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# Impact of socioeconomic factors on follow-up and health service use up to 5 years of age in a European cohort of children born very preterm

Anna-Veera Seppänen

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**THESE DE DOCTORAT DE  
SORBONNE UNIVERSITE**

Spécialité  
Epidémiologie  
Ecole Doctorale Pierre Louis de Santé Publique à Paris : Epidémiologie et Sciences de  
l'Information Biomédicale

Présentée par

Mlle Anna-Veera Seppänen

Pour obtenir le grade de

**DOCTEUR de SORBONNE UNIVERSITE**

Sujet de la thèse :

Impact des facteurs socio-économiques sur le suivi et l'utilisation des services de  
santé jusqu'à l'âge de 5 ans dans une cohorte européenne d'enfants nés très  
prématurément

*Impact of socioeconomic factors on follow-up and health service use up to 5 years  
of age in a European cohort of children born very preterm*

Soutenue le 10 décembre 2020

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*I dedicate this thesis to Max Öberg, born on the 13 April 2019 at 32 weeks of gestation, and his family, as to all children and their families who are living with the consequences of preterm birth.*



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## Abbreviations

BPD	Bronchopulmonary dysplasia
BW	Birth weight
CA	Congenital anomaly or corrected age (if years CA)
CI	Confidence interval
cPVL	Cystic periventricular leukomalacia
d	Days
EFCNI	European Foundation for the Care of Newborn Infants
EI	Early intervention
ENT	Ear-nose-throat
EPICE	Effective Perinatal Intensive Care in Europe
FU	Follow-up
GA	Gestational age
GP	General practitioner
HAS	National Health Authority (Haute Autorité de Santé) (France)
IUGR	Intrauterine growth restriction
IVH	Intraventricular haemorrhage
mo	Month/months
NEC	Necrotising enterocolitis
NICE	National Institute for Health and Care Excellence (UK)
NICU	Neonatal intensive care unit
ORL	Oto-rhino-laryngologist
ROP	Retinopathy of prematurity
SGA	Small for gestational age
SHIPS	Screening to improve Health In very Preterm infantS in Europe
VPT	Very preterm
WG	Weeks' gestation
y	Years





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# Chapter 1: Introduction

Very preterm (VPT) birth, defined as birth before 32 completed weeks' gestation, is a global concern; up to 2% of all children world-wide are born VPT (Blencowe et al. 2012). In Europe, rates of VPT births vary from 0.8% (Iceland, Lithuania and Finland) to 1.4% (Hungary) (Euro-Peristat project 2018). Although the causes of preterm birth are heterogeneous and not fully known, advanced maternal age and an increase in assisted reproductive technology, leading to more multiple births, have contributed to an increase in preterm birth rates (birth before 37 completed weeks' gestation) over the last decades (Zeitlin et al. 2013). At the same time, more of these infants are surviving until discharge as a result of improvements in medical care and more active management (Bonet et al. 2017; Ancel, Goffinet, and the Epipage Writing Group 2015).

Although mortality has decreased, infants born VPT remain at high risk of severe complications and morbidities in the neonatal period (Ancel, Goffinet, and the Epipage Writing Group 2015; Edstedt Bonamy et al. 2019; Saigal and Doyle 2008), with consequences that reach beyond the neonatal intensive care unit (NICU) hospitalisation. Children born VPT face a higher risk of health and developmental problems throughout childhood. Compared to infants born at term, they have more neuro-sensory, developmental, socio-behavioural and health problems such as cerebral palsy (MacLennan, Thompson, and Gecz 2015), neurodevelopmental and cognitive disabilities (Larroque et al. 2008; Johnson 2007), language and hearing difficulties (Vohr 2016), emotional and behavioural problems (Lemola 2015; Johnson 2007) and respiratory difficulties (Saigal and Doyle 2008) as they grow up. These risks may further be augmented by unfavourable social circumstances (Lemola 2015; Beaino et al. 2011; Dall'oglio et al. 2010; Sentenac, Johnson, et al. 2020). Moreover, the risk of preterm delivery is higher in women exposed to social disadvantage (Blumenshine et al. 2010), with rates twice as high in socially deprived areas (Bonet et al. 2013; Smith et al. 2009). Consequently, socially disadvantaged families are disproportionately affected by the adverse consequences of preterm birth.

Follow-up is recognised as essential for managing preterm birth-related consequences (EFCNI, van Kempen, et al. 2018). Although the sequelae of VPT birth have been well documented, the prognosis of future health and development for the individual infant is unknown at discharge from the neonatal unit. Follow-up programmes for VPT infants therefore aim to identify emerging health and developmental problems as early as possible in children at high risk due

to preterm birth. Early detection of emerging problems allows children to receive timely and appropriate health care services, to initiate early interventions (EI) to limit sequela, and to coordinate and manage subsequent, often multidisciplinary or complex care (Haute Autorité de Santé 2020; NICE 2017). Inadequate access to care can have adverse impact on the child's health (Lindly et al. 2020). Well-managed care after discharging home an infant born VPT should coordinate and streamline health care service use. This may ultimately improve the child's health and development and reduce family stress (Kuo et al. 2017), and help to avoid emergency room visits and hospitalisations (Kuo et al. 2017).

Although research on EI programmes have shown inconsistent results on long-term outcomes, there is evidence that EI may have a positive impact on motor outcomes in infancy, cognitive development (Spittle et al. 2012), behaviour (Nordhov et al. 2012) and parental wellbeing (Benzies et al. 2013). Some research has also suggested that EI programmes are most beneficial for children from socially disadvantaged families and that resources should be targeted (Ment et al. 2003). At the same time, studies suggest that there are social inequalities in follow-up (Callanan et al. 2001), EI (Barfield et al. 2008) and health care services use (Raspa et al. 2010; van Doorslaer, Koolman, and Jones 2004), which may counteract the benefits for those who need care the most.

In 2018, the European Foundation for the Care of Newborn Infants (EFCNI) published the European Standards of Care for the Newborn Infant, recommending follow-up across multiple domains until school age, and for some domains beyond, with special attention to children with additional social risk (EFCNI, van Kempen, et al. 2018). Many, but not all countries in Europe have established national or regional follow-up programmes for infants born preterm, some as early as in the 1980's, but in the absence of international guidelines or standards, these programmes differ in terms of content, eligibility criteria, duration and coverage.

Currently, we have no overview of post-discharge health care of the VPT population in Europe. We do not know to what extent routine follow-up and other post-discharge health care services are used, and to what extent child perinatal health and sociodemographic determinants are associated with the access to and use of these services. We also do not know whether routine follow-up has an impact on long-term care and equitable access to care. We aimed to address these knowledge gaps using data from a large cohort of VPT births from 19 regions across 11 European countries. As the organisation of follow-up and care for VPT infants differs greatly across regions in Europe, studying the use of follow-up and health services across 19 European

regions with similar standards of living and universal health care systems allows us to describe variations in follow-up coverage, health care service use and care inequalities in relation to these different organisations of care.

## 1.1 Aim and objectives

The aim of this doctoral project was to assess the use of post-discharge follow-up and health care services among children born VPT in Europe and associations with family socioeconomic characteristics. We use data from the population-based Effective Perinatal Intensive Care in Europe (EPICE) cohort of VPT births in 19 regions in 11 European countries, and the Screening to Improve Health in very Preterm Infants in Europe (SHIPS) project that follows up the cohort at five years of age. Specific objectives were to:

- 1) Describe post-discharge follow-up until five years of age and health care service use at two and five years of age by children born VPT in a contemporary European cohort
- 2) Investigate differences in follow-up and health care service use across countries, and whether there are socioeconomic disparities in follow-up and health service use
- 3) Assess whether follow-up is associated with health care service use and equity in care

To address these objectives, we carried out four studies. In the first study (chapter 4), we investigated the use of medical specialist services in the VPT population in the study regions until two years' corrected age (CA), and the association between service use and family sociodemographic characteristics. These results were published in a manuscript entitled *Developmental Medicine and Child Neurology*, entitled *Specialist health care services use in a European cohort of infants born very preterm* (Seppanen et al. 2019).

In the second study (chapter 5), we assessed parents' satisfaction and experiences with preterm birth-related healthcare received by their children after discharge from the neonatal unit until 5 years of age. In this mixed-methods study, we used data from parental questionnaires to investigate family sociodemographic and child health characteristics associated with parents' ratings of care (poor, fair, good, excellent) and to perform thematic analyses of free-text suggestions on how care could be improved. This manuscript, entitled *Parents' ratings of post-discharge healthcare for their children born very preterm and their suggestions for*

*improvement: a European cohort study*, has been published in the journal *Pediatric Research* (Seppanen et al. 2020).

In the third study (chapter 6), we described the use of follow-up services until five years of age across regions in the 11 study countries and identified the sociodemographic and perinatal risk factors that were associated with follow-up enrolment and continuation. These results, reported in a manuscript entitled *Follow-up after very preterm birth in Europe* is currently under review.

We addressed the last objective in the fourth study (chapter 7), exploring the association between perinatal and sociodemographic risk factors and elevated health service use and type of health service use at five years of age. We also assessed whether follow-up alters such associations. To do so, we developed a framework for describing and synthesising information on health service use. These results are reported in the form of a manuscript entitled *Elevated health care use at five years of age in children born very preterm in a European cohort: association with social circumstances and access to routine follow-up services* that will be submitted for publication shortly.

These studies were carried out within the SHIPS project consortium which includes researchers and clinicians from 13 collaborating institutions in 11 European countries, including a Health Economics team, qualitative researchers and the EFCNI, a network of parents of children born preterm, supported by clinical experts and scientists, that unites parent organisations across Europe. As part of this thesis, I coordinated a working group of eight researchers from France, Portugal and the UK to discuss and get feedback on definitions and analyses on these four studies. Preliminary results were presented at biannual meetings of the SHIPS consortium.

The following chapter (chapter 2) provides a general background for these four studies; we describe the consequences of preterm birth in terms of health and development and provide an overview of the purposes and organisation of follow-up services, overall and more specifically in the European regions participating in SHIPS. In this chapter, we also review the post-discharge health care and health care needs in the VPT population. In a final section, we give a description of the current knowledge on the sociodemographic determinants of VPT birth and subsequent care.

In chapter 3, we present the data source and the statistical methodology used for the four studies. We also discuss the challenges of investigating health service use in an international study and detail the work undertaken to harmonise data on follow-up and care across countries. In chapters 4 to 7 we present the published results addressing the objectives, and in the last chapter (chapter 8), we synthesise and discuss these findings and make a final conclusion to the project.



## **Chapter 2: State of the art**

### **2.1 Introduction**

This chapter provides a non-exhaustive review of the major topics of importance for this doctoral project. We start by reviewing the perinatal factors associated with short and long-term prognosis among infants born VPT and provide an overview of the main health and developmental consequences of VPT birth in childhood. We then review the knowledge about health service use and follow-up programmes for children born VPT generally, as well as in the countries participating in the EPICE cohort. This population-based cohort, which constitutes the data source for this thesis, was established in 2011/2012 in regions from 11 countries: Belgium, Denmark, Estonia, France, Germany, Italy, the Netherlands, Poland, Portugal, Sweden and the UK. This section also highlights the current knowledge gaps in the literature with regards to follow-up and health service use among children born VPT. A final section addresses social equity and summarises studies investigating how family social circumstances affect the prognosis and health care of children born VPT.

### **2.2 Health and developmental consequences of very preterm birth**

Very preterm birth has immediate consequences for the newborn infant. Survival decreases markedly with decreasing gestational age (GA) at birth, from 93.6% at 27-31 weeks' GA, 52.4% at 22-26 weeks, 31.2% at 24 weeks to <1.1% before 24 weeks' GA according to data from France (Ancel, Goffinet, and the Epipage Writing Group 2015). Survival in the EPICE cohort was 91.0% at 30-31 weeks, 84.9% at 28-29 weeks, 70.5% at 26-27 weeks, 44.6% at 24-25 weeks and 4.2% at 22-23 weeks' GA (Draper et al. 2017). Stillbirth and mortality rates differ across countries, and was 27.7% overall in the EPICE cohort, ranging between 19.9% to 35.9% by region (Draper et al. 2017). In addition to an increased risk of mortality, the immaturity of infants born VPT and other related perinatal characteristics expose them to a high risk of severe morbidities and complications in their first months of life that, in turn, increase their risks of future health and developmental problems (Saigal and Doyle 2008).

### ***2.2.1 Perinatal morbidities and characteristics***

#### *Intrauterine growth and small for gestational age*

Approximately one-third of infants born VPT in Europe have intrauterine growth restriction (IUGR) as measured by being born small for their gestational age (SGA) (Zeitlin et al. 2017). Growth restriction is one of the main causes of VPT birth and is also more frequent among VPT births due to other causes, such as maternal hypertensive disorders (Delorme et al. 2016). Compared to other infants born at the same gestational ages, infants with restricted growth face increased risks of perinatal death (Delorme et al. 2016; Monier et al. 2017; Zeitlin, El Ayoubi, et al. 2010) and respiratory morbidity (Monier et al. 2017; Zeitlin, El Ayoubi, et al. 2010), as well as of worse long-term cognitive outcomes (Sacchi et al. 2020). Definitions of SGA vary, and in the EPICE cohort it is defined as birthweight <10th centile for intrauterine norms for gestational age and sex, using references developed for the cohort to take into consideration its multi-country composition (Zeitlin et al. 2017).

#### *Congenital anomalies*

Congenital anomalies are birth defects of prenatal origin of different levels of severity. Major anomalies, such as spina bifida and heart defects require medical interventions, whereas minor anomalies such as cup ear or undescended testicle have more limited social or cosmetic consequences (Centers for Disease Control and Prevention 2019). Congenital anomalies are more than five times more likely to be present among VPT compared to term-born infants; approximately 16% of infants born VPT have a congenital anomaly (Honein et al. 2009), and infants born preterm have up to a doubled risk of cardiovascular anomalies compared to term-born infants (Tanner, Sabrine, and Wren 2005), including congenital heart defects (Mustafa et al. 2020). The risk of mortality is higher especially in infants exposed to both preterm birth and cardiovascular anomalies (Tanner, Sabrine, and Wren 2005). Many studies exclude infants with severe congenital anomalies, because the long-term prognosis of the infant is highly related to the severity of the anomaly, in addition to conditions surrounding the preterm birth. However, children with minor congenital anomalies are not generally excluded from prognostic studies and the presence of an anomaly may affect both short and long-term outcomes.

### *Other perinatal characteristics*

There are other perinatal characteristics related to VPT birth which can affect child outcomes that are often taken into consideration in prognostic models for short and longer term outcomes, such as multiple pregnancy (between 8 to 10 % of all multiples in Europe are born <32 weeks' gestation) (Blondel et al. 2006), maternal pregnancy complications such as hypertensive disorders (a risk factor for preterm delivery and associated with restricted intrauterine growth) (Delorme et al. 2016), and infant sex, with males being at higher risk of death and some morbidities (Wolke, Johnson, and Mendonça 2019).

#### **2.2.2 Neonatal morbidities and complications**

The prevalence of severe neonatal morbidities (brain lesions, necrotising enterocolitis and retinopathy of prematurity) and bronchopulmonary dysplasia in preterm survivors varies across Europe, as shown in the EPICE cohort; between 10.4% (Ile-de-France, France) and 23.5% (Wielkopolska, Poland) in infants born <32 weeks of gestation (Edstedt Bonamy et al. 2019). The rates of neonatal morbidities increase with decreasing gestational age, from 40.8% among infants born at 22-26 weeks to 12.4% among those born between 27-31 weeks in France (Ancel, Goffinet, and the Epipage Writing Group 2015). These morbidities, as well as other complications emerging in the neonatal period have been associated with an increased risk of adverse long-term outcomes.

#### *Cerebral lesions and white matter injuries*

Cerebral lesions and white matter injuries, including severe intraventricular haemorrhage (IVH, grades III-IV are the most severe lesions) and cystic periventricular leukomalacia (cPVL) occur in an estimated 3.9% and 3.2% in children surviving VPT birth in Europe, respectively (Edstedt Bonamy et al. 2019). These neonatal morbidities may be fatal, and are two of the major risk factors for cerebral palsy (Marret et al. 2013; Ancel et al. 2006; Beaino et al. 2010; Gotardo et al. 2019). Children with cPVL have a pooled relative risk of 19.4 to develop cerebral palsy compared to children without, in a recent meta-analysis (Gotardo et al. 2019). Cerebral lesions in the neonatal period have also been associated with adverse effects on brain (Lemola 2015) and cognitive development (Beaino et al. 2011; Marret et al. 2013).

### *Retinopathy of prematurity*

Retinopathy of prematurity (ROP) is a severe disorder of the eye that is unique to infants born preterm and is one of the major causes of blindness in children (Hartnett 2015). It is classified in five stages of which the most severe stages cause irreversible damage to the eye (Classification of Retinopathy of Prematurity Group 2005). Around 3.7% of children born VPT in Europe are estimated to develop ROP (stage 3+) (Edstedt Bonamy et al. 2019). In addition to an elevated risk of blindness, ROP also increases the risk of vision impairments after VPT birth particularly (Hirvonen et al. 2018), and has been associated with poor cognitive outcome (Johnson 2007).

### *Necrotising enterocolitis*

Necrotising enterocolitis (NEC) is a severe bowel condition with an immediate threat to the neonate. Pooled estimates from a recent meta-analysis show that 7% of infants born extremely preterm may develop NEC during NICU hospitalisation (Alsaied, Islam, and Thalib 2020), of whom 20-40% need surgery, followed by a high mortality rate of up to 50% (Lin and Stoll 2006). Data from the EPICE cohort showed that 1.9% of the children born VPT in Europe had severe NEC requiring surgery or peritoneal drainage (Edstedt Bonamy et al. 2019). Survivors of NEC needing surgery have shown to have a higher risk of neurological and neuro-motor delays and poor growth (Federici and De Biagi 2019).

### *Bronchopulmonary dysplasia*

Bronchopulmonary dysplasia (BPD) is a condition that affects the immature lung, where the infant becomes reliant on artificial respiratory support (O'Reilly, Sozo, and Harding 2013). Severe BPD, when defined as need for oxygen (fraction of inspired oxygen >30%) or mechanical or non-invasive respiratory support at 36 weeks' postmenstrual age, affects about 5.5% of children born VPT in European countries (Edstedt Bonamy et al. 2019). BPD increases the risk for being re-hospitalised because of respiratory infections in the first years of life (Laugier et al. 2017), developing asthma in childhood, and is one of the principal causes of impaired lung function or respiratory illness later in life (O'Reilly, Sozo, and Harding 2013). BPD has also been associated with poor cognitive outcomes at five years of age (Twilhaar et al. 2018). Due to the long-term consequences BPD has on respiratory health, there is reason for long-term follow-up until adulthood (Duijts et al. 2020).

## *Sepsis*

Sepsis is a major complication of preterm birth with multiple short and long-term outcomes (McGovern et al. 2020). It is a condition caused by virus, bacteria or fungus, classified into early and late onset sepsis based on timing, depending on the definition (in utero, neonatal period before 72h of life, after 7 days of life, etc.) (Shane, Sánchez, and Stoll 2017). Sepsis has been less often included in studies of preterm birth-related outcomes, especially population-based studies relying on data collection from different neonatal units, because of the difficulty of defining sepsis, i.e. using clinical or treatment criteria (McGovern et al. 2020).

### ***2.2.3 Health and development in childhood and early adolescence***

Children born VPT have a higher risk of adverse long-term sequelae compared to their term-born peers, which increases with decreasing gestational age. The long-term consequences are heterogeneous, and sometimes multiple (Wolke, Johnson, and Mendonça 2019) and although well documented, remain unknown for the individual infant when they are discharged home from the neonatal unit. The risk of long-term chronic conditions in children born VPT is higher (Luu et al. 2016), including asthma (Been et al. 2014) and epilepsy (Hack et al. 2005; Crump et al. 2011), with an increasing risk with decreasing gestational age. However, most research focus on sensory, motor and neuro-cognitive outcomes, which may not be detected until the child starts school and is exposed to cognitive and social requirements.

## *Sensory impairment*

The risk of sensory impairments increases with decreasing gestational age and with the presence of brain lesions (Hirvonen et al. 2018). Whereas the need for hearing aid is rare (<1%) (Larroque et al. 2011) the need for glasses is common. At the age of eight years, 41% of the children born VPT in the EPIPAGE cohort needed glasses, compared to 26% in the term control group (Larroque et al. 2011). A register-based study on over one million livebirths in Finland showed a seven-fold increased risk of hearing loss in children born VPT (2.5%) compared to term-born children (0.4%), and much higher rates of visual impairment and blindness (3.6% vs. 0.8%) and minor sensory or ophthalmologic disorders (12.9% vs 2.6%) (Hirvonen et al. 2018).

### *Cerebral palsy and motor development*

Cerebral palsy (CP) is one of the main motor-related consequences of VPT birth (Wolke, Johnson, and Mendonça 2019). Cerebral palsy is a heterogeneous condition associated with severe motor problems and several developmental consequences, including intellectual disability, autism and epilepsy (MacLennan, Thompson, and Gecz 2015). Pooled prevalence of motor delay and CP have been estimated to 30.6% and 6.8% respectively in pre-school aged (5-5,5 year-old) children born VPT, with increasing prevalence with decreasing gestational age (Pascal et al. 2018). Oskoui et al. estimated the prevalence to 8.2% at <28 weeks and 4.3% at 28-31 weeks (Oskoui et al. 2013). Mild and moderate motor problems in children who do not develop CP is also common in children born preterm (40.5% at <37 weeks) (Williams, Lee, and Anderson 2010). These are referred to as developmental coordination disorder and include deficits in coordination, balance, fine and gross motor skills and visuo-motor integration, and poorer performance in these domains tend to persist into adolescence (Wolke, Johnson, and Mendonça 2019).

### *Cognitive delay and IQ*

There is a large pool of evidence on the increased risk of cognitive delay in children born VPT (Johnson 2007; Lemola 2015; Sentenac, Boutron, et al. 2020; Wolke, Johnson, and Mendonça 2019), also in seemingly healthy children (Dall'oglio, Rossiello et al. 2010). Systematic reviews and meta-analyses have established that school-aged children born VPT have lower IQ scores compared to their term-born peers (Johnson 2007; Wolke, Johnson, and Mendonça 2019), sometimes with poorer results in boys compared to girls (Johnson 2007; Linsell et al. 2018). Low IQ scores (<2 SD) have been found in up to 25% of children born VPT, making it one of the main sequelae of VPT birth, which, in addition, does not seem to improve as the children grow older (Wolke, Johnson, and Mendonça 2019). A recent synthesis of all systematic reviews on cognitive delay showed a standardised mean difference of 11.6 to 12.9 IQ points lower for children born <32 weeks compared to term-born controls (Sentenac, Boutron, et al. 2020). Cognitive delay is more common in lower gestational ages; pooled prevalence of cognitive delay (until 5,5 years of age) has been estimated at 14.7% in children born VPT and 29.4% in children born extremely preterm (Pascal et al. 2018). This delay presents across several sub-domains, including executive functioning and processing speed (Brydges et al. 2018).

### *Language delay, school readiness and academic performance*

There is also growing evidence on language delay (Sentenac, Johnson, et al. 2020), poor school readiness (Carter and Msall 2017) and lower academic performance later in life (Brydges et al. 2018) in children born preterm. School-aged children born VPT have worse performance especially in mathematics and spelling, need more special educational support and have poorer academic attainment at the end of compulsory schooling, suggesting they do not catch up with their peers (Wolke, Johnson, and Mendonça 2019).

### *Psychiatric, behavioural and social problems*

An increased risk of psychiatric, behavioural and social problems, especially in early adolescence, have been documented (Wolke, Johnson, and Mendonça 2019). Attention deficit disorders and to some extent Autism spectrum disorders are the most commonly reported psychiatric disorders reported in VPT-born children and adolescents (Wolke, Johnson, and Mendonça 2019; Johnson 2007). Although less frequently studied, research also shows an increased risk in depressive and anxiety disorders and social withdrawal and peer relationship problems lasting into adulthood (Wolke, Johnson, and Mendonça 2019).

## **2.3 Follow-up of children born very preterm**

### ***2.3.1 What is follow-up and why is it important?***

#### *The mission*

Follow-up programmes provide screening for emerging health and developmental problems in children born VPT, in order to enable early interventions (EI) and coordinate follow-up and care from a range of medical care providers after discharge home (EFCNI, van Kempen, et al. 2018). Follow-up also aims to inform and guide families, and help them know whether their child is developing normally, and facilitate school entry (Doyle et al. 2014). Their broader missions include gaining more knowledge on long-term outcomes after VPT birth and to provide data for benchmarking (Doyle et al. 2014). These programmes, that are more structured and specialised than routine primary care check-ups, are developed to regularly assess children across multiple domains, ideally covering physical and mental health, learning and cognition and quality of life (Doyle et al. 2014), but as guidelines have not been standardised and resources vary, so do follow-up programmes.

### *Early interventions*

Early intervention (EI) programmes are multidisciplinary and heterogeneous, and aim to implement interventions as early as possible after suspicion of developmental delay (Benzies et al. 2013; Anderson, Treyvaud, and Spittle 2020). Interventions include, for instance, physiotherapy, support to enhance infant cognitive and social development, and family interventions to support parenting and infant-parent bonding (Spittle et al. 2015; Benzies et al. 2013; Anderson, Treyvaud, and Spittle 2020). EI has been shown to have positive effects on cognition and motor development in infancy (Spittle et al. 2015). Improvements in parental anxiety and depression have also been reported for EI programmes with parent-support and/or educational components, which, in turn, have been associated with improved short-term child outcomes (up to 24 months) (Benzies et al. 2013) such as behaviour (Anderson, Treyvaud, and Spittle 2020). There is also some evidence that EI programmes are most beneficial for children with more risk factors (such as lowest birth weights or with brain lesions) (Anderson, Treyvaud, and Spittle 2020) and from socially disadvantaged families in terms of early health (Waruingi, Iyer, and Collin 2015) and cognitive, language and motor outcomes (Spittle et al. 2018). There is some evidence that cognitive improvements persist until five years of age (Spittle et al. 2015), but research shows inconsistent results on long-term outcomes and there is a general lack of long-term evaluations of post-discharge EI programmes (Anderson, Treyvaud, and Spittle 2020). However, studies on *Head Start* programmes, i.e. pre-school programmes aimed at reducing social disparities in disadvantaged communities, suggest that the impact of interventions on school achievement, social and behavioural and health outcomes may show in school-age and early adulthood (Bauer and Schanzenbach 2016).

### *Effects of follow-up*

There is a consensus that follow-up is important for the long-term management of VPT birth because it detects health and developmental problems early and permits timely referral for early intervention (EFCNI, van Kempen, et al. 2018). However very few published studies have evaluated the impact of routine neonatal follow-up programmes on child outcomes. Existing studies focus on specific outcomes, are short-term or single unit studies, and/or have been performed in non-European health care contexts. These studies suggest that follow-up programmes may improve access to care and improved health outcomes.



One of the few existing randomised controlled trials on follow-up programmes for high-risk infants (low birth-weight infants and infants needing mechanical ventilation at NICU) showed that enforced follow-up could reduce intensive care visits and minimise the risk of life threatening illnesses during the first year of life without increasing overall care costs (Broyles et al. 2000). The enforced programme included improved access to care through a follow-up home visit, a 24/7 phone line, and access five days per week to the follow-up clinic for both routine care and acute health problems (Broyles et al. 2000). A recent European study suggests that routine follow-up may improve outcomes in children with CP (lower risk of contractures, but no effect on cognitive, motor and speech delays) (Bufteac et al. 2020). Studies from Australia and the US suggest that follow-up facilitates access to early intervention services (Pritchard et al. 2013; Greene and Patra 2016). Greene and Patra (2016), assessed EI referrals of infants born <30 weeks' gestation and/or with a birth weight (BW) <1000 g attending NICU follow-up with cognitive, language and motor assessments at 4, 8 and 20 months' CA. Their results showed that the increased time enrolled in follow-up increased the likelihood of being referred to EI services, with a peak in referrals at one year of CA. Referrals between 12 and 20 months were associated with delayed language development, lower gestational age and higher postmenstrual age at discharge (Greene and Patra 2016).

However, implementing follow-up programmes comes with its challenges; 19% of the infants, who were less likely to have abnormal brain ultrasounds and lung abnormalities and older mothers, did not attend any follow-up appointments (Greene and Patra 2016). Furthermore, the timing of evaluations during follow-up was crucial for appropriate referral to EI services, as too early developmental screening in infants <1000 g BW may not yet detect developmental delay which may manifest later in the most immature infants (Greene and Patra 2016). Another study from the US also reported that non-attendance to follow-up appointments and financing of these programmes were two major challenges, and that further improving the coordination of care could result in improved outcomes in the children (Bockli et al. 2014).

### ***2.3.2 Recommendations and programmes for follow-up and care after very preterm birth***

Until recently, there were no international recommendations for follow-up after VPT birth. Expert groups have previously outlined key components of follow-up programmes, recommendations for the follow-up of specific neonatal complications and local or regional recommendations for follow-up. A group of experts from Australia, New Zealand and the UK developed a framework for follow-up in 2014, outlining the main domains to be assessed,

including general health, growth, feeding, sensory and neurological problems, motor skills, cardiovascular and respiratory health, metabolism, reproductive health, cognitive and language development, pre-academic skills, behaviour, social skills, daily functioning, self-esteem, parents' mental health and parent-child interaction, family social support and impact on siblings (Doyle et al. 2014). However, while also suggesting time points and tools for assessments, the expert group acknowledged that the domains assessed and the methods and tools used will depend on the resources in units providing this follow-up, and that the timing and frequency of assessments will depend on the child's age, health and development (Doyle et al. 2014). Recommendations also exist for specific preterm birth-related pathologies and complications, such as BPD; an expert group on BPD recommended in a recent publication that children with BPD should be followed until adulthood, by multidisciplinary teams including subspecialists such as paediatric cardiologists, ENT specialists, physiotherapists etc. (Duijts et al. 2020).

#### *Follow-up programmes and recommendations in Europe: the SHIPS regions*

National and regional follow-up programmes and recommendations in Europe vary largely in terms of content (timing, number and types of assessments, tools used for the assessments), and duration across countries, regions and even neonatal units and networks. This is illustrated by the follow-up programmes and recommendations in the SHIPS regions.

As part of the SHIPS project's objectives and reporting to the European Commission, information was collected on national and regional follow-up policies and practices in all SHIPS study regions until 2017 and reported in two Deliverables, 3.2 and 4.1 (Johnson et al. 2016; Barros et al. 2018). This information is summarised in Table 1 below, where data has been completed for France and the UK for the most recent recommendations.

In 2017, national or regional follow-up programmes existed in all but four of the SHIPS study countries (Denmark, Portugal, Italy and the UK), where local programmes were in place and limited information was collected. All national and regional programmes involved neonatal units and hospitals and multidisciplinary teams. Follow-up programmes had been established as early as in the 1980's, but recent updates to programmes or guidelines in many countries shows that this continues to be an important policy area. Some countries had no official guidance or policy on follow-up in 2017 (UK and France). Recommendations have since been issued in both countries.

**Table 1** Characteristics of follow-up programmes and recommendations in the SHIPS regions\*

Country: Region	Programme (start date)	Characteristics of programme or recommendation
<b>Belgium:</b> Flanders	National programme (2014)	<p><b>Target:</b></p> <ul style="list-style-type: none"> <li>- GA&lt;31 wks +6 d and/or BW≤1500 g (4 developmental controls)</li> <li>- GA≥31 wks–31 wks +6 d and BW&gt;1500 g (2 developmental controls)</li> </ul> <p><b>Duration:</b> 5.5 y</p> <p><b>Assessments:</b></p> <ul style="list-style-type: none"> <li>- A (3-5 mo): General paediatric evaluation, neurological exam, growth, evaluation of sensory development, parenting and neuro-motor evaluation</li> <li>- B (9-13 mo): Growth evaluation</li> <li>- C (22-25 mo): A + mental examination + prosocial behaviour</li> <li>- D (4.5-5.5 y): C + language, preschool skills/spatial awareness, writing skills</li> </ul> <p><b>Performed by:</b> Neonatologist/neurologist, clinical psychologist, speech therapist, physiotherapist, social worker, in cooperation with paediatrician, social network etc.</p>
<b>Denmark:</b> Eastern region	Local programmes only	<p><b>Target:</b></p> <ul style="list-style-type: none"> <li>- GA&lt;32 wks and BW&lt;1500 g (usually 4 controls at hospital)</li> <li>- GA&lt;32 wks (physiotherapy or ergotherapy follow-up)</li> </ul> <p><b>Duration:</b> 2-5 y depending on hospital</p> <p><b>Assessments:</b> At 3, 5, 12 and 24 mo at most hospitals, if GA&lt;32 wks and BW&lt;1500 g</p> <p><b>Performed by:</b> Physiotherapists. Some are also followed-up by ergotherapists.</p> <p><b>Remarks:</b> Different follow-up programmes in different regions. Some hospitals do not have standardised follow-up programmes. Family practitioner follows up all children at the age of 1, 2, 3, 4 and 5 y. If neurological symptoms or delayed development are discovered, children are referred to a paediatric neurologist.</p>
<b>Estonia:</b> Entire country	National programme (2008)	<p><b>Target:</b> GA&lt;32 wks or BW&lt;1500g or if serious illness</p> <p><b>Duration:</b> 2 y</p> <p><b>Assessments:</b></p> <ul style="list-style-type: none"> <li>- At 2, 4, 6, 9 and 12 mo: Paediatrician at neonatal unit, physiotherapist</li> <li>- At 9 mo only: otoacoustic emissions, brainstem auditory evoked potential</li> <li>- At 12 mo: also a vision test</li> <li>- At 18 mo: physiotherapist assessment</li> <li>- At 24 mo: developmental and speech assessments</li> <li>- According to individual need: Child neurologist, other paediatric subspecialists</li> </ul> <p><b>Performed by:</b> Paediatricians, developmental psychologists, physiotherapists, child neurologist and other paediatric subspecialists</p> <p><b>Remarks:</b> Based on national guideline (2008) for follow-up of high-risk children. No official guideline for follow-up beyond 2 years</p>
<b>France**</b> Burgundy, Ile-de-France and the Northern region	Regional programme Ile-de-France (2014) and local programmes	<p><b>Target:</b> GA&lt;32 wks or GA&lt;37 wks with IUGR or SGA, or if other adverse perinatal outcome such as congenital anomalies or cardiopathies</p> <p><b>Duration:</b> 6 y in Ile-de-France, recommended until 5y</p> <p><b>Assessments:</b> motor, language, social and behavioural development, working memory, learning abilities, hearing, vision and growth assessments at 9,18, 24, 30-36 mo, 4 and 5 y</p> <p><b>Remarks:</b> Based on HAS national guidelines (2020). No clear follow-up policy for preterm births existed in France in 2017. Local or regional follow-up networks were being set up.</p>
<b>Germany:</b> Hessen and Saarland	National programme (2006) and regional programme in lower Saxony (2004)	<p><b>Target:</b></p> <ul style="list-style-type: none"> <li>- BW&lt;1500g (2 years' mandatory follow-up)</li> <li>- Additional voluntary inclusion criteria (e.g.&lt;32 WG) vary across units</li> </ul> <p><b>Duration:</b> national programme 2 y, regional programmes 5-10 y</p> <p><b>Assessments:</b> Organisation decided at unit level. Time points for assessment (e.g. 6, 12, 60 mo) vary across units and are voluntary</p> <p><b>Performed by:</b> Organisation decided at unit level. Most commonly performed in the neonatal unit, the department of neuropaediatrics or the social paediatric centre by paediatricians, developmental psychologists and physiotherapists</p> <p><b>Remarks:</b> Regulation stated by the <i>Gemeinsamer Bundesausschuss</i> Institution (Gemeinsamer Bundesausschuss 2020)</p>
<b>Italy:</b> Emilia-Romagna, Lazio and Marche	Local programmes only	<p><b>Target:</b> <i>not reported</i></p> <p><b>Duration:</b> Until 2, some until 3 years CA (regional difference)</p> <p><b>Assessments:</b> Majority followed in NICU although regional differences: some followed in other hospital unit or secondary care neonatal unit</p> <p><b>Performed by:</b> Majority followed by paediatrician or neonatologist from NICU. Some followed by other paediatrician or neonatologist, clinical/developmental psychologist, physiotherapist or nurse/midwife</p>
<b>The Netherlands:</b>	National programme (Early 1980's,	<p><b>Target:</b></p> <ul style="list-style-type: none"> <li>- GA&lt;30 wks and/or BW&lt;1000g</li> <li>- BW&lt;1500g and &lt;10 percentile</li> </ul>

Central and Eastern region	updated in 2015)	<ul style="list-style-type: none"> <li>- children with severe cerebral pathology, asphyxia/after hypothermia/severe white matter lesions (cPVL/meningitis), parenchymal lesions, cerebellar pathology, basal ganglia lesions or post haemorrhagic ventricular dilatation</li> <li>- children born after top referral care (like extracorporeal membrane oxygenation or laser therapy for twin transfusion syndrome)</li> </ul> <p><b>Duration:</b> 8 y</p> <p><b>Assessments:</b></p> <ul style="list-style-type: none"> <li>- 6 and 12 mo: background data, physical, neurological, motor examination</li> <li>- 2, 5, 8 y of CA: together cover anamnesis, paediatric, neurological, IQ, speech, language, visual-cognitive, motor and behavioural examinations</li> </ul> <p><b>Performed by:</b> Paediatricians, developmental psychologists, speech and physiotherapists</p> <p><b>Remarks:</b> Based on 2015 national guidelines</p>
<b>Poland:</b> Wielkopolska	Regional programme, Wielkopolska (1998)	<p><b>Target:</b> GA&lt;33 wks (included in the Multidisciplinary Health Care Program of Premature Infants until 3 years of age)</p> <p><b>Duration:</b> 2 y (programme in Wielkopolska)</p> <p><b>Assessments:</b> Assessment of postnatal growth, physical examination, laboratory tests, assessment of endocrinology activity, psychomotor development with standardised tests, eye examination and if needed: ENT, cardiology, speech</p> <p>Scheduled visits at:</p> <ul style="list-style-type: none"> <li>- 1<sup>st</sup> year CA: 5 visits (1, 3, 6, 9 and 12 mo)</li> <li>- 2<sup>nd</sup> year CA: 4 visits (compulsory at 18 and 24 mo)</li> <li>- 3<sup>rd</sup> year: 3 visits (according to calendar age)</li> </ul> <p><b>Performed by:</b> Regional Perinatal Centres, including paediatrician, developmental psychologist, physiotherapist, speech therapist and health visitor</p> <p><b>Remarks:</b> Based on guidelines by Polish Neonatal Society (2015)</p>
<b>Portugal:</b> Lisbon and Northern region	Local programmes only	<p><b>Target:</b> VPT-born infants</p> <p><b>Duration:</b> Recommendations up to 8 years</p> <p><b>Assessments:</b> Non-standardised, unit-based, routine follow-up: Hearing, vision, neurological, psychomotor, growth, mental development, gross motor, school performance assessments, with more specific assessments if dysfunctions (feeding, behaviour, autism, IQ, language and dyslexia)</p> <p><b>Performed by:</b></p> <ul style="list-style-type: none"> <li>- Clinicians at unit of hospitalisation (neonatologist, development paediatrician, psychologist, ORL, ophthalmologist, physiotherapist) or</li> <li>- Local hospital/health care centre (GP, specialists according to need, early childhood intervention programmes only for children specially identified and referred)</li> </ul> <p><b>Remarks:</b> Based on national recommendations (not compulsory) of the Neonatology Section of the Portuguese Society of Paediatrics for follow-up of VPT infants (2012)</p>
<b>Sweden:</b> greater Stockholm	National programme (2014)	<p><b>Target:</b></p> <ul style="list-style-type: none"> <li>- High-risk: GA&lt;28 wks or BW<math>\leq</math>3 SD or severe morbidities</li> <li>- Local/unit based follow-up for children born at 28-32 WG not high risk</li> </ul> <p><b>Duration:</b> 5 y</p> <p><b>Assessments:</b> Neurocognitive outcome assessment at 2 and 5,5 years (neurocognitive, development, motor and mental health)</p> <p><b>Performed by:</b> Paediatrician, neonatologist, developmental psychologist and speech therapist</p> <p><b>Remarks:</b> Based on neonatal follow-up program by the National Neonatal Association (2015)</p>
<b>UK**:</b> East Midlands, Northern, and Yorkshire & the Humber regions	Local programmes only	<p><b>Target:</b> GA&lt;30 or GA&lt;37 wks if perinatal risk factors (e.g. brain lesions, asphyxia)</p> <p><b>Duration:</b> 2 y</p> <p><b>Assessments:</b></p> <ul style="list-style-type: none"> <li>-12 mo: one at 3-5 mo and second at 12 mo</li> <li>-24 mo: in-depth assessment (development, motor, attention, emotional, behavioural, vision, hearing, feeding, sleeping, growth)</li> <li>- Additional developmental assessment if GA&lt;28 wks</li> </ul> <p><b>Performed by:</b> Multidisciplinary team</p> <p><b>Remarks:</b> Based on NICE guidelines published after this study (2017)</p>

*\*Table adapted from: Johnson, Draper et al. (2016) Deliverable 4.1: Report on developmental assessment batteries, p. 19 (available upon request); Barros, Saulyte et al. (2018) Deliverable 3.2: Final report on the study of follow-up programmes, accessible at: <https://cordis.europa.eu/project/id/633724/results> (Accessed on 2 October 2020)*

*\*\*Updated in September 2020 due to new recommendations*

### *European standards for follow-up care*

In 2019, the EFCNI published the European standards of care for new-born health, including guidelines for the long-term follow-up of preterm-born infants. The standards were developed in an iterative process, written by topic expert groups, with input from representatives from parent- and patient organisations, and finally voted by a Chair committee who also graded the level of scientific evidence for each standard (EFCNI, Walz, et al. 2018). The multi-disciplinary expert groups involved a total of 220 experts across Europe in psychology and child development, neonatology, developmental neurology, paediatric medicine and research, etc.

According to these standards of care, all infants born <32 weeks of gestation should have coordinated and integrated care, i.e. follow-up with specific assessments, until early school age, starting with hearing screening at one month's age, neuro-motor, speech, cognitive, socio-emotional and mental health screening at two years of age, and school readiness assessments including motor and vision tests before school start (EFCNI, Hadders-Algra, et al. 2018; EFCNI, van Kempen, et al. 2018; EFCNI, Jaekel, et al. 2018). Children who are identified as being at risk of neuro-motor abnormalities or motor delay should be further referred to appropriate specialists for interventions (EFCNI, Hadders-Algra, et al. 2018). Social and peer relationship problems should be annually screened for after school entry (EFCNI, Vaillancourt, et al. 2018) and respiratory problems until adolescence (EFCNI, Lehtonen, et al. 2018). Finally, parents should receive support and mental health screening at least during the first two years after delivery (EFCNI, Houtzager, et al. 2018).

### *Recommendations for follow-up in France (2020)*

The most recent recommendations for follow-up of high-risk children in France were published by the French National Health Authority (Haute Autorité de Santé 2020) in February 2020. In these recommendations, a child is considered at high risk when born <32 weeks' gestation or <37 weeks with IUGR or SGA, or if other adverse perinatal outcomes are detected, such as congenital anomalies, regardless of gestational age. Follow-up is recommended until five years, depending on the results of earlier evaluations.

A child at high risk of neurodevelopmental problems should have their first neurodevelopmental specialist appointment scheduled at the time of neonatal unit discharge. These assessments aim to detect delays in their motor, language, social and behavioural

development, working memory, learning abilities and possible hearing and vision impairments, as well as growth. Depending on the results of these evaluations, screening tests should be done at 9, 18, 24, 30-36 months CA and at 4 and 5 years of age. If there is a strong suspicion of developmental delay, referrals should be made and interventions started within 3 months for children younger than 18 months, and 6 months for children aged 18 months or older.

Recommendations are also made for the coordination across multiple care providers and for the communication with parents, who should be informed about the importance of follow-up, and have clear, comprehensible and complete information on adverse health and developmental outcomes (Haute Autorité de Santé 2020).

