Priorities for collaborative research using very preterm birth cohorts

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ABSTRACT

Objectives To develop research priorities on the consequences of very preterm (VPT) birth for the RECAP Preterm platform which brings together data from 23 European VPT birth cohorts.

Design and setting This study used a two-round modified Delphi consensus process. Round 1 was based on 28 research themes related to childhood outcomes (<12 years) derived from consultations with cohort researchers. An external panel of multidisciplinary stakeholders then ranked their top 10 themes and provided comments. In round 2, panel members provided feedback on rankings and on new themes suggested in round 1.

Results Of 71 individuals contacted, 64 (90%) participated as panel members comprising obstetricians, neonatologists, nurses, general and specialist paediatricians, psychologists, physiotherapists, parents, adults born preterm, policy makers and epidemiologists from 17 countries. All 28 initial themes were ranked in the top 10 by at least six panel members. Highest ranking themes were: education (73% of panel members' top 10 choices); care and outcomes of extremely preterm births, including ethical decisions (63%); growth and nutrition (60%); emotional well-being and social inclusion (55%); parental stress (55%) and impact of social circumstances on outcomes (52%). Highest ranking themes were robust across panel members classified by background. 15 new themes had at least 6 top 10 endorsements in round 2.

Conclusions This study elicited a broad range of research priorities on the consequences of VPT birth, with good consensus on highest ranks between stakeholder groups. Several highly ranked themes focused on the socioemotional needs of children and parents, which have been less studied.

What is already known on this topic?

- More knowledge is needed on the long-term health, behavioural, emotional and social status of children born very preterm.
- There appears to be little improvement in long-term outcomes of children born very preterm despite improved survival and neonatal care within the last three decades.
- Knowledge is limited on the efficacy of postdischarge follow-up programmes and other services for children and their families.
- Collaborative data platforms using data from existing very preterm cohorts could optimise research on the long-term consequences of preterm birth.

What this study adds?

- Diverse stakeholders identified a broad scope of priority themes related to the consequences of very preterm birth that can orient collaborative research.
- There is good consensus on several high ranking priorities among a wide range of themes.
- Socioemotional needs of children and parents, which have been less studied in this population, are highly ranked by all stakeholder groups.

INTRODUCTION

Every year between 1% and 2% of births are very preterm (VPT), occurring at <32 weeks of gestation, totalling over 50 000 babies in European Union countries.[1] Improved survival over past decades has led to more VPT babies being discharged home from the neonatal intensive care unit (NICU). These children face higher risks of cerebral palsy, visual and auditory deficits, poor respiratory outcomes, impaired motor and cognitive ability and psychiatric disorders than children born at later gestations.[2–4] While there are some reports of decreasing risks of cerebral palsy among VPT children,[5–7] several recent meta-analyses and cohort studies have found that the prevalence of neurodevelopmental impairment has not changed and may even be rising.[2,3,8] These studies call attention to the lack of progress in tackling the long-term consequences of VPT birth.

The need to promote research on the consequences of VPT birth was the motivation for the RECAP Preterm (Research on European Children and Adults Born Preterm) project, a European initiative to develop a research platform for VPT cohorts. Twenty-three cohorts from 15 European countries constituted over three decades are participating in this project to create the infrastructure, data dictionaries and harmonisation algorithms to facilitate collaborative research projects. As part of its development, the RECAP Preterm project will implement several demonstration projects to test the platform. This study sought to engage researchers from the participating cohorts as well as an external panel of stakeholders to guide the choice of the demonstration projects on the consequences of preterm birth for child and family outcomes up to 12 years of age. A secondary aim was to provide an overview of the current research concerns of stakeholders on the consequences of very preterm birth in childhood.

METHODS

This study implemented a modified two-round Delphi process with a multidisciplinary and geographically diverse panel of European stakeholders. The Delphi process is a formalised method for obtaining consensus, whereby participants respond to successive questionnaires that aim to identify common principles or proposals.[9 10] It is used for multiple purposes, including determining common priorities for research.[11–14] Responses are qualitative (free text comments) and quantitative (assigning ranks/scores). The Delphi process allows for anonymity, ensures an equal voice for all participants, provides feedback to the group to encourage iteration and interaction, and generates summary measures of agreement.[9 10] Unlike some Delphi processes, we did not aim to eliminate themes or to achieve a shortlist of the most important topics. As such, a two-round process was considered sufficient.

The starting point for the Delphi was establishing a list of research themes concerning child and family outcomes up to 12 years (figure 1). While the RECAP Preterm project includes adult and child cohorts (listed in online supplementary appendix 1), our aim was to establish a research agenda using data from all cohorts, including recent cohorts that do not have long-term follow-up. The list of themes was derived through iterative consultation using online surveys with researchers from participating cohorts (11 participants from contemporary child cohorts, followed by 25 participants from all cohorts). We also reviewed the discussion sections of published cohort studies. Integrating quantitative evidence from other sources would have been of great interest, but was not considered feasible. Twenty-eight themes were defined using this process. Each theme was summarised in plain language for round 1 of the Delphi questionnaire (online supplementary appendix 2).

Each cohort provided between three and six suggestions for Delphi panel members. Nominated candidates had to be external to the RECAP Preterm project, have good knowledge of preterm birth and represent diverse perspectives, including those of health professionals involved in the care of children born very preterm, researchers, policy makers (eg, health agency directors), parents, parent representatives and preterm-born adults. Parents and preterm adults were also identified with the help of The European Foundation for the Care of Newborn Infants (EFCNI), a parents' association participating in RECAP Preterm. The questionnaire was in English, but responses could be in national languages with cohort representatives contacted to provide clarifications.

