Epipage 2
Étude épidémiologique sur les petits âges gestationnels

Neurodevelopmental care policies, practices, and outcomes in France: The EPIPAGE-2 cohort study.

Véronique Pierrat, Pierre-Yves Ancel
For the EPIPAGE-2 group.

Obstetrical, Perinatal and Pediatric Epidemiology Team INSERM UMR 1153

Instituts thématiques Inserm
Institut national de la santé et de la recherche médicale

Epipage2.inserm.fr

PARIS DESCARTES IUT

Centre Hospitalier Régional Universitaire de Lille

France in 2011

22 regions in the metropolitan area

4 oversea regions

65.34 millions inhabitants

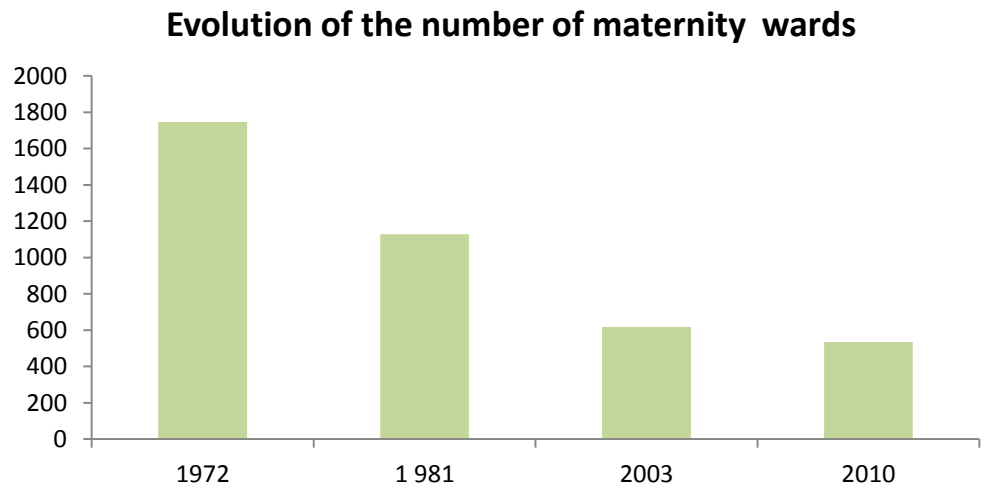
823 394 births

Prematurity rate 7.4% of all births/
6.6% of live births

Epipage 2
Étude épidémiologique sur les petits âges gestationnels

Organisation of perinatal care in 2011

- 535 maternity units
- 275 neonatal units
  - 66 level III units
  - 78 level IIb units
  - 131 level IIa units (128 in Epipage-2)



Epipage 2
Étude épidémiologique sur les petits âges gestationnels

Epipage-2

Epipage 2

Étude épidémiologique sur les petits âges gestationnels

Study design

- Prospective national population-based cohort
- Infants born at 22 to 34 completed WG in all maternity units in 25 French regions
- Recruitment: 8-month period (22 to 26 WG), 6-month period (27 to 31 WG), 5-week period (32-34 WG)
- All survivors were enrolled for longitudinal follow-up and included in the study at 2 years CA if parents consented
- Collection of data at $5^{1/2}$ years of age in progress

Ancel PY, BMC Pediatr, 2014

Epipage 2
Étude épidémiologique sur les petits âges gestationnels

Study design

EPIPAGE

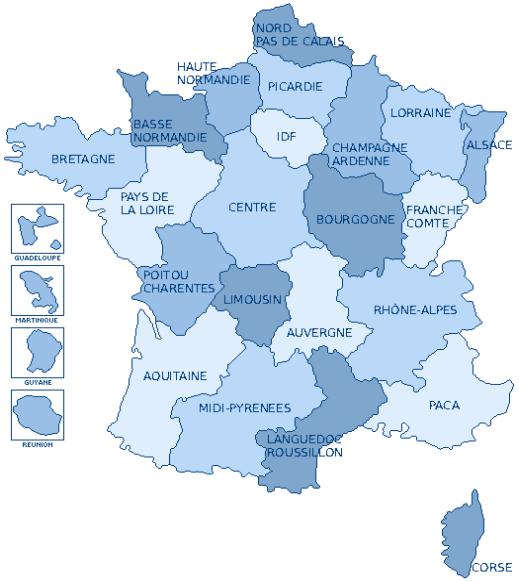
Very preterm infants born in 9 regions of France in **1997**

→ 8 years of age

EPIPAGE- 2

Very preterm infants born in 25 regions of France in **2011**

→12 years of age



Epipage 2
Étude épidémiologique sur les petits âges gestationnels

Aims of the study

- To describe short- and long-term outcomes in very and moderately preterm babies and their families
- To study medical practices and organization of care and assess their impact on child health and development
- To explore the etiology of preterm birth and identify early predictors of health and developmental problems.

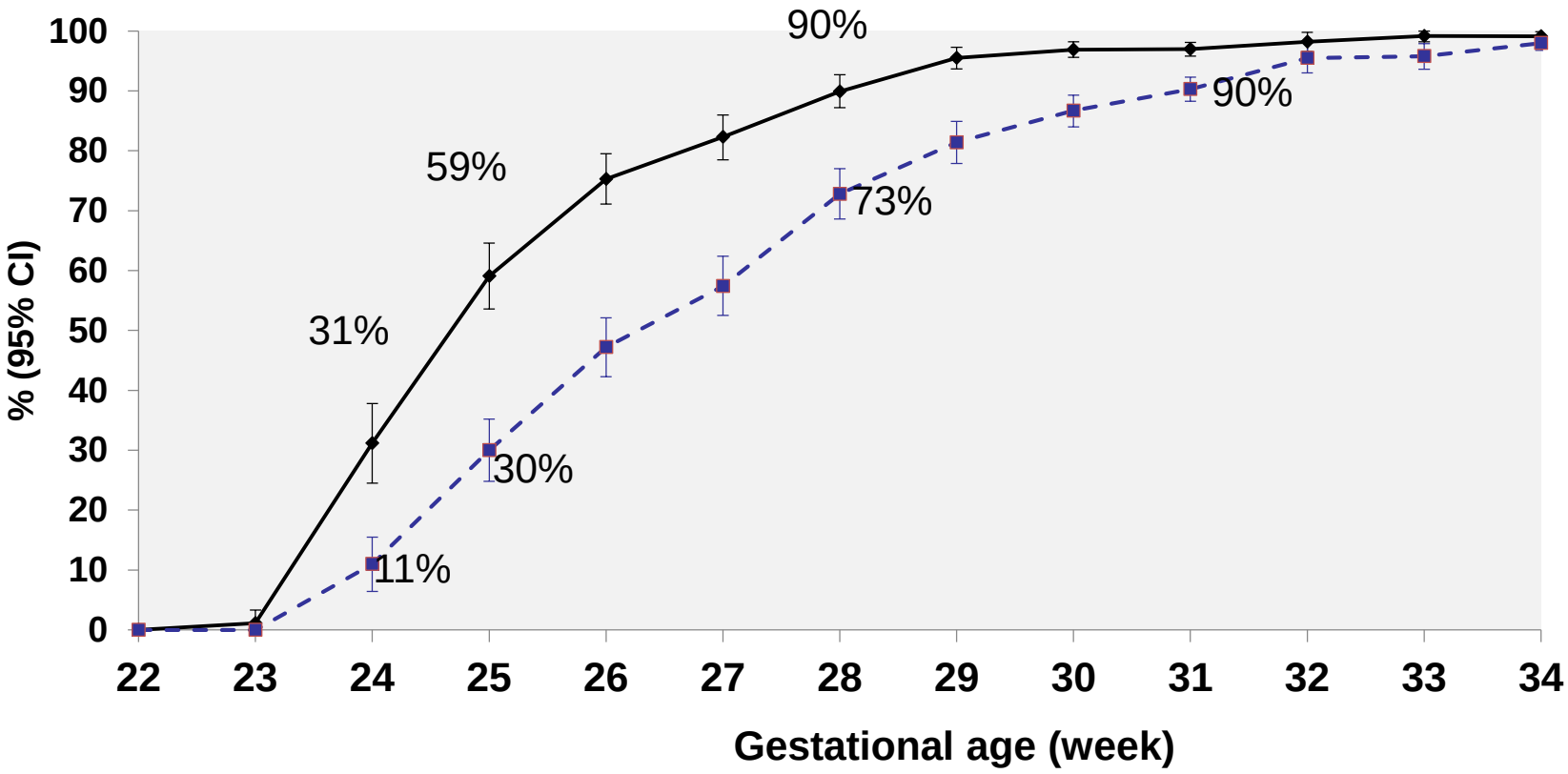
Epipage 2
Étude épidémiologique sur les petits âges gestationnels