#### *Recommendations for follow-up in the UK (2017)*

UK guidelines on follow-up were issued in 2017 for the first time by the National Institute for Care and health Excellence (NICE 2017). These guidelines recommend that enhanced developmental support and surveillance by a multidisciplinary team until two years of CA should be offered to children born before 30 weeks' gestation, or before 37 weeks' gestation if they have other perinatal risk factors such as brain lesions or perinatal asphyxia.

Two assessments are recommended during first year of life (at three to five months and by 12 months) and an in-depth assessment at two years of CA. The assessments include screening for developmental problems and disorders such as motor, attention, emotional and behavioural problems, vision and hearing impairment, feeding and sleeping problems and growth. An additional developmental assessment should be offered at four years of age for children born before 28 weeks' gestation and be advised for children born at later gestational ages.

If any assessments suggest that developmental problems are present, referral should be made to appropriate care providers, and information needs to be given to caregivers, primary health care teams, educational services and social care services where appropriate. Parents should be informed about follow-up at neonatal unit discharge (NICE 2017).

#### *Follow-up programmes worldwide*

The lack of national follow-up programmes and guidelines concerns countries worldwide, with large heterogeneity in local programmes as a consequence. Several studies have reviewed local follow-up programme organisation and, in line with the heterogeneity in follow-up programmes

and recommendations seen in the SHIPS study countries, these studies have shown high levels of heterogeneity as well.

In Australia and New Zealand, all NICUs are responsible for monitoring the health of the infants they treated and are expected to provide paediatric and neurodevelopmental assessments for all infants born <32 weeks' GA. This data is pooled into a national registry by the Australian and New Zealand Neonatal Network (ANZNN), but there are no national guidelines on follow-up (personal communication, Peter Anderson, Professor of Paediatric Neuropsychology, Monash University). A review of local routine follow-up programmes in New Zealand showed that inclusion criteria varied by GA, BW and clinical characteristics, and that follow-up duration remained at the discretion of the clinician (Gledhill, Scott, and de Vries 2018). When no developmental delays had been discovered until two years of age, follow-up was generally discontinued. However, the main reason for inadequate provision of follow-up to VPT-born infants was funding and resources (Gledhill, Scott, and de Vries 2018). The authors suggested that national guidelines and funding are needed for equal follow-up across the country.

Also in the US are neonatal units mandated to follow-up NICU graduates after discharge, however, at least in 2014, there were no standardised guidelines provided for the follow-up of infants born VPT (Bockli et al. 2014). A survey conducted in 2012 showed that variability in follow-up programmes for high-risk children in the US were dependent on the unit's association with academic centres, especially in terms of care providers available (Kuppala et al. 2012). Whereas growth, neurodevelopment and neurological problems were assessed in almost all programmes, around half offered speech assessments, social worker support and behavioural assessments (Kuppala et al. 2012).

In Canada, existing follow-up programmes were reviewed already in 1986, with large variability in follow-up eligibility criteria, assessments and timing of visits. These variations remained fifteen years later, regardless of the recommendations that been published in 1987, in all regions except Quebec, where programme implementation methods differed (Synnes, Lefebvre, and Cake 2006).

A Spanish study showed that 71% of NICUs in the country offered follow-up for VPT-born infants prior to their national recommendations being published (Pallás-Alonso et al. 2019). However, heterogeneity in programme content was high, and although almost half of the units (42%) provided long-term follow-up, none of them fulfilled the follow-up recommendations

that were later published by the Spanish Neonatal Society. The authors of this study concluded that the observed heterogeneity stemmed from a lack of recommendations for specific assessments (Pallás-Alonso et al. 2019).

## **2.4 Post-discharge health care and health care needs**

### *2.4.1 Health care service use*

Health care service use is an important outcome of VPT birth. It reflects how well the child is doing, and how children and their parents perceive their health and development (Forrest et al. 2004), even in the absence of diagnosis and designated treatments. For children with good access to screening and diagnostic services, the range and the types of care received provide an indication of the range of complications that children face after preterm birth. Furthermore, in populations with health care needs and low service use, the absence of health care contacts may signal unmet health care needs.

#### *Outpatient care*

There are studies showing that VPT birth may result in a higher use of outpatient care in early childhood, as well as specialist care and therapies later in childhood compared to children born at term (Saigal and Doyle 2008). Economic studies have shown higher overall health-care related costs (Petrou, Yiu, and Kwon 2019) and higher outpatient costs (Johnston et al. 2014) incurred from preterm birth after NICU discharge, especially during the first years of life. Few studies address GP or paediatrician visits specifically, but some have shown inconclusive results, with similar rates of GP consultations in children born VPT compared to term (Gray et al. 2006). Most studies focus on hospitalisations, early intervention services as well as sub-specialist outpatient care.

Results from the EPIPAGE 1 population-based cohort in seven regions of France showed a higher use of specialised health care services in children born VPT compared to the term control group at both five (Larroque et al. 2008) and eight years of age (Larroque et al. 2011). At eight years, for instance, 55% of VPT born children received specialist care compared to 38% in the control group (Larroque et al. 2011). Type of services also differed between term controls and VPT-born, who represented the majority of users in physiotherapy (8% vs <1%), occupational and psychomotor therapies (12% vs 3%) as well as eye specialist services (15% vs 5%)



(Larroque et al. 2011). The EPIPAGE 1 study included children born in 1997 and we were not able to find more recent population-based studies providing a comprehensive description of specialist care in Europe.

A single-centre cohort study from the US including children born before 30 weeks of GA (or very low birth weight) in 2008-2011 showed that by the age of two years, 29% of the children were followed by a medical paediatric specialist (excluding therapies included in EI programmes such as developmental, speech and physical therapy) (Patra and Greene 2018). As all children were enrolled in NICU follow-up and receiving early intervention services when required, the authors concluded that the paediatric specialist service use was high (Patra and Greene 2018). An earlier US study assessing the use of a larger range of outpatient services (social workers, visiting nurse, occupational therapy, physiotherapy speech therapy and neurodevelopmental and behavioural therapies) in children born <28 weeks' gestation found that 55% of the children had used more than three of these services before the age of 22 months CA and 37% reported needing services that had not been received (Hintz et al. 2008).

#### *Emergency room services*

The risk of needing emergency room (ER) services within 90 days of discharge from the neonatal unit increases with decreasing gestational age and in the presence of BPD and multiple birth (Vohr et al. 2018). Between 19-21% of the infants born <37 weeks' gestation in a US cohort used ER services within the first 90 days of discharge, mainly due to respiratory infections (Vohr et al. 2018). The US study by Patra and Greene (2018), found that 54% of the sample (born preterm) had visited the ER by two years of age (Patra and Greene 2018). One population-based study from England reported that 29% of the general paediatric population under 5 years of age had visited an ER at least once between 2011 and 2012 (Cecil et al. 2016). Our literature review did not identify any studies from Europe on use of ER services among children born VPT.

#### *Hospitalisations*

More studies focus on hospitalisations, which are considered less desirable care use outcomes for NICU graduates (Kuo et al. 2017), and for which data is more often available from routine data sources. Results from the EPICE cohort in Italy revealed hospitalisation rates of 38.2% (at least one hospital admission) between neonatal unit discharge and two years of CA, with

hospitalisation rates increasing with decreasing gestational age, mainly due to the presence of prematurity-related morbidities (Meregaglia et al. 2020). A French study found hospitalisation rates (minimum one hospitalisation) of 22% in the first year of life in children born <32 completed weeks' gestation that were included in a follow-up network for high-risk children (Laugier et al. 2017). The main reasons for hospitalisation were respiratory illness (44%), infections (17%), surgery (15%) and digestive conditions (14%) and almost 19% of all hospitalisations were emergencies (Laugier et al. 2017). In Norway, one study reported that 20% of VPT-born children have been hospitalised at least once between one and four years of age, and 13% between five and nine years of age (Klitkou et al. 2017). The VPT children had a IRR of 3.2 for being hospitalised compared to the general population (or 227 vs 72 hospitalisations per 1000) until four years of age. This difference was smaller in the five to nine-year olds but was still statistically significant (Klitkou et al. 2017).

Non-European studies show similar or higher rates; a US study (Patra and Greene 2018) on infants born before 30 weeks of GA found that 35% had been hospitalised by two years of age, and an Australian study on singletons showed higher hospitalisation rates across all gestational ages compared to term births (44% for children born between 28-31 weeks and 54% <28 weeks) during the first year of life (Slimings et al. 2014).

#### ***2.4.2 Complex health care needs***

Health care outcomes in the high-risk paediatric population are also conceptualised in terms of complex care needs, or medical complexity. Children who are at an increased risk of chronic health or developmental, emotional or behavioural conditions, such as children born VPT, are considered to have special health care needs as they are more likely to require more health services than children without special health need (McPherson et al. 1998). In the US, approximately 19% of all children aged 0 to 17 years have special care needs, and 13% have elevated special care needs, i.e. needing specialised services in addition to medications, or has a functional limitation regardless of care received (Child and Adolescent Health Measurement Initiative). There are few assessments on the prevalence of children suffering from complex care needs due to the heterogeneity in definitions (Brenner, O'Shea, Larkin, et al. 2018).

### *Definition of complex care needs*

Children with complex care needs have multiple clinical and/or social needs that require access to multidimensional health care services or social support, sometimes without having any known, unifying diagnosis (Brenner, Kidston, et al. 2018). The definition of complex health care needs varies in the literature, and includes children with a range of chronic conditions (intellectual disabilities, rare diseases, cerebral palsy, heart failure, technological dependence etc.) in various settings (school, community, home etc.) and from diverse family backgrounds (in terms of culture, ethnicity, employment status etc.) (Brenner, Kidston, et al. 2018). Complex health care needs can also be defined partly by health care service use (Cohen et al. 2011). Bramlett et al. define children with complex care needs as children with chronic functional limitations, or chronic conditions that require prescription medication or specialised therapies such as physiotherapy or speech therapy, or increased medical, mental health or educational services or developmental, emotional or behavioural counselling/treatment (Bramlett et al. 2009). Bramlett et al. consider care as complex when a child needs three or more doctor's visits for sick care, has two or more ER visits or any specialist visit during the past year, and becomes more complex with increasing amount of medical and ER visits and increasing amount of specialised services or devices needed (Bramlett et al. 2009). Kuo et al. define children as having medical complexity when, in addition to special care needs, children need care from providers across different domains, and have seen at least two medical specialists in the previous year (Kuo et al. 2014). As presented in chapter 7, we used this body of literature to guide the selection of criteria to identify children with elevated health service use at five years in our cohort.

### *Health care*

While this group of children with complex care needs are heterogeneous, they have a common elevated risk of poor health and development which impacts on their families (Bramlett et al. 2009) and high levels of unmet health care needs (Kuo et al. 2017; Bramlett et al. 2009). Complex care requires better care management to avoid developmental risks, family stress, and emergency department and hospital use (Kuo et al. 2017), whereas poor management may result in failure to meet health needs, worsening health outcomes, increased reliance on acute health care services and an additional stress on health care systems (Brenner, Kidston, et al. 2018). Recent research from a European multi-national project found that European countries are

poorly organised to respond to the health care needs in this population, with lacking policy for care coordination and care planning after discharge (Brenner, O'Shea, Larkin, et al. 2018).

## **2.5 Equity in health and health care**

### ***2.5.1 Sociodemographic risk factors in health and developmental outcomes***

Social inequalities in health are widely acknowledged in the general population, but also in early childhood, at the neighbourhood, household and national levels (Pillas et al. 2014). Different studies across Europe consistently find associations between poor health and developmental outcomes and low family income and educational level, job strain, no house ownership and poverty, and parental unemployment (Pillas et al. 2014).

#### *Preterm birth*

Very preterm birth disproportionately affects families with social risk factors (Carter and Msall 2017). The risk of VPT delivery is higher in expecting mothers in socially vulnerable populations (Blumenshine et al. 2010; Kramer et al. 2001), and in areas with higher rates of social deprivation (Bonet et al. 2013; Smith et al. 2009; Deguen et al. 2018). There are many hypotheses about the mechanisms that contribute to higher risks of preterm birth in socially vulnerable populations, including the impact of unhealthy behaviours, such as smoking, strenuous or otherwise deleterious working conditions, the poor accessibility or quality of prenatal care, stress and psychosocial factors, as well as genetic factors (Kramer et al. 2001). However, these mechanisms remain poorly understood with limited robust empirical evidence about their relative impacts (Kramer et al. 2009).

#### *Health and development*

Whereas there are few social disparities in the short-term mortality and morbidity in children born VPT (Bonet et al. 2013), there is a growing literature on the elevated risks of cognitive delays in early and later childhood in children with social risk. Preterm-born children in families with social risk factors based on parental educational level and/or occupation, have shown to have higher risk of cognitive deficiencies (Beaino et al. 2011; Dall'oglio et al. 2010) and delayed language development in early childhood (Wild et al. 2013; Sentenac, Johnson, et al. 2020), compared to children without social risk. Similarly, family social risk factors, including lower maternal education and unemployment, low family income, ethnic minority (or race in the US),

foreign language spoken at home and teenage parenthood, have been associated with less school readiness and poor academic skills in late preterm and term-born populations (Carter and Msall 2017).

### ***2.5.2 Equity in follow-up and health care***

Although neonatal care is considered equitable (Smith et al. 2009), research suggests that use of post-discharge services may be lower in socially disadvantaged families despite a worse long-term prognosis indicating greater need. Research mostly focuses on social disparities in the use of EI programmes, and to date, few studies have assessed whether socioeconomic characteristics are related to routine follow-up.

#### *Follow-up and EI programmes*

Research on post-discharge follow-up attendance show mixed results; most studies on follow-up include participants who are part of research studies, where the parents' motivation to participate and the resources to keep participants in follow-up may be very different from routine follow-up for NICU graduates (Orton et al. 2015). Callanan, Doyle et al. (2001) found a 94% participation rate in neurodevelopmental follow-up at five years of age in a research study on extremely preterm-born children, but with 25% of the children requiring more efforts to keep in follow-up, with cancelled appointments or reluctance from parents to attend, which was related to lower maternal educational level and single-parenthood, as well as multiple birth (Callanan et al. 2001). Similarly, a study from Australia showed 98% participation rates in neuro-developmental follow-up at two years of age in children born extremely preterm who were part of clinical research studies, but only 32% in children who were not enrolled in research (Orton et al. 2015). The main reason for non-attendance in non-research settings was loss to contact with families, and associations with sociodemographic factors were weak (Callanan et al. 2001). A US study showed an attendance rate of 68% for scheduled routine follow-up appointments after NICU discharge, where non-attendance was associated with having a boy or multiple gestation, living far from the hospital, and maternal drug use, whereas child morbidity was associated with higher compliance (Harmon et al. 2013). This shows the importance of studying routine follow-up unrelated to research studies and in different setting to assess challenges and access to follow-up and health services.

Socioeconomic factors, such as family income (Carter and Msall 2017) low parental educational level and ethnic minority (Barfield et al. 2008) or a combination (e.g. single-parenthood, low maternal education, low family income or ethnic minority) (Pritchard et al. 2013; Roberts et al. 2008) have been associated with less access to EI services in high-risk infants as well as lower use in children born VPT until two years of age (Roberts et al. 2008). The type of services delivered (e.g. educational vs. specialised therapies) within EI programmes may also be influenced by socioeconomic factors in addition to care needs, but interpretation of these results are complicated as they may indicate that care has been adapted to children with different needs due to social vulnerability, or, that there are inequalities in care provision (Raspa, Hebbeler et al. 2010).

### *Specialist services*

Fewer studies address social inequalities in specialist service use outside EI programmes in children born VPT. Social inequalities in specialised health care service use have been documented in adults in Europe (van Doorslaer, Koolman, and Jones 2004; Stirbu et al. 2011) as well as in high-risk children. Stirbu et al. found in a study in nine European countries that adults with lower educational level are less likely to see specialists in nearly all (eight out of nine) countries than those with higher educational level, even when care needs were higher, e.g. when living with chronic disease (Stirbu et al. 2011). In a recent study, Woolfenden et al investigated the impact of social disadvantage, determined by parental educational level, occupation and single-parenthood, on health service use, including specialists, in preschool-aged children with developmental vulnerability, i.e. physical, social or behavioural difficulties, health care needs or schooling difficulties. They concluded that children who have developmental vulnerability with an additional social disadvantage are less likely to use health services compared to children without social disadvantage (Woolfenden et al. 2020).

### *Emergency room visits and hospitalisations*

Higher use of certain services has also been reported in socially vulnerable children. For instance, higher risk of ER visits in newborn within 90 days of discharge have been associated with maternal mental health problems (Vohr et al. 2018), non-English speaking families (Vohr et al. 2018; Abdulla et al. 2020) and immigrant families (Abdulla et al. 2020) in the US. Parental immigration status has also been associated with higher re-hospitalisation rates and longer hospital stay in the US (Abdulla et al. 2020). Some of the hypotheses behind these differences

in the US include communication issues in immigrant families who do not speak the native language as well as increased poverty in immigrant families (Abdulla et al. 2020). Lower maternal educational level and occupation index have been associated with higher risk of rehospitalisation until two years of CA in children from the EPICE cohort in Italy (Meregaglia et al. 2020). The same characteristics were associated with increased medical and health care costs, mainly driven by the hospital admissions (Meregaglia et al. 2020). In a French study, neighbourhood-level social deprivation was associated with an increased risk of rehospitalisation in the first year of life in children born VPT; furthermore, children from the most deprived areas had an additional risk of multiple rehospitalisation as well as hospitalisation due to emergency (Laugier et al. 2017). These disparities existed although France has universal health care coverage and the children were included in routine follow-up for high-risk children with regular assessments throughout early childhood (Laugier et al. 2017).

#### *Origins of inequitable health care*

Studies of health care organisation and supply provide additional insight into mechanisms behind unequal care access, with shortcomings in referrals to EI services via care providers (Barfield et al. 2008) and higher hospitalisation rates in populations living in deprived areas where access to other, preventive health care services is restricted (Laugier et al. 2017). These are examples of the inverse care law, i.e. the inverse relationship with elevated care needs and quality care availability in more deprived populations, that was first described by Tudor Hart in 1971 (Hart 1971). Inequities in care were argued to arise from, and to be remedied with health care policy as it operates through restricted care provision in deprived areas, to where it is harder to recruit health care professionals, and where general practitioners have more patients but less hospital support, and more pressure but less resources (Hart 1971).

Qualitative studies have given more in-depth perspectives on the challenges faced by families with social disadvantage that may contribute to the unequal use of follow-up and health care services. Parents with children enrolled in neonatal follow-up programmes have expressed difficulties with attending appointments due to practical factors related to personal resources and social support, such as being a single parent, having long distances to health services and relying on public transport, or having multiple jobs or inflexible working hours (Ballantyne et al. 2015). Poorer health literacy in families with social risk have also been suggested (Pritchard et al. 2013).

## Chapter 3: Methods

### 3.1 Introduction

The aim of chapter 3 is to first give a short background on the EPICE cohort, the five-year follow-up project SHIPS, and how data was collected and harmonised. Secondly, this chapter provides an overview of the statistical and qualitative methods used for our analyses and some of the analytical challenges we confronted. A more detailed presentation of the analytic strategies and methods is provided in each article.

### 3.2 Data source and study population

All data analysed for this thesis come from the population-based Effective Perinatal Intensive Care in Europe (EPICE) cohort of births before 32 weeks' gestation, and its follow-up project Screening to improve Health In very Preterm infantS in Europe (SHIPS) (Zeitlin et al. 2020). The main aims of the SHIPS project were to evaluate preterm birth-related follow-up screening and prevention programmes on health, care and quality of life for VPT infants and their families as well as on coverage, ability to meet needs, health equity and costs at the population-level. More detail can be found at [www.epiceproject.eu](http://www.epiceproject.eu).

The cohort includes 19 regions in 11 European countries (Figure 1). The regions were selected for the study based on their geographic and organisational diversity, as well as resources for implementing the study protocol. The cohort included all still and live births and terminations of pregnancy (TOP) between 22 weeks and 0 days' and 31 weeks and 6 days' gestation from all maternity units in the regions over a twelve-month period (from April 2011 to September 2012), except for in France, where inclusions were done over a six-month period. The cohort was assessed at baseline, at two years of CA (EPICE project) and at five years of chronological age (SHIPS project). At baseline, the cohort included 2429 stillbirths and TOP, and 7900 live births before 32 weeks' gestation (Table 2). Of the live-born infants, 6792 (86.0%) survived to discharge home from the neonatal unit. At two years' CA, 4426 (65.5%) children participated in the follow-up, and 3687 (54.5%) participated in the five-year follow-up.



**Figure 1.** Map of countries and regions in the EPICE project



Source: *EPICE map* (EPICE project 2015)

Available at <https://www.epiceproject.eu/en/region.html> [Accessed on 3 September 2020]

**Table 2** Study population and participation rates by country

Regions in countries	All births	Live births	Survived to discharge (% of livebirths)	Death before 2y	Participated at 2 y (% of eligible <sup>a</sup> )	Death from 2 to 5y	Participated at 5y (% of eligible <sup>a</sup> )	Breakdown of participation			Participated at 2 and 5y (% of eligible)
								Questionnaire + NDA <sup>b</sup>	Questionnaire only	NDA <sup>b</sup> only	
Belgium	990	752	653 (86.8)	0	308 (47.2)	0	280 (42.9)	57	216	7	189 (28.9)
Denmark	441	351	286 (81.5)	0	180 (62.9)	0	152 (53.1)	42	110	0	122 (42.7)
Estonia	179	153	141 (92.2)	2	138 (99.3)	0	134 (96.4)	35	98	1	134 (96.4)
France	2047	1307	1109 (84.9)	6	986 (89.4)	0	779 (70.6)	168	608	3	745 (67.5)
Germany	855	758	662 (87.3)	5	435 (66.2)	1	280 (42.7)	63	215	2	237 (36.1)
Italy	1399	1134	975 (86.0)	7	732 (75.6)	0	693 (71.6)	140	552	1	586 (60.5)
Netherlands	550	393	330 (84.0)	0	229 (69.4)	0	155 (47.0)	65	81	9	132 (40.0)
Poland	400	316	250 (79.1)	1	199 (79.9)	0	189 (75.9)	37	152	0	175 (70.3)
Portugal	974	724	607 (83.8)	2	408 (67.4)	0	433 (71.6)	106	326	1	359 (59.3)
Sweden	308	267	241 (90.3)	1	165 (68.8)	0	144 (60.0)	32	110	2	123 (51.3)
UK	2186	1745	1538 (88.1)	7	646 (42.2)	1	448 (29.3)	105	317	26	336 (22.0)
Total	10329	7900	6792 (86.0)	31	4426 (65.5)	2	3687 (54.5)	850	2785	52	3138 (46.4)

<sup>a</sup>Survived to discharge deducting death before follow-up

<sup>b</sup>Neurodevelopmental Assessment (performed on a subsample of all children in the cohort born <28 weeks' gestation)

### ***3.2.1 Consortium***

The SHIPS consortium consists of thirteen European partners, including one principal investigator and coordinators, clinicians and researchers in each country, qualitative researchers, a health economics team as well as a parent organisation, the European Foundation for the Care of Newborn Infants (EFCNI), constituting the SHIPS research group. Both the EPICE and SHIPS projects were coordinated by a group led by Jennifer Zeitlin in the EPOPé team (where I was project manager) at the French National Institute of Health and Medical Research (INSERM UMR1153).

Working groups were created within the SHIPS research group on key research areas, including a group for follow-up and health care-related research which included eight researchers from France, Portugal and the UK (including health economists), with monthly meetings for feedback and discussions on definitions and analyses related to this PhD project. Results were also presented and discussed at biannual meetings for the SHIPS consortium, attended by 40-60 consortium researchers and invited guests, as well as the annual EFCNI Parent Organisations' meetings, attended by parent organisation representatives and parents of preterm infants. A closer collaboration was also established with the ISPUP team in Porto, Portugal, with annual research visits for work on data harmonisation and health care classifications. The EPICE cohort is now part of the Research on European Children and Adults born Preterm (RECAP) project that aims to bring together VPT and low birth weight cohorts in Europe in a federated database to improve research on preterm birth. The RECAP Early Career Research group meets two to three times per year and provides an additional multi-disciplinary environment to share knowledge and discuss analyses and results. Finally, the EPOPé team at INSERM has weekly research seminars where ongoing research, including results for this thesis, is presented regularly for the researchers, clinicians and statisticians in the unit.

### ***3.2.2 Consent, funding and permissions***

Consent was obtained from all mothers for being part of the EPICE cohort and follow-up and for the collection of both perinatal and follow-up data. Consent was also sought at the time of follow-up at 5 years for participating in the SHIPS project, according to local ethics authorisations. All regions obtained ethics approvals from appropriate local committees according to national legislations before the collection of any data. Both the EPICE and SHIPS European studies were approved by the French Advisory Committee on Use of Health Data in

Medical Research (CCTIRS) and the French National Commission for Data Protection and Liberties (CNIL). Both projects were funded by the European Commission; the 7<sup>th</sup> Framework programme (EPICE) and the H2020 innovation and research programme (SHIPS) respectively, under grant agreements No 259882 (EPICE) and 633724 (SHIPS).

### 3.3 Data

Perinatal data were abstracted from obstetric and neonatal records by medical staff or trained investigators and parents filled in questionnaires including questions on their child's development, health, follow-up and health care services use when their children were two years of CA (paper) and at five years of age (paper or online). The questionnaires were first developed in English, then translated and adapted to each study language, and finally back-translated to English. Variables collected at each time point are detailed in Table 3. Information on health care service use was collected using the following standardised question:

Two-year questionnaire:

***Has your child received care from any of the following since they were first discharged home from the neonatal unit? (Yes/No, number of times)***

Five-year questionnaire:

***How many times has your child seen these professionals or used these services over the last year? This includes appointments both at the health care office and at home. (Number of times)***

The question was followed by a list of proposed health care providers, adapted to local organisation of care for the paediatric population. The parents ticked each of the providers the child had seen and/or provided the number of times the service had been used. Any additional use of services could be reported as free-text response. Data from free-text responses at two years were used to complete the list of services when developing the five-year questionnaire. For full list of services in each country, see Appendices B2, D1 and E1.

In the two-year questionnaire, the proposed services included the options *Follow-up network for children born preterm* and/or *Follow-up in neonatal unit where child was hospitalised after birth* and *In the hospital as in-patient*. In the five-year questionnaire, the use of routine follow-up programmes and hospitalisations were asked in two separate questions for more detail:

*Does your child have routine check-ups for children who were born prematurely [optional description of regional service]? (No, never had such check-ups, No, not anymore (please specify age at last check-up), Yes, still has check-ups (at neonatal unit where he or she was born, at other place or health care professional...))*

*Has your child had to stay in hospital overnight over the last year? If yes, please give information below for each time your child stayed in hospital (Type of ward, Number of nights)*

**Table 3** Principal data used in the analyses, collected as part of the EPICE and SHIPS studies

	<b>Perinatal data (EPICE)</b> <i>Obstetric and neonatal records</i>	<b>Two years (EPICE)</b> <i>Parent-report questionnaire</i>	<b>Five years (SHIPS)</b> <i>Parent-report questionnaires</i>
<b><i>Pregnancy and perinatal</i></b>			
GA in completed weeks' gestation	X		
Child sex	X		
Birth weight	X		
Multiplicity (singleton, twin, triplet or quadruplet)	X		
Intraventricular haemorrhage	X		
Cystic periventricular leukomalacia	X		
Retinopathy of prematurity	X		
Necrotising enterocolitis	X		
Congenital anomaly	X		
Supplemental oxygen or artificial ventilation at 36 weeks' postmenstrual age	X		
<b><i>Child health and development</i></b>			
Asthma diagnosis			X
Parent-rated child health (poor, fair, good, excellent)			X
Parent-rated child development (very delayed, delayed, average, in advance)			X
Epilepsy diagnosis			X
Autism diagnosis			X
Vision impairment		X	X
Hearing impairment		X	X
Motor impairment		X	X
Cerebral palsy diagnosis		X	X
<b><i>Health care service use</i></b>			
Health care services (service and number of contacts)		X (since discharge)	X (past year)
Overnight hospitalisations		X	X
Use of follow-up services		X (since discharge)	X (since discharge)
Parents' rating of health care since discharge (poor, fair, good, excellent)			X
Parents' suggestions for improving care for children born very preterm (freetext)			X
<b><i>Sociodemographic</i></b>			
Mother's age at delivery	X		
Parity at delivery	X		
Mother's highest attained educational level		X	X
Mother's and partners occupational status		X	X
Mother's country of birth	X	X	X
Family situation/marital status		X	X

In the five-year questionnaires, parents were also asked to rate the preterm-related care their child had received since discharge from the neonatal unit (four-point scale from poor to excellent) and give free-text suggestions on how care can be improved (for more detail, see chapter 5).

### **3.4 Harmonising health care data**

#### *Standardising the data collection*

Although standardised, pretested questionnaires were used to collect data on follow-up and health care service use, the data had to be harmonised before performing any comparative analyses. When developing the questionnaire, health service definitions were adapted to the different health care systems and the paediatric services offered in each of the study countries. For instance, certain services, such as respiratory physiotherapy and osteopathy, are used in the paediatric population in some countries (in this case, France) but rarely in others. Furthermore, not all services are relevant for the age group in all countries. For instance, school nurse visits are only relevant in countries where children start school before six years of age, and was therefore not included in the five-year questionnaires for instance in Sweden, and was replaced by nursery health professional in Estonia. As a result, the pre-specified list of health services was slightly different across countries, adding complexity to cross-country comparisons.

#### *Validations from country representatives*

To assess differences and avoid misclassifications, translations and back-translations of each service proposed in the questionnaires were compared across countries, verifying that each service was appropriately classified and comparable (e.g. that motor development specialist in Estonia, physical therapist in Poland and psychomotor therapist in France correspond to the classification “Physiotherapist or motor development therapist”). This was particularly important for free-text answers that were translated, assessed and recoded into existing service classifications or new services after discussion with clinical experts and country representatives. These discussions were key, as free-text services sometimes referred to country-specific programmes or specialised clinics, such as the Centre for Developmental Disabilities in Belgium (recoded as multidisciplinary services) or country-specific services such as developmental paediatrician in Portugal (recoded as neurologist). Further validations were required for number of visits that were sometimes very high (e.g. 300 visits), frequently

reported in the free-text fields (e.g. “twice per week for three months”), and sometimes referred to scheduled visits in local programmes (e.g. “all scheduled U-exam visits” in Germany). Representatives from each country validated the correspondence between services within each classification and references to local programmes (see Appendices B2, D1 and E1 for comparisons).

### *Grouping variables*

Presenting and discussing data with representatives from each region was crucial for harmonisation, but also for understanding the data when comparing care across countries with different health care systems as well as for creating meaningful groupings of services for the analyses. Especially paediatric primary care differs across countries, between paediatrician-based, family practitioner or GP based, and mixed systems (van Esso et al. 2010), and is therefore likely to result in largely different rates for these services depending on the country. Other organisational differences were reflected in our data, such as the use of ER services, that were significantly higher in Portugal compared to other countries; emergency departments in Portugal commonly have on-call primary caregivers available for non-emergency consultations (personal communication at SHIPS meeting, Portugal, January 2020). Grouping together ER, GP, paediatrician and nurse consultations was therefore one solution for having comparable rates of outpatient primary-caregiver and emergency visits.

### **3.5 Analysis strategy: key points**

We confronted several common analytical challenges during the data analyses. These included the hierarchical structure of the data creating intra-cluster correlation, differences in case-mix between countries, and bias related to loss to follow-up in the cohort. These issues were approached with slightly different methods in our publications, as outlined below and described in detail in each article. Finally, while the SHIPS study was not a qualitative study, we applied qualitative methods to analyse the numerous free-text responses provided by parents to open ended questions in the five-year questionnaire. These methods were implemented with the help of a qualitative researcher. As these are described in detail in chapter 5, we provide only a brief summary of these methods at the end of this chapter.

### ***3.5.1 Hierarchical structure of the data***

The data analysed in this project has a hierarchical structure; it contains a higher than average proportion of twins, triplets and quadruplets, i.e. children clustered within mothers, and children clustered within neonatal units, which, in turn, are clustered within regions and countries. Siblings share primarily the same family characteristics and living environment, but may also be similar in terms of health or other unmeasured factors. Infants born in the same neonatal units may have been exposed to the same care policy and practice, and children living in the same regions and countries may be exposed to the same socioeconomic context, follow-up network and health care system and other unmeasured societal factors, and are therefore not truly independent.

This hierarchical structure with intra-cluster correlations violates the assumptions of independent observations in statistical models, requiring methods to relax these assumptions. Independence of observations is a commonly violated requisite, especially in health policy research where subjects are clustered in areas sharing the same policies and other environmental factors (French and Stuart 2020). If data is cluster-correlated, there will typically be an underestimation of the true variance and an inflation of Type I errors (Williams 2000), i.e. a risk of obtaining false associations, if this clustering is not taken into account. Several methods can be used to take into account this intra-group correlation, including stratification, robust variance estimators and multilevel modelling.

#### ***Multilevel modelling***

Multilevel modelling is a generally accepted method to remedy the issue of hierarchical samples in multivariate models (Maas and Hox 2004), and is commonly used to both take into account and study the effects of hierarchies in data (French and Stuart 2020), as they allow to quantify variance in outcome explained by variance *within* clusters as well as *between* them, or in other words, to measure the contextual influence on an outcome (Merlo et al. 2005). A single-level model (or fixed-effects model), would neglect the fact that observations are grouped (Merlo et al. 2005), violating the assumption of independent and identically distributed errors in fixed-effects models, which may bias standard errors and result in falsely statistically significant results (Maas and Hox 2004).



However, there are multiple methodological issues with multilevel modelling, and there has been an on-going debate within the EPICE/SHIPS cohort about the best way to model between country-heterogeneity. The main concerns include not meeting the underlying assumptions of the multilevel models which may bias the results. Multilevel models based on maximum-likelihood estimation methods 1) assume that the number of clusters are large, 2) require that the variance of the random effects are normally distributed for accurate tests of significance at the second level (Maas and Hox 2004) and 3) and that clusters are selected randomly.

The first issue with meeting model assumptions is that our data contains a small number of clusters (11 countries). According to Maas and Hox (2004), around ten clusters are acceptable if only studying fixed effects, whereas a minimum of 30 clusters has been suggested for studying contextual effects (Maas and Hox 2004). Our small number of clusters also makes it difficult to assess the distribution of variance to assess whether the normality assumption is met. Furthermore, the selection of countries for the study was not random, but based on geographic location and resources for participating in the study. This selection violates the assumption of exchangeability of residuals, i.e. that any other country in our sampling population of European countries could have replaced any of the countries in the cohort (Snijders and Bosker 1999). The biases resulting from small numbers of clusters will have a minimal effect on the first level regression coefficients or standard errors, but will bias the second-level variance components and their standard errors, complicating the assessment of contextual effects (Maas and Hox 2004). In general, when our focus was on assessing differences between countries, we used country-stratified analyses (chapter 4) or a country fixed-effects approach (chapter 5 and 6), in line with other analyses in the SHIPS cohort (Draper et al. 2017), while adjusting for intra-cluster correlation using sandwich estimators (see below). When the focus was on the pooled cohort or the effects of a second-level variable (chapter 7), we opted for multi-level models with second-level clustering for countries, which provided more accurate standard errors. As illustrated in the table below (Table 4) using data from the study of parental ratings, the choice of model has a minor effect on the coefficients of interest.

### *Robust estimators of variance*

It is possible to correct for non-independence of standard errors without using hierarchical modelling. Whereas stratification simply breaks up the clusters, a cluster-robust variance estimator, also called a clustered “sandwich” estimator, will relax the assumption of non-independent observations within clusters, although it retains the assumption of independence

between clusters (Stata Press 2013b). Calculation of robust variance estimators is a commonly used method in health policy research (French and Stuart 2020). Further, the Huber-White, or conventional robust variance estimator, is required for certain models, to relax model assumptions (Stata Press 2013b). This is the case for obtaining Risk Ratios for dichotomous outcomes when using generalised linear regression models with Poisson distributions and a log link; the Huber-White estimator will relax the assumption that the data must have a Poisson distribution (Cummings 2009; Zou 2004). When hierarchical models were not used in our study, sandwich estimators were used to correct standard errors for intra-cluster correlations between countries and multiple pairs.

**Table 4** Risk ratios of poor or fair ratings by sociodemographic characteristics and child health and development with (A) country as fixed effect, and (B) country as random effect

RR for poor and fair ratings by socio-demographic characteristics, perinatal risk, developmental and neurosensory difficulties	A) Country as fixed effect		B) Country as random effect	
	<sup>a</sup> RR	[95% CI]	<sup>a</sup> RR	[95% CI]
Mother's educational level (ref. lower)				
Intermediate	1.21	[0.82-1.79]	1.21	[0.87-1.69]
Higher	1.49	[1.01-2.20]	1.50	[1.15-1.97]
Mother's country of birth (ref. native)				
Born elsewhere in Europe	0.40	[0.18-0.90]	0.40	[0.23-0.71]
Born outside Europe	0.82	[0.53-1.25]	0.80	[0.66-0.97]
Single parent or other (ref. living with partner)	0.88	[0.58-1.34]	0.87	[0.59-1.28]
Perinatal risk (ref. lower)				
Moderate	0.97	[0.75-1.25]	0.97	[0.72-1.32]
Higher	1.09	[0.82-1.46]	1.10	[0.74-1.64]
Cerebral palsy	2.08	[1.44-3.00]	2.10	[1.55-2.86]
Epilepsy	1.92	[1.07-3.46]	1.90	[1.18-3.04]
Autism	1.37	[0.76-2.46]	1.35	[0.87-2.10]
Moderate/severe vision or hearing problem	1.65	[1.01-2.69]	1.66	[0.77-3.62]
Country	<i>Not shown</i>		<i>Not available</i>	

*Risk ratios are derived from multilevel generalised linear regression models using inverse probability weights and accounting for correlation between siblings*

### 3.5.2 Differences in case-mix

In this project, we estimate outcome measures, such as parents' satisfaction with care, and use of routine follow-up services, across eleven study countries. We also assess outcomes in populations based on social characteristics. To have estimates comparable across countries and social groupings, it is necessary to adjust for differences in case-mix, i.e. in underlying population characteristics across countries. This can be done by stratification, standardisation

and multivariate analysis adjusting for population characteristics and thereafter predicting estimates of the outcome.

In chapter 4, we compared the use of specialist services in VPT-born children across social groups (lower and higher maternal educational level, and native and foreign-born mothers) in each of the study countries. All analyses were stratified by country, making sample sizes smaller; therefore, we created a composite variable summarising perinatal risk factors, subsequently used in other EPICE studies (Sentenac, Johnson, et al. 2020), that we used for adjusting for underlying risk profiles with direct standardisation in STATA. This method applies the distribution of characteristics of the overall sample (or the weighted average) to each strata (Stata Press 2013a). However, standardisation is not optimal when adjusting for several covariates (Muller and MacLehose 2014).

In chapter 4, we also assessed the mean number of specialist services seen for social groups in each country, using the command for predicted margins in STATA (Williams 2012). Margins are statistics calculated after regression models where some covariates are fixed at certain values, for example the mean (Williams 2012). Using this method, we predicted the mean number of specialists seen, after regression models, holding perinatal risk constant at the mean across social groups, i.e. as if all children had the same (mean) perinatal characteristics across social groups. Thus, we can compare if a child with “average” perinatal risk and a native born mother sees the same amount of specialists as a child with “average” perinatal risk and a foreign-born mother. In chapter 6, we obtained proportions of post-discharge follow-up by country by marginal standardisation. This time, taking into account differences in several perinatal and social characteristics simultaneously, we predicted the proportions of follow-up as if the children in each country were drawn from the same overall population, as in direct standardisation. This is the most appropriate method for standardisation when multiple dichotomous covariates are included (Muller and MacLehose 2014).

### ***3.5.3 Loss to follow-up and missing data***

Loss to follow-up is a common problem in longitudinal studies (MacBean et al. 2019) that can bias the results and compromise the generalisability of the results. Study subjects lost to follow-up may differ from the participating sample on several areas, commonly on socioeconomic and demographic but also medical characteristics (MacBean et al. 2019).

As described in Table 2, the study response rates at five years of age varied largely, between 29.3% (UK) and 96.4% (Estonia), and with an overall participation rate of 54.5%. In our study sample, loss to follow-up may have several consequences. A study comparing participation in research-related follow-up and clinical routine follow-up found that research participants are more likely to attend follow-up appointments (Orton et al. 2015). Study participants in our cohort may be more motivated and able to participate in routine follow-up and be most adherent to medical appointments, which would lead to an overestimation of follow-up and health care service use.

Loss to follow-up in the EPICE cohort has been associated with mainly sociodemographic and some perinatal characteristics (Zeitlin, Maier et al. 2020). Several methods have been applied to account for study attrition. Initially, regions with high attrition rates were excluded from the analyses (UK Northern region), until a method was agreed upon in the consortium that allows to keep all regions in the analyses: inverse probability weights after multiple imputation. In this method, weights are created and applied to the sample, giving higher rates to observations with characteristics of non-responders, combined with multiple imputation by chained equations of any missing values in order to obtain more accurate weights (Seaman et al. 2012). All the variables that could be related to loss to follow-up, and thus contributing to these weights are described in the table below (Table 5). This method has been used in several of the cohort publications (Bonnet et al. 2019; Sentenac, Johnson, et al. 2020) and described in detail in chapter 5.

**Table 5** Factors associated with loss to follow-up at two and five years in the EPICE cohort

<b>Perinatal</b>	<b>Pregnancy/delivery</b>	<b>Sociodemographic</b>	<b>Child development at 2 years CA</b>
GA age at birth	Previous caesarean section	Maternal age at delivery	Gross motor impairment
Hospital transfer during neonatal care (inborn)	Singleton gestation	Mother's country of birth (foreign/native)	Cognitive delay
Bronchopulmonary dysplasia	Parity	Maternal educational level	
Small for gestational age	Premature rupture of membranes (PROM)	Breastfeeding at discharge	
Severe neonatal morbidity	Mode of delivery	Study region	
Surgery	Maternity unit level		
Mechanical ventilation	Antepartum haemorrhage		
CPAP			
Prophylactic surfactant			
Apgar score <7			
Congenital anomalies			

## 3.6 Qualitative analyses

### 3.6.1 Parental satisfaction with health care

In addition to assessing rates of follow-up and use of different types of health services across study regions, we assessed parents' satisfaction with care for their children born VPT, including parents' ratings of care as well as free-text suggestions on how care could be improved. A large number of parents, 971, provided detailed responses to this open-ended question, providing the opportunity to adopt a mixed-methods approach to analyse parents' lived experiences alongside the quantitative data.

The importance of patient satisfaction with health care services are increasingly recognised by service providers and researchers (Gibbons et al. 2016). Patient satisfaction is assessed for informing on perceived non-medical outcomes in health care evaluations, to assess areas of improvement in specific health care aspects, as a measure of health care quality or as basis for financial decisions (Gustavsson, Gremyr, and Kenne Sarenmalm 2016; Junewicz and Youngner 2015). Patient satisfaction has been associated with compliance with treatment plans and is considered important in attaining good medical outcomes (Junewicz and Youngner 2015).

Parent or caregiver satisfaction is assessed in the paediatric population, and has been used to evaluate specific paediatric health care settings such as NICU care (Pierrat et al. 2020; Russell et al. 2014; Conner and Nelson 1999) and specific services and care for specific conditions such as cerebral palsy (Shevell et al. 2019). Generally, extensive scales specifically developed for each purpose are used, but shorter scales have been shown to give equivalent results (Gibbons et al. 2016).

Qualitative methods are also used for assessing parents' experiences with care and confirm that parents are an imperative source of information when wanting to assess health care services and follow-up (Pritchard et al. 2008). Post-discharge care for children born VPT have been assessed in qualitative studies revealing drawbacks, for instance, in continuity of care (Rucci et al. 2015), service access and communication, that may have a negative impact on the use of post-discharge services in this population (Pritchard et al. 2008).