In round 1, panel members selected their top 10 priorities from the list of 28 themes, ranked their top 5 from 1 (highest) to 5 and identified missing themes. In round 2, we obtained feedback on the first-round rankings, asked whether newly suggested themes ranked in the top 10, and requested ideas for grouping themes and other comments. In the instructions, panel members were asked to select research themes needed to underpin clinical practice and/or health policy based on their own experience.

To analyse round 1 results, we created several summary scores: an average of rankings whereby the highest ranking theme was given a score of 10, the second highest given a score of 9 and so on. As only the top five were ranked, a score of 5 was given to non-ranked items in the top 10 and a 0 score was given to non-ranked items. We also counted the number of panel members ranking the theme in their top 10, 5 and 1. For round 2, we counted top 10 endorsements for new themes. Comments were analysed quantitatively (eg, number expressing agreement) as well as qualitatively to describe the panel's opinions.

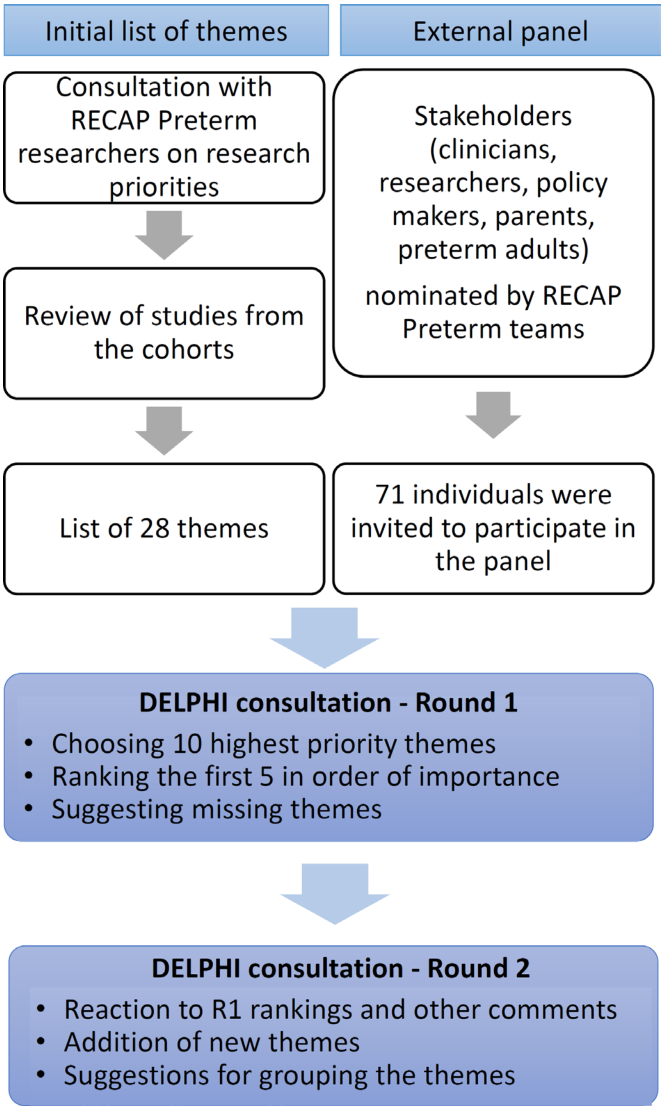

Figure 1 Methodology for the consultation process to identify research priorities on the consequences of very preterm birth.

RESULTS

Of the 71 individuals nominated by the cohorts or the EFCNI, 64 (90%) participated in at least one Delphi round with 60 (85%) in each round (table 1). The panel included participants from 17 countries and multiple backgrounds, further classified into: (1) health professionals involved in the perinatal period, (2) health professionals involved in follow-up, (3) parents and preterm-born adults and (4) other.

All 28 themes in round 1 were rated in at least six top 10 lists and every theme was in at least one top 5 list (table 2). Despite the support for a broad range of themes, there was high agreement on a smaller set of themes. Themes with highest rankings (average score ≥3.5 and >50% top 10 scores) were: education

Table 1 Characteristics of the external Delphi panel

	Total	Round1/Round2	Health professionals in perinatal period	Health professionals involved in follow-up	Parents and preterm adults	Other
Characteristics	n=64	n=60/60	n=19	n=19*	n=16*	n=*8* the star is misplaced
Country						
Austria	1	1/1	X			
Belgium	7	7/7	X	X	X	
Canada	2	2/2		X		
Czech Republic	1	1/1	X			
Denmark	1	1/1				X
Estonia	5	5/4		X	X	
Finland	2	2/2	X	X		
France	7	7/6	X	X	X	X
Germany	5	5/3	X		X	
Ireland	1	1/1			X	
Italy	5	5/5	X	X	X	X
The Netherlands	4	4/4	X	X		X
Norway	4	2/3	X	X		
Portugal	3	4/4		X	X	X
Spain	3	3/3			X	
Sweden	7	5/7	X	X	X	X
UK	6	4/6	X	X	X	
Discipline/Background*						
Obstetrician	4	4/4	X			
Neonatologist	17	14/17	X			
Nurse in neonatology	1	1/1	X			
Paediatrician	7	6/7		X		
Paediatrician subspecialist†	5	5/4		X		
Psychologist	7	7/7		X		
Physiotherapist	1	1/1		X		
Parent/Parent representative	11	11/10			X	
Adult born preterm	5	5/4			X	
Policy maker	4	4/3				X
Epidemiologist	3	3/3				X
Sociologist	2	1/2				X

*Three members were classified in two categories (parent/sociologist, parent/psychologist, sociologist/policy maker).
†Neurologist (n=2), endocrinologist (n=2), ophthalmologist (n=1).

of very preterm infants; care and outcomes of extremely preterm births, including ethical decisions; growth and nutrition; emotional well-being and social inclusion; parental stress and impact of social circumstances on outcomes.

