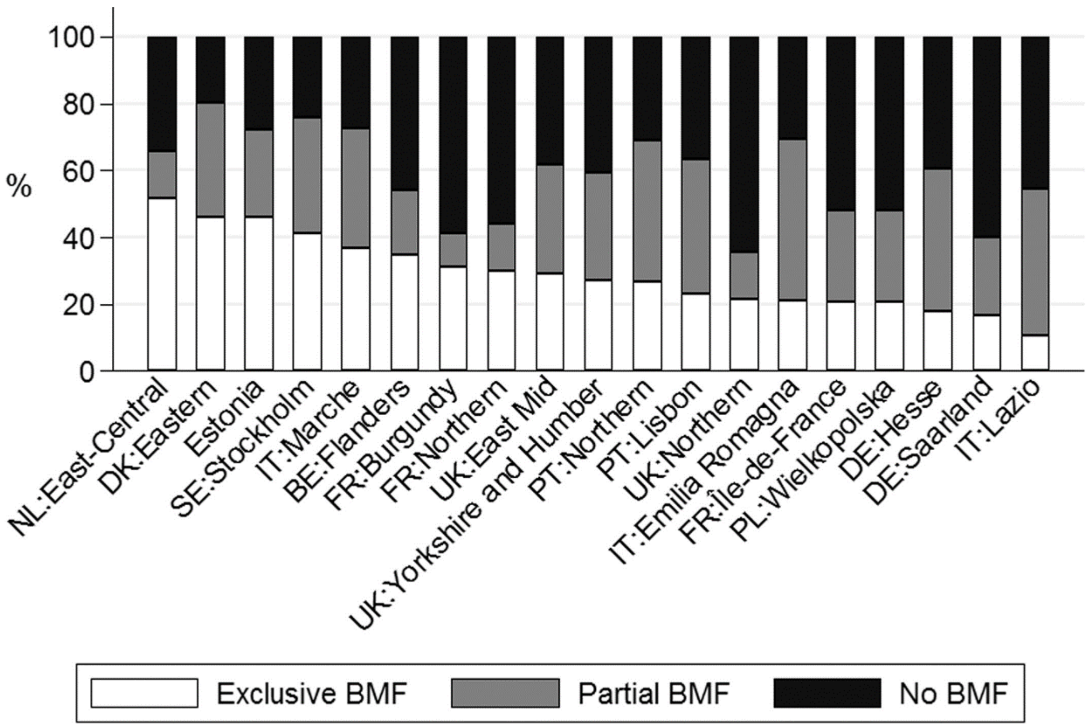
Across Europe, the *Models of Organising Access to Intensive Care for Very Preterm Births* (MOSAIC) study documented the overall BMF prevalence at discharge among VPT infants in eight European regions in 2003, which ranged from 19% in Burgundy (France) to 70% in Lazio (Italy), and exclusive BMF varied from 6% in the Northern region of Portugal to 29% in Trent (UK) (Figure 9) (137). This study showed a significant positive correlation with the national rates of breastfeeding for all infants. In particular, half of the Portuguese VPT infants were discharged on BMF (6% exclusive and 44% mixed) (137).



BE/FL, Belgium/Flanders; FR/BU, France/Burgundy; FR/IF, France/Ile-de-France; IT/LA, Italy/Lazio; NL/EC, Netherlands/East-Central; PL/WL, Poland/Wielkopolska-Lubuskie; PO/NO, Portugal/North; UK/TR, United Kingdom/Trent.

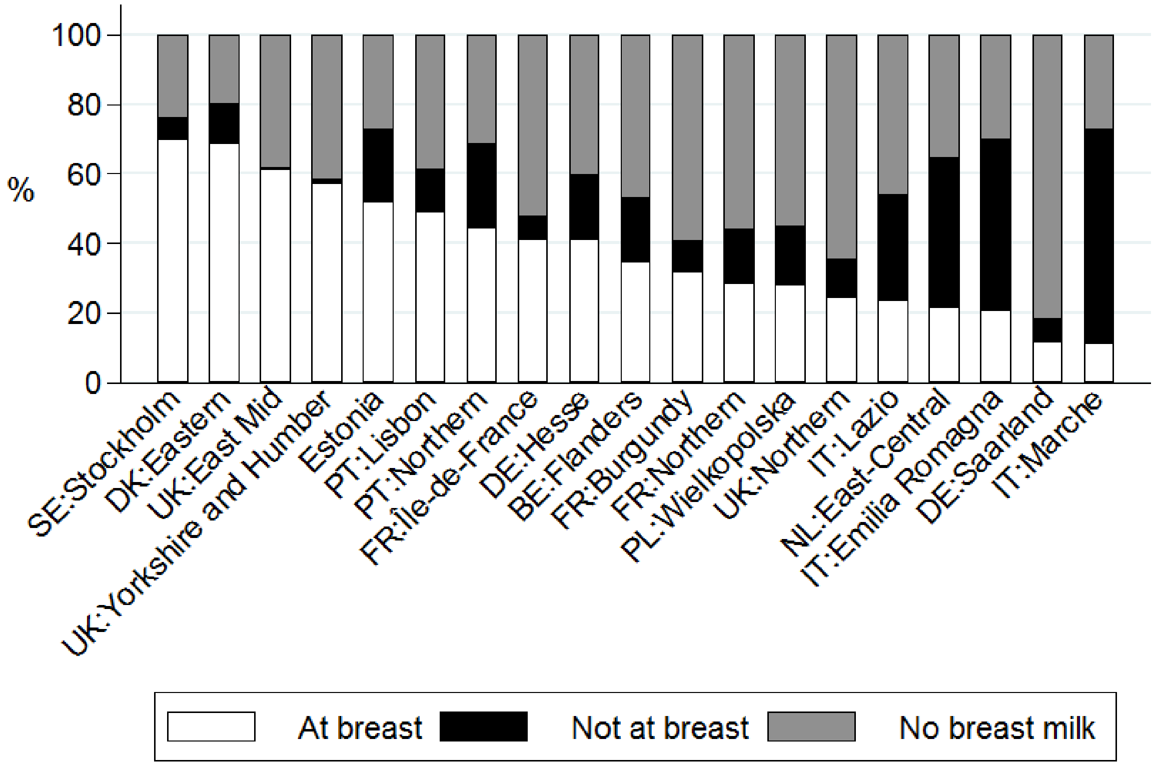
Figure 9. Breast milk feeding at discharge in very preterm infants in eight European regions, and overall national breastfeeding rates (black dots), in 2003. Reproduced from Bonet et al., 2011 (137).

Results from the EPICE cohort, providing data from 19 European regions (n=6 592 infants), showed that exclusive mother´s own milk feeding in the first 24 hours after the first enteral feed was administered to 37.5% of infants (138). At discharge, 58.0% of all infants received any BMF and 27.5% exclusively. Additionally, a wide variation between the regions and within countries was observed (Figure 10) (138). The Eastern region of Denmark presented the highest proportion of any BMF at discharge, with 80%, and the Northern region of the UK had the lowest proportion, at 36%. The East-central region of the Netherlands had the highest proportion of exclusive BMF at discharge, with 51.5%. In Portugal, 65% of infants received exclusive mother´s own milk in the first 24 hours after the first enteral feed (data not published), and nearly two-thirds of infants received breast milk at discharge and 25% exclusively (Figure 10) (138). As observed in Figure 11, among infants with any BMF at discharge, 68% were fed directly from the breast, which varied between 16% and 93% among the regions studied (almost 50% in Portuguese regions) (138).



BMF, Breast milk feeding. Countries: BE, Belgium; DE, Germany; DK, Denmark; FR, France; IT, Italy; NL, the Netherlands; PL, Poland; PT, Portugal; SE, Sweden; UK, the United Kingdom.

Figure 10. Breast milk feeding at discharge in very preterm birth across 19 European regions, in 2011/2012. Reproduced from Wilson et al., 2018 (138).



BE, Belgium; DE, Germany; DK, Denmark; FR, France; IT, Italy; NL, the Netherlands; PL, Poland; PT, Portugal; SE, Sweden; UK, United Kingdom.

Figure 11. Breast milk feeding directly at the breast at discharge in very preterm birth across 19 European regions, in 2011/2012. Reproduced from Wilson et al., 2018 (138).

Comparing the same regions participating in both the MOSAIC (2003) and the EPICE (2011/2012) studies, the prevalence of any BMF at discharge improved in all regions, except in Lazio (Italy); and exclusive BMF also increased over time, with the exception of Lazio (Italy) and Wielkopolska (Poland). In Portugal, there was a substantial increase in both any and exclusive BMF at discharge from 2003 to 2011/2012. Another Portuguese study, from 2013/2014, which included all level III NICUs located in the Northern region, showed that 96.7% of VPT infants (evaluated at 15-22 days after delivery) and 96.4% of full-term infants (in the puerperium period) received any BMF (139).

A study with data from the Swedish Neonatal Quality Register, using information from 2004 to 2013, found a decrease in the prevalence of exclusive BMF in extremely preterm infants (22-27 weeks) from 55% to 16%, as well as in VPT infants (28-31 weeks) from 41% to 34% (140).

Beyond the differences observed across countries and regions, there are also large disparities in BMF among neonatal units within the same country. Exclusive BMF at discharge varied by NICU from 53% to 83% in a prospective Danish cohort of preterm infants (141). The proportion of high-risk infants fed with exclusive human milk (mother's or donor's milk) ranged from 0% to 60% across centres in Italy (142). In the United States, variations from 35% to 71% were recorded when comparing low- versus high-use sites across the country (143). Finally, a recent study from France, using data from the EPIPAGE-2 cohort, revealed that 47% of all VPT infants received BMF at discharge, with proportions ranging from 21% to 84% among units (144).

Globally, rates of breastfeeding continuation for infants born VPT do not generally meet international recommendations. A prospective population-based cohort from Sweden showed that 79% of mothers were breastfeeding at two months, 62% at four, 45% at six, 22% at nine and 12% at twelve (145). Likewise, a study from Israel found that nearly 20% of infants received any BMF at least until six months (CA) (146), and another study from Sweden achieved a higher proportion, at 43% (147).

1.3.4. Determinants of breast milk feeding in very preterm infants

The low prevalence and short duration of BMF among VPT infants may be explained by several factors. Available research has shown that mothers who were not married, younger, foreign-born, had a lower educational level, were smokers, multiparous and did not attend prenatal care were less likely to BMF their infants (137, 145, 148-150). Furthermore, infants with lower gestational age, lower birth weight, severe neonatal morbidities and longer hospital stays were less likely to be fed with breast milk (137, 148, 149).

The EPICE cohort, using data from 19 European regions, has explored the maternal, obstetric and infant factors, as well as the maternal and neonatal unit policies that may influence BMF at hospital discharge (138). Primiparity, administration of antenatal corticosteroids, first enteral feed less than 24 hours after birth and mother's own milk at first enteral feed were positively associated with any BMF at discharge. Vaginal delivery, singleton birth and receiving mother's own milk at first enteral feed were associated with exclusive BMF. Additionally, this study demonstrated that units with a Baby-Friendly Hospital accreditation improved any BMF at discharge. On the other hand, units with protocols for BMF and units using donor milk had higher rates of exclusive BMF (138).

Numerous literature supports that the degree of promotion and support by NICU staff, as well as the unit's policies and practices also impact BMF rates among VPT infants (147, 151-155). The recently published results of the EPIPAGE-2 cohort also revealed that BMF at discharge, after adjustment for individual-level variables, was associated with the provision of kangaroo care (skin-to-skin contact) at any time during the first week of life, with policies supporting BMF initiation (BMF information systematically provided to mothers hospitalised for a potential preterm delivery and breast milk expression proposed within six hours after birth) and maintenance (availability of protocols for BMF and a special room for mothers to express) (144).

1.3.5. The challenges of providing breast milk feeding in very preterm infants

Providing BMF to hospitalized VPT infants is particularly challenging, as it requires the mother to express regularly until her child has acquired the capacity to suckle directly at the mother´s breast (156, 157). In the NICU setting, BMF is a complex task posing several logistic challenges, mainly due to mother-infant separation, with a negative impact on initiating milk expression in the immediate postpartum period and in maintaining the milk supply (156-159). Less than 30% of mothers can sustain their lactation to meet the needs of their infants when they are born VPT (155).

According to parents' perspectives, successful breast milk supply in the NICU depends on coherent and accurate knowledge about its techniques and benefits, the reinforcement of mothers' motivation, as well as alignment between the NICU's routines and the parents' needs (160). Parents perceived issues related to their own current breast milk supply experience as main facilitators and barriers simultaneously (Table 4) (160). The parental–professional relationship constituted the second group of facilitators, but the fourth of barriers. The characteristics of the NICU were more relevant as a barrier than as a facilitator (160). In Portugal, concerns related to inadequate milk supply, difficulties with expressing breast milk and physical separation from infants were identified by parents as the major barriers in providing breast milk to VPT infants in the NICU, while the contribution to infant growth and well-being, and the parent's knowledge about BMF benefits were the main facilitators (159).

This supports the importance of family-centred care and a family-friendly environment in NICUs that incorporate parents' needs, preferences and values, as well as stimulate their active participation and involvement in the infant's care (153, 158, 161-163). A recent cluster-randomised controlled trial, which aimed to analyse the effect of the Family Integrated Care (FICare) programme on infant and parent outcomes, demonstrated that exclusive BMF rate at discharge was higher for infants in the FICare group than those in the standard care group, and also found a decrease in the stress and anxiety of parents in the intervention group (164).

Thus, it is fundamental to study the role of general and local policies and practices that may overcome individual barriers and constraints to initiate and continue BMF in VPT infants.

Table 4. Facilitators and barriers to breast milk supply in neonatal intensive care units (NICUs), according to parents' expectations and experiences. Reproduced from Alves et al., 2013 (160).

	Facilitators Frequency (n)	**Barriers Frequency (n)**
Breast milk supply current experience	38	27
Nourishment and contribution to infant's growth and well-being	6[28–33]	
Support sense of 'normality'	6[28–33]	
Opportunity to hold and connect with infants	5[24 29–32]	
To learn about infant's and women's bodies and behaviours	5[24 29 31–33]	
To learn about techniques and strategies	5[24 29 31–33]	
Accurate/inaccurate knowledge regarding breast milk supply benefits	4[28 29 32 33]	2[29 30]
Awareness of infant vulnerability	3[28 29 32]	4[24 30–32]
To compensate the baby	3[31–33]	
Use of electric pump versus hand pump	1[28]	
Difficulties with pumping*		7[24 28–33]
Worries surrounding inadequate milk supply		6[24 28–30 32 33]
Delays in starting to express and supplying milk		4[24 28 29 31]
Desire for more rapid weight gain		2[28 32]
Feelings of failure		2[31 32]
Parents–professionals relationships	14	10
Positive reinforcement and feedback (motivation)	6[24 28 29 31–33]	
Provision of accurate information (guidance)	6[24 28 29 31–33]	
Confidence in healthcare providers	2[30 31]	
Staff perceptions of needs differ from those of parents		5[24 28 30–32]
Inconsistent information/conflicting advice		3[24 28 31]
Lack of expert advice		2[24 28]
Characteristics of NICU	11	20
Availability of peer counsellors	4[28 29 31 33]	
Availability/unavailability of sterile supplies	3[28 29 33]	1[28]
Comfortable/stressful NICU environment	3[28 29 31]	5[24 30–33]
Structured feeding routine	1[31]	3[24 31 32]
Physical separation from infants		4[24 28 30 31]
Lack of privacy		3[24 28 31]
Distance (home/hospital; NICU/maternity units)		2[24 30]
'Exclusion' of the father		1[31]
Inability of other family members to visit the infant		1[30]
Parents' social background and expectations	7	13
Parents' mutual commitment to provide breast milk	3[29–31]	
Existence/lack of social support	2[29 31]	3[28–30]
Hope that supplying breast milk will be easier once home	1[32]	
Take the decision before delivery	1[28]	
Competing time demands		3[24 29 30]
Lack of role models		3[28 29 33]
Separation from other family members/friends		3[24 30 31]
Low socio-economic status		1[31]

*Pain, transport of milk, levels of stimulation, feelings of exhaustion and frustration.

1.3.6. Short- and long-term benefits of breast milk feeding in very preterm infants

There is evidence regarding the short- and long-term health benefits of BMF for infants born at less than 32 weeks of gestation, namely, in decreasing multiple neonatal morbidity conditions related to prematurity, as well as in the improvement of neurodevelopmental outcomes (165). BMF significantly decreases the rate of necrotizing enterocolitis and is associated with a reduction of infections, bronchopulmonary dysplasia, retinopathy of prematurity and feeding intolerance in VPT infants (130, 156, 165-169). Additionally, BMF reduces the risk of hospital readmissions or emergency visits for subsequent illness (168).

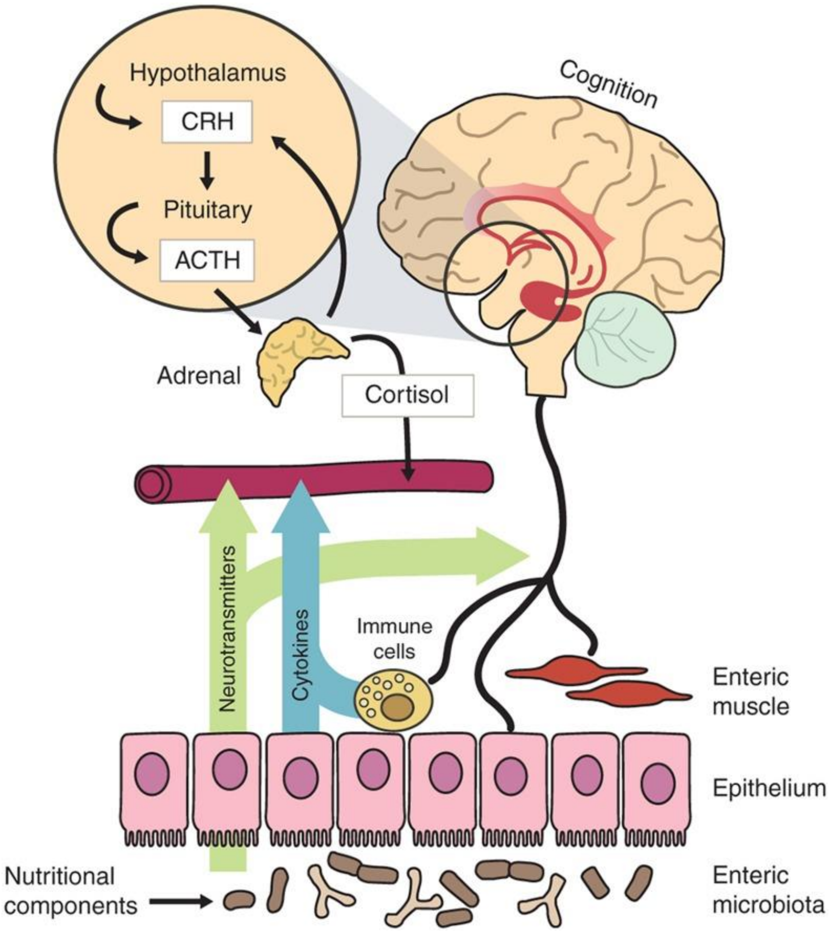
Children and young adults born VPT who received BMF during the neonatal period are less susceptible to infections and metabolic disorders, such as obesity and diabetes, as well as cardiovascular and respiratory diseases, and may have better health-related outcomes later in life (170-173).

1.3.6.1. The effect of breast milk feeding on neurodevelopmental and mental health

The potential effect of BMF on neurodevelopmental and mental health outcomes in children born before 32 weeks of gestation is an area of ongoing research. The evidence regarding its relationship is inconsistent and the mechanisms are still not fully understood (165, 174-176). Some observational studies found an independent positive association (177-181), while others have not (182-184).

Two cohorts of VPT infants in France, LIFT and EPIPAGE, found that any breastfeeding at discharge was associated with a decrease in the odds of suboptimal neurodevelopment at two and at five years of age, respectively (180). A randomized clinical trial of 363 very low birth weight (VLBW) infants found that the use of supplemental donor milk compared with preterm formula, as a supplement to a mother's own milk during hospitalization, did not improve neurodevelopment at 18 months of CA (185). Johnson and colleagues found that receiving breast milk during NICU admission was associated with a lower autism spectrum symptomatology in extremely preterm children at 11 years of age (186). More recently, a cohort study from Germany, which included 2 467 children born VLBW, showed that breastfeeding for at least three months was associated with lower parent-rated behavioural difficulty scores at five to six years of age, particularly for inattention/hyperactivity and conduct disorders (187).

The presence of biological components in breast milk, such as long-chain polyunsaturated fatty acids (LCPUFAs), especially docosahexaenoic acid and arachidonic acid, and human milk oligosaccharides, which are essential for an infant's brain development, might explain the association observed, as these components play an important role in neurogenesis and may modulate infant gut microbiota composition (188-191). Growing evidence supports the existence of a microbiome-gut-brain axis (Figure 12) (192). The microbiome is thought to interact with the brain through immunological, endocrine and neural pathways, although the exact mechanisms are not yet clear (192).



"*Gut microbiota may modulate brain function and development through immune signaling (e.g., pro- and anti-inflammatory cytokines, chemokines, and immune cells), endocrine, and neural pathways. Conversely, the brain may influence the gut through neurotransmitters that impact on immune function, and through alterations in cortisol levels, intestinal motility, and permeability. Nutritional components may exert effects on each of these communication pathways. ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone*." transcribed with permission from Keunen et al., 2015 (192).

Figure 12. The reciprocal interaction between gut microbiota and the brain. Reproduced from Keunen et al., 2015 (192).

A recent study including preterm infants (≤33 weeks) found that those who received exclusive breast milk for equal to or more than 75% of days of in-patient care presented higher connectivity in the fractional anisotropy (FA)-weighted connectome and increased FA within white matter tracts compared with the group who had less than 75% of days receiving exclusive BMF. The effect on structural connectivity and tract water diffusion parameters was greater with at least 90% exposure, suggesting a dose-effect response (Figure 13) (193). No significant group wise differences in brain volumes were observed (193).

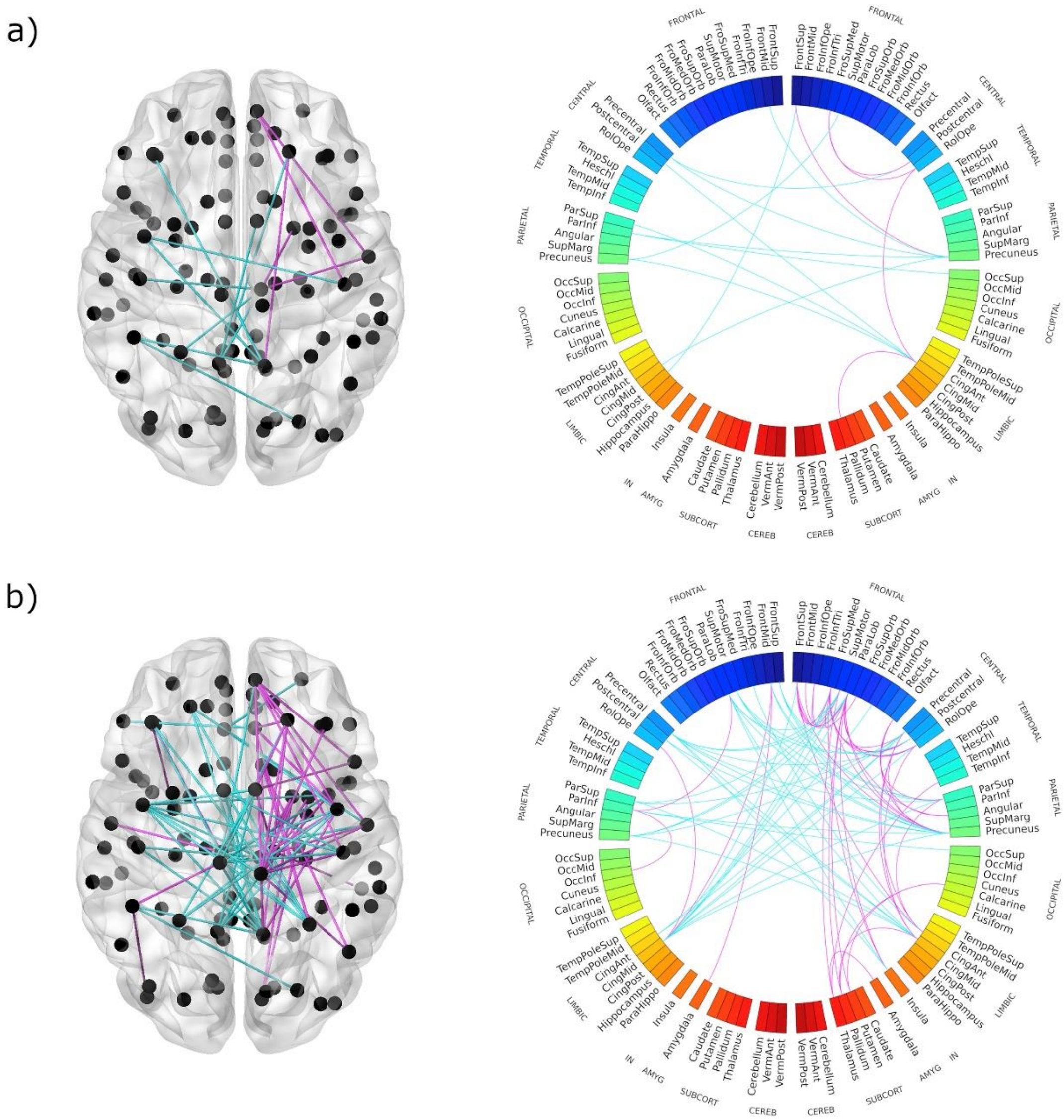


Figure 13. Network differences in the fractional anisotropy-weighted connectome for the two thresholds: ≥75% (a) and ≥90% (b). Inter-hemispheric connections are shown in blue, and intra-hemispheric connections in magenta. For visualization: anatomic left is on the right side of the image. Reproduced from Blesa et al., 2019 (193).

Another study demonstrated that VLBW/VPT infants receiving early breast milk exhibited significantly greater total brain volumes by term-corrected age, as well as higher volumes in the amygdala-hippocampus and cerebellum compared with formula-fed infants (194). Moreover, infants receiving breast milk also presented greater white matter microstructural organisation in the corpus callosum, posterior limb of internal capsule and cerebellum (194).

Therefore, the nutritional components of breast milk with immunomodulatory and/or anti-inflammatory effects may serve as neuroprotective agents. Overall, understanding the mechanisms and the impact of BMF practices in the medium- and long-term on neurodevelopmental and mental health outcomes of children born VPT merit further investigation.

2. RESEARCH OBJECTIVES

Providing BMF to VPT infants is a complex and challenging process. There is a wide disparity in BMF rates between and within countries that are not entirely explained by maternal and infant characteristics. These suggest that substantial gains are possible if the role of policies and practices operating in neonatal units is understood. Additionally, the research gap in the effect of BMF practices on the medium- and long-term health-related outcomes of children born VPT deserves further investigation.

Thus, this thesis aimed to study BMF practices in infants born VPT, and to prospectively assess the effect of such practices on neurodevelopmental and mental health outcomes during childhood. We intended to answer the following specific objectives:

1. To assess the influence of NICU policies and practices on BMF at hospital discharge among Portuguese VPT infants. *[Paper I]*

2. To describe the policies towards parental presence in European NICUs and test the hypothesis that liberal parental policies are associated with an increased likelihood of breastfeeding VPT infants at discharge from hospital. *[Paper II]*

3. To describe the prevalence and duration of exclusive and any BMF in VPT infants. *[Paper III]*

4. To determine the factors associated with BMF continuation until six months of age among breastfed VPT infants. *[Paper IV]*

5. To compare practices for managing mother's own milk in European NICUs. *[Paper V]*

6. To estimate the association between BMF initiation and duration with cognitive development at two years of CA in children born VPT. *[Paper VI]*

7. To estimate the association of BMF practices with behavioural and emotional outcomes at preschool age in children born VPT. *[Paper VII]*

3. METHODS

This thesis was developed with a unique European research infrastructure set up by the "*Effective Perinatal Intensive Care in Europe*" (EPICE) project (www.epiceproject.eu), which created a birth cohort with over 10 thousand VPT births with the active engagement of a research consortium comprised of scientific teams from 19 regions in 11 European countries (66). Using both quantitative and qualitative approaches, the EPICE project investigated the use of evidence-based practices for the care of VPT infants, and explored the associations between evidence-based care and their health and developmental outcomes, at three levels: patient, unit and regional.

The EPICE project aimed to improve the survival, and long-term health and development of VPT infants by ensuring that available medical knowledge is translated into effective perinatal care. To achieve this goal, this project constituted a *cohort study* of VPT births (the EPICE cohort) with a gestational age less than 32 weeks in 2011/2012. This knowledge base was completed through further surveys: a *case study* of recommendations from regional governance bodies and professional societies about interventions for VPT infants; a *unit study* of maternity and neonatal units about policies and practices related to VPT infants; and a *qualitative study* with in-depth interviews of doctors and nurses in neonatal units on processes for changing policies and practices.

The specific objectives of this thesis were accomplished through the analysis of data obtained from both cohort and unit studies. A general description of these studies is provided below. Additional information regarding the EPICE project was published elsewhere, at the European (66) and national levels (195).

The selection of eligible participants and the statistical analyses depend on the specific objectives of each manuscript. Thus, they are described in detail in the respective methods sections.

3.1. The EPICE cohort

The EPICE cohort is a population-based prospective study that includes all births from 22^{+0} to 31^{+6} weeks of gestation during a period of 12 months in 2011/2012 (six months in France), in 19 European regions (Figure 14). Regions were selected with respect to geographic and organisational diversity, feasibility and sample size considerations. The EPICE study in Portugal involved all of the public units from two regions, the Northern and Lisbon and Tagus Valley (n=27), as well as three private units in Lisbon. In 2011 and 2012, 68.6% and 66.3% of all VPT births in Portugal occurred in these two geographical regions, respectively.

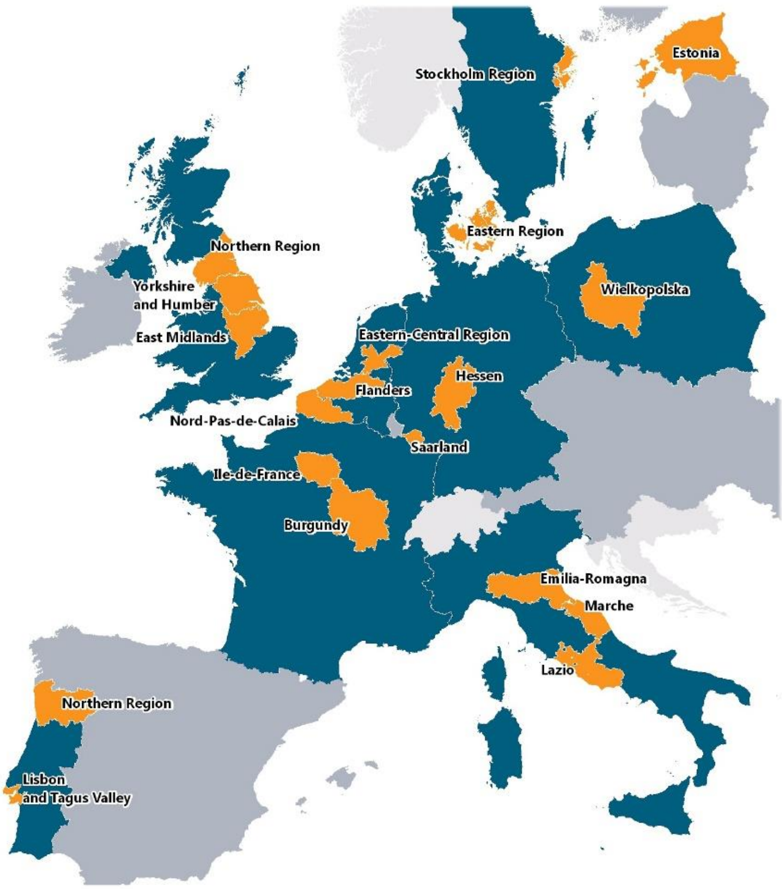


Figure 14. Regions included in the EPICE project. [Flanders in Belgium; the Eastern Region of Denmark; Estonia (entire country); Burgundy, Ile-de-France and the Northern regions of France; Hesse and Saarland in Germany; Emilia-Romagna, Lazio and the Marche regions of Italy; the Central and Eastern regions of The Netherlands; Wielkopolska in Poland; Lisbon and Tagus Valley and the Northern region of Portugal; the East Midlands, Northern and Yorkshire and Humber regions of the UK; and the Stockholm region in Sweden.]

3.1.1. Participants

During the study period, 10 329 VPT births were included and, of those, 815 were terminations of pregnancy, 1 614 were stillbirths and 7 900 were live births. Of the 6 792 infants discharged alive (86.0%), 6 761 survived to two years, of which 4 426 (65.5%) participated in the two-year CA follow-up. A subsequent follow-up of the cohort was performed at five years of age, which was integrated in the new European research project "*Screening to Improve Health in Very Preterm Infants in Europe*" (SHIPS), and 3 689 children were evaluated (54.6%) (66).

The EPICE-Portugal cohort recruitment occurred between 1st June 2011 and 31st May 2012, and identified 974 VPT births, of which 724 were live births, and with 607 infants discharged alive (83.8%). A written informed consent for the follow-up evaluations was obtained for 544 (89.6%) infants (of the 607 eligible). Two infants died after being discharged from the NICU (both before two years of age). Besides the follow-up waves conducted at the European level, the EPICE-Portugal cohort has been evaluated more frequently: at 12 months (n=456), at two years of CA (n=408), at three (n=466), at four (n=445) and at seven years of age (n=440). The eight-year follow-up is currently ongoing.

For the purposes of this thesis, data collected from baseline to the two-year follow-up, as well as data gathered at the three-year follow-up from the EPICE-Portugal cohort, were used.

3.1.2. Data collection

Perinatal data on maternal characteristics, pregnancy complications, birth and the neonatal course were abstracted from medical records in obstetric and neonatal units using a pretested standardized questionnaire with common definitions, which was completed by medical staff until discharge from the hospital and later verified by the research team (66).

At two years of CA, parents completed a questionnaire on health, neurodevelopmental outcomes, growth, breastfeeding, health service use and socio-demographic information (66). The questionnaire was developed in English, and translated into the different national languages, back translated into English and pretested in all regions by the research team. The evaluation included a validated developmental assessment tool, the *Parent Report of Children's Abilities-Revised for preterm infants* (PARCA-R), which comprises the short version of the *MacArthur Communicative Development Inventory* (CDI) for language abilities (196, 197). Four questions on language acquisition were developed for countries where the CDI was not available. The *Ages & Stages Questionnaire* (ASQ) was used in French regions, as this instrument was validated in France, whereas the PARCA-R was not (198).

In the EPICE-Portugal cohort, a structured questionnaire answered by the parents was applied at the three-year follow-up, using a computer-assisted telephone interview, by trained interviewers. This questionnaire focused on socio-demographic characteristics, health, growth, type of feeding (including breastfeeding) and health service use. Additionally, behavioural and emotional problems were measured using the *Child Behaviour Checklist for ages 1½-5 years* (CBCL/1½-5) (199, 200). The parents were asked to complete and return the questionnaire, which was sent by mail.

3.2. Unit study

The survey of maternity and neonatal units gathered information from the hospitals where the infants were born and hospitalized, using a structured questionnaire developed by the EPICE consortium and pretested in all countries with obstetricians and neonatologists working outside the study regions.

The questionnaire was completed by the head of each maternity and neonatal unit in the spring of 2012, and included information on the structural characteristics of the units (level of specialization), their activity levels in 2011, policies, protocols and practices related to selected medical interventions, ethical decisions, decision making processes and the existence of health-care quality monitoring systems. Neonatal units with at least 10 VPT admissions per year and their associated maternity units were included in this unit study.

There were 532 maternity hospitals and 270 neonatal units in the EPICE regions. Among the eligible units, the response rate was higher than 90% (134/135 for neonatal units and 123/134 for maternity units) (66). In Portugal, all of the questionnaires from eligible units (17 neonatal units and 17 maternity units) were obtained.

3.3. Ethics

Each country team received ethical authorizations from local regional and/or hospital ethics boards, as required by national legislation. Informed consent was obtained from all parents or legal representatives included in the follow-up study. The European study was approved by the French Advisory Committee on Use of Health Data in Medical Research, and by the French National Commission for Data Protection and Liberties. In Portugal, the EPICE study was approved by the Ethics Committee of the participating hospitals and by the Portuguese Data Protection Authority (authorization 7426/2011).

4. RESULTS

This thesis resulted in the following manuscripts:

Paper I. Rodrigues C, Severo M, Zeitlin J, Barros H; on behalf of the Portuguese EPICE Network. *The type of feeding at discharge of very preterm infants: neonatal intensive care units policies and practices make a difference*. Breastfeed Med 2018; 13(1):50-59. Doi: 10.1089/bfm.2017.0135.

Paper II. Cuttini M, Croci I, Toome L, Rodrigues C, Wilson E, Bonet M, Gadzinowski J, Di Lallo D, Herich LC, Zeitlin J; the EPICE Research Group. *Breastfeeding outcomes in European NICUs: impact of parental visiting policies*. Arch Dis Child Fetal Neonatal Ed. 2019; 104(2):F151-F158. Doi: 10.1136/archdischild-2017-314723.

Paper III. Rodrigues C, Teixeira R, Fonseca MJ, Zeitlin J, Barros H; on behalf of the Portuguese EPICE Network. *Prevalence and duration of breast milk feeding in very preterm infants: a 3-year follow-up study and a systematic literature review.* Paediatr Perinat Epidemiol 2018; 32(3):237-246. Doi: 10.1111/ppe.12457.

Paper IV. Bonnet C, Blondel B, Piedvache A, Wilson E, Bonamy AE, Gortner L, Rodrigues C, van Heijst A, Draper ES, Cuttini M, Zeitlin J; the EPICE Research Group. *Low breastfeeding continuation to 6 months for very preterm infants: a European multiregional cohort study*. Matern Child Nutr 2019; 15(1):e12657. Doi: 10.1111/mcn.12657.

Paper V. Rodrigues C, Zeitlin J, Wilson E, Toome L, Cuttini M, Maier RF, Pierrat V, Barros H; the EPICE Research Group. *Managing mother's own milk for very preterm infants in neonatal units in 11 European countries.* Acta Paediatr. 2020 Aug 4. Doi: 10.1111/apa.15518.

Paper VI. Rodrigues C, Zeitlin J, Zemlin M, Wilson E; Pedersen P, Barros H; the EPICE Research Group. *Breast milk feeding and cognitive development at 2 years of corrected age in children born very preterm: a European cohort study. [Manuscript submitted]*

Paper VII. Rodrigues C, Zeitlin J, Carvalho AR, Gonzaga Z, Henrique Barros; on behalf of the Portuguese EPICE Network. *Behavioural and emotional outcomes at preschool age in children born very preterm: the role of breast milk feeding practices. [Manuscript submitted]*

4.1. PAPER I

The type of feeding at discharge of very preterm infants: neonatal intensive care units policies and practices make a difference

Rodrigues C, Severo M, Zeitlin J, Barros H; on behalf of the Portuguese EPICE Network.

Breastfeed Med 2018; 13(1):50-59. Doi: 10.1089/bfm.2017.0135.

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The Type of Feeding at Discharge of Very Preterm Infants: Neonatal Intensive Care Units Policies and Practices Make a Difference

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on behalf of the Portuguese EPICE (Effective Perinatal Intensive Care in Europe) Network*

Abstract

Objective: To assess the influence of neonatal intensive care units (NICUs) on feeding practices at discharge of Portuguese very preterm infants.

Materials and Methods: We analyzed data from 580 very preterm infants (<32 gestational weeks) discharged home from NICUs of two Portuguese regions and enrolled during 2011–2012 in *Effective Perinatal Intensive Care in Europe* population-based cohort. Maternal and infant characteristics were abstracted from medical records, and heads of NICUs provided the units characteristics. Feeding at discharge was classified as exclusive formula, exclusive breast milk or mixed, and differences among NICUs were obtained by comparison with pooled geometric mean odds of all NICUs, using multinomial logistic regression. Median odds ratios (MOR) were calculated to quantify variability among NICUs using multilevel logistic regression.

Results: At discharge, 25.2% very preterm infants were exclusively on breast milk, 34.1% exclusively on formula, and 40.7% had mixed feeding, with a wide variation among NICUs. Exclusive breast milk increased in NICUs that had higher numbers of admissions, provided parents eating facilities, and by having designated members to support mothers who were breastfeeding. The individual NICU odds of mixed versus exclusive formula feeding ranged from 0.36 to 2.07 and for exclusive breast milk versus exclusive formula ranged from 0.16 and 5.11. Adjusting for individual and unit characteristics, heterogeneity across NICUs remained evident, being the MOR 1.33 for mixed feeding and 1.35 for exclusive breast milk.

Conclusions: NICUs influence feeding practices independently of individual characteristics, highlighting the importance of institution-based interventions to promote breast milk.

Keywords: breast milk, breastfeeding, intensive care units, neonatal, infant, premature, EPICE project

Introduction

There is an international consensus on the advantages of exclusive breast milk feeding from birth to 6 months of life,[1] a recommendation that is extended to preterm infants.[2] However, the prevalence of breast milk feeding in very preterm infants (<32 gestational weeks) is lower than among term infants,[3] even the health benefits being well established for these infants, both in preventing life-threatening conditions and in promoting development.[2,4–6]

Moreover, across Europe, there is a large variation in breast milk feeding, despite current clinical guidelines and public health policy.[7] The MOSAIC study documented a large variation in breast milk feeding at discharge among very preterm infants in eight European regions in 2003, ranging from 19% in Burgundy (France) to 70% in Lazio (Italy), and showed a significant positive correlation with the national rates of breastfeeding for all infants.[3] In that study, 50% of Portuguese very preterm infants were discharged on breast milk (6% exclusive and 44% mixed).[3]

Available research has shown that mothers who were not married,[8,9] younger,[3,8,9] of a lower social class,[10,11] smokers,[10] multiparous,[3] and not attending prenatal care[12] were less likely to provide breast milk to their infants. Infants with lower

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*Portuguese EPICE Network members are listed in "Members of the EPICE-Portugal Network" section at the end of the article.

gestational age,[3,9] lower birth weight,[3] bronchopulmonary dysplasia,[3] and longer hospital stay[13] were less likely to be fed with breast milk.