Although successful follow-up relies on parents' engagement (Little et al. 2015), parents' perceptions have not been commonly used to assess the post-discharge care offered to their

children; existing studies remain limited in terms of sample size and in being very context-specific. In the SHIPS project, the parental questionnaire was not designed to assess parents' evaluations of care, but included one question on parents' ratings of care, and therefore parents' free-text suggestions on how care can be improved allowed for more in-depth analysis of care satisfaction.

### ***3.6.2 Thematic analysis***

Parents' free-text responses on how to improve care were analysed with thematic analysis, in the collaboration with a qualitative researcher at INSERM, and in correspondence with qualitative researchers in Italy. Thematic analysis is a method commonly used in qualitative health-related research, mostly involving interviews, but has also been used to analyse open-ended text responses (Redshaw and Henderson 2018). Thematic analysis is to some extent more descriptive and less interpretative compared to other qualitative methods, such as content analysis, as it aims to identify, analyse and establish themes from patterns that emerge from qualitative text data (Vaismoradi, Turunen, and Bondas 2013). The data analysis and interpretation is an iterative process comprising several steps, including systematically generating codes when exploring data, reassessing data and codes over several cycles, collating codes into themes and refining these, as well as extracting examples from the text (Vaismoradi, Turunen, and Bondas 2013). The steps of the analysis process for analysing free-text responses in our data are described in detail in chapter 5, and the coding scheme is provided in Appendix A1.

As part of the SHIPS project's qualitative work package, coordinated by the Italian research team, interviews were conducted with parents from four study countries on their experiences with follow-up. Although results from these interviews have not yet been published, we were able to compare the themes from free-text responses with those from the qualitative interviews, finding similar experiences in both studies.

# **Chapter 4: Specialist health care services use in a European cohort of infants born very preterm**

## **4.1 Preface**

The first article of this doctoral project, published in *Developmental Medicine and Child Neurology* (Seppanen et al. 2019), gives a previously unavailable overview of post-discharge specialist service use at two years CA in children born VPT in Europe, including perinatal and sociodemographic factors associated with its use. We know that health care systems and post-discharge follow-up policies and programmes for VPT infants differ across Europe, and that health care access may be lower in children from families with social risk factors, regardless of their higher risk of health and developmental problems. Describing the specialist service use in children born VPT is a first step in understanding long-term management of VPT birth and care access in Europe.

We used data from the EPICE cohort, including 4322 children born before 32 weeks' gestation, followed up at two years CA in regions across 11 European countries, to describe their use of specialist health care services since discharge from the neonatal unit. We also investigated whether there are social disparities in service use in the regions after taking into account underlying differences in perinatal health across social groups. We found a high overall use of specialist services; 76% of the children had seen at least one specialist since discharge from the neonatal unit, ranging from 54% to 100% between countries. Large variations in service use were also observed in the sub-group of children at highest risk of health and developmental problems based on their perinatal characteristics. Perinatal risk factors, such as GA and neonatal morbidities, were associated with more specialist service use, but did not explain the regional differences. Lower maternal educational level was associated with less specialist service use in three countries.




This study illustrates the marked diversity in models of care for infants born VPT in their first two years of life in European countries. This diversity is not a result of differences in perinatal risk, and raises questions about the strengths and drawbacks of different health care models across Europe. These questions relate to whether some models achieve better outcomes in terms of health and development, the costs for society and families and their capacity to mitigate or accentuate social inequalities.

The work is presented here in its published form, with supplementary material presented at the end of the document: Appendix B1-B4.

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# Specialist health care services use in a European cohort of infants born very preterm

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## PUBLICATION DATA

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**AIM** Children born very preterm require additional specialist care because of the health and developmental risks associated with preterm birth, but information on their health service use is sparse. We sought to describe the use of specialist services by children born very preterm in Europe.

**METHOD** We analysed data from the multi-regional, population-based Effective Perinatal Intensive Care in Europe (EPICE) cohort of births before 32 weeks' gestation in 11 European countries. Perinatal data were abstracted from medical records and parents completed a questionnaire at 2 years corrected age (4322 children; 2026 females, 2296 males; median gestational age 29wks, interquartile range [IQR] 27–31wks; median birthweight 1230g, IQR 970–1511g). We compared parent-reported use of specialist services by country, perinatal risk (based on gestational age, small for gestational age, and neonatal morbidities), maternal education, and birthplace.

**RESULTS** Seventy-six per cent of the children had consulted at least one specialist, ranging across countries from 53.7% to 100%. Ophthalmologists (53.4%) and physiotherapists (48.0%) were most frequently consulted, but individual specialists varied greatly by country. Perinatal risk was associated with specialist use, but the gradient differed across countries. Children with more educated mothers had higher proportions of specialist use in three countries.

**INTERPRETATION** Large variations in the use of specialist services across Europe were not explained by perinatal risk and raise questions about the strengths and limits of existing models of care.

Children born very preterm (<32wks' gestation) face higher risks of motor impairment, including cerebral palsy, vision and hearing loss, language and developmental delay, and behavioural and cognitive difficulties compared to children born at later gestational ages.<sup>1–5</sup> These risks rise with declining gestational age at birth.<sup>1,2</sup> Between 21% and 35% of children born extremely preterm (22–27wks) have been shown to have moderate to severe neurological disability in childhood.<sup>2</sup> Other perinatal factors also affect the probability of health difficulties later in life, most

importantly, the presence of severe neonatal morbidities at discharge from the neonatal unit.<sup>2</sup> Up to 40% of infants born extremely preterm and 7% to 12% of infants born between 28 weeks and 31 weeks' gestation have a severe morbidity at discharge.<sup>6,7</sup> However, many children without severe morbidities also experience developmental problems.<sup>8</sup> Social factors may affect long-term prognosis, and children from socially disadvantaged families have more adverse outcomes in, for example, language development,<sup>9</sup> cognition,<sup>8</sup> and cerebral palsy.<sup>10</sup>

Equitable and timely access to high-quality health services is needed to ensure appropriate care for emerging health problems in this population. Studies show that health service use is higher in infants born very preterm compared to children born at term<sup>2</sup> and in children with developmental disabilities compared to those without.<sup>11</sup> Use of occupational and physical therapies is higher in children born very preterm at 18 months corrected age<sup>12</sup> and up to the age of 10 years to 12 years.<sup>13</sup> The type and number of services used depends primarily on gestational age at birth<sup>1,4</sup> and the severity of disabilities.<sup>1</sup> In the French Epidemiological Study on Small Gestational Ages (EPIPAGE)<sup>1</sup> cohort, one-third of children born very preterm used specialized care, including occupational, speech and physiotherapy, and psychologist or psychiatrist consultations at 5 years of age.<sup>1</sup> Other studies suggest that families' socio-economic characteristics affect children's use of health care services. Unfavourable social circumstances have been associated with increased outpatient service use in children born very preterm in Canada.<sup>14</sup> In the USA, low maternal education, poverty, and ethnic group have been associated with less access to early intervention services for high-risk infants.<sup>15</sup> Socio-economic characteristics have also been associated with the type of service providers consulted.<sup>16</sup>

While existing recommendations specify that paediatric specialist consultations, as well as sensory, developmental, and behavioral screening are needed for infants born preterm,<sup>17,18</sup> clear evidence-based guidelines governing post-discharge care do not exist. The importance of establishing more solid evidence-based and common guidelines has been highlighted by parent organizations and professional societies<sup>19,20</sup> but first, more information is needed about current practices. Existing studies provide an overview of the services used, but they are limited in their geographical coverage. Health service use may reflect both prevention and follow-up policies as well as how the health care system is organized, and are, therefore, highly context specific. In this study, the objective was to compare the use of specialist services by children born very preterm (<32wks' gestation) across Europe. The focus was on care received after discharge from hospital up to 2 years' corrected age and on investigating the differences by children's perinatal risk and mothers' social characteristics, across regions from 11 countries.

## METHOD

### Data source

Data were collected as part of the Effective Perinatal Intensive Care in Europe (EPICE) project, a population-based cohort of very preterm births in 19 regions in 11 European countries: Belgium (Flanders); Denmark (Eastern region); Estonia (entire country); France (Burgundy, Ile-de-France, and Northern region); Germany (Hesse and Saarland); Italy (Emilia-Romagna, Lazio, and Marche); the Netherlands (Central and Eastern region), Poland (Wielkopolska); Portugal (Lisbon and Northern region); Sweden (greater Stockholm) and the United Kingdom

### What this paper adds

- Use of specialist services by children born very preterm varied across Europe.
- This variation was observed for types and number of specialists consulted.
- Perinatal risk was associated with specialist care, but did not explain country-level differences.
- In some countries, mothers' educational level affected use of specialist services.

(East Midlands, Northern, and Yorkshire and the Humber regions). Regions were selected based on geographic location, organizational diversity, on-site infrastructure, and expertise for implementing the protocol. Still and live births between 22 weeks' gestation and 31 weeks and 6 days' gestation were included from all maternity hospitals over 12 months between April 2011 and September 2012. In France, the inclusions were performed over 6 months.

Perinatal data were abstracted from obstetric and neonatal records until the initial discharge from hospital, by medical staff or trained investigators. At 2 years' corrected age, parents were sent a questionnaire on the development and health of their child. Consistency and reliability were addressed in the design phase of the study; questionnaires included previously validated questions when possible and common definitions that were translated and pretested in each country.

Consent to participate in the EPICE cohort was obtained from all mothers included in the follow-up study, including for the collection of perinatal and follow-up data. Each region obtained approval from their local ethics board and/or hospital committee according to national legislations before the start of data collection. The 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.

### Study population

The EPICE cohort included 10 329 stillbirths, terminations of pregnancies, and live births before 32 weeks' gestation (Fig. S1, online supporting information). Out of 7900 live births, 6792 infants (86.0%) survived to discharge from the neonatal unit. Families whose child died before 2 years' corrected age ( $n=31$ ) were not contacted for follow-up. Of the 6761 children alive at 2 years, 2336 (34.6%) did not participate in the study. The Northern region in the UK (380 children alive at 2y) was excluded from the analyses because of concern about bias linked to a low response rate (27.1%). After excluding the UK Northern region, the loss to follow-up varied between 0.7% and 53.0% across the countries ( $p<0.001$ ). The final study sample included 4322 children (67.7% of those eligible).

### Data on use of specialist health services

Data on the use of health services were collected through the parent-report questionnaire at 2 years' corrected age. Parents were asked whether their child had seen any of the health care providers included on a prespecified list, or

whether their child had seen any other health care professionals which could be answered by a free-text response. The prespecified list of providers was developed in English, then translated and adapted to local health care systems; the providers thus differed slightly across countries (Table SI, online supporting information). This analysis focused on the most commonly used services provided by specialist physicians and other health care professionals that are not routinely provided by a general practitioner or paediatrician. Free-text responses were abstracted and the most common specialist services were described. Services for similar health problems, such as psychologist and psychiatrist, were analysed together. A variable ‘any specialist’ was defined as having consulted, at least once since first discharge from the neonatal unit, any of the prespecified specialists for all countries. Information on paediatricians was included to assess if these consultations were more frequent where specialist use was lower.

### Data on perinatal risk factors and socio-economic status

Perinatal and child characteristics included gestational age in weeks, sex, small for gestational age (birthweight <10th centile for gestational age and sex, using references developed for the cohort),<sup>21</sup> any congenital anomaly, bronchopulmonary dysplasia (based on need for supplemental oxygen or ventilation at 36wks’ postmenstrual age), retinopathy of prematurity (stages III–V, diagnosed before discharge), intraventricular haemorrhage (grades III and IV) or cystic periventricular leukomalacia, and necrotising enterocolitis needing surgery.

The mothers’ highest achieved educational level was collected in the 2-year questionnaire using the International Standard Classification of Education 2011 definition and categorized as (1) high school (upper secondary) or below and (2) more than high school (post-secondary or more). Whether the mother was foreign-born was also self-reported. The mother’s age at delivery was obtained from medical records.

### Statistical analysis

First, responders were compared with non-responders regarding child characteristics, perinatal risk, and mother’s sociodemographic factors. The use of specialist services was then described across the countries and by perinatal risk. Three risk groups were defined, based on perinatal characteristics associated with the risk of developing developmental or health problems in childhood:<sup>2,8</sup> (1) a high-risk group born before 28 weeks and/or with a severe neonatal morbidity (bronchopulmonary dysplasia, retinopathy of prematurity, intraventricular haemorrhage/cystic periventricular leukomalacia, or necrotising enterocolitis needing surgery) and/or a severe congenital anomaly; (2) a low-risk group born at 30 weeks or 31 weeks, not small for gestational age, without congenital anomalies, and without severe neonatal morbidity, and (3) a moderate-risk group including all other children, not classified as high or low risk. Proportions were compared using  $\chi^2$  test for

trend of odds and the mean number of different specialists seen across these risk groups was compared using the Kruskal–Wallis test.

To assess the effect of social factors, specialist use was compared by maternal education (high school or less vs more than high school) and birthplace (foreign vs native-born). Direct standardization was used to account for the distribution of perinatal risk within each country. Binomial regression models were used to obtain *p*-values for the risk differences in any specialist service use across the educational groups and between foreign and native-born mothers, adjusting for perinatal risk. Adjusted mean numbers of specialists were predicted holding risk constant at the mean across social groups. *p*-values were obtained by negative binomial regressions, a method appropriate for Poisson-distributed data where the variance is greater than the mean,<sup>22</sup> and the Wald test, adjusted for perinatal risk. For both adjusted models, a clustered sandwich estimator was used to take into consideration intrafamily correlation for multiples.

Sensitivity analyses were performed to assess the impact of non-response on the estimates of service use using inverse probability weighting. The weights were derived using sociodemographic and medical characteristics to estimate the probability of responding to the 2-year questionnaire, following methods previously used for this cohort.<sup>23</sup> All analysis was performed using STATA 14.0 (Stata Corp., College Station, TX, USA).

## RESULTS

The population at 2 years’ corrected age consisted of 2026 females and 2296 males, with a median gestational age of 29 weeks (interquartile range, [IQR] 27–31; Table I) and a median birthweight of 1230g (IQR 970–1511g). Bronchopulmonary dysplasia was present in 12.6% of the children, severe and non-severe congenital anomaly in 1.1% and 7.3% respectively, retinopathy of prematurity in 3.8%, intraventricular haemorrhage/cystic periventricular leukomalacia in 6.1%, and necrotising enterocolitis needing surgery in 1.6%. Based on gestational age and perinatal factors, 26.9% were classified into the low-risk group, 38.8% into the moderate-risk group, and 34.3% into the high-risk group. Mothers had a median age of 31 years (IQR 27–35y) and a majority had more than high school education (53.6%). Among non-responders at 2 years, mothers were younger ( $\leq 24$ y) and more often foreign-born with singleton pregnancies (Table SII, online supporting information). The questionnaires were completed by the mother (85.9%), father (6.0%), both (2.9%), or other responders (e.g. grandparents, 5.2%).

Overall, the highest reported specialist service use was for ophthalmologists and physiotherapists or motor development therapists (Table II). However, there was wide variation across countries: the use of ophthalmologists ranged from 23.9% in the Danish region to 99.3% in Estonia (overall 53.4%), and physiotherapists ranged from 29.5% in the UK regions to 96.4% in Estonia (overall 48.0%).

**Table I:** Sample characteristics

	<i>n</i> <sup>a</sup>	<i>n</i> (%) or <b>median [IQR]</b>
Gestational age in completed weeks	4322	<b>29 [27–31]</b>
<26		324 (7.5)
26–27		759 (17.6)
28–29		1152 (26.7)
30–31		2087 (48.3)
Birthweight, g	4322	<b>1230 [970–1511]</b>
Multiple birth		
Singleton	4322	2890 (66.9)
Twins		1259 (29.1)
Triplets or more		173 (4.0)
Sex: female	4322	2026 (46.9)
Small for gestational age	4322	
Yes (<10th centile)		1413 (32.8)
No (≥10th centile)		2909 (67.3)
Congenital anomaly	4321	
Severe		49 (1.1)
Non-severe		317 (7.3)
None		3955 (91.5)
Bronchopulmonary dysplasia at 36wks' postmenstrual age	4225	533 (12.6)
Retinopathy of prematurity stages III–V	4272	161 (3.8)
Intraventricular haemorrhage grade III or IV or cystic periventricular leukomalacia	4278	260 (6.1)
Necrotising enterocolitis needing surgery	4322	67 (1.6)
Perinatal risk <sup>b</sup>	4215	
Lower		1132 (26.9)
Moderate		1636 (38.8)
Higher		1447 (34.3)
Mother's age at delivery (y)	4322	<b>31 [27–35]</b>
≤24		537 (12.4)
25–34		2515 (58.2)
≥35		1260 (29.4)
Foreign-born mother	4308	956 (22.2)
Mother's educational level	4168	
High school or less		1936 (46.5)
More than high school		2232 (53.6)

Data reported as *n* (proportion) or in bold type for median [IQR].

<sup>a</sup>Percentages are calculated on all cases excluding missing values, as indicated. <sup>b</sup>Lower: over 29wks' gestation, without small for gestational age, severe neonatal morbidities, and congenital anomaly; Moderate: not classified as higher or lower risk; Higher: below 28wks' gestation or at least one neonatal morbidity or severe congenital anomaly. IQR, interquartile range.

Respiratory and asthma specialists were the third most used service (23.6% overall) but with a higher use of respiratory physiotherapy in French regions (63.5%). Psychologist/psychiatrist visits were more frequent in Estonia (42.0%) and in the Polish region (42.1%). Consultations with dieticians were reported more often in the UK (25.8%) and Swedish (27.9%) regions. Hearing specialists (including ear-nose-throat, audiology, and hearing screening) were reported as free-text answers in all countries except Estonia, where hearing examinations were prespecified and frequently reported (83.3%). However, the item in Estonia referred to the examination (not the specialist) and may have been provided in other settings. Use of any of the prespecified specialists varied from 53.7% (Italian regions) to 100% (Estonia). Consultations with paediatricians showed variability by country, but were not systematically higher when specialist service use was low.

Perinatal risk was associated with increased specialist use (Table III). In the lowest risk group, 64.3% had seen at least one specialist compared to 85.7% of the high-risk children ( $p<0.001$ ). On average 1.1 specialists were reported for low-risk, 1.4 for moderate-risk, and 1.9 for high-risk children ( $p<0.001$ ). This increase was seen in all countries except the Netherlands and Denmark.

Overall, the proportion of children having consulted at least one specialist was slightly higher for mothers with more than high school education (77.6% vs 74.2%;  $p=0.009$ ), after standardizing for risk group (Table IV). Significant differences by maternal educational level were found in Belgium, Germany, and Portugal. Differences were found between foreign and native-born mothers in France (any specialist use) and Germany (number of different specialists), after adjusting for risk.

The sensitivity analysis using inverse probability weights revealed slightly lower use of all services when loss to follow-up was taken into consideration (Table SIII, online supporting information). However, service use and differences between countries were otherwise very similar. The analysis by risk and educational groups yielded similar associations (data not shown).

## DISCUSSION

This study provides a previously unavailable overview of specialist service use among children born very preterm in their first 2 years of life in 11 European countries. A large variability existed in the reported use of services across the countries, with use of any specialist varying from 54% to 100%. Higher perinatal risk was associated with increased specialist consultations and number of specialists. Maternal education was associated with specialist use in regions from three countries. These results reveal highly diverse approaches to the use of specialists in care of children born very preterm across Europe and the challenges of benchmarking care across countries, even when they share similar standards of living and universal health care coverage.

Our findings corroborate previous studies showing a high use of specialist services by children born preterm, much higher than the 16% in children born at 39 weeks or 40 weeks in a previous study.<sup>1</sup> It also confirms the documented association with perinatal risk factors.<sup>1,14,24</sup> However, perinatal risk did not explain differences between countries, as these persisted after risk adjustment. This variation may be explained by differences in policies for the follow-up of infants born very preterm. For instance, Estonia, where almost all children had seen a specialist, has established national follow-up policies and a comprehensive programme including specialist care for all children born before 32 weeks. In the UK, Denmark, and Italy, where national protocols have not yet been established for follow-up of children born very preterm, specialist service use was lower, even when perinatal risk was high, possibly reflecting a focus on treatment more than prevention. Studying the content of established follow-up programmes and their ability to refer children to specialists

**Table II:** Use of specialist services by country (sorted by total use of services)

Regions from	Prespecified services <sup>a</sup>										Free text responses													
	Paediatrician, %	Any of the prespecified services, %	Ophthalmologist, %	Physiotherapist or motor development therapist, %	Respiratory, lung, or asthma specialist or pulmonologist, %	Developmental psychologist or psychiatrist, %	Dietician or nutritionist, %	Hearing examination ear-nose-throat/audiology/hearing specialist, %	Neurologist, %	Osteopath, %	Speech therapist, %	Total	Paediatrician, %	Any of the prespecified services, %	Ophthalmologist, %	Physiotherapist or motor development therapist, %	Respiratory, lung, or asthma specialist or pulmonologist, %	Developmental psychologist or psychiatrist, %	Dietician or nutritionist, %	Hearing examination ear-nose-throat/audiology/hearing specialist, %	Neurologist, %	Osteopath, %	Speech therapist, %	
Belgium	90.0	62.8	33.1	<b>41.0</b>	13.7	8.5	1.7	2.3	0.3	2.3	308	90.0	62.8	33.1	<b>41.0</b>	13.7	8.5	1.7	2.3	0.3	2.3	2.3	1.6	
Denmark	34.3	62.6	23.9	<b>45.8</b>	7.5	7.5	10.3	0.6	3.5 <sup>a</sup>	2.2	180	34.3	62.6	23.9	<b>45.8</b>	7.5	7.5	10.3	0.6	3.5 <sup>a</sup>	2.2	2.2	0.0	
Estonia	38.4 <sup>b</sup>	100.0	<b>99.3</b>	96.4	16.1	42.0	3.6	83.3 <sup>a</sup>	70.3 <sup>a</sup>	2.2	138	38.4 <sup>b</sup>	100.0	<b>99.3</b>	96.4	16.1	42.0	3.6	83.3 <sup>a</sup>	70.3 <sup>a</sup>	2.2	2.2	29.7 <sup>a</sup>	
France	96.1	92.9	61.9	46.3	<b>63.5</b>	17.6	0.2	32.0	2.2 <sup>a</sup>	26.9 <sup>a</sup>	986	96.1	92.9	61.9	46.3	<b>63.5</b>	17.6	0.2	32.0	2.2 <sup>a</sup>	26.9 <sup>a</sup>	4.6	6.3	
Germany	87.4	88.7	<b>78.5</b>	63.8	2.9	6.0	7.9	3.9	8.5 <sup>a</sup>	4.6	435	87.4	88.7	<b>78.5</b>	63.8	2.9	6.0	7.9	3.9	8.5 <sup>a</sup>	4.6	4.6	1.6	
Italy	86.4	53.7	<b>36.8</b>	30.2	7.8	10.0	3.1	5.9	26.1 <sup>a</sup>	2.2	731	86.4	53.7	<b>36.8</b>	30.2	7.8	10.0	3.1	5.9	26.1 <sup>a</sup>	2.2	2.2	1.2	
Netherlands	88.9	84.2	37.2	<b>79.0</b>	6.7	6.6	10.6	3.1	0.9	1.3	229	88.9	84.2	37.2	<b>79.0</b>	6.7	6.6	10.6	3.1	0.9	1.3	10.0	1.2	
Poland	90.9	94.9	<b>90.8</b>	82.2	28.4	42.1	3.6	6.5	69.0 <sup>a</sup>	0.0	199	90.9	94.9	<b>90.8</b>	82.2	28.4	42.1	3.6	6.5	69.0 <sup>a</sup>	0.0	0.0	10.6	
Portugal	84.2	79.7	<b>67.7</b>	44.4	17.6	18.9	9.6	12.5	14.5 <sup>a</sup>	0.0	408	84.2	79.7	<b>67.7</b>	44.4	17.6	18.9	9.6	12.5	14.5 <sup>a</sup>	0.0	0.0	1.2	
Sweden	74.5	74.1	47.8	<b>54.0</b>	39.7	4.5	27.9	7.3	3.6 <sup>a</sup>	0.0	165	74.5	74.1	47.8	<b>54.0</b>	39.7	4.5	27.9	7.3	3.6 <sup>a</sup>	0.0	0.0	1.8	
UK	56.2	58.7	<b>33.6</b>	29.5	11.4	3.3	25.8	4.1	5.6 <sup>a</sup>	0.0	543	56.2	58.7	<b>33.6</b>	29.5	11.4	3.3	25.8	4.1	5.6 <sup>a</sup>	0.0	0.0	6.5	
Total	81.0	75.9	53.4	48.0	23.6	13.3	7.9	14.0	13.7	7.4	4322	81.0	75.9	53.4	48.0	23.6	13.3	7.9	14.0	13.7	7.4	4.9	—	
n missing values	160	144	99	166	244	174	134	—	—	—		160	144	99	166	244	174	134	—	—	—	—	—	—

Most commonly used service in each country in bold type. <sup>a</sup>Prespecified services, i.e. services reported by the parent using a list of suggested services. <sup>b</sup>Paediatrician outside follow-up clinic. In Estonia, all children have a paediatrician consultation at a follow-up centre as part of follow-up. <sup>c</sup>Question asked in 35 of 165 cases (18.4%) in Sweden. Regions are: Belgium (Flanders); Denmark (Eastern region); Estonia (entire country); France (Burgundy, Ile-de-France, and Northern region); Germany (Hesse and Saarland); Italy (Emilia-Romagna, Lazio, and Marche); the Netherlands (Central and Eastern region), Poland (Wielkopolska); Portugal (Lisbon and Northern region); Sweden (greater Stockholm); and the UK (East Midlands and Yorkshire and the Humber regions).

**Table III:** Use of specialist services (proportion of any specialist and mean number of different services used) by country and level of perinatal risk

Regions from	Total	Lower			Moderate			Higher			$p^a$	$p^b$
		Number of children	Any service, %	Mean number of services	Number of children	Any service, %	Mean number of services	Number of children	Any service, %	Mean number of services		
Belgium	308	98	48.9	0.7	101	60.8	0.9	85	81.5	1.5	<0.001	<0.001
Denmark	180	33	50.0	0.7	64	59.4	0.9	69	72.5	1.1	0.022	0.053
Estonia	138	36	100.0	2.2	52	100.0	2.8	50	100.0	2.6	–	0.003
France	986	234	87.3	1.5	400	92.7	1.8	306	97.3	2.3	<0.001	<0.001
Germany	435	104	81.7	1.3	182	89.8	1.5	149	92.4	1.8	0.012	<0.001
Italy	731	215	42.3	0.6	284	51.9	0.8	225	66.1	1.3	<0.001	<0.001
Netherlands	229	53	81.1	1.4	86	82.6	1.3	89	88.6	1.5	0.200	0.194
Poland	199	53	96.1	2.1	62	91.8	2.3	83	96.4	2.9	0.798	<0.001
Portugal	408	98	64.8	1.1	173	80.4	1.4	137	89.2	2.0	<0.001	<0.001
Sweden	165	44	37.2	0.7	63	75.4	1.4	54	100.0	2.9	<0.001	<0.001
UK	543	164	44.9	0.6	169	51.2	0.8	200	76.8	1.6	<0.001	<0.001
Total	4322	1132	64.3	1.1	1636	75.1	1.4	1447	85.7	1.9	<0.001	<0.001

Data reported as number of children in each category, proportion of children having seen any of the prespecified services and mean number of different prespecified services seen. <sup>a</sup> $\chi^2$  test for trend of odds. <sup>b</sup>Kruskal–Wallis test for  $p$ -value for mean number of services. Regions are: Belgium (Flanders); Denmark (Eastern region); Estonia (entire country); France (Burgundy, Ile-de-France, and Northern region); Germany (Hesse and Saarland); Italy (Emilia-Romagna, Lazio, and Marche); the Netherlands (Central and Eastern region), Poland (Wielkopolska); Portugal (Lisbon and Northern region); Sweden (greater Stockholm); and the UK (East Midlands and Yorkshire and the Humber regions).

could give a better picture of the role of specialists in screening, prevention, and treatment. Variation across countries may also reflect differences in how paediatric primary care is organized more generally, and the accessibility of paediatric services. Systems with varying provision of paediatric services exist across Europe.<sup>25</sup> However, there was no clear pattern across the countries with respect to using paediatric versus specialist services.

The two most commonly used services were ophthalmologist and physiotherapist, as reported previously.<sup>12</sup> Some services were more country specific, such as respiratory physiotherapy in France, speech therapy in Estonia, dietician in Sweden and the UK, and neurologist and psychologist/psychiatrist in Estonia and Poland. In France, respiratory physiotherapy is commonly used in the general paediatric population.<sup>26</sup> Speech/language therapy, which is used for feeding difficulties in this age group, were also mentioned by parents, although they were not prespecified in the questionnaire and should be included in future studies.

Children of more educated mothers were more likely to see a specialist in 3 of the 11 countries, which has similarly been reported for out-patient services in children born very preterm.<sup>14</sup> The absence of these differences in the remaining countries might be explained by the organisation of care, such as having systematic follow-up in place, or referral or targeting practices focussing on socially disadvantaged families, and constitute areas for further investigation. Ensuring access to specialized health services for socially disadvantaged families is essential as these families are more likely to have a child born very preterm<sup>27</sup> and there is evidence that they may benefit more from some services.<sup>28</sup> Conversely, being foreign-born or not speaking the language may act as a barrier to contact with

service providers.<sup>29</sup> Reassuringly, few differences were found between foreign and native-born women in this study.

The strengths of this study include its population-based design, geographic spread, and standardized protocol across 11 European countries. However, with limited detail collected about the frequency of consultations and whether they were for prevention or treatment, we could not consider the appropriateness of the care, nor whether specialist care was provided as part of other health services, such as motor development tests that are sometimes performed at maternal and child health centres. Neither could we distinguish private from public providers, nor assess if services had out-of-pocket costs. Another limitation was loss to follow-up, which varied across regions. Comparison of non-responders with responders showed that younger and foreign-born mothers were underrepresented, but proportions of perinatal risk factors were very similar in both groups. Consideration of non-response using inverse probability weighting lowered estimates of specialist use, suggesting that non-responders were less likely to use health services, but associations with risk and educational level did not change. Finally, recall bias might have affected the accuracy of the answers, but there is no reason to believe that recall bias was differential across regions as the protocol and questionnaires were standardized.

In conclusion, these data show high heterogeneity in specialist health service use among children born very preterm across European regions using a standardized parent-report instrument in 10 languages. This heterogeneity cautions about generalizing research results on health care use from one country to others, and calls attention to the diverse models of care within Europe. Further studies on specialist service use in relation to health outcomes, use of

**Table IV:** Use of specialist services (proportion of any specialist and mean number of different specialists seen) by country and maternal education level, adjusted by perinatal risk

Regions from	Use of specialist services by educational level and birthplace, adjusted for risk															
	High school or less				More than high school				Foreign-born				Native			
	Number of children	Any service (%) <sup>a</sup>	Mean number of services <sup>b</sup>	<i>p</i> <sup>c</sup>	Number of children	Any service (%) <sup>a</sup>	Mean number of services <sup>b</sup>	<i>p</i> <sup>d</sup>	Number of children	Any service (%) <sup>a</sup>	Mean number of services <sup>b</sup>	<i>p</i> <sup>c</sup>	Number of children	Any service (%) <sup>a</sup>	Mean number of services <sup>b</sup>	<i>p</i> <sup>d</sup>
Belgium	308	57.1	0.8	0.036	174	67.8	1.0	0.197	58	67.2	0.9	0.836	250	62.2	0.9	0.615
Denmark	180	65.2	1.1	0.968	150	63.4	0.9	0.467	18	43.1	1.0	0.485	162	63.9	0.9	0.767
Estonia	138	100.0	2.7	–	89	100.0	2.5	0.104	9	100.0	2.6	–	129	100.0	2.6	0.757
France	986	91.9	1.9	0.295	481	94.0	1.9	0.434	335	90.3	1.8	0.045	646	94.1	1.9	0.439
Germany	435	221	88.1	0.008	200	93.0	1.7	0.186	122	82.1	1.3	0.145	311	91.0	1.7	0.006
Italy	731	459	54.6	0.406	266	51.0	0.8	0.512	188	53.2	0.8	0.994	543	53.5	0.8	0.935
Netherlands	229	39	87.5	0.873	187	84.0	1.4	0.173	27	76.2	1.2	0.377	202	85.4	1.4	0.269
Poland	199	114	93.8	0.081	83	97.6	2.6	0.069	1	–	2.2	–	198	–	2.5	0.062
Portugal	408	228	74.7	0.011	175	86.2	1.7	0.013	76	84.1	1.6	0.828	332	78.8	1.5	0.408
Sweden	165	71	70.6	0.396	93	75.3	1.5	0.537	48	66.4	1.3	0.280	117	75.5	1.5	0.535
UK	543	175	56.7	0.519	334	59.9	1.0	0.693	74	51.0	0.9	0.229	462	59.8	1.0	0.378
Total	4322	1936	74.2	0.009	2232	77.6	1.5	0.170	956	75.1	1.4	0.456	3352	76.2	1.4	0.227

Data reported as number of children in each category, proportion of children having seen any of the prespecified services and mean number of different prespecified services seen. <sup>a</sup>Proportions adjusted by level of perinatal risk by direct standardization. <sup>b</sup>Adjusted predictions of mean number of services holding risk constant at mean across social groups. <sup>c</sup>*p*-value for risk difference adjusted for perinatal risk and clustering for multiples, using binomial regression. <sup>d</sup>*p*-value for difference in mean number of specialists seen adjusted by risk and clustering for multiples, using Wald test after negative binomial regression. Regions are: Belgium (Flanders); Denmark (Eastern region); Estonia (entire country); France (Burgundy, Ile-de-France, and Northern region); Germany (Hesse and Saarland); Italy (Emilia-Romagna, Lazio, and Marche); the Netherlands (Central and Eastern region), Poland (Wielkopolska); Portugal (Lisbon and Northern region); Sweden (Greater Stockholm); and the UK (East Midlands and Yorkshire and the Humber regions).

emergency and in-patient services, parental experiences of care, and health care costs should investigate the advantages and drawbacks of these models in order to inform guidelines that are applicable across diverse health systems.

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## SUPPORTING INFORMATION

The following additional material may be found online:

**Figure S1:** Flowchart illustrating the participation in the study.

**Table S1:** Specialist services as defined in each country specific questionnaire

**Table SII:** Responder and non-responder characteristics

**Table SIII:** Use of specialist services by country using inversed probability weighting, sorted by total use of services

**Appendix S1:** Members of the Effective Perinatal Intensive Care in Europe (EPICE) research group

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# **Chapter 5: Parents' ratings of post-discharge healthcare for their children born very preterm and their suggestions for improvement: a European cohort study**

## **5.1 Preface**

In Chapter 4, we showed that the use of specialist services varies widely across countries in Europe, even in children at highest risk of health and developmental problems, and that there may be social disparities in access to specialist services in some countries at two years CA. These results led to further questions on the strengths and drawbacks of the post-discharge care offered to children born VPT across Europe.

Parents play a key role in the follow-up and care of children born VPT, but studies involving parents in evaluating post-discharge care are few, and remain limited in sample size and context. The second article of this doctoral project, published in *Pediatric Research* (Seppanen, Sauvegrain et al. 2020), uses a mixed methods approach to investigate parents' perceptions of the post-discharge care received by their children born VPT, until five years of age in regions from 11 European countries.

We used data from 3635 parental follow-up questionnaires, including parents' ratings of care received by their children until five years of age (poor, fair, good, excellent) and analysed over 900 free-text suggestions on how care can be improved. We assessed ratings by country, child health and development and family sociodemographic factors and sought to understand parents' perceptions of drawbacks with health care by thematic analysis.

The majority of children (86%) had received satisfactory care according to their parents, but care ratings varied across countries, and dissatisfaction with care was highest amongst families with children with health and developmental difficulties. Parents' suggestions on how care could be improved were similar across countries, and focused on the need for better care coordination and communication with parents. The comments by parents of children in the SHIPS cohort corroborate conclusions from previous studies suggesting that post-discharge care for children with complex care needs is poorly organised in Europe.

Knowing that routine follow-up policies and care satisfaction differ across Europe, and that dissatisfaction is high especially among parents of children with the most complex care needs, raises further questions on the use of routine follow-up services and role of such follow-up on accessing satisfactory care and on managing care for children with the most elevated and complex care needs beyond two years of age.

This work is presented here in its published form, and with supplementary material presented at the end of the document: Appendix C1-C3.

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## POPULATION STUDY ARTICLE

# Parents' ratings of post-discharge healthcare for their children born very preterm and their suggestions for improvement: a European cohort study

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**BACKGROUND:** Follow-up of very preterm infants is essential for reducing risks of health and developmental problems and relies on parental engagement. We investigated parents' perceptions of post-discharge healthcare for their children born very preterm in a European multi-country cohort study.

**METHODS:** Data come from a 5-year follow-up of an area-based cohort of births <32 weeks' gestation in 19 regions from 11 European countries. Perinatal data were collected from medical records and 5-year data from parent-report questionnaires. Parents rated post-discharge care related to their children's preterm birth (poor/fair/good/excellent) and provided free-text suggestions for improvements. We analyzed sociodemographic and medical factors associated with poor/fair ratings, using inverse probability weights to adjust for attrition bias, and assessed free-text responses using thematic analysis.

**RESULTS:** Questionnaires were returned for 3635 children (53.8% response rate). Care was rated as poor/fair for 14.2% [from 6.1% (France) to 31.6% (Denmark)]; rates were higher when children had health or developmental problems (e.g. cerebral palsy (34.4%) or epilepsy (36.9%)). From 971 responses, 4 themes and 25 subthemes concerning care improvement were identified.

**CONCLUSIONS:** Parents' experiences provide guidance for improving very preterm children's post-discharge care; this is a priority for children with health and developmental problems as parental dissatisfaction was high.

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**IMPACT:**

- In a European population-based very preterm birth cohort, parents rated post-discharge healthcare as poor or fair for 14.2% of children, with a wide variation (6.1–31.6%) between countries.
- Dissatisfaction was reported in over one-third of cases when children had health or developmental difficulties, such as epilepsy or cerebral palsy.
- Parents' free-text suggestions for improving preterm-related post-discharge healthcare were similar across countries; these focused primarily on better communication with parents and better coordination of care.
- Parents' lived experiences are a valuable resource for understanding where care improvements are needed and should be included in future research.

**INTRODUCTION**

Very preterm births (<32 weeks of gestation) represent up to 1.6% of births in high-income countries<sup>1</sup> or up to 2% of births worldwide.<sup>2</sup> Although survival for these infants has improved, they remain at increased risk of developing multiple health and developmental problems compared to infants born at term.<sup>3,4</sup> As the prognosis for each individual infant is unknown at discharge from hospital, follow-up is essential for the early identification of

health needs, the coordination of health services from multiple providers, and for enabling timely intervention.<sup>5</sup>

Parents' engagement is crucial for successful follow-up of preterm infants,<sup>6</sup> but few studies have reported on parents' own evaluations of the post-discharge care offered to their children. Parents may provide important insights for improving healthcare beyond aspects of medical, outcome-related quality,<sup>7,8</sup> and this knowledge may help to improve service adherence, care delivery,<sup>8</sup>

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and consequently health outcomes. Qualitative studies involving parents have suggested that there is room for improvement in the continuity of care for preterm infants<sup>9</sup> and that assistance with accessing services or providing comprehensive information to parents may impact on the use of post-discharge services in this population.<sup>10</sup> The use of early intervention services has been shown to improve outcomes in both children<sup>11</sup> and parents<sup>12</sup> and may be of most benefit to socially deprived families.<sup>13</sup> At the same time, unfavorable social factors such as poorer financial resources<sup>14</sup> or lower educational level<sup>15</sup> have been associated with multiple barriers for attending follow-up services<sup>14</sup> and follow-up discontinuation<sup>15</sup> for children at risk of developmental problems and morbidities.

Although parents are frequently involved in evaluating specific healthcare services or units,<sup>16,17</sup> pediatric specialties,<sup>18</sup> or aspects of care,<sup>9</sup> there have been no large-scale or international evaluations of post-discharge care involving parents of children born very preterm. The main aims of this study were to assess parents' ratings of their children's prematurity-related care from discharge from neonatal care until 5 years of age in a large cohort from 19 regions in 11 European countries by sociodemographic characteristics and child health outcomes. In addition, we aimed to provide a thematic synthesis of parents' suggestions on how healthcare can be improved.

## METHODS

### Data sources

The data were collected for the Screening to improve Health in very Preterm infantS (SHIPS) study, which followed up the area-based EPICE cohort of infants born before 32 weeks' gestation over 12 months in 2011–2012,<sup>19,20</sup> in all maternity units of 19 regions in 11 European countries: Belgium (Flanders); Denmark (Eastern region); Estonia (entire country); France (Burgundy, Ile-de-France, and Northern regions, 6 months' data collection only); Germany (Hesse and Saarland); Italy (Emilia-Romagna, Lazio, and Marche); the Netherlands (Central and Eastern regions), Poland (Wielkopolska); Portugal (Lisbon and Northern regions); Sweden (greater Stockholm); and the United Kingdom (East Midlands, Northern, and Yorkshire and the Humber regions). Children were followed up at 2 and 5 years of age using parental questionnaires. At 5 years of age, a subset of all children born before 28 weeks' gestation were also invited to participate in clinical assessments.<sup>19</sup>

### Ethics

Ethics approvals and parental consent were obtained according to national legislation in each country before data collection. The SHIPS project was approved by the French Advisory Committee on Use of Health Data in Medical Research and the French National Commission for Data Protection and Liberties.

### Study population

At baseline, the cohort included 7900 live births and 2429 stillbirths and terminations of pregnancies. Six thousand seven hundred and ninety-two infants were discharged alive from the neonatal unit (Supplementary Fig. S1 (online)). At 5 years, 6759 children were alive, of whom parents of 3687 (54.5%) children participated in the follow-up and 3635 (53.8%) returned a questionnaire.<sup>19</sup>

### Data collection

At inclusion, pregnancy and perinatal data were collected from obstetric and neonatal records. At 5 years of age, health, healthcare, and socioeconomic information was collected using parent-report questionnaires that had been pre-tested in all national languages. The questionnaires could be completed at home, in follow-up clinics, online, or using paper questionnaires, depending on local study protocols. Questionnaires could be filled in by mothers, fathers, or other primary caregivers. They were

asked the following question: "How would you describe the healthcare your child has received related to his or her preterm birth after being discharged from the neonatal unit; excellent, good, fair, poor, or has not received any healthcare related to very preterm birth?" The parents were also asked to provide suggestions for how healthcare for very preterm children can be improved, as free-text responses.

### Data analysis

Proportions of poor-to-fair ratings (considered to represent dissatisfaction) were described by country. The association between dissatisfaction and sociodemographic characteristics and child health was assessed using  $\chi^2$  tests. Sociodemographic characteristics included maternal educational level (lower: lower secondary [ISCED levels 0–2], intermediate: upper or post-secondary, non-tertiary or short cycle tertiary [levels 3–5], or higher: Bachelor degree or higher [levels 6–8]),<sup>21</sup> country of birth (native-born, born elsewhere in Europe, or born outside Europe), family situation (mother living with partner vs. single caregiver or other family situation), age at delivery ( $\leq 24$ , 25–34, or  $\geq 35$  years), parity at delivery (multiparous vs. nulliparous), and multiplicity (singleton vs. twins or more). As in previous analyses of this cohort, perinatal risk factors were used to create a variable representing overall risk of health and developmental problems at discharge from the neonatal hospitalization, classified as: lower (born over 29 weeks' gestation, not small for gestational age [SGA; birth weight <10th centile for intrauterine norms for gestational age and sex, using references developed for the cohort<sup>22</sup>] and without severe neonatal morbidities [bronchopulmonary dysplasia (BPD), i.e., need for supplemental oxygen or ventilation at 36 weeks' postmenstrual age, stages III–V retinopathy of prematurity (ROP), levels III–IV intraventricular hemorrhage (IVH), cystic periventricular leukomalacia (cPVL), or necrotizing enterocolitis (NEC) needing surgery] or congenital anomalies [CA]), moderate (not classified as higher or lower risk), or higher risk (born below 28 weeks' gestation or at least one neonatal morbidity or a severe CA).<sup>23</sup> Data on the child's health at 5 years included a parental rating of their child's overall health status (good/excellent vs. poor/fair) and asthma diagnosis. Data on developmental and neurosensory difficulties included the parent's rating of their child's development (average/advanced vs. delayed/very delayed); clinical diagnosis of cerebral palsy, epilepsy, and autism; and reports of moderate or severe vision or hearing problems (defined as having difficulties seeing even with glasses, being blind or seeing light only, requiring hearing aids, or being deaf).