Among themes with a score ≥2.0 (corresponding to 20 or more top 10 endorsements), we compared top 10 ratings by the panel member background classification. This comparison showed good agreement on several highest ranking themes (figure 2). Some differences were notable, however, with parents being more interested in education, emotional well-being, social inclusion, the impact of social circumstances and motor development, while neonatologists and obstetricians expressed more interest in obstetric and neonatal organisation.

Eighteen respondents (30%) had no further comments about the themes. Others requested clarification that specific topics were included in an existing theme (eg, parental presence in the NICU in *obstetric and neonatal organisation*, maternal milk/breast feeding in *growth and nutrition*) and suggested ways to regroup themes. Some suggested themes were outside the study's stated scope (adult outcomes, causes of preterm birth, issues specific to middle-income and low-income countries). Twenty new themes were suggested.

In round 2, 48 of 60 panel members commented on the rankings of which 30 were positive: "*Interesting and relevant, perceived as logical for me*" (Sweden, neonatal nurse). "*I feel that the themes with the highest scores really are appropriate*" (Spain, adult born preterm). "*The ranking reflects my view and I believe that this is a good starting point for prioritizing*" (Norway, psychologist). These are '*interesting results that are not unexpected*' (the UK, obstetrician). "*The list covered the most important topics. I agree with the order of priorities*" (France, neonatologist). Some endorsed the rankings even though they had different initial viewpoints "*after seeing the priority rankings and reading the description again, I think that these themes (care and outcomes of extremely preterm births and growth and nutrition) should be in the priority rankings*" (Portugal, parent representative).

Participants commented positively about the overlap between respondent groups: '*high correlation between the different subgroups indicates that this is a balanced composition*' (Belgium, physiotherapist) and this was seen to '*illustrate the concern,*

Table 2 Ranking of themes by the external panel (round 1, n=60)

Theme	Average ranking*	Top 10 count†	Top 5 count†	Top 1 count†
Education of very preterm infants	4.6	44	18	3
Care and outcomes of extremely preterm birth, including ethical decisions	4.5	38	23	8
Growth and nutrition, including breast feeding	4.1	36	19	7
Emotional well-being and social inclusion	3.5	33	13	2
Parental stress	3.5	33	14	4
Impact of social circumstances on outcomes	3.5	31	15	6
Obstetrical and neonatal unit organisation and practices, including policies towards parents	3.2	29	14	5
Perinatal factors/treatments and long-term complications	3.1	28	15	4
Minor impairments and impact on learning and quality of life	3.0	27	11	1
Changes in disability status over time	2.8	27	10	3
Autism spectrum disorder and attention deficit and hyperactivity disorder	2.3	23	7	1
Cardiometabolic and pulmonary outcomes	2.3	20	11	2
Epigenetics/Genetic markers of poor outcomes	2.1	21	6	2
Motor development	2.0	20	8	0
Very preterm children from migrant families	2.0	22	7	0
Very severe fetal growth restriction	1.9	18	10	2
Intraventricular haemorrhage (IVH), including severe and less severe lesions	1.6	15	6	2
Necrotising enterocolitis (NEC)	1.6	16	4	1
Multiples	1.4	14	3	0
The wider environment (environmental and neighbourhood exposures)	1.2	10	6	2
Cerebral palsy (CP), including linking to CP registers	1.2	13	1	1
Maternal obesity and/or diabetes	1.0	10	3	0
Sub-fertility treatment	0.9	11	3	0
Validating predictive models of hospitalisation after discharge	0.9	9	3	1
Severe maternal morbidity during childbirth	0.9	10	3	0
Malformations	0.9	9	3	1
Older maternal age	0.9	9	3	0
Neurosensory impairments (blindness and deafness)	0.7	6	3	2

*See 'Methods' section for calculation of average rank.
†Number listing the theme as one of their top 10, 5 and 1 priorities.

common to all participating groups, with long-term quality of life of the survivors' (Portugal, paediatrician). The diversity in responses was valued: '*It is good that the top 10 ranking covers topics from different areas… This provides a broader picture of research related to very preterm children'* (Estonia, psychologist). Some respondents expressed regret that some topics were not more highly ranked: "*In general, I do agree with large parts of the priority ranking, although I would definitely rank topics such as 'very severe fetal growth restriction' or 'NEC' or 'IVH' significantly higher'* (Austria, neonatologist).