Neonatal period

Ancel PY, JAMA Pediatr, 2015

Epipage 2
Étude épidémiologique sur les petits âges gestationnels

SURVIVAL TO DISCHARGE IN 2011

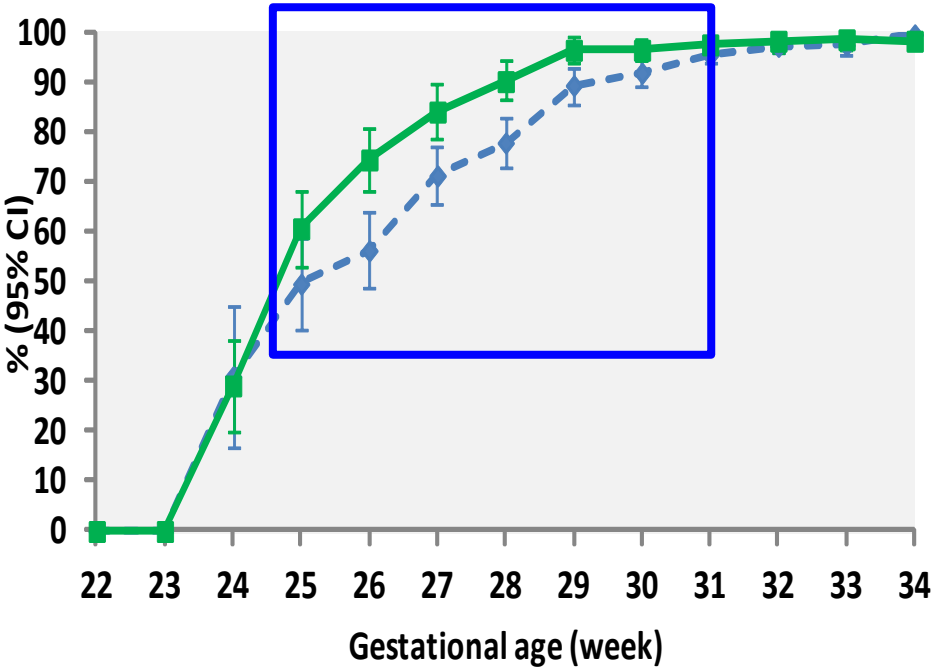


Severe neonatal morbidity : severe bronchopulmonary dysplasia or necrotising enterocolitis stage 2-3 or severe retinopathy of prematurity stage >3 or any of the following severe cerebral abnormalities on cranial ultrasonography: intraventricular haemorrhage grade III or IV or cystic periventricular leukomalacia

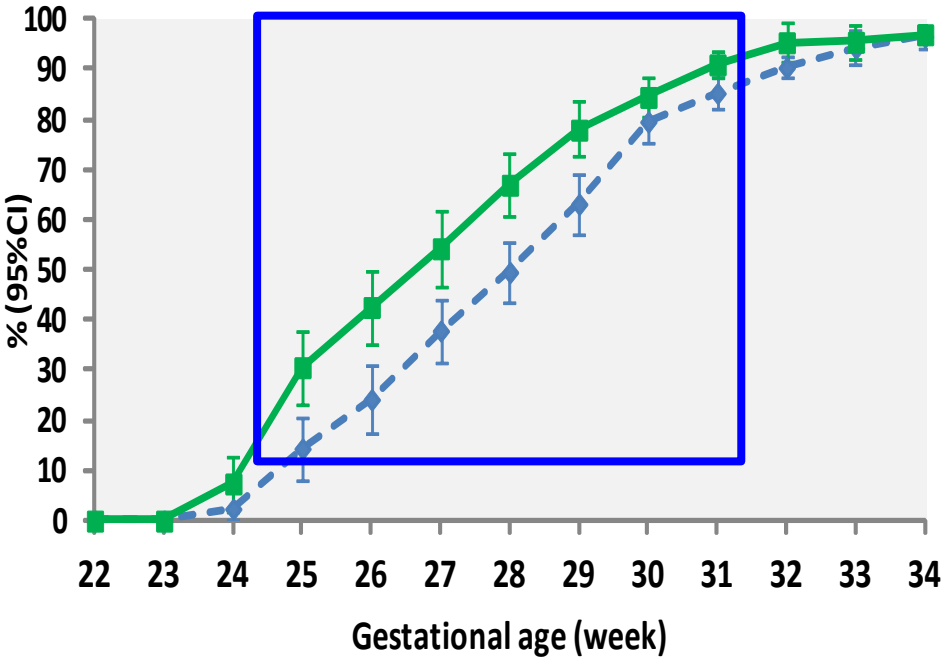
Epipage 2

SURVIVAL TO DISCHARGE

Survival to discharge



Survival to discharge without morbidity



- No survivor at 22-23 weeks
- No change at 24 weeks
- **Significant improvment between 25-31 weeks**

Epipage 2

Perinatal management

	22 weeks	23 weeks	24 weeks	25 weeks	26 weeks
Antenatal steroids					
France – EPIPAGE	2%	12%	57%	76%	81%
UK – EPICure	42%	65%	86%	88%	86%
USA – NICHD	13%	53%	85%	86%	86%
Sweden – EXPRESS	40%	85%	95%	89%	93%
Cesarean section					
France – EPIPAGE	9%	5%	14%	34%	60%
UK – EPICure	5%	6%	14%	31%	44%
USA – NICHD	7%	24%	60%	65%	65%
Sweden - EXPRESS	6%	16%	46%	62%	68%

Survival in the neonatal period

	22 weeks	23 weeks	24 weeks	25 weeks	26 weeks
France (2011) EPIPAGE 2	**0%**	**1%**	**31%**	**59%**	**75%**
England (2006) EPICure	3/152 2%	66/339 19%	178/442 40%	346/521 66%	448/580 77%
Australia (2005)	1/20 5%	7/32 22%	22/43 51%	31/46 67%	47/57 82%
USA – 2003-2007	25/421 6%	226/871 26%	748/1370 55%	1078/1498 72%	1319/1576 84%
Sweden (2004-07) EXPRESS	5/51 10%	53/101 52%	96/144 67%	167/205 81%	176/206 85%
Japan (2005)	33/97 34%	153/282 54%	324/423 77%	428/501 85%	486/542 90%