To obtain adjusted risk ratios for dissatisfaction with healthcare services, we used three multilevel generalized linear regression models with a log link, Poisson distribution, and a robust variance estimator,<sup>24</sup> with two levels to account for correlation between siblings: one including sociodemographic variables and country only, and two adding either parent-rated health and developmental problems or diagnosed developmental or neurosensory difficulties. We did not run a model with all variables due to collinearity between parent-reported health status and clinical diagnoses. The covariates were selected based on the scientific literature and bivariate analyses, including variables that were related to parental ratings with a  $p$  value <0.2. We used the sample average as the reference for presenting the country risk ratios for poor/fair ratings. In sensitivity analyses, regression models were (1) adjusted for all covariates without selection based on a  $p$  value cut-off and (2) restricted to cases where the questionnaire was answered by mothers only.

### Non-response and missing data

The response rate varied depending on the country (53.8% overall, range 29.3–96.4%); non-responders in the cohort were more likely to be younger, foreign-born mothers, and have a lower educational

level, as detailed elsewhere.<sup>19</sup> To take into consideration potential attrition bias, we generated inverse probability weights based on characteristics of non-responders available at baseline and at the 2-year follow-up, after multiple imputation of missing values,<sup>25</sup> following methods previously used in this cohort.<sup>26</sup> This approach gives a higher weight to children with characteristics that are underrepresented because of non-response. First, 20 imputations using multiple chained equations were performed to impute missing values for the variables used for predicting the inverse probability weights. Data were assumed to be missing at random. All variables associated with loss to follow-up were included in the regression: gestational age in completed weeks, Apgar score (<7), use of continuous positive airway pressure, use of mechanical ventilation, use of prophylactic surfactant within 2 h after birth, birth in level 3 unit, inborn status (no transfer within 48 h of birth), SGA, any CA (severe or non-severe vs. none), BPD, any severe morbidity at discharge (IVH, cPVL, ROP, or NEC), surgery (for patent ductus arteriosus, CA, NEC, or other reasons), infant received human milk at discharge, mode of delivery (vaginal/instrumental vs. cesarean), previous cesarean section, parity at delivery, antepartum hemorrhage after week 20, premature rupture of membranes (>12 h), multiplicity, mother's age at delivery, mother's country of birth, mother's educational level, gross motor impairment at 2 years corrected age,<sup>27</sup> cognitive delay at 2 years corrected age,<sup>27</sup> and study region. The weights were estimated on the total sample of infants eligible for follow-up at 5 years. All proportions in the tables are derived from the weighted sample and all models were run with weights. In sensitivity analyses, we ran models truncating weight values at the 95th percentile to assess whether the results were affected by the extremes of the weight distribution.

Missing data were not frequent among responders: 2.7% of healthcare ratings were missing and the proportion of missing data varied between 0.3% (maternal age) and 5.3% (country of origin) for co-variables.

**Analysis of free-text responses**

Free-text responses were explored using thematic analysis. We used an iterative process for the translation of responses and initial coding into keywords and subthemes. The approximately 1300 free-text responses were first automatically translated using Google Translate. Tables including the original juxtaposed with the automatically translated text were used for a first coding of

keywords and preliminary themes by the first author. In this step, specific ambiguities in the translations or where multiple interpretations were possible were highlighted. These tables were then sent to the country teams who reviewed the translations and key words. The focus of this step was to ensure that the text was correctly translated and that these translations, as well as the keywords, reflected the original content. As it was not possible to return questionnaires to the responders for clarifications, responses that could not be interpreted after review, due to poor wording or lack of detail, were removed. After this step, keywords were coded into themes and subthemes by the first author, which were reviewed and validated by a qualitative researcher (P.S.); a random sample of the responses were double-coded by P.S. and divergences were discussed with the first author until consensus was reached. Responses that contained more than one suggestion were coded into several themes and duplicate responses for multiple siblings were removed. Themes and subthemes were summarized and described by country and healthcare ratings. Citations were extracted to illustrate the most common subthemes, while ensuring the confidentiality of the responder. The citations selected for presentation in the manuscript were reviewed again by country team members to ensure the precision of the translation.

All data analyses were carried out with STATA 14.0 (Stata Corp., College Station, TX, USA) and Excel 2013.

**RESULTS**

Questionnaires were returned for 3635 children; by mothers (83%), fathers (15%), and other caretakers, such as grandparents (1.4%), all hereafter referred to as parents. Parents reported that 92.8% of the children had received post-discharge care for their prematurity.

For 14.2% of these children, parents judged the care to be poor or fair, but this varied from 6.1% in France to 31.6% in Denmark. (Table 1). Parents expressed more dissatisfaction with post-discharge care when maternal educational level was higher and when mothers were native-born or born outside Europe compared to mothers born elsewhere in Europe (Table 2). Proportions of poor/fair ratings were higher for children with parent-rated health or developmental problems, diagnosed cerebral palsy or epilepsy, or moderate-to-severe vision or hearing problem at 5 years of age.

**Table 1.** Parents' ratings of preterm birth-related healthcare by country, ordered by weighted proportion of poor or fair ratings.

How would you describe the healthcare your child has received related to his or her preterm birth, after being discharged from the neonatal unit?										
Country	N <sup>a</sup>	Excellent		Good		Fair		Poor		Poor or fair % <sup>b</sup>
		n	% <sup>b</sup>	n	% <sup>b</sup>	n	% <sup>b</sup>	n	% <sup>b</sup>	
France	688	343	49.8	303	44.1	40	5.8	2	0.3	6.1
The Netherlands	138	40	30.7	85	60.2	10	7.1	3	2.1	9.2
Portugal	409	223	54.6	142	34.9	37	8.9	7	1.7	10.5
Italy	659	327	47.6	259	41.3	58	8.8	15	2.2	11.1
Belgium	231	82	36.0	120	52.0	26	10.8	3	1.2	12.0
Estonia	111	52	46.9	44	39.6	13	11.7	2	1.8	13.5
Sweden	125	51	42.5	49	39.0	18	13.2	7	5.3	18.5
UK	376	179	47.8	132	33.0	48	12.9	17	6.3	19.2
Germany	228	84	37.4	99	42.7	37	16.7	8	3.2	19.9
Poland	173	26	15.0	103	59.7	34	19.6	10	5.6	25.2
Denmark	144	45	32.6	52	35.8	37	24.4	10	7.2	31.6
Total	3282	1452	44.0	1388	41.8	358	11.2	84	3.0	14.2

<sup>a</sup>Excluding missing values and cases where parents reported "no care received."

<sup>b</sup>Inverse probability weights have been used to adjust for non-response.

**Table 2.** Poor or fair ratings by sociodemographic factors, child health, and health service use.

	N	Poor or fair ratings		
		n	% <sup>a</sup>	p <sup>a</sup>
<b>Family sociodemographic factors</b>				
Mother's educational level				0.042
Lower secondary	535	53	10.5	
Upper or post-secondary	1355	169	14.5	
Higher education	1358	214	15.5	
Mother's country of birth				0.008
Native-born	2586	375	15.3	
Born elsewhere in Europe	146	9	6.3	
Born outside Europe	376	35	11.1	
Family situation				0.199
Mother living with partner	2875	395	14.6	
Single mother or other family situation	396	46	11.9	
Mother's age at delivery, years				0.946
≤24	365	45	14.7	
25–34	1896	256	14.0	
≥35	1011	138	14.0	
Parity at delivery				0.224
Multiparous	1271	188	15.1	
Nulliparous	1975	252	13.4	
Multiple birth				0.728
Singleton	2315	324	14.4	
Twins, triplets, or quadruplets	967	118	13.8	
<b>Child's perinatal health</b>				
Perinatal risk <sup>b</sup>				0.107
Lower	791	101	13.5	
Moderate	1244	155	12.9	
Higher	1164	179	16.2	
<b>Child's health and development at 5 years</b>				
Parent-rated child health				<0.001
Good or excellent	2928	333	12.0	
Poor or fair	329	104	32.3	
Asthma diagnosis				0.244
No	2609	342	13.8	
Yes	516	77	16.0	
Parent-rated child development				<0.001
Average or in advance	2580	268	11.1	
Delayed or very delayed	663	161	24.4	
Cerebral palsy diagnosis				<0.001
No	3080	380	12.7	
Yes	186	58	34.4	
Epilepsy diagnosis				<0.001
No	3100	399	13.6	
Yes	53	18	36.9	
Autism diagnosis				0.060
No	3089	399	13.6	
Yes	70	15	22.5	
Vision or hearing problems				0.008
None to mild	3072	395	13.7	
Moderate to severe	124	32	22.4	

Data are reported as the number of children in each category (N) and the number and proportion of children with poor or fair ratings (n, %).

<sup>a</sup>Proportions are calculated using inverse probability weights.

<sup>b</sup>Lower: >29 weeks' gestation, not small for gestational age, no severe neonatal morbidities, and no congenital anomaly; moderate: not classified as higher or lower risk; higher: <28 weeks' gestation or at least one neonatal morbidity or severe congenital anomaly.

Higher maternal educational level, being native-born, and child health and developmental difficulties remained associated with poor/fair ratings in the adjusted analyses (Table 3). Significant differences in risk ratios persisted across countries after adjustment, despite slight changes in point estimates. Incorporating remaining covariates (mother's age, parity, multiple birth, and asthma diagnosis, *p* value >0.2) in our sensitivity analysis did not change these associations (data not shown). Sensitivity analysis with only mothers as responders showed slightly higher rates of dissatisfaction (15.0% instead of 14.2%) but did not change the results from the main models (data not shown). Differences between weighted and unweighted proportions of poor and fair ratings were minimal: 13.5% [95% confidence interval (CI) 12.3–14.7] vs. 14.2% [95% CI 12.9–15.6] overall (see Supplementary Table S1 (online) for unweighted proportions by country) and associations with other co-variables in unweighted and weighted models were similar (Supplementary Table S2 (online)) but slightly increased in the association between mother's educational level and dissatisfaction as well as perinatal health and dissatisfaction. Sensitivity analyses truncating weights at the 95th percentile (*n* = 52 at weight = 4.24) did not affect results. See Supplementary Table S2 (online) for models (Model III) with and without truncated weights, compared to unweighted models.

Parents provided 1105 (30%) unique free-text responses, of which 85 stated "no comment" or "do not know" and 49 that the child had not received post-discharge care. The remaining 971 responses were analyzed thematically. Some themes did not relate to improvements in post-discharge healthcare but focused on positive experiences with healthcare (*n* = 232 suggestions) or care during the neonatal hospitalization (*n* = 137 suggestions) and were excluded. Four themes and 25 subthemes were related to healthcare improvements, as shown in Table 4. Among the parents who provided free-text responses, 956 also rated the post-discharge care; 25.7% (*n* = 246) rated the care as poor or fair and 74.3% (*n* = 710) as good or excellent (not shown).

The most frequent theme was (I) Coordination of follow-up and healthcare, with *Improving care coordination* as the most common subtheme. Parents reported a lack of coordination, having to take responsibility for the organization of healthcare and identification of the appropriate healthcare providers for their child, which was described as an exhausting, stressful, time consuming, or difficult task. Some parents experienced having numerous appointments with poor continuity of care and lack of communication between multiple healthcare providers or asked for a reference person to coordinate care or follow-up.

"Big disappointment that no one has overall responsibility for follow-up. Our daughter has many doctor visits at three different hospitals. Countless visits could have been avoided if someone had an overview of the situation." – Parent, Sweden (care rating: Poor)

Other reoccurring subthemes in this category included the need for further *training of generalists and nurses* (especially health visitors and Child Healthcare Centre nurses) on preterm birth, having more *equitable access to follow-up and services*, and *reducing waiting times* on waiting lists, especially for visits to specialists, and queuing in the waiting rooms.

"After finishing the follow-up at the neonatal unit, we find that both the Child Healthcare Centre nurse and the preschool lack knowledge of premature babies and their needs. Thus, more knowledge/education to Child Health Centre and preschool staff." – Parent, Sweden (care rating: Excellent)

"Unfortunately, help for premature babies is only available in larger cities. We live in the countryside and have limited access

**Table 3.** Risk ratios of poor or fair ratings by sociodemographic characteristics and child health and development.

	Unadjusted risk ratios	Model I: sociodemographic characteristics	Model II: socio-demographic characteristics and parent-rated health and development	Model III: socio-demographic characteristics, perinatal risk, and developmental and neurosensory difficulties
	RR [95% CI]	<sup>a</sup> RR [95% CI]	<sup>a</sup> RR [95% CI]	<sup>a</sup> RR [95% CI]
Mother's educational level (ref. lower)				
Intermediate	1.28 [0.90–1.83]	1.18 [0.81–1.72]	1.34 [0.95–1.90]	1.21 [0.82–1.79]
Higher	1.63 [1.15–2.32]	1.44 [0.99–2.09]	1.73 [1.22–2.46]	1.49 [1.01–2.20]
Mother's country of birth (ref. native)				
Born elsewhere in Europe	0.36 [0.16–0.77]	0.35 [0.15–0.81]	0.37 [0.17–0.83]	0.40 [0.18–0.90]
Born outside Europe	0.60 [0.40–0.90]	0.80 [0.53–1.21]	0.74 [0.50–1.09]	0.82 [0.53–1.25]
Single parent or other (ref. living with partner)	0.81 [0.56–1.18]	0.90 [0.61–1.33]	0.85 [0.57–1.26]	0.88 [0.58–1.34]
Poor/fair health (ref. good/excellent)	3.09 [2.45–3.92]		2.59 [1.98–3.39]	
Delayed/very delayed development (ref. average/in advance)	2.62 [2.13–3.23]		1.92 [1.52–2.42]	
Perinatal risk (ref. lower)				
Moderate	0.93 [0.71–1.23]			0.97 [0.75–1.25]
Higher	1.25 [0.95–1.66]			1.09 [0.82–1.46]
Cerebral palsy	2.91 [2.14–3.95]			2.08 [1.44–3.00]
Epilepsy	2.53 [1.57–4.08]			1.92 [1.07–3.46]
Autism	1.78 [1.04–3.05]			1.37 [0.76–2.46]
Moderate/severe vision or hearing problem	2.25 [1.52–3.34]			1.65 [1.01–2.69]
Country (ref. mean)				
Belgium	0.72 [0.47–1.11]	0.66 [0.43–1.03]	0.63 [0.41–0.97]	0.70 [0.44–1.11]
Denmark	2.67 [1.89–3.77]	2.81 [1.99–3.96]	2.95 [2.10–4.14]	2.91 [2.03–4.19]
Estonia	1.02 [0.60–1.73]	0.91 [0.53–1.56]	0.80 [0.46–1.40]	0.75 [0.41–1.38]
France	0.40 [0.29–0.56]	0.42 [0.30–0.60]	0.46 [0.33–0.65]	0.46 [0.32–0.66]
Germany	1.38 [0.97–1.97]	1.44 [0.92–2.23]	1.53 [1.00–2.34]	1.47 [0.93–2.32]
Italy	0.73 [0.55–0.96]	0.81 [0.61–1.07]	0.81 [0.62–1.05]	0.83 [0.62–1.10]
Netherlands	0.54 [0.29–1.00]	0.53 [0.29–0.98]	0.58 [0.32–1.07]	0.52 [0.27–1.02]
Poland	2.07 [1.49–2.88]	1.93 [1.39–2.68]	1.80 [1.31–2.48]	1.95 [1.40–2.72]
Portugal	0.72 [0.52–1.00]	0.77 [0.55–1.07]	0.83 [0.60–1.14]	0.78 [0.56–1.10]
Sweden	1.38 [0.88–2.18]	1.36 [0.87–2.15]	1.26 [0.81–1.98]	1.41 [0.85–2.34]
United Kingdom	1.13 [0.84–1.52]	1.12 [0.82–1.53]	1.06 [0.78–1.45]	1.03 [0.72–1.46]

All risk ratios are derived from weighted, multilevel generalized linear regression models, accounting for correlation between siblings.

to all specialists. A visit to a specialist is associated with an additional trip, and I do not always have a transport and unfortunately there is still a very long waiting time for some specialists." – Parent, Poland (care rating: Good)

The second most frequent theme was (II) Follow-up type and content. Two common suggestions included having *more frequent* or *longer follow-up*. The reasons included reassuring parents that the child was reaching important developmental milestones, to know whether the child was ready for school and/or needed school support. A few parents felt that follow-up was unnecessary when their child was doing well.

"There should be a follow-up when the children reach school age to see how they are developing and whether they are ready to go to school." – Parent, Denmark (care rating: Fair)

Improving follow-up with *additional examinations or therapies*, especially before school start, and *following up on other areas apart from physical health*, such as emotional and mental health, were two frequent subthemes in this category.

"Preterm children could have a check every year, especially hearing, vision and psychologist. There should definitely be a check before school." – Parent, Estonia (care rating: Good)

"Follow-up on physical health was fine. Follow-up on mental health and "invisible" late effects were non-existent. We were all alone with those things and ended up seeking help from a private consultant." – Parent, Denmark (care rating: Poor)

*Improving healthcare professionals' communication with parents*, in category (III) Communication and parent support, was the most

**Table 4.** Free-text themes and subthemes ordered by the number of suggestions and with ranking by healthcare rating.

In your experience, how could the healthcare for very preterm children be improved?						
Theme (N suggestions)	Subtheme	N suggestions	Rank			
			All	Good/excellent	Poor/fair	
Coordination of follow-up and healthcare (478)	<b>Improve care coordination between providers</b>	<b>150</b>	<b>2</b>	<b>2</b>	<b>1</b>	
	<b>Train generalists or follow-up staff about prematurity</b>	<b>69</b>	<b>6</b>	<b>9</b>	<b>5/6</b>	
	<b>Provide more equitable access to follow-up</b>	<b>68</b>	<b>7</b>	<b>6</b>	<b>5/6</b>	
	<b>Shorten waiting times and queuing</b>	<b>60</b>	<b>9</b>	<b>8</b>	<b>8</b>	
	Involve additional or more appropriate healthcare providers in follow-up	47	11		<b>10<sup>a</sup></b>	
	Improve timeliness of healthcare or follow-up	42	12			
	Improve hospital transfer and re-hospitalization practices	22	16			
	Reduce out-of-pocket costs	20	18			
	Follow-up type and content (377)	<b>Improve follow-up frequency</b>	<b>103</b>	<b>3</b>	<b>3</b>	<b>3</b>
		<b>Increase follow-up duration</b>	<b>84</b>	<b>4</b>	<b>5</b>	<b>4</b>
<b>Offer specific examinations or therapies</b>		<b>61</b>	<b>8</b>	<b>7</b>	<b>9</b>	
<b>Offer follow-up beyond physical health</b>		<b>56</b>	<b>10</b>	<b>10</b>	<b>10<sup>a</sup></b>	
Change nature or type of follow-up		27	14			
Improve general quality of follow-up or content		25	15			
Offer home visits or home care		21	17			
Communication and parent support (283)	<b>Improve communication with parents or interpersonal relationship</b>	<b>166</b>	<b>1</b>	<b>1</b>	<b>2</b>	
	<b>Offer parent follow-up and psychological or emotional support</b>	<b>75</b>	<b>5</b>	<b>4</b>	<b>7</b>	
	Offer practical support to parents	33	13			
	Facilitate parents' peer-to-peer communication	9	20			
Macro-social context (44)	Train school staff about prematurity	14	19			
	Increase length of parental leave	9	21			
	Offer school support for child	8	22			
	Invest in research on prematurity or related healthcare	5	23			
	Increase healthcare investment	5	24			
	Improve media coverage of premature birth	3	25			

In bold type: top 10 themes overall and by rating.

<sup>a</sup>Equal number of suggestions.

frequent subtheme overall. Main issues were lack of communication from healthcare providers and lack of information sharing with parents regarding medical procedures, follow-up and medical services available, how to care for a child born very preterm, and what to expect regarding the child's long-term health or schooling. Some suggestions concerned interpersonal aspects, such as lack of empathy or listening, or requesting a more humane or positive attitude from healthcare providers.

"It was explained in the neonatal unit that in the future we may come across problems such as learning difficulties, vision, hearing, developmental delay. However, it was never explained if and what services would help overcome any of these problems." – Parent, UK (care rating: Poor)

Parents also frequently suggested *psychological or emotional support for the parents* themselves as part of the long-term follow-up after discharge. They expressed a feeling of being left alone to cope with the trauma of very preterm birth and the burden of taking care of their child after discharge, without sufficient psychological support for both parents.

"I, as a mother, would have wished for better support after discharge. After the hospital stay, you are left alone with your worries and fears". – Parent, Germany (care rating: Excellent)

"Making room for parents too, because also the motherhood was premature." – Parent, Italy (care rating: Fair)

Subthemes were similar across countries (not shown) and similarly ranked for parents who rated the healthcare as poor or fair and those who rated healthcare as good or excellent.

## DISCUSSION

Overall, 14.2% of the children in our study received healthcare that their parents rated as poor or fair, with variation between 6.1% and 31.6% by country. However, dissatisfaction was significantly higher for children with health or developmental problems; up to over one-third when children had a diagnosis of cerebral palsy or epilepsy or when parents rated their children's health as poor or fair. Dissatisfaction with post-discharge care was more frequent among mothers with higher educational status. Thematic analysis



of 971 parental responses identified 4 themes and 25 subthemes about how healthcare could be improved, which were largely similar across countries.

The strengths of this study include its population-based design, geographic diversity, large sample size, and the use of a standardized, pre-tested questionnaire. A strength, but also a limitation, of the study is the wide definition of post-discharge healthcare covering the period between neonatal intensive care unit (NICU) discharge and 5 years of age. As follow-up programs and health services vary across countries in terms of availability, content, and duration, our questionnaire intentionally referred to a large range of services over a long period of time. Thus we are able to measure overall perceptions with how very preterm birth is managed in the long term across countries, but we cannot know if parents referred to specific care aspects in their ratings (medical quality, screening, interventions etc.), unless parents specified the service or time period in the free-text answers. The free-text question intentionally leads parents toward more negative experiences, as it focused on aspects requiring improvement in care. However, the long time period may lead parents to refer care ratings either to more recent care or care related to more difficult and stressful experiences, which may have happened around NICU discharge and in early childhood when medical follow-up is more intense. In the latter case, the ratings may be more negative than if the question had covered a more proximate period. Unfortunately, we did not have data on the characteristics of services received nor objective measures of the quality of services, such as waiting times or service availability, to contrast with parental perceptions. Another potential limitation relates to the multilingual nature of our sample, in particular when interpreting the free-text responses. When translation is part of the research process, it inevitably involves a degree of interpretation<sup>28</sup> and may increase the risk of misinterpretation of answers.<sup>29</sup> To minimize this risk, we used an iterative process for the translation and interpretation using automatic translation, followed by coding of keywords and finally a review of translation accuracy and interpretation by researchers in each of the study countries. A final limitation was the potential for bias linked to non-response, which was 45.5% for the overall sample and higher in some countries.<sup>19</sup> Loss to follow-up is a challenge in longitudinal cohort studies,<sup>30</sup> especially those with population-based designs, and can be related to characteristics that may affect healthcare perceptions. We used inverse probability weights to adjust for attrition bias. Reassuringly, results based on the unweighted and weighted analyses were similar but slightly increased the association between mother's educational level and dissatisfaction as well as perinatal health and dissatisfaction. Previous studies in this cohort have shown that the association between sociodemographic or perinatal factors and health-related outcomes may be accentuated when using these weights,<sup>21</sup> as increased loss to follow-up in socially disadvantaged groups is taken into account.

The proportion of poor/fair ratings varied widely across countries. The study countries differ on several structural aspects that may have contributed to these differences but that we were not able to measure, such as the organization of primary care,<sup>31</sup> level of integrated care in the case of multi-morbidity,<sup>31</sup> patients' ability to pay for out of pocket costs,<sup>32</sup> and the state's involvement in the healthcare system.<sup>33</sup> Furthermore, follow-up and subsequent care are likely to have been organized very differently across the regions, including access to specialists,<sup>23</sup> as no international standards for follow-up existed at the time. Follow-up programs aim to facilitate care coordination and timely intervention and might in its absence have contributed to differences in overall satisfaction. Our study was not designed to link parental perceptions to specific health system features and this remains an area for further research. Differences in ratings could also be related to factors unrelated to the healthcare system. Research on adult patients has proposed that care

satisfaction is to a large extent influenced by individual factors, such as personality, expectations about healthcare, and health status.<sup>34</sup> Patient expectations, in turn, have been associated with several characteristics, including patient age and educational level,<sup>34,35</sup> which could explain the association between parents' educational status and dissatisfaction in our study. Unknown broader societal factors<sup>34</sup> may explain the differences in ratings that remained across countries after adjusting for child health and parent sociodemographic factors. The subjectivity of the satisfaction measure in our study may accentuate the impact of individual and social factors,<sup>36</sup> which involve expectations and for which there is no common base level,<sup>36</sup> as well as different levels of "tolerance" toward service quality, which may depend on the general standard of living in the country.<sup>36</sup> This may partly explain the differences in ratings for native-, European-, and non-European-born mothers. Finally, the inclination to express dissatisfaction or complaints may also be cultural<sup>37</sup> and influence levels of dissatisfaction across countries, but there is, to our knowledge, little evidence on the impact of culture on care perceptions across Europe. The unexplained differences in parents' perceptions may partly mean that care satisfaction represents something different in each country.<sup>38</sup>

The parents' suggestions concerning how healthcare could be improved were predominantly the same across countries. The suggestions were mainly organizational (follow-up coordination, provider training, access to services, and timeliness), but the most frequently mentioned subtheme concerned interpersonal aspects (healthcare-provider communication and relationship with parents). Similar themes have been found in other studies,<sup>7,9,10,16,39,40</sup> suggesting that healthcare providers may be subject to similar shortcomings regardless of follow-up content and healthcare context. Of note was that many parents had suggestions for improving healthcare despite rating their care as good or excellent, and these were largely similar to parents expressing dissatisfaction. This apparently paradoxical result suggests that even parents who are satisfied with their care in general experience difficulties with care coordination or have unsatisfactory interactions with providers.

Parents of children with health or developmental problems were less satisfied with healthcare, but few suggestions centered on health outcomes, medical quality, or technical aspects of care. Other studies have found that dissatisfaction with healthcare services does not necessarily reflect poor medical quality of care<sup>7,22</sup> but rather poor communication, especially when patients have major disabilities<sup>41</sup> or complex healthcare needs.<sup>8</sup> Additionally, poor organization of healthcare may become more apparent for parents whose children require complex multidisciplinary care compared to those with less complex health problems, not seeking healthcare to the same extent. It is also possible that dissatisfaction with health services has an impact on the further use of follow-up and health services, such as change of care provider, seeking care in the private sector, or discontinuing follow-up. We do not have data on unmet service need, which is particularly difficult to define in our European cohort because of differences in healthcare systems and this remains an area for further investigation. Our results are consistent with those from the Models of Child Health Appraised (MOCHA) study, which showed that European countries are failing to manage complex healthcare needs in the general pediatric population, with no policies for care coordination and care planning after discharge.<sup>42</sup> The lack of integrated healthcare systems for complex care manifests as a lack of multidisciplinary care and inconsistent healthcare provision depending on where care is sought and may ultimately negatively affect quality of care and health outcomes.<sup>43</sup> The parents' suggestions in our study coincide with policy improvements currently being recommended for the follow-up of preterm births, such as multidisciplinary follow-up,<sup>44</sup> follow-up until school age,<sup>45</sup> and parent support.<sup>46</sup> Further improvements

based on parents' lived experiences should be considered in policy strategies.

Over one in ten children born very preterm received post-discharge care that their parents rated as poor or fair, with the highest rates for children who are most reliant on health services. Many parents provided suggestions for improving care, which centered on common themes, despite the wide geographic heterogeneity in ratings. Parents constitute a valuable resource for researchers and policy makers seeking to improve healthcare and for understanding failures in the healthcare system.

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A.-V.S., E.S.D., L.T., R.E.R., S.P., H.P., M.C., J.Z., and the SHIPS Research Group made substantial contributions to conception and design and acquisition of data. A.-V.S., P.S., and J.Z. analyzed the data. A.-V.S., P.S., E.S.D., L.T., R.E.R., S.P., H.P., L.J.J.Z., M.C., and J.Z. contributed to interpretation of data, drafting the article, revising it critically for important intellectual content, and approved the final version to be published. Members of the SHIPS research group approved the final version to be published.

## ADDITIONAL INFORMATION

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# Chapter 6: Follow-up after very preterm birth in Europe

## 6.1 Preface

Routine follow-up for children born VPT aims to detect emerging health and developmental problems early to enable timely interventions and appropriate management of care from multiple providers. However, studies suggest that some groups of children, especially from socially vulnerable families, have lower follow-up attendance and less access to early intervention services. We also showed in chapters 4 and 5 that use of specialist services and satisfaction with post-discharge care varies widely across countries in Europe and that there may be weaknesses in the care systems managing long-term care and follow-up for children born VPT, especially concerning care coordination and care for children who are most reliant on health care services. We know that follow-up policies differ across Europe, but we do not have an overview of the actual use of routine follow-up services in children born VPT and whether follow-up may be lower in certain sub-populations.

The third article in this doctoral project gives an overview of post-discharge routine follow-up in infants born VPT until five years of age in regions from 11 European countries. We used data from the parental questionnaires at two and five years of age to determine rates of starting and continuing routine follow-up until five years of age in the cohort. We also assessed whether perinatal risk and family sociodemographic determinants have any impact on follow-up enrolment and continuation.

We found that less than one-third of these children born VPT were still in follow-up at five years, with variations from 10% to 60% across countries. Children with perinatal risk factors were more likely to enter and continue follow-up, whether children from socially vulnerable families were less likely to enter follow-up.

Variations in routine follow-up rates are expected, as there is no consensus in Europe on optimal duration and coverage for follow-up. However, our study made it possible to illustrate the extent of these disparities. Further, the sociodemographic barriers to entering routine follow-up are concerning, as socially at-risk populations may benefit most from routine follow-up services. These results raise questions on whether these disparities may be related to geographical and sociodemographic disparities in care received by children born VPT until five years of age.

This work is presented here as a submitted, pre-peer review manuscript, with supplementary material presented at the end of the document: Appendix D1.

## Follow-up after very preterm birth in Europe

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## **Abstract**

**Background:** Long-term follow-up is essential for managing neurodevelopmental and health problems in children born very preterm, but data on follow-up are sparse, especially beyond two years of age.

**Methods:** We describe follow-up service use and associated perinatal and social characteristics in an area-based cohort of births <32 weeks' gestation in 19 regions from 11 European countries. Perinatal data were collected from medical records and data at two and five years from parental questionnaires.

**Results:** 27.3% of 3635 children used follow-up services at five years. Children of less educated, younger and migrant mothers were less likely to start follow-up; perinatal risk factors influenced continuation of follow-up. Follow-up rates at five ranged from 10.0% to 60.2% across countries after adjustment for perinatal and social risks.

**Conclusions:** Socially vulnerable children were less likely to use follow-up services. Marked disparities in five-year follow-up in Europe illustrate a lack of consensus on optimal follow-up duration.



## **Introduction**

Follow-up programs aim to facilitate detection of neurodevelopmental and health problems and to enable early intervention for children born very preterm, i.e. before 32 weeks of gestational age (GA), who have a higher risk of impairment compared to term-born infants.<sup>1</sup> However, research suggests that follow-up attendance may be lower in children from socially disadvantaged families,<sup>2</sup> who might benefit the most from interventions.<sup>3</sup> Comprehensive and multidisciplinary post-discharge follow-up has been recommended for all children born very preterm until school age,<sup>4</sup> but recommendations differ regarding eligibility, frequency, duration and content of long-term follow-up.<sup>5-9</sup> Although the importance of follow-up is widely acknowledged, data on its use is sparse, especially beyond the first two years of life. This study aimed to describe the use of routine follow-up services and associated perinatal and social characteristics among children born very preterm in 19 regions in 11 European countries.

## **Methods**

### *Study population*

The data were collected for the EPICE (Effective Perinatal Intensive care in Europe) and SHIPS (Screening to improve Health In very Preterm infantS) studies which constituted and followed up an area-based cohort of children born between 22+0 weeks and 31+6 weeks of gestation in 2011/2012 in all maternity units in 19 regions across 11 European countries.<sup>10</sup> Maternal and perinatal data were collected from obstetric and neonatal records using a standardised, pretested protocol and parents completed questionnaires at two years of CA and at five years. Out of 7900 live births, 6792 were discharged home from neonatal care; at five years, 6759 children were alive and 3635 (53.8%) participated in the study.

### *Follow-up services*

Our main outcome was parent-reported use of routine follow-up services for their children until five years of age. At two years' CA, parents provided information on use of routine follow-up services since discharge from neonatal care. In the five-year questionnaire, they were asked: "Does your child have routine check-ups for children born prematurely? No, never; No, not anymore; Yes, still has check-ups". For both questionnaires, the terminology was adapted to how care was organised locally (Supplemental table 1). Children were classified as never starting follow-up if no participation in follow-up was reported at either time point by parents. Children were classified as no longer in follow-up if they had started follow-up, but were not receiving check-ups anymore at five years.

### *Perinatal and sociodemographic risk factors*

Characteristics hypothesised to relate to child health and use of routine follow-up services included: maternal age at delivery, parity, multiple birth, mother's educational level (lower secondary, upper or post-secondary or short cycle tertiary, and bachelor degree or higher), maternal country of birth (native-born, born in Europe, born outside Europe), GA, small for gestational age (SGA), a composite variable of severe neonatal morbidity (retinopathy of prematurity stages III–V, grade III-IV intraventricular haemorrhage, diagnosis of cystic periventricular leukomalacia or necrotizing enterocolitis needing surgery), bronchopulmonary dysplasia (BPD), defined as supplemental oxygen or artificial ventilation at 36 weeks' postmenstrual age, any congenital anomaly and child sex.

### *Statistical analysis*

We assessed the association between perinatal and sociodemographic factors and country and the probability of never, no longer and still using routine follow-up services with Chi<sup>2</sup> tests and multinomial regression models with robust variance estimators to take into account correlation between siblings in multiple pairs. We estimated adjusted proportions of children still using routine follow-up services at five years by country, for the total sample and for a subsample of all children born <28 weeks' GA, using predicted margins. To account for study attrition bias, inverse probability weights were used to give higher weight to children with characteristics of non-responders.<sup>10</sup> STATA 14.2 was used for analyses (Stata Corp., College Station, TX, USA).

### *Ethics*

Each country team obtained ethical approvals locally. The French Advisory Committee on Use of Health Data in Medical Research (CCTIRS) and the French National Commission for Data Protection and Liberties (CNIL) provided authorisations for constituting the European database.

## **Results**

Parents reported that 27.3% of the children were still using routine follow-up services at five years of age, with variation between countries from 10.9% to 58.4%; 9.7% had never used follow-up services, ranging from 0.0% to 21.5% (Table 1). Never using follow-up services was associated with mothers' sociodemographic characteristics, including younger age, low educational level and being born outside Europe, as well as with lower perinatal risk. The risk of starting but no longer using follow-up services at five years was higher for children with mothers born outside of Europe but lower for children with perinatal risk factors (lower GA, SGA, BPD, male sex). Adjustment for perinatal and social characteristics failed to explain

differences between countries in use of follow-up services at five years of age which ranged from 10.0% to 60.2% in the whole sample and from 11.9% to 75.7% in children born <28 weeks' gestation (Figure 1).

## **Discussion**

Reported use of follow-up services was high (90.3%) for the children in our cohort; however, less than one-third (27.3%) reported still using follow-up services at five years. Perinatal risk factors were positively associated with starting and continuing follow-up. In contrast, sociodemographic risk factors were principally associated with a higher risk of never starting follow-up. Children with mothers born outside of Europe were also less likely to continue follow-up. The main factor associated with using follow-up services at five years was country.

This study's strengths are its use of population-based, standardised data on perinatal and social factors and common pretested questions about follow-up services from regions in diverse European countries. Some parents who reported not using follow-up at five years may not have accurately recalled using these services, although responses at two years allowed us to verify use of these services and complete data at five years. Another limit relates to cohort attrition which may lead to over-estimation of follow-up service use. To mitigate this, we adjusted for known correlates of non-response using inverse probability weights.

Children with younger, less educated and migrant mothers faced higher risks of never starting follow-up. Other studies have also shown that social barriers affect entering follow-up services.<sup>11</sup> Reasons for non-attendance may be both structural, such as failing to contact families, or lower referral rates in units that serve disadvantaged populations<sup>11</sup> and individual, such as declining appointments.<sup>2</sup> This is of major concern as these children are more vulnerable to the neurodevelopmental consequences of very preterm birth, and may benefit most from early interventions.

Children with perinatal risk factors, such as lower GA and neonatal morbidities, were more likely to start and continue using follow-up services, as found elsewhere.<sup>2</sup> This is expected, as enrolment criteria in follow-up programmes are based on perinatal risk factors for health and developmental problems.<sup>5,6</sup> After standardising on these characteristics, continued use was strongly influenced by country. These wide variations illustrate the absence of consensus on a common model for follow-up care, reflected in heterogeneous guidelines for enrolment criteria

and duration of routine follow-up services.<sup>5-9</sup> They may also result from differences in health service availability and organisation which should be investigated in future studies.

## **Conclusion**

Among children born very preterm, family sociodemographic characteristics were associated with never starting follow-up. This, together with the marked disparities in use of follow-up services at five years of age within European health systems, reveals the need for better evidence on optimal follow-up organisation and duration.

## **What is already known on this topic?**

- Follow-up programs for children born very preterm aim to facilitate detection of neurodevelopmental and health problems and to enable early intervention
- Follow-up policies differ regarding eligibility, frequency, duration and content across countries in Europe
- Attendance at routine follow-up programmes may be lower in children from socially disadvantaged families

## **What this study adds**

- Despite high use of routine follow-up services overall, less than one-third of children born very preterm continued follow-up at 5 years across regions in Europe
- Perinatal risk factors were positively associated with starting and continuing follow-up whereas sociodemographic risk factors were associated with a higher risk of never starting follow-up
- Country was the main determinant for using follow-up services with ranges from 10.0% to 60.2% after adjustment for population characteristics

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**Table 1:** Family sociodemographic and perinatal factors associated with routine follow-up for children born very preterm at five years of age

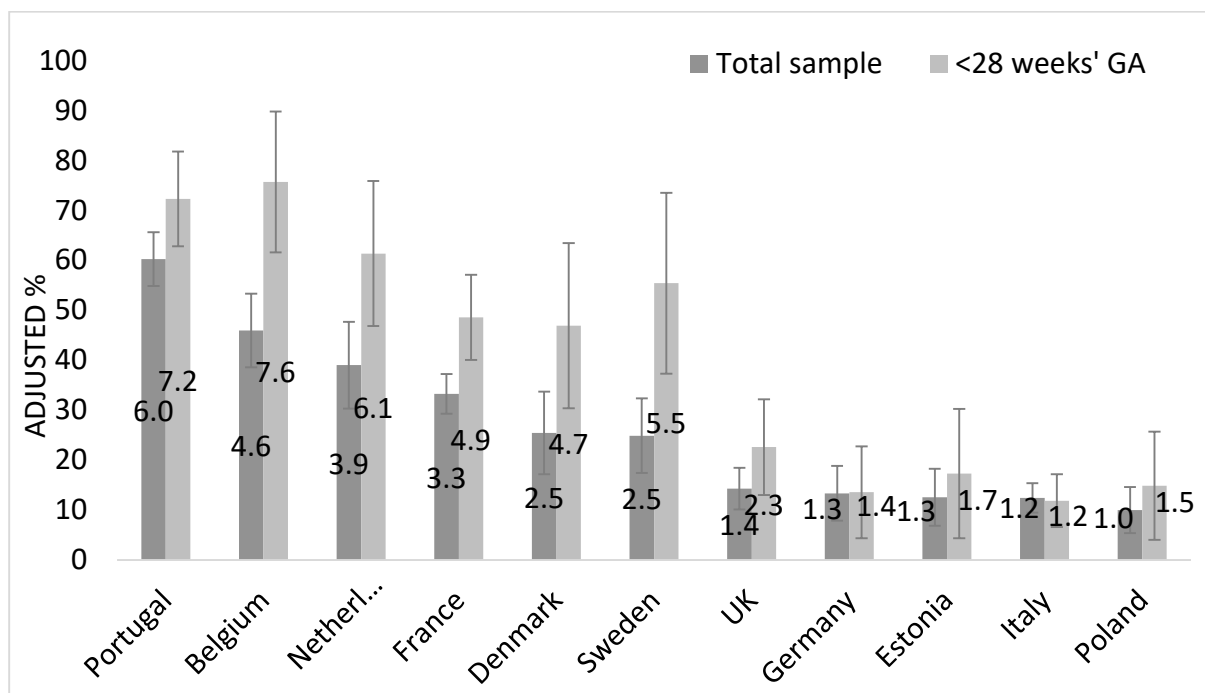
Does child have routine check-ups for children born very preterm at five years?	N	No, never %	Not anymore %	Yes, still %	Reference: Still in follow-up at 5 years			
					No, never		Not anymore	
					aRR	[95% CI]	aRR	[95% CI]
<b>Mother's age at delivery, years</b>								
<=24	422	17.3	55.2	27.5	2.0	[1.2 - 3.5]	1.1	[0.8 - 1.6]
25-34	2057	9.2	63.0	27.8	ref		ref	
35=<	1098	6.8	67.2	26.0	0.7	[0.5 - 1.2]	1.0	[0.8 - 1.3]
<b>Parity at delivery</b>								
Multiparous	2156	8.3	63.6	28.1	ref		ref	
Nulliparous	1390	11.2	62.7	26.1	1.1	[0.7 - 1.6]	1.0	[0.8 - 1.2]
<b>Multiple birth</b>								
No (singleton)	2531	10.6	62.0	27.4	ref		ref	
Yes (twins or more)	1056	7.5	65.4	27.1	0.5	[0.3 - 0.9]	1.0	[0.7 - 1.2]
<b>Mother's educational level<sup>a</sup></b>								
Lower	589	13.7	58.9	27.4	2.0	[1.1 - 3.5]	0.9	[0.7 - 1.3]
Intermediate	1474	9.7	64.0	26.3	1.4	[0.9 - 2.2]	0.8	[0.7 - 1.1]
Higher	1478	6.3	66.3	27.4	ref		ref	
<b>Country or birth</b>								
Native	2857	8.9	63.5	27.6	ref		ref	
European born	238	7.7	63.9	28.4	0.9	[0.4 - 2.0]	0.8	[0.5 - 1.2]
Born outside Europe	476	13.3	61.9	24.9	2.5	[1.4 - 4.2]	1.4	[1.0 - 1.9]
<b>Gestational age, completed weeks</b>								
<26	305	5.5	53.9	40.6	0.2	[0.1 - 0.4]	0.3	[0.2 - 0.5]
26-27	657	6.0	54.2	39.9	0.2	[0.1 - 0.4]	0.5	[0.4 - 0.6]
28-29	937	6.3	66.1	27.6	0.3	[0.2 - 0.5]	0.7	[0.6 - 0.9]
30-<32	1688	13.8	66.2	20.0	ref		ref	
<b>Small for gestational age</b>								
<3 centile	766	7.7	62.0	30.2	0.5	[0.3 - 0.7]	0.7	[0.5 - 0.9]
3 - 9 centile	417	11.0	59.3	29.6	1.0	[0.6 - 1.6]	0.7	[0.5 - 0.9]
≥10 centile	2404	10.2	63.8	26.0	ref		ref	
<b>Any severe neonatal morbidity<sup>b</sup></b>								
No	3141	10.4	63.5	26.1	ref		ref	
Yes	365	5.0	57.7	37.3	0.5	[0.2 - 1.1]	0.9	[0.7 - 1.3]
<b>Bronchopulmonary dysplasia</b>								
No	3034	10.7	64.4	24.9	ref		ref	
Yes	466	3.8	53.8	42.4	0.4	[0.2 - 0.8]	0.6	[0.5 - 0.9]
<b>Congenital anomaly</b>								
No	3292	9.9	62.7	27.4	ref		ref	
Yes	295	8.5	65.5	26.0	0.6	[0.3 - 1.2]	0.9	[0.6 - 1.2]
<b>Child sex</b>								
Male	1914	10.0	59.3	30.7	0.9	[0.6 - 1.3]	0.7	[0.6 - 0.9]
Female	1673	9.4	67.1	23.5	ref		ref	
<b>Country (Region)</b>					(ref Sample mean)		(ref Sample mean)	
Portugal (Lisbon, Northern Region)	425	4.8	36.8	58.4	0.6	[0.3 - 1.2]	0.2	[0.1 - 0.2]
Belgium (Flanders)	259	12.8	40.5	46.7	3.6	[2.0 - 6.3]	0.3	[0.2 - 0.4]
Netherlands (Central Eastern)	146	6.3	52.2	41.5	1.7	[0.7 - 4.1]	0.5	[0.3 - 0.7]
France (Burgundy, Ile-de-France, Northern Region)	770	10.3	58.6	31.2	3.0	[1.9 - 4.6]	0.6	[0.5 - 0.8]
Denmark (Eastern Region)	151	10.8	62.5	26.7	6.3	[2.9 - 13.8]	0.9	[0.6 - 1.4]
Sweden (greater Stockholm)	141	2.8	70.7	26.6	1.1	[0.2 - 6.3]	1.0	[0.7 - 1.5]
UK (East Midlands, Northern, Yorkshire & the Humber)	419	13.6	69.4	17.0	10.9	[6.1 - 19.4]	1.9	[1.4 - 2.7]
Germany (Hesse, Saarland)	266	21.5	65.4	13.0	21.1	[11.3 - 39.4]	1.9	[1.2 - 3.1]
Estonia (entire country)	133	0.0	87.2	12.8	0.0	[0.0 - 0.0]	2.6	[1.6 - 4.2]
Italy (Emilia-Romagna, Lazio, Marche)	691	4.5	83.2	12.3	4.5	[2.3 - 8.7]	2.5	[1.9 - 3.3]
Poland (Wielkopolska)	186	13.4	75.7	10.9	18.9	[9.4 - 38.3]	2.9	[1.8 - 4.8]

Inverse probability weights after multiple imputation were used for all analyses

<sup>a</sup> Lower: ISCED levels 0-2 (Lower secondary); Intermediate: ISCED level 3-5 (upper or post-secondary, non-tertiary or short cycle tertiary); Higher: ISCED level 6-8 (Bachelor degree or higher).