Other panel members expressed neutral opinions (ie, commenting on contrasts between stakeholders or suggesting alternative groupings). Six expressed more critical views related to missing themes and the overall process. One theme mentioned by two respondents was care in childhood: '*The monitoring and evaluation of care and outcomes over a long-term period (at least the whole preschool period) should have more votes'* (Italy, epidemiologist). Others criticised the scope "*Can we please try and PREVENT preterm birth…We have totally lost the relation with the factors that may cause prematurity*" (The Netherlands, policy maker) or the process itself: "*I am reluctant to prioritize themes—a grassroots type of approach that treats all ideas and initiatives as equal might be more appropriate*" (Germany, neonatologist) or "*Thinking about these issues in isolation is not, to me, as productive as discussing them in a broader group—so I struggle to devote enough time or thinking to the issues as they deserve*" (the UK, obstetrician).

In round 2, 15 new themes were ranked in the top 10 of 6 or more panel members, which corresponds to lowest ranking in the original list of 28 (table 3). No new theme received >27 votes which delineated the top 10 in round 1. New themes expanded the focus to economic costs and family organisation. Some themes overlapped somewhat with the original themes and overlap was noted by some panel members in the initial list. In round 2, we asked about regrouping or combining themes. The panel members' replies were divergent, with some proposing to subsume individual topics into a few thematic categories and others insisting strongly that themes be kept specific. Given the absence of consensus, the themes were left in their original formulation (online supplementary appendix 3 provides the compiled list of themes with a top 10 ranking ≥6).

The most highly rated themes informed RECAP Preterm's initial research agenda on childhood outcomes, with three demonstration projects considered to be immediately feasible (care and outcomes of extremely preterm birth, including ethical decisions; growth and nutrition; impact of social circumstances on outcomes) and two areas for further development (education of very preterm infants; Parental stress).

DISCUSSION

This study elicited a broad range of research priorities covering the health, developmental, psychological and social consequences of VPT birth based on an initial consultation with very preterm cohort researchers and a modified Delphi process with an external panel of 64 stakeholders. There was robust consensus among panel members around a set of most highly ranked themes which were used to structure the research agenda on child outcomes within the RECAP Preterm platform. Highly ranked themes focused on medical management around birth, including ethical questions and the organisation of care, and on broader social issues, such as education and parents' experiences. This study also revealed the diversity of stakeholder perspectives as reflected in some key differences in rankings by panel member background and in the high number of themes, 43, included in the top 10 lists of at least 6 panel members.

The study's strengths were high participation rates from the external panel, geographic and disciplinary diversity and the participation of parents and very preterm born adults. While some consensus processes include users, patients or laypeople, in many cases respondents are clinicians or researchers only and response rates are often below 60%.[11–14] One of the difficulties of the Delphi methodology is its complexity for laypeople and the ability to understand English constrained the people we invited to participate.[15] In line with recommendations for carrying out Delphi exercises,[16 17] the scope, objectives and intended outcomes of our study were predefined. However, some participants questioned the scope focusing on the consequences of VPT birth as opposed to the causes of prematurity.