Significant variations in the prevalence of breast milk feeding have also been observed among neonatal intensive care units (NICUs),[9,12–15] which could reflect suboptimal use of evidence-based care,[16] with different attitudes and practices operating locally and influencing the initiation and maintenance of breast milk feeding beyond individual factors.[17,18] One previous study showed that NICUs with better work environments, educated nurses, and providing breastfeeding support by nurses have higher rates of infants discharged on human milk.[15]

Thus, we aimed to assess the influence of NICUs characteristics on feeding practices at discharge among Portuguese very preterm infants.

Materials and Methods

Study design and participants

Data were collected as part of the Portuguese participation in the study *Effective Perinatal Intensive Care in Europe* (EPICE), that recruited a population-based prospective cohort of very preterm infants (22–31 completed weeks of gestational age) born in 2011–2012, in 19 European regions.[16]

In Portugal, all 724 very preterm live births that occurred between June 2011 and May 2012 in the two participating regions—North and Lisbon and Tagus Valley—were documented.[19] For analysis, only infants born in public maternity units ($n = 703$) and discharged home were considered ($n = 581$; 115 infants died and 7 infants were discharged to institutions). Infants were admitted to the NICU where they spent their first consecutive 48 hours of life.[3] We excluded one NICU with a single admission over the study period. The final sample comprised 580 infants admitted to 16 NICUs, with a median infants per unit of 29 (range 6–112).

Data collection

Data on maternal, pregnancy, infant, and clinical characteristics were abstracted from medical records by local healthcare professionals, using a pretested standardized questionnaire,[19] and later verified by the research team.

Data on NICU characteristics were obtained using a structured questionnaire, completed by the head of the unit or a coworker(s), to assess information about how the care of very preterm infants was organized in the unit, including questions about admissions and activity, services and equipment, staffing, protocols/guidelines, and perinatal practices.

Outcome

Feeding practices at discharge were classified in three categories: exclusive formula (no breast milk); exclusive breast milk (receiving only maternal breast milk, without differentiating between mother's own milk and donor milk); or mixed (a combination of breast milk and formula). Breast milk was considered regardless of the feeding method: directly from the breast, bottle, tube, or cup.

Individual-level variables

Gestational age was based on the best estimate of the obstetrical team, using information on ultrasound measures and the last menstrual period. Maternal hypertensive disorders comprised chronic hypertension, gestational hypertension, preeclampsia, eclampsia, or HELLP syndrome. Bronchopulmonary dysplasia was defined as oxygen dependence or respiratory support (including nasal cannula, nasal continuous positive airway pressure, or mechanical ventilation) at 36 weeks of postmenstrual age. Severe brain injury was considered when there was a diagnosis of intraventricular hemorrhage grades III or IV using the classification defined by Papile et al.[20] and/or cystic periventricular leukomalacia, which was recorded only if cystic abnormalities were present on ultrasound or CT scan. Necrotizing enterocolitis was considered if stage II or III of Bell's classification was verified. Congenital anomalies included major congenital anomalies at birth and/or minor congenital anomalies defined as those considered reportable to EUROCAT.[21]

Portuguese infants were georeferenced according to their home address using the ArcGIS Online World Geocoding Service and Google Maps, and it was possible to do so accurately for 574 (99.0%) infants. Neighborhood socioeconomic deprivation was assessed using the European Deprivation Index (EDI), used to classify small areas according to their level of socioeconomic deprivation.[22] The EDI classes were attributed to participants using ArcGIS version 10.4.1 by a point-in-polygon overlay operation. The EDI score was categorized in quintiles of increasing deprivation (1-least to 5-most deprived). The EDIs of England, Spain, and France were used for the four participants who resided in these countries. No EDI quintile could be attributed to two participants: one residing in Scotland and another in Angola. More details about the formula of EDI construction in those countries are reported elsewhere.[22]

Neonatal unit-level variables

The unit variables were selected based on previous research showing the characteristics that could potentially influence the breast milk feeding outcomes[23,24] and on the characteristics supporting family-centered care and family–friendly environment approaches.[18,25,26] Thus, the unit variables covered four specific NICUs characteristics: (1) general aspects of the NICU (e.g., number of admissions, level of care); (2) policies toward parents (e.g., kangaroo care, parents were allowed to spend the night in the NICU); (3) facilities available in the intensive care unit area (e.g., a room for parents to relax and talk, a room specifically for breast milk expression and/or breastfeeding); and (4) breastfeeding-related characteristics (e.g., *Baby-Friendly Hospital Initiative* accreditation, written protocol available).

As the specialization of units by level of care varies internationally, we categorized it as level II and III, according to Portuguese guidelines, which consider the hospital services and grade, being level II defined as medium intensive care (often termed "perinatal support unit") and level III as high-intensive care (often termed "differentiated perinatal support unit"). Baby-Friendly Hospital Initiative accreditation[27] variable was categorized as: (1) no accreditation; (2) in process of accreditation; and (3) maternity unit or both maternity and neonatal units accredited.

The variable "designated staff in the unit to support mothers expressing or breastfeeding" was considered if the unit had a healthcare professional with certified training in breastfeeding/lactation (e.g., lactation consultant/feeding coordinator) available, whose role is supporting mothers expressing or breastfeeding. Kangaroo care policies were based on the opportunity offered by the unit for parents to hold their baby close to their chest, skin-to-skin, categorized as offered routinely, sometimes, only on request, or generally no, and were recorded separately for mothers and fathers.

Ethical approval

The study was approved by the Portuguese Data Protection Authority (authorization 7426/2011) and by the Ethics Committee of each participating hospital.

Statistical analysis

Feeding practices at discharge by NICU were compared with the proportions in the whole sample, using the Chi-square goodness of fit test or the Fisher exact test, as appropriate. To evaluate differences among NICUs, we compared each NICU with the overall effect obtained as the pooled geometric mean odds of all NICUs, using the deviation contrast method.[28] Crude odds ratios (OR) and respective 95% confidence intervals were estimated using multinomial logistic regression, comparing mixed versus exclusive formula and exclusive breast milk versus exclusive formula, considering that the outcome has three categories.

Feeding practices at discharge by maternal, infant, and NICUs characteristics were described as counts and proportions for categorical variables, and median and 25–75 percentiles (P25–P75) for continuous variables. Proportions were compared using the Chi-square test and medians using the Kruskal–Wallis test for individual characteristics.

Multilevel mixed-effects multinomial logistic regression was fitted for each NICU characteristic with a random effect by NICU. The likelihood ratio test was used to compare the model with and without each NICU characteristic to evaluate the respective association with feeding practices at discharge. This comparison was provided if at least 2 of the 16 NICUs displayed each category of the characteristic considered.

A median odds ratio (MOR) was calculated to quantify the magnitude of variability, and can be conceptually described as quantifying the variation between clusters (second-level variation) by comparing two individuals from two randomly chosen different clusters. Thus, considering two infants with the same covariates, chosen randomly from two different NICUs, the MOR is the median value of the OR between the infant in the NICU with the highest breast milk feeding proportion and the infant in the NICU with the lowest breast milk feeding proportion. The MOR is equal to 1 (meaning no differences between clusters) or greater, and a greater variation between NICUs results in a larger MOR.[29,30]

We first estimated a null model, which only included a random intercept without any exposure variables. Then, we included maternal and infant characteristics in the model (Model 1) to assess the extent to which variability between NICUs was explained by individual characteristics. Afterward, additional models were computed incorporating each specific group of NICU characteristics as a block: (1) general aspects; (2) policies toward parents; (3) facilities available in the intensive care unit area; and (4) breastfeeding-related characteristics. NICUs characteristics included in each block were only the ones that were strongly associated with the variance between NICUs based on interval odds ratio (IOR) estimations calculated for each NICU characteristic (Supplementary Table S1; Supplementary Data are available online at www.liebertpub.com/bfm). The IOR was defined as the interval centered on the median of the distribution comprising 80% of the values of the odds ratio (IOR-80). If the interval does not contain the value 1, it indicates that the effect of the NICU characteristic considered accounts for a strong amount of the variance between NICUs.[30]

We calculated the relative increase of the variance between NICUs when moving from $\tau_0^{(1)}$ to $\tau_0^{(2)}$ $[(\tau_0^{(1)}-\tau_0^{(2)})/(\tau_0^{(1)})]$, where $\tau_0^{(1)}$ and $\tau_0^{(2)}$ were the variance of random effects of Model 1 and of each other model, respectively. The proportion of explained variance corresponds to the proportion of between-NICUs variance that could be explained by the variables selected. It is negative when the variance between NICUs increases, and it is positive when the difference decreases after adjustment. To evaluate how NICUs characteristics influence the variability between units independently of the individual level, we established the model adjusted for individual characteristics as the reference.

Analysis was performed using STATA 14.0 software (Stata Corporation, College Station, TX) or R version 3.2.3 using the MASS package.

Results

Feeding at hospital discharge was 25.2% exclusive breast milk, 34.1% exclusive formula, and 40.7% mixed feeding. As shown in Figure 1, feeding practices at discharge varied significantly among Portuguese NICUs, ranging from 3.3% to 50.0% for exclusive breast milk, 16.7–50.9% for exclusive formula, and from 21.4% to 61.5% for mixed feeding. Six of the 16 NICUs presented proportions of feeding practices significantly different from those observed in the total sample, but the two Portuguese regions, although they are administered by separate health authorities, presented similar results (26.7% North versus 24.0% Lisbon and Tagus Valley for exclusive breast milk; 43.3% North versus 38.7% Lisbon and Tagus Valley for mixed).

The individual NICU odds of mixed versus exclusive formula feeding compared with the pooled geometric mean odds are presented in Table 1 and ranged from 0.36 to 2.07 showing a wide heterogeneity. For 2 of the 16 NICUs, the differences were statistically significant. The odds for exclusive breast milk versus exclusive formula varied between 0.16 and 5.11 showing an even wider heterogeneity, with four NICUs being significantly different from the pooled geometric mean odds.

Table 2 summarizes feeding practices at discharge according to maternal and infant characteristics. The median length of hospital stay was greater in infants who received exclusive formula (64 days, P25: 47 – P75: 92; versus 47 days for mixed, P25: 34.5 – P75: 63; versus 46 days for exclusive breast milk, P25: 34 – P75: 63, $p < 0.001$).

Table 3 shows the prevalence of feeding practices at discharge considering NICU characteristics. In general, the units were very similar regarding the evaluated items. For example, all units allowed parents to stay with their baby as much as they wanted in each visit and routinely offered kangaroo care to the mother. Only one NICU reported to offer kangaroo care to the father sometimes. However, infants who were

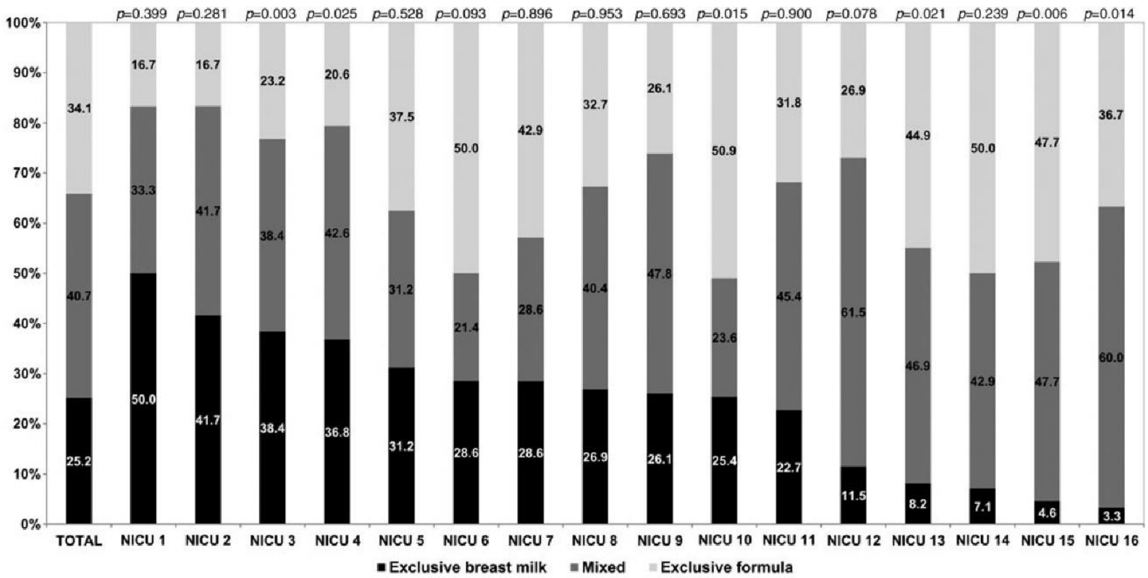

FIG. 1. Distribution of feeding practices at discharge in very preterm infants, by NICU, Portugal, 2011–2012. *p*-Values for the comparison of each unit with the total sample. If there was a transfer, infants were assigned to the NICU where they spent the first 48 hours of life. NICU, neonatal intensive care unit.

hospitalized in NICUs, which had a designated staff member to support mothers expressing or breastfeeding, had higher proportions of exclusive breast milk (30.7% versus 10.3%, $p < 0.001$), as was the case for NICUs that provided facilities for parents to heat food and/or make drinks (30.3% versus 15.9%, $p = 0.002$). On the contrary, infants who were hospitalized in NICUs, which provided a bathroom with a shower for parents, had lower proportions of exclusive breast milk (17.9% versus 32.4%, $p < 0.001$). NICUs that had higher numbers of admissions in 2011 presented higher proportions of exclusive breast milk (29.4% for ≥350 admissions versus 18.6% for <350, $p = 0.032$). Two NICUs reported use of human bank milk/donor's milk, one offered milk to infants with less than 32 gestational weeks and the other only to infants with less than 28 weeks.

Table 4 provides results from the random intercept model. After adjustment on maternal and infants characteristics, the MOR comparing mixed feeding with exclusive formula was 1.62, showing significant variation between NICUs. These variations decreased in Model 2 (1.55) and achieved a higher effect in Model 3 by adding the variable bathroom with a shower for parents (1.35), with an explained variance of 60.0%, without further changes, resulting from the addition of designated staff member to support mothers expressing or breastfeeding to Model 4 (1.33). When comparing exclusive breast milk with exclusive formula, the MOR results adjusted for maternal and infant characteristics revealed larger heterogeneity across NICUs (2.38). In Model 2, the variability between NICUs decreased to 2.23, a change associated with an explained variance of 11.5%. In Model 3, the additional adjustment resulted in an attenuation of the MOR estimate (1.88) with an explained variance that increased to 44.9%. Finally, we obtained 87.5% of the explained variation by adding the variable designated staff to support mothers expressing or breastfeeding (MOR = 1.35).

Discussion

In this first large sample of Portuguese very preterm infants representing approximately two-thirds of the national very preterm births during the study period, the overall prevalence of any breast milk feeding at discharge was 65.9%, ranging

Table 1. Odds of Exclusive Formula Versus Mixed and Versus Exclusive Breast Milk Feeding at Discharge in Portuguese Very Preterm Infants

	Mixed versus exclusive formula	*Exclusive breast milk versus exclusive formula*
	Crude OR (95% CI)	
NICU 1	1.66 (0.17–15.91)	5.11 (0.60–43.64)
NICU 2	2.07 (0.44–9.84)	4.26 (0.88–20.51)
NICU 3	1.37 (0.80–2.34)	2.82 (1.59–4.98)
NICU 4	1.72 (0.89–3.31)	3.04 (1.51–6.14)
NICU 5	0.69 (0.30–1.59)	1.42 (0.60–3.34)
NICU 6	0.36 (0.14–0.91)	0.97 (0.40–2.35)
NICU 7	0.55 (0.10–3.01)	1.14 (0.21–6.27)
NICU 8	1.02 (0.53–1.98)	1.40 (0.66–2.96)
NICU 9	1.52 (0.58–4.01)	1.70 (0.56–5.18)
NICU 10	0.38 (0.20–0.76)	0.85 (0.43–1.70)
NICU 11	1.18 (0.46–3.04)	1.22 (0.39–3.76)
NICU 12	1.89 (0.79–4.55)	0.73 (0.20–2.71)
NICU 13	0.87 (0.47–1.60)	0.31 (0.11–0.89)
NICU 14	0.71 (0.25–2.04)	0.24 (0.03–1.78)
NICU 15	0.83 (0.44–1.56)	0.16 (0.04–0.66)
NICU 16	1.36 (0.64–2.88)	0.16 (0.02–1.08)

A comparison of each individual NICU with the total sample. NICUs (where infants spent their first consecutive 48 hours of life). Reference class: Each NICU was compared to the overall effect obtained as the pooled geometric mean odds of all NICUs odds.

NICU, neonatal intensive care unit; OR, odds ratio; 95% CI, 95% confidence interval.

Table 2. Feeding Practices at Discharge According to Maternal, Pregnancy, Infant, and Clinical Characteristics

	Feeding practices at discharge (n = *580*)			
Characteristics	*Exclusive formula* (n = *198*), n (*%*)	*Mixed* (n = *236*), n (*%*)	*Exclusive breast milk* (n = *146*), n (*%*)	p
Maternal				
Age (years)				
≤24	44 (45.4)	34 (35.0)	19 (19.6)	0.170
25–29	44 (35.2)	47 (37.6)	34 (27.2)	
30–34	55 (29.0)	87 (45.8)	48 (25.3)	
≥35	55 (32.7)	68 (40.5)	45 (26.8)	
Country of birth				
Portugal	153 (32.2)	199 (41.9)	123 (25.9)	0.172
Other	40 (42.1)	35 (36.8)	20 (21.0)	
Parity				
Primiparous	123 (34.3)	151 (42.1)	85 (23.7)	0.627
Multiparous	75 (34.2)	85 (38.8)	59 (26.9)	
Neighborhood socioeconomic deprivation				
1 (Least deprived)	52 (29.2)	76 (42.7)	50 (28.1)	0.425
2	34 (31.8)	51 (47.7)	22 (20.6)	
3	34 (37.0)	35 (38.0)	23 (25.0)	
4	33 (36.8)	34 (37.8)	23 (25.6)	
5 (Most deprived)	44 (41.9)	36 (34.3)	25 (23.8)	
Pregnancy				
Multiple pregnancy				
No	147 (36.4)	146 (36.1)	111 (27.5)	0.003
Yes	51 (29.0)	90 (51.1)	35 (19.9)	
Intrauterine growth restriction				
No	157 (33.5)	194 (41.4)	118 (25.2)	0.513
Yes	41 (38.7)	38 (35.8)	27 (25.5)	
Hypertensive disorders				
No	149 (33.2)	189 (42.1)	111 (24.7)	0.369
Yes	48 (37.5)	45 (35.2)	35 (27.3)	
Premature rupture of membranes (before onset of labor)				
No	139 (34.8)	158 (39.5)	103 (25.8)	0.543
Yes	55 (31.2)	78 (44.3)	43 (24.4)	
Antenatal steroids				
No	22 (53.7)	13 (31.7)	6 (14.6)	0.020
Yes	175 (32.6)	223 (41.5)	139 (25.9)	
Mode of delivery onset				
Spontaneous	94 (31.9)	129 (43.7)	72 (24.4)	0.299
Induced/Caesarean before labor	104 (36.5)	107 (37.5)	74 (26.0)	
Mode of delivery				
Vaginal/instrumental	51 (31.9)	67 (41.9)	42 (26.2)	0.775
Caesarean	147 (35.0)	169 (40.2)	104 (24.8)	
Infants				
Sex				
Male	113 (34.1)	135 (40.8)	83 (25.1)	0.998
Female	85 (34.1)	101 (40.6)	63 (25.3)	
Gestational age at birth (weeks)				
24–27	76 (49.7)	47 (30.7)	30 (19.6)	<0.001
28–29	53 (33.8)	62 (39.5)	42 (26.8)	
30–31	69 (25.6)	127 (47.0)	74 (27.4)	
Birth weight (g)				
<1,000	94 (47.5)	67 (33.8)	37 (18.7)	<0.001
1,000–1,499	73 (27.8)	113 (43.0)	77 (29.3)	
≥1,500	31 (26.0)	56 (47.1)	32 (26.9)	
Apgar score at 5 minutes				
≤7	51 (45.5)	39 (34.8)	22 (19.6)	0.015
≥8	145 (31.2)	197 (42.4)	123 (26.4)	
Congenital anomaly				
No	181 (32.9)	228 (41.4)	141 (25.6)	0.028
Yes	17 (56.7)	8 (26.7)	5 (16.7)	

(*continued*)

TABLE 2. (CONTINUED)

Characteristics	Feeding practices at discharge (n=580) Exclusive formula (n=198), n (%)	Mixed (n=236), n (%)	Exclusive breast milk (n=146), n (%)	p
Clinical outcomes				
Bronchopulmonary dysplasia				
No	147 (29.4)	218 (43.6)	135 (27.0)	<0.001
Yes	51 (64.6)	18 (22.8)	10 (12.7)	
Severe brain injury				
No	181 (33.7)	218 (40.6)	138 (25.7)	0.399
Yes	17 (40.5)	18 (42.9)	7 (16.7)	
Early infection (≤72 hours of life)				
No	187 (33.6)	232 (41.7)	137 (24.6)	0.048
Yes	11 (45.8)	4 (16.7)	9 (37.5)	
Late infection (>72 hours of life)				
No	99 (27.7)	163 (45.7)	95 (26.6)	<0.001
Yes	99 (44.4)	73 (32.7)	51 (22.9)	
Necrotizing enterocolitis diagnosis				
No	186 (33.2)	231 (41.2)	143 (25.5)	0.046
Yes (Bell stage II/III)	12 (60.0)	5 (25.0)	3 (15.0)	
Any surgery during hospitalization				
No	158 (30.6)	223 (43.2)	135 (26.2)	<0.001
Yes	40 (62.5)	13 (20.3)	11 (17.2)	
No. of transfers between NICUs during hospitalization				
0	131 (30.0)	185 (42.4)	120 (27.5)	0.001
≥1	67 (46.5)	51 (35.4)	26 (18.1)	

In each variable, the total may not add up to 580 due to missing data.
NICU, neonatal intensive care unit.

from 49.0% to 83.4%, and of exclusive breast milk 25.2%, ranging from 3.3% to 50.0% across units. We found differences across NICUs, suggesting that unit characteristics are probably more important than available national orientations for breast milk feeding. Moreover, results from the adjusted MOR provided strong evidence for the observed heterogeneity across NICUs. Differences of this magnitude across units have also been found in other countries. Exclusive breast milk feeding at discharge varied significantly between units from 53% to 83% in a prospective Danish cohort of preterm infants.[14] The proportion of high-risk infants fed with exclusive human milk (mother's or donor's milk) varied from 0% to 60% across centers in Italy.[13] In the United States, variations from 35% to 71% were recorded comparing low use with high-use sites across the country,[9] or hospital risk-adjusted rates of breast milk feeding that ranged from 19.7% to 100% in California.[12]

It is considered critical to avoid mother–infant separation, by promoting early, prolonged, and continued skin-to-skin contact (kangaroo care).[31] A previous qualitative study, with mothers and fathers of preterm infants, identified the supportive factors and barriers for their performance of kangaroo care: parent-related factors, time, infants-related factors, and the NICU and home environment.[32] In our regions, all units provided unlimited visit duration throughout visitation, which was 24 hours for 11 of the 16 units, and 12 hours during the day for 3. Also, all NICUs routinely provided kangaroo care to mothers and 15 NICUs to fathers. Thus, per se, these factors cannot contribute much to the variation between units. However, maternity leaves in Portugal might not be fully paid if hospitalization periods are long and commuting from home to the NICU is not covered by social security, a difficulty confronted by many parents who have to travel long distances as a result of regionalization of care. Logistics and economic constraints may thus render parental visits rather challenging and increase the probability of mother–infant separation.[33] As we did not evaluate the actual length of parental presence and skin-to-skin contact in the NICU, this potential individual source of variability could not be addressed.

An appropriately trained health staff, with certified education and training in breastfeeding, has been shown to play a key role in NICUs for successfully establishing breast milk feeding, supporting mothers, informing about benefits and clarifying doubts, and helping to initiate and maintain lactation.[15,33–35] In our study, five NICUs had no designated staff member to support mothers expressing or breastfeeding, and they presented the lowest prevalence of exclusive breast milk. When we evaluated feeding practices using a random intercept model, this staff-related characteristic explained per se the largest proportion of variance (42.6%), being a major determinant of exclusive breast milk feeding. Considering that in Portugal the population is served by a universal and free maternal and child health system whose professionals follow a nationally defined standard training, we did not expect such heterogeneity of the NICUs. It is important to consider the personal experience, beliefs, attitudes, and involvement of professionals[17,36] as a major source of information, guidance, assurance, and support to parents,[37] but no such information was collected in the present study.

Parents are also key actors for successful breast milk feeding. A systematic review of studies describing their views showed that knowledge about infant's and women's

Table 3. Feeding Practices at Discharge According to Portuguese Neonatal Intensive Care Units Characteristics

		Feeding practices at discharge (n=*580*)			
	No. of NICUs (n=*16*)	*Exclusive formula* (n=*198*), n (*%*)	*Mixed* (n=*236*), n (*%*)	*Exclusive breast milk* (n=*146*), n (*%*)	p[a]
General NICUs characteristics					
Region					
North	9	74 (30.0)	107 (43.3)	66 (26.7)	0.277
Lisbon and Tagus Valley	7	124 (37.2)	129 (38.7)	80 (24.0)	
Level of care					
II	3	6 (24.0)	9 (36.0)	10 (40.0)	0.220
III	13	192 (34.6)	227 (40.9)	136 (24.5)	
No. of admissions in 2011					
<350	9	87 (38.5)	97 (42.9)	42 (18.6)	0.032
≥350	7	111 (31.4)	139 (39.3)	104 (29.4)	
Policies toward parents					
Total length of time, in which parents had access to the baby's room/cot in the intensive care area during the day (8 am–8 pm)					
<12 hours	2	19 (41.3)	16 (34.8)	11 (23.9)	0.691
12 hours (no limit)	14	179 (33.5)	220 (41.2)	135 (25.3)	
Total length of time, in which parents had access to the baby's room/cot in the intensive care area during the night (8 pm–8 am)					
<12 hours	5	49 (33.3)	64 (43.5)	34 (23.1)	0.677
12 hours (no limit)	11	149 (34.4)	172 (39.7)	112 (25.9)	
Parents were allowed to spend the night in the NICU					
No	3	45 (26.5)	69 (40.6)	56 (32.9)	0.158
Yes, in special circumstances only	3	45 (36.3)	55 (44.4)	24 (19.4)	
Yes, always	10	108 (37.8)	112 (39.2)	66 (23.1)	
Parents may stay during ward rounds					
No	5	81 (42.2)	73 (38.0)	38 (19.8)	0.116
Yes (always)	11	117 (30.2)	163 (42.0)	108 (27.8)	
Facilities available in the intensive care unit area					
Beds in other unit/maternity ward for parents staying overnight					
No	13	181 (33.9)	223 (41.8)	130 (24.3)	0.152
Yes	3	17 (37.0)	13 (28.3)	16 (34.8)	
A room specifically for breast milk expression and/or breastfeeding					
No	3	25 (29.8)	39 (46.4)	20 (23.8)	0.480
Yes	13	173 (34.9)	197 (39.7)	126 (25.4)	
A room for parents to relax and talk					
No	4	31 (41.3)	30 (40.0)	14 (18.7)	0.391
Yes	12	167 (33.1)	206 (40.8)	132 (26.1)	
A bathroom with a shower for parents					
No	7	75 (25.9)	121 (41.7)	94 (32.4)	<0.001
Yes	9	123 (42.4)	115 (39.7)	52 (17.9)	
Facilities for parents to heat food and/or make drinks					
No	8	80 (38.6)	94 (45.4)	33 (15.9)	0.002
Yes	8	118 (31.6)	142 (38.1)	113 (30.3)	
Breastfeeding-related characteristics					
Baby-Friendly Hospital accreditation					
No	3	16 (36.4)	19 (43.2)	9 (20.4)	0.137
In process of accreditation	7	68 (38.2)	78 (43.8)	32 (18.0)	
Yes	6	114 (31.8)	139 (38.8)	105 (29.3)	
Written protocol for breastfeeding and human milk use					
No	3	16 (28.6)	29 (51.8)	11 (19.6)	0.240
Yes	13	182 (34.7)	207 (39.5)	135 (25.8)	
Designated staff in the unit to support mothers expressing or breastfeeding					
No	5	63 (40.4)	77 (49.4)	16 (10.3)	<0.001
Yes	11	135 (31.8)	159 (37.5)	130 (30.7)	

NICUs (where infants spent their first consecutive 48 hours of life).
[a]*p*-Values corresponding to the results of the likelihood ratio test using multilevel mixed-effects multinomial logistic regression with a random effect by NICUs.
NICU, neonatal intensive care unit.

TABLE 4. NEONATAL INTENSIVE CARE UNITS CHARACTERISTICS VARIABILITY ON FEEDING PRACTICES AT DISCHARGE: RESULTS FROM A RANDOM INTERCEPT MODEL

	Feeding practices at discharge (n = 576)							
	Mixed versus exclusive formula				*Exclusive breast milk versus exclusive formula*			
	MOR	*Variance*	*Explained variance (%)*		*MOR*	*Variance*	*Explained variance (%)*	
Model 0	1.35	0.10	Reference	—	2.02	0.53	Reference	—
Model 1	1.62	0.25	−157.3	Reference	2.38	0.82	−48.3	Reference
Model 2	1.55	0.21	−113.0	17.2	2.23	0.71	−31.2	11.5
Model 3	1.35	0.10	−3.0	60.0	1.88	0.44	18.2	44.9
Model 4	1.33	0.09	8.8	64.6	1.35	0.10	81.5	87.5

Model 0 is a null model, baseline model without any exposure variable.
Model 1 is adjusted for maternal age, multiple pregnancy, antenatal steroids, gestational age, birth weight, apgar score, congenital anomaly, bronchopulmonary dysplasia, early infection, late infection, any surgery, and number of transfers between NICUs.
Model 2 is additionally adjusted for parents may stay during ward rounds.
Model 3 is additionally adjusted for bathroom with a shower for parents.
Model 4 is additionally adjusted for designated staff or other members in the unit to support mothers who were expressing or breastfeeding.
MOR, median odds ratio; NICU, neonatal intensive care unit.

bodies and behaviors, reinforcement of mother's motivation, and alignment between NICUs routines and parents' needs are essential.[38] In Portugal, concerns related to inadequate milk supply, difficulties with expressing breast milk, and physical separation from infants were identified by parents as major barriers to provide breast milk to very preterm infants in the NICU, while their knowledge about breastfeeding benefits was a major facilitator.[39] This supports the importance of family-centered care and a family–friendly environment in NICUs that incorporate parents' needs and stimulate their active participation in infants' care.[25] In the United Kingdom, a large variation within and across types of neonatal units was observed regarding indicators of family-centered care, namely facilities, information, and policies.[26] In our study, 13 NICUs provided a room specifically for breast milk expression and breastfeeding, but feeding practices were similar in the remaining units. Unexpectedly, we found that NICUs with a bathroom with a shower for parents had lower exclusive breast milk proportions. In fact, we did not evaluate the utilization of available facilities or what units were offering as resources, namely chairs near the infants' cots, equipment, and access to breast pumps. This type of information could provide a deeper understanding of the observed variability.[17,18,25]

Differences across NICUs can also be related to local regulations and adherence to guidelines, such as the management of mother's own milk for infants born very preterm regarding fresh versus pasteurized human milk, regular bacteriological analyses, or storage time.[17,40] We found that 13 NICUs followed written protocols for breastfeeding and human milk use, 8 had their own, and 5 used regional, national, or network protocols, but feeding practices were similar. In Portugal, there is only one human milk bank serving two NICUs, making a meaningful comparison impossible. Although donor human milk is recommended when mother's milk is not available, this is not a possible alternative in Portuguese NICUs for infants whose mothers choose not to breastfeed or cannot do it. However, it is well established that human milk banks are an instrument for breastfeeding promotion and support.[41]

The observed proportion of breast milk feeding at discharge in our study was higher than in 2003 in the North region of Portugal,[3] reflecting a regional increase in exclusive breast milk feeding from 6.0% to 26.7% for exclusive breast milk and 50.0% to 70.0% for any breast milk, probably following adherence to the *Baby-Friendly Hospital* accreditation.[27]

It is known that maternal, obstetric, and infant clinical factors influence breast milk feeding in NICUs. However, our study suggests that NICUs influence feeding practices independently of individual characteristics. A study from the EPICE cohort, including units from all 19 European regions, found that infants cared at NICUs with a *Baby-Friendly Hospital* Initiative accreditation were more often on any breast milk feeding at discharge and that those admitted to NICUs with protocols for breast milk feeding and access to donor milk had higher proportions of exclusive breast milk feeding at discharge.[23] Because of the heterogeneity of units across regions, this study was unable to investigate the organizational characteristics of the units or measure unit-level variability, as we were able to do within the Portuguese sample. International studies are, however, appropriate for investigating characteristics that vary more widely at the regional level.

A major strength of our study is the use of high-quality data, collected within a population-based prospective cohort, under common protocols and research tools, covering all NICUs in the two largest Portuguese regions. To avoid unnecessary confounding, infants were attributed to the NICU, where they spent their first consecutive 48 hours of life, as breast milk feeding success depends on establishing lactation in the period immediately after birth.[3] To the best of our knowledge, this is the first study using the MOR, which allows a multilevel analysis of heterogeneity between units within the same level.

Limitations should also be acknowledged. We have no information about duration of breast milk feeding in hospital, making it impossible to consider a time dimension in the comparison of feeding at discharge. Some variables potentially useful to understand the findings were not available, namely maternal intention and motivations to breastfeed or the reasons for not initiation or stopping breastfeeding, such as mother's own choice, physiological or psychological reasons, and mother's milk is not available or is insufficient. Detailed sociodemographic characteristics would be also helpful. However, we georeferenced the infants and used a neighborhood socioeconomic deprivation index, a valid proxy of individual socioeconomic position, and we did not find statistically significant differences.[22]

Conclusion

There was a significant variation in the prevalence of breast milk feeding of very preterm infants in Portuguese NICUs, independent of individual characteristics, and only partially explained by the evaluated NICUs' characteristics. This highlights the importance of a better understanding of the complex determinants of breast milk feeding among this specific group of vulnerable infants and the role of institution-based interventions to promote breast milk in NICUs as a component of healthcare quality.

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4.2. PAPER II

Breastfeeding outcomes in European NICUs: impact of parental visiting policies

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Breastfeeding outcomes in European NICUs: impact of parental visiting policies

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ABSTRACT

Objective The documented benefits of maternal milk for very preterm infants have raised interest in hospital policies that promote breastfeeding. We investigated the hypothesis that more liberal parental policies are associated with increased breastfeeding at discharge from the neonatal unit.
Design Prospective area-based cohort study.
Setting Neonatal intensive care units (NICUs) in 19 regions of 11 European countries.
Patients All very preterm infants discharged alive in participating regions in 2011–2012 after spending >70% of their hospital stay in the same NICU (n=4407).
Main outcome measures We assessed four feeding outcomes at hospital discharge: any and exclusive maternal milk feeding, independent of feeding method; any and exclusive direct breastfeeding, defined as sucking at the breast. We computed a neonatal unit Parental Presence Score (PPS) based on policies regarding parental visiting in the intensive care area (range 1–10, with higher values indicating more liberal policies), and we used multivariable multilevel modified Poisson regression analysis to assess the relation between unit PPS and outcomes.
Results Policies regarding visiting hours, duration of visits and possibility for parents to stay during medical rounds and spend the night in unit differed within and across countries. After adjustment for potential confounders, infants cared for in units with liberal parental policies (PPS≥7) were about twofold significantly more likely to be discharged with exclusive maternal milk feeding and exclusive direct breastfeeding.
Conclusion Unit policies promoting parental presence and involvement in care may increase the likelihood of successful breastfeeding at discharge for very preterm infants.

What is already known on this topic?

- ► Parental involvement in the care of very preterm infants in neonatal units has been associated with several benefits, including reduced morbidity and improved growth and neurobehaviour.
- ► The evidence on the relation between neonatal unit parental policies and breastfeeding outcomes at discharge is scarce.

What this study adds?

- ► Policies towards parental presence and involvement in neonatal units vary between and within European countries.
- ► More liberal parental policies are associated with increased likelihood of exclusive maternal milk feeding and exclusive direct breastfeeding at hospital discharge.

INTRODUCTION

The increased awareness of the benefits of breastfeeding for preterm infants in preventing morbidities and improving early brain development and, possibly, cognition has raised interest in modifiable factors, such as the organisation and policies of neonatal units, which can promote breastfeeding in this high-risk population.[1–5]

Reinforcing parental presence in the neonatal intensive care unit (NICU) may be one such factor. Programmes aimed at supporting parental presence and interaction with their infants in NICUs have been shown to reduce morbidity,[6 7] infant stress and pain[7] and length of hospital stay[6 8] and to improve early neurobehaviour,[7 9] infant growth,[7 10] language and cognitive skills at follow-up.[11 12] However, reports on the relation with breastfeeding are scarce. An Italian study carried out in five NICUs[13] found that a policy of free 'around the clock' parental visiting was associated with increased frequency of breast milk feeding in very low birth weight singletons at 4 weeks of life (58% vs 16%), while another pilot study in Canada reported increased breastfeeding in infants assigned to a care-by-parent programme.[10] Similarly, the higher breastfeeding rates documented at discharge among infants cared for in a single family room unit were attributed to the increased opportunity for maternal-infant interaction and kangaroo care (KC) compared with usual open-ward care.[14]

This study used the data of the international area-based project on 'Effective Perinatal Intensive Care in Europe' (EPICE) to describe the policies towards parental presence in NICUs in 19 European regions and test the hypothesis that liberal parental policies are associated with increased likelihood of breastfeeding very preterm (VP) infants at discharge from hospital.

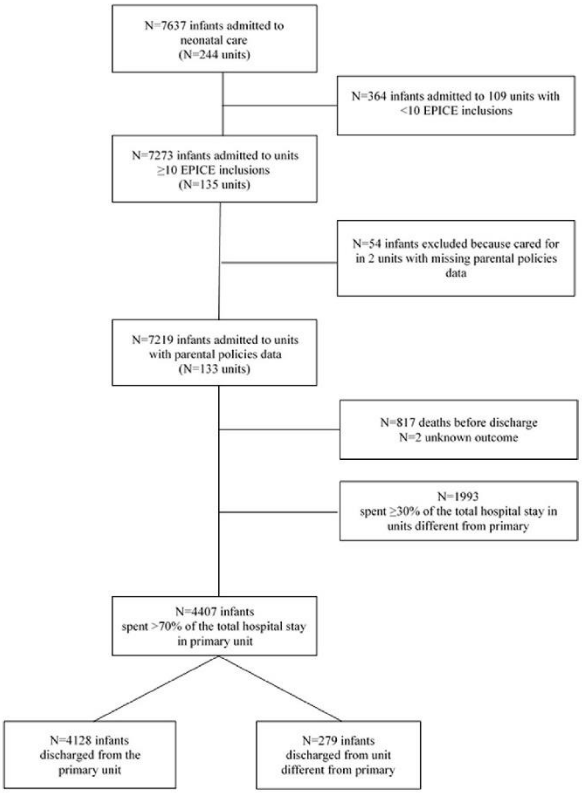

Figure 1 Flow chart of the study population. EPICE, Effective Perinatal Intensive Care in Europe.

METHODS

Study design and participants

EPICE aimed at assessing the use of evidence-based interventions and outcomes in a prospective, geographically defined cohort of births occurred at 22–31 completed weeks gestation in 19 regions[15]: Flanders in Belgium; Eastern region in Denmark; Estonia (entire country); Burgundy, Ile-de-France and Northern region in France; Hesse and Saarland in Germany; Emilia-Romagna, Lazio and Marche in Italy; the Central and Eastern regions in the Netherlands; Wielkopolska in Poland; Lisbon and Tagus Valley, and North region in Portugal; greater Stockholm in Sweden; East Midlands, Yorkshire and Humber and the Northern region in the UK. Recruitment started between March and July 2011 and lasted 12 months, except in France where it lasted 6 months. In addition, all neonatal units with at least 10 VP recruitments (n=135) were sent a standardised form to collect information on the unit organisation, policies and usual practices, including parental visiting and KC.

A total of 7637 very preterm admissions to neonatal care were recorded (figure 1); 7219 infants were admitted to the 133 NICUs with information on unit organisation and parental visiting policies, and 6400 of them were discharged alive. To achieve an adequate matching between the unit policies and patient outcomes, this study included only the 4407 infants discharged alive after spending >70% of their total hospital stay in the same primary NICU, defined as the unit of care in the first consecutive 48 hours of life.[16] Provided this criterion was met, infants transferred to lower level care before discharge (n=279) were retained in the study on the assumption that feeding habits were already well established at the time of back-transfer. The proportion of excluded infants (n=1993) varied by country (from 3.8%, 5.1% and 11.2% in Germany, Poland and Italy to a maximum of 82.6% in Estonia and 88.5% in the Netherlands), as result of local policies regarding regionalisation and transfers between units.

Written parental informed consent was obtained according to national legislation.

Variables

Unit policy variables

Questions regarding parental policies were selected based on a review of previous studies[17–19] and included the number of hours parents had access to the intensive care area during daytime and night-time, the maximum allowed length of stay per visit (as much as they want, up to a given time or other), whether they could spend the whole night in the unit—either in parent rooms or simply sitting near the baby's cot—and stay during medical rounds (both coded as yes always, yes in special circumstances only, no).