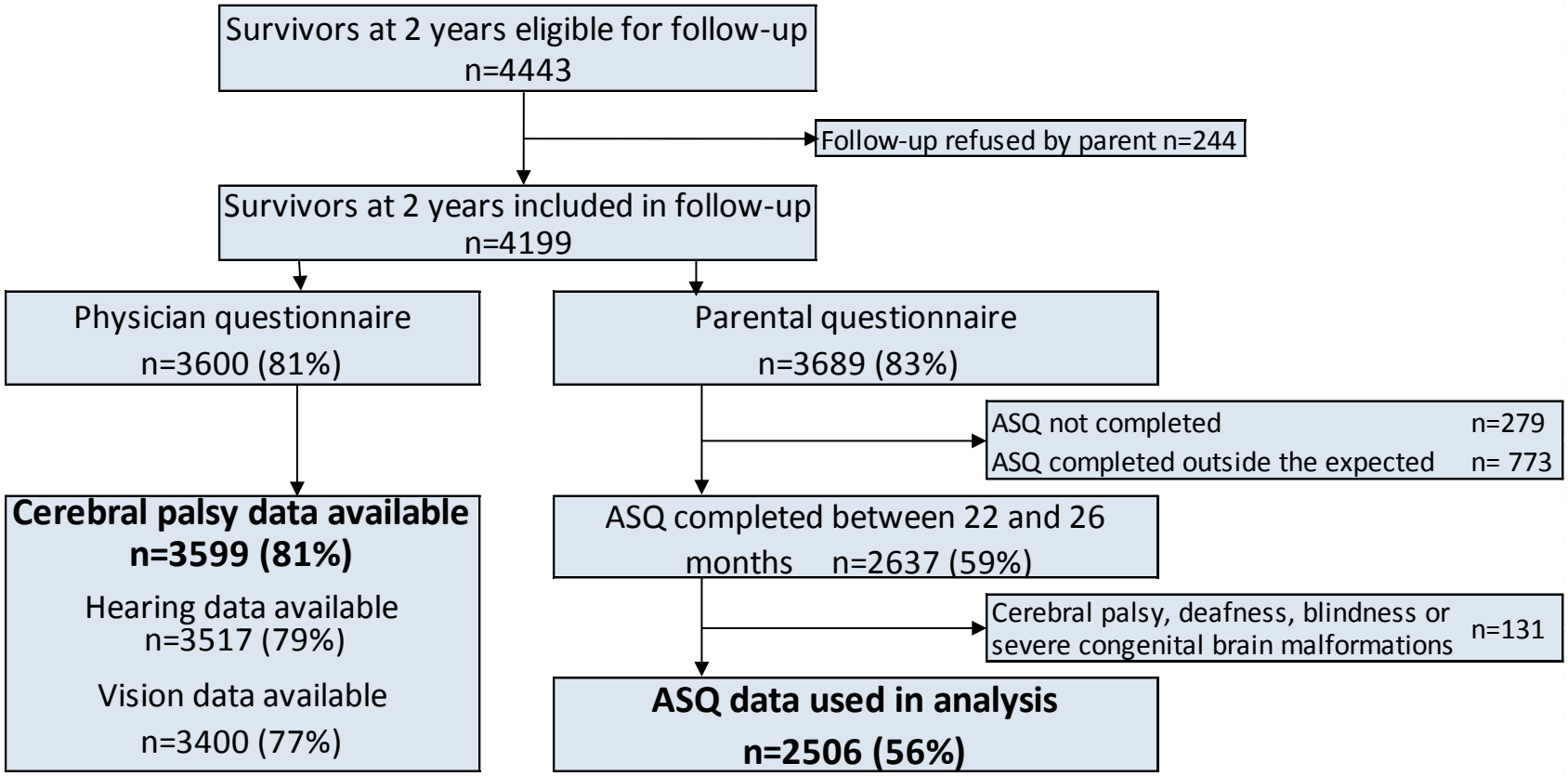
1. **FRANCE 2011** (EPIPAGE 2)
2. **ENGLAND 2006 (**EPICure, Costeloe et al 2012)
3. **AUSTRALIA 2005** (Doyle et al, 2009)
4. **USA – 2003-2007** (Stoll et al, 2010)
5. **SWEDEN 2004-07** (EXPRESS study group, 2009)
6. **JAPAN 2005** (Itabashi et al, 2009)

At 2 years corrected age

Pierrat V, BMJ, 2017

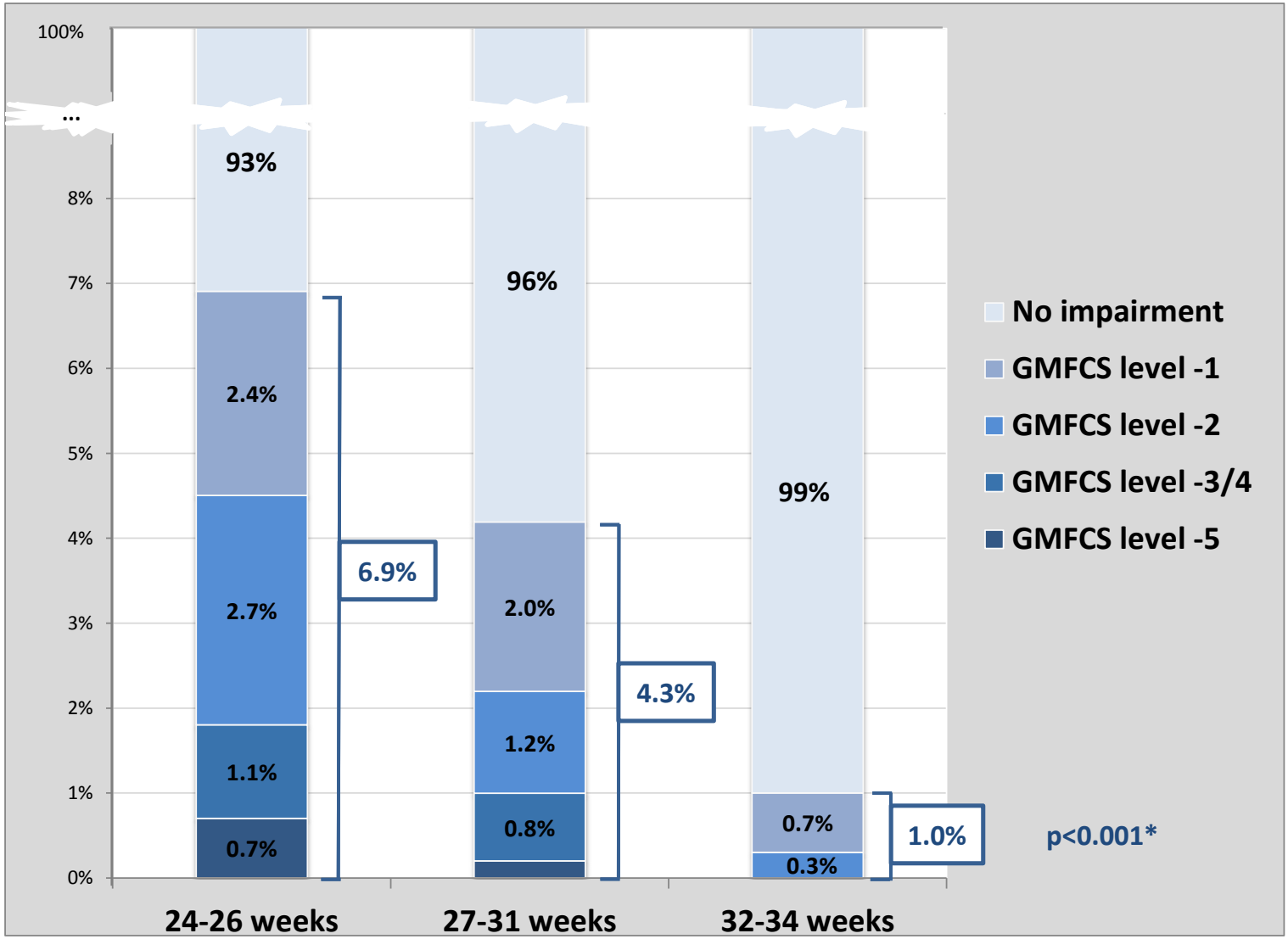
Epipage 2
Étude épidémiologique sur les petits âges gestationnels

Study population at 2 years corrected age.