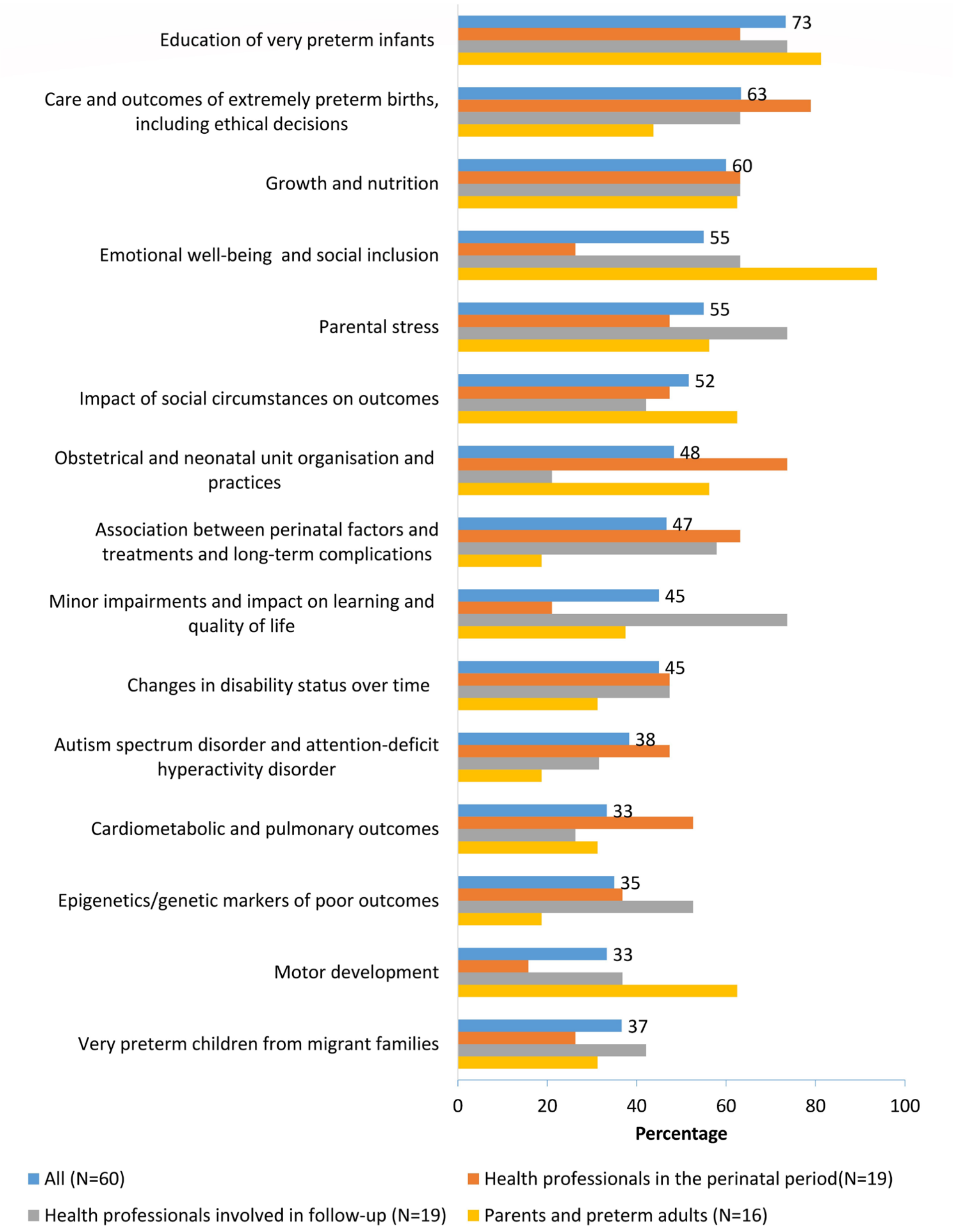

Figure 2 Themes most often selected in the top 10 priority lists by background of panel members (percentage of responses by group). Note: background category 'other' not included because of its small size and heterogeneous composition.

Furthermore, some panel members contested aspects of the methodology, including whether the technique lends itself to the level of reflection required. Finally, despite representation of a broad range of professionals who care for children born very preterm, not all specialties were included (ie, child psychiatrists, speech therapists), which may lead to under-representation of themes specific to these disciplines.

These results revealed a strong cross-disciplinary interest in the socioemotional repercussions of preterm birth. In particular, parental stress was ranked highly by all panel members, regardless of background. There is increasing awareness of the stressors on families linked to having a very preterm infant and the potential impact on children's health and development,[18] yet most research does not consider the topic of parental stress.[19] Much less is also known about prognostic factors associated with the emotional well-being and mental health of the child.[20] Finally, the strong interest in education, ranked in the top 10 of over 70% of panel members, suggests a need for an earlier and more comprehensive focus on the impact of VPT birth on life trajectories, a topic given visibility in the studies from cohorts of preterm born adults.[21] Other top ranked themes were anchored around care in the period around birth, known to be determinant for mortality and morbidity and amenable to intervention, including the organisation of care and perinatal factors.[22–24] While there is more research on these topics, this list highlights the limited knowledge about their long-term impact.

The range of themes in the final list illustrates the diversity of interests among stakeholders, the heterogeneous aetiology of VPT birth and the myriad ways that preterm birth impacts on child health and development and family function. Even among the highest ranking themes, professional background shaped priority rankings, with, for instance, less priority given to the organisation of care around birth by health professionals involved in follow-up and similarly less interest in emotional well-being by perinatal health professionals. Differences between professionals and parents also emerged, with the latter

Table 3 New themes suggested by the external panel by number rated in top 10 in round 2 (n=60)

Theme	Top 10 count	%
Included in final list (≥6 top 10 votes)1		
Cognitive development	21	35
Economic consequences for family (including stopping/reducing work) and for society	14	23
Longitudinal studies over time looking at changes in care and outcomes	14	23
Parental mental health	13	22
Feeding problems	9	15
Retinopathy of prematurity	9	15
Language development, including multilingual education	8	13
Impact on the organisation of the family and other children in the family	8	13
Chronic lung disease	8	13
Quality improvement initiatives	7	12
Territorial and geographical dispersion/distribution of very preterm births—important for policy and prevention	7	12
Pharmacology/Medication /Pharmacokinetics of drugs	6	10
Microbiome studies	6	10
Role of primary care physicians in care of very preterm children	6	10
Long-term impact of extreme preterm birth on maternal outcomes (eg, later cardiovascular disease and diabetes)	6	10
Not included in final list (<6 top 10 votes)1		
Minor visual impairments	5	8
Hygiene in the neonatal unit	5	8
Cystic periventricular leukomalacia	4	7
Adolescent pregnancy	1	2
Older paternal age	0	0

1; Six corresponds to the lowest ranking theme in the original list of 28 themes.

more interested in emotional well-being and social inclusion, education and growth and nutrition. The diversity of opinion in our panel was evident in questions about how the research themes should be grouped, leading us to retain themes as originally formulated without regrouping. These contrasting perspectives underscore the importance of including diverse opinions in consensus procedures and remind us the Delphi procedure is valuable for eliciting areas of common ground, and for sounding out the range of opinion and illuminating areas of difference.[16]

CONCLUSION

Our study illustrated the broad span of research themes on the consequences of VPT birth in childhood considered to be priorities by stakeholders and identified several highly ranked themes with broad consensus to shape the RECAP Preterm research agenda. Initiatives to develop federated research constitute a valuable opportunity to involve the research community and other stakeholders in reviewing research needs.