<sup>b</sup> Intraventricular haemorrhage grades III-IV, cystic periventricular leukomalacia, retinopathy of prematurity stages III-V or necrotising enterocolitis needing surgery

**Figure 1:** Continued routine follow-up at 5 years by country<sup>a</sup> after adjustment for perinatal and social characteristics<sup>b</sup> for all children born very preterm and for children born extremely preterm (<28 weeks of GA)



<sup>a</sup>Regions in: 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 and Northern region); Sweden (greater Stockholm) and the United Kingdom (East Midlands, Northern, and Yorkshire & the Humber regions)

<sup>b</sup>Mother's age at delivery, parity at delivery, multiple birth, mother's educational level, mother's country or birth, GA, SGA, any severe neonatal morbidity, BPD, congenital anomaly and child sex

# **Chapter 7: Elevated health care use at five years of age in children born very preterm in a European cohort: association with social circumstances and access to routine follow-up services**

## **7.1 Preface**

Follow-up has recently been recommended by a European expert group for all children born VPT until school age because of their elevated risk of health and developmental problems. Studies have shown that the use of health care services and the risk of hospitalisation increases with decreasing gestational age. Multiple, or complex, health and developmental needs require additional efforts from health care systems to avoid undesirable health and health care outcomes, and follow-up has an important role in identifying children with such need and in managing care access and early interventions for these children.

However, in chapters 4 and 6 we showed varying rates of specialist health service use and routine follow-up participation across the study countries that were not explained by differences in perinatal risk factors. In chapter 5, parents of children with health and developmental problems reported higher dissatisfaction with care, and in chapter 6, we found that children from socially vulnerable families were less likely to get enrolled in follow-up. This led us to ask questions on the impact of social factors on health care service use beyond two years of age, and the relationship between routine follow-up and equitable use of health care services, especially in children with the most elevated care needs. The existing literature on children born VPT has sparse data on longer-term post-discharge health care and existing studies have tended to focus on inpatient hospitalisations because these data are available in routine sources.

In the fourth and last study in this doctoral project, we give a comprehensive overview of health care service use at five years of age by children born VPT in the EPICE cohort. We investigate cross-country differences in elevated service use, whether social factors are associated with elevated service use, and whether extensive routine follow-up may alter such associations.

We found continued high use of health services at five years of age, including elevated use of outpatient and inpatient care as well as specialist services. Children from socially vulnerable



families were more likely to use outpatient or ER services or to be hospitalised, whereas children born in countries with higher routine follow-up coverage at five years of age were less likely to do so. These results suggest that VPT-born children with social disadvantage may be getting less optimal care, and that continued follow-up may play a role in helping parents navigate the complex care needs of their children born VPT.

This work is presented here as a draft manuscript, with supplementary material presented at the end of the document: Appendix E1-E4.

# **Elevated health care use at five years of age in children born very preterm in a European cohort: association with social circumstances and access to routine follow-up services**

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**Short title:** Elevated health care use at five years of age in children born very preterm in Europe

## **Abstract**

*Background:* Very preterm birth (<32 weeks' gestation) has long-term health and developmental consequences, with an increased risk especially in children from socially vulnerable families. While many studies have investigated long-term health and developmental outcomes, there is a paucity of data on health service use beyond early childhood in this population. We aimed to describe the use of health care services at five years of age, identify perinatal and social factors associated with elevated service use and assess associations with routine follow-up in children born very preterm.

*Methods:* We used data from the EPICE area-based cohort of births <32 weeks' gestation from 11 European countries. Perinatal data were collected from medical records and health care service use over the past year and sociodemographic data from parental questionnaires at five years of age. Using criteria from the literature, we defined elevated outpatient/inpatient care ( $\geq 4$  sick-care visits to general practitioner, pediatrician or nurse,  $\geq 3$  emergency room visits, or  $\geq 1$  overnight hospitalization) and specialist care ( $\geq 2$  different specialists consulted or  $\geq 3$  specialist visits) and assessed associated perinatal and social factors. To explore the association between routine follow-up and service use, we distinguished between children living in countries with higher versus routine follow-up rates at five years.

*Results:* 44% of children received elevated outpatient/inpatient care and 49% elevated specialist care at five years of age. Social factors were more strongly associated with use of outpatient/inpatient than specialist services. Lower gestational age and neonatal morbidities were the main predictors of elevated specialist service use. Living in a country with higher routine follow-up coverage was associated with less use of outpatient/inpatient but not specialist services.

*Conclusions:* Children born very preterm have high health care service use at five years of age. Children in socially vulnerable families may receive less optimal care, and routine follow-up until five years may help parents avoid frequent use of outpatient and inpatient services.

## **Introduction**

Very preterm (VPT) birth (<32 weeks' gestation) has long-term consequences beyond neonatal intensive care hospitalization. Health and developmental problems associated with VPT birth are heterogeneous and often multiple, including neurosensory, cognitive, motor, behavioral, mental health, pulmonary and growth problems (1-5). Studies have shown that children born VPT require more health care in childhood (1, 6), and have higher health care-related costs compared to children born at or close to term (7). To date, research has mainly focused on hospital admissions or health service use in the first two years of life (8). However, a more comprehensive assessment of health service use in this population is important to identify the range of services required, ensure adequate resources for families and evaluate the accessibility and quality of health care.

Follow-up programs for children born VPT aim to identify health and developmental problems early, initiate early interventions and coordinate care provision. Early interventions have shown benefits for early health (9) and cognitive, language and motor outcomes (10), particularly in children from socially disadvantaged families, who have higher risks of adverse health and developmental outcomes (5, 11-13). Thus, follow-up may help mitigate the negative impact of social circumstances on health and development and improve equity in healthcare. However, follow-up (14-16) and early intervention attendance (17) may be lower in children with social risk factors.

European countries face challenges managing care for the children most reliant on health services; the Models of Child Health Appraised (MOCHA) study showed a lack of post-discharge care coordination and policies for children with complex care needs (18), which could compromise care provision and quality (19). Efficient care coordination can prevent unnecessary family stress and undesirable care, such as emergency room visits and excess

hospitalizations (20), whereas inadequate access to health care can have adverse impact on the child's health and their family's wellbeing (21). Parents of children born VPT in the Effective Perinatal Intensive Care in Europe (EPICE) cohort were more dissatisfied with healthcare services when children had complex health problems, such as cerebral palsy or autism (22) and identified poor care coordination and organization as priority areas for improving post-discharge care.

This study aimed to provide a comprehensive description of health service use among children born VPT at five years of age in 19 regions in 11 European countries, identify children with elevated, i.e. the highest health service use, and assess perinatal and social factors associated with elevated service use. Given differences in routine follow-up for children born VPT at five years of age in participating countries (16), we also sought to determine whether living in a country with higher long-term routine follow-up coverage affected these associations.

## **Methods**

### *Data source*

The data were collected as part of the Screening to improve Health In very Preterm infantS (SHIPS) project, a five-year follow-up of the population-based EPICE cohort of VPT births in 19 regions in 11 European countries (23): 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 and Northern region); Sweden (greater Stockholm) and the United Kingdom (East Midlands, Northern, and Yorkshire & the Humber regions).

### *Study population*

The cohort included all children born between 22+0 weeks and 31+6 weeks of gestation in all maternity units over 12 months (between April 2011 and September 2012), except in France, where births were included over six months. Out of 7,900 live births; 6,792 infants were discharged home alive and 6,759 were alive and invited to the follow-up at five years, of whom 3,635 (53.8%) participated.

### *Data*

Pregnancy, perinatal and sociodemographic data were extracted from obstetric and neonatal records at baseline by trained study staff, using a standard, pretested questionnaire. When the children were five years of age, sociodemographic and health services data were collected via paper or online questionnaires filled in by mothers, fathers or other caregivers (hereafter parents).

### *Health care services*

In the five-year questionnaire, parents were asked how many times during the past year their child had seen each of the health care providers suggested in a list. Depending on the country, 15 to 17 care providers were suggested, based on options previously used in this cohort at two years corrected age (8), adapted to reflect local care practices relevant to the age group (see Supplementary Table 1 for providers in each country). Parents could report additional services used as free-text responses. The questionnaire also included separate questions on overnight hospitalizations and participation in routine follow-up for children born VPT. The latter was used to derive overall follow-up rates for the study countries, as reported elsewhere (16).



### *Perinatal and social risk factors*

Perinatal factors included gestational age (GA) at birth, small for gestational age (SGA) status, defined as birthweight <10<sup>th</sup> – 3<sup>rd</sup> percentile and <3<sup>rd</sup> percentile, using intrauterine norms (13), bronchopulmonary dysplasia (BPD) defined as need for supplemental oxygen and/or artificial ventilation at 36 weeks' postmenstrual age, any congenital anomalies, neonatal morbidities including retinopathy of prematurity (ROP) stages III–V, intraventricular hemorrhage (IVH) grades III-IV, cystic periventricular leukomalacia (cPVL), necrotizing enterocolitis (NEC) requiring surgery, child's sex, and multiple gestation (singleton, twins, triplets or quadruplets).

Family sociodemographic factors included maternal educational level at five years, categorized into three groups based on the International Standard Classification of Education (ISCED) 2011 definition: (I) lower secondary (ISCED levels 0–2), (II) intermediate: upper or post-secondary, non-tertiary or short cycle tertiary (levels 3–5), and (III) higher: Bachelor degree or higher (levels 6–8) (11), parents' employment status at five years (at least one parent being unemployed versus no parent being unemployed), maternal age at delivery, maternal country of birth classified into native, non-native European-born and born outside Europe, and parity at birth (nulliparous or multiparous).

### *Defining elevated health service use*

Because there is no consensus on what constitutes elevated health care service use in high-risk pediatric populations, we adapted criteria from the published literature and used exploratory methods based on latent cluster analysis to define elevated service use (24-26). Bramlett et al. (25) and Kuo et al. (26) investigated complex care needs in children with special health care needs in the U.S. National Survey of children and the National Survey of Children's Health. Bramlett et al. based their definitions on health service use, use of medical aids, unmet care needs and medical insurance (25) whereas Kuo et al. (26) considered multidisciplinary and

specialist care only. Patra and Greene studied high health care service use during the two first years of life in children born preterm (27), and Brenner et al. (19) performed a systematic concept analysis of complex care need. Their different definitions for complex or elevated service use are described in Table 1.

We used these criteria to describe the use for each healthcare provider separately as (1) no use, (2) occasional use (1-3 visits to GP, pediatrician and nurses, 1-2 ER visits, one hospitalization or 1-2 specialist visits), and (3) frequent use ( $\geq 4$  visits for GP, pediatrician and nurses,  $\geq 3$  ER visits,  $\geq 2$  hospitalizations,  $\geq 3$  specialist visits). We chose higher thresholds for frequent use, exceeding the number of visits for complex care, as children born VPT have a higher need of health care services compared to the general pediatric population.

Using these definitions, we explored profiles of service use in our sample with latent cluster analysis. Analyses using hierarchical clustering with Ward's linkage and Gower distance measures as well as K-means clustering yielded consistent typologies with clusters of 1) lower service use across all health care domains or with occasional outpatient care, 2) frequent outpatient care and hospitalizations and 3) frequent use of specialist care (Supplementary Table 2). Based on these typologies and the adapted thresholds for complex care, we defined elevated health service use along two dimensions: I) outpatient/inpatient service use and II) specialist service use. The thresholds for classifying children into these groups are described in Table 1.

### *Analytical strategy*

We described the health care received by the children for each health service provider and type of service, including the percentage of children who had no, occasional or frequent visits as well as number of visits (mean, SD and median, IQR) or number of different providers seen (specialist services only). We then investigated the proportion of children with elevated

outpatient/inpatient as well as specialist service use by country and in relation to the countries' overall routine follow-up rates. The association between perinatal risk and sociodemographic characteristics and elevated outpatient/inpatient and specialist service use was assessed using Chi<sup>2</sup> tests (not shown). Adjusted risk ratios (RR) for elevated outpatient/inpatient and specialist service use were derived using multilevel generalized linear regression models, to take into consideration clustering within mothers and countries, with a log link, Poisson distribution and robust standard errors (28). We assessed service use by perinatal (model I) and perinatal and sociodemographic (model II) factors. We defined whether children are living in a country with extensive follow-up policy by classifying countries based on observed routine follow-up rates (at or above the mean: Portugal, Belgium, the Netherlands, France, Denmark and Sweden versus below the mean: UK, Germany, Estonia, Italy and Poland), and added this to a third model (model III) to assess the effect of follow-up on health service use. We performed a sensitivity analysis by repeating model III for total number of contacts for both types of services, using multilevel negative binomial models, appropriate for count data where the variance is greater than the mean (29).

As the overall study response rate was 53.8% (range 29.3%– 96.4% between countries) (23), we used inverse probability weights after multiple imputation (30) to give a higher weight to children with characteristics of non-responders in all analyses, as described elsewhere (22, 31). STATA 14.2 was used for all analyses (Stata Corp., College Station, TX, USA).

### *Ethics and funding*

All study regions obtained ethical approval according to national legislations. The study was also approved by the French Advisory Committee on Use of Health Data in Medical Research (CCTIRS) and the French National Commission for Data Protection and Liberties (CNIL). The

SHIPS project received funding from the European Union's horizon 2020 research and innovation program under grant agreement number 633724.

## Results

In five year-old children born VPT, health care visits during the past year were frequent; 68.4% of the children had four or more health care visits in total for a median of 6 contacts (IQR: 3–17); 45.3% had four or more outpatient/inpatient visits and 44.2% had three or more specialist visits (Table 2). General practitioners and pediatricians were the most commonly used outpatient/inpatient services, regardless of number of visits. Thirty-two percent had at least one ER visit, and 6.5% had three or more ER visits; over 10% were hospitalized overnight once over the past year, and 1.7% were hospitalized more than once. Eye specialists and ear/hearing specialist were the most consulted specialists for occasional (1–2) visits (22.8% and 33.4% respectively), and speech therapists (17.5%) for frequent (four or more) visits.

Overall, 44.1% of the children were classified as having elevated outpatient/inpatient service use with variations between 23.9% (Denmark) and 77.6% (Poland) (Figure 1). This proportion was 48.8% for elevated specialist care and varied between 38.9% (the Netherlands) and 65.6% (Poland). Around one-third (n=1,213, 35.0%) of the children were considered as having neither elevated outpatient/inpatient nor specialist care.

Elevated outpatient/inpatient service use was associated with BPD (RR=1.15; CI 1.06–1.26), congenital anomalies (RR=1.19; CI 1.04–1.37) and neonatal morbidities (RR=1.18; CI 1.08–1.29) as well as social risk factors; children of mothers with lower or intermediate educational level (RR=1.18; CI 1.00–1.40 and RR=1.16; CI 1.03–1.30) and unemployed parents (RR=1.20; CI 1.05–1.38) had higher risk of elevated outpatient/inpatient service use, whereas children of older mothers ( $\geq 35$  years at delivery) had lower risk (RR=0.86; CI 0.78–0.94) (Table 3).

Presence of perinatal risk factors had a stronger association with elevated specialist service use than outpatient/inpatient care, including low gestational age at birth (RR=1.49; CI 1.20–1.84 for <26 weeks and RR=1.21; CI 1.09–1.35 for 26-27 weeks), SGA (RR=1.12; CI 1.00–1.25), BPD (RR=1.16; CI 1.06–1.26), congenital anomalies (RR=1.15; CI 1.04–1.27), neonatal morbidities (RR=1.43; CI 1.35–1.51) and sex of the child, with boys having higher risk of elevated specialist service use after adjustment for perinatal characteristics (RR=1.17; CI 1.04–1.32) (Table 4). Children of mothers with the lowest educational level had slightly higher risk (RR=1.10; CI 1.03–1.19) and non-European born mothers had lower risk (RR=0.79, CI 0.66–0.94) of having elevated specialist service use. Living in a country with higher follow-up coverage was associated with lower relative risk of using outpatient/inpatient services (RR=0.71; CI 0.53–0.96), but did not affect use of specialist services. Sensitivity analysis using the total number of outpatient/inpatient and specialist care contacts, respectively, identified similar risk factors for elevated care (Supplementary Table 3), and analyses without inverse probability weights had limited impact on model estimates (Supplementary Table 4).

## **Discussion**

Children born very preterm in the EPICE cohort were frequent users of health services at five years of age; 68.4% of the children had four or more health care visits during the past year, and 65.0% had either elevated outpatient/inpatient or specialist service use: 44.1% for outpatient/inpatient and 48.8% for specialist service use, with wide variations between countries. Both elevated outpatient/inpatient and specialist service use were associated with perinatal risk factors, but they had more influence on specialist service use. In contrast, the magnitude of the association between social risk factors and elevated service use was higher for outpatient/inpatient services than for specialist services. Living in a country with high rates

of routine follow-up for children born VPT was associated with lower relative risk of elevated outpatient/inpatient service use, but not specialist service use.

This study uses data from a large, population-based cohort from 19 regions in 11 European countries with comparable levels of development and universal health insurance, collected with a standardized, pre-tested questionnaire. We add novel, comprehensive information about health service use at five years of age in this population using harmonized definitions that were developed and verified by researchers in each country and refined based on parental responses at two years (8). Limitations include reliance on parent-report data and parents' recall of the number of healthcare visits over the past year, which may have led to an underestimation of outpatient service use. Previous studies in adult patients found self-reported hospitalization and ER visits to be consistent with those extracted from medical records, whereas GP visits were underreported with only 28% accurate reporting over an eight-month period (32). We also do not have data on the reason for the health care visits nor any measure of unmet health care needs and can therefore not estimate the appropriateness of care received by the children or assess foregone health care. Finally, although care definitions were harmonized and pretested, health care systems differ across countries, making international comparisons more difficult, which may explain some of the differences in service use across countries. Another limitation is the study participation rate, which was 53.6% at five years of age. We used inverse probability weights to take into account study attrition which slightly increased the associations between outpatient service use and sociodemographic variables, but had limited impact on model estimates.

Our results show elevated health service use at five years of age in children born VPT, corroborating previous studies (1, 6). Sixty-five percent of the cohort had high service use based on adapted classifications developed for the pediatric population. This contrasts markedly with

nationwide survey data from 2017 and 2018 from the U.S. showing that approximately 13.3% of all children aged 0 to 17 years in the general U.S. population had elevated special care needs not managed with medication only, but requiring specialized services and/or having a functional limitation (33).

Elevated care use, especially use of specialist services, was consistently associated with perinatal risk factors, principally low gestational age and neonatal morbidities. This is expected, as children with perinatal risk are at higher risk of health and developmental difficulties requiring more, and sometimes complex, care from multiple providers. Boys had a higher risk of elevated specialist use, which could be explained by their higher risks of neurodevelopmental delay (3).

Children with at least one unemployed parent and mothers with lower educational level had higher risk of elevated outpatient/inpatient service use. Although children with social disadvantage have an additional risk of poor health and developmental outcome (5, 11, 12), previous research has found that high-risk children with additional social disadvantage are less likely to use medical services (34) and more likely to discontinue follow-up (14, 35). Others have reported differences in types of service use by social factors; a study on children enrolled to early intervention programs found social disadvantage to be associated with interventions from child development specialists and early childhood special educators as opposed to speech and occupational therapy and physiotherapy, which could either reflect the different needs in these families or unmet care need (36).

Our results suggest that children with social disadvantage may be receiving less optimal care, as shown by the association between parental unemployment and low maternal educational level and elevated outpatient, ER and hospital care, and children of mothers born outside Europe being less likely to receive elevated specialist care. Furthermore, although risks of health and

developmental problems are higher in children with social risk factors, we did not find a higher risk of elevated specialist service use in these children, in contrast to findings for outpatient and inpatient services. Poorer access to care in socially disadvantaged populations may stem from inequitable referral by care providers (37), insufficient personal resources, single parenthood, lack of transportation and inflexible working conditions (14) or limited care provision in more deprived areas (38). We have previously shown that children of mothers born outside Europe have a higher risk of discontinuing follow-up at five years (16), possibly leading to more restricted access to specialists, which could explain their lower likelihood of using specialist services. Appropriate care management should limit ER visits and prevent avoidable hospitalizations (20), whereas poorer management, especially in the case of complex care needs, may result in failure to meet health needs and increased use of acute health care services (19).

Health service use varied between countries, as previously observed in this cohort for the use of specialist services at two years of corrected age, possibly due to differences in country follow-up policies (8), and the organization of primary pediatric care (39). Recent studies have also shown that care provision for children with complex care needs are inconsistent and depends on their place of residence (19), and that there is a lack of consensus on how to meet complex care needs (18). We explored the hypothesis that living in a country with more extensive follow-up might affect this variation and found that it was negatively associated with elevated outpatient/inpatient care use, but not elevated specialist care. This may suggest that well-established, inclusive follow-up programs can help avoid undesirable health service use. We were not able to analyze the eligibility criteria and content of the follow-up offered in the study countries, and we were not able to assess the appropriateness of care, but we know from previous analyses in this cohort that some countries do not have mandatory follow-up beyond two years and that children of younger, non-European born and low education mothers have a



higher risk of never entering follow-up (16). This raises questions about equitable access to follow-up and health care services in VPT populations and on the optimal organization of post-discharge care.

## **Conclusion**

This study provides previously unavailable data on types and amount of health care services used at five years of age among children born VPT across regions in Europe. Our results reveal high service use with large differences across countries, and less optimal care, defined as elevated use of outpatient and inpatient services, among socially disadvantaged groups. While many studies exist on developmental outcomes in children born VPT, our study emphasizes the importance of expanding research on the optimal management of health care to investigate the services that should be provided to meet the health needs of these children. Future studies can use these multinational data, as well as the classifications developed from the published literature, as a reference for exploring health care service use and equity in other populations with complex care needs.

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**Table 1** Health services and thresholds used in literature and for the EPICE cohort

Complex or elevated care in published literature	Elevated care definitions for the EPICE cohort
<p><b>Bramlett et al. (2009)</b>  <i>Children with special care needs aged 0-17 years, visits during past year:</i>            ≥3 doctor's visits for sick care, or            ≥2 ER visits, or            ≥1 specialist visit  <i>(Specialty doctor, physical, occupational or speech therapy, mental health care or counselling or home health care)</i>            More visits - increased complexity</p> <p><b>Patra and Greene (2017)</b>  <i>Children born very preterm, from discharge until 22 months:</i>            ≥2 hospitalizations, or            ≥2 ER visit, or            Follow-up by ≥2 medical pediatric specialist  <i>(Excluding therapies such as developmental, speech and physical therapy)</i></p> <p><b>Kuo et al. (2014)</b>            Multiple needs across different domains            ≥2 different specialists consulted  <i>(Specialty doctor, physical, occupational or speech therapy, mental health care or counselling or home health care)</i></p> <p><b>Brenner et al. (2018)</b>            Multidimensional care that manages multiple condition-related needs</p>	<p><b>Elevated outpatient/inpatient service use</b>            ≥4 doctor's visits for sick care in total including visits to GP, pediatrician, nurse and/or school nurse, or            ≥3 ER visits, or            ≥1 overnight hospitalization</p> <p><b>Elevated specialist service use</b>            ≥2 different specialists and/or            ≥3 visits to same specialist from the following list:            Neurologist            Ear-nose-throat (ENT), hearing or ear specialist            Ophthalmologist or eye specialist            Speech therapist            Psychologist            Psychiatrist            Physiotherapist or psychomotor therapist            Respiratory, asthma, lung or allergy specialist            Dietitian or nutritionist            Occupational therapist            Early intervention services            Multidisciplinary services</p>

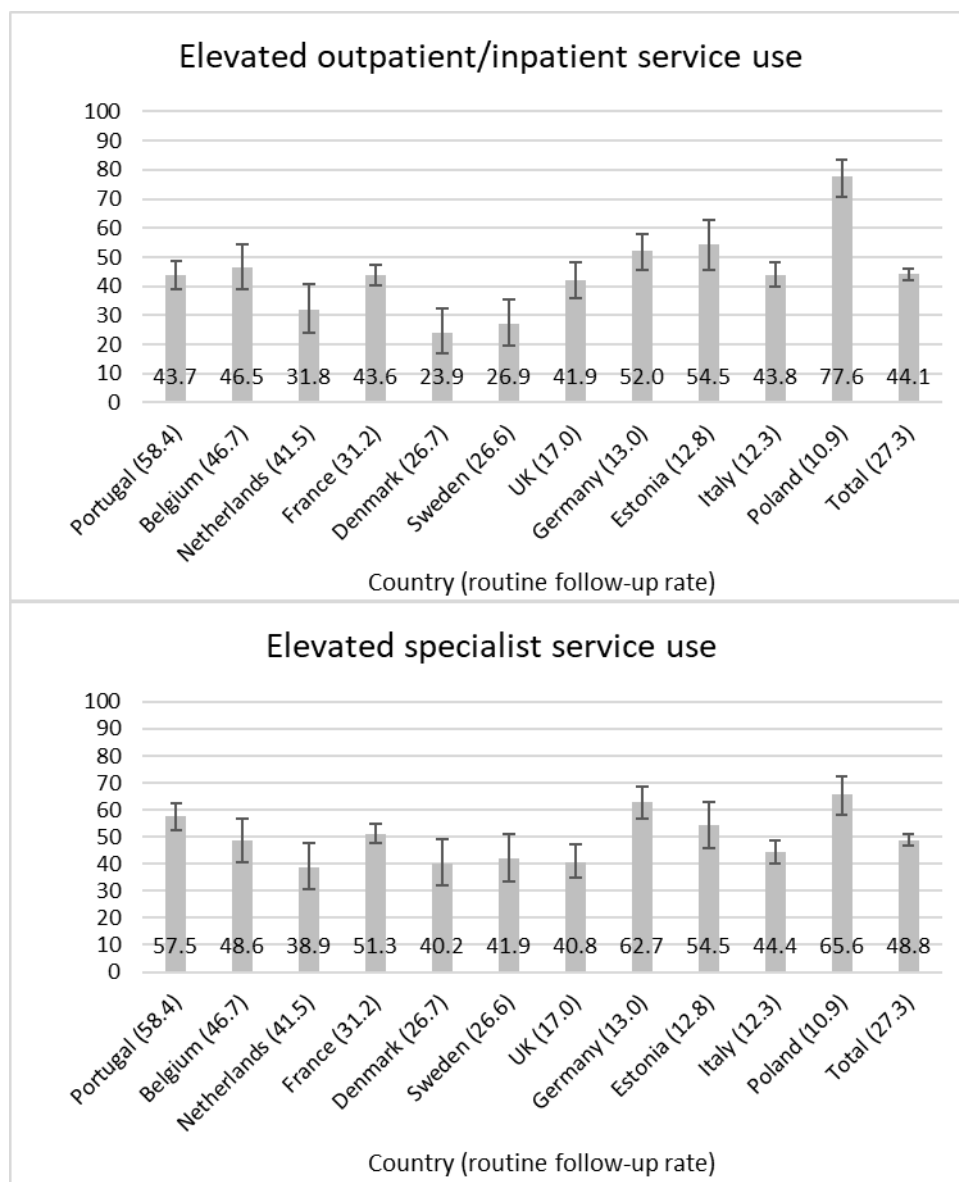
**Table 2.** Health care services used during the past year by five year-old children born VPT (excluding routine check-up and vaccination visits)

Health care service	Total	No, occasional, frequent visits*			Number of visits	
<b>Outpatient services</b>	N	No visits (%)	1-3 visits (%)	4 or more (%)	Mean (SD)	Median [IQR]
General practitioner (because of illness)	3537	1666 (45.9%)	1304 (37.8%)	567 (16.3%)	2.0 (4.0)	1 [0-3]
Pediatrician (because of illness)	3537	1572 (46.0%)	1337 (36.3%)	628 (17.7%)	2.1 (5.1)	1 [0-3]
Nurse	3537	3425 (96.7%)	78 (2.3%)	34 (1.1%)	0.2 (4.9)	0 [0-0]
School nurse	3537	3296 (91.3%)	222 (7.8%)	19 (0.9%)	0.2 (1.8)	0 [0-0]
Total number of visits to providers above	3537	529 (15.3%)	1657 (45.8%)	1351 (38.9%)	4.5 (8.8)	3 [1-5]
	N	No visits (%)	1-2 visits (%)	3 or more (%)	Mean (SD)	Median [IQR]
Emergency room	3537	2451 (68.0%)	878 (25.6%)	208 (6.5%)	0.7 (1.7)	0 [0-1]
<b>Inpatient services</b>	N	No visits (%)	1 visit (%)	2 or more (%)	Mean (SD)	Median [IQR]
Hospitalized over night	3527	3142 (88.5%)	333 (9.9%)	52 (1.7%)	0.1 (0.4)	0 [0-0]
<b>Outpatient and inpatient</b>	N	No visits (%)	1-3 visits (%)	4 or more (%)	Mean (SD)	Median [IQR]
Total number of visits, outpatient and inpatient	3586	450 (12.9%)	1528 (41.8%)	1608 (45.3%)	5.2 (9.4)	3 [1-6]
<b>Specialist services</b>	N	No visits (%)	1-2 visits (%)	3 or more (%)	Mean (SD)	Median [IQR]
Neurologist	3537	3164 (89.5%)	298 (8.5%)	75 (2.1%)	0.3 (2.3)	0 [0-0]
Ear-nose-throat or hearing specialist	3537	2474 (69.7%)	810 (22.8%)	253 (7.5%)	0.7 (1.8)	0 [0-1]
Ophthalmologist or eye specialist	3537	1982 (58.0%)	1236 (33.4%)	319 (8.6%)	1.0 (2.9)	0 [0-1]
Speech therapist	3537	2661 (75.6%)	243 (6.9%)	633 (17.5%)	6.7 (21.4)	0 [0-0]
Psychologist	3537	3094 (88.6%)	260 (6.7%)	183 (4.7%)	1.1 (8.1)	0 [0-0]
Psychiatrist	3537	3396 (95.8%)	105 (3.3%)	36 (0.9%)	0.1 (2.0)	0 [0-0]
Physiotherapist	3537	2955 (83.9%)	158 (3.9%)	424 (12.2%)	6.4 (24.4)	0 [0-0]
Respiratory or lung specialist or allergologist	3537	3134 (88.8%)	305 (8.2%)	98 (2.9%)	0.4 (5.1)	0 [0-0]
Dietitian or nutritionist	3537	3416 (95.4%)	79 (2.5%)	42 (2.1%)	0.1 (0.8)	0 [0-0]
Occupational therapist	3537	3299 (92.2%)	60 (2.0%)	178 (5.8%)	2.5 (13.1)	0 [0-0]
Early intervention service	3537	3325 (93.4%)	67 (2.0%)	145 (4.7%)	1.5 (10.5)	0 [0-0]
Multidisciplinary service**	3537	3382 (96.6%)	140 (3.0%)	15 (0.5%)	2.8 (10.9)	1 [1-1]
Total number of visits to specialists	3537	1002 (29.6%)	942 (26.2%)	1593 (44.2%)	20.5 (55.2)	2 [0-9]
		No specialist	1 specialist	2 or more	Mean (SD)	Median [IQR]
Number of different specialists seen	3537	1002 (29.6%)	1023 (28.6%)	1512 (41.9%)	1.7 (1.9)	1 [0-2]
<b>All services</b>	N	No visits (%)	1-3 visits (%)	4 or more (%)	Mean (SD)	Median [IQR]
Total number of visits, all services included	3586	229 (6.8%)	881 (24.7%)	2476 (68.4%)	25.4 (57.8)	6 [3-17]

All data are weighted with inverse probability weights after multiple imputation; \*Thresholds defined from the published literature, see methods.

\*\*Included in French questionnaire; answers derived from free-text answers in other countries

**Figure 1.** Proportions\* and 95% confidence intervals of children born VPT with elevated outpatient/inpatient<sup>a</sup> and specialist<sup>b</sup> service use at five years of age, by country, sorted by overall routine follow-up rates for children born VPT



\*Weighted with inverse probability weights

<sup>a</sup>  $\geq 4$  sick-care visits in total to general practitioner, pediatrician, nurse and/or school nurse,  $\geq 3$  emergency room visits, and/or at least one overnight hospitalization during the past year.

<sup>b</sup>  $\geq 2$  different specialists consulted or  $\geq 3$  visits in total to neurologist, ear-nose-throat, hearing or ear specialist, ophthalmologist or eye specialist, speech therapist, psychologist, psychiatrist, physiotherapist or psychomotor therapist, respiratory, asthma, or lung specialist or allergologist, dietitian or nutritionist, occupational therapist, early intervention services, and/or multidisciplinary services during the past year.

**Table 3.** Risk ratios of elevated outpatient/inpatient service use at 5 years in children born VPT by perinatal (Model I) and social (Model II) factors and follow-up context (Model III)

Elevated outpatient/inpatient service use			Model I		Model II		Model III	
	N	%	RR	[95% CI]	RR	[95% CI]	RR	[95% CI]
<b>Gestational age, completed weeks</b>								
<26	298	54.3%	1.22	[1.02-1.45]	1.16	[0.98-1.38]	1.16	[0.98-1.38]
26-27	653	44.1%	1.05	[0.96-1.15]	1.00	[0.91-1.10]	1.00	[0.91-1.11]
28-29	923	45.7%	1.11	[0.99-1.25]	1.12	[0.99-1.27]	1.12	[0.99-1.27]
30-31	1667	41.4%	ref		ref		ref	
<b>SGA (percentiles)</b>								
<3 <sup>rd</sup>	763	47.6%	1.10	[0.99-1.23]	1.08	[0.93-1.25]	1.08	[0.93-1.25]
3 – 9 <sup>th</sup>	411	40.5%	0.95	[0.84-1.07]	0.96	[0.87-1.05]	0.96	[0.87-1.05]
>10 <sup>th</sup>	2367	43.5%	ref		ref		ref	
<b>BPD</b>								
No	2992	42.7%	ref		ref		ref	
Yes	462	53.0%	1.13	[1.03-1.24]	1.16	[1.06-1.26]	1.15	[1.06-1.26]
<b>Congenital anomalies</b>								
No	3247	42.8%	ref		ref		ref	
Yes	294	59.1%	1.21	[1.04-1.40]	1.20	[1.04-1.37]	1.19	[1.04-1.37]
<b>Any neonatal morbidity<sup>a</sup></b>								
No	3103	42.6%	ref		ref		ref	
Yes	357	56.8%	1.17	[1.05-1.29]	1.19	[1.09-1.29]	1.18	[1.08-1.29]
<b>Child sex</b>								
Male	1893	45.3%	1.06	[0.96-1.17]	1.06	[0.96-1.17]	1.06	[0.96-1.17]
Female	1648	42.7%	ref		ref		ref	
<b>Multiple gestation</b>								
Singleton	2505	45.7%	ref		ref		ref	
Twins, triplets or quadruplets	1036	39.8%	0.91	[0.80-1.04]	0.90	[0.78-1.04]	0.90	[0.78-1.03]
<b>Maternal educational level<sup>b</sup></b>								
Lower	587	49.5%			1.18	[1.00-1.40]	1.18	[1.00-1.40]
Intermediate	1447	45.3%			1.16	[1.03-1.30]	1.16	[1.03-1.30]
Higher	1458	38.9%			ref		ref	
<b>Parents' employment status</b>								
No parent unemployed	3134	42.6%			ref		ref	
At least one parent unemployed	372	54.6%			1.20	[1.04-1.38]	1.20	[1.05-1.38]
<b>Maternal age at delivery (years)</b>								
≤24	418	45.0%			0.86	[0.72-1.04]	0.86	[0.72-1.04]
25-34	2021	46.0%			ref		ref	
≥35	1092	39.8%			0.86	[0.78-0.95]	0.86	[0.78-0.94]
<b>Maternal country or birth</b>								
Native	2825	44.5%			ref		ref	
European-born	238	42.9%			0.94	[0.83-1.05]	0.93	[0.83-1.04]
Born outside Europe	463	42.7%			0.94	[0.85-1.05]	0.95	[0.85-1.05]
<b>Parity</b>								
Multiparous	2129	44.4%			ref		ref	
Nulliparous	1372	43.7%			0.96	[0.82-1.14]	0.96	[0.82-1.13]
<b>Country routine follow-up rate</b>								
Lower (≤17%)	1689	47.7%					ref	
Higher (>26.6%)	1852	40.3%					0.71	[0.53-0.96]

Inverse probability weights after multiple imputation were used for all analyses.

SGA: small for gestational age; BPD: bronchopulmonary dysplasia.

<sup>a</sup> Intraventricular haemorrhage grades III-IV, cystic periventricular leukomalacia, retinopathy of prematurity stages III-V or necrotising enterocolitis requiring surgery

<sup>b</sup> Lower: ISCED levels 0-2 (Lower secondary); Intermediate: ISCED level 3-5 (upper or post-secondary, non-tertiary or short cycle tertiary); Higher: ISCED level 6-8 (Bachelor degree or higher).

**Table 4.** Risk ratios of elevated specialist health care service use at 5 years in children born VPT by perinatal (Model I) and social (Model II) factors and follow-up context (Model III)

Elevated specialist service use			Model I		Model II		Model III	
	N	%	RR	[95% CI]	RR	[95% CI]	RR	[95% CI]
<b>Gestational age, completed weeks</b>								
<26	298	73.7%	1.46	[1.19-1.78]	1.49	[1.20-1.84]	1.49	[1.20-1.84]
26-27	653	57.3%	1.26	[1.13-1.39]	1.21	[1.09-1.35]	1.21	[1.09-1.35]
28-29	923	48.7%	1.13	[0.99-1.30]	1.12	[0.98-1.28]	1.12	[0.98-1.29]
30-31	1667	41.1%	ref		ref		ref	
<b>SGA (percentiles)</b>								
<3 <sup>rd</sup>	763	50.7%	1.09	[0.97-1.21]	1.08	[0.95-1.24]	1.08	[0.95-1.24]
3 – 9 <sup>th</sup>	411	49.4%	1.09	[0.96-1.24]	1.12	[1.00-1.25]	1.12	[1.00-1.25]
>10 <sup>th</sup>	2367	48.2%	ref		ref		ref	
<b>BPD</b>								
No	2,992	46.2%	ref		ref		ref	
Yes	462	66.2%	1.14	[1.05-1.24]	1.16	[1.06-1.26]	1.16	[1.06-1.26]
<b>Congenital anomalies</b>								
No	3247	47.8%	ref		ref		ref	
Yes	294	61.3%	1.17	[1.06-1.30]	1.15	[1.04-1.27]	1.15	[1.04-1.27]
<b>Any neonatal morbidity<sup>a</sup></b>								
No	3103	45.5%	ref		ref		ref	
Yes	357	77.5%	1.43	[1.32-1.54]	1.43	[1.35-1.52]	1.43	[1.35-1.51]
<b>Child sex</b>								
Male	1893	52.1%	1.18	[1.05-1.33]	1.17	[1.04-1.32]	1.17	[1.04-1.32]
Female	1648	45.1%	ref		ref		ref	
<b>Multiple gestation</b>								
Singleton	2505	49.4%	ref		ref		ref	
Twins, triplets or quadruplets	1036	47.3%	1.02	[0.93-1.12]	1.00	[0.89-1.13]	1.01	[0.89-1.13]
<b>Maternal educational level<sup>b</sup></b>								
Lower	587	53.5%			1.10	[1.03-1.19]	1.10	[1.03-1.19]
Intermediate	1447	46.4%			1.00	[0.95-1.05]	1.00	[0.95-1.05]
Higher	1458	47.5%			ref		ref	
<b>Parents' employment status</b>								
No parent unemployed	3134	47.6%			ref		ref	
At least one parent unemployed	372	56.7%			1.08	[0.93-1.26]	1.08	[0.93-1.26]
<b>Maternal age at delivery (years)</b>								
≤24	418	47.0%			0.86	[0.71-1.05]	0.86	[0.71-1.05]
25-34	2021	49.3%			ref		ref	
≥35	1092	49.4%			1.02	[0.96-1.08]	1.02	[0.96-1.08]
<b>Maternal country or birth</b>								
Native	2825	50.1%			ref		ref	
European-born	238	49.9%			0.98	[0.88-1.09]	0.98	[0.88-1.09]
Born outside Europe	463	42.7%			0.79	[0.66-0.94]	0.79	[0.66-0.94]
<b>Parity</b>								
Multiparous	2129	49.8%			ref		ref	
Nulliparous	1372	48.3%			0.96	[0.86-1.08]	0.96	[0.86-1.08]
<b>Country routine follow-up rate</b>								
Lower (<17%)	1689	48.1%					ref	
Higher (>26.6%)	1852	49.6%					0.95	[0.76-1.17]

Inverse probability weights after multiple imputation were used for all analyses.

SGA: small for gestational age; BPD: bronchopulmonary dysplasia.

<sup>a</sup> Intraventricular haemorrhage grades III-IV, cystic periventricular leukomalacia, retinopathy of prematurity stages III-V or necrotising enterocolitis requiring surgery

<sup>b</sup> Lower: ISCED levels 0-2 (Lower secondary); Intermediate: ISCED level 3-5 (upper or post-secondary, non-tertiary or short cycle tertiary); Higher: ISCED level 6-8 (Bachelor degree or higher).