Epipage 2

Cerebral palsy at 2 years CA by GA groups

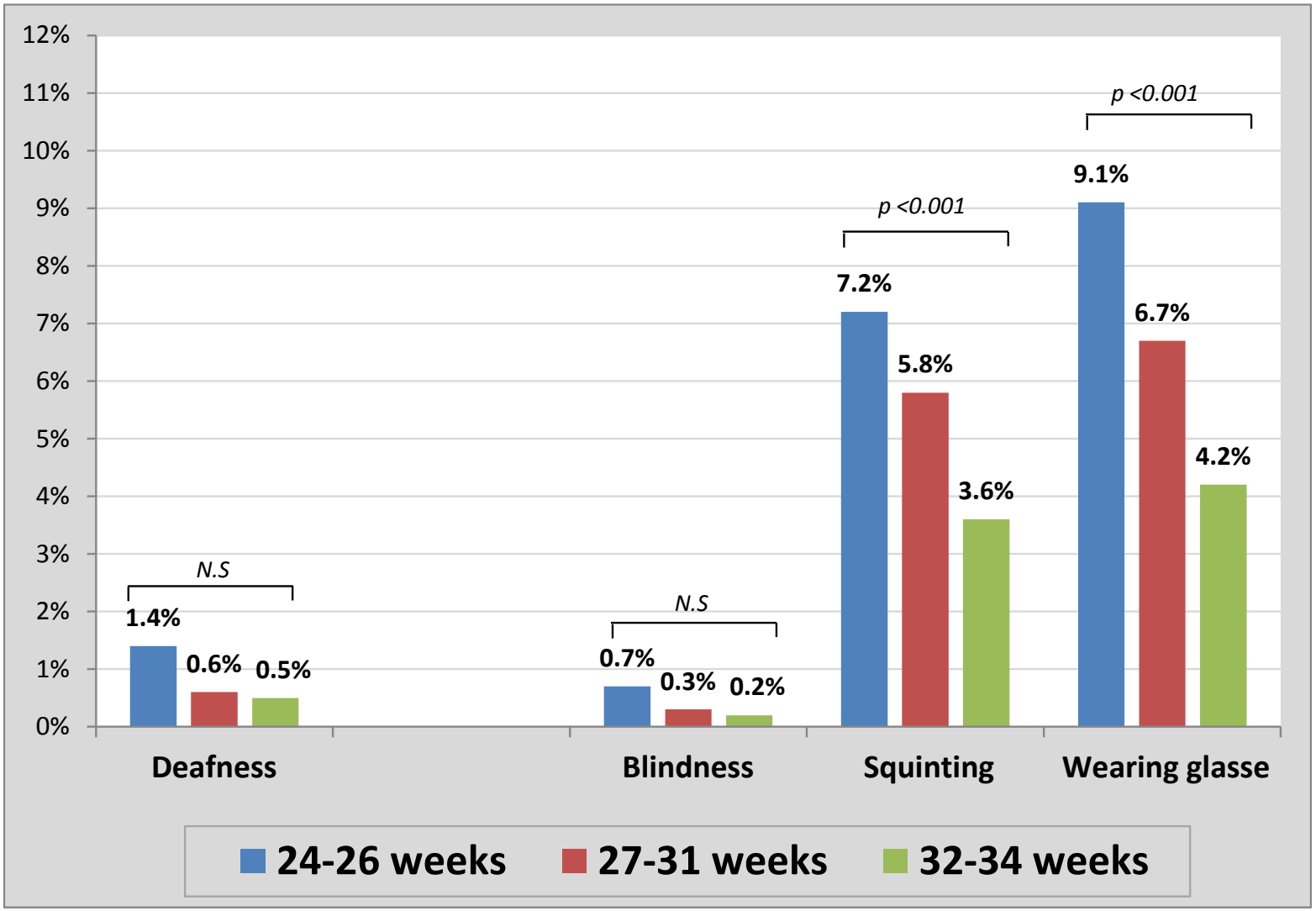


GMFCS : Gross Motor Function Classification System, a higher number indicates a higher degree of severity.

* Comparison between gestational age groups 24-26 weeks / 27-31 weeks / 32-34 weeks.

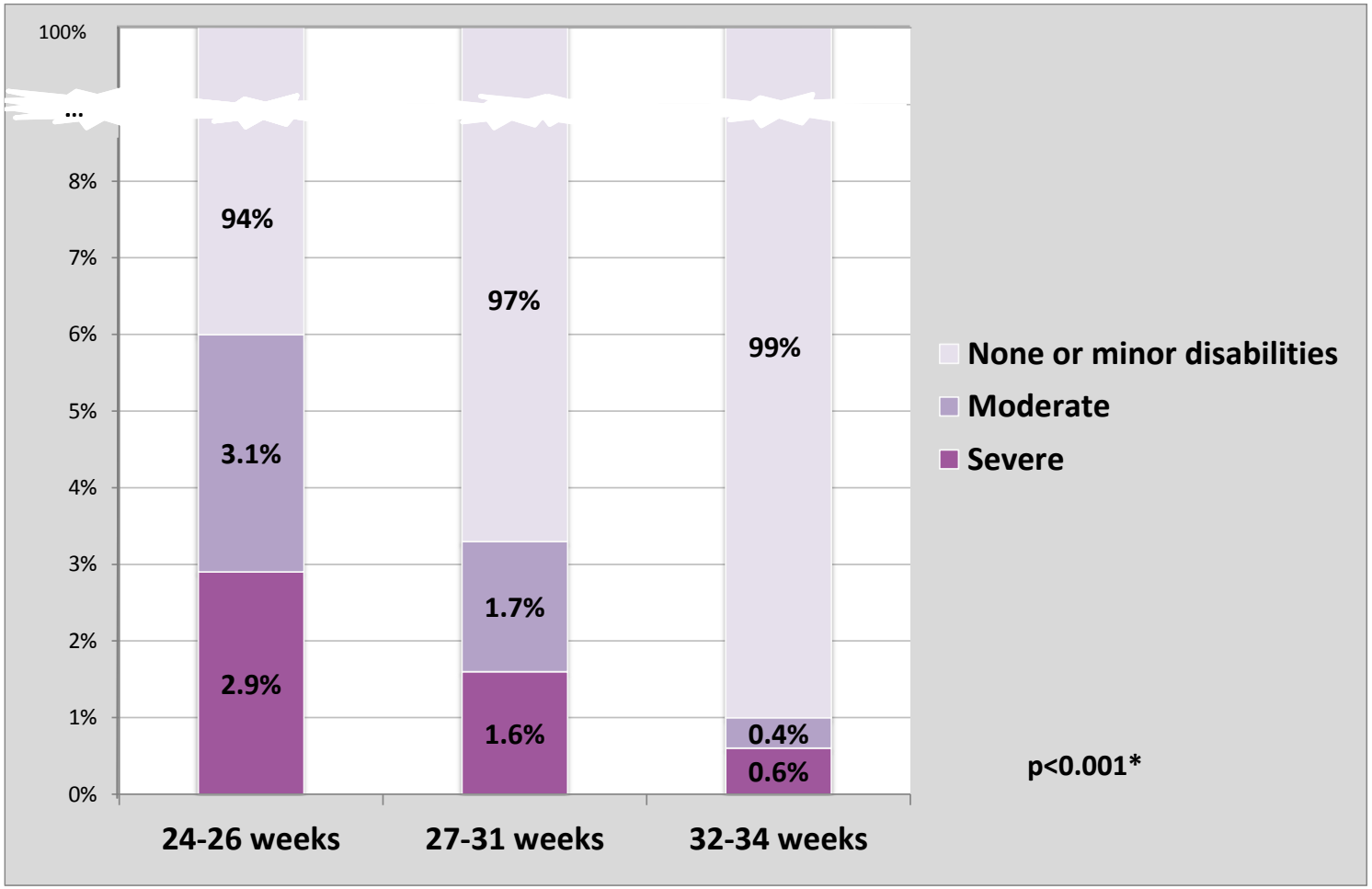
Epipage 2

Visual and hearing impairments at 2 years CA by GA groups



Epipage 2

Neuro-motor or sensory disabilities at 2 years corrected age by gestational age groups



* Comparison between gestational age groups 24-26 weeks / 27-31 weeks / 32-34 weeks.

Severe= cerebral palsy GMFCS levels 3-5 and/or bilateral deafness and/or bilateral blindness.
Moderate= cerebral palsy GMFCS levels 2 and/or unilateral deafness and/or unilateral blindness.