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Appendix 1

European very preterm cohorts participating in the RECAP Preterm platform

(for more information on the current European cohorts participating in the RECAP Preterm platform, including the number of inclusions, follow-up ages and data collected, see cohort profiles available on https://recap-preterm.inesctec.pt/cat/)

Cohort name	**Country**	**Birth years**
ACTION	Italy	2003-2005
AYLS	Finland	1985-1989
BEST-BLS	Germany	1985-1986
DNBC	Denmark	1996-2002
EPIBEL	Belgium	1999-2000
EPICE/SHIPS	Belgium, Denmark, Estonia, France, Germany, Italy, Netherlands, Poland, Portugal, Sweden, UK	2011-2012
EPICE-PT	Portugal	2011-2012
EPICURE 1	UK and Ireland	1995
EPICURE 2	UK	2006
EPIPAGE 1	France	1997-1998
EPIPAGE 2	France	2011
ESTER	Finland	1985-1989
Estonia 02-03	Estonia	2002-2003
Estonia 07	Estonia	2007-2008
ETFOL	Denmark	1994-1995
EXPRESS	Sweden	2004-2007
GNN	Germany	2009-2010
HeSVA	Finland	1978-1985
Pinkeltje/Lollipop	Netherlands	2002-2003
NTNU LBW Life	Norway	1986-1988
PEP	Norway	1999-2000
PIPARI	Finland	2001-2006
POPS	Netherlands	1983

Appendix 2 –
Initial list of themes with descriptions sent in Round 1 questionnaire (some clarifications made after Round 1, noted in bold italics)

Influence of family, social and environmental factors on child outcomes	
1. Very preterm children from migrant families	In some regions of Europe, up to 40% of very preterm infants have mothers who are migrants. Migrant families may live in difficult social circumstances and face language, communication and cultural barriers that limit their access to health and social services. In Europe, the characteristics and experiences of migrant populations are highly diverse depending on their country of origin, when they migrated and migrant policies in their host country. Another important issue for migrant children born preterm is how clinicians and researchers monitor their development and cognition since most clinical evaluations are designed for host-country children who speak only one language.
2. Impact of social circumstances on outcomes	Women with a low educational level or low incomes are more likely to have a preterm delivery. Very preterm children from socially disadvantaged families are also found to have worse neurodevelopment and health, although not in all studies or for all impairments. More understanding of these associations is needed to develop interventions to interrupt the transfer of health and social inequalities across generations. Importantly, early intervention in children from socially disadvantaged families may be particularly effective in improving developmental outcomes.
3. Parental stress	Having a very preterm infant can be stressful for parents. Knowledge is limited about how parental stress impacts on parent-infant interactions, child health and development as well as which interventions can effectively reduce stress for parents. Helping parents to cope with the stress of raising a very preterm child could improve the family environment and parents' ability to support their child. This could be an effective strategy for achieving better outcomes for very preterm children, especially with regards to their mental health and social inclusion.
4. The wider environment	The wider environment affects child health and development in many ways. Environmental exposures include pollution and other toxins as well as neighbourhood social and economic characteristics, such as social networks, crime rates, the availability of shops selling healthy food and fast-food restaurants. There are a growing number of studies on the impact of these environmental characteristics, but not specifically among very preterm children. Yet, children born very preterm may be particularly vulnerable to negative environmental conditions.
5. Education of very preterm infants	While many studies have investigated the cognitive, developmental and behavioural difficulties associated with very preterm birth, much less is known about how these affect performance and integration into school and how the school environment influences success in school. Within Europe, there is a large diversity in approaches to schooling, including age at school entry, policies related to staying behind a year and options for keeping children with difficulties in regular schools. This diversity provides an opportunity to learn from systems achieving good results. This theme covers children with moderate and severe motor

	and cognitive disabilities, who require specialised services at school, as well as children with minor difficulties. We will also study children with good school attainment to assess what promotes success in school.
Growth and later development	
6. Minor impairments and impact on learning and quality of life	Initial studies of the consequences of very preterm birth focused on major motor and neuro-developmental impairments, but children without these impairments are confronted with minor motor, cognitive and behavioural difficulties that impact on their health, learning and quality of life. Describing these difficulties and their consequences is essential for their prevention and treatment as well as for research on their causes.
7. Growth and nutrition	Finding optimal feeding and nutrition strategies, **including the promotion of breastfeeding,** represents a major challenge for the care of very preterm newborns. A wide range of policies currently exist, illustrating an absence of consensus. Research on this theme would aim to assess the impact of sub-optimal growth before and after birth (intra- and extra-uterine growth restriction) on longer term outcomes and to identify effective interventions to improve growth. Data from multiple cohorts could be used to develop robust tools for evaluating growth trajectories in very preterm children.
8. Autism spectrum disorder (ASD) and attention-deficit hyperactivity disorder (ADHD)	Preterm birth is a well-established risk factor for ASD and ADHD. The low prevalence of these conditions can make it difficult to study these disorders in small studies. There is also evidence that these disorders have a different clinical presentation and correlates in the preterm population. These results suggest that there may be differences in causes which has consequences for diagnosis, treatment and intervention. Combining data from several cohorts will provide more robust estimates of the prevalence of these disorders by gestational age and phenotypic profile, and will identify the specific risk factors and developmental mechanisms for ASD and ADHD among children born very preterm.
9. Emotional wellbeing and social inclusion	Studies on older children and adults born preterm find that emotional wellbeing and social inclusion are predominant concerns, yet much of the research on younger children focuses on physical health and development. This research theme would assess and evaluate existing data in cohorts of younger children on emotional disorders (panic disorders, anxiety and depression), as well as mental wellbeing and social participation.
10. Motor development	Many children born very preterm have mild to moderate motor problems that have an impact on their daily lives. Understanding the characteristics and the trajectory of these difficulties and relevant risk factors could inform physiotherapists and occupational therapists. Minor problems may also represent obstacles for learning in school and participation in social activities. Some cohorts have assessed motor outcomes at several ages and these could be combined to get a more complete picture of growth difficulties and their consequences during childhood.
11. Cardiometabolic and pulmonary outcomes	Children and adults born very preterm or very low birthweight have increased levels of several cardiometabolic risk factors including higher blood pressure and impaired glucose regulation, which can lead to increased risks of metabolic syndrome and type 2 diabetes in adulthood and possibly stroke and coronary heart disease. These children also