# Chapter 8: Discussion

## 8.1 Summary of main findings

The aim of this doctoral project was to assess the use and equity of post-discharge follow-up and health care services among children born VPT in 19 regions in 11 European countries. The objectives were to describe and investigate cross-country differences in post-discharge follow-up and health care service use at two and five years of age, to investigate whether there are socioeconomic disparities in follow-up and health service use, and to assess whether follow-up is associated with health care services use and equity in care.

Our results showed wide variations across Europe in the use of post-discharge follow-up for children born VPT and health care services until five years of age, that were not explained by differences in risk factors at birth. Reassuringly, a large majority of parents reported receiving routine follow-up services for their children, but by five years of age, differences in continued use were marked across countries, even after adjusting for case-mix: from 10.0% to 60.2% with even higher contrasts for children at highest risk born before 28 weeks of gestation (11.9% to 72.3%).

We documented high use of health care services at two years of age for specialists, as well as at five years of age, using a more comprehensive description of service use. Seventy-six percent of the children in our cohort had seen at least one specialist since discharge until two years of CA. At five years of age, health service use was still high; only one-third of the children in our cohort were not considered to have elevated health care service use based on definitions adapted from the literature on complex care needs, 44% had elevated outpatient or inpatient service use and 49% elevated specialist service use. Children with perinatal risk factors consistently used more follow-up and health services compared to children without in our analyses, which is expected. For instance, children who suffered from neonatal morbidities in the NICU had a 18% higher risk (RR=1.18) of having elevated use of outpatient and inpatient services and 43% higher risk (RR=1.43) of elevated specialist service use at age five compared to children without these morbidities. Variation in health service use persisted across countries, despite high levels of use overall and adjustments for the differences in population case-mix between the countries in the cohort. At two years of CA, use of any specialist service varied from 54% (Italy) to 100% (Estonia) and at 5 years of age, rates of elevated specialist use ranged from 39% (the

Netherlands) to 66% (Poland) and elevated outpatient and inpatient service use from 24% (Denmark) to 78% (Poland). These summary variables, composed of a number of care providers, obscured further heterogeneity in the types and amounts of care within specific categories of care providers. We also showed variation in dissatisfaction with care between countries ranging from 6% (France) to 32% (Denmark), although parents' satisfaction with care was high overall (14% poor or fair ratings overall).

Two findings were of particular concern: the higher rates of dissatisfaction with health care among parents of children with the most elevated health care needs as well as the lower use of follow-up services and elevated use of outpatient and inpatient services in children from socially vulnerable families. Parental rates of dissatisfaction were 34% when children had cerebral palsy and 37% when children had epilepsy at five years of age, compared to 14% overall. Children of mothers born outside Europe had an over two-fold risk ( $RR=2.5$ ) of never starting routine follow-up and 40% higher risk ( $RR=1.4$ ) of ending follow-up before age five compared to children of non-immigrant mothers. Children of unemployed parents had 20% higher risk ( $RR=1.2$ ) of having elevated outpatient and inpatient service use at five years compared to children of employed parents, and inversely, children of non-European born mothers had lower risk ( $RR=0.8$ ) of having elevated specialist service use. Children with complex health needs and those with social vulnerabilities represent two groups of children who are most in need of follow-up and health care and may benefit the most from interventions.

Finally, when we assessed the association with routine follow-up and health care service use, we found that children living in a country with high routine follow-up rates at five years of age, an indicator of a more comprehensive follow-up policy, were less likely to have an elevated use of outpatient and inpatient services ( $RR=0.8$ ) compared to children living in countries with lower routine follow-up rates.

To place these results and their implications for future research in a broader context, this section discusses the advantages and limitations of our multi-national population-based research project and the challenges it posed for answering our research questions. The interpretation of specific findings for policy and research have already been addressed in the accompanying publications. However, these broader challenges played a crucial role in how the research project developed as we gained knowledge on the strengths and drawbacks of long-term health care for children born preterm, and as we gained more understanding about the limitations in our data. We will address the benefits and drawbacks of (1) conducting research on follow-up

and health services use in the European context where there is high diversity in health care organisation and service provision, and (2) using a population-based cohort design with parent-report questionnaires to assess follow-up and health services use.

## **8.2 Europe, opportunities and challenges for research**

### *Opportunities in international research*

Europe provides many opportunities for studying health care, as the countries are similar in terms of wealth and universal health care coverage. International studies, especially in Europe, provide a setting in which outcomes can be compared across countries to identify where improvements can be made. Previous studies have used European multi-national settings so compare health and health care service-related outcomes. Mackenbach et al. (2008) compared socioeconomic inequalities in health in adults across 22 countries in Europe, and showed that the magnitude of inequality related to social status varies across Europe (Mackenbach et al. 2008), and the Models for Child Health Appraised (MOCHA) study group has been able to show differences in paediatric care policies (Brenner, O'Shea, McHugh, et al. 2018), health care delivery (Luzi, Pecoraro, and Tamburis 2017) and quality of care assessments (Luzi et al. 2017) across 30 European countries.

Multinational collaborations have been a central part of research on children born VPT; many publications on the EPICE cohort have shown inter-country variability in, for instance, severe neonatal morbidity rates (Edstedt Bonamy et al. 2019), duration in hospital stay (Maier et al. 2018), use of evidence-based interventions (Zeitlin et al. 2016), including antenatal steroids (Norman et al. 2017) and hypothermia prevention (Wilson et al. 2016), as well as breastfeeding rates at discharge (Wilson et al. 2018). Other collaborations, such as the Models of Organising Access to Intensive Care for very preterm births (MOSAIC) project, the International Network for Evaluations of Outcomes of Neonates (iNeo) collaboration and the Vermont-Oxford (VON) international collaborations have similarly been able to study and show variation in health care practice across high-income countries. These studies, mainly focused on the perinatal period, have made it possible to point out where there is room for improvement, by identifying widespread use of non-evidence based practices across units, for example in the use of surfactant (Horbar et al. 2004), by illustrating variations in outcomes, including survival rates in VPT across neonatal networks (Helenius et al. 2017), and specific interventions, such as

respiratory management (Beltempo et al. 2018), and caesarean sections for VPT births (Zeitlin, Di Lallo, et al. 2010), showing the need for more evidence for the optimal use of medical practices.

Whereas comparative studies on practices in the perinatal period benefit from the existence of practice guidelines and the relatively standard high-technology environment of the NICU, even though structural factors such as size, stipulations about level of care and staffing differ (Van Reempts et al. 2007), health care systems and the provision of post-discharge paediatric health care differ across countries, which pose multiple challenges for research which this study had to confront.

#### *Diversity in the European health care context – challenges for research*

Health care-related research in an international context poses a range of challenges, but the major complexities come from differences in health care systems and contexts. As described in chapter 2, national or regional follow-up programmes existed in seven of the study countries at the time of discharge. Recommended follow-up duration varied from two to eight years, and recommended assessments contained diverse, more or less extensive assessments across different time points and with different frequencies.

This diversity, together with the lack of information on the structural characteristics and availability of local programmes that vary across regions, cities and units, posed a particular challenge for our objective of studying the role of routine follow-up on health service use. Initially, our aim was to attribute exposure to types of follow-up programmes (based on organisational-level characteristics) to the children in the cohort, in order to assess their impact on health service use. However, classifying countries or regions according to the availability, enrolment criteria and content of national and regional follow-up programmes did not yield meaningful groupings due to the large variation in follow-up recommendations at the regional level and a lack of information on local programmes, making it difficult to attribute exposure to specific follow-up programmes or policies to the individual children in the cohort. Nonetheless, we were able to assess the association between routine follow-up and elevated health service use, based on patterns of parent-reported follow-up at five years as a proxy for the extensiveness of follow-up policy and programmes.

Finally, although statistical methods allow us to take into account differences in case-mix and intra-country clustering, there are a range of factors that may affect our outcome measures that we did not measure or could not take into account. Countries may differ in several aspects that may influence health care service use, such as general organisation of health care, e.g. GP or paediatrician-based primary care systems (van Esso et al. 2010; Poropat et al. 2017), gate-keeping systems and hospital versus community-based provisions (Wolfe et al. 2013), parents' ability to pay for out of pocket-costs (Stepurko, Pavlova, and Groot 2016) and other unmeasured societal factors. The diversity in health care environments in this project limits the interpretation of the variability found in health care service use; more research is needed to assess whether these differences are related to unmet health care needs.

When health care service use is studied in multi-national contexts, diversity in health systems needs to be addressed from the study-planning phase through to the interpretation of research results. Questionnaires need to be harmonised to represent the same concepts but simultaneously be adapted to local health care systems and cultural contexts (Gibbons et al. 2016). Answers need to be translated, understood and analysed in their health care and cultural context (Larkin, Dierckx de Casterle, and Schotsmans 2007), statistical methods need to take into account differences in population characteristics and the study design needs to be appropriate for studying cross-country differences. However, the researcher faces a complex situation, where this cross-country diversity is only fully understood after data collection, especially for topics, such as ours, that have not been previously studied. In this way, our work standardising and describing health systems provides an important foundation for future research on health care use among children born VPT.

### **8.3 Study design and methods**

#### *Observational cohort study design*

Observational cohort studies, i.e. studies without randomised interventions and controls, have benefits that makes them attractive for assessing care use and policy; they make it possible to assess interventions in their “natural”, uncontrolled setting and achieve better external validity, for instance, compared to randomised controlled trials (RCT) (Gillies et al. 2016).

However, observational studies are not sufficient for evaluating services in terms of causality between intervention and outcome. There is often a long and complex pathway between the

intervention and the outcome influenced by multiple external (unmeasured) factors and interactions (Barratt et al. 2016) that observational studies cannot take into account. In this project, we assessed the association between routine follow-up and health care service use. However, with our observational cohort study design, we were unable to assess the causal effects of routine follow-up on health services use. Although we found associations between follow-up coverage and elevated health service use, these results need to be interpreted with caution. For instance, a more “optimal” use of health care services (e.g. less reliance on outpatient and emergency services) can be a positive consequence of comprehensive follow-up policies and programmes, but it could also result from follow-up programmes and optimal service use patterns independently co-existing in the same health care and societal context, for instance, a region where the health care resources and service availability are better (Raine et al. 2016).

Whereas RCTs are considered the gold standard for assessing interventions, randomised trials using quasi-experimental methods are seen as the strongest designs for assessing causality in health policy research (French and Stuart 2020). These methods include intervention groups (e.g. hospital units) where a policy has been introduced and control groups not exposed to the policy, that are followed over time. Following these groups over time makes it possible to assess “difference in differences”, i.e. take into account changes that occur in measured outcomes due to other external reasons (such as societal change) and not necessarily the intervention (French and Stuart 2020). These trials cannot, however, show how and why interventions may work and need to be completed with other study methods (Barratt et al. 2016). Newer approaches have also been proposed for evaluating complex care and health care systems, including mixed methods and stepped wedge designs (Lamont et al. 2016), or combinations with observational studies and randomised controlled trials (Gillies et al. 2016).

#### *Treatment-selection bias*

Observational studies are also subject to treatment-selection bias, where study subjects with poorer health are more likely to be offered health-related interventions in the clinical setting (instead of being randomised to the intervention), which can result in worse outcomes or weaker effects (Gillies et al. 2016). In this project, we did not assess the association with routine follow-up and health and developmental outcomes at five years of age, as detection of health and developmental-related outcomes are interlinked with receiving follow-up checks. The inability to fully control for underlying health status and needs of the children would have likely given the impression of poorer outcomes in children exposed to follow-up programmes. The wide

heterogeneity in types and severity of health and developmental outcomes after VPT birth complicates these analyses further. One option, considered for future studies in this cohort, will be to focus on the follow-up and health care of specific sub-groups of children with more easily defined pathologies (with diagnoses of CP or severe motor coordination as measured by standardised clinical assessments).

#### *Non-response and study attrition*

Finally, an issue that relates to any study involving volunteers, study participants may differ from non-participants regarding many characteristics. We used inverse probability weights to take into account the most common factors related to non-response, such as sociodemographic characteristics. However, some level of bias might remain. Studies have shown that children participating in research studies are also much more likely to participate in routine neurodevelopmental follow-up (Orton et al. 2015). In our case, parents participating in the study might be more likely to use routine follow-up services for their children compared to parents who did not participate in the study. This may lead to an overestimation of the use of routine follow-up services in our analyses.

#### *Assessing equity in health services research*

In order for health care systems to be able to provide health care according to need, it is essential to address equity (Raine et al. 2016). In this project, we were able to study the association with family sociodemographic determinants and the use of routine follow-up and post-discharge health care services. Data on multiple sociodemographic characteristics were collected at several time points in the study, allowing us to verify and harmonise data for more accurate measures. We found that children from socially vulnerable families were less likely to use routine follow-up services and more likely to have an elevated use of hospital in- and outpatient services. However, evaluating health care equity is a complex task which requires addressing the issue from multiple angles. Inequities in care use may result from not having access to care (provider-related) or not using care to which there is access, due to structural or environmental barriers, or because care is not needed (user-related) (Raine et al. 2016). Therefore, to have a more precise assessment of care equity, all three components, supply, need and use need to be taken into account simultaneously, and assessed horizontally (equal care for equal need) and vertically (care in proportion to need) (Raine et al. 2016). Inequities may also happen at different phases of the health care process: screening participation, referral by practitioners,

access to and use of treatment (Raine et al. 2016). Assessing the impact of follow-up on equity of health care service use optimally needs taking into account that inequities may be created anywhere along the care process. A limitation of our study is that we did not have data on referrals to services to determine whether non-use is provider or user-related, nor a measure of unmet care need, which should be addressed in future studies.

*Relying on parental report of their children's health and satisfaction with care received*

In this project, we assessed the use of routine follow-up and health care services and the association between them. For this, we were reliant on parent-report data from questionnaires. We used a proxy of inclusive follow-up policy based on the proportion of children that were still receiving follow-up check-ups at five years of age according to their parents in each country. Although the overall use of routine follow-up rates in our cohort may give an indication on the availability and inclusiveness of follow-up programmes, it does not in itself provide information on the availability, quality or organisation of such follow-up. Not using follow-up services at five years may represent either a lack of follow-up availability (no programmes being provided until five years or child is not eligible), poor organisation of follow-up (e.g. failure to inform parents) (Callanan et al. 2001) or it may be a result of parents declining appointments (Callanan et al. 2001), experiencing difficulties in attending appointments (e.g. time or resources) (Ballantyne et al. 2015), not distinguishing follow-up programmes for children born VPT from general routine check-ups, or not recalling having used these services. Studies have shown that especially outpatient primary care visits may be underreported in self-reported data (Petrou et al. 2002). By translating the parent-reported use of routine follow-up services to a measure of inclusiveness of follow-up policies at five years of age, we have been able to, not draw conclusions on the effect of follow-up, but to raise more questions about the organisation of follow-up and how to evaluate their effects.

Other parent-report measures in this project included parents' ratings of post-discharge care and parents' open-ended free-text suggestions on how care can be improved. Patient, or in this case, parent satisfaction with health care, have previously been used for assessing health care quality and areas of improvement in health care (Junewicz and Youngner 2015). Parents' experiences in qualitative studies have previously revealed organisational weaknesses in the post-discharge care for children born VPT (Rucci et al. 2015; Pritchard et al. 2008), and informed policy development and recommendations (Bertoncelli 2020). Using these methods, we were able to



assess perceived care quality and drawbacks with the care offered to children born VPT across the study countries, that would not have been possible without parent-reported experiences.

While parent-reported outcomes describing their experiences and their children's health and development provide valuable information about how health services are performing, they are filtered through parents' own knowledge and expectations and are correlated with their social status, their children's health status, the health care they receive and their cultural beliefs. So, while we revealed sub-optimal patterns of care related to parental socioeconomic status, this was not reflected in their satisfaction, for instance, where lower education was associated with higher satisfaction with care. The strengths and weaknesses of relying on parents' reports informed the contours of our study questions and the interpretation of the results.

As far as we know, our study was novel in looking at differences in health service provision and care in children born VPT after discharge in Europe. Although the multi-national European context comes with its complexities for interpretation of results and harmonising data, it also provides unique opportunities for comparing outcomes and benchmarking health service provision. Multinational, observational cohort studies, although they cannot determine causal associations between health services and outcomes, constitute an important foundation by providing descriptive, population-based data and standardised methods for future research.

# Chapter 9: Conclusion

## 9.1 Conclusions on main findings

The organisation of follow-up and care for children born VPT differs greatly across regions in Europe, and studying the use of follow-up and health services across 19 European regions with similar standards of living and universal health care systems allowed us to show how this translates into large variations in follow-up coverage, health care service use and care satisfaction across the regions. These variations in the use of follow-up and health care services were documented even in children facing the greatest risks of health and developmental problems. Although we were not able to measure unmet care need, this variation raises questions about the optimal organisation and availability of care and follow-up for children across Europe, in relation to health and developmental outcomes, the satisfaction of parents and the costs for families and society. The studies part of this dissertation provide previously unavailable data on health care service use and follow-up until five years of age, constituting essential benchmarks for countries to evaluate their own services in light of the questions raised by this research.

Our findings also revealed some important strengths and limitations in the care and follow-up currently offered in Europe to children born VPT, which gives indications about care provision in the absence of common evidence-based follow-up guidelines. We have provided novel knowledge about the factors that are associated with the use health care and routine follow-up services among children born VPT, as well as areas that require improvements according to their parents. As expected, we found that children with perinatal risk factors were more likely to have an elevated use of health care services, but we also found higher rates of dissatisfaction with care in parents of children with health and developmental problems at five years of age, i.e. in children most reliant on health care services. Children with the most complex health problems need care that requires particular effort from the health care system in terms of care coordination and follow-up, making this group of children particularly exposed to potential failures in coordination and communication, as reflected in parents' satisfaction with care. These results add to other studies that have found that there is need for improved organisation of care for children with complex care needs (Brenner, O'Shea, Larkin, et al. 2018). Regardless of country, parents frequently reported care coordination, follow-up, communication and parent support as priority areas for improving long-term care for children born VPT.

Other important results from our studies concern access to care for children from socially vulnerable families. We found that children with social risk factors are less likely to use follow-up services and have higher risk of elevated outpatient and inpatient service use. These results raise concern about the equity in access to follow-up and health care services in Europe. Early childhood provides a critical window during which future health inequalities can be mitigated or even prevented, and needs to be addressed at all levels: the micro, meso and macro-levels (Pillas et al. 2014). These results suggest that social inequities need to be considered when informing and offering care and follow-up to families, when organising follow-up and care provision at hospitals and health care centres, and when developing recommendations for care and follow-up for children born VPT.

In conclusion, our study shows that improvements in follow-up for children born VPT in Europe are needed in terms of care coordination for complex care needs and their social inclusiveness to facilitate access to preventative and therapeutic care for children from socially vulnerable families. These concerns about care quality and equity help shape the priorities for research, notably concerning the availability and effectiveness of follow-up services for improving health and minimising unnecessary outpatient and inpatient care, how to improve care coordination to optimise support and intervention services, and how to ensure equitable access to services for children from socially vulnerable families.

## **9.2 Perspectives for future research**

The results from this doctoral project call attention to high service use in children born VPT until five years of age and particularly to the wide variation in service use across countries. These results also raise further questions and set the stage for future research needed for evidence-based health care in this population. Research should include studies that assess the effects of follow-up programmes on care access and use, as well as child health and development, especially in children with complex care needs and socially vulnerable children. Eligibility, content and duration of follow-up programmes should be assessed at national, regional at local levels. Drawing on health policy and health services disciplines, it would be useful to characterise the organisational and policy contexts that lead to the wide variation in the use of health care and follow-up services. Other study designs, including randomised trials using quasi-experimental methods would be valuable for evaluating the underlying causal patterns. Furthermore, as we have seen in this project, parents of these children constitute a

valuable resource, permitting mixed-methods investigations and should be included at all stages of research, together with the children themselves, as they grow older.

Our results also raise questions on the organisation of care, particularly for children with complex care needs in children and from socially vulnerable families. Parents of children born VPT have shown to be a valuable asset in understanding drawbacks in complex and multidisciplinary care systems and when aiming to improve care and follow-up in this population. More research is needed to understand inequitable provision and use of follow-up services, and where these inequities emerge in the care provision process. More detailed data collection on care offer and referral, follow-up inclusion and attendance as well as follow-up programme content can facilitate assessing where interventions are needed for high quality and equitable care in this population.

It is necessary to continually reinforce the descriptive evidence-base on the equity and use of health care services and the experiences of VPT children and their families, in order to call attention to their needs and to provide baseline information to inform policy. Without this data, shortcomings cannot be identified and solutions cannot be developed. In this project, we hope to have facilitated future research and evaluations of care. The standardised lists of health care providers relevant for this age group of children born VPT, harmonised across eleven European countries, can be used in future studies. We identified a range of variables that are associated with health care service use and follow-up and should be considered both in research as well as when developing guidelines and providing services to children born VPT and their families. Finally, the rates of routine follow-up and health care service use our research provided serve as a base, and hopefully an incentive, for new studies to benchmark care in other countries or to evaluate changes over time in the SHIPS countries. With improved knowledge on the optimal provision and management of health care, health systems will be better equipped to meet the needs of children born VPT and their families.

## Scientific communications

### *Publications in peer-reviewed journals*

**Seppänen, AV.**, Bodeau-Livinec, F., Boyle, E. M., Edstedt-Bonamy, A., Cuttini, M., Toome, L., Maier, R. F., Cloet, E., Koopman-Esseboom, C., Pedersen, P., Gadzinowski, J., Barros, H., Zeitlin, J. and the Effective Perinatal Intensive Care in Europe (EPICE) research group (2018) Specialist health care services use in a European cohort of infants born very preterm. *Dev Med Child Neurol.* 61: 832-39. doi:10.1111/dmcn.14112

**Seppänen AV.**, Sauvegrain P, Draper E S, Toome L, El Rafei R, Petrou S, Barros H, Zimmermann L J I, Cuttini M, Zeitlin J and the SHIPS Research group. Parents' ratings of post-discharge healthcare for their children born very preterm and their suggestions for improvement: a European cohort study. *Pediatric Research.* 1-9. doi: 10.1038/s41390-020-01120-y

### *Communications*

#### Oral communications

- FHU Préma Young Researchers' Afternoon, Sept. 2020, Paris, France
- 3<sup>rd</sup> joint European Neonatal Societies' Congress, Sept. 2019, Maastricht, The Netherlands
- 9<sup>th</sup> Europaediatrics Congress, Jun. 2019, Dublin, Ireland
- 15<sup>th</sup> EFCNI Parent Organisations Meeting, Jan. 2019, München, Germany
- 14<sup>th</sup> EFCNI Parent Organisations Meeting, Jan. 2018, München, Germany
- 2<sup>nd</sup> joint European Neonatal Societies' Congress, Nov. 2017, Venice, Italy
- Annual Congress of the Doctoral School, Oct 2017, Saint Malo, France

#### Poster presentations

- Annual Congress of the Doctoral school, Oct. 2019, Saint Malo, France
- Joint SSM 63rd Annual Scientific Meeting & IEA European Congress of Epidemiology, Sept. 2019, Cork, Ireland
- Pediatric Academic Societies Meeting, Apr. 2019, Baltimore, US
- Annual Congress of the Doctoral School, Oct. 2018, Saint Malo, France

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## Annex

### Appendix A1, Chapter 3. Coding scheme for free-text responses in SHIPS questionnaire

Theme	Subtheme	Coding	Quotes, examples 1 <sup>st</sup> draft
I. Coordination of follow-up and health care	'1. Improving care coordination between care providers	Better <b>coordination</b> of follow-up One <b>reference follow-up person/contact</b> Less <b>responsibility</b> on parent to organize care More <b>proactive</b> follow-up (offer not only on request) Take into account child's <b>context</b> in planning More <b>centralization</b> of services (physically) Better <b>continuity</b> of care <b>Follow through</b> with all appointments Better/more supportive <b>administration</b> (attestations, reimbursements etc.) Improved communication and information sharing <b>between practitioners/services</b> Collaboration with follow-up/health care provider and schools Less responsibility on schools for developmental screening	"Big disappointment that no one has overall responsibility for follow-up. Our daughter has many doctor visits at three different hospitals. Countless visits could have been avoided if someone had an overview of the situation." (Sweden)  "It would be better to have a written list of the visits to be carried out, possibly in a single hospital/place, with a team headed by a single referent person. Checks already scheduled autonomously." (Italy)
	'3. Involving additional or more appropriate care providers	Follow-up by <b>multidisciplinary team</b> Follow-up by <b>appropriate (PTB specialized) professional</b> More <b>specialized</b> support Follow-up by <b>paediatrician</b> instead of family doctor More <b>nurse</b> follow-up Follow-up by <b>other specialist</b> , e.g. neurologist or neonatologist	"There should be specific multidisciplinary health care teams from the beginning to accompany these children, with everyone being aware of and knowing the child, so that follow-up could be more complete and closer." (Portugal)  "Should have a Pediatrician in the Health Center (instead of being attended by any Doctor and each time a different one)" (Portugal)
	'22. Train generalists or follow-up staff about prematurity	Informing and training <b>generalists</b> (pediatricians, nurses, family doctors, health visitors) in PTB Training of <b>hospital staff</b>	"After finishing the follow-up at the neonatal unit, we find that both the BVC [Child Health Centre nurse] and the preschool lack knowledge of premature babies and their needs. Thus more knowledge / education to Child Health Centre and preschool staff." (Sweden)
	'4. More equitable access to follow-up	<b>Equal</b> follow-up regardless of where you live (city, countryside, region) General follow-up <b>protocol or national standard</b> for all units More <b>proximal</b> services (shorter distance)	"Unfortunately, help for premature babies is only available in larger cities. We live in the countryside and have limited access to all specialists. A visit to a specialist is associated with an additional trip, and I do not always have a transport [...]" (Poland)

		<p><b>Facilitated access</b> to care (via referrals, less restrictions)          Having <b>access to specialists</b>          Have appointments available/time slots          Having enough staff to get care  <b>Access</b> to services/care regardless of health insurance          Improved <b>wheelchair access</b>          Wider <b>inclusion</b> criteria to follow-up (e.g. 35 WG, not 30)</p>	<p>“There is a very large difference in the health care provided to premature infants between [Hospital A] (where [child] was born) and [Hospital B] (where s/he was later transferred). [...]” (Portugal)</p> <p>“Complicated to be followed by family doctor and to get referral to a specialist” (Estonia)</p>
	'33. Improved hospital transfer and re-hospitalization practices	<p>Facilitated transition to <b>general hospital</b> and care          Improve <b>communication</b> between units of transition  <b>Not force</b> transfer          Maintain <b>standards of care</b> and <b>hygiene</b> in transfer unit          Improve <b>privacy or security</b> in transfer unit          Improve care <b>coordination</b> at transfer unit</p>	<p>“After 97 days of neonatology, I went to paediatrics for one night because of inguinal hernia: from a problem child to a number in the corridor. That was hard.” (Belgium)</p> <p>“Nurses in intermediate care should be as careful as nurses in intensive care.” (Portugal)</p>
	'14. Shorter waiting times and queuing	<p><b>Shorter waiting</b> times/waiting lists  <b>Shorter queues/less waiting in line</b> at clinic  <b>Adapted</b> waiting environment</p>	<p>“[...] and unfortunately there is still a very long waiting time for some specialists. I have a problem with getting into sensory integration classes.” (Poland)</p>
	'15. Improve timeliness	<p>Timely <b>follow-up</b>          Timely <b>assessments</b>          Timely <b>referrals</b>          Timely <b>diagnosis</b>          Timely <b>interventions/care</b></p>	<p>“Autism was detected when s/he enrolled in kindergarten and it was the teacher who found his/her behaviour was not standard compared to other children of his/her age. We attributed the fact that s/he did not speak to her prematurity, because we see him/her every day and we do not see things as someone from outside [...]. We lost a little time before we decided to place him/her in a school adapted to his/her development. Between discharge from neonatology and school start children should have assessments of early detection of autism so that referrals are made as quickly as possible [...]” (Belgium)</p>
	'43. Reduce out-of-pocket costs	<p>Better <b>coverage</b> for rehabilitation by insurance  <b>Free</b> follow-up care (included specialist visits/exams)          Better (financial) access to <b>alternative treatment</b> methods  <b>Financial help</b> for non-reimbursed treatments          Compensate for lost income          Free or less expensive care          Faster reimbursement or support</p>	<p>“[...] support in terms of funding for medicines or equipment used during the rehabilitation at home.” (Poland)</p>
II. Follow-up type and content	'6. Improve follow-up duration	<p>Longer follow-up <b>beyond 2 years</b>          Longer follow-up <b>until school age</b>          Longer follow-up <b>beyond school age</b>  <b>Shorter follow-up</b> if no apparent need</p>	<p>“There should be a follow-up when the children reach school age to see how they develop and whether they were ready to go to school.” (Denmark)</p>
	'7. Improve follow-up frequency	<p>More <b>frequent</b> follow-up  <b>Less</b> follow-up appointments          More follow-up of <b>healthy children</b></p>	<p>“Preterm children could have a check every year, especially hearing, vision and psychologist. There could definitely be a check before school.” (Estonia)</p>

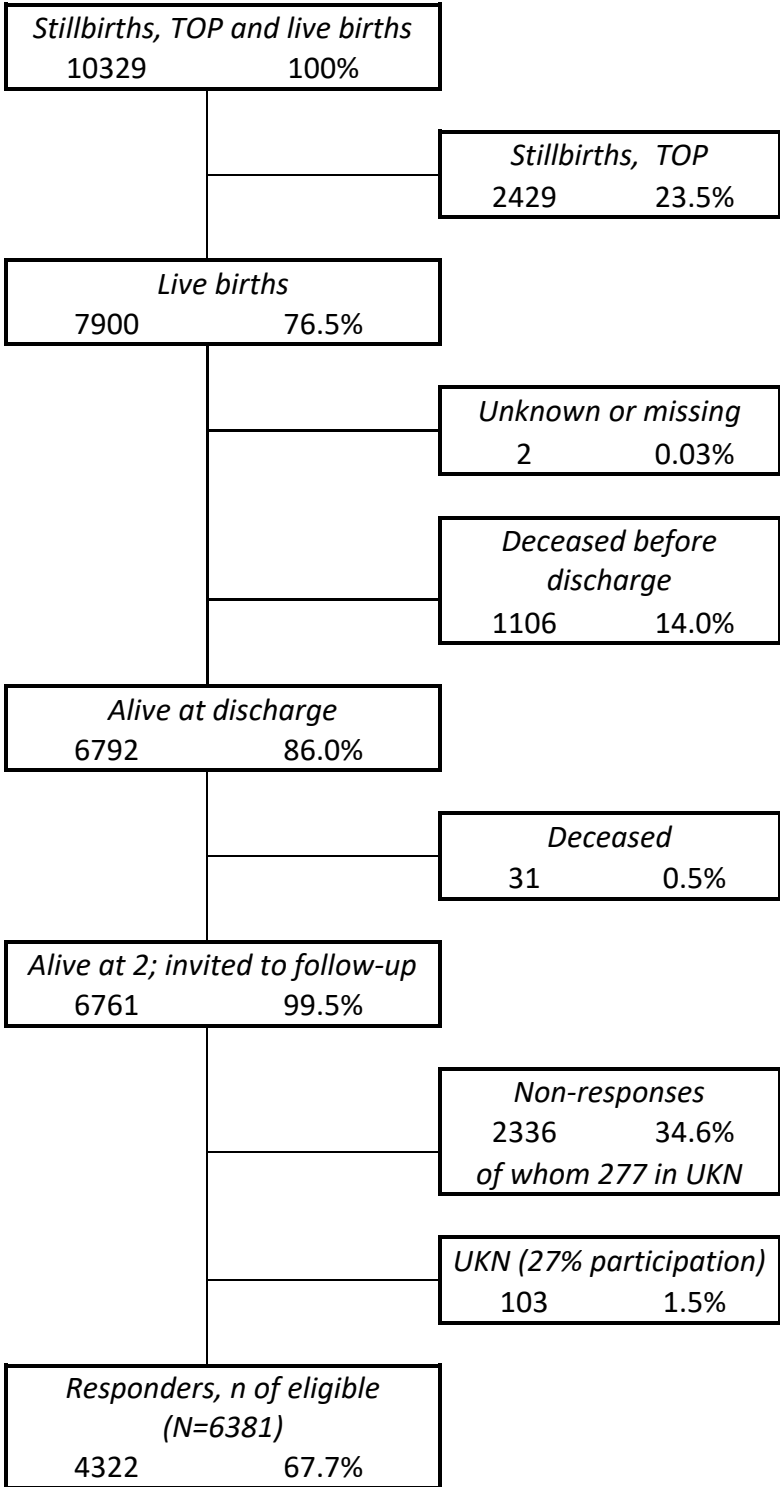
	'8. Offer follow-up beyond physical health	<b>Not only</b> focus on <b>physical</b> health (+ e.g. cognitive/emotional FUP) More <b>psychological</b> follow-up Assess more <b>development</b> Assess for <b>autism</b> Assess <b>socialization</b> problems	"Follow-up on physical health was fine. Follow-up on mental health and "invisible" late effects were non-existing. We were all alone with those things and ended up seeking private help from a consultant." (Denmark)
	'9. Offer home visits/home care	More follow-up <b>home visits</b> right <b>after discharge</b> <b>Home</b> visits/home care or assistance Assess child's <b>family/home conditions</b>	"Support for the home at an early stage in case of doubts or impossibility of travel, and medical follow-up; the possibility of having contact with a permanent nurse or health assistant in order to clarify some doubts, since not all parents have family support, which fortunately is not my case." (Portugal)
	'10. Offer specific examinations or therapies	<b>Eye</b> examinations <b>Motor</b> examinations <b>Heart</b> examinations <b>Brain/neurologic</b> examinations <b>Lung</b> examinations <b>Dentist</b> examinations <b>Hearing</b> tests Other specific examinations (e.g. palate, spine...) More <b>physio</b> or ergotherapy (occupational) / rehabilitation <b>Osteopathic</b> care <b>Speech</b> therapy <b>Eating/feeding</b> support	"Preterm children could have a check every year, especially hearing, vision and psychologist. There could definitely be a check before school." (Estonia)
	'12. Change nature/type of follow-up	More <b>prevention</b> More <b>interventions</b> Include <b>immunization</b> to RSV More <b>extensive/holistic</b> follow-up (more assessments) Not only phone calls	"Follow-up checks were too basic, no blood tests, no adequate visit by a child neuropsychiatrist" (Italy)
	'13. Improve general quality of content	More <b>quality</b> of offered care/visits/checks or <b>better FUP</b> <b>Adequate or sufficient</b> care	"During prematurity he/she was very well followed. Follow-up is no longer so rigorous, especially with regard to support in Speech Therapy." (Portugal)
<b>V. Communication and parent support</b>	'17. Improve communication with parents/ interpersonal relationship	Informing parents on <b>follow-up care</b> (medical procedures, care available, where to go, right to financial support...) Informing parents on what can be <b>expected in the future</b> (health, milestones, development schooling...) Preparing <b>parents</b> to take care of premature infant Giving <b>feedback on child's development</b> Informing parents about <b>PTB during pregnancy</b> Informing and communicate also with the <b>father</b> <b>Listening</b> more to parents More <b>humane relationship/empathy</b> towards parents More <b>positive attitude</b> / positive communication More <b>opportunities to communicate</b> with medical professionals	"Parents are not informed about many things. Such as orthopedic shoes, parents are left to themselves and only by accident they learn about some information." (Poland)  "It was explained in the neonatal unit that in the future we may come across problems such as learning difficulties, vision, hearing, developmental delay. However it was never explained if and what services would help overcome any of these problems." (UK)

		Involving parents in the care Less use of <b>medical terms</b> by medical professionals Removing foreign <b>language barrier</b>	
	'19. Facilitate peer-to-peer communication	Facilitating contact with <b>peers</b> (other parents of VPTB)	"To support the communication with other concerned parents" (Germany)
	'24. Offer parent follow-up and psychological/emotional support	Follow-up also for parents Emotional and psychological support for parents Psychological support also for father More parent support during NICU stay (staff, psychologist) Longer therapy sessions in NICU Facilitated/support in/less abrupt transition to <b>home</b> Support for parents after discharge home	"I, as a mother, would have wished for a better support after the discharge. After the stay in the hospital you are left alone with your worries and fears." (Germany)  "Making room for parents too, because also the motherhood was premature." (Italy)
	'26. Offer practical support to parents	Support for mother to breast-feed Guide parents in appropriate activities for child Expert advice Advice on developing bond with child <b>Child care</b> support (for siblings) Improved <b>discharge practices</b> (preparations for continued care, e.g. appropriate medications, care plan with appointments and parent training, e.g. first aid)	"More support over weekends when first discharged from hospital" (UK)
<b>VII. Macro-social context</b>	'47. Invest in more research	More research on <b>causes</b> of PTB More support for <b>long-term</b> studies Improve science	"The experience I had with [child] was excellent care, they should only improve science." (Portugal)
	'41. Increase length of parental leave	Parental leave <b>adapted</b> to prematurity <b>Long</b> enough parental leave	"More leave for fathers" (The Netherlands) "I find 12 weeks maternity leave inadequate when a child is born at 31 weeks. My child has spent more than 6 weeks in neonatology. When s/he finally got home I had to go back to work shortly, solved this with parental leave. But I do not think that parental leave should serve for this." (Belgium)
	'38. Offer school support for child	<b>Support</b> for <b>starting</b> school or kindergarten Attention to prematurity in <b>teaching</b> (adapting, e.g. pace)	"We had amazing care (health). However, educationally we've had nothing and school seem ill prepared to deal with ex prems and the support they may need - they just seem to think they should be at the same development point as their peers." (UK)
	'23. Train school staff in prematurity	Increased awareness in <b>school staff</b> who are not aware of prematurity-related issues	"After finishing the follow-up at the neonatal unit, we find that both the BVC [Child Health Centre nurse] and the preschool lack knowledge of premature babies and their needs. Thus more knowledge / education to Child Health Centre and preschool staff." (Sweden)
	'20. Improve media coverage on prematurity	Speaking more about prematurity in <b>media</b> (TV etc.)	"More divulgation about the seriousness of being a premature child (to the general public)" (Portugal)

	'48. Increase care investment	More government <b>investment</b> in care for PTB More resources to <b>developmental</b> health services More resources to <b>speech</b> therapy More resources to <b>physiotherapy</b> More resources for <b>equipment</b> [at hospitals?] More support to <b>associations</b>	"Government needs to give more money for equipment." (UK)
<b>VI. NICU environment and care transition</b>	'29. Facilitate NICU stay as family	Access to stay at <b>NICU overnight</b> for <b>mother</b> Access to stay at <b>NICU overnight</b> for <b>father</b> <b>Unlimited</b> stay or longer visiting hours in NICU <b>Housing</b> near NICU for parents Bigger <b>rooms</b> (e.g. family rooms) Do not <b>separate twins</b> Increased <b>privacy</b> Admit <b>access for siblings</b> to visit/stay	"By being able to be with your child 24 hours a day because of attachment and interaction." (The Netherlands)
	'30. Improved physical environment	<b>Nicer environment</b> (e.g. pictures or happy stories of PT children on the walls) Less <b>noise</b> Improved <b>hygiene</b> Having required/modern <b>equipment</b> available More <b>comfortable</b> chairs/beds Safer/more <b>secure</b> rooms	"More attention to viral infections in NICU. When [Child] was in NICU, some children developed viral infections." (Italy)  "More equipment for hospitals. When I was hospitalized, there was only one incubator that was occupied. Luckily my daughter was born only four days later and had access to one. It is very sad that babies have to be transferred because there is no essential equipment available for their survival. I also remember that there were few breathing equipment" (Portugal)
	'31. NICU staff training & interpersonal skills	More health care <b>personnel</b> Better <b>trained</b> health care personnel in NICU More <b>sensitive/empathic/understanding</b> staff	"Especially the first week in university hospital I was not always well informed and treated humane. We liked it better in peripheral hospital" (The Netherlands)
	'32. Facilitate parent-child connection in NICU	Improved parent-child <b>bonding</b> opportunities/being <b>close</b> <b>Advice</b> on developing bond while in NICU Involvement of parents in child <b>care</b> (bathing, diapers etc.) Involvement of parents in <b>feeding</b> Access to or mandatory <b>kangaroo care</b>	"More attention to the mother/child contact (eg. kangaroo therapy) and breastfeeding (more support)" (Italy)
	<b>Positive</b>	'50. Satisfied - general	Satisfied with care in <b>general</b> Satisfied with care in <b>NICU</b> Satisfied with <b>follow-up</b>
	'52. Parent communication	Parents were <b>listened to</b> Parents were <b>taken care of</b> Parents were <b>taken seriously</b> A good <b>parent-practitioner relationship</b> has been important <b>Attentiveness</b> of/in services Staff showed empathy	"We have always felt that we could contact the hospital at any time regarding concerns and were taken seriously. [...]" (Denmark)
	'53. Appropriate timing	Follow-up was <b>regular</b> Follow-up was <b>timely</b>	"I wouldn't know how to improve as the care I had for my twins can be considered both necessary and

		The <b>timing of referral</b> has been crucial for interventions	sufficient (as included in the follow-up program) and even timely for possible problems in need of appropriate specialist visits." (Italy)
	'54. Competency/trust in care provider	Important to <b>follow the advice</b> of the doctor <b>Trust</b> in doctors <b>Specialists</b> give advice and help <b>Empathy and professionalism</b>	"Personally we had excellent follow-up and the people we met were very competent." (France)
	'55. Kangaroo care	<b>Kangaroo care</b> has been important	"Be sure to start with the "kangaroo", I was probably one of the few who kept the baby for several hours in kangaroo. Later at home, the baby was a lot in the stomach bag near me. [...] (Estonia)
<b>No follow-up/care</b>	'0. No follow-up or care	No follow-up offered There is no follow-up Had no follow-up because child is healthy No experienced need for follow-up or care There should be follow-up, even if healthy The care given was unnecessary	"Was not necessary" (Belgium)
<b>No comment</b>	99. No suggestion, no comment or I don't know	Field is empty No suggestions I do not know Can't think of anything etc.	"Nothing to point out." (France) "Don't ask, not enough space" (UK)
<b>Twins</b>	88. See other twin		
<b>Other</b>	100. Other – to be recoded		

Appendix B1, Chapter 4. Figure SI: Flow-chart illustrating the participation in the study



TOP: Terminations of pregnancy; UKN: UK Northern Region

Appendix B2, Chapter 4. Table SI: Specialist services as defined in each country specific questionnaire.