Policies regarding skin-to-skin KC (offered routinely, sometimes, only on request or generally no) were recorded separately for mothers and fathers. The responses were combined into a single variable coded as: highly liberal for both parents (offered routinely to both); liberal for both parents (offered routinely or sometimes to mothers, and sometimes to fathers); liberal for mothers only (routinely to mothers and on request or not offered to fathers, or sometimes to mothers and on request to fathers) and restricted (offered sometimes to mothers and not offered to fathers, or on request for both). We recorded the presence of a written protocol for developmental care and for breastfeeding, and of dedicated staff to support breastfeeding (all coded as yes or no). Baby Friendly Hospital Initiative (BFHI) accreditation was recorded as no, in process or accredited.

Maternal and neonatal variables

Data describing the infants' health risks were abstracted from clinical records using common definitions and a precoded form. Gestational age was the best obstetric estimate based on information on last menstrual period and ultrasound measures. Small for gestational age (SGA) was defined as birth weight <10th percentile using European intrauterine references.[20] Severe congenital anomalies were those reported by European Registry of Congenital Anomalies and Twins (EUROCAT).[21] Bronchopulmonary dysplasia (BPD) was defined as oxygen supplementation at 36 weeks postmenstrual age.

Three questions recorded infant feeding at discharge from hospital: any use of formula; any use of maternal milk and, if this was the case, whether the infant was sucking at the breast, that is, direct breastfeeding.[22] Using this information, we computed four binary outcome variables: 1) any maternal milk feeding, defined as any use of mothers' own milk, exclusive or together with formula, independently of method of feeding (breast, bottle or other method); 2) exclusive maternal milk feeding, without formula, independently of method of feeding; 3) any direct breastfeeding, defined as sucking directly at the breast, exclusively or together with formula and 4) exclusive direct breastfeeding (no formula).

Statistical analysis

We computed a Parental Presence Score (PPS) using the unit variables on parental visiting (see online supplementary material). Following the original format of questions on length of stay per visit, whether parents could stay during medical rounds and could spend the night in unit, we scored responses from 2 (most liberal) to 0 (least liberal). The answers regarding visiting number of hours, originally measured on a quantitative scale (from 0 to 12), were recoded as 0 (<6 hours), 1 (6–11) and 2 (12 hours). Eight units (one in Belgium, two in Germany, five in France), caring for 380 infants, had missing values in one of these variables, which were replaced by the mean of the values of the other variables in the same unit. We then carried out exploratory factor analysis using a polychoric correlation matrix to take into account the ordinal nature of the scores.[23] As the five variables loaded on one single factor with high factor loadings (range 0.70–0.96), we added the unweighted individual scores to obtain the total PPS. The high ordinal reliability alpha (0.94) confirmed the internal consistency of the scale.[23] The PPS ranged from 1 to 10 (mean 8, SD 2.6), with higher values indicating more liberal visiting policies. To compute risk ratios (RR), we categorised it as low (<7), intermediate (7–9) and high (10). These cut-offs, corresponding to <25th, 25th–60th and >60th percentile respectively, were selected taking into account the negatively skewed score distribution and the need to have adequate numbers of infants in each category.

At unit level, we tested the correlation between the PPS and breastfeeding rates using the non-parametric Spearman's rank correlation coefficient. We then carried out univariable and multivariable multilevel modified Poisson regression analysis to estimate RRs.[24] For each feeding outcome we estimated three models. Model 1 included as predictor only the categorised PPS. Model 2 included the PPS and other unit variables that might confound the association between PPS and feeding outcomes: level (tertiary or otherwise), BFHI accreditation, written protocol for developmental care and for breastfeeding, dedicated staff to support breastfeeding and parental KC policies. Finally, model 3 included all predictors in model 2 plus the following maternal and infant variables: maternal age (coded as <25, 25–34, ≥35 years), country of birth (used as foreign born or native, ie, born in country), parity (0, 1, 2 or more), type of pregnancy (single or multiple), gestational age (22–25, 26–27, 28–29 and 30–31 weeks); caesarean delivery, male gender, inborn status, Apgar score <7 at 5 minutes SGA, any major congenital anomaly and BPD (all coded as yes or no). All models included region and unit of care as random effects to take into account the hierarchical nature of the database (babies, units, regions).

Multivariable models excluded infants with missing outcome information: 127 did not have information on any maternal milk feeding, 127 on use of formula and 241 on feeding directly at the breast. Two NICUs (45 infants) had missing information for KC policies and two (30 infants) for written breastfeeding protocol. Missing data were ≤1% for maternal age, parity, type of pregnancy, caesarean delivery and BPD, 5% for Apgar score and 7% for mother country of birth. Missing values for predictors were included as separate category in multivariable models.

In all models, because of the observational nature of our study and the use of several breastfeeding measures, we did not report p values but only point estimates and 95% CIs to allow, as suggested by Rothman KJ,[25] for the separate assessment of the magnitude and the precision of associations.

Finally, we carried out a sensitivity analysis by running all the multivariable models using the whole population after attributing the previously excluded 1993 infants to 1) the maximum and 2) the minimum PPS category of their region (see online supplementary material).

Data analysis was carried out using STATA V.14.0 SE (StataCorp, College Station, Texas, USA).

RESULTS

Table 1 shows the characteristics of the study population and feeding outcomes at hospital discharge. Overall, 53.3% were males and 31.9% multiples; 25.4% were born before 28 weeks gestation and 33.1% were SGA. Use of mother's milk at discharge varied between countries, with the Scandinavian regions and Estonia showing rates higher than the others.

Table 2 shows the characteristics and policies of the units. Most were tertiary NICUs, except in Sweden, Denmark, the UK and Poland. The average number of hours when parents had access to their babies' cots in the intensive care area was 10.9 during daytime and 9.9 during night-time. Only Italian units reported time restrictions regarding the visit length. Policies were more restrictive generally as regards the presence of parents during medical rounds and the possibility of staying overnight, whether in bedrooms for parents or simply sitting near the baby's cot (not possible in 16.8% and 28.9% of units, respectively), but differences between countries were large. Routine KC was widely offered to both parents in all countries except France and Poland, but restrictions were present for fathers also in Italy and Estonia. Written protocols for breastfeeding and developmental care were present in 90.8% and 57.9% of units respectively, and 81.7% had dedicated staff to support breastfeeding.

Figure 2 shows the distribution of NICUs by category of PPS. All units in Sweden, 64% in France and about half in Denmark, the Netherlands, the UK, Portugal and Estonia had a PPS of 10, corresponding to the most liberal policies towards parents. However Estonia, Portugal and France also had units with PPS<7. Poland had no unit with a score of 10, while in the Italian regions the proportion of units scoring <7 reached 73%.

At unit level, the PPS was significantly correlated with the rates of exclusive maternal milk feeding (Spearman's correlation coefficient 0.384, p<0.001), any and exclusive direct breastfeeding (correlation coefficients 0.300 and 0.418, respectively, p<0.001), but not with any maternal milk feeding. These results were confirmed by multivariable analyses, showing higher RRs of breastfeeding for these three outcomes when PPS scores were ≥7, independently from other unit and maternal or infant characteristics (table 3). The association was stronger and statistically significant for the variables measuring exclusive maternal milk feeding, either directly at the breast or not, with most of the adjusted point estimates ≥2. There was no dose-response effect.

The results of sensitivity analysis did not meaningfully change these conclusions.

When each of the five variables used in the PPS was entered separately in the models, we found that liberal (ie, ≥6 hours) access to NICU during daytime had the strongest effect, and qualified as the most important prerequisite for parental involvement and child breastfeeding (data not shown in tables).

DISCUSSION

This study found that policies towards parental presence and involvement in the care of their VP babies varied across European NICUs, particularly as regards participation in clinical rounds and the possibility to spend the night in the unit. KC was widespread but in several units, particularly in France, Poland and Italy, policies were still more restrictive for fathers than for mothers. More liberal parental presence policies, as measured by a PPS≥7, were significant predictors of exclusive maternal milk feeding at hospital discharge, directly at the breast or not. The association could not be explained by the offer of KC, nor by other unit and infants characteristics.

Table 1 Characteristics of the infants included in the study and feeding outcomes by country

	Sweden		Denmark		UK		Estonia		The Netherlands		Belgium		France		Poland		Germany		Portugal		Italy		Total	
	(n=157)		(n=181)		(n=941)		(n=23)		(n=33)		(n=379)		(n=535)		(n=224)		(n=609)		(n=497)		(n=828)		(n=4407)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Maternal age, years																								
<25	12	7.7	20	11.0	248	26.7	8	34.8	2	6.1	47	12.4	85	15.9	52	23.3	76	12.6	70	14.1	69	8.3	689	15.7
25–34	82	52.9	116	64.1	499	53.7	4	17.4	22	66.7	245	64.6	322	60.2	131	58.7	356	58.9	286	57.5	376	45.5	2439	55.6
≥35	61	39.4	45	24.9	183	19.7	11	47.8	9	27.3	87	23.0	128	23.9	40	17.9	172	28.5	141	28.4	382	46.2	1259	28.7
Parity																								
0	89	57.1	103	57.2	470	50.4	12	52.2	24	72.7	227	60.4	276	53.2	102	46.1	374	61.7	315	63.6	520	63.2	2512	57.6
1	54	34.6	43	23.9	225	24.1	4	17.4	8	24.2	77	20.5	129	24.9	89	40.3	134	22.1	470	26.9	203	24.7	1099	25.2
2 or more	13	8.3	34	18.9	237	25.4	7	30.4	1	3.0	72	19.1	114	21.9	30	13.6	98	16.2	89	9.5	100	12.1	753	17.2
Native mother	109	69.4	132	82.5	776	85.0	22	100.0	30	90.9	270	75.0	333	66.1	222	99.1	337	83.6	408	84.1	573	69.2	3212	78.6
Multiples	50	31.9	67	37.0	216	23.0	9	39.1	12	36.4	160	42.2	188	35.1	45	20.1	229	37.6	151	30.4	279	33.7	1406	31.9
Males	82	52.9	102	56.3	508	54.0	17	73.9	15	45.4	209	55.1	273	51.0	125	55.8	330	54.1	280	56.3	407	49.1	2348	53.3
Gestational age, weeks																								
22–25	12	7.6	11	6.1	74	7.9	1	4.4	8	24.2	39	10.3	44	8.2	24	10.7	67	11.0	27	5.4	51	6.2	357	8.1
26–27	13	8.3	22	12.2	133	14.1	1	4.4	13	39.4	60	15.8	125	23.4	38	17.0	113	18.5	102	20.5	140	16.9	760	17.3
28–29	52	33.1	57	31.4	264	28.0	4	17.4	2	6.1	105	27.7	156	29.2	51	22.8	157	25.9	130	26.2	222	26.8	1201	27.2
30–31	80	51.0	91	50.3	470	50.0	17	73.8	10	30.3	175	46.2	210	39.2	111	49.5	272	44.6	238	47.9	415	50.1	2089	47.4
Small for gestational age	53	33.8	60	33.1	293	31.2	4	17.4	9	27.3	112	29.6	187	35.0	52	23.2	227	37.3	188	37.8	273	33.0	1459	33.1
Caesarean delivery	117	75.0	134	74.0	537	57.4	8	34.8	15	45.4	238	64.3	330	62.5	148	66.1	532	88.4	371	74.7	682	82.4	3112	71.1
Apgar score<7 at 5′	33	21.3	18	9.9	134	15.2	3	13.0	9	27.3	42	11.2	87	17.4	59	27.6	94	15.9	45	9.1	84	11.3	608	14.5
Inborn	142	90.5	177	97.8	883	93.8	11	47.8	32	97.0	374	98.7	472	88.2	193	86.2	604	99.2	491	98.8	746	90.1	4125	93.6
Any major congenital anomaly	2	1.3	0	–	8	0.9	0	–	0	–	2	0.5	3	0.6	14	6.3	15	2.5	0	–	10	1.2	54	1.2
Bronchopulmonary dysplasia	19	12.2	16	9.1	223	24.2	1	4.4	10	30.3	61	16.1	68	13.0	22	9.8	62	10.2	62	12.5	71	8.7	615	14.1
Feeding outcomes at discharge:																								
Any maternal milk	127	80.9	139	79.9	444	47.6	17	73.9	22	66.7	210	57.1	254	47.5	99	44.6	297	57.2	336	68.0	507	62.2	2452	57.4
Exclusive maternal milk	71	45.2	67	41.1	280	30.0	11	47.8	15	45.5	132	35.6	137	25.6	38	17.1	85	16.2	130	26.2	130	16.0	1096	25.7
Any direct breastfeeding	116	73.9	123	71.1	402	44.0	11	47.8	8	25.8	141	39.5	210	39.6	53	25.6	178	37.0	232	49.2	180	22.3	1654	39.8
Exclusive direct breastfeeding	67	43.2	59	35.3	261	28.8	11	47.8	6	18.2	92	25.2	117	22.0	21	9.7	67	13.0	99	20.2	56	6.9	856	20.3

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Table 2 Characteristics and policies of the neonatal intensive care units by country

	Sweden		Denmark		UK		Estonia		The Netherlands		Belgium		France		Poland		Germany		Portugal		Italy		Total	
	(n=4)		(n=8)		(n=27)		(n=4)		(n=2)		(n=9)		(n=22)		(n=4)		(n=14)		(n=17)		(n=22)		(n=133)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Tertiary level	2	50.0	2	25.0	12	44.4	3	75.0	2	100.0	8	88.9	22	100.0	1	25.0	13	92.9	15	88.2	16	72.7	96	72.2
Visiting time (hours)																								
Daytime: mean (range)	12 (–)		11.9 (11–12)		11.9 (11–12)		11 (8–12)		12 (–)		12 (–)		11.5 (6–12)		12 (–)		11.3 (7–12)		11.8 (10–12)		7.2 (2–12)		10.9 (2–12)	
Night-time: mean (range)	12 (–)		12 (–)		11.9 (11–12)		6 (0–12)		12 (–)		12 (–)		11.7 (6–12)		10 (4–12)		9.1 (0–12)		10.4 (4–12)		4.2 (0–12)		9.9 (0–12)	
Length of time parents may stay per visit																								
As much as they want	4	100.0	8	100.0	27	100.0	4	100.0	2	100.0	9	100.0	22	100.0	4	100.0	13	100.0	17	100.0	15	68.2	125	94.7
Up to a given time	0	–	0	–	0	–	0	–	0	–	0	–	0	–	0	–	0	–	0	–	7	31.8	7	5.3
Parents may stay during ward rounds																								
Yes, always	4	100.0	8	100.0	24	88.9	3	75.0	1	50.0	6	75.0	19	90.4	4	100.0	8	57.1	12	70.6	7	31.8	96	73.3
Yes, in special cases only	0	–	0	–	3	11.1	0	–	0	–	2	25.0	1	4.8	0	–	2	14.3	0	–	5	22.7	13	9.9
No	0	–	0	–	0	–	1	25.0	1	50.0	0	–	1	4.8	0	–	4	28.6	5	29.4	10	45.5	22	16.8
Parents may spend the night in the unit																								
Yes, always	4	100.0	5	62.5	15	55.6	2	50.0	1	50.0	4	44.5	10	55.6	0	–	4	30.8	11	64.8	6	27.3	62	48.4
Yes, in special cases only	0	–	3	37.5	11	40.7	0	–	1	50.0	2	22.2	2	11.1	1	25.0	4	30.8	3	17.6	2	9.1	29	22.7
No	0	–	0	–	1	3.7	2	50.0	0	–	3	33.3	6	33.3	3	75.0	5	38.4	3	17.6	14	63.6	37	28.9
Parental kangaroo care																								
Highly liberal for both	4	100.0	8	100.0	24	88.9	1	25.0	2	100.0	8	88.9	9	40.9	3	75.0	14	100.0	16	94.1	16	72.7	105	79.0
Liberal for both	0	–	0	–	3	11.1	2	50.0	0	–	1	11.1	6	27.3	0	–	0	–	1	5.9	3	13.6	16	12.0
Liberal for mothers only	0	–	0	–	0	–	1	25.0	0	–	0	–	3	13.6	0	–	0	–	0	–	3	13.6	7	5.3
Restricted	0	–	0	–	0	–	0	–	0	–	0	–	2	9.1	1	25.0	0	–	0	–	0	–	3	2.3
Written unit protocol for developmental care	3	75.0	6	75.0	17	63.0	1	25.0	0	–	6	66.7	10	45.5	1	25.0	6	42.9	13	76.5	14	63.6	77	57.9
Written unit protocol for breastfeeding	4	100.0	8	100.0	26	96.3	4	100.0	2	100.0	6	66.7	17	85.0	4	100.0	12	85.7	15	88.2	21	95.5	119	90.8
Baby Friendly Hospital Initiative accreditation																								
No	0	–	6	75.0	2	7.5	3	75.0	0	–	6	66.7	20	90.8	1	25.0	13	92.9	3	17.6	18	81.8	69	51.9
In process	0	–	1	12.5	8	29.6	0	–	0	–	0	–	1	4.6	0	–	1	7.1	7	41.2	1	4.6	21	15.8
Accredited	4	100.0	1	12.5	17	62.9	1	25.0	2	100.0	3	33.3	1	4.6	3	75.0	0	–	7	41.2	3	13.6	43	32.3
Dedicated staff to support breastfeeding	4	100.0	6	75.0	19	73.1	3	75.0	2	100.0	8	88.9	20	95.2	4	100.0	11	78.6	12	70.6	18	81.8	107	81.7

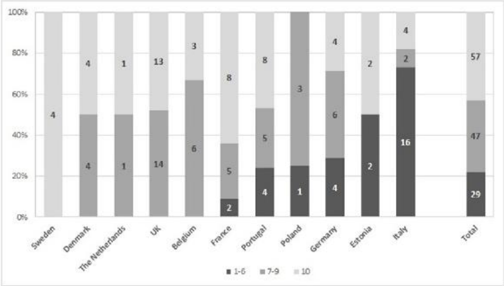

Figure 2 Distribution of neonatal intensive care units by category of Parental Presence Score.

Both feeding directly at the breast and exclusive maternal milk feeding are associated with longer duration of breastfeeding after discharge from NICU,[22 26] contributing to the prevention of chronic conditions such as obesity, metabolic syndrome, cardiovascular problems and type 2 diabetes.[27] Additionally, direct breastfeeding increases the opportunities for skin-to-skin contact, with possible benefits for the infant microbiota composition,[28 29] and may promote better infant self-regulation of energy intake and appetite later in childhood.[30 31]Compared with formula and even expressed maternal milk, direct breastfeeding appears to confer greater protection against respiratory problems and asthma.[32]

Our results suggest a threshold effect, as an 'intermediate' PPS (7–9) appeared sufficient to motivate parents towards breastfeeding and to achieve all the benefit as regard exclusive maternal milk feeding at discharge, without any additional advantage linked to the highest score of 10. While a dose-response effect is generally considered to support the hypothesis of a causal effect, lack of it does not necessarily imply otherwise,[33] particularly for complex interventions such as public health or clinical policy strategies. Inadequate compliance with the intervention proposed or, in our case, failure of parents to use all the options allowed by a fully open visiting policy might also explain the lack of dose-response detection.

The strengths of our study are the area-based design, the availability of both unit and individual patient data and the large sample size that allowed us to investigate policies in many NICUs in different countries. There are also limitations. Only a few regions per country participated and we cannot assume that our sample was nationally representative. For sake of internal validity, we included only infants who spent >70% of their total hospital stay in the same primary NICU, and it is possible that some of the exclusions were due to more severe child illness requiring transfer. Thus, strictly speaking, our findings apply to infants who spent >70% of their hospital time in the same unit. As is the case for all observational studies, we cannot prove that the association between PPS and breastfeeding outcomes is causal. Finally, we surveyed the unit policies but not the actual frequency of parental visiting and KC practice at individual level. In this regard, however, previous studies in this field have shown consistency between policies, staff attitudes and actual clinical practices and parents behaviours.[34 35]

Our results confirm those of previous reports on the relationship between parental presence and breastfeeding in NICUs[10 13 14] using a much larger, area-based international population and taking into account potential confounders, such as KC, BFHI accreditation, maternal and infant characteristics. The findings are also consistent with a recent qualitative study, carried out in three regions in France, Italy and the UK, that identified the restrictive parental visiting policies as possible determinant of the low rate of exclusive breastfeeding at discharge from NICU in the Italian region, despite its higher rate of any maternal milk feeding compared with the others.[36]

This study adds to the increasing body of evidence on the effectiveness of parent-based programmes, such as educational interventions,[8] increased involvement in babies' care[8 9 11] and family integrated care[10 12] to improve the health outcomes of VP infants. These strategies also affect parental outcomes, reducing stress and depression[8 10] and fostering feelings of empowerment and self-efficacy. In the light of this evidence, and of the many proven benefits of maternal milk, NICUs should aim at strengthening their policies to support the involvement of parents in the care of VP children.

Table 3 Association between unit PPS and breastfeeding outcomes at discharge from hospital*

		Model 1‡		Model 2§		Model 3¶	
Feeding outcomes at discharge	**PPS†**	**RR**	**(95% CI)**	**aRR**	**(95% CI)**	**aRR**	**(95% CI)**
Any maternal milk	Low	Ref		Ref		Ref	
	Intermediate	1.1	(1.0 to 1.2)	1.1	(0.9 to 1.2)	1.0	(0.9 to 1.2)
	High	1.1	(1.0 to 1.2)	1.0	(0.9 to 1.2)	1.0	(0.9 to 1.2)
Exclusive maternal milk	Low	Ref		Ref		Ref	
	Intermediate	2.4	(1.6 to 3.7)	2.4	(1.5 to 3.7)	2.5	(1.5 to 4.2)
	High	2.3	(1.4 to 3.8)	2.1	(1.2 to 3.6)	2.1	(1.1 to 4.0)
Any direct breast feeding	Low	Ref		Ref		Ref	
	Intermediate	1.4	(1.1 to 1.9)	1.3	(1.0 to 1.7)	1.3	(1.0 to 1.8)
	High	1.5	(1.1 to 2.0)	1.4	(1.0 to 1.8)	1.3	(1.0 to 1.8)
Exclusive direct breast feeding	Low	Ref		Ref		Ref	
	Intermediate	2.7	(1.6 to 4.6)	2.6	(1.5 to 3.7)	2.3	(1.4 to 3.8)
	High	2.6	(1.5 to 4.7)	2.1	(1.2 to 3.5)	1.9	(1.1 to 3.4)

*Univariable and multivariable RRs were computed using multilevel modified Poisson regression analysis. Random effects: unit and region.
†PPS: low 1–6, intermediate 7–9, high 10.
‡Model 1: only PPS as predictor.
§Model 2: adjusted for other unit variables: unit level, written protocol for developmental care and for breast feeding, Baby Friendly Hospital Initiative, dedicated staff to support breast feeding and parental KC policies.
¶Model 3: adjusted for all variables present in model 2 plus maternal and infant variables: maternal age, country of birth, parity, type of pregnancy, gestational age, caesarean delivery, male gender, inborn status, Apgar score<7 at 5', SGA, any major congenital anomaly and BPD.
aRR, adjusted RR; BPD, bronchopulmonary dysplasia; KC, kangaroo care; PPS, Parental Presence Score; RR, risk ratio; SGA, small for gestational age.

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Contributors MC conceived this work, supervised statistical analyses and drafted the paper. She contributed to designing the data collection instrument, and coordinated data collection in the Emilia Romagna and Marche regions. IC carried out statistical analyses and contributed to the interpretation of the findings. She made substantial contributions to data collection in Emilia Romagna and Marche regions. LT contributed to designing the data collection instrument, coordinated data collection in Estonia and critically revised the paper for important intellectual content. CR coordinated data collection in Portugal regions and participated in the preparation of the manuscript and interpretation of findings. EW contributed to designing the data collection instrument and to the acquisition of the data in Sweden; she participated in drafting the paper and in the interpretation of the findings. MB participated in designing the data collection instrument and in creation of the study database. She critically reviewed the paper for important intellectual content, and contributed to the interpretation of the findings. JG contributed to designing the data collection instrument, coordinated the study in Poland, critically revised the paper and contributed to finalise it. DDL contributed to designing the data collection instrument, coordinated the study in the Lazio region, participated in the interpretation of the results and critically revised the manuscript. LCH made substantial contributions to data analyses and interpretation and participated in drafting the paper. JZ initiated and coordinated the project at the international level, drafted the data collection instrument, made substantial contributions to the interpretation of the results and participated in drafting and finalising the paper. All authors have seen and approved the submission of this version of the manuscript, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Appendix

The Parental Presence Score (PPS) was computed using the following five variables included in the unit data collection form:

Original questions:	Scoring for computing the PPS:	
Total length of time when mother or both parents have access to the baby's room/cot in the intensive care area (please write n. of hours):		
1) During day-time (h. 08:00 – 20:00): ____ ____	12h	score 2
	6 – 11h	score 1
	<6h	score 0
2) During night-time (h. 20:00 – 8:00): ____ ____	12h	score 2
	6 – 11h	score 1
	<6h	score 0
3) When mother or both parents visit, how long can they stay with the baby?		
1. As much as they want		score 2
2. Up to *(specify max time per visit:________)*		score 1
3. Other *(specify:______________________)*		score 0
4) Can the mother or the parents stay with the baby during the doctors' ward rounds?		
1. Yes, always		score 2
2. Yes, in special circumstances only		score 1
3. No		score 0
5) Are mothers or parents allowed to spend the night in the intensive care area? (whether in parents' rooms or simple near their babies' cots)		
1. Yes, always		score 2
2. Yes, in special circumstances only		score 1
3. No		score 0

TABLE S_max. Association between unit PPS and breastfeeding outcomes at discharge from hospital (highest regional score category for all excluded children)[a]

Feeding outcomes at discharge	Parental Presence Score (PPS)[b]	Model 1[c]		Model 2[d]		Model 3[e]	
		RR	(95% CI)	aRR	(95% CI)	aRR	(95% CI)
Any maternal milk	Low	Ref		Ref		Ref	
	Intermediate	1.0	(0.9 – 1.2)	1.0	(0.9 – 1.1)	1.0	(0.8 – 1.2)
	High	1.1	(1.0 – 1.2)	1.0	(0.9 – 1.2)	1.0	(0.9 – 1.2)
Exclusive maternal milk	Low	Ref		Ref		Ref	
	Intermediate	2.4	(1.8 – 3.2)	2.2	(1.7 – 3.0)	2.3	(1.6 – 3.3)
	High	1.9	(1.3 – 2.7)	1.8	(1.2 – 2.5)	1.8	(1.2 – 2.8)
Any direct breastfeeding	Low	Ref		Ref		Ref	
	Intermediate	1.1	(0.8 – 1.6)	1.1	(0.8 – 1.5)	1.1	(0.8 – 1.5)
	High	1.2	(0.9 – 1.6)	1.2	(0.9 – 1.5)	1.2	(0.9 – 1.5)
Exclusive direct breastfeeding	Low	Ref		Ref		Ref	
	Intermediate	2.5	(1.7 – 3.7)	2.3	(1.6 – 3.2)	2.2	(1.4 – 3.3)
	High	1.8	(1.1 – 2.9)	1.6	(1.0 – 2.6)	1.5	(0.9 – 2.6)

[a] Uni- and multivariable Risk Ratios (RR) were computed using multilevel modified Poisson regression analysis. Random effects: unit and region. aRR indicates adjusted RR.

[b] Parental Presence Score: Low 1-6, Intermediate 7-9, High 10

[c] Model 1: only PPS as predictor.

[d] Model 2: adjusted for other unit variables: unit level, written protocol for developmental care and for breastfeeding, Baby Friendly Hospital Initiative, dedicated staff to support breastfeeding and parental KC policies.

[e] Model 3: adjusted for all variables present in Model 2 plus maternal and infant variables: maternal age, country of birth, parity, type of pregnancy, gestational age, caesarean delivery, male gender, inborn status, Apgar score <7 at 5', SGA, any major congenital anomaly and BPD.

TABLE S_min. Association between unit PPS and breastfeeding outcomes at discharge from hospital (lowest regional score category for all excluded children)[a]

Feeding outcomes at discharge	Parental Presence Score (PPS)[b]	Model 1[c]		Model 2[d]		Model 3[e]	
		RR	**(95% CI)**	**aRR**	**(95% CI)**	**aRR**	**(95% CI)**
Any maternal milk	Low	Ref		Ref		Ref	
	Intermediate	1.1	(1.0 – 1.3)	1.1	(1.0 – 1.2)	1.1	(1.0 – 1.3)
	High	1.1	(1.0 – 1.2)	1.0	(0.9 – 1.1)	1.0	(0.9 – 1.1)
Exclusive maternal milk	Low	Ref		Ref		Ref	
	Intermediate	1.4	(1.0 – 1.9)	1.4	(1.0 – 1.8)	1.4	(1.1 – 1.9)
	High	1.4	(1.1 – 1.9)	1.3	(1.0 – 1.7)	1.3	(1.0 – 1.7)
Any direct breastfeeding	Low	Ref		Ref		Ref	
	Intermediate	1.4	(1.1 – 1.8)	1.4	(1.1 – 1.7)	1.4	(1.1 – 1.7)
	High	1.3	(1.1 – 1.6)	1.2	(1.0 – 1.5)	1.2	(1.0 – 1.4)
Exclusive direct breastfeeding	Low	Ref		Ref		Ref	
	Intermediate	1.7	(1.2 – 2.3)	1.6	(1.1 – 2.2)	1.6	(1.2 – 2.2)
	High	1.8	(1.3 – 2.4)	1.6	(1.3 – 2.1)	1.5	(1.2 – 2.0)

[a] Uni- and multivariable Risk Ratios (RR) were computed using multilevel modified Poisson regression analysis. Random effects: unit and region. aRR indicates adjusted RR.

[b] Parental Presence Score: Low 1-6, Intermediate 7-9, High 10

[c] Model 1: only PPS as predictor.

[d] Model 2: adjusted for other unit variables: unit level, written protocol for developmental care and for breastfeeding, Baby Friendly Hospital Initiative, dedicated staff to support breastfeeding and parental KC policies.

[e] Model 3: adjusted for all variables present in Model 2 plus maternal and infant variables: maternal age, country of birth, parity, type of pregnancy, gestational age, caesarean delivery, male gender, inborn status, Apgar score <7 at 5', SGA, any major congenital anomaly and BPD.

4.3. PAPER III

Prevalence and duration of breast milk feeding in very preterm infants: a 3-year follow-up study and a systematic literature review

Rodrigues C, Teixeira R, Fonseca MJ, Zeitlin J, Barros H; on behalf of the Portuguese EPICE Network.

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ORIGINAL ARTICLE

WILEY Paediatric and Perinatal Epidemiology

Prevalence and duration of breast milk feeding in very preterm infants: A 3-year follow-up study and a systematic literature review

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Abstract

Background: The World Health Organization recommends exclusive breast milk feeding until 6 months and continuing up to 2 years of age; little is known about whether very preterm infants are fed in accordance with these recommendations. We aimed to describe the prevalence and duration of breast milk feeding in very preterm children and to systematically review internationally published data.

Methods: We evaluated breast milk feeding initiation and duration in very preterm children born in 2 Portuguese regions (2011-2012) enrolled in the EPICE cohort and followed-up to the age of 3 (n = 466). We searched PubMed® from inception to January 2017 to identify original studies reporting the prevalence and/or duration of breast milk feeding in very preterm children.

Results: 91.0% of children received some breast milk feeding and 65.3% were exclusively breast fed with a median duration of 2 months for exclusive and 3 months for any breast milk; only 9.9% received exclusive breast milk for at least 6 months, 10.2% received any breast milk for 12 months or more, and 2.0% for up to 24 months. The literature review identified few studies on feeding after hospital discharge (n = 9); these also reported a low prevalence of exclusive breast milk feeding at 6 months (1.0% to 27.0%) and of any breast milk at 12 months (8.0% to 12.0%).

Conclusions: The duration of breast milk feeding among Portuguese very preterm infants was shorter than recommended. However, this appears to be common globally. Research is needed to inform strategies to promote continued breast milk feeding.

KEYWORDS
breast feeding, breast milk, EPICE project, very preterm infants

*Members of the EPICE-Portugal Network are given in Appendix.

1 | INTRODUCTION

There is a general recommendation to provide exclusive breast milk feeding during the first 6 months of life to both full-term and preterm infants, and to continue up to 2 years or longer with complementary foods.[1,2] There is evidence regarding the health benefits of breast milk feeding for very preterm infants (born at <32 weeks of gestation), namely, in decreasing multiple neonatal morbidity conditions related to prematurity, such as infections and necrotizing enterocolitis, and also, in the improvement of neurodevelopmental outcomes.[2,3]

Despite these benefits, a low prevalence of breast milk feeding is still described and seems common in very preterm children.[4-6] Most research has focused on breast milk feeding in hospital or at discharge home from hospital with fewer studies able to describe the full duration of breast milk feeding.[6] In Portugal, the frequency of breast milk feeding in these children has only been evaluated twice, at discharge in 2003[4] and 15-22 days after delivery during Neonatal Intensive Care Unit (NICU) stay in 2013,[7] both studies described the North region. No information is available about the duration of exclusive or any breast milk feeding in Portuguese very preterm infants. Also, in the international context, a systematic evaluation of the prevalence and duration of breast milk feeding in very preterm infants is lacking.

Therefore, this study aimed to describe the frequency and duration of breast milk feeding in Portuguese very preterm infants and to systematically review the published literature on breast milk feeding in very preterm infants, with a focus on studies providing data on the duration of exclusive breast milk for the first 6 months and any breast milk through at least the first year.

2 | METHODS

2.1 | Design

A cohort of very preterm Portuguese children was followed. They were recruited as part of the longitudinal study Effective Perinatal Intensive Care in Europe (EPICE) that included all live births between 22 and 31 completed weeks of gestation occurring in 19 regions from 11 European countries, in 2011 to 2012.[8] The study was approved by the Ethics Committee of the participating hospitals and by the Portuguese Data Protection Authority (authorization 7426/2011). Informed consent was obtained from all parents or legal representative.

2.2 | Setting and sample

The EPICE study in Portugal involved all the public maternity and neonatal intensive care units (NICUs) from 2 regions [North and Lisbon and Tagus Valley (LTV)] (n = 27), along with 3 private units from LTV. In 2011 and 2012, 68.6% and 66.3% of all very preterm births in Portugal occurred in these 2 geographical regions, respectively.[9]

The sample included all infants discharged alive from all NICUs whose parents provided informed consent [544 (89.6%) of 607 eligible participants].[10] At the 3-year follow-up, 2 children had died, 2 children had been adopted and unavailable for further evaluation according to legal rules, 5 parents declined to participate, and 69 were unreachable. Thus, 466 infants remained for this analysis (Figure S1). Participants were compared to 78 non-participants regarding maternal and infant characteristics. Mothers of participants were older, and more frequently born in Portugal, primipara, and breast milk feeding at discharge (Table S1).

2.3 | Data collection

Data on maternal and infant characteristics at baseline were abstracted from medical records by local health care professionals using a pretested standardized questionnaire.[10] We collected data on maternal age, mother's country of birth, parity (primipara vs multipara), twinning, gender, gestational age at birth (weeks), birthweight (g), length of hospitalization (days), type of feeding at discharge, and neighbourhood socio-economic deprivation.

Information on breast milk feeding practices was obtained using a structured questionnaire completed by the parents or legal guardians when the children were 3 years of age (chronological age), using a computer-assisted telephone interview, by trained interviewers. Parents were asked if the child has ever received breast milk feeding, including donor's milk. If the answer was yes then they were asked for how long the child received breast milk exclusively and for how long the child received breast milk feeding combined with formula feeding or with other type of foods and/or beverages.

2.4 | Definition of variables

Gestational age was based on the best estimate of the obstetrical team, using information from ultrasound measures and last menstrual period. Infants were georeferenced according to their home address using the ArcGIS Online World Geocoding Service and Google Maps. Neighbourhood socio-economic deprivation was assessed using the European Deprivation Index (EDI) that is used to classify small areas according to their level of socio-economic deprivation. The construction of EDI, which was developed for 5 European countries, was fully described elsewhere.[11] In Portugal, EDI score resulted from the weighted sum of the following standardized variables at census block group level: % overcrowded households, % households with no bath or shower, % household with no indoor flushing, % households occupied by non-owners, % women aged 65 or more, % individuals with low education, % individuals in low-income occupation, and % unemployed individuals. The EDI score was categorized in quintiles of increasing deprivation (1-least to 5-most deprived).[12]

Regarding our outcome of interest, exclusive breast milk feeding was considered when the infant received no food or drinks other than the mother's own milk or donor's milk, regardless of route of administration. Any breast milk feeding was considered if the infant received some breast milk, regardless of route of administration, and independently if it was only exclusive or mixed (the addition of formula or other food and/or drink to breast milk). Duration of breast milk feeding was defined as the age of the child, reported in months of chronological age, when the exclusive and any breast milk feeding was stopped completely. Information on any breast milk feeding was obtained for all 466 participants, but 13 did not report the duration period, remaining 453 with information on any breast milk feeding duration. To compute exclusive breast milk feeding, we excluded 22 participants [19 did not report the information and 3 provided unreliable information (duration ≥12 months)], remaining 444 participants for analysis of exclusive breast milk feeding.

2.5 | Statistical analysis

Sample characteristics are presented as counts and proportions for all categorical variables, and median and percentile 25 and percentile 75 (p25-p75) for non-normally distributed continuous variables. We compared the maternal and infant characteristics of children receiving exclusive and any breast milk for shorter vs longer durations. Proportions were compared using a chi-square test and non-normally distributed continuous variables with the Kruskal-Wallis test. The duration of exclusive and any breast milk feeding was categorized in 3 groups: (1) never received the type of breast milk considered; (2) between >0 and <4 months for exclusive and between >0 and <6 months for any breast milk; (3) and ≥4 months for exclusive and ≥6 months for any breast milk. The cut-off point of 4 months for exclusive breast milk was considered because this is the length of the fully paid maternity leave in Portugal, and so the proportion of children on exclusive breast milk for at least 6 months was very low which would result in lack of statistical power. Also for any breast milk, we defined the cut-off point of 6 months as the proportion of children on any breast milk for at least 12 months was very low which would result in lack of statistical power.

Kaplan-Meier curves estimates were fitted to describe exclusive and any breast milk feeding duration (continuous variable) only among infants who initiated breast milk feeding.

Analyses were performed using STATA 11.0 software (Stata Corporation, College Station, TX, USA).

2.6 | Systematic literature review

The review was conducted based on the Preferred Reporting of Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[13,14] PubMed® was searched from inception to January 2017, to identify original published studies reporting the prevalence and/or duration of breast milk feeding in very preterm infants. The following search expression was used [("breast milk" OR breastmilk OR breastfeeding OR feeding OR "human milk") AND ("very preterm" OR "very premature" OR "extreme prematurity" OR "extremely preterm" OR "extremely premature" OR "extreme preterm" OR "very low birth weight" OR "very low birthweight") AND (duration OR prevalence OR frequency OR proportion)], 443 studies were identified.

Retrieved publications were screened by 2 researchers (CR and RT) following predefined criteria to determine eligibility. Studies were excluded if: (1) the full text was not written in English, French, German, Italian, Portuguese, or Spanish; (2) did not involve humans (e.g. in vitro or animal research); (3) non-original articles (e.g. book chapters, review articles, editorials, comments, guidelines); (4) reported qualitative research or case studies; (5) non-observational (e.g. randomized controlled trials); (6) case–control; (7) not focused on very preterm infants (≤32 weeks of gestational age) or very low birthweight (≤1500 g); (8) data not related to the prevalence and/or duration of breast milk feeding; and (9) duplicate studies or evaluating the same sample.

Two researchers (CR and RT) evaluated the included studies to extract the following data: year of publication, country, infants' year of birth, sample size, gestational age, and/or birthweight. The prevalence by type of breast milk feeding practices was extracted, also considering the reporting period (e.g. at initiation, at hospital discharge) and/or duration reported, whenever available. Differences in the data extracted by the 2 researchers were discussed involving a third researcher (HB) whenever necessary.

In this review, breast milk feeding practices were categorized as: exclusive breast milk, mixed (breast milk with formula) and any breast milk (receiving some breast milk, independently if it was exclusive or mixed). Breast milk was considered if it was the mother's own milk or a donor's milk and regardless of the feeding method (directly from the breast, bottle, tube, or cup).

3 | RESULTS

3.1 | Prevalence and duration of breast milk feeding

Our sample included 26.4% (n = 123) extremely preterm (<28 weeks) and 73.6% (n = 343) very preterm (28 to 31 weeks) infants with a median gestational age of 29 weeks (p25-p75: 27-31). The median birthweight was 1170 g (p25-p75: 945-1430) and the median length of hospital stay was 51 days (p25-p75: 37-71). Overall, the prevalence of exclusive breast milk feeding initiation was 65.3% (290/444) and 91.0% (424/466) for any breast milk feeding. No differences were found between North and LVT on exclusive (63.3% vs 67.1%) or any breast milk feeding (89.4% vs 92.4%).

Figure 1A shows that 34.7% of very preterm infants never received breast milk exclusively, 24.8% were exclusively fed with breast milk for <2 months, and 9.9% for at least 6 months or more. While only 9.3% (42/453) of very preterm infants never received any breast milk, 25.8% were fed for <2 months and 38.4% between 2 months and <6 months. Overall, 26.5% received any breast milk for 6 months or more, 10.2% for 12 months or more, and 2.0% 24 months or more (Figure 1B).