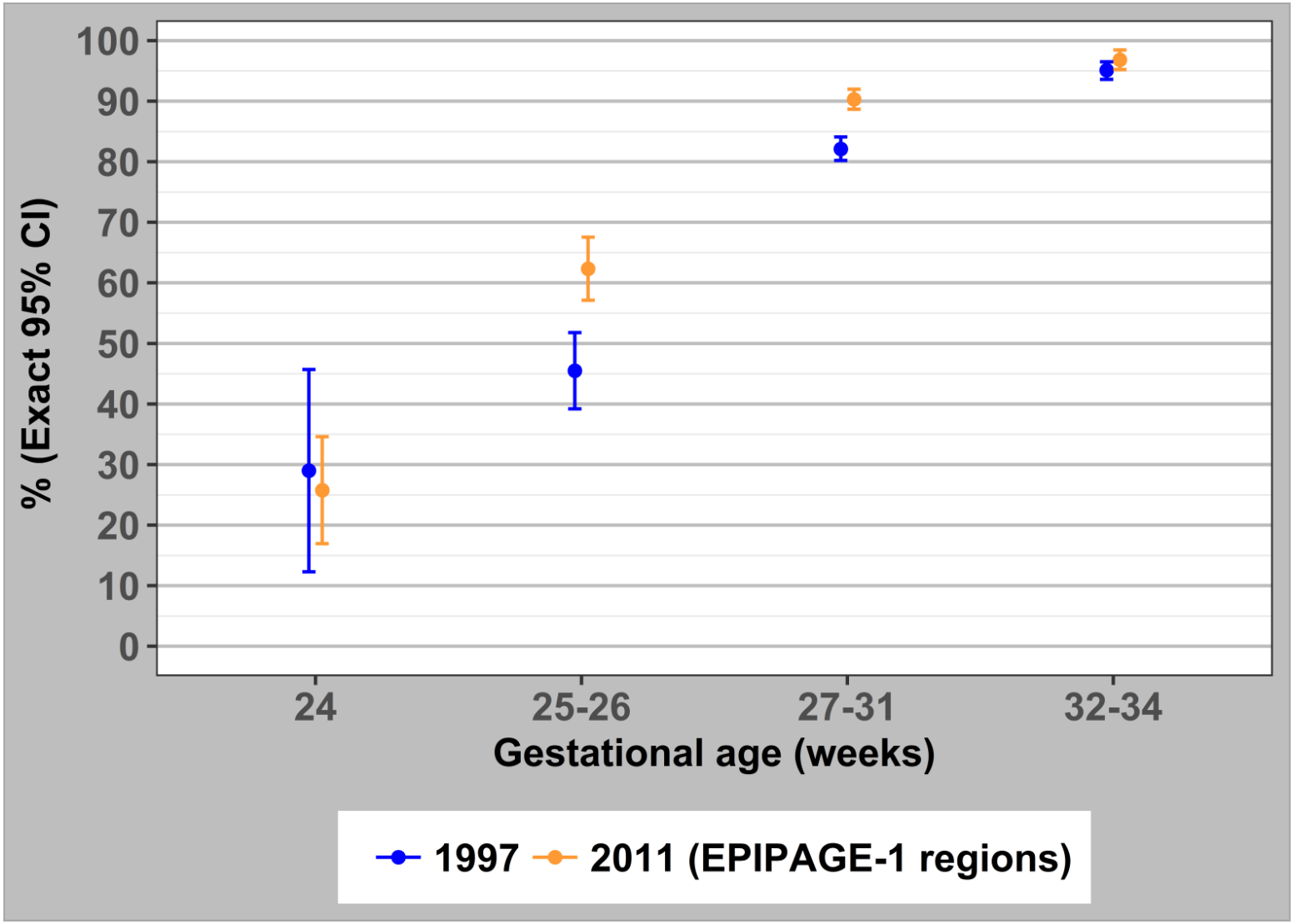
Epipage 2

Survival at 2 years CA among live births

Neuro-motor or sensory disabilities = cerebral palsy GMFCS levels 2-5 and/or deafness and/or blindness.

Comparison 1997 (EPIPAGE-1) *v* 2011

Survivors without neuro-motor or sensory disabilities at 2 years CA among live births



No survivor at 22-23 weeks in the 9 regions participating in both EPIPAGE studies.

Epipage 2

Ages and Stages Questionnaire (ASQ) at 2 years CA by GA groups

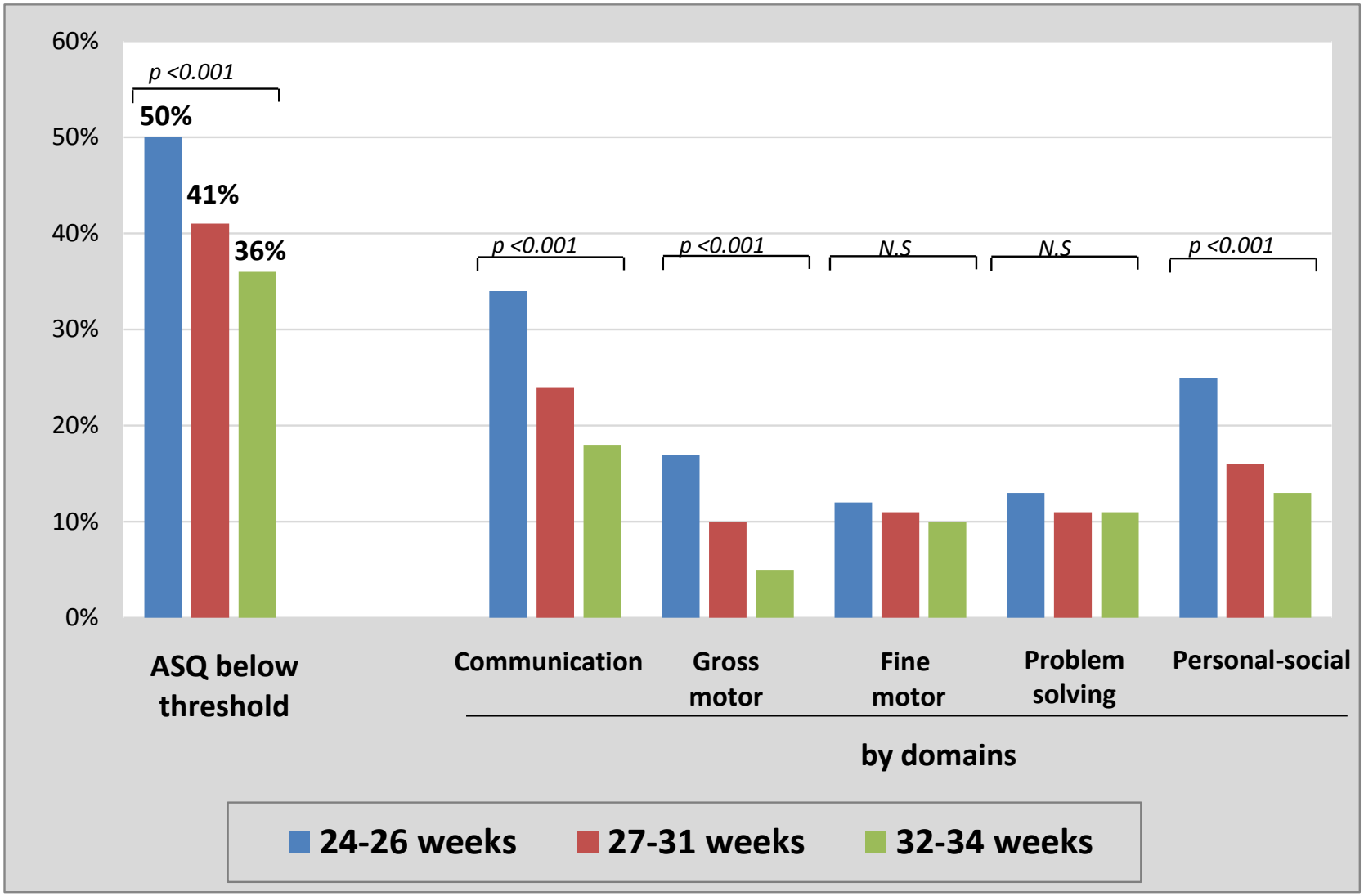
	24-31 weeks* (n = 1884)	24-26 (n = 313)	27-31 (n = 1571)	32-34 weeks (n = 235)	p-value†
ASQ score (median[IQR])	229 [199 to 255]	223 [185 to 250]	230 [200 to 255]	235 [205 to 260]	<0.001

*Including one survivor born at 23 weeks + 6 days

Cut-off of 220 identify children at risk of a developmental quotient (DQ) $\leq$ 85 sensitivity 85%, specificity 72% (Flamant, 2011)

Epipage 2

Ages and Stages Questionnaire (ASQ) at 2 years CA by GA groups



Using established screening cut-off points (Squire, 2009). Infants with cerebral palsy, deafness, blindness or severe congenital anomalies were excluded.

What this study adds

- In France from 1997 to 2011, severe neonatal morbidities in children born preterm decreased, accompanied by a significant increase in survival without severe/moderate neuro-motor or sensory disabilities at age 2 years.

- Despite improvements in neuro-motor and sensory outcomes, a high risk of developmental delay persisted for all children born preterm.