	have poorer pulmonary airflow than their peers born at term. The mechanisms underlying these associations are not well understood. Pooling data across cohorts increases the accuracy of risk estimates and could help to uncover additional risk and protective factors that could be targets for prevention.
12. Changes in disability status over time	While assessments of disability in early childhood are good predictors of later disability, many children change their disability status as they grow older. Some children are no longer considered to have a moderate or severe disability, whereas others are evaluated as moderately or severely disabled after a normal evaluation earlier in childhood. This research theme focuses on identifying the medical, social and healthcare factors leading to a change in disability status in order to improve prediction for clinical care and to understand what determines the clinical course of disability in this population.
Perinatal care	
13. Care and outcomes of extremely preterm births, including ethical decisions	Studying births at extremely early gestational ages is challenging due to their relatively low number. Lack of knowledge, particularly about longer term outcomes, has led to a range of attitudes in the management of these births by medical teams, with practices varying substantially between and within countries. A consortia approach would permit many questions around this topic to be tackled. These include methodological issues (how to assess gestational age, impact of stillbirths, definition of active management), better evaluation of the infants' potential for survival and survival without major disability (for example, by examining outcomes among births receiving active management), and evaluating the impact of perinatal management on rare (e.g. auditory or visual impairment) or subtle (cognitive or behavioural problems) outcomes later in childhood.
14. Validating predictive models for hospitalization after discharge	Understanding the risk factors for re-hospitalisation after discharge from the neonatal intensive care unit is needed for hospital staff to make the best discharge decisions. Discharging too early can expose the infant to adverse events, leading to re-hospitalization. However, prolonged stay in hospital lengthens exposure to risks associated with the hospital environment (for instance, nosocomial infections), may impede interactions between parents and the infant and can affect the hospital's capacity to admit other infants as well as their healthcare costs. European cohorts can contribute to defining generalisable predictive models to improve discharge decisions.
15. Obstetrical and neonatal unit organization and practices	The organization of healthcare services for very preterm infants is known to affect their survival free of morbidity. Factors within units like staffing adequacy, as well as hospital and regional level factors such as population density, geography and distances between hospitals, may have profound effects on hospital personnel and decision-making. The environment within the neonatal unit also differs across Europe based on the use of developmental care guidelines, including the number of children per room and **policies and facilities making it possible to facilitate** the presence of parents. The impact of different policies of care is unclear, particularly for longer-term child health. Combining information from different health systems could facilitate learning about best practices and optimal organization.
16. Association between perinatal factors and	There is a large literature investigating the associations between perinatal risk factors (such as medical complications at birth) and infant

treatments and long term complications	outcomes. This is also true for treatments and interventions used at birth and during the neonatal hospitalisation such as antenatal steroid administration, use of magnesium sulfate and hypothermia management. Short term effects of these treatments have been explored, but the impact on longer term outcomes remains unknown. Further research on health and development in children with these perinatal characteristics or receiving these treatments is needed to fully understand their impact and to develop optimal post-discharge healthcare strategies.
Research on specific population risk factors	
17. Maternal obesity and/or diabetes	Maternal obesity and diabetes are increasingly common in European countries and these are risk factors for very preterm birth. Research on term children finds that maternal obesity and diabetes are associated with specific developmental difficulties, such as language and other cognitive delays. Maternal obesity is also related to the child's future growth and in particular their risk of obesity in the future. These issues remain unexplored among very preterm children.
18. Sub-fertility treatment	Sub-fertility treatment increases risks of very preterm birth and is also linked to conditions such as preterm prolonged rupture of membranes which lead to preterm birth. Sub-fertility treatment is also a risk factor for congenital anomalies which are more common among children born very preterm. Given these links, it is important to describe the longer-term neurodevelopmental, physical and psychological morbidities related to sub-fertility treatment.
19. Older maternal age	In European societies, more women are having children after 35 and they are more likely than younger mothers to have pregnancy complications, such as very preterm birth. Investigating the specific risks associated with very preterm birth for children with mothers over 35 years of age could lead to improvements in care and counselling for parents.
20. Multiples	About one-third of very preterm infants are multiples. Multiple pregnancies have specific medical complications during pregnancy, which affect the children's later health and development and also pose specific challenges for parents. Areas for study include how to effectively breastfeed multiples, how to provide best care for children who may both require special services, and the impact of a co-twin's death - an occurrence in about one-quarter of deliveries - on maternal mental health. Multiple births are often excluded from population studies and there is less research on the long-term developmental outcomes of multiples compared to singletons in preterm populations.
Research on neonatal morbidities or subgroups of preterm births defined by their medical characteristics	
21. Intraventricular haemorrhage (IVH) including severe and less severe lesions	Severe bleeding in the brain (or severe intraventricular haemorrhage (IVH)) is one consequence of very preterm birth and leads to poor motor and neurodevelopmental outcomes. However, the health and developmental outcomes related to less severe bleeding are less well understood and some children with severe IVH develop normally. Preventive measures for IVH and how new imaging techniques can improve prediction and care are areas where research is needed.