Tables 1 and 2 summarize maternal and infant characteristics according to exclusive and any breast milk feeding duration respectively. No differences were found for exclusive breast milk feeding

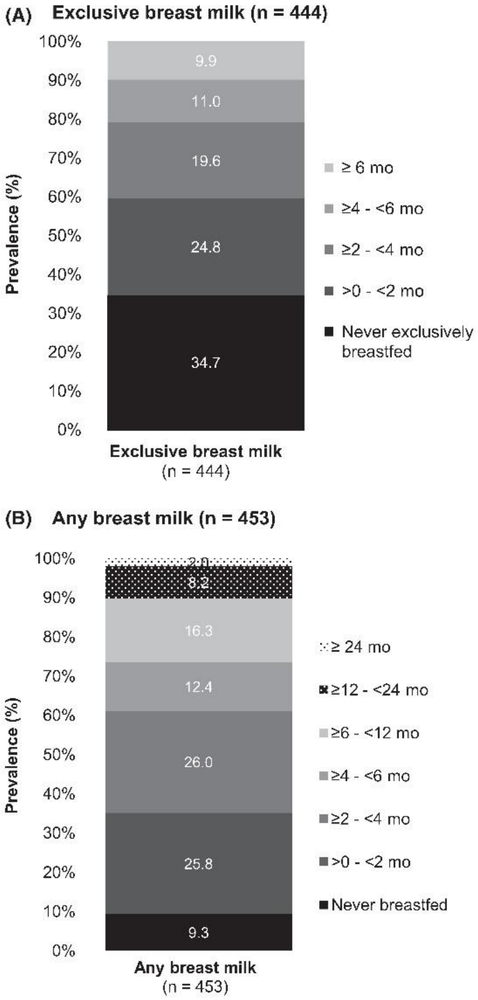


FIGURE 1 A and B, Duration of exclusive breast milk feeding (A) and any breast milk feeding (B) in Portuguese very preterm infants. The duration is reported in months of chronological age.

regarding the maternal and infant characteristics evaluated. We observed that among children who never received any breast milk feeding, 26.2% were of non-Portuguese mothers and 52.4% were of multiparae women; of those who received any breast milk for at least 6 months or more, 15.8% were of non-Portuguese mothers and 36.1% of multiparae women.

Figure 2A,B present the proportion of very preterm infants remaining on exclusive and any breast milk by month, up to 6 and 12 months, respectively, only among infants who initiated breast milk feeding. The duration of exclusive breast milk feeding ranged from 0.1 to 9.0 months, with a median duration of 2.0 months (p25-p75: 1.0-4.0). At 6 months of age <5% of children were on exclusive breast milk feeding. Any breast milk feeding duration ranged from 0.1 to 36.0 months, with a median duration of 3.0 months (p25-p75: 1.2-6.0). At the end of the first month, 25% of children had already

TABLE 1 Exclusive breast milk feeding duration (chronological age) according to maternal and infant characteristics (n = 444)

Characteristics	Exclusive breast milk feeding duration (chronological age) Never (n = 154) n (%)	<4 months (n = 197) n (%)	≥4 months (n = 93) n (%)
Maternal age at birth (y)			
≤29	49 (31.8)	80 (40.6)	31 (33.3)
30-34	54 (35.1)	67 (34.0)	43 (46.2)
≥35	51 (33.1)	50 (25.4)	19 (20.4)
Missing	0	0	0
Mothers' country of birth			
Portugal	131 (85.1)	179 (90.9)	82 (88.2)
Others	23 (14.9)	18 (9.1)	11 (11.8)
Missing	0	0	0
Neighbourhood socio-economic deprivation			
1 (least deprived)	40 (26.5)	65 (33.0)	33 (36.3)
2	36 (23.8)	42 (21.3)	16 (17.6)
3	22 (14.6)	23 (11.7)	14 (15.4)
4	26 (17.2)	32 (16.2)	18 (19.8)
5 (most deprived)	27 (17.9)	35 (17.8)	10 (11.0)
Missing	3 (1.9)	0	2 (2.2)
Parity			
Primipara	92 (59.7)	138 (70.0)	61 (66.3)
Multipara	62 (40.3)	59 (30.0)	31 (33.7)
Missing	0	0	1 (1.1)
Twin			
No	105 (68.2)	134 (68.0)	65 (69.9)
Yes	49 (31.8)	63 (32.0)	28 (30.1)
Missing	0	0	0
Child's gender			
Male	87 (56.5)	108 (54.8)	57 (61.3)
Female	67 (43.5)	89 (45.2)	36 (38.7)
Missing	0	0	0
Gestational age at birth (wk)			
24-27	44 (28.6)	51 (25.9)	23 (24.7)
28-29	35 (22.7)	61 (31.0)	27 (29.0)
30-31	75 (48.7)	85 (43.2)	43 (46.2)
Missing	0	0	0
Birthweight (g)			
<1000	49 (31.8)	73 (37.1)	28 (30.1)
≥1000	105 (68.2)	124 (62.9)	65 (69.9)
Missing	0	0	0
Length of hospitalization (d)			
Median (p25-p75)	52 (37-71)	52 (39-71)	47 (34-70)
Missing	0	0	0

p25, percentile 25; p75, percentile 75.

TABLE 2 Any breast milk feeding duration (chronological age) according to maternal and infant characteristics (n = 453)

Characteristics	Any breast milk feeding duration (chronological age)		
	Never (n = 42) n (%)	<6 months (n = 291) n (%)	≥6 months (n = 120) n (%)
Maternal age at birth (y)			
≤29	11 (26.2)	111 (38.1)	38 (31.7)
30-34	15 (35.7)	104 (35.7)	50 (41.7)
≥35	16 (38.1)	76 (26.1)	32 (26.7)
Missing	0	0	0
Mothers' country of birth			
Portugal	31 (73.8)	267 (91.8)	101 (84.2)
Others	11 (26.2)	24 (8.2)	19 (15.8)
Missing	0	0	0
Neighbourhood socio-economic deprivation			
1 (least deprived)	8 (19.0)	97 (33.6)	39 (33.3)
2	11 (26.2)	58 (20.1)	26 (22.2)
3	6 (14.3)	42 (14.5)	14 (12.0)
4	11 (26.2)	41 (14.2)	24 (20.5)
5 (most deprived)	6 (14.3)	51 (17.6)	14 (12.0)
Missing	0	2 (0.7)	3 (2.5)
Parity			
Primipara	20 (47.6)	197 (67.7)	76 (63.9)
Multipara	22 (52.4)	94 (32.3)	43 (36.1)
Missing	0	0	1 (0.8)
Twin			
No	26 (61.9)	196 (67.4)	90 (75.0)
Yes	16 (38.1)	95 (32.6)	30 (25.0)
Missing	0	0	0
Child's gender			
Male	21 (50.0)	165 (56.7)	71 (59.2)
Female	21 (50.0)	126 (43.3)	49 (40.8)
Missing	0	0	0
Gestational age at birth (wk)			
24-27	14 (33.3)	70 (24.0)	34 (28.3)
28-29	10 (23.8)	85 (29.2)	32 (26.7)
30-31	18 (42.9)	136 (46.7)	54 (45.0)
Missing	0	0	0
Birthweight (g)			
<1000	16 (38.1)	99 (34.0)	37 (30.8)
≥1000	26 (61.9)	192 (66.0)	83 (69.2)
Missing	0	0	0
Length of hospitalization (d)			
Median (p25-p75)	56.5 (39-88)	52 (37-70)	47.5 (36-70)
Missing	0	0	0

p25, percentile 25; p75, percentile 75.

stopped any breast milk feeding. At 12 months of age <10.0% of children received any breast milk and at 18 months <3%. In 34.4% of the cases, breast milk feeding stopped during hospital stay.

3.2 | Systematic literature review

From the literature review, we identified 31 studies[4,6,15-43] that address the prevalence and/or duration of breast milk feeding in very preterm infants (Table S2), reporting data from 34 different countries (1 study was multicenter): 16 European, 11 American, 3 Oceanian, 3 Asian, and 1 African. Articles were published between 1998 and 2016, and described data collected between 1986 and 2015. Among the 31 studies included, 11 reported the prevalence of breast milk feeding at initiation, 13 at hospital discharge, 9 at some other time (e.g. in the first 2 weeks after birth, at 36 weeks postmenstrual age), and 13 presented complete data on overall duration. Only 9 studies[6,18,21,28,35,36,39,41,42] presented data for breast milk feeding specifically at 6 months or more (chronological or corrected age) and 2 studies[6,36] at 12 months (chronological age) (Table 3). The prevalence of any breast milk feeding at 6 months or more (chronological or corrected age) ranged from 19.9% in Israel[18] to 50.0% in Denmark,[6] and for exclusive breast milk ranged between 1.0% in Sweden[28] and 27.0% in Denmark.[6] At 12 months, the prevalence of any breast milk was 8.0% in Denmark[6] and 12.0% in Sweden,[36] the only studies reporting this information. None of the studies presented data for breast milk feeding duration for more than 12 months.

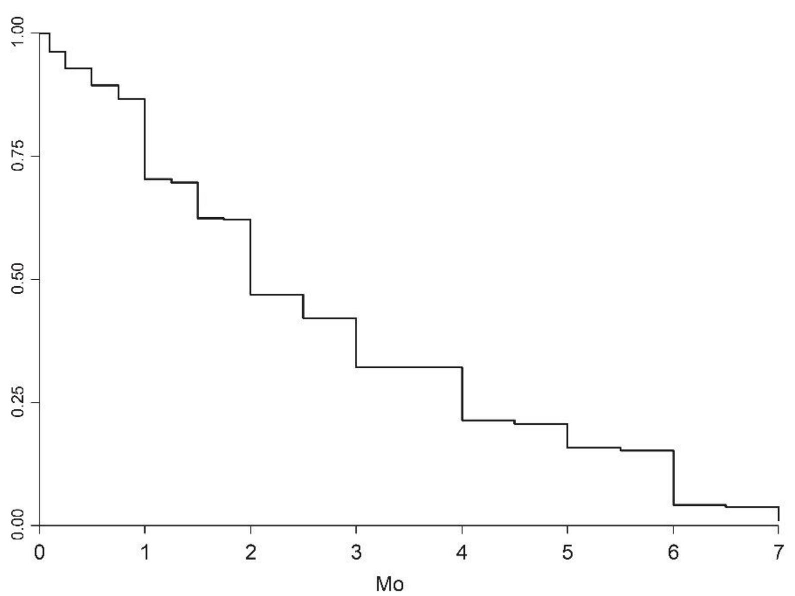
4 | COMMENT

4.1 | Principal findings

This is the first description of the duration of breast milk feeding in Portuguese very preterm infants. We found that 91.0% of the very preterm infants initiated any breast milk feeding and 65.3% exclusive breast milk feeding. The median duration of exclusive breast milk feeding was 2 months and of any breast milk feeding 3 months. The World Health Organization (WHO) recommends 6 months of exclusive breast milk with continued breast milk feeding along with complementary foods up to 2 years of age or beyond.[1,2] In Portugal, very preterm infants are clearly far from achieving this recommendation, despite high initiation rates for any breast milk feeding.

4.2 | Interpretation

In Generation XXI, a population-based Portuguese birth cohort, including live births with at least 24 weeks of gestation, and assembled in 2005/2006 in the metropolitan area of Porto, the proportion of infants that never received breast milk was similar to the observed in our very preterm sample (8.4% vs 9.0%).[44] The median durations of exclusive and any breast milk feeding in our study were shorter than in infants from the Generation XXI cohort, 2.0 vs 2.5 months for exclusive and 3.0 vs 5.5 months for any breast milk feeding, respectively.[44] In 2013, the prevalence of any breast milk feeding



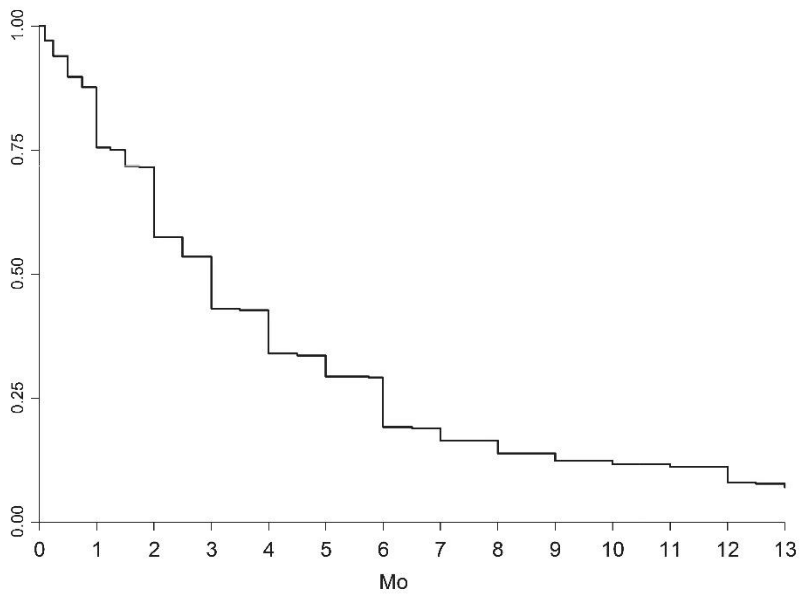


FIGURE 2 A and B, Kaplan-Meier curve with estimates of exclusive breast milk feeding duration (A) and of any breast milk feeding duration (B) in very preterm infants in Portugal, only among infants who initiated the type of breast milk feeding considered. The duration is reported in months of chronological age.

in the North region of Portugal was 96.7% in very preterm infants evaluated at 15-22 days after delivery and 96.4% in full-term infants analysed during the puerperium.[7]

Few studies reported breast milk feeding prevalence and duration in very preterm infants, and most of them described the prevalence at initiation, during hospitalization, and/or at discharge, as revealed our systematic literature review. In addition, we observed that the prevalence and duration of breast milk feeding in very preterm infants varies widely across countries. At initiation period, the prevalence of any breast milk feeding in very preterm infants was 99.0% in Denmark (2009/2010),[6] 96.8% in Australia (2011/2012),[21] and 75.5% in the USA (2007-2010).[20] The Australian study showed that the proportion of very preterm infants that received breast milk for more than 6 months was 41.7%,[21] while it was only 26.5% at 6 months or more in our sample. Similarly, in Denmark and Sweden, 50.0% and 45.0% of very preterm infants were being fed with breast milk at 6 months of age respectively.[6,36] At hospital discharge, results from a population-based study of very preterm infants born in 2003 in 8 European regions showed the prevalence of any breast milk feeding at discharge ranged between 19% in Burgundy (France) and 70% in Lazio (Italy),

TABLE 3 Main characteristics of the studies included in the systematic literature review with information on breast milk feeding practices at or after 6 months of age (chronological or corrected age)

First author, year of publication	Country	Infants' year of birth	Sample size	Gestational age (weeks) or Birthweight (g)	Breast milk feeding practices	Prevalence (%)	Duration of breast milk (months)
Morag, 2016	Israel	2012-2014	181	<32	Any	19.9	6 CA
Sharp, 2015	Australia	1990-1992	432	<32	Any	25.8	>6
		2011-2012	253			41.7	
Maastrup, 2014	Denmark	2009-2010	60	24-27	Exclusive	27.0	6
					Any	50.0	6
						8.0	12
			257	28-31	Exclusive	23.0	6
					Any	47.0	6
						14.0	12
Flacking, 2011	Sweden	2001-2002	103	<32	Exclusive	1.0	6 CA
					Any	43.0	6 CA
Åkerström, 2007	Sweden	1996, 2001, 2004	27	<28	Any	41.0	6 CA
			82	28-31	Any	47.0	6 CA
Flacking, 2007	Sweden	1993-2001	225	<32	Any	45.0	6
						22.0	9
						12.0	12
Smith, 2003	USA	1991-1993	361	≤1500	Any	21.6	>6
Horwood, 2001	New Zealand	1986	280	<1500	Any	21.1	≥8
Elder, 1999	Australia	1990-1991	538	<33	Any	26.9	>6

CA, Corrected age.

while 50% of participating Portuguese very preterm were fed with any breast milk at discharge (6% exclusive and 44% mixed).[4] This review did not find any study reporting data on breast milk feeding after 12 months in very preterm infants. Furthermore, there is a paucity of data from Southern and Eastern Europe countries.

The low prevalence and short duration of breast milk feeding among very preterm infants may be explained by several factors. First, by difficulties inherent to their higher neonatal morbidity, such as the delicate transition from enteral to oral feeding and the long stay in the stressful environment of the NICUs.[18,32] In addition, factors related to health care services may play an important role in the support and promotion of breast milk feeding as it has been shown that hospital policies and practices, independently of maternal sociodemographic factors, exert influence on the initiation and duration of breast milk feeding.[45] A previous study of the Portuguese infants in the EPICE cohort found a wide variation in the prevalence of breast milk feeding at discharge across Portuguese NICUs, ranging from 49.0% to 83.4% for any breast milk and from 3.3% to 50.0% for exclusive breast milk. This study found that NICUs characteristics, as having designated members to support mothers who were breast feeding, influence feeding practices independently of maternal and infant characteristics.[46] Furthermore, an inadequate legislation covering maternity protection may hinder women to breastfeed their child.[47] In Portugal, mothers have access to 4 months of fully paid parental leave, which is shorter than the WHO recommendation for exclusive breast milk feeding. Considering that the association between early return to work and shorter breast milk feeding duration has been reported in several studies, this may partially explain the differences between countries described here, as Sweden, Australia, and Denmark provide longer periods of maternity leave than Portugal.[48] Overall, our findings indicate a need for improvements in breast milk feeding supportive measures for mothers at neonatal units and after discharge.[21,49]

4.3 | Strengths of the study

A major strength of our study is the use of high-quality data, obtained from a population-based prospective cohort, using a structured questionnaire at 3 years of age. This allowed us to estimate the prevalence and total duration of exclusive and any breast milk feeding until the age of 3. In addition, our study also included a systematic review, and to the best of our knowledge, this is the first systematic review describing the prevalence and/or duration of breast milk feeding in very preterm infants.

4.4 | Limitations of the data

Our results could be affected by potential recall bias due to retrospective data collection, and the time between stopping breast milk feeding and reporting for most parents. In a birth cohort from Denmark, comparing data on breast milk feeding obtained from the self-administered questionnaire at 18 months with the weekly short message service (SMS) questions since birth, a longer duration of exclusive breast milk feeding using the self-administered questionnaire was observed, while the duration of any breast milk feeding was similar between the 2 methods.[50] In a Brazilian study, 70% of mothers correctly recalled breast milk feeding duration when their children were 4 years of age, while 21% reported higher duration and 9% reported lower duration.[51]

Another limitation was the lack of detailed information on sociodemographic characteristics, such as mother's employment and educational level. However, we georeferenced the infants and used the European Deprivation Index to classify neighbourhood socio-economic deprivation index, which has been used as a valid proxy of individual socio-economic position,[11] and we did not find differences. This result was unexpected considering that previous studies have shown that maternal socio-economic status is associated with initiation and duration of breast milk feeding in very preterm infants.[31,36] However, the European Deprivation Index is a validated and robust measure with very fine geographical scales and was used in other studies with Portuguese data that reported associations with different outcomes.[52,53]

Regarding our systematic literature review, a considerable heterogeneity was observed across the studies, not allowing us to conduct a meta-analysis. It is difficult to compare the findings of studies on breast milk feeding prevalence due to the different definitions of breast milk feeding used—only breast feeding or breast and bottle feeding; the misclassification of exclusive breast milk feeding; the different periods of assessment—during hospital stay, at or after hospital discharge; and the use of chronological/corrected age when reporting the duration. In this sense, the comparisons among studies should be performed carefully.

5 | CONCLUSIONS

Given that the duration of both exclusive and any breast milk feeding is positively associated with several optimal health outcomes and, as we found that in Portugal both were below the recommendations, more studies are needed to clarify the longitudinal obstacles to breast milk feeding beyond hospital discharge. Appropriate interventions are needed to increase both the prevalence and duration of exclusive and any breast milk feeding among this vulnerable population. Hence, enabling women to remain at home with their infants for a longer period through a more comprehensive labour policy and maternity leave provision (e.g. to establish 6 months mandatory paid maternity leave) represent public health measures that can contribute to improve breast milk feeding practices in Portugal.[47]

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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APPENDIX

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Supporting Information

Table S1. Comparison of participants' and non-participants' characteristics

Characteristics	**Non-participants (n=78)** n (%)	**Participants (n=466)** n (%)
Maternal age at birth (years)		
≤29	37 (47.4)	166 (35.6)
30-34	13 (16.7)	171 (36.7)
≥35	28 (35.9)	129 (27.7)
Missing	0	0
Mothers' Country of birth		
Portugal	49 (64.5)	411 (88.2)
Others	27 (35.5)	55 (11.8)
Missing	2 (2.6)	0
Neighborhood socioeconomic deprivation		
1 (least deprived)	20 (25.6)	147 (31.9)
2	11 (14.1)	97 (21.0)
3	21 (26.9)	66 (14.3)
4	9 (11.5)	78 (16.9)
5 (most deprived)	17 (21.8)	73 (15.8)
Missing	0	5 (1.1)
Parity		
Primipara	39 (50.0)	305 (65.6)
Multipara	39 (50.0)	160 (34.4)
Missing	0	1 (0.2)
Twin		
No	54 (69.2)	319 (68.4)
Yes	24 (30.8)	147 (31.6)
Missing	0	0
Child's gender		
Male	47 (60.3)	267 (57.3)
Female	31 (39.7)	199 (42.7)
Missing	0	0
Gestational age at birth (weeks)		
24-27	23 (29.5)	123 (26.4)
28-29	17 (21.8)	131 (28.1)
30-31	38 (48.7)	212 (45.5)
Missing	0	0
Birthweight (grams)		
<1000	25 (32.0)	159 (34.1)
≥1000	53 (68.0)	307 (65.9)
Missing	0	0
Type of feeding at discharge		
Exclusive formula	40 (51.3)	145 (31.1)
Mixed	31 (39.7)	193 (41.4)
Exclusive breast milk	7 (9.0)	128 (27.5)
Missing	0	0
Length of hospitalization (days)		
Median (p25-p75)	53 (39-84)	51 (37-71)
Missing	0	0

Abbreviations: p25, percentile 25; p75, percentile 75.

Supporting Information

Table S2. Main characteristics of all studies included in the systematic literature review

First author, year of publication	Country	Infants' year of birth	Sample size	Gestational age (weeks)	Birthweight (grams)	Breast milk feeding practices	Prevalence (%)	Reporting period	Duration of breast milk
Ericson, 2016	Sweden	2004 2013	1936	22-27		Exclusive	55.0 16.0	Discharge	
		2004 2013	4595	28-31			41.0 34.0		
Freitas, 2016	Brazil	2010-2015	32	<32		Exclusive	10.8	1 mo CA	
						Mixed	26.8	1 mo CA	
						Any			4.2 mo[a](median) 1.2 mo[b](median)
Herich, 2016	Italy	2011-2012	1047	<32		Exclusive	25.1	Initiation	
						Exclusive	17.6	Discharge	
						Any	62.7	Discharge	
Morag, 2016	Israel	2012-2014	181	<32		Any	80.6	14 dy	
							71.8	36 wk GA	
							48.0	6 wk after discharge	
							19.9		6 mo CA
Casavant, 2015	USA	2011-2013	96		≤1500	Any	99.0	Initiation	
							48.0	Discharge	
Hwang, 2015	USA	2007-2010	Not specified	23-33		Any	75.5	Initiation	
							59.3	⩾10 wk	
Sharp, 2015	Australia	1990-1992 2011-2012	432 253	<32		Any	65.6 96.8	Initiation	
		1990-1992					10.0 10.0 20.8 25.8		<1 mo 1-2 mo 3-6 mo >6 mo
		2011-2012					9.5 13.9 31.7 41.7		<1 mo 1-2 mo 3-6 mo >6 mo

First author, year of publication	Country	Infants' year of birth	Sample size	Gestational age (weeks)	Birthweight (grams)	Breast milk feeding practices	Prevalence (%)	Reporting period	Duration of breast milk
Wilson, 2015	Sweden	2011-2012	138	<32		Exclusive	55.0	36 wk PA	
						Mixed	25.0		
						Any	80.0		
Maastrup, 2014	Denmark	2009-2010	60	24-27		Exclusive	63.0		1 mo
							38.0		4 mo
							27.0		6 mo
						Any	95.0	Initiation	
							95.0		1 mo
							62.0		4 mo
							50.0		6 mo
							8.0		12 mo
			257	28-31		Exclusive	73.0		1 mo
							37.0		4 mo
							23.0		6 mo
						Any	99.0	Initiation	
							89.0		1 mo
							59.0		4 mo
							47.0		6 mo
							14.0		12 mo
Murase, 2014	Japan	2008-2012	85	<32		Any	58.0	Discharge	
Barois, 2013	France	2009-2011	77	<32		Exclusive	22.0	Discharge	
						Any	38.0		
Davanzo, 2013	Italy	2005-2006	613	<32		Exclusive	31.0	Discharge	
						Any	55.8		
Corpeleijn, 2012	Netherlands	2009-2010	349		<1500	Exclusive	2.0	10 dy	
						Mixed	86.0		

First author, year of publication	Country	Infants' year of birth	Sample size	Gestational age (weeks)	Birthweight (grams)	Breast milk feeding practices	Prevalence (%)	Reporting period	Duration of breast milk
Maayan-Metzger, 2012	Israel	2006-2008	400	≤32		Exclusive	13.5	1 mo	
						Mixed	74.0		
						Any	87.5		
Bonet, 2011	8 European regions	2003		<32				Discharge	
	Belgium/Flanders		342			Exclusive	17.0		
						Mixed	20.0		
						Any	37.0		
	France/Burgundy		305			Exclusive	14.0		
						Mixed	5.0		
						Any	19.0		
	France/Ile-de-France		694			Exclusive	7.0		
						Mixed	19.0		
						Any	26.0		
	Italy/Lazio		341			Exclusive	18.0		
						Mixed	52.0		
						Any	70.0		
	Netherlands/Central-East		297			Exclusive	22.0		
						Mixed	33.0		
						Any	55.0		
	Poland/Wielkopolska-Lubuskie		257			Exclusive	24.0		
						Mixed	13.0		
						Any	37.0		
	Portugal/North		179			Exclusive	6.0		
						Mixed	44.0		
						Any	50.0		
	United Kingdom/Trent		591			Exclusive	29.0		
						Mixed	6.0		
						Any	35.0		

First author, year of publication	Country	Infants' year of birth	Sample size	Gestational age (weeks)	Birthweight (grams)	Breast milk feeding practices	Prevalence (%)	Reporting period	Duration of breast milk
Flacking, 2011	Sweden	2001-2002	103	<32		Exclusive	51.0		1 mo CA
							45.0		2 mo CA
							34.0		3 mo CA
							15.0		4 mo CA
							4.0		5 mo CA
							1.0		6 mo CA
						Any	74.0		1 mo CA
							70.0		2 mo CA
							62.0		3 mo CA
							55.0		4 mo CA
							48.0		5 mo CA
							43.0		6 mo CA
Maia, 2011	Brazil	2005-2006	88		<1500	Exclusive	25.0	1 wk after discharge	
						Mixed	71.5		
						Any	96.5		
Pineda, 2011	USA	No information	135		<1500	Any	78.0	Initiation	
						Exclusive	34.0	Discharge	
						Any	48.0		
						Any			43 dy (mean)
Zachariassen, 2010	Denmark	2004-2008	478	≤32		Exclusive	60.0	Discharge	
						Mixed	5.0		
						Any			1.8 mo (mean)
Kirchner, 2009	Austria	2000-2005	239		<1500	Any	60.0	Discharge	
Lee, 2009	USA	2005-2006	6790		<1500	Any	61.1	Discharge	
Sisk, 2009	USA	2001-2003	184		700-1500	Mixed	86.0	2 wk	
						Any	62.0	Discharge	

First author, year of publication	Country	Infants' year of birth	Sample size	Gestational age (weeks)	Birthweight (grams)	Breast milk feeding practices	Prevalence (%)	Reporting period	Duration of breast milk
Akerström, 2007	Sweden	1996, 2001, 2004	27	<28		Any	76.0	Discharge	
							63.0		2 mo CA
							56.0		4 mo CA
							41.0		6 mo CA
			82	28-31		Any	84.0	Discharge	
							72.0		2 mo CA
							51.0		4 mo CA
							47.0		6 mo CA
Flacking, 2007	Sweden	1993-2001	225	<32		Any	79.0		2 mo
							62.0		4 mo
							45.0		6 mo
							22.0		9 mo
							12.0		12 mo
Were, 2007	Kenya	2002	175		≤1500	Exclusive	47.4	1 mo	
						Mixed	32.6		
Merewood, 2006	USA	2002	534	<32		Any	62.9	Initiation	
Smith, 2003	USA	1991-1993	361		≤1500	Any	60.0	Initiation	
							6.4		<1 wk
							23.8		1-4 wk
							32.1		1-3 mo
							16.1		4-6 mo
							21.6		>6 mo
Furman, 2002	USA	1997-1999	119	<32	<1500	Any	34.0		40 wk CA
							16.0		4 mo CA

First author, year of publication	Country	Infants' year of birth	Sample size	Gestational age (weeks)	Birthweight (grams)	Breast milk feeding practices	Prevalence (%)	Reporting period	Duration of breast milk
Horwood, 2001	New Zealand	1986	280		<1500	Any	72.8	Initiation	
							35.4		<4 mo
							16.4		4-7 mo
							21.1		≥ 8 mo
Elder, 1999	Australia	1990-1991	538	<33		Any	70.1	Initiation	
							9.5		< 1 mo
							33.6		1-6 mo
							26.9		> 6 mo
Hylander, 1998	USA	1992-1993	212		≤1500	Any	58.0	Initiation	

Abbreviations: CA, Corrected Age; GA, Gestational age; PA, Postmenstrual Age; USA, United States of America; dy, days; wk, weeks; mo, months.

[a] Infants who were receiving exclusive breast milk feeding in the 1st month CA.

[b] Infants who were receiving mixed breast milk feeding in the 1st month CA.

4.4. PAPER IV

Low breastfeeding continuation to 6 months for very preterm infants: a European multiregional cohort study

Bonnet C, Blondel B, Piedvache A, Wilson E, Bonamy AE, Gortner L, Rodrigues C, van Heijst A, Draper ES, Cuttini M, Zeitlin J; the EPICE Research Group.

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ORIGINAL ARTICLE

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Low breastfeeding continuation to 6 months for very preterm infants: A European multiregional cohort study

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Abstract

Breastfeeding confers multiple benefits for the health and development of very preterm infants, but there is scarce information on the duration of breastfeeding after discharge from the neonatal intensive care unit (NICU). We used data from the Effective Perinatal Intensive Care in Europe population-based cohort of births below 32 weeks of gestation in 11 European countries in 2011–2012 to investigate breastfeeding continuation until 6 months. Clinical and sociodemographic characteristics were collected from obstetric and neonatal medical records as well as parental questionnaires at 2 years of corrected age. Among 3,217 ever-breastfed infants, 34% were breastfeeding at 6 months of age (range across countries from 25% to 56%); younger and less educated mothers were more likely to stop before 6 months (adjusted relative risk [aRR] <25 years: 0.68, 95% CI [0.53, 0.88], vs. 25–34 years; lower secondary: 0.58, 95% CI [0.45, 0.76] vs. postgraduate education). Multiple birth, bronchopulmonary dysplasia (BPD), and several neonatal transfers reduced the probability of continuation but not low gestational age, fetal growth restriction, congenital anomalies, or severe neonatal morbidities. Among infants breastfeeding at discharge, mixed versus exclusive breast milk feeding at discharge was associated with stopping before 6 months: aRR = 0.60, 95% CI [0.48, 0.74]. Low breastfeeding continuation rates in this high-risk population call for more support to breastfeeding mothers during and after the neonatal hospitalization, especially for families with low socio-economic status, multiples, and infants with BPD. Promotion of exclusive breastfeeding in the NICU may constitute a lever for improving breastfeeding continuation after discharge.

KEYWORDS

breast milk, breastfeeding, inverse probability weighting, neonatal intensive care, prematurity, very preterm infants

*Members of the EPICE Research Group are listed in Appendix.

1 | INTRODUCTION

Breast milk is considered the best food for newborns and infants, and the World Health Organization recommends exclusive breastfeeding until 6 months of age (Bernard et al., 2017; Edmond et al., 2006; Ip et al., 2007; Kramer & Kakuma, 2002). The nutritional and immunological benefits of breast milk are particularly important for very preterm infants born at less than 32 weeks of gestation who are at higher risk of infection and other health and developmental problems than term infants. (Lechner & Vohr, 2017; Vohr et al., 2007; Vohr et al., 2017). Breastfeeding a very preterm infant also reinforces the mother's caregiving role in the neonatal intensive care unit (NICU) and can promote bonding (Flacking, Ewald, Nyqvist, & Starrin, 2006; Ikonen, Paavilainen, & Kaunonen, 2015). However, breastfeeding a very preterm infant is challenging, requiring the mother to pump milk regularly until her child has acquired the capacity to suckle at the breast and posing multiple logistic challenges during the long neonatal hospitalization (Callen & Pinelli, 2005; Nye, 2008). Consequently, breastfeeding rates for very preterm infants are lower than for full-term infants (Akerstrom, Asplund, & Norman, 2007; Flacking, Nyqvist, & Ewald, 2007; Merewood, Brooks, Bauchner, MacAuley, & Mehta, 2006).

Most research on breastfeeding very preterm infants has focused on breastfeeding initiation or at discharge from the NICU (Bonet et al., 2011; Lee & Gould, 2009; Sisk, Lovelady, Dillard, Gruber, & O'Shea, 2009; Zachariassen et al., 2010). These studies find that younger maternal age, being foreign-born, and having a low educational level reduce the probability of breastfeeding at discharge home from hospital. The child's clinical characteristics are also important: Breastfeeding is less likely among multiples and infants with low gestational ages, fetal growth restriction, severe neonatal morbidities, and congenital anomalies.

Finally, breastfeeding support policies in the NICU, including having designated members to support mothers, having a Baby-Friendly Hospital Initiative accreditation, and general cultural attitudes to breastfeeding also affect breastfeeding rates among very preterm infants (Bonet et al., 2015; Rodrigues, Severo, Zeitlin, & Barros, 2017; Santoro Junior & Martinez, 2007; Wilson et al., 2017).

We have less knowledge about factors that favour or hinder continued breastfeeding after discharge from the NICU. The same social and clinical characteristics that influence breastfeeding in the neonatal unit may affect continuation, but it is possible that salient factors differ. Social characteristics, for instance, may exert a stronger influence after the child returns home, whereas those related to care in the neonatal unit may have less impact. An understanding of the factors that promote continued breastfeeding is needed to develop effective postdischarge support and to prepare families at discharge for the difficulties they may face.

In this study, we sought to identify factors associated with breastfeeding continuation until 6 months of age among breastfed very preterm infants using data from a European multiregional population-based study.

Key messages

- In this multiregional European cohort, one third of ever-breastfed very preterm infants were breastfed at 6 months, varying from 25% (Portuguese and British regions) to 50% (Swedish and Danish regions).
- The probability of being breastfed to 6 months was lower for infants with less educated mothers.
- Neonatal factors associated with stopping were multiple birth, bronchopulmonary dysplasia, and multiple neonatal transfers but not low gestational age or other severe morbidities.
- Continuation was more likely with exclusive, as opposed to mixed, breastfeeding.
- Rates of breastfeeding continuation for very preterm babies in Europe fall short of international recommendations and are marked by strong social inequalities.

2 | METHODS

2.1 | Data source

This study uses data from the Effective Perinatal Intensive Care in Europe cohort, a population-based cohort study including all stillbirths and live births born below 32 weeks of gestation in 19 regions from 11 European countries over a 12-month period in 2011 and 2012 (Zeitlin et al., 2016). Participating countries (regions) were Belgium (Flanders), Denmark (Eastern region), Estonia (entire country), France (Burgundy, Ile-de-France, and the Northern region), Germany (Hesse and Saarland), Italy (Emilia-Romagna, Lazio, and Marche), the Netherlands (Central and Eastern region), Poland (Wielkopolska), Portugal (Lisbon, Tagus Valley, and North region), Sweden (greater Stockholm area), and the United Kingdom (East Midlands, Northern, and Yorkshire and Humber regions). For the three French regions, data were collected as part of the French study EPIPAGE2, where inclusions lasted 6 months in 2011–2012 (Ancel et al., 2015).

Perinatal and maternal characteristics were abstracted from obstetrical and neonatal medical records using a pretested standardized questionnaire filled in by a trained health care professional. Data were collected until the infant's discharge home and included information on breastfeeding at discharge. At 2 years of corrected age, a questionnaire was sent to parents to collect information about maternal sociodemographic characteristics and the child's health and development. The 2-year questionnaire included questions about whether the child was ever breastfed and the age of the child when breastfeeding was stopped.

2.2 | Ethical approvals

Ethics approval and parental consent were obtained in each study region from regional and/or hospital ethics committees, as required by national legislation. The European study was also approved by the French Advisory Committee on Use of Health Data in Medical Research and the French National Commission for Data Protection and Liberties.

2.3 | Study population

Our study population includes all infants followed up at 2 years of corrected age who were ever breastfed and for whom breastfeeding status at 6 months was available. Infants born in one of the regions, Northern UK, were excluded because of concern about selection bias among responders due to a very low response rate (<35%). Of 6,410 infants surviving to discharge in the 18 remaining regions, 26 died before 2 years of age. Of the 6,384 eligible infants for follow-up at 2 years, questionnaires were returned for 4,321 (67.7%). Follow-up rates differed between the regions: ranging from 47.2% in Belgium to 97.9% in Estonia. Among these infants, 951 were never breastfed (22.0%) and 153 (3.5%) had missing information on breastfeeding status at 6 months. The sample for this study therefore comprised 3,217 ever-breastfed infants (Figure 1).

2.4 | Outcomes

First, infants were considered to have ever been breastfed if the answer was yes to the question "Was your child breast fed" in the parental questionnaire at 2 years.

The primary outcome was whether the child was breastfed until at least 6 months of chronological age. Information on exclusive (only breast milk) and mixed (breast milk and formula) feeding, and on whether the child was feeding directly at the breast or received breast milk using a cup or a bottle was collected at discharge but not at 2 years.

Infants were considered to be breastfed until at least 6 months if mothers reported an age when breastfeeding was stopped that was greater or equal to 6 months. In few cases, the mother stated that she had breastfed but did not provide information on when she stopped. If the infant was not breastfed at discharge, as indicated in the medical notes, and was discharged home before 6 months of age, we considered that the infant was not breastfed at 6 months.

2.5 | Sociodemographic and infant health characteristics

We investigated maternal sociodemographic variables that were found in previous studies to affect breastfeeding initiation and breastfeeding in the NICU, including level of education, which was categorized in four groups according to the International Standard Classification of Education 2011 (Schneider), age in years, country of birth (Europe or other country), parity, and type of pregnancy (single or multiple). Infant characteristics were gestational age, whether the child had a severe neonatal morbidity diagnosed before discharge home—including intraventricular haemorrhage Papille's grades III or IV, cystic periventricular leukomalacia, retinopathy of prematurity III to V, necrotizing enterocolitis, and bronchopulmonary dysplasia (BPD), defined as respiratory support or oxygen at 36 weeks post menstrual age (Bonamy et al., 2017). We also included information on whether the infant was small for gestational age (<10th percentile) using intrauterine curves (Zeitlin et al., 2017), had any surgery, or was transferred during neonatal care. Finally for the subset of children who were no longer breastfed after discharge, we created a variable to describe their feeding status at discharge (receiving exclusive breast milk at the breast, exclusive breast milk but not from the breast, mixed feeding (breast milk and formula) with breast milk from the breast, mixed feeding with breast milk not from the breast). Missing data were low for maternal and neonatal variables (< 2%) and 2.5% for mother's education level. Missing data were excluded in multivariable models.