Pre-specified services and/or free-text answers	UK	FRANCE	SWEDEN	DENMARK	GERMANY	BELGIUM & THE NETHERLANDS	PORTUGAL	ITALY	POLAND	ESTONIA
Paediatrician	Paediatrician	Un(e) pédiatre <b>Paediatrician</b>	Barnläkare <b>Paediatrician</b>	Børnelæge <b>Paediatrician</b>	Kinderärztin/ Kinderarzt <b>Paediatrician</b>	Kinderarts <b>Paediatrician</b>	Pediatra <b>Paediatrician</b>	Pediatra (oltre le visite di controllo presso la neonatologia) <b>Paediatrician (outside check-up visit at neonatal unit)</b>	Pediatra <b>Paediatrician</b>	Lastearst väljaspool eelnevaid asutusi <b>Paediatrician outside the follow-up clinic</b>
Physiotherapist or motor development therapist	Physiotherapist/ Motor development therapist	Des séances de kinésithérapie motrice <b>Physiotherapy sessios</b>	Sjukgymnast <b>Physiotherapist</b>	Fysioterapeut <b>Physiotherapist</b>	Physiotherapeut(in)/ Krankengymnast(in) <b>Physiotherapist</b>	Fysiotherapeut <b>Physiotherapist</b>	Fisioterapeuta/ Terapeuta de desenvolvimento motor <b>Physiotherapist/ Motor development therapist</b>	Fisioterapista/ Terapista della motricità (oltre le visite di controllo presso la neo-natologia) <b>Physiotherapist/Motor development therapist (outside check-up visit at neonatal unit)</b>	Fizioterapeuta/ Rehabilitant <b>Physiotherapist/ Rehabilitation</b>	Füsioterapeut <b>Physiotherapist</b>
	Motor development therapist	Un(e) psychomotricien(ne) <b>Psychomotor therapist</b>				Therapeut voor motorische ontwikkeling <b>Motor development therapist</b>				
Resporatory, lung or asthma specialist, allergologist, pulmonologist	Respiratory/ Asthma specialist	Des séances de kinésithérapie respiratoire <b>Respiratory physiotherapy</b>	Andningsmottagning eller lungmottagning <b>Respiratory or lung specialist</b>	Lungespecialist / astmaspecialist <b>Lung specialist/ asthma specialist</b>	Lungenspezialist(in)/ Asthmaspezialist(in) <b>Lung specialist/ asthma specialist</b>	Ademhalings- /astmaspecialist <b>Respiratory/ asthma specialist</b>	Imuno-alergologista/ pneumologista <b>Immuno-allergist / pulmonologist</b>	Specialista in malattie respiratorie (oltre le visite di controllo presso la neo-natologia) <b>Specialist in respiratory diseases (outside check-up visit at neonatal unit)</b>	Pulmonolog <b>Pulmonologist</b>	Kopsuarst <b>Allergologist/ pulmonomlogist</b>
Psychologist or developmental psychologist	Developmental or behavioural psychologist	Un(e) psychologue <b>Psychologist</b>	Psykolog <b>Psychologist</b>	Udviklings- eller adfærdspsykolog <b>Developmental or behavioural psychologist</b>	Entwicklungspsychologin <b>Develomental psychologist</b>	Ontwikkelings- of gedragspsycholoog <b>Developmental or behavioural psychologist</b>	Psicólogo (do comportamento ou do desenvolvimento) <b>Psychologist (behavior or development)</b>	Psicologo dello sviluppo in età evolutiva (oltre le visite di controllo presso la neonatologia) <b>Developmental psychologist (outside check-up visit at neonatal unit)</b>	Psycholog <b>Psychologist</b>	Lastepsühhloog <b>Child psychologist</b>
Psychiatrist	Psychiatrist	Un(e) psychiatre <b>Psychiatrist</b>	Psykiater <b>Psychiatrist</b>	Børnepsykiater <b>Child psychiatrist</b>	Psychiater(in) <b>Psychiatrist</b>	Psychiater <b>Psychiatrist</b>	Psiquiatra <b>Psychiatrist</b>		Psychiatra <b>Psychiatrist</b>	Lastepsühhhaater <b>Child psychiatrist</b>
Dietician or nutritionist	Dietician	Un(e) diététicien(ne) <b>Dietician</b>	Dietist <b>Dietician</b>	Diætist <b>Dietician</b>	Ernährungsberater(in) <b>Dietician</b>	Diëtist(e) <b>Dietician</b>	Nutricionista/Dietista <b>Nutritionist/Dietist</b>	Dietista (oltre le visite di controllo presso la neonatologia) <b>Dietician (outside check-up visit at neonatal unit)</b>	Dietetyk <b>Dietician</b>	Dieetõde <b>Dietician</b>
Ophthalmologist or eye specialist	Ophthalmologist	Un(e) orthoptiste/ ophthalmologiste (spécialiste des yeux) <b>Optometrist/ ophthalmologist (eye specialist)</b>	Ögonläkare /Ortopst <b>Ophthalmologist/ orthoptist</b>	Øjenspecialist <b>Ophthalmologist</b>	Augenärztin/ Augenarzt <b>Ophthalmologist / eye doctor</b>	Oogspecialist <b>Ophthalmologist</b>	Oftalmologista <b>Ophthalmologist</b>	Oculista (oltre le visite di controllo presso la neonatologia) <b>Oculist (outside check-up visit at neonatal unit)</b>	Okulista <b>Oculist</b>	Silmaarst <b>Ophthalmologist</b>
Neurologist	Neurologist	Un(e) neurologue <b>Neurologist</b>	« Neurologist » asked in some questionnaires	Neurolog <b>Neurologist</b>	Neuropädiater(in) <b>Child neurologist</b>		Neurologista <b>Neurologist</b>	Neuropsichiatra infantile / Neurologo (oltre le visite di controllo presso la neonatologia) <b>Child neuro-psychologist / Neurologist (outside check-up visit at neonatal unit)</b>	Neurolog <b>Neurologist</b>	Lasteneuroloog <b>Child neurologist</b>
Speech therapist										Logopeed <b>Speech therapist</b>
Hearing examination/ ear specialist/ ENT/audiology										Kuulmisuuringud <b>Hearing examinations</b>
Osteopath		Ostéopathe <b>Osteopath</b>								



**Appendix B3, Chapter 4.** Table SII: Responder and non-responder characteristics

	Responders at 2 years (N=4322)	Non-responders at 2 years (N=2059)
	n(%) or median [IQR]	n(%) or median [IQR]
<b>Gestational age, weeks</b>	29 [27-31]	30 [28-31]
<26	324 (7.5)	175 (8.5)
26-27	759 (17.6)	297 (14.4)
28-29	1152 (26.7)	554 (26.9)
30-31	2087 (48.3)	1033 (50.2)
<i>Total</i>	4322 (100.0)	2059 (100.0)
<b>Birth weight, grams</b>	1230 [970-1511]	1250 [985-1525]
<b>Multiple birth</b>		
Singleton	2890 (66.9)	1456 (70.8)
Twins or triplets	1432 (33.1)	602 (29.3)
<i>Total</i>	4322 (100.0)	2058 (100.0)
<b>Sex of child</b>		
Male	2296 (53.1)	1115 (54.2)
Female	2026 (46.9)	943 (45.8)
Undetermined	0 (0.0)	1 (0.1)
<i>Total</i>	4322 (100.0)	2059 (100.0)
<b>Small for gestational age</b>		
No (>10 <sup>th</sup> percentile)	2909 (67.3)	1401 (68.1)
Yes (≤10 <sup>th</sup> percentile)	1413 (32.7)	657 (31.9)
<i>Total</i>	4322 (100.0)	2058 (100.0)
<b>Congenital anomaly</b>		
None	3957 (91.6)	1898 (92.2)
Non-severe	315 (7.3)	138 (6.7)
Severe	49 (1.1)	23 (1.1)
<i>Total</i>	4321 (100.0)	2059 (100.0)
<b>Bronchopulmonary dysplasia at 36 weeks postmenstrual age</b>		
No	3692 (87.4)	1740 (86.3)
Yes	533 (12.6)	276 (13.7)
<i>Total</i>	4225 (100.0)	2016 (100.0)
<b>Retinopathy of prematurity stages III-V</b>		
No	4111 (96.2)	1952 (96.6)
Yes	161 (3.8)	68 (3.4)
<i>Total</i>	4272 (100.0)	2020 (100.0)
<b>Intraventricular haemorrhage grades III-IV or cystic periventricular leukomalacia</b>		
No	4018 (93.9)	1882 (92.8)
Yes	260 (6.1)	146 (7.2)
<i>Total</i>	4278 (100.0)	2028 (100.0)
<b>Necrotising enterocolitis with surgery</b>		
No	4255 (98.5)	2020 (98.1)
Yes	67 (1.6)	39 (1.9)
<i>Total</i>	4322 (100.0)	2059 (100.0)
<b>Overall perinatal risk</b>		
Low	1132 (26.9)	575 (28.7)
Moderate	1636 (38.8)	764 (38.2)
High	1447 (34.3)	662 (33.1)
<i>Total</i>	4215 (100.0)	2001 (100.0)

*Data reported as median [IQR: interquartile range] or n(proportion)*

**Table SII, continued:** Responder and non-responder characteristics

	Responders at 2 years (N=4322)	Non-responders at 2 years (N=2059)
	n(%) or median [IQR]	n(%) or median [IQR]
<b>Mother's age in years at delivery</b>	31 [27-35]	29 [25-34]
≤24	537 (12.4)	488 (23.7)
25-34	2515 (58.2)	1098 (53.3)
≥35	1270 (29.4)	473 (23.0)
<i>Total</i>	4322 (100.0)	2059 (100.0)
<b>Mother's country of birth</b>		
Foreign-born	956 (22.2)	500 (38.4)
Native	3352 (77.8)	802 (61.6)
<i>Total</i>	4308 (100.0)	1302 (100.0)
<b>Mother's educational level<sup>a</sup></b>		
High school or less <sup>b</sup>	1936 (46.5)	
More than high school <sup>c</sup>	2232 (53.6)	
<i>Total</i>	4168 (100.0)	
<b>Country</b>		
Belgium	308 (7.1)	345 (16.8)
Denmark	180 (4.2)	106 (5.2)
Estonia	138 (3.2)	1 (0.1)
France	986 (22.8)	117 (5.7)
Germany	435 (10.1)	222 (10.8)
Italy	731 (16.9)	237 (11.5)
The Netherlands	229 (5.3)	101 (4.9)
Poland	199 (4.6)	50 (2.4)
Portugal	408 (9.4)	197 (9.6)
Sweden	165 (3.8)	75 (3.6)
UK	543 (12.6)	608 (29.5)
<i>Total</i>	4322 (100.0)	2059 (100.0)

*Data reported as median [IQR: interquartile range] or n(proportion)*

<sup>a</sup>Not available for non-responders at 2 years

<sup>b</sup>ISCED levels 0-3 (early childhood education to upper secondary)

<sup>c</sup>ISCED levels 4-8 (post-secondary to doctoral)

**Appendix B4, Chapter 4. Table SIII: Use of specialist services by country using inversed probability weighting, sorted by total use of services**

Specialised services											
Regions from:	Any of the pre-specified services		Pre-specified services*					Free text responses			
	Paediatrician %	%	Ophthalmologist %	Physiotherapist or motor therapist %	Respiratory, lung or asthma specialist or pulmonologist %	Developmental psychologist or psychiatrist %	Dietician or nutritionist %	Hearing examination/ ENT/audiology/ hearing specialist %	Neurologist %	Osteopath %	Speech therapist %
Belgium	89.3	61.2	33.0	<b>38.4</b>	13.5	7.5	1.4	2.1	0.3	2.2	1.4
Denmark	34.7	60.5	22.6	<b>44.5</b>	6.9	6.8	10.1	0.5	3.5*	2.2	0.0
Estonia	38.5 <sup>a</sup>	100.0	<b>99.3</b>	96.4	16.1	42.1	3.6	83.3*	70.3*	2.2	29.7*
France	96.0	92.8	61.6	46.5	<b>63.7</b>	17.5	0.2	32.1	2.2*	26.3*	6.3
Germany	87.0	87.9	<b>77.8</b>	63.8	2.9	6.0	8.7	3.8	8.9*	4.3	1.6
Italy	86.0	53.9	<b>36.5</b>	30.4	8.0	9.8	3.2	5.4	26.1*	2.1	1.0
Netherlands	88.7	84.7	37.7	<b>78.7</b>	7.1	7.1	11.2	3.2	0.9	1.3	9.6
Poland	90.7	95.0	<b>90.8</b>	82.4	28.9	41.9	3.7	6.3	69.5*	0.0	10.6
Portugal	84.4	79.9	<b>66.8</b>	45.5	19.3	20.5	10.6	12.1	15.7*	0.0	1.0
Sweden	75.2	71.3	46.9	<b>51.7</b>	37.9	4.9	27.8	6.4	3.4 <sup>b</sup>	0.0	2.0
UK	54.4	57.7	<b>33.4</b>	27.9	12.3	3.4	26.2	3.5	5.8*	0.0	6.5
Total	78.8	73.0	50.3	45.8	21.0	11.9	9.5	11.2	12.4	5.7	4.4

Most commonly used service in each country in bold. Weighted proportions derived using sociodemographic and medical characteristics to estimate the probability of responding to the two-year questionnaire. Variables used to construct weights include maternal age, foreign origin, parity, breastfeeding at discharge, previous caesarean, region of birth, gestational age, multiple pregnancy, pregnancy complications (premature rupture of membranes, antepartum haemorrhage), mode of delivery, small for gestational age, Apgar score, congenital anomalies, neonatal morbidities (bronchopulmonary dysplasia, any severe morbidity), neonatal transport, level of unit of discharge, neonatal care (respiratory support, surgery) as described in reference 23.

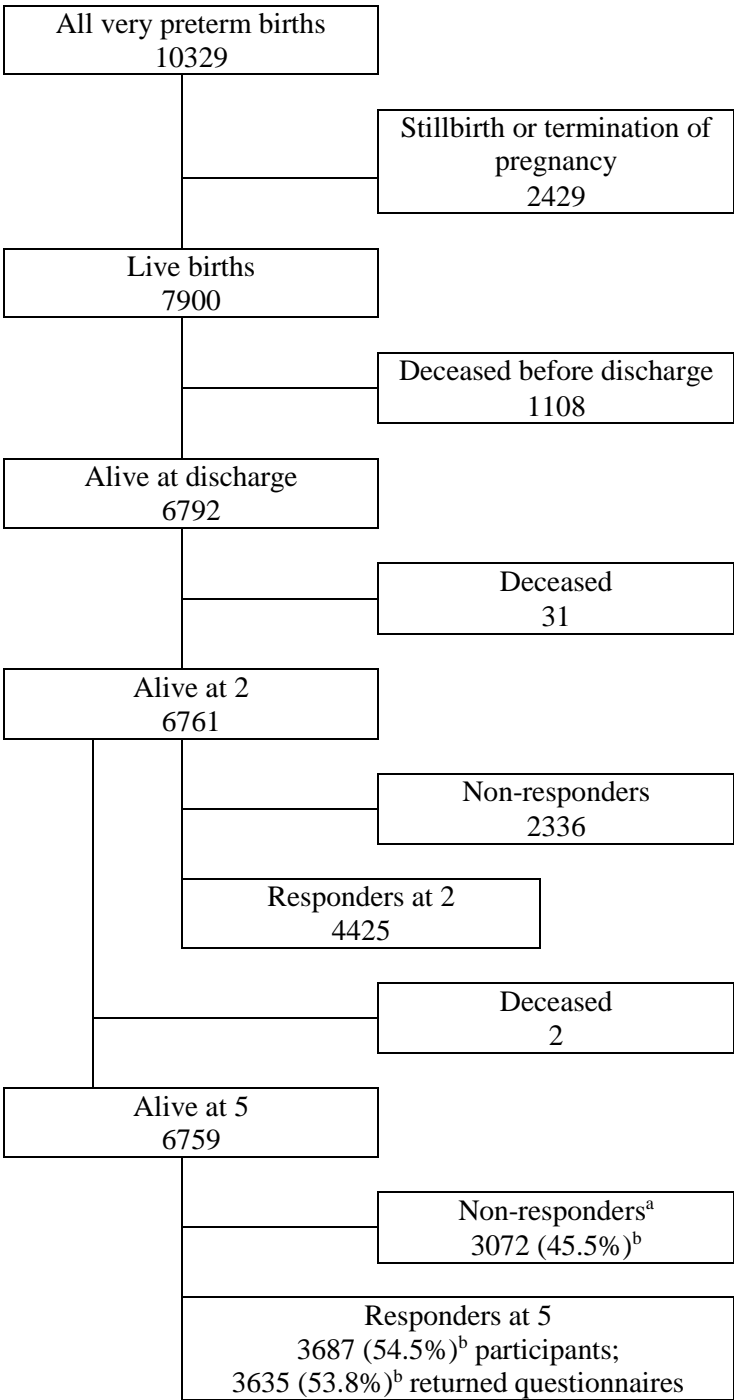
<sup>a</sup> Paediatrician outside follow-up clinic. In Estonia, all children have a paediatrician consultation at a follow-up centre as part of follow-up.

<sup>b</sup> Question asked in 35 of 165 cases (18,4%) in Sweden.

\*Pre-specified services, i.e. services reported by the parent using a list of suggested services

Regions are: 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 and Northern region); Sweden (greater Stockholm) and the United Kingdom (East Midlands and Yorkshire & Humber regions)

Appendix C1, Chapter 5. Supplemental Figure S1. Flowchart



<sup>a</sup>Non-responders include children for whom parents did not consent to follow-up, who were lost to follow-up or for whom a questionnaire was not returned

<sup>b</sup>Calculated over children alive at five year

**Appendix C2, Chapter 5.** Supplemental Table S1. Parents' ratings of preterm birth-related healthcare by country, ordered by unweighted proportion of poor or fair ratings

<i>How would you describe the healthcare your child has received related to his or her preterm birth, after being discharged from the neonatal unit?</i>										
		Excellent		Good		Fair		Poor		Poor or fair
Country	N <sup>a</sup>	n	%	n	%	n	%	n	%	%
France	688	343	49.9	303	44.0	40	5.8	2	0.3	6.1
The Netherlands	138	40	29.0	85	61.6	10	7.3	3	2.2	9.4
Portugal	409	223	54.5	142	34.7	37	9.1	7	1.7	10.8
Italy	659	327	49.6	259	39.3	58	8.8	15	2.3	11.1
Belgium	231	82	35.5	120	52.0	26	11.3	3	1.3	12.6
Estonia	111	52	46.9	44	39.6	13	11.7	2	1.8	13.5
UK	376	179	47.6	132	35.1	48	12.8	17	4.5	17.3
Germany	228	84	36.8	99	43.4	37	16.2	8	3.5	19.7
Sweden	125	51	40.8	49	39.2	18	14.4	7	5.6	20.0
Poland	173	26	15.0	103	59.5	34	19.7	10	5.8	25.4
Denmark	144	45	31.3	52	36.1	37	25.7	10	6.9	32.6
Total	3282	1452	44.2	1388	42.3	358	10.9	84	2.6	13.5

**Appendix C3, Chapter 5.** Supplemental Table S2. Risk ratios of poor or fair ratings by sociodemographic characteristics and child health and development (A) without weights, (B) using inverse probability weights, and (C) inverse probability weights truncated at 95<sup>th</sup> percentile

Socio-demographic characteristics, perinatal risk, developmental and neurosensory difficulties	A) Without weights		B) Using inverse probability weights		C) Inverse probability weights truncated at 95 <sup>th</sup> pct	
	<sup>a</sup> RR	[95% CI]	<sup>a</sup> RR	[95% CI]	<sup>a</sup> RR	[95% CI]
Mother's educational level (ref. lower)						
Intermediate	1.15	[0.81-1.64]	1.21	[0.82-1.79]	1.21	[0.82-1.79]
Higher	1.38	[0.97-1.96]	1.49	[1.01-2.20]	1.49	[1.01-2.20]
Mother's country of birth (ref. native)						
Born elsewhere in Europe	0.44	[0.21-0.90]	0.40	[0.18-0.90]	0.41	[0.18-0.91]
Born outside Europe	0.87	[0.60-1.26]	0.82	[0.53-1.25]	0.82	[0.54-1.26]
Single parent or other (ref. living with partner)	0.92	[0.64-1.33]	0.88	[0.58-1.34]	0.88	[0.58-1.33]
Perinatal risk (ref. lower)						
Moderate	0.95	[0.74-1.23]	0.97	[0.75-1.25]	0.97	[0.75-1.25]
Higher	1.02	[0.79-1.34]	1.09	[0.82-1.46]	1.09	[0.82-1.46]
Cerebral palsy	1.89	[1.35-2.64]	2.08	[1.44-3.00]	2.08	[1.45-3.00]
Epilepsy	1.85	[1.07-3.21]	1.92	[1.07-3.46]	1.91	[1.06-3.43]
Autism	1.32	[0.74-2.35]	1.37	[0.76-2.46]	1.36	[0.75-2.44]
Moderate/severe vision or hearing problem	1.37	[0.90-2.10]	1.65	[1.01-2.69]	1.66	[1.02-2.69]
Country (ref. mean)						
Belgium	0.82	[0.54-1.25]	0.70	[0.44-1.11]	0.70	[0.44-1.11]
Denmark	2.46	[1.83-3.31]	2.91	[2.03-4.19]	2.90	[2.02-4.16]
Estonia	0.73	[0.42-1.25]	0.75	[0.41-1.38]	0.75	[0.41-1.38]
France	0.47	[0.34-0.66]	0.46	[0.32-0.66]	0.46	[0.32-0.66]
Germany	1.39	[0.94-2.07]	1.47	[0.93-2.32]	1.47	[0.93-2.31]
Italy	0.83	[0.65-1.08]	0.83	[0.62-1.10]	0.83	[0.62-1.10]
Netherlands	0.61	[0.32-1.15]	0.52	[0.27-1.02]	0.53	[0.27-1.02]
Poland	1.71	[1.29-2.28]	1.95	[1.40-2.72]	1.94	[1.39-2.71]
Portugal	0.79	[0.59-1.07]	0.78	[0.56-1.10]	0.78	[0.56-1.10]
Sweden	1.40	[0.91-2.17]	1.41	[0.85-2.34]	1.40	[0.85-2.32]
United Kingdom	1.08	[0.80-1.44]	1.03	[0.72-1.46]	1.04	[0.74-1.47]

**Appendix D1, Chapter 6.** Supplemental Table 1: Translations and back-translations for questions on routine follow-up by country

	Two-year questionnaire		Five-year questionnaire	
	Translation	Back-translation	Translation	Back-translation
Introduction	<i>Has your child received care from any of the following since they were first discharged home from the neonatal unit? (Translations omitted)</i>		<i>Not applicable</i>	
Belgium	...Nazorg'-netwerk (regionaal netwerk voor nazorg voor te vroeg geboren kinderen) ...Een kraamafdeling waar uw kind werd opgenomen na de geboorte	...After care network (regional network for children born preterm) ...A maternity ward where your child was admitted after the birth	Heeft uw kind standaardcontroles voor kinderen die te vroeg zijn geboren? (Centrum voor Ontwikkelingsstoornissen, kinderarts) ...Bij de afdeling neonatologie/ kindergeneeskunde waar hij of zij is geboren ...Andere plaats of professionele zorgverlener:	Does your child receive standard check-ups for children who were born prematurely? (Centre for Developmental Disorders, paediatrician) ...Neonatology department where he or she was born ...Other location or the professional healthcare provider:
Denmark	...Opfølgning fra neonatalafdelingen eller ambulatoriet på sygehuset, hvor barnet var indlagt efter fødslen	...Follow-up from the neonatal ward or outpatient clinic at the hospital where child was hospitalised after birth	Bliver jeres barn fulgt op af rutine – eller opfølgningsundersøgelser for børn født for tidligt? ...Neonatal afdeling (afdeling for nyfødte) hvor vi var indlagt efter fødslen ...Andre steder og andet sundhedspersonale, angiv hvor og hvilke:	Is your child being followed up by routine or follow-up examinations for children born preterm? ...Neonatal unit (unit for newborn) where we were hospitalised after birth ...Other place or other health care professional, please specify where and which ones:
Estonia	...Jälgimisvõrgustik enneaegsete laste jälgimine (Tallinna või Tartu lastehaiglate juures) ...Järelekontroll sünnitusmaja lastearsti juures	...Follow-up network for premature infant monitoring (in a children's hospital in Tallinn or Tartu) ...Follow up check with a paediatrician at maternity unit	Kas Teie laps on käinud enneaegsetele lastele mõeldud rutiinses tervisekontrollis? ...Vastsündinute osakond, kus laps sündis ...Muu koht või terviseteenuse asutus:	Has your child gone through a routine health check for premature children? ...Neonatal unit the child was born in ...Other place or health care institution:
France	...Un « Réseau de suivi » (réseau régional de suivi des enfants nés prématurés) ou le service de néonatalogie dans lequel il a été pris en charge à sa naissance ?	...A “Follow-up” network (regional follow-up network of children born preterm) or neonatal services where your child was taken care of after birth?	Votre enfant a-t-elle/il des examens de santé dans le cadre d’un suivi spécifique aux enfants nés prématurés ? ... dans le service de néonatalogie dans lequel il a été pris en charge après sa naissance ... autre, préciser :	Does your child have health examinations as part of a follow-up specifically for children born preterm? ...in the neonatal service where he was taken care of after birth ...other, specify:
Germany	...Geplantes “Nachuntersuchungs-Programm” für Frühgeborene	...Planned “Follow-up” program for preterm babies	Erhält Ihr Kind spezielle Nachsorgeuntersuchungen für frühgeborene Kinder [zusätzlich zu den üblichen U-Untersuchungen]? ...Neugeborenenstation, wo es nach der Geburt betreut wurde ...Sonstige Einrichtung oder medizinische Fachkraft:	Does your child receive special follow up examination for preterm infants [in addition to the common examinations for all children]? ...Neonatal unit, where it was treated after birth ...Other facility or medical professional:

	<b>Two-year questionnaire</b>		<b>Five-year questionnaire</b>	
	<b>Translation</b>	<b>Back-translation</b>	<b>Translation</b>	<b>Back-translation</b>
Italy	Visite di controllo presso la Neonatologia dove era stato ricoverato e poi dimesso, o in altro servizio dello stesso ospedale.	...Check-ups at the Neonatal Unit where the child was hospitalised and then discharged from, or in other unit of the same hospital	Il suo bambino segue un programma di controlli periodici ("follow-up") per bambini nati pretermine? ... Unità di Terapia Neonatale/Neonatologia dell'Ospedale di nascita/dimissione ... Altra struttura sanitaria oppure figura sanitaria (ad es. pediatra di base, neuropsichiatra, psicologa...):	Does your child follow a program of regular check-ups ("follow-up") for children born preterm? ...NICU/neonatal unit of the hospital of birth or discharge ...Other institute or healthcare professional (e.g. paediatric GP, paediatric neurologist, psychologist...):
The Netherlands	...Nazorg'-netwerk (regionaal netwerk voor nazorg voor te vroeg geboren kinderen) ...Een kraamafdeling waar uw kind werd opgenomen na de geboorte	...After care network (regional network for children born preterm) ...A maternity ward where your child was taken after the birth	Wordt uw kind nog routinematig opgevolgd vanwege zijn/haar prematuriteit? (bijvoorbeeld in een Centrum voor Ontwikkelingsstoornissen (COS), kinderarts,...) ...Neonatologie waar hij/zij geboren werd ...Andere plaats of hulpverlener:	Does your child receive standard check-ups for children who were born prematurely? (Outpatient Follow-up Clinic) ... Neonatology department where he or she was born ...Other location or other healthcare provider:
Poland	...Wizyta kontrolna w oddziale neonatologicznym w którym było hospitalizowane dziecko po urodzeniu	...Check-up visit in the neonatal ward where the child was hospitalised after birth	Czy dziecko przechodzi rutynowe badania kontrolne dla dzieci urodzonych przedwcześnie? ...Oddział neonatologii, na którym dziecko przebywało po urodzeniu ...Inna placówka lub pracownik służby zdrowia	Does your child have routine check-ups for preterm children? ... Neonatology ward where the child stayed after birth ...Another facility or health care professional
Portugal	...Unidade de Neonatologia onde a criança esteve hospitalizada após o nascimento	...The neonatal unit where the child was hospitalised after birth	O/a seu/sua filho/a faz consultas de rotina específicas para crianças nascidas prematuramente? ...Unidade de cuidados neonatais onde a criança nasceu ...Outro local ou profissional de saúde:	Does your son/daughter have routine appointments specifically for prematurely born children? ...Neonatal care unit where the child was born ...Other location or healthcare professional:
Sweden	...Uppföljningsprogram för förtidigt födda barn ...På neonatalavdelningen där ditt barn vårdades	...Follow-up program for children born preterm ...The neonatal unit where the child received care	Följer ditt barn på ett uppföljningsprogram för prematurfödda, t.ex vid neonatalmottagning? ...Neonatal vårdenhet/mottagning där barnet vårdades som nyfödd ... Annan vårdinrättning eller vårdkontakt:	Is your child in a follow-up programme for children born preterm, e.g. at a neonatal clinic? ...Neonatal care unit/ facility where the child was cared for as newborn ...Other healthcare facility or healthcare contact:
UK	"Follow-up" network (regional follow-up network of children born preterm) or neonatal unit where your child was hospitalised after birth		Does your child have routine check-ups for children who were born prematurely? ...Neonatal unit where he or she was born ...in other place or health care professional:	



Appendix E1, Chapter 7. Supplemental Table 1: Services as defined in each country-specific five-year follow-up questionnaire

Service	UK	FRANCE	SWEDEN	DENMARK	GERMANY	BELGIUM	NETHERL.	PORTUGAL	ITALY	POLAND	ESTONIA
<b>A child doctor (paediatrician) (because of illness, not routine checks or vaccination visits)</b>	A child doctor (paediatrician) (because of illness, not routine checks or vaccination visits)	Un(e) pédiatre <b>Paediatrician</b>	Barnläkare (för att barnet varit sjukt, inte rutinkontroll eller vaccination) <b>Child physician (paediatrician) (because of illness, that is not included in routine check or vaccination visits)</b>	En børnelæge (pædiater) (pga sygdom, som ikke er inkluderet i rutine check eller vaccinations besøg) <b>Child physician (paediatrician) (because of illness, that is not included in routine check or vaccination visits)</b>	Kinderarzt (Pädiater) (wegen Krankheit, nicht wegen Vorsorgeuntersuchung oder Impfung) <b>Children's doctor (paediatrician) (because of illness, not because of preventive examination or vaccination)</b>	Kinderarts/Pediater (vanwege ziektes, geen routine check-up of vaccinatie) <b>A paediatrician (due to illness, not for standard check-ups or vaccination visits)</b>	Een kinderarts (pediater) (vanwege ziekte, niet voor standaardcontroles of vaccinatiebezoeken) <b>A paediatrician (due to illness, not for standard check-ups or vaccination visits)</b>	Pediatra (por motivo de doença; não considerar consultas de rotina ou vacinação) <b>Paediatrics (due to illness; please ignore routine or vaccination appointments)</b>	Pediatra (solo visite per malattia, esclusi controlli di routine e vaccinazioni) <b>Pediatrician (only visit for illness, excluding routine checkups and vaccinations)</b>	Pediatra (z powodu chorób, z wyłączeniem rutynowych wizyt kontrolnych oraz szczepień) <b>Pediatrician (due to illness, excluding routine checkups and vaccinations)</b>	Lastearst (pediaater) (haiguse, mitte rutiinse kontrolli või vaksineerimise pärast) <b>Children's doctor (paediatrician) (due to an illness, not routine check-up or vaccination)</b>
<b>A family doctor or general practitioner (because of illness, not routine checks or vaccination visits)</b>	A family doctor or general practitioner (because of illness, not routine checks or vaccination visits)	Un(e) médecin généraliste <b>General practitioner</b>	Allmänläkare (för att barnet varit sjukt, inte rutinkontroll eller vaccination) <b>General practitioner (because child was sick, not routine check or vaccination)</b>	Egen læge eller vagtlæge (pga. sygdom ikke inkluderet i rutine check eller vaccinations besøg) <b>Family doctor or on-call physician (because of illness, that is not included in routine check or vaccination visits)</b>	Hausarzt oder Allgemeinmediziner (wegen Krankheit, nicht wegen Vorsorgeuntersuchung oder Impfung) <b>Family doctor or general practitioner (because of illness, not because of preventive examination or vaccination)</b>	Een huisarts (vanwege ziektes, geen routine check-up of vaccinatie) <b>A general practitioner (due to illness, not for standard check-ups or vaccination visits)</b>	Een huisarts (vanwege ziekte, niet voor standaardcontroles of vaccinatiebezoeken) <b>A general practitioner (due to illness, not for standard check-ups or vaccination visits)</b>	Médico/a de família ou médico/a de clínica geral (por motivo de doença; não considerar consultas de rotina ou vacinação) <b>Family doctor or general practitioner (due to illness; please ignore routine or vaccination appointments)</b>	Medico di famiglia o generico (solo visite per malattia, esclusi controlli di routine e vaccinazioni) <b>Family doctor or general practitioner (only visit for illness, excluding routine checkups and vaccinations)</b>	Lekarz rodzinny lub lekarz medycyny ogólnej (z powodu chorób, z wyłączeniem rutynowych wizyt kontrolnych oraz szczepień) <b>Family doctor or general practitioner (due to illness, excluding routine checkups and vaccinations)</b>	Perearst või üldarst (haiguse, mitte rutiinse kontrolli või vaksineerimise pärast) <b>Family doctor or GP (due to an illness, not routine check-up or vaccination)</b>
<b>Hospital Accident and Emergency Department (A&amp;E)</b>	Hospital Accident and Emergency department (A&E)	Un service hospitalier d'urgences <b>Hospital emergency services</b>	Akutombtagning <b>Emergency department</b>	Skadestuen <b>Emergency Department</b>	Notaufnahme im Krankenhaus <b>Emergency department (in a hospital)</b>	Spoedgevallen van het ziekenhuis <b>The Accident &amp; Emergency department of a hospital</b>	Spoedeisende hulp in een ziekenhuis <b>The Accident &amp; Emergency department of a hospital</b>	Serviço de Urgência <b>Emergency Service</b>	Pronto Soccorso/ Dipartimento di Emergenza <b>Emergency room / Emergency department</b>	Szpitalny oddział ratunkowy (SOR) <b>Emergency Department (ED)</b>	Haigla erakorralise meditsiini osakond (EMO) <b>Emergency room of a hospital (ER)</b>
<b>Neurologist (brain specialist)</b>	Neurologist (brain specialist)	Un(e) neurologue/ Neurologue <b>Neurologist or paediatric neurologist</b>	Barnneurolog (neuropediatriker) <b>Child neurologist (neuropaediatrician)</b>	Neurolog (specialist i hjerneskader og udvikling) <b>Neurologist (specialist in brain damages and development)</b>	Neurologe (Hirnfacharzt) <b>Neurologist</b>	Neuroloog (specialist van de hersenen) <b>Neurologist (brain specialist)</b>	Neuroloog (hersenspecialist) <b>Neurologist (brain specialist)</b>	Neurologista(especialista do sistema nervoso: cérebro) <b>Neurologist (specialist of the nervous system: brain)</b>	Neurologo/Neuropsichiatra infantile (per problemi neurologici) <b>Neurologist/ Child Neuropsychiatrist (for neurological problems)</b>	Neurolog (specjalista chorób mózgu) <b>Neurologist (brain disease specialist)</b>	Neuroloog (aju spetsialist) <b>Neurologist (specialist on the brain)</b>
<b>An ear specialist or ENT (Ear, nose and throat specialist)</b>	An ear specialist or ENT (Ear, Nose and Throat specialist)	Un(e) Otho-Rhino-Laryngologiste « ORL » <b>Otorhinolaryngologist "ENT"</b>	Öron-näsa-hals läkare <b>Ear, nose and throat physician</b>	Ørelæge/specialist (Øre, næse, hals læge) <b>Ear doctor/specialist (Ear, nose and throat physician)</b>	Ohren- bzw. Hals-, Nasen-, Ohrenarzt (HNO) <b>Ear, nose and throat specialist (ENT)</b>	Neus-keel-oor Arts (NKO) <b>An ear/nose/throat specialist (ENT)</b>	Een oorspecialist of KNO-arts (keel/neus/oran) <b>An ear specialist or ENT doctor (ear/nose/throat)</b>	Otorinolaringologista (médico/a especialista dos ouvidos, nariz e garganta) <b>Otolaryngologists (doctor specialised in the ear, nose and throat)</b>	Otorinolaringoiatra (specialista delle malattie di orecchio, naso e gola) <b>Otolaryngologist (specialist on diseases of the ear, nose and throat)</b>	Laryngolog (specjalista chorób ucha, nosa i gardła) <b>Laryngologist (ear, nose, and throat specialist)</b>	Kõrvaarst või LOR (Kõrva-, nina- ja kurguarst) <b>Ear specialist or ENT (doctor of the ear, nose, and throat)</b>
<b>An eye specialist (ophthalmologist)</b>	An eye specialist (ophthalmologist)	Un(e) ophtalmologiste <b>Ophthalmologist</b> Un(e) orthoptiste <b>Orthoptist</b>	Ögonläkare <b>Eye physician</b>	Øjenlæge (ophthalmolog) <b>Eye physician (ophthalmologist)</b>	Augenarzt <b>Eye specialist</b>	Oogarts / Oftalmoloog <b>An eye specialist / ophthalmologist</b>	Een oogspecialist of oogarts (oftalmoloog) <b>An eye specialist (ophthalmologist)</b>	Oftalmologista (médico/a especialista dos olhos) <b>Ophthalmologist (doctor specialised in eye problems)</b>	Oculista (specialista dei problemi dell'occhio/vista) <b>Oculist (specialist of problems of the eye/vision)</b>	Okulista (specjalista chorób oczu) <b>Ophthalmologist (eye specialists)</b>	Silmaarst (oftalmoloog) <b>Eye specialist (Ophthalmologist)</b>
<b>Speech/language therapist</b>	Speech / language therapist	Un(e) orthophoniste <b>Speech therapist</b>	Logoped <b>Speech therapist</b>	Tale/sprog pædagog/specialist <b>Speech/language pedagogue/specialist</b>	Logopæde <b>Speech therapist</b>	Logopedist <b>Speech therapist</b>	Spraak-/taaltherapeut (logopedist) <b>Speech/language therapist</b>	Terapeuta da Fala <b>Speech Therapist</b>	Logopedista/terapista del linguaggio <b>Speech therapist/ language therapist</b>	Logopeda <b>Speech therapist</b>	Kõneteraapeut/logopeed <b>Speech therapist</b>
<b>Psychologist</b>	Psychologist	Un(e) psychologue <b>Psychologist</b>	Psykolog <b>Psychologist</b>	Psykolog <b>Psychologist</b>	Psychologe <b>Psychologist</b>	Psycholoog <b>Psychologist</b>	Psycholoog <b>Psychologist</b>	Psicólogo/a <b>Psychologist</b>	Psicologo <b>Psychologist</b>	Psycholog <b>Psychologist</b>	Pühholoog <b>Psychologist</b>
<b>Psychiatrist (because of anxiety, behavioural or developmental problems)</b>	Psychiatrist (because of anxiety, behavioural or developmental problems)	Un(e) psychiatre <b>Psychiatrist</b>	Barnpsykiater (för oro eller beteendeproblem) <b>Child psychiatrist (for anxiety or behavioural problems)</b>	Psykiater (pga. angst, adfærds- eller udviklingsproblemer) <b>Psychiatrist (for anxiety, behavioural or developmental problems)</b>	Psychiater (wegen Angstzuständen, Verhaltens- oder Entwicklungsproblemen) <b>Psychiatrist (because of anxiety states, behavioural or developmental problems)</b>	Psychiater (omdat mijn kind angstig is, gedrags- of ontwikkelingsproblemen heeft) <b>Psychiatrist (due to anxiety, behavioural or developmental problems)</b>	Psychiater (vanwege angst, gedrags- of ontwikkelingsproblemen) <b>Psychiatrist (due to anxiety, behavioural or developmental problems)</b>	Psiquiatra (devido a ansiedade, problemas comportamentais ou de desenvolvimento) <b>Psychiatrist (due to anxiety, behavioural or development problems)</b>	Psichiatra o neuropsichiatra (per ansia, problemi del comportamento o dello sviluppo) <b>Psychiatrist and neuropsychiatrist (for anxiety, behavioural or developmental problems)</b>	Psychiatria (z powodu stanów lękowych, zaburzeń zachowania lub rozwojowych) <b>Psychiatrist (due to anxiety disorders, behavioral and developmental disorders)</b>	Pühhiaater (ärevuse, käitumise või arenguprobleemide pärast) <b>Psychiatrist (because of anxiety, behaviour or developmental problems)</b>

<b>Physiotherapist or motor development therapist</b>	Physiotherapist or Motor development therapist	Un(e) psychomotricien(ne) <b>Psychomotor therapist</b>  Un(e) kinémothricien <b>Physiotherapist</b>	Sjukgymnast <b>Physiotherapist</b>	Fysioterapeut <b>Physiotherapist</b>	Physiotherapeut bzw. Förderung der motorischen Entwicklung <b>Physiotherapist respectively promotion of motor development</b>	Kinesist / fysiotherapeut <b>Therapist for motor skills development / physiotherapist</b>	Fysiotherapeut of therapist voor motorische ontwikkeling <b>Physiotherapist or therapist for motor skills development</b>	Fisioterapeuta ou Terapeuta de Psicomotricidade <b>Physiotherapist or Psychomotor Therapist</b>	Fisioterapista o psicomotricista <b>Physiotherapist or psychomotor therapist</b>	Fizioterapeuta lub terapeuta rozwoju psychomotorycznego <b>Physical therapist or psychomotor development therapist</b>	Füsioterapeut või liikumisterapeut <b>Physiotherapist or motor development therapist</b>
<b>Respiratory or asthma specialist</b>	Respiratory or asthma specialist	Un(e) pneumologue/ pneumopédiatre <b>Respirologist/paediatric respirologist</b>	Lungläkare <b>Pulmonary physician</b>	Lungelæge <b>Lung physician</b>	Atemwegs- oder Asthmaspezialist <b>Specialist for asthma or respiratory problems</b>	Arts voor ademhaling of astma <b>A specialist in the field of breathing or asthma</b>	Specialist op het gebied van ademhaling of astma <b>A specialist in the field of breathing or asthma</b>	Pneumologista (especialista em questões respiratórias ou asma) <b>Pulmonologist (specialist in respiratory problems or asthma)</b>	Specialista in malattie respiratorie e asma/pneumologo <b>Specialist in respiratory diseases and asthma/pneumologist</b>	Pulmonolog (specialista od chorób układu oddechowego/astmy) <b>Pulmonologist (specialist for respiratory system conditions / asthma)</b>	Kopsuarst või astma arst <b>Pulmonologist or asthma specialist</b>
<b>Dietician</b>	Dietician	<b>Free-text answers only</b>	Dietist <b>Dietician</b>	Dietist <b>Dietician</b>	Ernährungsberater <b>Nutritionist</b>	Diëtiste <b>Dietician</b>	Diëtist <b>Dietician</b>	Nutricionista <b>Nutritionist</b>	Dietista <b>Dietician</b>	Dietetyk <b>Dietician</b>	Dieetarst/dieetõde <b>Dietician</b>
<b>Nurse or Health visitor</b>	Health visitor	<b>Free-text answers only</b>	<b>Routine check-ups and vaccination visits excluded (BVC nurse)</b>	Sundhedsplejerske <b>Nurse</b>	Gesundheitsfürsorger <b>Health provider</b>	Sociaal verpleegster / <b>Infirmière spécialisée Community nurse</b>	Sociaal verpleegkundige <b>Community nurse</b>	Visita domiciliária <b>Home visit</b>	Assistenza domiciliare (professionista non medico) <b>Home assistance (non-medical professional)</b>	Pielęgniarka środowiskowa <b>Community nurse</b>	Pereõde <b>Family nurse practitioner</b>
<b>School nurse</b>	School nurse	<b>Free-text answers only</b>	<b>Free-text answers only</b>	Skolesygeplejerske <b>School nurse</b>	Schulkrankenschwester <b>School nurse</b>	Schoolverpleegkundige <b>School nurse</b>	Schoolverpleegkundige <b>School nurse</b>	Enfermeira escolar <b>School nurse</b>	Infermiera della scuola <b>School nurse</b>	Pielęgniarka szkolna <b>School nurse</b>	Kooliõde/Lasteaia tervishoiutõõtaja <b>School nurse / Health professional of a nursery school</b>
<b>Occupational therapist</b>	Occupational therapist	<b>Free-text answers only</b>	Arbeterapeut <b>Occupational therapist</b>	Ergoterapeut <b>Occupational therapist</b>	Ergotherapeut <b>Occupational therapist</b>	Ergoterapeut <b>Occupational therapist</b>	Ergotherapeut <b>Occupational therapist</b>	Terapeuta ocupacional <b>Occupational therapist</b>	Terapista occupazionale <b>Occupational therapist</b>	Terapeuta zajęciowy <b>Occupational therapist</b>	Tegelusterapeut <b>Occupational therapist</b>
<b>Early Intervention services (services that help children with disabilities or developmental delays to develop their skill and enhance their capacities)</b>	Early Intervention services (services that help children with disabilities or developmental delays to develop their skill and enhance their capacities)	<b>Free-text answers only</b>	Habilitering (vårdinrättning som hjälper barn med funktionsnedsättning eller utvecklingsförsening att utveckla sina färdigheter och förbättra sina funktioner). <b>Habilitation (health care facility that helps children with disabilities or delayed development to develop their skills and improve their functions)</b>	Forebyggende tiltag (tiltag som hjælper børn med funktions- eller udviklingsforsinkelse til at udvikle deres færdigheder). <b>Preventive measures (actions that help children with disability or developmental delay to develop their skills)</b>	Maßnahmen zur Frühförderung (um Kindern mit Beeinträchtigungen zu helfen, ihre Fähigkeiten zu entwickeln und zu verbessern) <b>Early education measures (to help children with impairments to develop and improve their skills)</b>	Dienst voor vroeg-behandeling (Diensten die kinderen met beperkingen of ontwikkelingsachterstand helpen om hun vaardigheden te ontwikkelen en verbeteren, bijvoorbeeld vroeg- en thuisbegeleidingsdiensten) <b>Services related to early intervention (services that help children with a handicap or developmental delay to develop their skills and increase their capabilities)</b>	Diensten op het gebied van vroegtijdige interventie (diensten die kinderen met een handicap of ontwikkelingsachterstand helpen om hun vaardigheden te ontwikkelen en hun capaciteiten te vergroten) <b>Services related to early intervention (services that help children with a handicap or developmental delay to develop their skills and increase their capabilities)</b>	Serviços de Intervenção Precoce (serviços que promovem o desenvolvimento de competências e capacidades em crianças com necessidades especiais ou perturbações do desenvolvimento) <b>Early Intervention Services (services promoting the development of skills and abilities in children with special needs or developmental disorders)</b>	Centro di riabilitazione dell'età evolutiva <b>Child rehabilitation center</b>	Świadczenia z zakresu wczesnej interwencji (pomoc dla dzieci z niepełnosprawnością lub opóźnieniem rozwojowym w celu rozwijania ich umiejętności i możliwości) <b>Early intervention services (supporting children with disability or developmental delay to develop their skills and abilities)</b>	Varajase sekkumise teenus (teenus, mis aitab puudega või arengu mahajäämusega lastel arendada nende oskusi ja toimetulekut) <b>Early intervention services (a service that helps disabled or developmentally delayed children to develop their skills and ability to manage)</b>
<b>Multidisciplinary service</b>	<b>Free-text answers only</b>	Votre enfant est-elle/il actuellement suivi dans un centre spécialisé? (CAMSP, CMP, CMPP, Autre) ? <b>Is your child currently followed in a specialized centre (CAMSP, CMP, CMPP, Other)?</b>	<b>Free-text answers only</b>	<b>Free-text answers only</b>	<b>Free-text answers only</b>	<b>Free-text answers only</b>	<b>Free-text answers only</b>	<b>Free-text answers only</b>	<b>Free-text answers only</b>	<b>Free-text answers only</b>	<b>Free-text answers only</b>
<b>If other care provider, please specify:</b>	If other care provider, please specify:	Autre (précisez la spécialité et la fréquence de consultation) <b>Other (specify the specialty and frequency of consultations):</b>	Om ni haft andra vårdkontakter, vänligen specificera vilka och skriv nedan: <b>If you have had other contacts with healthcare services, please specify which ones below:</b>	Hvis jeres barn er blevet tilset af andre personalegrupper eller services end de nævnte, vær venlig at angive hvilke og antal besøg: <b>If your child has been attended to by other professionals or services other than those mentioned, please specify which ones and number of visits</b>	Sonstige medizinische Dienste, nämlich: <b>Other medical services, namely:</b>	Indien een andere zorgverlener, gelieve dit aan te geven: <b>Please write down any other healthcare providers here:</b>	Indien andere zorgverleners, graag hier noteren: <b>Please write down any other healthcare providers here:</b>	Se recorreu a outro serviço ou profissional de saúde, por favor especificar: <b>If you sought other healthcare service or professional, please specify:</b>	Se il suo bambino ha usufruito di altri servizi o professionisti sanitari, la preghiamo di specificarli qui di seguito: <b>If your child has used other services or healthcare professionals, please specify them below:</b>	Jeżeli dziecko korzystało z innych świadczeń, proszę je wymienić: <b>If the child has used other services, please list them:</b>	Muu teenuse osutaja korral palun täpsustage: <b>If there are providers of other services, please specify:</b>