22. Necrotising enterocolitis (NEC)	Necrotising enterocolitis (NEC) is a serious condition affecting very preterm newborns where tissues in the intestine become inflamed and start to die. There is a large variability in NEC prevalence across neonatal units and regions in Europe. Understanding this variability and whether practices from hospitals or regions with less NEC can be applied more broadly is an important area for research. Questions also exist on the long-term health of children who survived NEC.
23. Very severe fetal growth restriction	Restricted fetal growth is common among pregnancies ending in very preterm delivery. However, some fetuses experience very severe growth restriction with birthweights up to 4 or 5 standard deviations below what would be expected given their gestational age. Studies of fetal growth restriction have tended to group all infants with growth restriction together, but these very severe cases may have different causes and health and developmental outcomes. Combing data from cohorts could provide new information on these uncommon, but severe, situations.
24. Severe maternal morbidity during childbirth	Severe maternal morbidity is defined as a life-threatening condition affecting the mother during pregnancy, childbirth or after delivery (such as eclampsia or post-partum haemorrhage). Severe maternal morbidity occurs between 1 to 2% of deliveries in high-income countries, but is more common for very preterm deliveries. The simultaneous management of high-risk situations for both the mother and the infant at delivery may affect health outcomes for both of them. Whether the mother suffered severe morbidity has been neglected in research on the health and development of very preterm infants, but these mothers may be less likely to breastfeed and they face higher risks of depression, which may affect mother and child interactions.
25. Malformations	There is a higher frequency of malformations among very preterm infant than infants born at term. Children with serious anomalies are often excluded from analyses of outcomes as researchers search to identify prognostic factors linked solely to preterm birth. Children with minor congenital anomalies are sometimes excluded as well. This means that the specific needs of these children are neglected in research. As the type and severity of anomalies are very different, sufficient sample sizes (i.e. large enough studies) to be able to study specific, uncommon anomalies are difficult to achieve using national cohorts alone.
26. Cerebral Palsy (with links to CP registers)	Between 5 and 15% of children born very preterm are diagnosed with cerebral palsy (CP). Because these children represent a small proportion of all very preterm infants, studies have not focused specifically on this population. However, many research questions remain about the causes and characteristics of CP among very preterm infants and the later consequences for health and quality of life. Combining data from the very preterm cohorts would lead to a larger number of study subjects and make it possible to explore multiple research topics. Joint collaboration with the European network of CP registers (SCPE) could be explored.

27. Neurosensory impairments (blindness and deafness)	Children who are blind or deaf constitute less than 2% of very preterm infants, but these impairments have a major impact on their quality of life. Hence it is essential to understand their root causes for future prevention and consequences, and this can only be achieved by combining cohorts to get sufficient numbers of subjects.
Other	
28. Epigenetics/genetic markers of poor outcomes	Epigenetic modifications* such as DNA methylation are thought to be involved in mediating the relations of early-life stressors with health trajectories over the full life cycle, including into subsequent generations. Preterm birth potentially disturbs these modifications in irreversible ways, however, little is known about how modifications vary according to gestational age at delivery or about the interactions between very preterm birth and other early ex-utero exposures. ** changes to gene function which can be inherited, but that do not affect DNA sequences.*

Appendix 3 – Priority research themes from Round 1 and Round 2 (N=43)

Theme	**Top 10 votes**[1]
Education of very preterm infants	44
Care and outcomes of extremely preterm birth, including ethical decisions	38
Growth and nutrition, including breastfeeding	36
Emotional wellbeing and social inclusion	33
Parental stress	33
Impact of social circumstances on outcomes	31
Obstetrical and neonatal unit organization and practices, including policies towards parents	29
Perinatal factors/treatments and long term complications	28
Minor impairments and impact on learning & quality of life	27
Changes in disability status over time	27
Austism spectrum disorder and Attention deficit and hyperactivity disorder	23
Very preterm children from migrant families	22
Epigenetics/genetic markers of poor outcomes	21
Cognitive development	21
Cardiometabolic and pulmonary outcomes	20
Motor development	20
Very severe fetal growth restriction	18
Necrotising enterocolitis	16
Intraventricular haemorrhage, including severe and less severe lesions	15
Multiples	14
Economic consequences for family (including stopping/reducing work) and for society	14
Longitudinal studies over time looking at changes in care and outcomes	14
Cerebral Palsy (CP), including linking to CP registers	13
Parental mental health	13
Sub-fertility treatment	11
The wider environment (environmental and neighbourhood exposures)	10
Maternal obesity and/or diabetes	10
Severe maternal morbidity during childbirth	10
Validating predictive models of hospitalization after discharge	9
Malformations	9
Older maternal age	9
Feeding problems	9
Retinopathy of prematurity	9
Language development, including multilingual education	8
Impact on the organization of the family and other children in the family	8
Chronic lung disease	8
Quality improvement initiatives	7
Territorial & geographical dispersion/distribution of very preterm	7

births – important for policy & prevention	
Neurosensory impairments (blindness and deafness)	6
Pharmacology/medication /Pharmacokinetics of drugs	6
Microbiome studies	6
Role of primary care physicians in care of very preterm children	6
Long term impact of extreme preterm birth on maternal outcomes (e.g. later cardiovascular disease and diabetes)	6

NOTE: the threshold of 6 corresponds to the lowest-ranking theme in our original list of 28 themes