2.6 | Analysis strategy

We first compared the characteristics of responders and nonresponders with the 2-year questionnaire. We used the Wald test from logistic regressions adjusting for region to take into consideration differences in the response rates by region (Table S1). To take into consideration potential biases due to nonresponse, we used the

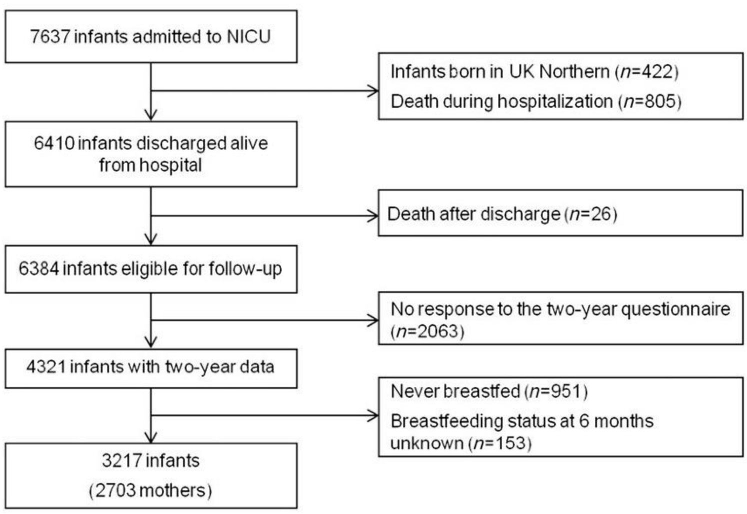

FIGURE 1 Flow-chart of study cohort

TABLE 1 Breastfeeding continuation at 6 months among ever-breastfed infants, according to maternal and neonatal characteristics

	Infants (N)	Unweighted (%)	Weighted (%)	Breastfed until 6 months weighted rates (%)	Unadjusted RR [95% CI]
TOTAL	3217			34.4	
Maternal age (years)					
<25	351	10.9	11.0	20.9	0.60 [0.48–0.75]
25–34	1925	60.0	60.0	34.7	Ref.
≥35	934	29.1	29.0	37.6	1.08 [0.97–1.21]
Mother's country of birth					
Europe	2716	85.6	84.4	31.8	Ref.
Other	457	14.4	15.6	45.8	1.44 [1.28–1.63]
Mother's educational level					
Lower secondary	426	13.6	13.6	25.3	0.52 [0.53–0.64]
Upper secondary	1265	40.3	40.4	29.9	0.61 [0.54–0.69]
Bachelor degree or less	846	27.0	28.0	34.9	0.72 [0.63–0.82]
Master/doctoral degree	598	19.1	18.1	48.6	Ref.
Parity					
0	2012	63.1	59.8	34.2	Ref.
1	754	23.6	24.2	35.1	1.03 [0.91–1.16]
2 or more	424	13.3	16.0	31.1	0.91 [0.77–1.07]
Type of pregnancy					
Singleton	2201	68.4	66.6	37.2	Ref.
Multiple	1016	31.6	33.4	27.7	0.74 [0.66–0.83]
Gestational age (weeks)					
23–25	227	7.1	7.2	35.8	1.10 [0.91–1.34]
26–27	544	16.9	16.1	39.9	1.23 [1.08–1.40]
28–29	648	26.9	27.0	33.0	1.02 [0.90–1.15]
30–31	1582	49.1	49.7	32.4	Ref.
SGA					
<10th percentile	1035	32.2	32.0	34.7	1.03 [0.93–1.15]
≥10	2182	67.8	68.0	33.7	Ref.
Severe neonatal morbidity[a]					
No	2866	90.9	90.5	34.3	Ref.
Yes	286	9.1	9.5	34.0	0.99 [0.83–1.18]
Bronchopulmonary dysplasia[b]					
No	2777	88.0	87.2	34.8	Ref.
Yes	380	12.0	12.8	29.1	0.84 [0.71–0.99]
Surgery[c]					
No	2919	90.7	91.1	33.4	Ref.
Yes	298	9.3	8.9	40.4	1.21 [1.04–1.41]
Transfer during neonatal care					
0	1923	59.8	60.2	35.9	Ref.
1	891	27.7	27.7	32.6	0.91 [0.81–1.02]
2 or more	403	12.5	12.1	28.0	0.78 [0.65–0.93]
Breastfeeding at discharge					
Exclusive at breast	865	29.5	29.0	56.8	-
Exclusive not at breast	305	10.4	9.4	44.4	-
Mixed at breast	796	27.2	27.4	31.0	-
Mixed not at breast	464	15.9	14.1	24.9	-
Not breastfeeding at discharge	498	17.0	20.0	0.0	-
Country[d]					
Belgium (Flanders)	245	7.6	10.3	30.6	0.85 [0.71–1.02]
Denmark (eastern region)	170	5.3	5.7	48.8	1.36 [1.17–1.59]

(Continues)

TABLE 1 (Continued)

	Infants (N)	Unweighted (%)	Weighted (%)	Breastfed until 6 months weighted rates (%)	Unadjusted RR [95% CI]
Estonia (entire country)	119	3.7	2.6	37.0	1.03 [0.83–1.28]
France (Burgundy, Ile-de-France, and the northern region)	526	16.4	12.3	36.2	1.01 [0.90–1.13]
Germany (Hesse and Saarland)	316	9.8	9.6	41.1	1.15 [1.01–1.31]
Italy (Emilia-Romagna, Lazio and Marche)	545	16.9	14.8	31.9	0.89 [0.79–1.01]
The Netherlands (central and eastern region)	199	6.2	5.9	33.8	0.94 [0.79–1.13]
Poland (Wielkopolska)	129	4.0	3.3	38.2	1.07 [0.81–1.37]
Portugal (Lisbon, Tagus Valley, and north region)	344	10.7	10.6	25.0	0.70 [0.58–0.83]
Sweden (greater Stockholm area)	152	4.7	4.7	52.5	1.47 [1.26–1.71]
UK (east midlands and Yorkshire & Humber regions)	472	14.7	20.3	28.1	0.78 [0.68–0.91]

Note. Ref.: reference; RR: risk ratio—95% CI: confidence intervals.

[a]Included retinopathy of prematurity, intraventricular haemorrhage, periventricular leukomalacia and necrotizing enterocolitis.

[b]Oxygen dependence or ventilation at 36 weeks of gestational age.

[c]During neonatal hospitalization.

[d]Sample average was used as reference for deriving risk ratio for each region.

inverse probability weighting method (Cole & Hernan, 2008). This method involves assigning a weight that is inversely proportional to the probability of response for each subject based on demographic, social, and medical characteristics; the weight was computed using the complete sample of eligible infants (*n* = 6,384). Probabilities were predicted using a logistic regression model with follow-up status at 2 years (yes or no) as the outcome. All demographic and health variables associated with nonresponse were included in this regression (maternal age, parity, pregnancy and neonatal characteristics of care, breastfeeding at discharge, and region, as shown in Table S1). Missing data from variables included in this regression model were imputed with chained equations. Data were assumed to be missing at random. All results presented in this study are based on weighted data.

We then described rates of breastfeeding continuation for each covariable in our study sample of ever-breastfed infants and used generalized linear multilevel regression models with a Poisson distribution and robust standard errors. This model makes it possible to estimate covariate adjusted risk ratios for binary outcomes (Zou & Donner, 2013). We used multilevel models to take into account the hierarchical structure of our data (infants within countries) and the nonindependence of observations within countries. Risk ratios were preferred to odds ratios as breastfeeding continuation at 6 months is not a rare event and our data study used a cohort design. In order to assess the potential impact of mode of feeding at discharge on breastfeeding continuation, we ran a second model using the subpopulation of infants breastfed at discharge, that is, excluding infants who stopped breast milk feedings before discharge. Finally, to estimate the impact of maternal and infant characteristics on country specific rates of breastfeeding continuation, we computed adjusted rates based on our final model in the overall sample and compared these with unadjusted rates.

We also carried out two sensitivity analyses. We first compared weighted with unweighted models to assess the impact of considering bias due to nonresponse. Second, we examined the potential impact of multiple births with a model using mothers (as opposed to babies) as our level of observation. In this model, a mother of multiples was considered to breastfeed until 6 months if at least one of her infants continued to this age. Variables describing neonatal risk factors (BPD, surgery, SGA, and morbidity) were considered present if at least one infant was affected.

All statistical analyses were performed using STATA V.14.

3 | RESULTS

Table 1 describes the maternal and neonatal characteristics of our sample of ever-breastfed infants included in the 2 years follow-up. Both the unweighted and weighted distributions of maternal and neonatal characteristics are shown. As seen by the changes in proportions after weighting, taking into consideration nonresponders led to slightly higher proportions of mothers born outside of Europe, multipara, and multiples. The other variables had very similar overall distributions.

About 11% of infants had a mother aged less than 25 years of age and 29% had a mother 35 years or older; about 60% were first-born children. Mothers were mainly born in Europe; almost 14% had only lower secondary education, whereas 18% had a master or doctoral degree. About one quarter of infants were born before 28 weeks of GA, with 7% at <26 weeks GA; 67% were from singleton pregnancies. About one in 10 had a severe neonatal morbidity, not including BPD, and 13% had BPD. Forty percent of children were transferred at least once during their neonatal hospitalization. At discharge, breastfeeding had already been discontinued for 20% of ever-breastfed infants, whereas 38% were exclusively receiving breast milk and 42% breast milk and formula.

Overall, 34.4% were still breastfed at 6 months of age. In univariate comparisons, also shown in Table 1, maternal characteristics associated with breastfeeding continuation were maternal age (mothers under 25 were more likely to stop before 6 months), being born outside of Europe and higher maternal education. Parity was not associated with breastfeeding continuation. Children from multiple pregnancies, with BPD and who were transferred two or more times were less likely to be breastfed at 6 months. Having had surgery and being born at 26 and 27 weeks of gestational age compared with being born at 30 or 31 weeks were associated with continued breastfeeding. Infants who were exclusively breastfed at the breast at discharge were more likely to continue to 6 months, 56.8%, versus 24.9% for those receiving breast milk not at the breast and formula.

Rates of breastfeeding continuation varied significantly by country of birth: from 25.0% in Portugal to 52.5% in Sweden. As shown in Figure 2, in addition to overall continuation rates, the proportion of infants who stopped breastfeeding during the neonatal hospitalization differed across countries, with a range from 10.7% in Poland, 11.0% in Estonia, or 11.4% in Italy to 25.8% in UK.

In the adjusted model conducted on the overall sample, presented in Table 2, most of the associations observed in Table 1 persisted. Infants with mothers less than 25 years of age were 30% less likely to be breastfed than infants with older mothers (aRR = 0.68 [0.53–0.88]), whereas educational level had a strong linear effect. Mothers born out of Europe were more likely to continue breastfeeding until 6 months (aRR = 1.47 [1.26–1.71]). Estimated relative risks for neonatal factors were similar in multivariable models.

In the second model which focused on the sample of infants still breastfed at discharge, we found that receiving formula at discharge was associated with a significantly lower probability of breastfeeding continuation until 6 months, for those feeding directly at the breast (aRR = 0.60 [0.48–0.74]) as well as those not feeding directly at the breast (aRR = 0.46 [0.31–0.69]). In the subpopulation of infants breastfed at discharge, young maternal age and BPD were no longer associated with breastfeeding continuation, even when feeding status at discharge was not present in the model (results not shown). Additional sensitivity analyses found that results of the final model were similar without weights (Table S2). When models were run using mothers, instead of infants, as the unit of observations, results were also similar (Table S3).

Maternal and neonatal characteristics explained only a small proportion of the difference between countries, as shown in Figure 3 which compares breastfeeding continuation to 6 months before and after adjustment. However, differences in population characteristics affected rankings in some countries. For instance, if maternal and infant characteristics were the same across all countries, Sweden would have lower rates (52% to 46%) and higher rates would be observed in Estonia (37 to 39%) and in the UK (28 to 31%).

4 | DISCUSSION

Among very preterm infants who were breastfed after birth, only 34.4% were breastfed up until 6 months, although breastfeeding continuation rates varied across countries. Lower rates were observed in regions from Portugal and the UK and higher rates in those from Sweden and Denmark, but even in the countries with higher rates, only about half of infants who started breastfeeding continued to 6 months of age. Most infants stopped breastfeeding after discharge from hospital, but in some countries up to one quarter of children had stopped before discharge. A low maternal educational level was a key risk factor for stopping breastfeeding. In contrast, women born outside of Europe breastfed longer. Infants from multiple pregnancies were also less likely to continue breastfeeding until 6 months. Two neonatal factors negatively affected continuation: BPD and multiple neonatal transfers, whereas other neonatal risk factors, such as severe neonatal morbidities and small for gestational age, found in previous research to negatively impact initiation of breastfeeding, were not associated with or favoured continuation. Finally, infants receiving breast milk and formula at discharge were half as likely to be breastfed to 6 months as those receiving only breast milk.

4.1 | Strengths and limitations

The main strengths of this study are the large multicountry population-based sample with data collected at birth and at 2 years using common, pretested protocols. It is therefore possible to estimate and to compare breastfeeding continuation rates until 6 months using the same methodology across a range of sociocultural contexts in Europe. This is important as previous studies have employed varying definitions, making international comparisons difficult (Rodrigues et al., 2018). The availability of data on many perinatal and socio-

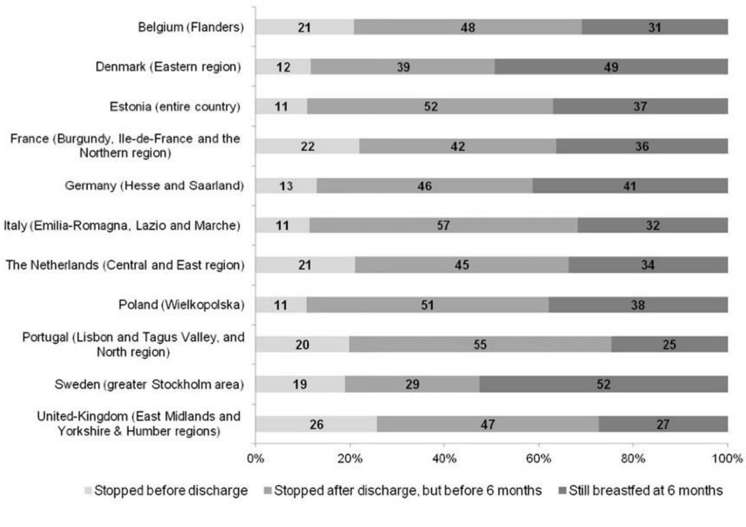

FIGURE 2 Distribution of infants by country according to the moment that breastfeeding was stopped

TABLE 2 Maternal and neonatal characteristics associated with breast milk feeding continuation until 6 months among all ever-breastfed infants and among infants still breastfeeding at discharge

	Model 1 all ever-breastfed infants		Model 2 infants breastfed at discharge	
	Adjusted RR	95% CI	Adjusted RR	95% CI
Maternal age (years)				
<25	0.68	0.53–0.88	0.92	0.77.–1.09
25–34	1.00	Ref.	1.00	Ref.
≥35	1.11	0.94–1.30	1.13	0.97–1.32
Mother born outside of Europe	1.47	1.26–1.71	1.44	1.29–1.62
Mother's educational level				
Lower secondary	0.58	0.45–0.76	0.65	0.49–0.85
Upper secondary	0.67	0.55–0.82	0.74	0.62–0.87
Bachelor degree or less	0.85	0.70–1.02	0.86	0.74–0.99
Master/doctoral degree	1.00	Ref.	1.00	Ref.
Parity				
0	1.00	Ref.	1.00	Ref.
1	0.97	0.86–1.10	0.91	0.82–1.01
2 or more	0.83	0.64–1.07	0.99	0.81–1.20
Type of pregnancy (multiple)	0.69	0.58–0.81	0.80	0.70–0.91
Gestational age (weeks)				
23–25	1.06	0.86–1.32	1.31	1.07–1.60
26–27	1.20	1.02–1.41	1.29	1.11–1.50
28–29	0.99	0.88–1.11	1.06	0.92–1.22
30–31	1.00	Ref.	1.00	Ref.
SGA (<10th percentile)	1.04	0.97–1.12	1.10	1.01–1.18
Severe neonatal morbidity[a]	0.95	0.76–1.18	0.93	0.72–1.19
Bronchopulmonary dysplasia[b]	0.83	0.73-0.94	0.97	0.84–1.12
Surgery[c]	1.21	1.05-1.41	1.17	0.97–1.42
Transfers during neonatal care				
0	1.00	Ref.	1.00	Ref.
1	0.92	0.78–1.09	0.89	0.79–1.00
2 or more	0.83	0.67–1.03	0.84	0.72–0.99
Breastfeeding at discharge				
Exclusive feeding at breast	-	-	1.00	Ref.
Exclusive feeding not at breast	-	-	0.86	0.71–1.05
Mixed feeding at breast	-	-	0.60	0.48–0.74
Mixed feeding not at breast	-	-	0.46	0.31–0.69

Note. aRR: adjusted risk ratio for all variables in the table; Ref.: reference.

[a]Included retinopathy of prematurity, intraventricular haemorrhage, periventricular leukomalacia and necrotizing enterocolitis.

[b]Oxygen dependence or ventilation at 36 weeks of gestational age.

[c]During neonatal hospitalization.

economic characteristics allowed us to consider multiple risk factors found to be of importance for breastfeeding initiation in previous studies. Finally, the majority of previous studies had smaller, more selected samples, being principally from single centres (Flacking, Wallin, & Ewald, 2007; Morag et al., 2016; Rodrigues et al., 2018).

Our study also has some limitations. About 32% of the infants discharged alive were not followed-up at 2 years corrected age. Infants whose parents answered the questionnaire at 2 years were more frequently breastfed at discharge from hospital. However, we were able to compare responders with nonresponders and took into consideration potential selection biases by using inverse probability weighting methods. Sensitivity analyses showed that results were not substantially affected by weighting for nonresponse. We also did not have information regarding exclusive breastfeeding after discharge, support after discharge, and the reasons for weaning. The duration of breastfeeding was collected retrospectively when the child was 2 years of age, and this may lead to some misclassification bias, although studies find good validity of maternal recall of breastfeeding duration (Amissah, Kancherla, Ko, & Li, 2017; Li, Scanlon, & Serdula, 2005). Finally, some important factors that might affect postdischarge decisions were not collected, including maternal smoking status which has been found to affect decisions to continue breastfeeding (Callen & Pinelli, 2005; Killersreiter, Grimmer, Buhrer, Dudenhausen, & Obladen, 2001).

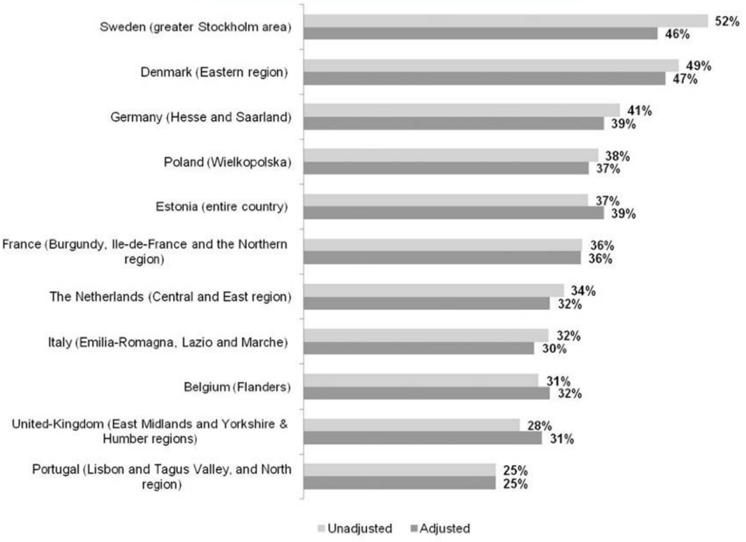

FIGURE 3 Percent breastfeeding at 6 months among breastfed very preterm infants by country

4.2 | Comparison with other findings and interpretation

Some of the maternal and neonatal characteristics that we found to be associated with continuation have been noted in smaller single-centre studies. In one single-centre study of 225 very preterm infants in Sweden, Flacking et al. (2007) reported that mothers with low socio-economic level were less likely to continue breastfeeding until 6 months. In general, maternal social status has been found to negatively impact on breastfeeding—including breastfeeding initiation in very preterm infants as well as among term infants (Flacking et al., 2007; Forster, McLachlan, & Lumley, 2006; Herich et al., 2017; Li, Darling, Maurice, Barker, & Grummer-Strawn, 2005; Scott & Binns, 1999). Previous studies have also observed that few neonatal morbidities impact on breastfeeding continuation. In an Israeli study including 181 very preterm infants, neonatal morbidities did not affect breastfeeding continuation between 6 weeks postdischarge and 6 months corrected age (Morag et al., 2016). In fact, cessation of breastfeeding before 6 months corrected age was more frequent for infants born at higher gestational age over 28 weeks (Morag et al., 2016). We also found that infants born below 28 weeks were more likely to be breastfed until 6 months compared with infants born at 30–31 weeks. One hypothesis for this finding is that motivation for breastfeeding may be increased for mothers with a particularly fragile infant; further, as initiation of breastfeeding is more challenging for these infants—as witnessed by the body of literature linking low gestational age to a reduced probability of breastfeeding (Lee & Gould, 2009)—less motivated mothers may be discouraged at the onset. Another hypothesis is that these mothers receive more support and attention from hospital staff because of their child's high-risk health status.

In contrast with other neonatal morbidities, BPD did affect continuation. BPD affects suck–swallow respiration coordination, and these infants may face sucking difficulties. Infants with BPD also have poor feeding endurance and performance (Mizuno et al., 2007). These difficulties could make continued breastfeeding more challenging. Rehospitalizations in the first year of life are also more than twice as frequent among infants with BPD compared with other very preterm infants and this may interfere with breastfeeding continuation (Smith et al., 2004). We found, however, that the relation with BPD was no longer significant among the subsample of infants breastfed at discharge, suggesting that this factor may hinder continuation during the neonatal hospitalization. A better understanding of this negative relationship could lead to targeted interventions to help breastfeeding mothers of infants with BPD. This is important as BPD is an independent risk factor for poor longer term health and development (Arnaud et al., 2007).

We also found that multiple neonatal transfers were associated with an increased risk of stopping breastfeeding before 6 months. This result could be explained by the discontinuity in information provided or practices across different NICUs leading to confusion or lack of support. The absence of common beliefs and practices within the NICU has been identified as an obstacle at the unit level to successful breastfeeding promotion (Bonet et al., 2015). The variation in the proportion of infants who stopped breastfeeding while still in hospital illustrates that neonatal unit policies can impact on continuation. In a previous qualitative study on breastfeeding with neonatal unit staff in several regions participating in the Effective Perinatal Intensive Care in Europe project, UK participants suggested that discharge policies may discourage continued breastfeeding when formula feeding is perceived to facilitate earlier discharge (Bonet et al., 2015). Other unit policies have been found to affect breastfeeding at discharge in our cohort, including the presence of dedicated personnel for breastfeeding support in the Portuguese regions (Rodrigues et al., 2017) and the baby-friendly hospital initiative in the overall sample (Wilson et al., 2017). Kangaroo Care has been found to be positively associated with breastfeeding duration in other studies (Flacking, Ewald, & Wallin, 2011). Our finding that exclusive as opposed to mixed breastfeeding at discharge was strongly related to the probability of continuation points to a modifiable practice that likely reflects unit policies, as rates of mixed versus exclusive feeding at discharge vary widely across Europe (Wilson et al., 2017). In contrast, we did not find that direct feeding from the breast had a significant impact on continuation, unlike a study conducted in one single-centre in Israel on 162 mothers of very preterm infants (Pinchevski-Kadir et al., 2017).

Consideration of maternal and neonatal factors did not substantially reduce the wide differences observed between countries in our study. The reasons for these persistent large disparities are likely linked to unit policies, as discussed above, as well as the support and counselling available to mothers after their discharge from hospital; the importance of these latter factors, which we could not include in our study, was highlighted in the integrative review by Briere et al. on breastfeeding duration after NICU discharge (Briere, McGrath, Cong, & Cusson, 2014). Broader policies promoting breastfeeding in the general population as well as structural measures related to the duration of maternity leave or employment regulations that facilitate combining work with breastfeeding also differ across the countries in our sample, but further research is needed to understand their impact on breastfeeding continuation in this population (Bonet et al., 2015).

5 | CONCLUSION

We found low breastfeeding continuation rates, marked by strong social inequalities, among very preterm infants in European regions. Given current international recommendations, knowledge about the positive effects of breastfeeding for child health and development and the need to address social inequalities in health, our results call for increased policy attention to the promotion of breastfeeding in this vulnerable population. Overall, a majority of ever-breastfed infants were weaned after discharge, highlighting the importance of postdischarge counselling and support. However, more support in the neonatal unit could target discontinuation during the neonatal hospitalization, which occurred more frequently in some of the study regions. Our results also point to specific areas where changes to neonatal policies could improve breastfeeding continuation more generally, including management of intrafacility transfers, breastfeeding support to the mothers of multiples and infants with BPD and promotion of exclusive feeding. Given the marked differences in continuation by maternal education, understanding the specific obstacles faced by women from more disadvantaged families is needed to design interventions to mitigate these negative effects. Finally, our study has an encouraging message for parents and providers: once breastfeeding initiation is successful, infants at highest risk are not more likely to stop. Thus, while it may be harder to start breastfeeding infants born at very low gestational age or with severe neonatal morbidities, these obstacles appear to be overcome in the long-run.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

CONTRIBUTIONS

JZ had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design was done by JZ, BB, AKEB, LG, AvH, ESD, and MC. All authors (including authors listed in EPICE Research Group) contributed to the acquisition, analysis, or interpretation of data. The drafting of the manuscript was done by CB and JZ. Also, the statistical analysis was done by CB, AP, and JZ. Lastly, the critical revision of the manuscript for important intellectual content and approval of final version of the manuscript was done by all authors (including authors listed in EPICE Research Group).

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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APPENDIX

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Table S1: Comparison of proportions of children followed up at 2 years by maternal and neonatal characteristics and country, all infants eligible for follow-up regardless of breastfeeding status

	Follow-up N=4321	No follow-up N=2063	
	n (%)	n (%)	p-values
Maternal age (years)			< 0.001
≤ 24	537 (52.4)	488 (47.6)	
25-34	2514 (69.5)	1101 (30.5)	
≥ 35	1260 (73.0)	466 (27.0)	
Born out of the country	765 (59.3)	526 (40.7)	< 0.001
Parity			< 0.001
0	2594 (71.6)	1029 (28.4)	
1	1044 (66.2)	533 (33.8)	
2 or more	639 (56.7)	488 (43.3)	
Type of pregnancy			0.001
Singleton	2889 (66.4)	1461 (33.6)	
Multiple	1432 (70.4)	602 (29.6)	
Gestational age at birth (weeks)			0.01
23-25	324 (64.9)	175 (35.1)	
26-27	759 (71.8)	298 (28.2)	
28-29	1152 (67.5)	554 (32.5)	
30-31	2086 (66.8)	1036 (33.2)	
Severe neonatal morbidity[a]	430 (65.2)	230 (34.8)	0.12
BPD[b]	584 (67.2)	285 (32.8)	0.76
SGA (< 10th percentile)	1413 (68.2)	659 (31.8)	0.55
Surgery[c]	438 (69.5)	192 (30.5)	0.30
Transfer during neonatal care			0.09
0	2508 (66.6)	1255 (33.4)	
1	1240 (69.5)	545 (30.5)	
2 or more	573 (68.5)	263 (31.5)	
Country			< 0.001
Belgium (Flanders)	308 (47.2)	345 (52.8)	
Estonia	138 (99.3)	1 (0.7)	
France (Ile-de-France, Bourgogne, Nord)	986 (89.4)	117 (10.6)	
Denmark (Eastern)	180 (62.9)	106 (37.1)	
Germany (Hesse, Saarland)	435 (66.2)	222 (33.8)	
Italy (Lazio, Marche, Emilia)	731 (75.3)	240 (24.7)	
The Netherlands (East-Central)	229 (69.4)	101 (30.6)	
Poland (Wielkopolska)	199 (79.9)	50 (20.1)	
Portugal (Lisbon and Tagus Valley, and North region)	408 (67.3)	198 (32.7)	
Sweden (Stockholm)	165 (68.8)	75 (31.2)	
UK (East Midlands, Yorkshire and Humber)	543 (47.2)	608 (52.8)	

[a]Included retinopathy of prematurity, intraventricular hemorrhage, periventricular leukomalacia and necrotizing enterocolitis

[b]Oxygen dependence or ventilation at 36 weeks of gestational age

[c]During neonatal hospitalization

Table S2: Maternal and neonatal characteristics associated with breast milk feeding continuation until 6 months among all ever-breastfed infants and among infants still breastfeeding at discharge – Unweighted models

	Model 1 All ever breastfed infants		**Model 2** Infants breastfed at discharge	
	Adjusted RR	95% CI	Adjusted RR	95% CI
Maternal age (years)				
< 25	0.71	0.56 - 0.91	0.90	0.74 - 1.09
25-34	1.00	*Ref.*	1.00	Ref.
≥ 35	1.12	0.98 - 1.29	1.16	1.04 - 1.29
Mother born outside of Europe	1.42	1.23 - 1.64	1.44	1.29 - 1.60
Mother's educational level				
Lower secondary	0.53	0.42 - 0.68	0.57	0.44 - 0.75
Upper secondary	0.69	0.59 - 0.82	0.73	0.63 - 0.84
Bachelor degree or less	0.87	0.74 - 1.03	0.83	0.73 - 0.94
Master/Doctoral degree	1.00	*Ref.*	1.00	*Ref.*
Parity				
0	1.00	*Ref.*	1.00	*Ref.*
1	0.94	0.82 - 1.09	0.94	0.85 - 1.04
2 or more	0.94	0.75 - 1.18	1.06	0.86 - 1.30
Type of pregnancy (multiple)	0.69	0.61 - 0.79	0.78	0.69 - 0.87
Gestational age (weeks)				
23-25	1.12	0.90 - 1.40	1.25	1.02 - 1.53
26-27	1.21	1.03 - 1.41	1.25	1.08 - 1.46
28-29	1.00	0.89 - 1.12	0.83	0.89 - 1.17
30-31	1.00	*Ref.*	1.00	*Ref.*
SGA *(< 10th percentile)*	1.03	0.97 - 1.10	1.07	1.01 - 1.13
Severe neonatal morbidity[a]	0.97	0.79 - 1.21	1.00	0.79 - 1.28
BPD[b]	0.85	0.76 - 0.95	0.93	0.81 - 1.07
Surgery[c]	1.21	1.05 - 1.41	1.23	1.07 - 1.42
Transfers during neonatal care				
0	1.00	*Ref.*	1.00	*Ref.*
1	0.92	0.81 - 1.04	0.91	0.82 - 1.01
2 or more	0.80	0.70 - 0.92	0.85	0.68 - 1.06
Breastfeeding at discharge				
Exclusive feeding at breast	-	-	1.00	*Ref.*
Exclusive feeding not at breast	-	-	0.85	0.73 - 0.99
Mixed feeding at breast	-	-	0.61	0.51 - 0.73
Mixed feeding not at breast	-	-	0.44	0.33 - 0.60

aRR : adjusted risk ratio for all variables in the table

[a]Included retinopathy of prematurity, intraventricular hemorrhage, periventricular leukomalacia and necrotizing enterocolitis

[b]Oxygen dependence or ventilation at 36 weeks of gestational age

[c]During neonatal hospitalization

Table S3: Maternal and neonatal characteristics associated with breast milk feeding continuation until 6 months among mothers of all ever breastfed infant and among mothers of infant still breastfeeding at discharge

	Model 1 All ever breastfed infants		**Model 2** Infants breastfed at discharge	
	Adjusted RR	95% CI	Adjusted RR	95% CI
Maternal age (years)				
< 25	0.69	0.54 - 0.88	0.90	0.76 - 1.06
25-34	1.00	*Ref.*	1.00	*Ref.*
≥ 35	1.14	0.99 - 1.32	1.12	0.99 - 1.37
Mother born outside of Europe	1.45	1.24 - 1.70	1.39	1.25 - 1.55
Mother's educational level				
Lower secondary	0.59	0.48 - 0.73	0.63	0.49 - 0.82
Upper secondary	0.67	0.55 - 0.81	0.72	0.62 - 0.85
Bachelor degree or less	0.84	0.71 - 0.98	0.83	0.73 - 0.95
Master/Doctoral degree	1.00	*Ref.*	1.00	*Ref.*
Parity				
0	1.00	*Ref.*	1.00	*Ref.*
1	0.98	0.87 - 1.11	0.93	0.84 - 1.03
2 or more	0.82	0.63 - 1.07	1.00	0.83 - 1.20
Type of pregnancy (multiple)	0.71	0.60 - 0.85	0.79	0.68 - 0.91
Gestational age (weeks)				
23-25	0.96	0.80 - 1.15	1.20	1.00 - 1.44
26-27	1.14	0.98 - 1.33	1.26	1.09 - 1.45
28-29	0.97	0.86 - 1.09	1.03	0.90 - 1.19
30-31	1.00	*Ref.*	1.00	*Ref.*
SGA *(< 10th percentile)*	1.04	0.95 - 1.14	1.09	1.00 - 1.19
Severe neonatal morbidity[a]	0.96	0.77 - 1.19	0.93	0.72 - 1.19
BPD[b]	0.86	0.73 - 1.00	1.00	0.85 - 1.17
Surgery[c]	1.27	1.09 - 1.47	1.22	1.03 - 1.44
Transfers during neonatal care				
0	1.00	*Ref.*	1.00	*Ref.*
1	0.95	0.81 - 1.10	0.91	0.82 - 1.00
2 or more	0.83	0.67 - 1.03	0.85	0.72 - 1.00
Breastfeeding at discharge				
Exclusive feeding at breast	-	-	1.00	Ref.
Exclusive feeding not at breast	-	-	0.84	0.70 - 1.00
Mixed feeding at breast	-	-	0.60	0.50 - 0.72
Mixed feeding not at breast	-	-	0.44	0.31 - 0.62

aRR : adjusted risk ratio for all variables in the table
[a]Included retinopathy of prematurity, intraventricular hemorrhage, periventricular leukomalacia and necrotizing enterocolitis
[b]Oxygen dependence or ventilation at 36 weeks of gestational age
[c]During neonatal hospitalization

4.5. PAPER V

Managing mother's own milk for very preterm infants in neonatal units in 11 European countries

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BRIEF REPORT

ACTA PÆDIATRICA NURTURING THE CHILD WILEY

Managing mother's own milk for very preterm infants in neonatal units in 11 European countries

Feeding with human milk has been recognised as an essential component of newborn care and is especially important for infants born very preterm (VPT, below 32 weeks of gestation) who face higher risks of adverse outcomes. WHO recommends that infants who cannot be fed mother's own milk (MOM) should receive donor human milk. Direct feeding at the breast takes time to establish after VPT birth and procedures are required for expressing, collecting, storing and administering breast milk that respect microbiological safety rules and ensure nutritional and immunological quality. However, as recommendations are scarce, these procedures appear to be dependent on organisational structures and policies of the units.[1-3]

Breast milk is one of the most common modes of postnatal human cytomegalovirus (HCMV) transmission in preterm infants with rates for fresh or frozen MOM ranging from 8% to 37% and about 10% probability of infant infection.[2] The debate on the risk of neonatal morbidity and long-term neurodevelopmental impairment in VPT infants with HCMV infection is ongoing,[4] raising additional challenges for establishing best practices for managing MOM.[1,2] In 2012, the American Academy of Paediatrics stated that the benefits of fresh MOM from HCMV-seropositive mothers outweighed the risk of HCMV infection. In 2018, the working group of the French Neonatal Society on fresh human milk use in preterm infants advised pasteurisation of MOM from HCMV-seropositive mothers for infants born <28 weeks or <1000 grams.[2] In addition to HCMV transmission, also bacterial contamination of expressed milk is suspected to lead to significant problems in VPT infants.[2]

Published reports have revealed differences in MOM management among neonatal intensive care units (NICUs) and countries.[1,3] We aimed to compare practices for handling MOM for VPT infants using standardised questions in European NICUs.

Data were collected as part of the area-based EPICE (Effective Perinatal Intensive Care in Europe) study set-up to investigate the use of evidence-based practices for the care of VPT infants in 19 regions in 11 countries.[5]

In 2012, structured questionnaires were sent to the head of all NICUs with at least 10 VPT admissions during the study period. The unit questionnaire recorded information on the units' characteristics and policies, including procedures for managing MOM. Of the 135 eligible NICUs, 134 (99.3%) replied.

Descriptive statistics are presented as numbers and valid proportions.

Ethical approval was obtained in each region from appropriate ethics committees, as required by national legislation, and for the European database by the French data protection committee.

As shown in Table 1, 72% of the 134 neonatal units were level III and 91% had a written protocol (developed at unit or regional level) for breastfeeding/human milk use; when MOM was not available, 34% used human banked milk for all VPT infants (range: 0%-100% in Sweden) and 13% for some groups only (range: 0%-50%).

Management of MOM varied widely across the countries. Overall, 56% of units reported using fresh MOM (not frozen and unpasteurised milk) without restrictions regarding gestational age, birthweight or risk of HCMV transmission (range: 0% in Germany to 100% in Netherlands and Denmark). Different practices were also observed between units in the same country, particularly in France and Italy. In most units (70%), MOM was not pasteurised (range: 23%-100%); and in 29 (22%) units, all VPT infants received pasteurised MOM (range: 0%-73% in France).

HCMV serology on all mothers who express their milk (or HCMV polymerase chain reaction of the milk) was required in 29% of units (range: 0% in 6 countries to 93% in Germany). Wide differences were found between NICUs in France and Italy. Among these units (n = 36), 47% used human bank/MOM pasteurised, 26% frozen-thawed MOM, 3% untreated fresh MOM and 24% formula in the case of HCMV-seropositive mothers.

Systematic bacteriological analyses of the fresh or frozen-thawed MOM were not performed in 76% of units (range: 29%-100%), performed in <10% for the first milk feeding only, and every week in 7%.

These large variations in practice between countries could reflect differences in local regulations or guidelines, as well as lack of strong recommendations at international and national level. Heterogeneity

EPICE (Effective Perinatal Intensive Care in Europe) Research Group: BELGIUM: Flanders (E Martens, G Martens, P Van Reempts); DENMARK: Eastern Region (K Boerch, A Hasselager, LD Huusom, O Pryds, T Weber); ESTONIA (L Toome, H Varendi); FRANCE: Burgundy, Ile-de France and Northern Region (PY Ancel, B Blondel, A Burguet, PH Jarreau, P Truffert); GERMANY: Hesse (RF Maier, B Misselwitz, S Schmidt), Saarland (L Gortner); ITALY: Emilia Romagna (D Baronciani, G Gargano), Lazio (R Agostino, I Croci, F Franco), Marche (V Carnielli), M Cuttini, D DiLallo; NETHERLANDS: Eastern & Central (C Koopman-Esseboom, A van Heijst, J Nijman); POLAND: Wielkopolska (J Gadzinowski, J Mazela); PORTUGAL: Lisbon and Tagus Valley (LM Graça, MC Machado), Northern region (Carina Rodrigues, T Rodrigues), H Barros; SWEDEN: Stockholm (AK Bonamy, M Norman, E Wilson); UK: East Midlands and Yorkshire and Humber (E Boyle, ES Draper, BN Manktelow), Northern Region (AC Fenton, DWA Milligan); INSERM, Paris (J Zeitlin, M Bonet, A Piedvache).

TABLE 1 Management of mother's own milk for very preterm infants in the neonatal unit, by country[b]

	Belgium		Denmark		Estonia		France		Germany	
	(n = 9)		(n = 8)		(n = 4)		(n = 23)		(n = 14)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Level of care										
Level III	8	(88.9)	2	(25.0)	3	(75.0)	22	(95.6)	13	(92.9)
Written protocol for breastfeeding and human milk use										
Yes, regional or network protocols	0	(0.0)	0	(0.0)	3	(75.0)	3	(14.3)	0	(0.0)
Yes, unit protocols	6	(66.7)	8	(100.0)	1	(25.0)	15	(71.4)	12	(85.7)
No	3	(33.3)	0	(0.0)	0	(0.0)	3	(14.3)	2	(14.3)
Use of human bank milk/donor's milk to feed VPT infants whose mothers do not express their milk										
Yes, for all infants less than 32 wk GA	0	(0.0)	7	(87.5)	1	(25.0)	19	(82.6)	0	(0.0)
Yes, for some infants	0	(0.0)	1	(12.5)	0	(0.0)	2	(8.7)	2	(14.3)
No	9	(100.0)	0	(0.0)	3	(75.0)	2	(8.7)	12	(85.7)
Infants whose mothers express breast milk receive fresh milk[a]										
Yes, with no restrictions	4	(50.0)	8	(100.0)	3	(75.0)	6	(28.6)	0	(0.0)
Yes, but with restrictions	2	(25.0)	0	(0.0)	1	(25.0)	11	(52.4)	14	(100.0)
No, all milk is frozen or pasteurised	2	(25.0)	0	(0.0)	0	(0.0)	4	(19.0)	0	(0.0)
Infants whose mothers express breast milk receive frozen-thawed milk										
Yes, with no restrictions	6	(66.7)	8	(100.0)	1	(25.0)	3	(13.0)	2	(14.3)
Yes, but with restrictions	2	(22.2)	0	(0.0)	1	(25.0)	1	(4.4)	11	(78.6)
No	1	(11.1)	0	(0.0)	2	(50.0)	19	(82.6)	1	(7.1)
Infants whose mothers express breast milk receive own mother's pasteurised milk										
Yes, all babies <32 wk GA	2	(22.2)	1	(12.5)	1	(25.0)	16	(72.7)	1	(7.1)
Yes, only some babies <32 wk GA	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.6)	3	(21.4)
No, own mother's milk is not pasteurised	7	(77.8)	7	(87.5)	3	(75.0)	5	(22.7)	10	(71.4)
Human cytomegalovirus (HCMV) serology on all mothers of VPT infants (or HCMV PCR of the milk) is required, if they express their milk										
Yes, according to GA or weight	1	(11.1)	0	(0.0)	0	(0.0)	5	(31.2)	13	(92.9)
Other criteria	0	(0.0)	0	(0.0)	0	(0.0)	3	(18.8)	0	(0.0)
No	8	(88.9)	7	(100.0)	4	(100.0)	8	(50.0)	1	(7.1)
Type of milk given to VPT infants born to HCMV-seropositive mothers, if HCMV serology performed										
	n = 1		n = 0		n = 0		n = 8		n = 13	
Human bank or MOM pasteurised	1	(100.0)					7	(100.0)	3	(23.1)
Frozen-thawed breast milk	0	(0.0)					0	(0.0)	4	(30.8)
Untreated fresh breast milk	0	(0.0)					0	(0.0)	0	(0.0)
Only formula	0	(0.0)					0	(0.0)	6	(46.1)
Systematic bacteriological analysis of the mother's fresh or frozen-thawed milk is performed										
Yes, for the first milk feeding	0	(0.0)	0	(0.0)	0	(0.0)	6	(28.6)	4	(28.6)
Yes, every week	0	(0.0)	0	(0.0)	0	(0.0)	9	(42.9)	0	(0.0)
Another frequency	1	(11.1)	1	(12.5)	2	(50.0)	0	(0.0)	1	(7.1)
No	8	(88.9)	7	(87.5)	2	(50.0)	6	(28.6)	9	(64.3)

Note: Differences in the total number of units for each item are due to missing data.

Abbreviations: GA, gestational age; HCMV, human cytomegalovirus; MOM, mother's own milk; PCR, polymerase chain reaction; UK, United Kingdom; VPT, very preterm.

[a]Fresh breast milk corresponds to not frozen and unpasteurised milk, including refrigerated milk.

[b]Regions included in the EPICE study by country: Flanders in Belgium; the Eastern Region of Denmark; Estonia (entire country); Burgundy, Ile-de France and the Northern regions in France; Hesse and Saarland in Germany; Emilia-Romagna, Lazio and Marche regions in Italy; the Central and Eastern regions of The Netherlands; Wielkopolska in Poland; the Lisbon and Northern regions of Portugal; and the East Midlands, Northern and Yorkshire and Humber regions in the UK; and the Stockholm region in Sweden.