**Appendix E2, Chapter 7.** Supplemental Table 2. Cluster characteristics, examples of Hierarchical and K-means clustering

Population characteristics for each service use cluster derived with hierarchical and K-means clustering methods	Hierarchical clustering				K-means clustering			
	Low service use, occasional outpatient	Moderate service use	Elevated specialist service use	Elevated service use - all	Low service use, occasional outpatient	Elevated specialist	Elevated, especially outpatient	
	n=985	n=1210	n=388	n=895	n=2182	n=896	n=400	
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
<b>Occasional visits to same specialist</b>								
No (no visits or frequent visits)	985 (100.0)	0 (0.0)	388 (100.0)	0 (0.0)	982 (45.0)	292 (32.6)	99 (24.8)	
Yes (1-2 visits)	0 (0.0)	1210 (100.0)	0 (0.0)	895 (100.0)	1200 (55.0)	604 (67.4)	301 (75.3)	
<b>Frequent visits to same specialist</b>								
No (no visits or occasional visits)	985 (100.0)	1210 (100.0)	0 (0.0)	0 (0.0)	2182 (100.0)	0 (0.0)	13 (3.3)	
Yes (3 or more visits)	0 (0.0)	0 (0.0)	388 (100.0)	895 (100.0)	0 (0.0)	896 (100.0)	387 (96.8)	
<b>GP, Paediatrician, Nurse or School nurse</b>								
No visit	214 (21.7)	159 (13.1)	57 (14.7)	82 (9.2)	373 (17.1)	135 (15.1)	4 (1.0)	
Occasional (1-3 visits)	544 (55.2)	615 (50.8)	149 (38.4)	319 (35.6)	1159 (53.1)	432 (48.2)	36 (9.0)	
Frequent (4 or more visits)	227 (23.1)	436 (36.0)	182 (46.9)	494 (55.2)	650 (29.8)	329 (36.7)	360 (90.0)	
<b>ER</b>								
No visit	746 (75.7)	847 (70.0)	267 (68.8)	543 (60.7)	1593 (73.0)	757 (84.5)	53 (13.3)	
Occasional (1-2 visits)	224 (22.7)	308 (25.5)	87 (22.4)	251 (28.0)	532 (24.4)	115 (12.8)	223 (55.8)	
Frequent (3 or more visits)	15 (1.5)	55 (4.6)	34 (8.8)	101 (11.3)	57 (2.6)	24 (2.7)	124 (31.0)	
<b>Hospitalised over night</b>								
No	944 (95.8)	1115 (92.2)	323 (83.3)	715 (79.9)	2059 (94.4)	866 (96.7)	172 (43.0)	
Once	38 (3.9)	85 (7.0)	55 (14.2)	151 (16.9)	111 (5.1)	29 (3.2)	189 (47.3)	
Twice or more	3 (0.3)	10 (0.8)	10 (2.6)	29 (3.2)	12 (0.6)	1 (0.1)	39 (9.8)	

**Appendix E3, Chapter 7.** Supplemental Table 3. Total number of outpatient/inpatient visits and total number of specialist services visits during the past year in five year-old children born VPT, by perinatal and social factors and follow-up context

	Total number of out/inpatient visits		Total number of specialist visits	
	exp(b)	[95% CI]	exp(b)	[95% CI]
<b>Gestational age, completed weeks</b>				
<26	1.50	[1.19-1.89]	2.10	[1.45-3.04]
26-27	1.14	[0.99-1.31]	1.40	[1.03-1.89]
28-29	1.15	[0.98-1.36]	1.50	[1.05-2.13]
30-31	ref		ref	
<b>SGA (percentiles)</b>				
<3 <sup>rd</sup>	1.06	[0.93-1.21]	1.03	[0.87-1.22]
3 – 9 <sup>th</sup>	0.95	[0.84-1.08]	1.26	[0.95-1.68]
≥10 <sup>th</sup>	ref		ref	
<b>BPD</b>				
No	ref		ref	
Yes	1.12	[0.90-1.39]	1.47	[1.31-1.65]
<b>Congenital anomalies</b>				
No	ref		ref	
Yes	1.24	[0.95-1.62]	1.67	[1.14-2.45]
<b>Any neonatal morbidity<sup>a</sup></b>				
No	ref		ref	
Yes	1.21	[1.05-1.40]	3.35	[2.66-4.22]
<b>Child sex</b>				
Male	1.03	[0.88-1.20]	1.64	[1.32-2.04]
Female	ref		ref	
<b>Multiple gestation</b>				
Singleton	ref		ref	
Twins, triplets or quadruplets	0.83	[0.69-1.00]	1.03	[0.82-1.29]
<b>Maternal educational level<sup>b</sup></b>				
Lower	1.42	[1.24-1.63]	1.04	[0.76-1.42]
Intermediate	1.29	[1.08-1.54]	1.08	[0.95-1.24]
Higher	ref		ref	
<b>Parents' employment status</b>				
No parent unemployed	ref		ref	
At least one parent unemployed	1.13	[0.90-1.43]	1.28	[0.85-1.92]
<b>Maternal age at delivery (years)</b>				
≤24	0.94	[0.77-1.14]	0.86	[0.53-1.40]
25-34	ref		ref	
≥35	0.86	[0.81-0.92]	1.03	[0.83-1.27]
<b>Maternal country or birth</b>				
Native	ref		ref	
European-born	1.12	[0.83-1.51]	0.80	[0.63-1.02]
Born outside Europe	0.97	[0.84-1.12]	0.67	[0.44-1.03]
<b>Parity</b>				
Multiparous	ref		ref	
Nulliparous	0.96	[0.84-1.08]	1.10	[0.78-1.56]
<b>Country follow-up rate</b>				
Lower (≤17%)	ref		ref	
Higher (>26.6%)	0.60	[0.41-0.88]	0.70	[0.33-1.50]

Inverse probability weights after multiple imputation were used for all analyses.

SGA: small for gestational age; BPD: bronchopulmonary dysplasia.

<sup>a</sup> Intraventricular haemorrhage grades III-IV, cystic periventricular leukomalacia, retinopathy of prematurity stages III-V or necrotising enterocolitis requiring surgery

<sup>b</sup> Lower: ISCED levels 0-2 (Lower secondary); Intermediate: ISCED level 3-5 (upper or post-secondary, non-tertiary or short cycle tertiary); Higher: ISCED level 6-8 (Bachelor degree or higher).

**Appendix E4, Chapter 7.** Supplemental Table 4: Risk ratios of elevated health care use at 5 years of age in children born VPT, by perinatal and social factors and follow-up context (Models III) without inverse probability weights

	Elevated outpatient/inpatient service use (Model III)		Elevated specialist service use (Model III)	
	RR	[95% CI]	RR	[95% CI]
<b>Gestational age, completed weeks</b>				
<26	1.20	[1.04-1.38]	1.42	[1.17-1.71]
26-27	1.03	[0.93-1.14]	1.20	[1.08-1.33]
28-29	1.09	[0.98-1.21]	1.13	[0.99-1.28]
30-31	ref		ref	
<b>SGA (percentiles)</b>				
<3 <sup>rd</sup>	1.07	[0.92-1.25]	1.03	[0.92-1.15]
3 – 9 <sup>th</sup>	0.92	[0.86-0.97]	1.06	[0.95-1.19]
≥10 <sup>th</sup>	ref		ref	
<b>BPD</b>				
No	ref		ref	
Yes	1.12	[1.03-1.22]	1.17	[1.07-1.27]
<b>Congenital anomalies</b>				
No	ref		ref	
Yes	1.16	[1.02-1.31]	1.13	[1.02-1.25]
<b>Any neonatal morbidity<sup>a</sup></b>				
No	ref		ref	
Yes	1.12	[1.04-1.20]	1.38	[1.29-1.47]
<b>Child sex</b>				
Male	1.07	[0.98-1.16]	1.20	[1.08-1.33]
Female	ref		ref	
<b>Multiple gestation</b>				
Singleton	ref		ref	
Twins, triplets or quadruplets	0.92	[0.84-1.01]	1.01	[0.91-1.13]
<b>Maternal educational level<sup>b</sup></b>				
Lower	1.10	[0.96-1.26]	1.10	[1.00-1.21]
Intermediate	1.14	[1.01-1.30]	1.01	[0.95-1.07]
Higher	ref		ref	
<b>Parents' employment status</b>				
No parent unemployed	ref		ref	
At least one parent unemployed	1.14	[1.00-1.30]	1.03	[0.91-1.17]
<b>Maternal age at delivery (years)</b>				
≤24	0.92	[0.78-1.07]	0.88	[0.76-1.01]
25-34	ref		ref	
≥35	0.89	[0.81-0.99]	1.03	[0.98-1.09]
<b>Maternal country or birth</b>				
Native	ref		ref	
European-born	0.93	[0.86-1.02]	1.05	[0.89-1.23]
Born outside Europe	0.90	[0.80-1.01]	0.77	[0.67-0.88]
<b>Parity</b>				
Multiparous	ref		ref	
Nulliparous	0.94	[0.78-1.13]	0.96	[0.85-1.08]
<b>Country follow-up rate</b>				
Lower (<17%)	ref		ref	
Higher (>26.6%)	0.71	[0.51-0.99]	0.96	[0.78-1.19]

SGA: small for gestational age; BPD: bronchopulmonary dysplasia.

<sup>a</sup> Intraventricular haemorrhage grades III-IV, cystic periventricular leukomalacia, retinopathy of prematurity stages III-V or necrotising enterocolitis requiring surgery

<sup>b</sup> Lower: ISCED levels 0-2 (Lower secondary); Intermediate: ISCED level 3-5 (upper or post-secondary, non-tertiary or short cycle tertiary); Higher: ISCED level 6-8 (Bachelor degree or higher).

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## Abstract

**Title:** Impact of socioeconomic factors on follow-up and health service use up to 5 years of age in a European cohort of children born very preterm

Children born very preterm, before 32 weeks' gestation, have a higher risk of adverse long-term health and developmental consequences compared to their term peers; risks that may further be augmented by social factors. Routine follow-up programmes for children born very preterm are essential for timely identification and management of emerging sequelae, but studies suggest that follow-up and health service use may be inequitable. We aimed to describe routine follow-up and health service use among children born very preterm in 19 regions in 11 European countries, and assess whether follow-up is associated with health care services use and care equity.

We used data from the population-based Effective Perinatal Intensive Care in Europe (EPICE) cohort of very preterm births in 2011/2012 to assess the use of specialist services until two years of age as well as follow-up and health care service use at five years of age. Our results reveal high rates of health care service use at two and five years, as well as large variation in service use and follow-up rates between countries, even in children at highest risk of health and developmental problems. Of concern was that children from socially vulnerable families were less likely to start and continue follow-up, and more likely to frequently use outpatient and inpatient services at five years of age. We also assessed parents' satisfaction and experiences with the care received by their children after discharge from the neonatal unit and found high satisfaction overall, with the exception of parents of children with the most complex health or developmental problems. One of the priority areas of improvement suggested by parents was care coordination.

This thesis provides novel data on health care service use and follow-up until five years of age in children born very preterm in Europe, and constitutes a basis for future research and benchmarking health service provision. Our results also raise further questions about the optimal organisation and availability of care and follow-up for children born very preterm across Europe.

**Key words:** Very preterm birth, health service use, follow-up, equity, cohort, Europe



## Résumé en Français

**Titre :** Impact des facteurs socio-économiques sur le suivi et l'utilisation des services de santé jusqu'à l'âge de cinq ans dans une cohorte européenne d'enfants nés très prématurément

### Introduction

Les naissances très prématurées avant 32 semaines d'aménorrhée ont augmenté au cours des dernières décennies et concernent jusqu'à 1,4 % des naissances en Europe. Bien que la mortalité ait diminué, les enfants nés très prématurément sont à risque de développer des complications sévères après la naissance. Ces risques perdurent après leur sortie d'hospitalisation et peuvent être majorés par un environnement social défavorable.

Les séquelles d'une naissance très prématurée sont bien documentées dans la littérature, mais le pronostic de chaque enfant est inconnu à sa sortie d'hospitalisation. Les programmes de suivi visent à identifier précocement les problèmes de santé et de développement afin de permettre des interventions précoces et des soins appropriés. Les interventions précoces peuvent améliorer le développement moteur, cognitif et comportemental, en particulier chez les enfants de familles les plus défavorisées. Parallèlement, des études ont montré qu'il existe des inégalités sociales dans le suivi, les interventions précoces et l'utilisation des soins et des services de santé, ce qui creuse l'écart avec ceux qui en ont le plus besoin.

Actuellement, il existe peu d'études sur l'utilisation des services de santé après la sortie de l'hôpital des enfants nés très prématurément en Europe. Nous ne savons pas dans quelle mesure les caractéristiques périnatales et sociodémographiques des enfants sont associées à l'utilisation de ces services ou si le suivi a un impact sur leur prise en charge médicale et sur les disparités sociales dans l'accès aux soins. Dans ce projet doctoral, nous avons cherché à répondre à ces questions (1) en décrivant le suivi après la sortie de l'hôpital et l'utilisation des services de santé jusqu'à l'âge de cinq ans chez les enfants nés très prématurément, (2) en étudiant les différences d'utilisation des services de suivi et de santé entre les pays, et les disparités socio-économiques dans l'utilisation de ces services, et (3) en évaluant l'association entre le suivi et l'utilisation de services de santé, en faisant l'hypothèse qu'un suivi plus complet conduit à réduire les inégalités dans l'utilisation de soins de santé.

Pour répondre à ces objectifs, nous avons réalisé quatre études (présentées dans les chapitres 4 à 7), en utilisant les données de la cohorte Effective Perinatal Intensive Care in Europe (EPICE), basée sur la population des naissances très prématurées dans 19 régions de 11 pays européens, et le projet Screening to Improve Health in very Preterm Infants in Europe (SHIPS) qui correspond au suivi de cette cohorte à l'âge de cinq ans.

Dans le chapitre 2 (Etat de l'art), nous décrivons les conséquences sur la santé d'une naissance prématurée et les connaissances actuelles sur les programmes de suivi et l'utilisation des services de santé après la sortie de l'hôpital chez les enfants nés prématurément. Le chapitre 3 présente les sources de données et les méthodes statistiques utilisées pour les quatre études. Enfin, les résultats ont été résumés et discutés dans le dernier chapitre (chapitre 8), avec une conclusion générale des travaux issus de la thèse présentée en fin de chapitre.

## **Etat de l'art**

### *Conséquences de la naissance très prématurée sur la santé et le développement*

Une naissance très prématurée a des conséquences immédiates pour le nouveau-né. La survie diminue nettement avec la diminution de l'âge gestationnel à la naissance tandis que le risque de morbidité et de complications graves augmente. D'autres caractéristiques périnatales liées à une naissance très prématurée, telles que certaines complications maternelles de la grossesse, le retard de croissance intra-utérin et les anomalies congénitales, ont également été associées à de moins bonnes issues à long terme. Les principales morbidités qui surviennent au cours des premiers mois de vie incluent les lésions cérébrales, la dysplasie broncho-pulmonaire, l'entérocolite ulcéro-nécrosante et la rétinopathie de la prématurité, lesquelles augmentent le risque de problèmes de santé et de développement ultérieurs. Les conséquences à long terme chez ces enfants sont hétérogènes et souvent multiples, comprenant l'asthme, l'épilepsie, les troubles de la vision et de l'audition, la paralysie cérébrale, les retards cognitifs et développementaux, y compris le retard de langage et des difficultés d'apprentissage et scolaires. Un risque accru de problèmes psychiatriques, comportementaux et sociaux a également été documenté, notamment des troubles de l'attention et, dans une certaine mesure, des troubles du spectre autistique.

### *Suivi des enfants nés très prématurément*

Les programmes de suivi dépistent les problèmes de santé et de développement des enfants afin de permettre des interventions précoces et de coordonner le suivi et les soins après la sortie d'hospitalisation. Le suivi vise également à informer et aider les familles sur le bon développement de leur enfant et à faciliter leur entrée à l'école. Ces programmes, qui sont plus structurés et spécialisés que le suivi médical habituel de routine en pédiatrie, évaluent la santé physique et mentale, le développement, la cognition et la qualité de vie de manière régulière. Peu d'études ont évalué ces programmes, mais celles-ci suggèrent que ces programmes pourraient améliorer l'accès aux soins et la santé de l'enfant. Jusqu'à très récemment, aucune recommandation internationale n'existait sur le suivi des enfants nés prématurés. Par conséquent, en Europe, le contenu et la durée du suivi recommandé, ainsi que les programmes de suivi sont hétérogènes. Par exemple, dans les pays participant à l'étude SHIPS, la durée du suivi varie entre deux et huit ans, et les bilans de santé et du développement sont plus ou moins approfondis et ont lieu à des âges et à des fréquences différentes.

### *Prise en charge après la sortie de l'hôpital et les besoins de soins*

L'utilisation des services de santé peut être considérée comme une mesure indirecte de la santé de l'enfant, même en l'absence de diagnostic et de traitements désignés. Ainsi, dans des populations ayant des besoins spéciaux en santé, par exemple chez les enfants avec des troubles neuro-développementaux, l'absence de consultations peut refléter des besoins de santé non satisfaits. Des études montrent qu'une naissance très prématurée, par rapport à une naissance à terme, peut entraîner un recours plus important des services ambulatoires, notamment des services d'urgences, ainsi que des services spécialisés dans l'enfance. Cependant, la plupart des études se concentrent sur les hospitalisations, montrant des taux plus élevés chez les enfants nés très prématurément que chez ceux nés à terme. Dans la population pédiatrique, le recours aux soins traduit également des besoins complexes, cliniques et/ou sociaux de ces enfants. Les enfants ayant des besoins complexes sont plus à risque de problèmes de santé et de développement plus tard à l'enfance, ce qui nécessite une gestion des soins encore meilleure.

### *Équité en santé et des soins*

Les disparités sociales en santé sont largement documentées dans la population générale et à la petite enfance. Le risque d'accouchement prématuré est plus élevé chez les femmes socialement

vulnérables, et les facteurs sociaux sont associés à un risque plus élevé de déficiences cognitives chez les enfants nés très prématurément. De même, les caractéristiques sociales des parents, tels qu'un faible niveau d'éducation, le chômage, un faible revenu, l'appartenance à une minorité ethnique et le très jeune âge, ont été associés à des difficultés d'apprentissage et scolaires chez les enfants, quel que soit l'âge gestationnel à la naissance. En même temps, la recherche suggère que l'utilisation des services de santé après la sortie de l'hôpital (services d'intervention précoce, hospitalisations et services d'urgence) est moins optimale chez les enfants issus de familles défavorisées, qui ont pourtant un pronostic à long terme moins favorable. À ce jour, les études évaluant les liens entre les caractéristiques sociales et la participation aux programmes de suivi restent peu nombreuses.

## **Méthodes**

### *Introduction*

Ce projet de thèse a été réalisé au sein du consortium SHIPS qui comprend des chercheurs et des cliniciens de treize institutions dans onze pays européens, dont une équipe d'économie de la santé, des chercheurs spécialisés en méthodes qualitatives et un réseau d'associations européennes de parents d'enfants nés prématurément (EFCNI). Les résultats de ces travaux ont été discutés lors de réunions semestrielles du consortium et plus fréquemment dans le cadre d'un groupe de travail sur les soins et le suivi avec des chercheurs français, portugais et anglais. Ces discussions ont permis d'interpréter les résultats par rapport à l'organisation des soins dans chaque pays et d'harmoniser les définitions et les catégories des services de soins.

### *Source des données et population étudiée*

Les données proviennent de l'étude EPICE qui a constitué une cohorte d'enfants nés avant 32 semaines d'aménorrhées avec un suivi à deux ans, et de l'étude SHIPS qui a suivi ses enfants à cinq ans. La cohorte comprend 19 régions en Belgique, au Danemark, en Estonie, en France, en Allemagne, en Italie, aux Pays-Bas, en Pologne, au Portugal, en Suède et au Royaume-Uni. Ont été incluses toutes les naissances vivantes et les interruptions médicales de grossesse entre 22 semaines et 0 jour et 31 semaines et 6 jours au sein de toutes les maternités issues des régions participantes. La période d'inclusion était de douze mois (ou six mois en France) en 2011 et 2012. Les enfants ont été évalués à l'inclusion, à deux ans d'âge corrigé et à cinq ans. Sur 7900

naissances vivantes, 6792 (86,0 %) enfants ont survécu jusqu'à la sortie d'hospitalisation, 4426 (65,5 %) ont participé à l'âge de deux ans et 3687 (54,5 %) au suivi à cinq ans.

#### *Données recueillies et harmonisation des données*

Les données périnatales ont été recueillies à partir des dossiers obstétricaux et néonataux par les soignants ou des enquêteurs formés pour l'étude. Les parents ont rempli des questionnaires sur le développement, la santé, le suivi et l'utilisation des services de santé de leur enfant à deux et à cinq ans. Pour les questions sur l'utilisation des services de santé, une liste standardisée des services pédiatriques a été établie dans chaque pays. Les définitions des services ont été adaptées aux systèmes de soins et aux services pédiatriques offerts dans chaque pays. Les parents devaient indiquer les services utilisés par leur enfant ainsi et que le nombre de visites au cours de l'année passée. Il a été également demandé aux parents d'évaluer les soins reçus par leur enfant sur une échelle de 1 (mauvais) à 4 (excellent), et de faire des propositions, en texte libre, sur les améliorations à apporter aux soins de santé pour les enfants nés très prématurément.

#### *Stratégie d'analyse : points clés*

Les méthodes statistiques utilisées pour analyser les données ont présenté plusieurs défis analytiques, notamment : la structure hiérarchique des données et le choix de modèles statistiques adaptés, la prise en compte des différences dans la population des enfants prématurés entre les pays, et le possible biais lié aux familles perdues de vue dans la cohorte. Pour relever ces défis liés à la structure hiérarchique, nous avons appliqué la modélisation multiniveau et des approches à effets fixes par pays combinée avec des estimations robustes de variance, détaillées au chapitre 3. Afin d'obtenir des estimations comparables entre les pays, nous avons pris en compte les caractéristiques des populations par la stratification, la standardisation directe et les ajustements à partir des modèles multivariés. Nous avons créé une variable composite pour classer les enfants en trois groupes selon leur niveau de risque périnatal. Pour prendre en compte les perdus de vue, nous avons pondéré nos analyses par l'inverse de la probabilité de participer au suivi, après imputation multiple des données manquants. Cette méthode attribue un poids plus élevé aux enfants ayant des caractéristiques semblables aux enfants perdus de vue. Enfin, nous avons utilisé une approche mixte comprenant des méthodes qualitatives (analyse thématique) pour analyser les réponses en texte libre fournies par les parents suggérant des améliorations de la prise en charge des prématurés.

*Résultats – article 1: Utilisation de services de santé spécialisés dans une cohorte européenne d'enfants nés très prématurément*

La première étude de ce projet de thèse, publiée dans la revue *Developmental Medicine and Child Neurology*, permet de décrire pour la première fois l'utilisation des services spécialisés au cours des deux premières années de vie chez les enfants nés très prématurément en Europe, ainsi que sur les facteurs périnataux et sociodémographiques associés à l'utilisation de ces services. La population d'étude comprend 4322 enfants nés très prématurément suivis à deux ans d'âge corrigé dans les onze pays étudiés. Nous avons également étudié les disparités sociales en lien avec l'utilisation des services dans chaque pays après ajustement sur le niveau de risque périnatal des enfants.

Nous avons constaté une utilisation élevée des services spécialisés : 76 % des enfants avaient vu au moins un spécialiste depuis leur sortie de l'hospitalisation néonatale, variant entre 54 % en Italie et 100 % en Estonie. Nous avons également observé de grandes variations dans l'utilisation de ces services chez les enfants présentant des facteurs de risque périnataux, tels que les morbidités néonatales : 86 % avaient consulté au moins un spécialiste avec une variation entre 66 % en Italie et 100 % en Estonie et en Suède ; ces enfants avaient consulté 1,9 différents services spécialisés en moyen (entre 1,1 au Danemark et 2,9 en Suède et en Pologne). Un niveau d'éducation maternel plus faible était associé à un recours moins fréquent aux services spécialisés dans trois pays sur onze. Ses résultats soulèvent des questions de recherche pour les études ultérieures sur les forces et les faiblesses en termes de résultats de santé et d'équité de ces modèles de prise en charge très différents en Europe.

*Résultats – article 2 - L'évaluation parentale des soins de santé reçus par leurs enfants nés très prématurément après la sortie de l'hôpital et leurs propositions pour améliorer ces soins au sein d'une étude de cohorte Européenne*

Pour la deuxième étude de ce projet de thèse publiée dans la revue *Pediatric Research*, nous avons utilisé une approche mixte pour évaluer, dans les onze pays européens participant à l'étude SHIPS, la perception des parents sur les soins reçus par leurs enfants nés très prématurément jusqu'à l'âge de cinq ans. Les données issues de 3635 questionnaires parentaux ont été utilisées, comprenant l'évaluation par les parents des soins reçus par leur enfant jusqu'à cinq ans (mauvais, moyen, bon ou excellent), ainsi que 900 suggestions en texte libre données par les parents sur les améliorations à apporter aux soins. Nous avons étudié les proportions

d'évaluation mauvaise ou moyenne (insatisfaction) par pays, ainsi que le lien entre l'insatisfaction et la santé, le développement de l'enfant et les facteurs sociodémographiques de la famille. Nous avons utilisé une analyse thématique pour classer les améliorations de soins souhaitées par les parents.

Une minorité des parents (14 %) étaient insatisfaits des soins reçus par leurs enfants, avec une variation de 6 % en France à 32 % au Danemark. L'insatisfaction à l'égard des soins était la plus élevée parmi les familles ayant des enfants souffrant de problèmes de santé. Les taux d'insatisfaction étaient de 34 % lorsque les enfants présentaient une paralysie cérébrale et de 37 % chez les enfants épileptiques. Les suggestions des parents pour améliorer les soins étaient similaires d'un pays à l'autre, avec un consensus autour de la nécessité, pour les professionnels de santé, d'améliorer leurs communications avec les parents et d'améliorer la coordination des soins. Les suggestions des parents de la cohorte SHIPS corroborent des études européennes antérieures qui montrent que les enfants ayant des besoins complexes rencontrent souvent des difficultés de prise en charge liés à une mauvaise organisation des soins. Sachant que les politiques en matière de suivi diffèrent en Europe, cela soulève des questions sur le rôle des programmes de suivi dans la coordination des soins chez des enfants avec des besoins complexes.

### *Résultats – article 3 - Suivi après une naissance très prématurée en Europe*

La troisième étude (actuellement soumis) porte sur l'utilisation des programmes ou des services de suivi après la sortie de l'hospitalisation néonatale chez les enfants nés très prématurés. Nous avons utilisé les données des questionnaires parentaux à l'âge de deux et cinq ans pour déterminer les taux de suivi pour les enfants nés très prématurés. Le questionnaire à deux ans a recensé l'utilisation des services de suivi au cours des deux premières années de vie avec des questions qui étaient adaptées à l'organisation des soins de suivi dans chaque pays. A cinq ans, la question suivante a été posée : Votre enfant a-t-elle/il des examens de santé dans le cadre d'un suivi spécifique aux enfants nés prématurés, dans le service de néonatalogie dans lequel il a été pris en charge après sa naissance ou autre (préciser) ? Non, il/elle n'en jamais eu ; Non, il/elle n'en a plus maintenant ; Oui, il/elle a actuellement des examens. Nous avons également évalué si les facteurs de risque périnataux et les facteurs sociodémographiques familiaux étaient liés à l'utilisation de ces services.

Une grande majorité des 3635 enfants grands prématurés ont eu un suivi spécifique aux enfants nés prématurés (90 %) entre la sortie de l'hôpital et cinq ans, mais moins d'un tiers était encore suivi à cinq ans, entre 10 à 60 % selon le pays après ajustement sur les facteurs de risques périnataux et sociaux. Les contrastes entre pays dans les pourcentages d'enfants suivis à cinq ans étaient encore plus marqués pour les enfants nés avant 28 semaines d'aménorrhée (12 à 72 %). Les enfants présentant des facteurs de risques périnataux étaient plus souvent suivis, tandis que les enfants de mères avec une éducation plus modeste, plus jeunes et migrantes avaient des risques plus importants de ne pas être suivis du tout. Les enfants de mères nées hors d'Europe avaient deux fois plus de risque de ne jamais être suivi et un risque majoré de 40 % d'arrêter le suivi avant l'âge de cinq ans par rapport aux enfants nés de mères non immigrées. Même si des variations entre pays dans les taux de suivi étaient attendues, la plus faible probabilité d'être suivi chez les enfants présentant des facteurs de risque sociaux est préoccupante, surtout dans la mesure où les bénéfices du suivi sont plus marqués dans cette population. Ces résultats laissent penser que des disparités géographiques et sociodémographiques peuvent exister dans l'accès aux soins de santé à l'âge de cinq ans.

*Résultats – article 4- Utilisation élevée des services de santé à l'âge de cinq ans chez les enfants nés très prématurément : association avec les circonstances sociales et le suivi*

Dans la quatrième et dernière étude de ce projet (manuscrit à soumettre), nous donnons un aperçu complet de l'utilisation des services de santé à l'âge de cinq ans dans la cohorte EPICE. Tout d'abord, nous avons défini "l'utilisation élevée" des soins ambulatoires/hospitaliers (médecins généralistes, pédiatres, infirmier-e-s, visites aux urgences, ou hospitalisation de nuit) et spécialisés (par exemple, neurologue, kinésithérapeute ou psychologue) en fonction de critères figurant dans la littérature sur les soins pédiatriques. Par la suite, nous avons étudié les différences entre pays en matière de recours élevé à ces deux types des services, et examiné si des facteurs sociaux étaient associés à une utilisation plus élevée de services. Nous avons également étudié si des politiques en faveur de suivi plus complet des enfants nés prématurés pouvait modifier ces associations. Pour explorer l'association entre la nature des politiques de suivi à l'échelle du pays et l'utilisation des services, nous avons comparé les enfants vivant dans des pays avec des taux de suivi plus élevés à cinq ans (reflétant des politiques de suivi plus complet) aux enfants vivant dans des pays avec des taux de suivi moins élevés (reflétant des politiques de suivi moins complet).



A l'âge de cinq ans : 44 % des enfants avaient une utilisation élevée des services ambulatoires/hospitaliers ( $\geq 4$  consultations avec un médecin généraliste, pédiatre, ou infirmière/infirmier, en dehors de visites de routine ou vaccinations, et/ou  $\geq 3$  visites aux urgences, ou au moins une hospitalisation de nuit), entre 24 % (Danemark) et 78 % (Pologne). En termes d'utilisation des services spécialisés, 49 % avaient une utilisation élevée ( $\geq 2$  spécialistes différents et/ou  $\geq 3$  visites à un spécialiste), entre 39 % (Pays-Bas) et 66 % (Pologne). Les enfants issus de familles socialement vulnérables étaient plus susceptibles de recourir aux services ambulatoires et aux urgences, ou d'être hospitalisés. Par exemple, les enfants de parents sans emploi avaient 20 % de risque en plus d'avoir un recours élevé aux services ambulatoires et hospitaliers à cinq ans, comparé aux enfants de parents qui travaillaient. Les enfants habitant dans des pays où les taux de suivi à cinq ans étaient plus élevés étaient moins susceptibles de recourir aux services ambulatoires et aux urgences ou être hospitalisés. Ces résultats suggèrent que les enfants nés très prématurément et socialement défavorisés reçoivent des soins moins optimaux, et qu'un suivi plus complet pourrait aider les parents à répondre au mieux aux besoins de santé complexes de leurs enfants.

## **Discussion**

### *Résumé des principales conclusions*

Nos résultats ont montré de grandes variations en Europe dans l'utilisation des services de suivi et de soins de santé par les enfants nés prématurément, après la sortie de l'hospitalisation néonatale et jusqu'à l'âge de cinq ans, et qui ne s'expliquent pas par des différences dans les facteurs de risque à la naissance. Une grande majorité de parents a déclaré avoir bénéficié de services de suivi pour leurs enfants, mais les différences dans l'utilisation des services de suivi à l'âge de cinq ans étaient marquées entre les pays, avec une variation encore plus importante chez les enfants nés avant 28 semaines. Nous avons aussi documenté une utilisation élevée des services de santé à l'âge de deux ans, ainsi qu'à cinq ans. Les enfants présentant des facteurs de risque périnataux ont systématiquement eu un suivi et des recours aux services de santé plus importants, mais les variations dans l'utilisation des services de santé persistaient entre les pays, même après la prise en compte des différences de niveau de risque périnataux et sociaux. Nous avons également constaté des variations entre les pays dans l'insatisfaction des parents à l'égard des soins, bien que le niveau de satisfaction soit globalement élevé. Deux résultats sont particulièrement préoccupants : (1) une insatisfaction élevée des parents à l'égard des soins quand leurs enfants avaient des besoins élevés ou complexes, et (2) une utilisation plus faible

des services de suivi et le recours plus élevé aux services ambulatoires et hospitaliers chez les enfants issus de familles socialement vulnérables comparés aux autres familles. Les enfants avec des besoins de santé complexes et des vulnérabilités sociales représentent deux groupes d'enfants qui ont le plus besoin de suivi et de soins de santé, et qui pourraient le plus bénéficier d'interventions. Enfin, nous avons constaté que le fait de vivre dans un pays doté d'un suivi plus complet, c'est-à-dire où les enfants étaient plus souvent suivis jusqu'à l'âge de cinq ans, était associé à une probabilité plus faible de recours élevé aux services ambulatoires et hospitaliers.

### *L'Europe, opportunités et défis pour la recherche*

Notre étude a bénéficié de la participation de multiples pays européens. L'Europe offre de nombreuses possibilités d'étudier les soins de santé, notamment pour comparer les états de santé et le recours aux soins, car les pays sont similaires en termes de richesse et de couverture universelle des soins de santé. Cependant, la recherche liée aux soins de santé dans un contexte international n'est pas sans difficultés. Les principaux défis proviennent des différences entre les systèmes et les contextes de soins de santé entre les pays et, comme dans notre cas, de la variabilité des programmes et des recommandations de suivi. Néanmoins, nous avons pu évaluer l'association entre le suivi et l'utilisation élevée des services de santé en nous basant sur les taux de suivi déclarés par les parents comme indicateur de l'étendue de la politique et des programmes de suivi. Les pays peuvent également différer sur plusieurs autres aspects susceptibles d'influencer l'utilisation des services de santé, tels que l'organisation générale des soins de santé, l'existence des contraintes financières quand il y a des frais non-couverts par l'assurance, et d'autres facteurs sociétaux non mesurés. La diversité des environnements de soins de santé dans ce projet limite l'interprétation de la variabilité constatée dans l'utilisation des services de santé, mais permet de définir les hypothèses pour des recherches futures.

### *Conception et méthodes d'étude : forces et limites*

Les études de cohortes observationnelles multinationales basées sur des questionnaires d'auto-évaluation sont des méthodes intéressantes pour la recherche sur les soins de santé, mais elles présentent également des limites. Tout d'abord, les études de cohortes observationnelles ne peuvent pas déterminer la causalité entre l'intervention et le résultat, comme le suivi et l'utilisation des services. Elles sont également sujettes à un biais de sélection car les participants de l'étude dont la santé est moins bonne sont plus susceptibles d'utiliser des services de suivi

ou de soins médicaux, ce qui rend difficile l'évaluation de l'effet de ces services sur la santé. En outre, comme la participation est volontaire, les participants à l'étude peuvent être très différents des perdus de vue. Bien que nous ayons utilisé la méthode de la pondération inverse par la probabilité de participer pour tenir compte d'un éventuel biais d'attrition, les parents participant à l'étude pourraient être plus susceptibles d'utiliser des services de suivi par rapport aux parents qui n'ont pas participé, ce qui conduirait à une surestimation des taux d'utilisation.

Nos données ont également des limites. Nous ne disposons pas de détails sur la disponibilité, la qualité et l'organisation du suivi. De plus, les informations sur les visites médicales sont rapportées par les parents, comportant certainement des erreurs de mémoire, sans informations sur les raisons de l'utilisation ou non des services. Par conséquent, nous n'avons pas pu déterminer si l'absence d'utilisation des services était le signe d'un besoin de soins non satisfait, si les obstacles à l'utilisation étaient liés à l'offre, à l'accès ou au choix des parents, et à quel moment des inégalités pouvaient apparaître dans le processus de soins. En revanche, les évaluations des parents concernant les soins après la sortie de l'hôpital ainsi que leurs commentaires en texte libre sur la façon d'améliorer les soins, ont fourni des données précieuses sur la perception de la qualité des soins et l'insatisfaction vis à vis des soins offerts aux enfants nés très prématurément.

## **Conclusions**

### *Conclusions sur les principaux résultats*

L'organisation du suivi et de la prise en charge des enfants nés très prématurément diffère fortement selon les régions d'Europe. Dans ce projet de thèse, nous avons montré comment ces différences se traduisent par de grandes variations du taux du suivi médical, de l'utilisation des services de santé et de la satisfaction des parents selon les régions, même chez les enfants ayant les risques les plus élevés de problèmes de santé et de développement. Les études faisant partie de cette thèse fournissent des données inédites sur l'utilisation des services de suivi de santé jusqu'à l'âge de cinq ans, constituant des points de référence essentiels pour les pays qui peuvent évaluer leurs propres services à la lumière des questions soulevées par ces résultats sur l'organisation et la disponibilité des soins de suivi en Europe.

Ces études ont également permis d'acquérir de nouvelles connaissances sur les facteurs associés à l'utilisation des services de santé et de suivi chez les enfants nés très prématurément, ainsi que

sur les domaines qui nécessitent des améliorations. Nous avons constaté que les enfants présentant des facteurs de risque périnataux étaient plus susceptibles d'avoir un recours élevé aux services de soins, mais nous avons également constaté des taux d'insatisfaction plus élevés chez les parents d'enfants présentant des problèmes de santé et de développement à l'âge de cinq ans. Ces résultats s'ajoutent à d'autres études qui ont montré qu'il est nécessaire d'améliorer l'organisation des soins pour les enfants ayant des besoins de santé complexes. Quel que soit le pays, les parents ont fréquemment indiqué que la coordination des soins, le suivi, la communication et le soutien aux parents devaient être améliorés.

D'autres résultats importants de nos études concernent l'accès aux soins pour les enfants issus de familles socialement vulnérables ; les enfants issus de familles plus désavantagées sont moins susceptibles d'utiliser les services de suivi et risquent davantage de recourir aux services ambulatoires et hospitaliers. Ces résultats suscitent des inquiétudes quant à l'équité dans le suivi et l'utilisation des services de santé en Europe et suggèrent que les inégalités sociales doivent être prises en compte lors de l'élaboration de recommandations et de l'organisation du suivi et des soins pour les enfants nés très prématurément.

#### *Perspectives pour la recherche future*

Des recherches supplémentaires sont nécessaires pour évaluer les effets causaux des programmes de suivi sur la santé et le développement de l'enfant, en particulier chez les enfants ayant des besoins complexes et chez les enfants socialement vulnérables. D'autres études sont également nécessaires pour mieux comprendre si les inégalités émergent dans l'offre, l'accès ou l'utilisation des services de suivi. En outre, comme nous l'avons vu dans ce projet, les parents de ces enfants constituent une ressource précieuse et devraient être inclus à tous les stades de la recherche, avec les enfants eux-mêmes, à mesure qu'ils grandissent.

Il est nécessaire de renforcer continuellement nos connaissances sur l'utilisation des services de santé ainsi que les expériences des enfants nés très prématurément et de leurs familles, afin d'attirer l'attention sur leurs besoins et de fournir des informations pour éclairer les politiques. Nous avons identifié une série de facteurs associés à l'utilisation des services de santé et aux services de suivi qui doivent être pris en compte dans les recherches futures, ainsi qu'une liste standardisée de services de santé utilisés par les enfants très prématurés en Europe qui facilite des comparaisons entre pays. Enfin, les taux de suivi spécifique aux enfants nés prématurés et d'utilisation des services de santé que nous avons fournis dans le cadre de nos recherches servent

de base et incitent à de nouvelles études afin de comparer les soins dans d'autres pays ou évaluer les changements au fil du temps dans les pays EPICE-SHIPS.

**Mots clés :** naissance très prématurée, utilisation des services de santé, suivi, équité, cohorte, Europe