- Depending on gestational age, between half and one third of children born preterm will need formal developmental evaluation, using parental questionnaire as a first step approach to assess development

Epipage 2

IMPLEMENTATION OF DEVELOPMENTAL CARE

Pierrat V, Pediatr Crit Care Med, 2016

Objectives:

To describe

- the unit's policies towards several DC measures in France in 2011
- the evolution since 2004
- the observed practices at the individual level

To compare

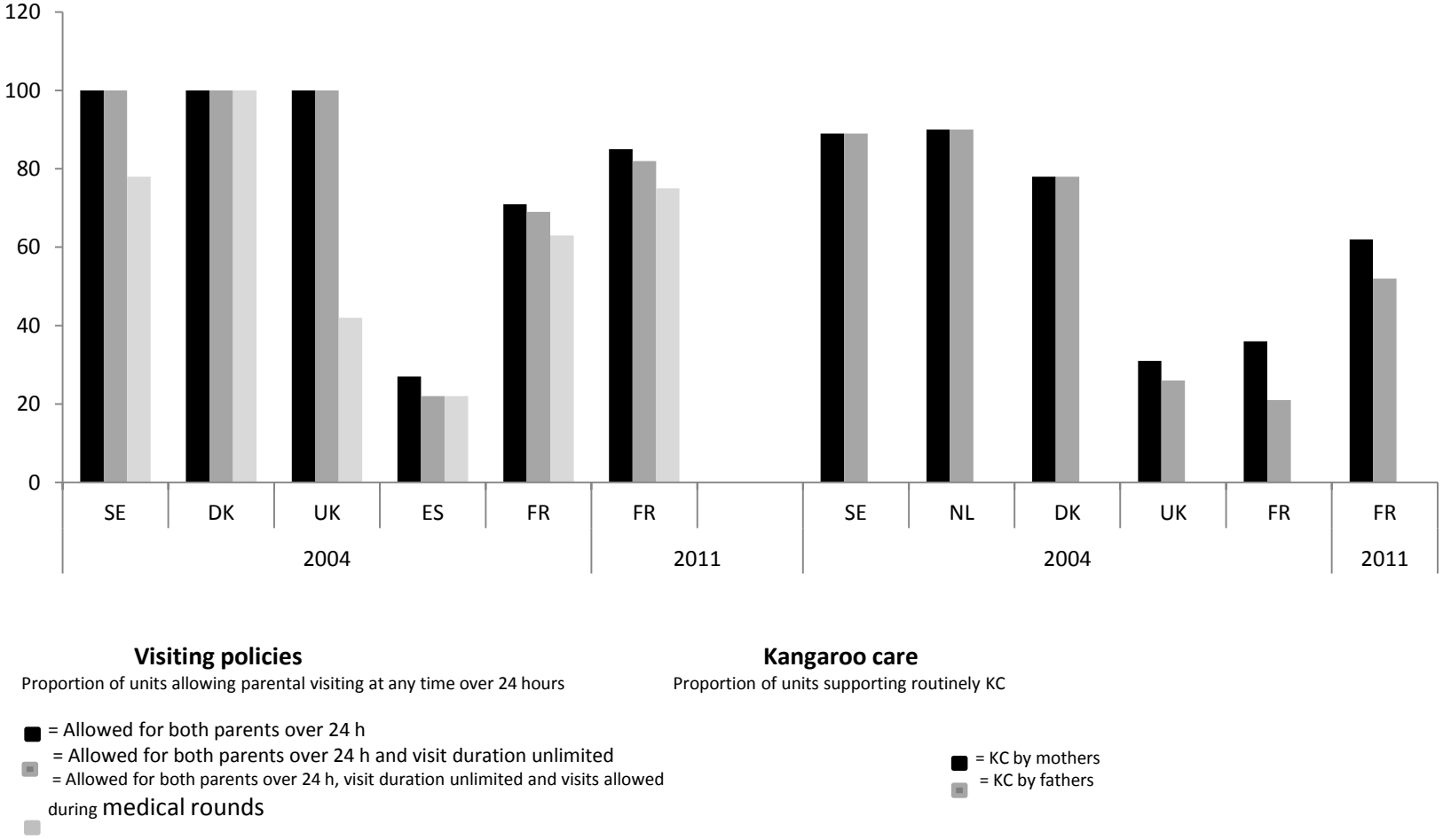
- the data with those of other European countries

DC policies for neonatal units in France from the 2004 European Science Foundation Survey (ESFs) and 2011 EPIPAGE-2 data

	2004 (n=43)	2011 (n=43)	P value*
Characteristics of the units			
In a teaching hospital	26 (60)	26 (60)	
No. VLBW admitted/year, median (range)	109 (50-300)	128 (30-392)	
Developmental care policies			
Visiting policy features			
Allowed for both parents over 24 h	29 (67)	38 (88)	0.03
Allowed for both parents over 24 h, visit duration unlimited and visits allowed during medical rounds	22 (51)	34 (79)	0.01
Facilities for parents			
Beds inside the units	7 (17)	20 (47)	< 0.01
Beds outside the units	22 (51)	23 (53)	0.83
Room to talk and relax	25 (58)	31 (72)	0.11
Bathroom with shower	10 (24)	17 (40)	0.16
Facilities to heat food and/or make drinks	17 (40)	21 (49)	0.32
KC for parents			
Mother routinely encouraged for KC	14 (35)	28 (65)	< 0.01
Father routinely encouraged for KC	8 (20)	25 (58)	< 0.01
Use of a neurobehavioral scale	21 (49)	12 (28)	0.04

Data are n° (%) unless indicated. * McNemar test for pairwise comparison

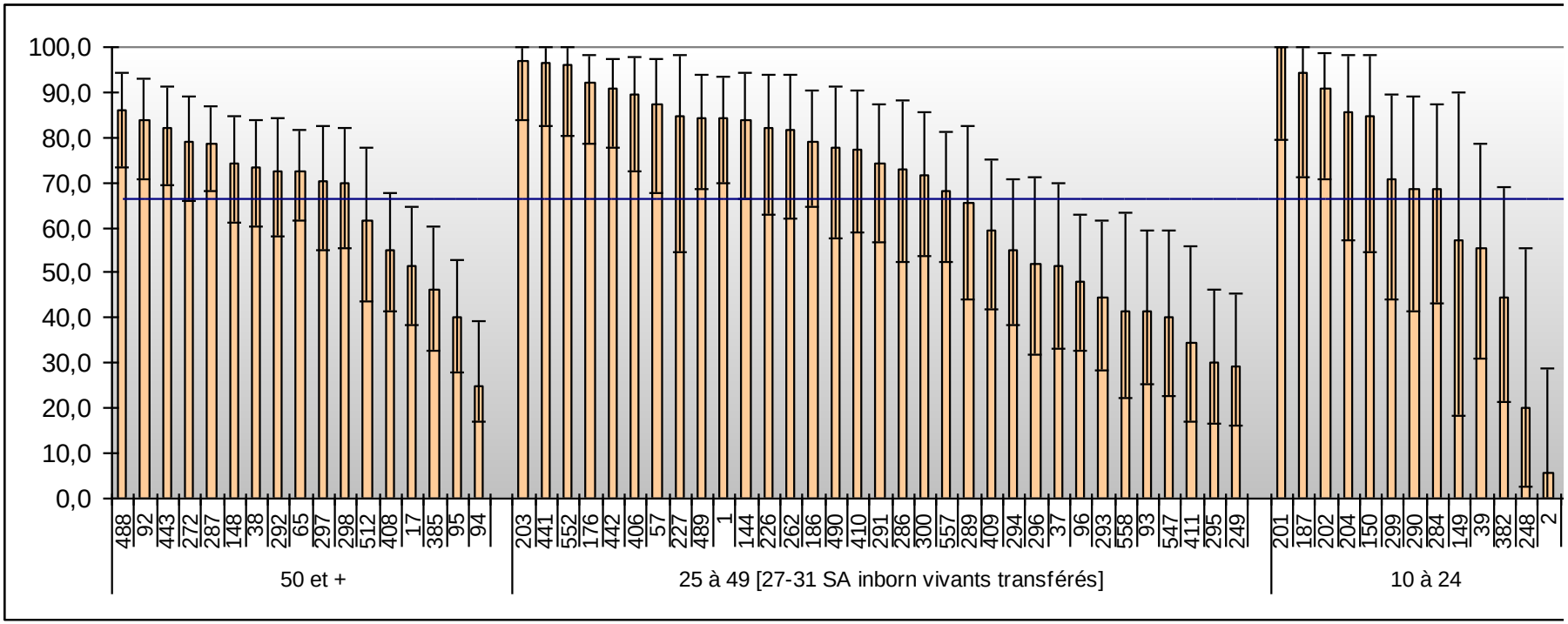
Comparison of visiting policies and kangaroo care with the 2004 European Science Foundation (ESFs) survey data by country and the 2011 EPIPAGE 2 data from France.