Italy		Netherlands		Poland		Portugal		Sweden		UK		Total	
(n = 22)		(n = 2)		(n = 4)		(n = 17)		(n = 4)		(n = 27)		(n = 134)	
n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
16	(72.7)	2	(100.0)	1	(25.0)	15	(88.2)	2	(50.0)	12	(44.4)	96	(71.6)
3	(13.6)	0	(0.0)	3	(75.0)	5	(29.4)	1	(25.0)	1	(3.7)	19	(14.4)
18	(81.8)	2	(100.0)	1	(25.0)	10	(58.8)	3	(75.0)	25	(92.6)	101	(76.5)
1	(4.6)	0	(0.0)	0	(0.0)	2	(11.8)	0	(0.0)	1	(3.7)	12	(9.1)
9	(40.9)	0	(0.0)	0	(0.0)	1	(5.9)	4	(100.0)	4	(14.8)	45	(33.6)
2	(9.1)	1	(50.0)	0	(0.0)	1	(5.9)	0	(0.0)	8	(29.6)	17	(12.7)
11	(50.0)	1	(50.0)	4	(100.0)	15	(88.2)	0	(0.0)	15	(55.6)	72	(53.7)
11	(50.0)	2	(100.0)	2	(66.7)	11	(64.7)	2	(50.0)	24	(88.9)	73	(56.1)
7	(31.8)	0	(0.0)	1	(33.3)	5	(29.4)	2	(50.0)	3	(11.1)	46	(35.4)
4	(18.2)	0	(0.0)	0	(0.0)	1	(5.9)	0	(0.0)	0	(0.0)	11	(8.5)
16	(72.7)	2	(100.0)	1	(25.0)	9	(52.9)	3	(75.0)	24	(88.9)	75	(56.0)
3	(13.6)	0	(0.0)	0	(0.0)	1	(5.9)	1	(25.0)	3	(11.1)	23	(17.2)
3	(13.6)	0	(0.0)	3	(75.0)	7	(41.2)	0	(0.0)	0	(0.0)	36	(26.9)
6	(27.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(7.4)	29	(21.8)
6	(27.3)	0	(0.0)	1	(25.0)	0	(0.0)	0	(0.0)	0	(0.0)	11	(8.3)
10	(45.4)	2	(100.0)	3	(75.0)	17	(100.0)	4	(100.0)	25	(92.6)	93	(69.9)
6	(27.3)	0	(0.0)	0	(0.0)	2	(11.8)	0	(0.0)	0	(0.0)	27	(21.4)
5	(22.7)	0	(0.0)	0	(0.0)	1	(5.9)	0	(0.0)	0	(0.0)	9	(7.1)
11	(50.0)	2	(100.0)	4	(100.0)	14	(82.4)	4	(100.0)	27	(100.0)	90	(71.4)
n = 11		n = 0		n = 0		n = 3		n = 0		n = 0		n = 36	
5	(45.4)					0	(0.0)					16	(47.1)
4	(36.4)					1	(50.0)					9	(26.5)
1	(9.1)					0	(0.0)					1	(2.9)
1	(9.1)					1	(50.0)					8	(23.5)
3	(13.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	13	(9.8)
0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	9	(6.8)
3	(13.6)	0	(0.0)	0	(0.0)	1	(5.9)	0	(0.0)	1	(3.7)	10	(7.6)
16	(72.7)	2	(100.0)	4	(100.0)	16	(94.1)	4	(100.0)	26	(96.3)	100	(75.8)

was also observed between units within the same country, revealing that different options can operate locally, such as milk bank availability which may differ between regions within countries. Study limitations include data collected in 2012, which may underestimate current human milk bank availability, and a smaller number of units in participating regions in some countries; however, no more recent comparable information on practices is available from so many European countries.

While it is recognised that MOM should be encouraged as the primary feeding method for VPT infants, this variation indicates substantial differences in attitudes about what constitutes best practices for the management of MOM among European neonatologists. To guide practice, further studies are needed to reinforce the evidence base on ensuing outcomes of HCMV infection as well as practices for managing these risks while ensuring that VPT infants can benefit from MOM.

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CONFLICT OF INTEREST

None to declare.

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4.6. PAPER VI

Breast milk feeding and cognitive development at 2 years of corrected age in children born very preterm: a European cohort study

Rodrigues C, Zeitlin J, Zemlin M, Wilson E, Pedersen P, Barros H, the EPICE Research Group.

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Breast milk feeding and cognitive development at 2 years of corrected age in children born very preterm: A European cohort study

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Conflict of interest

The authors declare that they have no conflicts of interest.

Contributions

Study concept and design was done by CR, JZ, and HB. All authors (including authors listed in EPICE Research Group) contributed to the acquisition, analysis, or interpretation of data. The first draft of the manuscript was done by CR. Also, the statistical analysis was done by CR, supervised by JZ and HB. Lastly, the critical revision of the manuscript for important intellectual content and approval of final version of the manuscript was done by all authors (including authors listed in EPICE Research Group).

ABSTRACT

The evidence about the relation between breast milk feeding (BMF) and neurodevelopment in very preterm (VPT) children is inconclusive. Thus, in a European cohort of infants born VPT, we investigated the association between BMF initiation and its duration on cognitive development at 2 years of corrected age (CA). Data were obtained from the Effective Perinatal Intensive Care in Europe (EPICE) population-based prospective cohort of infants born <32 weeks of gestation, in 11 European countries, in 2011–2012. The study sample included 4323 children (67.7% of those eligible for follow-up at 2 years CA). To determine the association between BMF (mother's own milk, regardless of the route of administration) and non-verbal and verbal cognition (categorized as an optimal and suboptimal outcome), adjusted risk ratios (aRR) were estimated fitting Poisson regression models, with inverse probability weights to account for non-response bias. Overall, 16% and 11% of the children presented suboptimal non-verbal and verbal cognition, respectively. Never BMF was associated with a significantly increased risk for suboptimal non-verbal (aRR=1.29, 95%CI=1.09-1.53) and verbal (aRR=1.45, 95%CI=1.09-1.92) cognitive development compared with those ever breastfed, after adjustment for perinatal and sociodemographic characteristics. Compared with infants breastfed 6 months or more, infants with shorter BMF duration exhibited a statistically non-significant elevated aRR. VPT infants fed with breast milk had both improved non-verbal and verbal cognitive development at 2 years CA in comparison with never breastfed, independently of perinatal and sociodemographic characteristics. This study encourages targeted interventions to promote BMF among these most vulnerable infants.

Keywords: Breast milk; Breastfeeding; Very preterm infants; Cognitive development; Neurodevelopment

KEY MESSAGES

- In a European cohort of children born very preterm, 16% and 11% presented suboptimal non-verbal and verbal cognitive development, respectively.

- Never breastfed children faced a higher risk of having suboptimal non-verbal and verbal cognition at 2 years of corrected age when compared to those who were breastfed, independent of multiple relevant perinatal and socio-demographic characteristics.

- The association between breast milk feeding and cognitive development among children born very preterm reinforces the importance of specifically targeted interventions to protect, promote and support it in neonatal intensive care units and after discharge.

1. INTRODUCTION

Despite ethical difficulties that hamper randomized trials, there is a solid evidence base showing that breast milk feeding (BMF) in healthy, full-term infants improves cognitive abilities in childhood, adolescence, and adulthood (Horta, Loret de Mola, & Victora, 2015; Victora et al., 2015). A meta-analysis of 17 observational studies reported that BMF was associated with higher scores in intelligence tests (+3.4 points) (Horta et al., 2015). This positive effect was also observed in a large cluster-randomized trial designed to evaluate a BMF promotion intervention, suggesting that the association is causal: the experimental group had a 5.9 higher cluster-adjusted mean difference in the full-scale intelligence quotient (IQ) (Kramer et al., 2008).

The presence of biological components in breast milk, such as long-chain polyunsaturated fatty acids (especially docosahexaenoic acid and arachidonic acid) and human milk oligosaccharides, essential for the infant's brain development, might explain the association, as these components play an important role in neurogenesis and modulate infant gut microbiota composition, respectively (Agostoni, 2008; Belfort, 2018; Innis, 2004; Mayer, Knight, Mazmanian, Cryan, & Tillisch, 2014). Another potential mechanism is related to the children's emotional environment. Mothers who breastfeed may provide stronger attachment security and be more sensitive to the needs of the infant (Peñacoba & Catala, 2019; Tharner et al., 2012) which have been associated with brain development and better neurocognitive outcomes (Treyvaud et al., 2016; Wang et al., 2019). However, BMF can also be an indirect indicator of other parenting behaviors which are independently associated with cognition. Further, in high income countries, higher maternal educational and socioeconomic status are positively associated with the prevalence and duration of BMF (Victora et al., 2016) and the link between BMF and cognitive development may therefore be partly confounded by family and parenting characteristics (Horta et al., 2015).

Very preterm (VPT, <32 weeks of gestation) infants experience a higher risk of short-term and long-term adverse health and developmental outcomes, including cerebral palsy, motor and cognitive delay (Ancel et al., 2015; Pierrat et al., 2017) and require more healthcare services (Seppanen et al., 2019). The importance of BMF on their neurodevelopment might be even more significant considering that they are particularly vulnerable to nutrient deficits and growth faltering, presenting very specific nutritional needs compared with full-term infants

(Belfort, 2018; EFCNI, 2018; El Rafei et al., 2020). At the same time, preterm neonatal morbidities which affect cognition, such as brain lesions, may operate through pathways that may not be affected by the nutritional or immunological benefits of BMF. Because of these specificities, studies based on full-term children cannot be generalized to this population.

The evidence about the relationship between BMF and neurodevelopment in VPT infants is inconclusive and the mechanisms are still not well understood (Koo, Tank, Martin, & Shi, 2014; Lechner & Vohr, 2017; Miller et al., 2018). Some observational studies found an independent positive association (Beaino et al., 2011; Belfort et al., 2016; Gibertoni et al., 2020; Johnson, Wolke, Hennessy, & Marlow, 2011; Roze et al., 2012), while others found none (Furman et al., 2004; Jacobi-Polishook et al., 2016; Pinelli, Saigal, & Atkinson, 2003). One randomized clinical trial of 363 very low birth weight (VLBW) infants found that the use of supplemental donor milk compared with preterm formula, as a supplement to mother's milk during hospitalization, did not improve neurodevelopment at 18 months' corrected age (CA) (O'Connor et al., 2016), raising further questions about the differences between donor human milk and mother´s own milk (Hård et al., 2019). Moreover, it remains unclear if prolonged BMF for more than 6 months CA has an influence on the neurodevelopmental outcome in VPT.

Recent systematic reviews and meta-analysis revealed that different methodological approaches such as population inclusion criteria (according to gestational age and/or birthweight), age at assessment, BMF indicators/definitions, methods and instruments for assessing and classifying neurodevelopment, the cognitive abilities considered as outcome, as well as design limitations (e.g. sample size) make a direct comparison between studies difficult (Koo et al., 2014; Lechner & Vohr, 2017; Miller et al., 2018; Sentenac, Boutron, et al., 2020).

Taking into account the inconsistent findings and also the lack of data on the total duration of BMF in this vulnerable population, we aimed to investigate the association of BMF (mother´s own milk) initiation and its duration with neurodevelopment, specifically on non-verbal and verbal cognition at 2 years of CA in a large prospective cohort of VPT infants from 11 European countries.

2. METHODS

2.1. Data source

This study uses data from the *Effective Perinatal Intensive Care in Europe* (EPICE) project, that recruited a geographically defined population-based prospective cohort of VPT infants (22–31 completed weeks of gestational age), born in 19 regions from 11 European countries (Zeitlin et al., 2020). As previously described, data were collected during 12 consecutive months in 2011-2012, starting between March and July 2011 (Zeitlin et al., 2020), except for the three French regions where inclusions lasted 6 months as part of the study EPIPAGE-2 (Ancel et al., 2015).

Data on infant, obstetric and maternal characteristics, and on neonatal course were retrieved from obstetrical and neonatal records using a pretested standardized questionnaire with common definitions filled in by medical staff until discharge from the hospital and later verified by the research team. At 2 years of CA, data on child's health and neurodevelopment outcomes, growth, health service utilization, BMF, and sociodemographic characteristics were collected using a structured questionnaire completed by parents. This questionnaire was translated into the different national languages, back translated in English, and pretested in all the regions (Zeitlin et al., 2020).

2.2. Ethical approvals

Informed consent was obtained from all parents or legal representative included in the follow-up study. Ethical approvals were obtained in each country as required by national legislation. The European study was also approved by the French Advisory Committee on Use of Health Data in Medical Research and the French National Commission for Data Protection and Liberties.

2.3. Study population

Of the 7900 VPT live births identified, 6792 infants were discharged alive (86.0%). Thirty-one infants died before 2 years CA, leaving 6761 eligible infants for follow-up at 2 years CA, and 4426 children provided information (65.5%). As the response rate in the Northern region in the UK was very low (27.2%, 103/379), this region was excluded from this analysis because of concern about a potential biased sample, in accordance with other studies at 2 years CA in this cohort (Bonnet et al., 2019; Seppanen et al., 2019). After excluding the UK Northern region, follow-up rates differed across countries, ranging from 47.2% in Belgium to 99.3% in Estonia. The final study sample included 4323 children (67.7% of those eligible) (Figure S1, supporting information).

2.4. Data on breast milk feeding (exposure)

Data on BMF was collected through the parental questionnaire at 2 years CA, considering only mother's own milk, independently of route of administration (nasogastric tube, bottle and/or directly at the breast). Infants were considered to have ever been breast fed if the answer was yes to the question "*Was your child breast fed?*". BMF duration was defined as the age of the child, reported in months of chronological age, at which BMF was stopped completely, regardless of if it was exclusive or partial. We categorized the BMF duration in five groups: (1) never breastfed; (2) between >0 and <2 months; (3) between 2 and <4 months; (4) between 4 and <6 months; and (5) 6 months or more.

2.5. Data on non-verbal and verbal cognitive development (outcome)

Regarding our outcome of interest, non-verbal and verbal cognitive abilities were measured at 2 years CA through a validated developmental assessment tool filled in by parents, the Parent Report of Children's Abilities-Revised (PARCA-R), which includes the short version of the MacArthur Communicative Development Inventory (CDI) for language abilities (Johnson et al., 2004; Johnson, Wolke, & Marlow, 2008). This tool has shown excellent test-retest reliability, and correlation with the Mental Development Index (MDI) of the Bayley Scales of Infant and Toddler Development-II (BSID-II) (Cuttini et al., 2012; Johnson et al., 2008). The full PARCA-R, which includes a non-verbal and verbal score, could not be completed in countries without a translation of the MacArthur short form available (Belgium, Denmark, the Netherlands, Poland, Portugal, and Sweden). Therefore, we additionally included questions on language acquisition which were asked in all regions. The Ages & Stages Questionnaire (ASQ) was used in French regions as this instrument was validated in France whereas the PARCA-R was not (Flamant et al., 2011).

For this study, we categorized both non-verbal and verbal cognition as a binary outcome, optimal and suboptimal. For non-verbal cognitive development, we established a cut-off of less than 22 for the non-verbal cognition score of the PARCA-R and less than 29.78 for the ASQ problem solving domain, which corresponds to less than 2 standard deviations (SD) below the mean of the standardisation sample to define suboptimal non-verbal cognition (Johnson et al., 2008). A negative response to the following question "*Does your child say as many as 10 words?*" (low expressive vocabulary indicator) was considered as suboptimal verbal cognition.

2.6. Data on perinatal and sociodemographic characteristics (covariates)

Perinatal and sociodemographic characteristics were used to describe the sample and as covariates in the analyses. We included child sex, gestational age (in completed weeks), small for gestational age (SGA) defined as birthweight <10^{th} percentile for gestational age (severe SGA as <3^{rd} percentile and moderate SGA as 3^{rd}-<10^{th} percentile) using intrauterine references developed for the cohort (Zeitlin et al., 2017), any congenital anomaly (none, non-severe vs. severe), bronchopulmonary dysplasia (BPD) defined as oxygen dependency or respiratory support at 36 weeks postmenstrual age, Intraventricular Haemorrhage Papille's grades III or IV (IVH III-IV), Cystic Periventricular Leukomalacia (cPVL), Retinopathy of Prematurity grades III-V (ROP III-V), and Necrotizing Enterocolitis (NEC) with surgery or peritoneal drainage. As defined previously for this cohort, we used a perinatal risk composite, considering three risk groups based on perinatal characteristics which represents the overall risk of health and developmental problems at discharge from the neonatal unit (Seppanen et al., 2019): (1) *Lower risk* - birth at 30-31 weeks of gestation, not SGA, no congenital anomaly and without severe neonatal morbidities (BPD, IVH III-IV, cPVL, ROP III-V, NEC with surgery or peritoneal drainage); (2) *Moderate risk* - birth at 28-29 weeks' gestation or SGA or any non-severe congenital anomaly, but no severe neonatal morbidities; and (3) *Higher risk* - birth before 28 weeks of gestation or at least one severe neonatal morbidity (BPD, IVH III-IV, cPVL, ROP III-V, NEC with surgery or peritoneal drainage) or severe congenital anomaly.

We assessed maternal and sociodemographic characteristics, including mother's age at delivery (≤24, 25-34 or ≥35 years), mother's country of birth (native-born, born in Europe and born outside Europe as in UK data were available only on ethnicity), family situation (mother living with partner vs. single caregiver or other family situation), parity at delivery, and type of pregnancy (singleton vs. multiple). We also included the mother's highest achieved educational level collected at the 2 years CA based on the International Standard Classification of Education (ISCED) 2011 definition and categorized in three groups, considering the cross-national differences in educational systems: (1) lower level (ISCED level 0-2: lower secondary); (2) intermediate level (ISCED level 3-5: upper or post-secondary, non-tertiary or short cycle tertiary); and (3) higher level (ISCED level 6-8: bachelor degree or higher) (UNESCO Institute for Statistics, 2012).

2.7. Statistical analysis

Responders and non-responders' characteristics were compared considering all eligible infants for follow-up at 2 years CA, excluding infants from UK Northern region (n=6382). We calculated the Wald test from the logistic regression adjusted for country because of differences in follow-up rates. The effects of potential bias due to attrition were accounted using the inverse probability weighting method in all analyses to give higher weight to children with characteristics of non-responders in order to obtain a sample that reflects the full set of observations (Bonnet et al., 2019; Seaman & White, 2013; Seaman, White, Copas, & Li, 2012). The probability of follow-up at 2 years CA (yes or no) was estimated with a multivariate logistic regression model including all variables available at baseline associated with nonresponse, as detailed elsewhere (Bonnet et al., 2019; Seppänen et al., 2020). The weight was computed using the total sample of eligible infants for follow-up at 2 years CA (n=6382). Before predicting the inverse probability weights, missing values from variables included in the regression model were imputed with multiple chained equations (twenty complete data sets generated) to have a more stable weight (Seaman & White, 2013; Seaman et al., 2012). Data were assumed to be missing at random. All results presented in this study are based on weighted sample.

BMF initiation, as well as non-verbal and verbal cognitive development were described by the study sample characteristics, and proportions compared performing Wald test from the logistic regression adjusted for country. To estimate the association between BMF and verbal and non-verbal cognition (optimal vs suboptimal), crude risk ratios (RR) and adjusted risk ratios (aRR) with 95% confidence intervals (95%CI) were estimated by fitting multilevel mixed-effects generalised linear regression models with a log link, Poisson distribution and robust standard errors. This model directly estimates the risk ratios and provides covariate-adjusted risk ratios and associated standard errors for binary outcomes (Zou & Donner, 2013). Risk ratios were preferred instead of odds ratios as suboptimal cognition is not a rare event in VPT infants (incidence of 10% or more) and our study used a prospective cohort design. We used multilevel models with random intercepts at the country and mother levels to consider the correlation of infants within countries and between siblings, respectively. To determine whether there is a dose-response relationship by BMF duration we performed a test for trend.

Variables selected for the adjusted models were based on the scientific literature and previous findings from the EPICE cohort (Bonnet et al., 2019; Draper et al., 2020; Sentenac, Johnson, et al., 2020; Wilson et al., 2018), including characteristics that were related or plausibility related with both BMF and cognitive development (potential confounders). Additionally, stratified analyses were performed to assess the association of BMF with non-verbal and verbal cognition by perinatal risk group (as an indicator of the overall risk of health and developmental problems) and maternal educational level (as an indicator of socioeconomic disadvantage), comparing the total crude risk ratios to the stratum-specific risk ratios.

Statistical analyses were performed using STATA version 15.1 software (Stata Corporation, College Station, Texas, USA).

3. RESULTS

Characteristics associated with loss to follow-up at 2 years CA are provided in detail in Table S1 (supporting information). Children born from singleton pregnancies and to younger, multiparous and migrant women were less likely to be followed-up. Children who received BMF at discharge were more likely to participate at 2 years CA.

Table 1 shows the infant and maternal characteristics of ever breastfed children (weighted distributions). We observed that proportions of never breastfed children were higher for younger, multipara, single and lower educational level mothers.

Of the 4092 children with available information, 16.0% presented suboptimal non-verbal cognitive development (weighted sample). This proportion varied among countries, with the lowest rate found in the Netherlands (10.6%) and the highest in Poland (24.8%) (Table 2). For verbal cognition, 11.1% (n=4134) of the children presented suboptimal ability (weighted sample) and this proportion ranged from 7.7% in Sweden to 19.1% in Poland (Table 2).

Suboptimal non-verbal and verbal ability at 2 years CA were more frequent in males, children born before 28 weeks of gestational age and at higher perinatal risk (Table 2). When mothers were born outside Europe and with lower educational levels, the proportions of children with suboptimal verbal and non-verbal cognition were higher.

As demonstrated in Table 3, never breastfed children faced a higher risk of suboptimal non-verbal cognition than those who had ever been breastfed (RR=1.48, 95%CI: 1.11-1.98). Similarly, when stratified by perinatal risk group, never BMF was associated with an increased risk in the three groups, with a gradient from the lower to higher risk groups (Lower: RR=1.02, 95%CI: 0.58-1.78; Moderate: RR=1.21, 95%CI: 0.97-1.51; Higher: RR=1.57, 95%CI: 1.12-2.18) (Table S2, supporting information). The stratified analysis by maternal educational level found that never BMF was associated with an increased risk of suboptimal non-verbal cognition in all groups, with a significant association in the intermediate level group (RR=1.55, 95%CI: 1.01-2.38) (Table S3, supporting information). Overall, after adjustment for sex, CA at assessment and perinatal risk, never BMF remained associated with an increased risk for suboptimal non-verbal cognition when compared with ever breastfed children (aRR=1.39, 95%CI: 1.11-1.75) (Table 3). This effect persisted after taking into maternal and sociodemographic characteristics (aRR=1.29, 95%CI: 1.09-1.53). The association between BMF duration and non-verbal cognition was stronger among shorter duration categories when comparing with infants breastfed until 6 months or more, with a dose-response relationship.

As shown in Table 4, we observed that children who were never breastfed presented 1.73 more risk to have suboptimal verbal cognition (95%CI: 1.19-2.52). The stratified analysis by perinatal risk found that never BMF was associated with an increased risk of suboptimal verbal cognition in the three risk groups, with a significant association in the moderate risk group (RR=2.17, 95%CI: 1.23-3.82) (Table S2, supporting information). In the same way, never BMF was also associated with an increased risk in all maternal educational level groups, with a significant association in both lower and intermediate groups (RR=1.70, 95%CI: 1.02-2.82; RR=1.76, 95%CI: 1.09-2.84, respectively) (Table S3, supporting information). Overall, this increased risk for never breastfed children remained significant after adjustment for sex, CA at assessment and perinatal risk (aRR=1.59, 95%CI: 1.16-2.19). Incorporating maternal and sociodemographic characteristics (maternal age, parity, type of pregnancy, mother's country of birth, mother's educational level, family situation), significant differences persisted, even with slight changes in point estimates (aRR=1.45, 95%CI: 1.09-1.92). We estimated crude and adjusted risk ratios considering the BMF duration and it was possible to verify a dose-response relationship (Table 4).

A sensitivity analysis was carried out considering only children hospitalized in NICUs without human bank milk/donor milk available. After adjustment for potential confounding factors, the risk was 1.70 (IC95%: 1.46-1.97) for non-verbal and 1.78 (IC95%: 1.49-2.14) for verbal suboptimal cognitive development, compared with those ever breastfed.

4. DISCUSSION

In a population-based cohort of children born VPT in Europe, we found that 16% and 11% of the children presented suboptimal non-verbal and verbal cognitive development, respectively. Never breastfed children faced a higher risk to have suboptimal cognition than those who had ever been breastfed, independently of perinatal and sociodemographic characteristics. When considering BMF duration, we observed a dose-response relationship with higher risks among short durations compared with longer durations.

Our findings support previous research indicating that BMF has an independent association with neurodevelopment for VPT children (Beaino et al., 2011; Gibertoni et al., 2020; Johnson et al., 2011; Roze et al., 2012). Two independent cohorts of VPT infants in France, LIFT and EPIPAGE, showed that any BMF at discharge was associated with a reduction in the odds of suboptimal neurodevelopment at 2 and at 5 years of age, respectively (Roze et al., 2012). Also, in the EPIPAGE cohort, it was observed that any BMF at discharge was highly associated with lower odds of mild and severe cognitive deficiencies at 5 years (Beaino et al., 2011). Another study from the United Kingdom and Ireland, using data from EPICure cohort, revealed that receiving any breast milk was a protective factor for reading scores at 11 years (Johnson et al., 2011). Recently, a study from Italy demonstrated that exclusively formula fed infants at discharge from the NICU had significantly lower neurodevelopment trajectories from 3 to 24 months of CA compared with those receiving exclusively human milk or mixed (Gibertoni et al., 2020). Data obtained from the United Kingdom Millennium cohort at 5 years showed a significant difference in mean score between children who were breastfed and who were never breastfed, after adjustment for potential confounders: in term children (≥37 weeks of gestation), a two-point increase in score for picture similarities (breastfed ≥4 months) and naming vocabulary (breastfed ≥6 months); in preterm children (28-36 weeks of gestation), a 4-point increase for naming vocabulary (breastfed ≥4 months) and picture similarities (breastfed ≥2 months) and a 6-point increase for pattern construction (breastfed ≥2 months) (Quigley et al., 2012).

The mechanisms linking BMF to neurodevelopment are still unclear, and even more so in VPT infants. Cognitive development is a complex multifactorial issue for VPT infants, depending on biological, clinical, and environmental events (Beaino et al., 2011; Draper et al., 2020; Gibertoni et al., 2020; Linsell, Malouf, Morris, Kurinczuk, & Marlow, 2015; Sentenac, Johnson, et al., 2020; Twilhaar et al., 2018) and BMF practices reflects many of these factors (Bonnet et al., 2019). A systematic review performed to identify the factors for poor cognitive development in children born VPT or VLBW found that the influence of perinatal risk factors on cognitive development appears to diminish over time as other social and environmental factors become more important (Linsell et al., 2015). In our study, although the risk ratios decreased consecutively when we adjusted for perinatal risk (model 1) and additionally for maternal and sociodemographic characteristics (model 2), never BMF remained associated with a significant increased risk for suboptimal non-verbal (RR=1.29) and verbal (RR=1.45) cognition comparing with those ever breastfed. This result is particularly important for clinical practice highlighting the crucial role of BMF as a minimum standard for newborn care, being a tool to mitigate the adverse neurodevelopmental outcomes among these vulnerable infants. Studies of BMF practices in neonatal units which are known to be effective for supporting VPT mothers, show there is a large margin for improvement in many countries (Cuttini et al., 2019; Rodrigues, Severo, Zeitlin, & Barros, 2018; Wilson et al., 2018).

Acting on modifiable risk factors that interfere with optimal neurodevelopment, such as those related to BMF, is important because despite many advances in perinatal care in the last decades, adverse neurodevelopmental outcomes among children born VPT are not declining over time (Pascal et al., 2018; Pierrat et al., 2017; Twilhaar et al., 2018). A meta-analysis from Blencowe et al., based on articles with a median birth year of 2000 or later, estimated that

52% of extremely preterm (born at <28 weeks) and 24% of VPT infants (born at 28-31 weeks) develop a certain degree of some neurodevelopmental impairment (Blencowe et al., 2013). A recent meta-analysis of 71 studies showed a large (0.86 SD) difference in intelligence scores between VPT children and full-term controls at age 5 years or older, in children born between 1990 and 2008 (Twilhaar et al., 2018). Pascal et al. estimated a pooled prevalence of cognitive delay of 16.9% (95%CI: 10.4–26.3) in VPT or VLBW infants born after 2006 and evaluated from 18 months CA until 6 years (Pascal et al., 2018). Pooled estimates of five meta-analyses affirmed the robust conclusion that VPT birth is associated with a lower IQ, compared with full-term children (Sentenac, Boutron, et al., 2020).

4.1. Strengths and limitations

The strengths of this study include the use of a large population-based prospective cohort, its geographic spread and range of sociocultural contexts, and standardized data collection tools, with common definitions, across 11 European countries. Another strength of our study is the information available on duration of BMF until the age of 2 years CA. To the best of our knowledge, there is not any published study from contemporary cohorts of children born VPT (<32 weeks) reporting the association between BMF duration and neurodevelopment outcomes. Most previous studies focused on BMF at time of discharge (any BMF versus exclusive formula) or during hospitalization period (ever vs. never), all of them with smaller samples sizes and being from single country-cohorts (Beaino et al., 2011; Gibertoni et al., 2020; Johnson et al., 2011; Roze et al., 2012). Additionally, we used both non-verbal and verbal cognitive development as outcomes, reinforcing the impact of our results. However, for verbal cognition we used a question about vocabulary production, reflecting a very low expressive vocabulary (less than 10 words), as a validated tool for assess language was not available for all countries (Zeitlin et al., 2020).

Our study also has other limitations. About 35% of the infants discharged alive were not followed-up at 2 years CA. Nevertheless, we were able to compare responders with non-responders using data at baseline and took into consideration potential bias related to cohort attrition by using inverse probability weighting methods. Sensitivity analyses showed that results were not substantially affected by weighting for non-response (data not presented), as observed previously in the EPICE cohort (Bonnet et al., 2019; Seppänen et al., 2020).

In addition, we did not collect detailed infant feeding data, namely we have no information about the total duration of exclusive BMF, type of formula used and route of BMF administration. The duration of BMF was collected retrospectively when the child was 2 years CA, which may lead to some potential recall bias, although previous studies reported good validity of maternal recall of BMF duration (Amissah, Kancherla, Ko, & Li, 2017). Also, this potential recall bias was mitigated by verifying the data reported by parents with the information on the type of feeding at discharge from hospital abstracted from clinical records, which made it possible to validate partially this information, in accordance with another study already published using EPICE data at 2 years CA (Bonnet et al., 2019).

In the EPICE cohort, 34% of units reported to use human bank milk/donor milk for all VPT infants when mother's own milk was not available (Rodrigues et al., 2021). Thus, within children classified as never breastfed (mother´s own milk) some of them may have received donor milk. A sensitivity analysis was carried out considering only children hospitalized in NICUs without human bank milk/donor milk available and we found that the association was even stronger for both non-verbal and verbal suboptimal cognitive development, compared with those ever breastfed.

Finally, maternal intelligence, which is an important potential confounder of the association between BMF and cognitive development, was not measured. However, in a recent meta-analysis of studies that controlled for maternal intelligence, BMF remained associated with a gain in performance in IQ testing (Horta et al., 2015).

5. CONCLUSION

BMF promotes both verbal and non-verbal cognitive development of VPT children at 2 years CA, independently of perinatal and sociodemographic characteristics. The most important conclusion is that any amount of BMF is better than none. Considering that any intervention that has the potential to increase cognitive ability among these most vulnerable infants is a significant window of opportunity, our results reinforce the importance of specifically targeted interventions to protect, promote and support BMF in neonatal intensive care units and after discharge. Further research is needed to understand the impact of BMF initiation and continuation at long-term neurodevelopmental outcomes in this vulnerable population.

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Table 1. Any breast milk feeding, according to the infant, neonatal morbidity, maternal, and socio-demographic characteristics.

	Any breast milk feeding (n=4305)		
Characteristics	Never n=952 (23.1%) n (%[a])	Ever n=3353 (76.9%) n (%[a])	p-value[b]
Infant and neonatal morbidity			
Child sex			
Male	504 (23.0)	1775 (77.0)	0.872
Female	448 (23.1)	1578 (76.9)	
Gestational age at birth			
22-25 weeks	84 (26.1)	239 (73.9)	0.007
26-27 weeks	192 (27.2)	563 (72.8)	
28-29 weeks	238 (20.7)	906 (79.3)	
30-31 weeks	438 (22.5)	1645 (77.5)	
SGA			
<3rd percentile	213 (23.9)	683 (76.1)	0.704
3rd – <10th percentile	115 (24.4)	396 (75.6)	
≥10th percentile	624 (22.6)	2274 (77.4)	
BPD			
No	781 (22.2)	2897 (77.8)	<0.001
Yes	142 (27.1)	388 (72.9)	
ROP stages III-V			
No	883 (22.5)	3213 (77.5)	<0.001
Yes	60 (39.0)	99 (61.0)	
IVH III-IV / cPVL			
No	871 (22.9)	3133 (77.1)	0.234
Yes	70 (25.6)	187 (74.4)	
NEC needing surgery or peritoneal drainage			
No	931 (23.0)	3308 (77.0)	0.037
Yes	21 (30.6)	45 (69.4)	
Any congenital anomaly			
None	850 (22.5)	3093 (77.5)	0.023
Non-severe	81 (27.1)	231 (72.9)	
Severe	21 (46.6)	28 (53.4)	
Perinatal risk			
Lower	222 (21.5)	907 (78.5)	<0.001
Moderate	326 (20.3)	1301 (79.7)	
Higher	379 (27.4)	1062 (72.6)	
Mother and sociodemographic characteristics			
Mother's age at delivery			
≤ 24 years	159 (29.3)	373 (70.7)	<0.001
25 - 34 years	508 (21.2)	1998 (78.8)	
≥ 35 years	282 (23.6)	975 (76.4)	

Parity at delivery			
0 previous births	508 (20.0)	2078 (80.0)	<0.001
1 previous birth	248 (24.8)	792 (75.2)	
2 or more previous births	181 (29.5)	454 (70.5)	
Type of pregnancy			
Singleton	680 (24.8)	2201 (75.2)	<0.001
Multiple	272 (19.3)	1152 (80.7)	
Mother's country of birth			
Native-born	714 (22.9)	2563 (77.1)	0.134
Born elsewhere in Europe	51 (31.0)	147 (69.0)	
Born outside Europe	131 (22.0)	449 (78.0)	
Mother's educational level [c]			
Low level (ISCED 0-2)	278 (34.7)	558 (65.3)	<0.001
Intermediate level (ISCED 3-5)	391 (22.6)	1366 (77.4)	
High level (ISCED 6-8)	214 (14.3)	1347 (85.7)	
Family situation			
Mother living with partner	812 (22.0)	3026 (78.0)	<0.001
Single mother or other family situation	102 (28.8)	280 (71.2)	
Country (region(s))			
Belgium (Flanders)	59 (21.7)	246 (78.3)	<0.001
Denmark (Eastern)	10 (6.2)	170 (93.8)	
Estonia (whole country)	19 (13.8)	119 (86.2)	
France (Burgundy, Northern, Ile-de-France)	357 (37.2)	629 (62.8)	
Germany (Hesse, Saarland)	111 (30.7)	319 (69.3)	
Italy (Emilia, Lazio, Marche)	183 (28.1)	549 (71.9)	
Netherlands (East-Central)	29 (14.1)	199 (85.9)	
Poland (Wielkopolska)	69 (36.8)	130 (63.2)	
Portugal (Lisbon and Tagus Valley, Northern)	52 (15.1)	350 (84.9)	
Sweden (Stockholm)	7 (5.0)	156 (95.0)	
UK (East Midlands, Yorkshire and Humber) [d]	56 (14.3)	486 (85.7)	

[a] Proportions were calculated using inverse probability weights to account for non-response bias; [b] Wald test from logistic regression adjusted for country; [c] ISCED=International Standard Classification of Education 2011; [d] UK Northern region was excluded from this analysis.

BPD, bronchopulmonary dysplasia; CA, corrected age; cPVL, cystic periventricular leukomalacia; IVH, intraventricular haemorrhage; NEC, necrotising enterocolitis; ROP, retinopathy of prematurity; SGA, small for gestational age.

Table 2. Non-verbal and verbal cognitive development, according to infant, neonatal morbidity, maternal, and socio-demographic characteristics.

	Non-Verbal cognition (n=4092)			Verbal cognition (n=4134)		
	Optimal n=3474 (84.0%)	Suboptimal n=618 (16.0%)		Optimal n=3691 (89.9%)	Suboptimal n=443 (11.1%)	
Characteristics	n (%[a])	n (%[a])	p-value[b]	n (%[a])	n (%[a])	p-value[b]
Infant and neonatal morbidity						
Child sex						
Male	1775 (81.1)	388 (18.9)	<0.001	1868 (85.9)	300 (14.1)	<0.001
Female	1699 (87.4)	230 (12.6)		1823 (92.3)	143 (7.7)	
Gestational age at birth						
22-25 weeks	229 (72.3)	83 (27.7)	<0.001	244 (76.8)	68 (23.2)	<0.001
26-27 weeks	576 (80.0)	128 (20.0)		599 (84.2)	108 (15.8)	
28-29 weeks	930 (83.8)	165 (16.2)		1016 (91.0)	93 (9.0)	
30-31 weeks	1739 (87.3)	242 (12.7)		1832 (91.3)	174 (8.7)	
SGA						
<3rd percentile	697 (80.9)	155 (19.1)	0.013	727 (84.5)	126 (15.5)	<0.001
3rd – <10th percentile	425 (86.1)	66 (13.9)		442 (89.9)	47 (10.1)	
≥10th percentile	2352 (84.6)	397 (15.4)		2522 (90.1)	270 (9.9)	
BPD						
No	3025 (85.5)	473 (14.5)	<0.001	3207 (90.4)	328 (9.6)	<0.001
Yes	368 (73.0)	135 (27.0)		399 (78.2)	110 (21.8)	
ROP stages III-V						
No	3334 (85.7)	556 (14.3)	<0.001	3529 (89.5)	402 (10.5)	<0.001
Yes	100 (64.5)	55 (35.5)		117 (73.9)	39 (26.1)	
IVH III-IV / cPVL						
No	3286 (85.8)	524 (14.2)	<0.001	3464 (89.9)	387 (10.1)	<0.001
Yes	153 (59.4)	87 (40.6)		188 (74.7)	51 (25.3)	
NEC needing surgery or peritoneal drainage						
No	3433 (84.3)	595 (15.7)	<0.001	3638 (89.0)	432 (11.0)	0.251
Yes	41 (66.3)	23 (33.7)		53 (83.8)	11 (16.2)	
Any congenital anomaly						
None	3207 (84.6)	544 (15.4)	0.025	3407 (89.5)	383 (10.5)	0.004
Non-severe	231 (78.0)	63 (22.0)		248 (83.0)	49 (17.0)	
Severe	35 (77.4)	11 (22.6)		35 (78.3)	11 (21.7)	
Perinatal risk						
Lower	970 (89.9)	104 (10.1)	<0.001	1023 (93.4)	72 (6.6)	<0.001
Moderate	1348 (86.0)	208 (14.0)		1431 (91.2)	138 (8.8)	
Higher	1064 (76.7)	296 (23.3)		1138 (83.3)	228 (16.7)	
Corrected age at assessment						
≤ 21 months	41 (83.9)	8 (16.1)	<0.001	44 (80.7)	11 (19.3)	0.052
22-26 months	3053 (83.1)	579 (16.9)		3211 (88.8)	389 (11.2)	
≥ 27 months	366 (92.8)	29 (7.2)		419 (90.6)	43 (9.4)	

Mother and socio-demographic characteristics						
Mother's age at delivery						
≤ 24 years	398 (82.4)	81 (17.6)	0.556	427 (86.6)	66 (13.4)	0.518
25 - 34 years	2027 (83.9)	363 (16.1)		2167 (89.9)	244 (10.1)	
≥ 35 years	1043 (85.3)	172 (14.7)		1092 (89.5)	128 (10.5)	
Parity at delivery						
0 previous births	2131 (85.8)	340 (14.2)	<0.001	2252 (90.3)	241 (9.7)	0.010
1 previous birth	830 (83.6)	158 (16.4)		880 (88.1)	119 (11.9)	
2 or more previous births	476 (78.4)	117 (21.6)		522 (86.7)	80 (13.3)	
Type of pregnancy						
Singleton	2297 (83.2)	436 (16.8)	0.075	2461 (89.9)	296 (11.1)	0.923
Multiple	1177 (85.7)	182 (14.3)		1230 (89.0)	147 (11.0)	
Mother's country of birth						
Native-born	2681 (84.6)	467 (15.4)	0.139	2888 (90.1)	308 (9.9)	0.003
Born elsewhere in Europe	162 (84.4)	28 (15.6)		156 (87.5)	26 (12.5)	
Born outside Europe	430 (81.1)	91 (18.9)		440 (84.4)	81 (15.6)	
Mother's educational level [c]						
Low level (ISCED 0-2)	646 (82.4)	130 (17.6)	0.006	673 (85.1)	118 (14.9)	<0.001
Intermediate level (ISCED 3-5)	1420 (83.2)	268 (16.8)		1532 (89.9)	172 (10.1)	
High level (ISCED 6-8)	1316 (86.0)	200 (13.8)		1389 (91.3)	132 (8.7)	
Family situation						
Mother living with partner	3154 (84.5)	550 (15.5)	0.115	3345 (89.6)	384 (10.4)	0.024
Single mother or other family situation	297 (80.8)	59 (19.2)		319 (85.1)	51 (14.9)	
Country (region(s))						
Belgium (Flanders)	246 (80.9)	57 (19.1)	0.001	273 (90.1)	26 (9.9)	0.009
Denmark (Eastern)	152 (85.2)	27 (14.8)		162 (90.6)	17 (9.4)	
Estonia (whole country)	123 (89.1)	15 (10.9)		126 (91.3)	12 (8.7)	
France (Burgundy, Northern, Ile-de-France)	734 (86.2)	116 (13.8)		729 (86.7)	110 (13.3)	
Germany (Hesse, Saarland)	376 (86.6)	53 (13.4)		397 (90.5)	36 (9.5)	
Italy (Emilia, Lazio, Marche)	624 (84.9)	107 (15.1)		649 (89.1)	80 (10.9)	
Netherlands (East-Central)	206 (89.4)	21 (10.6)		205 (90.2)	20 (9.8)	
Poland (Wielkopolska)	149 (75.2)	48 (24.8)		162 (80.9)	37 (19.1)	
Portugal (Lisbon and Tagus Valley, Northern)	344 (85.0)	60 (15.0)		362 (91.6)	34 (8.4)	
Sweden (Stockholm)	130 (79.9)	33 (20.1)		151 (92.3)	13 (7.7)	
UK (East Midlands, Yorkshire and Humber) [d]	390 (81.1)	81 (18.9)		475 (87.7)	58 (12.3)	

[a] Proportions were calculated using inverse probability weights to account for non-response bias; [b] Wald test from logistic regression adjusted for country; [c] ISCED=International Standard Classification of Education 2011; [d] UK Northern region was excluded from this analysis. BPD, bronchopulmonary dysplasia; CA, corrected age; cPVL, cystic periventricular leukomalacia; IVH, intraventricular haemorrhage; NEC, necrotising enterocolitis; ROP, retinopathy of prematurity; SGA, small for gestational age.