SE, Sweden; DK, Denmark; UK, United Kingdom; ES, Spain; FR, France; NL, The Netherlands

Pallas-Alonso C, Pediatr Crit Care Med, 2012

Variability of KC practices* among French units



Population : 27-31 weeks of GA, inborn, admitted in level III units

* KC during the first week of life

Burguet A, in preparation

Epipage 2

KANGAROO CARE AND BREAST FEEDING INITIATION

Pierrat V, Pediatr Crit Care Med, 2016

Objective: To investigate the association of maternal and infant characteristics and unit factors (policies and DC training) with KC initiation

Outcome measure: KC initiation during the first week of life

Variables of interest : KC policies and training in DC

Potential confounders: GA, SGA, single or multiple pregnancy
Nationality, employment before pregnancy, education level

Analysis strategy: Two-level hierarchical logistic regression analysis with patients (patient characteristics; level 1) nested within units (policies and training in DC; level 2).

KC during the first week of life by gestational age (GA) for neonates admitted to level III neonatal units in France in 2011

	Total n = 3005	23-26 weeks GA n = 545 (14%)	27-31 weeks GA n = 2460 (86%)	p-value**
GA, mean (SD)	28.8 (1.8)	25.5 (0.7)	29.4 (1.4)	< 0.01
Weight, mean (SD)	1206.1 (337.4)	813.3 (133.8)	1270.8 (318.1)	< 0.01
KC during the first week of life				
Yes	1694 (61)	159 (32)	1535 (66)	< 0.01
Day 1–3	776 (47)	49 (32)	727 (48)	< 0.01
Day 4–7	891 (53)	105 (68)	786 (52)	
No	1143 (39)	344 (68)	799 (34)	< 0.01
Main causes				
Policy of the unit or nursing staff unavailable	181 (18)	42 (13)	139 (20)	< 0.01
Parents unavailable or anxious	252 (26)	41 (13)	211 (30)	
Infant unstable	575 (55)	235 (74)	340 (49)	
Other	4 (0)	1 (0)	3 (0)	

Epipage 2

KC during the first week of life by groups of units' policies for neonates admitted to level III neonatal units in France in 2011

	KC group 1 n = 6	KC group 2 n = 20	KC group 3 n = 40	p
KC initiation (N, %)	99 (39)	508 (55)	1087 (68)	<0.001

KC group 1: KC allowed only on request for the mother and/or the father, with restrictions on minimal and maximal durations.
KC group 2: KC allowed often or routinely for the mother, only on demand for father, with restriction on minimal duration.
KC group 3: KC encouraged often or routinely for mothers and fathers without any limitation on duration.

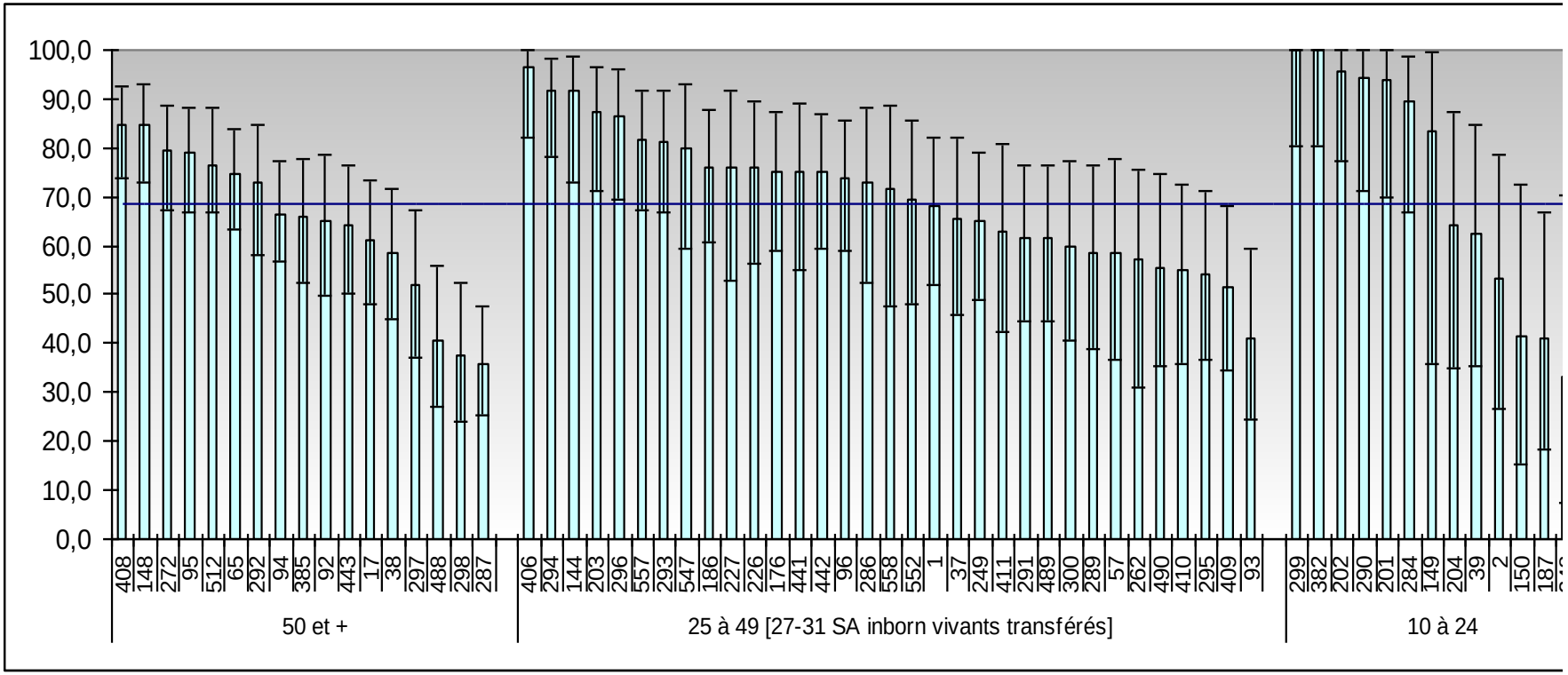
Multilevel logistic regression analysis of patient and unit factors associated with KC initiation

	Model 1 (empty model) n=2636	Model 2 (patient characteristics) n=2636		Model 3 (patient and unit factors) n=2636		
Patient characteristics		OR	95% CI	p-value	OR	95% CI	p-value
Gestational age							
23–26 weeks		1		< 0.01	1		< 0.01
27–31 weeks		5.8	4.5-7.5		5.9	4.5-7.6	
Pregnancy							
Single		1.7	1.4-2.0	< 0.01	1.7	1.4-2.0	< 0.01
Multiple		1			1		
Small-for-gestational age							
No		1.3	1.1-1.6	< 0.01	1.3	1.1-1.6	< 0.01
Yes		1			1		
Mother employed before pregnancy							
Yes		1.8	1.5-2.2	< 0.01	1.8	1.5-2.2	< 0.01
No		1			1		
Unit factors							
KC policies							
Group 1					1		0.02
Group 2					2.3	1.0-5.4	
Group 3					3.3	1.5-7.4	
DC training							
NIDCAP					3.5	1.8-7.0	< 0.01
Sensory motor program					0.6	0.3-1.2	
Introductory course					2.7	1.5-4.7	
No training					1		

Multilevel logistic regression analysis of patient and unit factors associated with KC initiation

	Model 1 (empty model) n=2636	Model 2 (patient characteristics) n=2636	Model 3 (patient and unit factors) n=2636
Random effect			
P value	< 0.01	< 0.01	< 0.01
Variance for neonatal units	1.0757	1.2063	0.6440
Standard error	0.238	0.2668	0.1647
Proportional change in variance (PCV)*		-0.12	0.40

Variability of BF initiation among French units



- Population : 27-31 weeks of GA, inborn, admitted in level III units
- Breast feeding initiation: 1549/2266 (68.4%)
- Units'factors associated with breast feeding initiation: Professional trained in human lactation, fully available for breastfeeding support (OR 1.4 95%CI 1.04-2.0). Nidcap (OR 1.4 95%CI 1.04-1.9).