Table 3. Prevalence and risk ratios for non-verbal cognitive development, by breast milk feeding (BMF) initiation and duration.

	Non-verbal cognitive development				
	Optimal	Suboptimal	Crude RR [b]	Adjusted RR [b] (95% CI)	
	n (% [a])	n (% [a])	(95% CI)	Model 1	Model 2
BMF initiation			*(n=4075)*	*(n=3959)*	*(n=3592)*
Never breastfed	713 (79.8)	170 (20.2)	1.48 (1.11-1.98)	1.39 (1.11-1.75)	1.29 (1.09-1.53)
Ever breastfed	2749 (85.4)	443 (14.6)	Reference	Reference	Reference
BMF duration			*(n=3870)*	*(n=3765)*	*(n=3422)*
Never breastfed	713 (79.8)	170 (20.2)	1.58 (1.17-2.13)	1.52 (1.17-1.97)	1.42 (1.09-1.85)
> 0 to <2 months	379 (82.8)	72 (17.2)	1.26 (0.80-1.98)	1.49 (0.98-2.26)	1.44 (0.89-2.34)
2 to <4 months	761 (86.4)	115 (13.6)	0.97 (0.74-1.27)	0.97 (0.75-1.26)	1.01 (0.74-1.37)
4 to <6 months	485 (86.5)	73 (13.5)	0.99 (0.71-1.38)	0.94 (0.68-1.31)	0.95 (0.63-1.43)
≥ 6 months	959 (86.4)	143 (13.6)	Reference	Reference	Reference
p-for-trend			*0.007*	*<0.001*	*0.003*

BMF, Breast milk feeding (mother's own milk); RR, Risk ratio.
[a] Proportions were calculated using inverse probability weights to account for non-response bias.
[b] Risk ratios were derived from the weighted sample (inverse probability of participating at the 2 years CA follow-up), multilevel mixed-effects generalised linear regression models with random intercepts at the country and mother level.
Model 1: Adjusted for child sex, corrected age at assessment, perinatal risk.
Model 2: Adjusted for child sex, corrected age at assessment, perinatal risk, maternal age, parity, type of pregnancy, mother's country of birth, mother's educational level, family situation.

Table 4. Prevalence and risk ratios for verbal cognitive development, by breast milk feeding (BMF) initiation and duration.

	Verbal cognitive development				
	Optimal n (% [a])	Suboptimal n (% [a])	Crude RR [b] (95% CI)	Adjusted RR[b] (95% CI) Model 1	Adjusted RR[b] (95% CI) Model 2
BMF initiation			*(n=4118)*	*(n=3999)*	*(n=3625)*
Never breastfed	753 (84.3)	134 (15.7)	1.73 (1.19-2.52)	1.59 (1.16-2.19)	1.45 (1.09-1.92)
Ever breastfed	2926 (90.4)	305 (9.6)	Reference	Reference	Reference
BMF duration			*(n=3894)*	*(n=3787)*	*(n=3440)*
Never breastfed	753 (84.3)	134 (15.7)	1.78 (1.23-2.59)	1.65 (1.19-2.31)	1.50 (1.12-2.00)
> 0 to <2 months	416 (89.4)	47 (10.6)	1.18 (0.77-1.79)	1.42 (1.00-2.03)	1.21 (0.93-1.59)
2 to <4 months	798 (91.3)	77 (8.7)	0.93 (0.78-1.10)	0.92 (0.76-1.13)	0.97 (0.74-1.26)
4 to <6 months	516 (92.8)	43 (7.2)	0.80 (0.50-1.27)	0.72 (0.46-1.12)	0.80 (0.49-1.31)
≥ 6 months	1010 (90.8)	100 (9.2)	Reference	Reference	Reference
p-for-trend			*0.017*	*0.005*	*0.011*

BMF, Breast milk feeding (mother's own milk); RR, Risk ratio.

[a] Proportions were calculated using inverse probability weights to account for non-response bias.

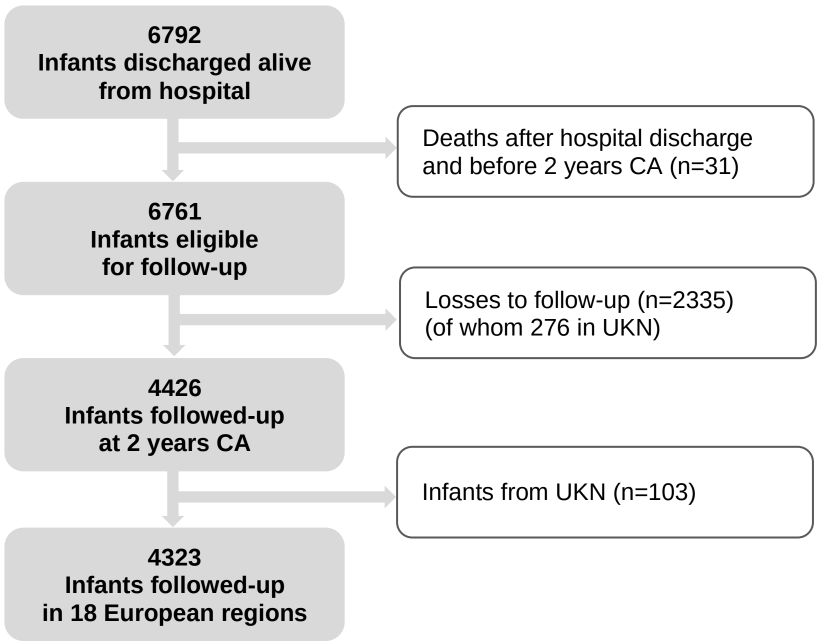
[b] Risk ratios were derived from the weighted sample (inverse probability of participating at the 2 years CA follow-up), multilevel mixed-effects generalised linear regression models with random intercepts at the country and mother level.

Model 1: Adjusted for child sex, corrected age at assessment, perinatal risk.

Model 2: Adjusted for child sex, corrected age at assessment, perinatal risk, maternal age, parity, type of pregnancy, mother's country of birth, mother's educational level, family situation.

SUPPORTING INFORMATION

Figure S1. Study population.



CA: Corrected age; UKN: UK Northern Region.

Table S1. Characteristics associated with loss to follow-up at 2 years corrected age, considering all eligible infants for this study (n=6382).

Characteristics	N[a]	Non-responders at 2 years CA n=2059 (32.3%) n (%)	Responders at 2 years CA n=4323 (67.7%) n (%)	p-value[b]	p-value[c]
Mother and pregnancy					
Mother's age at delivery	6364			<0.001	<0.001
≤ 24 years		488 (23.8)	537 (12.4)		
25-34 years		1098 (53.5)	2516 (58.3)		
≥ 35 years		465 (22.7)	1260 (29.2)		
Mother's country of birth	5940			<0.001	<0.001
Native-born		1319 (70.5)	3288 (80.8)		
Born elsewhere in Europe		117 (6.3)	198 (4.9)		
Born outside Europe		434 (23.2)	584 (14.4)		
Parity at delivery	6325			<0.001	<0.001
0 previous births		1029 (50.3)	2595 (60.6)		
1 previous birth		532 (26.0)	1044 (24.4)		
2 or more previous birth		485 (23.7)	640 (15.0)		
Type of pregnancy	6381			0.002	0.001
Singleton		1455 (70.7)	2891 (66.9)		
Multiple		603 (29.3)	1432 (33.1)		
Infant and neonatal morbidity					
Child sex	6381			0.320	0.581
Male		1118 (54.3)	2291 (53.0)		
Female		940 (45.7)	2032 (47.0)		
Gestational age at birth	6382			0.013	0.165
22-25 weeks		175 (8.5)	326 (7.5)		
26-27 weeks		297 (14.4)	757 (17.5)		
28-29 weeks		553 (26.9)	1153 (26.7)		
30-31 weeks		1034 (50.2)	2087 (48.3)		
Birth weight	6382			0.160	0.492
<1000 grams		545 (26.5)	1217 (28.2)		
≥1000 grams		1514 (73.5)	3106 (71.8)		
SGA	6381			0.818	0.998
<3rd percentile		417 (20.2)	901 (20.8)		
3rd – <10th percentile		240 (11.7)	512 (11.8)		
≥10th percentile		1402 (68.1)	2910 (67.3)		
BPD	6241			0.233	0.153
No		1739 (86.3)	3693 (87.4)		
Yes		276 (13.7)	533 (12.6)		
ROP stages III-V	6292			0.429	0.226
No		1951 (96.6)	4112 (96.2)		
Yes		68 (3.4)	161 (3.8)		

IVH III-IV / cPVL	6306			0.089	0.119
No		1881 (92.8)	4019 (93.9)		
Yes		146 (7.2)	260 (6.1)		
NEC needing surgery or peritoneal drainage	6382			0.314	0.725
No		2020 (98.1)	4256 (98.4)		
Yes		39 (1.9)	67 (1.6)		
Any congenital anomaly	6380			0.696	0.412
None		1897 (92.2)	3958 (91.6)		
Non-severe		138 (6.7)	315 (7.3)		
Severe		23 (1.1)	49 (1.1)		
Perinatal risk	6215			0.282	0.505
Lower		575 (28.8)	1132 (26.9)		
Moderate		763 (38.2)	1636 (38.8)		
Higher		662 (33.1)	1447 (34.3)		
BMF at discharge	6218			<0.001	<0.001
No		931 (47.6)	1596 (37.4)		
Yes		1023 (52.4)	2668 (62.6)		
Country (region(s))	6382			<0.001	<0.001
Belgium (Flanders)		345 (16.8)	308 (7.1)		
Denmark (Eastern)		106 (5.2)	180 (4.2)		
Estonia (whole country)		1 (0.1)	138 (3.2)		
France (Burgundy, Northern, Ile-de-France)		117 (5.7)	986 (22.8)		
Germany (Hesse, Saarland)		222 (10.8)	435 (10.1)		
Italy (Emilia, Lazio, Marche)		236 (11.5)	732 (16.9)		
Netherlands (East-Central)		101 (4.9)	229 (5.3)		
Poland (Wielkopolska)		50 (2.4)	199 (4.6)		
Portugal (Lisbon and Tagus Valley, Northern)		197 (9.6)	408 (9.4)		
Sweden (Stockholm)		75 (3.6)	165 (3.8)		
UK (East Midlands, Yorkshire and Humber) [d]		609 (29.6)	543 (12.6)		

[a] Proportions were calculated on all cases excluding missing values.
[b] Chi-squared test and did not include missing category.
[c] Wald test from logistic regression adjusted for country and did not include missing category.
[d] UK Northern region was excluded from this analysis.
BMF, breast milk feeding; BPD, bronchopulmonary dysplasia; CA, corrected age; cPV, cystic periventricular leukomalacia; IVH, intraventricular haemorrhage; NEC, necrotising enterocolitis; ROP, retinopathy of prematurity; SGA, small for gestational age.

Table S2. Stratified analysis by perinatal risk for non-verbal and verbal cognitive development, according to BMF practices.

	Lower perinatal risk			Moderate perinatal risk			Higher perinatal risk		
	Non-verbal cognition			Non-verbal cognition			Non-verbal cognition		
	Optimal n (% [a])	Suboptimal n (% [a])	Crude RR [b] (95% CI)	Optimal n (% [a])	Suboptimal n (% [a])	Crude RR [b] (95% CI)	Optimal n (% [a])	Suboptimal n (% [a])	Crude RR [b] (95% CI)
BMF initiation	*(n=1072)*			*(n=1547)*			*(n=1354)*		
Never breastfed	189 (89.4)	21 (10.6)	1.02 (0.58-1.78)	256 (84.7)	45 (15.3)	1.21 (0.97-1.51)	247 (68.8)	101 (31.2)	1.57 (1.12-2.18)
Ever breastfed	779 (89.9)	83 (10.1)	Reference	1086 (86.6)	160 (13.4)	Reference	813 (79.8)	193 (20.2)	Reference
BMF duration	*(n=1032)*			*(n=1477)*			*(n=1270)*		
Never breastfed	189 (89.4)	21 (10.6)	0.88 (0.45-1.73)	256 (84.7)	45 (15.3)	1.74 (1.10-2.75)	247 (68.8)	101 (31.2)	1.54 (1.21-1.96)
>0 to <2 months	138 (86.9)	19 (13.1)	1.16 (0.64-2.09)	160 (80.0)	36 (20.0)	2.19 (1.24-3.88)	74 (81.3)	16 (18.7)	0.90 (0.52-1.58)
2 to <4 months	231 (93.6)	15 (6.4)	0.53 (0.30-0.92)	305 (84.5)	54 (15.5)	1.64 (1.03-2.61)	205 (82.5)	43 (17.5)	0.85 (0.61-1.20)
4 to <6 months	136 (91.9)	11 (8.1)	0.66 (0.29-1.48)	162 (89.9)	19 (10.1)	1.10 (0.75-1.62)	171 (79.1)	42 (20.9)	1.02 (0.76-1.37)
≥ 6 months	241 (88.8)	31 (11.2)	Reference	401 (90.5)	39 (9.5)	Reference	300 (79.5)	71 (20.5)	Reference
p-for-trend			*0.707*			*0.006*			*0.071*
	Verbal cognition			Verbal cognition			Verbal cognition		
	Optimal n (% [a])	Suboptimal n (% [a])	Crude RR [b] (95% CI)	Optimal n (% [a])	Suboptimal n (% [a])	Crude RR [b] (95% CI)	Optimal n (% [a])	Suboptimal n (% [a])	Crude RR [b] (95% CI)
BMF initiation	*(n=1093)*			*(n=1560)*			*(n=1361)*		
Never breastfed	193 (91.2)	19 (8.8)	1.25 (0.68-2.31)	261 (85.2)	42 (14.8)	2.17 (1.23-3.82)	277 (78.3)	71 (21.7)	1.40 (0.92-2.11)
Ever breastfed	828 (93.8)	53 (6.2)	Reference	1164 (92.6)	93 (7.4)	Reference	857 (84.0)	156 (16.0)	Reference
BMF duration	*(n=1048)*			*(n=1484)*			*(n=1269)*		
Never breastfed	193 (91.2)	19 (8.8)	1.01 (0.44-2.30)	261 (85.2)	42 (14.8)	3.06 (1.39-6.73)	2778 (78.3)	71 (21.7)	1.42 (0.94-2.14)
>0 to <2 months	153 (92.0)	14 (8.0)	1.19 (0.53-2.65)	180 (89.9)	19 (10.1)	2.04 (0.82-5.05)	74 (82.2)	14 (17.8)	1.08 (0.55-2.14)
2 to <4 months	234 (96.4)	9 (3.6)	0.48 (0.11-2.19)	331 (92.0)	28 (8.0)	1.50 (0.81-2.79)	209 (84.3)	40 (15.7)	1.02 (0.72-1.43)
4 to <6 months	140 (95.1)	7 (4.9)	0.63 (0.26-1.48)	173 (94.8)	11 (5.2)	1.15 (0.52-2.57)	188 (90.0)	23 (10.0)	0.66 (0.34-1.28)
≥ 6 months	260 (91.7)	19 (8.3)	Reference	414 (94.5)	25 (5.5)	Reference	317 (84.7)	56 (15.3)	Reference
p-for-trend			*0.533*			*0.029*			*0.158*

BMF, Breast milk feeding (mother's own milk); RR, Risk ratio.

[a] Proportions were calculated using inverse probability weights to account for non-response bias; [b] Risk ratios were derived from the weighted sample (inverse probability of participating at the 2 years CA follow-up), multilevel mixed-effects generalised linear regression models with random intercepts at the country and mother level.

Table S3. Stratified analysis by mother´s education level for non-verbal and verbal cognitive development, according to BMF practices.

	Low educational level			Intermediate educational level			High educational level		
	Non-verbal cognition			Non-verbal cognition			Non-verbal cognition		
	Optimal n (% [a])	Suboptimal n (% [a])	Crude RR [b] (95% CI)	Optimal n (% [a])	Suboptimal n (% [a])	Crude RR [b] (95% CI)	Optimal n (% [a])	Suboptimal n (% [a])	Crude RR [b] (95% CI)
BMF initiation	*(n=768)*			*(n=1683)*			*(n=1514)*		
Never breastfed	209 (81.2)	47 (18.8)	1.13 (0.78-1.62)	293 (77.7)	75 (22.3)	1.55 (1.01-2.38)	171 (82.1)	37 (17.9)	1.52 (0.96-2.43)
Ever breastfed	431 (83.4)	81 (16.6)	Reference	1124 (85.0)	191 (15.0)	Reference	1144 (86.9)	162 (13.1)	Reference
BMF duration	*(n=723)*			*(n=1604)*			*(n=1448)*		
Never breastfed	209 (81.2)	47 (18.8)	1.30 (0.81-2.07)	293 (77.7)	75 (22.3)	1.74 (1.05-2.87)	171 (82.1)	37 (17.9)	1.47 (0.93-2.31)
>0 to <2 months	80 (84.2)	15 (15.8)	1.11 (0.66-1.87)	183 (82.9)	35 (17.1)	1.24 (0.58-2.66)	107 (83.5)	18 (16.5)	1.24 (0.62-2.49)
2 to <4 months	139 (83.7)	27 (16.3)	1.16 (0.63-2.13)	348 (86.9)	51 (13.1)	0.92 (0.63-1.35)	264 (87.3)	36 (12.7)	0.93 (0.62-1.38)
4 to <6 months	66 (88.5)	8 (11.5)	0.76 (0.32-1.82)	189 (82.6)	39 (17.4)	1.30 (0.84-2.00)	229 (89.8)	26 (10.2)	0.75 (0.34-1.63)
≥ 6 months	114 (86.3)	18 (13.7)	Reference	342 (86.9)	49 (13.1)	Reference	487 (86.3)	73 (13.7)	Reference
p-for-trend			*0.101*			*0.070*			*0.037*
	Verbal cognition			Verbal cognition			Verbal cognition		
	Optimal n (% [a])	Suboptimal n (% [a])	Crude RR [b] (95% CI)	Optimal n (% [a])	Suboptimal n (% [a])	Crude RR [b] (95% CI)	Optimal n (% [a])	Suboptimal n (% [a])	Crude RR [b] (95% CI)
BMF initiation	*(n=783)*			*(n=1700)*			*(n=1519)*		
Never breastfed	207 (80.8)	50 (19.2)	1.70 (1.02-2.82)	321 (85.8)	51 (14.2)	1.76 (1.09-2.84)	184 (88.8)	22 (11.2)	1.33 (0.73-2.42)
Ever breastfed	460 (86.1)	66 (13.9)	Reference	1208 (91.4)	120 (8.6)	Reference	1204 (91.6)	109 (8.4)	Reference
BMF duration	*(n=735)*			*(n=1607)*			*(n=1453)*		
Never breastfed	207 (80.8)	50 (19.2)	1.79 (0.71-4.51)	321 (85.8)	51 (14.2)	2.02 (1.20-3.41)	184 (88.8)	22 (11.2)	1.26 (0.71-2.24)
>0 to <2 months	84 (83.9)	15 (16.1)	1.41 (0.59-3.35)	203 (92.1)	20 (7.9)	1.08 (0.60-1.93)	120 (91.7)	8 (8.3)	0.81 (0.42-1.53)
2 to <4 months	154 (92.6)	13 (7.4)	0.66 (0.23-1.91)	359 (90.8)	37 (9.2)	1.15 (0.78-1.70)	274 (91.2)	26 (8.8)	0.98 (0.64-1.52)
4 to <6 months	67 (90.9)	7 (9.1)	0.71 (0.22-2.38)	205 (92.0)	20 (8.0)	1.23 (0.78-1.96)	243 (94.2)	16 (5.8)	0.60 (0.21-1.69)
≥ 6 months	121 (87.1)	17 (12.9)	Reference	361 (92.4)	30 (7.6)	Reference	512 (91.4)	48 (8.6)	Reference
p-for-trend			*0.098*			*0.030*			*0.473*

BMF, Breast milk feeding (mother's own milk); RR, Risk ratio.

[a] Proportions were calculated using inverse probability weights to account for non-response bias; [b] Risk ratios were derived from the weighted sample (inverse probability of participating at the 2 years CA follow-up), multilevel mixed-effects generalised linear regression models with random intercepts at the country and mother level.

4.7. PAPER VII

Behavioural and emotional outcomes at preschool age in children born very preterm: the role of breast milk feeding practices

Rodrigues C, Zeitlin J, Carvalho AR, Gonzaga Z, Barros H; on behalf of the Portuguese EPICE Network.

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Behavioural and emotional outcomes at preschool age in children born very preterm: the role of breast milk feeding practices

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Conflict of interest

The authors report no conflict of interest.

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Abstract

Children born very preterm (VPT, <32 weeks of gestation) present a higher risk of adverse behavioural and emotional outcomes. Because little is known on the effect of breast milk feeding (BMF) practices on such outcomes we assessed a Portuguese cohort of VPT children (N=263) at the age of 3, using the Child Behaviour Checklist. Behavioural or emotional subclinical/clinical problems were found in 51 (19.8%) children. BMF consistently had a preventive effect in adverse behavioural and emotional outcomes, particularly by reducing the risk of externalizing problems, somatic complaints, aggressive behaviour, as well as autism spectrum and attention deficit/hyperactivity symptoms.

Introduction

Very preterm (VPT) birth (<32 weeks of gestation) accounts for about 1% of live births worldwide (Blencowe et al., 2012). Survival rates of children born VPT have improved greatly in the last decades (Saigal & Doyle, 2008; Santhakumaran et al., 2018) but these children remain at higher risk of health and neurodevelopmental adverse outcomes than term infants (Saigal & Doyle, 2008).

Children born VPT are more likely to present behavioural and emotional difficulties, either internalizing (e.g., depression, anxiety, somatic complaints) or externalizing problems (e.g., hyperactivity, oppositional and aggressive behaviour) (Arpi & Ferrari, 2013; Cassiano, Gaspardo, & Linhares, 2016; Delobel-Ayoub et al., 2006; Samuelsson et al., 2017). They are particularly at risk for inattention, social-emotional problems and autism-related symptoms, but not for disruptive or oppositional behavioural problems (Johnson & Marlow, 2011; Samuelsson et al., 2017). This suggests a specific phenotype or profile of disorders in line with the neurodevelopmental immaturity conferred by VPT birth (Johnson & Marlow, 2011, 2017; Samuelsson et al., 2017). Behavioural and emotional development is influenced by biological, social and environmental factors, some present as early life stressful experiences, that may contribute to distinct neurodevelopmental trajectories (Cassiano et al., 2016; Delobel-Ayoub et al., 2006; Faure et al., 2017; Montirosso et al., 2016; Provenzi et al., 2016).

Behavioural and emotional problems in infancy tend to persist into adulthood (Linsell et al., 2019) and therefore identifying early modifiable factors could improve short and long-term outcomes. One of these may be infant feeding practices. Robust evidence shows the breast milk feeding (BMF) confers multiple benefits for VPT children, such as decreasing neonatal morbidity, including necrotizing enterocolitis, sepsis, bronchopulmonary dysplasia, and retinopathy of prematurity, and improving neurodevelopment (Miller et al., 2018; Ottolini, Andescavage, Kapse, Jacobs, & Limperopoulos, 2020). However, research on the benefits of BMF on behavioural and emotional outcomes in VPT is scarce (Cassiano et al., 2016; Härtel et al., 2020; Johnson et al., 2010) and findings in full-term infants are inconsistent (Belfort et al., 2016; Heikkilä, Sacker, Kelly, Renfrew, & Quigley, 2011; Kramer et al., 2009).

Thus, information is lacking in the international context about the effect of BMF practices on specific behavioural and emotional outcomes in this vulnerable population (Linsell et al., 2016).

This study estimates the association of BMF practices with behavioural and emotional problems at preschool age among VPT children in a Portuguese population-based cohort.

Methods

Study design and population

Data were obtained as part of the *Effective Perinatal Intensive Care in Europe* (EPICE) project, that recruited a population-based prospective cohort of children born from 22 to 31 completed weeks of gestation in 2011/2012, in 19 regions from 11 European countries, including Portugal (Zeitlin et al., 2020). The EPICE cohort in Portugal involved all the public maternity and neonatal intensive care units (NICUs) from 2 regions (n=27), Northern and Lisbon and Tagus Valley, along with three private units from Lisbon (Barros et al., 2014). They represented almost 70% of all VPT births that occurred in Portugal in this period. In addition to the European EPICE follow-up waves at 2 and 5 years, the Portuguese team carried out a follow-up of the cohort when the children were 3 years of age. This report therefore only includes the Portuguese cohort.

Out of the 724 live births, 607 infants survived to discharge from the NICU (83.8%), and we obtained informed consent for 544 infants (89.6%). At the 3-year follow-up, we identified two deaths, two children had been adopted and unavailable for further evaluation according to legal rules, five parents declined to participate, and 69 were unreachable. Of the 466 children that participated in the 3-year follow-up, 265 (57%) returned the parent-report *Child Behaviour Checklist for ages 1½-5 years* (CBCL/1½-5) (Achenbach & Rescorla, 2000; Achenbach et al., 2014) and 263 children had CBCL/1½-5 valid completed information for analysis.

Ethics

The EPICE study was approved by the Ethics Committee of participating hospitals and by the Portuguese Data Protection Authority (authorization 7426/2011). Informed consent was obtained from all parents or legal representatives included in the cohort.

Data on behavioural and emotional problems

Behavioural and emotional problems were assessed using a validated Portuguese version of CBCL/1½-5 (Achenbach et al., 2014). The parents were asked to fill in and return the questionnaire that was sent by mail at three years (chronological age) describing the child's behaviour within the preceding two months. The CBCL/1½-5 comprises 100 problem items (99 closed and 1 open-ended item), which are rated on a 3-point Likert-type scale. The instrument provides seven syndromes' scales (Emotionally reactive, Anxious/depressed, Somatic complaints, Withdrawn, Sleep problems, Attention problems, and Aggressive behaviour) and six of these scales (Sleep problems excluded) derive two second-order dimensions: Internalizing (Emotionally reactive, Anxious/depressed, Somatic complaints, Withdrawn) and Externalizing (Attention problems and Aggressive behaviour) problems. A total score is computed - Total Problems - that compiles the sum of all 99 items (Achenbach & Rescorla, 2000; Achenbach et al., 2014). CBCL/1½-5 also provides a Stress Problems scale (Achenbach & Rescorla, 2010; Rescorla et al., 2011). Scores were also computed for five scales oriented to *Diagnostic and Statistical Manual of Mental Disorders*, *5th edition* (DSM5) categories: Depressive Problems; Anxiety Problems; Autism Spectrum Problems; Attention Deficit/Hyperactivity Problems; and Oppositional Defiant Problems. All data were entered and coted using the *Assessment Data Manager* (ADM) software (version 9.1). The scores for the seven syndromes scales, as well as for the Stress Problems and DSM5-oriented scales, were categorized into normal (P<93), subclinical (P93-P97), and clinical (P>97). The scores for internalising, externalising and total problems, were also classified as normal (P<83), subclinical (P83-P90) and clinical (P>90) (Achenbach & Rescorla, 2000; Achenbach et al., 2014). For analysis, we combined the subclinical and clinical categories into one binary variable.

Data on breast milk feeding

Data on BMF practices were collected by trained interviewers using a computer-assisted telephone interview and a structured questionnaire, completed by the parents or legal guardians at the 3-year follow-up. Parents were asked if the child had ever received BMF, including donor's milk. If the answer was positive, then they were asked for how long BMF was exclusive or combined with formula feeding or with other types of foods and/or beverages. As previously described for this cohort (Rodrigues, Teixeira, Fonseca, Zeitlin, & Barros, 2018), exclusive BMF was considered when the child received no food or drinks other than the mother's own milk or donor's milk, regardless of the route of administration. Any BMF (never vs. ever) was considered if the child received some breast milk, despite the route of administration, exclusive or not. Duration of BMF was defined as the age of the child, reported in months of chronological age, when feeding was stopped completely (collected as continuous variable, ranging from 0-9 months for exclusive and 0-36 months for any). Exclusive BMF duration was categorised into <1 month (including never-breastfed) vs. ≥1 month; any BMF was categorized into <3 months (comprising never-breastfed) vs. ≥3 months. Besides previous studies (Härtel et al., 2020), these cut-offs were defined considering the sample median duration and the small number of never-breastfed children (9.9%, n=26).

Covariables

Clinical and sociodemographic characteristics at birth were abstracted from obstetric and neonatal records by local health care professionals using a pretested standardized questionnaire (Barros et al., 2014; Zeitlin et al., 2020). Small for gestational age (SGA) was defined as birthweight <10th percentile for gestational age using intrauterine references developed for the cohort (Zeitlin et al., 2017); bronchopulmonary dysplasia (BPD) was defined as oxygen dependency or respiratory support at 36 weeks postmenstrual age; severe neonatal morbidity diagnosed before discharge home included intraventricular haemorrhage Papille's grades III-IV (IVH III-IV), cystic periventricular leukomalacia (cPVL), ROP grades III-V (ROP III-V), and necrotizing enterocolitis (NEC) with surgery or peritoneal drainage. Maternal and sociodemographic variables included age at delivery (<35 years vs. ≥ 35 years), country of birth (native vs. foreign-born), type of pregnancy (singleton vs. multiple), the family structure at 3 years (mother living with father or partner vs. single caregiver), and the number of siblings (0 vs. ≥1). We also included the mothers' highest achieved educational level collected at two years of corrected age (CA) based on the International Standard Classification of Education (ISCED) 2011 definition and categorized in three groups: lower level (ISCED level 0-2: lower secondary); intermediate level (ISCED level 3-5: upper or post-secondary, non-tertiary or short-cycle tertiary); and higher level (ISCED level 6-8: bachelor degree or higher).

Statistical analysis

Descriptive statistics are presented as numbers and proportions. We compared responders to non-responders regarding maternal and neonatal characteristics using the Chi-square test. Twins and children born to younger (<35 years of age), multiparous, and migrant women were less likely to provide the CBCL/1½-5 at the 3-year follow-up (Table S1). On the other hand, children who received BMF at discharge were more likely to participate. We did not find differences in the frequency of neonatal morbidities among respondents and non-respondents.

The effects of potential bias due to attrition were accounted for using inverse probability weights to give higher weight to children with characteristics of non-responders (Bonnet et al., 2019; Seaman & White, 2013; Seaman, White, Copas, & Li, 2012). Weights were derived from a logistic regression as the probability of response to CBCL/1½-5 based on characteristics available at baseline (perinatal characteristics) and at the two-year follow-up (mother's educational level, gross motor impairment and cognitive delay at two years of CA), after multiple imputation of missing values (Bonnet et al., 2019; Seaman & White, 2013; Seaman et al., 2012). Missing data from variables included in this regression model were imputed by chained equations (20 complete datasets generated).

We described the characteristics of the overall sample, as well as by total problems, internalizing and externalizing problems (normal vs. subclinical/clinical) and weighted proportions were calculated excluding missing values and compared using the Chi-square test. Then, the prevalence of each type of behavioural and emotional problem in the clinical and combining subclinical and clinical range was estimated (weighted sample).

To assess the association between BMF practices and behavioural and emotional problems (binary outcome), crude risk ratios (RR) and adjusted (aRR) with 95% confidence intervals (95%CI) were estimated by fitting a modified Poisson regression model (Zou & Donner, 2013) with robust standard errors to account for the correlation between twins (adjusted for clustering mothers). Considering our sample size, we adjusted for gestational age, child sex, maternal age, and maternal education level. Thus, we used gestational age as a proxy of the overall risk of health and neurodevelopmental adversity (Allotey et al., 2018; Cassiano et al., 2016), as well as maternal age and education level as a proxy of socioeconomic status which have already been associated with behavioural problems in childhood (Alexandra Carneiro, Dias, & Soares, 2016). We carried out a sensitivity analysis, comparing weighted with unweighted models to assess the impact of considering bias due to nonresponse.

Numbers in tables are the observed, but proportions and RR provided in this study are based on weighted data. Statistical analysis was performed using STATA 15.1 software (Stata Corporation, College Station, Texas, USA).

Results

Table 1 summarizes the maternal and neonatal characteristics of the total sample and according to behavioural and emotional problems, specifically for total, internalizing and externalizing problems. Overall, 60.5% were males, 25.5% extremely preterm (≤27 weeks), 13.2% had BPD and 10.5% presented any other severe neonatal morbidity. Most had a younger (69.2%) and native mother (85.3%). A low maternal educational level was observed in 33.5% of the sample. Regarding BMF practices, 13.2% (26/263) of children never received BMF, 55.6% (149/255) were exclusively fed with breast milk for ≥1 month, and 45.8% (131/259) received any BMF for at least 3 months or more. Maternal and neonatal characteristics differed between normal and subclinical/clinical range children for behavioural and emotional problems. Subclinical/clinical total problems were more frequent in children born before 28 weeks of gestational age and with at least one severe neonatal morbidity and BPD. Children in subclinical/clinical range more frequently had mothers 35 years or older, who were foreign-born and had lower educational levels (Table 1).

The prevalence of the assessed behavioural and emotional problems at preschool age in Portuguese children born VPT is presented in Table 2. Twenty percent of children presented behavioural or emotional problems in subclinical/clinical range for total score. The combined prevalence of subclinical and clinical problems was higher for internalizing problems than externalizing problems (23.7% vs. 15.2%). Considering subclinical and clinical cases, emotionally reactive problems presented the higher prevalence (16.0%), while withdrawn scale presented the highest prevalence in the clinical range (7.4%). On the DSM5-oriented scales, the highest prevalence rate in the clinical range, as well as in the combining prevalence with subclinical cases, was observed for anxiety problems and autism spectrum problems.

The proportion of any type of behavioural and emotional problems in the subclinical/clinical range, by breast milk feeding practices, is provided in supplemental information (Table S2). In the crude model, never BMF was associated with an increased risk of 4.3 (95%CI:1.43-13.18) for attention deficit/hyperactivity problems, according to DSM5-Oriented Scales (Figure 1a). The adjustment for gestational age, sex, maternal age, and maternal education slightly attenuated this association (aRR=3.6, 95%CI: 0.98-13.18).

Children who were exclusively breast fed less than one month presented a significant greater risk for total behavioural and emotional problems (RR=1.8, 95%CI:1.00-3.21), externalizing problems (RR=2.0, 95%CI:1.00-3.82), somatic complaints (RR=2.4, 95%CI:1.05-5.42) and aggressive behaviour (RR=3.1, 95%CI:1.14-8.18) (Figure 1b). Also, considering the DSM5-Oriented Scales, children who received exclusive BMF less than one month had a 2.4 (95%CI: 1.15-5.24) higher risk of autism spectrum problems and 4.1 (95%CI: 1.27-12.93) for attention deficit/hyperactivity problems in crude models. After considering relevant confounders, these effects were consistent, but not statistically significant.

Receiving any BMF for less than three months was associated with a higher risk of externalizing problems (RR=2.0, 95%CI:1.01-3.90), but adjustment attenuated the association (aRR=1.8, 95%CI: 0.90-3.47) (Figure 1c).

Discussion

Our findings support that receiving any BMF, as well as the prolonged duration of exclusive and any BMF, may play an important role in protecting adverse behavioural and emotional outcomes, even though we did not find statistically significant associations after adjustment for potential confounders. Nevertheless, from a public health viewpoint, we should not disregard these results, which are in line with previous research (Härtel et al., 2020; Johnson et al., 2010), particularly for attention deficit/hyperactivity, autism spectrum problems and aggressive behaviour. Johnson and colleagues found that receiving BMF during NICU admission was associated with lower autism spectrum symptomatology in extremely preterm children at 11 years of age (Johnson et al., 2010). A cohort study from Germany, which included 2467 children born very low birth weight (VLBW), shown that BMF for ≥3 months was associated with lower parent-rated behavioural difficulty scores at 5-6 years of age measured by *Strengths and Difficulties Questionnaire* (SDQ), mainly for inattention/hyperactivity and conduct disorders (Härtel et al., 2020). A recent meta-analysis indicated a strong association between non-breastfeeding and attention-deficit/hyperactivity disorder including term and preterm children (adjusted OR=3.71; 95%CI=1.94-7.11) (Tseng et al., 2019). However, a large randomized controlled trial with generally healthy children (born at term and weighed at least 2500 grams) revealed no effect of extended or exclusive BMF on any SDQ scores at early primary school age (Kramer et al., 2008). Thus, the effect of BMF practices on mental health outcomes of children born VPT deserves further investigation.

Children born VPT require differentiated care to guarantee survival and a healthy development (Zeitlin et al., 2016). Despite the undeniable positive impact of BMF on health and development of VPT children (Miller et al., 2018; Schanler, 2011), its potential effect on behaviour and emotional outcomes remains unclear, because of the need to disentangle multiple interactions of perinatal, neurological, and environmental factors. Differing hypotheses have been put forth about the potential mechanisms for the perceived relation between BMF and behaviour outcomes in children born VPT. It may be the result of the essential long-chain polyunsaturated fatty acids (LCPUFAs) found in large amounts in breast milk, as well as human milk oligosaccharides (HMOs), growth factors and hormones, which arguably have a significant role in the development and function of the brain and central nervous system (Belfort, 2018; Victora et al., 2016). A recent study including preterm infants (≤33 weeks) found that exclusive BMF for ≥75% of days of in-patient care resulted in higher connectivity in the fractional anisotropy (FA)-weighted connectome and increased FA within white matter tracts (Blesa et al., 2019). VLBW/VPT infants receiving early BMF exhibited significantly larger total brain volumes by term-corrected age, as well as volumes in the amygdala-hippocampus and cerebellum compared with formula-fed infants (Ottolini et al., 2020). Moreover, infants receiving BMF also presented greater white matter microstructural organisation in the corpus callosum, posterior limb of internal capsule and cerebellum (Ottolini et al., 2020). The amygdala and hippocampus are regions of the brain that are particularly vulnerable to perinatal stress, and previous research has demonstrated that alterations in the amygdala and hippocampus are associated with cognitive and behavioural difficulties (Beauchamp et al., 2008; Thompson et al., 2008). Additionally, it has been suggested that BMF may lead to reduced behavioural and emotional problems in children born VPT as a result of greater maternal sensitivity, stronger infant attachment security, and more mother-infant interaction during feeding (Peñacoba & Catala, 2019). The quality of early mother-child interaction is associated with better neurocognitive outcomes in infants born before 28 gestational weeks (Rahkonen et al., 2014).

We found that multiple behaviour and emotional problems are common at preschool age in Portuguese children born VPT, with almost 20% of children presenting these problems. More internalizing than externalizing problems were observed. Looking at specific domains, the emotionally reactive problems, somatic complaints, and anxiety were more frequent. Considering the DSM5-oriented scales, the highest prevalence in the clinical range was observed for anxiety and autism spectrum problems. These results were consistent with previous studies in which a "preterm behavioural phenotype" was found, characterized by an increased risk for problems associated with inattention/hyperactivity, anxiety, social and emotional difficulties and, in general, a greater risk for internalizing rather than externalizing problems (Arpi & Ferrari, 2013; Johnson & Marlow, 2011, 2017). In the EPIPAGE cohort, based on SDQ completed by parents at three years, the prevalence of high total difficulties was 20% in VPT children and 9% in term (Delobel-Ayoub et al., 2006).

Despite the difficulties in diagnosing psychopathology in preschool age, early screening of behavioural and emotional problems should be included as a crucial part of healthcare follow-up programmes of children born VPT. Behavioural and emotional difficulties are potentially modifiable during early childhood, being this period a window of opportunity for early detection and early intervention, allowing to mitigate the medium and long-term adverse outcomes (Johnson & Marlow, 2017).

A major strength of our study is the use of high-quality data, obtained from a population-based prospective cohort, using a gold standard tool to assess behavioural and emotional problems. The CBCL/1½-5, which integrates a comprehensive evidence-based assessment system (*Achenbach System of Empirically Based Assessment* – ASEBA) (Achenbach & Rescorla, 2000), is widely used in diverse clinical settings and research, and in many countries to assess psychopathological problems (Rescorla et al., 2011). This is the first description in Portugal of the prevalence of behavioural and emotional problems at preschool age in children born VPT. Furthermore, this is one of the few studies assessing the potential effect of BMF practices on behavioural and emotional outcomes in VPT children, particularly exploring its effect in a wide range of specific domains. Also, most of the previous research included only healthy children. However, we decided not to exclude infants with any type of impairment because the health and developmental outcomes of children born VPT cannot be adequately investigated without studying these children. In this study, 0.4% of children presented hearing impairment, 1.6% cerebral palsy and 2.8% gross motor impairment; no children had visual impairment. The proportion of total behavioural and emotional problems, as well as receiving any BMF did not differ according to these characteristics (data not shown).