Conclusion

- Conceptual models to guide clinical care appear to affect French practices

- The application of such models to disseminate and strengthen the implementation of a wider range of DC measures should be explored in different cultural backgrounds

BREAST FEEDING AT DISCHARGE

Mitha A, in preparation

Objective: To investigate the association of maternal and infant characteristics and unit factors (policies and DC training) with BF at discharge

Outcome measure: BF at discharge

Variables of interest : Availability of professionals trained in human lactation and training in DC

Potential confounders: GA, SGA, single or multiple pregnancy
Nationality, employment before pregnancy, education level

Analysis strategy: Two-level hierarchical logistic regression analysis with patients (patient characteristics; level 1) nested within units (policies and training in DC; level 2).

Mitha A, in preparation

Breastfeeding at discharge

- GA: 24-31 weeks
- 47% 95% CI 45-49
- Variations between units: 21% to 84%
- Factors associated with BF at discharge
  - Kangaroo care during the first wek of life
  - Professional trained in human lactation, full-time available for BF support
  - Nidcap

MATERNAL INFORMATION ON PAIN ASSESSMENT AND MANAGEMENT

Pierrat V, in preparation

Epipage 2

Objective: To identify individual and organizational factors associated with maternal information on pain.

Outcome measure: Maternal information on pain

Variables of interest : Training in DC

Potential confounders: GA, SGA, single or multiple pregnancy
Nationality, employment before pregnancy, education level

Analysis strategy: Multinomial multilevel logistic regression analysis with patients (patient characteristics; level 1) nested within units (training in DC; level 2).

Outcome measure: Maternal information on pain

- GA: 24-31 weeks
- N = 1997
- MIP: assessment and management

  Sufficiently informed: 22%
  Somewhat: 45%
  No: 22%

Epipage 2

Factors associated with pain information

Individual characteristics of mothers

Level of education

Cohabitation

Individual characteristics of infants

GA

Characteristics of mothers related to unit organization

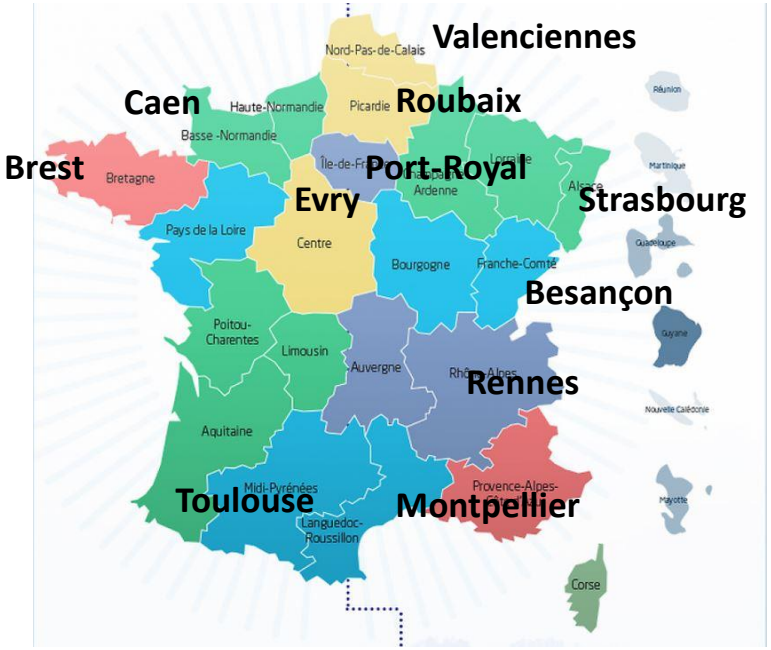
Daily visits of mothers

Team support perceived by mothers

Unit characteristics

Nidcap

NIDCAP IMPLEMENTATION IN 2011



- 1997-2011
- 1 NIDCAP training center (Brest)
- 11 level III units/ 1 level IIb unit

Acknowledgements

We thank all members of the EPIPAGE 2 Study Group who participated to the study for its substantial contribution to the conception, design, and acquisition of data.

- **Alsace:** D Astruc, P Kuhn, B Langer, J Matis (Strasbourg), C Ramousset; **Aquitaine:** X Hernandorena (Bayonne), P Chabanier, L Joly-Pedespan (Bordeaux), MJ Costedoat, A Leguen; **Auvergne:** B Lecomte, D Lemery, F Vendittelli (Clermont-Ferrand); **Basse-Normandie**: G Beucher, M Dreyfus, B Guillois (Caen), Y Toure; **Bourgogne:** A Burguet, S Couvreur, JB Gouyon, P Sagot (Dijon), N Colas; **Bretagne:** J Sizun (Brest), A Beuchée, P Pladys, F Rouget (Rennes), RP Dupuy (St-Brieuc), D Soupre (Vannes), F Charlot , S Roudaut; **Centre:** A Favreau , E Saliba (Tours), L Reboul; **Champagne-Ardenne:** N Bednarek**,** P Morville (Reims), V Verrière; **Franche-Comté:** G Thiriez (Besançon), C Balamou; **Haute-Normandie:** L Marpeau , S Marret (Rouen), C Barbier; **Ile-de-France:** G Kayem (Colombes), X Durrmeyer (Créteil), M Granier (Evry), M Ayoubi , A Baud , B Carbonne , L Foix L'Hélias, F Goffinet, PH Jarreau , D Mitanchez (Paris), P Boileau (Poissy), L Cornu, R Moras; **Languedoc-Roussillon:** P Boulot , G Cambonie , H Daudé (Montpellier), A Badessi, N Tsaoussis; **Limousin:** A Bédu, F Mons (Limoges), C Bahans; **Lorraine:** MH Binet, J Fresson, JM Hascoët, A Milton, O Morel, R Vieux (Nancy), L Hilpert; **Midi-Pyrénées:** C Alberge, C Arnaud, C Vayssière (Toulouse), M Baron; **Nord-Pas-de-Calais:** ML Charkaluk, V Pierrat, D Subtil, P Truffert (Lille), S Akowanou, D Roche; **PACA et Corse:** C D'Ercole, C Gire, U Simeoni (Marseille), A Bongain (Nice), M Deschamps; **Pays de Loire:** B Branger (FFRSP), JC Rozé, N Winer (Nantes), V Rouger, C Dupont; **Picardie:** J Gondry, G Krim (Amiens), B Baby; **Rhône-Alpes:** M Debeir (Chambéry), O Claris, JC Picaud, S Rubio-Gurung (Lyon), C Cans, A Ego, T Debillon (Grenoble), H Patural (Saint-Etienne), A Rannaud; **Guadeloupe:** E Janky, A Poulichet, JM Rosenthal (Point à Pitre), E Coliné; **Guyane:** A Favre (Cayenne), N Joly; **Martinique:** S Châlons (Fort de France), V Lochelongue; **La Réunion :** PY Robillard (Saint-Pierre), S Samperiz, D Ramful (Saint-Denis).
- **Inserm UMR 1153:** PY Ancel, V Benhammou, B Blondel, M Bonet, A Brinis, ML Charkaluk, A Coquelin, M Durox, L Foix-L'Hélias, F Goffinet, M Kaminski, G Kayem, B Khoshnood, C Lebeaux, L Marchand-Martin, V Pierrat, J Rousseau, MJ Saurel-Cubizolles, D Sylla, D Tran, L Vasante-Annamale, J Zeitlin.

Fundings

Epipage 2
Étude épidémiologique sur les petits âges gestationnels

Institute for Research in Public Health and its Financial partners and EQUIPEX investment program for the future coordinated by the National Research Agency (ANR-11-EQX-0038)

The PREMup foundation

La Fondation de France (N° 00050329)

La Fondation pour la Recherche Médicale (N°SPF20160936356)

AGENCE NATIONALE DE LA RECHERCHE ANR

Institut de Recherche en Santé Publique IReSP

Projet soutenu par Fondation de France

70 ANS FONDATION RECHERCHE MÉDICALE

Fondation premup
LE BIEN NAÎTRE, C'EST LA SANTÉ DE DEMAIN