Another strength of our study is the availability of different BMF indicators, including any and exclusive BMF, as well as its total duration. Most of the previous studies described BMF only at discharge or during NICU hospitalization (Johnson et al., 2010; Johnson et al., 2018; Rodrigues, Teixeira, et al., 2018). Nevertheless, in this study, we were not able to distinguish between donor human milk and mother's own milk. O´Connor et al did not find differences in neurodevelopment outcomes (Bayley III) at 18 months of CA in VLBW infants between those who had received supplemental donor human milk and preterm formula (O'Connor et al., 2016). Anyway, only two NICUs reported use of human bank milk/donor's milk in Portugal (Rodrigues, Severo, Zeitlin, & Barros, 2018). Almost 22% (57/263) of the children included in this analysis were born in these two NICUs, but of those just 5% (3/57) received exclusive donor human milk in the first 24 hours after first enteral feed.

Recall bias on behavioural and emotional problems can affect data. Moreover, we did not collect information from both parents and from the day-care providers or preschool teachers, which did not allow us to confirm the agreement between different informants in different contexts. In our cohort, almost 70% of CBCL/1½-5 was completed only by the mother. A recent meta-analysis showed that the level of cross-informant agreement between parents and teachers tends to be low, which could happen because different informants may observe diverse behaviours as they interact with the child in certain specific settings, such as school and home (A. Carneiro, Soares, Rescorla, & Dias, 2020).

It is important to mention that BMF practices were retrospectively collected when the child was three years. However, we do not expect relevant information bias. Previous studies reported good validity of maternal recall of BMF duration, especially when a short period (three years) was considered (Amissah, Kancherla, Ko, & Li, 2017; Li, Scanlon, & Serdula, 2005). An additional measure to address this potential recall bias was the comparison of data reported by parents with the information on the type of feeding at discharge from hospital as abstracted from clinical records, as well as with the data obtained from parents at two years of corrected age. For the incongruences or missing information (n=17), we further checked the clinical information registered in the Child Health Book.

Although 86% of children were followed-up at three years, we only have information for behavioural and emotional problems for 48.5% (263/542). We were able to compare responders with non-responders and took into consideration potential bias by using inverse probability weighting methods. Overall, sensitivity analyses showed that results were not substantially affected by weighting for nonresponse, being the point estimates in the same direction, but with larger confidence intervals. Anyway, we observed a slight effect on risk ratios with weighting that reflects the characteristics of non-responders that could be associated with a specific type of behavioural and emotional problems at preschool age, such as young maternal age and low education level (Delobel-Ayoub et al., 2006).

In conclusion, almost 20% of Portuguese children born VPT presented behavioural and emotional problems at three years of age, internalizing problems being more prevalent than externalizing ones. Although the magnitude of the associations was slightly attenuated after adjustment for relevant confounders, BMF seemed to prevent adverse behavioural and emotional outcomes in children born VPT, particularly by reducing the risk of externalizing problems, somatic complaints, aggressive behaviour, as well as autism spectrum problems and attention deficit/hyperactivity. Therefore, public health efforts should be targeted for early, exclusive, and continued BMF in VPT children, ensuring that these vulnerable infants receive the full benefits for the best start in life, so they can achieve their greatest potential.

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Table 1. Characteristics of total sample and of children with subclinical/clinical behavioural and emotional problems (total, internalizing and externalizing problems).

	Characteristics of total sample N=263	CBCL/1½-5 Subclinical/Clinical					
		Total problems n=51 (19.8%)		Internalizing problems n=57 (23.7%)		Externalizing problems n=40 (15.2%)	
Characteristics	n [a] (% [b])	n [a] (%[b])	p-value	n [a] (%[b])	p-value	n [a] (%[b])	p-value
Mother's age at delivery			0.065		0.322		0.436
< 35 years	177 (69.2)	30 (16.5)		35 (21.7)		25 (14.0)	
≥ 35 years	86 (30.8)	21 (27.3)		22 (28.1)		15 (18.0)	
Mother's country of birth			0.001		0.011		0.131
Native-born	238 (85.3)	39 (15.6)		45 (20.1)		33 (13.6)	
Foreign-born	25 (14.7)	12 (44.6)		12 (44.6)		7 (25.0)	
Mother's educational level [c]			0.016		0.001		0.023
Low level (ISCED 0-2)	69 (33.5)	21 (28.6)		24 (36.0)		18 (23.2)	
Intermediate level (ISCED 3-5)	81 (30.8)	18 (21.3)		21 (26.1)		13 (15.3)	
High level (ISCED 6-8)	112 (35.7)	12 (10.6)		12 (10.4)		9 (8.0)	
Type of pregnancy			0.564		0.355		0.378
Singleton	191 (67.5)	41 (21.0)		45 (25.7)		33 (16.9)	
Multiple	72 (32.5)	10 (17.4)		12 (19.5)		7 (11.9)	
Family situation at 3 years			0.914		0.753		0.641
Mother living with father/partner	236 (90.5)	47 (20.2)		51 (23.3)		36 (15.0)	
Single mother or other situation	24 (9.5)	4 (19.1)		5 (26.6)		4 (19.1)	
Number of siblings at 3 years			0.368		0.901		0.260
0	123 (41.3)	27 (22.9)		27 (24.0)		21 (18.6)	
≥1	137 (58.)	24 (18.1)		29 (23.3)		19 (13.2)	

Child sex			0.215		0.061		0.053
Male	158 (60.5)	36 (22.6)		41 (28.2)		31 (19.1)	
Female	105 (39.5)	15 (15.7)		16 (16.8)		9 (9.4)	
Gestational age at birth			0.003		0.018		0.483
≤ 27 weeks	72 (25.5)	23 (35.0)		26 (38.5)		14 (20.0)	
28-29 weeks	80 (30.4)	13 (16.7)		14 (18.9)		10 (12.9)	
30-31 weeks	111 (44.1)	15 (13.3)		17 (18.4)		16 (14.1)	
Small for gestational age			0.591		0.726		0.254
≥10th percentile	170 (65.2)	35 (20.9)		37 (24.4)		23 (13.3)	
<10th percentile	93 (34.8)	16 (17.9)		20 (22.3)		17 (18.9)	
Severe neonatal morbidity [d]			0.001		0.011		0.849
No	231 (89.5)	39 (17.0)		45 (21.3)		35 (15.1)	
Yes	32 (10.5)	12 (43.8)		12 (44.2)		5 (16.5)	
Bronchopulmonary dysplasia			0.003		0.026		0.368
No	229 (86.8)	37 (16.7)		43 (21.1)		32 (14.4)	
Yes	34 (13.2)	14 (40.9)		14 (40.7)		8 (20.5)	
Any congenital anomaly			0.689		0.261		0.781
No	252 (95.6)	48 (19.6)		53 (23.0)		39 (15.4)	
Yes	11 (4.4)	3 (24.6)		4 (38.8)		1 (11.9)	

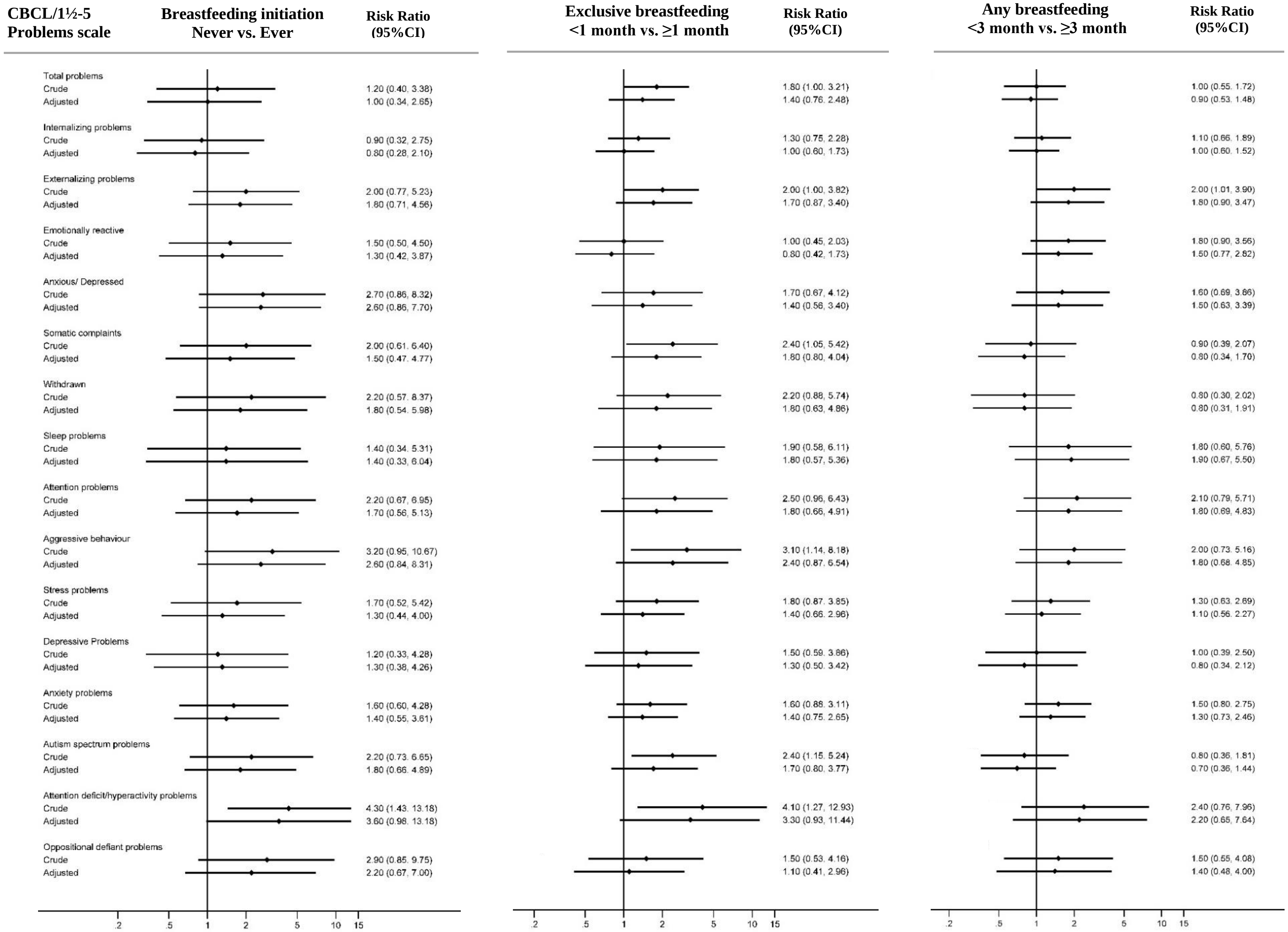
CBCL/1½-5, Child Behaviour Checklist for ages 1½-5 years.
[a] Number observed.
[b] Proportions were calculated using inverse probability weights to account for non-response bias.
[c] ISCED, International Standard Classification of Education 2011.
[d] Defined as intraventricular haemorrhage grades III–IV, cystic periventricular leukomalacia, surgical necrotizing enterocolitis, retinopathy of prematurity grades ≥3.

Table 2. Prevalence of each type of behavioural and emotional problems at preschool age in Portuguese children born very preterm.

	Behavioural and emotional problems (N=263)	
	Clinical n [a] (%[b])	Subclinical/ clinical n [a] (%[b])
CBCL/1½-5 Problems Scale		
Total problems	31 (11.8)	51 (19.8)
Internalizing problems	36 (15.0)	57 (23.7)
Externalizing problems	24 (8.8)	40 (15.2)
Emotionally reactive	16 (6.8)	36 (16.0)
Anxious/ Depressed	11 (5.2)	26 (10.3)
Somatic complaints	13 (6.3)	29 (12.0)
Withdrawn	19 (7.4)	24 (9.5)
Sleep problems	9 (2.9)	14 (4.8)
Attention problems	11 (4.0)	18 (6.5)
Aggressive behaviour	9 (4.2)	22 (8.4)
Stress problems	15 (6.1)	34 (13.5)
CBCL/1½-5 – DSM5-Oriented Scale		
Depressive Problems	11 (4.5)	19 (7.4)
Anxiety Problems	29 (11.5)	45 (17.2)
Autism Spectrum Problems	19 (7.4)	31 (12.0)
Attention Deficit/Hyperactivity Problems	10 (3.4)	14 (5.0)
Oppositional Defiant Problems	11 (4.4)	18 (6.8)

CBCL/1½-5, Child Behaviour Checklist for ages 1½-5 years; DSM5, Diagnostic and Statistical Manual of Mental Disorders, 5th edition.
[a] Number observed.
[b] Proportions were calculated using inverse probability weights to account for non-response bias.

Figure 1. Behavioural and emotional problems at preschool age in children born very preterm, by breast milk feeding practices.



CBCL/1½-5, Child Behaviour Checklist for ages 1½-5 years; CI, Confidence Interval; * DSM5-Oriented Scale; Model adjusted for gestational age, child sex, maternal age, maternal education level.

Supporting Information

Table S1. Comparison of responders to Child Behaviour Checklist for ages 1½-5 years (CBCL/1½-5) and non-responders' characteristics.

	CBCL/1½-5		
	Non-responders n=277 (51.1%)	Responders n=265 (48.9%)	
Characteristics	n (%)	n (%)	p-value
Mother and pregnancy			
Mother's age at delivery			0.002
≤ 24 years	58 (20.9)	27 (10.2)	
25-34 years	148 (53.4)	152 (57.4)	
≥ 35 years	71 (25.6)	86 (32.4)	
Missing	0	0	
Mother's country of birth			<0.001
Native-born	214 (79.3)	240 (90.6)	
Foreign-born	56 (20.7)	25 (9.4)	
Missing	7	0	
Mother's educational level [a]			0.053
Low level (ISCED 0-2)	52 (34.9)	70 (26.5)	
Intermediate level (ISCED 3-5)	51 (34.2)	82 (31.1)	
High level (ISCED 6-8)	46 (30.9)	112 (42.4)	
Missing	128	1	
Parity at delivery			0.002
Nulliparous	158 (57.0)	185 (69.8)	
Multiparous	119 (43.0)	80 (30.2)	
Missing	0	0	
Type of pregnancy			0.039
Singleton	179 (64.6)	193 (72.8)	
Multiple	98 (35.4)	72 (27.2)	
Missing	0	0	
Infant and neonatal morbidity			
Child sex			0.262
Male	153 (55.2)	159 (60.0)	
Female	124 (44.8)	106 (40.0)	
Missing	0	0	
Gestational age at birth			0.199
≤27 weeks	72 (26.0)	73 (27.5)	
28-29 weeks	68 (24.5)	80 (30.2)	
30-31 weeks	137 (49.5)	112 (42.3)	
Missing	0	0	
Small for gestational age			0.642
≥10th percentile	184 (66.4)	171 (64.5)	
<10th percentile	93 (33.6)	94 (35.5)	
Missing	0	0	

Bronchopulmonary dysplasia			0.946
No	242 (87.4)	231 (87.2)	
Yes	35 (12.6)	34 (12.8)	
Missing	0	0	
ROP stages III-V			0.917
No	265 (95.7)	254 (95.8)	
Yes	12 (4.3)	11 (4.2)	
Missing	0	0	
IVH III-IV / cPVL			0.757
No	259 (93.5)	246 (92.8)	
Yes	18 (6.5)	19 (7.2)	
Missing	0	0	
NEC needing surgery or peritoneal drainage			0.438
No	274 (98.9)	260 (98.1)	
Yes	3 (1.1)	5 (1.9)	
Missing	0	0	
Any congenital anomaly			0.168
No	258 (93.1)	254 (95.8)	
Yes	19 (6.9)	11 (4.2)	
Missing	0	0	
Breast milk feeding at discharge			0.047
No	105 (37.9)	79 (29.8)	
Yes	172 (62.1)	186 (70.2)	
Missing	0	0	
Region of birth			0.095
Lisbon and Tagus Valley	113 (40.8)	127 (47.9)	
Northern	164 (59.2)	138 (52.1)	
Missing	0	0	

ISCED, International Standard Classification of Education 2011.
[a] Data collected at 2 years of corrected age.
cPVL, cystic periventricular leukomalacia; IVH, intraventricular haemorrhage; NEC, necrotising enterocolitis; ROP, retinopathy of prematurity.

Table S2. Proportions of behavioural and emotional problems at preschool age in children born very preterm, by breast milk feeding practices.

	Behavioural and emotional problems	
	Normal	Subclinical/ Clinical
CBCL/1½-5 Problems Scale	n [a] (% [b])	n [a] (% [b])
Total problems		
BMF initiation		
Never breastfed	20 (77.5)	6 (22.5)
Ever breastfed	192 (80.6)	45 (19.4)
Exclusive BMF		
<1 month	78 (74.0)	28 (26.0)
≥1 month	128 (85.5)	21 (14.5)
Any BMF		
<3 months	101 (80.1)	27 (19.9)
≥3 months	107 (79.6)	24 (20.4)
Internalizing problems		
BMF initiation		
Never breastfed	20 (77.5)	6 (22.5)
Ever breastfed	186 (76.1)	51 (23.9)
Exclusive BMF		
<1 month	78 (72.9)	28 (27.1)
≥1 month	122 (79.3)	27 (20.7)
Any BMF		
<3 months	98 (74.8)	30 (25.2)
≥3 months	104 (77.4)	27 (22.6)
Externalizing problems		
BMF initiation		
Never breastfed	19 (73.0)	7 (27.0)
Ever breastfed	204 (86.6)	33 (13.4)
Exclusive BMF		
<1 month	83 (78.8)	23 (21.2)
≥1 month	133 (89.2)	16 (10.8)
Any BMF		
<3 months	101 (80.0)	27 (20.0)
≥3 months	118 (90.0)	13 (10.0)
Emotionally reactive		
BMF initiation		
Never breastfed	20 (77.5)	6 (22.5)
Ever breastfed	207 (85.0)	30 (15.0)
Exclusive BMF		
<1 month	90 (84.1)	16 (15.9)
≥1 month	130 (83.4)	19 (16.6)

Any BMF		
<3 months	107 (79.6)	21 (20.4)
≥3 months	116 (88.6)	15 (11.4)
Anxious/ Depressed		
BMF initiation		
Never breastfed	20 (77.5)	6 (22.5)
Ever breastfed	217 (91.6)	20 (8.4)
Exclusive BMF		
<1 month	92 (86.8)	14 (13.2)
≥1 month	138 (92.0)	11 (8.0)
Any BMF		
<3 months	112 (87.3)	16 (12.7)
≥3 months	121 (92.2)	10 (7.8)
Somatic complaints		
BMF initiation		
Never breastfed	21 (79.0)	5 (21.0)
Ever breastfed	213 (89.3)	24 (10.7)
Exclusive BMF		
<1 month	89 (82.3)	17 (17.7)
≥1 month	138 (92.6)	11 (7.4)
Any BMF		
<3 months	115 (88.8)	13 (11.2)
≥3 months	116 (87.5)	15 (12.5)
Withdrawn		
BMF initiation		
Never breastfed	22 (82.0)	4 (18.0)
Ever breastfed	217 (91.8)	20 (8.2)
Exclusive BMF		
<1 month	92 (86.7)	14 (13.3)
≥1 month	140 (94.1)	9 (5.9)
Any BMF		
<3 months	117 (91.4)	11 (8.6)
≥3 months	118 (89.0)	13 (11.0)
Sleep problems		
BMF initiation		
Never breastfed	23 (93.7)	3 (6.3)
Ever breastfed	226 (95.4)	11 (4.6)
Exclusive BMF		
<1 month	97 (93.2)	9 (6.8)
≥1 month	144 (96.4)	5 (3.6)
Any BMF		
<3 months	119 (93.8)	9 (6.2)
≥3 months	126 (96.6)	5 (3.4)
Attention problems		
BMF initiation		
Never breastfed	23 (87.8)	3 (12.2)
Ever breastfed	222 (94.4)	15 (5.6)

Exclusive BMF		
<1 month	95 (90.0)	11 (10.0)
≥1 month	142 (96.0)	7 (4.0)
Any BMF		
<3 months	116 (91.3)	12 (8.7)
≥3 months	125 (95.9)	6 (4.1)
Aggressive behaviour		
BMF initiation		
Never breastfed	21 (79.2)	5 (20.8)
Ever breastfed	220 (93.5)	17 (6.5)
Exclusive BMF		
<1 month	92 (86.6)	14 (13.4)
≥1 month	142 (95.6)	7 (4.4)
Any BMF		
<3 months	113 (89.0)	15 (11.0)
≥3 months	124 (94.4)	7 (5.6)
Stress problems		
BMF initiation		
Never breastfed	21 (79.2)	5 (20.8)
Ever breastfed	208 (87.6)	29 (12.4)
Exclusive BMF		
<1 month	87 (81.8)	19 (18.2)
≥1 month	135 (90.1)	14 (9.9)
Any BMF		
<3 months	109 (84.7)	19 (15.3)
≥3 months	116 (88.2)	15 (11.8)
CBCL/1½-5 DSM5-Oriented Scale		
Depressive Problems		
BMF initiation		
Never breastfed	23 (91.4)	3 (8.6)
Ever breastfed	221 (92.8)	16 (7.2)
Exclusive BMF		
<1 month	95 (90.6)	11 (9.4)
≥1 month	141 (93.8)	8 (6.2)
Any BMF		
<3 months	118 (92.5)	10 (7.5)
≥3 months	122 (92.4)	9 (7.6)
Anxiety problems		
BMF initiation		
Never breastfed	19 (74.4)	7 (25.6)
Ever breastfed	199 (84.0)	38 (16.0)
Exclusive BMF		
<1 month	81 (77.6)	25 (22.4)
≥1 month	130 (86.4)	19 (13.6)
Any BMF		
<3 months	101 (79.4)	27 (20.6)
≥3 months	113 (86.2)	18 (13.8)

Autism spectrum problems		
BMF initiation		
Never breastfed	20 (77.2)	6 (22.8)
Ever breastfed	212 (89.7)	25 (10.3)
Exclusive BMF		
<1 month	88 (81.6)	18 (18.4)
≥1 month	136 (92.5)	13 (7.5)
Any BMF		
<3 months	114 (89.1)	14 (10.9)
≥3 months	114 (86.4)	17 (13.6)
Attention deficit/hyperactivity problems		
BMF initiation		
Never breastfed	22 (85.0)	4 (15.0)
Ever breastfed	227 (96.5)	10 (3.5)
Exclusive BMF		
<1 month	96 (91.2)	10 (8.8)
≥1 month	145 (97.8)	4 (2.2)
Any BMF		
<3 months	118 (93.1)	10 (6.9)
≥3 months	127 (97.2)	4 (2.8)
Oppositional defiant problems		
BMF initiation		
Never breastfed	22 (84.4)	4 (15.6)
Ever breastfed	223 (94.6)	14 (5.4)
Exclusive BMF		
<1 month	97 (91.8)	9 (8.2)
≥1 month	141 (94.5)	8 (5.5)
Any BMF		
<3 months	117 (91.9)	11 (8.1)
≥3 months	124 (94.6)	7 (5.4)

BMF, breast milk feeding; CBCL/1½-5, Child Behaviour Checklist for ages 1½-5 years.

[a] Number observed.

[b] Proportions were calculated using inverse probability weights to account for non-response bias.

5. OVERALL DISCUSSION

This chapter intends to integrate the key findings of our research, by recognizing the major strengths and weaknesses, since each specific objective of this thesis resulted in one manuscript and the interpretation of the results were addressed in detail in each discussion section. Finally, the main public health implications are discussed, simultaneously providing suggestions for further research.

5.1. Key findings and publications

Below, a summary of the main findings of this thesis derived from each manuscript is presented, along with the corresponding research question.

Paper	Research question	Key findings
I	How do NICUs influence feeding practices at discharge in infants born VPT in Portugal?	Feeding practices at discharge varied significantly among Portuguese NICUs, ranging from 3% to 50% for exclusive BMF, and from 21% to 62% for mixed feeding.
		A designated staff member to support mothers expressing or breastfeeding in the NICU was the major determinant of exclusive BMF, explaining the largest proportion of variance observed among Portuguese units (43%).
		The availability of a bathroom with a shower for parents in the NICU explained the wide variance observed in the prevalence of any BMF across Portuguese units.
II	Are the policies towards parental presence in the NICU different across European countries?	Policies regarding visiting hours, duration of visits and possibility for parents to stay during medical rounds and spend the night in the NICU differed within and between countries.
	Are more liberal parental policies associated with increased BMF at discharge from the NICU?	More liberal parental visiting policies were associated with an increased likelihood of exclusive BMF and exclusive direct feeding at the breast at hospital discharge.

III	What is the prevalence and the total duration of exclusive and any BMF in children born VPT in Portugal and worldwide?	The duration of BMF among VPT infants did not meet international recommendations. In Portugal, only 10% of infants received exclusive BMF for at least six months and 10% received any BMF for 12 months or more (median duration of two months for exclusive and three months for any BMF). Worldwide, based on a systematic literature review, the prevalence of exclusive BMF at six months ranged from 1% to 27%, and of any BMF at 12 months varied between 8% and 12%.
IV	What are the factors associated with BMF continuation until six months of age among breastfed VPT infants?	One-third of ever breastfed VPT infants were breastfed at six months, varying from 25% (Portuguese and British regions) to 50% (Swedish and Danish regions). The probability of being breastfed to six months was lower for infants of mothers with a lower educational level. Neonatal factors associated with stopping breastfeeding were multiple pregnancy, bronchopulmonary dysplasia and multiple neonatal transfers. Infants receiving any BMF and formula at discharge were half as likely to be breastfed to six months as those receiving exclusive BMF.
V	Do the practices for handling the mother´s own milk for VPT infants vary between European NICUs?	There were large variations in managing the mother´s own milk across countries and between NICUs in the same country. In 22% of the inquired units, all VPT infants whose mothers expressed breast milk received their own mother's pasteurised milk (country range: 0%-73%). When mother´s own milk was not available, 34% of NICUs used human banked milk for all VPT infants.

VI	Do BMF initiation and duration affect the cognitive development of VPT children at 2 years of CA?	16% and 11% of children presented suboptimal non-verbal and verbal cognitive development, respectively. Compared to those who were breastfed, never breastfed children faced a higher risk of having suboptimal non-verbal and verbal cognition at two years of CA, independent of perinatal and sociodemographic characteristics.
VII	Do BMF practices have a role in behavioural and emotional outcomes of children born VPT at preschool age?	Nearly 20% of children presented behavioural or emotional problems at three years of age. BMF seemed to protect children born VPT from adverse behavioural and emotional outcomes at preschool age, as shown by a reduced risk for externalizing problems, somatic complaints, aggressive behaviour, as well as autism spectrum and attention deficit/hyperactivity symptoms.

5.2. Strengths and limitations

This thesis used data collected from one of the most important and large international prospective population-based cohorts of children born VPT – the EPICE cohort, which covered a diverse set of regions across Europe, including 7 900 live births (66). This is one of the major strengths of this thesis, considering that our findings could be generalisable to neonatal units across Europe as well as other settings with similar resources and characteristics. Regarding the Portuguese sample, this is the first geographically broad cohort of VPT infants, covering all maternity and neonatal units from the two largest regions of the country (Northern and Lisbon and Tagus Valley), which represent about two-thirds of all VPT births occurring in Portugal in the same period (2011/2012) (195).

Other strengths should be recognized, particularly the availability of high-quality data at both the individual- and unit-level, with a wide range of characteristics including information on units' policies and practices. All data were collected under rigorous protocols and research tools, based on pretested standardised questionnaires with common definitions in all regions. This enables robust comparisons between and within countries, giving us a range of sociocultural contexts in Europe. Another strength is that all regions checked for completeness of inclusions against delivery ward registries and/or another external data source. In Portugal, we cross-checked with hospital registries and through the *National Registry of Very Low Birth Weight Infants*.

A final strength is the involvement of the research teams in each region. The active participation of scientific experts from each region is necessary to ensure that the data are well harmonized and interpreted appropriately. This feedback contributes to the accuracy of the results and their broader contextualization.

Nonetheless, this research has limitations that need to be acknowledged. We have no information about the timing of feeding practices during the hospitalization period, making it impossible to consider a time dimension in the comparison of feeding at discharge. During hospitalization, there might be periods of exclusive BMF and other moments with different feeding approaches. Information on the chronology of BMF decisions would increase our capacity to understand their role in the results obtained. Also, we were unable to differentiate between the mother's own milk and donor human milk at discharge. However, given that only 34% of units stated that they provided donor human milk for all infants less than 32 weeks, and considering the general insufficiency of donor milk and the volumes needed for an infant at near-term equivalent age, it is unlikely that the infants would be receiving donor human milk at discharge, although this may have occurred in a few cases.

Additionally, it would be useful to have more detailed information on feeding practices, such as if fortified or unfortified breast milk was used and the duration of exclusive BMF for the entire cohort, particularly when investigating the association between BMF practices and health-related outcomes. In this context, we would like to point out as a strength the availability of total duration of exclusive and any BMF until the age of three years in the Portuguese cohort, while in the entire cohort, we only have the total duration for any BMF. Nevertheless, considering that this information was collected retrospectively when the child was two years of CA, as well as at three years for the Portuguese sample, the possibility of some recall bias cannot be disregarded. Nevertheless, we do not expect that this significantly affects the quality of the data retrieved, since previous studies have reported good validity of maternal recall of BMF initiation and duration (201, 202), especially when the duration is recalled after a short period of time (three years) (202).

Another limitation is the lack of detailed information on socio-demographic characteristics at baseline, such as the mother's employment and educational level, which were only collected in the follow-up evaluations. Also, other variables, which could potentially be useful to understand our findings, were not available, namely, maternal intention and motivations to breastfeed, as well as the reasons for not initiating or stopping breastfeeding (e.g., mother's own choice, by medical or psychological reasons, return to work).

Finally, the main challenge in dealing with large cohort studies is attrition due to loss to follow-up. In the EPICE cohort, 65.5% of infants were included in the two-year follow-up, with rates ranging from 42% in the UK to 99% in Estonia (67% in Portugal) (66). Children born from singleton pregnancies, and to younger, multiparous and migrant women were less likely to be followed-up at two years. Inversely, children who received BMF at discharge were more likely to participate in the follow-up evaluations (66). Indeed, loss to follow-up can undermine the representativeness and validity of estimates by introduce selection bias that might be differential (203). Multiple analytical strategies for handling missing data make it possible to estimate outcomes by reducing the impact of attrition. Two approaches commonly used to deal with missing data are multiple imputation (MI) and inverse probability weighting (IPW) (204, 205). Another possibility is to combine MI and IPW (204). In our analysis, the effects of potential selection bias due to attrition were accounted for by combining both MI and IPW methods (80, 204, 206). Thus, we used IPW to give a higher weight to children with characteristics of non-responders to obtain a sample that reflects the full set of observations. Weights were obtained from a logistic regression model as the probability of participation in the follow-up derived from relevant socio-demographic and perinatal characteristics. Before predicting the IPW, missing values from variables included in the regression model were imputed using MI by chained equations. This approach allowed us to generate more accurate estimates overall (204).

5.3. Implications for public health and research

Results from this thesis add new and important insights to the available knowledge landscape about BMF at discharge and its continuation at both the national and European levels, that can contribute to a better understanding of the policies and practices available in neonatal units to influence health services performance and, consequently, the health outcomes of infants born VPT.

Our investigation reveals that two-thirds of Portuguese infants born VPT received any BMF at discharge, but only 25% were exclusively breastfed *(Paper I)* (207). A wide variation was observed among Portuguese neonatal units and having designated members to support mothers in NICUs, as well as the access to a bathroom with a shower for parents were the main determinants of exclusive and any BMF at discharge, respectively (207). At the European level, policies regarding visiting hours, the duration of visits and the possibility for parents to stay during medical rounds and spend the night in the NICU differed between and within countries. These differences between NICUs were very marked in Portugal, where nearly half of the units reach the highest parental presence score (range 1–10, with higher values indicating more liberal policies), and 23.5% of NICUs presented a score below seven. Furthermore, we found that more liberal parental visiting policies were associated with an increased probability of exclusive BMF and exclusive BMF direct at the breast at hospital discharge *(Paper II)* (208). Taken together, these results highlight that there is a clear potential for improving BMF through policies and support in the NICU. Therefore, and in line with previous research showing that having a BFHI accreditation also affects BMF rates among VPT infants (138), it is crucial to obtain a commitment from governments, health authorities and health professionals to promote a supportive and collaborative environment in the NICU, as well as to offer adequate facilities, allowing the involvement of parents in the care of infants, based on a family-centred and integrated care approach (163, 164, 209-211). Thus, every woman should receive all of the support that she needs and be provided a designated staff member to help her during hospitalization, not only in the Portuguese context but worldwide (25).

Considering that there is much more research on BMF at discharge than on the maintenance of lactation following NICU discharge, our work provides useful information to address this gap in research. Therefore, we found that the total duration of exclusive and any BMF among Portuguese VPT infants is shorter than the recommended and this appears to be common globally *(Paper III)* (212). Additionally, across European countries, we observed that rates of breastfeeding continuation at six months fall short of recommendations, with a considerable variability across countries and with Portuguese regions presenting the lowest proportion (25%) *(Paper IV)* (206). Although some individual factors were relevant for the outcome studied, once again, NICU practices continued to exert influence even after discharge, as shown by the negative impact of multiple neonatal transfers. This result could reflect the differences in practices across NICUs leading to confusion or lack of support for mothers. Another key finding is that continuing BMF was more likely with exclusive BMF at discharge, suggesting an opportunity for intervention since the large variations observed in rates of mixed and exclusive BMF across European countries were also partly explained by unit policies and practices (138). Additionally, given that most ever-breastfed infants were weaned after discharge in the EPICE cohort, this emphasizes the importance of continuing counselling and support in the post-discharge period (25).

Furthermore, our data highlight that BMF continuation was marked by strong social inequalities, as the probability of being breastfed to six months was lower for infants of mothers with a lower educational level *(Paper IV)* (206). Understanding the specific obstacles faced by women from more disadvantaged families is crucial to design specific interventions to mitigate the negative effects of not BMF. It is well documented that socio-economic disadvantages, often measured by maternal educational level, affect short- and long-term developmental outcomes of children born VPT in several domains (80, 213). Thus, taking into account the lower proportion of BMF among women from more disadvantaged families across European countries, protecting and supporting BMF in this specific group of women is a major priority, and would make it possible to reduce other greater health inequalities (20).

Our results also reinforce the evidence base on the importance of BMF on health-related outcomes in childhood, particularly in neurodevelopmental and mental health outcomes *(Papers VI and VII)*. Never breastfed children faced a higher risk of suboptimal non-verbal and verbal cognition at two years of CA than those who had ever been breastfed *(Paper VI)*. The most significant conclusion is that any amount of BMF is better than none, highlighting the crucial role of BMF as a minimum standard for newborn care among these vulnerable infants.

This implies a global effort to guarantee equitable access to human milk to each newborn (102). Citing Victora and colleagues from the Lancet Breastfeeding Series (2016) "*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*" (20).

However, despite the acknowledged benefits of human milk, our data also showed that we are unable to give the best start in life to all VPT infants throughout Europe. By international recommendations, when a mother´s own milk is not available, pasteurized donor human milk should be provided by a well-established human milk bank. However, only 34% of units used human banked milk for all infants born VPT *(Paper V)* (214). In Portugal, there is currently only one human milk bank available in the Lisbon region, which services two NICUs. Although another human milk bank is being planned for the Northern region, this is clearly insufficient to cover all of Portugal's NICUs. Thus, we expect that the results of the current thesis could be a call to action for governments to support more human milk banks in Portugal and in other countries as well (215). We recognize the administrative and financial challenges of setting up a human milk bank (126), but it is indisputable that providing BMF to all VPT infants will reduce the negative socio-economic impact for families, as well as for health and social systems, and more broadly for society (100). Additionally, previous research illustrated that NICUs using donor milk had higher rates of exclusive BMF at discharge, demonstrating that an available human milk bank might be a driver to improve BMF rates in NICUs (138). Still in this context, it is crucial to emphasize the importance of providing a common regulation for human milk banks at the European level to ensure a minimum quality and safety standard for procurement, storage, processing, and distribution of donor milk. A call to European legislators was recently powered by EFCNI *("Making Human Milk Matter - The need for regulation in the European Union")* (135).

Large variations in the practices of the management of a mother´s own milk between and within countries were found, which indicate substantial differences in attitudes about what constitutes the best practices *(Paper V)* (214). This huge variability was also observed in previous studies and could reflect the lack of evidence for some points (116, 151). If there are challenges in translating scientific knowledge into practice in areas where there is robust evidence, this is even more difficult when the evidence is less strong (91, 216). Thus, to guide practice, further studies are needed to reinforce and provide evidence-based knowledge for the best practices on handling a mother´s own milk, for example, on ensuing outcomes of postnatal human cytomegalovirus infection, as well as practices for managing these risks (214).

This is in line with research priorities identified for collaborative research in the *Research on European Children and Adults Born Preterm* (RECAP Preterm) project, that brings together data from 23 VPT birth cohorts from 15 European countries. In fact, growth and nutrition, including breastfeeding, was one of the themes with the highest rankings, followed by themes focusing on the socio-emotional needs of children and parents, which have been less studied (217). In a systematic review conducted in 2016, several gaps were identified in research addressing the prognostic factors associated with the behavioural problems and psychiatric disorders in children born VPT/VLBW (176). In this context, this thesis also contributes for improving knowledge on this topic *(Paper VII)*. On the one hand, this is the first study reporting the prevalence of behavioural and emotional problems in children born VPT at preschool age, in Portugal. On the other hand, our data seem to indicate that receiving any BMF, as well as the prolonged duration of exclusive and any BMF may play an important role in protecting against adverse behavioural and emotional outcomes, even though we did not find statistically significant associations after adjustment for potential confounders. Nevertheless, from a public health perspective, we should not disregard these results, which are in line with previous research (186, 187).

Overall, to better understand the impact of nutrition on the neurodevelopmental and psychological outcomes of children born VPT over the life-course, further longitudinal studies are needed to analyse the exposure to different feeding practices, including BMF initiation and total duration (exclusive and any), type of human milk (mother´s own milk vs. donor), as well as the fortification method (e.g., individual vs. standard) and composition/quality of fortifiers (e.g., human milk-derived fortifier vs. bovine milk-derived fortifier) (124, 165, 218). Therefore, it would be of the utmost interest for future studies to use data from the European VPT birth cohorts, within the RECAP Preterm platform, to investigate the potential effect of BMF practices in different health-related outcomes throughout life.

From a public health perspective, we would also like to raise awareness to the importance of continued surveillance of BMF practices, monitoring their prevalence and trends overtime, enabling comparisons across countries, regions and units. In the Portuguese context, it is time to re-establish and improve the national Breastfeeding Registry, which was set up in 2010 and whose last report was published in 2014 (22). However, it is essential to invest in widespread coverage across the country and include all infants, regardless of gestational age. A national and well-established epidemiological system to monitor BMF indicators is crucial to provide continuous and systematic information allowing timely action-research to improve BMF outcomes.

Finally, efforts should be exhausted at the global, regional, national and local level by governments, policymakers, health workers, communities and families, working together to protect, promote and support human milk and breastfeeding for vulnerable infants, as well as for all infants and young children globally (25). Increasing breastfeeding practices for all infants worldwide is a public health concern, as it is an essential driver to achieve the Sustainable Development Goals by 2030 (219), including by improving child nutrition, preventing child mortality and decreasing the risk of non-communicable diseases, as well as supporting cognitive development.

6. CONCLUSIONS

Although providing BMF to infants born VPT is a complex and challenging process, there is a high potential for improving BMF through policies and support in NICUs, as shown by the main findings of our research in which neonatal unit characteristics exert a key role in BMF rates at discharge, as well as in its continuation to six months. The duration of BMF among VPT infants falls short of international recommendations across European countries, including Portugal, and low BMF continuation rates were marked by strong social inequalities. To target specific interventions to the groups and contexts with the greatest needs is of the utmost significance to mitigate even greater gaps in health outcomes among disadvantaged families.

Our results also highlight the contribution of BMF towards better health outcomes of infants born VPT, particularly in neurodevelopmental and mental health outcomes, which reinforce the importance and need of a comprehensive public health strategy to improve BMF rates among this vulnerable population. Neonatal units' characteristics are to a large extent modifiable and amenable to intervention. Parents are key actors for successful BMF in the neonatal unit environment. Thus, changes in policies and practices towards more family-centred and integrated care might be expected to cost-effectively increase BMF and, consequently, mitigate adverse health outcomes in the medium- and long-term in children born VPT.

In conclusion, our work provides novel results at the national and European levels, to underpin the action of public health stakeholders. Protection, promotion and support of BMF is a collective responsibility that implies a global effort, assuring that all VPT infants receive the full benefits for the best start in life.

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assunto
Provas de Doutoramento.

Informo V. Exª. que, por meu despacho de 2021.02.03, proferido no âmbito de delegação reitoral, nomeei o júri das provas de doutoramento em Saúde Pública, requeridas por V. Exª., com a seguinte constituição:

Presidente: Doutora Raquel Ângela Silva Soares Lino, Professora Catedrática da Faculdade de Medicina da Universidade do Porto.

Vogais:

- Doutor Livio Provenzi, Investigador Principal do Istituto di Ricovero e Cura a Carattere Scientifico, Itália;

- Doutora Rosa Maria Soares Madeiras Domingues, Professor da Escola Nacional de Saúde Pública Sérgio Arouca, Brasil;

- Doutor Manuel Gonçalo Cordeiro Ferreira, Professor Auxiliar Convidado da Universidade Nova de Lisboa;

- Doutor Alberto António Moreira Caldas Afonso, Professor Catedrático Convidado do Instituto de Ciências Biomédicas Abel Salazar da Universidade do Porto;

- Doutor Doutor José Henrique Dias Pinto Barros, Professor Catedrático da Faculdade de Medicina da Universidade do Porto;

- Doutora Carla Maria de Moura Lopes, Professora Associada com Agregação da Faculdade de Medicina da Universidade do Porto.

Com os melhores cumprimentos,

A Vice-Reitora,

Assinado por: **MARIA DE LURDES CORREIA FERNANDES**
Num. de Identificação: 052371573
Data: 2021.02.04 13:57:06+00'00'
Certificado por: **Diário da República Eletrónico.**
Atributos certificados: **Vice-Reitora - Universidade do Porto.**
CARTÃO DE CIDADÃO

(Profª. Doutora Maria de Lurdes Correia Fernandes)

(1/4)/PV

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